Outcome Evaluation of the In Vivo Cellular and Molecular Imaging Centers (ICMIC) Program

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Executive Summary

Rationale for the Evaluation and Approach

During the mid-1990s, the promise of molecular imaging had not yet been universally recognized, and the necessary tools and approaches for imaging at the molecular level were still in the early stages of development. Therefore, in 1997, the National Cancer Institute (NCI) convened an Imaging Sciences Working Group in order to identify high priority investment opportunities.

NCI created the *In Vivo* Cellular and Molecular Imaging Centers (ICMIC) program as a direct programmatic response to one of the Working Group's recommendations. The overall goal of the ICMIC program was to help molecular imaging realize its full potential as a tool to improve diagnosis and treatment of cancer patients in the clinic and interrogation of biological pathways relevant to cancer in the laboratory. NCI released the first ICMIC Request for Applications (RFA) in 1999. Using the P50 Specialized Centers mechanism, RFA-99-004 solicited applications for ICMIC centers grants of up to $2,000,000 per year in total costs for five years from institutions that already had ongoing investigator-initiated research programs in molecular imaging. RFA 99-002, also issued in 1999, requested applications for "pre-ICMIC" P20 planning awards of up to $400,000 per year for three years from institutions with scientific components necessary for productive interaction but lacking a proven track-record of multidisciplinary scientific research in molecular imaging. Subsequent ICMIC RFAs were issued in 2001 (RFA-01-016) and 2003 (RFA-03-010) before the program transitioned to a Program Announcement (PA) format, with PAs released in 2004 (PAR-04-069) and 2006 (PAR-06-406). The pre-ICMIC RFA was re-issued in 2001 (RFA-01-014).

As of the end of fiscal year 2007, the ICMIC program had funded eight full awards (Johns Hopkins, MGH, MSKCC, Stanford, UCLA, University of Michigan, University of Missouri-Columbia, and Washington University) and sixteen pre-ICMIC awards (five translating into full ICMICs). Total cost for the ICMICs and pre-ICMICs between FY 2000 and 2007 was $115.3 million, including $97.2 million for the ICMICs and $18.2 million for the pre-ICMICs.

NCI decided to conduct an outcome evaluation of the ICMIC program to inform program management about the effectiveness of the ICMIC program in meeting its goals as well as the aspects of the ICMIC program that were most (and/or least) effective in driving progress in cancer molecular imaging. NCI contracted with the Science and Technology Policy Institute (STPI) to conduct the evaluation between August 2007 and October 2008; the evaluation built upon a Feasibility Study conducted by STPI in 2006-2007.

The main unit of analysis for the ICMIC evaluation was either the ICMIC institution or the ICMIC award as appropriate. For certain outcome variables where data can meaningfully be aggregated across institutions (e.g. publications, trainees), the ICMIC program as a whole (sum of all ICMIC institutions) served as an alternate unit of analysis. The main target for the evaluation was the eight institutions that received

ICMIC P50 awards. Of these eight, a sub-sample of three "focal" ICMICs were chosen for more in-depth study: UCLA, MGH, and the University of Missouri-Columbia.

The study design was cross-sectional rather than quasi-experimental. As such, there were no formal comparison groups for the ICMIC institutions. However, because some familiarity with alternative strategies for developing cancer molecular imaging programs is critical to making decisions and recommendations about the program, the evaluation approach included an attempt to characterize the defining features as well as the strengths and weaknesses of non-ICMIC cancer molecular imaging programs. The University of California San Francisco, University of Massachusetts Medical Center, and University of Washington were selected as comparators because their historical strengths in imaging were roughly comparable to the ICMIC institutions. Data were also collected from three of the P20 pre-ICMICs that did not convert to full ICMIC status in order to assess the contribution of the pre-ICMICs.

The study used a diverse set of data sources and analytical techniques, including:

- Analysis of administrative data (ICMIC applications and progress reports, program documentation)
- Analyses of data gathered from NIH and other US Government databases (NIH Query/View/Report system, MEDLINE, clinicaltrials.gov, NIH iEdison database, US Patent and Trademark Office database)
- Interviews with ICMIC PIs, researchers, and trainees, with additional interviews conducted at the three focal ICMIC institutions
- Interviews with investigators at the three comparison institutions and with three pre-ICMIC PIs whose awards did not translate to P50 status
- Bibliometric data (actual and expected citations, journal impact factors) were collected and analyzed for ICMIC publications
- Social network analysis tools were used to visualize collaboration in the conduct and publication of ICMIC-supported research

The study was supported by a panel of three extramural experts (Dr. H. Kim Lyerly, Duke University; Dr. Claude Meares, University of California Davis; and Dr. Juan Rogers, Georgia Institute of Technology). Two NCI staff members (Dr. Anne Menkens, NCI/Cancer Imaging Program; Dr. Lawrence Solomon, NCI/Office of Science Planning and Assessment) served as observers to the panel, providing factual clarification as needed. The expert panel advised study design, commented upon interview guides, and reviewed draft analyses to ensure the quality of the interpretation of study findings.

Attainment of Program Goals and Other Overarching Findings

The Feasibility Study identified six specific programmatic goals, five of which have been present throughout the program and a sixth goal added beginning with the 2004 Program Announcement. The Evaluation's findings with respect to each goal are summarized below:

Program Goal #1: Stimulate, facilitate and enhance high-quality research in the area of cancer molecular imaging.

This goal has been met. Two lines of evidence support this finding. As described in Chapter 4, publication counts show that the publication output of the ICMICs is strong, although there is some variation in publication rate by ICMIC. A total of 755 publications were attributed to the full ICMICs; the steady-state ratio of dollars per publication per year was approximately $100,000 after an initial two-year ramp-up period. An additional 160 publications were identified as associated with the sixteen pre-ICMICs. ICMIC publications appear in a range of journals, including journals specifically targeted to molecular imaging or nuclear medicine, general cancer biology journals, journals aimed at clinical cancer research, chemistry journals, and general-biomedical journals. Bibliometric analysis also shows that the quality of the P50 ICMIC publications is strong, with many publications in high-impact journals and several highly-cited papers. Forty-one ICMIC publications (6%) were in journals with impact factors of twenty or higher, including six papers in *Science*, three in *Nature*, and one each in the *New England Journal of Medicine* and *JAMA*. Looking across all of the ICMIC publications, the average impact factor was 7.08[1], and the median was 4.986.

Program Goal #2: Direct cancer molecular imaging research towards bettering imaging technologies that have potential clinical or laboratory applications.

This goal was added in 2004, so an assessment is premature. The evaluation, however, did identify those clinically-translated discoveries of ICMIC research that have occurred. As described in Chapter 4, ten ICMIC projects have involved clinical trials in some fashion, but only five of those trials rely upon ICMIC discoveries: two trials using new imaging agents or techniques that an ICMIC first developed have been conducted with ICMIC funding, and three other trials have been conducted using techniques first developed at an ICMIC but the trials were funded through other awards. The evaluation also identified several additional discoveries – both agents and imaging techniques – that may enter the clinic in the next year or two.

As described in Chapter 3, ICMIC PIs place varying emphases on translational and clinical research in the conduct of their ICMIC awards. Most PIs agree with the translational focus that began with the 2004 Program Announcement, though some believe that the program shouldn't necessarily require translation because of the continuing need for enabling technology and the opportunities still remaining for imaging to catalyze advances in the understanding of cancer biology.

[1] While there is not a commonly accepted definition of "high-impact-factor journal", or publications of "average" impact factors across biomedical research, for comparison with the average of 7.08, the impact factor of *Cancer Research* is 7.66, and the impact factor of *Molecular and Cellular Biology* is 6.77. The paper with the median impact factor was in the *Journal of Nuclear Medicine*.

Program Goal #3: Support the formation of vibrant, multi-disciplinary communities of cancer molecular imaging researchers at grantee institutions.

This goal has largely been met, but not completely, as the extent of community formation varied across institutions. The assessment of this program goal aimed to answer two questions:

- "Did the research funded by the ICMICs involve a multidisciplinary group of faculty" and
- "Do funded researchers span the community of researchers at ICMIC institutions."

The answer to first of these two questions is described Chapter 5, which assesses the multidisciplinarity of ICMIC-supported research. Faculty from different disciplines and departments collaborate on the majority of individual ICMIC Research Components, though there is some variation across ICMICs. Publications attributed to ICMIC funding support the collaborative and multidisciplinary nature of ICMIC research.

The answer to the second of these questions is described in both Chapter 5 and Chapter 6. Most of the ICMICs included senior faculty spanning imaging technology development, basic cancer biology, and clinical researchers. Moreover, the evaluation finds that the ICMICs have clearly promoted the integration of imaging into the cancer research programs at their institutions, by involving junior and senior faculty from departments where imaging research does not typically occur. At most of the ICMICs, the Developmental Projects played a vital role in integrating new faculty.

Program Goal #4: Provide unique training and cross-training experiences for cancer-imaging researchers.

This goal has been met, though not as originally envisioned. The 1999 and 2001 RFAs described a training focus on graduate students and postdoctoral researchers. However, as described in Chapter 3, ICMICs have selected training strategies based upon local conditions, including the presence of other institutional sources of training funds. While six of the ICMICs train postdoctoral researchers and four train graduate students, two concentrated their Career Development funds on supporting junior faculty, one devoted resources to undergraduate training, and two funded visiting scientists.

Chapter 7 describes the results of ICMIC training efforts. The ICMICs appear to have been successful in providing cross-training opportunities to faculty, postdoctoral researchers, and graduate students. Evidence of a positive impact on overall career trajectory for junior faculty members is already apparent:

- Of the 18 non-tenure track faculty (mostly with Instructor rank) receiving Career Development funding from the ICMICs, twelve (67%) to date have received faculty positions – nine at the ICMIC institutions and three at other institutions.
- Of the 31 postdocs receiving Career Development funding, nine (29%) to date have received tenure-track faculty positions, and seven (23%) others have received non-tenure track instructorships or research staff positions.

Program Goal #5: Enable the acquisition of physical infrastructure to facilitate cancer molecular imaging research.

This goal has been met. As described in Chapter 7, ICMIC Specialized Resources have developed a set of capabilities and expertise that serve ICMIC researchers and other cancer imaging communities at their institutions (and in some cases other institutions as well). Most of the ICMICs developed new imaging techniques as part of research conducted by their Specialized Resources; several developed radiochemistry/synthesis capabilities for the synthesis of new imaging agents.

ICMIC Specialized Resource funds are not typically used to purchase large-scale equipment. These purchases are more likely to be supported through institutional resources, SAIR awards, or the NCRR Shared Instrumentation/High-end Instrumentation programs. As described in Chapter 6, the ICMIC (and pre-ICMIC) programs were identified by principal investigators as helping to leverage institutional investment for the purchase of capital equipment. At several ICMICs the leveraged funds were identified as having exceeded $2 million.

Program Goal #6: Build sufficient organizational infrastructure to effectively coordinate the cancer molecular imaging research enterprise at ICMIC institutions.

This goal has been advanced at most of the ICMIC institutions. The assessment considered two questions: (1) does the ICMIC represent a key portion of the coordinating infrastructure for cancer molecular imaging activity at the institution and (2) does the ICMIC influence the degree to which molecular imaging is incorporated into the basic and clinical research occurring at the institution? The assessment of the attainment of this goal is found in Section 6.4. At six of the ICMIC institutions (MGH, MSKCC, UCLA, Washington University, Michigan, Stanford) there appears to be evidence that the ICMIC program has built organizational infrastructure for coordinating the cancer molecular imaging research enterprise. ICMICs at those institutions are a primary hub for molecular imaging research applied to cancer; have senior clinicians participating in ICMIC research; and are well-integrated into the local Cancer Center and SPOREs.

In addition to the findings specific to individual program goals, the evaluation results also suggest a set of general findings:

1. ***The ICMIC program is a successful example of an NIH P50 program.*** The P50 Specialized Centers mechanism aims to balance research, infrastructure, and training efforts using a team-based approach to science. The individual findings above suggest that the ICMIC program has been successful in meeting the objectives that are common to P50s, and that the ICMICs are exhibiting "Centerness." The Developmental Projects, especially, have been valuable disproportionate to their funding level, as they have both provided opportunities to expand the users of molecular imaging at ICMIC institutions and catalyzed new research efforts, many of which have led either to new ICMIC Research Components or R01-funded awards.

2. ***The addition of the clinical/laboratory application development goal in 2004 may have been overly ambitious.*** Given the various activities carried out in a P50 centers context, adding a clinical research or laboratory application development goal may not have been beneficial. Asking ICMICs to advance the frontiers of molecular imaging techniques, establish multidisciplinary collaborations, train researchers and also move findings from those endeavors toward clinical trials or laboratory application development may have set too many goals for a single program to achieve. As a result, individual ICMIC principal investigators, based upon their interests and the strengths at their institutions, have chosen a varying balance among developing new imaging techniques or agents; on using imaging for discovery research; and clinical translation; the variation in strategy has continued through renewal of individual ICMIC awards. Therefore, the role of the ICMIC program in the "practical application" of imaging technology in the clinic has been limited to date and should be reassessed.

3. ***The program funding level is constraining.*** Especially because of the large number of programmatic objectives (and given high institutional overhead rates at some of the ICMIC institutions), maximum funding of individual ICMICs at $2 million in total costs is overly limiting and threatens the capability of ICMIC investigators to meet all the programmatic goals.

Recommendations: A Next-Generation ICMIC Program Design

Especially because the ICMIC program has been successful to date, recommending options for the future poses challenges. The recommendations assume that NCI leadership believes that the "Center" concept continues to be valuable for advancing molecular imaging because of fostering collaboration, building infrastructure, and training the next generation of researchers. However, it is recommended that the ICMIC program announcement should differentiate between new institutions aiming to enter the ICMIC program and those aiming to renew existing ICMIC awards. New and renewing ICMICs would have different goals, organizational structures, and review criteria.

New ICMICs

The goals and review criteria laid out in the original (1999 and 2001) RFAs would form the basis of proposals by new teams to form ICMICs. The primary objective of the first five years of ICMIC funding would be to support the formation of vibrant, multi-disciplinary communities of cancer molecular imaging researchers at grantee institutions where to date molecular imaging had not yet been well-integrated into the practice of cancer researchers. The P50 Specialized Centers mechanism – which supports a balance of R01-sized Research Components, facilities, training, and pilot projects – is ideal for this purpose.

Because not all new ICMICs would transition automatically to one of the renewing-ICMIC forms described below, applications for new ICMICs should include a sustainability plan that would describe how Specialized Resources initially funded through the ICMIC program could be sustained by the home institution at the end of the

five-year award period. Sustainability planning would involve the ICMIC institution and PI in working to ensure that the Specialized Resources and organizational capabilities developed during the ICMIC funding period would continue regardless of whether the ICMIC award itself was renewed.

Renewing ICMICs

Renewing ICMICs should be designed and reviewed quite differently from how they are envisioned in the current Program Announcement. Two varieties of renewing ICMICs are suggested – "translational" ICMICs and "basic research" ICMICs: Each variety of ICMIC would have its own set of guidelines regarding leadership structure, research and training emphases, support for specialized resources, and prospects for further renewal.

1. ***Translational ICMICs.*** One variety of renewing ICMIC would be explicitly focused on translating successful research from previous iterations of funding into clinical trials while continuing to devote a portion of its funding to the generation of a new round of discoveries. These ICMICs would focus on bringing imaging agents and techniques into the clinic, while continuing preclinical research aiming to ensure a robust pipeline of translatable concepts.
2. ***Basic research ICMICs***. A second variety of renewing ICMICs would be explicitly focused on extending and deepening the initial community-building efforts of the initial iteration. These ICMICs would aim to further expand the use of molecular imaging at their institutions or to address a set of high-priority basic cancer research challenges previously-unstudied using imaging techniques.

Chapter 1: Introduction

1.1: Program Origin and Structure

Over the past several years, molecular imaging has begun to influence many aspects of clinical cancer management. Examples of direct clinical applications include development and testing of targeted molecular imaging agents for the detection and diagnosis of cancer as well as for guiding and monitoring therapeutic interventions. Molecular imaging has also figured prominently in pre-clinical development, for example by facilitating model systems for the discovery and *in vivo* testing of novel cancer therapeutics and systems to validate emerging biomarkers.[2] At this point, the importance of molecular imaging technologies to cancer diagnosis and treatment are well-established, and there is every reason to believe that molecular imaging will continue to play critical roles in the cancer clinic and in the laboratory for many years to come.

During the mid-1990s, however, the promise of molecular imaging had not yet been universally recognized, and the necessary tools and approaches for imaging at the molecular level were still in the early stages of development. In 1997, the National Cancer Institute (NCI) convened an Imaging Sciences Working Group in order to engage in discussions of the issues and needs related to high priority investment opportunities. The Working Group formed seven task forces to provide recommendations to NCI in the following areas:

- Technology Assessment
- Training
- *In Vivo* Molecular Imaging Development
- Match Clinical and Biological Needs with Emerging Technologies
- Screening and Early Detection
- Technology Development
- Image-Guided Treatment[3]

In early 1998, the *In Vivo* Molecular/Genetic Imaging Development task force made a series of recommendations to NCI. These included the following:

> Funding for "Imaging Centers of Excellence." Develop and maintain centers dedicated to molecular/functional imaging research in accordance with the NCI. Staff such centers with personnel from a variety of fields who have a common goal to develop technology to image aspects of human cancer, noninvasively. Assure that the personnel in these centers are in sufficiently close physical proximity, engendering development of strong collaborative ties. Support nascent molecular/functional

[2] This paragraph draws upon National Institutes of Health, "IN VIVO CELLULAR AND MOLECULAR IMAGING CENTERS (ICMICS)", Program Announcement PAR-04-069, Release Date February 27th 2004, "Purpose of this PAR" Section.

[3] NCI Cancer Imaging Program, "Initial Meeting of the NCI Imaging Sciences Working Group", July 17-18, 1997, "Introduction and Purpose of Meeting" and "Recommendations and Actions" Sections http://imaging.cancer.gov/reportsandpublications/ReportsandPresentations/ImagingSciencesWorkingGroup ; last accessed May 15th, 2008.

imaging centers with services and facilities already available in industry or at the NIH.[4]

NCI created the *In Vivo* Cellular and Molecular Imaging Centers (ICMIC) program as a direct programmatic response to this recommendation. As described in the 2004 ICMIC Program Announcement, the overall goal of the ICMIC program has been to help molecular imaging to realize its full potential as a tool to improve diagnosis and treatment of cancer patients in the clinic and interrogation of biological pathways relevant to cancer in the laboratory.[5] The Small Animal Imaging Resource (SAIR) Program, funded through the R24 Resource-Related Research Projects mechanism, was created at the same to address other recommendations from the task force.

NCI released the first ICMIC Request for Applications (RFA) in 1999. Using the P50 Specialized Centers mechanism, RFA-99-004 solicited applications for ICMIC centers grants of up to $2,000,000 per year for five years from institutions that already had ongoing investigator-initiated research programs in molecular imaging. RFA 99-002, also issued in 1999, requested applications for "Pre-ICMIC" P20 planning awards of up to $400,000 for three years from institutions with scientific components necessary for productive interaction but lacking a proven track-record of multidisciplinary scientific research. Subsequent ICMIC RFAs were issued in 2001 (RFA-01-016) and 2003 (RFA-03-010) before the program transitioned to a Program Announcement (PA) format, with PAs released in 2004 (PAR-04-069) and 2006 (PAR-06-406). The Pre-ICMIC RFA was re-issued in 2001 (RFA-01-014).

1.2: Rationale for Evaluation[6]

The ICMIC Program Announcement is due for renewal. This outcome evaluation, conducted during FY2007-08, is intended to inform program management about the effectiveness of the ICMIC program in meeting its goals as well as the aspects of the ICMIC program that were most (and/or least) effective in driving progress in cancer molecular imaging. It will also allow program staff and the NCI Cancer Imaging Program – the Program within the NCI Division of Cancer Treatment and Diagnosis that administers the ICMICs to suggest programmatic improvements in advance of the next competition.

The results of the outcome evaluation are also expected to be of broad interest to a variety of NIH Institutes and Centers (ICs) and other funding agencies for two reasons. First, molecular imaging technology is gaining in importance across a range of basic,

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[4] NCI Cancer Imaging Program, "In Vivo Molecular/Genetic Imaging Development" (Elias Zerhouni, MD, Chair), February 18-19, 1998, Recommendation #1. http://imaging.cancer.gov/reportsandpublications/ReportsandPresentations/ImagingSciencesWorkingGroup/page4; last accessed May 15th, 2008.

[5] National Institutes of Health, "IN VIVO CELLULAR AND MOLECULAR IMAGING CENTERS (ICMICS)", Program Announcement PAR-04-069, Release Date February 27th 2004, "Purpose of this PAR" Section.

[6] The "Rationale for Evaluation" section is reproduced with minor modifications from the NIH Set-Aside Application for the evaluation of the ICMIC Program, Section 2.3, "Timeliness of the Evaluation".

translational, and clinical areas of biomedical science. However, there are currently few comparably large-scale research efforts in molecular imaging supported by NIH. The National Institute of Biomedical Imaging and Bioengineering (NIBIB), National Institute of Mental Health (NIMH), and the NIH-wide Bioengineering Consortium (BECON) have already expressed interest in understanding the extent to which ICMIC Program is driving scientific progress in this area.

Second, a wide range of NIH ICs rely on P-series "Centers" mechanisms to advance research goals. This outcome evaluation will be designed to provide insight into the factors that influence whether Centers programs succeed or fail, as well as potential benchmarks for P50 programs that could be used across NCI or other ICs.

1.3: Structure of this Report

The balance of the report is organized into eight chapters. In Chapter 2, the evaluation design is described in detail, including a description of methods for data collection. Chapter 3 describes the attributes of the various ICMICs, including an analysis of management strategies. Chapters 4-7 report on evaluation findings in the following outcome areas:

- ICMIC Research (Chapter 4)
- Multidisciplinarity (Chapter 5)
- Role of the ICMICs in the context of their institutions (Chapter 6)
- Capacity building (Chapter 7)

The final chapter (Chapter 8) summarizes evaluative findings and recommendations.

Six Appendices include supplemental information collected as part of the Outcome Evaluation.

Chapter 2: Methods

2.1: Evaluative Approach

A Feasibility Study for the ICMIC Outcome Evaluation was conducted between August 2006 and March 2007.[7] The Feasibility Study assembled programmatic information, built initial databases of publications and key personnel, and concluded that a full Outcome Evaluation was both warranted and feasible. A preliminary evaluation design was developed as part of the Feasibility Study, and this was used by NCI program staff and the Office of Science Planning and Assessment to submit a proposal to the NIH Office of Evaluation set-aside fund in summer 2007.

The main unit of analysis for the ICMIC evaluation was either the ICMIC institution or the ICMIC award as appropriate. For certain outcome variables where data can meaningfully be aggregated across institutions (e.g. publications, trainees), the ICMIC program as a whole (sum of all ICMIC institutions) served as an alternate unit of analysis.

The main target population for the evaluation was the eight institutions that received ICMIC P50 awards. Of these eight, a sub-sample of three "focal" ICMICs were chosen for more in-depth study. The ICMICs chosen were the University of California-Los Angeles (UCLA), Massachusetts General Hospital (MGH), and the University of Missouri-Columbia (UMC). These three ICMICs were selected because they were believed to represent the full spectrum diversity across the following variables:

- Type of institution (e.g., Research hospital versus university medical school)
- ICMIC cohort
- Originating as a Pre-ICMIC or not
- Type of research conducted at the ICMIC
- Size/underlying strength of institution

For reasons identified in the Feasibility Study[8], the study design was cross-sectional rather than quasi-experimental. As such, there were no formal comparison groups for the ICMIC institutions. However, because some familiarity with alternative strategies for

[7] Science and Technology Policy Institute, "Feasibility Study for an Evaluation of the In Vivo Cellular and Molecular Imaging Centers Program", March 2007

[8] See Feasibility Study Report for more information. As described on page 27 of the report, reasons include:

- The small number of ICMICs (and the variable influence of ICMICs within home institutions) suggests that statistical power would be insufficient to detect differences between ICMICs and non-ICMICs.
- It was not evident that information could be consistently collected regarding independent variables that may influence cancer research and cancer imaging. Examples of important variables for which comparison data are unlikely to be available include number of investigators carrying out research and level of infrastructure and core support.
- ICMICs do not necessarily account for a sizable fraction of the cancer imaging research occurring at awarded institutions. To the extent that this is true, it is difficult to distinguish the impact of an ICMIC at a given institution.

developing cancer molecular imaging programs is critical to making decisions and recommendations about the program, the evaluation approach included an attempt to characterize the defining features as well as the strengths and weaknesses of non-ICMIC cancer molecular imaging programs. The University of California San Francisco (UCSF), University of Massachusetts Medical Center (UMass), and University of Washington (UW) were selected as comparators because of their historical strengths in imaging that were roughly comparable to the ICMIC institutions. Additional data were also collected from three of the P20 pre-ICMICs that did not convert to full ICMIC status in order to assess the contribution of the Pre-ICMICs.

2.2: Logic Model/Study Questions

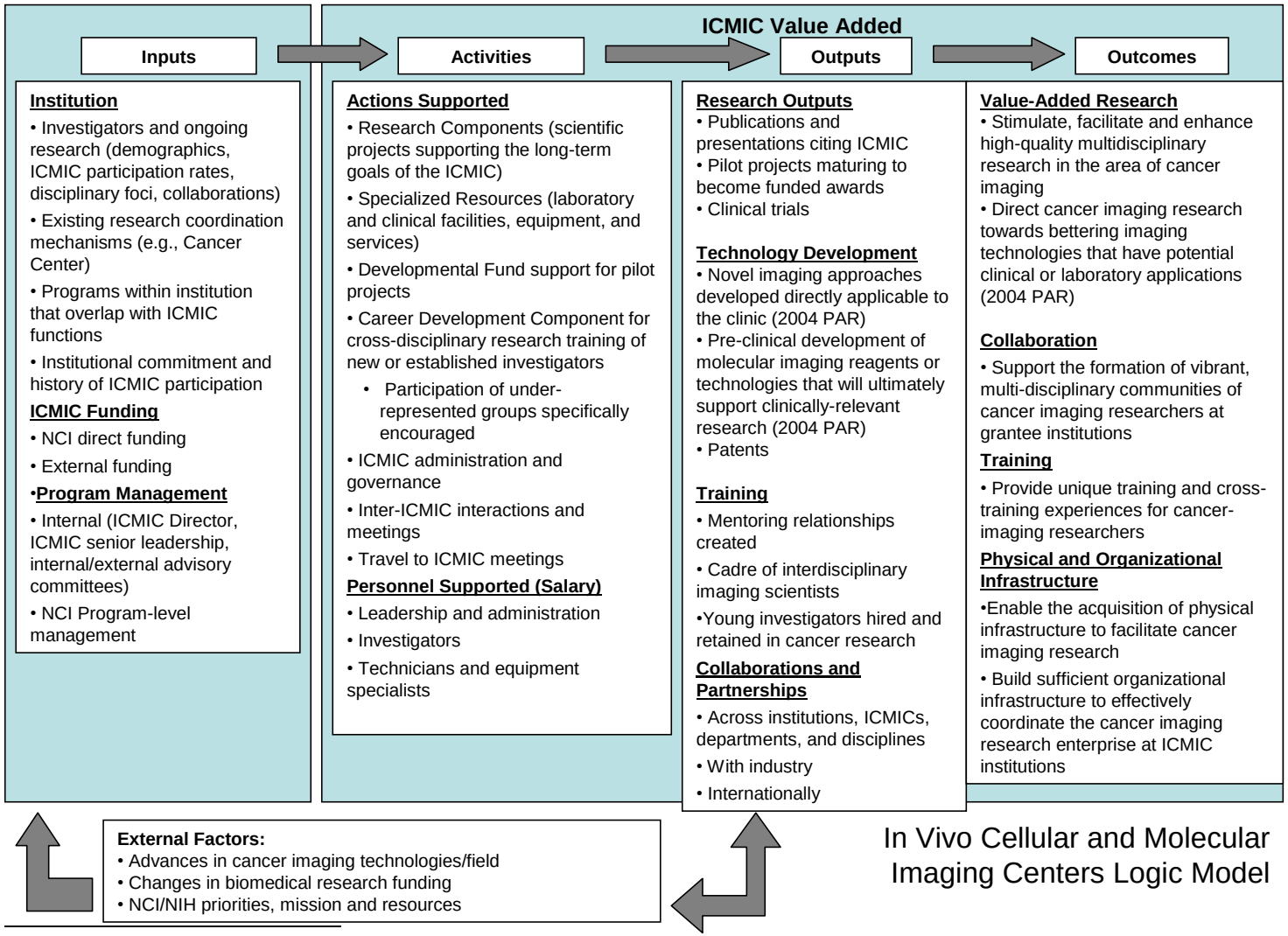
The Feasibility Study identified six specific programmatic goals, five of which have been present throughout the program and a sixth goal added beginning with the 2004 Program Announcement:[9]

1) Stimulate, facilitate and enhance high-quality research in the area of cancer molecular imaging;
2) Direct cancer molecular imaging research towards bettering imaging technologies that have potential clinical or laboratory applications (added beginning with the 2004 PAR);
3) Support the formation of vibrant, multi-disciplinary communities of cancer molecular imaging researchers at grantee institutions;
4) Provide unique training and cross-training experiences for cancer-imaging researchers;
5) Enable the acquisition of physical infrastructure to facilitate cancer molecular imaging research;
6) Build sufficient organizational infrastructure to effectively coordinate the cancer molecular imaging research enterprise at ICMIC institutions.

The extent to which each of these goals has been realized, how they were realized, and to what effect, are all relevant to the proposed outcome evaluation. Based upon review of the RFAs and PAs, a logic model was created to describe the programmatic inputs (e.g., institutional capabilities, funding, program management), activities, outputs, and outcomes of the ICMIC program. As the only substantial programmatic change was to add specifically translational and clinical goals beginning with the 2004 Program Announcement, only a single logic model was developed for the program's entire lifecycle, which is shown as Figure 2.1.

[9] Ibid, reproduced with minor modifications from pages 3-4.

Figure 2.1: ICMIC Program Logic Model[10]



[10] Ibid, reproduced with minor modifications from page 7.

The study questions correspond to the program goals and logic model. Specific study questions for the outcome evaluation were:[11]

1. Has the ICMIC program affected the **quantity or quality of research outputs** in the area of cancer-related molecular imaging at ICMIC institutions? (corresponds to program goal 1)
   - Are there differences in the quantity or quality of cancer molecular imaging research outputs produced by ICMIC institutions relative to comparator institutions?
   - To what extent and with what degree of confidence can any differences in quantity or quality of research outputs be attributed to ICMIC funding?
   - What mechanisms, features, or components of the ICMIC program are most important in improving or hindering research progress?
2. Has the ICMIC program affected **discovery, development, and translation** of imaging-related technologies that will have eventual impact in the clinic or in the laboratory? (corresponds to program goal 2)
   - Have ICMIC-funded institutions produced more translational outputs (e.g., imaging agents, new devices, device improvements, algorithms, protocols)?
   - Do discoveries from ICMICs advance more often or more quickly into clinical trials, preclinical development, or clinical practice?
   - To what extent and with what degree of confidence can translational outcomes be attributed to ICMIC funding?
   - What mechanisms, features, or components of the ICMIC program are most important in accelerating or hindering translational outcomes?
3. Has the ICMIC program affected the **number and/or the quality of multi-disciplinary collaborations** related to cancer molecular imaging? (corresponds to program goal 1)
   - Do the research outputs of ICMIC institutions show evidence of broader, deeper, more integrated, or more frequent multi-disciplinary collaborations?
   - Do ICMIC-affiliated researchers perceive their multi- and interdisciplinary collaborations to be productive and sufficiently integrated?
   - Is there evidence that the "Pre-ICMIC" P20 awards contribute to the formation of new multi-disciplinary collaborations or enhanced existing collaborations?
   - To what extent and with what degree of confidence can multi-disciplinary outcomes be attributed to ICMIC funding?

[11] Study questions reproduced with minor modifications from the ICMIC Outcome Evaluation set-aside application, Section 3.1, "Study Questions", pages 6-7.

- What mechanisms, features, or components of the ICMIC program are most important in accelerating or hindering multi-disciplinary collaboration?

4. Has the ICMIC program lead to the creation or enhancement of **multi-disciplinary communities** of cancer molecular imaging investigators at ICMIC institutions? (corresponds to program goal 3)
    - Does affiliation with ICMIC advance the career goals of junior faculty members, postdocs, and/or graduate students? Are they more likely to continue with careers in cancer molecular imaging research as a result?
    - Do imaging investigators form an unusually large, strong, tight-knit, and/or cohesive "community" at ICMIC institutions?
    - To what extent and with what degree of confidence can community and collaborative outcomes be attributed to ICMIC funding?
    - What mechanisms, features, or components of the ICMIC program are most important in accelerating or hindering community-building?
5. Has the ICMIC program enhanced or built **infrastructure** for cancer-related molecular imaging research at the institutional level? (corresponds to program goals 4-6)
    - Is imaging-related physical infrastructure at ICMIC institutions adequate to the needs of the affiliated imaging researchers?
    - Do ICMIC institutions provide adequate opportunities for training and cross-training?
    - Is organizational infrastructure at ICMIC or “Pre-ICMIC” institutions sufficient to ensure efficient allocation of resources, realize potential synergies (e.g., with Cancer Center Support Grant resources), and successfully advocate for the imaging community within the institution?
    - At “Pre-ICMIC” institutions that did not receive P50 awards, is there evidence that any improvements in organizational infrastructure were sustainable?
    - To what extent and with what degree of confidence can imaging-related infrastructure be attributed to ICMIC funding?
    - Does adequate imaging-related infrastructure exist at comparator institutions? If yes, how was it developed and funded?

2.3: Role of Expert Panel

The study was supported by a panel of three extramural experts from a variety of backgrounds relevant to the evaluation retained as consultants to STPI:

- Dr. H. Kim Lyerly, Duke University
- Dr. Claude Meares, University of California Davis
- Dr. Juan Rogers, Georgia Institute of Technology

Two NCI staff members served as observers to the panel, providing factual clarification as needed

- Dr. Anne Menkens, NCI/Cancer Imaging Program
- Dr. Lawrence Solomon, NCI/Office of Science Planning and Assessment

The expert panel advised study design, commented upon interview guides, and reviewed draft analyses to ensure the quality of the interpretation of study findings. The expert panel also played a key role in selecting focal ICMIC institutions and comparator cases. The expert panel met twice by teleconference, on October 30th 2007 and April 1st 2008, and reviewed materials electronically between teleconferences.

2.4: Data Collection and Analysis

Data Compiled from NIH and Public Records

Information regarding ICMIC awards and outputs was collected from a variety of sources at NCI including NIH databases, ICMIC applications and investigator progress reports, and other administrative documents. Where relevant, data were also extracted from public sources including the USPTO database and MEDLINE. The following information was extracted from these sources for every ICMIC award:

- ***Funding provided to ICMICs by NCI.*** ICMIC funding data from fiscal years 2001-2008 are available from NIH through its Query/View/Report (QVR) datasystem. QVR pulls were supplemented by programmatic data for fiscal year 2000. QVR data were also used to identify molecular imaging-related research themes and Shared Resources at ICMIC institutions.
- ***ICMIC-supported publications.*** An initial database of ICMIC-supported publications had been collated during the Outcome Evaluation Feasibility Study. The final database incorporated additional publications from recent progress reports, applications, and a MEDLINE search. PIs were also invited to review the publications lists and add any publications they thought should be included. The ICMIC publications database covers the period from program inception in 2000 to the end of fiscal year 2007.
- ***Demographic data for selected co-authors of ICMIC publications.*** For individuals appearing as co-authors on three or more ICMIC-supported publications, demographic information was collected from NIH biosketches (supplemented by curriculum vitae where necessary). Demographic information coded from these sources included department, highest degree, and field of highest degree. Medical residency fields were coded based upon the American Council for Graduate Medical Education's characterization, (http://www.acgme.org/adspublic/reports/accredited_programs.asp), while PhD fields were coded based upon the NSF characterization used in the Survey of Earned Doctorates (http://www.nsf.gov/statistics/srvydoctorates/surveys/srvydoctorates_2006.pdf, page 7).
- ***Demographic information for ICMIC key personnel.*** ICMIC key personnel were identified from the budget tables in ICMIC applications and progress

reports. Demographic information was collected for these individuals using the same process described for co-authors above.

- ***Names and demographic information of ICMIC Developmental Project leaders and Career Development awardees.*** Names of Developmental Project leaders and Career Development awardees were identified from the bodies of applications and progress reports. PIs were also invited to review the lists of awardees and add any missed by the initial search. Demographic information was collected for these individuals using the same process described for co-authors above.
- ***Patents attributable to ICMIC-sponsored research.*** USPTO searches were conducted on the names of ICMIC key investigators; patents associated with those investigators were examined to identify where the NIH or the ICMIC award was cited in the patent. A supplemental search was conducted of the NIH iEdison database to identify invention disclosures and patent applications associated with the program; due to confidentiality considerations, the supplemental search results were provided for the program as a whole and do not identify individuals or ICMIC institutions.
- ***Clinical trials conducted or supported by the ICMICs.*** Applications and progress reports were the primary source for identifying clinical trials that were in process or had been completed that either were conducted by the ICMIC directly or where ICMIC resources supported the conduct of the trial (e.g., a radiochemistry core producing radiotracers for an imaging trial). Administrative data were supplemented by a search of clinicaltrials.gov to identify trials conducted at the ICMIC institutions that used imaging agents developed or produced at the ICMICs that had not been mentioned in applications.

Interviews with ICMIC Program Participants and Comparators

A series of semi-structured interviews were conducted with ICMIC program participants and investigators at comparator institutions (Table 2.1). Interviewees were selected from each of the major strata of participants in the following manner:

- *ICMIC Principal Investigators.* All eight PIs were interviewed.
- *Pre-ICMIC Principal Investigators.* Three Pre-ICMIC PIs who also have SAIR awards were asked questions about the role played by ICMIC in building research capacity at their institutions. These questions were asked in the context of a separate Outcome Evaluation for SAIR that is being conducted in parallel with the ICMIC Outcome Evaluation.
- *Investigators serving as current Research Component leaders (focal ICMICs only).* For UCLA and MGH, all current leaders (two from each institution) were interviewed. For UMC, three leaders were interviewed at the suggestion of the ICMIC PI.
- *Investigators who were formerly Research Component leaders or Developmental Project leaders (focal ICMICs only).* STPI developed a draft list based upon information in the applications and progress reports, which was finalized in consultation with the PIs. A total of eight Research Component leaders and four Developmental Project leaders were interviewed.

- *Current and former ICMIC Career Development awardees (focal ICMICs only).* STPI developed a draft list based on information in the applications and progress reports, which was finalized in consultation with the PIs. A total of six current and four former Career Development awardees were interviewed.
- *External advisers (focal ICMICs only).* As part of the UMC case, the PI suggested STPI speak with the chair of their Scientific Advisory Board. While he is not formally a "Comparator" and a different protocol was used many of his insights are similar to those of the members of the comparison group
- *Principal Investigators at Comparator Institutions (UCSF, UW, UMass Medical).* STPI developed a draft list based recipients of imaging-related NCI awards as identified from a search of the NCI Cancer Research Portfolio, which was finalized in consultation with NCI program staff. A total of nine individuals were interviewed.

Table 2.1: Quantity of Interviews Conducted, by Interviewee Stratum

Interviewee Stratum	**Number Conducted**
ICMIC Principal Investigators	8
ICMIC Research Component Leaders	8
ICMIC Former Research Component/ Developmental Project Leaders	4
ICMIC Current Trainees	6
ICMIC Former Trainees	4
Comparators	9
Pre-ICMIC PIs	3
External Advisers	1
Totals	**43**

A separate interview discussion guide was developed for each of the groups described above. Each interview protocol was designed to facilitate "semi-structured" discussions comprised of open-ended questions and responses. Interviews occurred between January 2nd and March 7th 2008, each lasting from 30 to 60 minutes. The interviews were conducted over the telephone with an audio recording service. Transcripts were coded to facilitate analysis of responses by theme.

Analysis of Research Quality

A number of analytical methods were used to assess research quality. These include the following:

Bibliometric Analysis. The following information was purchased from Thomson/ISI in for each ICMIC-supported publication: 1) number of citations to that publication; 2)

expected number of citations to that publication; and 3) journal impact factor.[12] Thomson/ISI matched 717 (95% of the 755) ICMIC publications to their database of bibliometric information.

Analysis of Key Discoveries. ICMIC Principal Investigators were asked during interviews to identify up to three notable discoveries that were supported by their ICMIC funding. STPI performed short literature reviews of four of those discoveries (attached as Appendix C), using published literature, applications, and the interviews to identify: 1) the origins of the discovery and research performed before ICMIC involvement; 2) the nature of ICMIC support, including project origin/design, and collaborations; 3) outcome of the ICMIC-conducted research and any post-ICMIC continuation; and 4) interactions of this research with other ICMIC Research Components and with ICMIC Specialized Resources.

Analysis of ICMIC Personnel as Leaders in the Field. The names of ICMIC key personnel were cross-referenced against the list of conference organizers of the Joint Molecular Imaging Conference (2007); leadership of the Society of Molecular Imaging[13]; leadership of the Academy of Molecular Imaging[14]; and editors of the journals *Molecular Imaging* and *Molecular Imaging and Biology*.

Social Network Analysis

Coded demographic information was used as the input to social network diagrams of authors on ICMIC-supported publications and participants on ICMIC Research Components and Specialized Resources. Those data were analyzed through the social network analysis software UCI-NET 6.0 and visualized as social network diagrams to provide visual interpretations of collaboration patterns across the ICMIC.

Analysis of Overlap between ICMIC Publications and Other NIH Funding

For each of the 755 ICMIC-supported publications, MEDLINE searches were performed to identify any NIH-funded awards that were cited in the acknowledgement section of the paper. Acknowledgements were identified for 559 of the papers (74%), totaling 370 unique NIH awards cited 1,618 times. Where possible, attributes of the cited awards were identified using NIH databases.[15] Attributes coded for each cited award included:

- Principal Investigator and home institution for the cited award

[12] The journal impact factor is calculated by Thomson/ISI for any given year X, as the ratio of (the total number of citations by articles in that journal in years X-1 and X-2 in all Thomson/ISI indexed journals in year X) divided by (the total number of 'citeable' articles in that journal in years X-1 and X-2). Scale runs from zero to infinity. For more detail, see http://en.wikipedia.org/wiki/Impact_factor.

[13] See http://www.molecularimaging.org/electionresults07.php; accessed May 30, 2008

[14] See http://www.ami-imaging.org/index.php?option=com_content&task=blogcategory&id=31&Itemid=115), accessed May 30, 2008.

[15] 1,589 of the cited awards (98%) were successfully matched against NIH records; most awards for which information was unavailable appeared to be contracts, which are not uniformly captured by NIH's enterprise-wide awards datasystems.

- NIH activity code (e.g., P50)
- The NIH Institute or Center administering the award (e.g., NCI)
- Whether the cited award belonged to a large-scale NCI program, including:
    - ICMIC, or the P20 Pre-ICMIC
    - SAIR
    - Cancer Center Support Grants
    - Specialized Programs of Research Excellence (SPORE)
    - Network for Translational Research: Optical Imaging (NTROI)
    - Early Detection Research Network (EDRN)
    - Mouse Models of Human Cancer Consortium (MMHCC)
    - Centers of Cancer Nanotechnology Excellence (CCNE)
    - The Washington University Radionuclide Resource (R24)

From this database of the attributes of cited awards, it was possible to answer a variety of questions about the overlap between ICMIC-affiliated papers and other NIH funding.

Focal ICMIC Case Studies

For the three "focal" ICMICs (MGH, UCLA, and UMC), case studies were developed from interview and other data (attached as Appendix B). The case studies summarize information from the Outcome Evaluation on the following topics for each institution:

- Research Objectives and Research Strategy
- Institutional Context, Funding, and Infrastructure
- Structure of ICMIC Research: Collaboration and Rationale for Participation
- Imaging Research at the ICMIC Institution and the Role of the ICMIC in Fostering the Use of Imaging, and
- Education, Training, and the Role of ICMIC Career Development Funding

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Chapter 3: ICMIC Attributes, Management Strategies, and Institutional Context

3.1: ICMIC Awards and Funding

Between fiscal years 2000 and 2007, a total of sixteen pre-ICMICs and eight ICMICs were funded (Table 3.1). Of the ten pre-ICMICs funded in the FY2000 cohort, five eventually transitioned to ICMIC status; none of the pre-ICMICs funded in the second cohort have transitioned so far. Of the seven full ICMICs funded prior to 2004 that would have been eligible so far for renewals, four had successfully competed for them by the end of FY2007. Several more are expected to compete for renewal in FY2008. In total, therefore, there have been twelve P50 awards funded: four institutions have received one round of ICMIC funding, while four have received two.

Table 3.1 Year of Award for Pre-ICMICs and ICMICs, 2000-2007

Awardee	Year Awarded: Pre-ICMIC	Year Awarded: ICMIC	Year Renewed: ICMIC
University of Michigan	2000	2002	
Stanford University	2000	2005	
Vanderbilt University	2000		
University of Missouri-Columbia	2000	2003	
Johns Hopkins University	2000	2003	
Washington University	2000	2002	2006
University of Pennsylvania	2000		
Indiana University-Purdue University Indianapolis	2000		
Duke University	2000		
University of California- Irvine	2000		
Massachusetts General Hospital		2000	2006
Memorial Sloan-Kettering Cancer Center		2000	2006
University of California-Los Angeles		2000	2006
University of Southern California	2001		
University of Wisconsin	2001		
University of California- San Diego	2001		
Case Western Reserve University	2001		
University of Texas-Southwest Medical Center	2001		
University of Iowa	2001		

Total cost for the ICMICs and pre-ICMICs between FY 2000 and 2007was $115.3 million, including $97.2 million for the ICMICs and $18.2 million for the Pre-ICMICs. Although ICMIC awards were capped at $2 million per year in total costs, there were substantial differences in indirect rates across the ICMICs. During ICMIC PI interviews, one Principal Investigator mentioned that changes in the institution's overhead rate

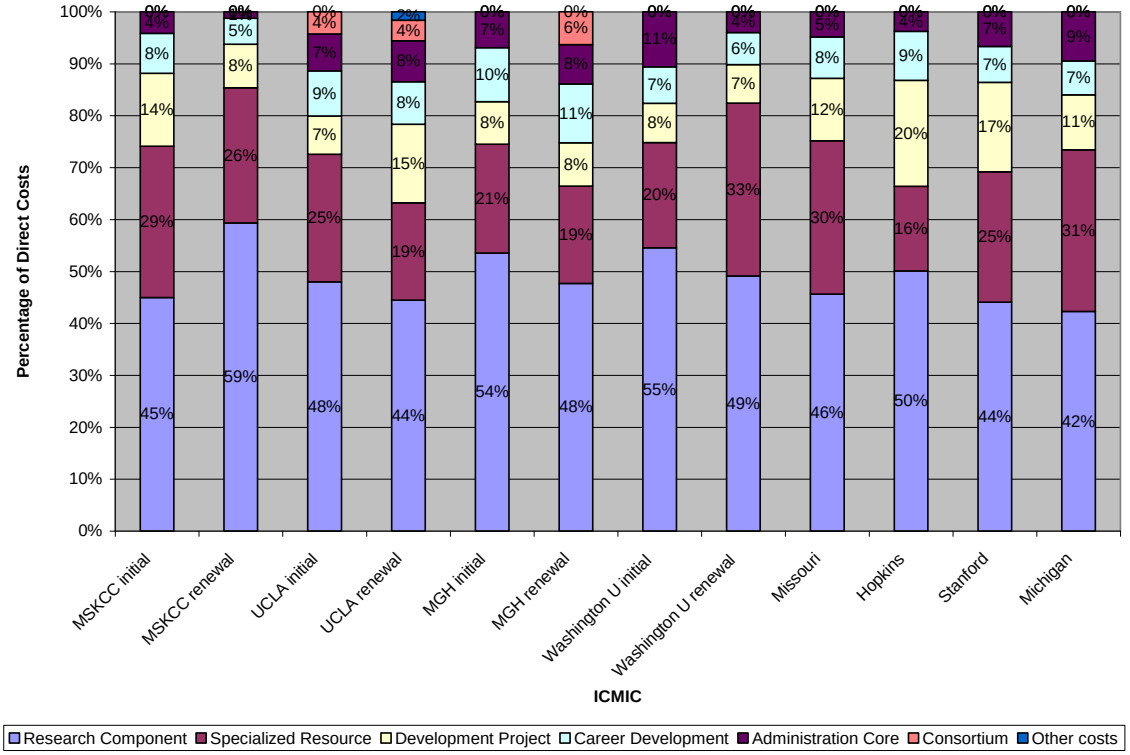
between the initial and the renewal applications reduced funding available for direct costs by more than $200,000 between iterations. Three of the ICMIC awards also included subcontracts: the University of Michigan partnered with the Van Andel Research Institute, resulting in a large subcontract, while individual Research Components of the UCLA and MGH renewals also involved subcontracts.

Expected budget components for ICMIC applications as described in the RFAs included the following:

- **Administrative infrastructure and leadership.** Generally, this was expected to consist of support for a Principal Investigator (PI) and one or more co-PIs plus dedicated administrative support, an internal management committee, and an external advisory body.
- **Research Components.** Three or more research subprojects, comparable in size and scope to an R01 or P01.
- **Specialized Resources.** Core facilities that support the Research Components and other ICMIC research.
- **Developmental Fund.** Funds used to support pilot projects.
- **Career Development Awards.** Intended to support training and career development for ICMIC-affiliated investigators.
- **Consortium.** Subcontracts from the lead institution to other institutions. At the Michigan ICMIC, the subcontract (to the Van Andel Research Institute) comprised approximately one-third of the ICMIC budget and included the cost of one Research Component and one Specialized Resource, while at other ICMICs subcontracts included subawards within individual Research Components to incorporate expertise not available at the lead institution.
- **Other Costs**. For example, a small portion of the budget could be dedicated to supporting travel to ICMIC investigator meetings.

The eight ICMICs were fairly similar with respect to distribution of direct funds across budget categories; at these institutions between 40 and 60% of award funds supported the Research Components, with an additional 16 to 33% supporting Specialized Resources (Figure 3.1).

Figure 3.1: Breakdowns of Spending, by ICMIC



Source: ICMIC applications
Note: For the Michigan award, consortium costs for the subcontract to the Van Andel Research Institute were allocated to functional budget categories, and F&A costs were allocated proportionately to the direct costs.

Despite this apparent similarity in budget structure, there were significant differences among the ICMICs with respect to management goals and strategies. These differences are discussed below in the context of management strategies for each of the ICMIC components.

3.2: Leadership Structure

Aspects of the ICMICs' leadership structures considered in the evaluation included the appointment of a co-PI; the composition of the executive committee or governing body that assists the PI in management; and the composition of advisory bodies that assist the ICMIC in setting future strategic directions. While there were similarities in organization across many of the ICMICs, there were variations among them (Table 3.2). Six of the eight ICMIC institutions included a co-PI (all but MGH, Washington University). Of those six, two (Johns Hopkins, MSKCC) included two co-PIs – and the MSKCC renewal application envisioned a transfer of the PIship mid-way through the funding period from Dr. Blasberg to Dr. Larson as research moved toward the clinic.

The composition of ICMIC executive committees also varied. Eight of the twelve funded ICMIC iterations included Research Component and/or Specialized Resource leaders on the executive council. UCLA, in its renewal, used a variation, including both current and former Research Component leaders on its executive committee. Stanford, Missouri, and

Washington University, on the other hand, included senior researchers with research interests and expertise considered valuable in managing the ICMIC on their executive councils. MSKCC combined both approaches; the MSKCC executive board included Research Component, Specialized Resource, and Developmental Project leaders, as well as department chairmen and heads of cross-cutting programs (e.g., Molecular Pathology and Chemistry).

Table 3.2: Categorization of ICMIC Administration

ICMIC-Funding Round Pair	Has co-PI	Executive Committee Membership includes RC/SR leaders?	Executive Committee Membership includes others?	Has internal advisory board?	Composition of external advisory board
MGH Initial	No	RC and SR	No	Yes (5 faculty)	4 faculty
MGH Renewal	No	RC and SR	No	No	6 faculty
MSKCC Initial	Yes	RC, SR, and DP	4 department chairs, 3 program directors	No	4 faculty
MSKCC Renewal	Yes	RC, SR, and DP	3 department chairs, 3 program directors	No	5 faculty
UCLA Initial	Yes	RC	No	Combined advisory board: 3 external, 3 internal	
UCLA Renewal	Yes	Current and former RC	No	Combined advisory board: 3 external, 3 internal	
Washington University Initial	No	Not necessarily	10 senior faculty	No	2 faculty
Washington University Renewal	No	Not necessarily	8 senior faculty	No	3 faculty
Johns Hopkins	Yes	SR and head of Career Development program	No	Yes (6 faculty)	4 faculty
Michigan	Yes	RC and SR	No	Yes (3 faculty)	3 faculty
Missouri-Columbia	Yes	Not necessarily	4 senior faculty	No	4 faculty
Stanford	Yes	Not necessarily	3 senior faculty	Yes (9 faculty)	4 faculty

Source: ICMIC administrative data

The cost of administration was included in each ICMIC's Administrative Core, which covered the cost of advisory board meetings, some of the time of the PI (and co-PI), and administrative support. All of the ICMICs also described supporting a seminar series as well as periodic meetings for conveying the research results and capabilities of their ICMIC to a broader community of cancer researchers and oncologists. The costs of ICMIC-wide meetings such as seminar series or annual retreats generally were covered under the Administrative Core as well.

3.3: Research Components

Although the ICMICs share a common goal of advancing the frontiers of biomedical and molecular imaging related to cancer, the ICMICs used different strategies in choosing which research projects to fund. Some ICMICs pursued particular strategies based on existing research strengths. For instance, the Johns Hopkins ICMIC has a focused biological theme, the study of hypoxia, metabolism, and the tumor microenvironment in creating or harboring stem-like cancer cells. Other ICMICs focused on specific technological problems, such as radiolabeled molecular imaging constructs capable of *in vivo* uptake and retention in cancer cells (University of Missouri-Columbia); probes with enzyme and transporter specificity to pinpoint molecular events within cells (Washington University); or novel molecular imaging reporters for specific biological events (University of Michigan). The other four ICMICs stated broader aims similar in scope to the overall program goals that did not significantly narrow the spectrum of possible research topics. Similarly, interviewees at comparator institutions reported using a variety of imaging modalities (e.g., PET, SPECT, MRI) for imaging, and their activities ranged from developing new imaging agents for cancer detection to the use of imaging for detecting treatment response or cancer progression.

When asked to explain how they selected Research Components, PIs reported using a range of strategies. Some PIs conducted an internal call for proposals across their institution or within the ICMIC core group, while others selectively targeted individuals or teams with ongoing research projects of interest to join the team. In some cases, there was a conscious effort made to include junior faculty as either PIs or co-PIs. Some PIs reported looking for projects they believed could stand alone as R01 proposals, while others made a point of choosing projects that they did not believe would be fundable as separate R01s but would benefit from the synergies established through the ICMIC.

> The four projects that were ultimately chosen represent the interface of important problems where we had sufficient initial data and local expertise to make a dent in the equation – ICMIC PI

> They were chosen by an enlightened bureaucracy, I like to think, because we didn't have a general call. We discussed with people the people we thought could put together the best applications, and those were the people who were included – ICMIC PI

PIs of the four ICMICs that had been renewed described that they had substantially changed the Research Components included in their renewal applications relative to their initial iterations. In most cases, "change" involved either forming new teams of researchers or for ICMIC collaborators from the initial iteration to initiate new lines of research; in a different approach, both the UCLA and MSKCC ICMICs, in their renewals, proposed to translate research begun through Research Components during the initial iteration into the clinic. There was substantial turnover of faculty between the initial and renewal iterations of these four ICMICs (Table 3.3), with the percentage of faculty participating in both iterations ranging from 15% (UCLA) to 38% (MSKCC).

ICMIC Research Components were categorized by intended research outcome based on an analysis of their specific aims (Table 3.4). Projects that focus on pre-clinical development of reagents and technologies that were not intended to be used in patients

were placed in one category, while projects that if, successful, could be translated directly into human clinical use were placed in another. Of the projects that were considered "directly clinically applicable", Research Component descriptions and budgets were assessed to identify whether funding for that Research Component included studies in humans.

Table 3.3: Faculty Participation in Renewed ICMICs

ICMIC	Both Iterations	Initial Only	Renewal Only	Total Faculty	Percentage of Total in Both Iterations
MGH	6	4	12	22	27%
MSKCC	10	8	8	26	38%
UCLA	4	8	15	27	15%
Washington University	8	13	4	25	32%

Source: STPI analysis of ICMIC Administrative data
Note: Table 3.3 includes faculty who were listed on budgets of Research Components or Specialized Resources, and does not include faculty who served only as unpaid collaborators.

Table 3.4: Categorization of ICMIC Research Components

ICMIC-Funding Round Pair	Include pre-clinical development of reagents or technologies, but no research whose products were intended for human clinical trials	Include research whose products, if successful, were intended for human clinical trials	Of the "directly clinically-applicable" Research Components, number that included funding for research involving human subjects in the RC itself
MGH Initial	0	4	0
MGH Renewal	0	4	0
MSKCC Initial	0	4	1
MSKCC Renewal	0	5	4
UCLA Initial	3	1	0
UCLA Renewal	0	4	2
Washington University Initial	3	1	1
Washington University Renewal	3	1	1
Johns Hopkins	2	2	0
Michigan	2	1	0
Missouri-Columbia	0	5	0
Stanford	2	2	1
Total	15	34	10

Source: STPI analysis of ICMIC Research Components

Of the forty-nine ICMIC Research Components, nearly three-quarters (34 of 49 or 69%) were intended to transition to the clinic, and at least ten projects involved actual clinical research funded as part of the Research Component. Some ICMICs included more clinically-oriented Research Components than others. In fact, six applications proposed Research Components that were all clinical in intent (MGH initial and renewal, MSKCC initial and renewal, UCLA renewal, Missouri-Columbia), while the remaining six account for only nine additional clinically-oriented projects and funding for three trials. In interviews, most ICMIC trainees and Research Component leaders stated that they expect their research to have an eventual clinical impact, but much work remains to be done before it can enter the clinic.

When asked whether they would support a shift in ICMIC program goals towards more exclusive focus on clinically-oriented research, most PIs supported the current program goals, which allow for a mix of basic and clinical research activities. At least one PI defended the continued inclusion of basic research components:

> Taking the impact that ICMICs have had on basic cancer biology, that's what's really new, and that's what has tremendous impact on how the way science is done [at] major medical centers and how drugs are assessed at big pharma.

However, another PI strongly disagreed with the idea that using molecular imaging to probe fundamental biological problems should remain a goal of the ICMIC program, stating about basic science research at ICMICs that, "a lot of the research is really very fundamental research that probably ought to be funded by a more basic [research program], and not as an imaging center itself." Several interviewees cautioned that, although they support inclusion of clinically-oriented research in the ICMIC program goals, ICMIC should not seek to support projects beyond early-stage clinical trials.

> I see it more as a seed for proving the principle, and then other entities meet to help fund this multi-center trials.... I don't know what the mission of ICMIC is with regards to large clinical trials, but I don't think that that should be it. – ICMIC trainee

3.4: Developmental Fund

One purpose of the Developmental Fund as described by the PIs was to provide pilot data that supported new grant applications for independent funding and yielding publishable results. Principal Investigators of three of the four ICMICs that have been renewed indicated that they relied heavily upon findings from Developmental projects during the first ICMIC in setting the research agenda for their renewal applications. In several cases, Developmental Components from the initial ICMIC were converted directly into Research Components for the renewal (Table 3.5).

Table 3.5: Research Components in the Renewal with Influenced by Developmental Projects from the Original ICMIC

ICMIC	Number of Research Components in Renewal	Number of Renewal Research Components that Originated as Developmental Projects	Number of Renewal Research Components that were Influenced by Developmental Projects
MGH	4	0	1
MSKCC	5	1	1
UCLA	4	2	1
Washington University	4	3	0

Source: STPI analysis of ICMIC Research Components

For example, at UCLA, the Principal Investigator described identifying the results of the initial ICMIC that were ripe for clinical translation and proposing them as Research Components in the renewal. At MGH, one of the renewal Research Components relied on a technology that had been validated as a developmental project. Also at MGH, two of the renewal Research Component leaders had been Developmental Project.

The Developmental Projects also create opportunities for collaboration. Several of the ICMICs managed their Developmental Funds in order to promote collaboration or multidisciplinary research. Eight of the ICMIC applications (all but MSKCC, Washington University renewal, Missouri) make reference to a requirement that Developmental Projects be "interdisciplinary" or "multidisciplinary" in their description of the overall operation of the Developmental Fund or of review criteria that ICMICs' governing bodies will use for selecting Developmental Projects. Although the MSKCC ICMIC did not describe a requirement that its Developmental Projects be "interdisciplinary" or "multidisciplinary", the ICMIC created a structure for considering and identifying new Developmental Fund ideas called the "Think Tank." The "Think Tank" is a multidisciplinary group of junior and senior investigators who meet bi-monthly to discuss and sharpen potential ideas for Developmental Projects. It was expected (though not explicitly required) that participation in the Think Tank would ensure the multidisciplinarity of the resulting Developmental Projects.

A third purpose of the Developmental Funds described by most of the PIs was to encourage the submission of proposals from investigators not traditionally involved in molecular imaging in the service of cancer research – either in soliciting ideas from across the institution or in including new investigators as a Developmental Project review criterion.

3.5: Specialized Resources

The Specialized Resources were intended to provide centralized services across the ICMIC, using dedicated funds, personnel, and infrastructure to support ICMICs'

research. The Stanford and Washington University applications specifically described features of the Specialized Resources (though the features are general across all of the ICMICs) that make these core resources instrumental in facilitating collaboration. Specialized Resources were generally utilized by multiple ICMIC Research Components, often as an informal convening point where ICMIC participants might meet and discuss their research.

Despite the substantial differences in the overall level of funding devoted to Specialized Resources (Figure 3.1), there were commonalities across the types of resources provided to ICMIC researchers. Table 3.6 identifies the functions funded through ICMIC Specialized Resources. All of the ICMICs supported Specialized Resources devoted to chemical/radiochemical synthesis, and virtually all of them devoted funds to small animal imaging and image analysis – with Washington University not funding imaging directly (a SAIR-supported function) and Missouri-Columbia not specifying the inclusion of image analysis in its imaging Specialized Resource. Most ICMICs supported some form of molecular biology Specialized Resources, and individual ICMICs funded Specialized Resources for producing transgenic mice, tissue banks, high-throughput screening, or for translating results toward the clinic.

Table 3.6: ICMIC Support for Specialized Resources

ICMIC-Funding Round Pair	Chemical synthesis	Imaging	Image Analysis/ statistics	Molecular Biology	Mouse Models	Tissue Bank	Translational Support	High-Throughput Screening
MGH Initial	Yes	Yes	Yes					
MGH Renewal	Yes	Yes	Yes	Yes				
MSKCC Initial	Yes	Yes	Yes	Yes				
MSKCC Renewal	Yes		Yes	Yes				
UCLA Initial	Yes	Yes	Yes					
UCLA Renewal	Yes	Yes	Yes					
Washington University Initial	Yes		Yes	Yes				
Washington University Renewal	Yes			Yes	Yes			Yes
Johns Hopkins	Yes	Yes	Yes	Yes			Yes	
Michigan	Yes	Yes	Yes		Yes			
Missouri-Columbia	Yes	Yes		Yes		Yes		Yes
Stanford	Yes	Yes	Yes	Yes				

Source: STPI Characterization of ICMIC Specialized Resources
Note: "Molecular Biology" includes Vectors, Assays [e.g. blots], Cell lines) Cell Sorting, Pathology, Histology, Xenograft Studies

3.6: Career Development Funds

Interviews with ICMIC PIs and review of application materials identified a range of career development strategies employed by individual ICMICs to meet local needs (Table 3.7). ICMICs devoted Career Development resources to:

> We started recruiting people who had either a background in imaging and we trained them in molecular techniques, or we recruited people who had a background in basic sciences or in molecular techniques, and we cross trained them in imaging. – ICMIC PI

- ***Faculty support at the Instructor or Associate Professor level.*** Four ICMICs devoted Career Development resources to supporting junior faculty members – with faculty support representing the sole use of Career Development funds at Johns Hopkins and at MGH. MGH focused on faculty at the Instructor level, while Johns Hopkins supported tenure-track Associate Professors.
- ***Postdoctoral fellows.*** All the ICMICs except for Johns Hopkins and MGH provided support to postdoctoral fellows. Several of the ICMICs made specific reference to cross-training investigators as part of their Career Development programs; and some described co-mentorship opportunities where postdoctoral fellows would be supervised by a cancer biologist and an imaging scientist. One economic incentive mentioned by several ICMIC faculty during interviews for focusing on postdoctoral-level trainees is that paying the costs of tuition (especially for graduate students) can be quite expensive, and so it is possible to train a larger number of postdocs than graduate students for the same expenditure of funds.
- ***Graduate Students.*** Four of the ICMICs devoted Career Development resources to graduate student training.
- ***Undergraduates.*** One ICMIC (Missouri-Columbia) chose to devote substantial resources to undergraduate training. The goal of undergraduate training was to expand the pipeline of future molecular imagers by catalyzing pre-medical students to pursue specialization in radiology or scientists to pursue training in chemistry or other imaging-related disciplines; undergraduate training through the University of Missouri-Columbia was also considered to be inexpensive relative to other forms of training. Undergraduates worked part-time during the semester and then full time in the laboratories of their mentors during the summer, with their internships concluding with a capstone presentation at Missouri-Columbia. Many interns apply for funds to present student papers at molecular imaging conferences.
- ***Visiting faculty.*** Two ICMICs devoted Career Development resources to training visiting faculty in molecular imaging, giving faculty the opportunity to change their career trajectories and return to their home institutions to create molecular imaging programs or departments.

Table 3.7: Career Development Strategies Employed by ICMICs

ICMIC	Faculty	Postdocs	Graduate Students	Undergraduates	Visiting Faculty
MGH	Yes	No	No	No	No
MSKCC	No	Yes	No	No	No
UCLA	No	Yes	Yes	No	Yes
Washington University	Yes	Yes	Yes	No	No
Johns Hopkins	Yes	No	No	No	No
Michigan	Yes	Yes	Yes	No	Yes
Missouri-Columbia	No	Yes	Yes	Yes	No
Stanford	No	Yes	No	No	No

Source: ICMIC Administrative Data

> Now, we also have a training program, a Cancer Imaging Training Program, a T32. So, the vast majority of people who we bring in for training are covered under that training program. So, we didn't think that there was a need of having yet another training program for post docs – ICMIC PI

The strategies pursued by ICMIC principal investigators in selecting training approaches depended upon the availability of other institutional training funds for cancer imagers, as will be discussed in greater detail below. During the interviews with ICMIC Principal Investigators, several mentioned that training funds (through T32s or R25Ts) was increasingly becoming available for the training of graduate students and postdoctoral researchers.

Two of the ICMICs described holding trainee-specific meetings. The UCLA ICMIC conducts a weekly meeting of all trainees, including a rotating schedule of presentations. The meeting is intended to update the trainees as to the progress of research across the ICMIC, and also serves to provide the trainees with practice in giving scientific presentations. The MGH ICMIC requires its trainees to attend Cancer Center research presentations and MGH Grand Rounds, in order to provide them with experience with oncology practice.

Three of the ICMICs (MGH, Johns Hopkins, and Michigan) described using Career Development funding to support junior faculty (either at Instructor or Assistant Professor level) as they began their independent research careers. Career Development funding was in some cases mentioned as being an instrumental part of offer packages to new investigators. The UCLA PI, both in an interview and in the UCLA applications, made reference to actively seeking out cancer researchers who were not previously users of molecular imaging but who might be appropriate to include as future leaders of ICMIC Research Components.

3.7: Other Imaging-Related Infrastructure at ICMIC Institutions

In order to understand the institutional context for the ICMICs, it is important to understand where and how the ICMIC awards overlapped with other NCI-supported imaging resources such as the SAIRs and Centers of Cancer Nanotechnology Excellence (CCNEs), other large-scale infrastructure and translational research efforts such as the SPOREs– as well as with NIH funding for instrumentation (e.g., NCRR-funded Shared Instrumentation Grants). While these overlaps are described in more detail in Chapter 6, Table 3.8 summarizes the other infrastructural elements that were present at each of the ICMIC-funded institutions:

Table 3.8: Other Awards at the ICMICs

ICMIC	SAIR	CCNE	NCRR Shared Instrumentation Awards for Molecular Imaging-Related Equipment	Radionuclide Resource	SPOREs
MGH	Yes	Partner (on MIT CCNE)	No	No	No (though present at other Harvard-area hospitals)
MSKCC	Yes	No	Yes (4)	No	Yes (1 SPORE, 1 pre-SPORE P20)
UCLA	Yes	Partner (on Caltech, Stanford CCNEs)	No	No	Yes (2)
Washington University	Yes	Yes	Yes (6)	Yes	No
Johns Hopkins	Yes	No	No	No	Yes (7)
Michigan	Yes	No	Yes (2)	No	Yes (2)
Missouri-Columbia	No	No	Yes (1)	No	No
Stanford	Yes	Yes	Yes (1)	No	No

Source: ICMIC Administrative Data

A related infrastructural consideration is the integration of molecular imaging at the Cancer Center level. All of the ICMICs except for Missouri-Columbia are affiliated with NCI-designated Cancer Centers (MGH, while not itself an NCI-designated Cancer Center, is affiliated with the Dana-Farber/Harvard Cancer Center). While these overlaps are described in more detail in Chapter 6, Table 3.9 shows whether the local Cancer Center had identified a research program related to imaging/molecular imaging, and whether the Cancer Center provided support to a molecular imaging or small animal imaging Shared Resource.

Table 3.9: Molecular Imaging Integration into Cancer Center

ICMIC	Cancer Center has "molecular imaging" research theme (theme name)	CCSG funds small animal imaging/molecular imaging Shared Resource?
MGH	Under development (Cancer Imaging)	None identified
MSKCC	Yes (Imaging and Radiation Sciences)	Yes
UCLA	None identified	Yes
Washington University	Yes (Oncologic Imaging)	Yes
Johns Hopkins	None identified	Yes
Michigan	Yes (Molecular Imaging)	Yes
Missouri-Columbia	Not applicable -- no affiliated NCI-designated Cancer Center	
Stanford	Yes (Cancer Imaging)	Yes

Source: STPI analysis of NIH Administrative Data; supplementary searches of Dana-Farber Cancer Center Internet site (http://www.dfhcc.harvard.edu/research-programs/discipline-based-programs/cancer-imaging/)

Chapter 4: ICMIC-Supported Research

As stated in Chapter 2, six programmatic goals have been identified for ICMIC:

1) Stimulate, facilitate and enhance high-quality research in the area of cancer molecular imaging;
2) Direct cancer molecular imaging research towards bettering imaging technologies that have potential clinical or laboratory applications (added beginning with the 2004 PAR);
3) Support the formation of vibrant, multi-disciplinary communities of cancer molecular imaging researchers at grantee institutions;
4) Enable the acquisition of physical infrastructure to facilitate cancer molecular imaging research;
5) Provide unique training and cross-training experiences for cancer-imaging researchers;
6) Build sufficient organizational infrastructure to effectively coordinate the cancer molecular imaging research enterprise at ICMIC institutions.

This chapter will focus on evidence for progress made by the ICMIC program towards meeting Goals 1 and 2.

4.1: Publication Counts and Research Productivity: P50 ICMICs

As described in Chapter 2, the database of ICMIC publications was assembled from programmatic records (e.g., applications, progress reports) and searches of MEDLINE-indexed peer reviewed journals in which authors acknowledge ICMIC funding. ICMIC Principal Investigators were also asked to review the publications lists.[16]

Using these methods, a total of 755 publications were attributed to the P50 ICMICs (Table 4.1), of which two were associated with more than one P50 ICMIC. Analysis of publication patterns reveals several points. First, the number of publications per P50 ICMIC varied substantially, with MGH and Washington University each exceeding 100 publications, MSKCC, UCLA, Michigan, and Stanford publishing nearly 100 papers, and Johns Hopkins and Missouri-Columbia publishing closer to 50. Average number of publications per year also varied across ICMICs. Assuming that the first two years of the MGH, UCLA, and MSKCC represented a "ramp-up" period comparable to the P20 Pre-ICMIC awards of the other five P50 institutions, MSKCC, UCLA, Johns Hopkins, Michigan, and Missouri-Columbia published between ten and fifteen papers per year; Washington University twenty per year; and MGH and Stanford have published close to thirty P50-associated publications per year.

[16] P20 ICMIC publications were obtained from searches of NIH databases, but not reconfirmed with the PIs, as the goal was to focus on the full ICMIC publications.

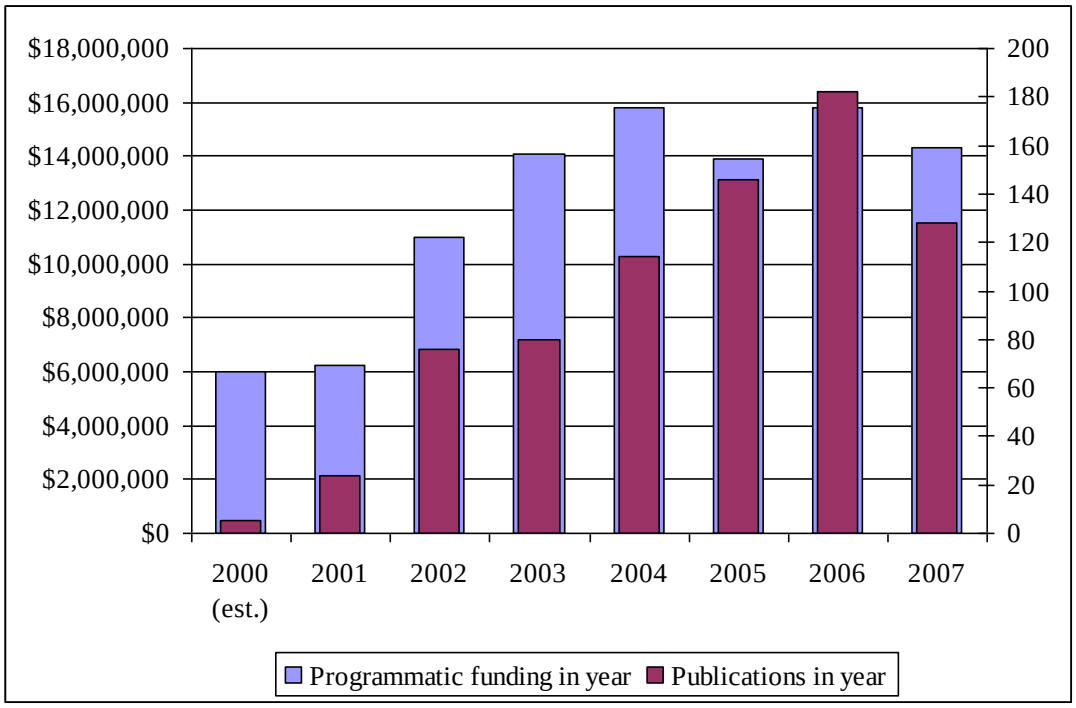
Table 4.1: P50 ICMIC-affiliated publications by year of publication

ICMIC	2000	2001	2002	2003	2004	2005	2006	2007 to 9/30	Average Publications per Year of P50 ICMIC Funding 2002-2007
MGH	4	6	28	15	27	33	46	21	28.3
MSKCC	1	6	8	10	22	14	14	8	12.7
UCLA	0	12	16	13	9	15	20	13	14.3
Washington University			13	18	24	24	18	18	19.2
Johns Hopkins				5	7	11	16	16	11
Michigan			11	9	17	26	20	8	15.2
Missouri-Columbia				10	7	10	12	14	10.6
Stanford						13	39	30	27.3

Source: ICMIC Publications database. Blue denotes years in which institution had P50 ICMIC, green years denote the period of P20 funding.
Note: The final "Average publications per year of P50 ICMIC funding 2002-2007" column includes only those ICMIC-affiliated publications published during the years the P50 was active. Two FY 2006 publications – one jointly acknowledging UCLA and Stanford ICMICs and one jointly acknowledging MGH and Missouri-Columbia – are double-counted

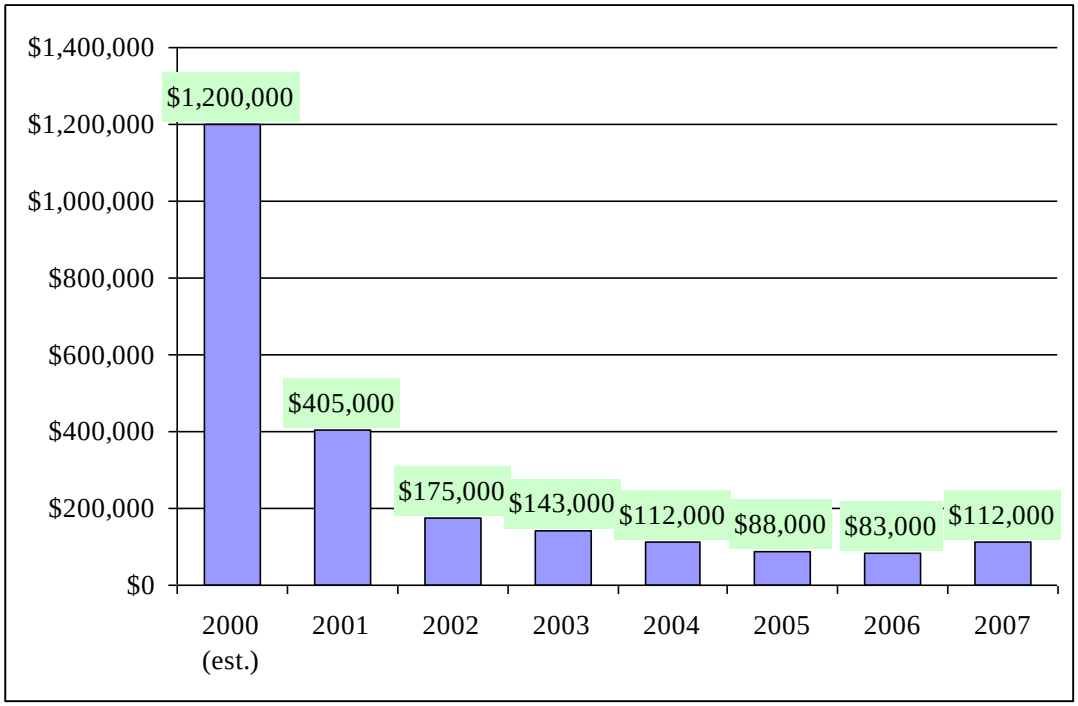
Taken together, the total number of publications per year associated with the ICMICs and has increased over time, while total programmatic funding has remained roughly constant since FY 2003 (Figure 4.1). The steady-state ratio of dollars per publication in a given year was approximately $100,000, although there was a substantial ramp-up period during the first two years of ICMIC program operations (Figure 4.2).

Figure 4.1: ICMIC P50 Funding and Publications, 2000-2007



Source: ICMIC Publications Database, administrative records.
Note: FY 2000 funding is estimated; publications are shown for full calendar years (except for 2007)

Figure 4.2: Ratio of Programmatic Funding to Number of Publications, 2000-2007



Source: ICMIC Publications Database, administrative records.
Note: FY 2000 funding is estimated; publications are shown for full calendar years (except for 2007)

4.2: Publication Quality

As described in Section 2.4, the publications of the ICMIC P50 institutions were submitted to Thomson/ISI for bibliometric analysis, and data on 717 were matched to their database.[17] The following analyses are based on the bibliometric data.

ICMIC papers were published in 208 distinct journals spanning a range of fields, including fundamental biology, chemistry, cancer biology, clinical oncology, molecular imaging, and nuclear medicine. A total of nine journals (5% of the 208 total) accounted for 38% of the total papers (275 of 717 papers); impact factors of those journals ranged between three and ten (Table 4.2). The journals in which the largest number of articles appears include dedicated molecular imaging and nuclear medicine journals (*Journal of Nuclear Medicine, Molecular Imaging, Molecular Imaging and Biology*), journals devoted to cancer biology (*Cancer Research, Neoplasia*), clinical cancer journals (*Clinical Cancer Research, Molecular Therapy*), a chemistry journal (*Bioconjugate Chemistry*), and a general journal (*Proceedings of the National Academy of Sciences*).

Table 4.2: Journals with Largest Number of Articles Thomson/ISI Indexed

Journal	Number of papers	Journal impact factor
Journal of Nuclear Medicine	52	4.986
Cancer Research	51	7.656
Proceedings of the National Academy of Sciences U S A	45	9.643
Bioconjugate Chemistry	38	3.823
Clinical Cancer Research	24	6.177
Neoplasia	21	4.913
Molecular Imaging	15	N/A
Molecular Imaging and Biology	15	2.961
Molecular Therapy	14	5.841

Source: Thomson/ISI bibliometrics for ICMIC P50 publications database
Note: Thomson/ISI began indexing Molecular Imaging in 2006. Table 4.2 understates the number of ICMIC publications in this journal.

Forty-one ICMIC publications (6%) were in journals with impact factors of twenty or higher, including six papers in *Science*, three in *Nature*, and one each in the *New England Journal of Medicine* and *JAMA* (Table 4.3). Looking across all of the ICMIC publications, the average impact factor was 7.08[18], and the median was 4.986. Impact factor was not available for 33 publications.

[17] An additional 27 P20 pre-ICMIC publications at ICMIC institutions were not identified until after the bibliometrics run was completed.

[18] While there is not a commonly accepted definition of "high-impact-factor journal" or publications of "average" impact factors across biomedical research, for comparison with the average of 7.08, the impact factor of *Cancer Research* is 7.66, and the impact factor of *Molecular and Cellular Biology* is 6.77. The paper with the median impact factor was in the *Journal of Nuclear Medicine*, which has an impact factor of 4.986.

Table 4.4: ICMIC Publications in Very High-Impact-Factor Journals

Journal	Impact factor	Number of Publications
New England Journal of Medicine	51.296	1
Nature Reviews. Cancer	31.583	1
Nature Reviews. Molecular Cell Biology	31.354	1
Science	30.028	6
Cell	29.194	3
Nature Medicine	28.588	9
Nature Immunology	27.596	2
Nature	26.681	3
Cancer Cell	24.077	7
JAMA	23.175	1
Nature Biotechnology	22.672	7

Source: Thomson/ISI bibliometrics for ICMIC P50 publications database

Another measure of the quality of ICMIC publications is the number of times they have been cited by other researchers. Table 4.4 presents the number of times that the 717 papers for which bibliometric data are available have been cited. Seventeen papers (2%) have been cited more than 100 times, and an additional fifty-five (8%) have been cited between fifty and one hundred times. These ten percent of papers represent forty-nine percent of the cumulative citations to ICMIC research.

Table 4.4: Citations to ICMIC Publications

Citations per paper	Papers with # of citations	Percentage of papers	Number of citations	Percentage of citations
101+	17	2%	3,375	23%
51-100	55	8%	3,738	26%
21-50	138	19%	4,342	30%
1-120	423	59%	3,039	21%
0	84	12%	0	0%

Source: Thomson/ISI bibliometrics for ICMIC P50 publications database

Listed below are the ten most-cited papers (with the ICMIC supporting those publications in parentheses). Seven of the ten most cited-papers are from first-cohort ICMICs (5 from UCLA, 2 from MGH), and three are from ICMICs first funded in 2002 (2 from Washington University, 1 from Michigan).

1. Michalet, X. Quantum dots for live cells, in vivo imaging, and diagnostics. SCIENCE Vol. 307 (2005). Pages 538-544 (UCLA). 543 citations.
2. Neshat, MS. Enhanced sensitivity of PTEN-deficient tumors to inhibition of FRAP/mTOR. P NATL ACAD SCI USA Vol. 98 (2001). Pages 10314-10319 (UCLA). 394 citations.
3. Massoud, TF. Molecular imaging in living subjects: seeing fundamental biological processes in a new light. GENE DEV Vol. 17 (2003). Pages 545-580 (UCLA). 304 citations

4. Birchmeier, C. Met, metastasis, motility and more. NAT REV MOL CELL BIO Vol. 4 (2003). Pages 915-925 (Michigan). 293 citations.
5. Ji, H. Arthritis critically dependent on innate immune system players. IMMUNITY Vol. 16 (2002). Pages 157-168 (MGH). 220 citations.
6. Bremer, C. In vivo molecular target assessment of matrix metalloproteinase inhibition. NAT MED Vol. 7 (2001). Pages 743-748 (MGH). 203 citations.
7. Krug, A. Herpes simplex virus type 1 activates murine natural interferon-producing cells through toll-like receptor 9. BLOOD Vol. 103 (2004). Pages 1433-1437 (Washington University). 190 citations.
8. Groszer, M. Negative regulation of neural stem/progenitor cell proliferation by the Pten tumor suppressor gene in vivo. SCIENCE Vol. 294 (2001). Pages 2186-2189 (UCLA). 182 citations.
9. Araki, T. Increased nuclear NAD biosynthesis and SIRT1 activation prevent axonal degeneration. SCIENCE Vol. 305 (2004). Pages 1010-1013 (Washington University). 162 citations.
10. Bhaumik, S. Optical imaging of Renilla luciferase reporter gene expression in living mice. P NATL ACAD SCI USA Vol. 99 (2002). Pages 377-382 (UCLA). 150 citations.

Journal impact factor is intended as a measure of the "quality" of the journals in which a paper is published, while the number of citations is normally interpreted as a measure of how useful the paper has been to the research community. Expected number of citations to a publication is a measure that aims to combine the two, normalizing the number of citations to an individual paper against others in the same journal and issue to determine whether the paper has been cited more often than expected. Actual citations were compared to expected citations for the papers published 2000-2006; papers published in 2007 were excluded because it is not always reasonable to expect citations to new publications within one year of their appearance. The median actual-to-expected ratio was 1.1 and the mean 1.52, suggesting that ICMIC-supported publications are at least as highly-cited as others in their peer cohorts.

Another use of the expected-to-actual citation ratio is to identify "hot" publications – papers that have been recently published but which have high citation rates relative to expectations. The ten "hottest" publications (including only publications with ten or more citations to date) include six from MGH, and one each from Johns Hopkins, UCLA, Washington University, and Stanford. Two of them are among the ten most highly cited papers.

1. Weissleder R. Molecular imaging in cancer. Science. 312:5777 (2006). Pages 1168-71 (MGH). Ratio 37/3.13 = 11.82.
2. Zhang X, Cai W, et. al. 18F-labeled bombesin analogs for targeting GRP receptor-expressing prostate cancer. J Nucl Med. 47:3 (2006). Pages 492-501. (Stanford). Ratio 15/1.32 = 11.36
3. Jaffer FA, Weissleder R. Molecular imaging in the clinical arena. JAMA. 293:7 (2005). Pages 855-62. (MGH). Ratio 74/6.95 = 10.65

4. Ventura A , Kirsch DG, et. al. "Restoration of p53 function leads to tumour regression in vivo." *Nature*. 445:7128 (2007). Pages 661-5 (MGH). Ratio 43/4.27 = 10.07
5. Krug, A. Herpes simplex virus type 1 activates murine natural interferon-producing cells through toll-like receptor 9. BLOOD Vol. 103 (2004). Pages 1433-1437 (Washington University). Ratio 190/25.79 = 7.36
6. Michalet, X. Quantum dots for live cells, in vivo imaging, and diagnostics. SCIENCE Vol. 307 (2005). Pages 538-544 (UCLA). Ratio 543/76.86 = 7.06
7. Graves EE, Ripoll J, et. al. A submillimeter resolution fluorescence molecular imaging system for small animal imaging. Med Phys. 30:5 (2003). Pages 901-11. (MGH). Ratio 80/11.53 = 6.94.
8. Jaffer FA, Nahrendorf M, et. al. Cellular imaging of inflammation in atherosclerosis using magnetofluorescent nanomaterials. Mol Imaging. 5:2 (2006). Pages 85-92. (MGH). Ratio 13/1.9 = 6.84.
9. Swirski FK , Libby P , et. al. Ly-6Chi monocytes dominate hypercholesterolemia-associated monocytosis and give rise to macrophages in atheromata. J Clin Invest. 117:1 (2007). Pages 195-205. (MGH). Ratio 13/1.96 = 6.63.
10. Semenza GL. Development of novel therapeutic strategies that target HIF-1. Expert Opin Ther Targets. 10:2 (2006). Pages 267-80. (Johns Hopkins). Ratio 21/3.25 = 6.46.

4.3: Key Discoveries as Identified by ICMIC Investigators

ICMIC Principal Investigators were asked during interviews to identify the signature discoveries or developments which were supported by ICMIC funding. Researchers were not asked to identify "basic" or "clinical" discoveries specifically, although certain PIs chose to selectively highlight particular aspects of their work. These discoveries are described briefly below; Appendix C develops four of these "stories of discovery" in more detail, describing both the research and the ICMIC's contribution to it.

One set of discoveries fell into the category of pre-clinical reagent and technology development. These discoveries constitute tools that become enabling technology at the ICMICs or within laboratories around the world:

- Advances in optical imaging technology, particularly in tomographic imaging (MGH).
- Split luciferase constructs for studying protein-protein interactions (Washington University)
- Imaging kinase activity *in vivo* (Michigan).
- Molecular imaging reporter constructs for cell-based high-throughput screening assays of pro-apoptotic and anti-apoptotic compounds for drug discovery (Michigan).
- Advances in the development of phage display technology (Missouri-Columbia).

A second set of discoveries use imaging to identify fundamental discoveries related to cancer biology:

- Examination of the role of choline metabolism, including as it relates to resistance to chemotherapy (Johns Hopkins).

- Investigation of the relationship of hypoxia to breast tumor invasiveness and metastasis (Johns Hopkins).

The ICMIC PIs identified a third set of signature discoveries, which are either in the process of entering clinical trials or are appear likely to be translated into the clinic in the near future:

- Combined virus and cell biotherapy (Stanford). Protocols have been approved by institutional committees and an IND is under development.
- Use of the HSV1-sr39tk PET reporter to monitor the treatment of melanoma by genetically modified T cells (UCLA). IRB approval has been initiated.
- Development of a PET probe for imaging T-cell activation (UCLA).
- Development of magnetic nanoparticles as a clinical product (MGH). Clinical protocols are currently awaiting FDA approval.
- Melanoma-targeting imaging peptides (Missouri-Columbia). Toxicology data have been collected, and a proposal for a Phase I clinical trial, in collaboration with Washington University, is in progress.
- Image-guided pro-drug enzyme therapy (Johns Hopkins). ICMIC researchers are consulting with the FDA as to how to translate promising preclinical developments.
- Angiogenesis imaging agent (Stanford). Preclinical developments are promising, and clinical trials are expected to begin in 2009.
- Use of inducible reporter genes to image T-cell antitumor activity (MSKCC). Imaging techniques are being developed for a clinical trial to be funded through an ICMIC Research Component.
- Developing proton MRSI to monitor tumors and predict therapeutic response (MSKCC). Initial clinical studies were performed during the first ICMIC funding period, and will continue during the renewal period.
- Use of FLT-PET to monitor inhibition of DNA synthesis (MKSCC). FLT-PET imaging will be incorporated into planned clinical trials of Hsp90 inhibitors.
- Use of diffusion-contrast enhanced MRI to determine the effectiveness of novel anti-angiogenesis agents in planned clinical trials (MSKCC).
- Development of imaging techniques to assess treatment response in castrate-resistant metastatic prostate cancer (MSKCC). Techniques developed in the initial ICMIC funding period will be refined to allow imaging to be incorporated into planned clinical trials.

Matching between the hot/highly-cited publications (identified during the previous section) and the self-identified key discoveries, three (all from MGH) of the eighteen hot and/or highly-cited publications were linked to two of the nineteen key discoveries. The "Advances in optical imaging technology, particularly in tomographic imaging" discovery was linked to the Graves and Bremer publications, while the "Development of magnetic nanoparticles as a clinical product" discovery was linked to the Jaffer paper.

Analysis of the ICMIC PI interviews and of the hot/highly-cited publications identifies several partial explanations for the disjuncture: (1) all ICMIC PIs identified key discoveries, but the hot/highly-cited publications did not include all of the ICMICs; (2) several PIs listed recent discoveries as what they felt to be among their most important, which at the time either had not been published or had been very recently published; and (3) several of the hot/highly-cited publications were review articles that, while often-cited, may not necessarily have reflected solely ICMIC-supported discoveries.

4.4: ICMIC-Supported Clinical Trials

The Outcome Evaluation identified ten clinical trials that have been supported at least in part by ICMIC technologies and resources. Some of these clinical trials are specifically supported by ICMIC-funding and research, while others capitalize on ICMIC-developed technology or make use of ICMIC Specialized Resources but were not ICMIC-funded.

ICMIC-Supported Clinical Trials of Imaging Agents First Synthesized by an ICMIC or Imaging Techniques First Developed Using ICMIC Funds

- The MSKCC is conducting first-in-man trials of a novel protein called 68Ga-F(ab')2-trastuzumab fragments – a PET-imageable protein developed at MSKCC that binds to HER2 (NCT00613847). This Phase 0 study, carried out as part of an ICMIC Research Component, aims to determine agent uptake and binding specificity in HER2+ patients.
- The Stanford ICMIC conducted a Phase 0 proof-of-principle clinical trial on twenty-four patients that examined the feasibility and effectiveness of three-dimensional rendering of PET/CT images as a "virtual" bronchoscopy and colonoscopy approach to treatment planning.

ICMIC-Supported Clinical Trials of Imaging Agents First Synthesized by Others or Techniques First Developed by Others

- The MSKCC ICMIC has begun recruiting patients for a trial entitled "[18F]-Fluoro-2-Deoxy-D-Glucose and [18F]-Dihydro-Testosterone Pet Imaging in Patients With Progressive Prostate Cancer" (NCT00588185). This clinical trial, as part of an ICMIC Research Component, attempts to image metastases of prostate cancer using the PET imaging compound FDHT (developed at Washington University in the mid-1990s) in addition to FDG.
- The Washington University ICMIC supported a clinical trial entitled, "MDR1 P-glycoprotein Transport Activity In Vivo with 94mTc-Sestamibi PET To Predict Response To Chemotherapy in Lung Cancer" as a Research Component in its initial funding period.

Clinical Trials Supported by Other Funds of Imaging Agents First Synthesized by the ICMIC or Techniques First Developed Using ICMIC Funds

- Three University of Michigan Developmental Projects using diffusion MRI as a biomarker of treatment response have been successful and incorporated into clinical trials of:
    - Breast cancer (Dr. Ann Schott)

- Prostate cancer (Dr. Kenneth Pienta)
- Head and neck cancer (Dr. Bradford Moffatt)

Clinical Trials Supported by Other Funds Where ICMIC Specialized Resources Contributed to Synthesis of the Imaging Agent or where ICMIC Career Development Awards Contributed to the Training of the Trial PI

- The MSKCC ICMIC has completed a clinical trial entitled "Imaging Brain Tumors with FACBC and Methionine" (NCT00597246). This clinical trial images brain tumors using the novel [18F]-FACBC PET as compared to standard methionine PET. The ICMIC Radiochemistry Specialized Resource provided the compound for the trial.
- The MSKCC ICMIC has begun recruiting patients for a clinical trial entitled, "Pilot Study Investigating the Biodistribution and Potential Diagnostic Ability of 18F FACBC in Patients With Head and Neck, Breast, and Prostate Cancer" (NCT00605488). The ICMIC Radiochemistry Specialized Resource provides the compound for the trial.
- Dr. Harasinghani, an MGH Career Development Awardee, has completed a clinical trial entitled, "Magnetic Resonance Imaging of Lymph Nodes Using Ferumoxytol in Patients With Primary Prostate or Breast Cancer" (NCT00087347).

4.5: Patents and Other Intellectual Property

Searches of the USPTO database were performed to identify whether ICMIC was acknowledged as providing support to US patents awarded to ICMIC-affiliated investigators. Two patents were identified that acknowledged ICMIC support:

- #7,153,905, "Hyperbranched dendron and methods of synthesis and use thereof." This relates to their nanoparticles research. (MGH)
- #6,567,684, "Imaging system, computer, program product and method for detecting changes in rates of water diffusion in a tissue using magnetic resonance imaging (MRI)." (Michigan)

Given the long lead times associated with patent filings, the small number of granted patents attributable to ICMIC activities was not unexpected. A search of the NIH iEdison database was also performed to identify whether any invention disclosures have been filed or patent applications submitted. Due to NIH confidentiality procedures, only summary information could be provided. As of July 2008, twenty-one patent applications from six ICMICs were listed as acknowledging support from an ICMIC award. One ICMIC (the identity of which could not be disclosed) was responsible for fourteen of those applications.

4.6: Research Outcomes of Developmental Projects

The purpose of the Developmental Projects was to pursue small-scale, potentially high-impact research. To assess the outcomes of the Developmental Projects, investigators

were asked to identify papers, grants, and clinical trials that were associated with Developmental Projects. Seven of the eight ICMICs reported outcomes in at least one of these categories (Table 4.5).

While data are not fully comparable across the ICMICs, it appears that at least twenty-six Developmental Projects have led to the funding of other awards based on pilot data from the ICMICs (in addition to an unknown number of awards funded based on Washington University pilot projects), and three clinical trials have been based on Development Project results. At least fifty-six of the Developmental Projects have led to published papers.

Table 4.5: Outcomes of Developmental Projects

ICMIC	Number of Developmental Projects	Number of projects leading to grants	Number of projects leading to clinical trials	Number of projects resulting in one or more publications
MGH	26	13	0	21
MSKCC	8	2	0	7
UCLA	15	1	0	10
Washington University	24	N/A	0	3
Johns Hopkins	11	4	0	7
Michigan	9	2	3	8
Missouri-Columbia	8	4	0	N/A
Stanford	6	N/A	0	N/A

Source: STPI analysis of ICMIC applications and administrative data
Note: Washington University identified 32 grant applications that resulted from Developmental Projects, but did not identify the number of Developmental Projects from which those applications originated. Number of projects leading to awards was not available for Stanford, and number of projects resulting in publications was not available for Stanford or the University of Missouri-Columbia

4.7: Synergies Between ICMIC and Other NCI-Funded Research

In order to identify possible synergies between ICMIC research and other NIH-funded research, the Outcome Evaluation analyzed acknowledgements of NIH-funded research for ICMIC-affiliated publications as reported on MEDLINE. MEDLINE searches of the publications affiliated with the P50 ICMICs identified 483 publications (64% of ICMIC publications) that acknowledged at least one award other than the ICMIC, including acknowledgements for a total of 362 distinct NIH non-ICMIC awards. Table 4.6 summarizes the awards co-cited with the ICMIC publications.

Table 4.6: Awards Acknowledged on ICMIC-Affiliated Publications (not including ICMIC Awards)

Type of Award	Number of publications	Number of distinct awards
All NCI-funded awards:	417	195
R01s	195	83
P01s	80	18
SAIR	185	7
SPORE	19	6
CCNE	21	3
Cancer Center	38	9
Non NCI-funded awards	195	167

Source: STPI analysis of ICMIC publications and administrative data

- ***MGH/Harvard:*** No ICMIC-supported publications acknowledged support from a SPORE award. Two ICMIC personnel named on Research Components or Specialized Resources are project leaders on SPORE research projects or pilot projects (DePinho, Scadden) and the leaders of two of the Harvard SPOREs (Haber, Kantoff) on SPOREs were listed as collaborators on an ICMIC Research Component in the most recent MGH application. Interviews with ICMIC key personnel and NIH database searches identified two projects in the newly-funded Dana-Farber GI SPORE (first funded as of 2007) that use imaging; interest in imaging grew out of connections and collaborations with the ICMIC PI.

> Well, the way that happened was [Name Redacted] had a developmental fund project from the ICMIC, it went beautifully....The other people in the SPORE all got wound up about that.... And so, the Prostate SPORE applications and utilization of molecular imaging grew out of the fact that there were people who had been involved in the ICMIC – ICMIC PI

- ***MSKCC:*** Two ICMIC-supported publications acknowledged support from the MSKCC Prostate SPORE award (P50CA092629); the papers described the use of imaging to assess metastasis and response to therapy in animal models. Interviews and application materials also identified the inclusion of imaging as among the research projects of a MSKCC P20 Brain Tumor pre-SPORE.
- ***UCLA:*** Ten ICMIC-supported publications acknowledged support from two UCLA SPOREs: six to the Prostate SPORE (P50CA092131) and four to the Lung SPORE (P50CA90388). NIH database searches identified ICMIC-affiliated investigators as either project PI or co-investigators on four of the five projects of the 2007 renewal of the Prostate SPORE. No direct personnel overlap could be identified with the Lung SPORE; publications citing both the Lung SPORE and the ICMIC described uses of PET in lung cancer detection and in assessment of treatment response.
- ***Johns Hopkins:*** Three ICMIC-supported publications acknowledged support from two Johns Hopkins SPOREs, two to the GI SPORE (P50CA062924) and

one to the Breast SPORE (P50CA88843). Both of these SPORE leaders serve as participants on ICMIC Research Components, and the ICMIC PI leads a pilot project on the Breast SPORE.

- ***Michigan:*** One ICMIC-supported publication acknowledged support from the Michigan Prostate SPORE (P50CA69568); the PI on the Prostate SPORE was a Developmental Project leader on the Michigan ICMIC.

The ICMICs vary substantially regarding the number of publications that acknowledge P30 Cancer Center Support Grants.

- ***UCLA:*** 10 ICMIC-supported publications acknowledge support from the UCLA Cancer Center, of which four also acknowledge support from Cancer Centers other than UCLA. One acknowledges support from the MSKCC Cancer Center.
- ***MSKCC:*** 9 ICMIC-supported publications acknowledge support from the MSKCC
- ***Washington University:*** 9 ICMIC-supported publications acknowledge support from the Siteman Cancer Center at Washington University
- ***Michigan:*** 3 ICMIC-supported publications acknowledge support from the Michigan Cancer Center
- ***MGH:*** 1 ICMIC-supported publication acknowledges support from the MIT Cancer Center, and one acknowledges support a Cancer Center outside of the Boston area.
- ***Johns Hopkins:*** 2 ICMIC-supported publications acknowledge support from Cancer Centers other than Johns Hopkins.
- ***Missouri-Columbia:*** 1 ICMIC-supported publication acknowledges support from the Washington University Cancer Center, and one acknowledges support from the MSKCC.

The co-citations suggest that integration with the local Cancer Center is relatively strong at MSKCC, UCLA, and Washington University, with more limited (or no) integration at the other ICMIC institutions.

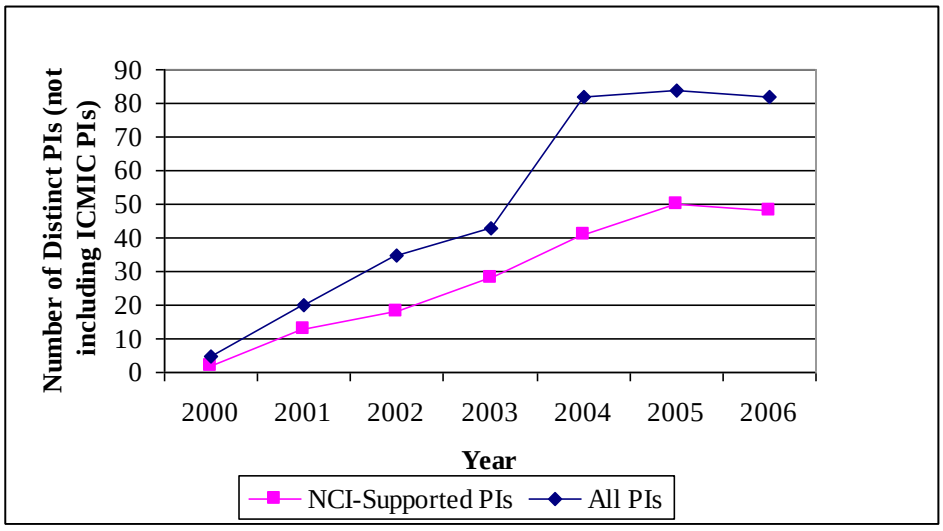
There is some evidence that, as the ICMICs matured, the integration between their research and other NCI-funded research expanded as well. Table 4.7 shows the expansion of the number of NCI-funded P01, R01, and R21 awards that were co-cited on ICMIC publications between 2000 and 2006. By 2004, approximately thirty to forty NCI awards were being cited on ICMIC papers each year. Another measure of the breadth of synergies between ICMICs and other NCI-funded research is to tabulate the number of distinct PIs (not counting the ICMIC PIs themselves) whose awards are being acknowledged on ICMIC-supported publications. Figure 4.3 shows a rapid rise in the number of NCI-funded investigators being acknowledged on ICMIC publications each year, with a steady state of approximately fifty distinct NCI-funded PIs (and eighty total PIs) being reached beginning in 2004-5.

Table 4.7: Number of NCI-funded Research Project Grants of Various Types Acknowledged on ICMIC Publications, 2000-2006

Year	P01s	R01s	R21s
2000	2	1	0
2001	3	12	0
2002	4	14	1
2003	6	22	1
2004	4	28	6
2005	7	20	3
2006	9	30	9

Source: STPI analysis of acknowledgement information from ICMIC-supported publications

Figure 4.3: Number of Principal Investigators (not counting ICMIC PIs) on Awards Acknowledged by ICMIC-Supported Publications, 2000-2006



Source: Source: STPI analysis of acknowledgement information from ICMIC-supported publications

4.8: Publications of the P20 Pre-ICMICs

While Chapter 4 has focused on the P50 ICMICs, publication data were collected for the P20 pre-ICMICs as well. An additional 160 publications were identified as associated with the sixteen pre-ICMICs (Table 4.8). Table 4.8 suggests substantial diversity in the publication rates of the Pre-ICMICs, especially of the non-transitioning Pre-ICMICs. Seven pre-ICMIC institutions (e.g., Johns Hopkins, Stanford, Vanderbilt, IUPUI, UT-Southwest, UC Irvine, University of Pennsylvania) published between ten and twenty papers attributed to their pre-ICMIC funding, while the other nine published fewer than ten – including two who produced a single paper. Table 4.9 compares across the transitioning and non-transitioning pre-ICMICs, and suggests that publication rates were similar between the transitioning and non-transitioning pre-ICMICs.

Table 4.8: Publications of P20 Pre-ICMICs

Institution	Pre-ICMIC Cohort	2000	2001	2002	2003	2004	2005	2006	2007	Total
Johns Hopkins University	2000		1	4	8	3				16
Stanford University	2000			1	7	10	1			19
University of Michigan	2000	2		4	1					7
University of Missouri-Columbia	2000			1	6	1				8
Washington University	2000	2	4	3						9
Subtotal: ICMICs transitioning to P50		4	5	13	22	14	1	0	0	59
Duke University	2000					1	1			2
Indiana University-Purdue University Indianapolis	2000		1	2	6	4	3	2		18
University of California-Irvine	2000			4	6	2	1	2		15
University of Pennsylvania	2000		1	2	2	4	3			12
Vanderbilt University	2000			3	7	6	2	2		20
Case Western Reserve University	2001					1	1	2		4
University of California-San Diego	2001						1			1
University of Iowa	2001				1	3	2			6
University of Southern California	2001							3	1	4
University of Texas-Southwest Medical Center	2001			2	2	4	4	4	2	18
University of Wisconsin	2001						1			1
Subtotal: P20s that did not transition		0	2	13	24	25	19	15	3	101

Source: ICMIC Publications database.

Table 4.9: Summary of Publication Rates

ICMIC Group	Funding (M$)	Publications	Ratio of funding to publications
11 Not transitioning ICMICs	$13.0	101	$128,713
5 Transitioning ICMICs	$5.2	59	$88,136
All 16 ICMICs	$18.2	160	$113,750

Source: ICMIC Publications database and ICMIC publication data.

4.9: ICMIC Participants as Leaders in the Scientific Community

A final consideration in the assessment of the ICMICs lies in the identification of the role of ICMIC participants in the broader molecular imaging community. Several approaches were taken to assess "leadership" of ICMIC investigators and their institutions, as described below.

Analysis of Leadership of Journals and Molecular Imaging Societies

STPI identified the current editorial boards of three imaging-related journals, *Molecular Imaging*, *Molecular Imaging and Biology*, and the *Journal of Nuclear Medicine*, and matched editors against the database of ICMIC key personnel (Table 4.10). Of the 122 journal-editor pairs (double-counting individuals who serve as editors on multiple journals), eighty-five were at US institutions. Forty-eight of the individual editors were at ICMIC or pre-ICMIC institutions (56% of editors at US institutions, 39% of all editors). Of those forty-eight, thirty-nine (81%) were ICMIC-affiliated. Forty-five of the editors were ICMIC-affiliated (53% of editors at US institutions, 36% of all editors): in addition to the thirty-nine ICMIC-affiliated editors, six editors were formerly ICMIC-affiliated but who have since moved to non-ICMIC institutions.

Table 4.10: ICMIC Affiliations of Molecular Imaging Journal Editors

	ICMIC-affiliated	Not ICMIC-affiliated	Total	Percentage ICMIC-affiliated
Not US-based	0	37	37	0%
ICMIC institution	30	5	35	86%
Pre-ICMIC institution	9	4	13	69%
Subtotal: All ICMIC institutions	39	9	48	81%
Not an ICMIC institution	6	31	37	16%
Subtotal: US-based	45	40	85	53%
Total:	45	77	122	37%

Source: STPI Analysis of journal editorial boards; lists of editors (which included affiliations) downloaded May 30th, 2008.

Of the forty-five editors who were ICMIC-affiliated, thirteen were ICMIC PIs (all ICMICs but University of Missouri, plus 3 P20 pre-ICMIC PIs), eight were co-PIs, eleven were Research Component or Specialized Resource leaders, two were Developmental Project leaders, and eleven investigators did not play formal leadership roles.

Another method of identifying leadership roles in the community played by ICMIC investigators was to analyze the leadership of the 2007 Joint Academy of Molecular Imaging/Society of Molecular Imaging Conference. Of the seventeen members of the organizing committee, seven were ICMIC-affiliated, including four of the eight ICMIC PIs; Dr. Gambhir of Stanford served as one of the two conference co-chairs.

Comparators' Perceptions of Institutions with Molecular Imaging Strengths

Comparators were asked to identify up to five of the strongest molecular imaging programs in the United States. Of the ten institutions named in response to this question, seven were ICMIC institutions. ICMIC institutions named most frequently were MGH and Washington University (each mentioned by five of nine interviewees). MSKCC, Johns Hopkins, and Stanford were each named by three interviewees, UCLA was mentioned by two, and Michigan was mentioned by one. Non-ICMIC institutions named included University of Washington (three mentions), University of Pennsylvania (two mentions), and University of California San Francisco (one mention).

Chapter 5: Collaboration and Multidisciplinarity

This chapter focuses on progress made by the ICMICs towards meeting the third program goal:

- Goal 3: Support the formation of vibrant, multi-disciplinary communities of cancer molecular imaging researchers at grantee institutions

5.1: Institutional Factors that Influenced Collaboration

The original ICMIC Request for Applications (RFA-99-004) stated that the ICMIC award is appropriate for, "those Institutions in which investigator-initiated multidisciplinary research involving imaging and molecular technologies are currently ongoing" and expected the ICMIC to provide, "an organizational structure specifically designed to facilitate scientific cross-fertilization between seemingly disparate groups of investigators." Future announcements (e.g., RFA-01-014, RFA-03-015) used similar language to describe the expected collaborative structure of the ICMICs.[19]

In their original applications and in interviews, all of the ICMIC Principal Investigators described pre-existing collaborations between members of what became the ICMIC team. Each of the applications in the first cohort of awards (MSKCC, MGH, UCLA) described a long-standing set of collaborations among a core nucleus of participants dating back to the early-to- mid 1990s, but the dynamics were slightly different at each institution. At UCLA, there appear to have been two distinct groups of collaborators that were united in the mid-1990s: a group of imaging faculty led by ICMIC co-PI Dr. Phelps and a group of cancer biologists led by PI Dr. Herschman. The MGH ICMIC originated with a nucleus of imaging scientists at the Center for Molecular Imaging Research that began a series of bilateral collaborations with cancer biologists including Dr. Breakefield in 1995 and Dr. Scadden in 1997. At MSKCC, a complex set of collaborations that formed the initial ICMIC was described, with no single individual acting as a catalyst or serving as the hub of the emerging ICMIC.

> "The goal for our first submission ... was to try and bring technologies of non-invasive imaging, PET scanning, and optical imaging, into the portfolio, into the toolbox of cancer researchers, who were preclinical" – ICMIC PI

> "Well, so the P20 basically allowed us to pull together this group of investigators that has pretty much remained the same now through the P50, the initial award, and then the competitive renewal. And so, the P20 in my opinion was just critically important in establishing that initial collaborative program, which is so important for these multidisciplinary projects to take off." – ICMIC PI

The other five ICMICs (Washington University, Stanford, Missouri, Michigan, and Johns Hopkins) each received a P20 pre-ICMIC award (see Table 5.1) before becoming a full ICMIC. These PIs credited the pre-ICMIC with

[19] The 1999 and 2001 RFAs also identified the role played by pre-ICMICs in establishing a collaborative infrastructure, stating for example in the 1999 RFA, "The 3-year P20 Pre-ICMIC awards described in RFA CA-99-002 will be appropriate for those Institutions that have most of the separate scientific components necessary for productive interaction but have no previous track-record of performing multidisciplinary scientific research" (RFA-99-004).

fostering collaborations that enabled the success of their ICMIC applications. At Washington University, Michigan, and Johns Hopkins, an existing nucleus of collaborations appears to have preceded the pre-ICMIC, but the P20 award helped to expand the depth and breadth of those collaborations. At Stanford and Missouri, PIs described the pre-ICMIC as having helped to leverage institutional support for the recruitment of new faculty and the building of other institutional infrastructure.

Several of the ICMIC institutions have particular types of organizational infrastructure that may have helped to facilitate collaboration. For example, four of the ICMIC institutions (MGH, UCLA, Missouri-Columbia, Stanford) have established multidisciplinary molecular-imaging related academic research centers (Table 5.1). These centers function as large-scale organizational structures for convening faculty and research staff from departments across the institution. There is significant overlap of leadership between the academic centers and the ICMIC at three of the four institutions, and at all four the ICMIC is integrated with the activities of the multidisciplinary center.

Table 5.1: Structural Features Promoting Collaboration and Multidisciplinarity

ICMIC	Had Pre-ICMIC	Multidisciplinary Imaging Center	Year of Formation of Multidisciplinary Center	Other Structural Features Promoting Multidisciplinarity
MGH	No	Center for Molecular Imaging Research at MGH/Harvard (CMIR)	1994	
MSKCC	No			Matrix organization of MSKCC faculty
UCLA	No	Crump Institute for Molecular Imaging	1990	Department of Molecular & Medical Pharmacology
Washington University	Yes			Division of Biology and Biological Sciences
Johns Hopkins	Yes			
Michigan	Yes			
Missouri-Columbia	Yes	Radiopharmaceutical Sciences Institute (RSI)	1999	
Stanford	Yes	Molecular Imaging Program at Stanford (MIPS)	2003	

Source: STPI Analysis of ICMIC applications and PI interviews, supplemented by internet searches to identify detail on structural features

Memorial Sloan-Kettering, UCLA, and Washington University each possess additional institutional features believed to promote collaboration. Research faculty at the Sloan-Kettering Institute (the MSKCC's research arm) are associated with one of eight "Research Programs" (e.g., Immunology, Molecular Pharmacology & Chemistry) rather than more traditional academic department structures. Faculty may also have appointments at Memorial Hospital and its research programs (e.g., the Experimental Therapeutics Center with which several ICMIC-participating faculty are affiliated), or with the clinical departments of Memorial Hospital (e.g., the ICMIC PI is affiliated with the Department of Neurology). Research Programs are described in application materials as cross-cutting structures that promote interdisciplinary interaction – molecular imaging

may be used as a tool for understanding angiogenesis or signaling networks by the Cell Biology or Cancer Biology and Genetics programs, or for assessing response to therapy by the Molecular Pharmacology and Chemistry or Clinical Immunology programs; each program draws upon researchers from across multiple departments. As described in Chapter 3, the ICMIC's executive committee, drawn from within the ICMIC, and from relevant department chairs and program heads (e.g., Radiology, Molecular Pharmacology and Chemistry, Clinical Immunology) reflects this matrixed approach to the organization of research.

The ICMIC co-PI at UCLA organized a Department of Molecular and Medical Pharmacology in 1993, merging the pharmacology and nuclear medicine programs. The department then recruited eighteen new faculty with a diverse array of backgrounds encompassing basic biological sciences, chemistry, and clinical research. According to the UCLA applications, the department acts as a microcosm of the broader UCLA cancer research community, with a particular focus on molecular imaging.

The Division of Biology and Biological Sciences (DBBS) at Washington University was formed in 1973, and currently consists of twelve interdisciplinary PhD programs, drawing upon faculty from twenty departments at Washington University. Faculty in DBBS have two primary appointments – one in an academic department, and one in an interdisciplinary program. Senior investigators often support graduate students from multiple disciplinary PhD programs, which brings a diverse set of perspectives into the research operations of their laboratories. As with the MSKCC ICMIC, the Washington University applications describe the hybrid Division-program structure as facilitating collaboration.

5.2: Collaborations and Multidisciplinarity of Individual Research Components

One approach to assessing the multidisciplinarity of the ICMICs is to analyze the content of the research itself. As a proxy for research content, the Outcome Evaluation considered the disciplinary affiliations of the personnel involved with the Research Components. This typically included a mix of faculty, research staff (either senior non-faculty researchers or research technicians), postdoctoral researchers, and students. However, since the research staff, postdocs, and students generally were attached to the laboratories of the faculty members who lead the Research Components, the faculty themselves were the focus of the assessment of disciplines. As described in Chapter 2, the discipline of a faculty member was determined by analyses of departmental affiliation and researchers' highest degrees.

Faculty associated with the 49 distinct ICMIC Research Components (counting research components of the four ICMICs that had been renewed as of FY 2007 separately in each iteration) were associated with more than twenty disciplinary groupings across both basic sciences (e.g., Anatomy/Physiology, Cell Biology, Biochemistry, Immunology, Virology, Genetics, Biophysics, Neuroscience, Bioinformatics, Chemistry (organic and inorganic), Physics, Engineering) and clinical medicine (e.g., Radiology, Internal Medicine, Pediatrics, Oncology, Pathology, Pharmacology, Surgery, and Veterinary Medicine) . Forty-five of the 49 Components (92%) provided funding to multiple faculty members as

part of their participation on the Research Component. Of these, 43 (96%) included faculty from two or more academic disciplines and 37 (82%) included faculty from two or more academic departments.[20] A total of six Research Components (one in each round of the MGH and UCLA ICMICs, one in the Michigan ICMIC, and one in the Stanford ICMIC) involved subcontracts or consulting agreements with collaborators outside the ICMIC home institution. By these measures, the ICMICs were heavily multidisciplinary in their approach to individual research tasks, although these data do not support conclusions regarding the character and quality of the scientific interactions.

5.3: Collaborations and Multidisciplinarity Across Multiple Research Components

Another approach to assessing the multidisciplinarity of within-ICMIC collaborations is to consider overlap of faculty between different Research Components and/or between Research Components and Specialized Resources. To explore this overlap, the evaluation considered faculty members who received salary support for their participation on a given ICMIC Research Component as well as faculty members named as "collaborators" who did not receive salary support[21]. A total of 11 Research Components (22%) had one or more paid faculty members who also received support from another Research Component, and 21 (43%) had one or more paid faculty members who received support from one of the Specialized Resources. When unpaid collaborators were included, more than half of all Research Components (60%) had one or more overlapping faculty members.

Overlap of faculty on Research Components varied substantially by ICMIC, with some (e.g., UCLA, MGH, Michigan, MSKCC renewal, Missouri, Washington University renewal) having no faculty members receiving salary from more than one Research Component, while half or more Research Components from the JHU, Washington University Initial, MSKCC initial, and Stanford ICMICs included faculty members receiving salary support from multiple Research Components. Faculty overlapping between Research Components and Specialized Resources, however, was more common across the ICMICs; only the UCLA ICMIC during its second round of funding had no Research Components where faculty members also received salary support from Specialized Resources.

Application materials were also analyzed to assess the inter-relatedness of the ICMIC Research Components as described. Eight of the twelve applications (all but UCLA initial, UCLA renewal, MSKCC initial, Michigan) specifically described the interrelationships and synergies among the ICMIC Research Components. Six of the ICMIC applications (Washington University initial, Washington University renewal,

[20] Analysis does not include faculty who were listed as "Collaborators" but who did not receive salary as part of their participation on the project.

[21] Six of the twelve ICMIC-round pairs (MGH renewal, MSKCC initial, MSKCC renewal, Missouri, Washington University initial, Washington University renewal) listed unpaid collaborators in their Research Component budgets and budget justifications. It is likely that had the others (UCLA both rounds, Stanford, MGH initial funding round, Michigan, Johns Hopkins) listed unpaid collaborators the broader measure of collaborativeness on Research Components would be still higher.

Stanford, MGH initial, MGH renewal, University of Missouri-Columbia) describe the transfer of tools and technologies across Research Components; the majority of Research Components are considered synergistic in that they can use the results of each others' research to advance their own techniques and approaches. Two of the ICMIC applications (Johns Hopkins, MSKCC renewal) describe a common theme or aspect of their research – an emphasis on understanding the role of hypoxia in the JHU application, and the two subthemes of human reporter gene constructs to study and better understand T cell activation and adoptive T cell therapy in patients and of imaging the biology of drug treatment response in the MSKCC renewal.

5.4: Collaborations and Multidisciplinarity at the ICMIC Level

Faculty departmental affiliations were assessed for each ICMIC. The percentage of faculty affiliated with a Radiology department or a multidisciplinary center devoted to molecular imaging (e.g., CMIR at MGH) varied substantially across the ICMICs (Table 5.2). Between 40% and 60% of all faculty were affiliated with a Radiology department or multidisciplinary imaging center at seven of the twelve ICMICs. An additional three ICMICs had fewer than forty percent, and two ICMICs (Stanford and the UCLA initial funding period) had more two-thirds or more (Table 5.2). Other faculty affiliations varied substantially from ICMIC to ICMIC. For example, several ICMICs had multiple members affiliated with medical schools or clinical departments, and others had multiple faculty members affiliated with a "basic science" department (MGH renewal, Washington University renewal, Missouri-Columbia). The MGH ICMIC (renewal period) was unique in that all of its Research Components involved unpaid collaborators from other institutions; including collaborators at two other Harvard hospitals (Brigham and Women's, Dana-Farber), Boston University Medical Center, Harvard University, and MIT. One Research Component at five of the other ICMICs (MGH initial, UCLA initial, UCLA renewal, Michigan; Stanford) involved a collaboration with a researcher from another institution (data not shown in Table 5.2).

Given the emphasis on translational research in the current ICMIC program announcement, another measure to consider is the number of ICMIC-participating faculty who have clinical backgrounds as indicated by an MD or MD-PhD degree. The percentage of faculty with an MD was between forty and sixty percent for nine of the twelve ICMICs and somewhat lower for the other three (Table 5.2); all of the ICMICs except for Missouri-Columbia had involved at least one senior-level clinician/oncologist/clinical trialist. Perhaps significantly, one of the ICMICs in the latter category (University of Missouri-Columbia) was among the ICMICs that had not brought any discoveries to clinical trials during their first five years of funding.[22] While clinician involvement is not sufficient for ICMIC discoveries to enter human trials, it is a necessary condition.

[22] Stanford, which had not initiated any clinical trials, first received ICMIC funding in 2004 and at the end of fiscal year 2007 had just completed its third year of funding.

Table 5.2: ICMIC-Level Assessment of Multidisciplinarity by Faculty Affiliation

ICMIC-Funding Round Pair	Total Faculty (total including unpaid collaborators in parentheses)	Number of supported faculty in Radiology or at Interdisciplinary Imaging Center	Percent. of Faculty in Radiology / Imaging	Departments with Two or More Faculty Named as Having Primary Affiliation	Highest Degree Where Known (PhD/ MD-PhD/ MD)	Percentage of Faculty with MD
MGH Initial	10 (29)	6	60%	None	5/4/1	50%
MGH Renewal	18 (32)	12	38%	Medicine (4); Pathology (4) Chemistry (2); Neurology (2); Neuroscience (2),	20/6/6	38%
MSKCC Initial	18 (20)	5	28%	Medicine (3), Epidemiology/ Biostatistics (2)	9/5/4	50%
MSKCC Renewal	18 (18)	6	33%	Medicine (4)	7/4/7	61%
UCLA Initial	12 (12)	9	75%	None	7/3/2	42%
UCLA Renewal	19 (19)	10	53%	Hematology/ Oncology (3)	8/4/7	58%
Washington University Initial	21 (23)	11	53%	Pathology (3)	13/3/5	38%
Washington University Renewal	12 (13)	4	33%	Medicine (2), Molecular Biology (2)	7/3/2	42%
Johns Hopkins	25 (25)	13	52%	Oncology (7)	13/5/7	48%
Michigan	12 (12)	7	58%	Radiation Oncology (2)	10/1/1	17%
Missouri-Columbia	18 (19)	8	44%	Biochemistry (3), Chemistry (2), Veterinary Medicine (2)	13/1/2 (+2 DVM)	17%
Stanford	15	10	67%	None	12/2/1	20%

Source: STPI Analysis of ICMIC applications and progress reports, supplemented by internet searches to identify faculty demographic information
Note. Columns 2-6 include only faculty listed as key personnel on Specialized Resources or Research Components, and not collaborators.

Another way to identify "Multidisciplinarity" is to group faculty members by area of research. Table 5.3 subdivides senior faculty (full professor or equivalent) participating in the ICMICs into three categories: (1) those primarily involved in the development of new imaging technologies and approaches; (2) cancer biologists; and (3) clinicians. The table suggests that at most of the ICMICs, there were senior faculty members involved from each of the categories. Missouri-Columbia did not include a senior-level clinician

as an ICMIC participant, while MGH, Michigan and Washington University involved a single senior clinical faculty member.

Table 5.3: ICMIC-Level Assessment of Multidisciplinarity of Senior Faculty at Full Professor Level

ICMIC	Professor-Level Imagers/ Radiologists/Chemists	Professor-Level Cancer Biologists	Professor-Level Oncologists/ Trialists
MGH	Weissleder, Fischman, Langer, Schreiber	Breakefield, Brown, Cantley, DePinho, Mathis; Murphy, Scadden, von Andrian, von Boehmer	Kantoff
MSKCC	Finn, Zanzonico	Blasberg, Rosen, Sadelain, {Bertino}	Larson, Gorelick, Scher, Scardino, O'Reilly
UCLA	Barrio, Czernin, Huang, Phelps, Satyamurthy	Herschman, Braun, McBride, Anna Wu, Hong Wu, Witte	Curiel, Economou
Washington University	Piwnica-Worms, Dehdashti, Welch	Kopan, Piwnica-Worms, Ratner, {Gordon}	DiPersio
Johns Hopkins	Bhujwalla, Wahl, Bluemke, Bottomley, Bulte, {van Zijl}	Kern, Murphy, Semenza, Sukumar, {Dang}	Davidson, Grossman, Jaffee
Michigan	Ross, Chenevert, Kilbourn, Meyer	Rehemtulla, vandeWoude	{Pienta}
Missouri-Columbia	Volkert, Quinn, Jurisson, Katti, Robertson, Singh	Deutscher, Forte, Hannink, Huxley, Sauter, Smith	None
Stanford	Gambhir, {Boyer}	Blau	Negrin, {Recht}

Source: STPI Analysis of ICMIC applications and progress reports, supplemented by Internet searches to identify faculty demographic information
Note: Senior faculty involved through Developmental Projects included in brackets. Does not include collaborators

Social network analysis is a method for representing interactions among groups of individuals. Social network diagrams were created to describe the collaborations (including unpaid collaborators) among ICMIC faculty as measured through their participation on Research Components and Specialized Resources (Appendix D). Individuals are represented as nodes of the diagram, and interactions (in this case co-participation on projects and Cores) as lines joining the individual nodes. Nodes can be colored to reflect attributes of the individual faculty – for each ICMIC, the first diagram shows departmental affiliation, and the second highest degree. Table 5.4 summarizes the interactions shown in the network diagrams, by ICMIC. The social network diagrams fall into three primary patterns.

Four ICMICs (UCLA initial, UCLA renewal, Michigan, Stanford) show limited cross-participation among the Research Components and Specialized Resources; a small number of investigators are affiliated with multiple Cores/projects and the social network diagram of faculty consists largely of small "islands" of researchers and includes several faculty members unconnected to others.

In contrast, two ICMICs (JHU and Missouri) are relatively highly collaborative and integrated; all (at JHU) or almost all (at Missouri) of the Research Components and

Specialized Resources are linked to the "main island" and the degree of interaction across Research Components and Specialized Resources is relatively high.[23] The other six ICMICs (MGH initial, MGH renewal; MSKCC initial, MSKCC renewal; Washington University initial; Washington University renewal) fall between these two extremes; there is substantial interaction within individual Research Components or Specialized Resources (shown as dense clusters of faculty), but fewer linkages across the diagram denoting individuals who are affiliated with multiple Research Components or Specialized Resources. At Washington University, especially, unpaid collaborators appear to provide key links across Research Components or Specialized Resources; excluding them from the social network diagram substantially decreases the degree of connectedness across the network.

Table 5.4: Summary of Co-Participation of Faculty on ICMIC Research Components and Specialized Resources, by ICMIC

ICMIC	Number of faculty (including collaborators)	Number of Faculty Participating on N Research Components/Specialized Resources					Interactions per Faculty Member
		0	1	2	3	4+	
MGH Initial	29	0	25	4	0	0	1.14
MGH Renewal	32	0	28	3	0	1 (5)	1.22
MSKCC Initial	22	0	12	6	2	0	1.36
MSKCC Renewal	18	0	13	4	1	0	1.33
UCLA Initial	12	1	9	1	1	0	1.17
UCLA Renewal	19	1	18	0	0	0	0.95
Washington University Initial	23	0	18	3	1	1	1.35
Washington University Renewal	13	0	10	2	0	1	1.38
Johns Hopkins	25	0	18	4	0	3	1.52
Michigan	12	0	12	0	0	0	1.00
Missouri-Columbia	19	0	12	3	4	0	1.58
Stanford	15	0	13	2	0	0	1.13

Source: STPI Analysis of ICMIC applications and progress reports
Note: Participation in Administrative Specialized Resources not included in the analysis. One UCLA ICMIC faculty member participates in the Administrative Core, but not on any of the other Specialized Resources, and so is identified as participating on "0" Research Components or Specialized Resources.

[23] The social network diagrams show two forms of interactivity – the number of faculty collaborating on each individual Research Component or Specialized Resource (all participants on a particular Research Component/Specialized Resource are shown as being linked to each other) as well as the number of faculty who span multiple Research Components or Specialized Resources. The table only shows the second of these forms of interactivity.

Examining the departmental affiliations of authors on ICMIC-affiliated publications offers a different measure of the multidisciplinarity of ICMIC research. Table 5.5 shows the departmental affiliations of authors on three or more publications, by ICMIC. The third column shows the number of authors affiliated with a Radiology department or molecular imaging center. As is shown in column five of the table, while program-wide approximately half of the identified authors are affiliated with the core department, the percentage varies substantially across ICMICs. Johns Hopkins is at the low end (21% of known authors outside of Radiology), while more than sixty percent at MSKCC and Missouri-Columbia are outside of Radiology.

Table 5.5: ICMIC-Level Assessment of Multidisciplinarity by Author Affiliation

ICMIC	Total Individual Co-Authors on Three or More ICMIC-Affiliated Papers	Number of co-Authors Where Departmental Affiliation Could Be Identified	Number in Radiology Department or Imaging Center	Percentage of Known Authors in Other Departments[24]
MGH	79	52	35	33%
MSKCC	70	42	15	64%
UCLA	68	41	20 (in M&MP)	51%
Washington University	54	29	19	34%
Johns Hopkins	29	19	15	21%
Michigan	63	26	12	54%
Missouri-Columbia	40	22	8	64%
Stanford	49	28	17	39%
Total	452	259	141	46%

Source: STPI Analysis of ICMIC publications database, and ICMIC applications and progress reports, supplemented by Internet searches to identify faculty demographic information

> "Just being involved in this project, people do come to me asking for advice and so on and so forth, with use of imaging applications in cancer, and those are hard to document clearly, but certainly I have given advice to many people here at UCLA on this issue. "
> – former ICMIC project leader

Eight of the Research Component leaders (current and former) interviewed were asked about the relative collaborativeness of their ICMIC research as compared with the research they conducted outside the ICMIC. All of them mentioned that their ICMIC-supported research was more collaborative than their non-ICMIC research. The Research Component leaders generally identified the multidisciplinary nature of the work as requiring collaboration (as the quote in the text box suggests); respondents also mentioned the interactions fostered by the ICMIC, through seminar series/ICMIC

[24] This measure likely underestimates the multidepartmental nature of ICMIC research. It would be expected that unknowns are more likely not to be affiliated with the core department or program, as most of the ICMIC institutions and interdisciplinary molecular imaging programs maintain on their Internet sites lists of past participants.

meetings and more informal discussions, as facilitating the interactions among researchers that are required.

The ICMIC PIs also were asked whether ICMIC-supported research is more collaborative than other imaging research occurring at their institutions. Most of the PIs, in contrast to the Research Component leaders, mentioned that all imaging research at their institution tended to be highly collaborative and that ICMIC research was not more collaborative than non-ICMIC research. Some of the PIs, on the other hand, did mention that ICMIC-supported research was more collaborative than other cancer imaging research at their institution. These PIs tended to be located at institutions that did not possess structural features promoting collaboration in imaging.

5.5: Collaborations Across ICMICs

Analysis of the ICMIC publications indicates that there was some collaboration across the various ICMICs that resulted in publications with authors from multiple awards as co-authors; as mentioned in Chapter 4, two publications acknowledged support from two P50 ICMICs each. The social network diagrams of ICMIC publications shown in Appendix E, however, include collaborators from other ICMICs who are co-authors (e.g., Professors Welch and Siegel of Washington University appearing as collaborators on MSKCC publications) – but generally only one ICMIC award is cited as supporting the research (e.g., the Washington University Radionuclide facility, of which Dr. Welch is the PI, is acknowledged on two MSKCC publications).

Washington University researchers appear to have been most likely to co-publish with researchers at other ICMIC institutions. Investigators from MGH, Stanford, Missouri-Columbia, MSKCC, and Michigan appear on three or more publications associated with the Washington University ICMIC; senior Washington University faculty members (e.g., Dr. Piwnica-Worms, Dr. Welch, Dr. Siegel) appear on three or more publications associated with the Missouri-Columbia, MSKCC, and Stanford ICMICs.

Researchers who moved from one ICMIC to another tended to be associated with cross-ICMIC publications.[25] As described in Chapter 6, Dr. Gambhir of UCLA moved to Stanford (along with several other researchers) to assume leadership of the Molecular Imaging Program at Stanford (MIPS) program; as might be expected, there is substantial and continuing cross-ICMIC publication between UCLA and Stanford. In another example described in Chapter 7, the movement of two researchers from Washington University to Michigan led to publications that involve a mix of authors from those institutions.

[25] Cross-ICMIC publications could represent either investigators who moved after the research was conducted, but before its publication, or investigators who remained involved in collaborations with their former colleagues. Dr. Gambhir's remaining on UCLA publications through 2007 suggests that he remains in active collaboration with colleagues at UCLA on ICMIC-related research, while on the other hand co-authorships by the Lukers on Washington University publications ended in 2005.

5.6: Insights on Multidisciplinarity from Comparator Institutions

Almost all of the interviewees at comparator institutions (University of Washington, UCSF, and University of Massachusetts Medical Center) also indicated that they collaborated outside their own research groups and laboratories to perform cancer imaging research. Their descriptions of how their collaborations occurred varied substantially, including:

- ***Individual initiative of investigators, actively seeking out new collaborations and building new research teams.*** Comparators indicated that they pursued new collaborations through their own efforts, identifying appropriate collaborators and encouraging them to join research teams. Researchers who were PIs on P-series awards described using renewals as a singular opportunity to introduce new investigators as collaborators, with one PI stating that approximately half of the researchers on the award changed from iteration to iteration.
- ***Creation of imaging-related seminar series to assemble cancer biologists, oncologists, and molecular imagers to share insights and catalyze collaborations.*** Seminar series were identified by several comparators as catalyzing collaborations, both by promoting the sharing of concepts across researchers in the institution and by bringing in imagers from other programs who suggested new lines of research to pursue.
- ***Historically close working relationships in small departments or institutions with a strong history of interdisciplinary collaboration.*** Several researchers pointed to cultural factors within their institutions as facilitating collaboration, describing the culture at their institutions as "naturally curious" or "wonderful" for collaboration.

Chapter 6: Community-Building and Organizational Infrastructure for Cancer Molecular Imaging

Two program goals are related to expanding the use of imaging at ICMIC institutions:

- Goal 3: Support the formation of vibrant, multi-disciplinary communities of cancer molecular imaging researchers at grantee institutions
- Goal 6: Build sufficient organizational infrastructure to effectively coordinate the cancer molecular imaging research enterprise at ICMIC institutions

This chapter discusses the strategies and activities utilized at ICMIC institutions to achieve these goals, as well as identifiable results to date.

6.1: Institutional Factors That Influenced Community-Building

As described in Chapter 3, ICMIC PIs employed a variety of strategies to build community among imaging researchers. These included a variety of mechanisms for drawing junior and senior faculty into imaging as well as seminar series and other mechanisms intended to facilitate networking and interaction. However, when considering community-building outcomes, it is important to recognize that the ICMICs do not operate in isolation from their institutional contexts. Table 6.1 summarizes the non-ICMIC activities carried out by ICMIC institutions aimed at expanding the institutional infrastructure available for research at the intersection of molecular imaging and cancer biology. The table shows that institutional funds were expended at every ICMIC institution to expand available capabilities for molecular imaging and cancer. Stanford University provided the largest single investment in molecular imaging infrastructure (more than $45 million); the creation of the MIPS program involved the hiring of eleven new faculty members (including Dr. Gambhir to lead the program), substantial expansion of laboratory space, and investment in equipment. Institutional expenditures in the millions of dollars occurred at MGH, MSKCC, Michigan, Missouri-Columbia, and Johns Hopkins, including the purchase of equipment and laboratory expansion or modernization– and in the case of Missouri, creating new faculty positions in the Radiopharmaceutical Sciences Institute. UCLA and Washington University also made institutional investments in molecular imaging – although exact dollar figures could not be determined, they likely were on the order of $1 million or less.

> Our major goal in the first ICMIC submission ...was to try to bring non-invasive imaging technologies into the hands of people who used animal models of cancer to develop technologies... And, also to try and make these kinds of technologies transparent and available, not just to people with an imaging background, but to cancer researchers – ICMIC PI

> When we submitted the original P50 application, the Vice Dean had by that time become very committed to imaging. –ICMIC PI

Table 6.1: Institutional Support for Community-Building

ICMIC	Equipment	Laboratory space	Faculty	Other	Total Dollar Value of Support (if stated)
MGH	PET/CT	4000 square feet added			> $2 million
MSKCC	Cyclotron upgrade, 4.7T and 7.0 MRI, 7.0T NMR,			Expansion of small animal facility, creation of Molecular Imaging Laboratory	
UCLA				Laboratory, animal facility remodeling, support for Small Animal Resource, career development funds	
Washington U			2 faculty (during P20)	Institutional support for HT Screening Specialized Resource	
Johns Hopkins	9.4T MRI spectrometer	1400 square feet added		Support for molecular biologist, pilot projects, postdoc, administrative assistant	At least $2.6 million
Michigan	7T MRI spectrometer, 9.4T MRI spectrometer, 2 IVIS optical systems, NIR equipment	4600 square feet added			$7 million
Missouri-Columbia	MicroSPECT/CT, 7T MRI, Xenogen optical		3 faculty		
Stanford	Cyclotron, other equipment not mentioned specifically in application	> 7,000 square feet added	11 faculty	Departmental funding for two postdocs	At least $45 million

Source: STPI Analysis of ICMIC applications and PI interviews

6.2: Estimates of Cancer Imaging Community Size

The size of the "cancer imaging community" at an ICMIC institution is difficult to measure for a number of reasons. While some faculty devote the bulk of their research effort to developing new imaging tools and techniques in the service of cancer research, others use imaging tools only sporadically as part of a larger research program. Imaging technology developers vary in the extent to which their approaches are aimed towards (or more broadly useful in) cancer research. For the purposes of the Outcome Evaluation, therefore, a variety of plausible definitions were used to estimate the size of the cancer imaging community.

First, the total number of participants in the ICMIC itself was considered. Most of the ICMICs included between twenty and thirty participants, with Johns Hopkins and the initial Washington University iteration including a larger number of participants (Table 6.2). This pattern may be explained by the fact that Washington University funded a large number of Developmental Projects (twenty projects, with twenty-five named investigators) while the Johns Hopkins ICMIC devoted the largest percentage of its budget (more than twenty percent of its direct costs) to pilot funding. A partial explanation for the small number of participants to date on the Washington University renewal is that as the renewal was only funded in 2007 few Developmental Projects have been awarded during the time period covered by the evaluation.

An alternate and perhaps more realistic measure of the size of the cancer molecular imaging community at the ICMIC institutions is the number of individuals identified as co-authors on ICMIC-supported publications. The ICMIC publications, however, included a total of 1,955 distinct co-authors, and it was not feasible within the evaluation to identify each individual researcher. Demographic information for the 386 researchers who were co-authors on three or more publications was identified. As is shown in Table 6.3, by this measure the number of authors participating in ICMIC-supported imaging research is between thirty and eighty individuals, varying substantially by ICMIC. As would be expected, the number of total authors tended to be higher for those ICMICs that have been renewed to date than for those ICMICs that are in their first iteration – but there is substantial variation within the newer cohorts. The information in Table 6.3, therefore, should be considered a lower bound on the total number of researchers who can be considered members of the "cancer molecular imaging" community at each institution.

Table 6.2: Participation in the ICMIC: Leading Roles

ICMIC-Funding Round Pair	Total Faculty on Research Components and Specialized Resources (including collaborators)	Individuals Involved On Developmental Projects Only or Faculty on Career Development Awards	ICMIC Participants in Leading Roles (sum of first two columns)
MGH Initial	29	17	46
MGH Renewal	32	7	39
MSKCC Initial	20	4	24
MSKCC Renewal	18	2	20
UCLA Initial	12	11	23
UCLA Renewal	19	2	21
Washington University Initial	23	17	40
Washington University Renewal	13	2	15
Johns Hopkins	25	10	35
Michigan	12	8	20
Missouri-Columbia	19	3	22
Stanford	15	4	19

Source: STPI analysis of ICMIC Administrative data

Table 6.3: Co-Authorship on Three or More ICMIC Publications

ICMIC	Total Individuals Co-Authors on Three or More ICMIC-Affiliated Papers	Number of Co-Authors Affiliated with the ICMIC	Number of Co-Authors Not - Affiliated with the ICMIC (affiliated with other ICMICs in parentheses)	Percentage ICMIC-affiliated
MGH	79	36	43 (1)	46%
MSKCC	70	34	36 (2)	49%
UCLA	68	39	29 (8)	57%
Washington University	54	25	29 (6)	46%
Johns Hopkins	29	18	11 (2)	62%
Michigan	63	22	41 (2)	35%
Missouri-Columbia	40	19	21 (2)	48%
Stanford	49	14	35 (5)	29%

Source: STPI analysis of ICMIC publications database, ICMIC administrative data

The ICMICs that have been renewed averaged thirty ICMIC-affiliated authors of three or more ICMIC publications, while the first iterations averaged between fourteen and twenty-two. On average, between forty and sixty percent of the authors of three or more ICMIC-affiliated publications are ICMIC-affiliated themselves, although the percentage is closer to one-third at Stanford and Michigan. At least part of this difference may be explained by the organization of the Michigan and Stanford ICMICs. Because of the bi-institutional nature of the Michigan ICMIC and the large research group at Van Andel who are subcontractors to the University of Michigan, each group has its own network of local collaborators, resulting in a two-island network of co-authorships (see Figure Appendix E-7 for the Michigan co-authorship diagram). It is not surprising that collaborators unaffiliated with the ICMIC at both institutions would be involved in ICMIC publications. At Stanford, the multidisciplinary MIPS center in which the Stanford ICMIC is situated, coupled with the rapid influx of other funds for molecular imaging research and training (discussed in greater detail below), could be expected to result in a set of ICMIC publications that involved a relatively large number of non-ICMIC co-authors.

6.3: Integration of Additional Faculty Members into Imaging Research

As described in Chapter 3, the Developmental Projects were intended to play a key role in integrating faculty from departments other than Radiology or an imaging research center into the cancer molecular imaging community. Table 6.4 summarizes attributes of Developmental Project participants. For most ICMICs, approximately half of the individuals who participated in Developmental Projects did come from other departments, with certain exceptions. One exception was MGH, where the Developmental Fund appears to have resulted primarily in building community within the MGH Center for Molecular Imaging Research (CMIR). MGH during its initial funding period awarded five individuals multiple Developmental Projects, including two individuals who received three awards each and three who received two awards. MGH also was quite likely to award developmental funds to Career Development awardees – four of whom received a total of five awards. Finally, MGH awarded less than one-quarter (3 of 13 or 23%) of its Developmental Projects to individuals outside the CMIR.

> In 1999-2000, we were starting, we were taking anybody kind of interested, you know in applying these types of strategies to their work, and bringing them in, whether they were senior investigators inside the department, outside the department didn't matter, you know just sort of trying to bring a working group together. And now, you know we are a well established paradigm. And so now, we can kind of prioritize a bit... there is internally a bit of a, I mean a clearly stated bias for people outside the Department of Radiology rather than in. – ICMIC PI

Table 6.4: Participation in Developmental Projects

ICMIC	Number of Developmental Projects to Date	Number of Participants	Number Not Involved with Research Components or Specialized Resources	Number Outside Radiology Departments or Imaging Centers
MGH Initial	20	13	12	3
MGH Renewal	6	6	6	3
MSKCC Initial	6	6	4	6
MSKCC Renewal	2	2	2	2
UCLA Initial	11	12	12	7
UCLA Renewal	4	4	2	2
Washington University Initial	20	25	17	15
Washington University Renewal	4	6	4	2
Johns Hopkins	11	11	8	5
Michigan	9	11	8	8
Missouri-Columbia	8	8	3	2
Stanford	6	6	4	3

Source: STPI analysis of ICMIC administrative data

Missouri-Columbia was another exception, awarding less than half (3 of 8 or 38%) of its Developmental Projects to researchers who were not affiliated with ICMIC Research Components or Specialized Resources and one quarter (2 of 8) to researchers outside the Radiopharmaceutical Sciences Institute (RSI). Its allocation of Developmental Projects appears to reflect the relatively small size of the cancer biology and molecular imaging communities at the institution.

As described in Chapter 4, ICMIC PIs were asked about the strategies they used in identifying and funding Developmental Projects. In addition to criteria related to the research content, most of the ICMIC PIs stated that they specifically sought to involve researchers from outside the ICMIC using the Developmental Fund, although their description of the process and of the types of researchers they aim to involve varied across the ICMICs. In general, the ICMIC PIs described looking to involve researchers outside their "core" department, and to involve researchers who could develop new techniques and approaches (e.g., imaging agents, instrumentation). One of the ICMIC PIs described a more translational research strategy, using the Developmental Fund to involve clinicians and to identify a set of pilot projects that, if successful, might incorporate imaging into the design and conduct of a clinical trial.

> And so, it was an active process, where ICMIC investigators would seek out key people that we thought we could have an impact on the clinic. – ICMIC PI

In order to be sustainable, community-building must involve changes in the career trajectories of individual researchers. Interviews with Research Component leaders and Career Development awardees identified two groups of participants whose career trajectories have been influenced by the ICMIC. One group included postdocs and junior faculty who received ICMIC funding for career development. Participation in the ICMIC facilitated cross-training, which enabled investigators with backgrounds in cancer biology to learn molecular imaging techniques and vice versa. More junior investigators also reported that participation broadened the range of imaging techniques with which they were familiar.

> One is certainly to get me more exposed to tumor biology, like basic research, then also, technical imaging skill sets, my background when I joined was magnetic resonance imaging but this has broadened; we also do nuclear and a lot of optical imaging, so that has certainly widened my horizon. – ICMIC Career Development Awardee

> I was getting very tired of doing experiments, where I called them the black box experiments. Put cells into an animal, and wait two weeks, two months, two years, whatever it was, and then come back to see what happens; and I was getting tired of that, and running into people who were thinking more carefully about biological imaging of live animals and people. I learned more about PET scan[ning], MRI, ultrasound, etcetera, and then got very interested in it, and decided having achieved a reasonably high level of success in other areas to literally shut down portions of my lab and start up new projects in imaging. So, the ICMIC was a[n] absolutely seminal event for me, to get funding to transition my lab into a new area of research. ICMIC Developmental Project leader

Interviewees also pointed to several notable cases where established researchers decided to make a major career shift to begin research in a new area or to begin to incorporate

imaging in their work. For those investigators, Developmental Awards provided a mechanism to begin to use imaging in their research, and they cited the ICMIC as an enabler and an opportunity to make that career shift. Additionally, several Developmental Fund recipients cited the guidance and mentorship of the ICMIC PIs as helpful in making career trajectory changes possible. The investigators interviewed mentioned that in addition to their continuing ICMIC involvement, they subsequently pursued R01/P01 funding for projects that involve molecular imaging. One example was Lily Wu of UCLA. Her postdoctoral training and initial research at UCLA after joining the faculty was focused on the use of adenovirus molecular genetics and function as a basis for gene therapy of prostate cancer; subsequent to receiving an ICMIC Developmental Project, her subsequent R01 and R21 incorporate bioluminescence and PET imaging to monitor the efficacy of gene therapy treatment approaches.

6.4: Organizational Infrastructure for Coordinating the Cancer Molecular Imaging Research Enterprise

Program Goal 6 is to "build sufficient organizational infrastructure to effectively coordinate the cancer molecular imaging research enterprise at ICMIC institutions." Looking across the eight ICMIC institutions, there was no single model for the manner in which the ICMIC influenced the "organizational infrastructure" at their institutions to provide "effective" coordination. Rather, the approach used to achieve this program goal depended upon the nature, extent and timing of other imaging related activities at their home institutions, including:

- The presence of academic centers (e.g., the MGH Center for Molecular Imaging Research) that serve as an institutional locus for cancer molecular imaging (described in Section 6.1 above)
- The existence of collaborations between ICMIC participants and participants in other large-scale NCI cancer research awards (described in Chapter 4).
- The other leadership roles played by the ICMIC PI (and co-PIs), including leadership of other large-scale awards devoted to cancer molecular imaging and role within the Cancer Center (if any) affiliated with the institution (described below)

The assessment of Program Goal 6 thus revolves around the answers to two questions:

1. Does the ICMIC represent a key portion of the coordinating infrastructure for cancer molecular imaging activity at the institution?
2. Does the ICMIC influence the degree to which molecular imaging is incorporated into the basic and clinical research occurring at the institution?

Coordinating Infrastructure for Cancer Molecular Imaging Activity at ICMIC Institutions

This section summarizes findings elsewhere in the report concerning the infrastructure responsible for coordinating cancer molecular imaging activity at the ICMIC institutions and the role played by ICMIC personnel in that coordination. Four specific coordination issues are discussed: (1) the relationship of ICMICs to multidisciplinary molecular

imaging research centers or to other coordinating structures, such as Cancer Center programs; (2) participation of Cancer Center senior leadership in the ICMIC's operations; (3) participation of ICMIC leadership in any molecular imaging-related research theme at the Cancer Center; and (4) synergies between ICMICs and SAIRs. Table 6.5 summarizes coordination efforts, by ICMIC.

Relationships between ICMICs and Multidisciplinary Imaging Research Centers or Other Coordinating Structures

As shown in Table 6.5, at seven of the eight ICMIC institutions, the ICMIC appears to be either a key component of imaging activity or is otherwise well-connected with the other loci of cancer molecular imaging activity. As described in Section 5.1, four of the ICMICs (MGH, UCLA, Missouri-Columbia, and Stanford) are housed inside institutional multidisciplinary imaging research centers led by the ICMIC PI or co-PI.[26] These multidisciplinary centers are devoted to molecular imaging research and represent the hubs of such activity at their institutions. At MSKCC, UCLA, and Washington University, institutional structures that facilitate the coordination of molecular imaging research are more virtual: the matrixed research structure of MSKCC and Washington University; and the emphasis of the UCLA Department of Molecular and Medical Pharmacology (a department led by the ICMIC co-PI) on molecular imaging and its application to cancer research.

Participation of Cancer Center Leadership in the ICMIC

Another measure of coordination is participation by leadership of the Cancer Center in ICMIC research or governance. At three ICMICs, members of the Cancer Center leadership play a direct role in the ICMIC.

- UCLA. Dr. Herschman is the Director for Basic Research of the UCLA-Jonsson Comprehensive Cancer Center. The Cancer Center Deputy Director (Dr. Economou) participates on an ICMIC Research Component.
- Washington University. Dr. Piwnica-Worms serves on the Executive Committee of the Washington University Siteman Cancer Center, and is co-Director of the Developmental Therapeutics Program of the Cancer Center. Two other members of the Siteman Cancer Center leadership team (Dr. Welch, Dr. DiPersio) participate on ICMIC Research Components
- MGH. The MIT Cancer Center Director (Dr. Jacks) is a collaborator on an ICMIC Research Component.

Four ICMICs (MGH, UCLA, Johns Hopkins, University of Michigan), include at least one member of their Cancer Center leadership – the Director or a Deputy/Associate Director – on their advisory boards, which allows for two-way transfer of information regarding ICMIC management and imaging research opportunities. Finally, as described in Section 3.2, the MSKCC ICMIC includes department chairmen and heads of cross-

[26] Although the cancer imaging enterprise at Missouri-Columbia appears to be more limited than at other ICMIC institutions, the Radiopharmaceutical Sciences Institute appears to form the locus for coordination.

cutting programs (e.g., Molecular Pathology and Chemistry) on its Executive Committee, which allows similarly for coordination and information exchange.

Table 6.5: Organizational Infrastructure for Imaging Research at ICMIC Institution

ICMIC	Freestanding Multidisciplinary Molecular Imaging Research Center or other coordinating structure	Cancer Center Leadership Participates or Has Governance Role in ICMIC	SAIR/SAIR PI Role in ICMIC?	Cancer Center "molecular imaging" research theme (theme name)	Theme leader	Strong Evidence for Coordination
MGH	Multidisciplinary Imaging Research Center led by PI	Yes	Yes/PI	Under Development (Cancer Imaging)	*Weissleder*	Yes
MSKCC	Other Coordinating Structure	Yes	Yes/co-PI	Yes (Imaging and Radiation Sciences)	*Larson*/ Zelefsky	Yes
UCLA	Both (MIRC led by co-PI)	Yes	Yes/co-PI	None identified		Yes
Washington University	Other Coordinating Structure	Yes	Yes/No	Yes (Oncologic Imaging)	Welch	Yes
Johns Hopkins	No	Yes	Yes/co-PI	None identified		No
Michigan	No	Yes	Yes/PI	Yes (Molecular Imaging)	*Ross/ Rehemtulla*	Yes
Missouri-Columbia	Multidisciplinary Imaging Research Center led by PI	No	No	Not applicable – no NCI-designated Cancer Center		Yes
Stanford	Multidisciplinary Imaging Research Center led by PI	No	Yes/co-PI	*Gambhir/ Contag*	Yes	Yes

Source: STPI analysis of NIH Administrative data
Note: Names in italics are ICMIC PIs or co-PIs

Existence of Molecular Imaging-Related Research Theme at the Cancer Center

Another measure of the ability of the ICMIC and its personnel to serve a coordinating function is whether a molecular imaging-related research theme at the Cancer Center level – and whether the theme is led by the ICMIC PI. At five of the ICMIC institutions (MGH, MSKCC, Washington University, Michigan, and Stanford) the Cancer Center has created (or in the MGH case, is in the process of creating) a research theme devoted to molecular imaging. At all institutions but Washington University, the theme is led by the

ICMIC PI. At the other three institutions, there is not a specific research theme devoted to molecular imaging at Cancer Center level. [27]

Synergies between ICMICs and SAIRs

A final point of coordination is whether the ICMICs are closely integrated with SAIRs at their institutions; seven of the eight ICMIC institutions (all but Missouri-Columbia) also have received SAIR awards. Three of the ICMICs (MSKCC, Washington University, Michigan) received SAIR funding before receiving ICMIC funding (either P20 or P50); MSKCC and MGH received P50 ICMIC funding before SAIR funding; and Johns Hopkins and Stanford received SAIR funds during the pre-ICMIC period of support. At these seven institutions, SAIRs and ICMICs are closely intertwined:

- ***Common leadership.*** At two institutions, the SAIR and ICMIC have the same PI (MGH, Michigan). At four institutions, the SAIR and ICMIC leadership teams are interwoven, with the SAIR PI acting as a co-PI on the ICMIC (MSKCC, UCLA, JHU, Stanford). Only at Washington University is the SAIR PI not a member of the ICMIC inner leadership – and there the SAIR PI serves on the ICMIC Internal Advisory Board.
- ***Common-pool resources.*** Small animal imaging is a widely-used technology at all of the ICMICs. As described in detail in Section 7.3, all of the ICMICs have provided funds to support small animal imaging, paying equipment and consumables costs and in most cases partially supporting the salaries of imaging personnel. Five ICMICs[28] (MGH, UCLA, Johns Hopkins, Michigan, Stanford) provide support though Specialized Resources devoted to animal imaging. MSKCC does not have a single "animal imaging" core (nor is there is single physical space that constitutes the SAIR), but in the initial ICMIC application there were distinct NMR and PET/Gamma cores that provided support to these specific facets of MSKCC's small animal imaging infrastructure. Washington University provided funds to the SAIR through the Administrative Core in its initial iteration.[29]

Summary: Integration of ICMIC into the Coordination of Molecular Imaging Research at ICMIC Institutions

At MGH, UCLA, Missouri-Columbia, and Stanford, evidence for coordination is direct. There exists a multidisciplinary research center headed by the ICMIC PI or co-PI; the

[27] Similar analyses were performed for those Cancer Centers that were not affiliated with ICMICs. While five of the seven (71%) of the ICMICs also had a molecular imaging-related theme at their Cancer Center, only seven of the other fifty-six Cancer Centers (13%) had a comparable molecular imaging theme; including three of nine pre-ICMIC institutions (33%) and four of forty-seven non-ICMIC institutions (9%). When only Comprehensive Cancer Centers were included, seventeen percent (6 of 35) had a molecular imaging theme, representing three of eight pre-ICMICs and three of twenty-seven non-ICMICs. It was not feasible to compare current CCSG support for molecular imaging with that present at the beginning of the ICMIC program.

[28] Although Missouri-Columbia does not have a SAIR, the ICMIC maintains a Specialized Resource devoted to small animal imaging.

[29] At six of the seven ICMICs with SAIRs (all but MGH), review of NIH administrative data shows that the Cancer Center Support Grant provides funding to the small animal imaging facility at the institution.

SAIR (if any) is also headed by the ICMIC leadership team; and at both MGH and UCLA other members of Cancer Center senior leadership are directly involved in the ICMIC as participants or in its governance. At both MGH and Stanford, there is a molecular imaging research program sponsored by the Cancer Center headed by the ICMIC PI.

At Washington University and at MSKCC, although there is not a single multidisciplinary center or organizational structure that forms the hub of imaging research, the linkage of senior ICMIC participants to the multiplicity of ongoing activities likely is sufficient. At Washington University, the ICMIC is closely linked to the Siteman Cancer Center (where Oncologic Imaging is an official research program), and to the other foci of imaging research (e.g., the Radionuclide Resource and the SAIR) at the university. At MSKCC, while the matrixed structure works against the coalescence of a singular point of coordination, the ICMIC appears to be well-integrated across the institution.

Although the scope of non-ICMIC imaging research at the University of Michigan is somewhat limited, the ICMIC and its leadership appear to be involved in its coordination. Although there is a named Center for Molecular Imaging, the research listed on the Center's Internet site includes only three awards, all of which are associated with Dr. Ross, the Michigan ICMIC PI.[30] Dr. Ross also serves as the leader of the molecular imaging-related research theme at the Michigan Cancer Center.

The evidence for institutionalization of imaging research at Johns Hopkins during the first ICMIC iteration, however, is more equivocal. While the ICMIC has become well-established, it is more difficult to identify strong linkages to the balance of the Hopkins cancer research enterprise that would suggest that the ICMIC is operating as a mechanism for coordinating all molecular imaging research occurring across the institution. The ICMIC is closely linked with the SAIR (which is itself funded by the Cancer Center Support Grant) and Cancer Center leadership is involved in the ICMIC's governance. However, Johns Hopkins has neither a stand-alone multidisciplinary molecular imaging-related research center linked to the ICMIC nor a molecular-imaging related research theme at Cancer Center level.

Integrating Molecular Imaging into Basic and Clinical Research at the Institution

The second question regarding the ICMIC's impact on coordination of cancer molecular imaging research is whether there is evidence that molecular imaging is being integrated into the overall cancer research program at the institution. Table 6.6 summarizes the results of the assessment of this question.

The first two columns of Table 6.6 summarize information shown in other chapters regarding whether the Cancer Center is funding molecular imaging research (through an imaging theme; through Cancer Center funding of the SAIR/small animal imaging

[30] http://www.med.umich.edu/msair/research.htm, accessed June 2008.

facility; or through pilot projects funded from the Cancer Center's Developmental Fund. All of the Cancer Centers that have ICMICs provide CCSG funding for molecular imaging research; at three of those institutions (MSKCC, UCLA, and Washington University) five or more ICMIC publications co-cite the Cancer Center Support Grant – suggesting more direct integration of the Cancer Center into ICMIC-related research at these institutions than at the others.

The third column draws from Table 6.3, showing the number of researchers at the ICMIC institution who were not ICMIC participants but have three or more co-authorships on ICMIC publications. The ICMICs fall into three groups: institutions with 30 or more such co-authors (MGH, MSKCC, Michigan, and Stanford); institutions with approximately twenty co-authors (UCLA, Washington University, and the University of Missouri-Columbia); and Johns Hopkins, with nine researchers not participating in the ICMIC who were co-authors on three or more ICMIC publications.

Table 6.6: Integration of Cancer Imagers with Other Cancer Researchers at ICMIC Institutions

ICMIC Institution	Molecular Imaging Supported by CCSG (Ch 3)	5+ ICMIC Publications co-Cite CCSG (Ch 4)	Number of Co-Authors Not - Affiliated with the ICMIC at the ICMIC Institution (Table 6.3)	Senior Clinicians Involved with ICMIC Beyond PI (Ch 5)	ICMIC Research(ers) Integrated into SPOREs (Ch 4)	5+ ICMIC Pubs co-Cite SPORE (Ch 4)
MGH	Yes	No	42	Yes	Yes	No
MSKCC	Yes	Yes	34	Yes	Yes	No
UCLA	Yes	Yes	21	Yes	Yes	Yes
Washington University	Yes	Yes	23	Yes	N/A	N/A
Johns Hopkins	Yes	No	9	Yes	Yes	No
Michigan	Yes	No	39	Yes	Yes	No
Missouri-Columbia	N/A	N/A	19	No	N/A	N/A
Stanford	Yes	No	30	Yes	N/A	N/A

Source: STPI analysis of NIH administrative data, co-citations of ICMIC publications

The three final columns of Table 6.6 summarize information from Chapters 4 and 5 regarding the integration of clinicians into the ICMIC and into clinical research at the institution. All of the ICMICs except Missouri-Columbia involve as active researchers senior clinicians beyond the ICMIC PI or co-PI. ICMIC research is integrated with local SPOREs (with integration potentially deepest at UCLA given the relatively large number of acknowledgements of SPORE funding on ICMIC publications).

At five of the ICMIC institutions (MSKCC, UCLA, Washington University, Michigan, and Stanford), the ICMIC and its personnel appear to be well-integrated into both the basic and clinical research communities at their institutions. As Stanford is a new Cancer Center, while there is a molecular imaging-related research theme as described above, it

may be premature to expect that the Cancer Center would be cited on ICMIC publications.

At Johns Hopkins, while on balance there appears to be integration, the evidence is more equivocal. On the one hand, the number of investigators involved with ICMIC publications (especially the number of non-ICMIC-affiliated investigators) is low relative to the other ICMICs; there are no publications acknowledging local support from the Cancer Center. On the other hand, senior clinicians participate actively in the ICMIC, and there are co-citations to two of the seven Johns Hopkins P50 SPORE awards active as of 2007.

At MGH and Missouri-Columbia, while there is strong integration of the ICMIC into the basic research at their institutions, there does not appear to be as strong a linkage between the ICMIC and the clinical oncology community. At Missouri-Columbia, one potential explanation lies in the limited strength of the clinical oncology community itself; Missouri-Columbia is the only ICMIC institution not affiliated with an NCI-designated Cancer Center, and there were no active SPORE or even clinically-focused P01 awards at the institution. At MGH, the MGH ICMIC involves a large number of collaborations with researchers at multiple universities, but there does not appear to be strong clinical integration with any particular institution. The strength of the CMIR itself, coupled with the scope of the clinical oncology community at the Harvard-affiliated hospitals, may to a certain extent hinder formal integration. The Dana-Farber/Harvard Cancer Center is currently developing a program in Cancer Imaging, which is categorized as one of its clinical research programs; the MGH CMIR is described as being central to this new effort.[31]

In summary, at six of the ICMIC institutions (MGH, MSKCC, UCLA, Washington University, Michigan, Stanford) there appears to be evidence that the ICMIC program is well integrated with the organizational infrastructure for coordinating the cancer molecular imaging research enterprise. At one institution (Johns Hopkins) there appears to be integration into clinical research, but there was not strong evidence that the ICMIC or its leadership served as an institution-level point of coordination for imaging research; the reverse may be the case at Missouri-Columbia.

6.5: Synergies Between Pre-ICMIC P20 and SAIR Programs

Another set of synergies identified is between the P20 pre-ICMIC program and the SAIR program. Of the fifteen institutions that have received funding through the SAIR program:

- Seven received funding through the ICMIC program
- Two (Duke, University of Pennsylvania) received SAIR funding and pre-ICMIC P20 funding simultaneously
- Three (Case Western, University of Texas-Southwest Medical Center, Vanderbilt) received ICMIC P20 funding before receiving SAIR funding

[31] Based upon the DF/HCC research program Internet site; http://www.dfhcc.harvard.edu/research-programs/discipline-based-programs/cancer-imaging/

- Three (University of Arizona, University of California-Davis, University of Texas – M.D. Anderson Cancer Center) have never received ICMIC funding

Principal investigators of the SAIRs that received ICMIC P20 funding in advance of SAIR funding were asked, as part of the ongoing SAIR evaluation, about the role played by the ICMIC P20 program in building multi-disciplinary collaborative teams of imagers and institutional infrastructure for molecular imaging at their institutions. Some of the PIs identified the ICMIC P20 as playing a vital role in building community, comparable to the responses of the ICMIC P50 PIs who had received P20 awards.

Chapter 7: Human and Physical Capital for Imaging Research

Training and physical infrastructure comprise two of the ICMIC program goals:

- Goal 4: Provide unique training and cross-training experiences for cancer-imaging researchers
- Goal 5: Enable the acquisition of physical infrastructure to facilitate cancer molecular imaging research;

This chapter describes outcomes associated with the ICMIC Career Development and Specialized Resource programs; and insights from interviews with comparators. The first part of the chapter describes human capital, and the second physical capital.

7.1: ICMIC Training and Its Outcomes

Career Development Awards

As shown in Table 7.1 below, a total of 4 tenure-track faculty members, eighteen non-tenure track faculty or research staff, 31 postdocs, 13 graduate students, 16 undergraduates, and five visiting faculty have received training through the use of ICMIC Career Development funds.

Table 7.1: Counts of Career Development Awardees

ICMIC	Tenure-Track Faculty	Non-Tenure-Track Faculty or Research Staff	Postdocs	Graduate Students	Undergraduates	Visiting Faculty
MGH	1	14	0	0	0	0
MSKCC	0	0	6	0	0	0
UCLA	0	0	9	6	0	4
Washington University	1	0	4	4	0	0
Johns Hopkins	1	2	0	0	0	0
Michigan	1	2	3	1	0	1
Missouri-Columbia	0	0	7	2	16	0
Stanford	0	0	2	0	0	0
Total	4	18	31	13	16	5

Source: STPI analysis of ICMIC administrative Data

One measure of the success of a career development program is whether participants' careers appeared to progress following training. Career-related outcomes of interest for Career Development Awardees included the following:

- New faculty appointments at the ICMIC institution;
- New faculty appointments at other academic institutions;
- Acceptance of a position in industry;
- Continuation of imaging training at the next appropriate level (e.g. undergraduates beginning graduate study, graduate students becoming postdoctoral fellows);

- Visiting scholars who returned to their home institutions.

Table 7.2 describes, where known, the current status of the ICMIC Career Development awardees (with the exception of the visiting scholars, who are described below). The table identifies several evident successes to date:

- Of the 18 non-tenure track faculty (mostly with Instructor rank), twelve to date have received faculty positions – nine at the ICMIC institutions and three at other institutions.
- Of the 31 postdocs, nine to date have received tenure-track faculty positions, and seven others have received non-tenure track instructorships or research staff positions.
- Of the 16 undergraduates, seven are known to be in graduate school, either in medical school or in the sciences.

Table 7.2: Transitions of ICMIC Career Development Recipients

Result	Tenure-Track Faculty	Non-TT Faculty	Postdocs	Graduate Students	Undergraduates	Total
Faculty: Received Tenure-Track Position at Same Institution	2	9	5	0	0	16
Faculty: Received Tenure-Track Position at Other Institution	1	3	4	0	0	8
Faculty: Received Non-Tenure-Track Position or Research Staff Position at Same Institution	0	5	3	1	0	10
Faculty: Received Non-Tenure-Track Position at Other Institution	0	1	4	0	0	4
Postdoctoral Fellow	N/A	N/A	12	1	0	13
Graduate Student	N/A	N/A	N/A	6	7	13
Undergraduate	N/A	N/A	N/A	N/A	8	8
Moved to Industry	1	0	1	1	0	4
Left Biomedical Research	0	0	0	2	1	2
Unknown	0	0	2	2	0	4
Total	4	18	31	13	16	82

Source: STPI analysis of ICMIC administrative data
Note: "N/A" = "Not applicable"

All four faculty who were visiting scientists at UCLA supported by Career Development funds have begun imaging programs at their universities – University of Tokyo, Kyoto University, Cambridge University, and Seoul National University. The visiting scientist trained at the University of Michigan is now in industry.

Trainees' Perceptions

Interviews with current and former trainees at the three focal ICMICs (MGH, UCLA, Missouri-Columbia) aimed to identify aspects of the training experience associated with receiving Career Development funds through the ICMIC program. A number of insights emerged from these interviews.

First, most trainees were not aware in advance they were joining an ICMIC; they were initially attracted to the research group that happened to have an ICMIC grant. Some trainees were not aware that they had specifically received an ICMIC "Career Development Award" to support their training, while others knew that their funding came from this designated source. Regarding the research that the trainees were pursuing, it was generally not possible for them to identify how much of that funding came from the ICMIC and how much from other sources, as research money is pooled. Trainees were aware of several other sources of funding supporting cancer molecular imaging at their institution; ICMIC was always referred to as the anchor support source. Post-doctoral trainees added that Career Development awards were instrumental in ensuring the continuity of their research.

> I have an electrical engineer in my group who now has learned some basic biology and has learned some chemistry, I mean not that he will synthesis things but knows what's possible in those areas. So that if either from, while he is here or later on in his career, if he wants to go and say build a new device, he can talk to a chemist in a reasonable way – ICMIC former trainee

Several trainees mentioned that participation in the ICMIC allowed them to cross-train or otherwise gain a set of technical skills that facilitated their development as well-rounded cancer imagers. For trainees, the use of equipment was the key "soft skill" gained through ICMIC participation. When probed for learned skills, trainees interpreted the question as referring specifically to gaining laboratory skills. Interviews identified that ICMICs allowed trainees to pursue research that requires more advanced equipment than might be available at other institutions. Nevertheless, there were other soft skills gained as well. Trainees noted that grant writing, publication, and presentation-writing skills were fostered through ICMIC participation.

Interviewees indicated that the ICMICs were stronger at fostering participant collaboration, especially interdisciplinary collaboration, relative to other training opportunities of which they were aware. They pointed out that, as expected of any laboratory-group environment, they benefited from peer interactions within their individual laboratories, but that the ICMICs have created opportunities for collaboration across laboratories as well.

ICMIC was cited by trainees and former trainees as having expanded and enhanced the community of cancer imagers, especially through weekly seminars and colloquia that facilitated the exchange of ideas at their institutions. Trainees had very positive views of the local cancer-imaging research community, referring to its cohesiveness, interdisciplinary nature, and the willingness to openly share. On the other hand, trainees were not aware of the research at the other ICMICs: cross-ICMIC/pan-ICMIC interactions were not evident.

PIs' commitment to trainees was evident in former trainees' comments about the quality of their experience. Former trainees reaffirmed the value of interactions with the PIs and their willingness to offer opportunities for trainees to learn and grow. Moreover, interviews with the former trainees revealed that they were aware of other former trainees' successes; they could identify graduates who have gained faculty positions elsewhere and progressed in their imaging research careers.

Training Through Participation in Research

Several ICMIC PIs observed during interviews that training also occurred through the participation of graduate students and postdoctoral fellows in ICMIC Research Components, Specialized Resources, and Developmental Projects; some estimated that more students were trained through research participation than the number receiving Career Development support. Although it was not feasible to generate a complete list of students receiving training through research for each ICMIC, the Washington University renewal application identified thirty-six individuals who had participated in research during the initial ICMIC funding period. Applying this rate of participation across all of the ICMICs suggests that several hundred individuals (including both students and laboratory technicians) likely will participate in ICMIC-sponsored research over the course of the twelve ICMIC awards funded to date.

Cancer Molecular Imaging Training at ICMIC Institutions Not Occurring Through the ICMIC

Prior to the initiation of the ICMIC program in 2000, all NCI-supported training in molecular imaging appears to have occurred as part of individual Research Project Grants; the evaluation identified no institutional training programs (e.g., T32s) that focused exclusively on providing training in molecular imaging or that included training in molecular imaging as part of a cancer biology training program at that time.[32] Subsequent to the funding of the ICMICs, four of the eight ICMIC institutions (all three of the first-cohort ICMICs, plus Stanford) have received NCI T32 or R25T awards for training in molecular imaging.[33] All of the PIs of those training awards have been involved with the ICMIC, including two awards won by ICMIC PIs and one by an ICMIC co-PI: In addition, a NIBIB T32 was recently awarded to the University of Missouri-Columbia in radiopharmaceutical sciences. At five of the eight ICMIC institutions, therefore (all but Johns Hopkins, Michigan, and Washington University) there are institutional training mechanisms in place to provide formal training to graduate students and/or postdoctoral researchers in molecular imaging.[34]

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[32] Based on searches of the NIH CRISP database for T32 or R25T awards prior to 2000 that included "molecular imaging" in the title or abstract. The first uses of the phrase by abstracts of training awards are in 2000.

[33] MGH (PI: Dr. Weissleder, T32CA079443, awarded 2001); MSKCC (PI: Dr. Hricak, R25CA096945, awarded 2002); UCLA (PI: Dr. Phelps, R25CA098010, awarded 2003);Stanford (PI: Dr. Gambhir, R25CA118681, awarded 2006). University of Missouri-Columbia (PI: Dr. Jurisson, T32EB004822) is not for "molecular imaging" per se, but it is closely tied to the activities of the Missouri-Columbia ICMIC.

[34] At ICMIC institutions, an additional five T32 awards (two at MGH, and one each at MSKCC, Michigan, and Stanford) provide general training in cancer biology but also explicitly mention "molecular imaging" in

7.2: Training Opportunities at Non-ICMIC Institutions

Only one comparable NCI-funded training award specific to molecular imaging was identified for a non-ICMIC institution during the same period; that award went to Vanderbilt (PI: Dr. Price, R25CA092043, awarded 2003), which was one of the recipients of a P20 pre-ICMIC that did not transition successfully to a P50. Eight non-NCI-funded molecular imaging T32 programs at non-ICMIC institutions were identified – all funded by NIBIB. Awardees include Vanderbilt (2 NIBIB T32s), Harvard University, Georgia Institute of Technology, University of California Davis, University of Arizona, Case Western Reserve University, and Duke University.

None of the comparator institutions (UCSF, University of Washington, University of Massachusetts Medical Center) possessed a molecular imaging-related T32 funded by NCI or by NIBIB as identified through the NIH database searches. Imaging trainees were usually supported by Research Project Grants or through individual fellowships. Interviewees reported that there also existed focused training opportunities that tended to focus on laboratory skills (e.g., PET fellowships that support trainees to gain advanced skills in PET imaging).

7.3: Physical Capital: Capabilities Built at ICMIC Institutions

Given the limited availability of funds for Specialized Resources (approximately $200,000-$400,000 at the various ICMICs), it is not surprising that ICMIC PIs interviewed stated that they generally did not invest in large-scale capital equipment. As described in Chapter 3, institutional support and NIH funding through NCRR instrumentation programs provides support for most large-scale equipment purchase. Several PIs mentioned the purchase of optical imaging or bioluminescence imaging equipment (which is less costly than a microPET scanner or a small animal MRI), and one described the purchase of SPECT equipment. Others described the importance of ICMIC funding in providing operating support for capabilities and equipment that required continuing maintenance and upkeep in order to provide utility to ICMIC researchers.

The ICMIC PIs did, however, identify particular materials, capabilities and expertise created or expanded by use of funds for Specialized Resources. Examples of capabilities included:

- ***MGH.*** Development of techniques for optical imaging of gene expression and protein activity; synthesis of nanoparticles and novel fluorescently labeled compounds as imaging agents and for cell tracking and distribution studies
- ***MSKCC.*** Synthesis of novel radiolabeled PET imaging agents (e.g., FLT, FlAU, FDHT); production of GMP-quality material for use in immune response modification clinical trials.
- ***UCLA.*** Synthesis of novel radiolabeled PET imaging agents (e.g., FLT, FDOPA, FEC, FHBG, FESP); development of microPET equipment and imaging techniques.

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their descriptions of training provided. These awards therefore may support graduate students or postdoctoral fellows in imaging-related topics, but do not necessarily do so.

- ***Washington University.*** Development of PET- and optical-based strategies for imaging protein-protein interactions *in vivo*,
- ***Johns Hopkins.*** Creation of Imaging Rapid Assessment Team for bringing imaging into Cancer Center and clinical trials; synthesis of novel constructs for gene silencing.
- ***Michigan.*** Development of high-resolution MRI-based serial tumor volume measurements and diffusion MR-based measurement of tumor water diffusion as potential indicators of therapeutic response; bioluminescence imaging of apoptosis
- ***Missouri-Columbia.*** Synthesis of novel radiolabeled SPECT imaging agents; discovery and optimization of tumor-avid peptides through phage display
- ***Stanford.*** Analysis of multi-component intracellular signaling by flow cytometry.

> So, the critical aspect of ICMIC Core support ... is, for the development of multimodality imaging that involves micro PET and the use of micro PET, and its extension into the clinic. PET is the technology that you bring to the clinic, as opposed to optical imaging, for the most part. And, I think that the key value of the shared research support that's provided through the ICMIC is to the preclinical PET research, and the translation of that research to the clinical applications. – ICMIC PI

Most of the ICMIC PIs indicated that the physical infrastructure and equipment at their institutions was adequate for the imaging research conducted at their institutions; only one PI indicated that more equipment and space would be necessary for their researchers to progress in their imaging capabilities. Information technology, however, was one area where investigators identified a need for improvements. Due to improvements in image capture and analysis that have occurred over the last several years, PIs suggested that hardware and software upgrades would improve the speed and quality of image processing.

Several of the ICMIC PIs identified increasing institutionalization of core services through support provided by the university or through other awards, especially associated with small animal imaging. For example, support for imaging resources and image analysis was removed from the MSKCC and Washington University ICMIC renewal applications, respectively. In both cases, SAIR funding was identified as supporting services that had originally been partially funded through the ICMIC Specialized Resources. At UCLA, the Jonsson Cancer Center created a shared small animal resource as a CCSG Core Facility, resulting in the contribution of Cancer Center funds in addition to SAIR, ICMIC, and other sources. At the University of Missouri-Columbia, Congressionally-appropriated funds created a Biomolecular Imaging Center at the Harry S. Truman VA Hospital; not only did the center purchase additional small animal imaging equipment but also the costs of maintenance and personnel are supported through the VA Hospital.

At comparator institutions, interviewees reported that the primary funding sources for large equipment are NIH and industry, supplemented with departmental investments. Like ICMIC PIs, interviewees indicated that the physical infrastructure at their

institutions was generally adequate, but they were more likely than their ICMIC counterparts to identify infrastructural limitations. For example, some interviewees stated they felt they were behind the ICMICs in terms of being state of the art because of older or even obsolete equipment. Others cited a lack of technicians and the difficulties of operating multiple imaging systems with a small number of personnel. Still others considered their institutions weak with respect to their support equipment, especially supplies and peripheral equipment.

Chapter 8: Findings and Recommendations

8.1: Findings Relative to Specific Program Goals

Program Goal #1, to stimulate, facilitate and enhance high-quality multidisciplinary research in the area of cancer molecular imaging, has been met.

Two lines of evidence support this finding. As described in Section 4.1, publication counts show that the publication output of the ICMICs is strong, although there is some variation in publication rate by ICMIC. A total of 755 publications were attributed to the full ICMICs; the steady-state ratio of dollars per publication per year was approximately $100,000 after an initial two-year ramp-up period. All of the ICMICs published at least ten papers citing the ICMIC award per year, while one (Washington University) averaged nearly twenty, and two (MGH, Stanford), nearly thirty published papers per year citing the award. An additional 160 publications were identified as associated with the sixteen pre-ICMICs.

As described in Section 4.2, ICMIC publications appear in a range of journals, including journals specifically targeted to molecular imaging or nuclear medicine, general cancer biology journals, journals aimed at clinical cancer research, chemistry journals, and general-biomedical journals. Bibliometric analysis also shows that the quality of the P50 ICMIC publications is strong, with many publications in high-impact journals and several highly-cited papers.

Program Goal #2, to direct cancer molecular imaging research towards bettering imaging technologies that have potential clinical or laboratory applications, was added in 2004, so an assessment is premature.

As described in the Feasibility Study for the ICMIC Outcome Evaluation and in Section 2.2, the clinical goal was first made explicit in Program Announcement PAR-04-069 in February 2004. Given the recent change to program goals, it is premature to have expected that new applications would have entered the clinic by the end of fiscal year 2007.

The evaluation nevertheless identified those discoveries of ICMIC research that have been clinically translated. As described in Section 4.4, few ICMIC discoveries have yet reached the clinic. The evaluation identified ten ICMIC projects that have involved clinical trials in some fashion, but only five of those trials rely upon ICMIC discoveries: two trials using new imaging agents or techniques that an ICMIC first developed have been conducted with ICMIC funding, and three other trials have been conducted using techniques first developed at an ICMIC but the trials were funded through other awards. The evaluation also identified several additional discoveries – both agents and imaging techniques – that may enter the clinic in the next year or two.

As described in Chapter 3 (the "Research Components" section on pages 20-22), ICMIC PIs place varying emphases on translational and clinical research in the conduct of their

ICMIC awards. Most PIs agree with the translational focus that began with the 2004 Program Announcement, though some believe that the program shouldn't necessarily require translation because of the continuing need for enabling technology, and the opportunities still remaining for imaging to catalyze advances in the understanding of cancer biology. Of the four ICMICs that had been renewed as of the end of fiscal year 2007, two (MSKCC and UCLA) specifically designed their renewal applications to focus on bringing successful discoveries from their first funding periods into the clinic, while the other two (MGH and Washington University) did not.

Program Goal #3, to support the formation of vibrant, multi-disciplinary communities of cancer molecular imaging researchers at grantee institutions, has largely been met, but not completely.

The assessment of this program goal aims to answer, "Did the research funded by the ICMICs involve a multidisciplinary group of faculty" as well as the broader question of whether funded researchers span the community of researchers at ICMIC institutions.

The answer to first of these two questions is described Chapter 5, which assesses the multidisciplinarity of ICMIC-supported research. As described in Sections 5.2 to 5.4, faculty from different disciplines and departments collaborate on the majority of individual ICMIC Research Components, though there is some variation across ICMICs regarding the degree of multidisciplinary collaboration. Section 5.4 (especially Table 5.5) also shows that the publications supported through ICMIC funds are collaborative and multidisciplinary.

The answer to the second of these questions is addressed in both Chapter 5 and Chapter 6. Chapter 5 (especially Table 5.3) shows that most of the ICMICs (with the exception of MGH and Missouri-Columbia) included senior faculty spanning imaging technology development, basic cancer biology, and clinical researchers. Section 6.3 describes the results of ICMICs' efforts to integrate imaging into cancer research communities at their institutions. The evaluation finds that the ICMICs have clearly promoted the integration of imaging into the cancer research programs at their institutions, by involving junior and senior faculty from departments where imaging research does not typically occur. At most of the ICMICs, the Developmental Projects played a vital role in integrating new faculty.

Program Goal #4, to provide unique training and cross-training experiences for cancer-imaging researchers, has been met, although not as originally envisioned.

The 1999 and 2001 RFAs described a training focus on graduate students and postdoctoral researchers. However, as described in Section 3.6, ICMICs have selected training strategies based upon local conditions, including the presence of other institutional sources of training funds. While six of the ICMICs train postdoctoral researchers and four train graduate students, two (MGH and Johns Hopkins) concentrated their Career Development funds on supporting junior faculty, one (University of

Missouri-Columbia) devoted resources to undergraduate training, and two (Michigan and UCLA), funded visiting scientists.

Section 7.1 describes the results of ICMIC training efforts. The ICMICs appear to have been successful in providing cross-training opportunities to faculty, postdoctoral researchers, and graduate students. Evidence of a positive impact on overall career trajectory for junior faculty members is already apparent:

- Of the 18 non-tenure track faculty (mostly with Instructor rank), twelve to date have received faculty positions – nine at the ICMIC institutions and three at other institutions.
- Of the 31 postdocs, nine to date have received tenure-track faculty positions, and seven others have received non-tenure track instructorships or research staff positions.
- Of the 16 undergraduates, seven are in graduate school – either medical school or sciences.

Program Goal #5, to enable the acquisition of physical infrastructure to facilitate cancer molecular imaging research, has been met.

As described in Section 7.3, ICMIC Specialized Resources have developed a set of capabilities and expertise that serve ICMIC researchers and other cancer imaging communities at their institutions (and in some cases other institutions as well). Most of the ICMICs developed new imaging techniques as part of research conducted by their Specialized Resources (e.g., MGH, UCLA, Washington University, Johns Hopkins, Michigan, Stanford) and several developed radiochemistry/synthesis capabilities for the synthesis of new imaging agents (e.g., MGH, MSKCC, UCLA, Missouri-Columbia).

ICMIC Specialized Resource funds are not typically used to purchase large-scale equipment. These purchases are more likely to be supported through institutional resources, SAIR awards, or the NCRR Shared Instrumentation/High-end Instrumentation programs. As described in Chapter 6 (the "Institutional Factors That Influenced Community-Building" section, pages 57-58), the ICMIC (and pre-ICMIC) programs were identified by principal investigators as helping to leverage institutional investment for the purchase of capital equipment. At several ICMICs (MGH, Johns Hopkins, Michigan, Stanford) the leveraged funds were identified as having exceeded $2 million.

Program Goal #6, to build sufficient organizational infrastructure to effectively coordinate the cancer molecular imaging research enterprise at ICMIC institutions, has been advanced at most of the ICMIC institutions.

The assessment considered two questions: (1) does the ICMIC represent a key portion of the coordinating infrastructure for cancer molecular imaging activity at the institution and (2) does the ICMIC influence the degree to which molecular imaging is incorporated into the basic and clinical research occurring at the institution? The assessment of the attainment of this goal is found in Section 6.4. At six of the ICMIC institutions (MGH, MSKCC, UCLA, Washington University, Michigan, Stanford) there appears to be

evidence that the ICMIC program has built organizational infrastructure for coordinating the cancer molecular imaging research enterprise. ICMICs at those institutions are a primary hub for molecular imaging research applied to cancer; have senior clinicians participating in ICMIC research; and are well-integrated into the local Cancer Center and SPOREs.

The evidence for institutionalization of imaging research at Johns Hopkins during the first ICMIC iteration, however, is more equivocal. While the ICMIC has become well-established, it is more difficult to identify strong linkages to the balance of the Hopkins cancer research enterprise that would suggest that the ICMIC is operating as a mechanism for coordinating all molecular imaging research occurring across the institution. The ICMIC is closely linked with the SAIR (which is itself funded by the Cancer Center Support Grant) and Cancer Center leadership is involved in the ICMIC's governance. However, Johns Hopkins has neither a stand-alone multidisciplinary molecular imaging-related research center linked to the ICMIC nor a molecular-imaging related research theme at Cancer Center level. The evidence regarding the integration of molecular imaging and the ICMIC into clinical research is equivocal as well. On the one hand, the number of investigators involved with ICMIC publications (especially the number of non-ICMIC-affiliated investigators) is low relative to the other ICMICs; there are no publications acknowledging local support from the Cancer Center. On the other hand, senior clinicians participate actively in the ICMIC, and there are co-citations to two of the seven Johns Hopkins P50 SPORE awards active as of 2007.

At Missouri-Columbia, one potential explanation lies in the limited strength of the clinical oncology community itself; Missouri-Columbia is the only ICMIC institution not affiliated with an NCI-designated Cancer Center, and there were no active SPORE or even clinically-focused P01 awards at the institution. At MGH, the MGH ICMIC involves a large number of collaborations with researchers at multiple universities, but there does not appear to be strong clinical integration with any particular institution. The strength of the CMIR itself, coupled with the scope of the clinical oncology community at the Harvard-affiliated hospitals, may to a certain extent hinder formal integration. The Dana-Farber/Harvard Cancer Center is currently developing a program in Cancer Imaging, which is categorized as one of its clinical research programs; the MGH CMIR is described as being central to this new effort.

The ICMIC institutions (and to a lesser extent, pre-ICMIC institutions that did not receive an ICMIC award) appear to be different from non-ICMIC institutions in the extent to which molecular imaging has been incorporated at Cancer Center level. As described in Section 6.4, while Cancer Centers affiliated with five of the seven (71%) ICMIC institutions had a molecular imaging-related theme, three of nine pre-ICMIC institutions (33%) and four of forty-seven non-ICMIC institutions (9%) had comparable research themes organized at their Cancer Centers as of fiscal year 2007. It was not feasible, however, to establish the directionality of cause and effect associated with this finding.

8.2: Overarching Findings

In addition to the findings specific to individual program goals, the evaluation results also suggest a set of general findings:

1. ***The ICMIC program is a successful example of an NIH P50 program.*** The P50 Specialized Centers mechanism aims to balance research, infrastructure, and training efforts using a team-based approach to science. The individual findings above suggest that the ICMIC program has been successful in meeting the objectives that are common to P50s, and that the ICMICs are exhibiting "Centerness." The Developmental Projects, especially, have been valuable disproportionate to their funding level, as they have both provided opportunities to expand the users of molecular imaging at ICMIC institutions and catalyzed new research efforts, many of which have led either to new ICMIC Research Components or R01-funded awards.
2. ***The addition of the clinical/laboratory application development goal in 2004 may have been overly ambitious.*** Given the various activities carried out in a P50 centers context, adding a clinical research or laboratory application development goal may not have been beneficial. Asking ICMICs to advance the frontiers of molecular imaging techniques, establish multidisciplinary collaborations, train researchers and also move findings from those endeavors toward clinical trials or laboratory application development may have set too many goals for a single program to achieve. As a result, individual ICMIC principal investigators, based upon their interests and the strengths at their institutions, have chosen a varying balance among developing new imaging techniques or agents; using imaging for discovery research; and clinical translation; the variation in strategy has continued through renewal of individual ICMIC awards. Therefore, the role of the ICMIC program in the "practical application" of imaging technology in the clinic has been limited to date and should be reassessed.
3. ***The program funding level is constraining.*** Especially because of the large number of programmatic objectives (and given high institutional overhead rates at some of the ICMIC institutions), maximum funding of individual ICMICs at $2 million in total costs is overly limiting and threatens the capability of ICMIC investigators to meet all the programmatic goals.

8.3: Recommendations: A Next-Generation ICMIC Program Design

Especially because the ICMIC program has been successful to date, recommending options for the future poses challenges. The recommendations below assume that NCI leadership believes that the "Center" concept continues to be valuable for advancing molecular imaging because of fostering collaboration, building infrastructure, and training the next generation of researchers. However, it is recommended that the ICMIC program announcement should differentiate between new institutions aiming to enter the ICMIC program and those aiming to renew existing ICMIC awards. New and renewing ICMICs would have different goals, organizational structures, and review criteria.

New ICMICs

The goals and review criteria laid out in the original (1999 and 2001) RFAs would form the basis of proposals by new teams to form ICMICs. The primary objective of the first five years of ICMIC funding would be to support the formation of vibrant, multi-disciplinary communities of cancer molecular imaging researchers at grantee institutions where to date molecular imaging had not yet been well-integrated into the practice of cancer researchers. The P50 Specialized Centers mechanism – which supports a balance of R01-sized Research Components, facilities, training, and pilot projects – is ideal for this purpose.

Because not all new ICMICs would transition automatically to one of the renewing-ICMIC forms described below, applications for new ICMICs should include a sustainability plan that would describe how Specialized Resources initially funded through the ICMIC program could be sustained by the home institution at the end of the five-year award period. Sustainability planning would involve the ICMIC institution and PI in working to ensure that the Specialized Resources and organizational capabilities developed during the ICMIC funding period would continue regardless of whether the ICMIC award itself was renewed.

Renewing ICMICs

Renewing ICMICs, however, should be designed and reviewed quite differently from how they are envisioned in the current Program Announcement. Two varieties of renewing ICMICs are suggested:

1. ***"Translational" ICMICs.*** One variety of renewing ICMIC would be explicitly focused on translating successful research from previous iterations of funding into clinical trials while continuing to devote a portion of its funding to the generation of a new round of discoveries. These ICMICs would focus on bringing imaging agents and techniques into the clinic, while continuing preclinical research aiming to ensure a robust pipeline of translatable concepts.
    - Leadership: The ICMIC PI would be a clinician (or clinician-scientist) with imaging background and expertise. A senior clinician (either a Cancer Center Director, Associate Director, or equivalent) would serve on the ICMIC executive committee to ensure bidirectional communication between the ICMIC and clinical trialists at the home institution regarding opportunities for integrating ICMIC-generated agents and techniques into upcoming trials at the institution and the needs of clinicians for new imaging agents or approaches.
    - Research Components: The majority of Research Components proposed would incorporate trials – either human studies of new imaging agents or the incorporation of new imaging techniques into treatment trials otherwise ongoing at the ICMIC institution. A minority of Research Components would be used to continue to create a "pipeline" of new clinically-translatable discoveries for future iterations.
    - Developmental Projects: Used to continue to create a "pipeline" of new clinically-translatable discoveries for future iterations.

- Career Development: Concentrated on training clinician-scientists – either postdoctoral fellows or junior investigators – to lead the next generation of translational research in cancer molecular imaging.
- Specialized Resources: Focus on clinical capabilities (e.g., synthesis of clinical-grade imaging agents); infrastructure associated with more basic research such as animal imaging would be expected to be supported by the institution.
- Further renewals: ICMICs could be renewed beyond the second funding period, based upon the success of their research.

2. ***"Basic research" ICMICs***. A second variety of renewing ICMICs would be explicitly focused on extending and deepening the initial community-building efforts of the initial iteration. These ICMICs would aim to further expand the use of molecular imaging at their institutions or to address a set of high-priority basic cancer research challenges previously-unstudied using imaging techniques. Proposers would be required to demonstrate community-building accomplishments in their first iteration as well as the need for and benefits of expanding community-building efforts through the renewal.
    - Leadership: The ideal ICMIC PI (or PI/co-PI team) would involve both a leader in molecular imaging technology development (especially someone heading a pre-existing large-scale interdisciplinary molecular imaging center) and a cancer biologist occupying a senior position in the institution's Cancer Center (e.g., Associate Director for Basic Research) or equivalent. An alternate leadership model would be for the executive committee/governing council (not the advisory board that meets infrequently to provide strategic advice and oversight) to include representation from Cancer Center leadership and/or leadership of departments or programs where the ICMIC aims to expand the use of molecular imaging in the service of cancer research.
    - Research Components: Research Components would involve either eminent cancer biologists who had not been previously users of molecular imaging or the extension of the use of molecular imaging to address a set of high-priority basic cancer research challenges previously-unstudied using imaging techniques.
    - Developmental Projects: As in the current ICMIC program announcement, Developmental Projects would be used for technique development and as a means for further extending the ICMIC community. It would be recommended that 10% or more of direct costs would be reserved for Developmental Projects, and that involving new investigators would be a key consideration in the selection of new pilot projects.
    - Career Development: Career Development funding would not be aimed specifically at a career stage of investigators, but would explicitly incorporate a community-building element that extended well beyond other molecular imaging training efforts (e.g., T32s, R25Ts) at the institution.
    - Specialized Resources: Specialized Resources would need to have capacity for, and usefulness to, the Research Components/Developmental Projects and other investigators across the institution.

- Further renewals: ICMICs could be renewed beyond the second funding period, but only if the applicants could demonstrate both successes in extending the use of molecular imaging in the service of cancer research during the current funding period and the need for further community-building during the next period.

Appendix A: List of Research Components and Specialized Resources

Research Components

MGH, Initial Iteration

1. In Vivo Imaging of Enzyme Activity (PI: Ralph Weissleder)
2. Angiogenesis Imaging (PI: Alexei Bogdanov)
3. Novel Vectors (PI: Xandra Breakefield)
4. Hematopoetic Cell Tracking (PI: David Scadden)

MGH, Renewal Iteration

1. Molecular libraries (PI: Ralph Weissleder)
2. Kinase Imaging (PI: Lee Josephson)
3. Novel Reporters and Delivery Vehicles (PI: Xandra Breakefield, Miguel Sena-Esteves)
4. Imaging CD8 Activity in Cancer (PI: Mikael Pittet, David Scadden, Ulrich von Andrian)

MSKCC, Initial Iteration

1. Imaging Gene Expression and Signal Transduction Pathways (PI: Juri Tjuvajev)
2. Pharmacokinetics and Optimization of Chemotherapy by NMR (PI: Jason Koutcher)
3. Imaging the In Vivo Antitumor Effects of Ansamycins (PI: Neal Rosen)
4. Imaging Progression and Response in Prostate Cancer (PI: Steven Larson)

MSKCC, Renewal Iteration

1. Imaging T cell interactions in adoptive therapy of EBV-associated malignancies (PI: Ronald Blasberg)
2. PET imaging of genetically modified human T cells in prostate cancer (PI: Vladimir Ponomarev)
3. Non-invasive markers of tumor response: a study of antiangiogenic therapy and development of non-invasive markers (PI: Jason Koutcher)
4. Development of methodologies for the in vivo imaging of the effects of novel inhibitors of signal transduction (PI: Neal Rosen)
5. Molecular imaging of castrate-resistant metastatic prostate cancer (PI: Steven Larson)

UCLA, Initial Iteration

1. Imaging Tumor Progression and Metastasis Caused by the Deletion of the Pten Tumor Suppressor Gene (PI: Hong Wu)
2. Imaging Prostate Cancer Bone Metastasis (PI: Charles Sawyer)
3. Imaging of VEGF Induction and Recruitment of Stromal Elements for Tumor Neovascularization (PI: Sanjiv Sam Gambhir)
4. In Vivo Analyses of Retargeted Adenovirus Vectors for Gene Therapy of Cancer (PI: Harvey Herschman)

UCLA, Renewal Iteration

1. In Vivo Imaging of Antigen-Specific T Cells in Mice and Humans (PI: Antoni Ribas)
2. Metabolic Phenotyping with PET to Monitor and Predict Responses to Kinase Inhibition in Cancer (PI: Johannes Czernin)
3. Recombinant Carcinoembyonic Antigen as a PET Reporter Gene (PI: Anna Wu)
4. Transductionally Redirected and Transcriptionally Restricted Adenovirus Therapy of Metastatic Colorectal Cancer (PI: Harvey Herschman)

Washington University, Initial Iteration

1. In Vivo Imaging of Gene Expression in Prostate Cancer (PI: Jeffrey Milbrandt)
2. Non-Invasive Monitoring of T Cell-Mediated Tumor Ablation (PI: Timothy McCarthy, Paul Allen)
3. Imaging Cancer Viruses with Tat Transducible Peptides (PI: Lee Ratner)
4. Imaging MDR1 P-glycoprotein Transport Activity In Vivo with Tc-94m-Sestamibi PET to Predict Response to Chemotherapy in Extensive Stage Small Cell Lung Cancer (PI: David Piwnica-Worms)

Washington University, Renewal Iteration

1. Imaging Notch Interactions with Members of Its Pathway (PI: Raphael Kopan)
2. Molecular Imaging Strategies to Study Cdc25A Regulation in vivo (PI: Helen Piwnica-Worms)
3. Imaging HTLV-1 Tax Induced Lymphomas (PI: Lee Ratner)
4. PET Imaging of GVHD and GVL Modulation Using Genetically-Modified Regulatory T Cells (PI: John Dipersio)

Johns Hopkins University

1. Combined Anti-Angiogenic Therapy and siRNA Targeting of Choline Kinase (PI: Zaver Bhujwalla)
2. Imaging the Role of HIF-1 in Breast Cancer Progression (PI: Gregg Semenza)
3. Imaging and Targeting Hypoxia in Solid Tumors (PI: Venu Raman)
4. Molecular and Functional Imaging of the HER-2/neu Receptor (PI: Dmitri Artemov)

University of Michigan

1. Imaging of Apoptosis (PI: Brian Ross)
2. Imaging of Carcinogenesis (PI: Alnawaz Rehemtulla)
3. Imaging of Oncogene Activation (PI: George Vande Woude)

University of Missouri-Columbia

1. Phage Display for Prostate, Breast, and Ovarian Tumor Imaging Agents (PI: Susan Deutscher)
2. Site-Specific Targeting of a Novel Receptor-Like Protein Expressed on Human Pancreatic and Breast Cancer Cells (PI: Leonard Forte)

3. Opioid Receptors and Ligands: Novel Markers for Cancer Imaging (PI: John Lever)
4. Development of New Peptidepeptide Nucleic Acid Conjugates for In Vivo Imaging of bcl-XL Expression in Lymphoma (PI: Michael Lewis)
5. Imaging Malignant Melanoma With Radiolabeled Alpha-MSH Peptide Analogs (PI: Thomas Quinn)

Stanford University

1. Development and Validation of Sensors for Imaging Protein Phosphorylation in Living Subjects (PI: Sanjiv Sam Gambhir)
2. Multi-Modality Imaging of Oncogene-induced Tumorigenesis (PI: Dean W. Felsher)
3. Dual Biotherapy for the Treatment of Malignancy (PI: Chris Contag)
4. PET Imaging of Brain Tumor Angiogenesis and Anti-Angiogenic Treatment (PI: Xiaoyuan Chen)

Specialized Resources

MGH, Initial Iteration

1. Chemistry (PI: C.H. Tung)
2. Small Animal Imaging (PI: Ralph Weissleder)

MGH, Renewal Iteration

1. Chemistry (PI: C.H. Tung, Lee Josephson)
2. Mouse (PI: Umar Mahmood)

MSKCC, Initial Iteration

1. NMR Imaging (PI: Jason Koutcher)
2. Gamma Camera Imaging (PI: Steven Larson)
3. Quantitative Autoradiographic and Optical Imaging (PI: Ronald Blasberg)
4. Organic Chemistry (PI: William Bornmann)
5. Cyclotron and Radiochemistry (PI: Ronald Finn)
6. Molecular Biology and Vector Development (PI: Michel Sadelain)
7. Image and Data Storage Analysis and Biostatistics (PI: Bradley Beattie)

MSKCC, Renewal Iteration

1. Cyclotron/Radiochemistry (PI: Ronald Finn)
2. Gene Transfer and GMP (PI: Isabella Riviere)
3. Image Analysis and Biostatistics (PI: Bradley Beattie)

UCLA, Initial Iteration

1. Cyclotron and Radiochemistry (PI: Jorge Barrio, N. Satyamurthy)
2. Molecular Imaging (PI: Simon Cherry, Sanjiv Sam Gambhir)
3. Quantitative Data Analysis (PI: Simon Cherry, Sanjiv Sam Gambhir)

UCLA, Renewal Iteration

1. Cyclotron and Radiochemistry (PI: N. Satyamurthy)
2. Molecular Imaging (PI: David Stout)
3. Quantitative Data Analysis (PI: Henry Huang)

Washington University, Initial Iteration

1. Molecular Imaging Reporter (PI: Kathryn Luker)
2. Molecular Imaging Chemistry (PI: Vijay Sharma)
3. Analytical and Image Processing (PI: Richard LaForest)

Washington University, Renewal Iteration

1. Molecular Imaging Reporter (PI: David Piwnica-Worms)
2. Molecular Imaging Chemistry (PI: Vijay Sharma)
3. Molecular Imaging High Throughput Screening (PI: Helen Piwnica-Worms, Raphael Kopan, David Piwnica-Worms)

Johns Hopkins University

1. Molecular Biology, Pathology and Viral Vectors (PI: Saraswati Sukumar)
2. Imaging, Image Analysis and Statistical Analysis (PI: Paul Bottomley)
3. Contrast agent development, Synthetic Chemistry and Radiopharmaceuticals (PI: Martin Pomper)
4. Translational Applications (PI: Nancy Davidson)

University of Michigan

1. Small Animal Imaging (PI: Thomas Chenevert)
2. Transgenic Animal (PI: Pam Swiatek)

University of Missouri-Columbia

1. Radiopharmacology/Imaging (PI: Timothy Hoffman)
2. Biochemistry (PI: George Smith)
3. Radiochemistry and Bioconjugation (PI: Kattesh Katti)
4. Human Cancer Tumor Bank (PI: Edward Sauter)

Stanford University

1. Chemistry/Radiochemistry (PI: Xiaoyuan Chen, Jianghong Rao)
2. Flow Cytometry (PI: Garry Nolan)
3. Small Animal Imaging (PI: Craig Levin; Michael Moseley)
4. Quantitation and Visualization (PI: Sylvia Plevritis; Sandy Napel)

Appendix B: Case Studies of Focal ICMICs

MGH

I. Research Objectives and Research Strategy

Overall research strategy: In both the first and second funding periods, the scientific aim of the MGH ICMIC was to develop next-generation imaging technologies to address important imaging research problems where expertise and preliminary data were available at MGH. Before the initial application was submitted, Dr. Weissleder reached out across the Harvard/MGH community through workshops and contacts with translational research groups such as the SPOREs. After initial project concepts were submitted by interested researchers, projects were selected as Research Components for the ICMIC based upon their potential clinical importance, rather than as part of an overarching theme or set of topics in cancer biology for the ICMIC to address. Two of the projects in each funding period have been aimed at improving imaging technologies, while two used imaging to support research studies focused on improving genetic or immunotherapeutic approaches to cancer treatment. All of the MGH ICMIC Research Components are aimed at creating new probes and agents and are expected to reach clinical trials during or soon after their five-year funding period. See Table A.1: MGH Research Component Descriptions for more detail.

Leadership continuity: There is some continuity in the leadership of the Research Components funded during the first and second funding periods of the ICMIC; three of the four Research Component leaders in the first funding period were involved in the leadership of Research Components in the second period, while the leader of the fourth Research Component in the second funding period was a Developmental Project leader during the first funding period.

Role of Developmental Projects: The overall goal of the Developmental program is to provide seed funding for novel, high-risk, pilot projects, with the expectation that the pilots will lead to publications and to other sources of funding for successful pilots. Other aims include promoting interdisciplinary research and catalyzing the use of imaging by new investigators. Interviewees relate that three of the four Research Components in the second funding period were influenced by research conducted through Developmental Projects – the Josephson and Pittet/Scadden/von Andrian projects (see Table A.1) were partially based on pilot projects conducted by those investigators during the first funding period, while the Breakefield/Sena-Esteves project was influenced by findings from a pilot project conducted by Yoshi Saeki, a former postdoc in imaging research at MGH.

II. Institutional Context, Funding, Infrastructure

Institutional home: The ICMIC resides at the Center for Molecular Imaging Research (CMIR), which was established in 1994 and has served as a focal point for molecular

imaging at MGH. The research culture at MGH and at the CMIR is highly collaborative. ICMIC participants interviewed reported that the large majority of people who engage in imaging associated with cancer research at MGH do so collaboratively, identifying approximately 150 collaborative projects around imaging at MGH.

Physical infrastructure: While space was very constrained in the early years, MGH made additional space available, today making the CMIR one of the largest programs at MGH (50,000 – 60,000 sq. ft of designated space). Although the large majority of dollars for the imaging equipment at CMIR did not come from ICMIC, the ICMIC award made notable contributions to the CMIR's infrastructure, especially during the first funding period. ICMIC funded a small animal imaging Specialized Resource, which preceded NCI funding for a Small Animal Imaging Resource R24 award to MGH, and was used to upgrade the animal imaging MRI system, purchase a scintigraphic imaging system, construct a near-infrared mouse imager, and install computer systems for image capture and analysis. (See Table A.2: Specialized Resource Descriptions for more detail.)

III. Structure of ICMIC Research: Collaboration and Rationale for Participation

Collaboration pre-ICMIC: Many of the key participants in the initial ICMIC had collaborated before the initial proposal. Between 1998 and early 2000, Dr. Weissleder had co-published on imaging-related topics with all three other Research Component leaders, and had worked closely with Dr. Bogdanov. He had also published on imaging-related topics with three of the four pilot project leaders (Basilion, Chiocca, and Josephson), between 1998 and 1999.

Incentives for Research Component leaders: The Research Component leaders interviewed fell into two groups regarding their rationale for participating in the ICMIC. For those who were already imaging researchers, participation in the ICMIC allowed them to expand the scale of their projects. The other leaders identified the ability to apply imaging approaches to their particular cancer research interests in order to better understand the fundamental biological processes they were investigating as the major incentive for joining the ICMIC. Junior investigators mentioned the opportunity to lead a Research Component which allowed them to collect data to support future R01 applications and advance their careers.

Structure of ICMIC: In both the first and second funding periods, the ICMIC was organized as four distinct Research Components. All Research Components have different Project PIs and virtually no overlap in research staff. The only exception is Dr. Weissleder, the overall ICMIC PI, who is part of two Research Components. There was more substantial personnel overlap between participants in the Research Components and the Specialized Resources, with several investigators overlapping during both funding periods. Figures Appendix D-1 and D-2 visualize the structure of the ICMIC as a social network diagram; individual investigators represent nodes of the network and lines show their interconnection through participation in Research Components or Specialized Resources. Applications and progress reports show that the Specialized Resources are used by all of the Research Components.

Multidisciplinarity: In the first funding period, two of the four Research Components were led by MGH faculty from outside the ICMIC core at CMIR and the MGH Department of Radiology (Dr. Breakefield, from the MGH Neurogenetics Department, and Dr. Scadden, from the MGH Hematology/Oncology Department). The pattern continued in the second funding period; two Research Components are led by non-CMIR MGH faculty (#2, #3), and one is co-led by CMIR and non-CMIR faculty (#4) – Research Component #4 includes a subaward to the Von Andrian group at Dana-Farber Cancer Center. All Research Components involved researchers from a mix of backgrounds, generally including at least two PhDs, MDs, or MD/PhDs in addition to research technicians.

IV. Imaging Research at MGH and the Role of the ICMIC in Fostering the Use of Imaging

Investigators' perceptions: The use of imaging in cancer research has expanded substantially at MGH and across the Harvard-affiliated research community since the advent of the ICMIC. Interviewees cited several roles played by the ICMIC in expanding the use of imaging. First, the process of applying for and receiving an ICMIC catalyzed interest. For example, as described above, the application process led Dr. Weissleder to interact with researchers across MGH as part of identifying the initial set of Research Components. Second, the ICMIC and its investigators serve as a resource for other investigators who wish to incorporate imaging into their research. As an example, interviewees cited the new Dana-Farber GI SPORE (Dr. Charles Fuchs), which has two molecular-imaging related projects and uses the ICMIC as a resource for developing new probes and agents and for information technology supporting image registration and capture. Interviewees mentioned that the older Harvard community SPOREs in contrast tend not to use imaging in their research. In this context, interviewees also considered ICMIC funding to be vital in encouraging researchers from diverse backgrounds to perform multidisciplinary research. Interviewees also described the joint seminar series which has been initiated between the ICMIC and other large-scale NCI-funded projects that pursue imaging as one of their research tools, specifically the MIT/Harvard Center for Cancer Nanotechnology Excellence (CCNE) and MIT U54 Tumor Microenvironment award.

Role of Developmental Projects: As described above, one of the goals of the Developmental Projects is to expand the base of imaging researchers and to draw new investigators into the ICMIC. Recipients of Developmental Project funding during the ICMIC's first years included investigators from across MGH (from CMIR, the MGH NMR center, and Neurosurgery) as well as one industry researcher (Lee Josephson) who subsequently joined the Harvard Medical School faculty. Recipients in subsequent years tended to be drawn from the CMIR.

Role of Specialized Resources: The CMIR's small animal imaging facilities serve as an enabling resource -progress reports and applications mention that the resource is used by 20-plus Harvard community investigators, as well as by investigators outside the Boston

area. The animal Specialized Resource is closely aligned with two Boston-area groups of mouse modelers; Dr. DePinho's P01 (Dana-Farber) and Dr. Jacks's Mouse Models of Human Cancer Consortium site (MIT) who serve as sources of new mouse models for imaging studies.

Co-citation of other awards on ICMIC publications: One measure of the collaboration between ICMIC awardees and others is to analyze the citations to non-ICMIC NIH grants on publications that were identified as being "ICMIC-supported." The number of investigators whose grants were co-cited on ICMIC publications rose from an average of seven per year between 2000 and 2002 (of whom two per year were not ICMIC participants during the first funding period) to eighteen in 2005 (of whom seven were not involved with the ICMIC in its first iteration) and twenty in 2006 (of whom eight were not ICMIC-involved).

Although an increasing number of grantees' awards were co-cited on ICMIC publications, the awards most likely to be co-cited along with the ICMIC grant were associated with core ICMIC participants. Awards often co-cited include the MGH SAIR where Dr. Weissleder is the PI (51 co-citations), a Tung R01[35] (24 citations), a P01 where Dr. Fred Hochberg is the PI and Dr. Breakefield is a project leader[36] (23 citations), the CMIR imaging training program where Dr. Weissleder is the PI[37] (20 citations), a Tung R21/R33[38] (15 citations), and an NHLBI-funded translational program of excellence in nanotechnology where Dr. Weissleder is the PI[39] (13 citations).

V. Education, Training, and the Role of ICMIC Career Development Funding

Molecular imaging training: MGH has an NCI T32 grant for molecular imaging training, which funds four postdoctoral researchers per year. The ICMIC Career Development program has been designed to complement the T32 training program, and supports primarily junior faculty or instructors at MGH, focusing on those who wish to change research directions and/or who need additional time in a productive scientific environment to establish an independent research program (2005 application). Fifteen junior faculty members (all but one of Instructor rank) have received career development funds through the MGH ICMIC. Interviewees related that while ICMIC Career Development funds are not used to support graduate students (because of Harvard overhead cost considerations), MIT graduate students can participate on ICMIC projects and receive project-based training.

Outcomes of the Career Development program: Seven of the eleven junior faculty who have completed their funding remain on the MGH faculty as either Associate or Assistant Professors and one additional awardee has Instructor rank. Three other completed trainees received faculty appointments at other institutions. In the second round of

[35] R01CA099385, 2003-7
[36] P01CA069246, 1997-2011
[37] T32CA079443, 2000-11
[38] R33CA088365, 2000-5
[39] U01HL080731, 2005-10

ICMIC funding, two former Career Development awardees became, respectively, a Research Component co-leader (Miguel Esteves-Sena) and a leader of the Mouse Specialized Resource (Umar Mahmood).

Career Development awardees often receive Developmental Project funding in parallel with their training award. Of the fifteen trainees, five received pilot project funding. Out of the twenty-five total Developmental Project awards, seven went to Career Development awardees; two received two Developmental Project awards each, three received one award of the twenty-five total Developmental Project awards. Some former trainees stated that without ICMIC funding, their research would have been focused on more immediate, short term goals.

Trainees' perceptions of the Career Development program: Current and former trainees interviewed were not aware in advance that they were joining an ICMIC. Instead, they were initially attracted to the CMIR and the researchers who happened to have an ICMIC grant. Interviewees stated that the MGH ICMIC training program aims to create multidisciplinary investigators at the intersection of molecular imaging and cancer biology. Most trainees are cross-trained through the ICMIC, having been trained initially either in imaging or in cancer biology, adding the complementary skill through their Career Development funding. Former trainees cited positive experiences that caused them to stay involved with ICMIC researchers once their Career Development awards concluded. Trainees interviewed who are now current faculty members at MGH and members of the CMIR cite the interactions with the ICMIC leaders and the collegiality of the center as an important incentive for faculty retention. Former trainees also cite the importance of being able to form collaborations that would have not been possible without the ICMIC.

Table A.1: MGH Research Component Descriptions

Initial iteration	Renewal iteration
In Vivo Imaging of Enzyme Activity (lead, Ralph Weissleder). Short Description: Imaging cathepsin D and other proteases to study tumorigenesis and to assist in cancer detection and staging.	Molecular libraries (lead, Ralph Weissleder). Short Description: Explore novel synthetic approaches to create ligands that target dextran-coated magnetic nanoparticles to prostate cancer cell surface antigens, testing different library methods and differentially screening thousands of molecules against known (hepsin, PAR-1, SPARC, PMSA, PSCA) and yet to be determined prostate cancer cell surface antigens
Angiogenesis Imaging (lead, Alexei Bogdanov). Short Description: Develop and test imaging tools to monitor angiogenesis in vivo, including both testing existing probes (sterically protected graft copolymer), developing new probes, and using imaging to evaluate therapeutic gene delivery to tumor neovasculature.	Kinase Imaging (lead, Lee Josephson). Short Description: Explore novel chemistries to develop probes that will enable imaging of the kinases involved in signaling transduction in humans, focusing on the lipid kinase PI3K (phosphoinositide 3-kinase) and the protein kinase AKT.
Novel Vectors (lead, Xandra Breakefield). Short Description: Develop novel targeting vectors and use imaging technologies to monitor transgene delivery and expression in tumor cells and animal models in order to allow the comparison and optimization of strategies for genetic therapies.	Novel Reporters and Delivery Vehicles (lead, Xandra Breakefield/Miguel Sena-Esteves). Short Description: Explore therapeutic strategies for glioma (endogenous neuroprecursor cells genetically modified to deliver new therapeutic proteins such as S-TRAIL and decoy receptors for VEGF to block angiogenesis) and develop imaging probes to assess whether the strategies are effective
Hematopoetic Cell Tracking (lead, David Scadden). Short Description: Develop imaging tools that allow tracing of stem and immune cell migration, facilitating experiments to determine if alterations in chemokine receptors on the surface of hematopoeic stem cells affect stem cell migration or if chemokine levels affect immune cell migration.	Imaging CD8 Activity in Cancer (lead, Mikael Pittet, David Scadden, Ulrich von Andrian). Short Description: Validate and employ noninvasive intravital imaging techniques to objectively monitor spontaneously arising tumor-specific T cell responses as well as measure the impact that immunotherapeutic modalities have on these responses.

Table A.2: MGH Specialized Resource Descriptions

Initial iteration	Renewal iteration
Chemistry Resource (C.H. Tung). Short Description. Provide resources to the CMIR Chemistry Core (formed in 1994) to synthesize radiochemicals, peptides, and imaging agents for use in ICMIC research, and to conduct research to improve imaging agent design and synthesis.	Chemistry Resource (C.H. Tung, Lee Josephson). Short Description. Provide resources to the CMIR Chemistry Core (formed in 1994) to synthesize radiochemicals, peptides, and imaging agents for use in ICMIC research, and to conduct research to improve imaging agent design and synthesis.
Small Animal Imaging Resource (Ralph Weissleder). Short Description. Develop new technologies and provide imaging services to investigators seeking to image small animals. Imaging capabilities include MR, MicroPET, near infrared, optical, scintigraphy.	Mouse Resource (Umar Mahmood). Short Description. Develop new technologies and provide imaging services to investigators seeking to image small animals. Imaging capabilities include intravital confocal microscopy, fluorescence reflectance imaging, fiberoptic fluorescence imaging, fluorescence-mediated tomography (FMT), bioluminescence imaging, SPECT, MicroPET, x-ray CT, and MR.

UCLA

I. Research Objectives and Research Strategy

Overall research strategy:

UCLA has historical strengths in imaging technology development, imaging probe development, and nuclear medicine, including the development of the first PET scanners and the first microPET for small animal imaging in 1997; in the late 1990s, however, those tools were not yet well-integrated into the work of the cancer biology community at the university. The goal of the ICMIC during its initial funding period was to catalyze the use of imaging across the cancer biology research community at UCLA. In soliciting Research Components, Dr. Herschman and Dr. Phelps, in consultation with the head of the UCLA Jonsson Cancer Center identified eminent investigators and approached them to discuss possible projects for the ICMIC application; there was not a formal call for proposals. Five projects emerged from the discussions, all of which were aimed to understand facets of cancer biology (only four of them were funded). They all used PET as the imaging modality – reflecting UCLA's historical strengths in PET imaging.

The goal of the second funding period was to move selected projects from the first funding period toward clinical trials. The ICMIC leadership solicited mini-proposals from its investigators (both Research Component leaders and Developmental Project leaders) and chose from among the ten received concept papers the four projects that were submitted as Research Components. Selection decisions were made based on the "ripeness" of the science for clinical testing; selected proposals had both therapeutic potential and made use of imaging for tumor detection (Research Component #3), monitoring of therapeutic response (Research Component #2), or identifying gene delivery to tumor cells (for Research Components #1 and #4). See Table A.3: UCLA Research Component Descriptions for more detail.

Leadership continuity: There is little continuity in the leadership of the Research Components funded during the first and second funding periods of the ICMIC; only Dr. Herschman continued as a Research Component leader from the first funding period – and two Research Component leaders (Dr. Sawyers and Dr. Gambhir) as well as a Specialized Resource leader (Dr. Cherry) were hired away by other universities; the four Research Component leader (Dr. Hong Wu) was selected as a Howard Hughes Investigator, and won R01 awards to continue his research outside the ICMIC. Two of the four Research Components in the second funding period are led by Developmental Project leaders from the first funding period, whose pilot projects became the foundation for their Research Components. For the fourth Research Component, the PI identified an investigator who had not been previously involved with the ICMIC but who had the clinical background to advance the concept and suggested that he lead the project.

Role of Developmental Projects: The overall goal of the Developmental program during the first funding period was to provide seed funding for novel, high-risk, projects that catalyze the introduction of molecular imaging techniques into the research of cancer

biologists who previously did not use these approaches. The program aimed to include both established, senior UCLA investigators and more junior faculty. During the second period, a second goal of the Developmental Fund was added, to sponsor projects that bridge the gap between animal models and human applications (translational research) and projects that extend into clinical trials. Interviewees relate that three of the Research Components in the second funding period were influenced by research conducted through Developmental Projects – #2 and #3 directly, while Research Component #1 united research performed through two of the Developmental Projects (by Dr. Witte and Dr. Braun).

II. Institutional Context, Funding, Infrastructure

Institutional home: The ICMIC resides at the Crump Institute for Molecular Imaging, which was established in 1990 and has served as a focal point for biological and molecular imaging at UCLA. Many ICMIC investigators have their academic appointments through the Department of Molecular and Medical Pharmacology. The research culture at Crump is highly collaborative. ICMIC participants interviewed reported that the large majority of people who engage in imaging associated with cancer research at UCLA do so collaboratively.

Physical infrastructure: The demand created for imaging services led to the expansion of the associated physical infrastructure at UCLA, which approximately doubled the small animal imaging capacity. The Jonsson Cancer Center, Crump, and the UCLA School of Medicine created a Small Animal Imaging Core as part of the Cancer Center that is now supported from a variety of sources, including DOE, the CCSG itself, two SPOREs, a SAIR, and the ICMIC. The ICMIC uses approximately 20-25% of the Small Animal Imaging Facility's capacity, and provides 15-20% of the support for the facility. Interviewees related that the ICMIC plays a crucial role in supporting radiochemistry and data analysis services to the imaging community; those two Specialized Resources support the use of PET imaging and its use in translational research (See Table A.4: UCLA Specialized Resource Descriptions for more detail).

III. Structure of ICMIC Research: Collaboration and Rationale for Participation

Collaboration pre-ICMIC: Interviewees related that the formation of the ICMIC was the catalyst for forging a bridge between developers of imaging technologies and the broader cancer biology community at UCLA. Between 1998 and early 2000, Dr. Herschman had co-published on imaging-related topics with one other Research Component leader (Dr. Gambhir), and had worked closely with him, Dr. Phelps, and the other Specialized Resource leaders. Two of the four pilot project leaders (Toyokumi, Berk), were also included on those imaging-related publications – especially regarding reporter gene techniques –between 1998 and 1999.

Incentives for Research Component leaders: The Research Component leaders interviewed fell into two groups regarding their rationale for participating in the ICMIC. For those who were already imaging researchers, participation in the ICMIC allowed

them to expand the scale of their projects. The other leaders identified the ability to apply imaging approaches to their particular cancer research interests in order to better understand the fundamental biological processes they were investigating as the major incentive for joining the ICMIC. The cancer biologists described a range of outreach activities that influenced their decision to participate in the ICMIC, including personal contacts with the PI and the discussion of the utility of molecular imaging at departmental seminars.

Structure of ICMIC: In both the first and second funding periods, the ICMIC was organized as four distinct Research Components. All Research Components have different Project PIs and virtually no overlap in research staff. There was some personnel overlap between participants in the Research Components and the Specialized Resources during the first funding period; Dr. Gambhir both led a Research Component and was a co-leader of two of the Specialized Resources; during the second funding period personnel are distinct. Figures Appendix D-7 and D-8 visualize the structure of the ICMIC as a social network diagram; individual investigators represent nodes of the network and lines show their interconnection through participation in Research Components or Specialized Resources. Applications and progress reports show that the Specialized Resources are used by all of the Research Components.

Multidisciplinarity: In the first funding period, three of the four Research Components were led by UCLA faculty with appointments in the Molecular and Medical Pharmacology Department (Dr. Sawyers, from the UCLA Medical School's Department of Hematology and Oncology, was the exception). The pattern continued in the second funding period; one Research Component is led by a faculty member from Hematology and Oncology (Dr. Ribas), while the rest involve faculty from M&MP. All Research Components involved researchers from a mix of backgrounds, generally including at least two PhDs, MDs, or MD/PhDs in addition to research technicians.

IV. Imaging Research at UCLA and the Role of the ICMIC in Fostering the Use of Imaging

Investigators' perceptions: The use of imaging in cancer research has expanded substantially at UCLA since the advent of the ICMIC. Interviewees cited several roles played by the ICMIC in expanding the use of imaging. First, the process of applying for and receiving an ICMIC catalyzed interest. For example, as described above, the application process led Dr. Herschman to interact with researchers across UCLA as part of identifying the initial set of Research Components. Second, the ICMIC and its investigators serve as the nucleus of a set of imaging-related collaborations that have developed among investigators funded through a range of NCI programs. The integration of the ICMIC and imaging into the Cancer Center Support Grant was mentioned as both a result of the ICMIC and as a stimulant for further expansion of collaborations; Dr. Herschman's dual role as director of basic research for the Jonsson Cancer Center and as the ICMIC PI was identified as being critical to the integration. Interviewees also mentioned that the ICMIC and its investigators are integrated into the Lung and Prostate SPOREs at UCLA. In the current funding period of the Prostate SPORE, one of the five

projects is explicitly imaging-based, and the project leaders or co-leaders of four of the five projects are ICMIC-affiliated; one of the projects in the Lung SPORE is imaging-based as well.

Several of the ICMIC investigators interviewed also mentioned that they found their work through the ICMIC to be more collaborative and multidisciplinary than other research that they perform; one senior scientist mentioned that the ICMIC served as an "intellectual incubator" at UCLA for stimulating new lines of cancer research.

Role of Developmental Projects: As described above, the primary goal of the Developmental Fund during the first ICMIC, and one of the goals during the second funding period, is to expand the base of imaging researchers and to draw new investigators into the ICMIC. Recipients of Developmental Project funding during the ICMIC's first five years included faculty from across UCLA (from M&MP, Pharmacology, Biological Chemistry, Microbiology, and Pathology); all of the Developmental Projects funded in the ICMIC's first two years went to faculty from outside the ICMIC's core at M&MP/Crump. Beginning with the end of the first funding period, and continuing through the second funding period, Developmental Projects have been awarded primarily to M&MP/Crump faculty, with some awarded to other faculty at UCLA.

Role of Specialized Resources: The Specialized Resources are funded by a variety of sources and serve the entire UCLA community; only approximately one-quarter of the capacity at those resources is directly devoted to ICMIC-funded projects. Many ICMIC "alumni" funded during the first cycle as Research Component or Developmental Project leaders continue to use imaging in their research, and are specifically mentioned in application materials as core users of the animal imaging facility; the renewal application mentions that the majority of users are non-ICMIC investigators. As many of the ICMIC-supported projects use PET and require radiochemistry resources, DOE funding through the UCLA-DOE Institute of Molecular Medicine was mentioned by interviewees as a critical contributor to the funding of the Specialized Resources.

Co-citation of other awards on ICMIC publications: One measure of the collaboration between ICMIC awardees and others is to analyze the citations to non-ICMIC NIH grants on publications that were identified as being "ICMIC-supported." The number of investigators whose grants were co-cited on ICMIC publications rose from an average of eight per year between 2001 and 2002 (of whom four per year were not ICMIC participants during the first funding period) to eleven in 2005 (of whom seven were not involved with the ICMIC in its first iteration) and eighteen in 2006 (of whom ten were not ICMIC-involved). Several investigators were located at institutions outside of UCLA (including City of Hope, USC, Scripps, and Washington University), and several of the UCLA investigators were funded by other NIH Institutes (including NIBIB, NIAID, NIMH, NIA, and NINDS) or through NCI SPOREs. These non-ICMIC awards included grants to support imaging technology development (where the publications reflect collaborations between ICMIC-supported technology developers such as Dr. Gambhir and others at UCLA and outside); grants to support cancer biology research; and non-

NCI supported researchers who are using PET imaging and likely are making use of ICMIC-supported Specialized Resources.

The awards most likely to be co-cited along with the ICMIC grant included both awards associated with core ICMIC participants and other NCI-funded P-awards to investigators at UCLA. Awards often co-cited include the UCLA SAIR where Dr. Phelps is the PI (24 co-citations), a Gambhir R01[40] (24 citations), a Herschman R01[41] (12 citations), the UCLA Jonsson Cancer Center Support Grant[42] (10 citations), a City of Hope P01 where Dr. Raubitschek is the PI and Anna Wu of the ICMIC (who had been an Associate Professor at City of Hope before coming to UCLA) was a project leader (2000-5) and continuing collaborator[43] (8 citations), and the UCLA Prostate SPORE[44] (6 citations).

V. Education, Training, and the Role of ICMIC Career Development Funding

Molecular imaging training: At the time of the first funding period, UCLA did not have dedicated training awards intended for molecular imaging training. The initial proposal identified the goal of training investigators at the intersection of cancer biology and imaging sciences, expecting to train three graduate students and three postdoctoral fellows each year, with the possibility of expending some funds to support faculty (either at UCLA or visiting from other institutions) who desired to cross-train. UCLA received a R25 award (entitled "Scholars in Molecular Imaging") award in 2004 to train post-doctoral fellows; in the ICMIC's renewal application the ICMIC leadership suggested that having the SOMI award would allow the ICMIC to provide still greater flexibility in their choice of Career Development awardees.

Nineteen individuals were identified as receiving support through the career development fund, including six graduate students, nine post-doctoral fellows, and four visiting faculty members.

Outcomes of the Career Development program: All four of the faculty members who were trained as visiting scholars returned to their original institutions to work in cancer imaging; three of them were known to have initiated molecular imaging programs at their universities. One of the post-docs (Dr. Mellinghof) has joined the UCLA faculty, and was a recipient of a Development Project in 2007; two others were identified as obtaining research positions at UCLA and Stanford, respectively. Of the six graduate students, three are in progress, one is a lecturer at UCLA, and two did not complete their studies.

Trainees' perceptions of the Career Development program: All of the trainees interviewed are currently at UCLA, either as graduate students or post-doctoral fellows. Some of the interviewees knew that they were joining the ICMIC when they first received funds, while others stated that they joined the laboratory of their mentors, who

[40] R01CA082214, 1999-2003 (at UCLA), 2003-2008 (at Stanford)
[41] R01CA084572, 1999-2010
[42] P30CA016042, 1977-2008
[43] P01CA043904 1988-2012
[44] P50CA092131, 2001-2012

had received ICMIC Career Development funds to support them. Interviewees described themselves as learning molecular imaging skills to supplement their biological science backgrounds.

Table A.3: UCLA Research Component Descriptions

Initial iteration	Renewal iteration
Imaging Tumor Progression and Metastasis Caused by the Deletion of the *Pten* Tumor Suppressor Gene (Hong Wu). Short Description: Design and test a PET imaging system to track Pten tumor suppressor gene deletion in an animal tumor model and to monitor tumor formation, metastasis, and the effectiveness of treatment in those animals.	In Vivo Imaging of Antigen-Specific T Cells in Mice and Humans (Antoni Ribas). Short Description: Builds on *in vivo* imaging of antigen-specific T cell responses in mice during the first funding period to conduct preclinical and clinical testing of the ability use PET to image tumor antigen-specific T cell responses against malignant melanoma.
Imaging Prostate Cancer Bone Metastasis (Charles Sawyer). Short Description: Use PET to image the metastasis of prostate cancer to the bone of mouse models, aiming to identify the role of angiogenesis and the origins of the osteoblastic response.	Metabolic Phenotyping with PET to Monitor and Predict Responses to Kinase Inhibition in Cancer (Johannes Czernin). Short Description: Introduce "metabolic phenotyping" with PET to monitor treatment responses to targeted kinase inhibition in cancer patients.
Imaging of VEGF Induction and Recruitment of Stromal Elements for Tumor Neovascularization (Sam Gambhir). Short Description: Use imaging of PET reporter genes to understand facets of the tumor microenvironment (especially the hypothesized correlation between VEGF induction and GMEC cell recruitment) required for new blood vessel growth.	Recombinant Carcinoembyonic Antigen as a PET Reporter Gene (Anna Wu). Short Description: Develop a new class of PET reporter probes based on CEA-binding peptides, in order to monitor gene expression and to track modified immune cells first in mice and eventually in humans.
In Vivo Analyses of Retargeted Adenovirus Vectors for Gene Therapy of Cancer (Harvey Herschman). Short Description: Optimize previously-developed PET reporter viruses and probes and investigate their distribution, targeting to tumor cells, and gene transfer capability in mouse models.	Transductionally Redirected and Transcriptionally Restricted Adenovirus Therapy of Metastatic Colorectal Cancer (Harvey Herschman). Short Description: Builds on the previous funding period to create an adenovirus vector for a gene therapy protocol that incorporates a firefly luciferase reporter gene to image successful gene delivery.

Table A.4: UCLA Specialized Resource Descriptions

Initial iteration	Renewal iteration
Cyclotron and Radiochemistry Facility (Jorge Barrio and N. Satyamurthy). Short Description: Add resources to a DOE-funded core laboratory to produce radiopharmaceuticals for ICMIC use.	Cyclotron and Radiochemistry Facility (N. Satyamurthy). Short Description: Add resources to a DOE-funded core laboratory to produce radiopharmaceuticals for ICMIC use.
Molecular Imaging Facility (Simon Cherry, Sam Gambhir). Short Description: Image mice using microPET and digital whole-body autoradiography	Molecular Imaging Facility (David Stout). Short Description: Image mice using microPET, microCT, optical, and digital whole-body autoradiography
Quantitative Data Analysis Facility (Simon Cherry, Sam Gambhir). Short Description: Acquire and extract data from mouse imaging performed in the Molecular Imaging Facility, and develop new software for image registration and analysis.	Quantitative Data Analysis Facility (Henry Huang). Short Description: Acquire and extract data from mouse imaging performed in the Molecular Imaging Facility, and improve the software for image registration and analysis developed during the first funding cycle.

University of Missouri-Columbia

I. Research Objectives and Research Strategy

Overall research strategy:

The University of Missouri-Columbia has historical strengths in the radiopharmaceutical sciences; the Missouri University Research Reactor, first brought online in 1966, is used by investigators to support the development of novel radiopharmaceuticals. The University of Missouri-Columbia received a P20 pre-ICMIC in 2000 for a Center for Single Photon-Emitting Cancer Imaging Agents to pursue the development of SPECT diagnostic imaging agents. The pre-ICMIC formed the basis for the creation of three Core facilities (In vivo Radiopharmacology and Microimaging; Biotechnology/Combinatorial Chemistry; and Radiochemistry/Bioconjugation Chemistry) as well as for the assembly of multidisciplinary research teams. At the time of the ICMIC application, the PI, working with the pre-ICMIC internal and external advisory boards, sent out a call for Research Components from University of Missouri faculty. Ten concepts were received, of which five were selected for inclusion in the ICMIC proposal. Building upon pre-existing strengths at Missouri in radiopharmaceutical sciences and technetium-99m chemistry, all five Research Components employed SPECT/radiolabeling as an imaging modality. See Table A.5: Missouri-Columbia Research Component Descriptions, for more detail.

Leadership continuity: There was substantial continuity between the P20 pre-ICMIC and the ICMIC investigators. Dr. Volkert led both the pre-ICMIC and the ICMIC. Three of the five Research Components funded in the ICMIC were outgrowths of pre-ICMIC work, and the leaders of the three Specialized Resources first funded during the pre-ICMIC retained those positions on the ICMIC as well.

Role of Developmental Projects: The overall goal of the Developmental program was to provide seed funding for novel, high-risk, projects to obtain preliminary results in support of further grant applications rather than to specifically involve new faculty in cancer imaging. Four of the eight Developmental Projects were identified as having led to the award of subsequent funds.

II. Institutional Context, Funding, Infrastructure

Institutional home: The ICMIC resides at the Radiopharmaceutical Sciences Institute (RSI), which was established in 1999. During the early 2000s, the University of Missouri committed to expand the RSI from its nucleus of radiochemists to include clinicians, biologists and biochemists, with a focus on applications to cancer research. The university had committed to hire an oncologist and two cancer biologists at the time of the original ICMIC application submission.

Physical infrastructure: The Missouri University Research Reactor (MURR) represents one pillar of the physical infrastructure available to the Missouri ICMIC; the pre-ICMIC

led to the creation of additional physical infrastructure, including the development of the three Specialized Resources and the purchase of small animal microSPECT and microCT equipment (partially funded by the pre-ICMIC, partially with institutional resources). See Table A.6: Missouri-Columbia Specialized Resource Descriptions, for more detail.

Subsequent to the establishment of the ICMIC, the University of Missouri invested, with additional support from the Department of Veterans' Affairs, in two other research centers that interact with the RSI and the ICMIC, the Biomolecular Imaging Center and the International Institute for Nano and Molecular Medicine. The Biomolecular Imaging Center was part of the expansion of the research capabilities of the Harry S. Truman VA Hospital; additional small animal imaging equipment purchased included combined SPECT/CT, micro-MRI, and optical equipment (a Xenogen 200), expanding the imaging modalities available for research. Interviewees noted that the expansion of the VA's research facilities helps to institutionalize the core resources available to imaging researchers, decreasing the requirement for individual programs such as the ICMIC or pre-ICMIC to fund equipment purchase and infrastructure support. The International Institute for Nano and Molecular Medicine was founded with $10 million in institutional support in 2006, and attracted Dr. Frederick Hawthorne from UCLA as its first head. Imaging aspects of the new center intersect with the ICMIC's activities.

III. Structure of ICMIC Research: Collaboration and Rationale for Participation

Collaboration pre-ICMIC: Interviewees related that the pre-ICMIC was the catalyst for forging a bridge between developers of imaging technologies and the broader cancer biology community at Missouri; the ICMIC application process – and its funding – further deepened those relationships. That collaboration on imaging topics was relatively new at the time of the ICMIC is reflected in publication records; between 1998 and 2000, Dr. Volkert had co-published on imaging-related topics with none of the Research Component leaders, and with two of the Specialized Resource leaders (Dr. Hoffman, Dr. Katti). The other ICMIC Research Component leaders historically had not co-published with each other, either; there was only one 1998-2000 publication involving two or more ICMIC Research Component leaders (a 2000 *Cancer Research* paper with Dr. Quinn as last author and Dr. Deutscher as a collaborating author). Dr. Volkert co-published with two of the Research Component leaders (Dr. Forte, Dr. Quinn) in 2001.

Incentives for Research Component leaders: The Research Component leaders interviewed had all previously participated in the pre-ICMIC and considered involvement in the full ICMIC as the natural extension of their activities. Investigators described the ICMIC as more collaborative and multidisciplinary than the balance of their research activities. As with other ICMICs, investigators identified ICMIC meetings and seminar series as a vehicle to convene investigators and foster collaboration. One difference between the Missouri ICMIC and others is the overall size of the cancer research community; with approximately fifty cancer researchers affiliated with the University of Missouri-Columbia, half or more of them were directly involved in the ICMIC through participation on the Research Components, Specialized Resources, or Developmental Projects by the end of the five years of funding.

Structure of ICMIC: There is substantial overlap in the participants on the ICMIC Research Components. While all five Research Components have different Project PIs, there are faculty investigators who collaborate on multiple Research Components, and there is substantial overlap between participants in the Research Components and the Specialized Resources. While Dr. Volkert is not the lead investigator on any of the ICMIC Research Components, he is listed as a collaborator on one of the Research Components, and on two of the Specialized Resources. Appendix D-17 and D-18 visualize the structure of the ICMIC as a social network diagram; individual investigators represent nodes of the network and lines show their interconnection through participation in Research Components or Specialized Resources. Applications and progress reports show that all but one of the Specialized Resources is used by all of the Research Components (the Human Tissue Bank was expected to be used by only four of the five Research Components), as well as by several of the Developmental Projects.

Multidisciplinarity: Research Components were led by faculty from four departments: including biochemistry (Deutscher, Quinn), Radiology (Lever), Pharmacology (Forte), and Veterinary Medicine (Lewis). Unlike other ICMICs, the faculty or senior scientists participating in two of the five Missouri Research Components were composed only of PhDs, with the others including one or more MD/PhDs or MDs in addition to PhD faculty, trainees, and research technicians.

IV. Imaging Research at Missouri and the Role of the ICMIC in Fostering the Use of Imaging

Investigators' perceptions: The use of imaging in cancer research has expanded substantially at Missouri since the advent of the pre-ICMIC and ICMIC; the mechanisms by which imaging has come to be more often used have been described above. In 2002, Dr. Volkert was the only University of Missouri investigator with NCI awards for cancer imaging (R01CA095075 in addition to the pre-ICMIC), while Dr. Deutscher had a 2002 DoD prostate cancer award (Prostate Cancer Imaging and Therapeutic Agents from in Vivo Tumor -Targeting Phage Display). By 2007, additional investigators had won awards from NCI for cancer imaging, including Dr. Katti (Hybrid Nanoparticles in Imaging and Therapy of Prostate Cancer, an Alliance for Cancer Nanotechnology Platform R01); Dr. Kannan (R21CA128460, Targeted Gold Nanoparticle-Bioconjugates for Imaging Breast Cancer); and Dr. Hawthorne (R21CA114090; Targetable Exploratory Multinuclear MRI Contrast Agents). ICMIC investigators had also received funding from DoD (e.g., Dr. Sauter, Molecular Staging of Breast Cancer Using PET) and from the VA (Dr. V. Glinskii; Dr. M. Giblin).

Role of Developmental Projects: As described above, the primary goal of the Developmental Fund is to catalyze new concepts that can be funded independently. Four of the eight investigators (three of the first cohort of Developmental Projects, one of the second cohort) have received additional NIH funding, of which two projects appeared to be related to their Developmental Awards. Recipients of Developmental Project funding

during the ICMIC's first five years included faculty from across the university (from RSI/Radiology, Biochemistry, Physics, Chemistry, and the MURR).

Role of Specialized Resources: The Radiochemistry, Biotechnology, and Tissue Specialized Resources primarily served the ICMIC (and pre-ICMIC); the Radiopharmacology/Imaging Core served investigators in addition to the ICMIC participants; interviewees reported that the Core is now integrated into the Truman VA Hospital's Biomolecular Imaging Center and facility fixed costs (e.g., technical staff, maintenance contracts) have been institutionalized.

Co-citation of other awards on ICMIC publications: One measure of the collaboration between ICMIC awardees and others is to analyze the citations to non-ICMIC NIH grants on publications that were identified as being "ICMIC-supported." The number of investigators whose grants were co-cited on ICMIC publications remained roughly constant, with five in 2003, six in 2004, six in 2005, four in 2006, and eight in 2007. In all years two of the investigators were listed as participating in the ICMIC. Several investigators were located at institutions outside of Missouri (including Washington University, Michigan, and the University of Virginia), and several of the Missouri investigators were funded by other NIH Institutes (including NHLBI, NIBIB, NIGMS, and NCRR). These non-ICMIC awards cited included grants to support radiopharmaceuticals development (e.g., NIBIB R21EB000833 to Charles Smith); a High-end Instrumentation Award (RR011962) for a 300 MHz spectrometer; and NHLBI-supported coronary biology research. In addition to the ICMIC and pre-ICMIC, only two NCI-funded awards for cancer biology (a Volkert R01 for radiopharmaceuticals development, the Katti nanotechnology R01) were co-cited along with the ICMIC on ICMIC publications.

The awards most likely to be co-cited along with the ICMIC grant were awards associated with the ICMIC PI. Awards often co-cited include a Volkert R01[45] (7 citations), the Missouri pre-ICMIC[46] (6 co-citations), and an NIGMS R01 by Dr. Hannink, who is a Developmental Project leader of the ICMIC[47] (4 citations).

V. Education, Training, and the Role of ICMIC Career Development Funding

Molecular imaging training: At the time of the first funding period, Missouri did not have dedicated training awards intended for molecular imaging training, although Missouri did have a doctoral training program in radiopharmaceutical science. Given the existence of a PhD program, the ICMIC leadership identified two areas of focus for Career Development funding – at the undergraduate and postdoctoral levels. It was felt that undergraduates generally are not exposed to radiopharmaceutical sciences or molecular imaging during training in biology, chemistry, or pre-medical courses; the ICMIC therefore aimed to involve undergraduates in research in order to raise awareness of these scientific areas as students decided upon science or medical careers. The undergraduate

[45] R01CA072942, 1997-2002 (Volkert PI), 2002-2007 (Hoffman PI)
[46] P20CA086290, 2000-2002
[47] R01CA059213, 2000-2004

training experience included part-time research during the semester and full-time research during the summer; interns participated in summer educational enrichment activities and presented their work at the close of the internship. The ICMIC also proposed to fund two postdoctoral fellows per year interested in topics related to the ICMIC. Missouri received a T32 award (Sylvia Jurisson PI) from NIBIB in 2007 for postdoctoral training in radiopharmaceutical chemistry.

Twenty-five individuals were identified as receiving support through the career development fund, including sixteen undergraduates, seven postdocs and two graduate students. None of the awards made through ICMIC's Developmental Fund were given to Career Development recipients.

Outcomes of the Career Development program: One of the post-docs (Dr. Balaji) has joined the Missouri faculty; one other has obtained a faculty position at Lincoln University. Two were identified as returning to their institutions of origin - one in India, and one in France. Three of the undergraduates started medical school (with a fourth in a post-baccalaureate program), and another three are pursuing graduate education at the University of Missouri – one in engineering, one in chemistry, and one in medical pharmacology and physiology.

Trainees' perceptions of the Career Development program: Both trainees interviewed are currently at the University of Missouri. Trainees stated that they originally joined the laboratories of their mentors, and did not know at the time that they were ICMIC affiliated; even after being integrated into their respective laboratories they did not know whether they were receiving Career Development funds or were paid through the individual Research Components. In terms of skills obtained through the ICMIC, one of the trainees (who arrived as a postdoc) had an organic chemistry background, and gained both radiochemistry skills as well as cell biology skills and understanding. The other trainee (who arrived as an undergraduate) initially learned simple research techniques before learning radiochemistry techniques and obtaining her own research project within the mentor's laboratory. This trainee also spoke of "soft skills" experiences, including presenting at a poster session on Capitol Hill and speaking to high school students and alumni about scientific research.

Table A.5: Missouri-Columbia Research Component Descriptions

Phage Display For Prostate, Breast, and Ovarian Tumor Imaging Agents (lead, Susan Deutscher). Short Description: Use phase display techniques to identify peptides binding to tumor-specific surface antigens (or phage bearing those peptides) for radiolabeling for detection of tumors via scintigraphy. Pharmacokinetic studies of promising imaging agents will be performed.
Site-Specific Targeting of a Novel Receptor-Like Protein Expressed on Human Pancreatic and Breast Cancer Cells (lead, Leonard Forte). Short Description: Characterize the newly-identified and distinct E. Coli Heat-Stable Enterotoxin STh(1-19) binding protein (SThBP), which is highly expressed on pancreatic and breast cancer tumors, and test radiolabeled STh(1-19) analogs in vitro and in vivo as SPECT imaging agents.
Opioid Receptors and Ligands: Novel Markers for Cancer Imaging (lead, John Lever). Short Description: Opioid receptors are over-expressed by a variety of human and animal tumors. Develop and validate imaging radioligands and mouse tumor models for in vivo studies of opioid receptors' overexpression by on breast and lung cancer cells in order to provide a foundation for future SPECT imaging studies of opioid receptor involvement in human cancers.
Development of New Peptidepeptide Nucleic Acid Conjugates for In Vivo Imaging of bcl-XL Expression in Lymphoma (lead, Michael Lewis). Short Description: Develop new radiolabeled peptide-peptide nucleic acid (peptide-PNA) constructs as SPECT imaging agents for molecular imaging of proto-oncogene bcl-XL expression in cancer to test the hypothesis that bcl-XL expression is correlated with poor treatment response in lymphoma.
Imaging Malignant Melanoma With Radiolabeled Alpha-MSH Peptide Analogs (lead, Thomas Quinn). Short Description: Develop new radiolabeled constructs of a new class of metal-cyclized peptides (CCMSH) that target the Alpha-MSH receptor present on melanoma cells for PET imaging of melanoma in murine and human melanoma mouse models; employ phage display technology to discover new melanoma targeting vectors.

Table A.6: Missouri-Columbia Specialized Resource Descriptions:

Radiopharmacology/Imaging Core (lead, Timothy Hoffman). Short Description: Provide researchers with the resources and expertise necessary to perform in vivo pharmacokinetic studies on normal and human tumor xenografted rodents, as well as provide scintigraphic imaging equipment and expertise to complement the pharmacokinetic data.
Biochemistry Core (lead, George Smith). Short Description: Provide researchers with resources to exploit biotechnology and combinatorial chemistry (phage peptide display, peptide synthesis) to rapidly evolve and improve peptide based molecules as cancer imaging agents.
Radiochemistry and Bioconjugation Core (lead, Kattesh Katti). Short Description: Design and develop ligands/bifunctional chelating agents (BFCAs), including radiochemistry optimization in labeling with ^{99m}Tc and ^{111}In, and bioconjugation chemistry for linking BFCAs to tumor-avid target-specific peptides.
Human Cancer Tumor Bank (lead, Edward Sauter). Short Description: Create tissue bank of malignant and benign specimens (blood, tissue sections – where possible both malignant and benign sections from the same individuals), correlated with clinical data to support breast cancer, ovarian cancer, and melanoma studies.

Appendix C: Stories of Discovery

In vivo imaging of enzyme activity

Institution: Massachusetts General Hospital
Project Leader: Ralph Weissleder
Research Component 1 (initial funding period)

In Brief
Developing optical technology to detect proteins specific to precancerous and cancerous cells for use in cancer detection, treatment planning, and future basic research.

Origins of the Research
There are many biological processes associated with tumorigenesis and metastasis that cannot be easily monitored with NMR, PET, or CT because key molecules involved in these processes are not distinguishable by currently used imaging techniques. The focus of this research was on tumor associated proteases. Tumor proteases have been implicated in angiogenesis, local aggression and metastases formation and have received attention as therapeutic targets.

The goal of this project was to investigate near infrared probes and optical imaging technologies in order to acquire biological and molecular information *in vivo*. Near infrared (NIR) probes are more ideally suited for *in vivo* imaging than are fluorescent probes, of which hundreds have been developed in the past, because NIR light (700-1000nm) penetrates tissues more efficiently than light in the visible spectrum (1). In preliminary studies, the Weissleder group had developed novel auto-quenched NIR fluorescent (NIRF) probes that only become fluorescent after interaction with their target.

Project Description
It was hypothesized that tumor associated proteases could be used as the source of image contrast to 1) improve tumor detection, 2) facilitate molecular characterization of tumors (e.g. metastatic potential), 3) study protease activity during tumorigenesis, regression, and relapse, and 4) to measure therapeutic efficacy of anti-protease treatments in vivo. The specific aims were as follows:

1. Synthesize and characterize novel NIRF probes against tumor associated proteases. Potential target enzymes include lysosomal proteases, intracellular proteases, and metalloproteinases.

2. Characterize optimized NIRF probes in cell cultures.

3. Test feasibility *in vivo* using animal models of human breast cancer.

Interactions with ICMIC Research Components and Specialized Resources
This project was intended to closely interact with other Research Components in the ICMIC. Research Component 3 ("Novel Vectors") will monitor vector-mediated transgene expression in tumor cells using imaging probes developed in this project. Research Component 2 ("Angiogenesis Imaging") included delivery and transvascular transport of the imaging probes developed in this project. This project and Research Component 4 ("Cell Tracking") planned to use common schemes for peptide synthesis and labeling and loading of cells with imaging probes.

This project also depended on both of the ICMIC's Specialized Resources. The Chemistry Resource provided raw materials and labeling of probes. The Small Animal Imaging Resource performed all imaging experiments and assisted with quantitation and analysis.

Finally, this project was designed to interact with other MGH research projects conducted outside of the ICMIC. One collaboration was with a DoD-funded project led by James Basilion (PC010692, fiscal year 2001), entitled "Non-Invasive Imaging of Gene Expression in Prostate Tumors", in which smart probes would be developed with specificity against forms of Prostate Specific Antigen. A second collaboration was with a 1999 Research Seed Grant from the Radiological Sciences of North America Research & Education Foundation led by C.H. Tung entitled, "Molecular Imaging of Tumor Matrix Metalloproteinases". In that project, probes were developed with specificity for matrix metalloprotease 2. Finally, in collaboration with Chance, Weissleder, and Tung's project "800 nm imaging probes", autoquenched imaging probes operating at 800 nm are being developed.

Results of the Research to Date (2007)
The project has led to the publication of over 30 manuscripts (3-24), licensing of the technology to the private sector, and pending clinical trials for colorectal cancer. In its 5th year of funding, the research was extended to include MR probes. Some highlights of this research include:

1. First demonstration that matrix metalloproteinases (MMPs) can be imaged and the efficacy of inhibitors quantified in vivo (5). This result led to one of the top 10 most highly cited papers in the entire ICMIC program.

2. First demonstration that proteases can be quantified in deep organs (3). NIRF probes were used to image *in vivo* protease activity in orthopic gliomas.

3. Development and validation of optical beta-galactosidase agent (6). A beta-gal conjugate was developed, the cleavage of which allows *in vivo* NIR imaging.

4. Development and validation of the first HIV protease imaging agent (15). A novel probe which is specific for HIV-1 protease which is detectable via NIRF imaging.

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In vivo imaging of antigen-specific T cells in mice and humans

Institution: UCLA
Project Leader: Antoni Ribas
Research Component 1 (renewal funding period)

In Brief
Treating melanoma with melanoma-targeted immune cells and monitoring the process in real time via PET scans.

Origins of the Research
Malignant melanoma is notoriously resistant to cytotoxic therapies but has shown some responsiveness to adoptive transfer of cloned antigen-specific T-cells. Because large scale, ex-vivo expansion of clonal T-cells is prohibitive for routine clinical use, an alternative is to adoptively transfer hematopoietic stem cells engineered to express a melanoma antigen-specific T-cell receptor (TCR) [1, 2]. These stem cells should yield stable engraftment and continuous endogenous generation of antigen-specific T-cells. Availability of a non-invasive in-vivo imaging technique for tracking reconstitution of the peripheral lymphocyte pool and homing of the antigen-specific T-cells to antigen-matched tumor cells [3] would greatly facilitate the preclinical development and clinical testing of such an approach.

Two Developmental Projects funded during the initial UCLA ICMIC award period - "Monitoring Functional and Regulatory States of Lymphocytes During Immunity" (2001-2003) and "Quantitation of the T cell Anti-Tumor Immune Response by Positron Emission Tomography" (2001-2003) - provided preliminary findings on which this project is based. In these developmental projects, Dr. Jonathan Braun and Dr. Owen Witte investigated in vivo imaging of T cell migration to tumor sites in mice utilizing the PET reporter gene HSV1-sr39tk [4]. Independent of the ICMIC, Dr. Ribas has performed pre-clinical and early clinical testing of similar cell-based therapeutic interventions.

Project Description
In their competitive renewal, the UCLA ICMIC proposed to use HSV1-sr39tk reporter gene based in vivo imaging techniques to investigate TCR-based tumor antigen-specific T cell responses against malignant melanoma in both pre-clinical animal models and human subjects. The specific aims are as follows.

1. Create retroviral and lentiviral vectors co-expressing HSV1-sr39tk and a melanoma-specific TCR and test TCR expression and reporter functionality *in vitro*.

2. Genetically modify murine lymphocytes and hematopoietic stem cells with the HSV1-sr39tk/TCR vectors and adoptively transfer into mice. Monitor reconstitution of the peripheral lymphocyte pool and trafficking to antigen-specific tumor cells by immunological assays and PET imaging.

3. Conduct a Phase I clinical trial in which immune cells are collected from patients, genetically modified with an HSV1-sr39tk/TCR vector, and re-infused under a dose escalation regimen. The primary end points are safety and feasibility with reconstitution of the peripheral lymphocyte pool and trafficking to antigen-specific tumor cells as secondary endpoints. Tumor responses will be monitored as a tertiary endpoint.

Interactions with ICMIC Research Components and Specialized Resources
The project was expected to benefit from interactions with each of the other three Research Components. Understanding of the effect of inflammation on imaging would be supplied by Research Component 2 ("Metabolic Phenotyping with PET to Monitor and Predict Responses to Kinase Inhibition in Cancer"). A novel reporter system being developed in Research Component 3 ("Recombinant Carcinoembryonic Antigen as a PET reporter gene") would supply an additional PET reporter to be compared against the HSV1-sr39tk system. The clinical infrastructure generated by Research Component 4 ("Transductionally Redirected and Transcriptionally Restricted Adenovirus Therapy of Metastatic Colorectal Cancer") would also benefit this project.

This project is expected to utilize all three of the UCLA ICMCI Specialized Resources. The Radiochemistry Specialized Resource produces the imaging compounds for microPET imaging. Imaging is performed by the Molecular Imaging Specialized Resource and data analysis by the Quantitative Image Analysis Specialized Resource.

Results of the Research to Date (through July 2007)
1. A lentiviral vector expressing the melanoma-specific TCR, HSV1-sr39tk, and GFP was constructed and scheduled for manufacture by the National Gene Vector Laboratory in October 2007. The retroviral vector could not be constructed as planned because the vector could not accommodate all of the required genes.

2. The UCLA-Caltech-CHLA-USC-UConn Translational Program in Engineered Immunity was formed and had an initial meeting to discuss feasibility of clinical trials. IRB review has been initiated and Recombinant DNA Advisory Committee approval has been obtained for the clinical trial.

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Imaging malignant melanoma with radiolabeled alpha-MSH peptide analogs

Institution: University of Missouri – Columbia
Project Leader: Thomas Quinn
Research Component 5

In Brief
The development of novel molecules for the diagnosis and staging of melanoma.

Origins of the Research
While melanoma is treatable if detected early, existing approaches to early detection are not adequate. Traditionally, melanoma has been diagnosed and staged invasively via biopsy [1] (which requires visual identification of a suspected cancer), or non-invasively – but non-specifically – via FDG-PET [2, 3, 4, 5]. While molecular probes specific for melanoma antigens have been developed [e.g. NR-ML-05], they are not routinely used in the clinic. A promising new class of melanoma probes targets the alpha-MSH receptor present on melanoma cells.

Project Description
Prior to the start of the ICMIC, the laboratory of Dr. Quinn developed two novel melanoma-targeting peptide classes, called CCMSH [6, 7] and DOTA-ReCCMSH [8, 9]. Preliminary binding properties and bioactivity assays had been performed *in vitro* for these compounds, and *in vivo* studies of biodistribution and tumor targeting of ^{99}Tc-CCMSH had been performed in mice.

In their application, the University of Missouri – Columbia ICMIC proposed to continue this research as part of a Research Component within the ICMIC. Their specific aims were as follows:

1. Determine the melanoma imaging specificity and sensitivity of ^{99}Tc-CCMSH, ^{11}In[DOTA]-ReCCMSH, and ^{64}Cu[DOTA]-ReCCMSH. This would be performed by SPECT in mice carrying metastatic melanoma.

2. Determine the *in vitro* tumor binding characteristics and *in vivo* biodistribution properties of ^{64}Cu[DOTA]-ReCCMSH by micro-PET in mice with solid and metastatic melanoma.

3. Monitor chemotherapy of melanoma-bearing mice using ^{99}Tc-CCMSH, ^{11}In[DOTA]-ReCCMSH, or ^{64}Cu[DOTA]-ReCCMSH and micro-SPECT.

4. Identify novel melanoma imaging targets using *in vivo* bacteriophage display selection strategies by injecting human melanoma-bearing SCID mice with phage libraries.

5. Image tumors with melanoma-homing bacteriophage via a pre-target approach by injecting tumor-bearing mice with alpha-MSH sequence bearing phage.

Interactions with ICMIC Research Components and Specialized Resources
The first three specific aims of the project were not expected to benefit from interactions with any of the four other Research Components. The phage display-related research was expected to interact with Research Component 1.

This project was expected to utilize all of the UM-C ICMIC Specialized Resources. The Radiopharmacology/Imaging Core would be used for animal studies. Synthesis of the peptide analogs would by performed by the Biotechnology Core, which would also provide the phage libraries. Clearing agents, to remove imaging agents from circulation, would be obtained from the Radiolabeling and Bioconjugation Core. Finally, the Human Tissue Bank Core would supply human melanoma samples for the phage selection experiments.

This research plan utilized several other collaborations:

- Clinical expertise in melanoma management would be provided by Clay Anderson, M.D.
- PET imaging access and support would be provided by Jason Lewis, Ph.D. of Washington University.
- The radiolabeling and characterization of ^{64}Cu[DOTA]-ReCCMSH would be performed in collaboration with Michael Welch, Ph.D. of Washington University.

Results of the Research to Date (through 2007)
As of the end of the funding cycle, the project's proposed aims had been accomplished and in several cases exceeded. For example, peptide conjugates were evaluated not only as imaging agents, but also as therapeutics.

1. The specificity, sensitivity, stability, binding, and biodistribution of a series of probes specific to the CCMSH receptor was determined including (1) three SPECT probes: ^{99m}Tc-CCMSH [10, 11], ^{111}In[DOTA]-ReCCMSH [10, 12], and ^{203}Pb[DOTA]-ReCCMSH [13]; (2) four PET probes: ^{64}Cu[DOTA]-ReCCMSH [16], ^{64}Cu[CBTE2A]-ReCCMSH [*15]; ^{68}Ga[DOTA]-ReCCMSH [14, 15], and ^{86}Y[DOTA]-ReCCMSH [16]; and (3) two radiotherapeutics: ^{212}Pb[DOTA]-ReCCMSH [13] and ^{177}Lu[DOTA]-ReCCMSH [18, 19].

2. One imaging agent was selected for preclinical development. Of the diagnostic SPECT probes, the ^{111}In[DOTA]-ReCCMSH probe had the best tumor uptake and imaging properties [2007 PR]; it appeared to be promising both for melanoma diagnosis and staging and for assessing the therapeutic efficacy of radiotherapeutics. Toxicity screening had begun. Translation was to be performed in collaboration with AlphaMed, Inc.

3. Four other probes were identified in mouse model studies as being potentially superior to currently used imaging probes and were proceeding toward preclinical development at the end of the project period. Of the diagnostic PET probes, while several had imaging properties superior to FDG-PET, ^{64}Cu[CBTE2A]-ReCCMSH had the best combination of

imaging properties and ease of synthesis and was selected for further development. The combination of ^{203}Pb[DOTA]-ReCCMSH as an imaging agent to assess the therapeutic efficacy of ^{212}Pb[DOTA]-ReCCMSH was also recommended for further assessment. The two combination therapeutic-and-imaging agents ^{118}Re-CCMSH [17] and ^{177}Lu[DOTA]-ReCCMSH [18, 19] were promising, and mouse model studies were continuing.

4. The pre-target phage imaging approach has resulted in the injection of libraries into SCID mice. These experiments are on-going.

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Dual biotherapy for the treatment of malignancy

Institution: Stanford
Project Leader: Chris Contag
Research Component 3

In Brief
Use imaging technology to develop a treatment for cancer in which tumor-killing viruses are delivered by the Trojan horse of the body's own anti-cancer immune cells.

Origins of the Research
This project investigates the potential of vaccinia-infected cytokine induced killer (CIK) cells for the treatment of cancer. In preliminary studies, CIK cell immunotherapy has been shown to reduce the risk of relapse following hepatoma resection [1] while GM-CSF recombinant vaccinia virus has been shown to induce an immune-generated anti-melanoma response at the site of injection [2]. Vaccinia-infected CIK cells have the potential for synergy because (a) viral replication in tumor cells increases expression of the NKG2D ligand which, when recognized by the NKG2D receptor on CIK cells, induces cell killing via the phosphorylation cascade [3-6] and (b) CIK cells could serve as a vehicle for delivering a higher virus payload to the tumor.

Project Description
The Stanford ICMIC proposed to use advanced in vivo imaging techniques involving reporter genes and bioluminescence to refine a CIK-vaccinia combination therapy in preclinical animal models and use the resulting data to design and conduct preliminary clinical trials. The specific aims were as follows.

1. Characterize vaccinia-CIK interactions in cell culture by (a) optimizing the timing and level of infection for effective virus release at the tumor site, (b) examining the effect of infection on expression levels of NKG2D ligand in tumor cells and (c) examining the phosphorylation cascade induced by CIK cell binding to normal, transformed and virally-infected tumor cells.

2. Examine CIK cell trafficking and viral infection in mice by (a) monitoring trafficking of normal and virally-infected CIK cells to CIK responsive and non-responsive tumors using different ratios of infected and uninfected cells, (b) developing a computer model of virus spread within a tumor when delivered alone versus via CIK cells, (c) determining whether any CIK subpopulations have greater efficacy in the combination therapy, (d) examining different tumor models for differential effects and (e) evaluating the ability of microPET imaging to monitor the effects of therapy.

3. Examine the potential clinical efficacy of the vaccinia-CIK therapy in lymphoma patients by conducting a Phase I safety trial followed by a small efficacy trial using FDG PET to measure tumor regression.

Interactions with ICMIC Research Components and Specialized Resources
This project was designed to interact directly with each of the other three ICMIC Research Components. Research Component 1 (Development and validation of sensors for imaging protein phosphorylation in living subjects) would contribute tools for the imaging of tumor regression subsequent to vaccinia-CIK therapy. Collaboration with Research Component 2 (Multi-modality imaging of oncogene-induced tumorigenesis) would analyze whether vaccinia-CIK therapy could eradicate minimal residual disease remaining after oncogene inactivation. Research Component 4 (PET imaging of brain tumor angiogenesis and anti-angiogenic treatment) would contribute imaging probes for the analysis of angiogenesis in the vaccinia-CIK treated tumors.

The project was also designed to take advantage of all four of the specialized resources of the ICMIC. The Chemistry/Radiochemistry Resource would generate FDG (and FHBG if necessary) for use in PET imaging. The Flow Cytometry Resource would be used to characterize CIK cell populations. Bioluminescence imaging, microPET, and microCT preclinical studies would be performed by the Small Animal Imaging Resource. Finally, the Image Quantitation/Visualization Core would be used to integrate and analyze the imaging data.

Results of the Research to Date (through 2007)
1. CIK-vaccinia interactions in cell culture. The ratio of infected to uninfected cells which is optimal for virus release and cell viability has been determined. Vaccinia infection of tumor cells was shown to increase expression of NKG2D ligand which may account for the synergy between viral infection and CIK killing of cells. Phosphorylation levels of ERK1 and p56 in CIK cells were demonstrated to shift in response to NKG2D activation.

2. CIK cell trafficking in mice. The trafficking and timing of infected CIK cells were examined. The examination of different ratios of infected to uninfected cells has been begun but not completed. The surface receptors of the CIK cells at various times post-treatment have been examined using four tumor types. The distribution of virus within the tumor, required for the computer simulation, has been sent to a collaborator for analysis. The beneficial effect of dual biotherapy on relapse in mice has been examined and the delivery of virus by CIK cells in mice has been published [7, 8]

3. Protocols for the first clinical study have been approved by Stanford's institutional review committees and an IND is in preparation.

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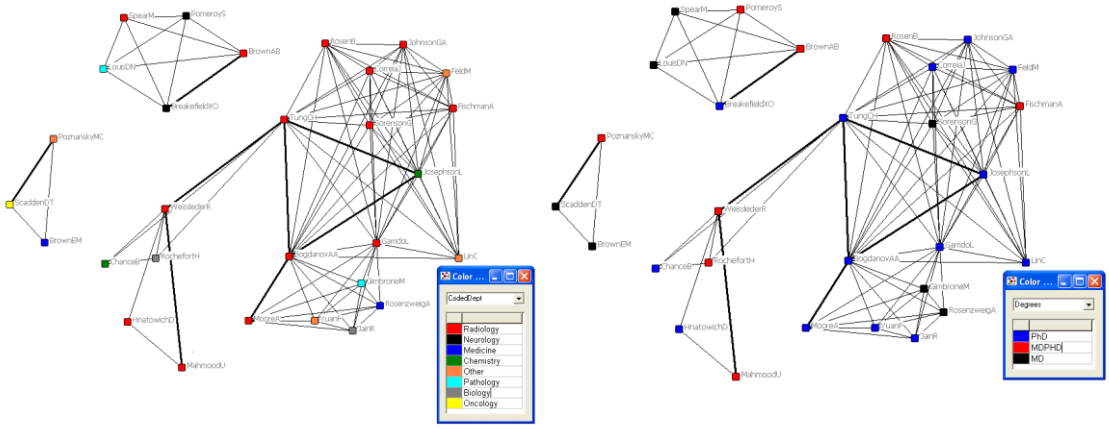
Appendix D: Social Network Diagrams Showing Multidisciplinarity

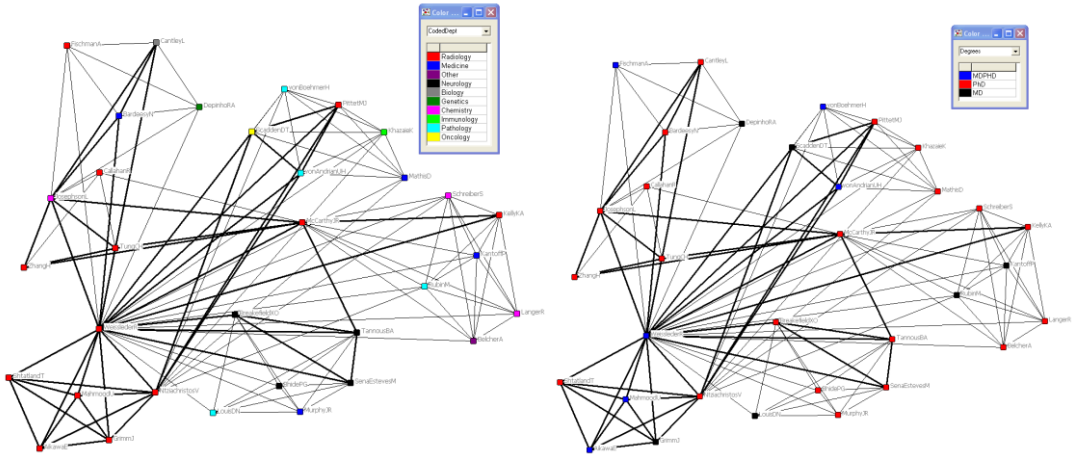
MGH

Figure Appendix D-1: MGH Initial Round, SNA Diagram of Research Component/Specialized Resource Participation, by Department and Degree of Faculty



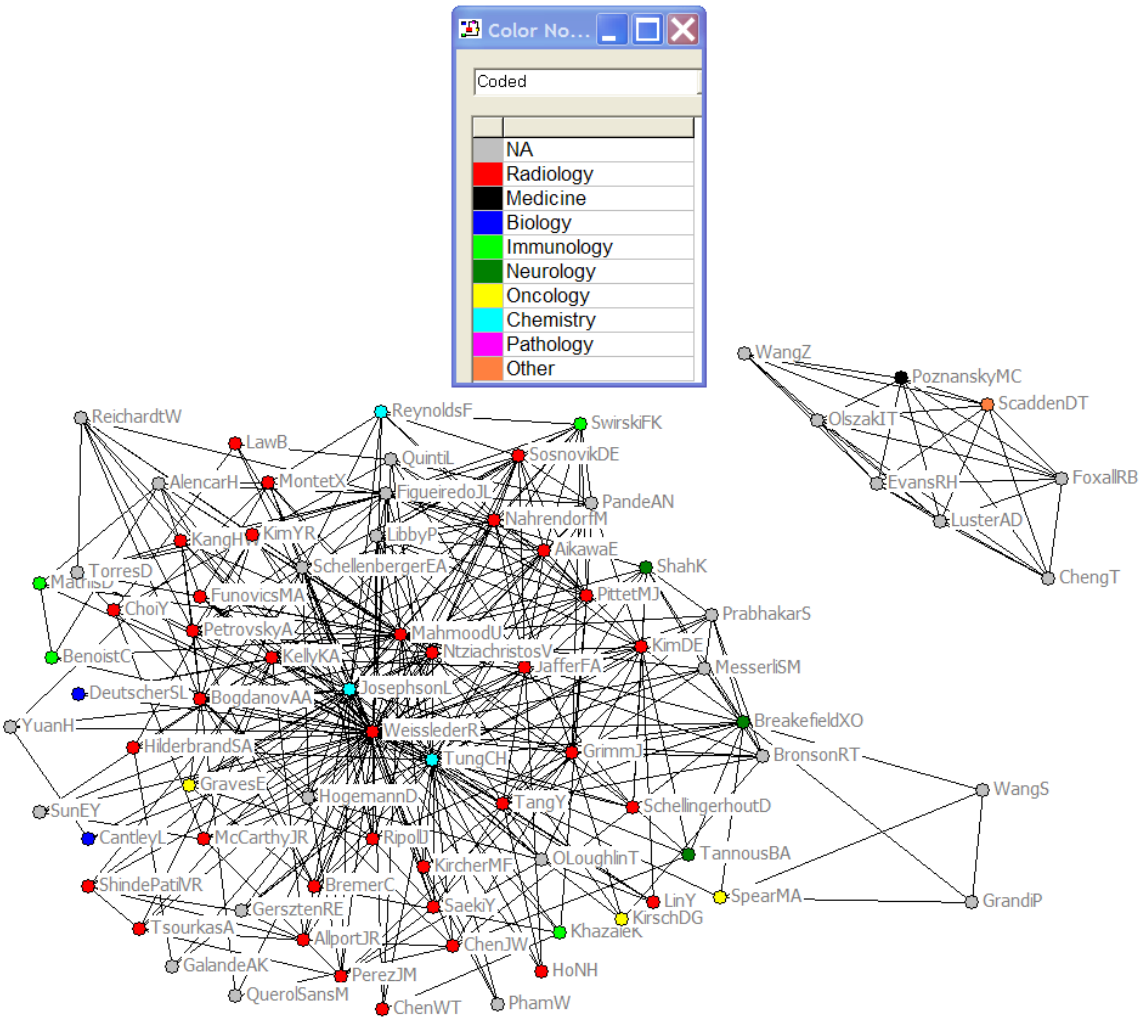
Source: Applications, supplemented by Internet searches. Thick lines denote supported personnel; thin lines denote unpaid collaborators.

Figure Appendix D-2: MGH Renewal Round, SNA Diagram of Research Component/Specialized Resource Participation, by Department and Degree of Faculty



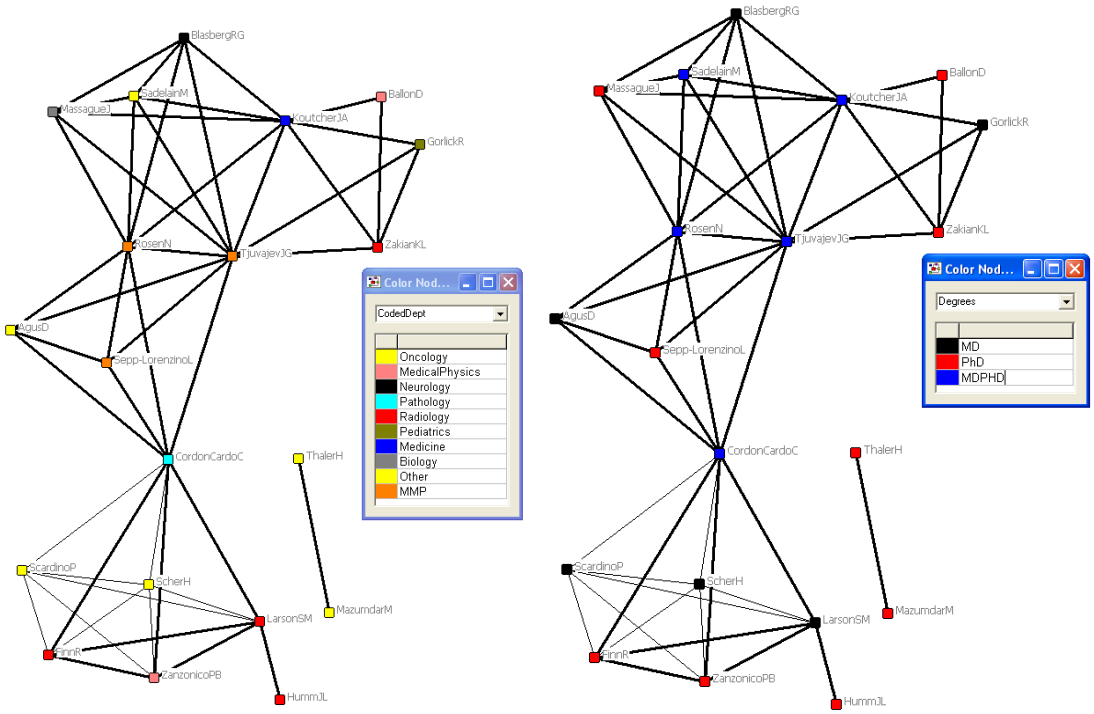
Source: Applications, supplemented by Internet searches. Thick lines denote supported personnel; thin lines denote unpaid collaborators.

Figure Appendix D-3: MGH Both Rounds, SNA Diagram of Co-Authorship, by Department of Participant, for All Individuals with Three or More co-Authorships on P50 ICMIC-Affiliated Publications



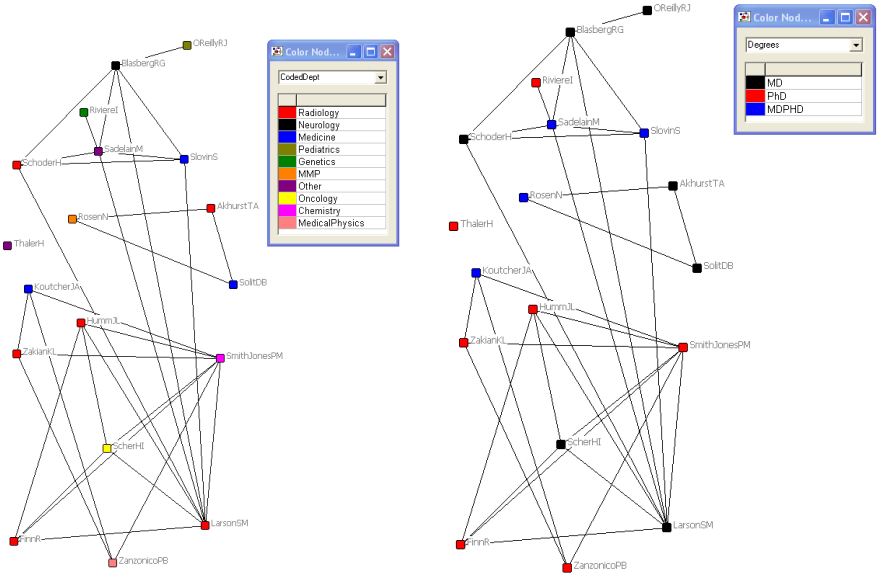
MSKCC

Figure Appendix D-4: MKSCC Initial Round, SNA Diagram of Research Component/Specialized Resource Participation, by Department and Degree of Faculty



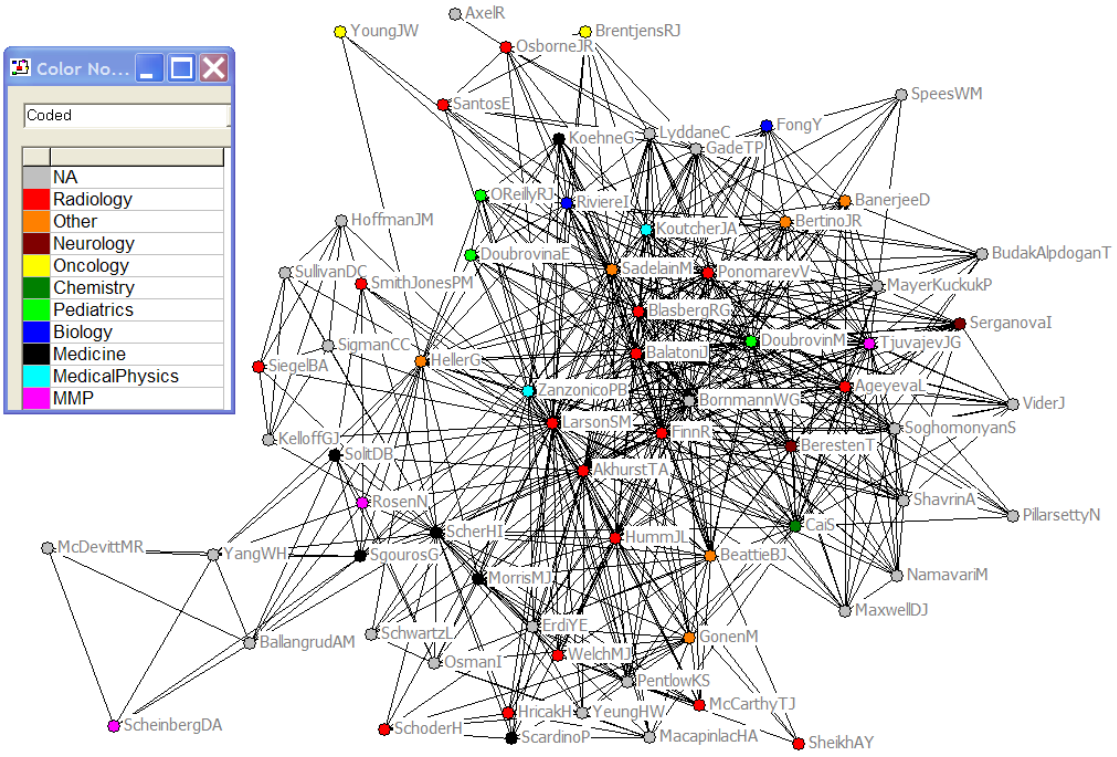
Source: Applications, supplemented by Internet searches. Thick lines denote supported personnel; thin lines denote unpaid collaborators.

Figure Appendix D-5: MKSCC Renewal Round, SNA Diagram of Research Component/Specialized Resource Participation, by Department and Degree of Faculty



Source: Applications, supplemented by Internet searches. Thin lines denote supported personnel; application does not include unpaid collaborators.

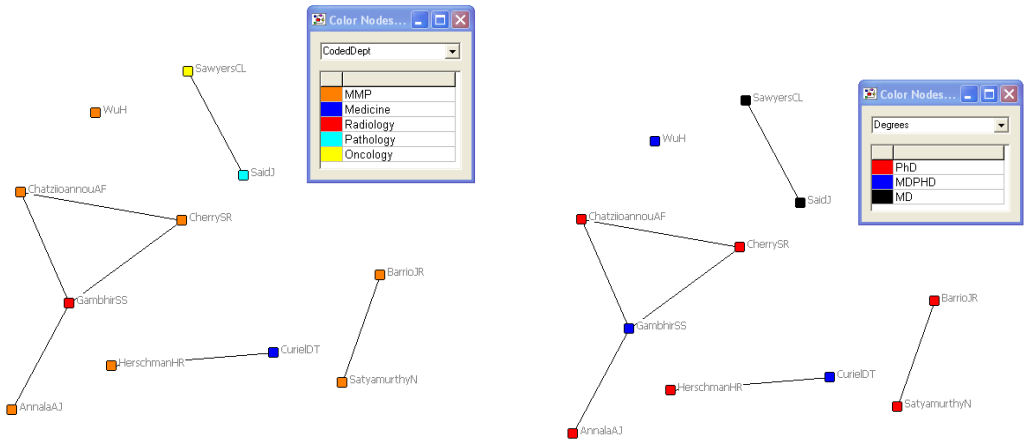
Figure Appendix D-6: MSKCC Both Rounds, SNA Diagram of Co-Authorship, by Department of Participant, for All Individuals with Three or More co-Authorships on P50 ICMIC-Affiliated Publications



Source: Database of ICMIC Publications. Affiliation information source: applications, supplemented by Internet searches.

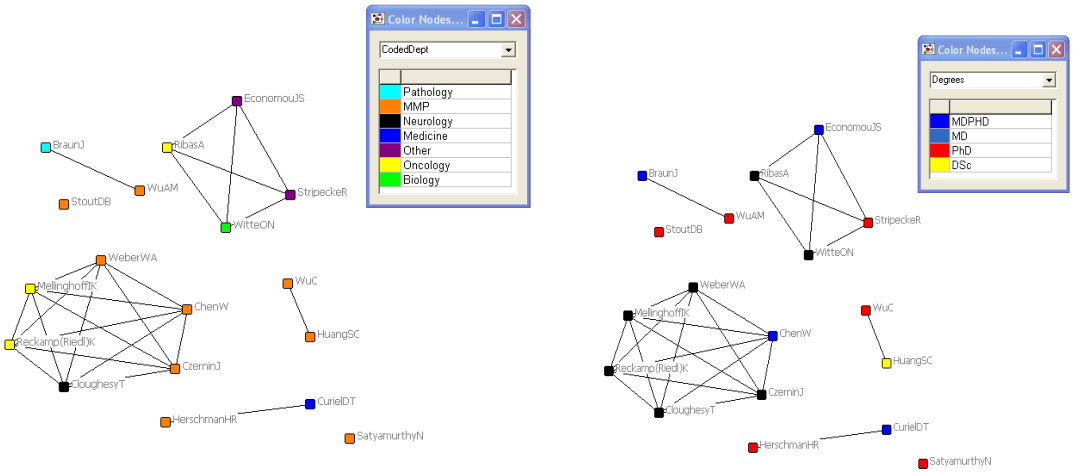
UCLA

Figure Appendix D-7: UCLA Initial Round, SNA Diagram of Research Component/Specialized Resource Participation, by Department and Degree of Faculty



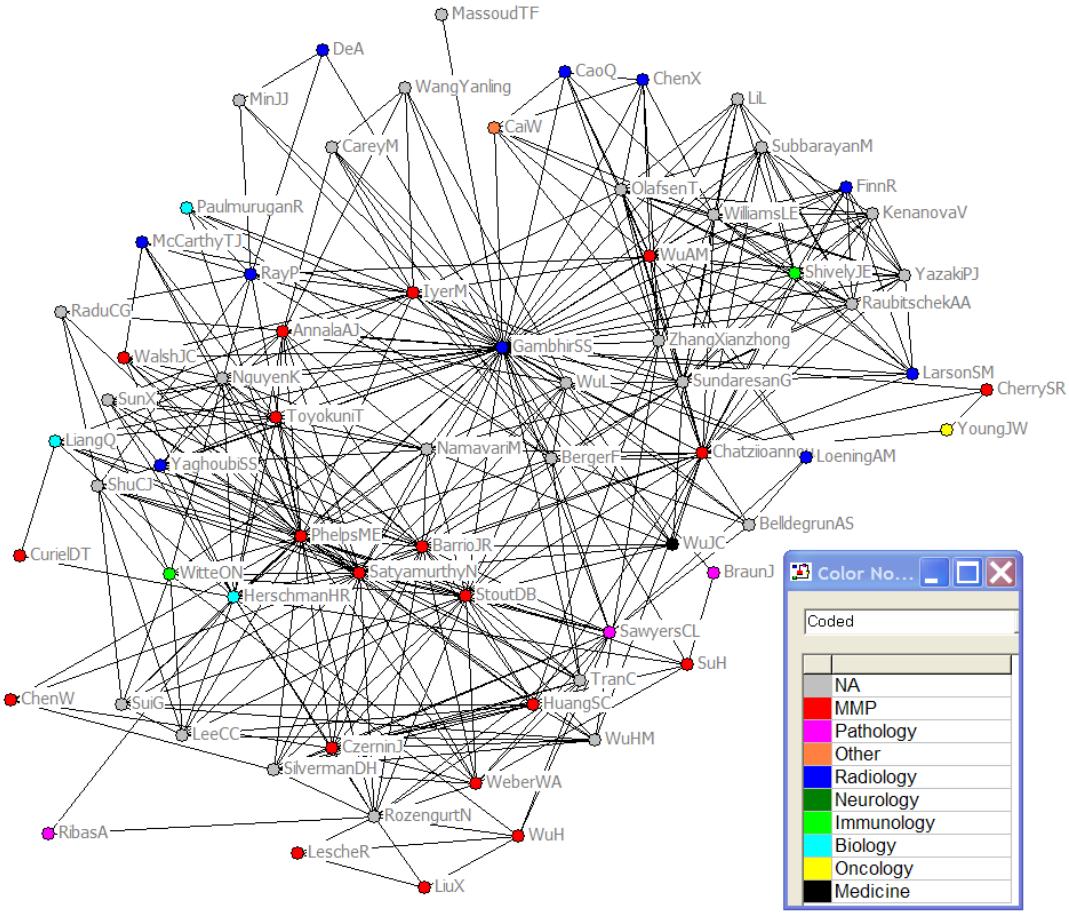
Source: Applications, supplemented by Internet searches. Thin lines denote supported personnel; application does not include unpaid collaborators.

Figure Appendix D-8: UCLA Renewal Round, SNA Diagram of Research Component/Specialized Resource Participation, by Department and Degree of Faculty



Source: Applications, supplemented by Internet searches. Thin lines denote supported personnel; application does not include unpaid collaborators.

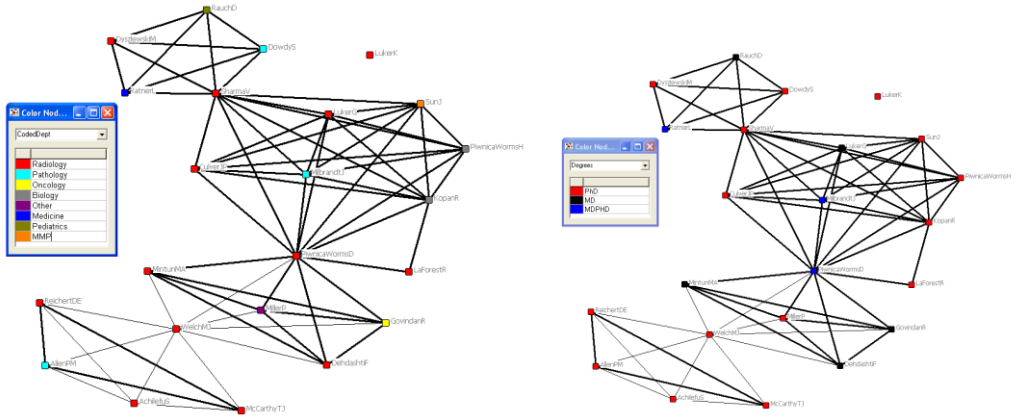
Figure Appendix D-9: UCLA Both Rounds, SNA Diagram of Co-Authorship, by Department of Participant, for All Individuals with Three or More co-Authorships on P50 ICMIC-Affiliated Publications



Source: Database of ICMIC Publications. Affiliation information source: applications, supplemented by Internet searches.

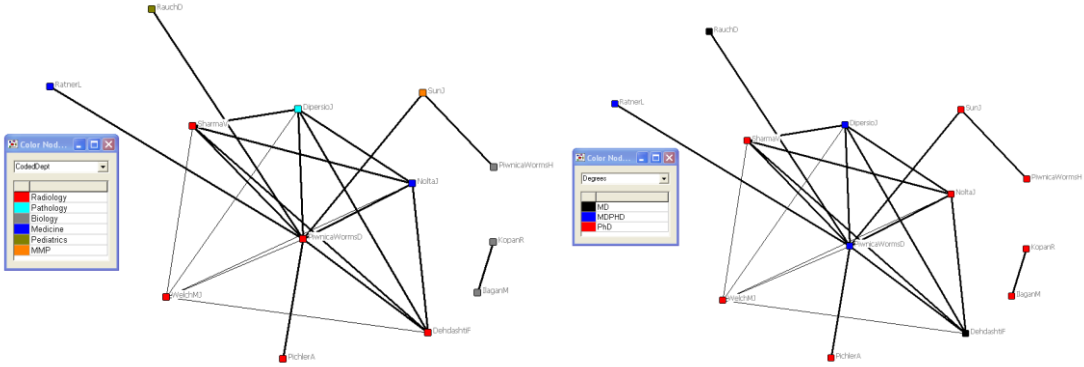
Washington University

Figure Appendix D-10: Washington University Initial Round, SNA Diagram of Research Component/Specialized Resource Participation, by Department and Degree of Faculty



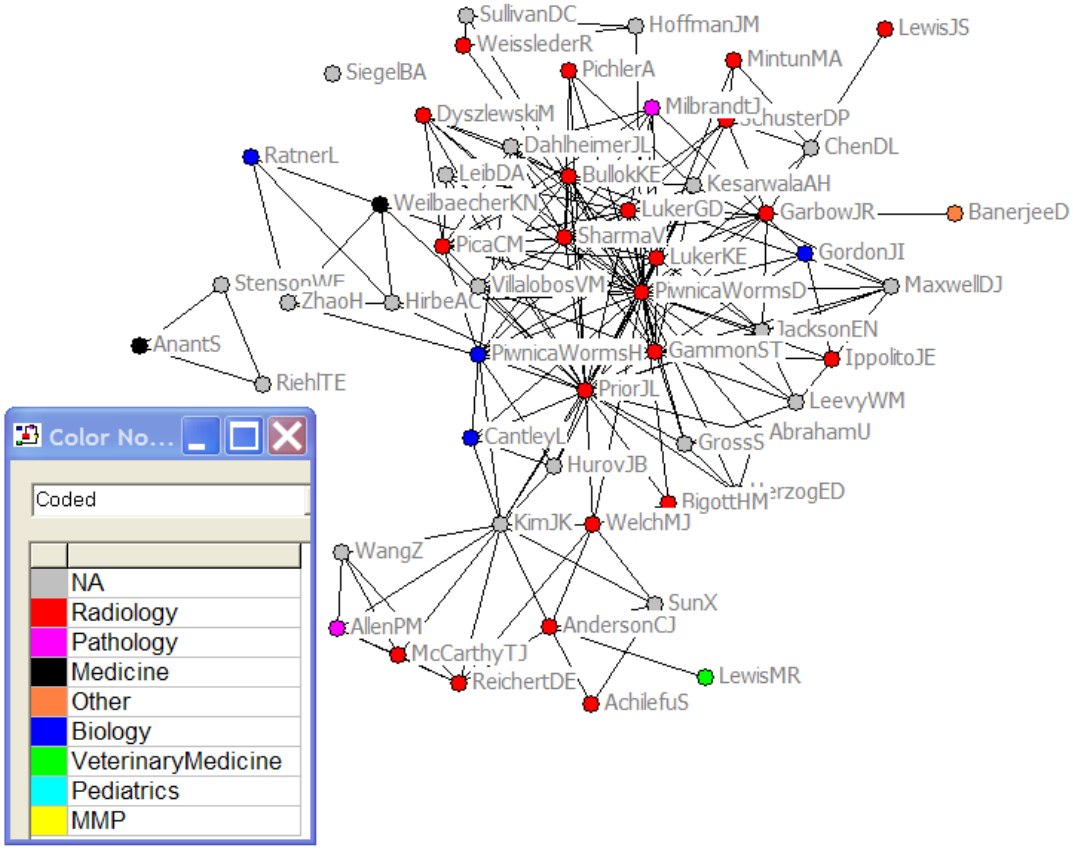
Source: Applications, supplemented by Internet searches. Thick lines denote supported personnel; thin lines denote unpaid collaborators.

Figure Appendix D-11: Washington University Renewal Round, SNA Diagram of Research Component/Specialized Resource Participation, by Department and Degree of Faculty



Source: Applications, supplemented by Internet searches. Thick lines denote supported personnel; thin lines denote unpaid collaborators.

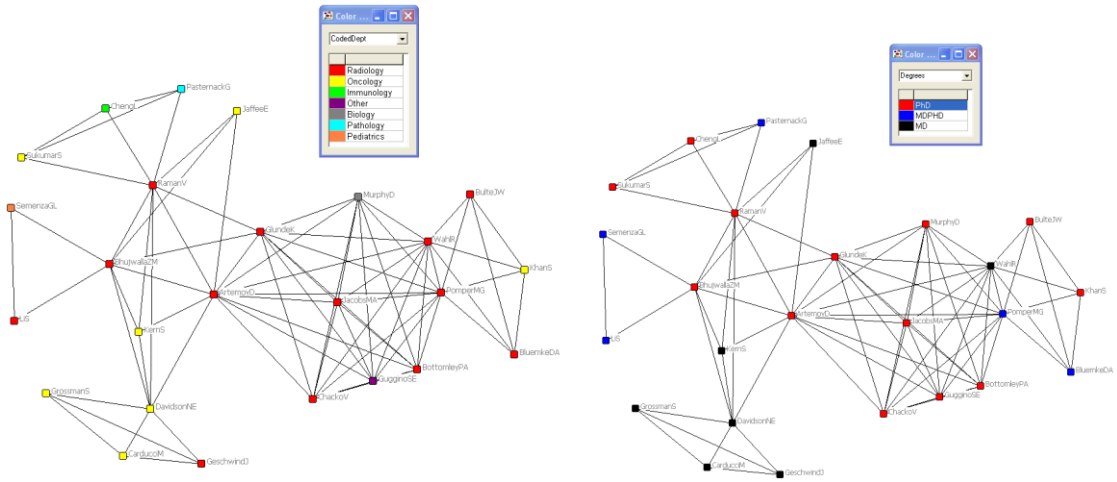
Figure Appendix D-12: Washington University Both Rounds, SNA Diagram of Co-Authorship, by Department of Participant, for All Individuals with Three or More co-Authorships on P50 ICMIC-Affiliated Publications



Source: Database of ICMIC Publications. Affiliation information source: applications, supplemented by Internet searches.

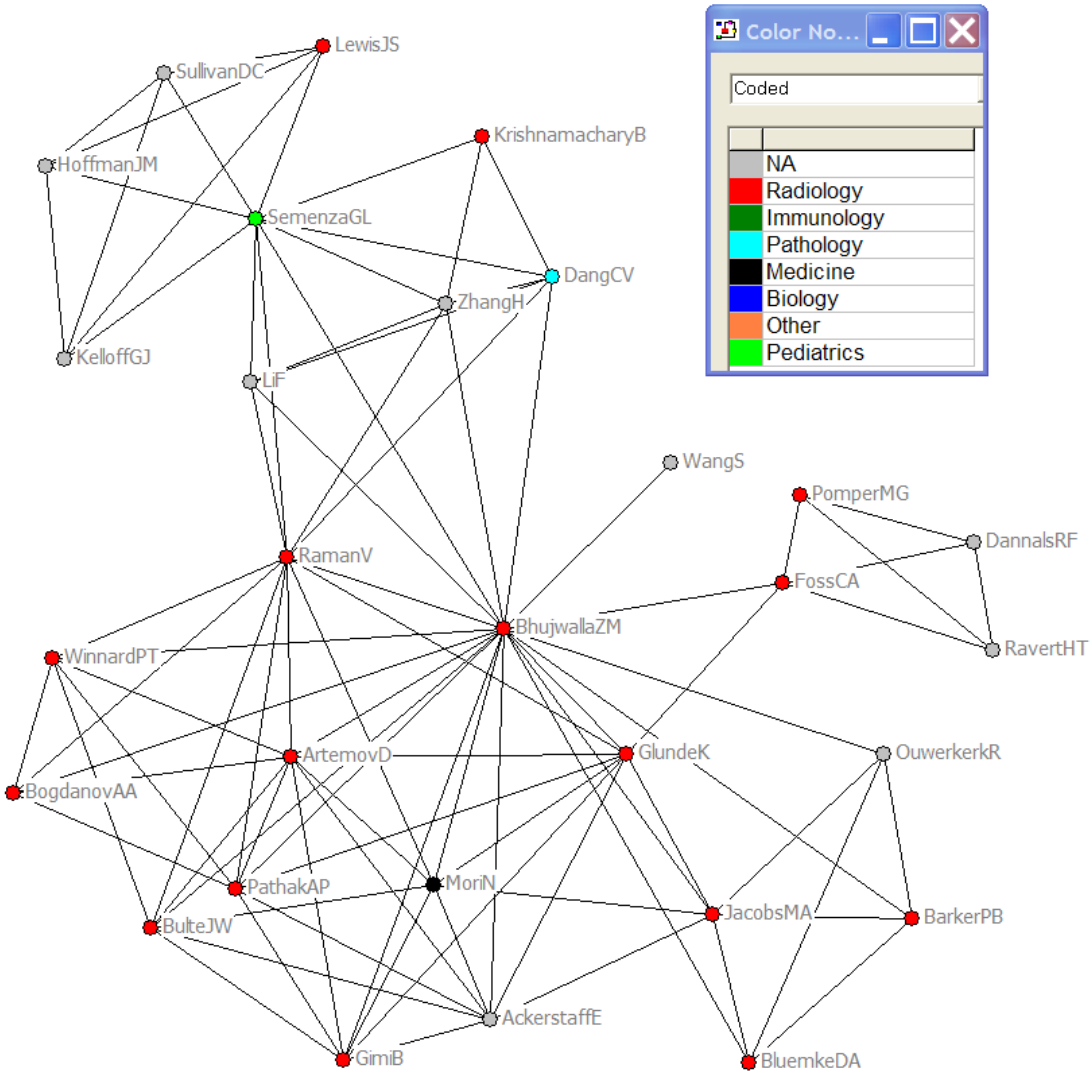
Johns Hopkins

Figure Appendix D-13: Johns Hopkins University, SNA Diagram of Research Component/Specialized Resource Participation, by Department and Degree of Faculty



Source: Applications, supplemented by Internet searches. Thin lines denote supported personnel; application does not include unpaid collaborators.

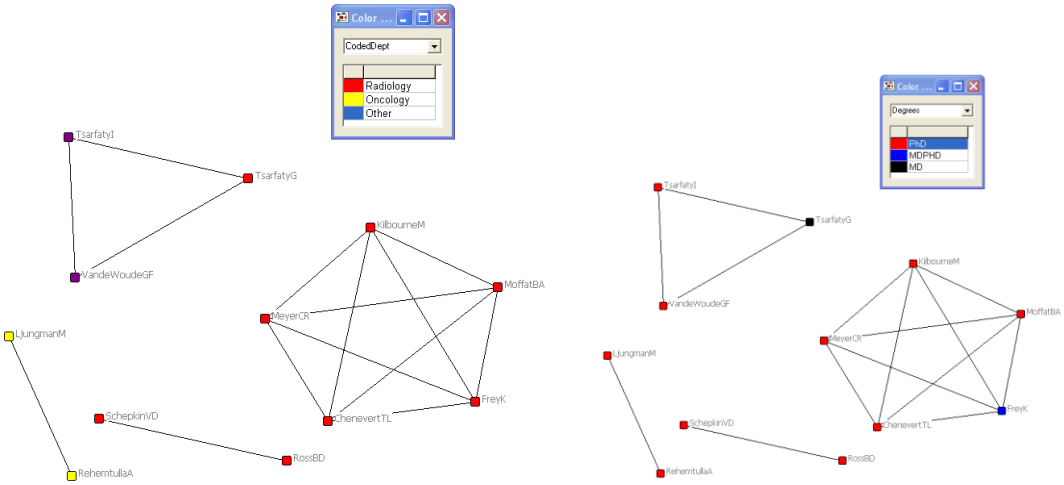
Figure Appendix D-14: Johns Hopkins, SNA Diagram of Co-Authorship, by Department of Participant, for All Individuals with Three or More co-Authorships on P50 ICMIC-Affiliated Publications



Source: Database of ICMIC Publications. Affiliation information source: applications, supplemented by Internet searches.

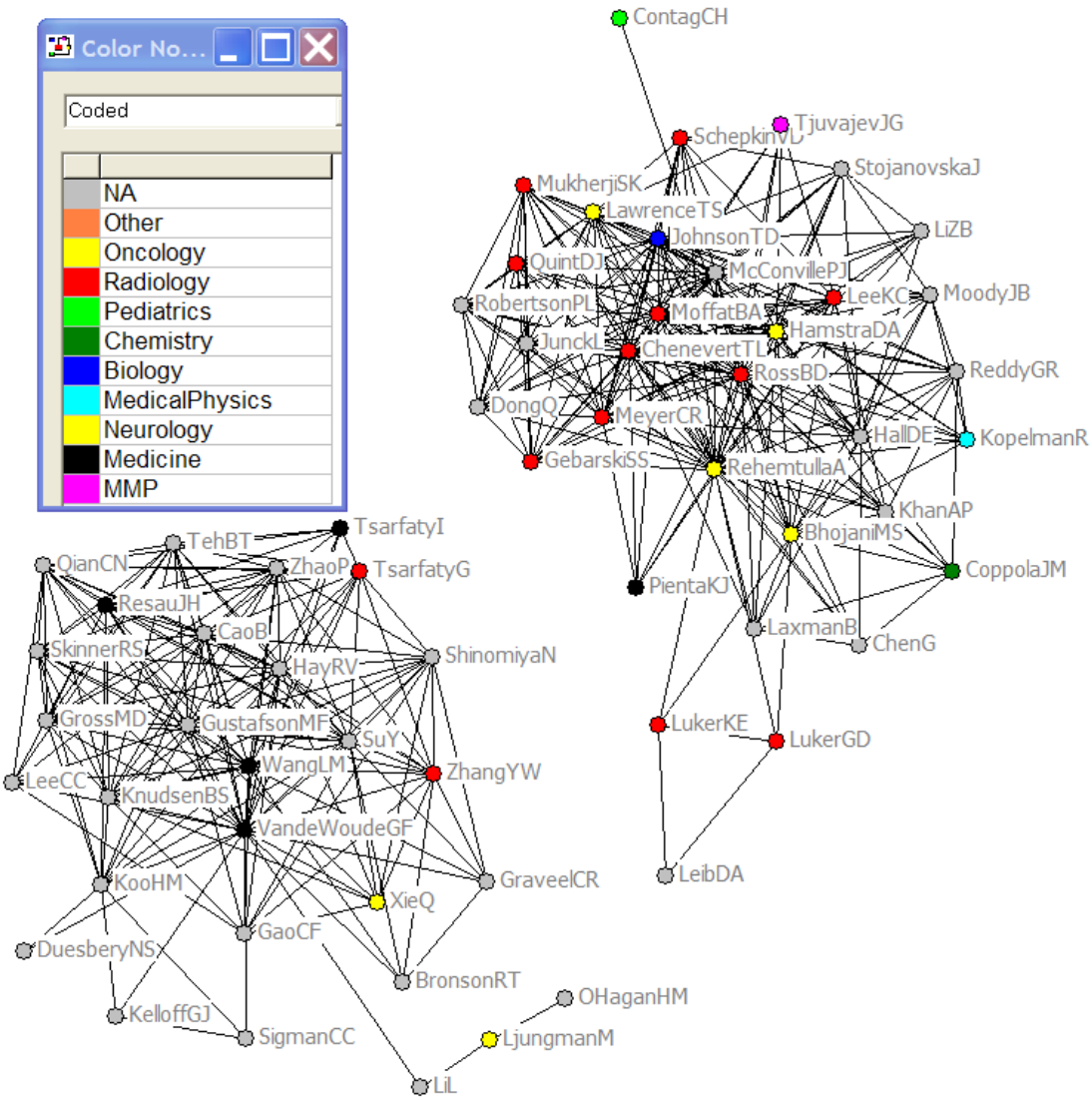
University of Michigan

Figure Appendix D-15: University of Michigan, SNA Diagram of Research Component/Specialized Resource Participation, by Department and Degree of Faculty



Source: Applications, supplemented by Internet searches. Thin lines denote supported personnel; application does not include unpaid collaborators.

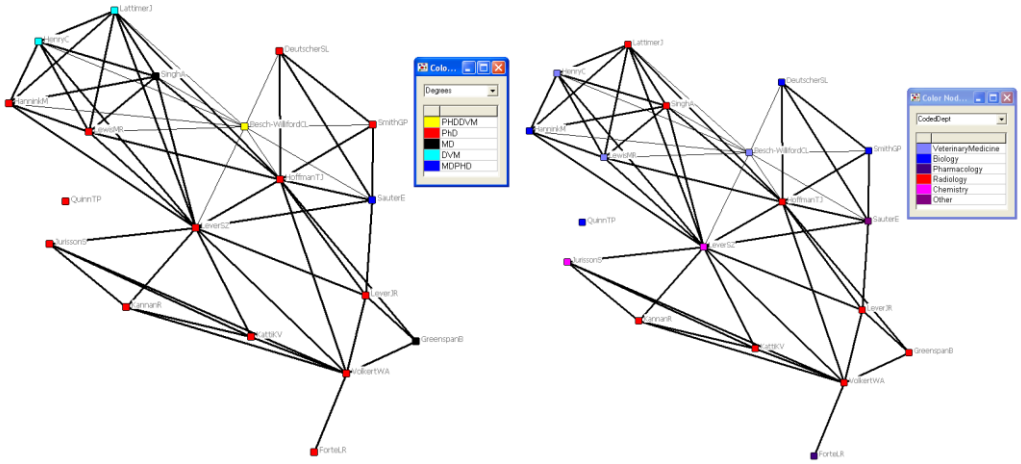
Figure Appendix D-16: University of Michigan, SNA Diagram of Co-Authorship, by Department of Participant, for All Individuals with Three or More co-Authorships on P50 ICMIC-Affiliated Publications



Source: Database of ICMIC Publications. Affiliation information source: applications, supplemented by Internet searches.

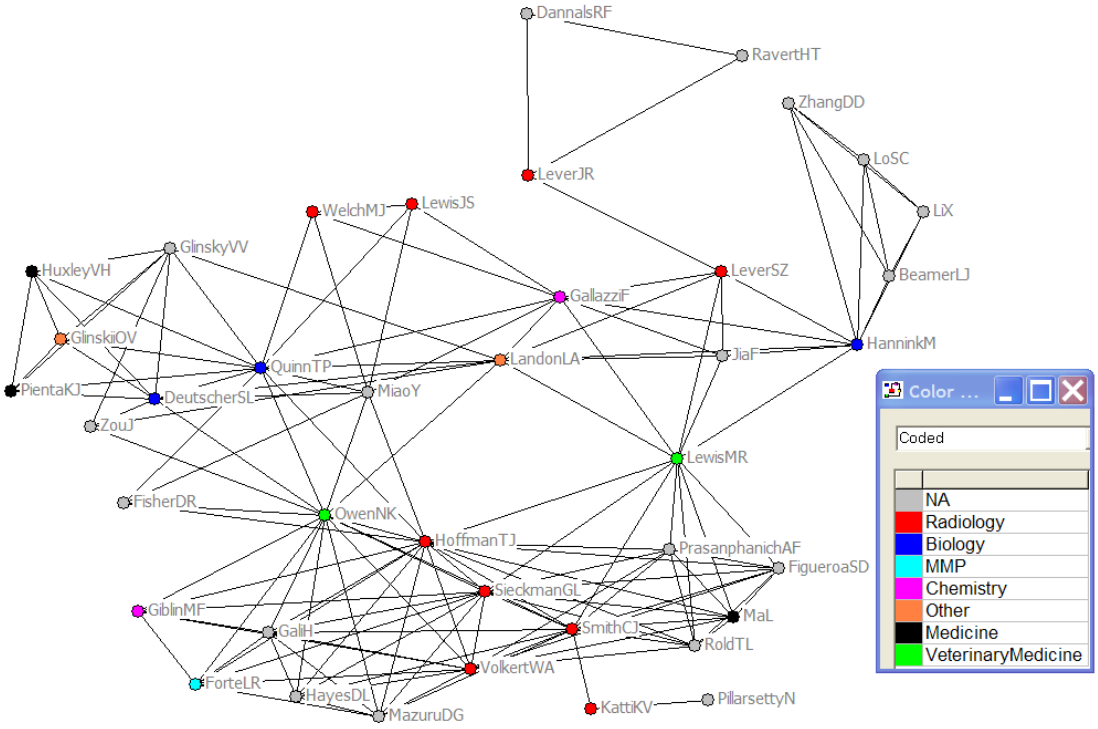
University of Missouri-Columbia

Figure Appendix D-17: University of Missouri-Columbia, SNA Diagram of Research Component/Specialized Resource Participation, by Department and Degree of Faculty



Source: Applications, supplemented by Internet searches. Thick lines denote supported personnel; thin lines denote unpaid collaborators.

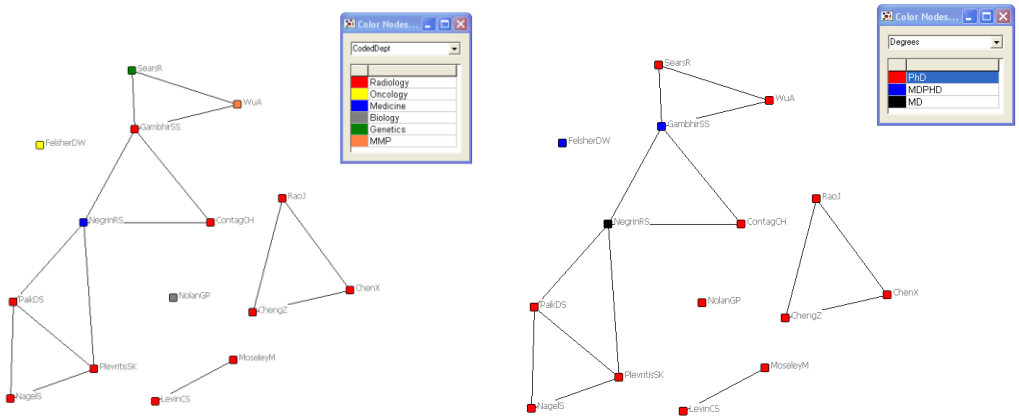
Figure Appendix D-18: University of Missouri-Columbia, SNA Diagram of Co-Authorship, by Department of Participant, for All Individuals with Three or More co-Authorships on P50 ICMIC-Affiliated Publications



Source: Database of ICMIC Publications. Affiliation information source: applications, supplemented by Internet searches.

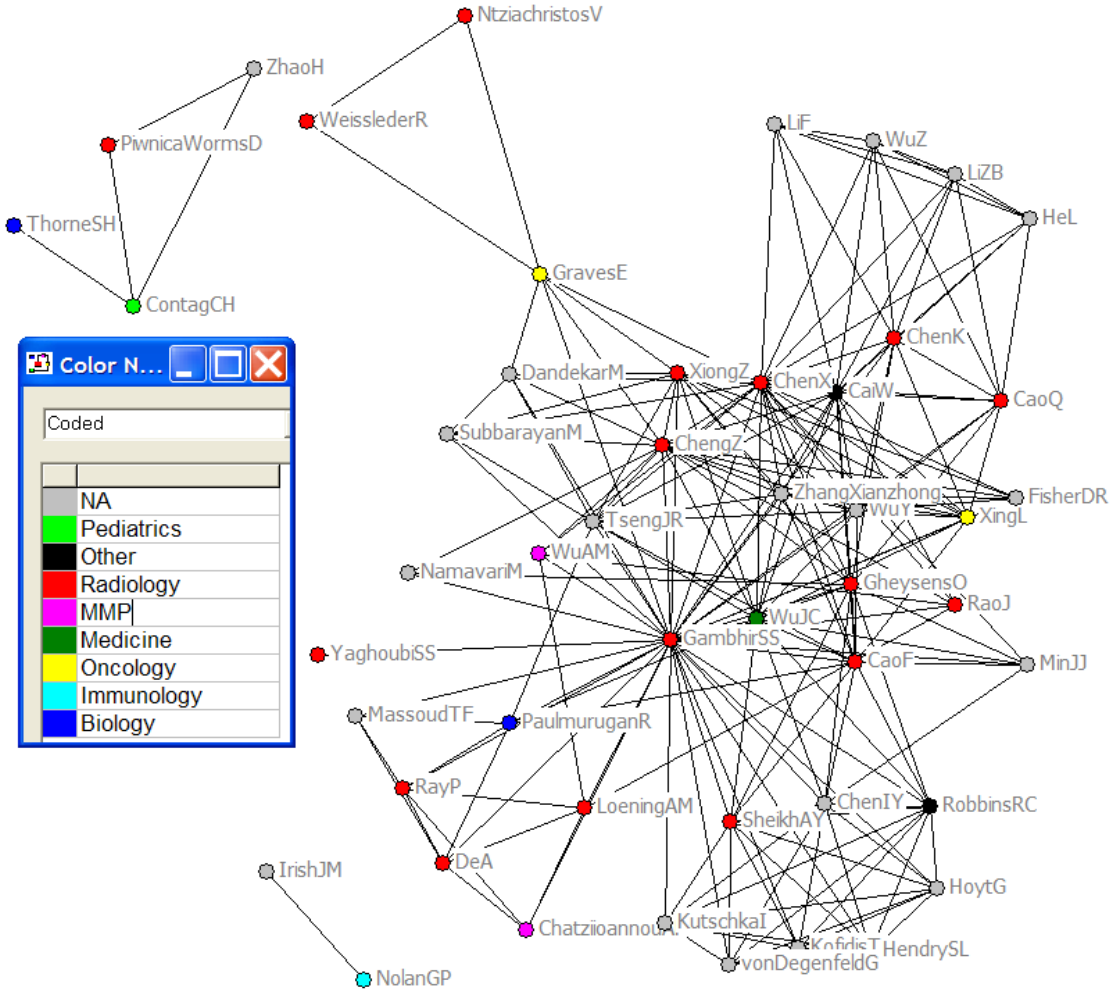
Stanford University

Figure Appendix D-19: Stanford University, SNA Diagram of Research Component/Specialized Resource Participation, by Department and Degree of Faculty



Source: Applications, supplemented by Internet searches. Thin lines denote supported personnel; application does not include unpaid collaborators.

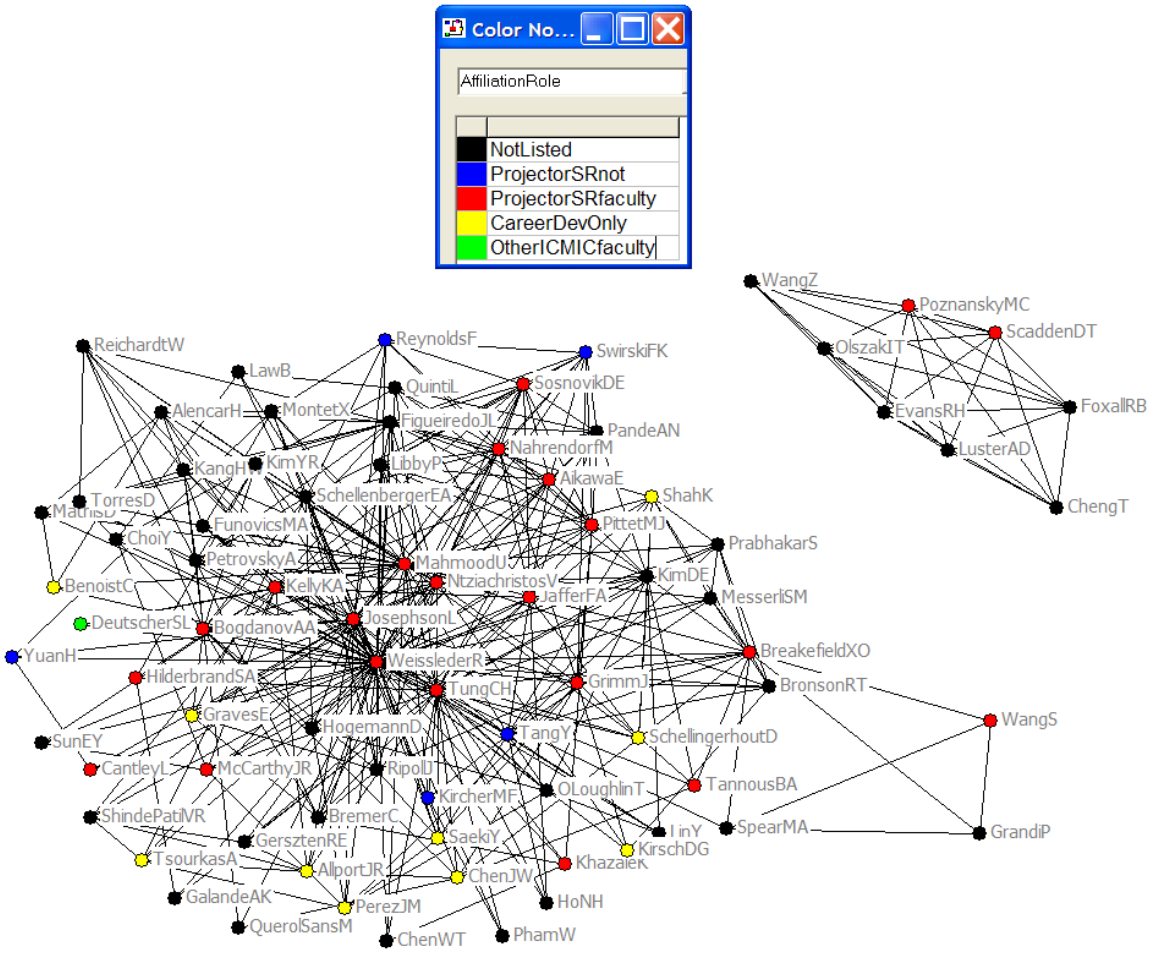
Figure Appendix D-20: Stanford, SNA Diagram of Co-Authorship, by Department of Participant, for All Individuals with Three or More co-Authorships on P50 ICMIC-Affiliated Publications



Source: Database of ICMIC Publications. Affiliation information source: applications, supplemented by Internet searches.

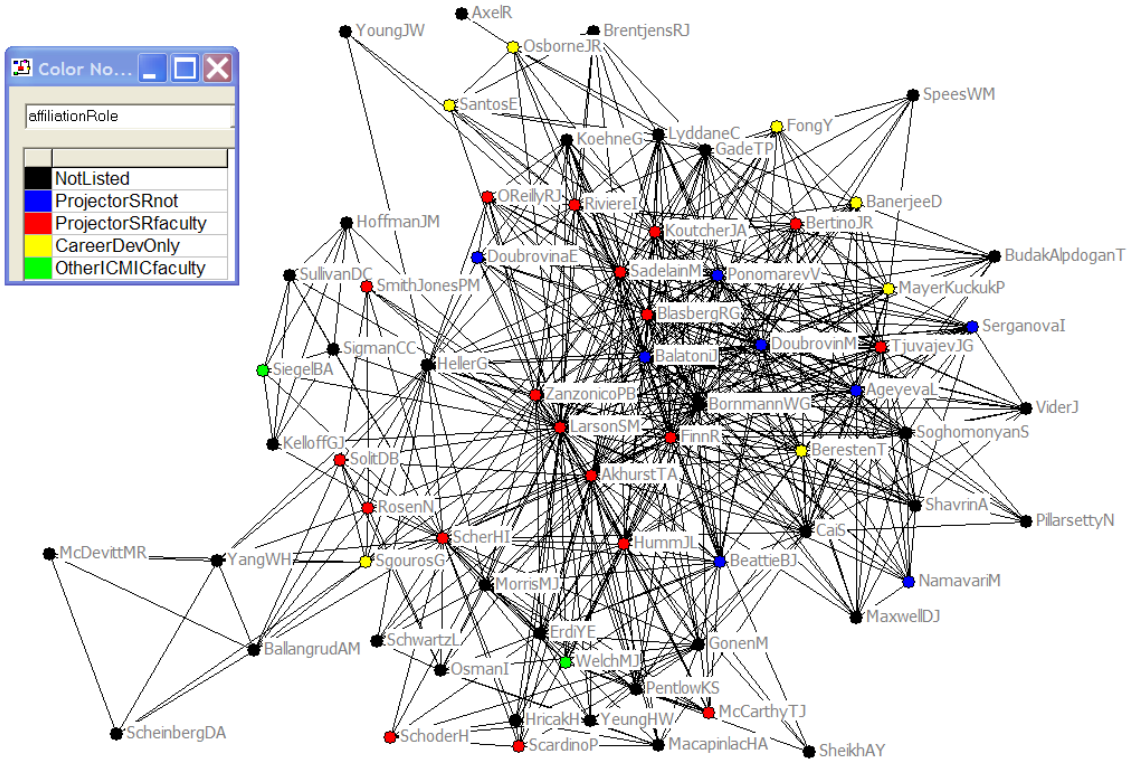
Appendix E: Social Network Diagrams Showing Participation in ICMIC Publications

Figure Appendix E-1: MGH Both Rounds, SNA Diagram of Co-Authorship, by Department of Participant, for All Individuals with Three or More co-Authorships on P50 ICMIC-Affiliated Publications



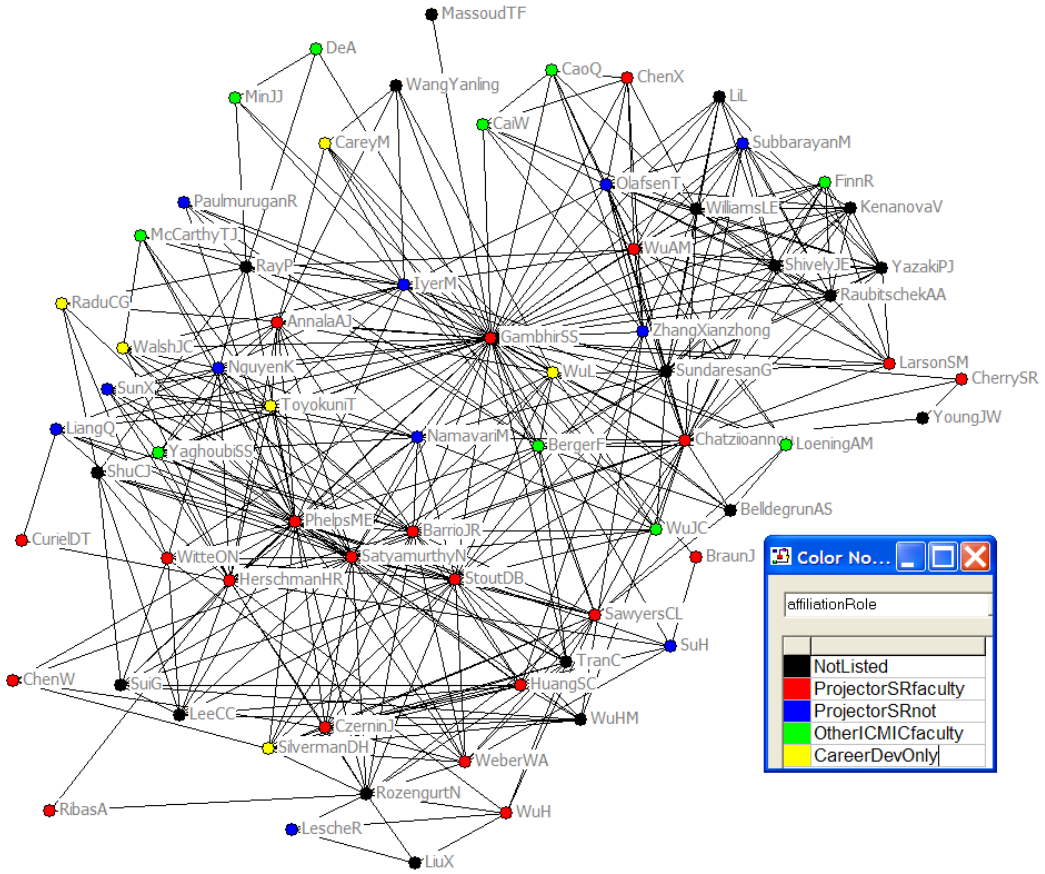
Source: Database of ICMIC Publications. Affiliation information source: applications, supplemented by Internet searches.

Figure Appendix E-2: MSKCC Both Rounds, SNA Diagram of Co-Authorship, by Department of Participant, for All Individuals with Three or More co-Authorships on P50 ICMIC-Affiliated Publications



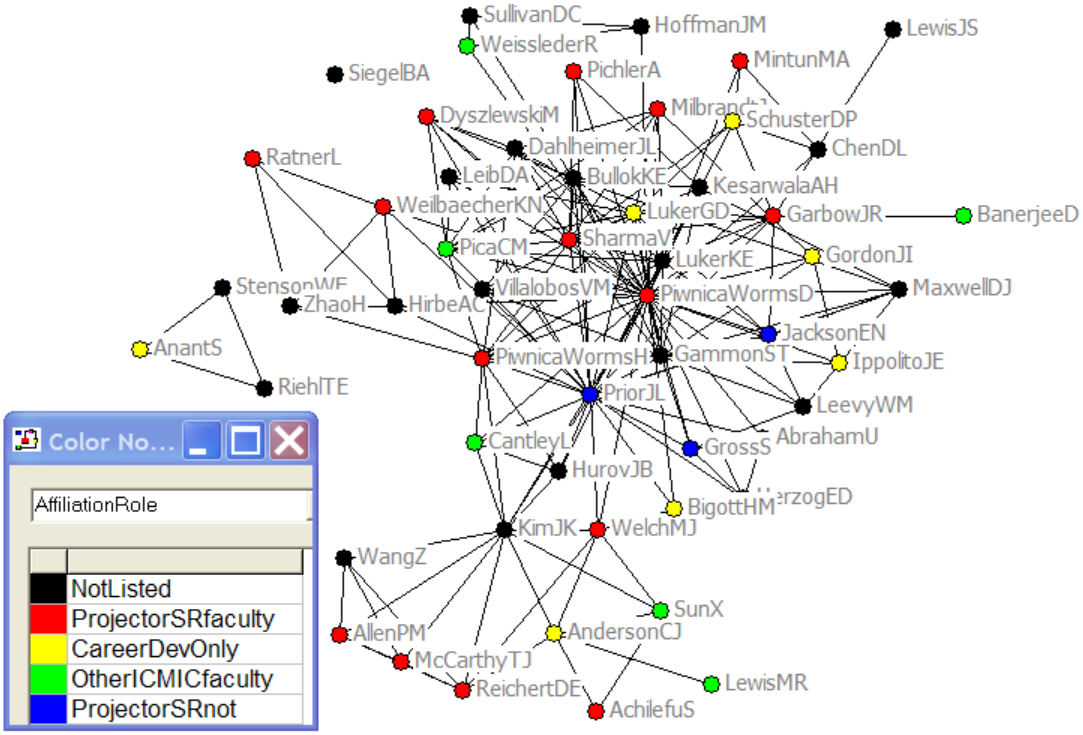
Source: Database of ICMIC Publications. Affiliation information source: applications, supplemented by Internet searches.

Figure Appendix E-3: UCLA Both Rounds, SNA Diagram of Co-Authorship, by Department of Participant, for All Individuals with Three or More co-Authorships on P50 ICMIC-Affiliated Publications



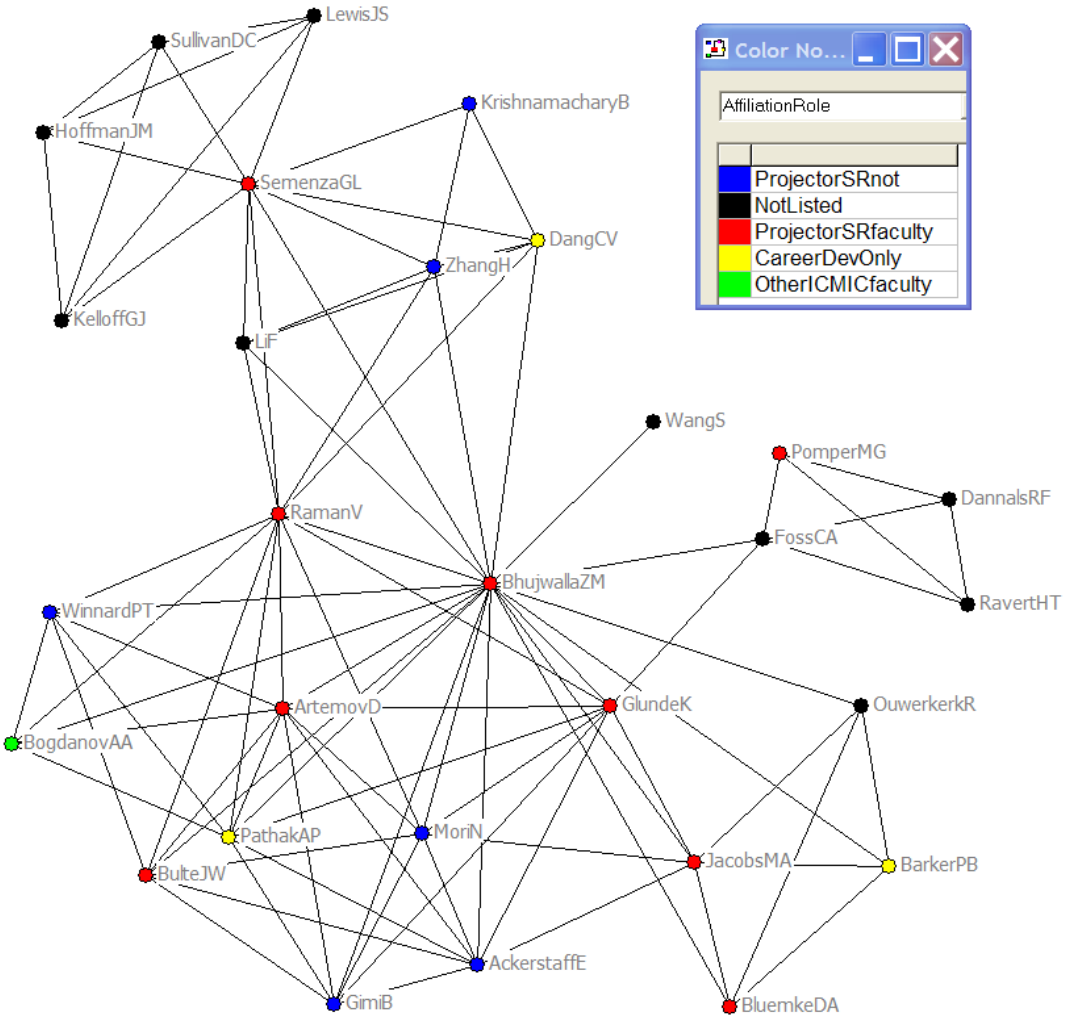
Source: Database of ICMIC Publications. Affiliation information source: applications, supplemented by Internet searches.

Figure Appendix E-4: Washington University Both Rounds, SNA Diagram of Co-Authorship, by Department of Participant, for All Individuals with Three or More co-Authorships on P50 ICMIC-Affiliated Publications



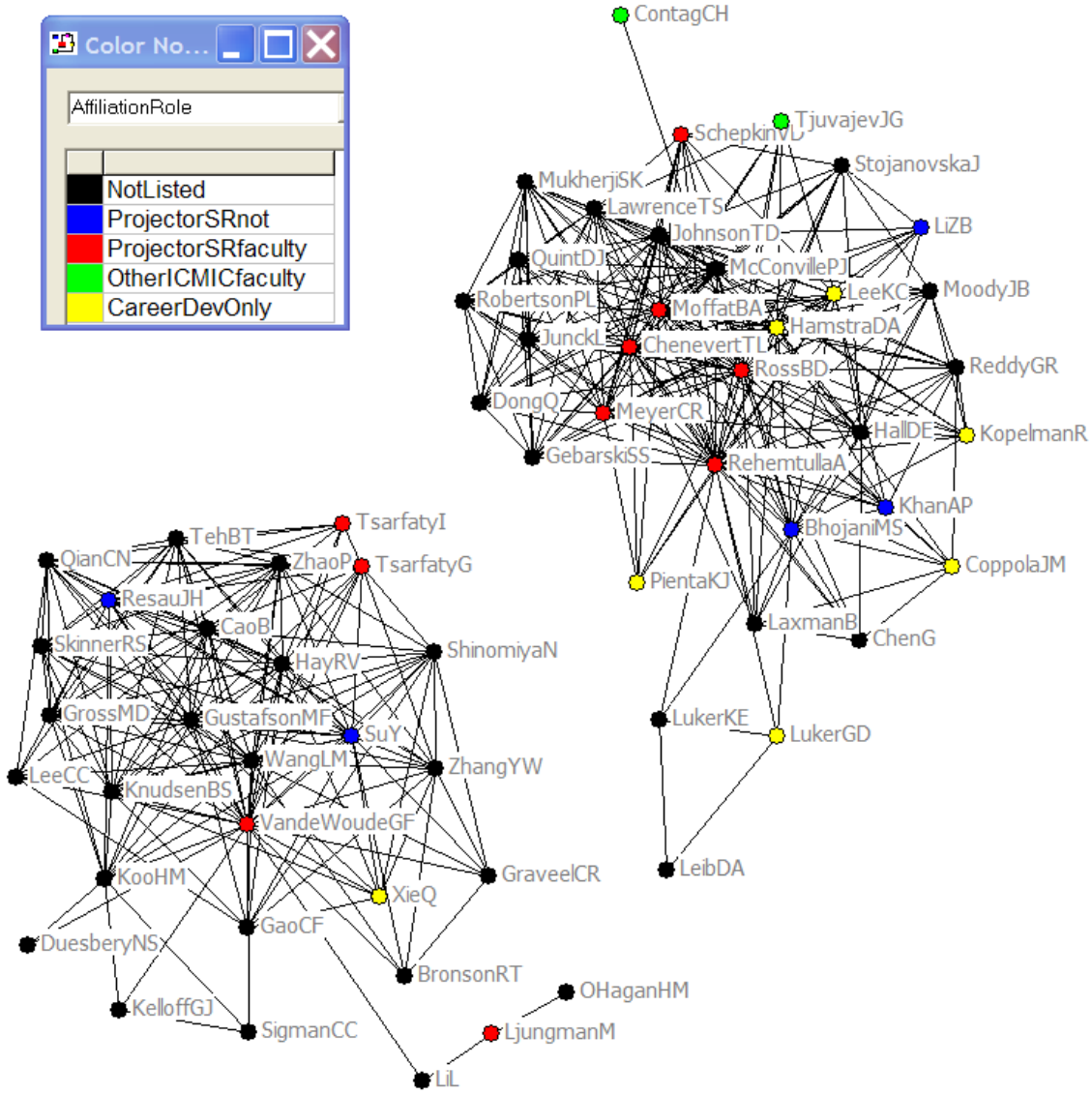
Source: Database of ICMIC Publications. Affiliation information source: applications, supplemented by Internet searches.

Figure Appendix E-5: Johns Hopkins, SNA Diagram of Co-Authorship, by Department of Participant, for All Individuals with Three or More co-Authorships on P50 ICMIC-Affiliated Publications



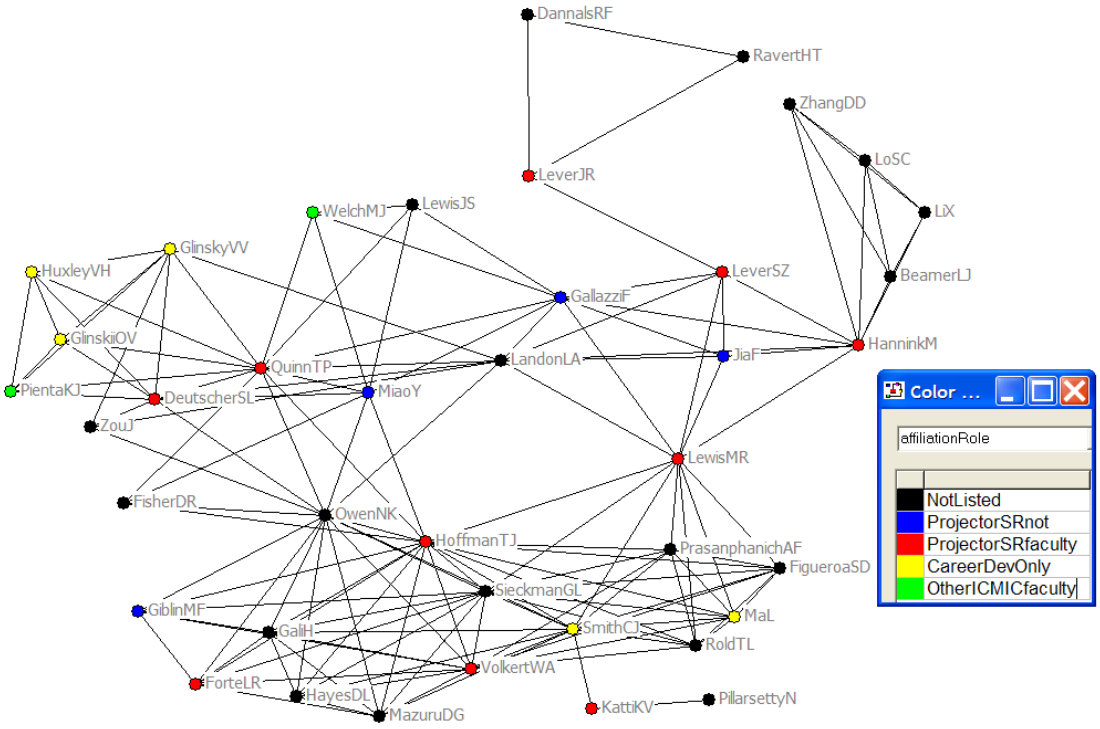
Source: Database of ICMIC Publications. Affiliation information source: applications, supplemented by Internet searches.

Figure Appendix E-6: University of Michigan, SNA Diagram of Co-Authorship, by Department of Participant, for All Individuals with Three or More co-Authorships on P50 ICMIC-Affiliated Publications



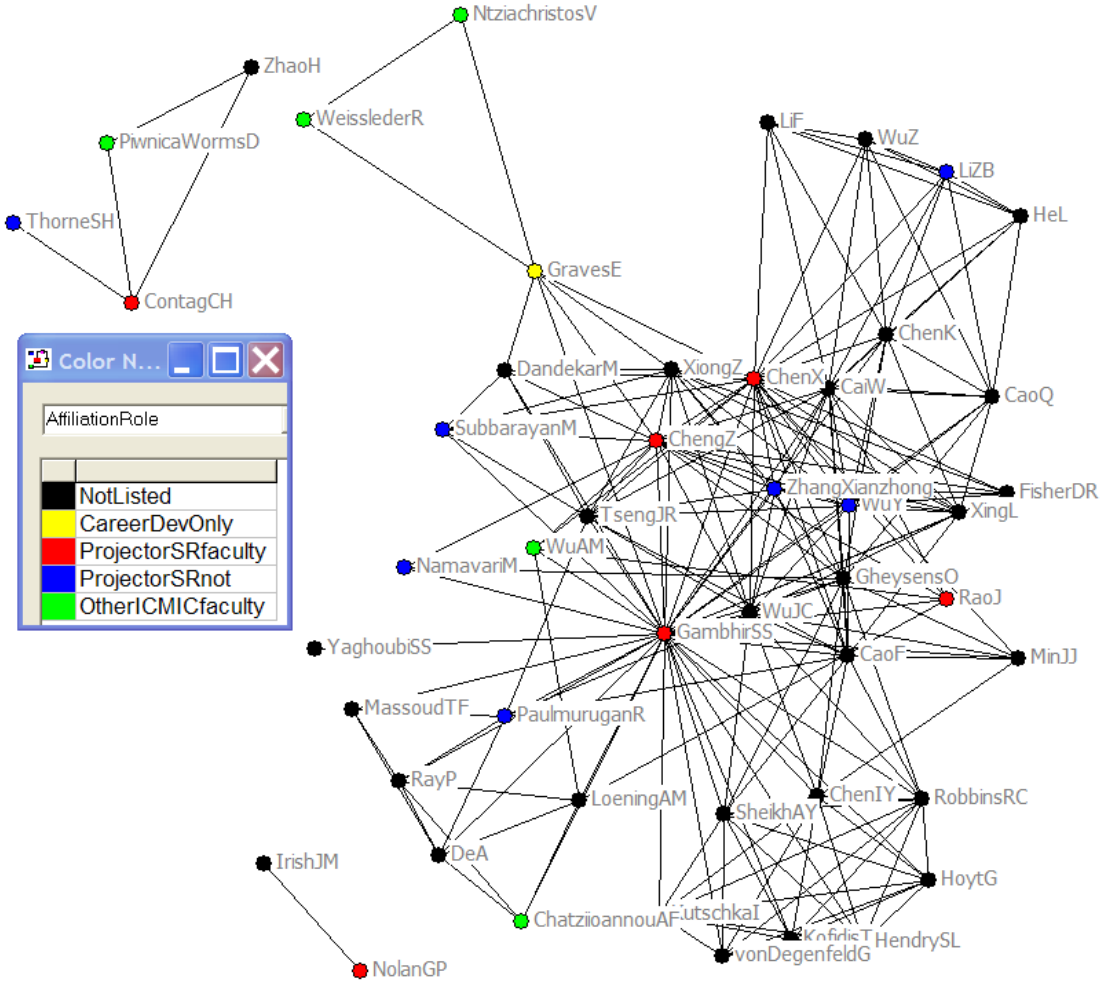
Source: Database of ICMIC Publications. Affiliation information source: applications, supplemented by Internet searches.

Figure Appendix E-7: University of Missouri-Columbia, SNA Diagram of Co-Authorship, by Department of Participant, for All Individuals with Three or More co-Authorships on P50 ICMIC-Affiliated Publications



Source: Database of ICMIC Publications. Affiliation information source: applications, supplemented by Internet searches.

Figure Appendix E-8: Stanford, SNA Diagram of Co-Authorship, by Department of Participant, for All Individuals with Three or More co-Authorships on P50 ICMIC-Affiliated Publications



Source: Database of ICMIC Publications. Affiliation information source: applications, supplemented by Internet searches.

Appendix F: Interview Information

List of Interviewees

ICMIC Principal Investigators:

1. Ralph Weissleder-MGH
2. Harvey Herschman-UCLA
3. David Piwnica-Worms-WashU
4. Brian Ross-Michigan
5. Samuel Gambhir - Stanford
6. Ronald Blasberg-MSKCC
7. Wynn Volkert – University of Missouri-Columbia (UM-C)
8. Zaver Bhujwalla – JHU

Research Component Leaders/Affiliated Researchers:

1. Mikael Pittet-MGH
2. Antoni Ribas-UCLA
3. Johannes Czernin-UCLA
4. Anna Wu-UCLA
5. Xandra Breakefield-MGH
6. John Lever - UM-C
7. Susan Deutscher - UM-C
8. Thomas Quinn - UM-C
9. Michael Welch, Washington University

Former Research Component/Developmental Project Leaders:

1. Hong Wu-UCLA
2. Lily Wu -UCLA
3. Owen Witte-UCLA
4. Jonathan Braun-UCLA

Current Career Development Awardees

1. Jennifer Shu - UCLA
2. Kimberly Kelly -MGH
3. Ken-Ichiro Kamei-UCLA
4. Jason McCarthy -MGH
5. Matthias Nahrendorf-MGH
6. Helen Su – UCLA

Former Career Development Awardees:

1. Baghavathy Balaji - UM-C
2. Stephanie Lane - UM-C
3. Alex Guimaraes -MGH
4. Umar Mahmood-MGH

Comparator Institution Researchers:

1. Thea Tlsty - UCSF
2. Kenneth Krohn – University of Washington
3. Jonathan Tait - University of Washington
4. Donald Hnatowich – University of Massachusetts Medical Center
5. Mary Rusckowski - University of Massachusetts Medical Center
6. Hubert Vesselle - University of Washington
7. Mitchel Berger - UCSF
8. Nola Hylton - UCSF
9. Alexei Bogdanov - University of Massachusetts Medical Center

Discussion Guides: ICMIC Principal Investigators

The purpose of this interview is to collect information about your ICMIC award and more generally about cancer imaging research at your institution. The information you provide will be used as part of an evaluation of the ICMIC program and may be shared with NCI and/or with other NIH stakeholders. Evaluation results will be reported in the aggregate wherever possible, and expert informants will not be identified by name, but it is possible that individuals with knowledge of the program could identify you or your institution from context.

You are under no obligation to participate, and your decision to participate will not affect the current or future status of your NIH funding. If you choose to participate, you may withdraw your consent at any time by contacting Dr. Brian Zuckerman of the Science and Technology Policy Institute (bzuckerm@ida.org). If it's ok with you, we'd like to make an audio recording of this session so that we can refer back to the tape while summarizing the results, but the tape will be kept confidential to the extent allowed by law and will be destroyed after the report is final.

Do you understand what I've just told you? Do you have any questions? Do we have your consent to proceed with the interview?

Planning, Management, and Organization

1. What are the most important goals of your ICMIC award?
    a. PROBE: Developing new imaging agents/tools/techniques for clinical or research use? Using imaging agents to understand aspects of cancer biology? Strengthening or supporting the cancer imaging research enterprise in other ways (e.g. community-building, networking, etc.)?
    b. Have the goals changed or evolved over time?
2. In general, what is your strategy for meeting those goals?
    a. How do specific research components align with the goals?
    b. What is the process for adding, updating, or eliminating projects?
    c. Is any particular emphasis placed on "collaborative" or "multi-disciplinary" projects?
    d. Is there any particular emphasis on including translational/clinical research?
3. Do the developmental projects fit in with this strategy?
    a. Is there a separate process for selecting and funding developmental projects?
    b. Did any research components originate as developmental projects?
    c. Have developmental projects enhanced or influenced research components in any other ways?
4. How did/do you recruit faculty to join the ICMIC?
    a. Approximately what percentage of the imaging researchers at your institution are affiliated with the ICMIC? Cancer researchers?
    b. Are researchers from "outside" disciplines/communities also involved? If yes, were they intentionally targeted for recruitment?
    c. Are there any groups/communities/individuals you would like to include that don't currently participate? [PROBE: Discipline? Seniority? Basic/Clinical?]
5. [Ask only if they had a P20] Can you please describe the activities funded through the P20 planning award that preceded your ICMIC award?

   a. PROBE: Forging new collaborations between researchers who had not previously worked together (who/which departments)? Developing research goals/strategy for full ICMIC proposal? Physical infrastructure support?
   b. Do you feel that the P20 activities contributed significantly to the success of your ICMIC? In what ways?

Research and Collaboration

6. What have been 1-3 the most important research discoveries made with ICMIC support?
   a. Which researchers/projects contributed to those results?
   b. If collaborations were involved, had the collaborators worked together before the ICMIC award? Do you think the ICMIC enhanced the collaboration?
   c. Did the research rely on physical infrastructure funded through the ICMIC?
   d. Did the ICMIC contribute in any other way?
7. Have any ICMIC research findings or outputs impacted translational research/clinical trials?
   a. If yes, please give details of the chain of events: which researchers were involved? How did it happen? Were non-ICMIC researchers involved?
   b. If no, do you anticipate this happening in the future?
8. Do you believe that ICMIC-supported research is more collaborative and/or multidisciplinary than other imaging-related research at your institution?
   a. Are there ICMIC-supported activities that actively promote collaboration among researchers?
   b. If yes, do you think collaboration/multidisciplinarity enhances the research? [PROBE: Quality? Productivity? Speed of translation?]

Imaging Infrastructure

9. Do you think the imaging-related physical infrastructure at your institution is adequate to meet the needs of the affiliated imaging researchers?
   a. What percentage of existing physical infrastructure is supported by ICMIC?
   b. What other funding sources have contributed?
   c. If additional funds were available for physical infrastructure, what would you do with them?

Training and Career Development

10. Please describe the training opportunities provided to graduate students/postdoctoral fellows at your ICMIC.
    a. From which departments do you draw your graduate students?
    b. What are the skill sets that the graduate students/postdocs learn through the ICMIC?
    c. Do you know of former trainees/fellows who are currently conducting cancer imaging research?
11. Are there other sources of funding for cancer imaging <u>training</u> at your institution?
    a. If yes, are the same students or fellows typically supported by multiple sources?
    b. Is ICMIC training distinct from other types of training?
12. How are career development funds used?
    a. Who uses these funds? [PROBE: postdocs? graduate students? junior faculty?]
    b. What types of activities are they used for?
    c. What is the process for selecting career development projects?
    d. If the ICMIC did not exist, how else might these activities be funded?

Community-Building

13. How would you describe the cancer-imaging research community at your institution?
    a. PROBE: Size? Cohesiveness? Diversity of disciplines? Diversity of age/experience? Frequency of interaction? Willingness to share resources/knowledge/expertise/etc.?
    b. Can you give any examples of ways in which the ICMIC has helped to expand or enhance the community of cancer/imaging researchers?

Role of ICMIC

14. What role does the ICMIC play at your institution relative to other funding sources for cancer imaging research?
    a. Are there other funding streams/organizations supporting cancer imaging at your institution? (IF ANY KNOWN, e.g. SPOREs, USE AS PROBES)
    b. If yes, is there a distinct role played by the ICMIC funding? Do the funding streams support different people/activities/equipment/research, or are the funds largely commingled?
    c. In what order (chronologically) were these funds awarded or organizations formed? Is it likely that ICMIC helped the institution to obtain additional funds or that the presence of other infrastructure helped you to obtain ICMIC funding?
    d. Can you give examples of spill-overs or synergies between ICMIC-affiliated research and other cancer research/imaging research at your institution?

Summary and Conclusion

15. Overall, has there been an increase in the use of cancer imaging techniques at your institution since the ICMIC began?
    a. Are non-ICMIC-affiliated (e.g., SPORE/R01-funded) researchers using imaging in their research more frequently?
    b. If yes, has this been a positive development for cancer research in general? For cancer treatment/prevention?
    c. To what extent do you believe any increases are attributable to ICMIC funding (as opposed to other funding sources or simply the evolution/diffusion of the technology)?
    d. Are there aspects of the ICMIC program that you think have been particularly important or particularly unimportant in achieving these results?
16. Are there any changes you would like to see made to the ICMIC program? Do you have any suggestions for NCI?
17. Is there anything else we haven't asked that you'd like to tell us about your ICMIC or the ICMIC program?

Discussion Guides: ICMIC Current Research Component Leaders

Informed Consent Statement for ICMIC Interviews:

The purpose of this interview is to collect information about your ICMIC award and more generally about cancer imaging research at your institution. The information you provide will be used as part of an evaluation of the ICMIC program and may be shared with NCI and/or with other NIH stakeholders. Evaluation results will be reported in the aggregate wherever possible, and expert informants will not be identified by name, but it is possible that individuals with knowledge of the program could identify you or your institution from context.

You are under no obligation to participate, and your decision to participate will not affect the current or future status of your NIH funding. If you choose to participate, you may withdraw your consent at any time by contacting Dr. Brian Zuckerman of the Science and Technology Policy Institute (bzuckerm@ida.org).

Do you understand what I've just told you? Do you have any questions? Do we have your consent to proceed with the interview?

{Interview group is ICMIC Research Component leaders. Any RC leaders who are junior faculty members should have questions 8 (if they have had career development funding) added from the trainee protocol as a followon probe to replace question 12a and question 9 (for all junior faculty, after question 12 is complete)}

Research and Collaboration

1. Why did you decide to join the ICMIC?
2. What percentage of your research is ICMIC-supported?
    a. When you present your research/speak outside your institution, under what circumstances do you wear an "ICMIC hat" as opposed to mentioning your affiliation with your department/other research center affiliation?
3. What has been the most important research discovery (or discoveries) associated with your individual Research Component?
    a. If collaborations were involved, had the collaborators worked together before the ICMIC award? Do you think the ICMIC enhanced the collaboration?
    b. Did the research rely on physical infrastructure funded through the ICMIC?
    c. Did the ICMIC contribute in any other way?
4. Have your research findings or outputs influenced translational research/clinical trials?
    a. If yes, please give details of the chain of events: which researchers were involved? How did it happen? Were non-ICMIC researchers involved?
    b. If no, do you anticipate this happening in the future?
5. Did your Research Component originate as a developmental project?
    a. Have developmental projects enhanced or influenced research components in any other ways?
6. IF ICMIC research time < 75%: Do you believe that your ICMIC-supported research is more collaborative and/or multidisciplinary than the other research you conduct?

7. Do you believe that your ICMIC-supported research is more collaborative and/or multidisciplinary than other imaging-related research at your institution?
    a. Are there ICMIC-supported activities that actively promote collaboration among researchers?
    b. If yes, do you think collaboration/multidisciplinarity enhances the research? [PROBE: Quality? Productivity? Speed of translation?]

Imaging Infrastructure

8. Do you think the imaging-related physical infrastructure at your institution is adequate to meet your needs?
    a. Which of the Specialized Resources does your Research Component specifically use?
    b. If additional funds were available for physical infrastructure, what would you do with them?

Training and Career Development

9. Please describe the training opportunities provided to your graduate students/postdoctoral fellows. {NOTE: Assumes that researchers have distinct "ICMIC" and "non-ICMIC" students
    a. Do you have distinct "ICMIC-supported" and "non-ICMIC-supported" graduate students/postdocs/fellows who you train?
    b. From which departments do you draw your ICMIC-supported graduate students?
10. What are the skill sets that the graduate students/postdocs learn through the ICMIC?
    a. Do they learn different skills from your "non-ICMIC" trainees?
    b. Do they learn different skills from other cancer imaging trainees in your department/institution?
11. Have any of your ICMIC-supported trainees moved on to other institutions to conduct cancer imaging research after they completed their training?
    a. Where are they currently located?
    b. Are they different from your "non-ICMIC" trainees?
    c. From other cancer imaging trainees in your department/institution?
12. Have you or your trainees used any of the ICMIC career development funds?
    a. What types of activities are they used for?
    b. What is the process for selecting career development projects?
    c. If the ICMIC did not exist, how else might these activities be funded?

Planning, Management, and Organization

13. What are the most important goals of the ICMIC?
    a. PROBE: Developing new imaging agents/tools/techniques for clinical or research use? Using imaging agents to understand aspects of cancer biology?
    b. Have the goals changed or evolved over time?
    c. Approximately what percentage of the imaging researchers at your institution are affiliated with the ICMIC? Cancer researchers?
    d. Are there any groups/communities/individuals you would like to be included in the ICMIC as a whole that don't currently participate? [PROBE: Discipline? Seniority? Basic/Clinical?]
14. [Ask only if they had a P20] Were you involved in the activities funded through the P20 planning award that preceded your ICMIC award?
    a. PROBE: Forging new collaborations between researchers who had not previously worked together (who/which departments)? Developing research goals/strategy for full ICMIC proposal? Physical infrastructure support?

b. Do you feel that the P20 activities contributed significantly to the success of the ICMIC? In what ways?

Community-Building

15. How would you describe the cancer-imaging research community at your institution
    a. PROBE: Size? Cohesiveness? Diversity of disciplines? Diversity of age/experience? Frequency of interaction? Willingness to share resources/knowledge/expertise/etc.?
    b. Can you give any examples of ways in which the ICMIC has helped to expand or enhance the community of cancer/imaging researchers?

Role of ICMIC

16. What role does the ICMIC play at your institution relative to other funding sources for cancer imaging research?
    a. Are there other funding streams/organizations supporting cancer imaging at your institution? (IF ANY KNOWN, e.g. SPOREs, USE AS PROBES)
    b. If yes, is there a distinct role played by the ICMIC funding? Do the funding streams support different people/activities/equipment/research, or are the funds largely commingled?
    c. In what order (chronologically) were these funds awarded or organizations formed? Is it likely that ICMIC helped the institution to obtain additional funds or that the presence of other infrastructure helped you to obtain ICMIC funding?
    d. Can you give examples of spill-overs or synergies between ICMIC-affiliated research and other cancer research/imaging research at your institution?

Summary and Conclusion

17. Overall, has there been an increase in the use of cancer imaging techniques at your institution since the ICMIC began?
    a. Are non-ICMIC-affiliated (e.g., SPORE/R01-funded) researchers using imaging in their research more frequently?
    b. To what extent do you believe any increases are attributable to ICMIC funding (as opposed to other funding sources or simply the evolution/diffusion of the technology)?
    c. Are there aspects of the ICMIC program that you think have been particularly important or particularly unimportant in achieving these results?
18. Are there any changes you would like to see made to the ICMIC program? Do you have any suggestions for NCI?
19. Is there anything else we haven't asked that you'd like to tell us about your ICMIC or the ICMIC program?

Discussion Guides: ICMIC Former Research Component Leaders

Interview guide for former Research Component leaders

Informed Consent Statement for ICMIC Interviews:

The purpose of this interview is to collect information about your ICMIC award and more generally about cancer imaging research at your institution. The information you provide will be used as part of an evaluation of the ICMIC program and may be shared with NCI and/or with other NIH stakeholders. Evaluation results will be reported in the aggregate wherever possible, and expert informants will not be identified by name, but it is possible that individuals with knowledge of the program could identify you or your institution from context.

You are under no obligation to participate, and your decision to participate will not affect the current or future status of your NIH funding. If you choose to participate, you may withdraw your consent at any time by contacting Dr. Brian Zuckerman of the Science and Technology Policy Institute (bzuckerm@ida.org).

Do you understand what I've just told you? Do you have any questions? Do we have your consent to proceed with the interview?

Past affiliation

1. If you can recall, why did you decide to join the ICMIC?
2. If you can recall, at the time, what percentage of your research was ICMIC-supported?
3. What was the most important research discovery (or discoveries) associated with your individual Research Component Project?
    a. PROBE: If collaborations were involved, had the collaborators worked together before the ICMIC award? Do you think the ICMIC enhanced the collaboration?
    b. PROBE: Did the ICMIC contribute in any other way?
4. Did your research findings or outputs influence translational research/clinical trials?
    a. PROBE: If yes, please give details of the chain of events: which researchers were involved? How did it happen? Were non-ICMIC researchers involved?
    b. PROBE: If no, do you anticipate this happening in the future?
5. Was the imaging-related physical infrastructure at your institution at that time adequate to meet your needs?

Current research/imaging

6. Does your <u>current</u> research build upon your Research Component Project?
7. Are you using imaging techniques in your current research?
8. Are you still collaborating with the ICMIC PI? Current ICMIC RC leaders?

9. Are you affiliated currently with any large NIH centers/projects (e.g., P50, P01)? If yes, which ones?
    a. PROBE: Are they currently incorporating imaging into their research?
    b. PROBE: Did the ICMIC (either through your affiliation or otherwise) introduce imaging techniques and approaches into their work?

Collaborativeness

10. Do you believe that your ICMIC-supported research was more collaborative and/or multidisciplinary than the research you currently conduct?
11. Do you believe that your ICMIC-supported research was more collaborative and/or multidisciplinary than other imaging-related research currently conducted at your institution?
12. Can you give any examples of other ways in which the ICMIC has helped to expand or enhance the community of cancer/imaging researchers?

Summary and Conclusion

13. Overall, has there been an increase in the use of cancer imaging techniques at your institution since the ICMIC began?
    a. PROBE: Are non-ICMIC-affiliated (e.g., SPORE/R01-funded) researchers using imaging in their research more frequently?
    b. PROBE: To what extent do you believe any increases are attributable to ICMIC funding (as opposed to other funding sources or simply the evolution/diffusion of the technology)?
    c. PROBE: Are there aspects of the ICMIC program that you think have been particularly important or particularly unimportant in achieving these results?
14. Are there any changes you would like to see made to the ICMIC program? Do you have any suggestions for NCI?
15. Is there anything else we haven't asked that you'd like to tell us about the ICMIC program?

Discussion Guides: ICMIC Current Trainees/Career Development Awardees

Informed Consent Statement for ICMIC Interviews:

The purpose of this interview is to collect information about your ICMIC award and more generally about cancer imaging research at your institution. The information you provide will be used as part of an evaluation of the ICMIC program and may be shared with NCI and/or with other NIH stakeholders. Evaluation results will be reported in the aggregate wherever possible, and expert informants will not be identified by name, but it is possible that individuals with knowledge of the program could identify you or your institution from context.

You are under no obligation to participate, and your decision to participate will not affect the current or future status of your NIH funding. If you choose to participate, you may withdraw your consent at any time by contacting Dr. Brian Zuckerman of the Science and Technology Policy Institute (bzuckerm@ida.org).

Do you understand what I've just told you? Do you have any questions? Do we have your consent to proceed with the interview?

{Interview group is ICMIC-trained postdocs/graduate students, as well as junior faculty who are not RC leaders but who have received career development funds.}

Research and Collaboration

1. Why did you decide to join the ICMIC?
    a. Did you know you were joining the ICMIC when you first affiliated with it?
2. What percentage of your support comes from the ICMIC?
    a. When you present your research/speak outside your institution, under what circumstances do you wear an "ICMIC hat" as opposed to mentioning your affiliation with your department/other research center affiliation?

3. What has been the most important research discovery or discoveries associated with your ICMIC-supported research?
    a. With whom do you collaborate on your research?
    b. Does the research rely on physical infrastructure funded through the ICMIC?
    c. Did the ICMIC contribute in any other way?
4. Have your research findings or outputs impacted translational research/clinical trials?
    a. If yes, please give details of the chain of events: which researchers were involved? How did it happen? Were non-ICMIC researchers involved?
    b. If no, do you anticipate this happening in the future?
5. {FOR GRADUATE STUDENTS AND POSTDOCS} Who is your research mentor?
    a. FOR GRADUATE STUDENTS: Is that the same person as the leader of your research project?
6. Is your research funded through ICMIC career development or developmental funds, or as part of a "Research Component"?

Training and Career Development

7. {GRADUATE STUDENTS/POSTDOCS ONLY} What are the skill sets that you have been learning through the ICMIC?

   a. Have you had the opportunity to build skills/learn to use equipment beyond what is required directly for your research?
   c. Have you had the opportunity to gain "soft skills" such as project management, grantwriting, management of more junior trainees?
   d. Do you learn different skills from other "non-ICMIC" trainees in your mentor's research group?
   e. Do they learn different skills from other cancer imaging trainees in your department/institution?
8. {JUNIOR FACULTY ONLY} What has been the influence of the ICMIC career development funding on your career?
   a. Factor in joining the faculty?
   b. Pursue new research directions?
   c. Gain new skills?
   d. How does this approach compare with NIH K-series career development awards?
9. {FOR JUNIOR FACULTY} Has any ICMIC-affiliated senior faculty member served as a mentor as part of your affiliation with the ICMIC?
   a. If yes, please describe

ICMIC Community

10. How would you describe your interactions with the leaders of the ICMIC Research Components?
11. How would you describe your interactions with the ICMIC PI?
12. {GRADUATE STUDENTS/POSTDOCS ONLY} How would you describe the {GRADUATE STUDENT OR POSTDOC} cancer-imaging research community at your institution?
   a. PROBE: Size? Cohesiveness? Diversity of disciplines? Frequency of interaction? Willingness to share resources/knowledge/expertise/etc.?
13. {JUNIOR FACULTY ONLY} Is there a community of junior faculty members associated with the ICMIC?
14. Can you give any examples of ways in which the ICMIC has helped to expand or enhance the community of cancer/imaging GRADUATE STUDENTS OR POSTDOCS?
15. How would you describe the cancer-imaging research community overall at your institution?
   a. PROBE: Size? Cohesiveness? Diversity of disciplines? Diversity of age/experience? Frequency of interaction? Willingness to share resources/knowledge/expertise/etc.?
   b. Can you give any examples of ways in which the ICMIC has helped to expand or enhance the community of cancer/imaging researchers?

Planning, Management, and Organization

16. Are there other centers/large programs supporting cancer imaging at your institution? (IF ANY KNOWN, e.g. SPOREs, USE AS PROBES)
   a. If yes, is there a distinct role played by the ICMIC?

Summary and Conclusion

17. Are there any changes you would like to see made to the ICMIC program? Do you have any suggestions for NCI?
18. Is there anything else we haven't asked that you'd like to tell us about your ICMIC or the ICMIC program?

Discussion Guides: ICMIC Former Trainees/Career Development Awardees

Informed Consent Statement for ICMIC Interviews:

The purpose of this interview is to collect information about your ICMIC award and more generally about cancer imaging research at your institution. The information you provide will be used as part of an evaluation of the ICMIC program and may be shared with NCI and/or with other NIH stakeholders. Evaluation results will be reported in the aggregate wherever possible, and expert informants will not be identified by name, but it is possible that individuals with knowledge of the program could identify you or your institution from context.

You are under no obligation to participate, and your decision to participate will not affect the current or future status of your NIH funding. If you choose to participate, you may withdraw your consent at any time by contacting Dr. Brian Zuckerman of the Science and Technology Policy Institute (bzuckerm@ida.org).

Do you understand what I've just told you? Do you have any questions? Do we have your consent to proceed with the interview?

Interview Guide for Former Trainees

Research and Collaboration

1. If you can recall, why did you decide to join the ICMIC?
    a. PROBE: Did you know you were joining the ICMIC when you first affiliated with it?
2. If you can recall, what percentage of your support came from the ICMIC?
3. Who was your research mentor?
    a. Do you still collaborate with him/her? If so, can you describe your current collaborative research with him/her?

Training and Career Development

4. What were the primary skills/skill sets that you learned through the ICMIC?
    a. Possible Probes: Did you have the opportunity to build skills/learn to use equipment beyond what is required directly for your research?
    b. Did you have the opportunity to gain "soft skills" such as project management, grantwriting, management of more junior trainees?
    c. Did you learn different skills from other "non-ICMIC" trainees in your mentor's research group?
    d. Did you learn different skills from other cancer imaging trainees in your department/institution?
5. What has been the influence of the ICMIC career development funding on your career?
    a. PROBES: What is your current position?
    b. What role did your participation in the ICMIC play in your attaining this position?

   i. Pursue new research directions?
   ii. Gain new skills?
   iii. Association with ICMIC mentor?
6. How does the ICMIC approach compare with other NIH training approaches you know of (T-series training grants, F-series fellowships)?

ICMIC Community

7. If you can recall, how would you describe your interactions with the leaders of the ICMIC Research Components?
8. {If PI was not mentor} How would you describe your interactions with the ICMIC PI?
9. Can you give any examples of ways in which the ICMIC has helped to expand or enhance the community of cancer/imaging graduate students and postdocs while you were affiliated with it?

Summary and Conclusion

10. Are there any changes you would like to see made to the ICMIC program? Do you have any suggestions for NCI?
11. Is there anything else we haven't asked that you'd like to tell us about your ICMIC or the ICMIC program?

Discussion Guides: Comparison Group Investigators

Comparison ICMIC PI Guide

Required Statement of Informed Consent

The purpose of this interview is to collect information about [imaging-research and] cancer imaging research and activities at your organization. The information you provide will be used as part of an evaluation of the ICMIC program and may be shared with NCI and/or with other NIH stakeholders.

You are under no obligation to participate, and your decision to participate will not affect the current or future status of your NIH funding. If you choose to participate, you may withdraw your consent at any time by contacting me (name of interviewer), (name of second listener) or Dr. Brian Zuckerman at the Science and Technology Policy Institute. Evaluation results will be reported in the aggregate wherever possible, and expert informants will not be identified by name.

If it's ok with you, we'd like to make an audio recording of this short interview so that we can refer back to the tape while summarizing the results-- the tape will be kept confidential and will be destroyed after the report is final. Is this ok?

Do we have your consent to proceed with the interview?

Research

1. Can you begin by describing the imaging research that you perform?
    a. PROBES: Approximately when did you begin using imaging techniques?
    b. Which modalities are you using?
    c. Can you recall why you chose to begin working in imaging?
2. In your research, do you collaborate with other imaging scientists beyond those in your laboratory?
3. Do you collaborate with clinicians at your institution?
4. Have any of your research findings or outputs impacted clinical trials?
    a. If yes, please give details of the chain of events: which researchers were involved? How did it happen?
    b. If no, do you anticipate this happening in the future?
5. If you are looking to pursue a new avenue of research, how do you do it?
    a. PROBE: Use existing R01 as means to start new line of research?
    b. Submit R21 application?
    c. Other ways?

Imaging Infrastructure

6. Do you think the imaging-related physical infrastructure at your institution is adequate to meet your needs?
7. What sources fund the purchase of large equipment?
8. What sources fund the maintenance and operations of that equipment?

a. If additional funds were available for physical infrastructure, what would you do with them?

Training and Career Development

9. Please describe the training opportunities available to graduate students/postdoctoral fellows at your organization in imaging-related fields
    a. Are there NIH training awards (Ts or R25Ts)?
    b. Is training done through individual R01s/P01s?
    c. From which departments do you draw your graduate students?
10. FOR SENIOR SCIENTISTS: Have you had difficulties attracting top candidates (graduate students, postdocs, junior faculty) to your institution?
    a. Are there candidates who turn down opportunities to go elsewhere? Where do they go?
11. FOR JUNIOR SCIENTISTS: Why did you choose to come to this institution?
    a. Were there issues regarding laboratory startup that you needed to overcome after taking your position?
    b. Was there formal mentoring by more senior faculty when you first began your position?

Community-Building

12. Is there a community of researchers at your institution who use imaging in cancer research?
    a. PROBE: To what extent do "community" members collaborate?
    b. Are there separate research efforts in each laboratory?
    c. Is there a common theme/set of strands that unite the research at a level above the single laboratory?
13. Are there mechanisms at your institution to actively promote imaging-related collaboration?
    a. Is there set of symposia/seminars that the cancer imaging researchers attend?
    b. Are there mechanisms for promoting collaborations between basic imaging scientists and clinicians?
14. During the past few years, has there been an increase in the use of cancer imaging techniques at your institution?

Community Leadership

15. Which institutions do you think are the leading (say top 5) institutions in the US in using imaging techniques in cancer research?
    a. If your institution is among them: Why?
    b. If your institution isn't among them – do you feel your institution is falling behind the leaders?

The ICMIC Program

16. Do you know anything about the NCI's ICMIC program?
17. Do you have any thoughts about it that might be relevant to this external evaluation of the program?
18. Is there anything else we haven't asked that you'd like to tell us about your imaging-related research in general at your organization, or the ICMIC program specifically?