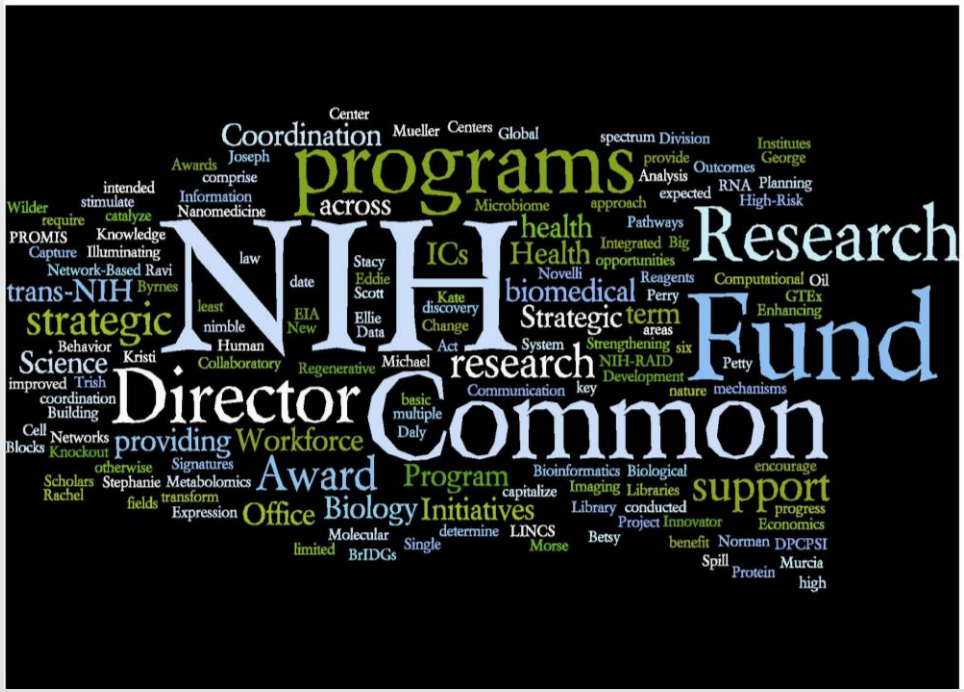
The NIH Common Fund:

Planning for Transformation



Council of Councils

January 29, 2016

National Institutes of Health
Office of Strategic Coordination - The Common Fund

Outline of FY 2018 Strategic Planning Process Phase 1

Ideas gathered from three sources:

- Invited meeting (~24 participants)
- Invited online discussion forum (300+ invitees)
- NIH ICs

- Prioritize ideas to select a few for discussion with all IC Directors
  Outcome: 5 prioritized ideas to bring to ICDs

- ICDs will consider ideas; can also raise others for discussion
- **Outcome: ideas with broad enthusiasm recommended for further planning**

- Dr. Collins has final decision about which ideas to bring to Council of Councils

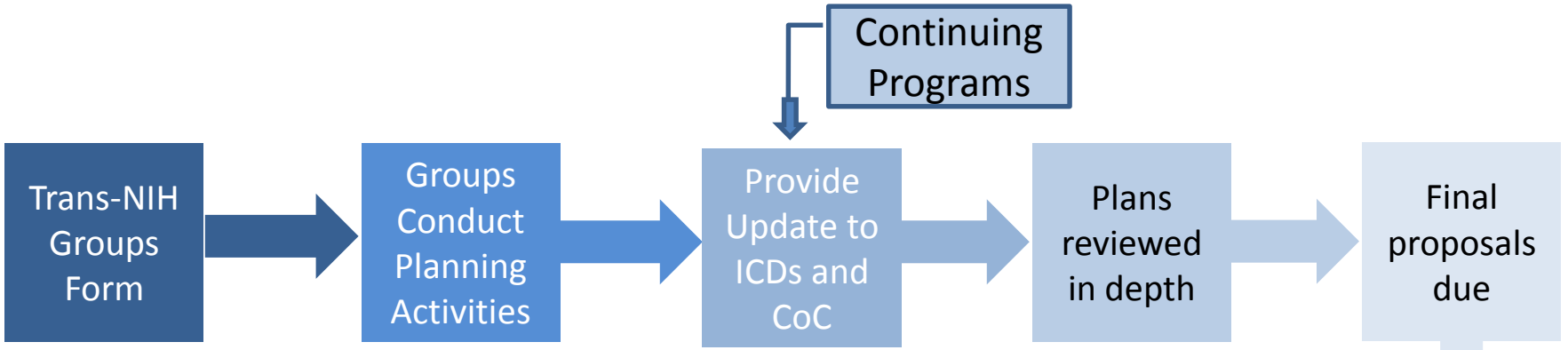
After Council clearance, ideas will move into Phase 2 strategic planning

July - October

December 14

Jan 29, 2016

Phase 2 Strategic Planning



- Working Groups Chaired by IC Directors, day to day leadership by IC and OSC staff

- Portfolio Analysis
- Workshops
- Focus Groups at national or international conferences
- RFIs, Social Media approaches

- Draft Plans for New and Continuing Programs will be presented to ICDs
- ICDs provide input on relative priorities
- Update provided to Council of Councils

- Small group of volunteer ICDs will provide feedback to groups
- Feedback allows refinement of plans

- Proposals presented to NIH Director and small group of ICDs
- Go/no go decisions made

Jan-Feb 2016

May 2016

June 2016

Aug-Sept, 2016

MECHANISMS OF FATIGUE IN HEALTH AND DISEASE

Mechanisms of Fatigue in Health and Disease

NINDS – Vicky Whittemore, PhD & Walter Koroshetz, MD
NIDA – David Thomas, PhD & Nora Volkow, MD
NINR – Leorey Saligan, PhD, RN, CRNP, FAAN
NIAID – Joseph Breen, PhD
NIA – Basil A. Eldadah, MD, PhD
NHLBI – Cheryl McDonald, PhD
NIAMS – James Witter, MD, PhD FACR
NICHD - Lynne Haverkos, MD, MPH
NIMH - Matthew Rudorfer, MD
ORWH – Cheryl Kitt, PhD

National Institutes of Health
Turning Discovery Into Health

Definition of Fatigue

- **Fatigue:** Fatigue can be defined as difficulty in initiating or sustaining voluntary activities (Chaudhuri and Behan, 2004)

- **Fatigue Model:** "Work" output is a function of:
  A. Motivational input (reward) – *subject of intense study*
  B. Feedback from motor, sensory, autonomic and cognitive systems that establishes the level of perceived exertion – *the biological basis of "exertion" for cognitive tasks, and how relevant feedback from the body is processed in the CNS is poorly understood.*
  C. Sense of fatigue occurs when value of B>>A
     - *Poorly understood **how** and unclear **where** that calculation happens*

- **Persistent Illness-related Fatigue:** The subjective sense of persistent "tiredness" or "loss of energy" that interferes with the performance of daily life activities and is not relieved by rest.

Acute versus Chronic Fatigue

- Acute fatigue is ubiquitous and likely involves a neural circuit for survival benefit. The mechanisms are unknown.

- Chronic fatigue is a condition that occurs normally during infectious illness, pregnancy, sleep deprivation, etc.

- Debilitating (persistent) chronic fatigue is a pathological condition that occurs in conjunction with many disorders and illness.

Two Major Categories of Fatigue

- **Physical fatigue** is an exercise-induced reduction in maximal voluntary muscle force.
  - The central nervous system fails to drive the motor neurons maximally.
  - How the brain interprets signals from muscle to produce sense of fatigue is not clear.

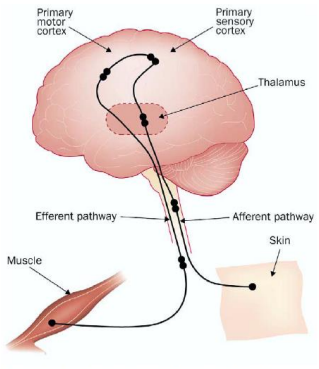
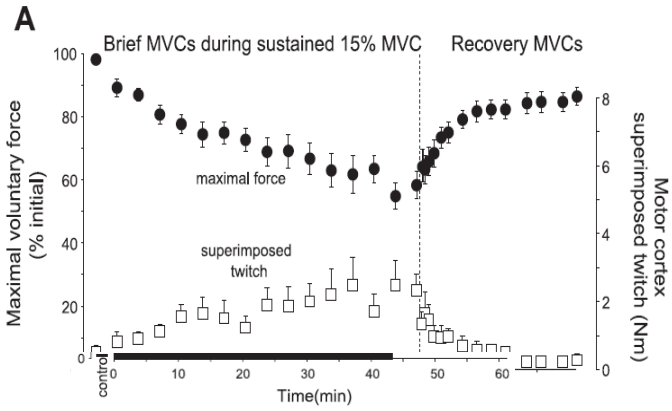


Figure 2: **Integration of sensory and motor pathways for physical activities**



- **Mental fatigue** is associated with affective, behavioral, and cognitive impairments especially in attention, planning, increased distractibility.
  - N.B. It is not related to ↓ATP.

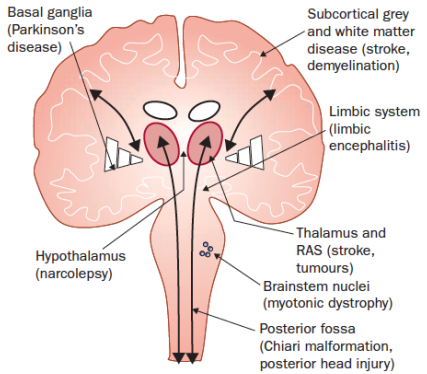


Figure 5: **General sites of pathology in central fatigue**
RAS=reticular activating system.

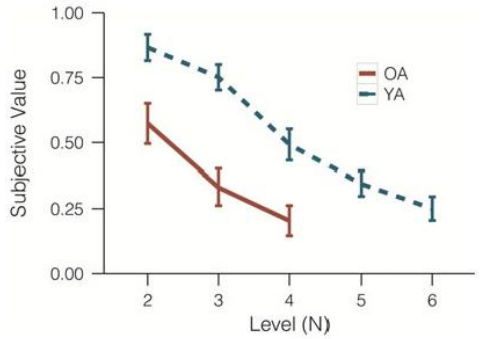


Figure 1 (Westbrook & Braver). Subjective value of a cash offer, or conversely, motivation to engage with a task, decreases with increasing working memory load for both young adults (YA) and older adults (OA).

Fatigue: Population Burden of Illness

Persistent Illness-Related Fatigue: a snapshot from cancer and rheumatic disease.

Table 2. Number of patients who endorsed Criterion A and B items.

Fatigue Case Definition Items	SSc Sample		Cancer Sample		p
	Completed Item, n	Endorsed Item, n (%)	Completed Item, n	Endorsed Item, n (%)	
A1. Two weeks of fatigue in past month	291	145 (49.8)	278	144 (51.8)	0.68
A2. General weakness	145	107 (73.8)	144	94 (65.3)	0.13
A3. Trouble concentrating	145	81 (55.9)	143	97 (67.8)	0.04
A4. Decreased motivation	145	96 (66.2)	143	87 (60.8)	0.39
A5. Insomnia/hypersomnia	145	118 (81.4)	144	119 (82.6)	0.88
A6. Non-restorative sleep	145	111 (76.6)	144	120 (83.3)	0.19
A7. Having to push to do things	144	123 (85.4)	144	107 (74.3)	0.03
A8. Sadness or frustration	145	105 (72.4)	144	94 (65.3)	0.21
A9. Trouble completing daily tasks	145	109 (75.2)	144	99 (68.8)	0.24
A10. Short-term memory problems	145	87 (60.0)	141	104 (73.8)	0.02
B. Impairment in functioning	122	102 (83.6)	116	105 (89.7)	0.13

SSc: systemic sclerosis.

Prominence of Fatigue in Many Disorders

Central Nervous System

Multiple Sclerosis
Post Stroke
Post TBI
Post Polio Syndrome
Post posterior fossa surgery/path

Neuroendocrine

Hypothyroidism
Hypothalamic Pituitary Adrenal Axis

Drug AEs

Metabolic

Renal Failure
Heart Failure
Anemia

Inflammatory/Rheumatic Diseases

Muscle Nerve

Overtraining Syndrome
Myasthenia Gravis
Mitochondrial disorders
Chronic Guillain Barre

Infectious and Post Infectious

Mononucleosis
Lyme
Influenza

Environmental

Heat
Altitude Sickness

Psychological

Depression
Post traumatic stress disorder
Anxiety Disorder
Addiction

Cancer

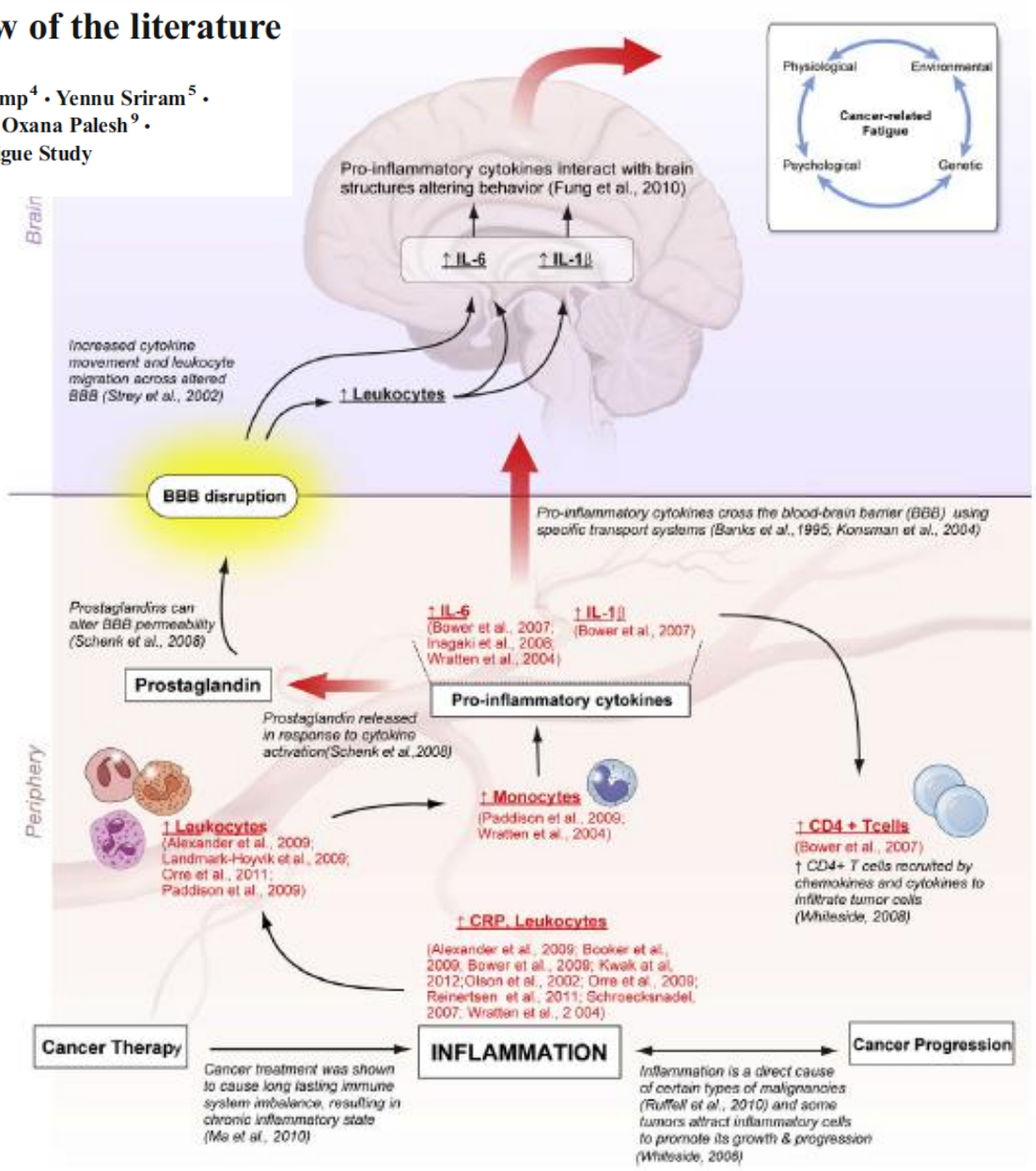
Cancer and Post cancer
Radiation and Chemotherapy

Mechanisms of Fatigue in Cancer

The biology of cancer-related fatigue: a review of the literature

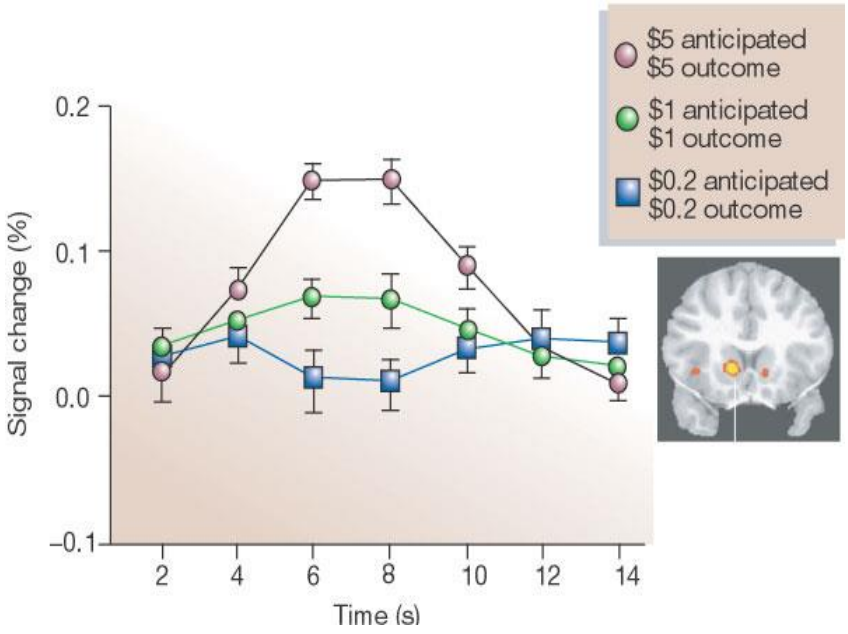
Leorey N. Saligan[1] · Karin Olson[2] · Kristin Filler[1] · David Larkin[3] · Fiona Cramp[4] · Yennu Sriram[5] · Carmen P. Escalante[5] · Auro del Giglio[6] · Kord M. Kober[7] · Jayesh Kamath[8] · Oxana Palesh[9] · Karen Mustian[10] · Multinational Association of Supportive Care in Cancer Fatigue Study Group–Biomarker Working Group

- No causation between a specific biomarker and CRF has been established
- Cytokine receptors present in brain. Peripheral measures of cytokine and inflammatory activity in CRF have been inconsistent.
- Some promising genomic and mitochrondrial markers
- In longitudinal studies mechanisms associated with CRF were immune/inflammatory, disruption of blood cell indices and sympathetic nervous system dysfunction



Neuroeconomics: A Potential Means to Understand Neural Mechanisms of Fatigue

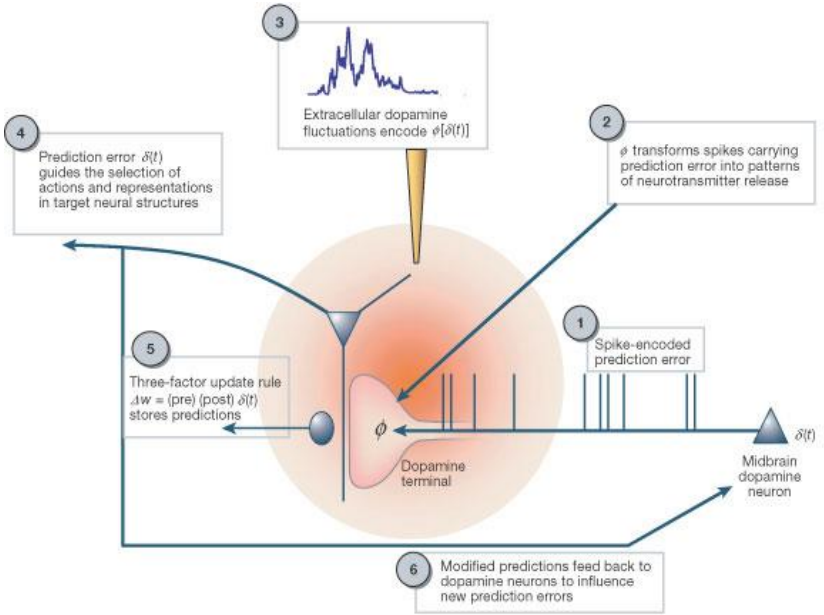
Nature **431**, 760-767 (14 October 2004)
Computational roles for dopamine in behavioural control
P. Read Montague[1,2], Steven E. Hyman[3] & Jonathan D. Cohen[4,5]



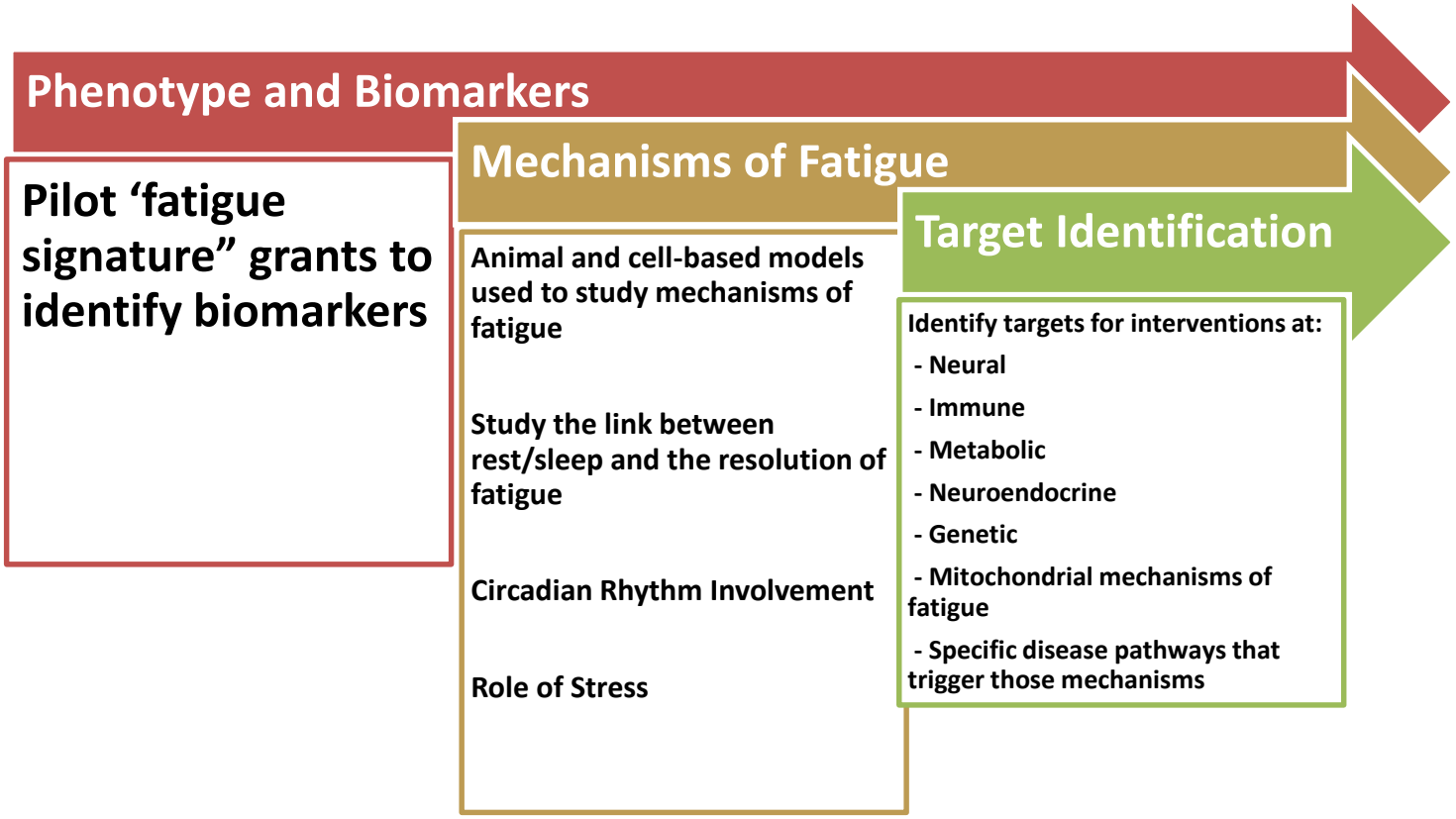
Subsecond dopamine fluctuations in human striatum encode superposed error signals about actual and counterfactual reward

Kenneth T. Kishida[a,1], Ignacio Saez[a,2], Terry Lohrenz[a], Mark R. Witcher[b], Adrian W. Laxton[b], Stephen B. Tatter[b], Jason P. White[a], Thomas L. Ellis[b,3], Paul E. M. Phillips[c,d], and P. Read Montague[a,e,f,1]

Dopamine release in human brain translates computations about actual and simulated experiences to embodied states of feeling



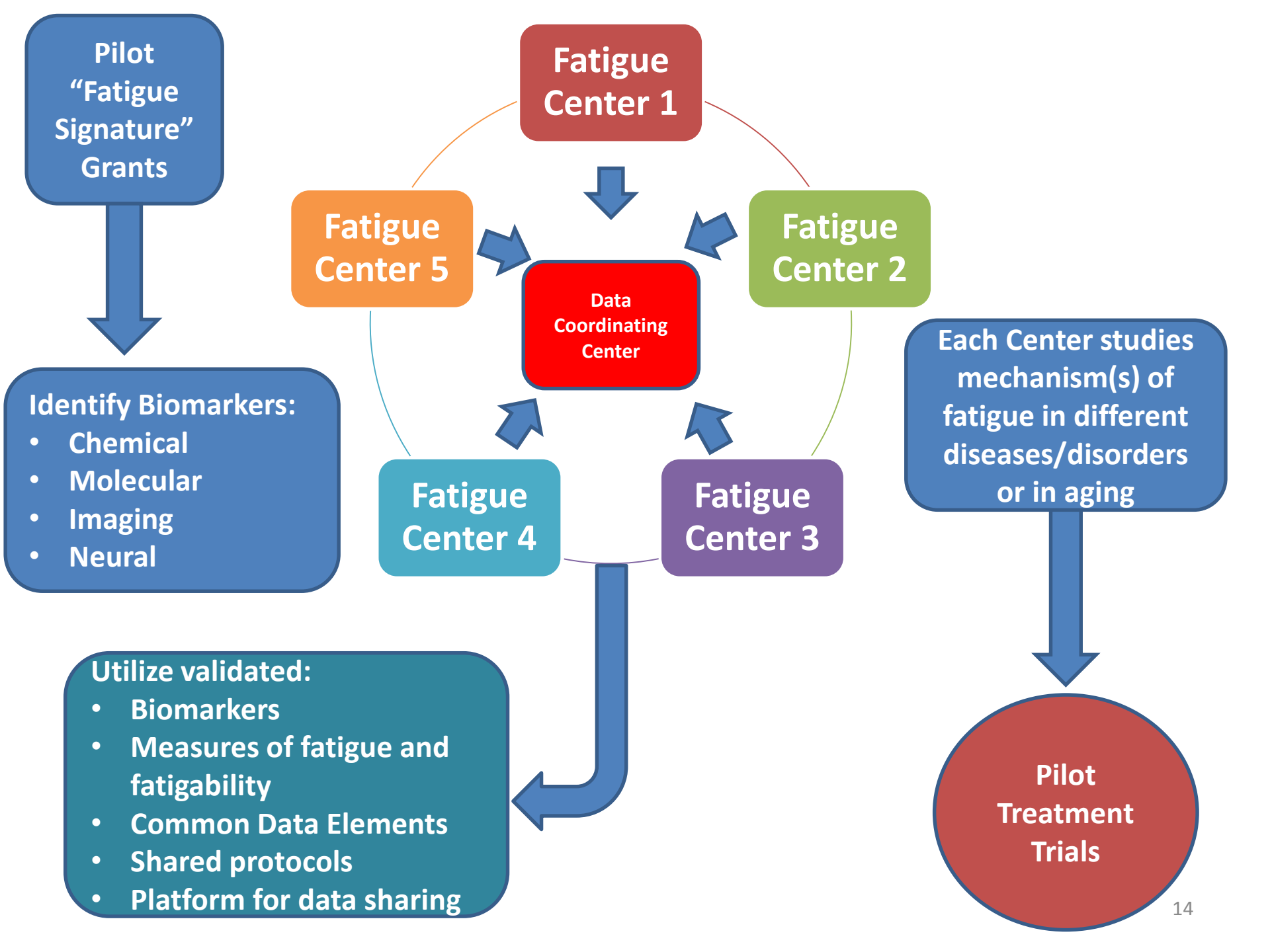
Statement of Work for a Program on Mechanisms of Fatigue



Deliverables:

- Improved diagnostics
- Development of targeted therapies
- Reduction of disease and aging-related burden of fatigue
- Profound public health benefits that improve quality of life across the wide spectrum of disease

Establish a "new normal" for future studies focused on effectively treating this devastating condition that affects the entire body and individuals across the lifespan


Pilot "Fatigue Signature" Grants
Identify Biomarkers:
• Chemical
• Molecular
• Imaging
• Neural
Fatigue Center 1
Fatigue Center 2
Fatigue Center 3
Fatigue Center 4
Fatigue Center 5
Data Coordinating Center
Each Center studies mechanism(s) of fatigue in different diseases/disorders or in aging
Pilot Treatment Trials
Utilize validated:
• Biomarkers
• Measures of fatigue and fatigability
• Common Data Elements
• Shared protocols
• Platform for data sharing

Why a Common Fund Program on Mechanisms of Fatigue in Health and Disease

- **Need:**
  - Fatigue affects everyone
  - Persistent illness-related fatigue represents a tremendous burden of illness
- **Gap:**
  - Fatigue is a common physiological state that has yet to be understood
  - Relatively little ongoing mechanistic research
  - Knowledge is limited and treatments absent
- **Solution:**
  - Requires diverse expertise & multidisciplinary approaches that cross multiple Institutes and Centers

Mechanisms of Fatigue in Health and Disease: *Goals of the Program*

- **Physical fatigue:**
  - Define the role of molecular regulators of physical fatigue in animal models and in humans.
    - metabolites, inflammatory cytokines and other circulating substances autonomic nervous systems, muscle afferents, respiratory, heat
  - Define how the supraspinal neural fatigue system integrates peripheral inputs to cause fatigue.
  - Define how the fatigue system is altered in disorders of illness-related fatigue.
- **Mental Fatigue:**
  - Define in animals and humans the neural system that calculates the cost/benefit of continued task engagement.
  - Define how that neural system is altered in disorders of illness-related fatigue.
- Identify factors that confer **vulnerability & resilience** to developing fatigue.
- Develop and validate fatigue and fatigability **measures, and biomarkers** to enable therapeutic trials.
- Establish **methods, CDEs, tools, and common platform** for study of fatigue in animal models and humans.
- Identify mechanisms underlying resolution of fatigue by **rest**/sleep and why it fails in disorders.
- Develop **targets for interventions** that attenuate persistent illness-related fatigue.



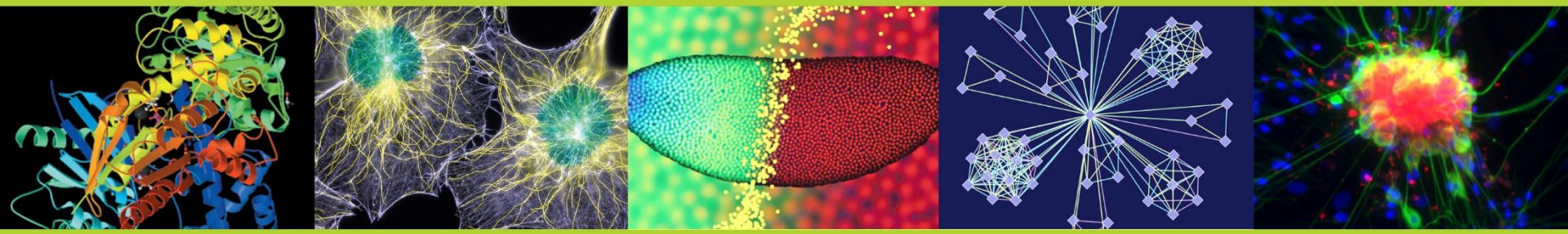
Mechanisms of Fatigue in Health and Disease: *Impact*

- Establishment of common measures and biomarkers of fatigue ('fatigue signature") would enable many future IC-supported projects and inform phase 2 trials of science-based interventions.
- Identification of peripheral and/or central targets that modulate the physiological state of fatigue would enable testing science-based interventions.
- Intervention(s) that attenuate fatigue would have enormous benefit for patients with a wide variety of disorders.

Transformative Potential of High Resolution Cryo-Electron Microscopy

Sponsoring ICOs: NIGMS, NEI, NHLBI, NIDDK, NINDS, ORIP

Interested ICOs: NCI, NIAID, NIDA

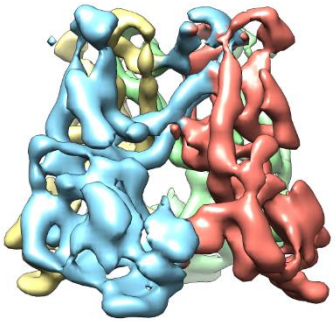


NIH National Institute of General Medical Sciences

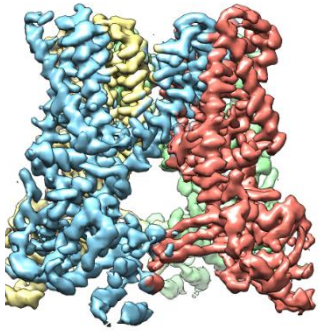
Why Now? New Technological Breakthroughs in Cryo-EM

1) **New electron microscopy technology dramatically improves our ability to see biological molecules**

Old Methods

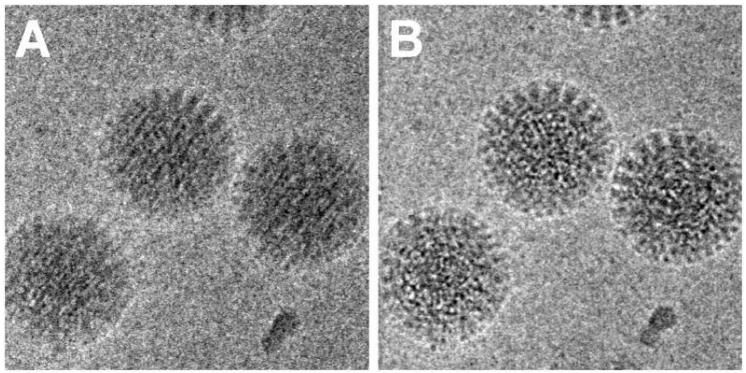


New Methods



TRPV1 Ion Channel:
Mediates burn sensation,
Yifan Cheng UCSF

2) **New motion correction methods resolve blurring of images due to movement of particles in electron beam**



Rotavirus Particles
Niko Grigorieff, Janelia Farms

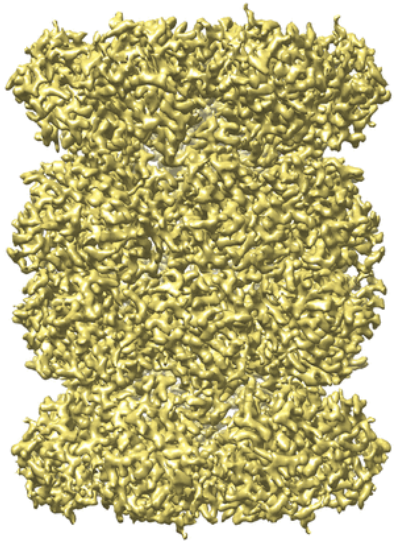
Scientific Opportunities through Cryo-EM

- **Determine structures more rapidly and easily**

> Venki Ramakrishnan: "*It's safe to predict that cryo-EM will largely supersede crystallography*." ***Nature*** (2015)

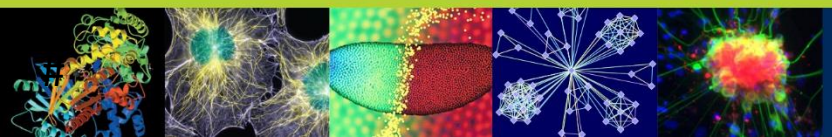
- **Direct visualization of subcellular structures, *in situ***

> Richard Henderson: "*If it carries on, and all the technical problems are solved, cryo-EM could indeed become, not just a first choice, but a dominant technology. We are probably halfway there*." ***Nature*** (2015)

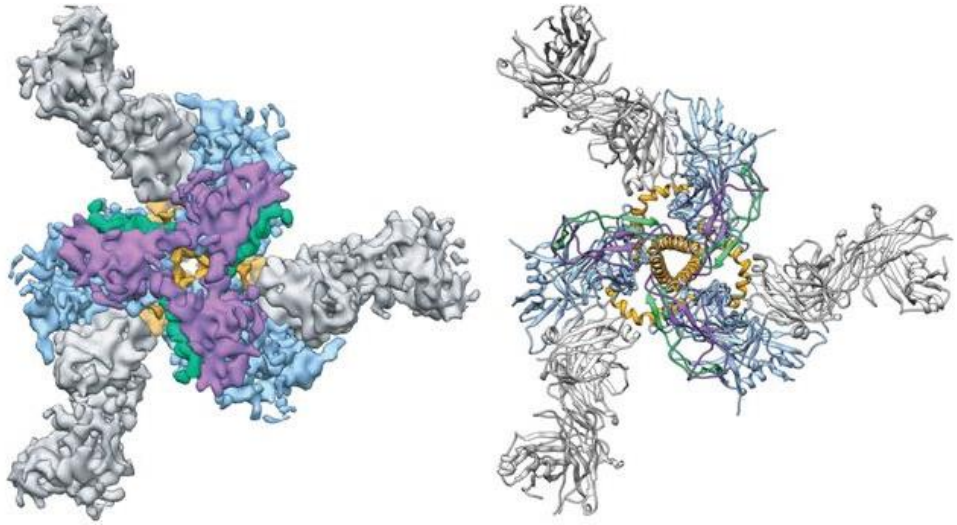


2.8 Å structure of proteasome.
Campbell et. al, eLife (2015)

Impacts on Research: Structures of hard to crystallize and complex molecules, such as channels and receptors; elucidating conformational changes in complexes; rapid determination of effects of mutations on structure; structural basis of drug action; structures of molecules determined inside of (or on) cells.



Cryo-EM Was Crucial for Recent Advances Towards an HIV Vaccine

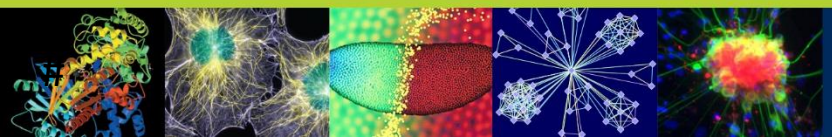


“Another major advance toward developing an effective HIV vaccine came in 2013 when a team of researchers led by John Moore at Weill Cornell Medical College in New York City and Ian Wilson at the Scripps Research Institute in La Jolla, California, obtained an atomic-level image of the HIV envelope trimer, the principal target for broadly neutralizing antibodies.”

-Wayne Koff, *The Scientist*, May 1, 2015

The U.S. Is Falling Behind Asia and Europe in Cryo-EM

- Initial Investment, 1-2 Cryo-EM microscopes, shared facility
- Moderate Investment, 3-4 Cryo-EM microscopes, regional facility
- Significant Investment, 5+ Cryo-EM microscopes, HTP user facility



National Institute of General Medical Sciences

Challenges for Researchers Today

Infrastructure

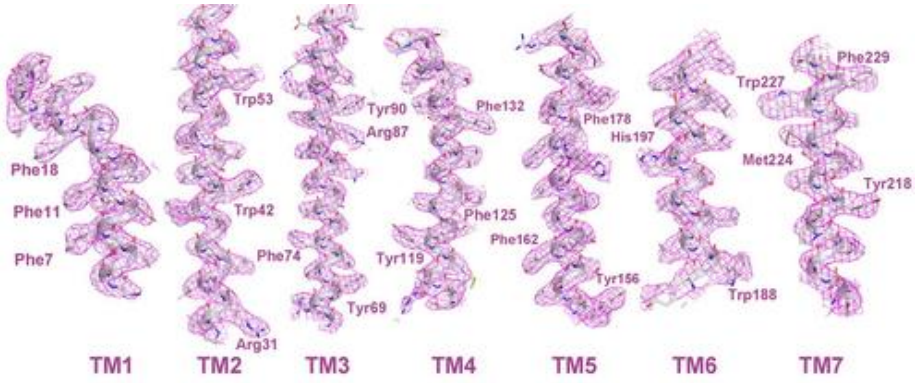
- Current technology only available to a few experts
- Inadequate to take advantage of scientific opportunity

Investigator base

- Workforce bottleneck: major training need
- Crystallographers want to move to EM

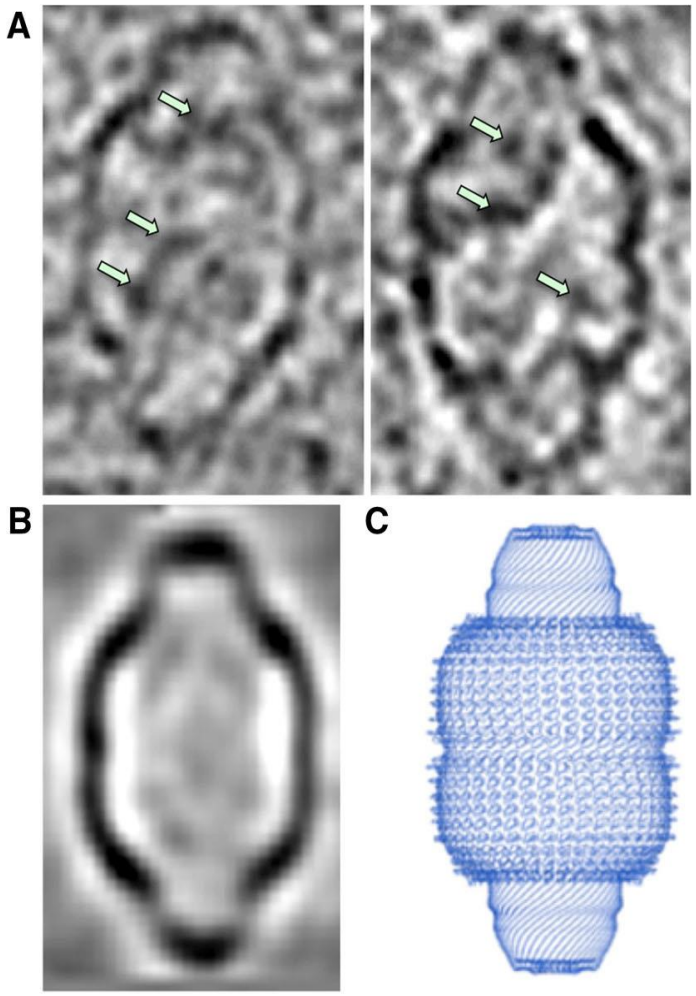
Equipment

- Expensive, limited numbers
- Inaccessible to most potential users
- Highly inefficient for each institution to buy and maintain its own cryo-EM



3.4 Å EM density map for all seven transmembrane segments of the APH-1 component of γ-secretase. Bai et al., Nature (2015)

Technology Development Needed for Tomography



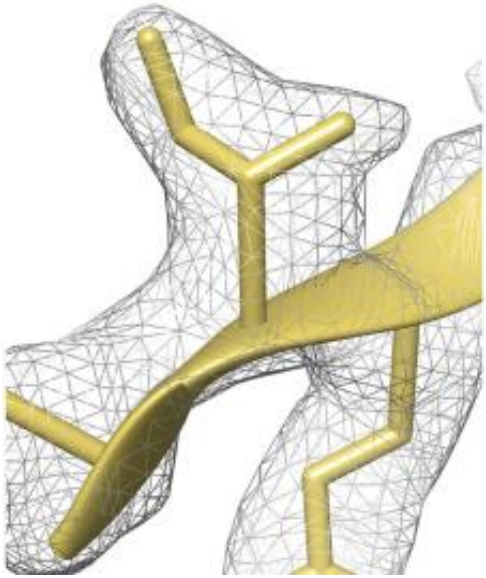
- Reconstruction of the structures of molecules inside of cells
- Recognition of molecules in tomograms is still done largely by eye
- More sensitive, automated, better resolution methods for tomography are needed

Crystal structure of purified rat liver vaults (~13 MDa).
Woodward et al. *Cell. Mol. Life Sci.* (2015)

Short-term Strategy: NIGMS Regional Consortia

NIGMS Regional Consortia Program (RFA- GM-16-001)

- Supports only equipment upgrades for expert laboratories
- No research assistance for screening or computational analysis
- No training



Unambiguous establishment of the rotameric conformation of an isoleucine residue in a 2.8 Å structure of *Thermoplasma acidophilum* 20S proteasome, , Campbel et al., *eLife* (2015)

Long Term Strategy – The Synchrotron Model

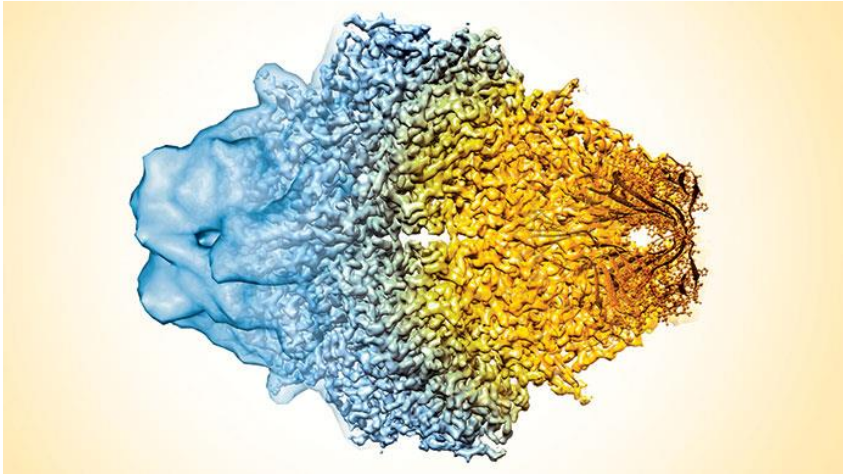
The Synchrotron Model for Cryo-EM

- State of the art regional user facilities
- Access open to all through peer review process
- Training for users
- Professional and technical staff to assist with data collection and analysis; maintain and upgrade equipment; provide training
- Wet lab facilities & lodging
- High-throughput and mail-in services

Advanced Photon Source, Argonne National Laboratory

Goals, Deliverables, Impact

- Move U.S. to the forefront of cryo-EM research
- Provide efficient and economical access to cryo-EM technologies and training: create economies of scale
- Develop new technologies and computational methods to lower cost, improve resolution, and increase throughput and ease of use
- Push the frontiers of *in situ* Cryo-EM (tomography)



BETTER RESOLUTION
This composite image of the protein β-galactosidase shows how cryo-EM has progressed over the years, from the indistinct blobs once obtained with the technique (left) to the nearly 2-Å-resolution structures possible today (right).
Credit: Sriram Subramaniam/NCI

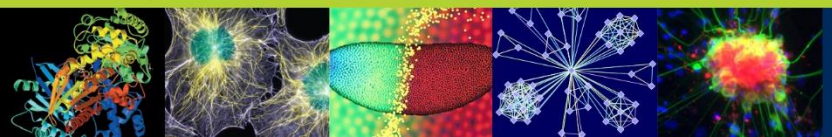
Draft Proposed Budget

3 Comprehensive Centers

		Year 1	Year 2	Year 3	Years 4-5	5 Year Total
Equipment	4 microscopes @ 3 centers	$22M	$22M	$ 22M	0	**$66M**
Operating Cost	Staff, facilities, maintenance	$4M	$6.4M	$8.7M	$7.1M	**$33.3M**
Training Cost	3 FTEs @ 3 centers	$0.6M	$1.2M	$1.8M	$1.8M	**$7.2M**
		$26.6M	**$29.6M**	**$32.5M**	**$8.9M**	**$106.5M**

Investigator-Initiated Research

	Activity	TC yearly	5 Year Total
Cryoelectron Tomography TR&D	R21, R01	$5M	**$25M**
Single Particle Analysis CryoEM TR&D	R21, R01	$2.5M	**$12.5M**
		$7.5M	**$37.5M**

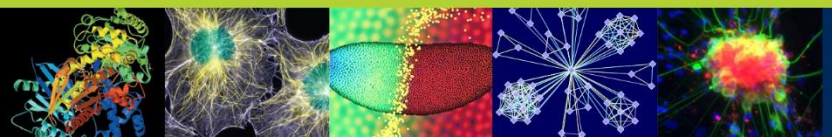


Sustainability Plan

- Depending on future needs and technological developments, we could enhance or expand the number of regional facilities in a second phase of Common Fund support.

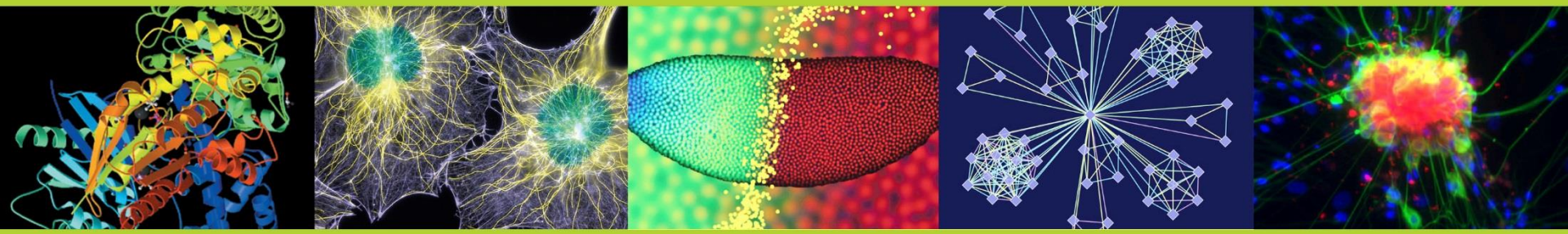
- Support for regional facility operations and maintenance would shift from the Common Fund to ICs, other federal agencies (e.g., NSF, DoE, DoD), other funders (e.g., HHMI) and industry.

    - Analogous to current model for supporting synchrotrons



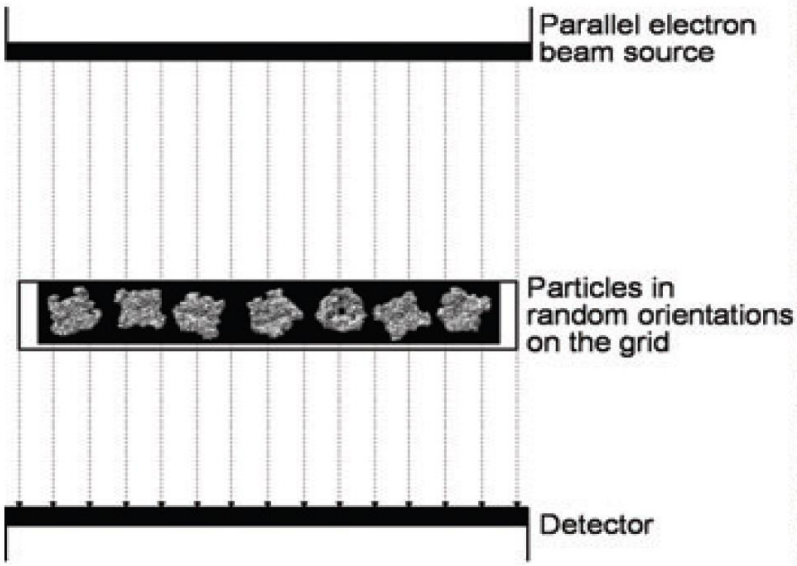
Thank You!

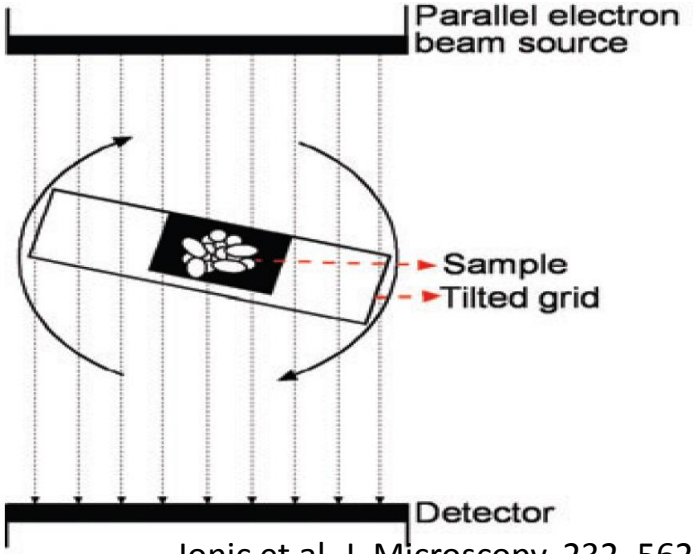
Questions?



EXTRA SLIDE

Technology Development for Tomography





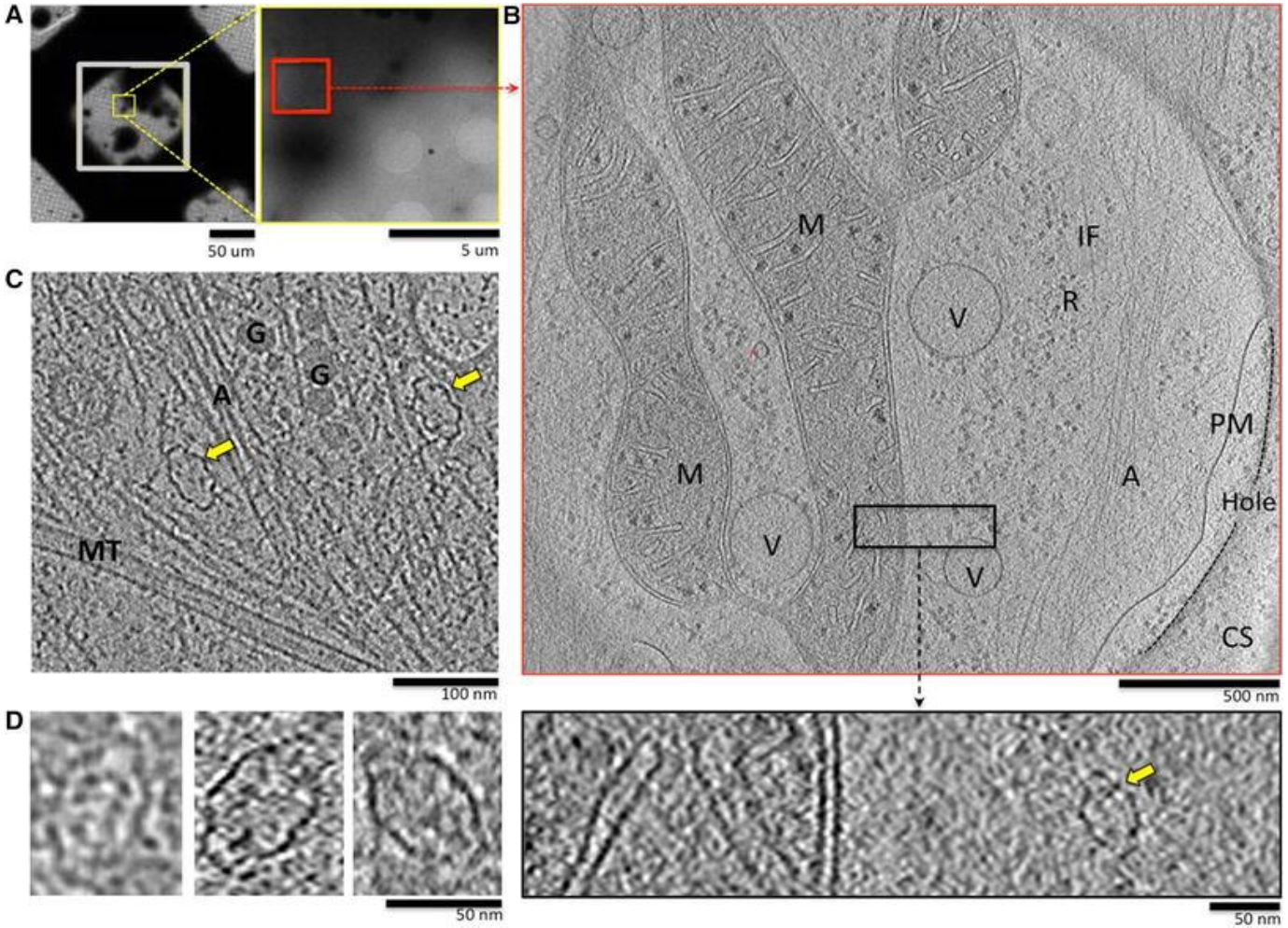
Jonic et al. J. Microscopy, 232, 562, 2008

Single Particle Reconstruction

For molecules in ice. Many particles, one orientation and image per particle, low electron dose, high resolution. Particles must all be the same. Ultimate achievable resolution 2Å or better.

Tomographic Reconstruction

For frozen hydrated cells. All images (~100) are recorded from the same specimen. One-of-a-kind objects. High electron dose. Ultimate achievable resolution will be limited by radiation damage (15-20Å?).



Woodward et al. Cell. Mol. Life Sci. 72, 3401, 2015

Tomographic reconstruction of frozen hydrated human cells. *A* actin, *G* granule, *IF* intermediate filament, *M* mitochondria, *MT* microtubule, *PM* plasma membrane, *R* ribosomes, *V* vesicle, *CS* edge of carbon support hole, yellow arrows, vault particles.