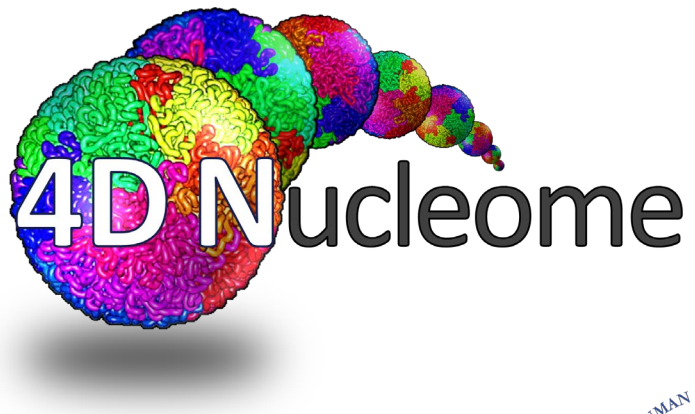
Common Fund 4DN Program: Proposal for a Second Stage



Ananda L Roy, PhD

Program Leader, 4DN

NIH Council Of Councils

May 17th, 2019

National Institutes of Health

Office of Strategic Coordination - The Common Fund

Finishing the Job: Understanding Genome Organization

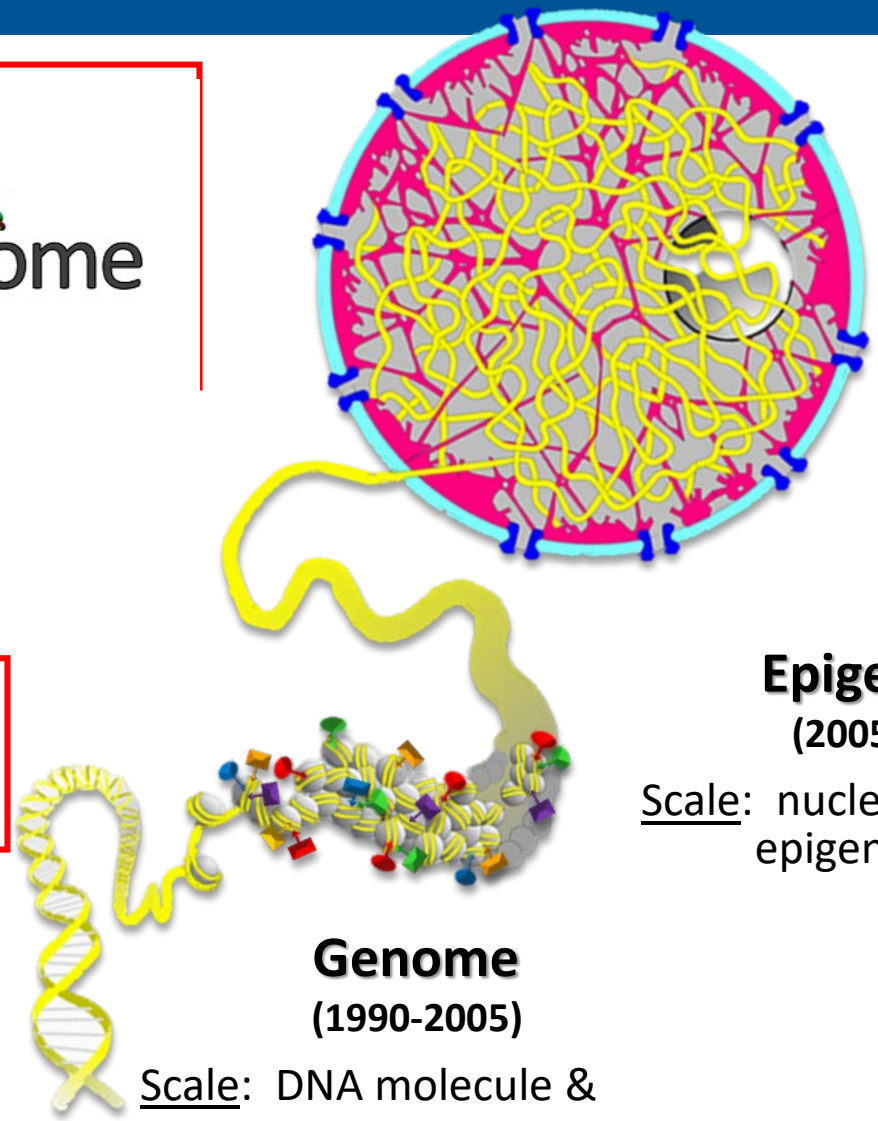
The Common Fund

4D Nucleome

ENCODE

ROADMAP epigenomics PROJECT

Human Genome Project



4D Nucleome
(2015-2022?)

Scale: cell nucleus & chromosome domains

Epigenome
(2005-2015)

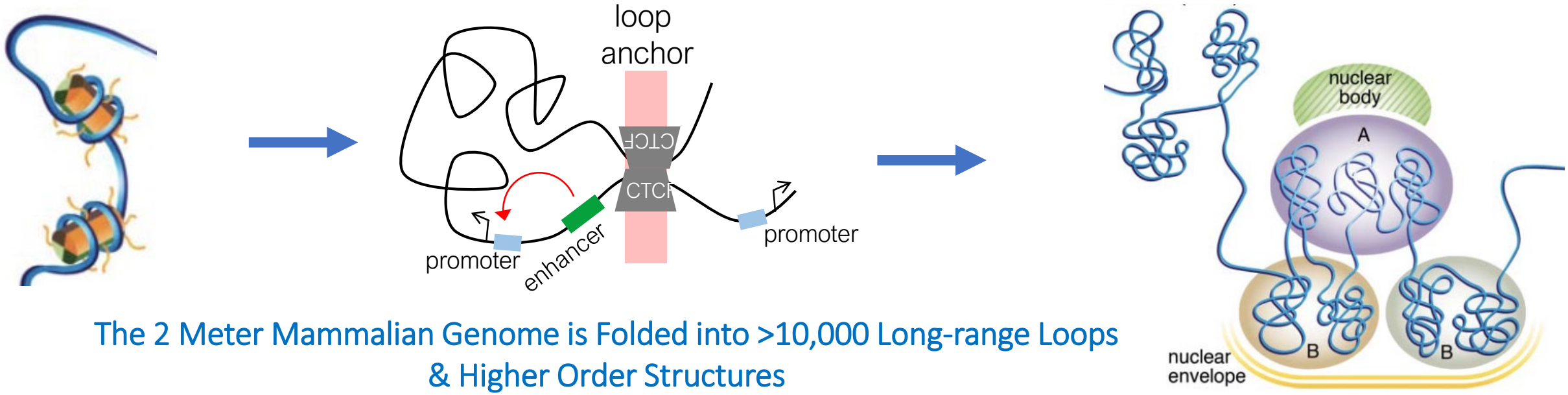
Scale: nucleosome & epigenetic marks

Genome
(1990-2005)

Scale: DNA molecule & sequence

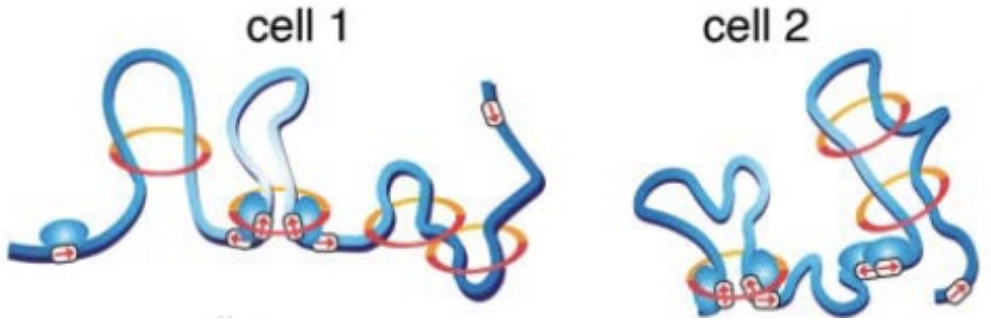
Red outline denotes Common Fund supported effort

Why Study Genome Topology?



The 2 Meter Mammalian Genome is Folded into >10,000 Long-range Loops & Higher Order Structures

- The spatial distribution of the genome is not random
- Chromatin is organized in chromosomal neighborhoods & associated with nuclear structures of unknown function
- This organization is dynamic in time and space



Rao et. al, *Cell*, 2014
Hansen et al., 2018

Why We Need a Common Fund Program

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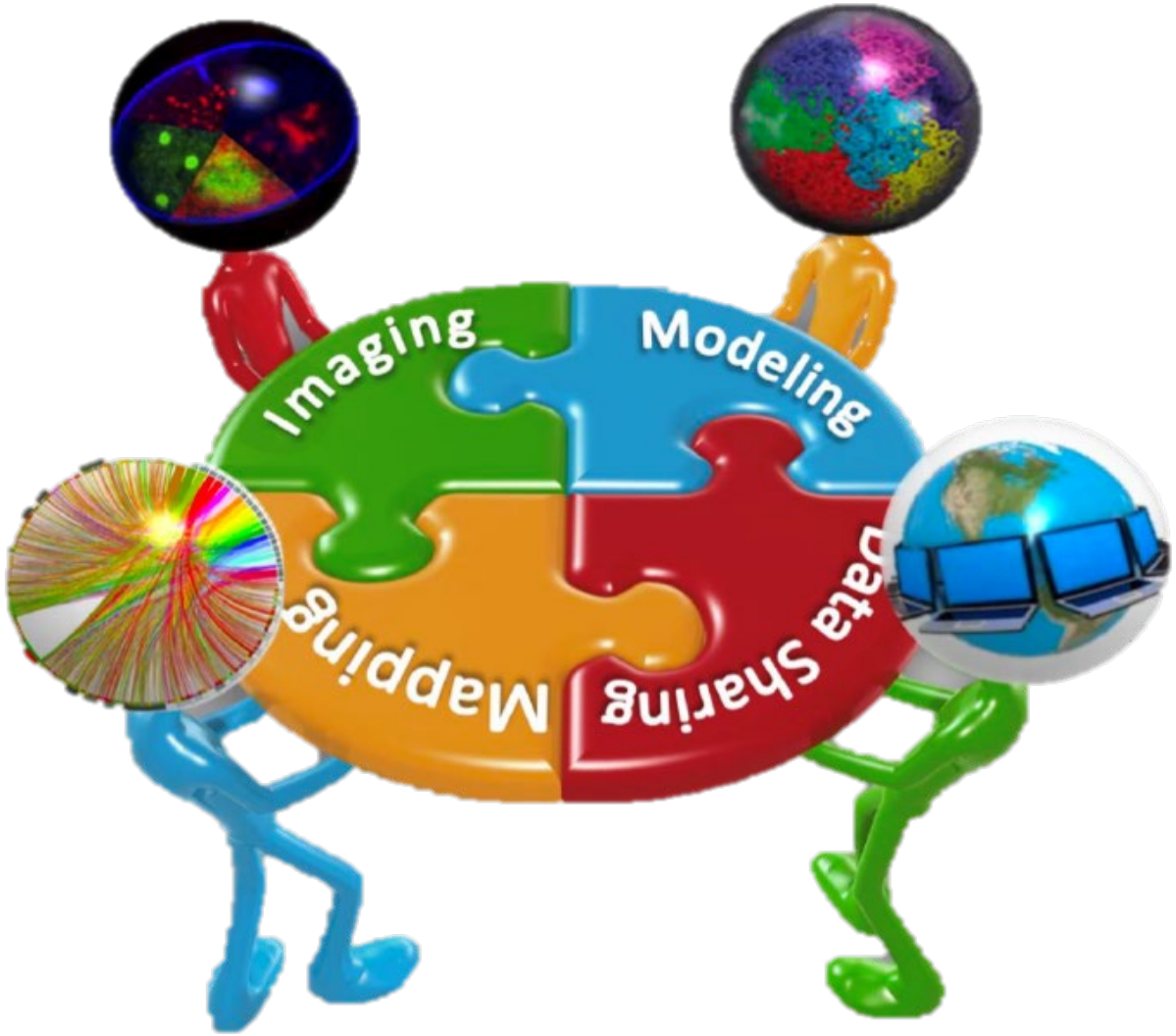

- Mapping the functional organization of the genome is **critical** to fully understand disease pathways and develop next generation diagnostics and therapeutics:
- 4DN tools and reference maps will **transform** many areas of biomedical research, but their development will require a **synergistic** effort;
- **Metrics and standards** need to be developed and adopted by a community of investigators, not just individuals.

Building on U.S. and International Efforts to Establish a Community of Practice

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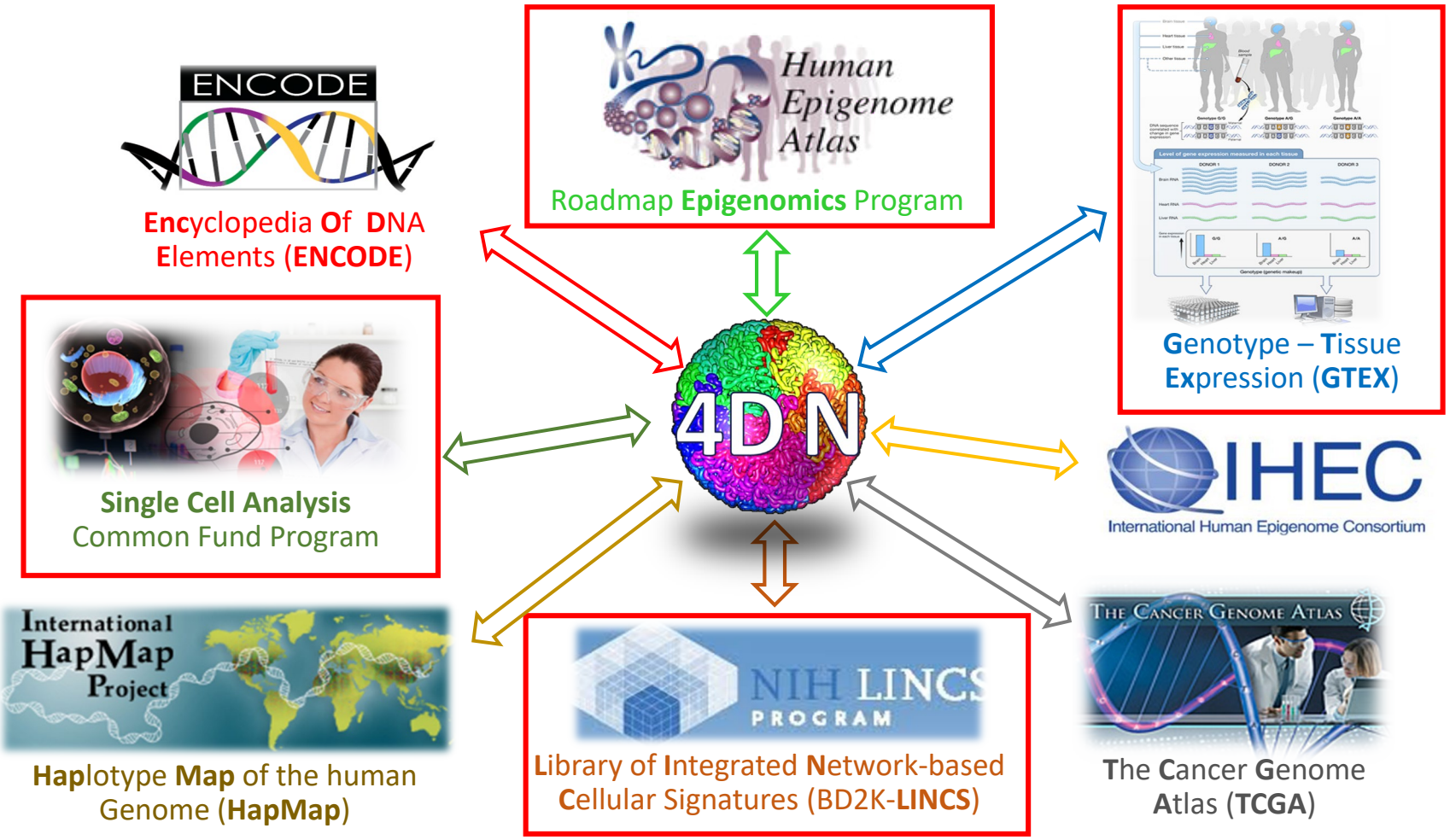

International data standards, rapid data and information exchange

Red outline denotes Common Fund supported effort

Goals of the 4DN Consortium – Stage 1

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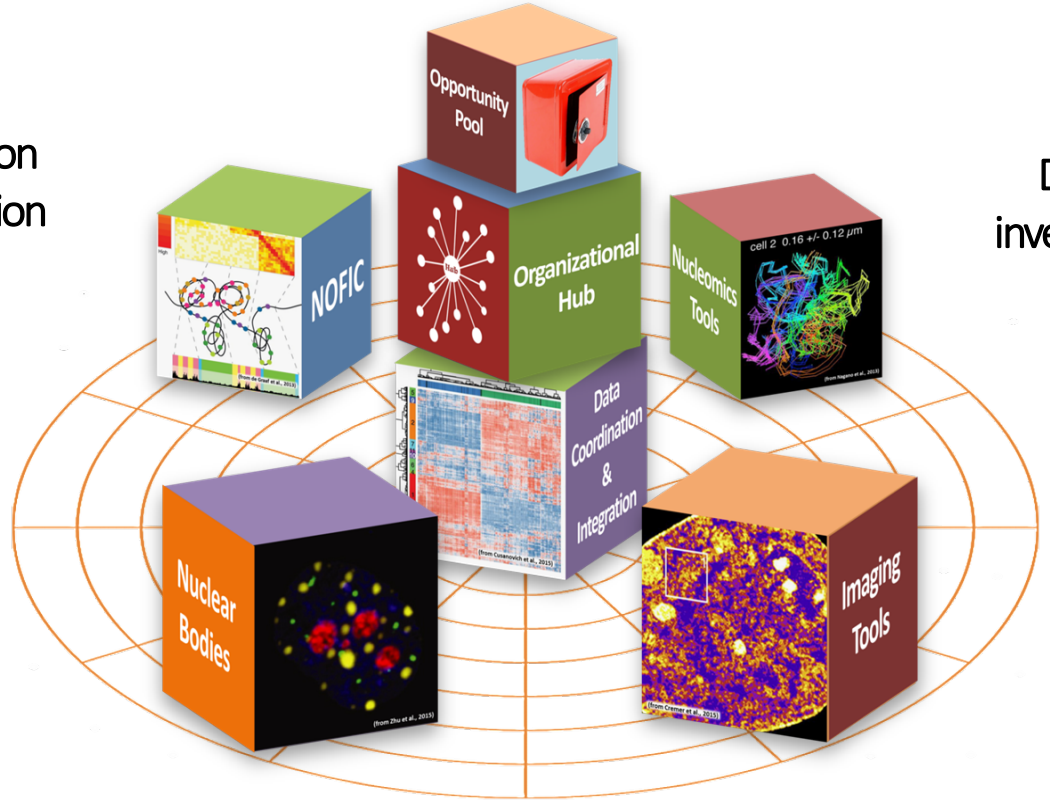
Administrative infrastructure: Develops and maintains the 4DN Portal, organizes outreach activities, coordinates the Opportunity Pool of funds (1 award)

Technology development and data production to understand 4D Nucleome structure/function (6 awards)



Develop & validate novel technologies to investigate the 4D organization of the genome (5 awards)

Develop tools & technologies to investigate the structure and function of nuclear bodies/domains (6 awards)

Develop & validate imaging technologies to visualize the structural/functional organization of the genome and its dynamics (9 awards)

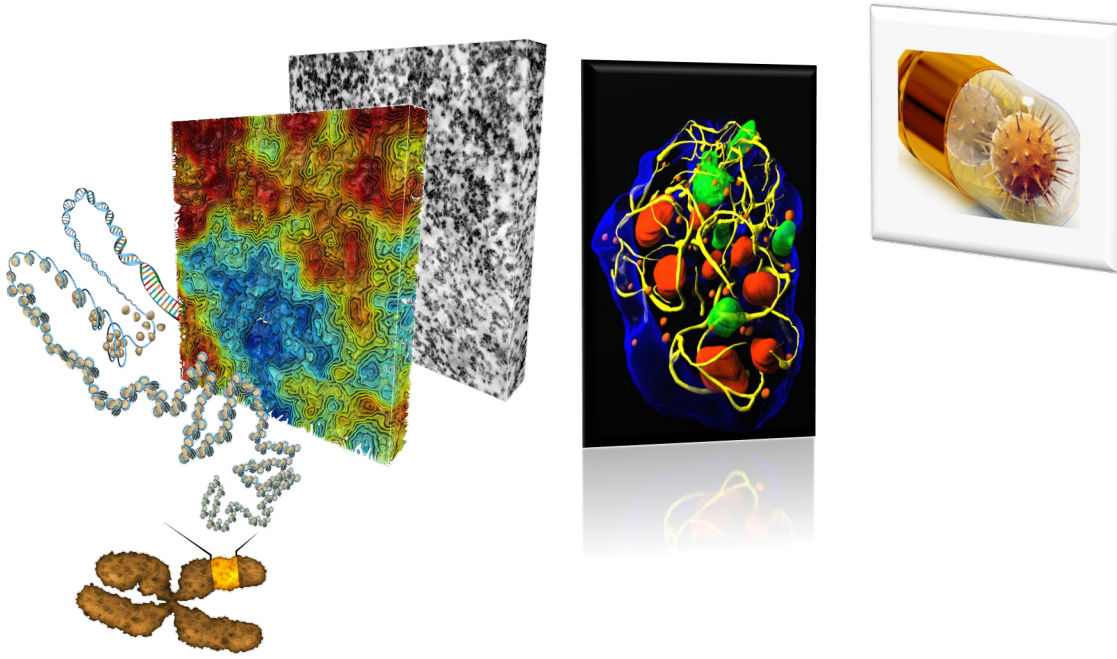
Collect, store, curate, & display data, metadata, and analysis tools
Disseminate to the scientific community (2 awards)

4DN Achievements: Consortium Structure Enabled Success

The Common Fund

- ~30 omics and ~25 imaging technologies in use
- ~60 new and existing software packages
- ~650 publicly available datasets: 256 omics datasets and ~25 protocols; 393 imaging datasets; Common cell line repository available to all
- Joint Analysis projects for data & technology integration in multiple cell lines; 8 omics pipeline in use
- A computational method (SPRITE) for estimating 3D spatial distance in the nucleus; Optogenetic method to study nuclear structure-function

Nearly 300 publications



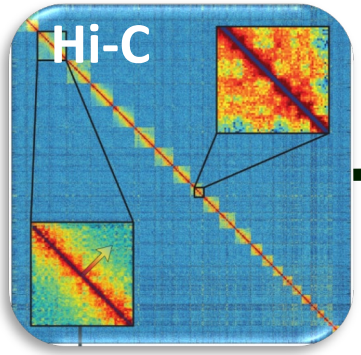
ChromeEMT: Visualizing 3D chromatin structure & compaction in interphase & mitotic cells

Clodagh C. O'Shea, 2017

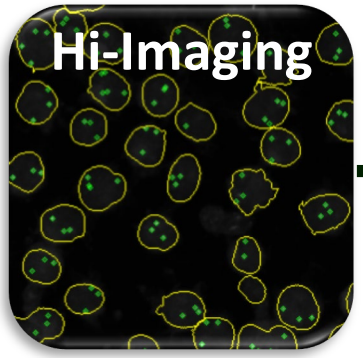
https://data.4dnucleome.org

Merging ‘Omics with Imaging: Single Cell Analysis Reveals Heterogeneity

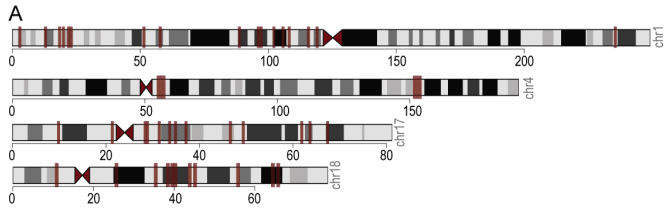
The Common Fund



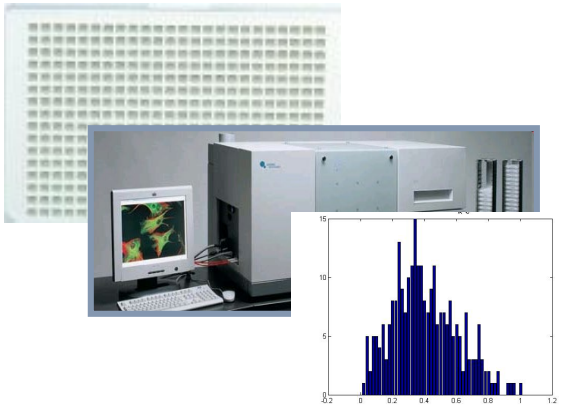
10^6 cells
Population-averages
Interaction data



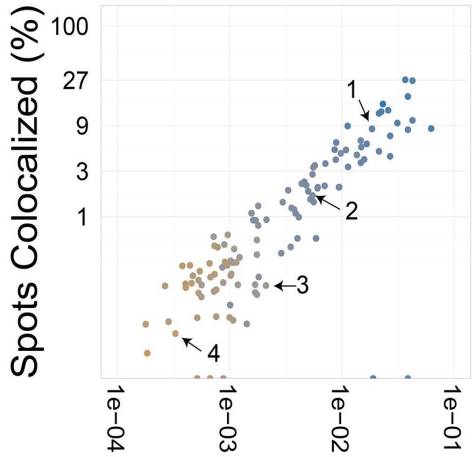
1000 cells
Single cell data
Spatial information

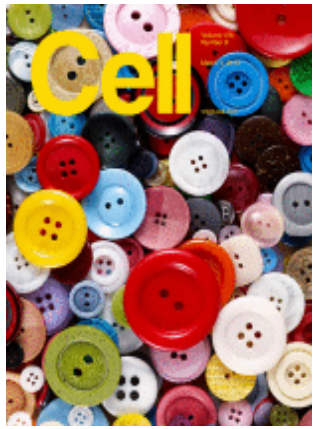


Imaging probes targeting 200 Hi-C interactions



3D location of interaction partners
Distance measurements





New Information:
Frequency of interactions in single cells Allele-specific behavior of interactions

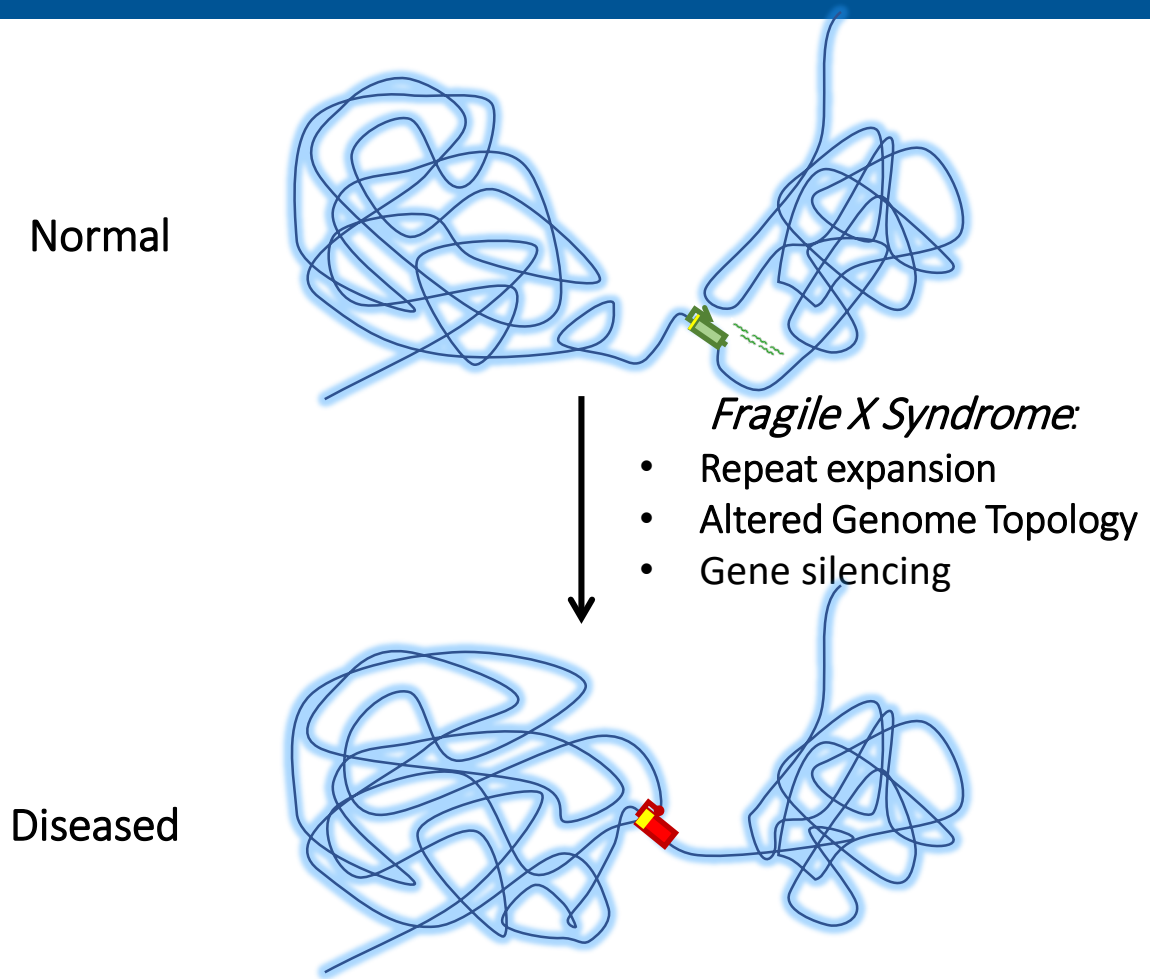
New Insight:
The organization of the genome is highly variable in individual cells

New Opportunities:
Probe the stochasticity of gene expression in single cells
Constrain structural models of genomes

Finn, Misteli, Cell, 2019

Rewired Genome Topology in Neurological Disorders

The Common Fund



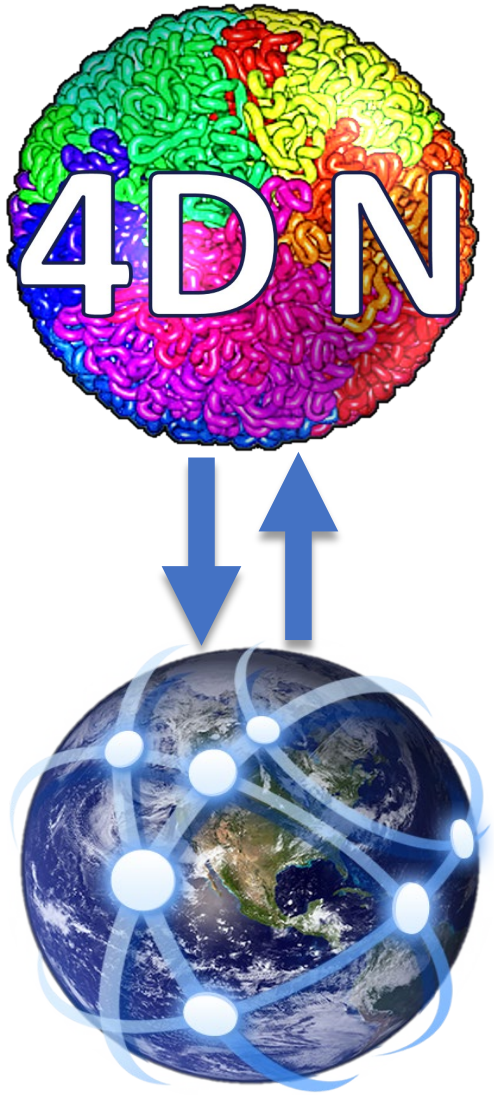
- Nearly all short tandem repeat tracts susceptible to unstable expansion co-localize to 3D chromatin domain boundaries
- Boundary encompassing *Fmr1* is severely disrupted in Fragile X Syndrome in a manner that correlates with pathogenic gene silencing

James Sun*, Linda Zhou*.....Phillips-Cremins, *Cell*, 2018

Outreach and Partnerships to Build Community of Practice

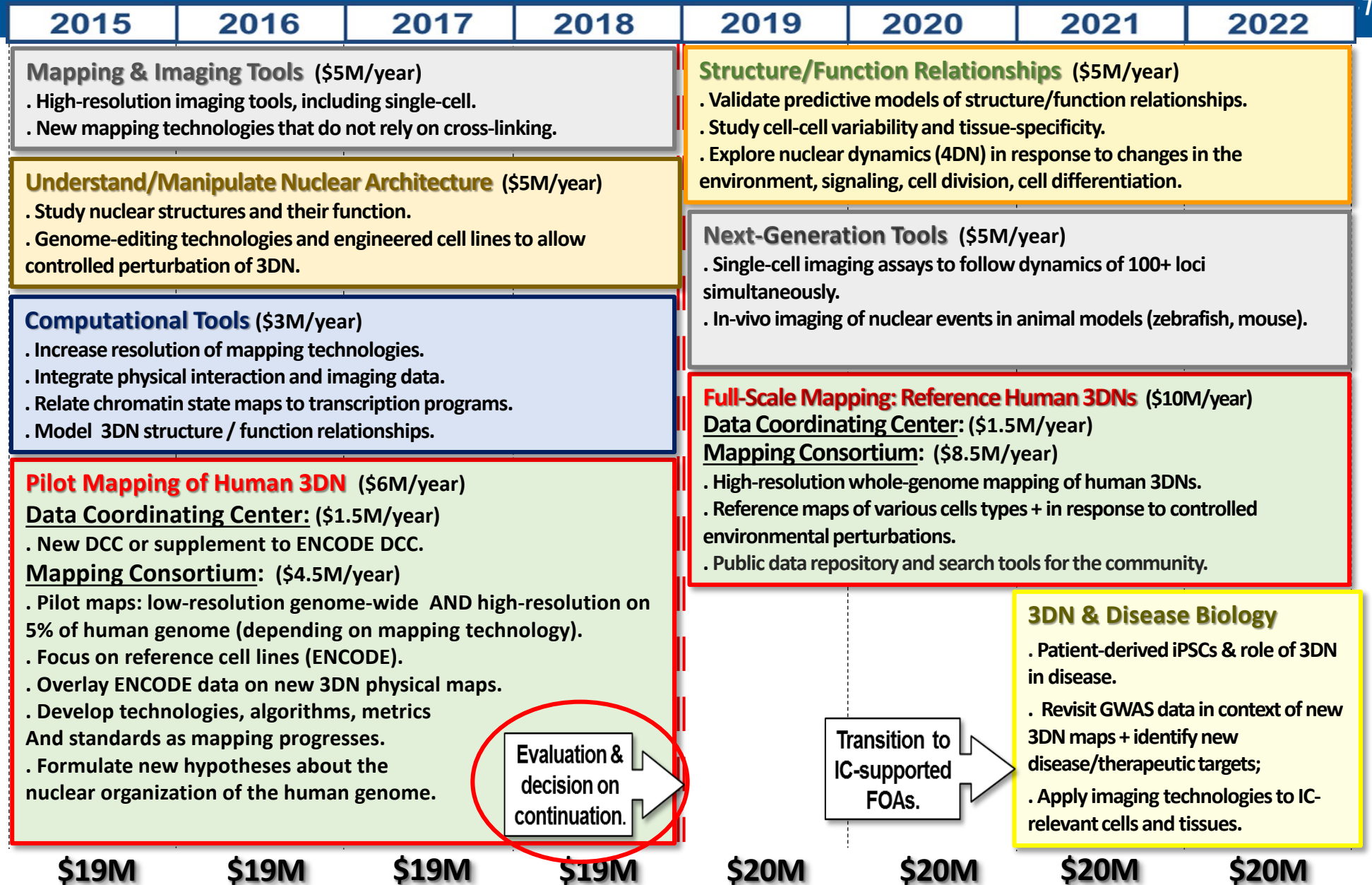
The Common Fund

- Early sharing of pre-prints through bioRxiv (2016)
- Transformative Collaborative Project Awards (2016)
- Joining the International Human Epigenome Consortium (2017)
- Jointly organized 4DN-American Society of Cell Biology Satellite Meetings: Bridging the 4D Genome with Cell Biology (2018-2019)
- Opening 4DN annual meetings to the public (2018-2019)
- 4DN Associate Membership (2018)
- Collaboration with ENCODE (2018)
- Collaboration with AICS (2018)



Initial Timeline and Budgets from 2014

The Common Fund



4DN Assessment and Planning for Stage 2

The Common Fund

- **4DN focus group webinars:**

  NIH staff solicited two separate panels of non-4DN investigators and non chromatin biologists. Identification of gaps in knowledge and need for further development in this space were consistent between the two groups.

- **Community feedback through the 2018 4DN Request For Information (RFI):**

  60 responses were collected from 4DN and non-4DN investigators worldwide: overlapping areas were identified

- **4DN-relevant NIH-wide portfolio analysis:**

  4DN research, technologies and publications are having a meaningful impact on the field

Stage 2 Challenges Identified

The Common Fund

- **Tools to identify the molecular machinery behind genome organization and function (proteins, ncRNAs, elements and properties contributing to nuclear compartmentalization, etc.**
- **Analysis of structure-function relationships in live cells using disruptors of genome architecture**
- **Single cell-resolution technologies for tissues, organoids and animal models – moving away from cultured cells; analysis over the lifespan and in health vs disease**
- **Technology development to assess relationship between genome organization, genetic and epigenetic signatures, and disease risk**
- **User-friendly technologies, databases, analytical and visualization tools**
- **Navigable reference maps to describe 4DN organization and dynamics for distinct population of cells and cellular states**

Proposed 4DN Stage 2 Initiatives

The Common Fund

Initiative 1: Chromatin Dynamics and Function

Interdisciplinary consortium to develop a comprehensive suite of technologies and analytical tools to describe high resolution nuclear/chromatin dynamics in individual cells

Goal: *To develop and apply tools to study chromatin dynamics in live cells; develop tools to model nuclear organization dynamics during cell division and differentiation; develop strategies to perturb nuclear organization to understand structure/function; develop approaches to define requirements for specific or optimal gene function.*

Initiative 2: Data Generation, Integration, Modeling and Visualization

Interdisciplinary teams to produce reference datasets through application of robust and complementary technologies to a limited number of consensus cell lines and/or 3D systems

Goal: *Produce navigable 4D reference maps and models of genome organization.*

Initiative 3: Nuclear Architecture over the Lifespan and in Human Health and Disease

Individual projects to investigate the role of nuclear organization during development and lifespan and in health and disease

Goal: *Develop and apply tools to investigate the role of nuclear organization during development and lifespan and in human health and disease*.

Proposed 4DN Stage 2 Initiatives

The Common Fund

Initiative 4: 4DN Organizational Hub

Goal: ***Coordinating center for the Network, promoting cross-site interaction to develop and disseminate standards for the field, enhancing collaborations among 4DN investigators, maintaining community website and serve as the focal point for outreach.***

Initiative 5: Data Coordination & Integration Center (4DN-DCIC)

Goal: ***To track, store, and display all data generated by the 4D Nucleome Program and provide a Data Analysis Center to assist with integrated analyses and with the development of metrics and standards to be adopted by the community at large. All data generated by 4D Nucleome participants will be rapidly released to the public.***

Stage 2 Timeline and Budget

The Common Fund

2020	2021	2022	2023	2024

Chromatin Dynamics and Function ($10M/year)
- Interdisciplinary consortium to study nuclear/chromatin dynamics in individual cells
- Tools to study chromatin dynamics in live cells
- Tools to model nuclear organization dynamics during cell division/differentiation

Data Generation, Integration, Modeling, Visualization ($8M/year)
- Interdisciplinary teams to produce navigable 4D reference maps and models of genome organization
- Limited number of consensus cell lines or 3D systems

Nuclear Architecture Over the Lifespan and in Human Health/Disease ($6M/year)
- Individual projects to investigate the role of nuclear organization over lifetime and in health/disease
- Using primary cells, organoids, organs-on-chips, primary tissues, model organisms

4DN Organizational Hub ($1.5M/year)
- Coordinating center for network, promoting cross-site interactions
- Develop/disseminate standards, enhance collaborations, maintain community website, outreach

Data Coordination and Integration Center ($2.5M/year)
- Track, store, display all date generated by 4DN program
- Data Analysis Center to assist with integrated analysis and development of metrics/standards

$28M	$28M	$28M	$28M	$28M

Stage 2 total = $141.5M*

**budget also includes $0.3M/year in Research Management Support for NIH staff salary, travel, and NIH-organized workshops*

The NIH 4DN Working Group

The Common Fund

Program Co-Chairs:

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Phil Smith (NIDDK)
*Roderic Pettigrew (NIBIB)**

Program Coordinators:

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Judy Mietz (NCI)
*Krishna Kandarpa (NIBIB)**

Common Fund Program Leader:
Ananda L. Roy (OD)

Coordinating Team:

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Ian Fingerman (NCI)
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Mike Pazin (NHGRI)

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Max Guo (NIA)
Matt Reilly (NIAAA)
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Geetha Senthil (NIMH)
Fred Tyson (NIEHS)
Paul Barrett (OD)
Jill Beaver(OD)

**Former*