3D Nucleome Program

January, 2014
Council of Councils

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Finishing the Job:
Understanding Genome Organization

Genome
(1990-2005)

Scale: DNA molecule & sequence

Human Genome Project

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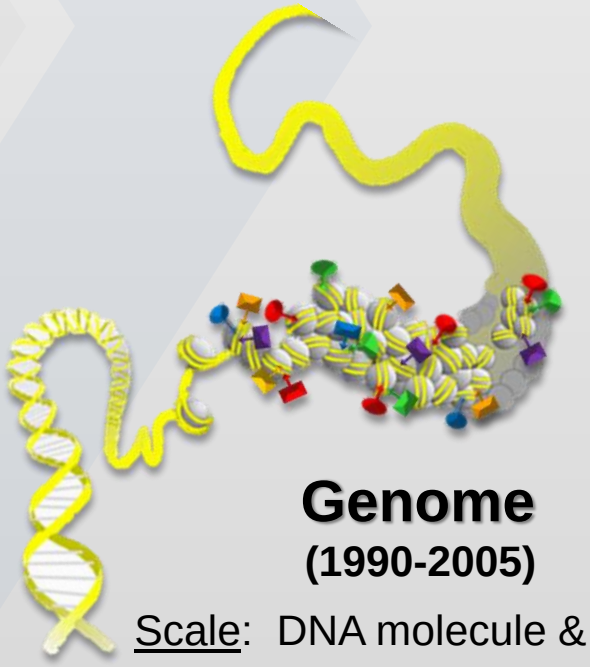
Finishing the Job:
Understanding Genome Organization



Epigenome
(2005-2015)

Scale: nucleosome & epigenetic marks

Genome
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Scale: DNA molecule & sequence

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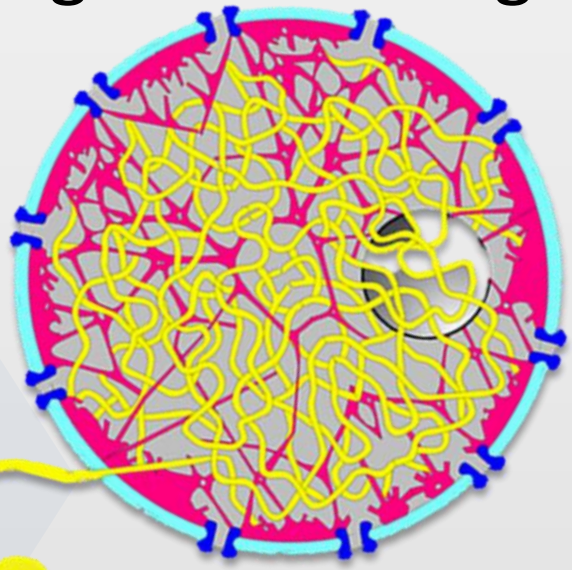
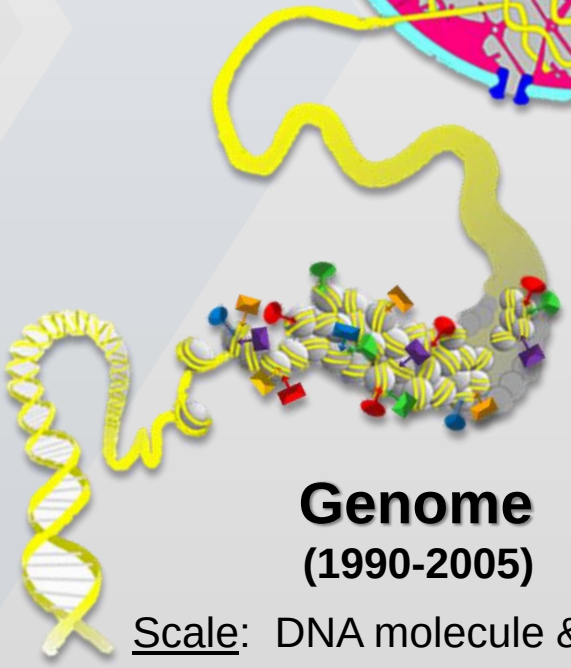
Finishing the Job:
Understanding Genome Organization



3D Nucleome
(2015-2022?)

Scale: cell nucleus & chromosome domains



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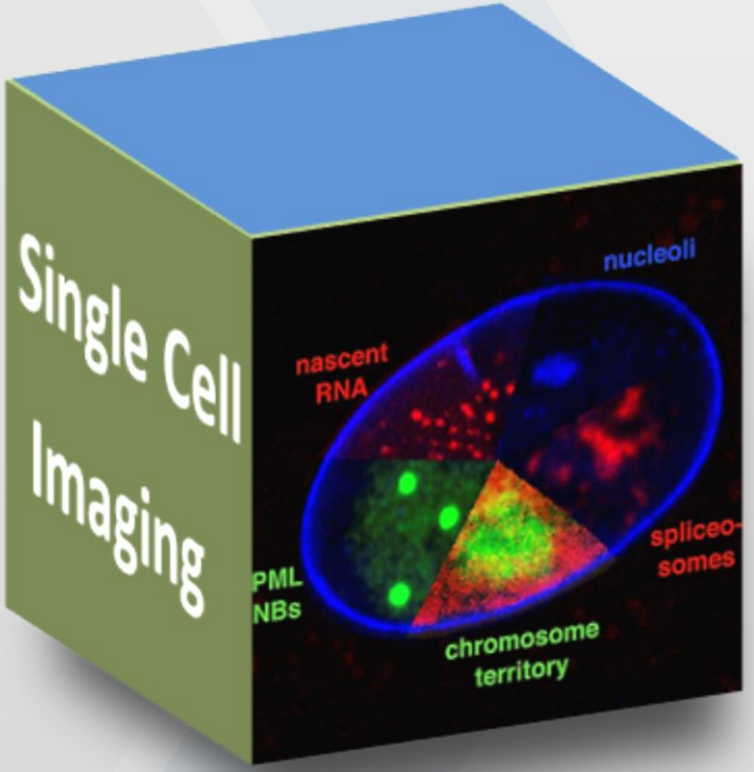
Mounting Evidence:
The Third Dimension Matters



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

Mounting Evidence:
The Third Dimension Matters

- Alterations of genome organization are associated with laminopathies, cancer and premature aging syndromes;

- Features are often cell- or tissue-specific, and include:
  - loss of genome integrity;
  - global changes in epigenetic marks;
  - widespread modifications of gene expression programs.

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Mounting Evidence:
The Third Dimension Matters

- 93% of disease-associated genetic variants reside in noncoding regulatory sequences with unknown targets;
- Mapping physical interactions between variants and promoters will help identify disease-associated target genes;
- Disease variants may belong to disease-specific modules within the nucleus.

Mounting Evidence:

The Third Dimension Matters

- **C**hromosome **C**onformation **C**apture (**3C**) allows mapping of long-range looping interactions between genes and regulatory elements.

- First-generation maps suggest that the genome is organized in physically defined **T**ranscription **A**ssociated **D**omains (**TAD**s) and “transcription factories”.

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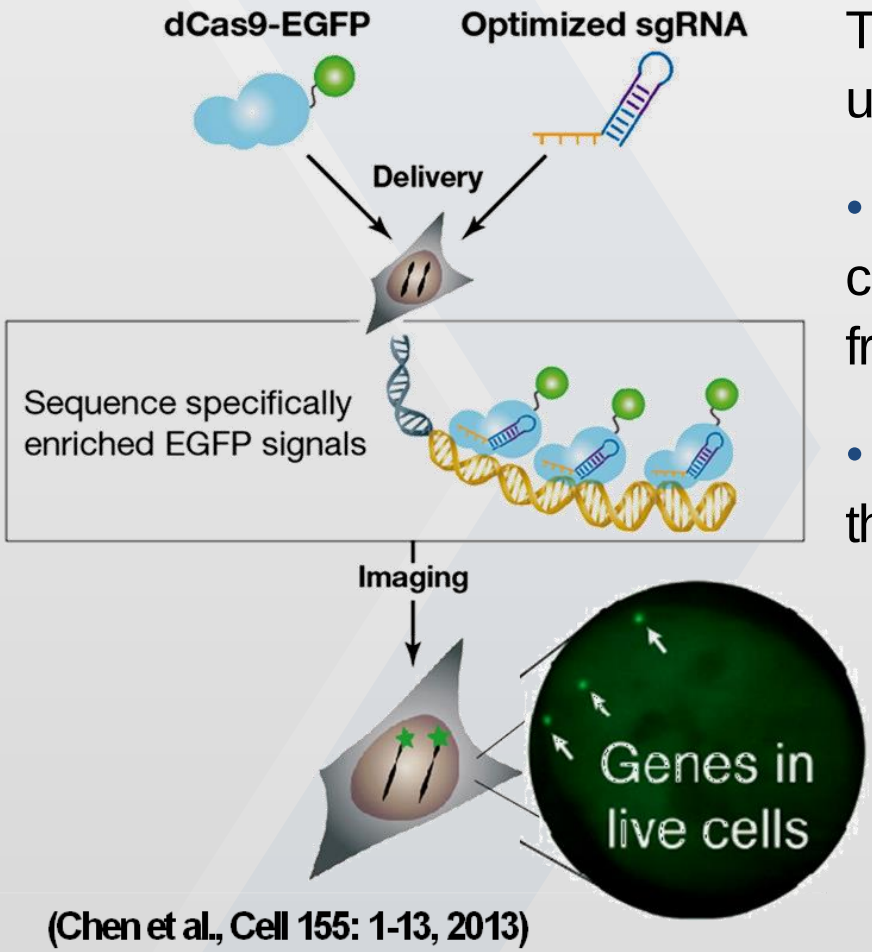
A CRISPR Picture Of The Nuclear Genome



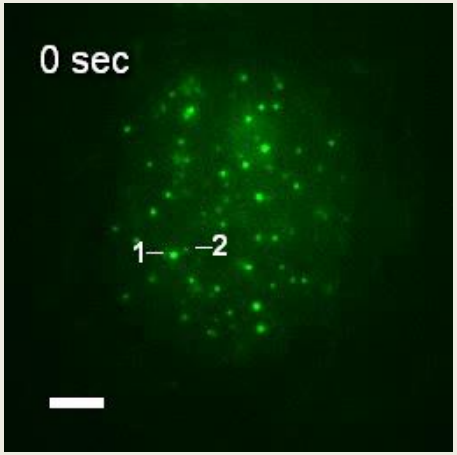
(Chen et al., Cell 155: 1-13, 2013)

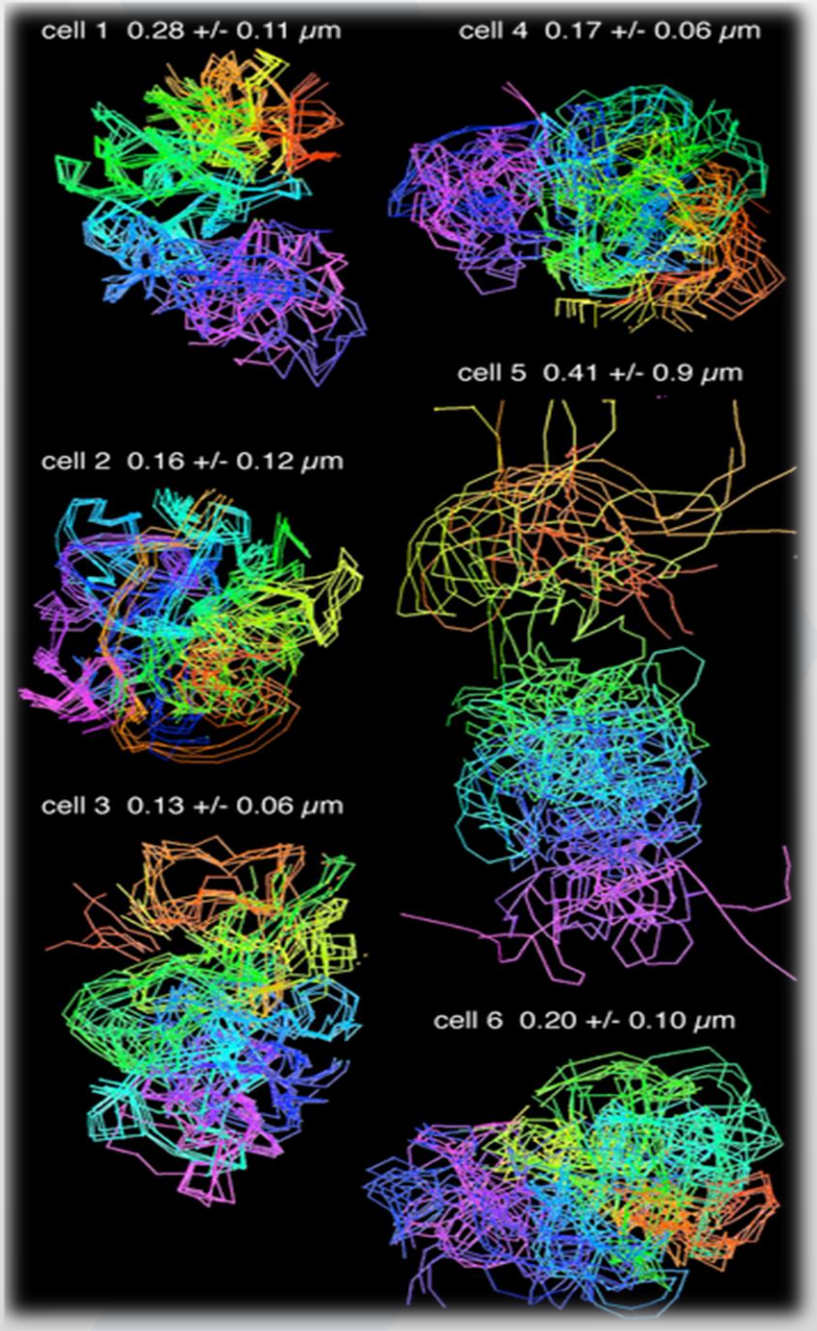
The gene-editing **CRISPR/Cas** system can be used to:

- modify gene regions & regulatory elements in cells to test the organizational models inferred from the mapping of chromatin interactions;
- directly image genetic elements and follow them dynamically in live cells.

Imaging telomere dynamics:

(Lei Qi Lab, UCSF)





Single-cell Genome Conformation Capture (Hi-C)

- Single-cell Hi-C imaging can detect thousands of simultaneous chromatin contacts within a nucleus.

- Individual chromosomes maintain domain organization at the megabase scale, but chromosome structures vary from cell to cell at larger scales.

From Nagano T et al., *Nature* 502: 59–64, 03 October, 2013

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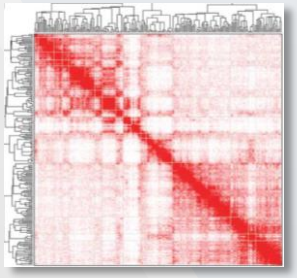
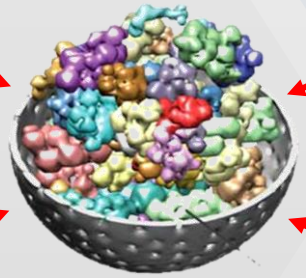
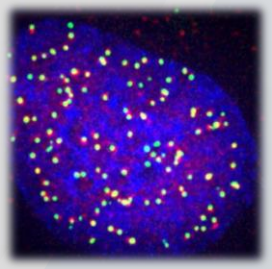
Deliverables of the 3DN Program



Global interactions between gene loci and regulatory elements.



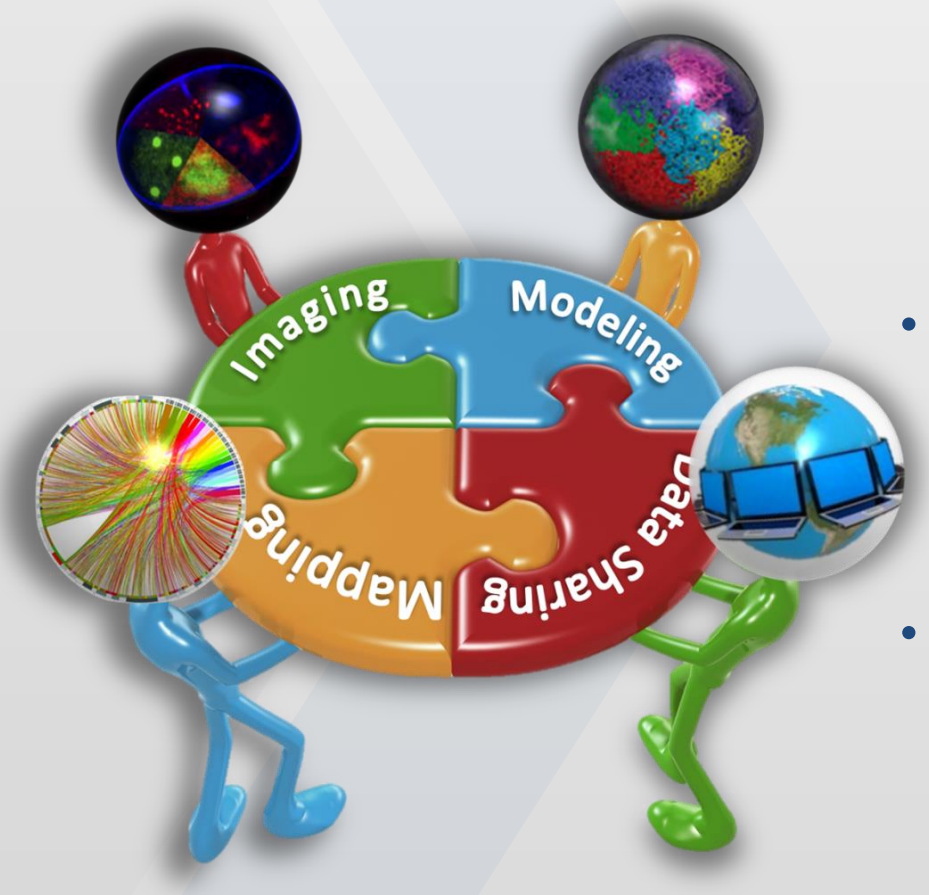
Predictive modeling of structure/function relationships.



Imaging dynamics of nuclear interactions in single cells.

- **Next generation tools** to explore the relationship between nuclear organization and regulation of gene expression programs in development and disease;
- **Reference maps** of the 3D architecture of the interphase nucleus for a variety of human cells and tissues;
- **Predictive models** of genome structure/function relationships;
- **Model validation** through controlled disruption of nuclear architecture and single-cell imaging.

Why We Need A Common Fund Program



- Mapping the functional organization of the genome is **critical** to fully understand disease pathways and develop next generation diagnostics and therapeutics;
- 3DN 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.

3DN Initiatives, Timeline And Budgets

2015	2016	2017	2018	2019	2020	2021	2022

Mapping & Imaging Tools ($5M/year)
. High-resolution imaging tools, including single-cell.
. New mapping technologies that do not rely on cross-linking.

Understand/Manipulate Nuclear Architecture ($5M/year)
. Study nuclear structures and their function.
. Genome-editing technologies and engineered cell lines to allow controlled perturbation of 3DN.

Computational Tools ($3M/year)
. Increase resolution of mapping technologies.
. Integrate physical interaction and imaging data.
. Relate chromatin state maps to transcription programs.
. Model 3DN structure / function relationships.

Pilot Mapping of Human 3DN ($6M/year)
Data Coordinating Center: ($1.5M/year)
. New DCC or supplement to ENCODE DCC.
Mapping Consortium: ($4.5M/year)
. Pilot maps: low-resolution genome-wide AND high-resolution on 5% of human genome (depending on mapping technology).
. Focus on reference cell lines (ENCODE).
. Overlay ENCODE data on new 3DN physical maps.
. Develop technologies, algorithms, metrics And standards as mapping progresses.
. Formulate new hypotheses about the nuclear organization of the human genome.

Evaluation & decision on continuation.

Structure/Function Relationships ($5M/year)
Validate predictive models of structure/function relationships.
. Study cell-cell variability and tissue-specificity.
Explore nuclear dynamics (4DN) in response to changes in the environment, signaling, cell division, cell differentiation.

Next-Generation Tools ($5M/year)
. Single-cell imaging assays to follow dynamics of 100+ loci simultaneously.
. In-vivo imaging of nuclear events in animal models (zebrafish, mouse).

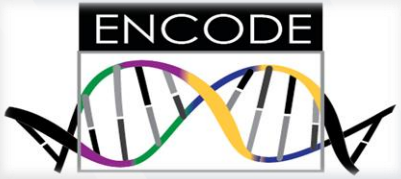
Full-Scale Mapping: Reference Human 3DNs ($10M/year)
Data Coordinating Center: ($1.5M/year)
Mapping Consortium: ($8.5M/year)
. High-resolution whole-genome mapping of human 3DNs.
. Reference maps of various cells types + in response to controlled environmental perturbations.
. Public data repository and search tools for the community.

Transition to IC-supported FOAs.

3DN & Disease Biology
. Patient-derived iPSCs & role of 3DN in disease.
. Revisit GWAS data in context of new 3DN maps + identify new disease/therapeutic targets;
. Apply imaging technologies to IC-relevant cells and tissues.

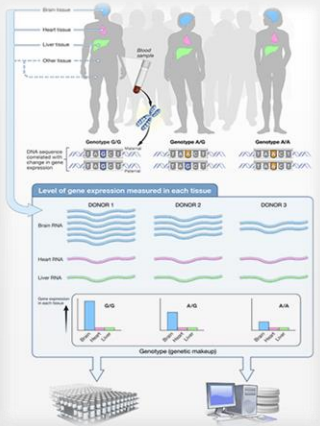
$19M	$19M	$19M	$19M	$20M	$20M	$20M	$20M

Building On U.S. And International Efforts



Encyclopedia **O**f **D**NA **E**lements (**ENCODE**)

Roadmap **Epigenomics** Program



Genotype – **T**issue **Ex**pression (**GTEX**)

Single Cell Analysis
Common Fund Program

Haplotype **Map** of the human Genome (**HapMap**)

Library of **I**ntegrated **N**etwork-based **C**ellular Signatures (BD2K-**LINCS**)

The **C**ancer **G**enome **A**tlas (**TCGA**)

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3DN Working Group

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Phil Smith, **NIDDK**

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Olivier Blondel, **NIDDK**

Lisa H. Chadwick, **NIEHS**

Richard Conroy, **NIBIB/Single Cell**

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Expert Panel

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