4D Nucleome

Applicant Webinar

January 21, 2020

We will start @ 1:05 PM EST

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Webinar Logistics

WebEx

- Slides used in this webinar will be available on the Common Fund Website: https://commonfund.nih.gov/4Dnucleome
- A list of commonly asked **FAQs** are posted and will be updated on the Common Fund Website: https://commonfund.nih.gov/4Dnucleome/faq
- All attendees will be muted for the entire webinar. You will have the opportunity to ask questions during Q&A session at the end of webinar.
- Please ask your questions via WebEx Chat or via email to 4DNucleome@mail.nih.gov.
- This webinar is being recorded for internal NIH use only.

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Agenda

- **Introduction & WebEx overview** – 3 min; Ian Fingerman (NCI)
- **Common Fund and 4DN overview** – 5 min; Ananda Roy, Common Fund (OD/OSC)
- **Application guidelines and Cooperative Agreements**– 5 min; Olivier Blondel (NIDDK)
- **Review procedure** – 5 min; David Balasundaram (CSR)
- **Funding announcement overviews** – 20 min (5 min each); Olivier Blondel (NIDDK), Mike Pazin (NHGRI), Lisa Postow (NHLBI)
- **Q&A session** – Until we run out of questions or 60 min, whichever comes first

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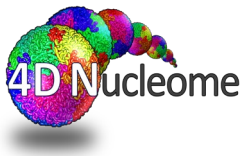
Criteria for Common Fund Programs

The Common Fund

- **Transformative:** Must have high potential to dramatically affect biomedical and/or behavioral research over the next decade
- **Catalytic**: Must achieve a defined set of high impact goals within 5-10 years
- **Synergistic:** Outcomes must synergistically promote and advance individual missions of NIH Institutes and Centers to benefit health
- **Cross-cutting:** Program areas must cut across missions of multiple NIH Institutes and Centers, be relevant to multiple diseases or conditions, and be sufficiently complex to require a coordinated, trans-NIH approach
- **Unique:** Must be something no other entity is likely or able to do

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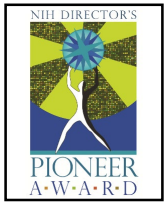

Why We Need a Common Fund 4DN Program

The Common Fund

- 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.

Goal was to establish a coordinated effort with other NIH and international initiatives to build a community of practice with rapid data sharing and information exchange.

Key Deliverables 4DN Phase I

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- **Next-generation genomic, imaging and computational tools to explore nuclear organization and its relationship with the regulation of gene expression programs;**
- **Pilot reference maps of the 3D architecture of the interphase nucleus for a select set of eukaryotic cells;**
- **Validated predictive models of genome conformation/function relationships;**
- **Next-generation tools to explore nuclear dynamics through controlled disruption of nuclear architecture and imaging in live cells and tissue;**
- **Community data and metadata standards.**

Goals of 4DN Phase II

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- **Understanding the biological significance of nuclear architecture through controlled perturbation;**
- **Determining how genome organization changes in biological time scales and in different diseases via biophysical, biochemical and visualization studies;**
- **Ascertain how we can use this information to improve human health.**

The ultimately goal for this endeavor is to deliver data and tools to be used by the broader community to understand and address the role of nuclear organization in health, disease and in lifespan.

4DN Stage 2 Timeline & Budget

The Common Fund

2020	2021	2022	2023	2024

Real Time Chromatin Dynamics and Function (U01) ($7M/year)

- **To support the development and application of tools that would enable the monitoring in real-time of the dynamic three-dimensional structure of mammalian genomes and provide insight into how organizing components of 4D genome architecture affect biological processes in live cells.**

4DN Centers for Data Integration, Modeling and Visualization (UM1) ($7M/year)

- **The purpose of this FOA is to solicit applications for research projects to generate reference datasets and to create navigable maps for the study of the spatial and temporal organization of the nucleus, using genomic and imaging data as well as newly developed**

4DN Organization and Function in Human Health and Disease (U01) ($10M/year)

- **To support projects that apply new or existing tools to monitor and/or manipulate the 4D nucleome in the context of human health and disease. Any human disease or biological process relevant to NIH's mission may be proposed including environmental exposures (e.g. addictive substances, toxins, psychosocial stress), or studies across development or lifespan. Other relevant timeframes may include but are not limited to: circadian rhythms, fasting and feeding cycles, reproductive cycles, and sleep/wake cycles.**

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

4D Nucleome

Information common to all RFA

Application Considerations

- **Read RFA carefully for suggestions on what to include in your application!!!**
- Submit a couple days early, do not wait until the last minute!
- Provide timeline and detailed quantitative annual milestones spanning funding period.
- Key personnel/consultants/team should demonstrate strong scientific expertise.
- Applicants are eligible to apply to multiple FOAs.
- This is a consortium effort.
  - Applicants will be expected to work collaboratively with all members of the 4D Nucleome Network, the 4DN Network OH and the 4DN DCIC
  - Applicants will help develop common standards, metrics for data generation and storage, and data analysis and visualization tools that can be used by the broader scientific community.
  - Collaborative projects across the network will be encouraged.

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Application Considerations

- All applications, regardless of the amount of direct costs requested for any one year, should **address a Data Sharing Plan**.

- **All awardees will be required to comply with existing 4DN Network policies.** This includes the data release and use policy, publication policy, and software sharing policy. See: https://www.4dnucleome.org/policies.html

- Applicants should **explicitly state their willingness to cooperate with the 4DN Program, 4DN Network Steering Committee (4DN-SC), NIH staff, and other stakeholders** in the development and implementation of research and standardization methods, data standards and formats, metadata requirements, and quality control metrics for this resource.

- Protocol, tool and reagent sharing: The applicant should **discuss plans for sharing and distribution of non-data resources that will be generated by the proposed project,** including models, protocols, computational tools, biomaterials, and reagents. As one of the essential goals of this program, NIH intends that tools and reagents generated by the 4DN Network be broadly available and distributed at minimal cost, and without undue intellectual property constraints, so that they can be as widely used as possible.

Application Budget Considerations

- Collaborative research opportunities

  - Funds equivalent to 15% (RFA-RM-20-003) or 20% (RFA-RM-20-005, RFA-RM-20-006) must be allocated to support new collaborative research opportunities in consultation with NIH staff in grant funding years 2, 3, 4 and 5.
  - The collaborative project does not need to be completely defined in the initial application, but applicants are encouraged to include a paragraph about a project that may be proposed in the future.

- Applicants must budget appropriate funds to support travel of investigators to the initial in-person 4DN Network kick-off meeting and to attend the annual 4DN Consortium meetings within the continental United States.

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These FOAs Use Cooperative Agreements (e.g. U01)

- Used when substantial programmatic involvement is anticipated between NIH and the recipient
- For roles and expectations see Cooperative Agreement "Terms and Conditions of Award" in FOA.
- For example:
  - Participate in 4D Nucleome annual meeting and in regular conference calls
  - Make satisfactory progress towards proposed scientific milestones

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Scientific Review Information

- Applications that are complete and responsive to the 4DN FOAs will be evaluated for scientific and technical merit by various Special Emphasis Panels (SEPs) convened by the Center for Scientific Review (CSR). Applications deemed unresponsive will be administratively withdrawn.
- Reviews will likely take place during the months of May through June, 2020.
- Meeting rosters will be posted online 30 days prior to the review meeting.
- For further review information, refer to **Section V** of the FOA – "**Application Review Information**". Read Review Criteria carefully.
- **Pay special attention and address "Specific to this FOA" review questions under each criterion.**

Scientific Review Information

- **Post Submission Materials:** NIH accepts limited information between the time of initial submission of the application and the time of initial peer review. Please see NOT-OD-19-083 for information https://grants.nih.gov/grants/guide/notice-files/NOT-OD-19-083.html. Post-submission materials must be received by the Scientific Review Officer (SRO) from the Authorized Organization Representative (AOR) of the applicant organization no later than 30 calendar days prior to the peer review meeting. Preprints and Other Interim Research Products (NOT-OD-17-050: https://grants.nih.gov/grants/guide/notice-files/not-od-17-050.html) are not accepted as post-submission materials because they do not represent unforeseen events.

- Questions regarding the review process may be directed to Dr. David Balasundaram at balasundaramd@csr.nih.gov.

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Information specific to individual RFA

Six Related Funding Opportunity Announcements

- Real Time Chromatin Dynamics and Function (U01) (RFA-RM-20-003): Support the development and application of tools for demonstrating how organizing components of 4D nucleome govern biological processes and will promote the generation of maps and models of the dynamic three-dimensional structure of the functional genome inside living cells.

- 4DN Centers for Data Integration, Modeling and Visualization (UM1) (RFA-RM-20-004): Support creation of reference models for the study of the spatial and temporal organization of the nucleus, using genomic and imaging data as well as newly developed visualization and analysis.

- 4DN Organization and Function in Human Health and Disease (U01) (RFA-RM-20-005): Support projects that apply new or existing tools to monitor and/or manipulate the 4D nucleome in the context of human health and disease.
- New Investigator Projects on 4DN Organization and Function in Human Health and Disease (U01) (RFA-RM-20-006): To support projects from scientists who are in the early stages of establishing an independent research career that apply new or existing tools to monitor and/or manipulate the 4D nucleome (4DN) in the context of human health and disease.
- Limited competition: 4D Nucleome Network Organizational Hub (U01) (RFA-RM-20-007)
- Limited competition: 4D Nucleome Network Data Coordination and Integration Center (U01) (RFA-RM-20-008)

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RFA-RM-20-003: Real Time Chromatin Dynamics and Function (U01 Clinical Trial Not Allowed)

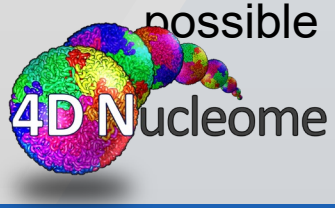
Contact: Olivier Blondel, Ph.D. (NIDDK) blondelol@niddk.nih.gov

Purpose

The CDF RFA will support the development and application of tools that would enable the monitoring in real-time of the dynamic three-dimensional structure of mammalian genomes and provide insight into how organizing components of 4D genome architecture affect biological processes in live cells.

Minimum requirements & research objectives

- To develop and combine next-generation tools and technologies to study chromatin dynamics in living cells, and generate corresponding high-content datasets;
- To develop tools to model dynamic nuclear structure during natural cellular transitions and explore the contribution of chromatin dynamics to biological processes in live mammalian cells;
- To work collaboratively with other CDF investigators to produce datasets, models and maps of three-dimensional chromatin dynamics of the highest possible resolution on a series of common cell types or cell systems.



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RFA-RM-20-003: Real Time Chromatin Dynamics and Function (U01 Clinical Trial Not Allowed)

Other supported areas of investigation:

- Identify the molecular components (e.g. DNAs, RNAs, proteins, etc.) and mechanisms that underly and drive dynamic changes in nuclear organization
- Develop strategies to perturb aspects of nuclear genome organization in a dynamic and regulated fashion (chromatin looping events, formation of nuclear compartments or biomolecular condensates) and study the impact of these perturbations on a variety of nuclear and cellular functions;

Experimental systems:

- Live mammalian cells (either cell lines or primary cells) or tissues (including but not limited to tissue slices, organoids and organs-on-a-chip);
- Use of model organisms is permitted to accelerate technology-development, but all applications must include validation in a mammalian system;
- Omics-based technologies that require the destruction of the cells for genome-wide exploration of chromatin organization are allowed, but all proposals must include imaging-based validation of chromatin dynamics predictions and models in live cells.

RFA-RM-20-003: Real Time Chromatin Dynamics and Function (U01 Clinical Trial Not Allowed)

Special Review Questions

Innovation and Significance:

- Will the proposed work significantly enhance our ability to study and understand aspects of chromatin dynamics?
- Are the proposed new technologies and tools likely to be adopted by the scientific community, thereby significantly increasing the impact of the work beyond the project itself?

Approach:

- Are the projected timeline and proposed milestones feasible and appropriate?
- If the use of model organisms is proposed in addition to mammalian cells and tissues, how appropriate are the justifications for not using exclusively a mammalian system?

Environment:

- Does the team have access to appropriate equipment required for the proposed studies?

RFA-RM-20-004: 4DN Centers for Data Integration, Modeling and Visualization (UM1 Clinical Trial Not Allowed)

Contact: Mike Pazin, Ph.D. (NHGRI) michael.pazin@nih.gov

Purpose

- To support projects to generate reference datasets and to create navigable maps for the study of the spatial and temporal organization of the nucleus, using genomic and imaging data as well as newly developed visualization and integrative analysis tools.

RFA-RM-20-004: 4DN Centers for Data Integration, Modeling and Visualization (UM1 Clinical Trial Not Allowed)

Contact: Mike Pazin, Ph.D. (NHGRI) michael.pazin@nih.gov

Objectives/key activities

- to collect reference nuclear architecture datasets using a combination of imaging and genomic methods;
- to collect data related to genome function (such as gene expression) in parallel to data on genome architecture, in order to develop models of structure/function relationships;
- to develop next-generation analysis, visualization and modeling tools for describing the three-dimensional organization of mammalian genomes in a genome-wide fashion;
- to derive genome-wide navigable reference maps for the study of genome organization and function.

RFA-RM-20-004: 4DN Centers for Data Integration, Modeling and Visualization (UM1 Clinical Trial Not Allowed)

Responsiveness

- Applications that are not responsive to this RFA will not be reviewed. Projects with the following properties will be considered non-responsive:
  - No new nuclear structure data collection
  - No new methods for integrative analysis, data visualization, or navigable maps
  - Modeling/analysis does not incorporate both imaging and genomic data
  - No funds budgeted for common project
  - Work not performed in mammalian systems
  - External data sets used in the project are not publicly available

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RFA-RM-20-004: 4DN Centers for Data Integration, Modeling and Visualization (UM1 Clinical Trial Not Allowed)

Make sure to address the following in your application:

- Management plan; milestones, timeline, project manager, roles
- Rationale for balance between depth in the number of assays used versus breadth in the number of cell fate/cell state combinations sampled
- Budget instructions; common project, project manager
- External data may be incorporated, so long as those data are publicly shared at the time of application
- Applications must set aside 20% of their Direct Costs from years 2-5 of the award for coordinated work on common samples in collaboration with NIH staff. However, detailed plans for a common project are not required, as the other projects will not be known to the applicants or the NIH at the time the applications are submitted.

High Altitude thoughts:

- What makes your approach different, and better? What will put your application into the reviewer's top 10% of applications?
- Significance may be perceived by the reviewers as being important. Common Fund supports work of interest to all NIH institutes and centers. Will your study have implications for other diseases or biological processes relevant to NIH?

RFA-RM-20-004: 4DN Centers for Data Integration, Modeling and Visualization (UM1 Clinical Trial Not Allowed)

Special Review Questions

Significance:

- Will the proposed project meet the 4DN goals of producing reference datasets and development of novel integrative analysis and visualization tools, leading to the production of navigable 4D reference maps and predictive models of genome organization?
- Will the proposed technologies and strategies enable the study of critical aspects of genome organization that cannot be adequately measured with existing technologies?
- What is the potential for the proposed approach to be widely adopted and easily used by the research community?
- Will the proposed assay(s) generate data that will be of high utility to the research community?
- Do the proposed navigable maps appropriately balance accuracy and usefulness

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RFA-RM-20-004: 4DN Centers for Data Integration, Modeling and Visualization (UM1 Clinical Trial Not Allowed)

Special Review Questions

Investigators:

- Has the team demonstrated a track record in interdisciplinary research and/or team science?
- Has adequate leadership for the day-to-day project management activities (e.g., a project manager or sufficient PD(s)/PI(s) effort) been described?
- Does the applicant indicate a willingness to work with other centers and participate in Consortium activities?
- Does the project team have appropriate experience with developing, optimizing, and validating this type of technology?
- Does the project team have a track record of disseminating novel tools and techniques broadly?

RFA-RM-20-004: 4DN Centers for Data Integration, Modeling and Visualization (UM1 Clinical Trial Not Allowed)

Special Review Questions

Approach

- Are the proposed samples well justified, including their relevance to human health and disease?
- Are the proposed assay(s) high-throughput, cost effective and state-of-the-art, and capable of producing high quality data?
- Is the rationale for balancing the number of samples versus the number of assays/sample scientifically compelling, with respect to meeting 4DN goals and utility to the community?
- Are the proposed integrative and modeling approaches state-of-the-art, and capable of producing high quality models?
- Are the plans for quality assessment and quality control reasonable and adequate?
- Are the plans for submitting data to the relevant database(s) appropriate and reasonable and is there evidence that systems are in place to support the data submission process?
- Are the milestones, timelines and goals proposed for the research project reasonable and appropriate?
- Is the management plan well-described and commensurate with the level of complexity required for this FOA?

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RFA-RM-20-005: 4DN Organization and Function in Human Health and Disease (U01 Clinical Trial Not Allowed)

Contact: John Satterlee, Ph.D. (NIDA) satterleej@nida.nih.gov

- Anyone may apply

RFA-RM-20-006: New Investigator Projects on 4DN Organization and Function in Human Health and Disease (U01 Clinical Trial Not Allowed)

Contact: Lisa Postow, Ph.D. (NHLBI) lisa.postow@nih.gov

- The proposed PD/PI(s) MUST be investigator(s) who has/have not previously received substantial, independent funding from NIH. This includes those with early stage investigator (ESI) status (https://grants.nih.gov/policy/early-investigators/index.htm).

RFA-RM-20-005, RFA-RM-20-006 4DN Organization and Function in Human Health and Disease

Purpose

- To support projects that apply new or existing tools to monitor and/or manipulate the 4D nucleome in the context of human health and disease.

- Any human disease or biological process relevant to NIH's mission may be proposed including environmental exposures (e.g. addictive substances, toxins, psychosocial stress), or studies across development or lifespan.

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RFA-RM-20-005, RFA-RM-20-006 4DN Organization and Function in Human Health and Disease

Responsiveness

Applications that are not responsive to this RFA will not be reviewed. In order to be responsive to this FOA:

- The primary thrust of the application MUST be to apply new or existing tools to monitor and/or manipulate 4D nucleome organization in the context of human health and disease. Any human disease or biological process relevant to NIH's mission may be proposed.

- At least one Specific Aim MUST propose to use human primary cells, tissues, organoids, or xenografts to understand human health and disease, unless human tissue is difficult or impossible to obtain (e.g. embryo, brain, heart, bone). In such cases the applicant instead may propose to use mammalian tissues if the applicant can justify how the proposed work would facilitate transition to the study of human tissues in the future. The human primary cells, tissues, organoids, or xenografts proposed should be directly relevant to the disease or biological process being studied.

RFA-RM-20-005, RFA-RM-20-006 4DN Organization and Function in Human Health and Disease

Responsiveness (continued)

Applications that are not responsive to this RFA will not be reviewed. In order to be responsive to this FOA

- Although applications composed entirely of computational approaches will not be responsive to this FOA, applications with computational, data analysis, or modeling components are encouraged.
- No more than 25% of the budget may be proposed to be used for the development of new technologies.
- All applications must set aside 20% of their Direct Costs from years 2-5 of the award to support new collaborative research opportunities in consultation with NIH staff. These projects are anticipated to further both the needs of the funded project and the 4DN consortium

RFA-RM-20-005, RFA-RM-20-006 4DN Organization and Function in Human Health and Disease

Special Review Questions

- Significance: Specific for this FOA: How will the proposed study transform our ability to understand the mechanisms of 4DN organization and function for a particular disease or human health process (including environmental exposures or changes during development or across lifespan)? How will this work dramatically improve our understanding of the health or disease mechanisms or lay a strong foundation for future prevention, diagnosis, or therapeutic efforts? What foundational knowledge will be provided by the study to inform the design of tools to monitor or manipulate the human health process or disease being investigated? How will the proposed work advance our ability to understand and develop new therapeutic approaches to alter or treat the human health process or disease being investigated?

- Investigators: Specific for this FOA: What expertise does the investigative team have in 4D Nucleome approaches and in the disease or human health process of interest?

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RFA-RM-20-005, RFA-RM-20-006 4DN Organization and Function in Human Health and Disease

Special Review Questions (continued)

- Innovation: Specific for this FOA: If development of a new technology is proposed, will it be significantly faster, cheaper

- Approach: Specific for this FOA: Is the projected timeline feasible and appropriate? Are the proposed milestones quantitative and appropriate for each phase of the project? If only non-human tissues were proposed, how appropriate are the justification and description of how the proposed work would facilitate transition to the study of human tissues in the future? Does the team have access to the human tissues or cells required for the proposed experiments?, more sensitive, or more robust than existing technologies?

- Environment: Specific for this FOA: Does the team have access to appropriate equipment required for the 4DN analysis approaches they propose to use?

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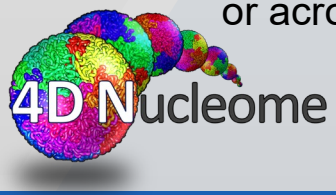
RFA-RM-20-005, RFA-RM-20-006 4DN Organization and Function in Human Health and Disease

Make sure to address the following in your application:

- **Significance**:
  - Explain how the proposed study transforms our ability to understand the mechanisms of 4DN organization and function for a particular disease or human health process (including environmental exposures or changes during development or across lifespan).
  - Explain how this work will dramatically improve our understanding of the health or disease mechanisms or lay a strong foundation for future prevention, diagnosis, or therapeutic efforts.
  - Describe what foundational knowledge will be provided by the study to inform the design of tools to monitor or manipulate the human health process or disease being investigated.
  - Explain how the proposed work will advance our ability to understand and develop new therapeutic approaches to alter or treat the human health process or disease being investigated.
  - Describe studies that, if fully successful, will transform the ability to understand the mechanisms of 4DN organization and function for a particular disease or human health process (including environmental exposures or changes during development or across lifespan).



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4DN Data Coordination and Integration Center: Roles and Responsibilities

What the DCIC <u>will do</u>

- Provide data wrangling expertise for data submission
- Work with 4DN working groups to develop and manage approved data and metadata formats
- Process data on approved 4DN data pipelines (e.g., DNase Hi-C, in situ Hi-C, dilution Hi-C, Repli-seq, TSA-seq, DAM-ID-seq, ATAC-seq, ChIP-seq)
- Accessioning of raw and processed omics and imaging datasets; share open-access data with the 4DN and broader research community in a timely fashion
- Manage approved submission to repositories for long-term data storage and access (e.g., GEO and dbGaP)
- Host broadly useful data analysis and visualization tools

What the DCIC <u>won't do</u>

- Project-specific data analysis and visualization; the DCIC will not conduct analysis for individual 4DN research projects

https://data.4dnucleome.org

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4DN Organizational Hub: Roles and Responsibilities

- Organize scientific meetings
- Provide administrative support to 4DN Network including the Steering Committee, subcommittees, and working groups.
- Maintain the 4DN Network public web portal that is the main entry point for the sharing of resources and information related to 4DN Network activities.
- Provide tiered access (public vs. 4DN-PI) to resources generated by all 4DN Network projects, including experimental models, protocols, biomaterials, resources, tutorials, reagents, and omics- and image-based data collections.
- Facilitate other 4DN Network activities, including: outreach activities and managing the social media presence of the 4DN Network, organizing sessions at scientific meetings, and facilitating consortium opinion and perspective pieces.
- **Ensure that members adhere to existing 4DN policies (e.g. data sharing, publication/preprint, and software sharing. See https://www.4dnucleome.org/policies.html for more information)**

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Important Dates

- **Letter of Intent Due Date**: - February 2, 2020: Health and Disease, New Investigator projects
  - February 17, 2020: Dynamics and Function, Mapping, OH, DCIC
- **Application Receipt**: - March 2, 2020: Health and Disease, New Investigator projects
  - March 17, 2020: Dynamics and Function, Mapping, OH, DCIC
- **Scientific Merit Review**: - June - July 2020
- **Advisory Council**: - August 2020
- **Earliest Start Date**: - September 2020

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Contacts

RFA-RM-20-003: Real Time Chromatin Dynamics and Function
Contact: Olivier Blondel, Ph.D. (NIDDK) blondelol@niddk.nih.gov

RFA-RM-20-004: 4DN Centers for Data Integration, Modeling and Visualization
Contact: Mike Pazin, Ph.D. (NHGRI) michael.pazin@nih.gov

RFA-RM-20-005: 4DN Organization and Function in Human Health and Disease
Contact: John Satterlee, Ph.D. (NIDA) satterleej@nida.nih.gov

RFA-RM-20-006: New Investigator Projects on 4DN Organization and Function in Human Health and Disease
Contact: Lisa Postow, Ph.D. (NHLBI) lisa.postow@nih.gov

Questions?

Submit questions via WebEx chat

Or email to 4DNucleome@mail.nih.gov

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Additional Information

Important points to remember…

RFA-RM-20-003: Real Time Chromatin Dynamics and Function (U01)

- Development and application of tools that would enable the monitoring of the 4D Nucleome in real-time of and how 4D genome architecture affect biological processes in live cells.
- **Eligibility:** Anyone may apply
- **Special consideration:** Must include at least one mammalian system.

RFA-RM-20-004:4DN Centers for Data Integration, Modeling and Visualization (UM1)

- Reference datasets and navigable maps for the study of the spatial and temporal organization of the nucleus.
- Develop visualization and integrative analysis tools.
- **Eligibility:** Anyone may apply
- **Special consideration:** Projects **MUST** be in mammalian systems relevant to human health and disease.

RFA-RM-20-005: 4DN Organization and Function in Human Health and Disease (U01)

- Support projects that apply new or existing tools to monitor and/or manipulate the 4D nucleome in the context of human health and disease.
- **Eligibility**: Anyone may apply
- **Special considerations:** At least ONE aim **MUST** propose to use human samples or tissues (exceptions may be allowed for hard to obtain tissues e.g. brain, fetal)

RFA-RM-20-006: New Investigator Projects on 4DN Organization and Function in Human Health and Disease (U01)

- Same goals as RFA-RM-20-005
- **Eligibility:** Limited to NIH Early Stage Investigator. No foreign institutions. Foreign components allowed.
- **Special consideration:** At least ONE aim **MUST** propose to use human samples or tissues (exceptions may be allowed for hard to obtain tissues e.g. brain, fetal)

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RFA-RM-20-004: 4DN Centers for Data Integration, Modeling and Visualization (UM1 Clinical Trial Not Allowed)

Navigable maps

- First-generation maps can be based on the datasets developed using the experimental system proposed in the application
- Awardees will collaborate to the building of higher-resolution genome-wide maps through the combination of datasets generated with complementary technologies by multiple teams using a consortium-defined set of samples
- Navigable maps must incorporate data from both imaging and genomic assays

- The utility of the reference maps can be piloted using biological problems; examples include (but are not limited to):
  - comparison of single cell and ensemble measurements of nuclear structure,
  - exploring the heterogeneity of nuclear structure across single cells,
  - studying the connectivity of promoters and other regulatory regions
  - examining the relationship between nuclear structure and function across developmental or disease states

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RFA-RM-20-005, RFA-RM-20-006 4DN Organization and Function in Human Health and Disease

Make sure to address the following in your application:

- **Investigators:**
  - Describe the expertise that the investigative team has in 4DN approaches and in the disease or human health process of interest.
- **Innovation**:
  - If development of a new technology is proposed, explain in what ways it will be significantly faster, cheaper, more sensitive, or more robust than existing technologies.
- **Approach**:
  - If only non-human tissues were proposed, describe how the proposed work would facilitate transition to the study of human tissues in the future.
  - Describe how your team will have access to the human tissues or cells required for the proposed experiments.
- **Project timeline**:
  - A timeline (Gantt chart) including milestones should be provided for all studies. Milestones are goals that create decision points in the project and should include clear criteria for success. Yearly milestones should provide clear indicators of a project's continued success or emergent difficulties and may be used to evaluate the application not only in peer review but also in consideration of the awarded project for funding of non-competing award years.
  - Milestones and the timeline should be provided in a separate heading at the end of the Approach section.

RFA-RM-20-005, RFA-RM-20-006 4DN Organization and Function in Human Health and Disease

Some general high altitude thoughts:

- These FOAs cover all health and disease areas relevant to NIH.
- What is your "special sauce"? What will put your application into the reviewer's top 10% of applications?
- Related to your special sauce, significance may be perceived by the reviewers as being important. Will your study impact a single disease/process? If your project is fully successful, will your study have implications for other diseases or biological processes relevant to NIH?
- Do you have a solid rationale for a role of 4DN in the disease or process of interest?
- Do you have a reasonable plan to apply 4DN tools to human primary cells, tissues, organoids, or xenografts?

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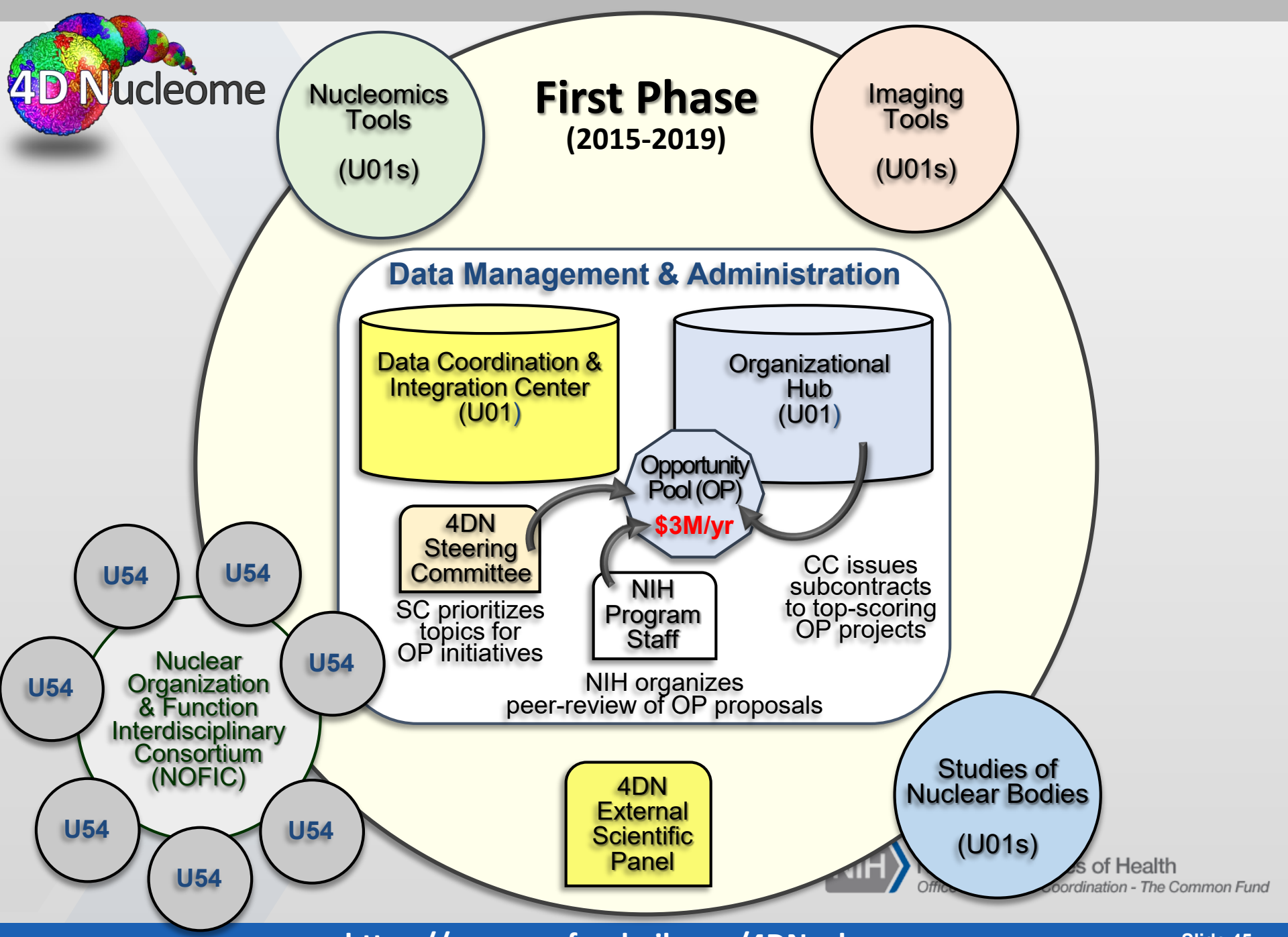
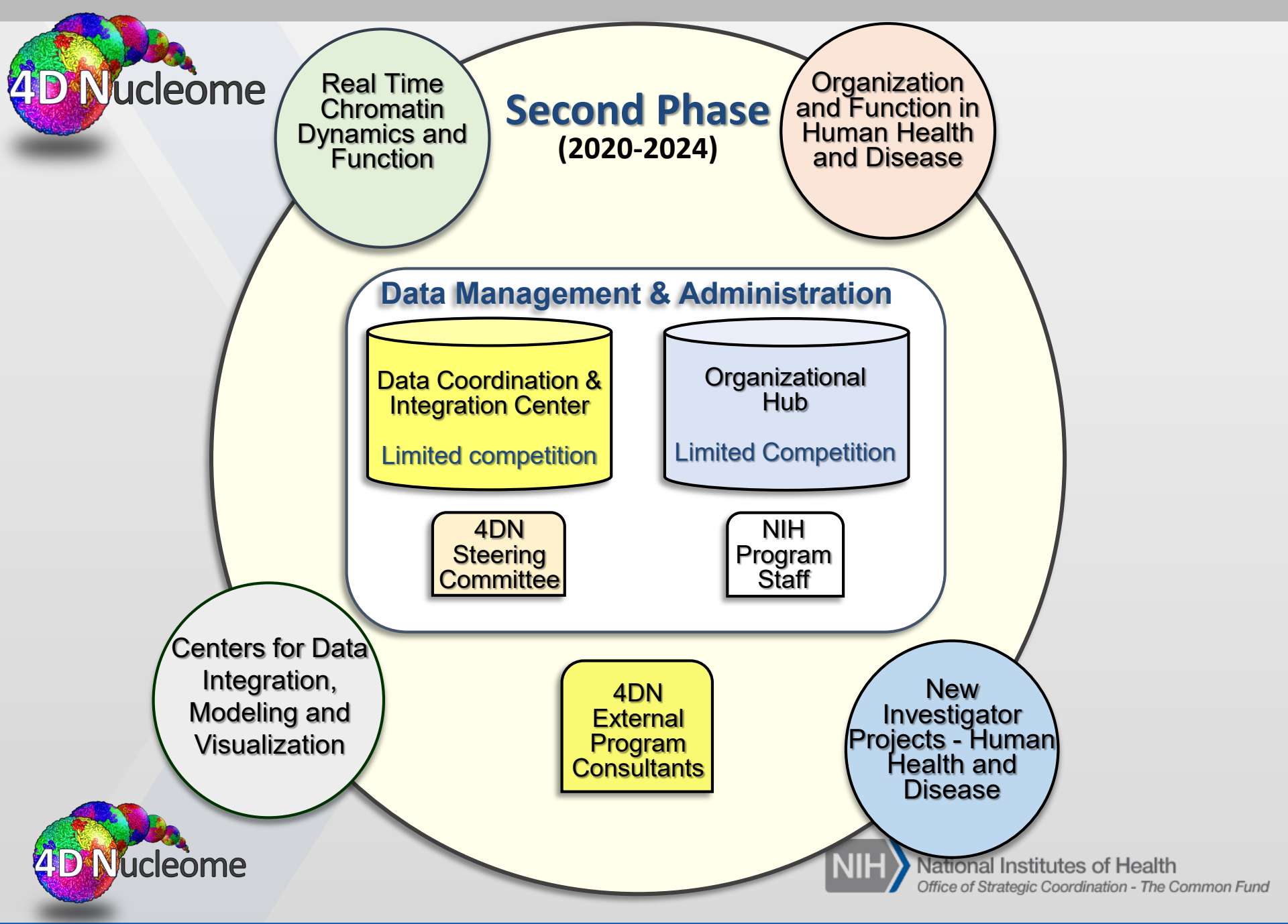
Some Additional Advice for New Investigator Applicants to RFA-RM-20-006

- Eligibility will be determined at the time of *submission*
- If awarded, this will remove you from ESI status so plan accordingly
- Multi-PI applications are allowed as long as all PIs are New Investigators
- You may consider including an established investigator(s) as a co-Investigator(s)
- Will the reviewers believe you can get it done?


4D Nucleome
First Phase
(2015-2019)
Nucleomics Tools
(U01s)
Imaging Tools
(U01s)
Data Management & Administration
Data Coordination & Integration Center (U01)
Organizational Hub (U01)
Opportunity Pool (OP)
$3M/yr
4DN Steering Committee
SC prioritizes topics for OP initiatives
NIH Program Staff
NIH organizes peer-review of OP proposals
CC issues subcontracts to top-scoring OP projects
U54
U54
U54
U54
U54
U54
Nuclear Organization & Function Interdisciplinary Consortium (NOFIC)
4DN External Scientific Panel
Studies of Nuclear Bodies
(U01s)


4D Nucleome
Real Time Chromatin Dynamics and Function
Second Phase
(2020-2024)
Organization and Function in Human Health and Disease
Data Management & Administration
Data Coordination & Integration Center
Limited competition
Organizational Hub
Limited Competition
4DN Steering Committee
NIH Program Staff
Centers for Data Integration, Modeling and Visualization
4DN External Program Consultants
New Investigator Projects - Human Health and Disease
4D Nucleome
NIH
National Institutes of Health
Office of Strategic Coordination - The Common Fund