National Advisory Council for Human Genome Research

Concept Clearance for Genomic Technology Development

May 18, 2015

Timeline for initiatives

Concept Clearances Council Review:	May 2015
FOAs Released:	Summer 2015
Initial Review:	Winter 2016
Council Review:	May 2016
Funding:	Summer 2016

Overview

We propose a Concept based on discussions at recent NHGRI planning webinars: *Genomic Technology Development*. The proposed initiatives are directed to meet the goal of developing technologies that enable:

- single cell methods for genomic technologies discussed here,
- high throughput/high information content functional analysis with genomic readout,
- DNA sequencing (sequencing technologies ripple through all the other needs and opportunities),
- foundational technologies (e.g., sample preparation, novel sensors and detectors),
- transcriptome analysis, and
- genome-wide functional analyses.

The resulting genomic technologies are critical for enabling innovative research that enhances our understanding of human biology and disease, and will be pursued as two initiatives.

1. **Novel Nucleic Acid Sequencing Technology Development**
   Purpose: facilitate development of novel DNA and direct RNA sequencing technologies using slightly larger and longer duration awards than are typical.
   ($2M total costs (TC) for new awards in each of four consecutive years; 2-4 awards/year, plus parallel small business grants)
2. **Genomic Technology Development Awards**
   Purpose: enable the best and most opportune investigator-initiated genomic technology development using slightly larger and longer duration awards. The planning meeting process identified a wide gamut of opportunities for investment.
   ($3M TC for new awards in each of four consecutive years; 3-6 awards each year, plus parallel small business grants)

Background

One of the major contributions by NHGRI has been in the genomic technology domain. Those efforts have been so transformative that it is hard to remember genomics without, for example, a reference human genome, inexpensive short-read sequencing, efficient bacterial artificial chromosome methods, microarrays, defined common human haplotypes, single molecule sequencing, and many more significant technical advances. Achieving the goals of the current and future strategic plans will require

further technological innovation and development. Bright prospects for future success motivate investing in genomic technology development specifically for 1) novel sequencing methodologies, and 2) general support for investigator-initiated especially opportune research.

Funding for NHGRI's $1000 genome sequencing technology development effort ended in FY14. NHGRI convened a planning workshop "*Genomic Technology Development*" on April 10 and April 16, 2105, in the form of two parallel webinars, to obtain advice about particularly opportune areas for future efforts in the field. These webinars built upon recommendations from two recent NHGRI planning workshops, "*Future Opportunities for Genome Sequencing and Beyond"* and "*From Genome Function to Biomedical Insight: ENCODE and Beyond.*" A follow-up survey enabled webinar attendees to identify priorities among the range of opportunities discussed. A workshop report is currently being drafted.

The workshop discussions and follow-up survey made it very clear that there are significant opportunities across a wide swath of genomics related research. There was wide recognition that new chemistries and methods for DNA and direct RNA sequencing are areas of significant and fundamental opportunity that, if successful, would have ever broadening impact on genomics, biomedical research, biomedicine and biology. Very high priority was also attributed to simultaneous analysis of DNA, RNA, epigenome, protein, etc. from the same sample; and high throughput genome modifications (by recombination and transient assays) for replacement, activation and inhibition, with genomic readout. These were followed closely by further scaling up high-throughput DNA sequencing, transcriptome and functional technologies to operate on 10^4 samples (with ultimate goal of analyzing 10^8 samples cost-effectively) for, e.g., single cell/small samples and for population studies; *in situ* methods (tissue context) for DNA, epigenome, RNA, and protein; and measuring proximal transcription dynamics, and transcriptome dynamics over time, from cells to organs.

The broad range of priorities and opportunities in technology development lead NHGRI to adopt an approach that encourages investigators to pursue their best ideas, and makes an accompanying investment in foundational sequencing technologies.

What's new

These initiatives complement and differ from the $1000 genome technology development program in several key ways:

- Novel Nucleic Acid Sequencing Technology Development (Initiative 1) continues an investment in nucleic acid sequencing technologies with emphasis on data quality, while not abandoning cost, emphasizing entirely new approaches, and broadening the focus to include direct RNA sequencing.
- Genomic Technology Development Awards (Initiative 2) expands beyond sequencing to areas of highest opportunity through investigator initiated applications to provide new foundational approaches for solving vexing problems in the field.

Funding note

To optimize the mix of genomic technologies supported, NHGRI will need the flexibility to build a balanced portfolio at the time of funding each RFA and PAR, which may entail funding across the score range.

1: Novel Nucleic Acid Sequencing Technology Development

What's new: Will provide support for novel DNA and direct RNA sequencing chemistries and instrumentation.

Purpose

The purpose of this initiative is to support development of novel nucleic acid sequencing technologies for DNA and direct RNA sequencing. Advances in genomics and more broadly in biomedical research have been greatly facilitated by significant and sustained DNA sequencing throughput increases and cost decreases. The goal now is to achieve longer read lengths, greater accuracy and lower costs with the anticipation that advances in any of these three areas will make significant contributions to the mission of NHGRI and beyond, including to many of the other technology development goals.

Proposed Scope and Objectives

The initiative will support novel chemistries and instrumentation for DNA and direct RNA sequencing. New methodologies and very substantial advances beyond existing approaches will be encouraged. A significant expectation will be that the methods proposed would, if successful, significantly propel forward the field of genomics.

The specific components of this initiative will include:

- Development of new DNA sequencing technologies, and
- Development of new direct RNA sequencing technologies.

Examples of potential research topics include:

- Novel chemistries, physics or instrumentation for entirely new ways to perform DNA sequencing. Examples of important sequencing needs include:
    - Exhaustive and quantitative sequencing of every DNA and/or RNA molecule in a sample, and
    - Very long reads (e.g., ≥150 Kb) with accuracy and error structure sufficient to *de novo* assemble human genomes.
- Direct RNA sequencing of full length transcripts without a cDNA intermediate, and
- Orders of magnitude improvements to existing sequencing technologies.

Relationship to Ongoing Activities

The proposed initiative will uniquely focus on new nucleic acid sequencing technologies.

Related Projects

Commercial interests are developing novel sequencing technologies. Some of those are announced or advancements to current technology. To the extent possible we will attempt to avoid overlap with those efforts, and leverage those efforts wherever possible. In addition, commercial efforts in these areas will be encouraged via the SBIR and STTR programs of NHGRI.

Mechanism of Support

RFAs for R01 and R21 grants that have slightly higher dollar amounts and timeframes than are typical for these activity codes. Parallel RFAs will be published for small business grants.

Funding Anticipated
$2M TC in additional RPG funding/year for four years (FY16-19). SBIR/STTR funds will be in addition to those listed in the previous sentence.

We anticipate funding 2-4 nucleic acid sequencing technology development awards (R01 and R21) per year in each of four years. Additional receipt dates will allow for amended applications, stimulate new applications across the funding period, and allow R21 funded work that leads to R01 applications. In addition, a predictable funding source is likely to stimulate additional work in this area of genomic technology development. Sufficient funds are necessary to catalyze efforts towards novel nucleic acid sequencing technologies.

Activity*	FY16	FY17	FY18	FY19	FY20	FY21	FY22
Novel Nucleic Acid Sequencing Technologies	$2M	$4M	$6M	$8M	$6M	$4M	$2M

*R01s of up to four years and R21s of up to three years are anticipated in these budget calculations. Small business activity is not included here since it comes from a separate dedicated budget.

2: Genomic Technology Development Awards

What's new: This is a new activity. The workshop identified several critical shortcomings that are poised to be overcome if activities are stimulated with a modest investment.

Purpose

The purpose of this initiative is to catalyze technology development for genomics (beyond initiative 1). The goal is to provide a mechanism for support of very novel and high impact work from across the gamut of genomics technology development. This initiative seeks to support technologies that will have an impact in the next five to seven years.

Proposed Scope and Objectives

The genomics technology development supported can broadly range across areas including: 1) single cell/small sample genomics, 2) high throughput biochemical and other tools to modulate gene expression, 3) foundational technologies (e.g., efficient sample prep for any of the other technologies), 4) transcriptomics, 5) genome-wide functional analyses, and 6) other high-impact genome technology needs that may arise over the 4 years of the initiative.

The objective is to catalyze novel work in these areas, and ensure a critical mass of genomics technology development for future impact in a five to seven year time frame. The broad range of priorities and opportunities in technology development will encourage investigators to pursue their best ideas and thereby move the genomics field forward.

Examples of possible research topics are:

- DNA, RNA, epigenome, protein, etc. from the same sample;
- high throughput genome modifications (by recombination and transient assays), for replacement, activation and inhibition, with genomic readout;
- scaling DNA sequencing, transcriptome, and functional technologies to operate on 10^4 samples (with ultimate goal of 10^8 cost-effectively) for, e.g., single cell/small samples and for population studies;
- *in situ* methods (tissue context) for DNA, epigenome, RNA, and protein analyses; and
- measuring proximal transcription dynamics, and transcriptome dynamics over time, from cells to organs.

Relationship to Ongoing Activities

The Common Fund Single Cell Analysis effort could overlap with these efforts. We will encourage development of technologies that could be applied to single cells and small amounts of biological material, and seek not to significantly overlap with this effort. This common fund activity is currently funded through FY17 and is not currently seeking new applications.

NCI Innovative Molecular Analysis Technologies (IMAT) Program could have overlap. We will coordinate with NCI colleagues to insure coordination of these goals with IMAT.

There are also certainly commercial efforts in these areas. We will aim to be aware of those that are public and stay appraised of those that are developing. In addition, commercial efforts in these areas will be encouraged via the SBIR and STTR programs of NHGRI.

Mechanism of Support
PARs for R01 and R21 that will have slightly larger budget caps and years of support than are typical for these activity codes. Parallel PARs will be published for small business grants.

Funding Anticipated
$3M TC in additional RPG funding/year for four years (FY16-19).
SBIR/STTR funds will be in addition to those listed in the previous sentence.

We anticipate funding 3-6 genomic technology development awards (R01 and R21) per year in each of four years. Additional receipt dates will allow for amended applications, stimulate new applications across the funding period, and allow R21 funded work that leads to R01 applications. In addition, a predictable funding source is likely to stimulate additional work in genomic technology development. Sufficient funds are necessary to catalyze efforts towards genomic technology development.

Activity*	FY16	FY17	FY18	FY19	FY20	FY21	FY22
Genomic Technology Development Awards	$3M	$6M	$9M	$12M	$9M	$6M	$3M

*R01s of up to four years and R21s of up to three years are anticipated in these budget calculations. Small business activity is not included here since it comes from a separate dedicated budget.

Summary of Request (R01 and R21 only)

Activity*	FY16	FY17	FY18	FY19	FY20	FY21	FY22
Novel Nucleic Acid Sequencing Technologies	$2M	$4M	$6M	$8M	$6M	$4M	$2M
Genomic Technology Development Awards	$3M	$6M	$9M	$12M	$9M	$6M	$3M
Total	$5M	$10M	$15M	$20M	$15M	$10M	$5M

* The $1,000 sequencing technology development program funded ~$5M in new grants per year in FY12-14. The current concept stays at that level, but it's now split between sequencing ($2M new grants per year) and the wider genome ($3M per year) technology development. As the new program ramps up it will be offset by decreased costs of the previous $1,000 genome effort (see below).

For perspective, past RPG spending for the $1,000 Genome RFAs.

FY06	FY07	FY08	FY09	FY10	FY11	FY12	FY13	FY14
$22.8M	$22.2M	$15.8M	$20.8M	$18.1M	$15.7M	$15.1M	$14.2M	$13.8M

Current year and future expected RPG spending from the $1,000 Genome RFAs.

FY15	FY16	FY17
$9.9M	$5.5M	$1.2M

Note funding decreases by $4.4M in FY 16 and a further $4.3M in FY17 nearly offsetting the costs of the first two years of the new Concept for Genomic Technology Development.