**National Advisory Council for Human Genome Research**
**Concept Clearance for Genomic Technology Development**
**February 12-13, 2018**

## Novel Nucleic Acid Sequencing Technology Development

### Purpose:

The purpose of this initiative is to reissue a series of requests for applications (RFAs) 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 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 genomic technology development goals. Advancing sequencing technologies is critical for enabling innovative research that enhances our understanding of human biology and disease.

### Background:

Major contributions by NHGRI have been in the technology development 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 (exemplified by the $1000 genome), defined common human haplotypes, single molecule and nanopore sequencing, and many more significant technical advances. Current and future strategic goals in genome sciences and genomic medicine necessitate continued technological innovation in sequencing technology development, and specifically in novel sequencing approaches and methodologies.

NHGRI has supported sequencing technology development since the inception of the institute, through programs such as the NHGRI Advanced Sequencing Technology Program (the $1000 Genome Program). Most recently we issued Requests for Applications (RFAs) addressing Novel Nucleic Acid Sequencing Technology Development (RFA-HG-15-031 (R21), -032(R01), -033 (R43/R44) and -039(R44)). Two years of awards have been made (14 total, Appendix 1) with FY18 awards pending. The current novel nucleic acid sequencing technology development RFA will end soon, with the last awards being made FY18. NHGRI would like to continue to support this fruitful area of technology development by reissuing this RFA in 2018 for funding in FY19-21.

### Proposed Scope and Objectives:

The initiative will support novel chemistries and instrumentation for DNA and direct RNA sequencing by continuing the novel nucleic acid sequencing technology development program. Novel methodologies and very substantial advances beyond existing approaches (at least 10-fold better) will be encouraged. The initiative will invest in nucleic acid sequencing technologies with emphasis on data quality, while not abandoning cost, emphasize entirely new approaches, and continue to broaden the focus with opportune investments in direct RNA sequencing. A significant expectation will be that the methods proposed would, if successful, propel forward and transform the field of genomics.

The specific components of this initiative will include:

- Development of new DNA sequencing technologies.
- Development of new direct RNA sequencing technologies.
- Substantial advances to existing nucleic acid sequencing technologies.

Examples of potential research topics include:

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

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

**Relationship to Ongoing Activities:**

Technology Development for genomics is a significant and signature effort by NHGRI. The proposed initiative will uniquely focus on novel nucleic acid sequencing technologies. Parallel efforts have also been encouraged through Novel Genomic Technology Development PARs (PAR-14, 15, 16 & 17). Some applications in both of these areas are also received through the Parent R01 and R21 along with the Omnibus SBIR and STTR FOAs. The RFAs stimulate additional sustained work in this area, with a strong focus on the significance, innovation and approach needed to catalyze advances in this field.

Commercial interests are developing novel sequencing technologies. To the extent possible we will attempt to avoid overlap with those efforts, and leverage those efforts wherever possible. Commercial efforts in these areas will be encouraged via the Small Business Innovation Research (SBIR) and Small Business Technology Transfer Research (STTR) programs of NHGRI.

**Mechanism of Support:**

RFAs for R01 (Research Project Grant) and R21 (Exploratory/Developmental Research Grants) grants provide more support than is typical for these activity codes. For R01s we will allow direct costs of up to $700,000 per year, with a maximum project period of 4 years. For R21s we will allow costs of up to $200,000 per year and no more than $400,000 for the entire budget period, with a maximum project period of 3 years. Because the nature and scope of the proposed research will vary from application to application, it is anticipated that the size and duration of each award will also vary, and will also be informed through the peer review and Council advisory processes. Parallel RFAs will be published for small business grants for the R43 and R44 SBIR Project Grant mechanisms.

**Funding Anticipated:**

NHGRI intends to commit $2,000,000 in total costs in additional RPG funding/year for three years (FY19-21) to support R01 and R21 applications. We anticipate funding 3-5 novel nucleic acid sequencing technology development awards (R01 and R21) per year in each of three years. Additional yearly 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 new work in this area of sequencing technology development. Sufficient funds are necessary to catalyze efforts towards developing novel nucleic acid sequencing technologies.

SBIR funds (R43 and R44 mechanisms) come from a separate dedicated budget and will be in addition to the funds set aside for R01/R21 applications.

<u>Funding note</u>

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

Appendix 1: Novel Sequencing Technology Development awards (FY16-FY17)

**Academic**

| Project | Actv | PI Name(s) All | Title | Awarded 1st year ($) |
|---|---|---|---|---|
| HG005115-09 | R01 | GUNDLACH, JENS | High Accuracy Nanopore Sequencing | 794,407 |
| HG009180-01 | R01 | LINDSAY, STUART | Recognition Tunneling for Single Molecule RNA Sequencing | 512,738 |
| HG009186-01 | R01 | WANUNU, MENI | Direct picogram DNA and RNA sequencing using nanopore Zero-mode waveguides | 711,477 |
| HG009188-01 | R01 | COLLINS, PHILIP; BOYANOV, BOYAN; WEISS, GREGORY A | DNA Sequencing Using Single Molecule Electronics | 584,552 |
| HG009189-01 | R01 | SHEPARD, KENNETH L; DRNDIC, MARIJA | Enzyme-less DNA base discrimination using solid-state nanopores with high-frequency integrated detection electronics | 461,366 |
| HG009190-01A1 | R01 | TIMP, WINSTON | Nanopore based profiling of epigenetic state | 784,452 |
| HG009187-01A1 | R21 | BESTOR, TIMOTHY H | Comprehensive Single Molecule Enhanced Detection of Modified Cytosines in Mammalian Genomes | 320,000 |
| HG009576-01 | R21 | ZHANG, SHENGLONG; LI, WENJIA | Development of LC/MS-Based Direct RNA Sequencing with Concomitant Basecalling and Modification Analysis Capability | 177,750 |
| | | | **Total** | **4,346,742** |

**Small Business**

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|---|---|---|---|---|
| HG009184-01 | R43 | SCHIBEL, ANNA | Achieving Single Nucleotide Resolution to Enable DNA Flossing Through Alpha-Hemolysin | 224,980 |
| HG009196-01 | R43 | ERVIN, ERIC | Nanopore Enabled Exonuclease Sequencing | 224,997 |
| HG009573-01 | R43 | RECZEK, ELIZABETH | Methods to enable direct RNA sequencing without amplification | 223,465 |
| HG009578-01 | R43 | ALDEN, JONATHAN | Epigenetic fingerprinting of label-free DNA using a solid-state nanopore | 279,974 |
| HG009580-01 | R43 | DAPPRICH, JOHANNES | Amplification-Free Target Enrichment and Direct Sequencing of Large Chromosomal Segments | 276,252 |
| HG009584-01 | R44 | SELVARAJ, SIDDARTH | Commercialization of a low-cost user-friendly DNA preparation kit that produces chromosome-span contiguity from conventional short-read sequencing for a wide range of applications | 848,530 |
| | | | **Total** | **2,078,198** |