Concept Clearance: Technology Development for Single-Molecule Protein Sequencing

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Purpose

- Accelerate innovation and development in single-molecule protein sequencing (SMPS)
  - Achieve tech advances to the level where SMPS can be used for genome-wide surveys;
  - Improve speed, sensitivity, quantitation and accuracy to use routinely in genome biology and function
  - Apply lessons learned from DNA sequencing to proteome at scale
  - Explore feasibility within budget constraints

Background

- Human proteome is extremely complex
  - Typical cell expresses >10,000 unique proteins
  - Can contain 100X as many proteoforms
  - Dynamic range 7 to 10 orders of magnitude
- Two main approaches
  - Affinity reagents
  - Mass spectrometry (MS)
- Currently, no technologies for routine proteome-scale sequencing and quantification

SMPS – Why now?

- Recent promising technological advances
  - Nanopore, Edman chemistry; companies
- Significant opportunity to advance state-of-art
- Facilitate low abundance protein detection and single cell analysis at high throughput.
- Enable improved cataloguing of protein gene products and “missing proteins”

SMPS- Why NHGRI?

- Extension of DNA seq tech into proteome world
  - scale, towards quantitation and de novo sequencing
- Expand understanding of genome biology and function
  - Genotype to phenotypes
  - Enable single cell genomic analysis
  - Establish roles of genes in pathways and networks
  - Multi-omic molecular diagnostics

Scope and Objectives

- Support investigator-initiated novel research with aim to significantly advance SMPS technologies
  - Novel, high-risk; not incremental advances
- Example techniques appropriate for development:
  - Nanopore
  - Edman-like degradation with parallel measurements
  - Fluorescence-based measurements
  - Recognition tunneling
  - Other technologies that have potential to scale genome-wide
- Not appropriate
  - Mass spectrometry
  - Technologies that are not on a path to scale

Mechanisms and Budget

	FY21	FY22	FY23	FY24	FY25
R01	2.0	4.0	6.0	4.0	2.0
R21	0.5	1.0	1.0	0.5	
SBIR	1.0	2.0	2.0	2.0	1.0
Total	**3.5**	**7.0**	**9.0**	**6.5**	**3.0**
dollars in millions	Grand Total = $29M with SBIR *($21M without SBIR)*				

- RFA R01 (Research Project) up to $500K direct costs/year; project period up to 3 years
- RFA R21 (Exploratory/Developmental Research) up to $200K DC/year; project period up to 2 years
- RFA R43/R44 SBIR; up to total costs $250K for Phase I, $2M for Phase II
- Seek sign-on from other ICs
    - *NHGRI is small player in proteomics – 1-2% of NIH*

NHGRI Technology Development Program

Sept 2019 Council

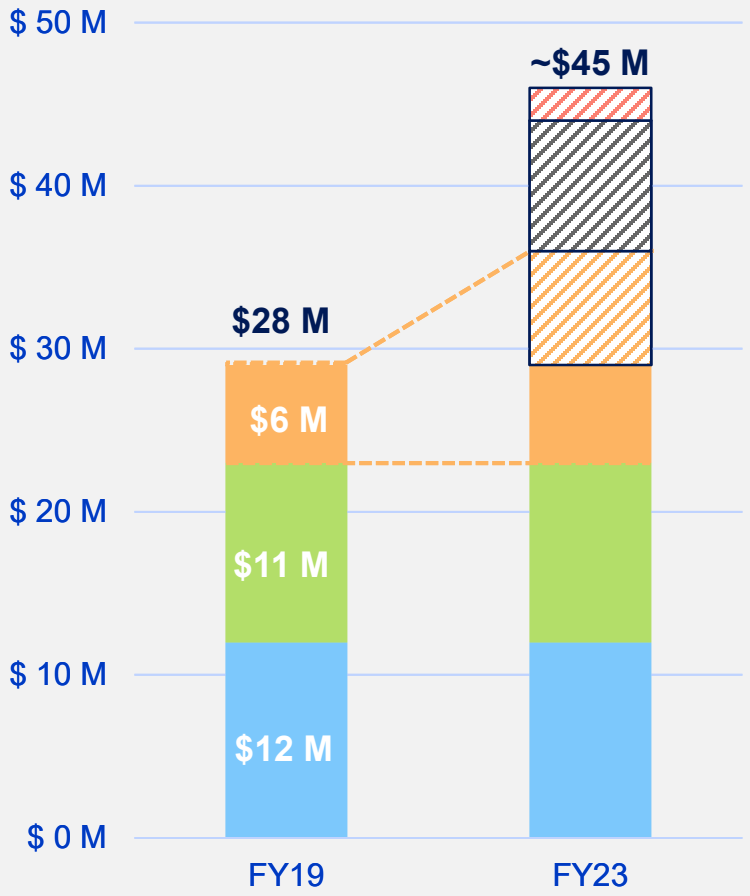
R01/R21

Grow to $45M/yr

SMPS

R01/R21

Grow to $7M/yr



Council approved

$1.5 M Coordinating Center RFA

$8 M Synthetic Tech RFA set

Sequencing Tech

$7 M Approved growth

Current RFA set

Unsolicited (PA/PAR)

Genomic Tech Dev

"Parent" FOAs

thank you Mike Smith

Questions / Discussion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