The NIH Nanomedicine Initiative
& NHGRI $1,000 Genome Sequencing Technology Program

Jeffery A. Schloss, PhD.
National Human Genome Research Institute
National Institutes of Health

National Nanotechnology Initiative at Ten:
NANOTECHNOLOGY INNOVATION SUMMIT
December 8, 2010 Washington, D.C.
Overarching Goals

- Accelerate basic research discoveries and speed translation of those discoveries into clinical practice
- Explicitly address roadblocks that slow the pace of biomedical research to improve health
- Develop new ways to fund innovative, potentially transformative research
- Develop programs that no single institute would fund that would be relevant to much or all of NIH
New Pathways to Discovery

Molecular Libraries and Imaging
Building Blocks, Biological Pathways and Networks
Structural Biology
Bioinformatics and Computational Biology

Nanomedicine
Human Microbiome Project
Epigenomics
Genotype-Tissue Expression (GTEx)
Protein Capture Reagents
Regulatory Science
Science of Behavior Change
Library of Integrated Network-Based Cellular Signatures (LINCS)
NIH Center for Regenerative Medicine
NIH’s Major Opportunities

• Applying high throughput technologies to understand fundamental biology, and to uncover the causes of specific diseases
• Translating basic science discoveries into new and better treatments
• Putting science to work for the benefit of health care reform
• Encouraging a greater focus on global health
• Reinvigorating and empowering the biomedical research community

Francis S. Collins  Science  1 January 2010
Nanoscience and Nanotechnology Definition

- research and development at the atomic, molecular, or macromolecular levels, at a scale of about 1 – 100 nm,
- providing a fundamental understanding of phenomena and materials at this scale, and
- creating and using structures, devices and systems that have novel properties and functions because of their small size.
New capabilities that were not possible before:

- novel phenomena, properties and functions at nanoscale that are non-scalable outside of the nm domain
- the ability to measure, control and manipulate matter at the nanoscale in order to change those properties and functions
- integration across length scale and fields of application
NIH Nanomedicine Initiative

Developed in context of but distinct from the ongoing nanotechnology research at NIH:

Learn to manipulate and re-engineer biology \textit{in vivo} with the same exquisite precision with which material scientists manipulate other materials

Use that capability to treat disease
NIH Vision for the Nanomedicine Initiative

- Uncover novel properties; quantitatively characterize these and other known properties of biomolecules and their complexes inside cells.

- Gain an understanding of the engineering principles used in living cells to "build" molecules, molecular complexes, organelles, cells, and tissues.

- Develop new technologies, and engineer devices and hybrid structures, for repairing tissues as well as preventing and curing disease.

A 10-year program engaging basic scientists and clinicians to move from discovery to preclinical model.
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A 10-year program engaging basic scientists and clinicians to move from discovery to preclinical model.
NIH Nanomedicine Initiative

• Multidisciplinary
  – biology, chemistry physics, math and computational science, engineering, clinical

• Translational
  – connects basic scientists with clinicians to develop new knowledge of basic biological mechanisms and transition it to pre-clinical testing within 10 years.

• Novel and risky
  – proposes new scientific and team science concepts:
    • engineering biology based on quantitative knowledge
    • basic science shaped by clinical goals
<table>
<thead>
<tr>
<th>Year</th>
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<tbody>
<tr>
<td>2003-4</td>
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<td>Midcourse Program Review</td>
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NDC = Nanomedicine Development Center
Nanomedicine Development Centers

2005

W. Chiu  Center for Protein Folding Machinery
         Baylor College of Medicine

W. Lim   Engineering Cellular Control: Synthetic Signaling
         and Motility Systems
         UCSF

M. Sheetz Nanotechnology Center for Mechanics in
           Regenerative Medicine
           Columbia University

E. Jakobsson National Center for the Design of Biomimetic
             Nanoconductors
             University of Illinois Urbana-Champaign
Nanomedicine Development Centers

2006

G. Bao       Nanomedicine Center for Nucleoprotein Nanomachines
             Georgia Institute of Technology

P. Guo       Phi29 DNA-Packaging Motor for Nanomedicine
             Purdue University

E. Isacoff   NDC for the Optical Control of Biological Function
             University of California Berkeley/LBNL

C. Ho        The Center for Systemic Control of Cyto-Networks
             University of California Los Angeles
Nanomedicine Development Centers

33 Institutions

Baylor College Medicine
Cold Spring Harbor Lab
Columbia
Duke
Emory
ETH Polyteknikum, Zurich
Georgia Institute Technology
Heidelberg University
Lawrence Berkeley National Lab
Medical College of Georgia
MIT
Mount Sinai School Medicine
North Carolina State
Northwestern
New York University
Oak Ridge National Lab
Oxford University, UK
Purdue
Sandia National Labs
Scripps
Stanford
U Cincinnati
UC Berkeley/LBNL
UC Davis
UCLA
UCSF
Univ Chicago
Univ Ill Urbana-Champaign
Univ New Mexico
Univ Southern Mississippi
Weizmann Institute, Israel
Yale

12 States

CA, CT, GA, IL, IN, MA, MS, NC, NM, NY, TX, OH

6 Countries

Israel, Germany, Switzerland, Canada, UK
# Nanomedicine Development Centers

<table>
<thead>
<tr>
<th>Center</th>
<th>Total</th>
<th>PIs</th>
<th>Postdocs</th>
<th>Students</th>
<th>Other</th>
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<tbody>
<tr>
<td>Nanomedicine Center for Nucleoprotein Machines</td>
<td>45</td>
<td>10</td>
<td>14</td>
<td>13</td>
<td>8</td>
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<tr>
<td>Center for Protein Folding Machinery</td>
<td>75</td>
<td>16</td>
<td>24</td>
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<td>Nanotechnology Center for Mechanics in Regen. Med.</td>
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<td>12</td>
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<td>The Center for Systemic Control of Cyto-Networks</td>
<td>31</td>
<td>10</td>
<td>8</td>
<td>10</td>
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<td>NDC for the Optical Control of Biological Function</td>
<td>63</td>
<td>18</td>
<td>13</td>
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<td>Engineering Cellular Control: Synthetic Signaling and Motility</td>
<td>44</td>
<td>13</td>
<td>10</td>
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<td>Phi29 DNA-Packaging Motor for Nanomedicine</td>
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<td>17</td>
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<td>National Center for the Design of Biomimetic Nanoconductors</td>
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<td>12</td>
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<td><strong>Average/NDC</strong></td>
<td>49</td>
<td>14</td>
<td>14</td>
<td>12</td>
<td>10</td>
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<td><strong>TOTAL</strong></td>
<td>344</td>
<td>96</td>
<td>100</td>
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### High Impact NDC Research Publications (219)

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<tr>
<th>Journal Name</th>
<th>Number of Publications</th>
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<tr>
<td>Nature</td>
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<tr>
<td>Cell</td>
<td>9</td>
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<tr>
<td>Science</td>
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<tr>
<td>Nature Immunology</td>
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<tr>
<td>Nature Photonics</td>
<td>1</td>
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<tr>
<td>Nature Biotechnology</td>
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<tr>
<td>Immunity</td>
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<tr>
<td>Nature Nanotechnology</td>
<td>4</td>
</tr>
<tr>
<td>Nature Cell Biology</td>
<td>2</td>
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<tr>
<td>Nature Physics</td>
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<tr>
<td>Nature Chemical Biology</td>
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<td>Nature Neuroscience</td>
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<tr>
<td>Neuron</td>
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<tr>
<td>Nature Methods</td>
<td>6</td>
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<tr>
<td>Molecular Cell</td>
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<tr>
<td>PLoS ONE</td>
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<tr>
<td>PLoS Biology</td>
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<tr>
<td>Nature Struct Mol Biol</td>
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<td>Nano Letters</td>
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<tr>
<td>PNAS</td>
<td>22</td>
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<tr>
<td>J Cell Biology</td>
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<tr>
<td>Advanced Materials</td>
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<td>Molecular Microbiology</td>
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<td>Biophysical Journal</td>
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<td>Faraday Discussions</td>
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<td>Human Gene Therapy</td>
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<td>Molecular BioSystems</td>
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<tr>
<td>J Physical Chemistry B</td>
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<td>J Molecular Biology</td>
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<td>Langmuir</td>
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<td>J Structural Biology</td>
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<td>European J Cell Biology</td>
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<td>Optics Express</td>
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<td>Optics Letters</td>
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<tr>
<td>Applied Physics Letters</td>
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<td>Matrix Biology</td>
<td>1</td>
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<td>Virology</td>
<td>1</td>
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<tr>
<td>Nanotechnology</td>
<td>3</td>
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<td>Total NDC Pubs: &gt;300</td>
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<td>2006-present</td>
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### Timeline and Evolution of the Program

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<td>Midcourse Program Review</td>
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<td>2010</td>
<td>NDC Reviews/ Renewals (4)</td>
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<td>Multi-PI Awards (clinical + basic)</td>
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<td>Clinical Consulting Boards</td>
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NDC = Nanomedicine Development Center
Continuing Centers (n=4)

- Protein Folding
- Nucleoprotein Machines
- Mechanobiology of Immune Synapse
- Optical Control of Biology
The ultimate goal is to engineer chaperonins with new functional properties, and/or substrate adaptor molecules, to prevent aggregation and/or refold proteins responsible for misfolded-protein diseases.

Select disease targets
Engineer folding
Move experiments in vivo
Deliver in organism
Perform pre-clinical tests

Elucidate detailed structure & function of chaperonins

Chaperonin blocks huntingtin aggregation

The center is developing methods for rapidly turning ion channels and enzymes in cells on and off with light to treat disease through the non-invasive manipulation or restoration of cell and circuit function in vivo.

Elucidate fundamental properties of target proteins, develop photoswitches, design instruments to stimulate in vitro and in vivo.

Demonstrate in intact animals

- Develop vectors and delivery methods
- Develop animal models
- Improve photoswitches for deep stimulation
- Test in relevant animal models

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The Road to the $1000 Genome — A Roundup of Sequencing Technology Developments

Recent news articles marking the tenth anniversary of the announcement of the first draft sequence of the human genome also predicted the rise of DNA sequencing technologies that sequence a human genome for $1,000 or less in the next three to five years, a development that would change the face of biomedical research and clinical practice.

The effort to bring the cost of high-quality human genome sequencing down to $1,000 or less began in 2004 with the award of the first grants from the National Human Genome Research Institutes' (NHGRI) Advanced DNA Sequencing Technology Program. At the time, Sanger sequencing employed during the Human Genome Project, using 100 machines over three to four months, produced a high-quality draft of a human or mammalian-sized genome for about $10 million.

The initial five-year goal of the program was to develop second, or next generation (NextGen) sequencing technologies that could reduce the cost of sequencing a human genome by two orders of magnitude to $100,000. That sequencing goal has been met and surpassed, thanks in part to the NHGRI program and other academic and private efforts. Such efforts have miniaturized the technologies that use exponentially less of the expensive chemical reagents needed in the first generation sequencing machines, and perhaps more importantly, are able to simultaneously read millions of sequencing reactions rather than just hundreds.

With NextGen DNA sequencing technologies being used in laboratories today, the cost of sequencing a human genome is now about $20,000, and sequencing can be completed with one machine in about a week because these machines process more than 100 million samples a run. Still, getting from a $10,000 genome sequence to a $1,000 genome sequence will not be a trivial endeavor.

For that reason, NHGRI continues to fund the development of revolutionary sequencing technologies. In 2009, NHGRI awarded approximately $19 million to 10 sequencing technology development projects. In addition, NHGRI named as its Recovery Act signature project the development of third generation sequencing technologies (3Gen), able to sequence an individual human genome for $1000. Seven additional projects were awarded more than $1.3 million in Recovery Act funds to further accelerate these efforts.

This article is the first in a series of periodic updates that will summarize breakthroughs recently published in the scientific literature by NHGRI-funded researchers who address or overcome obstacles to developing revolutionary 3Gen sequencing technologies.

Such efforts will integrate engineering with biochemistry, chemistry, nanotechnology and physics to enhance breakthrough DNA sequencing and analysis technologies. The expected result will be solutions to the analytical challenges researchers face in achieving the goal of a $1,000 genome.

"For example, one type of innovation our grantees are developing would eliminate the current need for expensive optical systems and other custom reagents," said Jeffery Schloss, Ph.D., NHGRI's program director for Genome Technology Development. "It's important to explore a wide range of innovative approaches. Instead of using fluorescence to identify DNA base pairs, some groups we fund are designing a technology that could feature a chip containing thousands to millions of nanopores."

A nanopore is a hole about two nanometers in diameter. One nanometer is one-billionth of a meter.
Quantum leaps

“...‘technological leaps’ that seem so far off as to be almost fictional but which, if they could be achieved, would revolutionize biomedical research and clinical practice.”

......Genome sequencing at $1000 or less for a mammalian genome.....
Zero mode waveguide
Optipore DNA sequencing

B McNally, et al. 2010 Nano Lett. 10,2237-2244
© 2010 American Chemical Society

MJ Kim et al. 2006 Adv. Mater. 18,3149-3153
© 2006 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim
Single-stranded nucleic acid molecules passing through a nanometer-sized pore modulate the ionic conductance across the membrane. This observation may one day lead to a device for single molecule DNA sequencing.
Bases cleaved from DNA by exonuclease block the nanopore and disrupt ion flow. Each of the four bases creates a characteristic signal.
Direct electronic readout of A, C, G, T and methyl-C

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Single walled Carbon Nanotubes as Nanopores

H Liu, et al. 2010 Science 327:64-67
© 2010 American Association for the Advancement of Science
IBM
Gustavo Stolovitzky

DNA Transistor

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