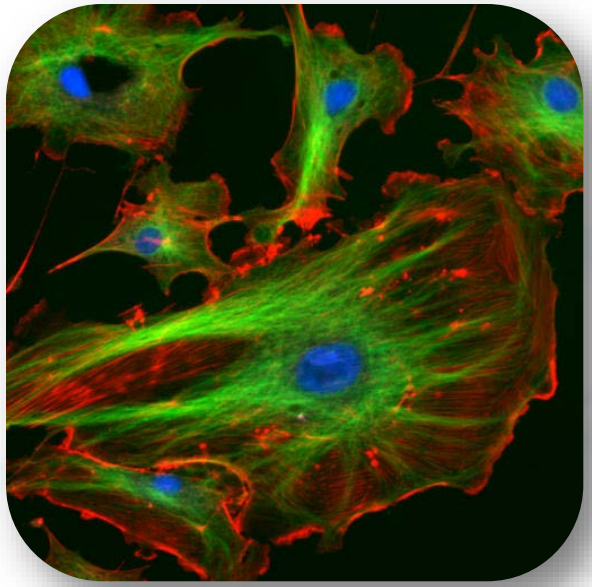


NIST and the Biosciences

Laurie E. Locascio, Ph.D.
Director, Material Measurement Laboratory

NIST
National Institute of Standards and Technology
U.S. Department of Commerce

MATERIAL MEASUREMENT LABORATORY

Bioscience at NIST beside some discoveries that changed the industry

1920

Radiation Physics Program (1920s)
Partnership with ADA, dosimetry standards (1928-)

1930

Standards for clinical markers(1969-)

1970

- Monoclonal antibodies (’74)
- Antibody based technologies

1980

Center for Advanced Research in Biotechnology (1988)
NIST plans national effort to support emerging biotechnology industry; NIST Biotechnology Division formed (1991)

1990

- PCR (’83)
- DNA analysis techniques

2000

Bio becomes NIST focus program - Biosciences Div formed
NIST gets strategic in bio (2006)

- Genome sequenced (’03)
- Next gen Sequencing and Omics measurements

2010

MML formed with 2 bioscience divisions (‘12)
Partnership with Stanford in synthetic bio/genomics (’14)
NIST emerging as an influencer- shaping discussion in standards for bio (‘15)

- Induced Pleuripotent Stem Cells (‘12)
- Technologies for engineering biology

2020

Vision for NIST bioscience – 2005-2015

Leverage our vast expertise in the quantitative physical sciences to provide the measurement infrastructure to underpin innovation in the biosciences

---

- *Strengthen partnerships with the medical, environmental and agricultural communities*
- *Grow our in-house knowledge of interdisciplinary bio-related fields*
- *Teach our federal and private partners in the biotechnology/healthcare fields about NIST's broad capabilities and strengths*

TARGETED AREAS OF STRATEGIC IMPORTANCE FROM 2005-2015

Omics Measurements

Develop the measurement capabilities to support growing needs in genomics, proteomics, metabolomics (health)

Biomanufacturing

Develop measurement science, standards and technologies for biopharma industry focusing on protein therapies (health, manufacturing)

Cell and System Analysis

New methods and technologies for probing cells and systems including tissue and organism level measurements (health)

Targeted Budget Growth for Bioscience at NIST 2005-2015

Budget Initiatives	Year	Amount
Bioimaging (cell and medical)	2006, 2007	3.8 M (MML, PML)
Bioscience/Health (measurement assurance for genomics/proteomics)	2009, 2010	7.5 M (MML, ITL)
Biomanufacturing (protein therapeutics)	2012, 2013, 2014	9.9 M (MML, PML, NCNR)
Synthetic Biology	2015	1.5 M (MML)
Biomanufacturing (nano)	2015	1.0 M (CNST)
Total 10 year base increase in bio		**23.7 M**

Who works in bio at NIST

- In 2012 reorganization, bio became primary focus area for MML
- Currently 5 laboratories have activities in bio area (MML, PML, ITL, NCNR, CNST)

What NIST does

- Performs cutting edge measurement science research to support better measurements
- Develops highest quality measurement science and standards for confidence in biological data

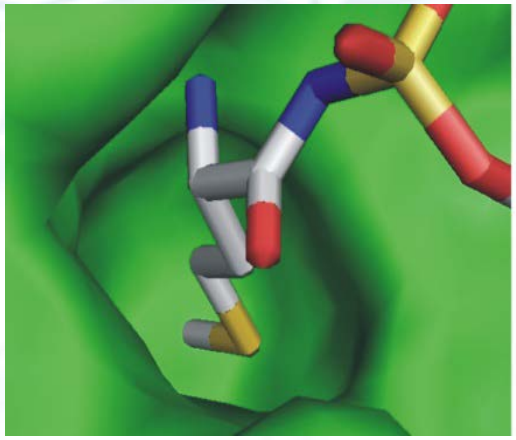
NMR-readable nanosensors for potential application in *in vivo* imaging: G. Zabow, S. J. Dodd, A. P. Koretsky-

Genome in a bottle reference genome: Zook, Munro, Salit

Measurement Science Research

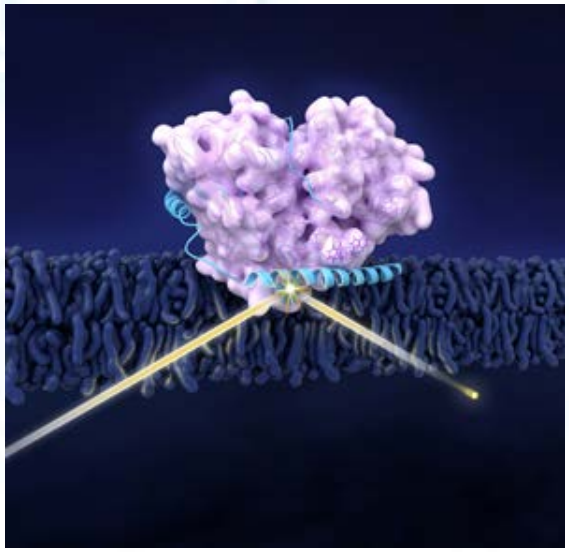
New tools and technologies taking advantage of our strengths in physical sciences

New methods based on existing technologies that enhance their measurement science capabilities



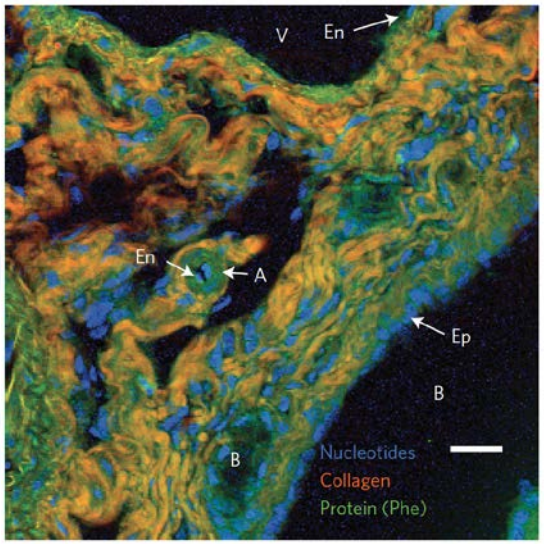
Next gen Protein Sequencing

NIST-invented technology for large scale, massively parallel protein sequencing to access whole proteome without bias (with UMD)



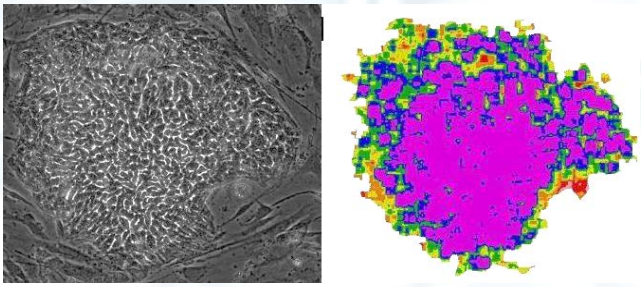
Neutron methods provide insight into Parkinson's disease

Using unique NIST facilities provide high resolution images of protein-protein interactions to elucidate mechanism of disease (with NIH, Carnegie Mellon)



Label-less 3D Chemical Imaging for Cells/Tissues

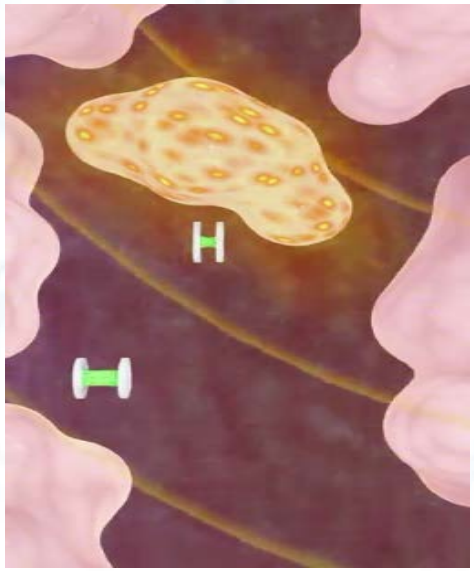
NIST-invented broadband coherent anti-Stokes Raman scattering microscopy can acquire full chemical spectrum at each pixel with high speed and without chemical labels to provide functional and molecular information for understanding of disease



Score = 4.6
(good)

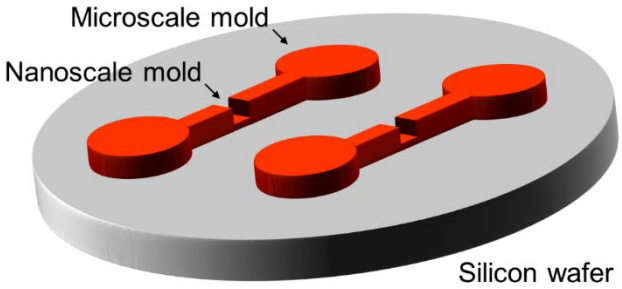
Algorithms and Visualization Tools for Qualification of Stem Cells for Cell Therapies

NIST-developed algorithms to provide objective metrics to qualify stem cell colonies prior to implantation or topical application in order to predict successful outcome. (with NIH)



Shape shifting Probes

NIST-invented shape-shifting probes are first-of-its-kind for sensitive, high-resolution remote biological sensing with application to deep tissue imaging. (with NIH)



Nanofluidic devices for cancer diagnosis

NIST-invented technologies for measuring 'circulating DNA' that results from tumor growth or metastasis. Fluorescence intensity and molecular diffusivity of DNA molecules confined in nanofluidic slits independently analyzed as orthogonal measures of molecular size.

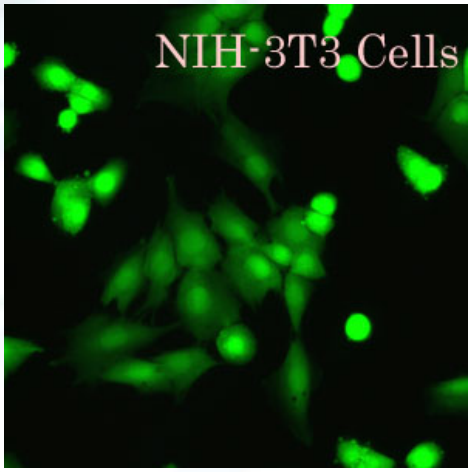
Measurement Science and Standards to Assure Confidence in Biological Data

- Providing standard reference materials, standard methods or community based consensus methods for measurements of RNA, DNA, proteins and cells

from standards for metabolomics to the first standard for global monitoring of HIV

Forensic DNA Typing

An extensive suite of standards, analysis tools, and teaching tools to ensure accurate genotyping. In support of the FBI Quality Assurance Standards followed by all forensic labs, our standards underpin that Nation's confidence in DNA for forensics. (Partners: FBI, NIJ, forensics labs, industry)



Standards for Cell Line Authentication

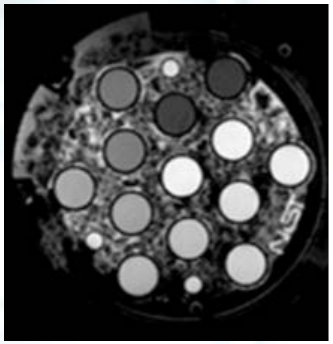
Methods, standards to solve problem of contaminated or misidentified cell lines used for basic research and industrial testing protocols. Estimates of 30% of cells misidentified, leading to incorrect research interpretation and estimates of billions of wasted dollars in our research enterprise. (Partners: ATCC,DNA Diagnostics Center, MedImmune)

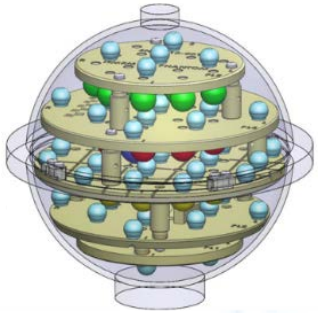
ISO Biotechnology Standards Committee

NIST serves as Chair and Executive Secretary of US Delegation developing documentary standards for biobanking, bioanalytical methods, and bioprocessing and promoting US agenda in international standards impacting trade.(Partners: FDA, USDA, USTR, NIH, DOE, ITA, US industry)

DNA Microarray Measurements

Reference methods, data analysis tools providing confidence in DNA microarray measurements addressing the wide variability in results from different commercial platforms. Developed in NIST-led consortium with >90 public, private, academic partners, standard sequences **now on products of every major microarray producer.** (Partners: NIH, FDA industry)





NIST MRI Phantoms

Medical Imaging

Standards, phantoms, and improved contrast agents for ionizing and non-ionizing (optical and magnetic) radiation medical imaging technologies to promote reproducibility, reduce uncertainty associated with various imaging modalities. First commercially-available traceable **PET phantoms to be shipped with every GE Healthcare PET-MRI scanner.**

Mass Spectral Library

Reference standard mass spectra for chemical, protein, peptide identification- largest selling NIST purchased data product. World's most widely used MS library with validated software for spectrum matching. **Integrated into virtually every mass spectrometry instrument vendor software systems.**

For greatest impact, we:

- Develop deep ties with our federal agencies (NIH and FDA are key)
- Establish close relationships with our industry stakeholders who keep us abreast of current issues affecting the sector
- Strategically partner with US biotechnology leaders to leverage federal dollars against private sector investment

Ties with Federal Agencies

- FDA/CDRH: Whole Genome Sequencing - genomic reference materials for personalized medicine; FDA used pilot NIST material to aid in approving the first next generation sequencer
- FDA/CDER, CBER: Biotherapeutics- ~ 65 FDA scientists and review staff participate in joint workshops to reconcile results from different sample processing, chromatographic, and mass spectral methods that sponsors use; MML serves on FDA advisory panel for biosimilar license applications
- NIH/NCI, Early Detection Research Network : Cancer Biomarkers- Validation and verification of new biomarkers for early cancer detection conducting Interlaboratory comparisons, producing standards, data analysis protocols for miRNA, genetic biomarkers
- NIH/NCI, Clinical Proteomics Tumor Analysis Consortium: Proteomics- Standards and data to support 'Common data analysis pipeline' (CDAP) for mass spectrometry consortium data in proteomics
- NIH/NIDCR: Dental Materials- Standard Reference Materials (SRMs) for measurement assurance of calcium phosphate based biomaterials; standardized measurements for improved dental materials and oral health care
- NIH/NIGMS, NSF/BIO, NIST: Co-organizing WH Symposium on confidence in data for innovation and data sharing (early 2016).

Ties with Federal Agencies

- FDA/CDRH: Whole Genome Sequencing - genomic reference materials for personalized medicine; FDA used pilot NIST material to aid in approving the first next generation
- FDA/CDER, CBER: Biotherapeutics- collaborate to reconcile and understand results from different methods that sponsors use in FDA applications for approval of new technologies and products; serve on panel for biosimilar license applications
- NIH/NIGMS, NSF/BIO, NIST: Co-organizing WH Symposium on confidence in data for innovation and data sharing (early 2016).
- support 'Common data analysis pipeline' (CDAP) for mass spectrometry consortium data in proteomics
- NIH/NIDCR: Dental Materials- Standard Reference Materials (SRMs) for measurement assurance of calcium phosphate based biomaterials; standardized measurements for improved dental materials and oral health care
- NIH/NIGMS: co-organizing a WH Symposium on reproducibility and confidence in data (early 2016) working with Jon Lorsch (NIGMS) and Jim Olds (NSF-BIO).

Ties with Federal Agencies

- NASA: worked with NASA to create strategic plan for materials research in the International Space Station including biological materials, biomaterials and biomimetics
- DARPA, Living Foundries program: standards for Synthetic Biology
- DHS Office of Science and Technology: Biosecurity Threat Detection- Engineered yeast with known genetic sequences for testing detection of unknowns

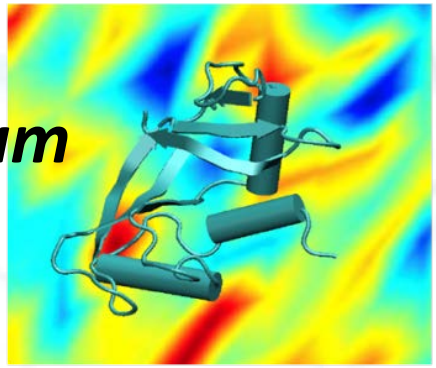
Working with Industry Stakeholders through Consortia

Genome in a Bottle Consortium

- NIST led consortium with more than 75 public, private, academic partners
- Developing whole genome reference materials and bioinformatics tools for quality assurance of whole genome sequencing technologies (next gen and next/next gen).
- FDA used this to approve the first high-throughput DNA sequencer.

NY Times (5/14/15): "The federal government opened a new era of genetic medicine on Thursday by introducing a standard way to ensure the accuracy of DNA tests used to tailor treatments for individual patients."

nSoft consortium

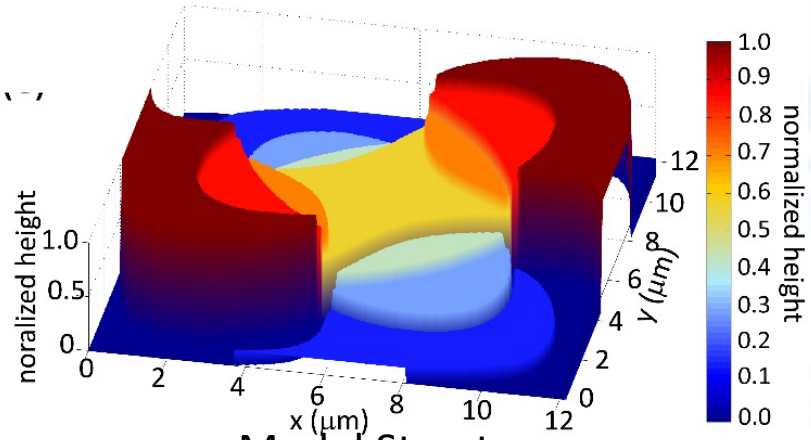


- NIST-led consortium for neutron measurement of soft materials
- Developing neutron instrumentation, sample environments, data analysis methods to attack issues in manufacturing of soft materials including polymers, colloids, and proteins (biopharma).
- Issues addressed include understanding protein instability in freeze-dried formulation; protein aggregation in needles (Dupont, Genentech, MedImmune, Chevron Phillips, Kimberly Clark, Dow, Solvay)

Nanofabrication and NanoBio

Multiple projects underway in CNST:

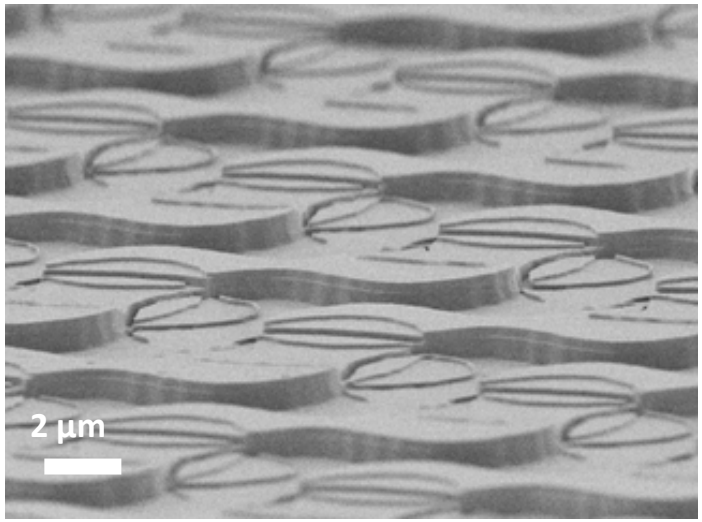
DNA sequencing; regenerative medicine; medical devices; medical diagnostics; drug delivery; neural probes; imaging (MRI, X-ray, & fluorescence); cell sorting and manipulation.



Model Structure

One example: 3D imaging of DNA transcription

- New method enables simultaneous imaging of multiple focal planes in live cells
- Collaborative microscope development project with HHMI Janelia Farm
- Diffractive optic produced in the NanoFab will dramatically improve throughput



Fabricated Structure

Strategic Partnerships

Institute for Bioscience and Biotechnology Research Partnership with University of Maryland System

Precision biomolecular structure/function measurements & standards to support biopharma and biotechnology

- NIST focus area: Biomanufacturing
- Funding: Grant to UMD $2.2M/annual) for infrastructure, operations, scientific programs
- IBBR NIST Staff, Associates and Affiliates (~ 50)

Joint Initiative in Measuring Biology (JIMB) Partnership with Stanford University

Measurements, standards and informatics tools for the genomics and the emerging synthetic biology enterprise.

NIST focus areas: Genomics, Synthetic Biology
Funding: 2 grants to Stanford (~2M) for research, training, seed funding for metrology
JIMB NIST Staff: 11

NIST labs reminded me of one of my favorite places, a hardware store, where I'm fascinated with all of the small objects in the bins and wonder what they are used for. NIST's bins are no secret to chemists, physicists, and engineers, but there hasn't been much for biologists. But now biologists have a bin or two at NIST…

The great news for us is that NIST has decided to help…by developing standards we can all use as benchmarks for our research and clinical applications. But they won't make a big deal of it; NIST does their work quietly choosing projects not on the basis of headline-grabbing potential, but on the potential to improve the quality of our science.

Jeanne P. Loring, Ph.D., Scripps Research Institute
Member, NRC Review Panel

What’s next?

Microbes and Humans

In Good Health? Thank Your 100 Trillion Bacteria By Gina Kolatajune, NY Times, 6/13/12

Dr. Barnett Kramer, director of the division of Cancer Prevention at {the NCI} had another image. Humans, he said, in some sense are made mostly of microbes. From the standpoint of our microbiome, he added, "we may just serve as packaging."

A. Bouslimani et al., Molecular Cartography of the human skin surface in 3D, PNAS, 3/30/15

Cancer continued

Thinking Ahead: From 'The Emperor Of All Maladies' To Precision Medicine In Cancer

While precision medicine is enhancing oncologists' capacity to predict effectiveness of treatment for individuals with particular mutations, this approach is new to most clinicians and doesn't yet apply in many cases.

By Elaine Schattner, Forbes, 3/15

Biological bad luck blamed in two-thirds of cancer cases

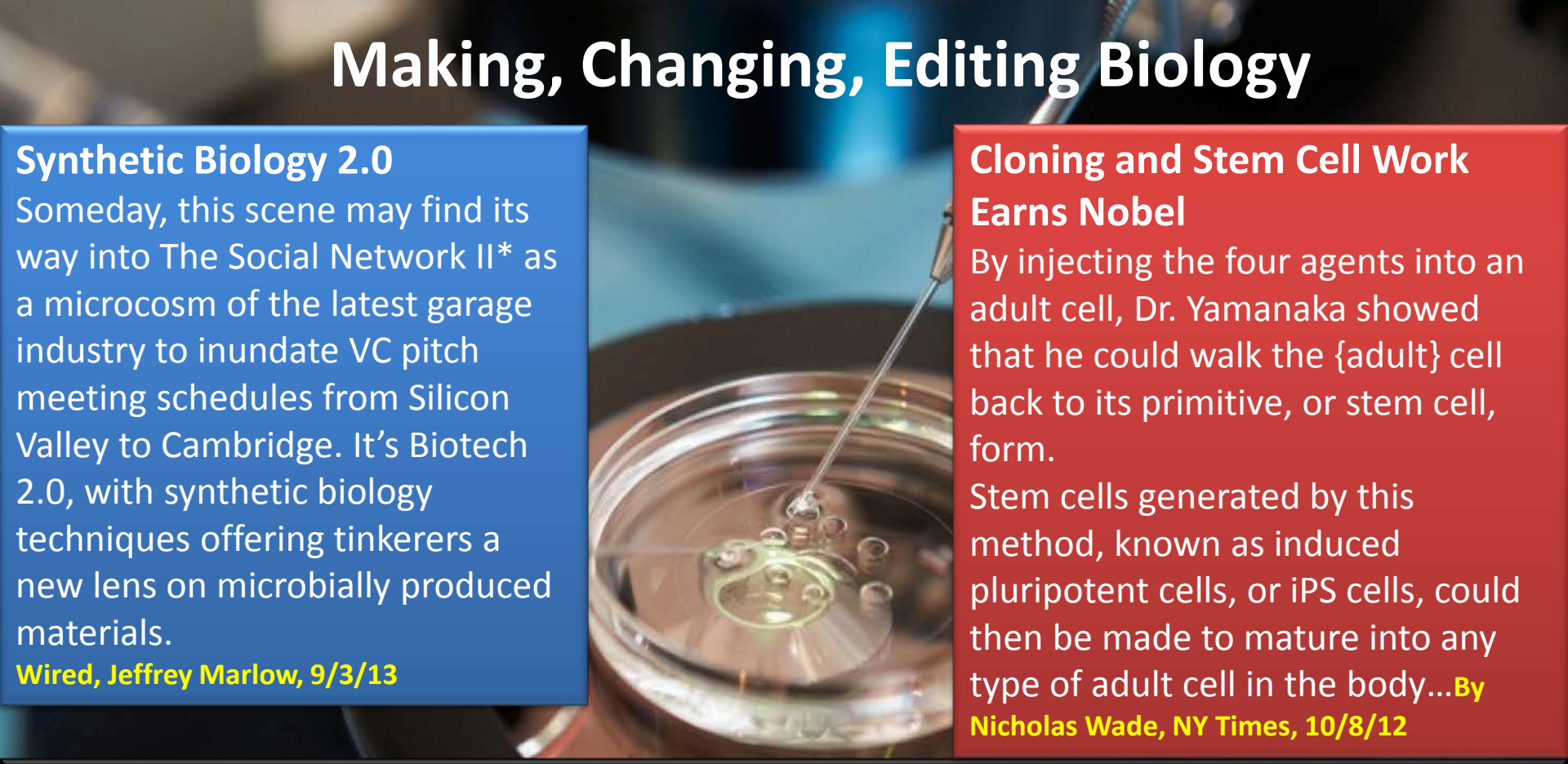
Tomasetti said harmful mutations occur for "no particular reason other than randomness" as the body's master cells, called stem cells, divide in various tissues. "Thus, we should focus more research and resources on finding ways to detect such cancers at early, curable stages," Tomasetti added.

By Will Dunham, Reuters, 1/1/15

Tomasetti and Vogelstein, Science, Jan 2 2015

Male cancer patients lose out in deadly research divide, The London Times, Jan 2013

Making, Changing, Editing Biology



Synthetic Biology 2.0

Someday, this scene may find its way into The Social Network II* as a microcosm of the latest garage industry to inundate VC pitch meeting schedules from Silicon Valley to Cambridge. It's Biotech 2.0, with synthetic biology techniques offering tinkerers a new lens on microbially produced materials.

Wired, Jeffrey Marlow, 9/3/13

Cloning and Stem Cell Work Earns Nobel

By injecting the four agents into an adult cell, Dr. Yamanaka showed that he could walk the {adult} cell back to its primitive, or stem cell, form.

Stem cells generated by this method, known as induced pluripotent cells, or iPS cells, could then be made to mature into any type of adult cell in the body…**By Nicholas Wade, NY Times, 10/8/12**

The rumors were true: Scientists edited genomes of human embryos for the first time

In March, a rumor surfaced in the scientific community that was intriguing, and perhaps a bit chilling: According to those in the know, researchers in China had successfully edited the genomes of human embryos, altering their DNA in a way never accomplished in our own species.

By Rachel Feltman, Washington Post, 4/22/15

P. Liang et al., CRISPR/Cas9-mediated gene editing in human tripronuclear zygotes, Protein & Cell, 4/18/15

3-D Printed Body Parts

Custom Organs, Printed to Order
Laboratories have successfully recreated human ears, noses, skull bones, jaw bones, tracheas, ears, noses, skin sections, bladders, arteries, and fat. Rather than cutting squares of healthy skin from a patient to help cover an injury, a 3D printer could print skin perfectly shaped to fit. Patients marred by disfigurement may soon be able to customize a nose on a computer.

Nova Next, By Jenny Morber, 3/18/15

A 10 YEAR VISION FOR 2015

NIST MEASUREMENT SCIENCE AND INNOVATION ENABLE 21ST CENTURY HEALTHCARE AND THE BIOECONOMY

In 10 years we have developed strong core capabilities in target areas of molecular and cellular analysis.

To have impact in the next wave of the building bioeconomy requires a great deal of additional sophistication to examine system-level complexity.

AREAS OF STRATEGIC IMPORTANCE (2015-2020)

Engineering biology
Develop the measurements and models for engineering biology to map out the fundamental principles that drive development of next generation bio-based products (high tech manufacturing, health)

Microbial Measurements
Develop measurement infrastructure for microbial measurements (health, environment)

Data and Informatics
Provide validated data and informatics tools to support confident decision-making (all sectors)

Quantitative Tools for Characterization of Complex Biologics
Define complex biomolecules/biologics through quantitative measurements to enable prediction of biological function in healthcare applications (manufacturing, health)

Precision Medicine
Develop measurement science and standards to ensure confidence in clinical decision-making, and ultimately enable adoption of precision medicine (health)