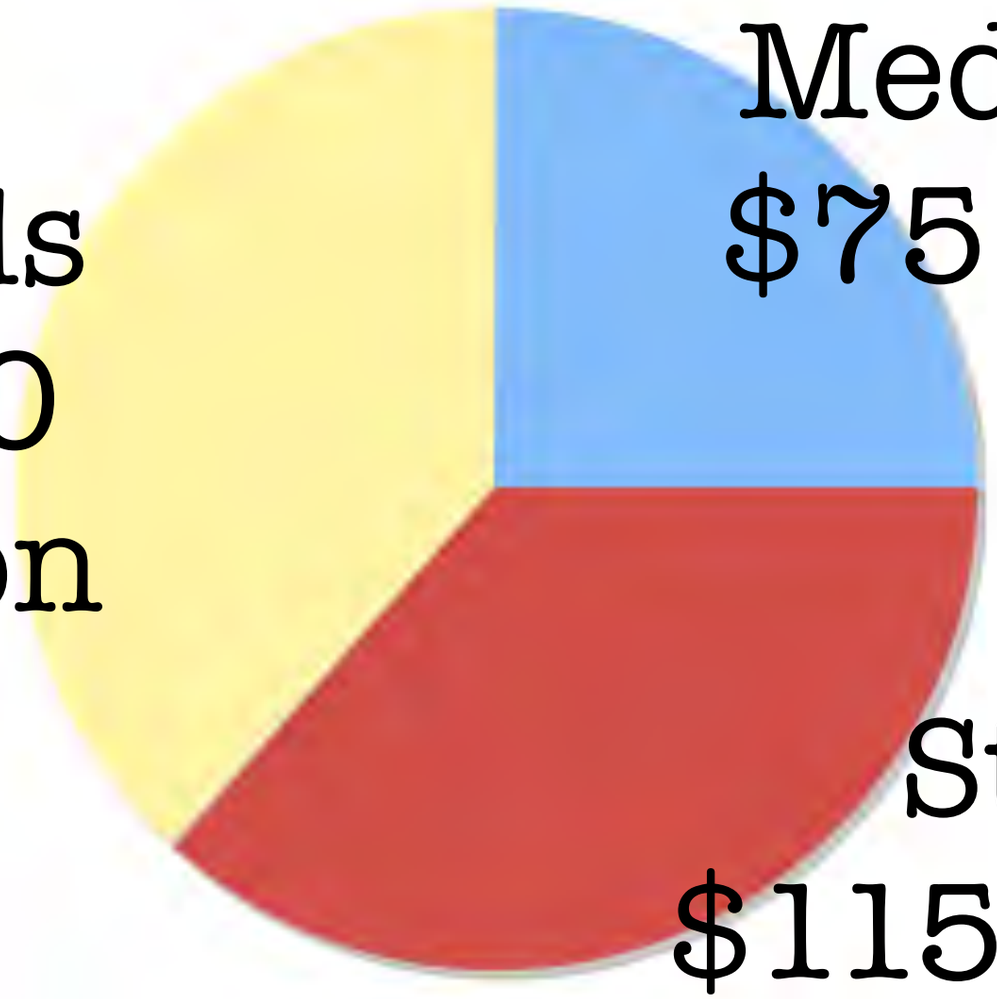
Bio(technology) in the 21st century

Drew Endy
Stanford Bioengineering
The BioBricks Foundation

12 September 2014
Lehigh University

Genetic engr. is >2% of US economy



Foods
$110
billion

Medicines
$75 billion

Stuff
$115 billion

10-15%
past y.o.y.
growth

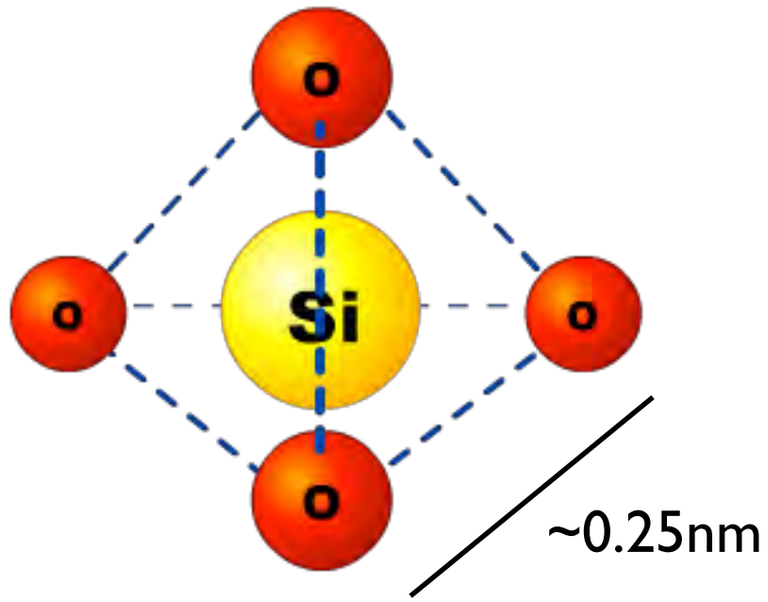
Biodesic DocID: 20110811_01

Biodesic 2011 Bioeconomy Update

Rob Carlson

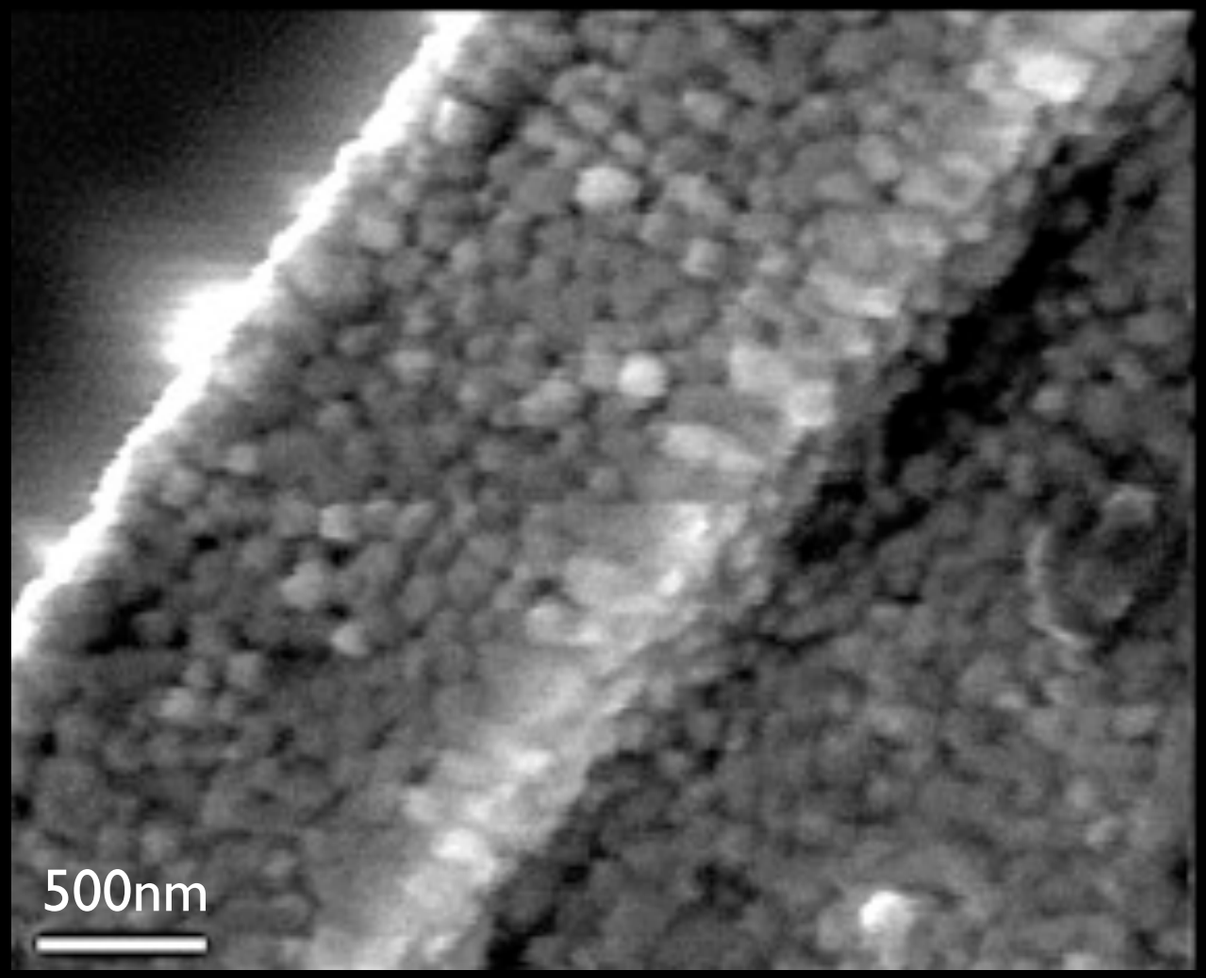
Genetically modified (GM) crops continue to see extensive global adoption. Revenues are growing rapidly and are substantially larger than commonly reported. Within the United States, more than 50% of cropland is now planted in GM seed resulting in 2010 revenues of nearly $110 billion. Together with 2010 revenues from biologics of $75 billion and revenues from industrial biotechnology of $115 billion, I estimate that total 2010 revenues from genetically modified products exceeded $300 billion, or the equivalent of more than 2% of Gross Domestic Product (GDP).

Yet, most of biotechnology
has not been imagined
or made true.



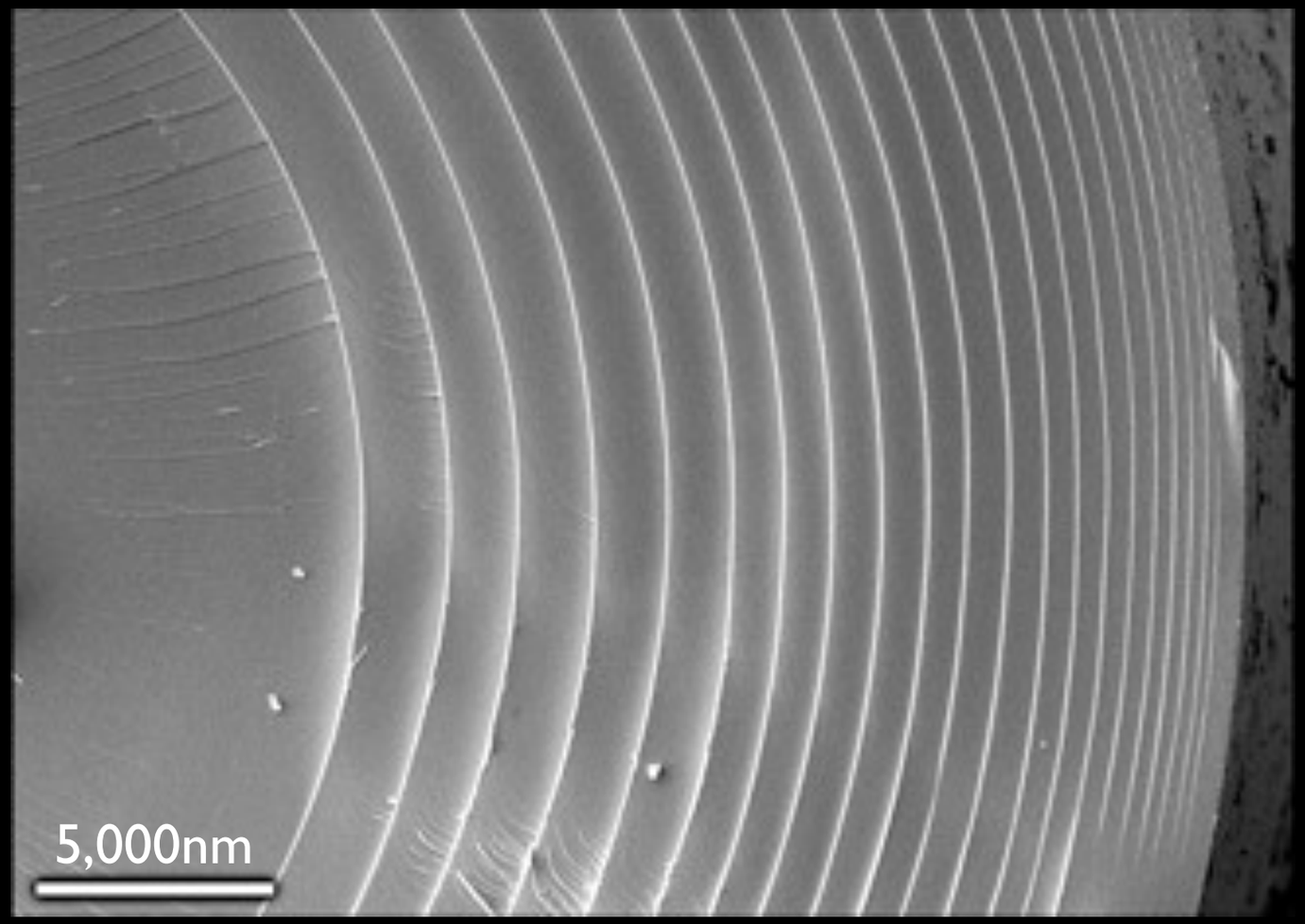
"Tetrahedral coordination of silica (SiO_2), the basic building block of the most ideal glass former."

http://en.wikipedia.org/wiki/Silicon_dioxide



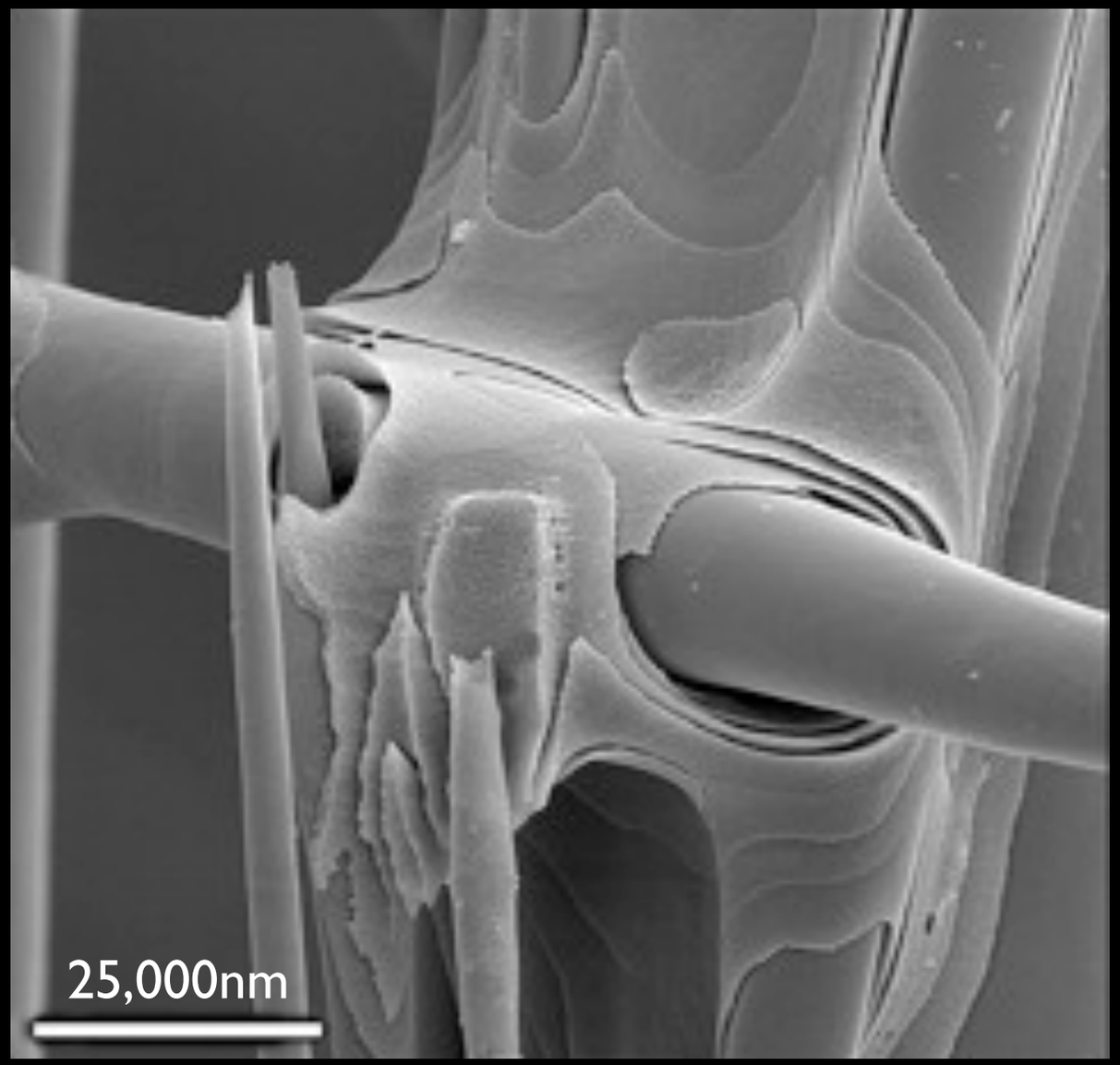
Sponge biosilica

Joanna Aizenberg et al., *Science* v.309 no.5732 pp.275-278, 8 July 2005



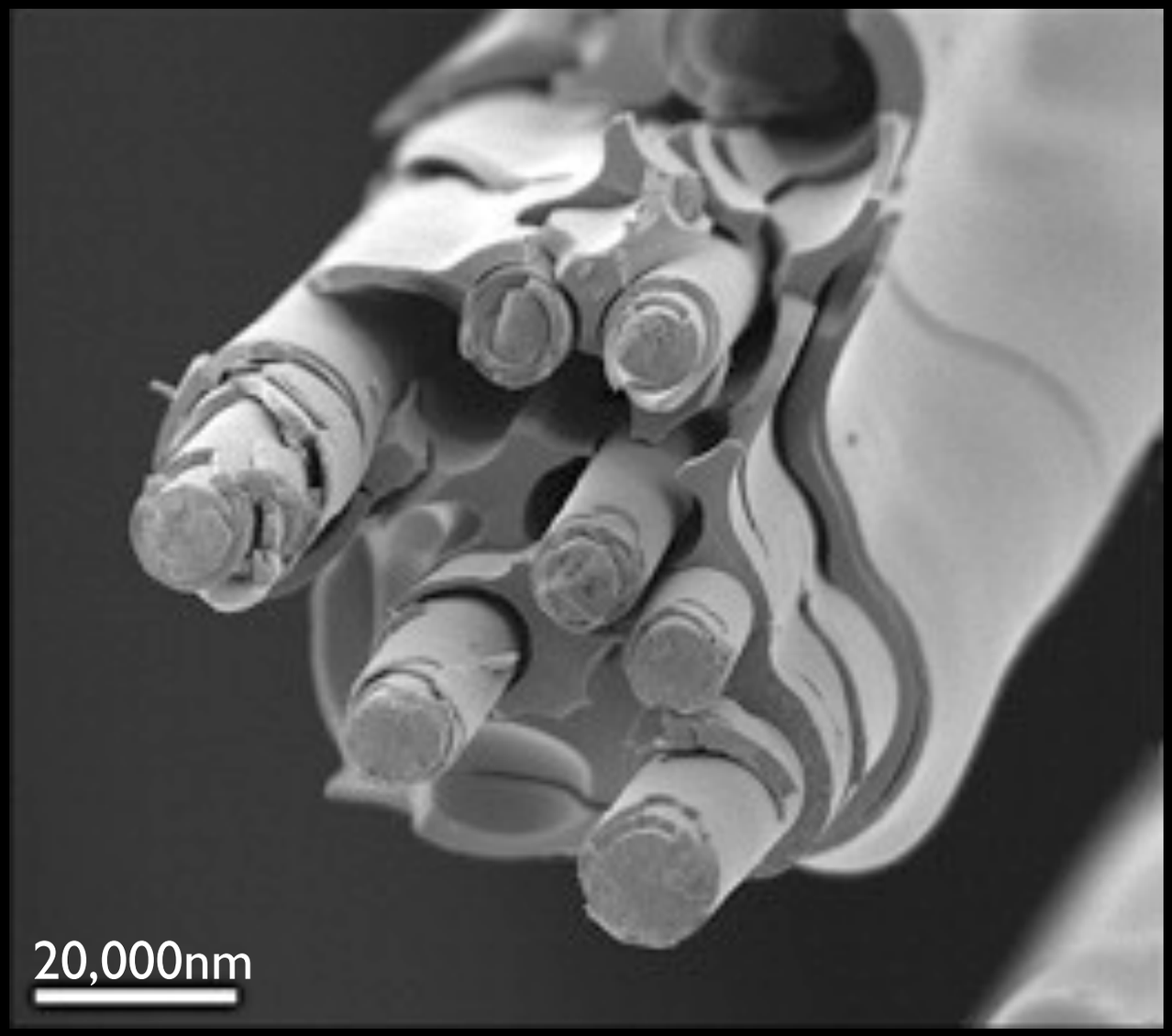
Laminated biosilica comprising sponge spicule

Joanna Aizenberg et al., *Science* v.309 no.5732 pp.275-278, 8 July 2005



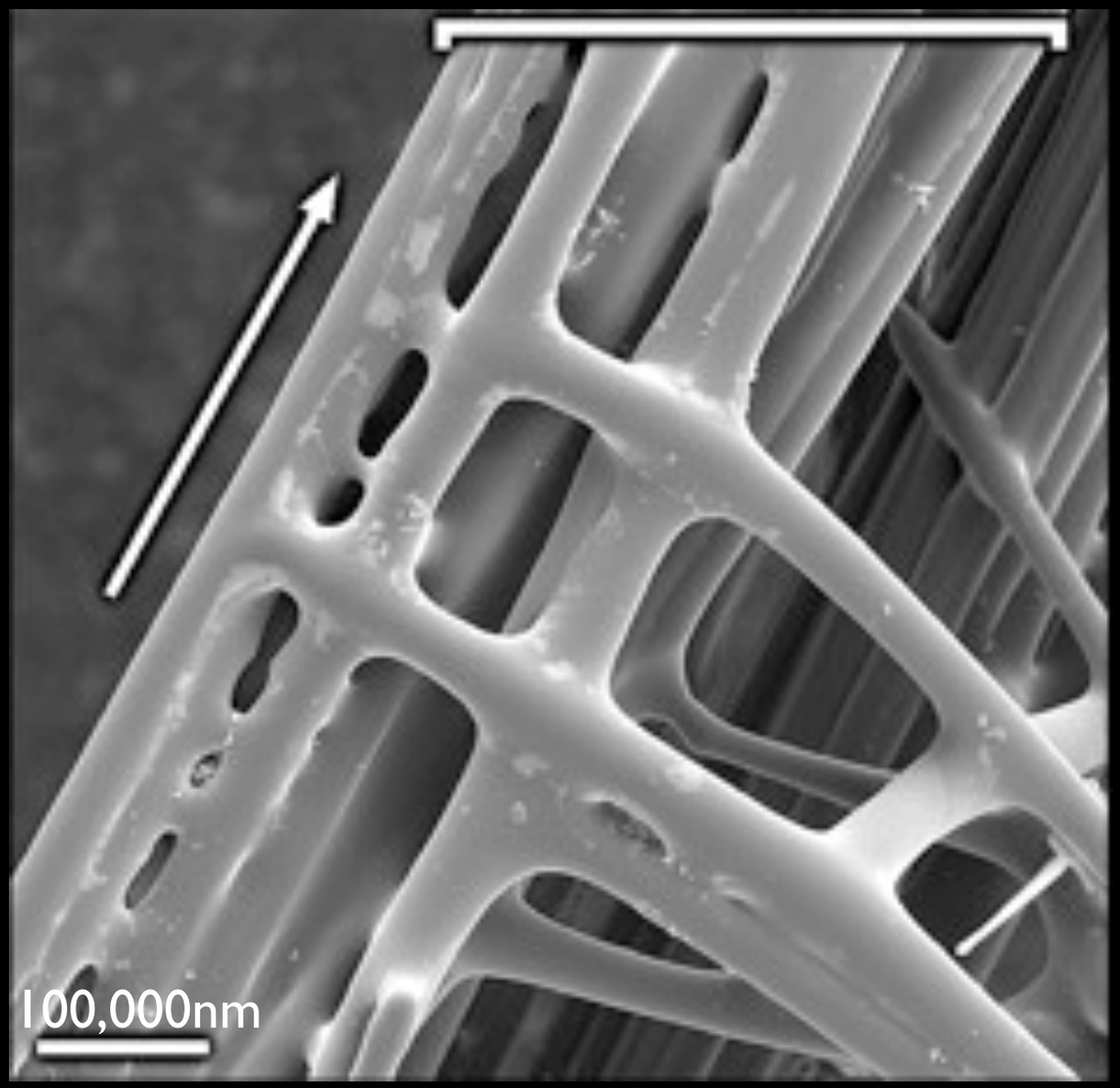
Sponge spicule lattice junction

Joanna Aizenberg et al., *Science* v.309 no.5732 pp.275-278, 8 July 2005



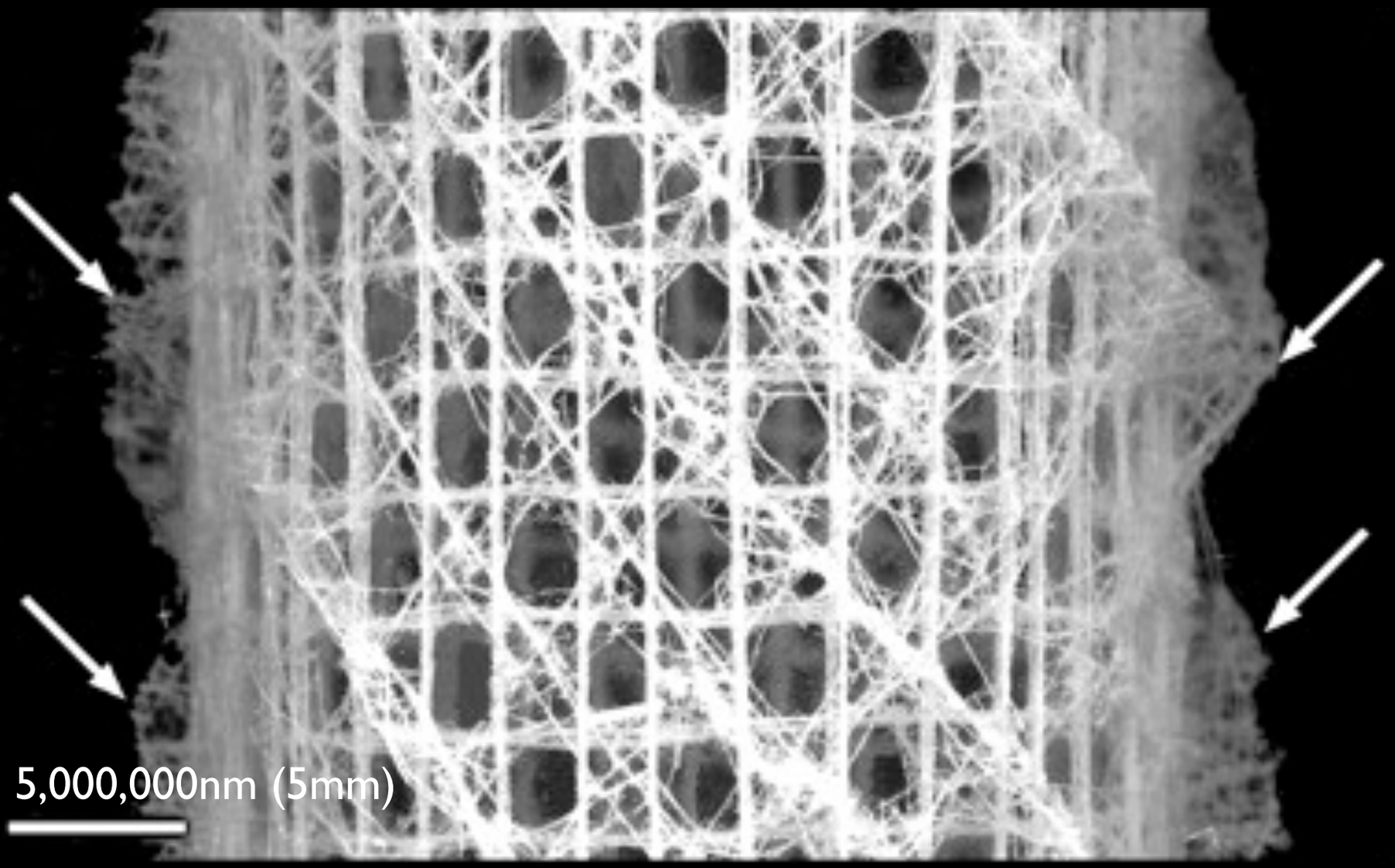
Cross section of biosilica spicule composite beam

Joanna Aizenberg et al., *Science* v.309 no.5732 pp.275-278, 8 July 2005



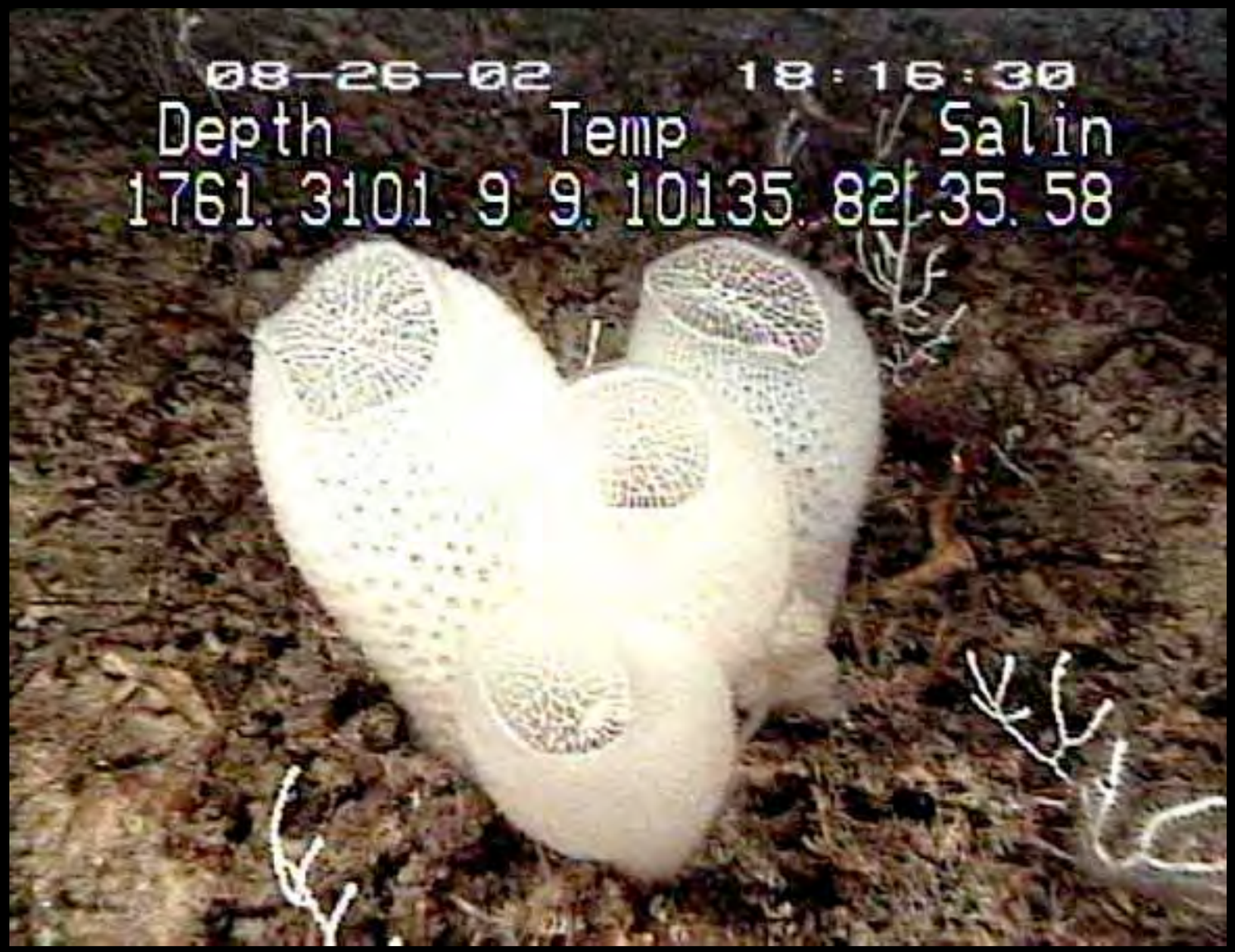
Bracketed junctions of biosilica spicule composite beams

Joanna Aizenberg et al., *Science* v.309 no.5732 pp.275-278, 8 July 2005

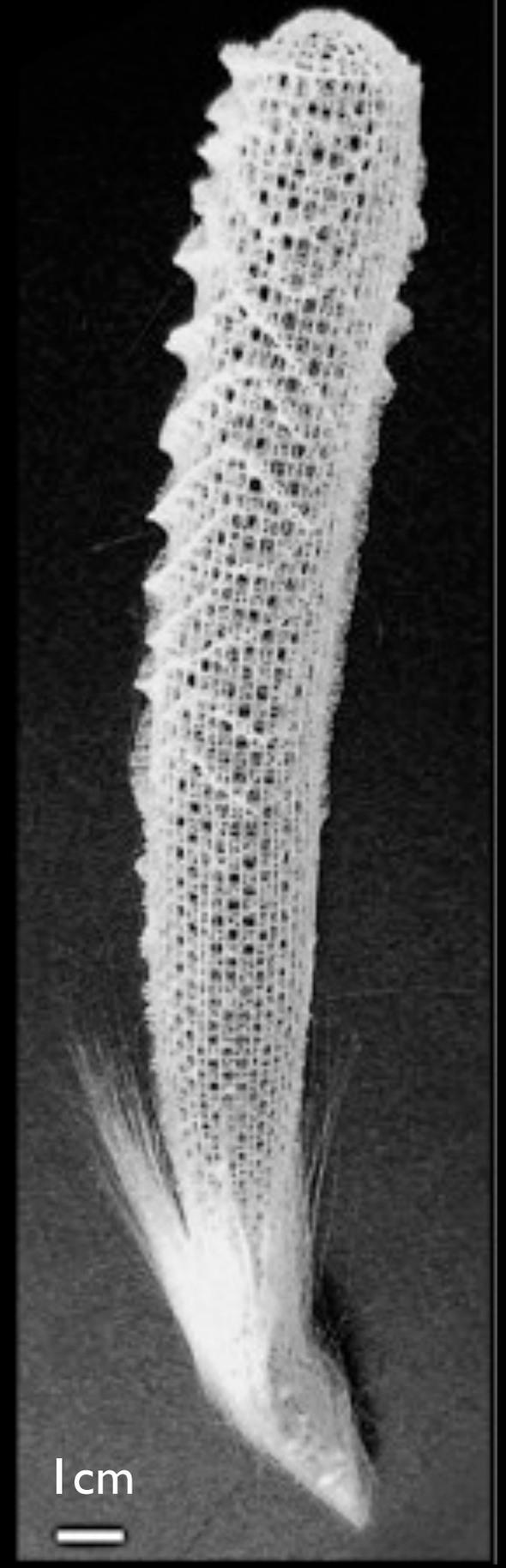


Biosilica cage

Joanna Aizenberg et al., *Science* v.309 no.5732 pp.275-278, 8 July 2005



http://en.wikipedia.org/wiki/Venus%27_Flower_Basket



Joanna Aizenberg et al., *Science* v.309 no.5732 pp.275-278, 8 July 2005

What could we do with Menlo Park, now a California "Shangri La" ?

http://sjl.blogs.com/photos/sharon_park/

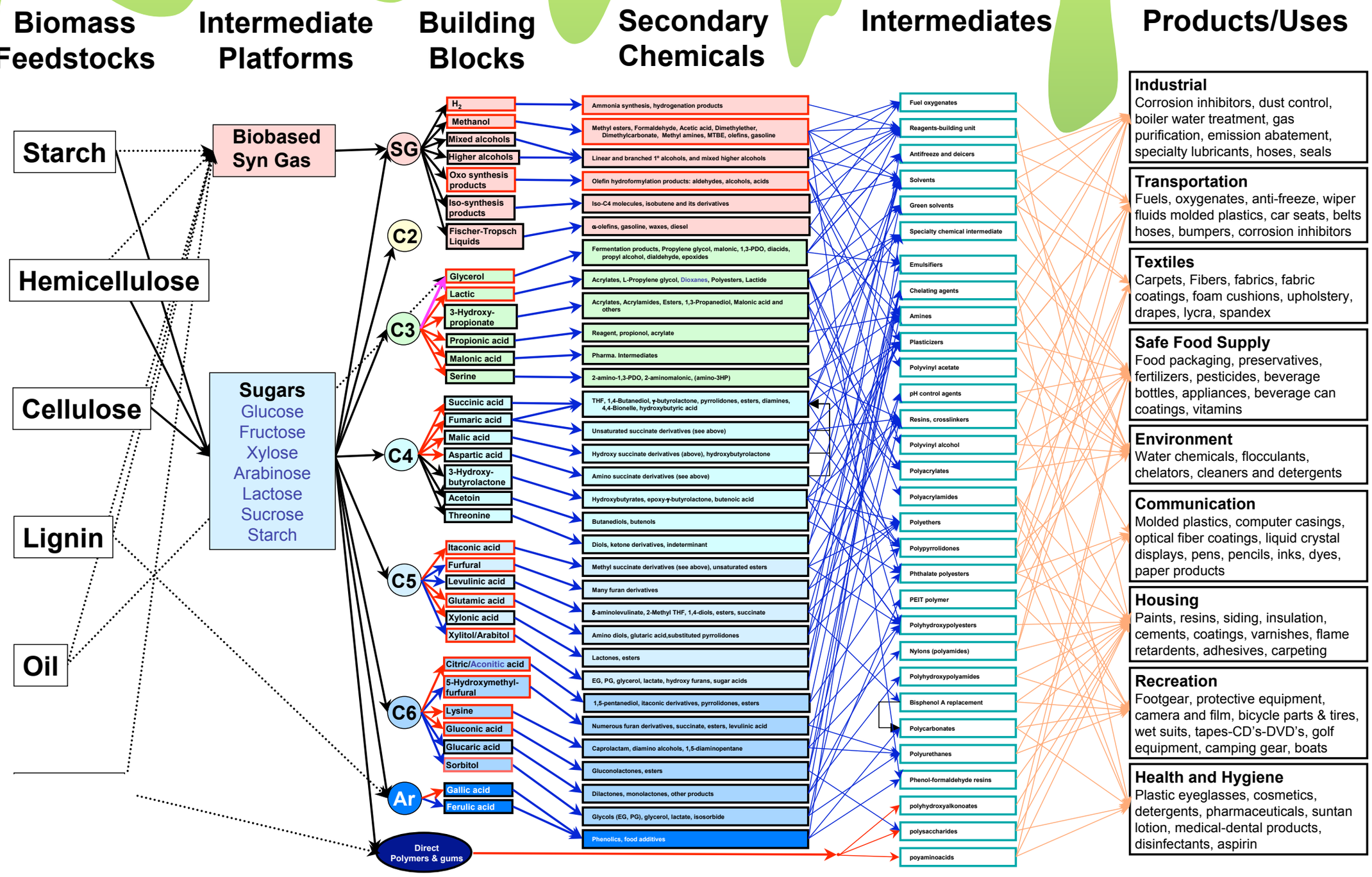
~16,000,000 pounds lawn & garden clippings per year...

The living bridges of Cherrapunji, India are made from the roots of the Ficus elastica tree. (http://rootbridges.blogspot.com/)

Fungal Chair, c/o Phil Ross (www.philross.org)

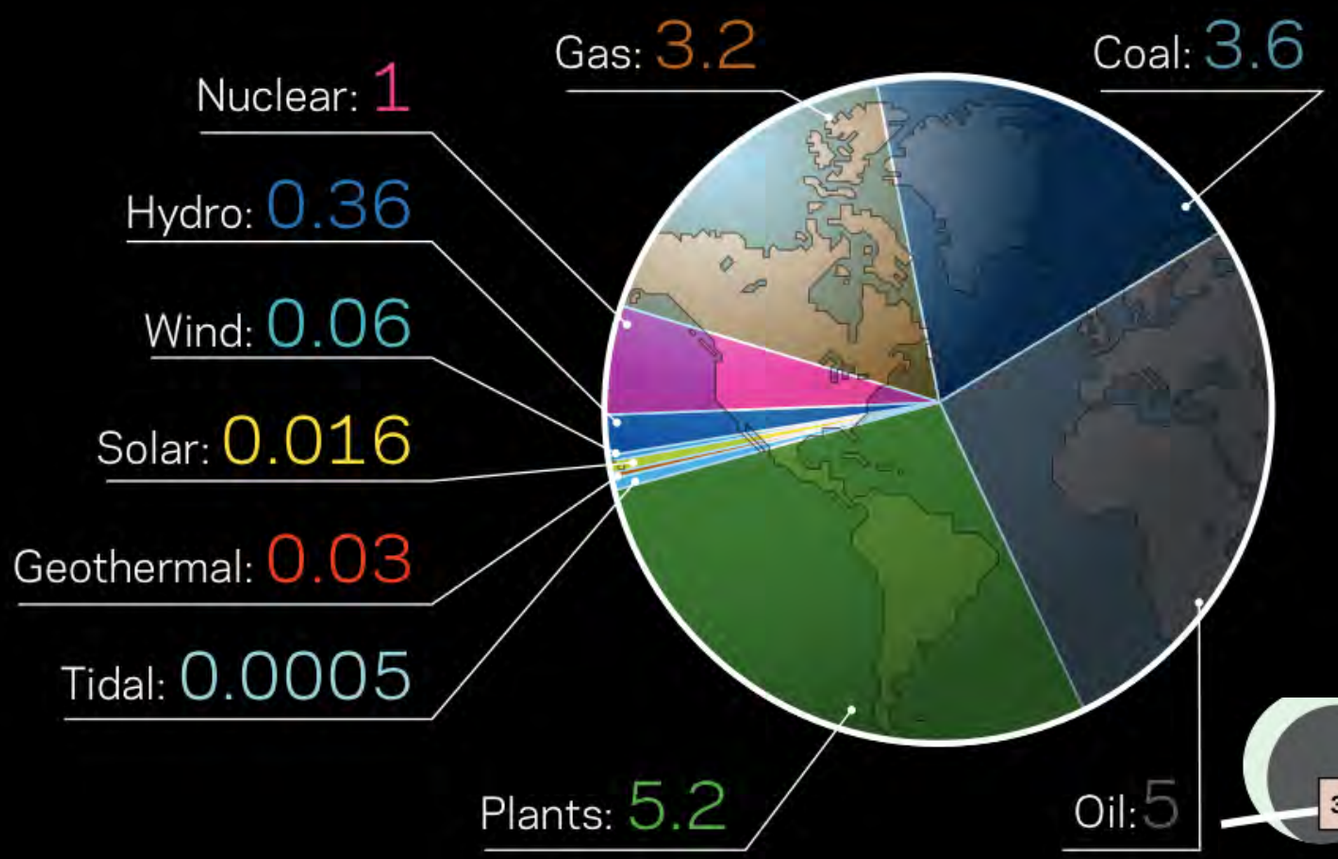
Food | Energy | Environment | Agriculture | Health | Chemicals & Materials | Security

2004 DOE report lists 120 highvalue chemicals for biomanufacturing



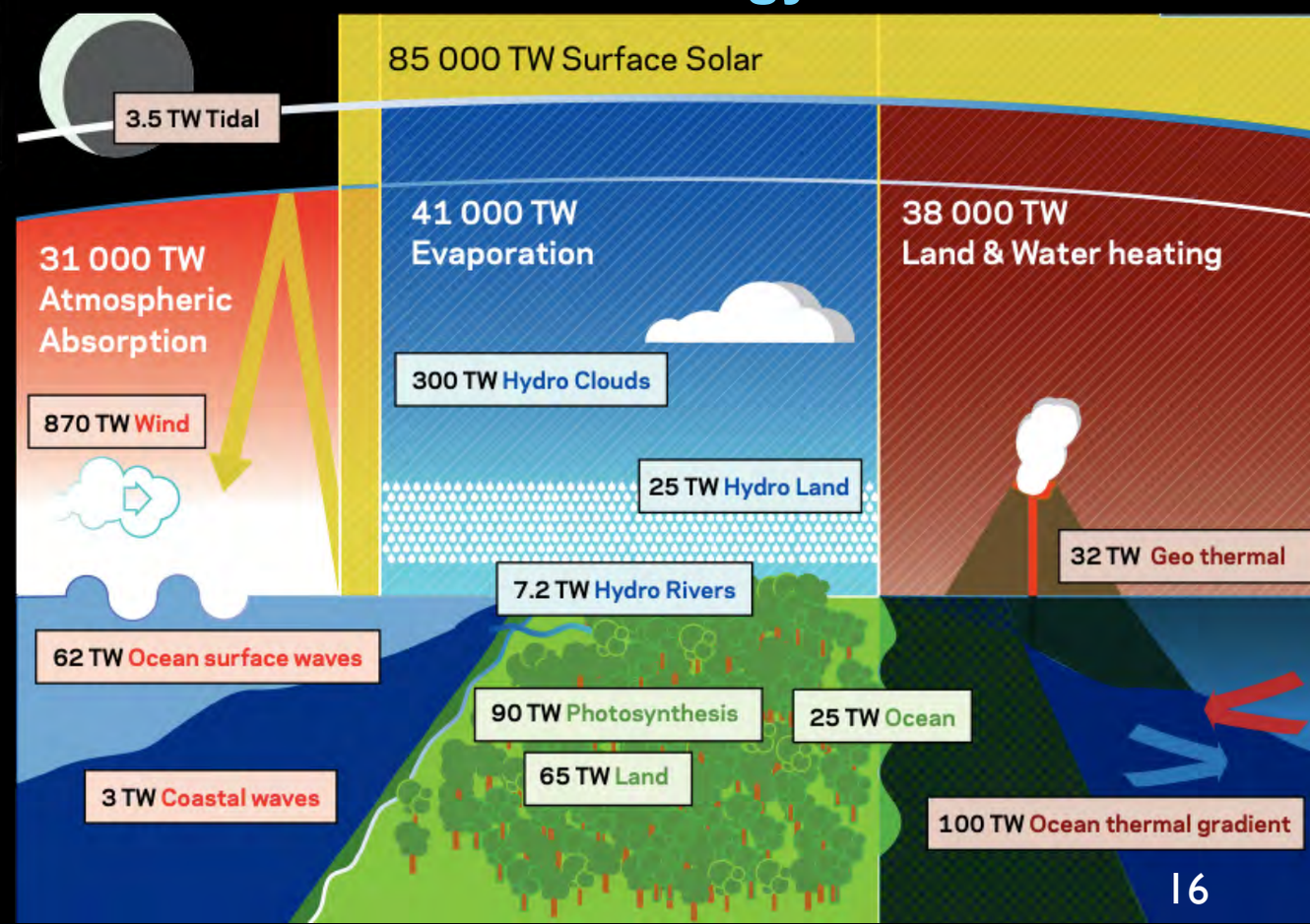
E.g., how much can we make with biology?

Current energy sources (15-17TW)



***Biology is ~90TW**

Renewable energy sources



"The Game Plan" v1, S. Griffith et al.

24% How will it be used?

c/o Jon Hoekstra, Chief Scientist, World WildLife Fund

Could we make biology easy to engineer?

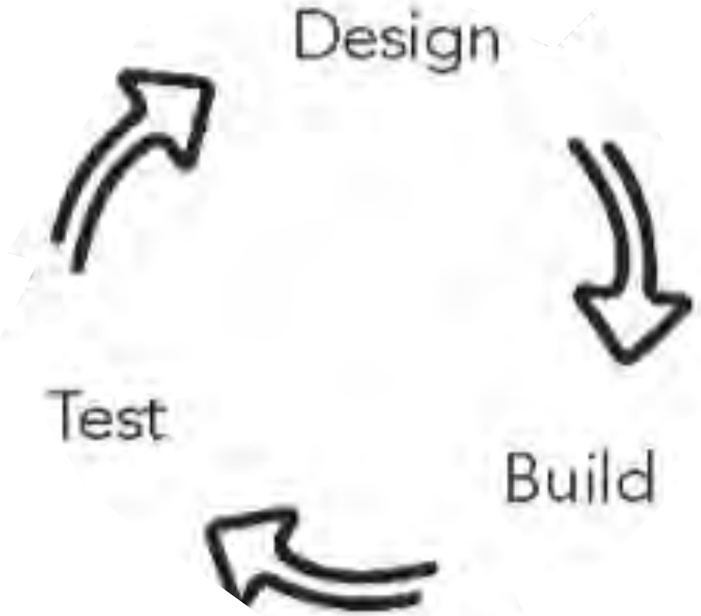
Self-mixing molecular systems

Atomic-scale thermal noise

Reproducing "machines"

High heterogeneity

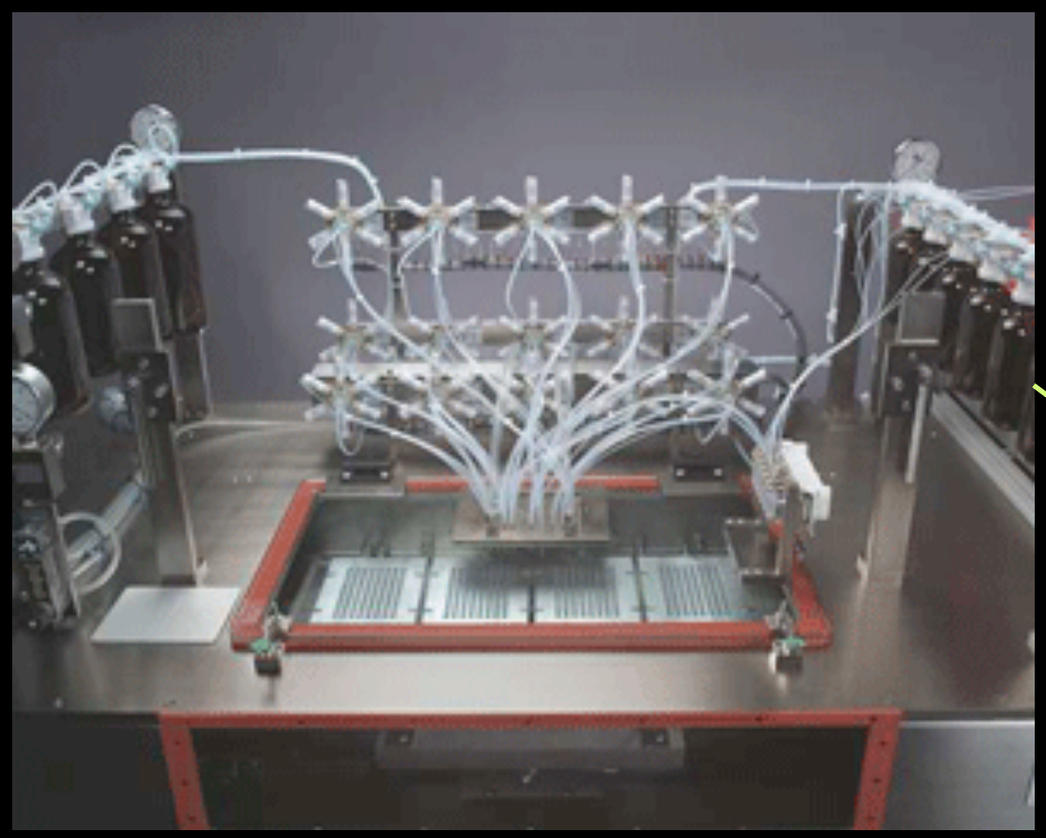
Living ramifications



DNA Construction = #1 Tech. of 21st Ctry.

From absract information to physical, living DNA designs.

TAATACGACTCACTATAGGGAGA



2004: 10,000 bp
2010: 1,000,000 bp
2016: 100 million?

Abstraction to enable engineered bio-simplicity!

8 Bit Synchro. Counter

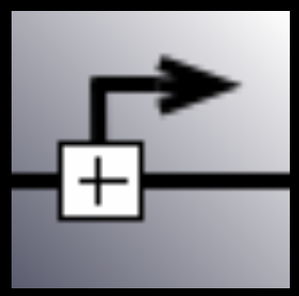
Systems = One or more devices encoding a human defined function(s).

Abstraction barrier! Do not cross!

DNA Inversion Data Latch

Devices = One or more parts encoding a human defined function(s).

Abstraction barrier! Do not cross!



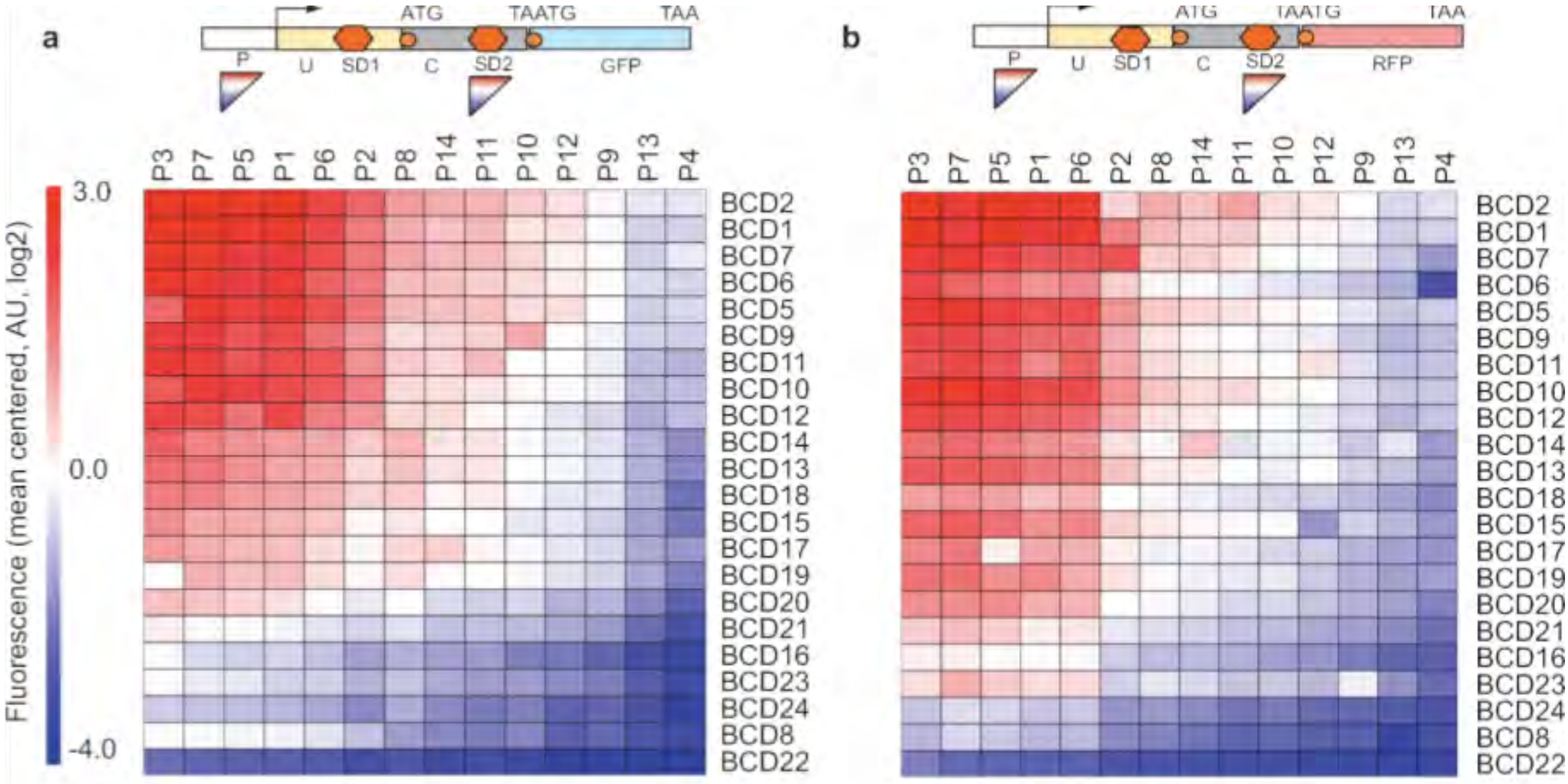
Parts = Basic biological functions encoded via DNA.

Abstraction barrier! Do not cross!

CTATAGGGAGA

DNA = Primary sequence and material.

c.2012, Standard Promoters & UTRs, 2 genes



**unpublished BIOFAB data c/o Dr.Vivek Mutalik et al. of BIOFAB Emeryville, funded via NSF and several corporate gifts.*

What do standards & abstraction enable?

1. Coordinate work over time

2. Coordinate work among parties

3. Enable the otherwise impossible

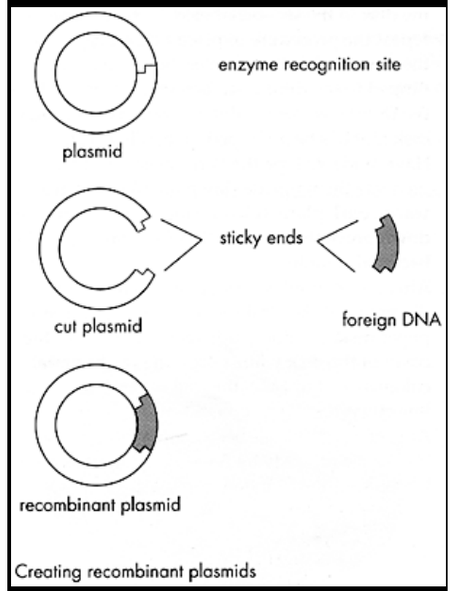
MIT 2003

iGEM 2010

21st Century Biotech. via Tools Revolutions

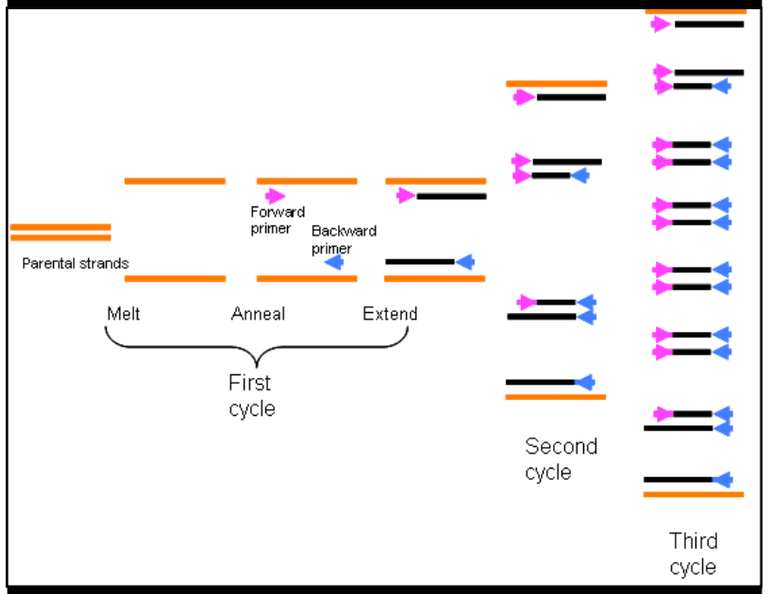
First Gen. Biotech =

Recombinant DNA



Basic "Cut" & "Paste"

Polymerase Chain Reaction



Amplify & Make Simple Changes

DNA Sequencing

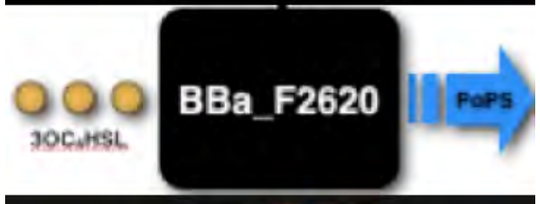
Read Out the Genetic Code

Next Gen. Biotech Adds New Tools =

Synthesis

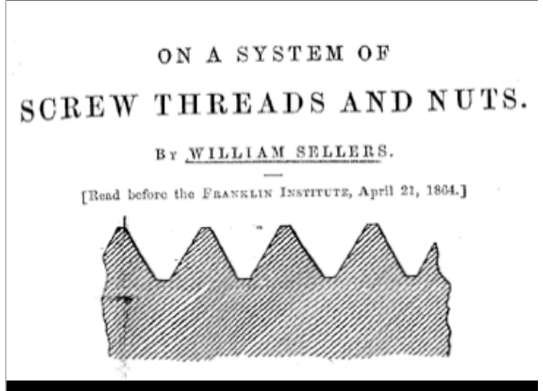
Decoupling of design & fabrication, leading to CAD and EDA.

Abstraction



Engineered simplicity enabling many component systems.

Standardization


ON A SYSTEM OF
SCREW THREADS AND NUTS.
By WILLIAM SELLERS.
[Read before the FRANKLIN INSTITUTE, April 21, 1864.]

Refined genetic components supporting "off the shelf" reuse.

...

Keep going for the next 70 years

One engineer's tools wish list

Get better at building DNA (**time**, reliability, cost)	4
Develop "rules" enabling functional composition	8
Populate genome-scale operating systems c/o rules	2
Refine sensors and actuators in accordance w/ rules	2
Develop libraries of molecular sensors to all primary and secondary metabolites	7-9
Develop reference materials for quantifying in vivo activities across time and place	4-8
Develop free-to-use data exchange standards for engineered genetic parts, devices, and systems	2-4

degree of difficulty (1=easy, 10=impossible)

"No matter who you are, most of the smartest people work for someone else" - Bill Joy

http://www.andyross.net/bill_joy.htm

Joy's Law meets engineering biology

"No matter who you are most of the smartest biologists work for someone else"

"No matter who you are most of the smartest biological engineers work for someone else"

"No matter who you are most of the best bio. parts you need will be discovered & refined by someone else"

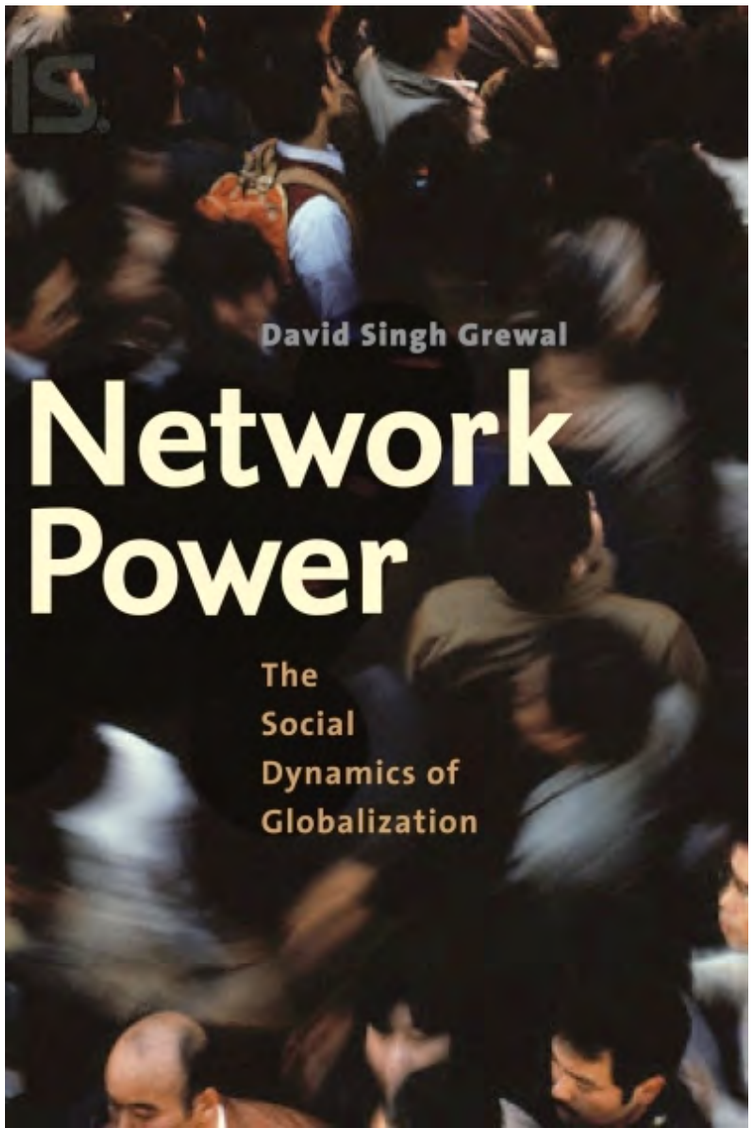
"No matter who you are, most of the needs & opportunities for what you can engineer exist somewhere else"

"No matter who you are, most of the aspects & issues arising from what you engineer ramify somewhere else"

"No matter who you are, most of the best bioterrorists & bioweaponeers work for someone else"

"No matter who you are, most of the best biotechnology ideas will be imagined and made true somewhere else"

So, what can we do about it?



"... globalization is best understood in terms of a power inherent in social relations, which he (Grewal) calls network power. Using this framework, he demonstrates how our **standards of social coordination both gain in value the more they are used and undermine the viability of alternative forms of cooperation**. A wide range of examples are discussed, from the spread of English and the gold standard to the success of Microsoft and the operation of the World Trade Organization, to illustrate how global standards arise and falter."

Could we realize the future of biotech by developing tools that lead the scaling of particular communities?

We can find many such opportunities

	degree of difficulty (1=easy, 10=impossible)
Prevent remilitarization of biological tech (globally).	5
Define and lead strategy for biological security.	8-10
Get biology recognized as a technology.	4
Increase and sustain support for improved fundamental engineering tools (many free-to-use)	3
Enable application areas that are beneficial, reasonably threatening, & that need improved tools.	5
Lead and partner globally with others. E.g., NIST et al. to establish open "network power."	5
Better public/private partnerships in biotech (open).	3

NATIONAL BIOEC
BLUEPRINT

April 2012

THE WHITE HOUSE
WASHINGTON

I. Background and Impacts of the U.S. Bioeconomy

"Innovation also demands basic research."

—President Obam

A bioeconomy is one based on the use of research and innovation in the biolo economic activity and public benefit. The U.S. bioeconomy is all around us: new for improved human health, higher-yielding food crops, emerging biofuels to r oil, and biobased chemical intermediates, to name just a few. The public benef logical research can be seen through the eyes of a patient who receives a critic not exist a decade ago, a farmer whose higher-yield crops are turned into fuels, f chemicals, and a small-business owner whose innovative biobased products are in manufacturing. Increased societal needs for food and energy, combined wit coveries in biology and new methods for harnessing biological processes, have the economic potential of the bioeconomy.[11]

Today's bioeconomy grew from several scientific and technological developm the practice and potential of biological research, including three of particula engineering, DNA sequencing, and robotic technologies that perform high t operations rapidly and accurately. These technological advances have led to the of the important drugs, products, and processes in widespread use today.

However, a growing U.S. population requires increased health services and more animal feed, fiber for clothing and housing, and sources of energy and chemical short, it needs a new and more potent bioeconomy fueled by innovative ideas help address these needs in new, more powerful ways.

The 2009 National Research Council report *A New Biology for the 21st Century*[12] st biological research—the potential to improve health outcomes for all American lations with higher-yield crops of improved nutritional value, and decrease Am petroleum-based products while increasing domestic biomanufacturing of fu report examined the state of biological research in the United States and recomm "capitalize on recent technological and scientific advances that have allowed bio logical research findings, collect and interpret vastly increased amounts of data, a of complex biological systems." The report also emphasized the benefit of coor to integrate biology with other sciences—namely physics, chemistry, and co with mathematics and engineering to address societal challenges in health, ene agriculture that provides food, feed, fiber, and fuel.

11. http://www.oecd.org/document/48/0,3746,en_2649_35831301_42864368_1_1_1_1
12. http://www.nap.edu/catalog.php?record_id=12764

II. Federal Bioeconomy Strategic Objectives

Strengthening Research and Development

"And if you have any doubt about the importance of this Federal investment in research and development, I would suggest that you talk to the cutting-edge businesses in your own states. They will tell you that if we want the next big breakthrough, the next big industry to be an American breakthrough, an American industry, then we can't sacrifice these investments in research and technology."

—President Obama, February 2011

Strategic Objective: Support R&D investments that will provide the foundation for the future bioeconomy.

A critical factor in leveraging biological systems to drive an innovation-based bioeconomy is the strength of the scientific enterprise investigating those systems, including basic and applied research. A robust biological/biomedical R&D enterprise, backed by government, foundations, and for profit investments, is necessary to produce the new knowledge, ideas, and foundational technologies required to develop products and services that support businesses and industries and help create jobs.

Nature has evolved countless biologically based systems with potential for new applications to address problems in health, energy, food, and the environment. Expanding basic knowledge of living systems and their molecular machinery will inspire new concepts for the creation of artificial processes and products that will address current and future needs. A sustained effort to understand and take advantage of natural living systems will produce novel solutions and encourage the growth of the bioeconomy.

Many government departments and agencies fund biological research with intramural and/or extramural funding programs (see box next page). Hence, the President has called for agencies to identify strategic R&D investments, as well as increase the use of flexible funding mechanisms to improve program efficiency and provide the best opportunity to enhance economic growth. Federal agencies are answering the call. As shown below, agencies are supporting development of the bioeconomy in a variety of ways: identifying strategic R&D progress to inform future efforts to enhance the bioeconomy; developing foundational transformative technologies; integrating approaches from engineering, physical sciences, and computational sciences; and implementing new flexible funding mechanisms. Shown below is a fraction of the bioeconomy projects and programs already started by Federal agencies.

Six-Party Joint Symposium on "Synthetic Biology for the Next Generation"
Under the Auspices of NAS/NAE in conjunction with RS/RAE & CAS/CAE
The NAS Building, Washington, DC, June 12-13, 2012

Synthetic Biology : China's perspectives

Xian-En Zhang 张先恩
Basic Research Department
China Ministry of Science & Technology
zhangxe@most.cn

5-year targets

Technology

- Synthesis
- Engineere
- Databases
- Computati

Industrial app

- Module de
- Design an
  transport

Medical appli

- Module de
  traditional
- Synthetic

Agricultural a

- Design an
  salinity

10-year targets

Technology

- Minimal g
- Expanded
- Computati

Industrial and

- Commerci
- Synthetic
- Synthetic
  pollutants

Medical appli

- Commerci
- Synthetic
  targeted t
- Synthetic

Agricultural a

- Design an
- Design and validation of synthetic devices (or artificial leaf) for photosynthesis

Ethic and biosafety/biosecurity issues

20-year targets

Technology

- Databases of full ranges of parts and devices for chassis organisms.
- Integrated technology platforms for design, modeling and validation of bio-systems

Applications

- Commercial production of a range of natural compounds, drugs, chemicals and biofules.
- Clinical applications of devices and bio-systems for surveillance, control, or therapy of selected major diseases.
- Development of commercial plants and crops with high tolerances and improved photosynthesis, and of engineered microbes with improved N2 fixation.
- Super bugs for environmental implementation for degradation of pollutants
- Creation of artificial microbial life.

Synthetic Yeast Genome, Sc2.0

The first international coordination meeting on synthetic yeast genome, Sc2.0, April 16, 2012, Beijing

Funders: NSF (USA); MoST (China); NSFC (China); BBSRC (UK); Council of Scientific and Industrial Research (India); Hong Kong Research Grants Council

Academia: Johns Hopkins University (USA); BGI, Tianjin University, Tsinghua University (China); Imperial College London, The University of Edinburgh (UK); Institute of Genomics and Integrative Biology, Pondicherry University (India); Hong Kong University, Hong Kong University of Science and Technology, Chinese University of Hong Kong (Hong Kong); Institut Pasteur (France); Catholic U Louvain la Neuve (Belgium)

The Sc2.0 PROJECT, initiated by Johns Hopkins University School of Medicine, is the first synthetic eukaryotic cell genome project. The project leader Dr. Jef Boeke, Director of the High Throughput Biology Center, Johns Hopkins University School of Medicine, said, "This meeting provides an opportunity for further boosting the research and applications of the Sc2.0 PROJECT. With the achievements of this project, I believe that we can seek much better solutions to face the challenges of the future, such as world energy shortage."

... to benefit all people & the planet?

	degree of difficulty (1=easy, 10=impossible)
Who will lead biosafety into the future?	4
What is our strategy for biological security?	8-10
How much can we make in partnership with biology?	2-8
What is the best balance of private and common wealth?	4-6
Who will choose what problems and opportunities are explored, pursued, and realized?	7-9
How can we invigorate new schools of engineering and art? Not just about industrialization.	4-6
How can we best work together?	?

Two Sections

The Real Paper

...ly newspaper July 16, 1977 35¢

DOING DNA AT HOME: A RECIPE FOR BOTULISM

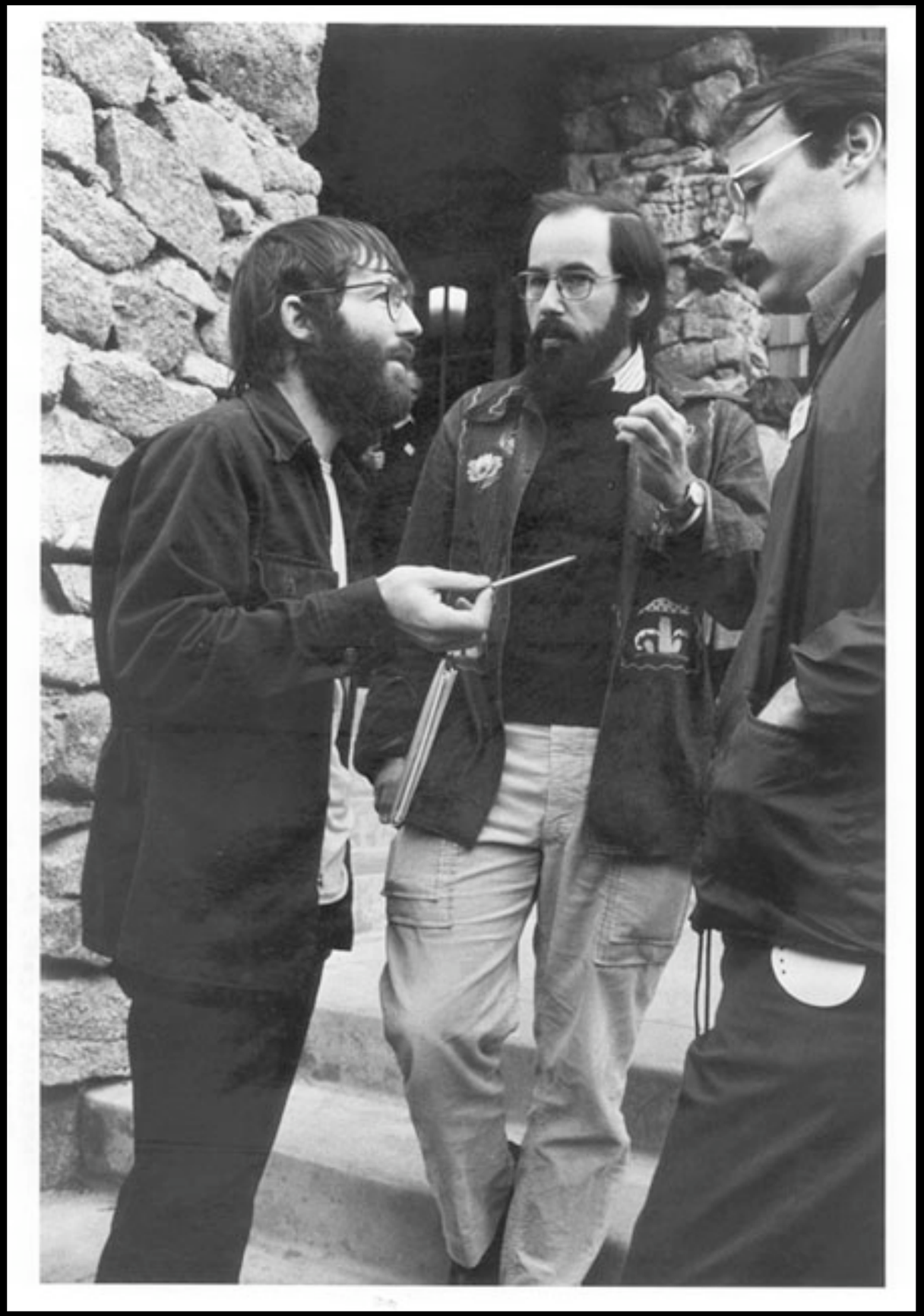
PAT CADDELL: CARTER'S GREASY POLLSTER

SHAPIRO: THEY'RE BANNING ABORTIONS AGAIN

Mark Fisher

E.g., biosafety ~1975 Asilomar

c/o http://cr4.globalspec.com/blogentry/8698



(c/o US NAS Archives)

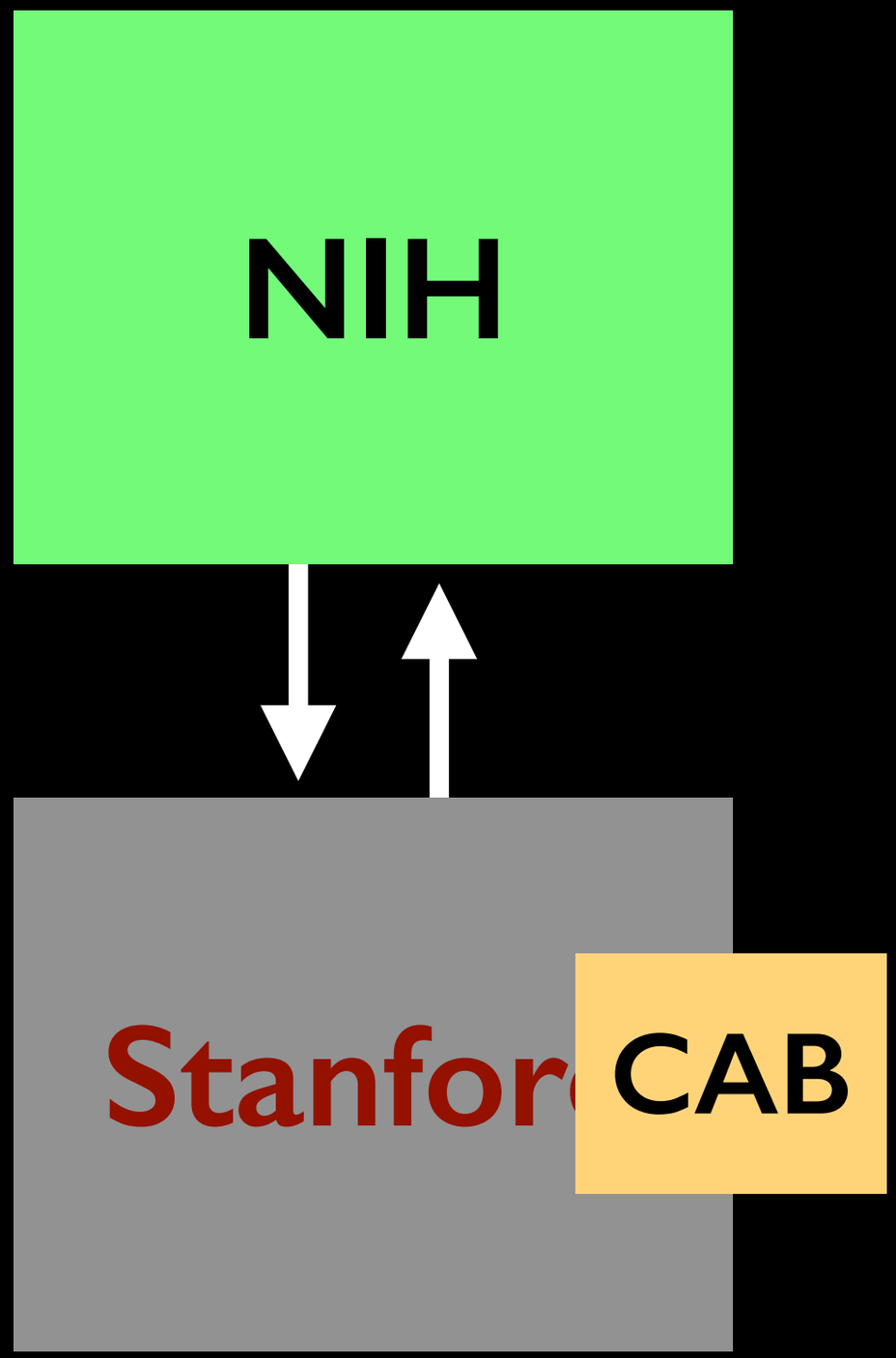
Biosafety Level 1 practices, safety equipment, and facility design and construction are appropriate for undergraduate and secondary educational training and teaching laboratories, and for other laboratories in which work is done with defined and characterized strains of viable microorganisms not known to consistently cause disease in healthy adult humans. Biosafety Level 1 represents a basic level of containment that relies on standard microbiological practices with no special primary or secondary barriers recommended, other than a sink for handwashing.

Biosafety Level 2 practices, equipment, and facility design and construction are applicable to clinical, diagnostic, teaching, and other laboratories in which work is done with the broad spectrum of indigenous moderate-risk agents that are present in the community and associated with human disease of varying severity. With good microbiological techniques, these agents can be used safely in activities conducted on the open bench, provided the potential for producing splashes or aerosols is low. Hepatitis B virus, HIV, the salmonellae, and Toxoplasma spp. are representative of microorganisms assigned to this containment level.

Biosafety Level 3 practices, safety equipment, and facility design and construction are applicable to clinical, diagnostic, teaching, research, or production facilities in which work is done with indigenous or exotic agents with a potential for respiratory transmission, and which may cause serious and potentially lethal infection. Mycobacterium tuberculosis, St. Louis encephalitis virus, and Coxiella burnetii are representative of the microorganisms assigned to this level. Primary hazards to personnel working with these agents relate to autoinoculation, ingestion, and exposure to infectious aerosols. At Biosafety Level 3, more emphasis is placed on primary and secondary barriers to protect personnel in contiguous areas, the community, and the environment from exposure to potentially infectious aerosols.

Biosafety Level 4 practices, safety equipment, and facility design and construction are applicable for work with dangerous and exotic agents that pose a high individual risk of life-threatening disease, which may be transmitted via the aerosol route and for which there is no available vaccine or therapy. Agents with a close or identical antigenic relationship to Biosafety Level 4 agents also should be handled at this level. When sufficient data are obtained, work with these agents may continue at this level or at a lower level. Viruses such as Marburg or Congo-Crimean hemorrhagic fever are manipulated at Biosafety Level 4. The primary hazards to personnel working with Biosafety Level 4 agents are respiratory exposure to infectious aerosols, mucous membrane or broken skin exposure to infectious droplets, and autoinoculation. All manipulations of potentially infectious diagnostic materials, isolates, and naturally or experimentally infected animals, pose a high risk of exposure and infection to laboratory personnel, the community, and the environment.

http://www.cdc.gov/od/ohs/biosfty/bmbl4/bmbl4toc.htm



http://mit.edu/cab/

Published online before print October 31, 2006
Genome Research, DOI: 10.1101/gr.5565706

Letter

Identification of an infectious progenitor for the multiple-copy HERV-K human endogenous retroelements

Marie Dewannieux[1,3], Francis Harper[2,4], Aurélien Richaud[1,4], Claire Letzelter[1], David Ribet[1], Gérard Pierron[2], and Thierry Heidmann[1,5]

[1] Unité des Rétrovirus Endogènes et Eléments Rétroïdes des Eucaryotes Supérieurs, UMR 8122 CNRS, Institut Gustave Roussy, 94805 Villejuif Cedex, France; [2] Laboratoire de Réplication de l'ADN et Ultrastructure du Noyau, UPR1983 Institut André Lwoff, 94801 Villejuif Cedex, France

Human Endogenous Retroviruses are expected to be the remnants of ancestral infections of primates by active retroviruses that have thereafter been transmitted in a Mendelian fashion. Here, we derived in silico the sequence of the putative ancestral "progenitor" element of one of the most recently amplified family—the HERV-K family—and constructed it. This element, *Phoenix*, produces viral particles that disclose all of the structural and functional properties of a bona-fide retrovirus, can infect mammalian, including human, cells, and integrate with the exact signature of the presently found endogenous HERV-K progeny. We also show that this element amplifies via an extracellular pathway involving reinfection, at variance with the non-LTR-retrotransposons (LINEs SINEs) or LTR-retrotransposons, thus recapitulating ex vivo the molecular events responsible for its dissemination in the host genomes. We also show that in vitro recombinations among present-day human HERV-K loci can similarly generate functional HERV-K elements, indicating that human cells still have the potential to produce infectious retroviruses.

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[3] Present address:

Safety precautions

All manipulations involving the reconstructed HERV-K were carried out in our lab according to the rules established by the "Commission de Génie Génétique" from the "Ministère délégué à l'Enseignement supérieur et à la Recherche" French authority that regulates handling of genetically modified organisms in all research institutions in France.

Albeit the HERV-K virus has a very low infectivity and does not sustain multiple-cycle infection, at least in all the cells tested, *Phoenix* is a retrovirus, and as such, is a priori eligible to BL3 conditions for manipulation. Accordingly, the material will only be sent to other labs in appropriate sealed containers in the form of small amounts of plasmid DNA that will require it to be amplified before use as a transfection vector to produce viral particles. At the present time and as a precautionary principle, it will only be distributed under a material transfer agreement specifying the commitment of the recipient labs to carry out every experiment using the material under BL3 conditions and accompanied by a duly signed authorization form from the Biosafety Committee responsible for genetic manipulations in their country of origin.

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Deadly infection claims San Francisco VA lab worker

By Matt O'Brien Bay Area News Group San Jose Mercury News
Posted:

MercuryNews.com

State and federal health officials are investigating how a rare and virulent bacteria strain appears to have killed a young researcher at a VA Hospital's infectious diseases lab in San Francisco, setting off alarms that the man's friends and fellow researchers also may have been exposed.

The 25-year-old laboratory researcher at San Francisco Veterans Affairs Medical Center died Saturday morning shortly after asking friends to take him to the hospital. For the week and months before his death, he had been handling a bacteria linked to deadly bloodstream infections at the VA Hospital's Northern California Institute for Research and Education, said Peter Melton, a spokesman for the California Occupational Safety and Health Administration.

The man, whose name has not been released, was working with fellow researchers to develop a vaccine for a bacterial strain that causes septicemia and meningitis. Hours after he left work, however, the germ that he was studying took his own life.

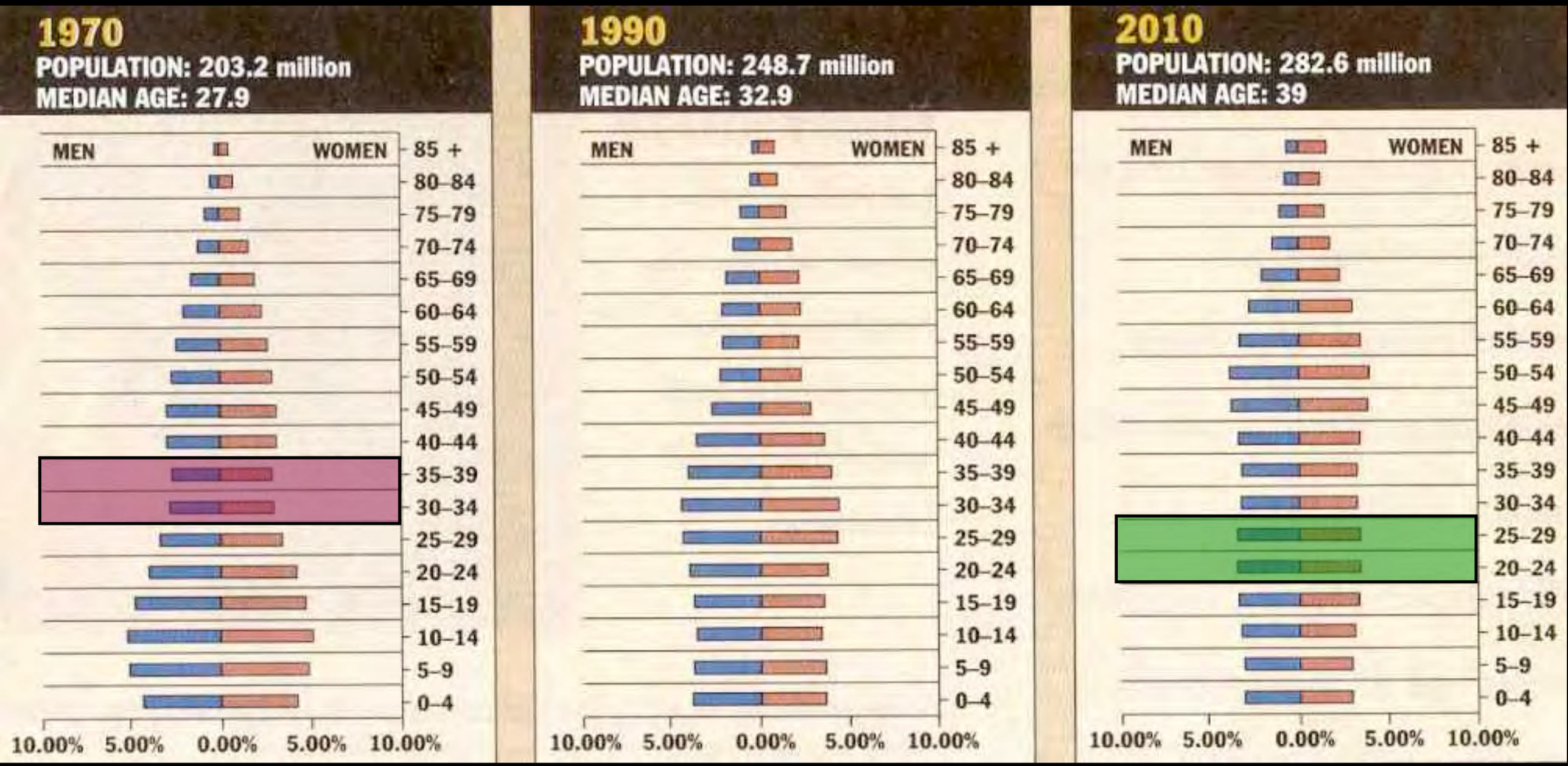
"He left the lab around 5 p.m. (Friday)," said Harry Lampiris, chief of the VA Hospital's infectious diseases division. "He had no symptoms at all."

Two hours later, however, the Treasure Island resident reported to his girlfriend he was feeling sick with a headache, fever and chills, Lampiris said. Not until Saturday morning did the symptoms grow worse with a body rash. He asked friends to take him to the hospital but fell unconscious in the car and had no pulse by the time he arrived. He died later in the morning.

"It starts out so non-specifically, people don't think it's anything serious," Lampiris said. "Obviously, he didn't suspect it."

The San Francisco Department of Public Health is trying to identify everyone who had close contact with the worker during the time he was infected, said city health spokeswoman Eileen Shields.

Who will lead biosafety in 2020?



Can you catalyze a renewal of biosafety leadership?

What's the difference between safety & security?

Hint: <u>Safety</u> belts vs. <u>security</u> locks in a car.

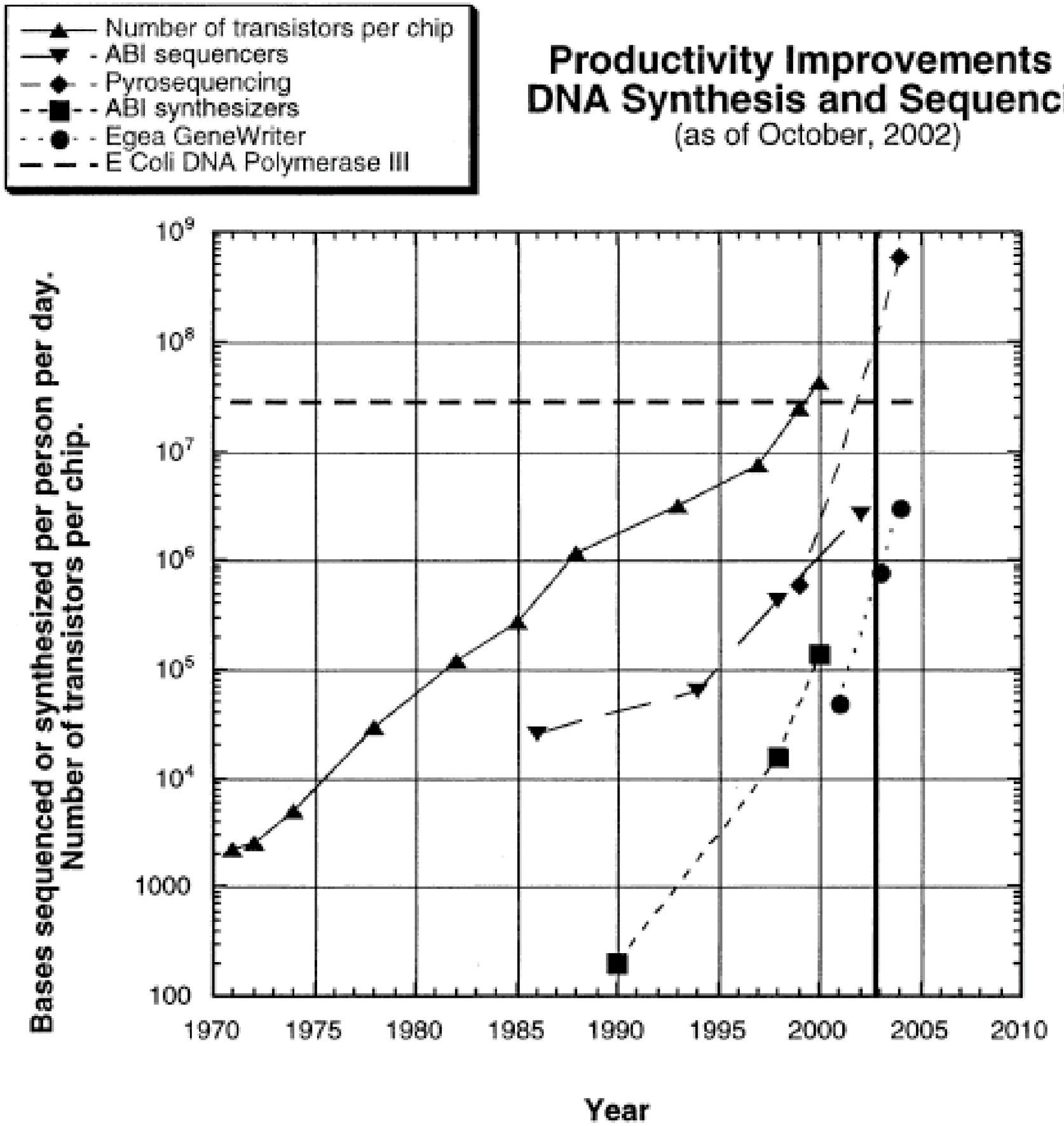
What's changed since the 1970s?

1. Databases populated with sequence information.
2. The internet.
3. Early improvements in automated DNA construction technology.
4. Overnight shipping.
5. Expanded concern re: active misapplication of biotech.

http://en.wikipedia.org/wiki/2001_anthrax_attacks

Productivity Improvements in DNA Synthesis and Sequencing

(as of October, 2002)



Carlson, Pace & Proliferation of Biological Technologies, Biosec. & Bioterror. 1(3):1 (2003)

Information (DNA Sequence)

Sequencing

Synthesis

Material (Physical DNA)

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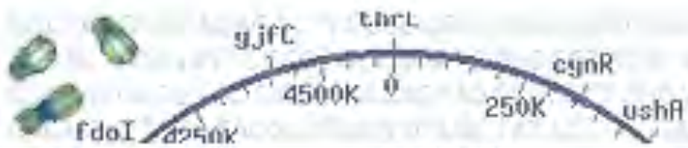
ebola – Genome Results

http://www.ncbi.nlm.nih.gov/sites/entrez

MIT OWW

NCBI



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DraftAssembly

Bacteria
Chromosome
Plasmid
DraftAssembly

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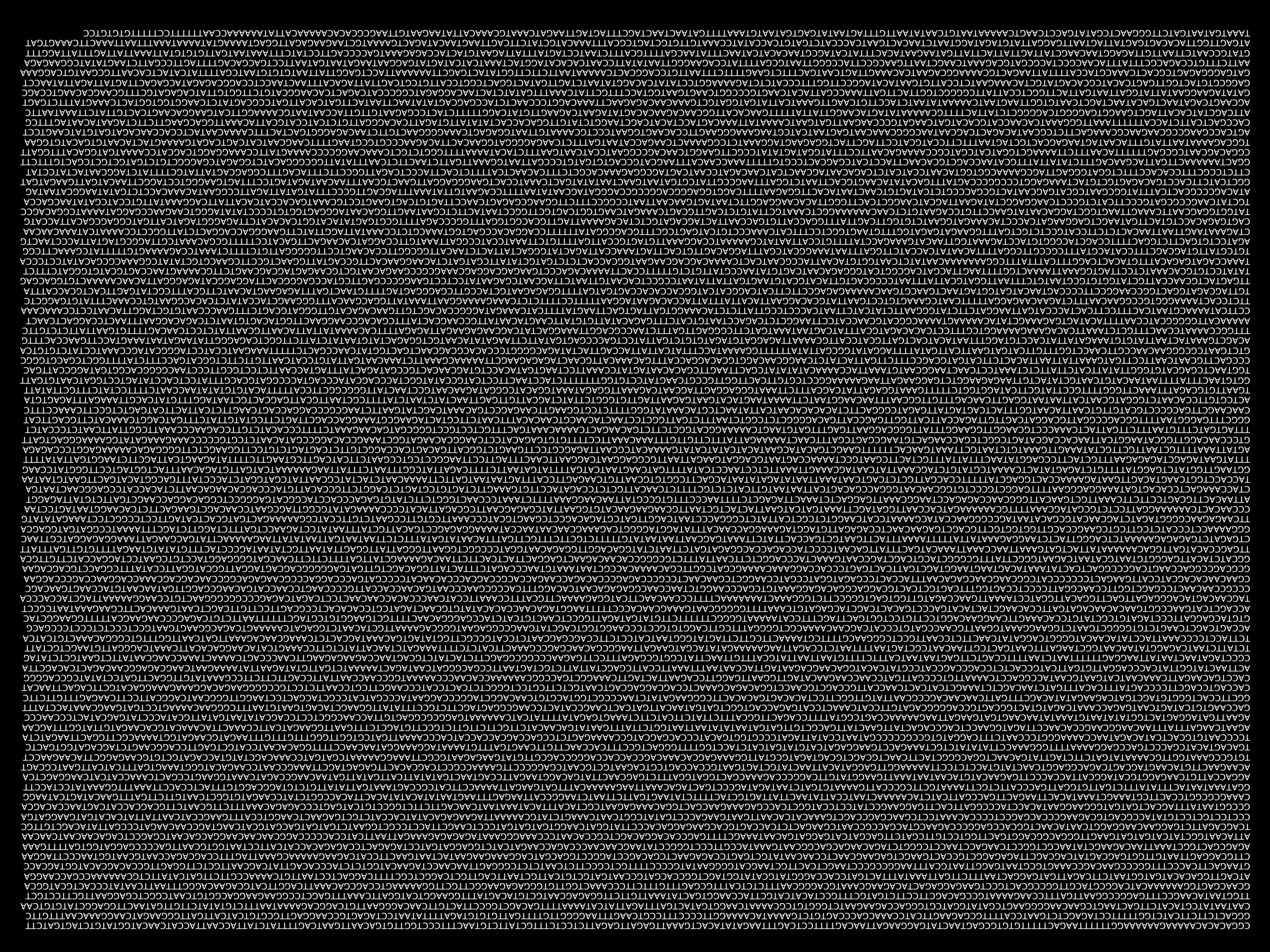
Items 1 - 3 of 3

1: NC_004161
Reston Ebola virus, complete genome
ssRNA; linear; Length: **18,891 nt**
Created: **2002/09/04**

2: NC_002549
Zaire ebolavirus, complete genome
ssRNA; linear; Length: **18,959 nt**
Created: **1999/02/10**

3: NC_006432
Sudan ebolavirus, complete genome
ssRNA; linear; Length: **18,875 nt**
Created: **2004/11/15**



Unknown reservoir →

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Lake Victoria marburgvirus, complete genome
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Created: **1994/01/26**

2: NC_006432
Sudan ebolavirus, complete genome
ssRNA; **linear**; Length: **18,875 nt**
Created: **2004/11/15**

3: NC_004161
Reston Ebola virus, complete genome
ssRNA; **linear**; Length: **18,891 nt**
Created: **2002/09/04**

4: NC_002549
Zaire ebolavirus, complete genome
ssRNA; **linear**; Length: **18,959 nt**
Created: **1999/02/10**

Locked-up →

NC_008291
Taterapox virus, complete genome
dsDNA; **linear**; Length: **198,050 nt**
Created: **2006/08/24**

NC_001611
Variola virus, complete genome
dsDNA; **linear**; Length: **185,578 nt**
Created: **1993/05/04**

NC_006966
Mule deer poxvirus, complete genome
dsDNA; **linear**; Length: **166,259 nt**
Created: **2005/04/08**

Don't exist →

1: DQ208309 Reports
Influenza A virus (A/Brevig Mission/1/1918(H1N1)) polymerase PB2 (PB2) mRNA, complete cds
gi|76786704|gb|DQ208309.1|[76786704]

1: DQ208310 Reports
Influenza A virus (A/Brevig Mission/1/1918(H1N1)) polymerase PB1 (PB1) mRNA, complete cds
gi|76786706|gb|DQ208310.1|[76786706]

Should the DNA sequences encoding human pathogens be freely available online?

1918 Flu and Responsible Science

The influenza pandemic of 1918 is estimated to have caused 50 million deaths worldwide; 675,000 in the United States. The reconstruction of the 1918 virus by the synthesis of all eight subunits and the generation of infectious virus are described on p. 77 of this issue,* and the sequences of the final three gene segments of the virus are described in a concurrent *Nature* paper.† Predictably, but alarmingly, this virus is more lethal to mice than are other influenza strains, suggesting that this property of the 1918 virus has been recovered in the published sequence. The good news is that we now have the sequence of this virus, perhaps permitting the development of new therapies and vaccines to protect against another such pandemic. The concern is that a terrorist group or a careless investigator could convert this new knowledge into another pandemic.

Should the sequence of the 1918 virus have been published, given its potential use by terrorists? The dual-use nature of biological information has been debated widely since September 11, 2001. In 2003, a committee of the U.S. National Academies chaired by Gerald Fink considered this issue, weighing the benefits against the risks of restricting the publication of such biological information. They outlined the tradeoff between erring on the side of prudence, thus potentially hindering the progress of critical science, and erring on the side of disclosure, thus potentially aiding terrorists. The U.S. National Science Advisory Board for Biosecurity (NSABB) was established to advise governmental agencies and the scientific community on policies relative to public disclosure. This board has begun to deliberate, but the questions are complex, as typified by these papers on the 1918 virus. It is reassuring that the NSABB was asked to consider these papers before publication and concluded that the scientific benefit of the future use of this information far outweighs the potential risk of misuse. People may be reassured that the system is working, because agencies representing the public, the scientific community, and the publishing journals were involved in the decision.

I firmly believe that allowing the publication of this information was the correct decision in terms of both national security and public health. It is impossible to forecast how scientific observations might stimulate others to create new treatments or procedures to control future pandemics. For example, in the *Nature* article, sequence comparisons suggest that the 1918 virus was generated not by incremental changes in the polymerase genes, but by the movement of these genes, in total, from an avian source into a human influenza virus. The availability of these sequences will permit identification of their avian origin and should show why this particular set of genes was selected. Similarly, the results in the *Science* article suggest that the cleavage of a protein on the surface of the 1918 virus, a step critical for virulent infection, may occur by a previously unknown mechanism—a hint that could lead to new drugs for inhibiting this step and thus preventing future pandemic eruptions.

Influenza is highly infectious, and a new strain could spread around the world in a matter of months, if not weeks. The public needs confidence that the 1918 virus will not escape from research labs. All of the described experiments were done in a Biosafety Level 3 laboratory, a high-containment environment recommended by the U.S. Centers for Disease Control and Prevention and the National Institutes of Health on an interim basis, whose use should become a permanent requirement for such experiments. Current evidence suggests that some available drugs and possible future vaccines could suppress infections by the 1918 virus. Given the prospect of another natural influenza pandemic, the recent decision by the U.S. administration to stockpile antivirals for influenza treatment seems wise. Finally, although a sequence of the 1918 virus has been determined and is highly virulent in mice, this may not be the specific form of the virus that caused the pandemic of 1918. An article in the same issue of *Nature*‡ reports the existence of sequence variation in a natural population of influenza virus; yet we have only one sequence for the 1918 pandemic strain, and the reconstructed virus described in the *Science* article was built into the backbone of a laboratory strain. Because a pandemic infection is dependent on many unknown properties, there is no certainty that the reconstructed 1918 virus is capable of causing a pandemic.

Phillip A. Sharp

Phillip A. Sharp is Institute Professor at the Massachusetts Institute of Technology, 77 Massachusetts Avenue, Cambridge, MA 02139, USA.

10.1126/science.1120820

OP-ED CONTRIBUTORS

Recipe for Destruction

By RAY KURZWEIL and BILL JOY

Published: October 17, 2005

AFTER a decade of painstaking research, federal and university scientists have reconstructed the 1918 influenza virus that killed 50 million people worldwide. Like the flu viruses now raising alarm bells in Asia, the 1918 virus was a bird flu that jumped directly to humans, the scientists reported. To shed light on how the virus evolved, the United States Department of Health and Human Services published the full genome of the 1918 influenza virus on the Internet in the GenBank database.

This is extremely foolish. The genome is essentially the design of a weapon of mass destruction. No responsible scientist would advocate publishing precise designs for an atomic bomb, and in two ways revealing the sequence for the flu virus is even more dangerous.

First, it would be easier to create and release this highly destructive virus from the genetic data than it would be to build and detonate an atomic bomb given only its design, as you don't need rare raw materials like plutonium or enriched

DNA synthesis and biological security

Hans Bügl, John P Danner, Robert J Molinari, John T Mulligan, Han-Oh Park, Bas Reichert, David A Roth, Ralf Wagner, Bruce Budowle, Robert M Scripp, Jenifer A L Smith, Scott J Steele, George Church & Drew Endy

A group of academics, industry executives and security experts propose an oversight framework to address concerns over the security of research involving commercial DNA synthesis.

DNA synthesis allows the direct construction of genetic material starting from information and raw chemicals[1]. Improvements in synthesis technology are accelerating innovation across many areas of research, from the development of renewable energy to the production of fine chemicals, from information processing to environmental monitoring, and from agricultural productivity to breakthroughs in human health and medicine. Like any powerful technology, DNA synthesis has the potential to be purposefully misapplied. Misuse of DNA-synthesis technology could give rise to both known and unforeseeable threats to our biological safety and security. Current government oversight of the DNA-synthesis industry falls short of addressing this unfortunate reality.

Here, we outline a practical plan for developing an effective oversight framework for the DNA-synthesis industry[2]. The resulting framework serves three purposes. First, it promotes biological safety and security. Second, it encourages the further responsible development of synthetic biology technologies and their continued, overwhelmingly constructive application. And third, it is designed to be international in scope. Our plan is informed by past and ongoing discussions of biological security issues associated with DNA-synthesis technology[3–5] and represents the collective views of all founding members of the

Hans Bügl, John P. Danner, Robert J. Molinari, John T. Mulligan, David A. Roth & Ralf Wagner are members of the International Consortium for Polynucleotide Synthesis; Hans Bügl and Ralf Wagner are at GENEART; John P. Danner, George Church & Drew Endy are at Codon Devices; Robert J. Molinari & David A. Roth are at CODA Genomics; John T. Mulligan is at Blue Heron Biotechnology; Han-Oh Park is at Bioneer; Bas Reichert is at BaseClear B.V.; Ralf Wagner is at the University of Regensburg Molecular Virology & Gene Therapy Unit, Institute of Medical Microbiology and Hygiene; Bruce Budowle, Robert M. Scripp, Jenifer A. L. Smith & Scott J. Steele are at the US FBI; George Church is in the Department of Genetics, Harvard Medical School; Drew Endy is in the Department of Biological Engineering, MIT; George Church & Drew Endy are at the multi-institution US National Science Foundation Synthetic Biology Engineering Research Center. e-mail: endy@mit.edu

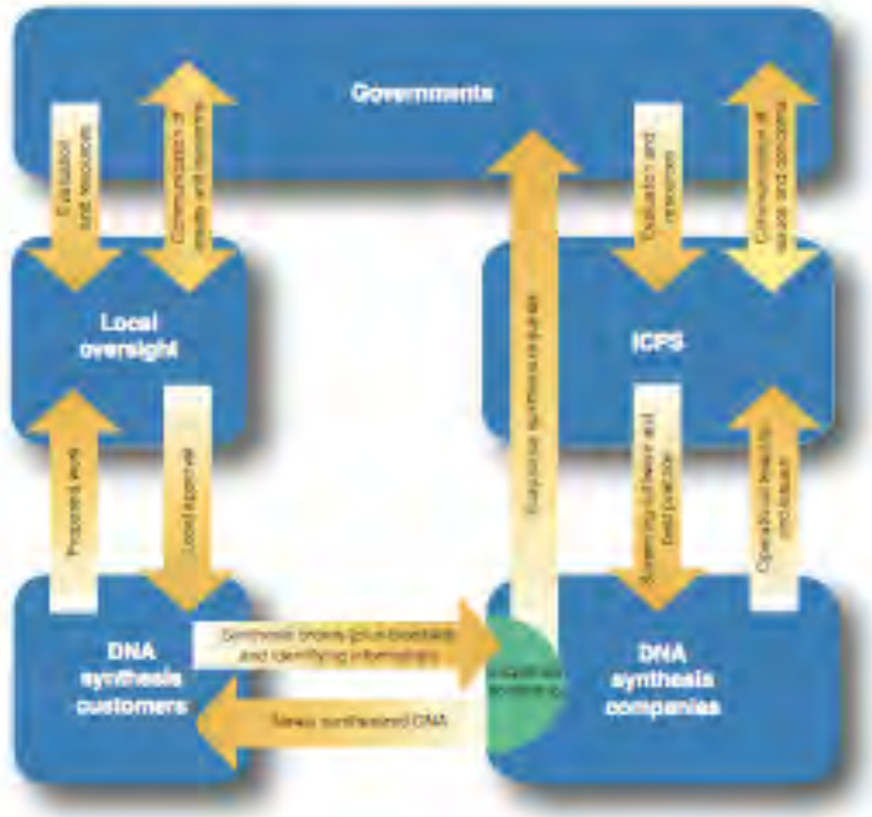

Figure 1 Our framework calls for the immediate and systematic implementation of a tiered DNA synthesis order screening process. To promote and establish accountability, individuals who place orders for DNA synthesis would be required to identify themselves, their home organization and all relevant biosafety information. Next, individual companies would use validated software tools to check synthesis orders against a set of select agents or sequences to help ensure regulatory compliance and flag synthesis orders for further review. Finally, DNA synthesis and synthetic biology companies would work together through the ICPS and interface with appropriate government agencies (worldwide) to rapidly and continually improve the underlying technologies used to screen orders and identify potentially dangerous sequences, as well as develop a clearly defined process to report behavior that falls outside of agreed-upon guidelines. ICPS, International Consortium for Polynucleotide Synthesis.

Property rights are important

X000001
July 31, 1790

The United States.

To all to whom these Presents shall come. Greeting.

Whereas Samuel Hopkins of the City of Philadelphia and State of Pensylvania hath discovered an Improvement, not known or used before such Discovery, in the making of Pot ash and Pearl ash by a new Apparatus and Process, that is to say, in the making of Pearl ash 1st. by burning the raw Ashes in a Furnace, 2d. by dissolving and boiling them when so burnt in Water, 3rd. by drawing off and settling the ley, and 4th. by boiling the ley into salts which then are the true Pearl ash; and also in the making of Pot ash by fluxing the Pearl ash so made as aforesaid; which Operation of burning the raw Ashes in a Furnace, preparatory to their Dissolution and boiling in Water, is new, leaves little Residuum; and produces a much greater Quantity of Salt: These are therefore in pursuance of the Act, entitled "An Act to promote the Progress of useful Arts", to grant to the said Samuel Hopkins, his Heirs, Administrators and Assigns, for the Term of fourteen Years, the sole and exclusive Right and Liberty of using, and vending to others the said Discovery, of burning the raw Ashes previous to their being dissolved and boiled in Water, according to the true Intent and Meaning of the Act aforesaid. In Testimony whereof I have caused these Letters to be made patent, and the Seal of the United States to be hereunto affixed. Given under my Hand at the City of New York this thirty first Day of July in the Year of our Lord one thousand seven hundred & Ninety.

G. Washington

City of New York July 31st. 1790.

I do hereby Certify that the foregoing Letters patent were delivered to me in pursuance of the Act, entitled "An Act to promote the Progress of useful Arts", that I have examined the same, and find them conformable to the said Act.

Edm: Randolph Attorney General for the United States.

The first U.S. patent, issued to Samuel Hopkins on July 31, 1790, for an innovative way of making "pot ash and pearl ash" -- source, Wikipedia

1. Disclose how to do something useful.

2. Define and scale relationships among parties

3. Support investment and returns

Current practice in biotech.

"Method" or "utility" **patents** provide ownership of exclusive rights to the practice of research processes, or uses of genetically encoded functions, respectively.

Patent-based rights can be used to protect an investment for a period of time (e.g., your future startup company).

Such rights can be licensed to others in order to make money.

Public domain also used to support giving things away.

United States Patent [19]
Cohen et al.

[11] 4,237,224
[45] Dec. 2, 1980

[54] PROCESS FOR PRODUCING BIOLOGICALLY FUNCTIONAL MOLECULAR CHIMERAS

[75] Inventors: Stanley N. Cohen, Portola Valley; Herbert W. Boyer, Mill Valley, both of Calif.

[73] Assignee: Board of Trustees of the Leland Stanford Jr. University, Stanford, Calif.

[21] Appl. No.: 1,021

[22] Filed: Jan. 4, 1979

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 959,288, Nov. 9, 1978, which is a continuation-in-part of Ser. No. 687,430, May 17, 1976, abandoned, which is a continuation-in-part of Ser. No. 520,691, Nov. 4, 1974.

[51] Int. Cl.³ C12P 21/00
[52] U.S. Cl. ..... 435/68; 435/172; 435/231; 435/183; 435/317; 435/849; 435/820; 435/91; 435/207; 260/112.5 S; 260/27R; 435/212
[58] Field of Search ..... 195/1, 28 N, 28 R, 112, 155/78, 79; 435/68, 172, 231, 183

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Chemical and Engineering News, p. 4, May 30, 1977.
Chemical and Engineering News, p. 6, Sep. 11, 1978.

Primary Examiner—Alvin E. Tanenholtz
Attorney, Agent, or Firm—Bertram I. Rowland

[57] ABSTRACT

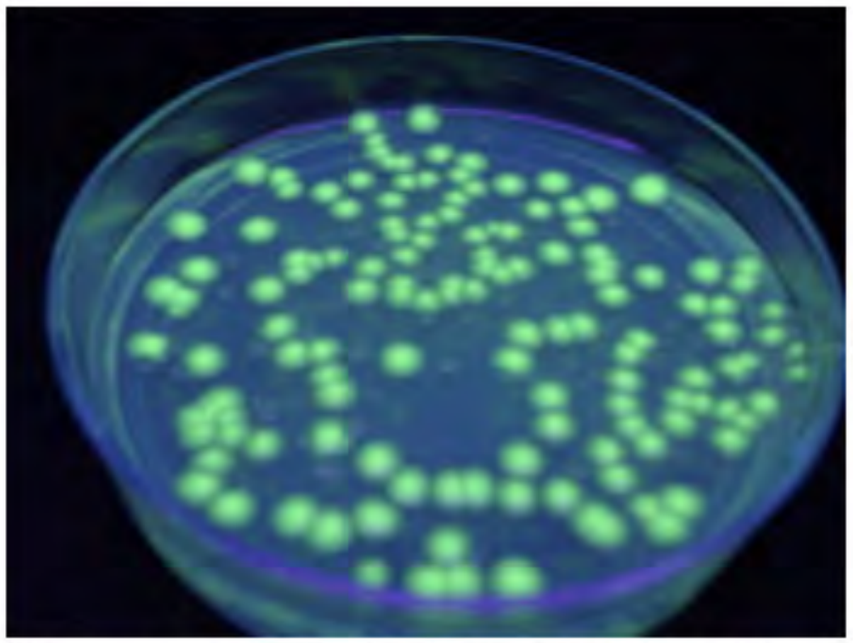
Method and compositions are provided for replication and expression of exogenous genes in microorganisms. Plasmids or virus DNA are cleaved to provide linear DNA having ligatable termini to which is inserted a gene having complementary termini, to provide a biologically functional replicon with a desired phenotypical property. The replicon is inserted into a microorganism cell by transformation. Isolation of the transformants provides cells for replication and expression of the DNA molecules present in the modified plasmid. The method provides a convenient and efficient way to introduce genetic capability into microorganisms for the production of nucleic acids and proteins, such as medically or commercially useful enzymes, which may have direct usefulness, or may find expression in the production of drugs, such as hormones, antibiotics, or the like, fixation of nitrogen, fermentation, utilization of specific feedstocks, or the like.

14 Claims, No Drawings

Best personal Regards
Herb Boyer
Stan Cohen

rDNA method patent generated $200+ million in licensing revenue for Stanford and UCSF.

http://www.yildizindunyasi.net/bilim%20dunyasi/gfp.htm



http://homepage3.nifty.com/nature_of_minamino/

http://www.brown.edu/Courses/BI0105_Miller/read/optical.html

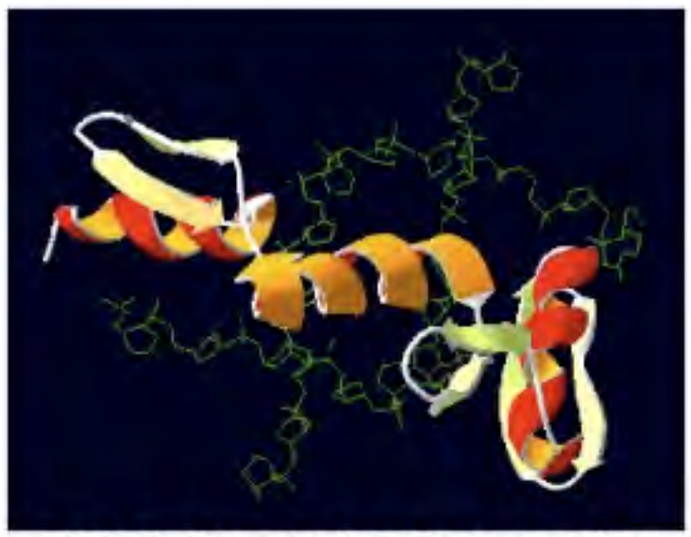
United States Patent *5,491,084*
Chalfie , et al. **February 13, 1996**

Uses of green-fluorescent protein

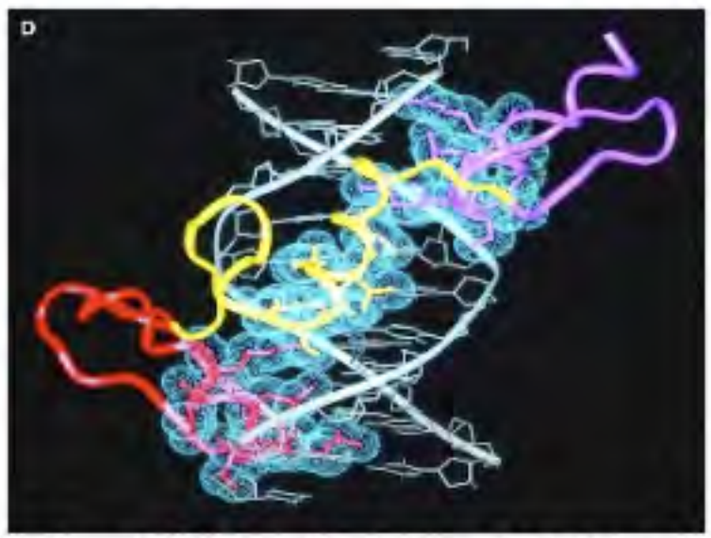
Abstract

This invention provides a cell comprising a DNA molecule having a regulatory element from a gene, other than a gene encoding a green-fluorescent protein operatively linked to a DNA sequence encoding the green-fluorescent protein. This invention also provides a method for selecting cells expressing a protein of interest which comprises: a. introducing into the cells a DNAI molecule having DNA sequence encoding the protein of interest and DNAII molecule having DNA sequence encoding a green-fluorescent protein; b. culturing the introduced cells in conditions permitting expression of the green-fluorescent protein and the protein of interest; and c. selecting the cultured cells which express green-fluorescent protein, thereby selecting cells expressing the protein of interest. Finally, this invention provides various uses of a green-fluorescent protein.

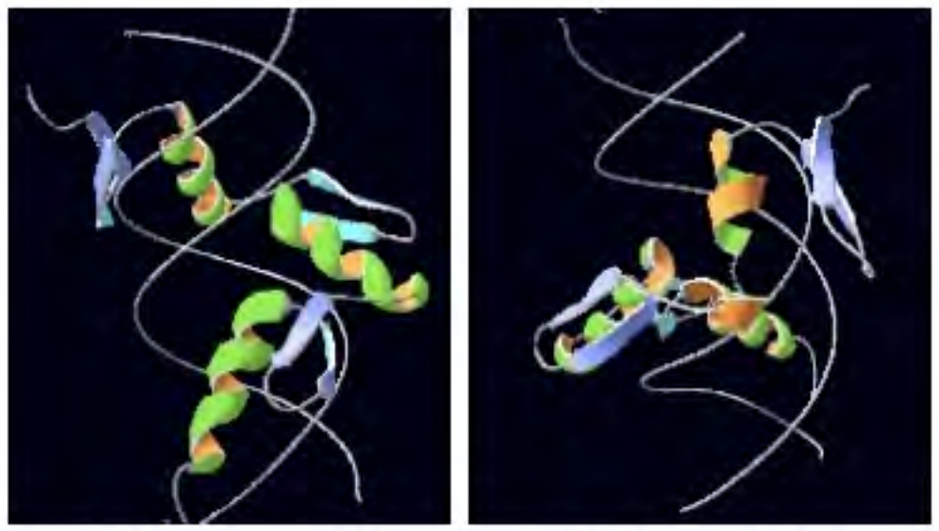
Inventors: **Chalfie; Martin** (New York, NY); **Prasher; Douglas** (East Falmouth, MA)
Assignee: **The Trustees of Columbia University in the City of New York** (New York, NY); **Woods Hole Oceanographic Institution** (Woods Hole, MA)
Appl. No.: **119678**
Filed: **September 10, 1993**



Zif268, Paveltich & Pabo c. 1991



Random Zif268s, Greisman & Pabo c. 1997



$TATA_{ZF-6}$ & $TATA_{ZF-2'}$ Wolfe et al. c. 2001

United States Patent **6,903,185**
Kim , et al. **June 7, 2005**

Poly *zinc* finger proteins with improved linkers

Abstract

Chimeric proteins, and methods for their production and use are disclosed. The chimeric proteins comprise a flexible linker between two *zinc* finger DNA-binding domains, wherein the linker comprises eight or more amino acids between the second conserved histidine residue of the carboxy-terminal *zinc* finger of the first domain and the first conserved cysteine residue of the amino-terminal *zinc* finger of the second domain.

Inventors: **Kim; Jin-Soo** (Inchon, KR); **Pabo; Carl O.** (Newton, MA)
Assignee: **Massachusetts Institute of Technology** (Cambridge, MA)
Appl. No.: **146221**
Filed: **May 13, 2002**

Costs of patent based framework

Patents take time and money to obtain (~$25k and 18-36 months).

What a patent claim covers often not 100% clear.

Searching patent claims not trivial (e.g., machine readable but not machine knowable).

Patent claims often disputed and not resolved until trial years later (i.e., more time and money).

Patents can be used to restrict access to methods and functions that others could benefit from.

Restrictive access to technologies can lead to public anger and rejection of tools and technologies.

For example, standards-based sharing

2008 iGEM competition resulted in 1,500 new BioBrick parts being developed, produced by ~1000 students across 30 countries.

1. 2008 iGEM budget worldwide ~$4 million

2. Utility filings on all 2008 parts would cost ~$37.5 million

3. Commercial freedom to operate unclear (e.g., competing claims?)

4. iGEM and the parts collections continue to grow (geometric)

E.g., designer genomes

SYNTHETIC GENOMICS®

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What We Do -

Our Science and Capabilities

SGI is built on pioneering science that has furthered biological knowledge. From rapidly discovering genes and developing advances to sequence whole genomes, to making innovations in synthesizing and constructing whole chromosomes and genomes, Drs. Venter, Smith and their teams are trailblazers in the use and development of these disruptive technologies. Today, that legacy of pioneering basic science research leading to transformative applications continues. At SGI, our scientists have a wide array of expertise and apply their skills to the development of our core products. In short, our science is the platform upon which all of our commercial applications are built. Our scientific capabilities include: synthetic biology/genomics, environmental genomics, plant genomics, microbiology, bioinformatics, genome engineering, analytical chemistry, fuel chemistry, and biochemistry and assay development.

What We Do

Our Science & Capabilities

Next Generation Fuels & Chemicals

Hydrocarbon Recovery & Conversion

Agricultural Products

Quick, do a freedom to operate search on 1000 genes in your company's designer genomes...

E.g., automated engineering

A company (real but anonymous) can make ~5000 engineered strains of microbes per week to support internal R&D.

Suppose each strain has, on average, 5 heterologous genetic functions.

How will their lawyers search for claims on 25,000 functions per week? 1,250,000 per year...

How will they license the uses as needed?

Changes in foundational tools...

Stress, strain, and swamp existing systems (capital costs, turn times, giving up)

Vitalize new venues?

OPEN ACCESS Freely available online

PLoS BIOLOGY

Essay

Synthetic Biology: Caught between Property Rights, the Public Domain, and the Commons

Arti Rai*, James Boyle

Novel artificial genetic systems with twelve bases instead of four [1]. Bacteria that can be programmed to take photographs [2] or form visible patterns [3]. Cells that can count the number of times they divide [4]. A live polio virus "created from scratch using mail-order segments of DNA and a viral genome map that is freely available on the Internet" [5]. These are some of the remarkable, and occasionally disturbing, fruits of "synthetic biology," the attempt to construct life starting at the genetic level. In terms of their scale and ambition, these efforts go beyond traditional recombinant DNA technology. Rather than simply transferring a pre-existing gene from one species to another, synthetic biologists aim to make biology a true engineering discipline.

In the same way that electrical engineers rely on standard DNA, its developers believe that, as DNA synthesis technology becomes increasingly inexpensive [7], the registry will be composed largely of information and specifications that can be executed in synthesizers just as semiconductor chip designs are executed by fabrication firms.

Synthetic biology has already produced important results, including more accurate AIDS tests and the possibility of unlimited supplies of previously scarce drugs for malaria [8]. Proponents hope to use synthetic organisms to produce not only medically relevant chemicals but also industrial materials, including biofuels such as hydrogen and ethanol [9]. At the same time, synthetic biology has engendered numerous policy concerns. From its inception, commentators have raised issues ranging from bioethical and environmental worries to fears of bioterrorism—indeed, the US Central

tension between different methods of creating "openness." On the one hand, one standard mechanism for creating openness has involved putting material in the public domain, outside the world of property. On the other, synthetic biology researchers may want to use intellectual property rights to create a "commons," just as developers of free and open source software use the leverage of software copyrights to impose requirements of openness on future programmers, requirements greater than those attaching to a public domain work. But synthetic biology, unlike software, is not necessarily protected by copyright. Should we rethink the boundary lines between intellectual property and the public domain as a result?

The Perfect Storm: Flawed Biotech Law Meets Flawed Software Law?

Intellectual property law in the US has

Ownership, sharing, and innovation frameworks can "evolve."

Early 1970s

"The first Unix application would be a word-processing program to be used by AT&T's patent-writing group."

http://www.spectrum.ieee.org/print/1571

Mid 70s to Mid 90s

"Who can afford to do professional work for nothing? ... Nothing would please me more than being able to hire ten programmers and deluge the hobby market with good software."
Bill Gates, Microsoft, Inc.

http://www.time.com

"Proprietary software divides the users and keeps them helpless, and that is wrong."
Richard Stallman, Free Software Foundation

http://www.boycottnovell.com/2009/03/14/

Today

And, changes in property rights law can be critical

The Copyright Act of 1976 stipulates (section 102):

(b) In no case does copyright protection for an original work of authorship extend to any idea, procedure, process, system, method of operation, concept, principle, or discovery, regardless of the form in which it is described, explained, illustrated, or embodied in such work.

Congress attempted to clarify the situation for computer programs (Rep. No. 473, 94th Cong., 1st Sess. 54 (1975)):

Section 102(b) is intended, among other things, to make clear that the expression adopted by the programmer is the copyrightable element in a computer program, and that the actual processes or methods embodied in the program are not within the scope of the copyright law.

and the National Commission on New Technological Uses of Copyrighted Works (CONTU), wrote in its final report (1978):

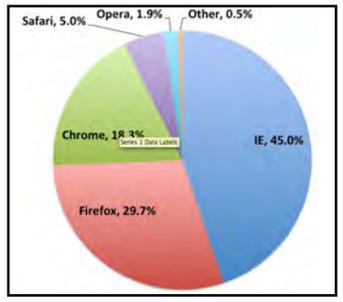
Where could a meaningful line of demarcation be drawn? Between flow chart and source code? Between source code and object code? . . . The Commission believes that none of these is appropriate. The line which must be drawn is between the expression and the idea, between the writing and the process which is described.

From MIT Course 6.805/STS085: Software and copyright law

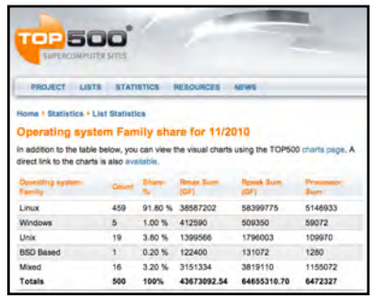
E.g., copyright law was extended to cover software decades ago. More recently software patents have been pursued.

What do we want to become true?

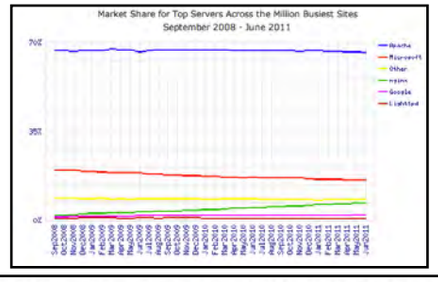
Free Software



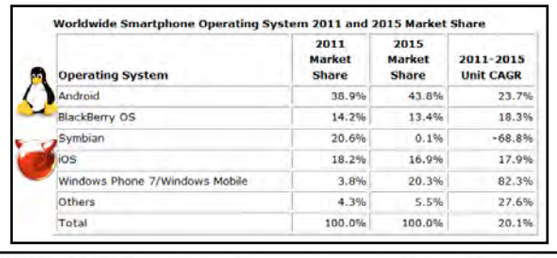
>50% browsers



>90% HPC



>80% servers



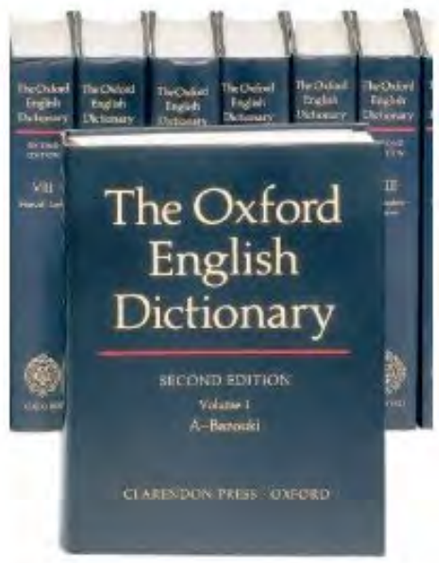
Worldwide Smartphone Operating System 2011 and 2015 Market Share			
Operating System	2011 Market Share	2015 Market Share	2011-2015 Unit CAGR
Android	38.9%	43.8%	23.7%
BlackBerry OS	14.2%	13.4%	18.3%
Symbian	20.6%	0.1%	-68.8%
iOS	18.2%	16.9%	17.9%
Windows Phone 7/Windows Mobile	3.8%	20.3%	82.3%
Others	4.3%	5.5%	27.6%
Total	100.0%	100.0%	20.1%

>60% smart phones

Position Jun 2011	Position Jun 2010	Delta in Position	Programming Language	Ratings Jun 2011	Delta Jun 2010	Status
1	2	↑	Java	18.580%	+0.62%	A
2	1	↓	C	16.278%	-1.91%	A
3	3	=	C++	9.830%	-0.55%	A
4	6	↑↑	C#	6.844%	+2.06%	A
5	4	↓	PHP	6.602%	-2.47%	A
6	5	↓	(Visual) Basic	4.727%	-0.93%	A
7	10	↑↑↑	Objective-C	4.437%	+2.07%	A
8	7	↓	Python	3.899%	-0.20%	A
9	8	↓	Perl	2.312%	-0.97%	A
10	20	↑↑↑↑↑↑↑↑↑↑	Lua	2.039%	+1.55%	A
11	12	↑	JavaScript	1.501%	-0.58%	A
12	11	↓	Ruby	1.484%	-0.61%	A
13	9	↓↓↓↓	Delphi/Object Pascal	1.070%	-1.50%	A
14	16	↑↑	Lisp	0.935%	+0.28%	A

12 of 15 languages

"Just" the DNA Dictionary + Rules of Grammar



I.e., for me (DE) I want to see a future in which the "operating systems for life" are free to use.

http://i.pbase.com/u47/hodero/large/30691408.jungle.jpg

Dreams

Make biology easy to engineer (tools).

Understand life.

Opportunities

Enable all constructive biotechnology.

Renew humanity in partnership with nature.