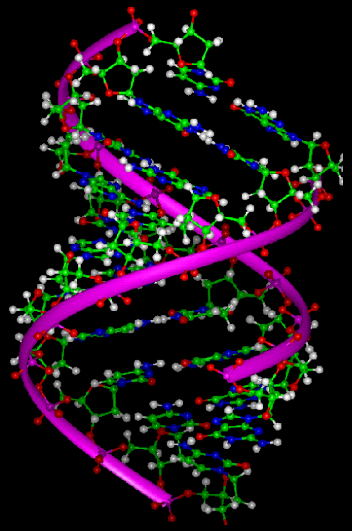

Biology Futures

The revolution in personalized genomics and synthetic biology: technological status and ethical issues

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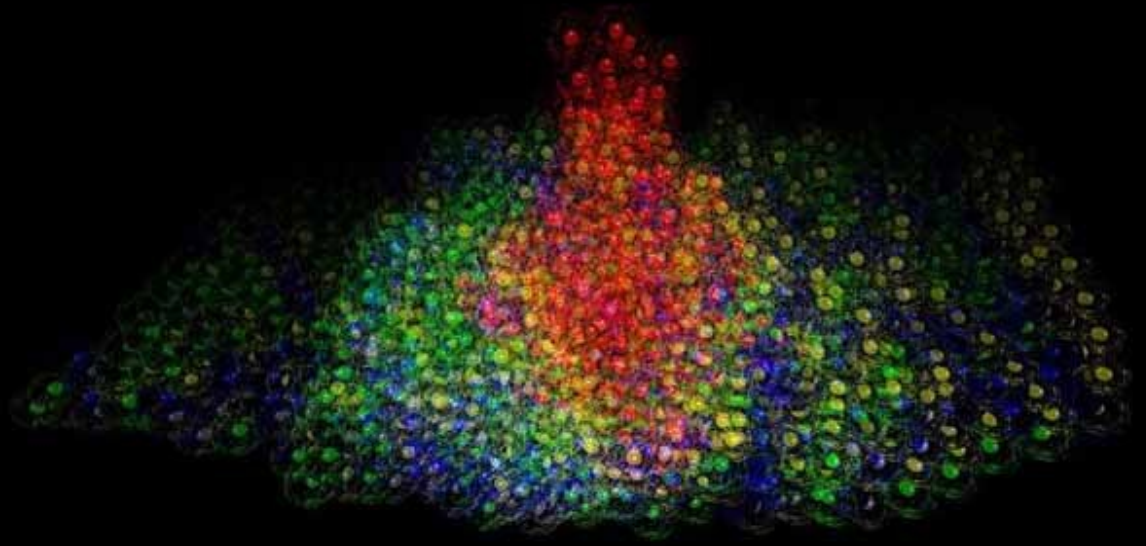
Slides: http//www.melanieswan.com/presentations/biology_futures.ppt

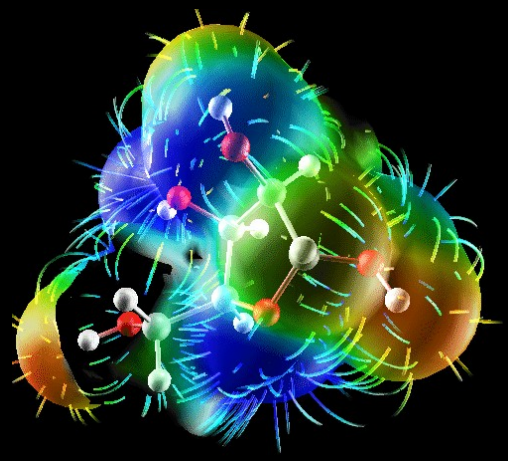
Summary

- Broad biology problem space: increasing worldwide demand for natural resources and healthcare services
- Traditional approaches stalled: soaring costs, slow innovation, static rate of annual drug discovery
- Conceptual and practical transformation
  - Art to digitized information science to engineering problem
  - Trial and error tools replaced by direct design



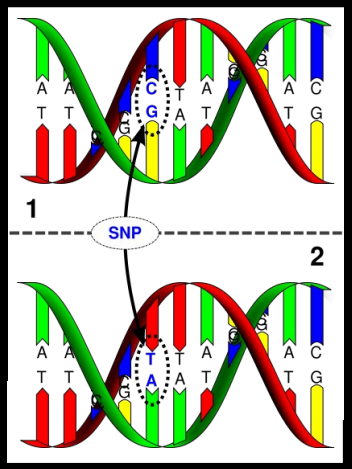
Agenda

- Genomics tools: sequencing and synthesizing
- Personal genomics revolution (sequencing)
- Synthethic biology revolution (synthesizing)
  - Biofuels, biofood
- Ethics
- Other areas
  - Advances in brain research
  - Long-term biology futures



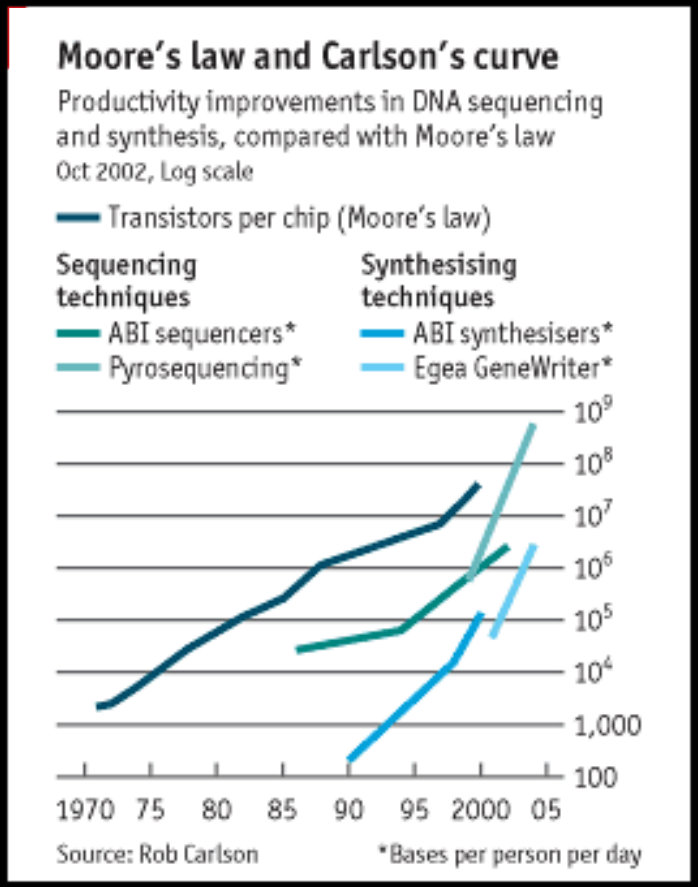
Key genomics tools

- DNA Sequencing (reading)
  - Human: 3b base pairs
- DNA Synthesizing (writing)
  - Replaces oligo synthesis, PCR
- Variation: SNPs (analysis)



Variation: SNP

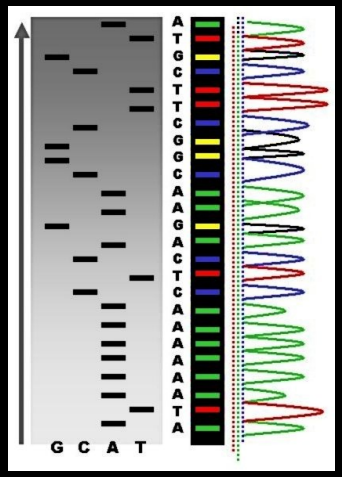
DNA Synthesizer

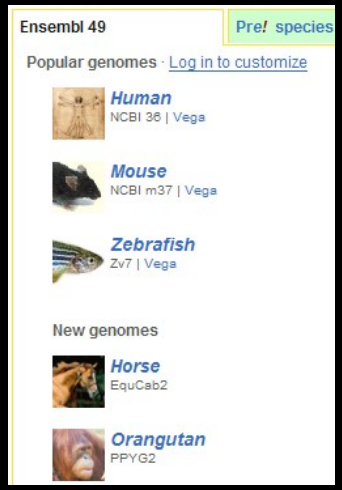


Sources: http://www.economist.com/background/displaystory.cfm?story_id=7854314, http://www.molsci.org/%7Ercarlson/Carlson_Pace_and_Prolif.pdf

Status of DNA sequencing

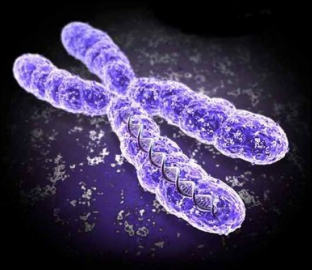
- Human Genome Project (1990-2003)
  - Sequence genome, identify genes
  - E. coli, fruit fly, mouse, chimp, etc.
- International HapMap Project (2002-2007)
  - DNA Bank: haplotype map
  - 4 populations: U.S., Japan, China, Nigeria
- High-throughput sequencing
  - Helicos, 454, Illumina, ABI, Pacific Biosciences
  - Whole genome $1,000 vs. $250,000
  - Archon X Prize: $10m, 100 genomes, 10 days, $10,000 per genome; expires 2013, 7 teams



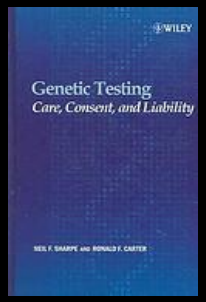


Ensembl gene browser

Genetic testing revolution



- $730m market growing 20% per year[1]



- Medical diagnosis (one-offs)
  - 1,000 existing genetics tests
- Direct-to-consumer genomics services ($100-$2,500)
  - Specific or multi-SNP array
  - DNA Direct, Navigenics, 23andme, deCODEme
- Uses of genetic testing
  - Disease diagnosis, risk assessment and monitoring
  - Drug response evaluation

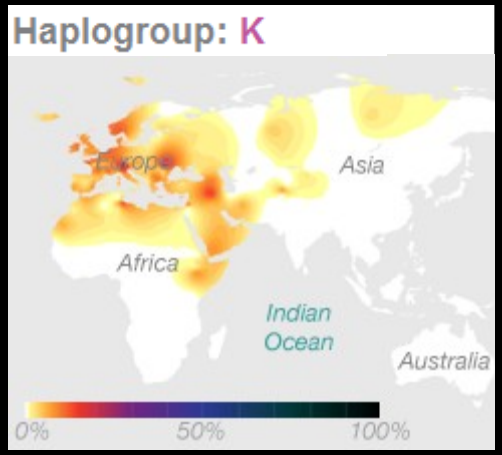
[1] *http://www.forbes.com/free_forbes/2007/0618/052_2.html*

Direct-to-consumer genomics service 23andme

gene journal

580,000 SNPs scanned and mapped to 70 conditions

Age-related Macular Degeneration	Crohn's Disease	Malaria Resistance (Duffy Antigen) new
Alcohol Dependence	Developmental Dyslexia	Male Infertility ♂
Alcohol Flush Reaction	Earwax Type	Measures of Intelligence
Ankylosing Spondylitis	Eye Color new	Memory
Antidepressant Response	Eye Color	Multiple Sclerosis
Atrial Fibrillation	Food Preference	Muscle Performance
Attention-Deficit Hyperactivity Disorder	Freckling	Obesity
Avoidance of Errors	Glaucoma	Obesity
Back Pain	Gout new	Obsessive-Compulsive Disorder ♂
Baldness	HDL Cholesterol Level	Odor Detection
Bipolar Disorder	HIV and AIDS	Pain Sensitivity
Birth Weight	HIV/AIDS Infection	Persistent Fetal Hemoglobin
Bitter Taste Perception	Hair Color	Placental Abruption ♀
Blood Groups new	Heart Attack	Prostate Cancer ♂
Breast Cancer	Height	Restless Legs Syndrome
Caffeine Metabolism	Heroin Addiction	Rheumatoid Arthritis
Celiac Disease new	High Blood Pressure (Hypertension)	Tardive Dyskinesia
Celiac Disease	Lactose Intolerance	Type 1 Diabetes
Cluster Headaches	Longevity	Type 2 Diabetes
Colorectal Cancer	Lou Gehrig's Disease (ALS)	Venous Thromboembolism



# rsid	chromosome	position	
rs3094315	1	742429	AG
rs12562034	1	758311	GG
rs3934834	1	995669	CC
rs9442372	1	1008567	GG
rs3737728	1	1011278	GG
rs11260588	1	1011521	GG
rs6687776	1	1020428	CC
rs9651273	1	1021403	GG
rs4970405	1	1038818	AA
rs12726255	1	1039813	AA
rs11807848	1	1051029	TT
rs9442373	1	1052501	AA
rs2298217	1	1054842	CC
rs12145826	1	1055892	GG

23andme colorectal cancer marker

Karen Jacobs

0.21 out of 100

people of European ethnicity who share Karen Jacobs's genotype will get Colorectal Cancer between the ages of 30 and 49.

Average

0.26 out of 100

people of European ethnicity will get Colorectal Cancer between the ages of 30 and 49.

8q24 region **Marker:** rs6983267

This SNP occurs in a hypothetical gene called LOC727677. Little is known about the gene's function; however, it is located in a region of DNA that often acquires extra copies in colorectal cancers. This suggests that the SNP is linked to a change in the activity of a nearby gene that influences cancer development.

One group found that the riskier version of this SNP is associated not only with an increased risk of colorectal cancer, but also with formation of the precancerous adenomatous polyps. This suggests that the SNP is linked to a gene that affects the very early stages of colorectal cancer.

Citations

Haiman et al. (2007) . "A common genetic risk factor colorectal and prostate cancer." *Nat Genet* 39(8):954-6..

Tomlinson et al. (2007) . "A genome-wide association scan of tag SNPs identifies a susceptibility variant for colorectal cancer at 8q24.21." *Nat Genet* 39(8):984-988.

Zanke et al. (2007) . "Genome-wide association scan identifies a colorectal cancer susceptibility locus on chromosome 8q24." *Nat Genet* 39(8):989-994.

Genes vs. Environment

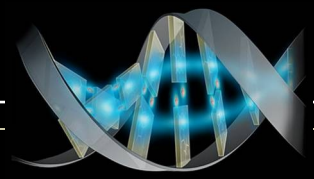
35 %
Attributable to Genetics

The heritability of colorectal cancer is estimated to be 35%. This means that environmental factors contribute more to differences in risk for this condition than genetic factors. Genetic factors that play a role in colorectal cancer include both unknown and known factors. Known factors include rare mutations in the MSH2 and MLH1 genes that appear in familial cases of colon cancer (which 23andMe does not genotype), and the SNP we describe here. Other factors include a history of previous colorectal cancer, colorectal polyps, or inflammatory bowel disease, being an Ashkenazi Jew or of African descent, a diet high in animal fat, physical inactivity, obesity, smoking, heavy alcohol use, and diabetes. (Note: The contribution of the SNP reported by 23andMe to inherited colorectal cancer risk is minor. If you have a strong family history of early-onset colon cancer, you should consider mutation testing of MSH2 and MLH1.) (sources)

Direct-to-consumer genomics controversy

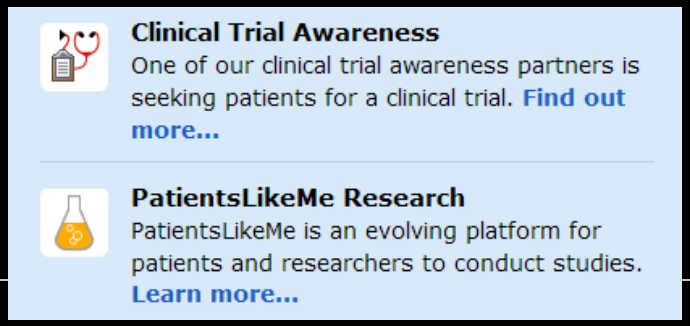
Drawbacks	Advantages

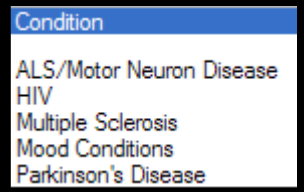
▪ Unregulated
▪ Usefulness of information
  ▪ Unclear correlation
  ▪ Multigenic diseases
  ▪ Lack of therapies
▪ Results interpretation
  ▪ Genetic counseling
  ▪ False positives, false negatives
▪ Insurance and employment discrimination
	▪ Fact-based information
	▪ Improved consumer experience
	  ▪ Consumer-owned data
	  ▪ Empowered
	  ▪ Health literacy
	▪ Significant demand
	▪ Impact on healthcare
	  ▪ Consumer more active, better outcomes

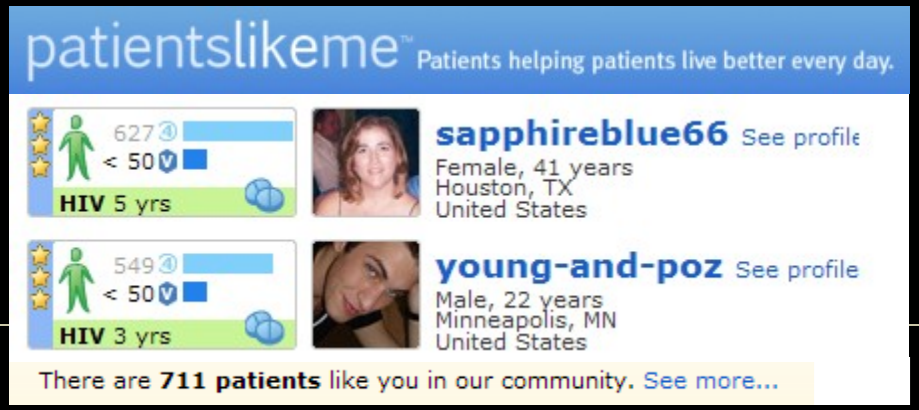


Implications of personalized genomics

- System must change: healthcare and insurance
- Long tail of medicine
  - Member communities and social networking
  - Online databases for field studies and clinical trials
  - Research priorities enumerated, funding directed
- Key step towards personalized medicine
  - Genomic data + medical history + biological markers
- Upstreams focus to prevention vs. therapy





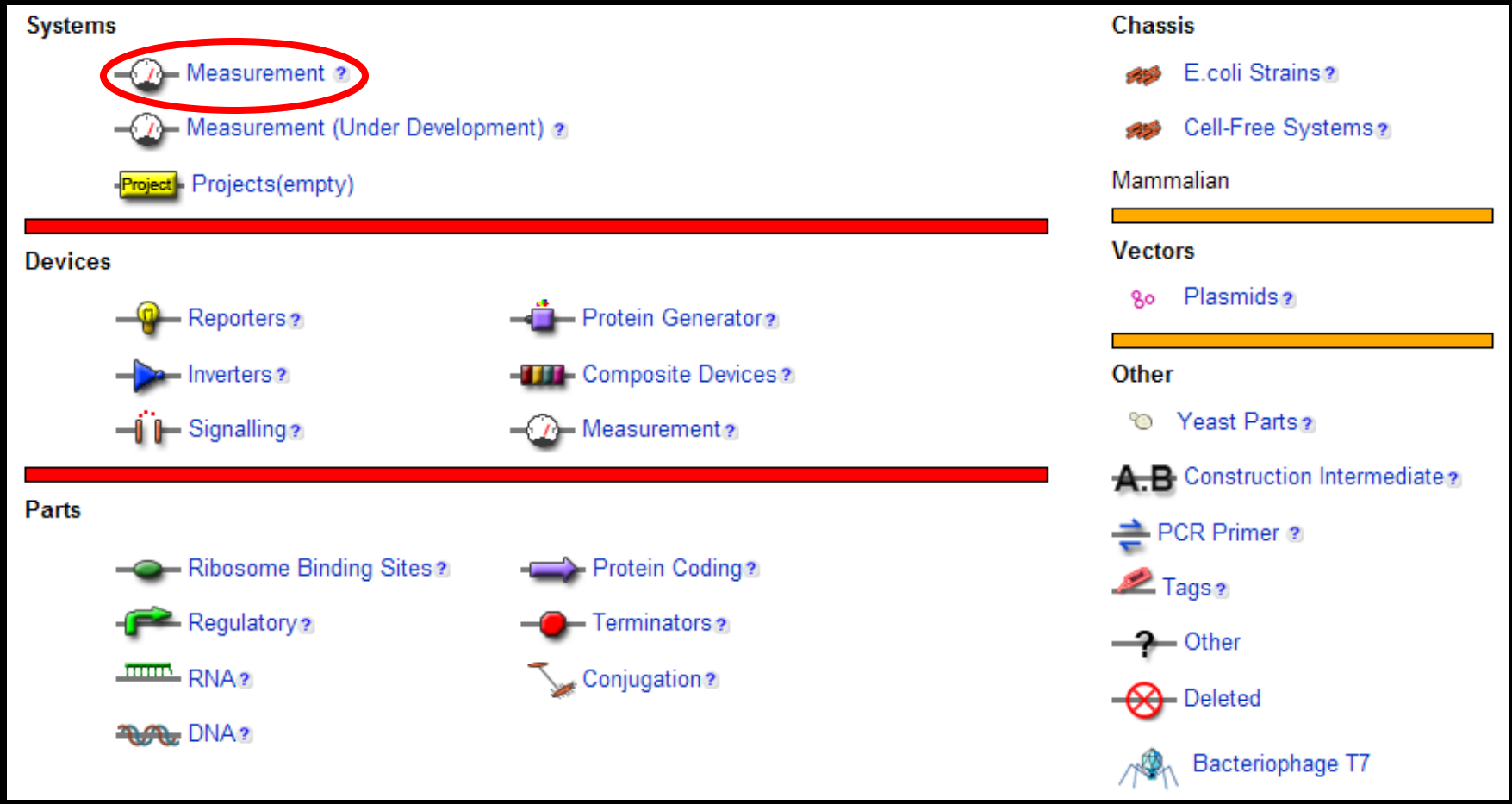


Synthetic biology revolution

- Vision
  - Understand and harness biological design rules
- Definition
  - Using engineering to redesign existing and construct new biological parts, devices and systems
- Wide-ranging applications
  - Energy, nutrients/food, pharmaceuticals, structural materials, chemicals, environment
- Result
  - Encoded DNA executed by a cellular chassis
  - Directed design vs. trial and error

BioBricks: Registry of Standard Biological Parts

- Modular building block components



Source: http://partsregistry.org (MIT)

BioBricks example: measurement device selection

Measurement Devices

Information about measurement systems

Table of promoter output high measurement system parts

Available Measurement Devices *Show 165 more parts* *Edit*

-?-	Name	Type	Description	Output	Length
A W	BBa_I13513	Measurement	Screening Plasmid 2		2885
A W	BBa_I13515	Measurement	Screening Plasmid 4		2825
A W	BBa_I5131	Measurement	[illegible]		906
A W	BBa_I7100	Measurement	TetR repressible GFP generator		940
A W	BBa_I732901	Measurement	[illegible]		3438
A W	BBa_I732902	Measurement	R0010 I732020		597
A W	BBa_I732903	Measurement	R0011 I732020		452
A W	BBa_I732913	Measurement	[aTC] -> RFP		1757
A W	BBa_I732914	Measurement	P_NAND_U073O26D001O16 + RFP		989
A W	BBa_I732916	Measurement	P_NOR_U037O11D002O22 + RFP		954
A W	BBa_I732917	Measurement	P_NOR_U035O44D001O22 + RFP		951
A W	BBa_J5517	Measurement	Arabinose -> LacI ts -| GFP		3473
A W	BBa_J5518	Measurement	Arabinose -> LacI ts -| mRFP		3458
A	BBa_I13008	Measurement	RBS Test R0011.B0031.E0130		942
A	BBa_I13011	Measurement	RBS Test R0040.B0030.E0130		943
A	BBa_I13012	Measurement	RBS Test R0040.B0031.E0130		942
A	BBa_I13013	Measurement	RBS Test R0040.B0032.E0130		941
A	BBa_I13014	Measurement	RBS Test R0040.B0033.E0130		939
A	BBa_I13512	Measurement	Screening plasmid 1		2887
A	BBa_I13514	Measurement	Screening Plasmid 3		2825
A	BBa_I13529	Measurement	Screening Plasmid 2.1		2911
A	BBa_I13530	Measurement	Screening Plasmid 2.2		2911
A	BBa_I13533	Measurement	Screening Plasmid 2.5		2945
A	BBa_I13534	Measurement	Screening Plasmid 2.6		2945
A	BBa_I13606	Measurement	Reporter Construct (Ty+Lc+)		1966
A	BBa_I13614	Measurement	Cascaded Tet (medium) and Lac (medium) QPIs		2284
A	BBa_I13617	Measurement	Cascaded Tet (elowitz) and Lac (medium) QPIs		2282
A	BBa_I13623	Measurement	Cascaded Lac (medium) and Tet (weak) QPIs		2281
A	BBa_I13624	Measurement	Cascaded Lac (medium) and Tet (medium) QPIs		2284

BioBricks example: obtain part sequence

Part:BBa_I7100

DNA Available
Experience: Works

Designed by Jennifer Braff

Entered: 2004-10-26

TetR repressible GFP generator

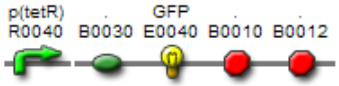
BBa_I7100 is a composite part consisting of a TetR repressible promoter (BBa_R0040) and a GFP generator (BBa_E0840). Thus, BBa_I7100 produces fluorescence in either the absence of TetR or in the presence of the inducer aTC.

Usage and Biology

See BBa_R0040 for details on the TetR repressible promoter.

Sequence and Features

Format: Subparts | Ruler | SS | DS Search: Length: 940 bp Context: Part only Get selected sequence



Part-only sequence for BBa_I7100(940 bp)

```
tccctatcagtgatagagattgacatccctatcagtgatagagatactgagcactactagagattaaagaggagaaatactagatgcgtaaaggagaaga
acttttcactggagttgtcccaattcttgttgaattagatggtgatgttaatgggcacaaattttctgtcagtggagagggtgaaggtgatgcaacatac
ggaaaacttacccttaaatttatttgcactactggaaaactacctgttccatggccaacacttgtcactactttcggttatggtgttcaatgctttgcga
gatacccagatcatatgaaacagcatgacttttcaagagtgccatgcccgaaggttatgtacaggaaagaactatatttttcaaagatgacgggaacta
caagacacgtgctgaagtcaagtttgaaggtgatacccttgttaatagaatcgagttaaaaggtattgattttaaagaagatggaaacattcttggacac
aaattggaatacaactataactcacacaatgtatacatcatggcagacaaacaaaagaatggaatcaaagttaacttcaaaattagacacaacattgaag
atggaagcgttcaactagcagaccattatcaacaaaatactccaattggcgatggccctgtccttttaccagacaaccattacctgtccacacaatctgc
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taatactagagccaggcatcaaataaaacgaaaggctcagtcgaaagactgggcctttcgttttatctgttgtttgtcggtgaacgctctctactagagt
cacactggctcaccttcgggtgggcctttctgcgtttata
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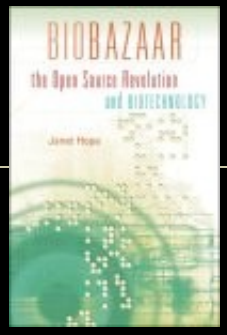
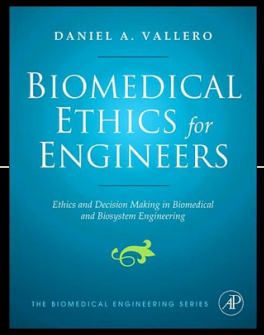
Synthetic biology status



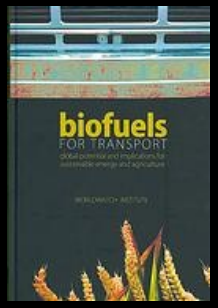


- Initiatives
  - BioBricks parts registry database
  - Working groups on design, interoperability and legal standards
  - Small scale directed experiments vs. large scale random
  - Improvement from error correction techniques
  - Focus on yield, stability, refinement
- Key efforts
  - Craig Venter (Synthetic Genomics): genome synthesis, biofuels
  - Drew Endy (MIT): standardized parts, BioBricks Foundation
  - Jay Keasling (Berkeley): biofuel, anti-malarial treatment
  - Joe Jackson (Harvard): Open Source Biotech Brazil
  - George Church (Harvard): synthetic cells, novel amino acids
  - iGEM competition

Biofuels

Algal Oil

- First generation
  - Food feedstock: sugar, starch, vegetable oil or animal fats using conventional technology (food for fuel debate)
  - Fuel types: vegetable oil, biodiesel, butanol, ethanol, syngas
- Second generation
  - Non food crop feedstock: cellulose, waste biomass: wheat, corn, wood
  - Fuel types: biohydrogen, biomethanol, DMF, bio-DME, Fischer-Tropsch diesel, biohydrogen diesel, mixed alcohols and wood diesel
- Third generation
  - Algae feedstock
- Fourth generation
  - CO_2 feedstock: CO_2 converted to methane by bacteria

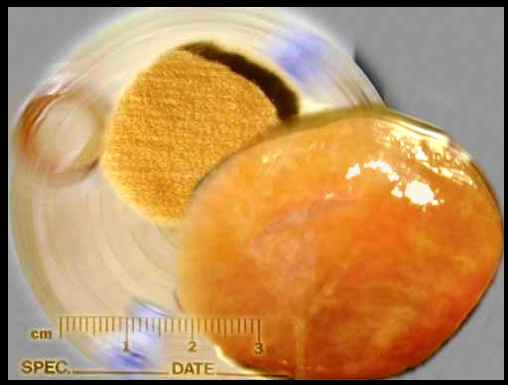


Biofood

- Continuum of precision in plant and animal selection
  - Selective breeding
  - Artificial selection
  - High-tech breeding (IVF)
  - Genetic engineering, tissue engineering
- Per capita long-term world production trends
  - Decline in rice, wheat, potatoes and rye
  - Increase in maize, sugar cane, soybean, palm oil
- Competition for food resources
  - Human and animal feedstocks
  - Energy
  - Industrial inputs

Wild type corn

Enhanced corn

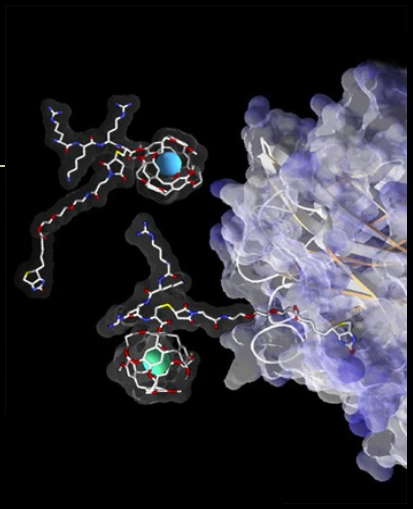


In vitro meat

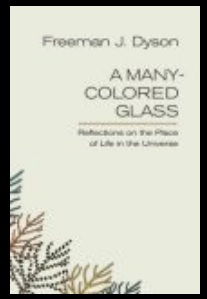
Corn images: http://www:science-interactive.co.uk

Implications of synthetic biology

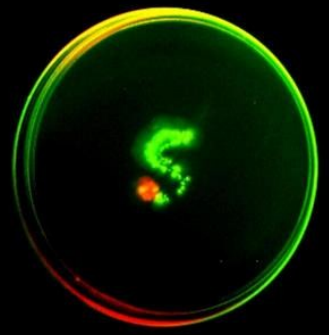
- Geopolitics
  - Petrochemical industry replacement
  - Technology as policy, energy independence
  - Access: economic and social polarization
  - Competitive advantage
- Public health
  - Combinatorial vaccine library, DNA bank
  - Healthcare: prevention, costs, Social Security
  - Embryonic genetic modification, designer babies
- Culture of life design



Spore Creature Creator



Bioethics and society



- Fundamental setting for bioethics: humanity

- Legislative status
  - UN Convention on Human Rights and Biomedicine
  - U.S. Presidential Council on Bioethics (est. 2001)
  - U.S. genetic nondiscrimination
    - Federal: Genetic Information Nondiscrimination Act, May 2008
    - State: genetic non-discrimination legislation in 40 states

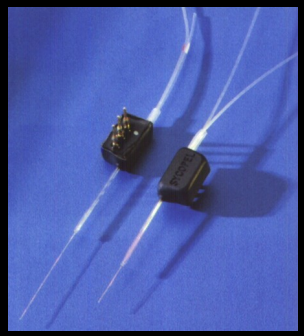
- Heterogeneous cultural response to technology
  - Paternity testing (Europe), stem cell research (U.S.)

Ethics of new technology: dual-use

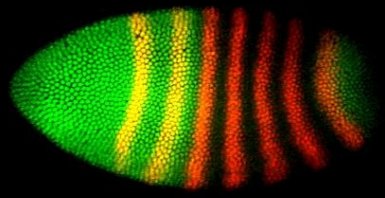
"evil" Technophobic (Bill Joy)	"good" Technophilic (Ray Kurzweil)
▪ Control and if necessary extinguish technology ▪ Top-down monitoring and control, hierarchical, few in power (surveillance) ▪ Philosophy of secrecy ▪ Licensing, monitoring, gated access, tracking, inspection ▪ Challenges are concentrated, government provides national security	▪ Technology is inevitable ▪ Bottom-up monitoring, democratic, participatory, many in power (sousveillance) ▪ Philosophy of openness ▪ Proliferation of open source projects (OpenWetWare, diybio, biopunk, biohack) ▪ Challenges are distributed, citizen defense, biosensors

Biological warfare and public health

- Can these technologies be weaponized?
- Biological Weapons Convention (1972)
  - Offense prohibited; defensive research
- Open publishing (AIDS, SARS)
- Risk assessment
  - Access to existing samples
  - Creating pathogens is difficult
  - Superbugs (Staph aureus), emerging infections
- Simultaneous development of defenses
  - Sensors



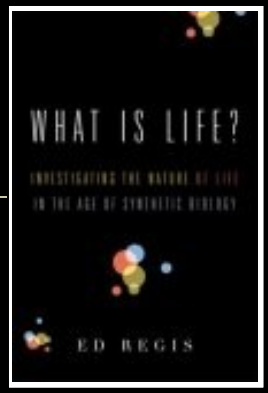
Ethics: practitioner standards



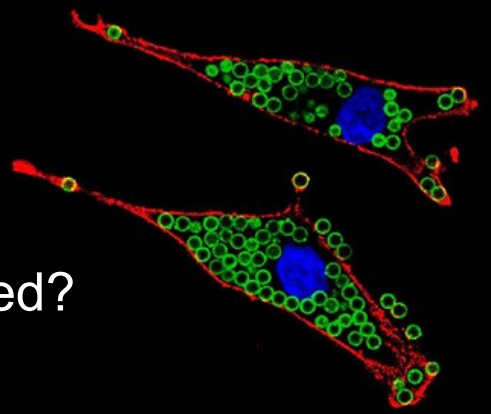
- Hippocratic oath principles: autonomy, privacy, beneficence
- Research Ethics Recommendations for Whole-Genome Research: Consensus Statement[1] March 25, 2008
  - Consent
  - Withdrawal from research
  - Return of results
  - Public data release
- Synthetic biology biosafety
  - Reviews: external pre-experimental and ongoing
  - Responsibility-taking: signature, documentation
  - Safe design: non-reproductive, activation-based, suicide gene
  - Safeguards for unintended consequences

[1] *http://biology.plosjournals.org/perlserv/?request=get-document&doi=10.1371/journal.pbio.0060073*

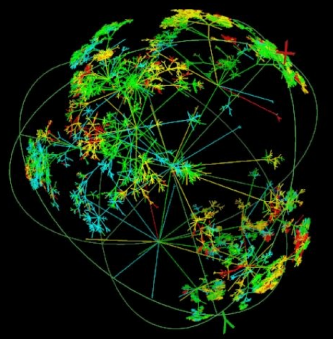
Ethics: intellectual property



- Models
  - Protected, open-source, shared foundation
  - Successive tiers cleared to public use
    - 1996 Bermuda Principles
    - 2000 Clinton: genome sequences ineligible for patent
- Considerations
  - Product window, cost of development, market demand
  - Open-source information, fee-based services
- Definitional issues
  - What is life?
  - Can genetically modified organisms be patented?
    - Diamond v. Chakrabarty, 1980



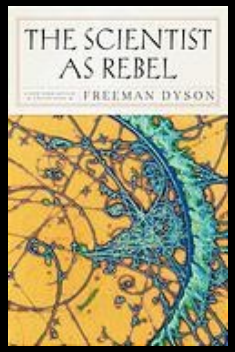
Pedagogy and scientific method



- High dynamism in the field of biology
  - Mathematical biology (SMB), computational biology
- 21c skillsets: the new literacy

"From this combination of passion and inventiveness I sense that students are reinventing literacy. Literacy has been boiled down to reading and writing, but the means have changed since the Renaissance. In a very real sense post-digital literacy now includes 3D machining and microcontroller programming." – Neil Gershenfeld, MIT[1]

  - The educated person of today must be able to express thoughts in a variety of technology-based media
- Evolution of the scientific method
  - Combinatorial era focuses on empiricism and simulation



[1] *http://en.wikipedia.org/wiki/Synthetic_biology*

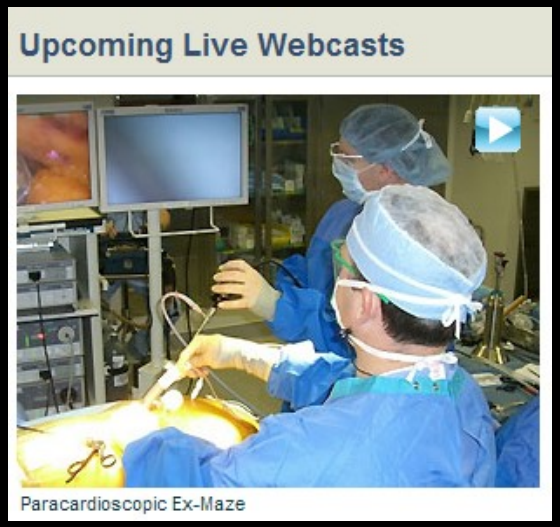
Advances in brain research

- IBM Blue Brain: multidisciplinary advances
  - Neocortical anatomy and microscopy recording
- Genomics and the brain
  - Functional genomics and gene expression
- Neuro-imaging
  - Synapse activity, vesicles and transporters
  - Small systems in specialized tissues
  - Molecular scale activities with PET
  - Neuronal interactions with magneto-electroencephalography
  - Bloodflow and structure of the brain using MRI and fMRI
- Intelligence
  - James Flynn – IQ increasing
  - Bruce Lam – continuing evolution
  - Christine Kenneally – language suite (FoxP2)

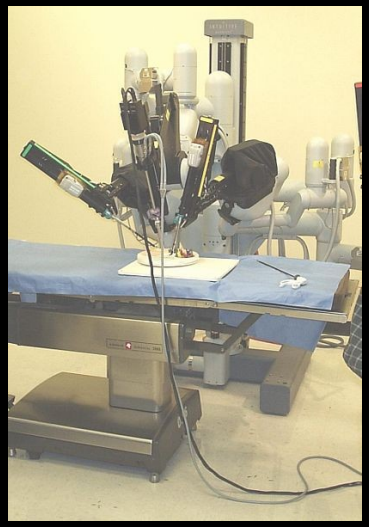
Innovations underway

- Virtual health services
- Telemedicine
- InterpretMyXRray
- Robotic surgery

Second Health Operating Theatre, Second Life



OR-Live.com



da Vinci Robotic Surgery

Teraradiology

Telemedicine

Long-term biology futures

- Neuroplasticity and brain fitness
- Human genetic modification
- Anti-aging, life extension
- Neuroengineering
- Transhuman, posthuman

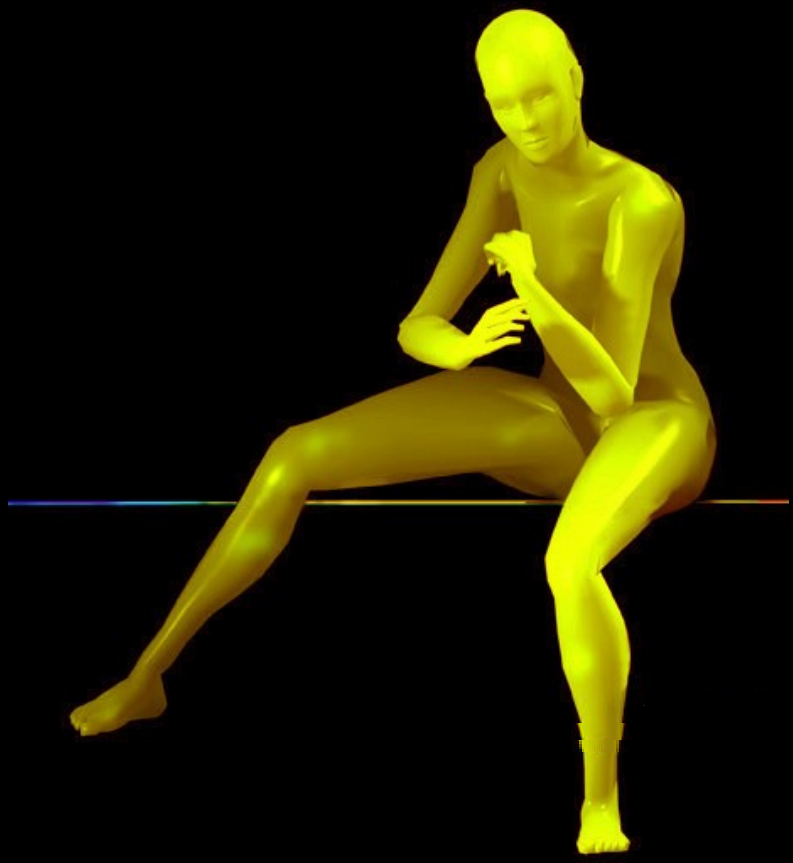
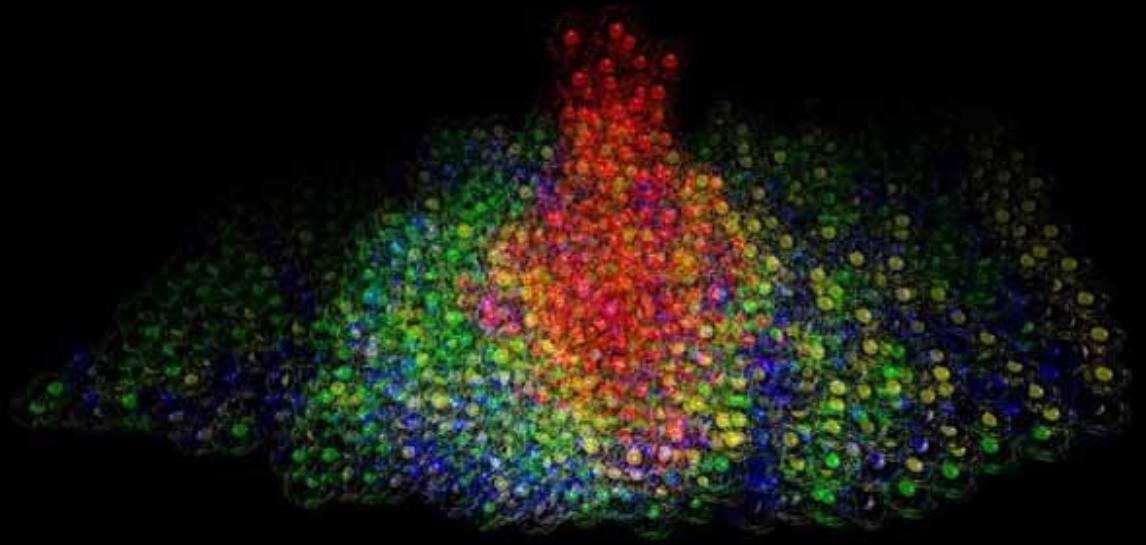


Image: Natasha Vita-More, Primo Posthuman

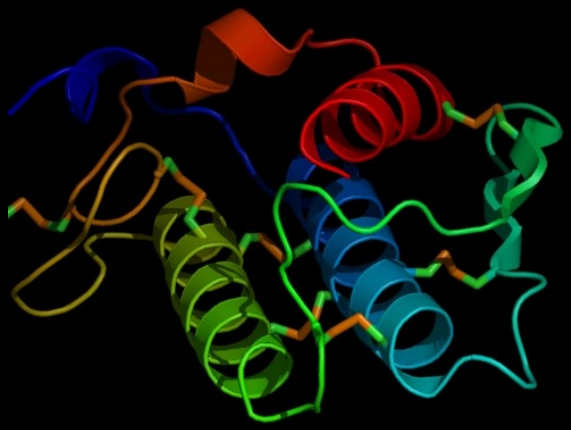
Summary

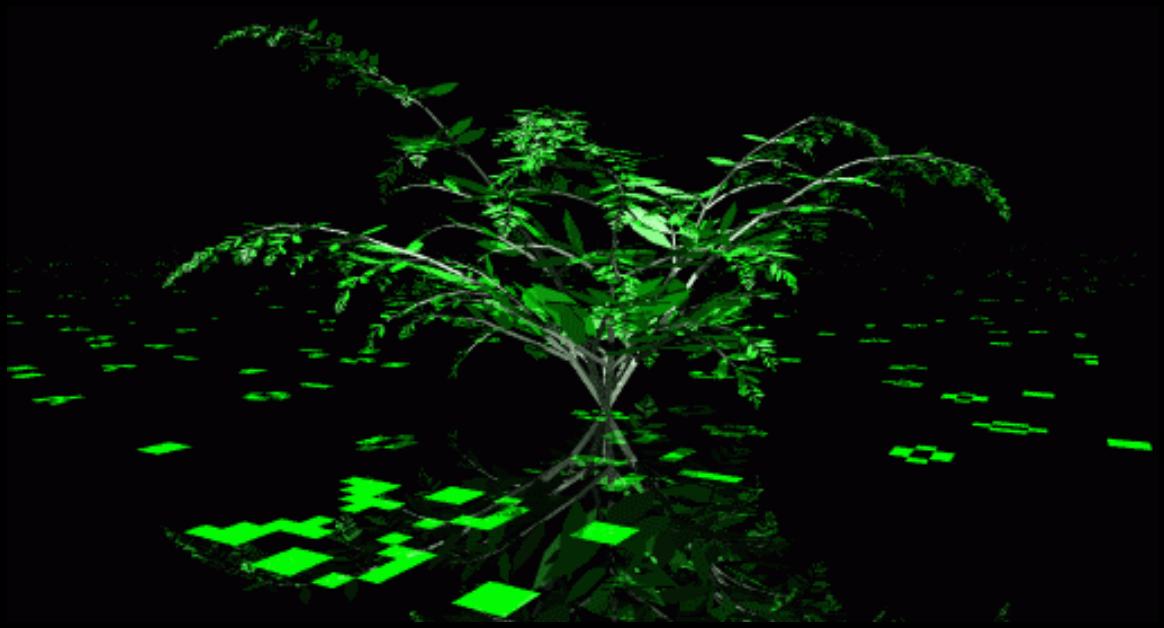
- Broad biology problem space: increasing worldwide demand for natural resources and healthcare services
- Traditional approaches stalled: soaring costs, slow innovation, static rate of annual drug discovery
- Conceptual and practical transformation
  - Art to digitized information science to engineering problem
  - Trial and error tools replaced by direct design



Resources

- Ethics and biotechnology industry watch groups
  - http://www.bioethics.net/ (American Journal of Bioethics)
  - http://www.etcgroup.org/
- News, blogs, advocacy groups, etc.
  - http://www.eyeonDNA.com/
  - http://phylogenomics.blogspot.com/
  - http://www.personalizedmedicinecoalition.org/
- Podcasts and video
  - http://www.cbc.ca/ideas/features/science/
  - http://www.onemedplace.com/
  - http://or-live.com/
- Synthetic biology
  - http://partsregistry.org/
  - http://igem.org/
  - http://openwetware.org/
  - http://www.synbiosafe.eu/forum/





Thank you

Slides: http//www.melanieswan.com/presentations/biology_futures.ppt

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