Synthetic Viruses Targeting Cancer

Andrew Hessel

September 7, 2007

SENS 3, Cambridge, UK

pinkarmy.org

Why is a new strategy necessary?

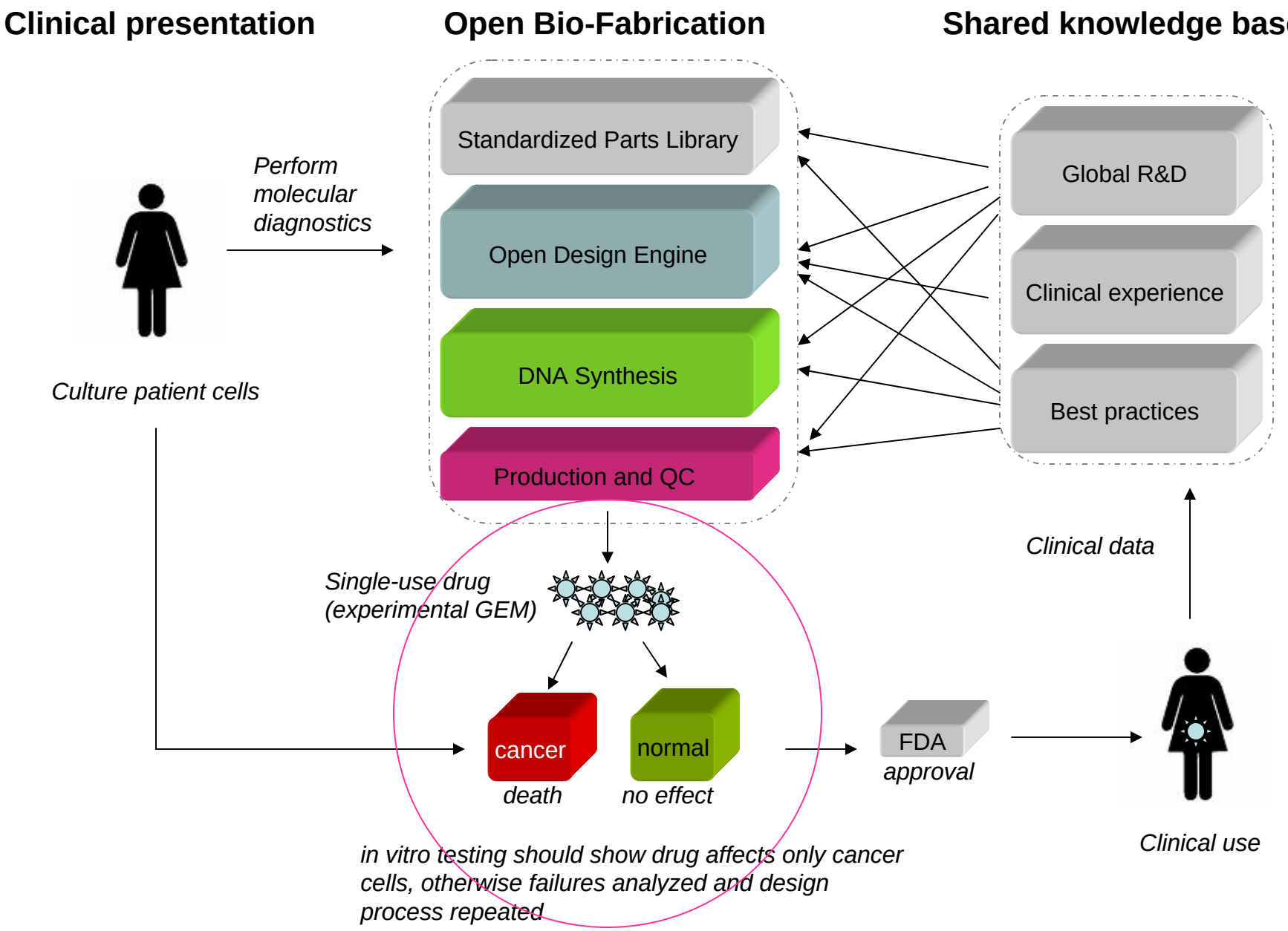
- Breast cancer remains a significant cause of illness and death
- The treatment options for breast cancer have remained virtually the same for the last 30 years, despite great advances in molecular biology
- The rate of new therapeutic development is too slow
- The economics of the current drug development model are unsustainable
- Current drug development strategies do not address the fact that *each cancer is a unique disease*
- Even the most modern cancer treatments work far downstream from the fundamental root of cancer, namely damage to DNA

The *Ideal* Cancer Drug

- Highly specific to an individual cancer
- Works at the level of DNA
- Effective, well-tolerated, with mild side effects
- Inexpensive and widely available
- Based on the best current biological understanding and technology
- Rapidly reconfigurable to target any resistant cell populations or for mixed cell populations

Strategy Framework

Desired outcome	Can be accomplished by
Works at level of DNA	Gene-based agents such as viruses or, better, genetically engineered machines
Personalized and targeted	Incorporate molecular knowledge of individual cancer into the design; obviates need for wide clinical testing
Rapid development, reconfigurable	Modular components, semi- or fully-automated drug design and production
Best technology available	Open access to research data, development data, and clinical use results, allowing continuous innovation
Low cost	Free market competition leading to non-monopolistic pricing


Clinical presentation
Open Bio-Fabrication
Shared knowledge base
Perform molecular diagnostics
Culture patient cells
Standardized Parts Library
Open Design Engine
DNA Synthesis
Production and QC
Global R&D
Clinical experience
Best practices
Clinical data
Single-use drug (experimental GEM)
cancer
death
normal
no effect
FDA approval
Clinical use
in vitro testing should show drug affects only cancer cells, otherwise failures analyzed and design process repeated

CELL GENESYS

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Clinical Trials | Trials Open for Enrollment | Patient's Library

Patient's Library

- What are Clinical Trials?
- What are Cancer Immunotherapies?
- What are Oncolytic Viruses?
- Bibliography

WHAT ARE ONCOLYTIC VIRUSES?

Oncolytic ("onco" meaning cancer, "lytic" meaning "killing") viruses represent an innovative potential cancer therapy known as "virotherapy"—a therapy that seeks to harness the natural properties of viruses to aid in the fight against cancer.

geron

ONCOLYTICS BIOTECH INC

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Technology Changing Life

Oncolytics Biotech Inc. was formed in 1998 to develop its proprietary product, REOLYSIN®, as a potential therapeutic for a wide variety of human cancers.

Oncolytics has completed six clinical trials with REOLYSIN® in Canada, the U.K. and the U.S. and is currently conducting seven Phase I or Phase II REOLYSIN® trials in the U.K. and the U.S.

The current clinical program includes local or systemic delivery of REOLYSIN® as a monotherapy, and local or systemic delivery of REOLYSIN® in combination with radiation or chemotherapy for patients with advanced cancers.

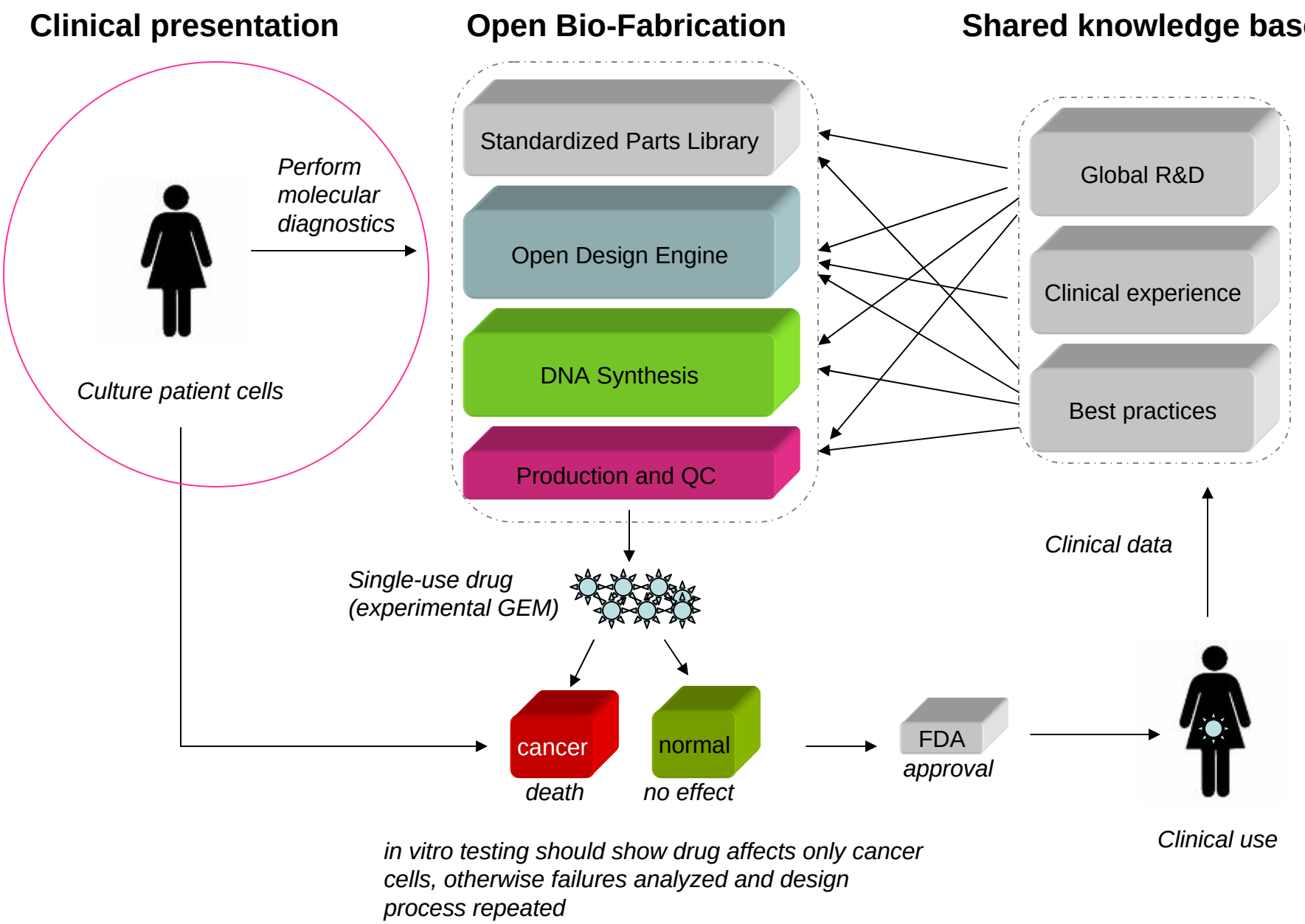
News Releases & Announcements

$6.3M from Terry Fox Foundation to link researchers across Canada developing oncolytic virus therapies for cancer

OTTAWA, May 24, 2007 — Seven Canadian research teams, led by Dr. John Bell of Ottawa, will share a $6.3 million grant to collaboratively develop and test oncolytic viruses as cancer therapeutics. The grant was awarded by the Terry Fox Foundation through the National Cancer Institute of Canada after a competitive peer-review process.

"Canada is a leading country for oncolytic virus research. This grant will allow us to expand our efforts and work together to ensure that cancer patients benefit from our research as soon as possible," said Dr. Bell, a Professor and Senior Scientist at the University of Ottawa, the Ottawa Health Research Institute and The Ottawa Hospital Regional Cancer Centre.

Oncolytic viruses infect and destroy cancer cells without harming normal cells. They work because many anti-cancer genes are also anti-viral genes, so when cells develop genetic mutations that lead to cancer, they often lose their viral defenses at the same time. While oncolytic viruses have been known to exist for decades, there has been a resurgence of interest in recent years as scientists have discovered new oncolytic viruses and engineered them to be better and safer. Studies in laboratory models have shown that these viruses are very effective against many cancers and early clinical studies in patients have been encouraging.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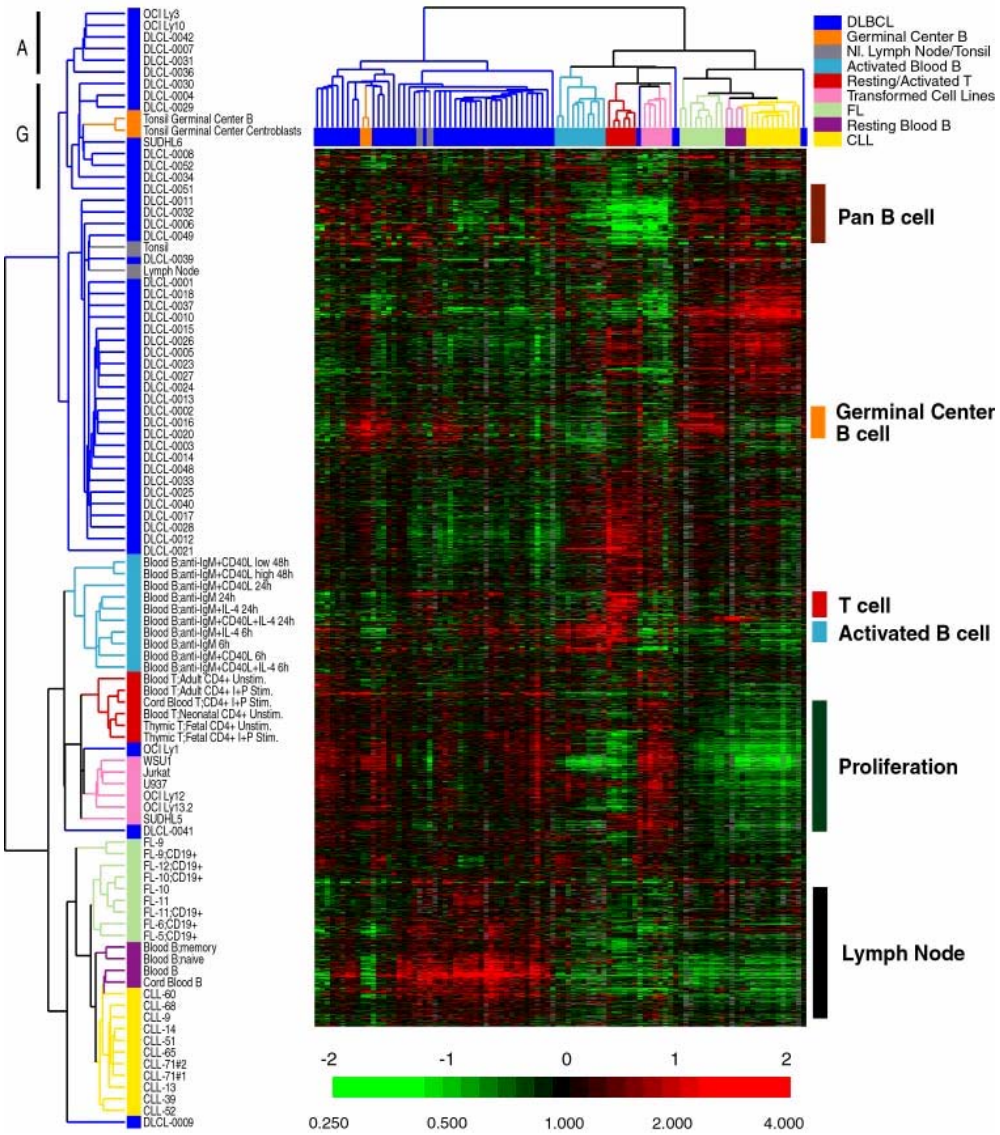
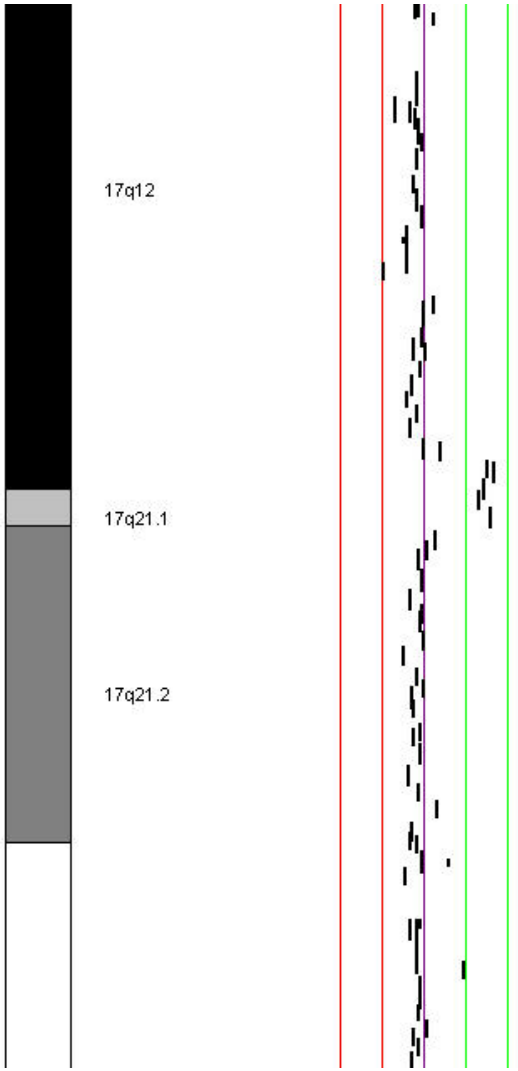
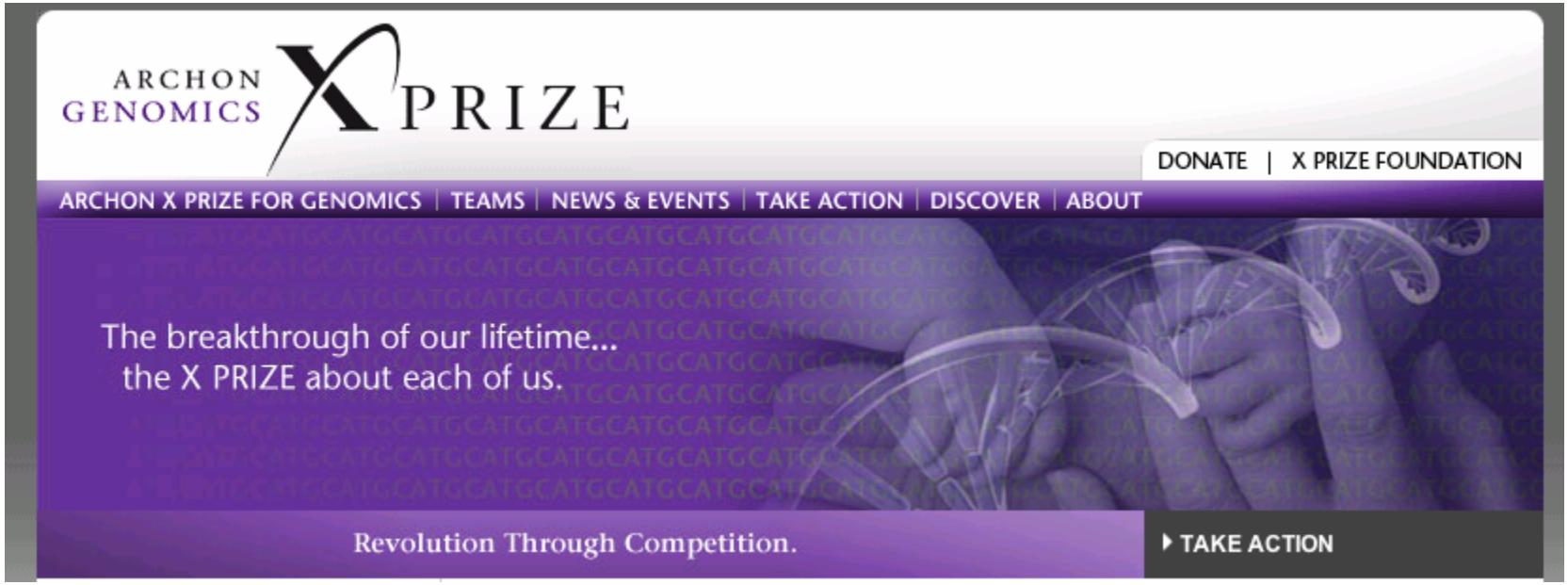
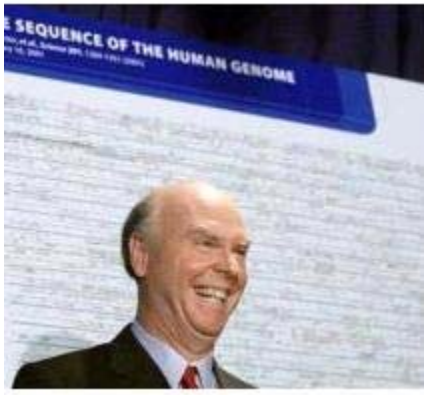
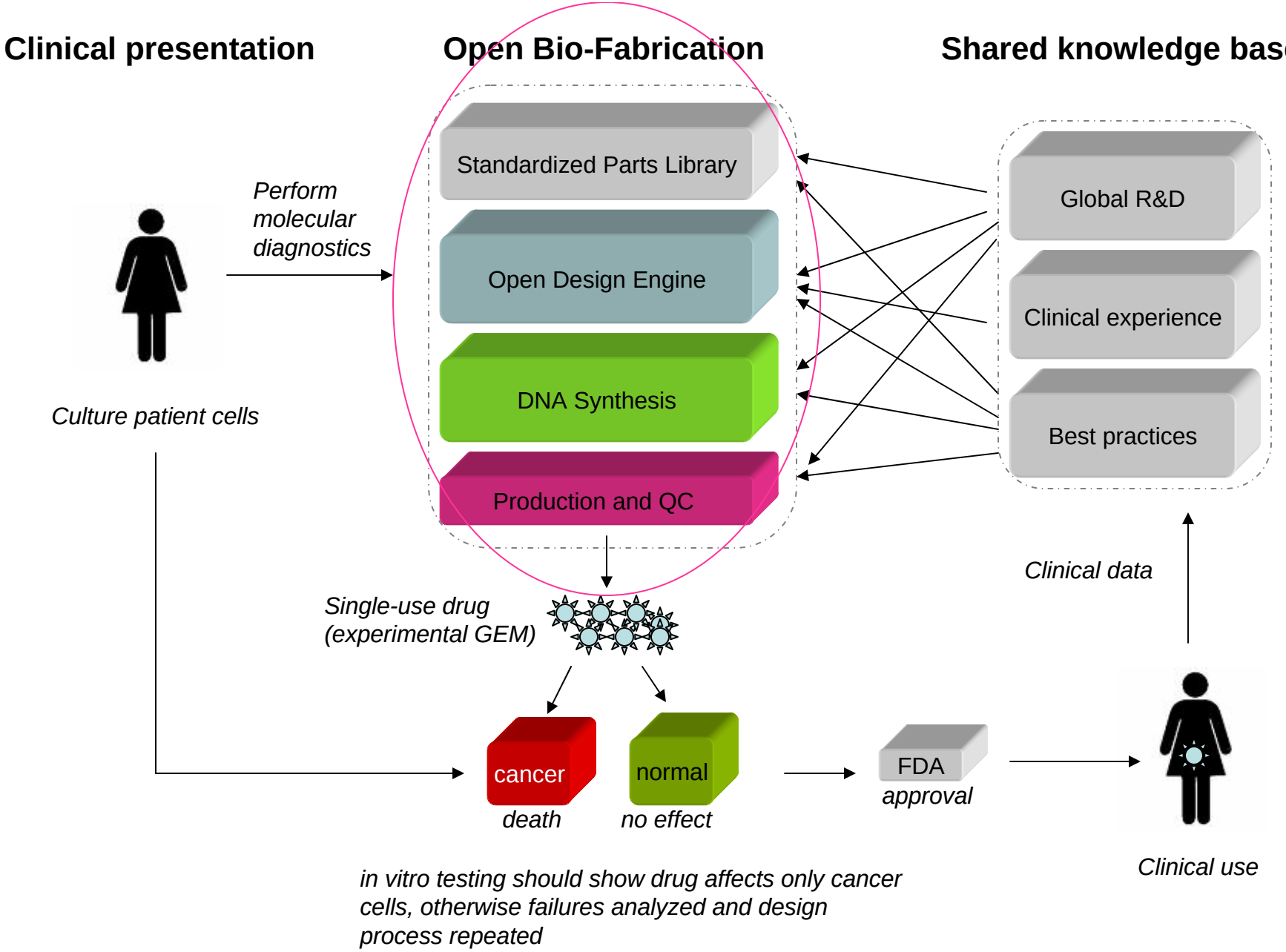








First individual genome published online; shows humans less alike than thought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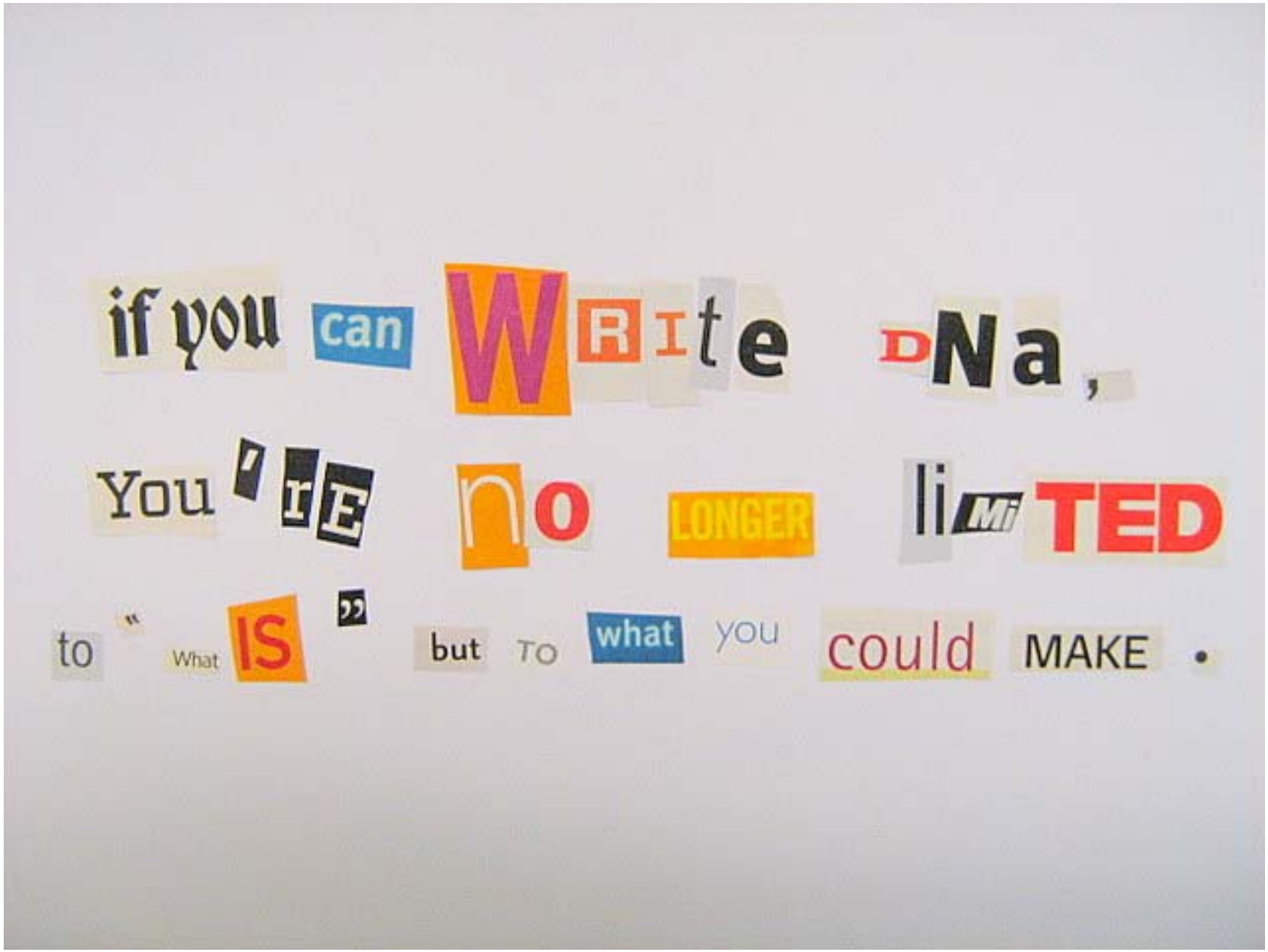
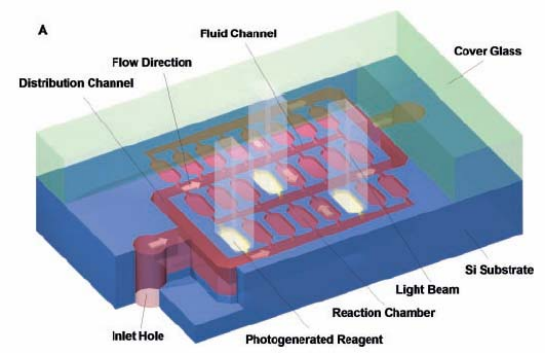
Synthetic Biology

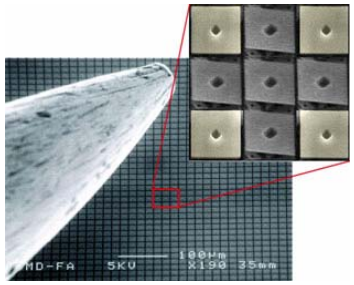
"**Synthetic biology** is an emerging area of research that can broadly be described as the design and construction of novel artificial biological pathways, organisms or devices, or the redesign of existing natural biological systems."

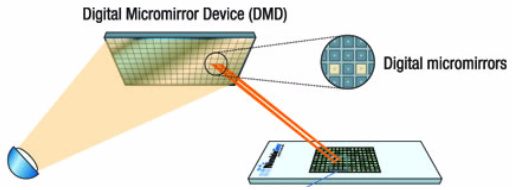
Effectively transforms DNA into a programming language

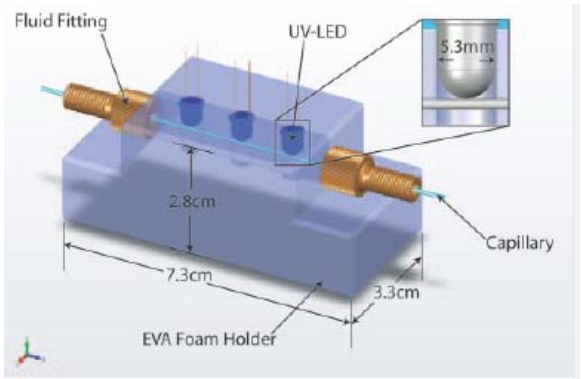

WARNING


if you can WRITE DNA,
You 're no LONGER limiTED
to " What IS " but TO what you could MAKE .









- -5 years: 0.5 - 5kb, $10-$15/bp
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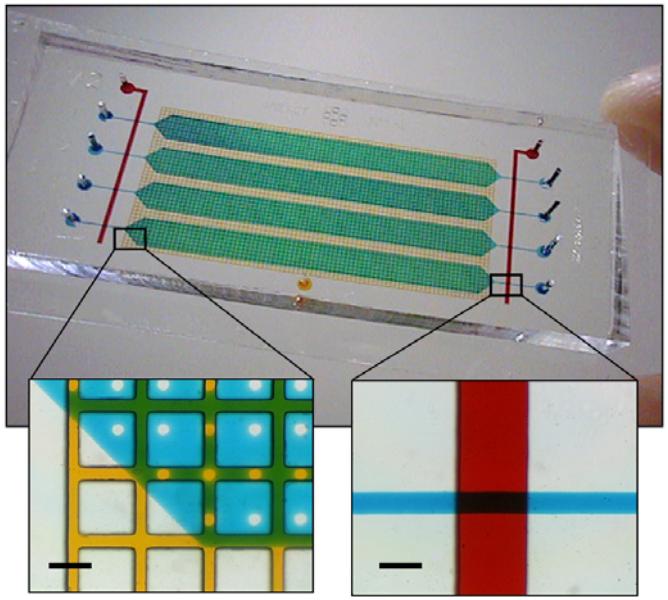

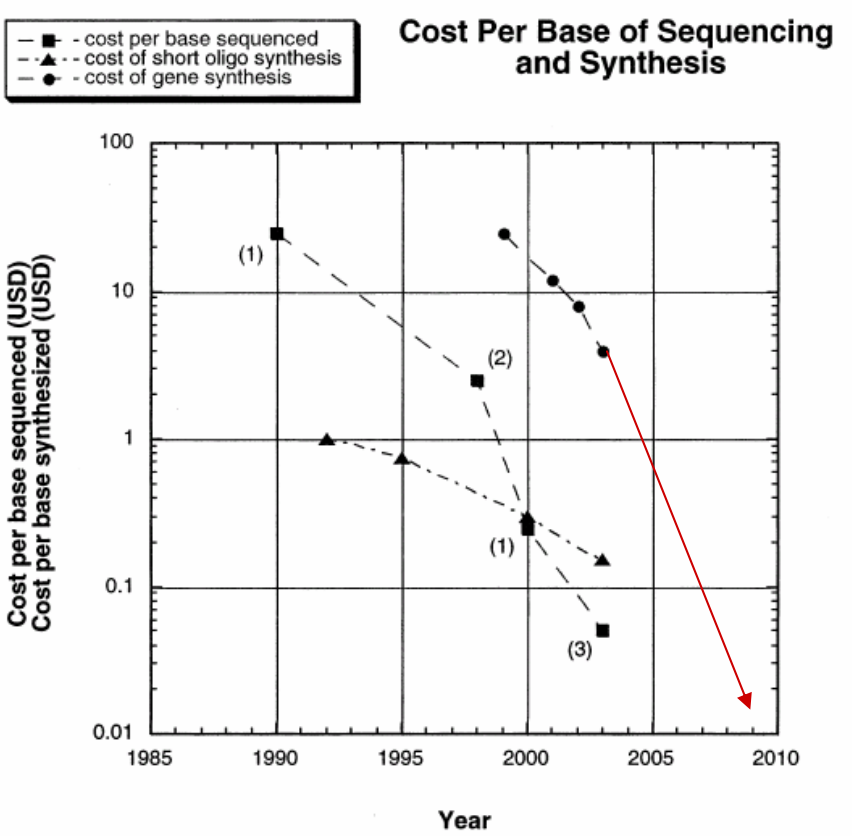

Carlson, R. (2003) The Pace and Proliferation of Biological Technologies

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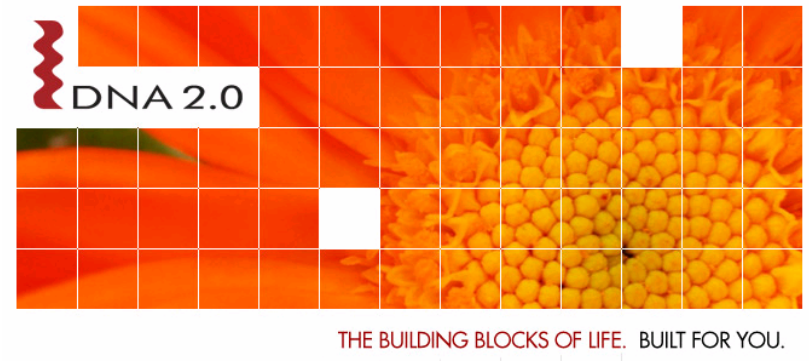

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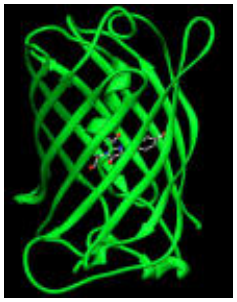
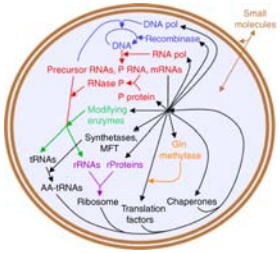
Applications dependent on synthetic capabilities



single genes*

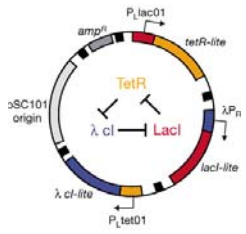


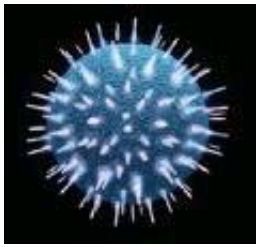
minimal life

base pairs

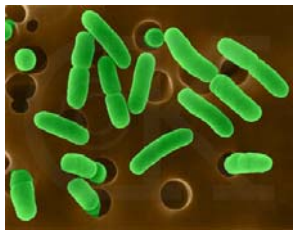
10^2 10^3 10^4 10^5 10^6 10^7

genetic circuits, viruses, GEMs





Engineered organisms



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Synthetic Oncolytic Viruses

- Designed using standardized genetic modules
- Similar to code libraries in computing

- Develop minimal oncolytic viral core

- Create libraries of functional components (targeting, gene knockdown, transgenes, selective promoters, control systems)

- Permits rapid development of individualized viruses based on well-characterized, standardized parts

Transcriptional Regulators

jump to part

BBa_

navigation

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search

Go Search

toolbox

- What links here

Available repressible regulators (normally ON) -?-

Show 0 more parts

Edit

-?-	Name	Description	Direction	Control -?-	Output Low	Output High	Length
A W	BBa_I14032	promoter P(Lac) IQ	Forward				37
A W	BBa_R0040	promoter (tetR, negative)	Forward	aTc, tetracyline			54
A W	BBa_R0051	promoter (lambda cI regulated)	Forward	lambda cI			49

Available inducible regulators (normally OFF) -?-

Show 0 more parts

Edit

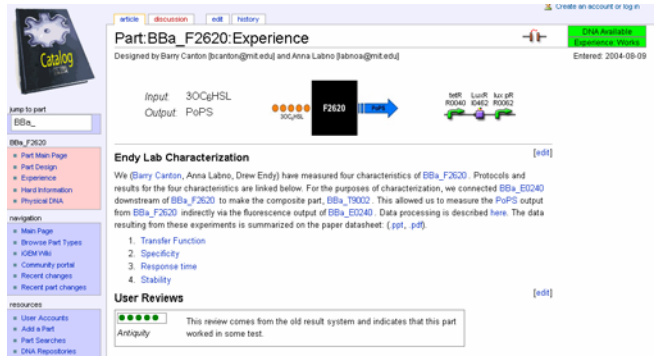
-?-	Name	Description	Direction	Control -?-	Output Low	Output High	Length
A	BBa_I12007	Modified lambda Prm promoter (OR-3 obliterated)	Forward	cI			82
A	BBa_R0062	Promoter (luxR & HSL regulated -- lux pR)	Forward	luxR, HSL			55
A	BBa_R0079	Promoter (LasR & PAI regulated)	Forward	PAI			157
A	BBa_R0080	Promoter (AraC regulated)	Forward	araC			149

Available other regulators

Show 172 more parts

Edit

-?-	Name	Description	Direction	Control -?-	Output Low	Output High	Length
A W	BBa_I0500	Inducible pBad/araC	Forward	araC, arabinose			1210
A W	BBa_I13453	Pbad promoter					130
A W	BBa_J13002	TetR repressed POPS/RIPS generator	Forward	ATc			74
A W	BBa_J13023	3OC6HSL+LuxR dependent POPS/RIPS generator					117
A W	BBa_J23100	constitutive promoter family member					35
A W	BBa_J23101	constitutive promoter family member					35
A W	BBa_J23102	constitutive promoter family member					35
A W	BBa_J23103	constitutive promoter family member					35
A W	BBa_J23104	constitutive promoter family member					35
A W	BBa_J23105	constitutive promoter family member					35
A W	BBa_J23106	constitutive promoter family member					35
A W	BBa_J23107	constitutive promoter family member					35
A W	BBa_J23108	constitutive promoter family member					35
A W	BBa_J23109	constitutive promoter family member					35
A W	BBa_J23110	constitutive promoter family member					35
A W	BBa_J23111	constitutive promoter family member					35



BBa_F2620

3OC$_6$HSL → PoPS Receiver

http://parts.mit.edu/registry/index.php/Part:BBa_F2620

Authors:
Barry Canton [bcanton@mit.edu]
Anna Labno [labnoa@mit.edu]

Last Update: 15 January 2007

Description

A transcription factor (LuxR, BBa_C0062) that is active in the presence of cell-cell signaling molecule 3OC$_6$HSL is controlled by a TetR-regulated operator (BBa_R0040). Device input is 3OC$_6$HSL. Device output is PoPS from a LuxR-regulated operator. If used in a cell containing TetR then a second input signal such as aTc can be used to produce a Boolean AND function.

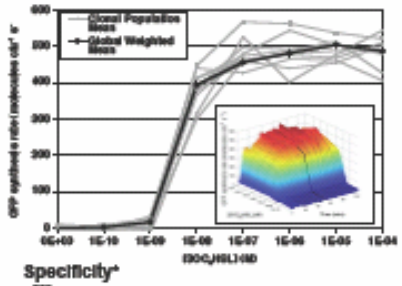
Characteristics

Input Swing: 1E-9 to 1E-6 M 3OC$_6$HSL, exogenous
Output Swing: 0±1 to 503±1 GFP molecules cfu^{-1} s^{-1}
Switch Point: 7±1 nM 3OC$_6$HSL, exogenous
LH Response: 9 min ($t_{50\%}$), 27 min ($t_{90\%}$)

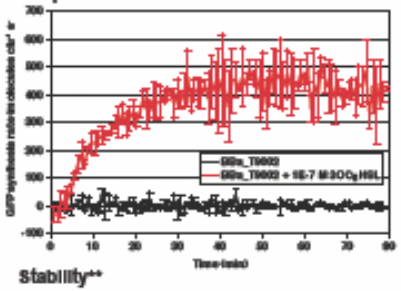
Key Parts

BBa_R0040: TetR-regulated operator
BBa_C0062: luxR ORF
BBa_R0062: LuxR-regulated operator

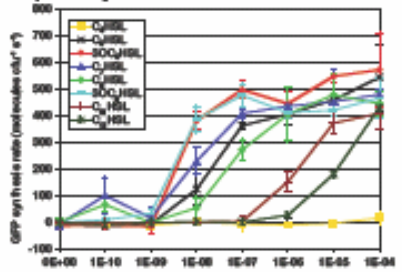
Transfer Function*



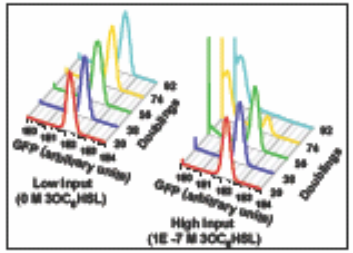
Response Time*



Specificity*



Stability**



Demand (low/high input)

Translational: 256/8048 ribosomes cfu^{-1}
3.8E3/1.2E5 charged tRNA cfu^{-1} s^{-1}

Stability (low/high input)

Genetic: >92/74 replication events**
Performance: >92/74 replication events**

Compatibility

Chassis: Compatible with *MC4100*, *MG1655*, and *DH5α*
Plasmids: Compatible with *pSB3K3* and *pSB1A2*
Devices: Compatible with *E0240*, *E0430* and *E0434*
Crosstalk with systems containing *TetR (C0040)*
Signaling: Crosstalk with input molecules similar to 3OC$_6$HSL

Conditions (abridged)

Output: Indirect via *BBa_E0240*
Vector: pSB3K3
Chassis: MG1655
Culture: Supplemented M9, 37°C
**Equipment:* PE Victor3 plate reader
***Equipment:* BD FACScan cytometer

Registry of Standard Biological Parts
making life better, one part at a time

License: Public

Signaling Devices

Open Source Biology

- Maximally drives innovation
- Very low development costs
- Permits wide oversight and review
- Inclusive and non-proprietary
- Results in diverse, empowered, technically competent community
- Speeds wide dissemination of ideas and technologies

iGEM 2006 THE INTERNATIONAL GENETICALLY ENGINEERED MACHINE CO

LEARN ABOUT iGEM 2007 HERE

RESULTS

the iGEM 2006 Jamboree has officially concluded. Find the results HERE

THE iGEM STORY

Hear the story and meet the people behind the Competition

MEET THE TEAMS

Review the international roster of iGEM teams

WIKI LIVE!

See how the teams are getting on right now. Visit the iGEM wiki site.

The Jamboree

November 4-5, 2006

Massachusetts Institute of Technology, Cambridge, MA, USA

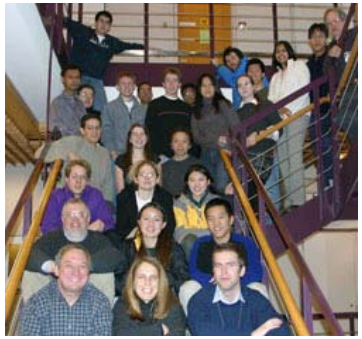
This summer, 37 teams from around the world participated in a biology competition. The challenge: design and build biological systems and run them in living cells.

What they did in four months will astound you.

Find out more here...

iCampus

MIT



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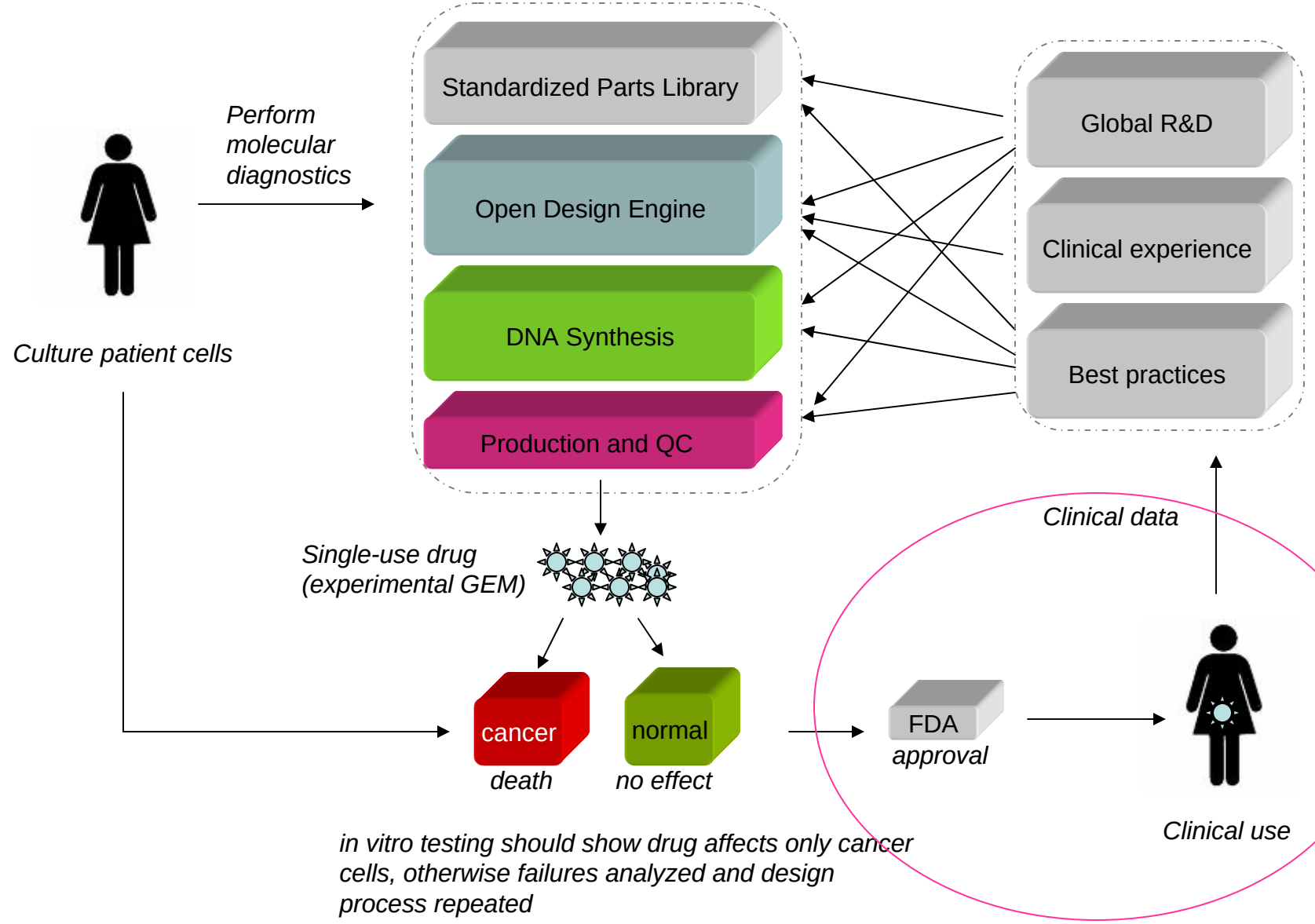
Clinical presentation

Open Bio-Fabrication

Shared knowledge base



Funding and political support

CIBC Run for the Cure
CANADIAN BREAST CANCER FOUNDATION

Summary

- Rapid development of state-of-the-art GEMs at minimal cost
- Each cancer is treated as it should logically be treated: as a unique instance of disease.
- All the components pre-exist and are becoming increasingly accepted and validated. The innovation here is assembling them
- Cost vs. performance, the strategy will be *more effective* yet *cost less* over time (as is the case with computing)
- The process can be used multiple times with the same speed and efficacy
- Minimal potential for harm (n = 1), problematic designs or parts never reused