Regenerating the Future, Again

Peter Goodfellow

President

Institute of Advanced Biological Analytics

The Future Is Here

iABA

UniQure

EMEA approval of Glybera

Spark Therapeutics

FDA Advisory Board recommends approval of Luxturna

Novartis

CAR-T, FDA approval of Kymriah

Institute of Advanced Biologic Analytics

iABA

- Rooted in the interface between Genetics, Genomics and Computational Science

- Applying advances in AI, cloud computing and novel chip design for accelerated analytics

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"Il n'y a de nouveau que ce qui est oublié"

Marie Antoinette to her dressmaker Rose Bertin

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Mission Statement:

”There is nothing new - except opportunity”

Current Focus of iABA

- The ‘3Rs’ for therapeutic application
  - Replace
  - Repair
  - Regenerate

Replace

- Non-biological
  - Artificial joints – over 7 million Americans have artificial joints
  - Artificial kidneys – over 400,000 Americans depend on dialysis
  - Pacemakers – 600,000 implanted each year world wide
  - Artificial pancreas -

Medtronics Minimed – Wearable Artificial Pancreas

Replace

- Non-biological
  - Artificial joints – over 7 million Americans have artificial joints
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  - Pacemakers – 600,000 implanted each year world wide
  - Artificial pancreas

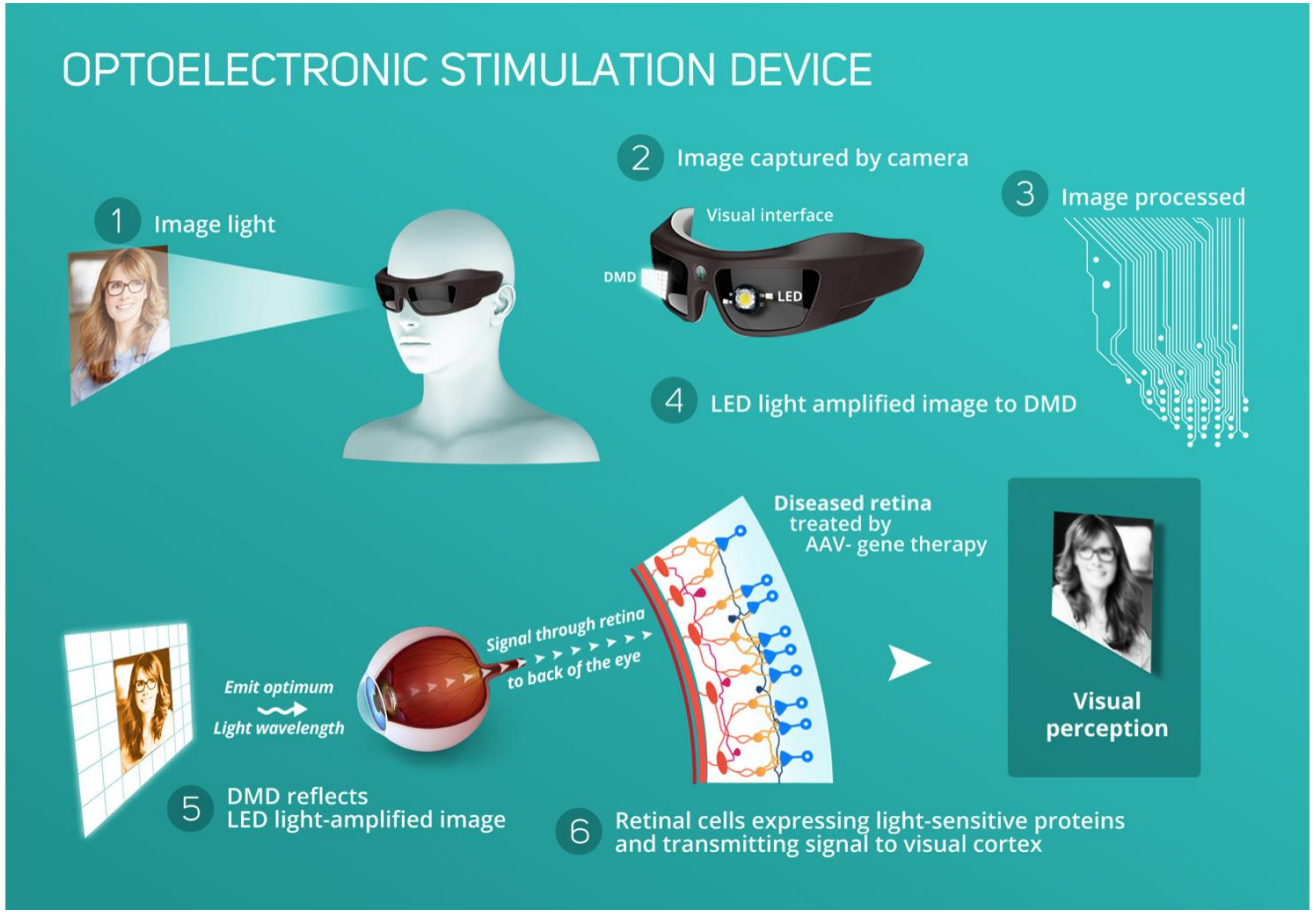
- *The future*
  - *Further miniaturisation*
  - *Application of AI techniques*
  - *Remote supervision*

Replace

- Biological
  - Syngeneic and allogeneic: blood transfusions (>100 million), kidney (84,000), liver (27,000), bone marrow (20,000), heart (7,300), lung (5,200), pancreas (2400), small bowel, face, hand etc
  - Xenogeneic

- *The future*
  - *Modulation of the immune system better facilitating allogeneic and xenogeneic transplants – learnings from immuno-oncology*
  - *Humanisation of xenogeneic donors (especially using genome editing)*
  - *Mixed biological and non-biological devices*

Gensight – a Combination of Device and Gene Therapy



Repair

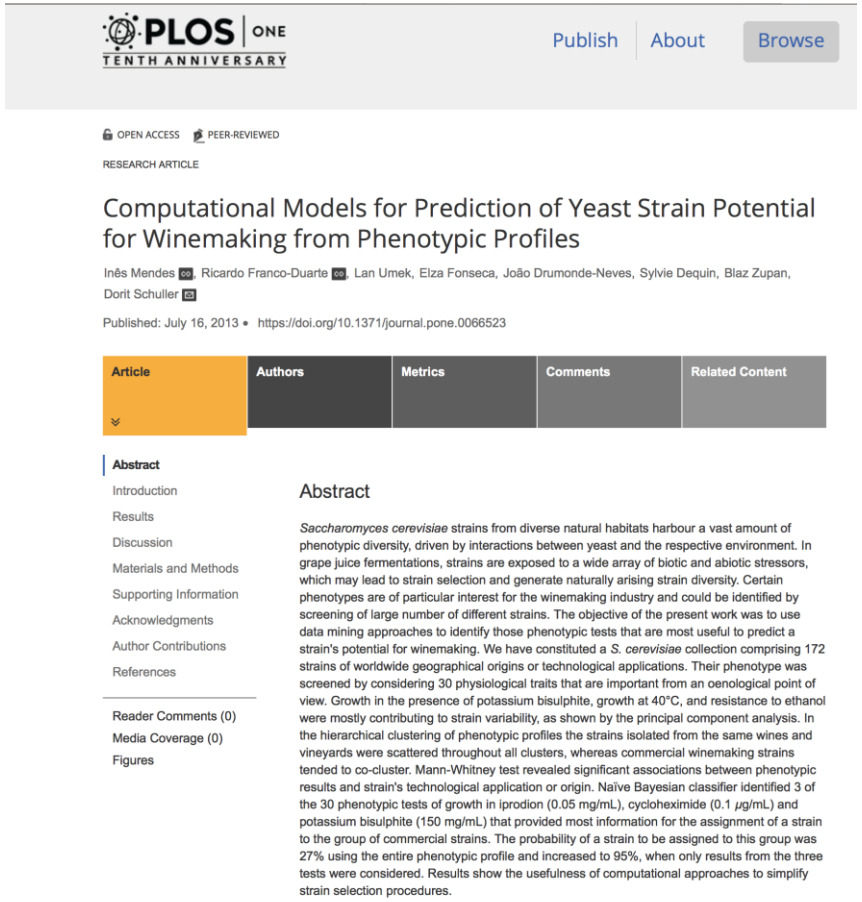
- A problem of stem cells

Project 1: The Human Yeast

iABA

- Define essential genes – approximately 1100
- Check essential genes for human homologues – majority are shared
- *Create computational model of yeast based on gene-gene, protein-protein and protein-gene data etc.*
- Replace yeast gene with human gene and select for fast growing variants
- *Use analytics to predict likely genes affected*
- Sequence the whole genome
- *Refine model*
- Repeat

Other Yeast Computational Models



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RESEARCH ARTICLE

Computational Models for Prediction of Yeast Strain Potential for Winemaking from Phenotypic Profiles

Inês Mendes, Ricardo Franco-Duarte, Lan Umek, Elza Fonseca, João Drumonde-Neves, Sylvie Dequin, Blaz Zupan, Dorit Schuller

Published: July 16, 2013 • https://doi.org/10.1371/journal.pone.0066523

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Abstract
Introduction
Results
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Materials and Methods
Supporting Information
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Author Contributions
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Reader Comments (0)
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Abstract

Saccharomyces cerevisiae strains from diverse natural habitats harbour a vast amount of phenotypic diversity, driven by interactions between yeast and the respective environment. In grape juice fermentations, strains are exposed to a wide array of biotic and abiotic stressors, which may lead to strain selection and generate naturally arising strain diversity. Certain phenotypes are of particular interest for the winemaking industry and could be identified by screening of large number of different strains. The objective of the present work was to use data mining approaches to identify those phenotypic tests that are most useful to predict a strain's potential for winemaking. We have constituted a *S. cerevisiae* collection comprising 172 strains of worldwide geographical origins or technological applications. Their phenotype was screened by considering 30 physiological traits that are important from an oenological point of view. Growth in the presence of potassium bisulphite, growth at 40°C, and resistance to ethanol were mostly contributing to strain variability, as shown by the principal component analysis. In the hierarchical clustering of phenotypic profiles the strains isolated from the same wines and vineyards were scattered throughout all clusters, whereas commercial winemaking strains tended to co-cluster. Mann-Whitney test revealed significant associations between phenotypic results and strain's technological application or origin. Naïve Bayesian classifier identified 3 of the 30 phenotypic tests of growth in iprodion (0.05 mg/mL), cycloheximide (0.1 μg/mL) and potassium bisulphite (150 mg/mL) that provided most information for the assignment of a strain to the group of commercial strains. The probability of a strain to be assigned to this group was 27% using the entire phenotypic profile and increased to 95%, when only results from the three tests were considered. Results show the usefulness of computational approaches to simplify strain selection procedures.

Project 2: The Human Cell Lineage

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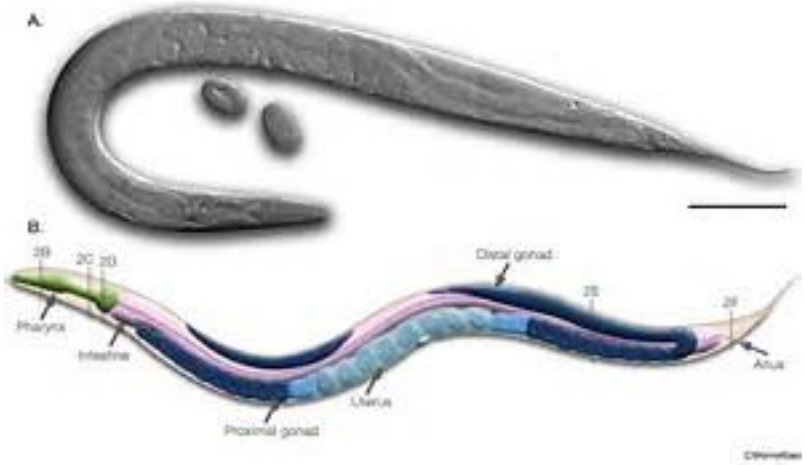
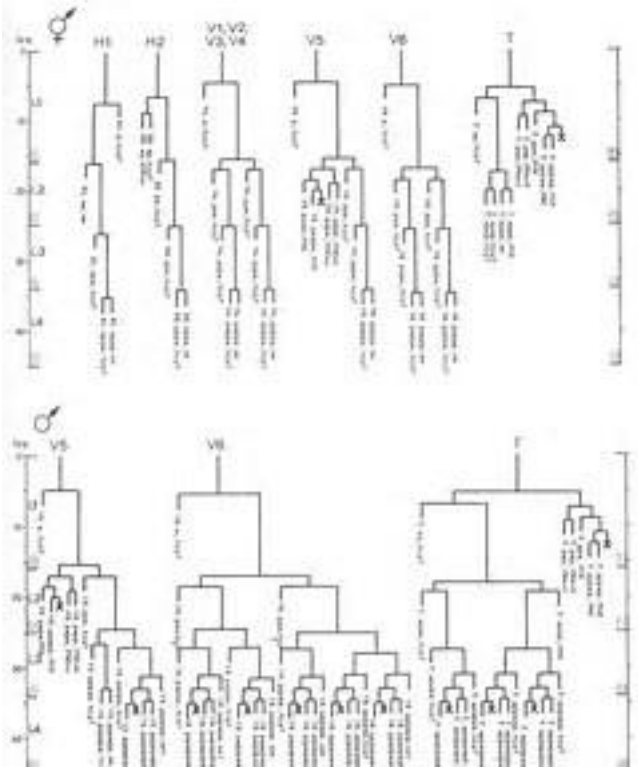
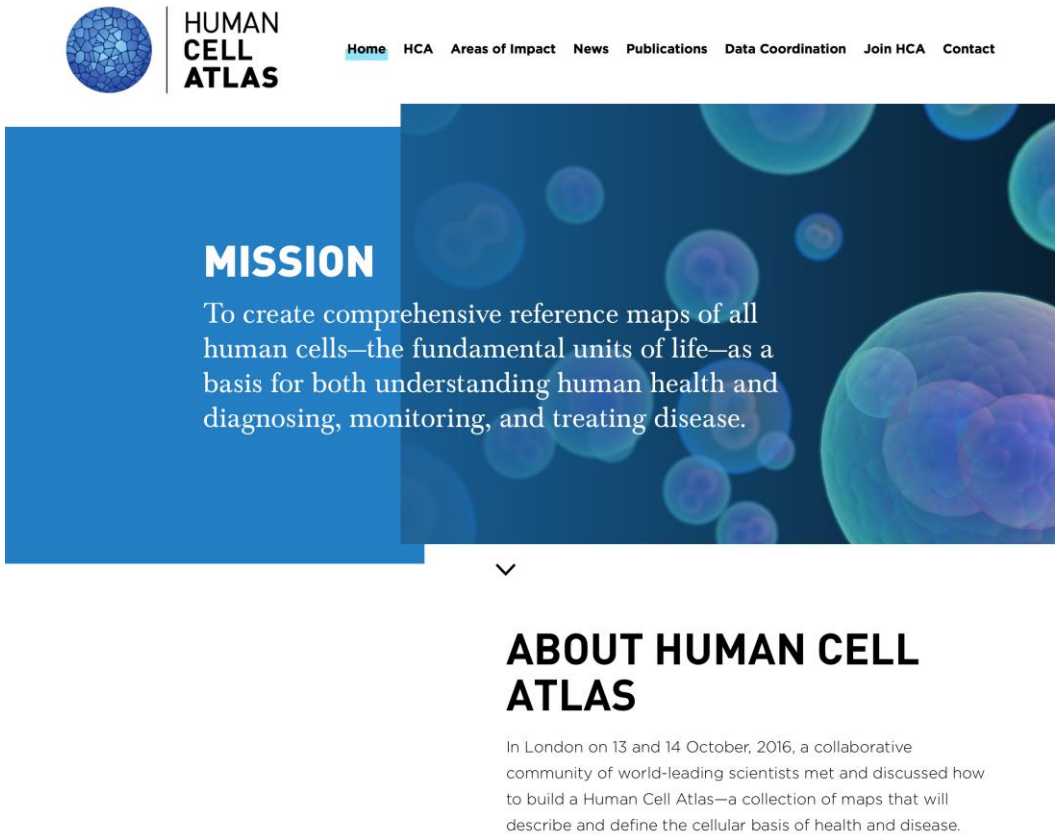




The Human Cell Atlas



The Lineage Tracing by CRISPR/CAS

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Project 2: The Human Cell Lineage

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- CRISPR based (or cre-lox) barcode lineage tracing in mouse
- Single cell transcriptomics to define cell types in developing and adult mouse
- Single cell transcriptomics in human tissues to translate the mouse data to human
- Confirm in human using random (naturally occurring) mutations in human cell lineage tracing

Project 3: Sourcing cells

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Cell

Volume 126, Issue 4, 25 August 2006, Pages 663–676

CellPress

Article

Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors

Kazutoshi Takahashi[1], Shinya Yamanaka[1, 2],

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https://doi.org/10.1016/j.cell.2006.07.024

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Transdifferentiation

- Almost any cell to iPSC: Oct3/4, Sox2, c-Myc, and Klf4 (Nanog, Lin28)
- Fibroblast to neuron: Ascl1, Brn2 and Myt1l
- Fibrobast to cardiomyocyte: Gata4, Mef2c and Tbx5

The Barriers to Replacement

- Introduction of cells – the niche problem

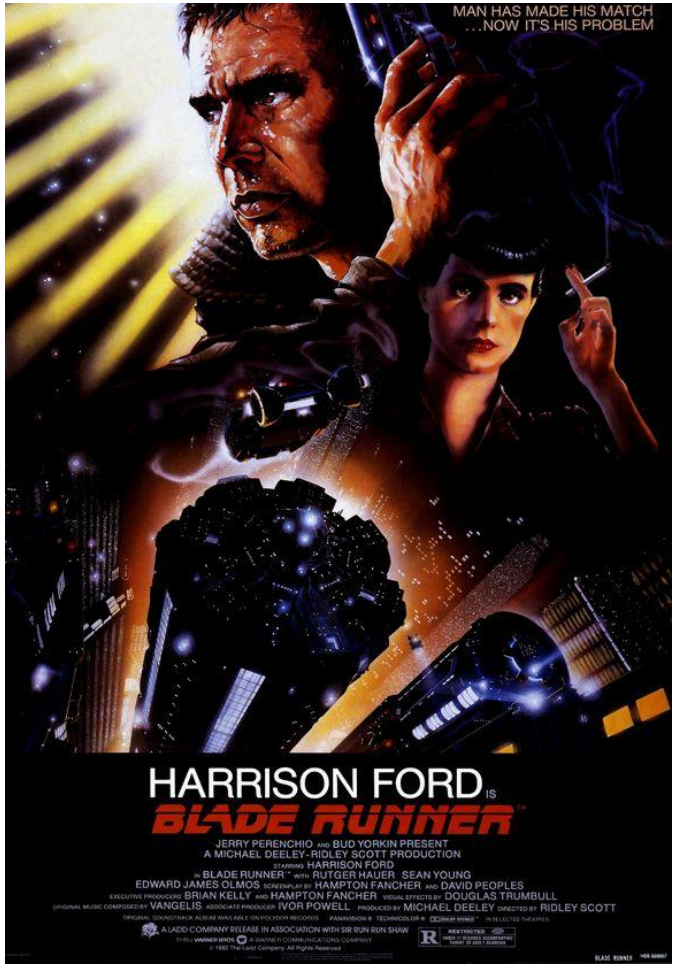
- Epigenetics

Regeneration

- Organ regeneration is a problem of co-ordination of multiple stem cells

- Organoids

The Blade Runner Paradox



Thanks to my colleagues at iABA