Regenerating the Future, Again

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The Future Is Here

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

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

• Applying advances in AI, cloud computing and novel chip design for accelerated analytics
"Il n'y a de nouveau que ce qui est oublié”

Marie Antoinette to her dressmaker Rose Bertin
Institute of Advanced Biologic Analytics

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 worldwide
  • Artificial pancreas -
Medtronics Minimed – Wearable Artificial Pancreas
Replace

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• 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

**OPTOELECTRONIC STIMULATION DEVICE**

1. **Image light**
2. **Image captured by camera**
3. **Image processed**
4. **LED light amplified image to DMD**
5. **DMD reflects LED light-amplified image**
6. **Retinal cells expressing light-sensitive proteins and transmitting signal to visual cortex**
Repair

• A problem of stem cells
Project 1: The Human Yeast

• 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
Project 2: The Human Cell Lineage
The Human Cell Atlas

MISSION
To create comprehensive reference maps of all human cells—the fundamental units of life—as a basis for both understanding human health and diagnosing, monitoring, and treating disease.

ABOUT HUMAN CELL ATLAS
In London on 13 and 14 October 2016, a collaborative community of world-leading scientists met and discussed how to build a Human Cell Atlas—a collection of maps that will describe and define the cellular basis of health and disease.
The Lineage Tracing by CRISPR/CAS
Project 2: The Human Cell Lineage

• 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

Cell

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

Article

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

Kazutoshi Takahashi¹, Shinya Yamanaka¹, ²

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

• Almost any cell to iPSC: Oct3/4, Sox2, c-Myc, and Klf4 (Nanog, Lin28)

• Fibroblast to neuron: Ascl1, Brn2 and Myt1l

• Fibroblast 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