Using Stem Cells to Predict Drug Effect

Jason T Maynes, PhD/MD
Wasser Chair in Anesthesia and Pain Medicine
Associate Chief of Perioperative Services (Research)
Director of Research, Anesthesia and Pain Medicine
Staff Anesthesiologist, Hospital for Sick Children
Departments of Anesthesia and Biochemistry, University of Toronto
Disclosures:

- Current and past funding/drug discovery agreements with:
  - Merck
  - GSK
  - Novartis
  - MaRS Innovation
  - Blueline Bioscience
  - Versant Ventures
  - Acea Biopharma
  - Ontario Center of Excellence
  - IRiCOR
Intelligent Clinical Decision Making

- An oncology patient needs chemotherapy:
  - What regimens risk cardiac disease?
- A post-surgical patient needs pain treatment:
  - Are they at a high risk for opiate side effects?
  - Are they likely to develop chronic pain?
- An ICU patient has poor cardiac function:
  - Will this patient respond to milrinone, and at what dose?
Is this your patient?
Patient Phenotyping

Diagram showing the concept of patient phenotyping, moving from ideal health to risk factors to disease. The left section of the diagram illustrates the distribution of individuals in terms of measurement, with a normal distribution curve. The right section shows the response magnitude of these individuals, with bars representing different levels of response.
Stem Cells and Stem Cell Tissue

Existing Stem Cells:
- Hematopoietic
- Mesenchymal
- Neuronal
- Cardiac
- Umbilical
eSC
iPSC

What is a stem cell?
A single cell that can replicate itself, or...

differentiate into many cell types.
Utility of Stem Cell-Derived Tissue

Disease and Tissue Modeling: Cardiac

Complex Dynamic Tissue: rate, rhythm, contractility, conduction
Quantifying Cardiac Conduction

• > 70% of drug recalls are for unexpected cardiotoxicity
• Comprehensive in Vitro Proarrhythmia Assay (CiPA)
• A majority are for arrhythmogenic side effects
• Cardiac conduction diseases - ARVC
• Anesthesia pharmacopeia has high cardiac interactions

• To measure cardiac conduction, you need functional tissue (not isolated cells, patch clamping)
Quantifying Cardiac Conduction

[Images of laboratory equipment and data charts showing dye transfer distances for different concentrations of substances like 18-aGA and Rotigaptide]
Quantifying Cardiac Conduction

- Mutations in Plakophilin 2 (PKP2) cause ARVC
- Screened 1000 compounds known to affect ion channels
Therapeutic Design
Healthy Cardiomyocyte iPSC-CM Layers

Physical Contraction  Ion Channel Activity
Healthy Cardiomyocyte iPSC-CM Layers

Impaired Physical Contraction

Loss of Ca++ Wave

Hypertrophic Cardiomyopathy iPSC-CM Layers (MYH7)
JC-1 Treatment Improves Ca++ Cycling in HCM

Baseline

+JC-1
Concentration (mcg/ml) vs. Normalized beat rate (%)

- **Lidocaine**
  - 4h
  - 24h

- **Bupivacaine**
  - 4h
  - 24h

- **Levobupivacaine**
  - 4h
  - 24h

- **Ropivacaine**
  - 4h
  - 24h
Bupivacaine (6µg/ml)

Ropivacaine (6µg/ml)

Control

\[ \text{Ca}^{2+} \quad \text{Na}^+ \quad \text{K}^+ \]
Ca$^{2+}$ Corrects Bupivacaine Arrhythmia

![Graph showing the effect of Ca$^{2+}$ on Bupivacaine arrhythmia]

Arrhythmogenicity

- CV of beating period (0-8h)

- Media
- Ca$^{2+}$
- LO Bup
- HI Bup
- HI Bup + Ca$^{2+}$
- LO Rop
- HI Rop
- HI Rop + Ca$^{2+}$

* * *

NS
Isoproterenol

(A) Graph showing the effect of Isoproterenol on cell resistance over time.

(B) Graphs illustrating the dose-dependent increase in contractility and rate.

Contractility

Rate (dose dep increase Hz)
Verapamil

Contractility

Rate (dose dep decrease Hz)
Omecamtiv

Contractility

Rate (no change Hz)
Ivabradine

Contractility

Rate (dose dep decrease Hz)
Dangerous cut

The numbers of surgeons involved in research are falling — the trend must be reversed.

27 APRIL 2017 | VOL 544 | NATURE | 393

More than half said that basic research was a priority in their departments — but just one-third said that it was realistic to expect surgeons to succeed in basic research. Most respondents said they had neither the time nor the motivation for research, and in any case lacked adequate departmental support and funding. Nearly two-thirds believed that basic research among trainees should be limited to a select few residents with the ambition and talent to be successful in future research activities.

"Policymakers must stop seeing surgeons as easy sources of revenue."

that includes regenerative medicine and possibly xenotransplantation (transplantation of tissues and organs from other species). They are also much needed for crucial research into surgically treated diseases that only rarely hit the headlines — particularly in the correction of congenital birth defects, but also in adult diseases such as spinal cord injury, diabetes, and many others.
Stimulation of Innovation at The Hospital for Sick Children

- Innovation Fund: ~$150,000 per year in peer-adjudicated funding
  - starter funding to stimulate further applications
- Formal collaborative programme with BME:
  - Clinicians pitch ideas to students (course)
  - Graduate student collaborative programme (CIGITI)
  - Many graduate appointments of physicians
- High success rate summer student programme
  - Formal mentorship, educational initiatives
- Customized educational pathways for peri-operative physicians
- Research chair funding used for research
Conclusions

• Preclinical models for prediction of drug activity are poorly translational
• Significant inter-individual variance in drug response, with dynamic changes (not necessarily genetic)
• Stem-cell derived tissue can be used to model:
  • Conductive diseases
  • Cardiac physiology
• Drug discovery can be facilitated using iPSC tissue:
  • Impedance-based electrode devices
  • Dynamic CNT contractility systems
• Future: packaging of pro-regenerative neonatal cardiac secretomes into nanoparticles
Acknowledgements

- Maynes Lab:
  - Dr. Ramesh Vanama
  - Dr. Michael Tropak
  - Julia Plakhotnik
  - Manpreet Malhi
  - Dr. Yanan Tang
  - Dr. Olga Chernya
  - Kaley Hogarth
  - Henry Mah
  - Dr. Libo Zhang
  - Doorsa Tarazi
  - David Pompili

- Coles Lab:
  - Alex Traister
  - Chris Welsh
  - Sarv Patel

- Collaborators:
  - Boris Hinz
  - Yu Sun

- COLLABORATORS:
  - BORIS HINZ
  - YU SUN

- ORGANS:
  - COlLABORATORS
  - BORIS HINZ
  - YU SUN

- ORGANIZATIONS:
  - MaRS Innovation
  - HEART & STROKE FOUNDATION
  - INNOVATION.CA
  - CIHR-IRSC
  - NSERC CRSGN