Novel Translational Strategies for Drug Discovery

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The Translational Challenge in Drug Discovery

Clinical trial failure rate >90%

75% of drugs terminated due to safety or efficacy issues not predicted by animal models

Nature Reviews Drug Discovery, 12, 569, 2013
The Translational Challenge in Drug Discovery

Clinical trial failure rate >90%

- Poor study design
- Cross-species differences
- Genetic uniformity of models
- Heterogeneity of patient population
- Poor understanding of disease mechanism

75% of drugs terminated due to safety or efficacy issues not predicted by animal models

Efficacy

Safety

Strategic

Nature Reviews Drug Discovery, 12, 569, 2013
The Pain Patient Population is Heterogeneous

Baron et al., PAIN (2017)

Sensory manifestation

- Sensory loss > Thermal hyperalgesia >> Mechanical hyperalgesia
- Thermal hyperalgesia > Mechanical hyperalgesia > Sensory loss
- Sensory loss = Thermal hyperalgesia >> Mechanical hyperalgesia
- Mechanical hyperalgesia > Thermal hyperalgesia > Sensory loss
Unclear How Rodent Pain Models Map on the Diversity of Human Pain Patient Population
Unclear How Rodent Pain Models Map on the Diversity of Human Pain Patient Population

Rodent models do not help in matching a specific drug with the appropriate indication.
Ex-Vivo Study in Human Primary Cells and Tissues to Improve Translational Research
Human Primary Hepatocytes in Drug Discovery

Acknowledgement of the species differences in the DMPK profile of molecules


The use of human microsomes and hepatocytes is introduced


Reduction of Ph-1 attrition due to issues related to pharmacokinetics or bioavailability

Drug Discovery Using Human Tissue from Disease Donors: Cystic Fibrosis Case Study

**Kalydeco for Cystic Fibrosis**

- Genetic defect in CFTR chloride channel
- No relevant animal model
- Cultured bronchial epithelia isolated from human tissue
- Differentiated human epithelia show the same defective ion transport as observed in vivo
- Used as the key pharmacology model for Vertex CFTR modulators

Van Goor et al. (2006)
Predictive of clinical outcomes

- Lower development risks related to interspecies differences

- Study of drug action in healthy or pathological states

- Reliable assessment of potency to guide first-in-human dosing
Key Challenges of Human Tissue-Based Research

- **Viability**
  - Functional assessment of drug effect
  - Data quality & reliability

- **Velocity**
  - Access
  - Scalability

- **Variability**
  - Recovery methods and timeline
  - Inter-donor variability
Cellular and Tissue Loss of Function is a Process

- **Alive**
  - Blood flow
  - Ionic pumps
  - Depolarization
  - ATP
  - O₂

- **Dead**
  - Cytoplasmic Ca²⁺
  - Mitochondrial Ca²⁺
  - MPTP opening
  - Ion channel downregulation
  - Apoptosis/Necrosis
  - Tissue disintegration
  - Cellular disintegration
Enabling Drug Discovery in Human Tissues

- **Method standardization**
- **Prevent ischemia and reperfusion injury**
- **High volume of organs**
- **Each sample is extensively annotated**

Organs are collected and perfused with solutions that prevent ischemic damage.

Measurement of drug effect

Organ donor

Expedited shipping
Human Sensory Neurons for Pain Drug Discovery
Assessment of Drug Activity in Pathological States

1- In vitro-sensitized hDRG

- Prevalence of pain cases in the donor population

- Spontaneous firing in hDRG neuron from chronic pain donor

2- Chronic pain donor hDRG

- Peripheral neuropathy

- Inflammation
Inhibition of Human Sensory Neurons’ Activity by Raxatrigine and Carbamazepine

Normal nociception

Remaining APs (%)

Frequency (Hz)

PREDICTED ANALGESIA

0 2 4 6 8

0 20 40 60 80 100 120

0.3 µM Raxa

1 µM Raxa

3 µM Raxa

Normal nociception

Remaining APs (%)

Frequency (Hz)

PREDICTED ANALGESIA

0 2 4 6 8

0 20 40 60 80 100 120

3 µM CBZ

10 µM CBZ

30 µM CBZ
Sensory Neurons Sensitized With Inflammatory Agents Are Not Inhibited by Raxatrigine and PF-05089771

Inflammation

**PREDICTED ANALGESIA**

- 0.3 $\mu$M Raxa
- 1 $\mu$M Raxa
- 3 $\mu$M Raxa

- 10 nM PF-771
- 30 nM PF-771
- 100 nM PF-771

**REMAINING APs (%)**

Frequency (Hz)
Raxatrigine Fails to Inhibit the Activity of Human Sensory Neurons from Low Back Pain Donors
Cardiac Safety Assessment in Human Heart Ex-Vivo

**Drug A**

- Human adult cardiomyocytes
- Reduction in cardiomyocyte contractility only at very high concentrations
- No evidence of drug-induced arrhythmia

**Dofetilide**

- Human adult ventricular trabeculae
- After-contraction pro-arrhythmia marker

**Control**

- ANB-504 1 µM
- ANB-504 3 µM
- ANB-504 10 µM
- ANB-504 30 µM

No evidence of pro-arrhythmia markers up to 30 µM

Cardiac safety margin ~100x of the target effective concentration
1) AZD7762 is a potent and selective Chk1 kinase inhibitor for solid tumors
2) Development halted due to serious AE
   a) Decrease left ventricular ejection fraction
   b) Increased troponin I
3) In conscious dogs, transient dose-dependent decrease in contractility (-22% at high dose)
4) No effects on systolic or diastolic arterial blood pressure
5) In vitro human cardiomyocytes exhibit 10-30x higher sensitivity compared to dog myocytes
6) Dogs are not good predictors of inotropy effects in human

Sausville et al. (2014)
Human Ex-Vivo Systems are Increasingly Utilized in Translational Research
Human Tissues in Drug Discovery

**LEAD IDENTIFICATION**
Establish compound potency and selectivity in primary adult human cells and tissues.

**TARGET IDENTIFICATION**
Identify novel therapeutic targets directly in human tissues.

**LEAD OPTIMIZATION**
Maximize efficacy and safety of lead compounds using authentic human targets.

**CLINICAL CANDIDATE SELECTION**
Make informed decisions about candidate selection and clinical study design leveraging preclinical human data.

**CLINICAL TRIALS**
De-risk clinical stage toxicity signals in ex vivo human models.

**REGULATORY APPROVAL**

Summary

Assessment of drug effects in ex-vivo *human* models

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Study of drug action in the context of *pathological* states

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*Quantitative* assessment of potency
Thank You

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