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Novel Translational Strategies for Drug Discovery

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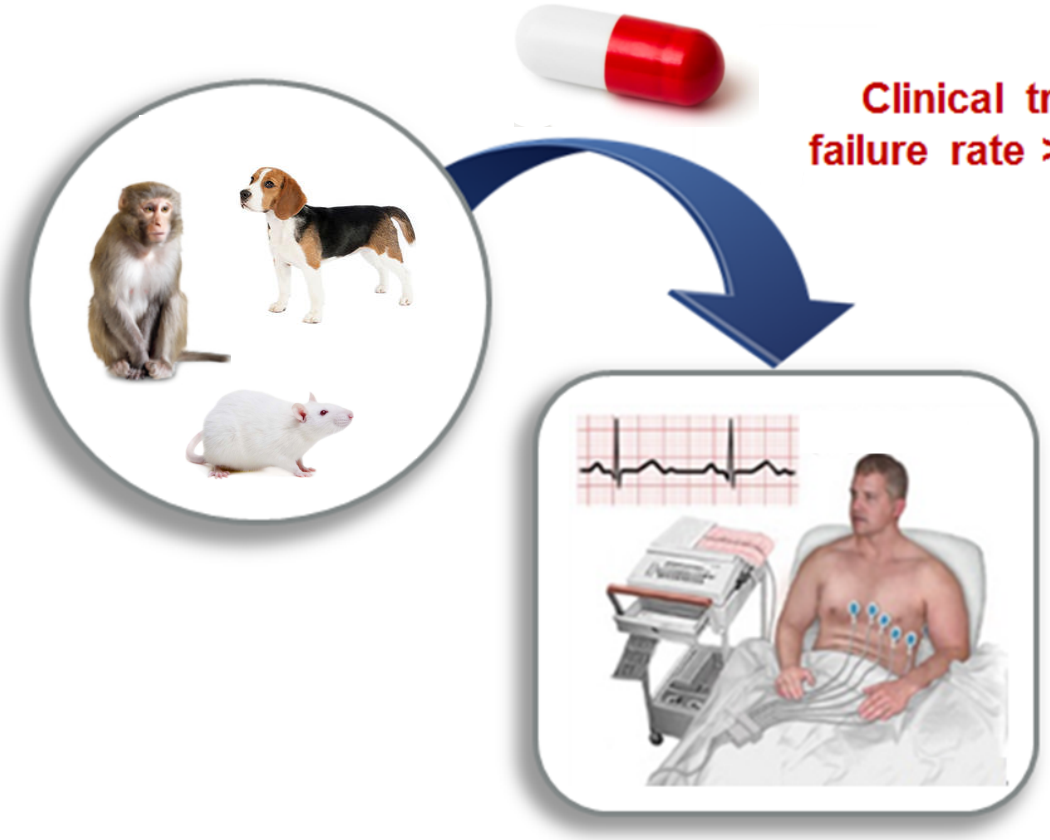
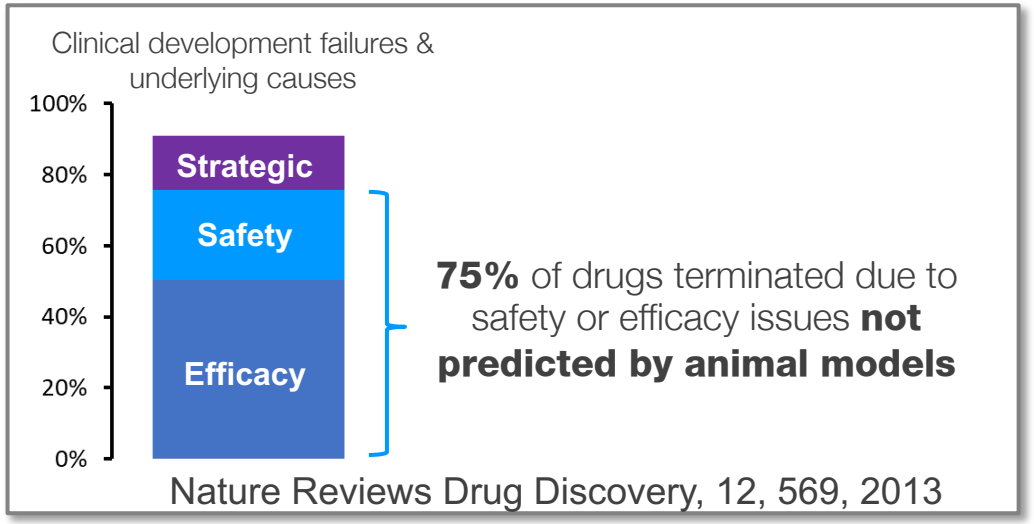
The Translational Challenge in Drug Discovery



Clinical trial failure rate >90%



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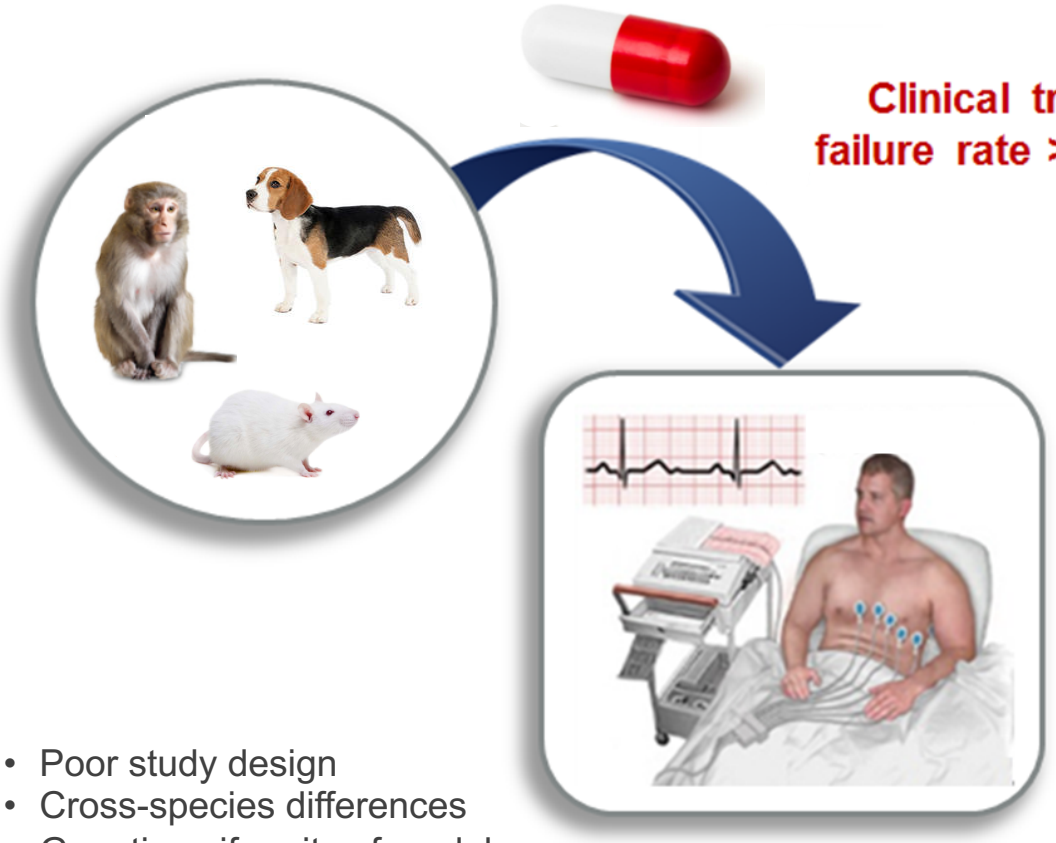
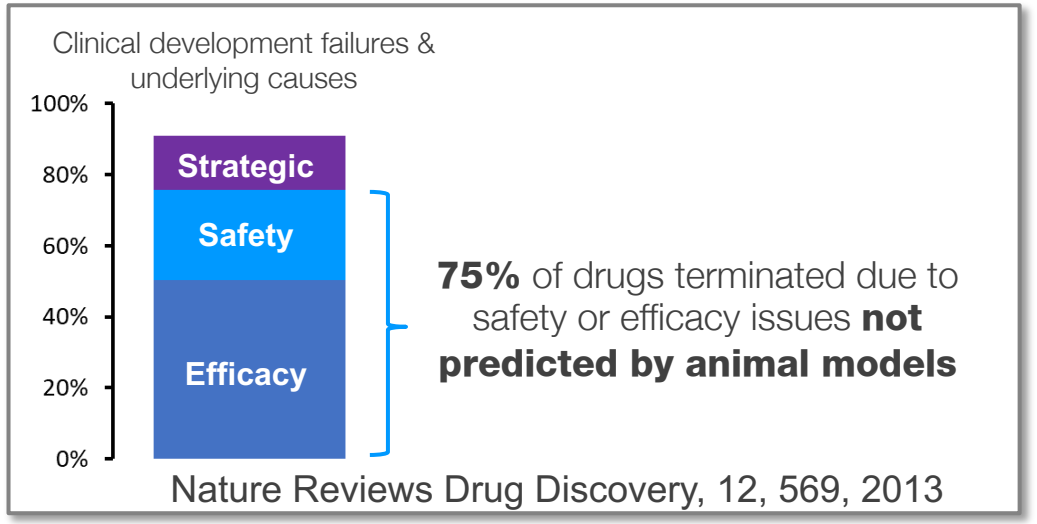
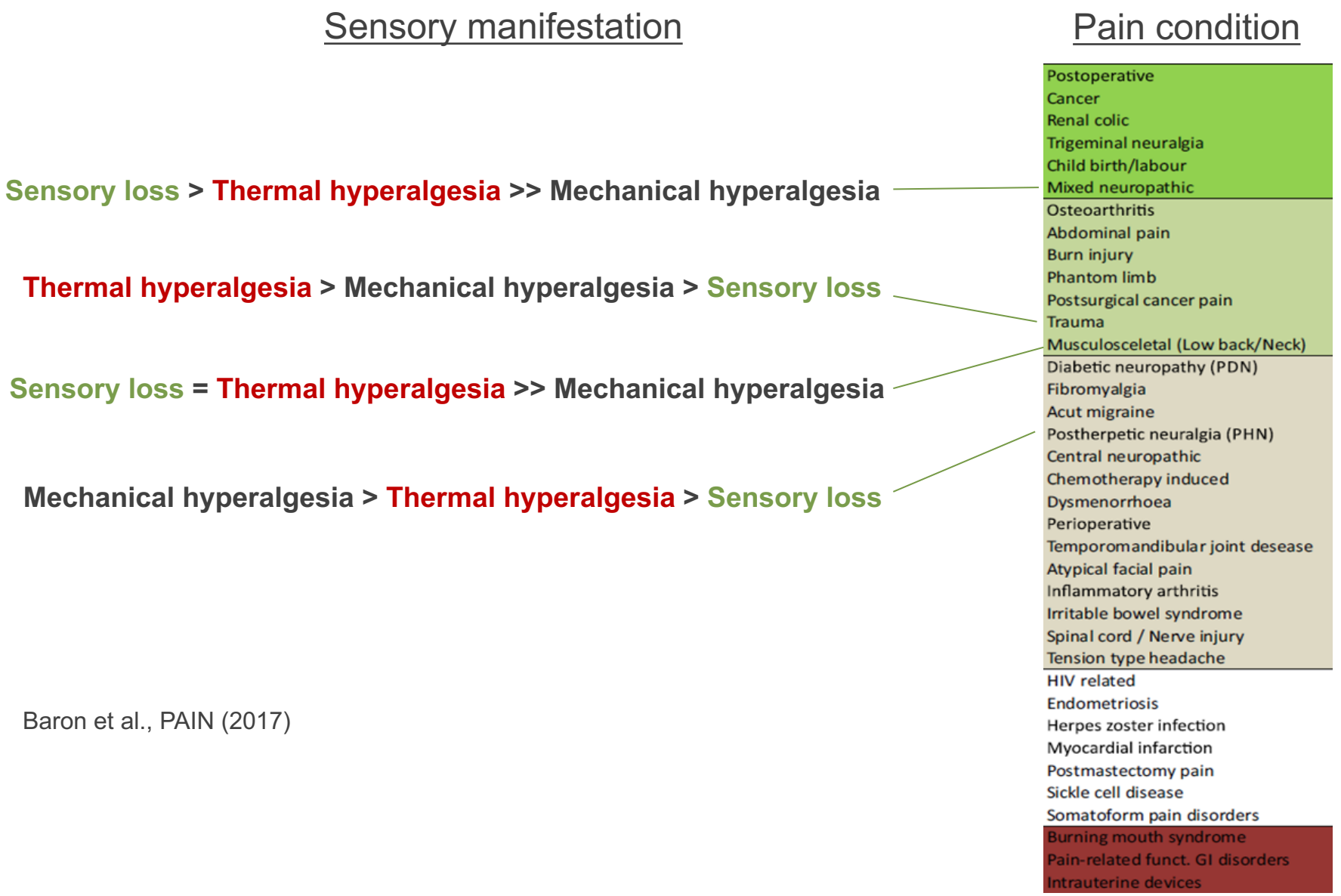




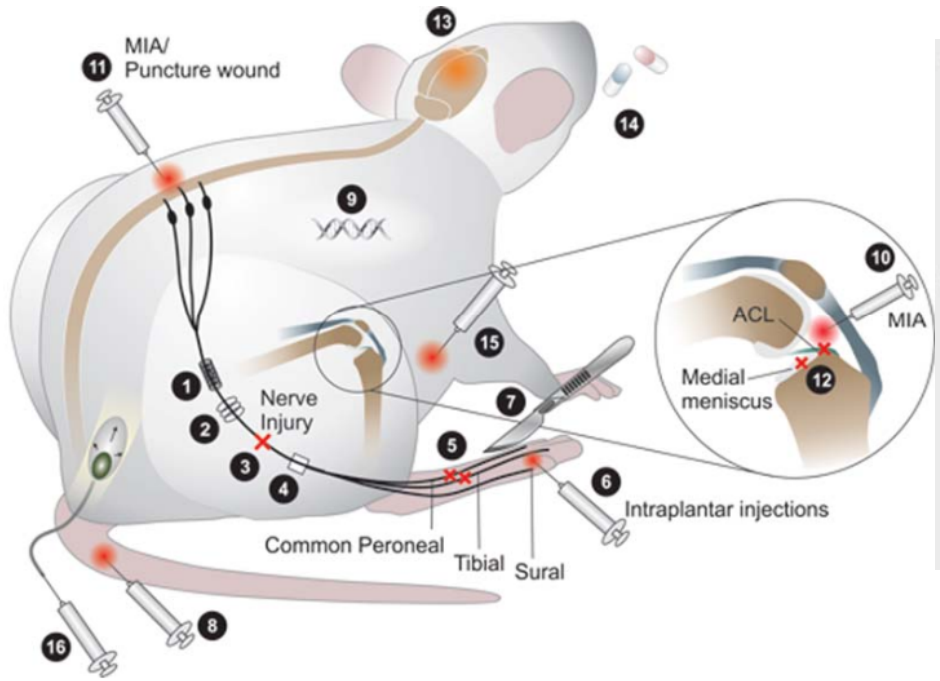
- Poor study design
- Cross-species differences
- Genetic uniformity of models
- Heterogeneity of patient population
- Poor understanding of disease mechanism

The Pain Patient Population is Heterogeneous



Baron et al., PAIN (2017)

Unclear How Rodent Pain Models Map on the Diversity of Human Pain Patient Population



1 → 5 Nerve injury
6 Chemical irritants
7 Incision wound
8 Collagen injection
9 Transgenic animals
10 → 11 Chemically-induced arthritis
12 Mechanically-induced arthritis
13 Migraine
14 Pharmacological agents
15 Systemic Injection
16 Distension

?

Postoperative
Cancer
Renal colic
Trigeminal neuralgia
Child birth/labour
Mixed neuropathic

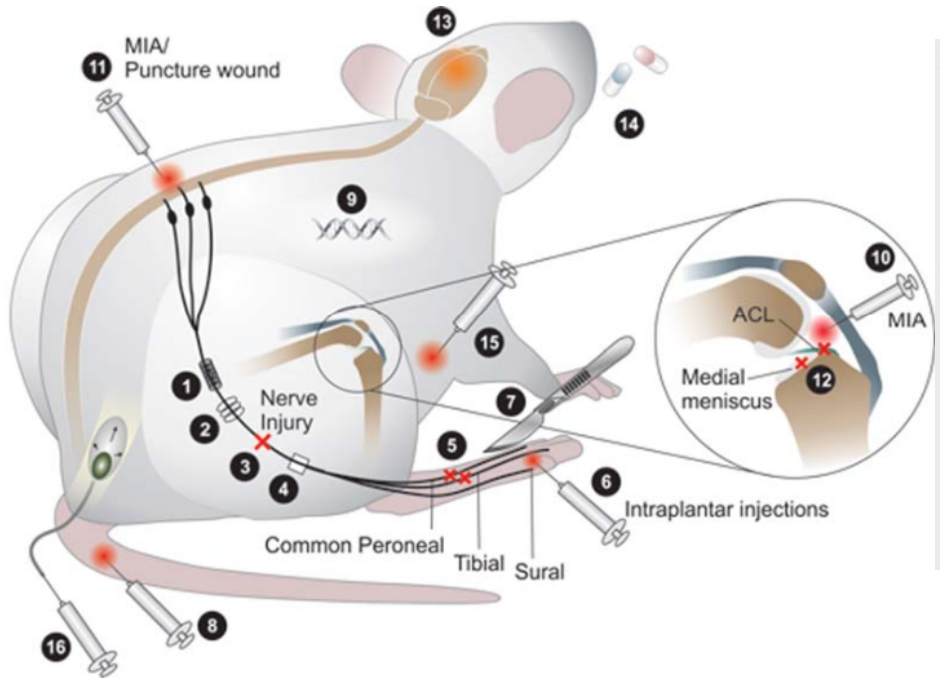
Osteoarthritis
Abdominal pain
Burn injury
Phantom limb
Postsurgical cancer pain
Trauma
Musculosceletal (Low back/Neck)

Diabetic neuropathy (PDN)
Fibromyalgia
Acut migraine
Postherpetic neuralgia (PHN)
Central neuropathic
Chemotherapy induced
Dysmenorrhoea
Perioperative
Temporomandibular joint desease
Atypical facial pain
Inflammatory arthritis
Irritable bowel syndrome
Spinal cord / Nerve injury
Tension type headache

HIV related
Endometriosis
Herpes zoster infection
Myocardial infarction
Postmastectomy pain
Sickle cell disease
Somatoform pain disorders

Burning mouth syndrome
Pain-related funct. GI disorders
Intrauterine devices

Unclear How Rodent Pain Models Map on the Diversity of Human Pain Patient Population



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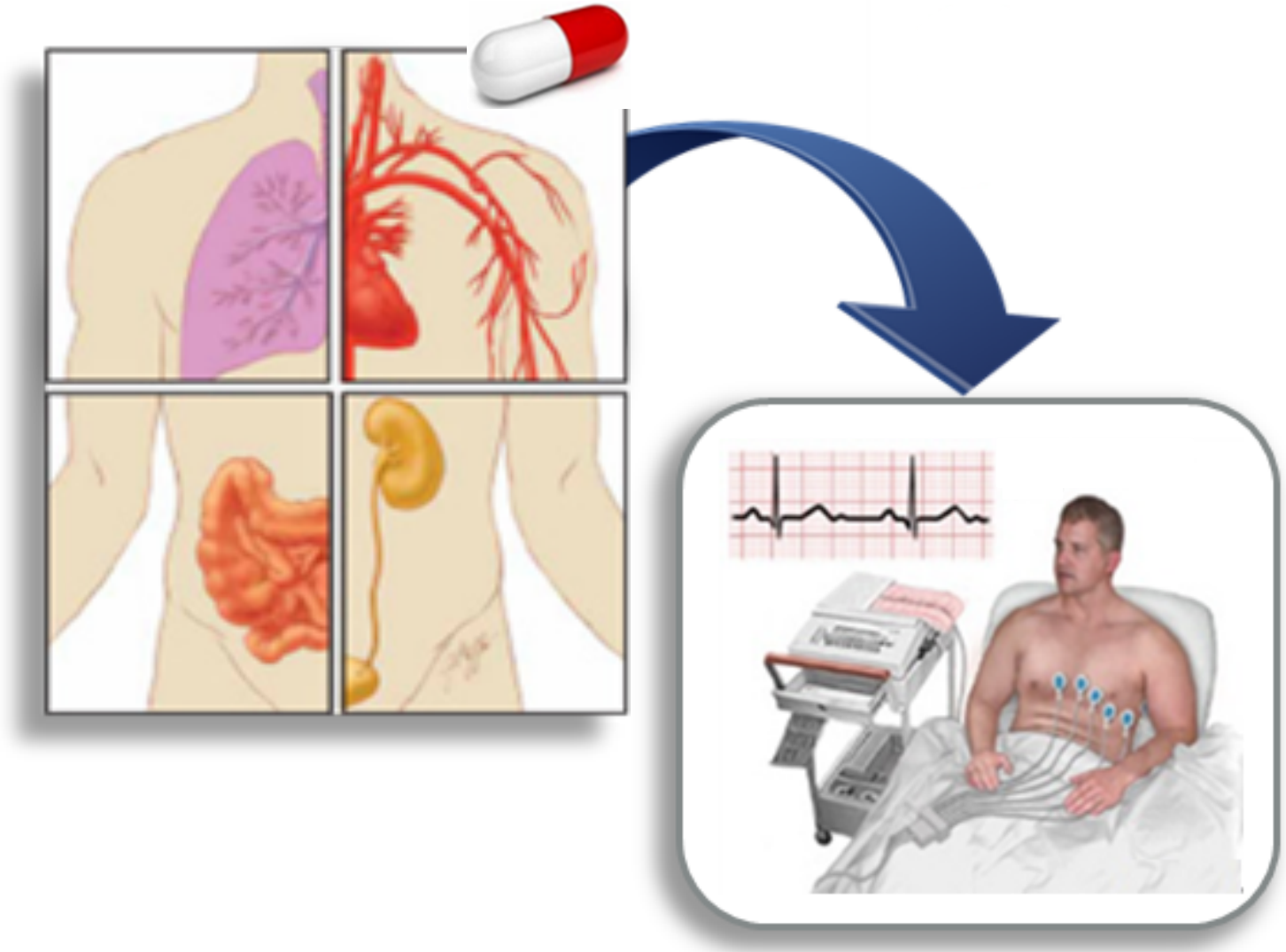
Rodent models do not help in matching a specific drug with the appropriate indication.

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

Hucker HB. Species differences in drug metabolism.
Annu Review Pharmacology. 1970;10:99-118

The use of human microsomes and hepatocytes is introduced

Houston JB. Utility of in vitro drug metabolism data in predicting in vivo metabolic clearance.
Biochem Pharmacol. 1994;47(9):1469-1479.

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

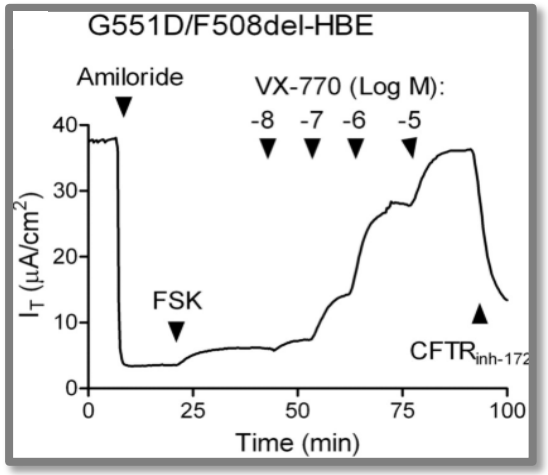
Kola I, Landis J. Can the pharmaceutical industry reduce attrition rates? Nat
Rev Drug Discov. 2004;3(8):711-715.

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

VERTEX



Van Goor et al. (2006)

Predictive of clinical outcomes

Lower development risks related to interspecies differences

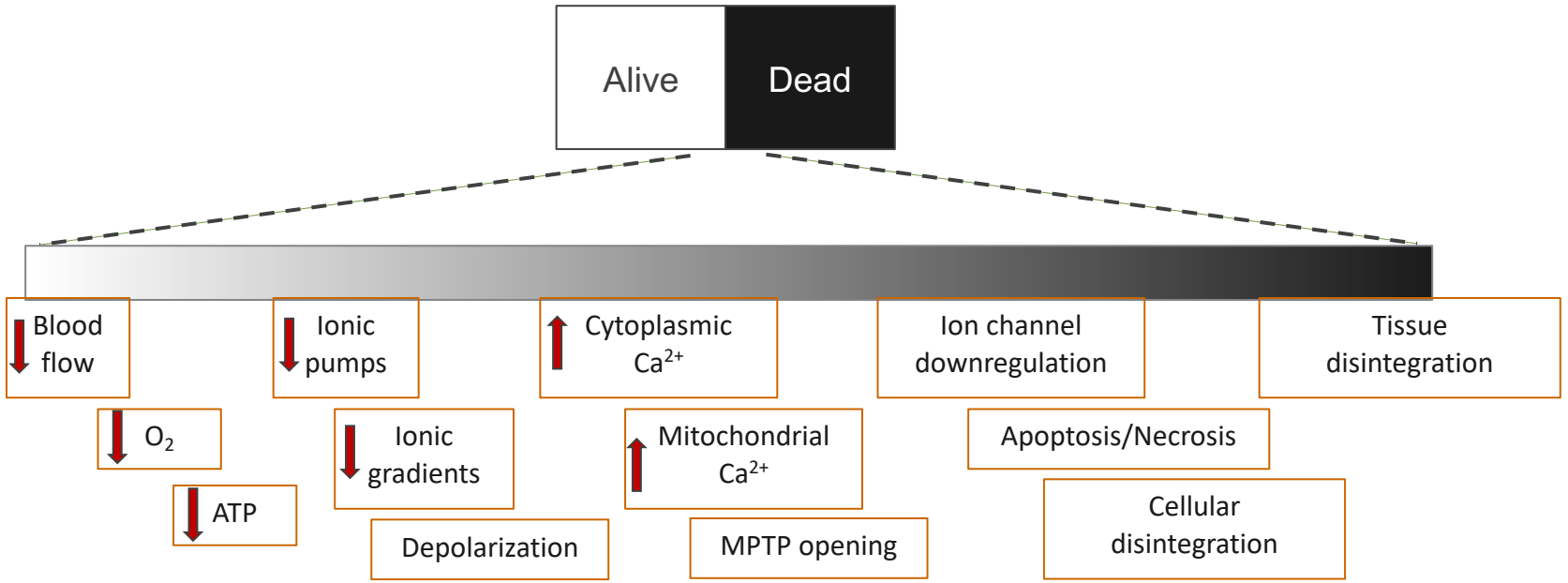
Study of drug action in healthy or pathological states

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 Process



Enabling Drug Discovery in Human Tissues

Organ donor

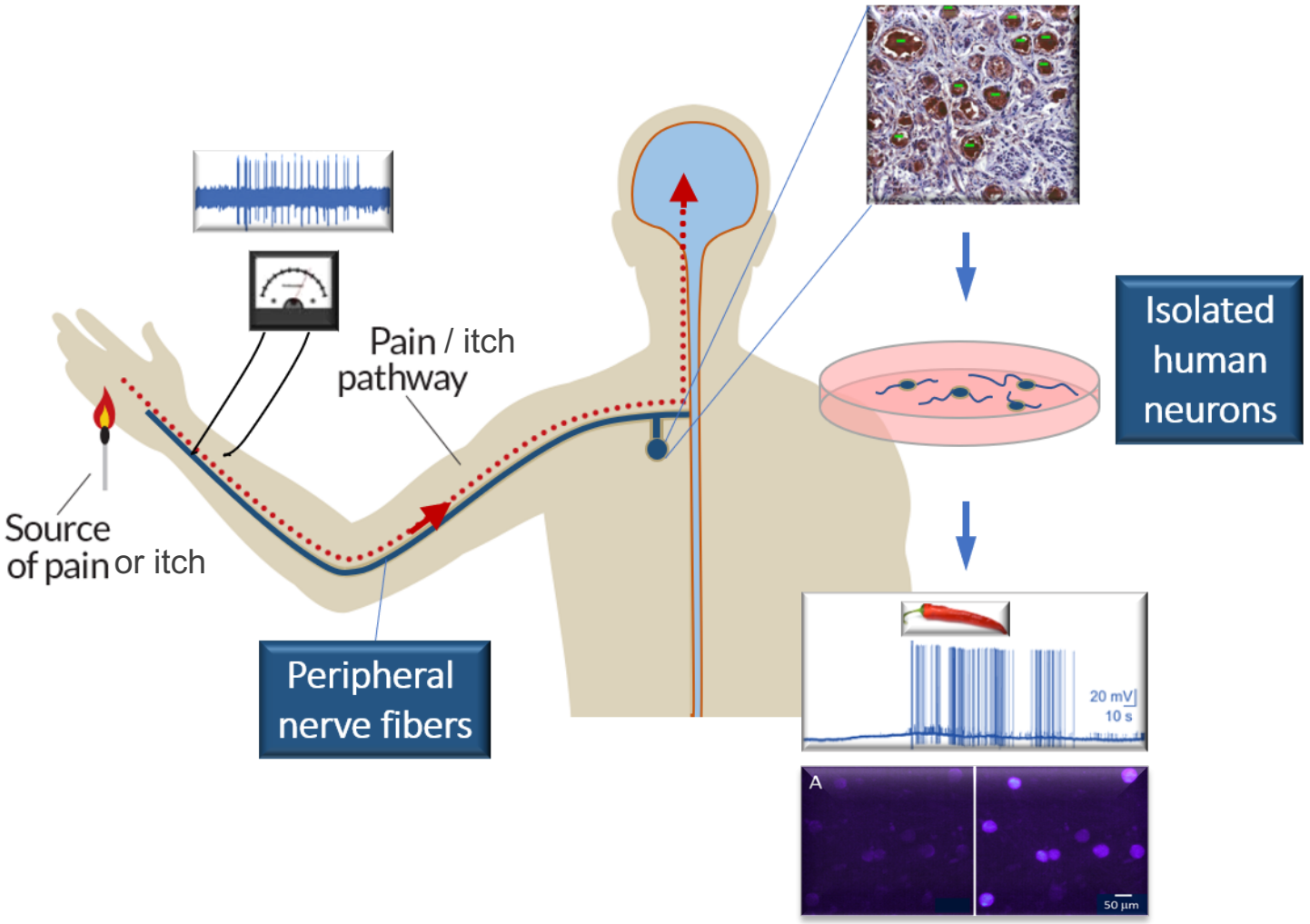
Organs are collected and perfused with solutions that prevent ischemic damage

Expedited shipping

Measurement of drug effect

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

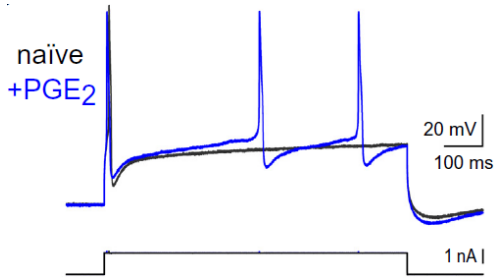
Human Sensory Neurons for Pain Drug Discovery



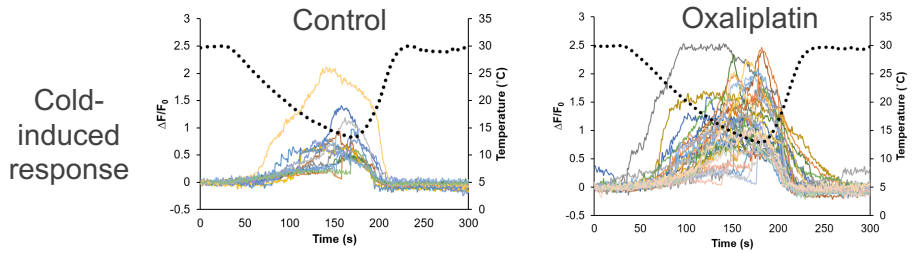
Assessment of Drug Activity in Pathological States

1- In vitro-sensitized hDRG

Inflammation

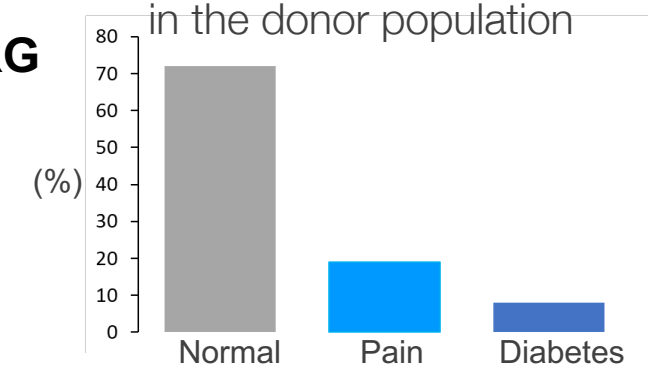


Peripheral neuropathy

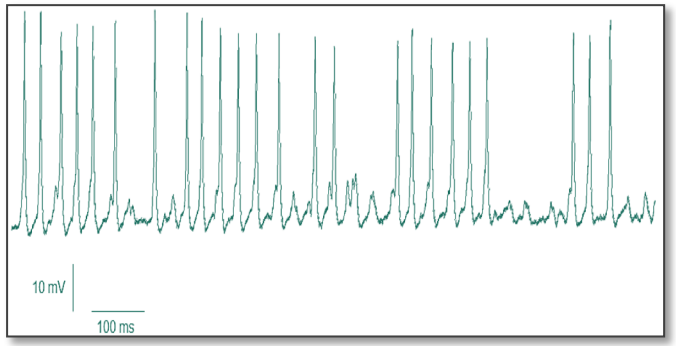


2- Chronic pain donor hDRG

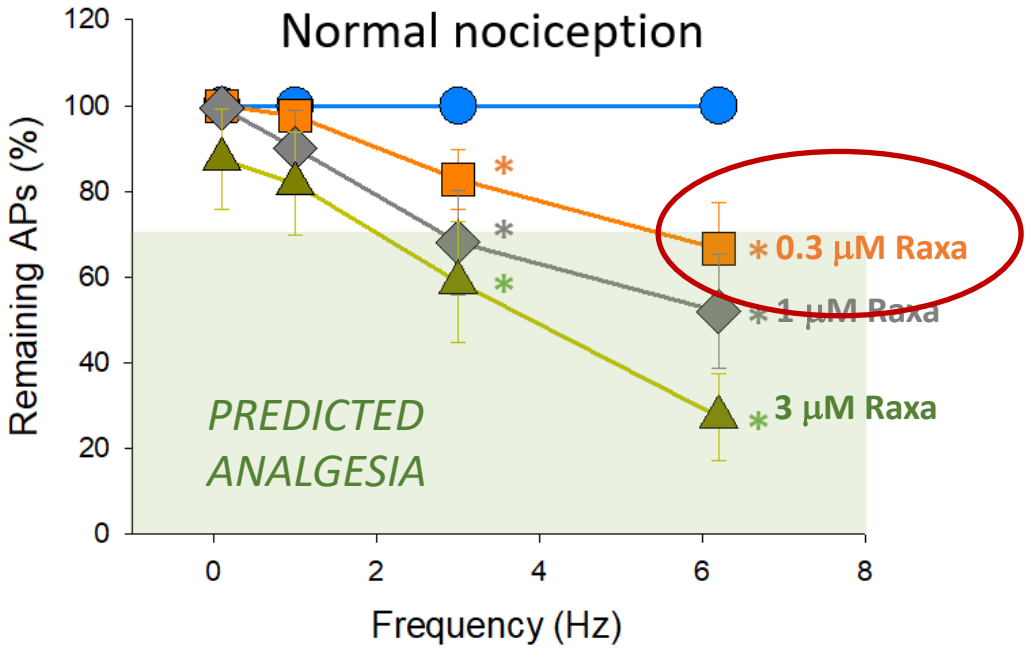
Prevalence of pain cases in the donor population

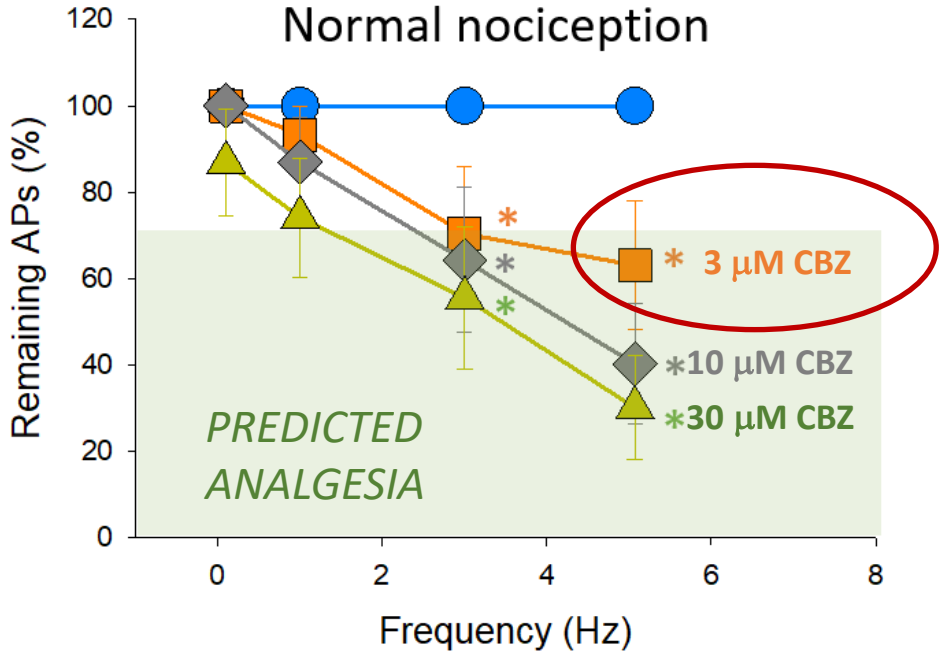


Spontaneous firing in hDRG neuron from chronic pain donor

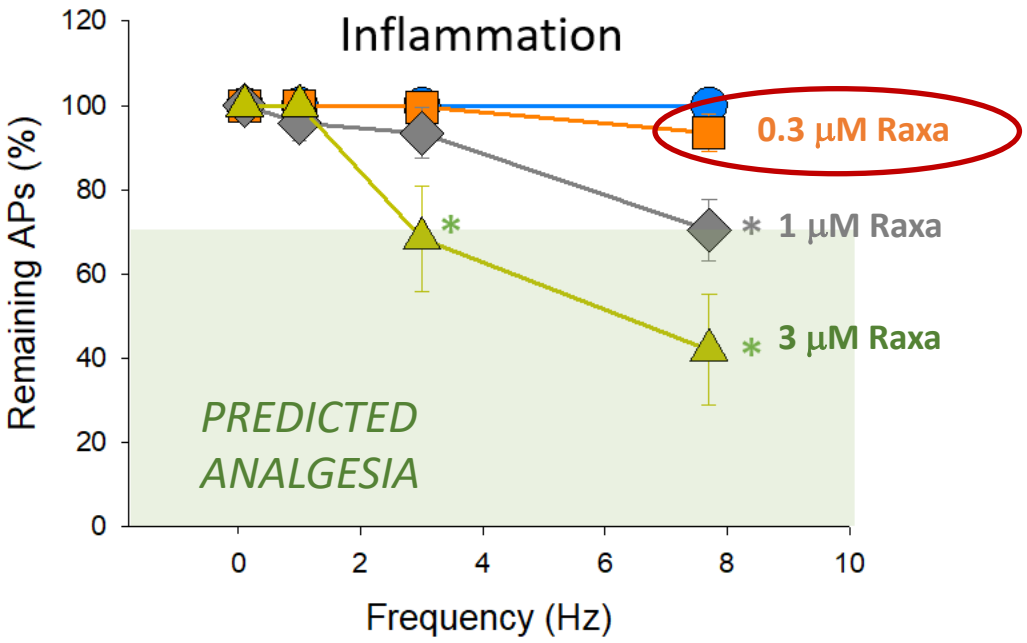


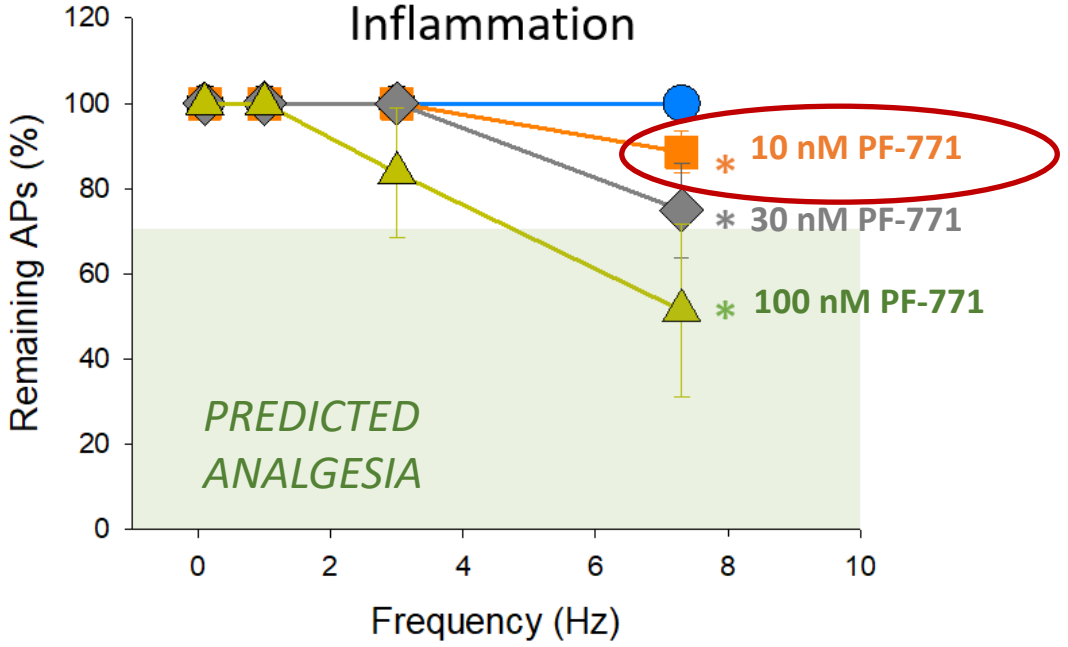
Inhibition of Human Sensory Neurons' Activity by Raxatrigine and Carbamazepine



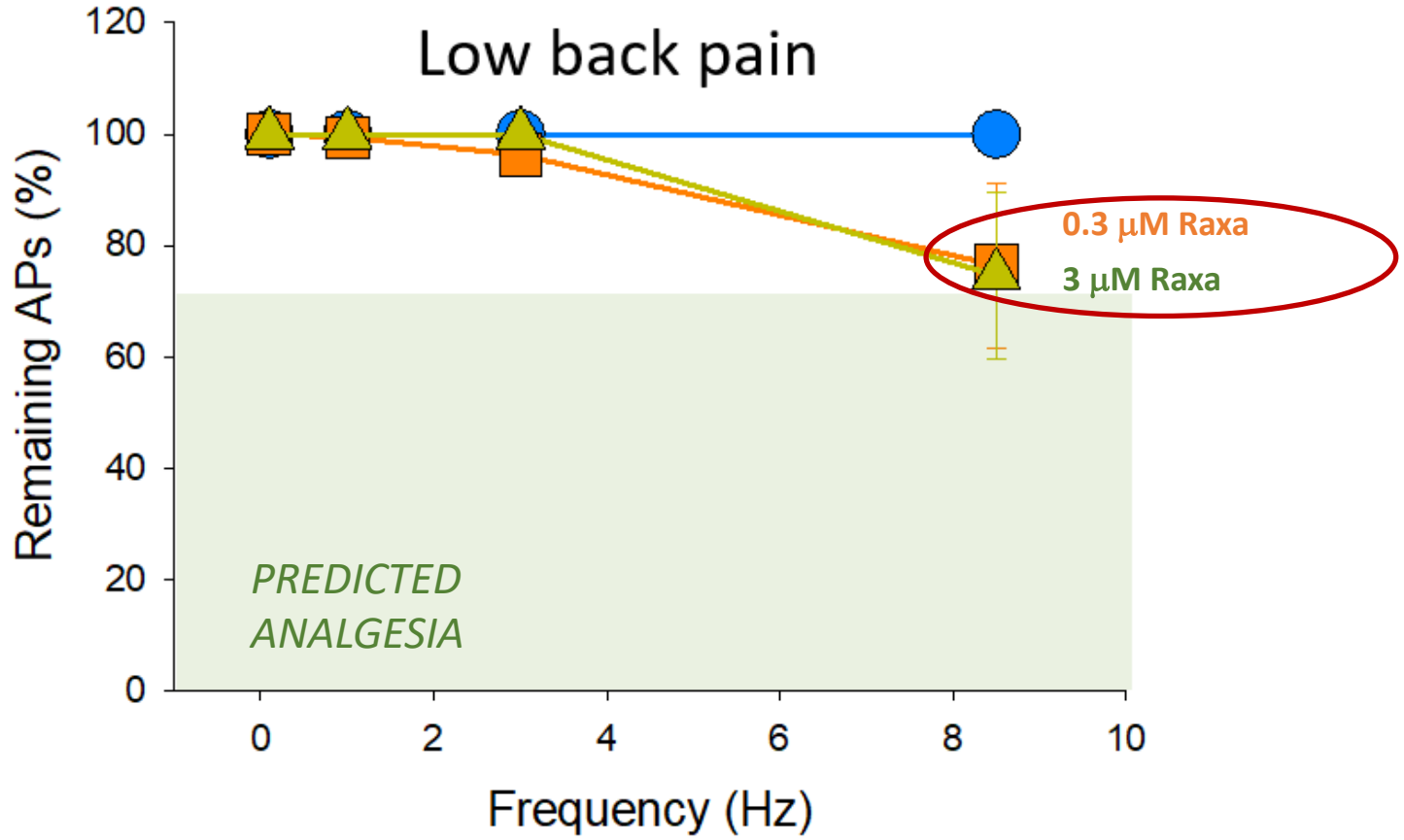


Sensory Neurons Sensitized With Inflammatory Agents Are Not Inhibited by Raxatrigine and PF-05089771

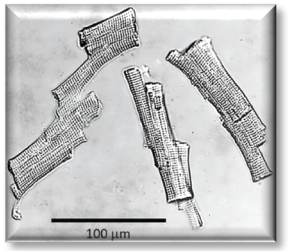




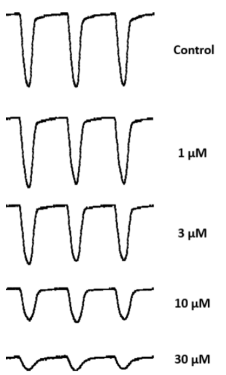
Raxatrigine Fails to Inhibit the Activity of Human Sensory Neurons from Low Back Pain Donors

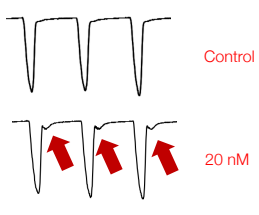


Cardiac Safety Assessment in Human Heart Ex-Vivo

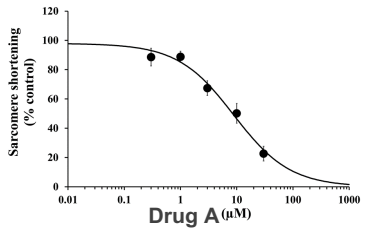


Human adult cardiomyocytes

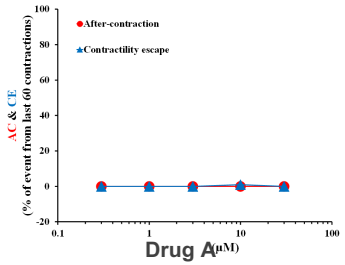




After-contraction pro-arrhythmia marker

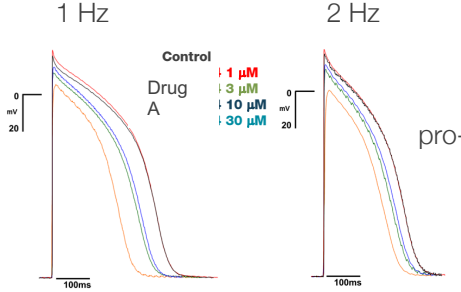


Reduction in cardiomyocyte contractility only at very high concentrations

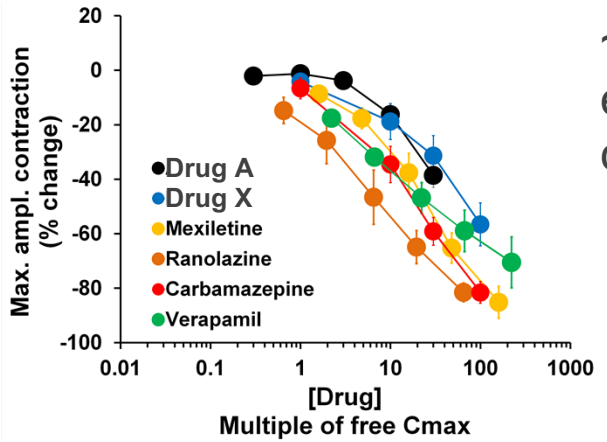


No evidence of drug-induced arrhythmia

Human adult ventricular trabeculae



No evidence of pro-arrhythmia markers up to 30 µM



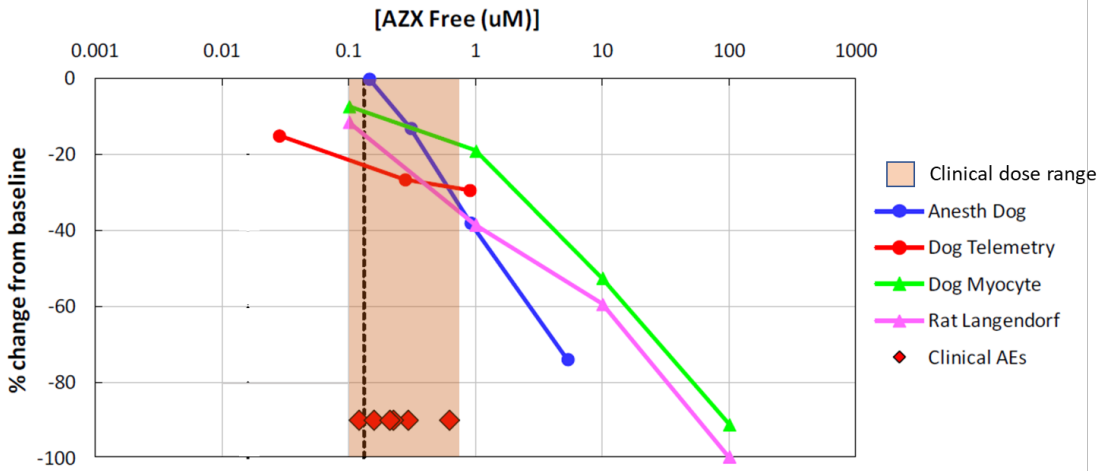
Cardiac safety margin ~100x of the target effective concentration

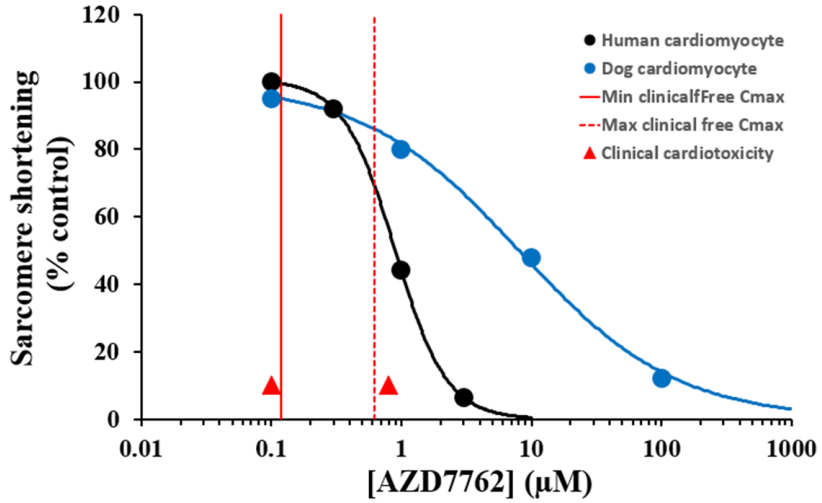
Poor Translation Can Result in Serious Adverse Events

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

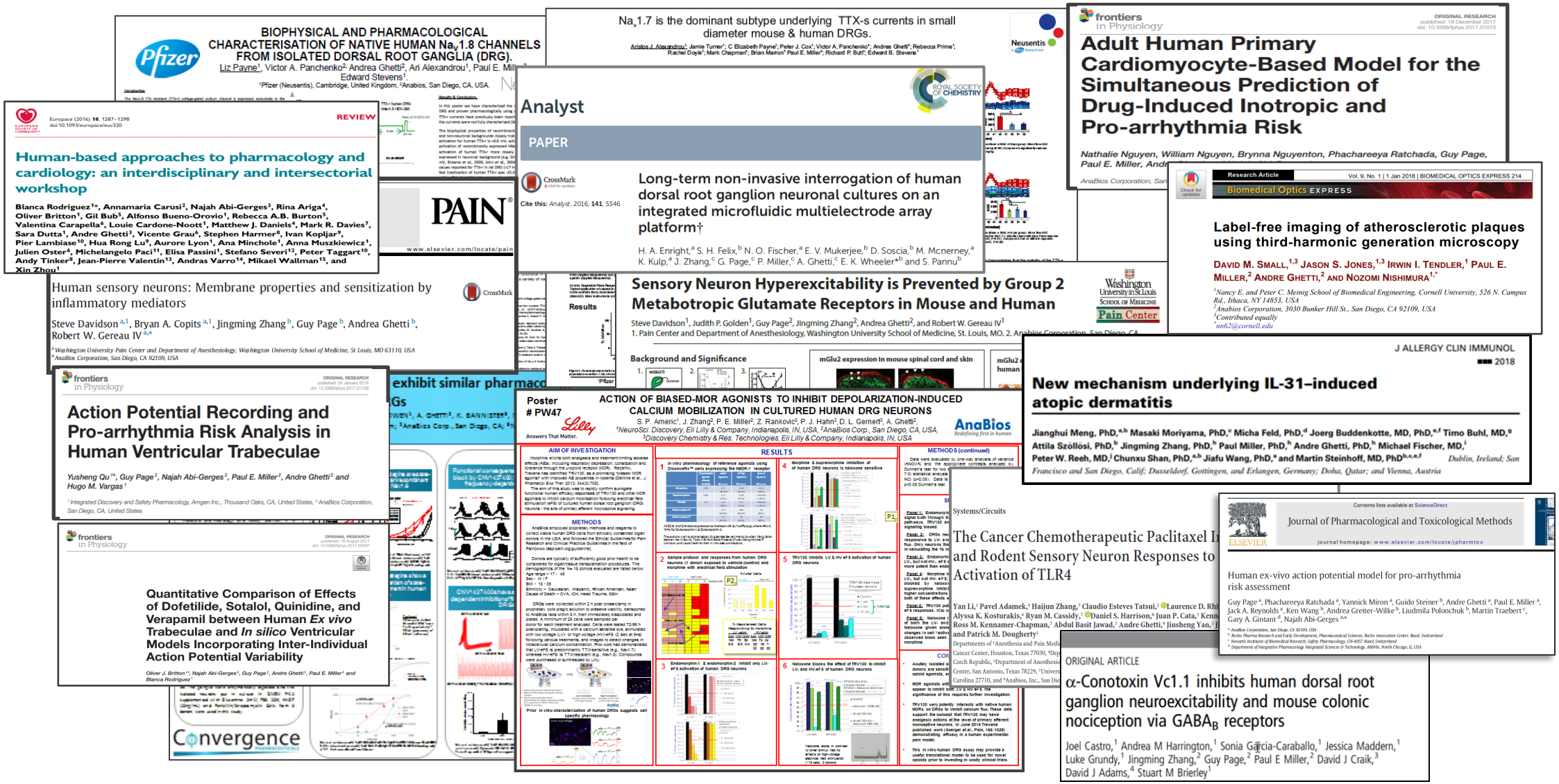
Sausville et al. (2014)

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

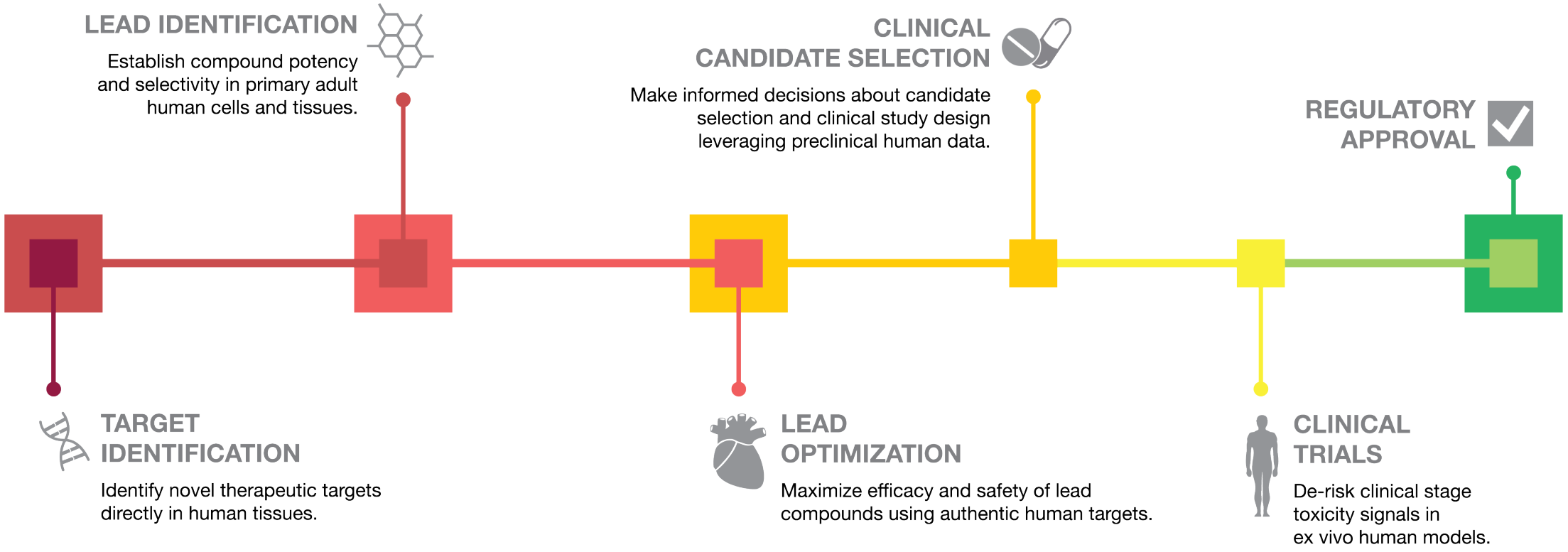




Human Ex-Vivo Systems are Increasingly Utilized in Translational Research



Human Tissues in Drug Discovery



Summary

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

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

Quantitative assessment of potency

Thank You

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