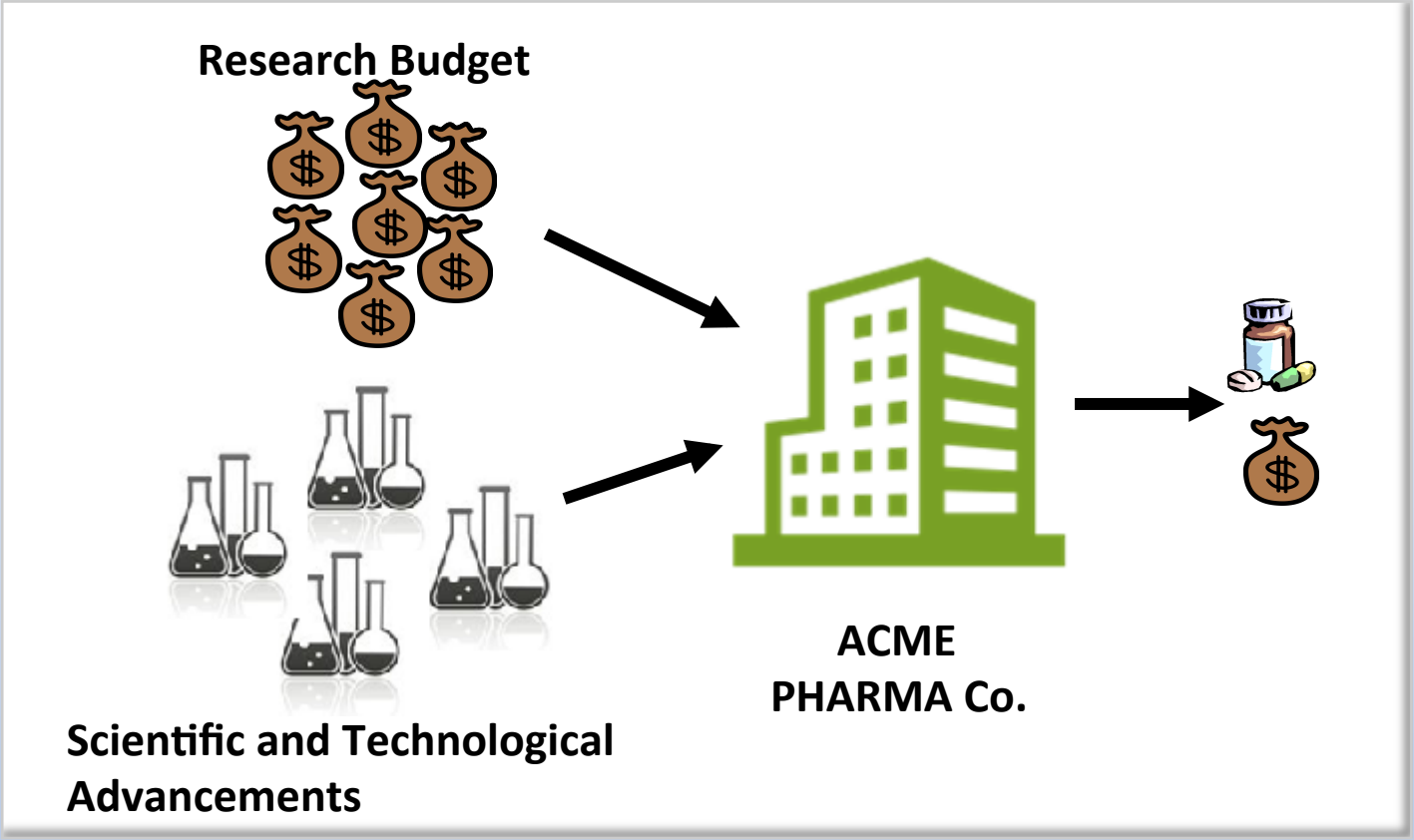
“If mice were only people….”

Re-thinking Pre-Clinical In Vivo Models To Increase the Probability of Clinical Success

Beth Ann Murphy, PhD

Nina Jochnowitz

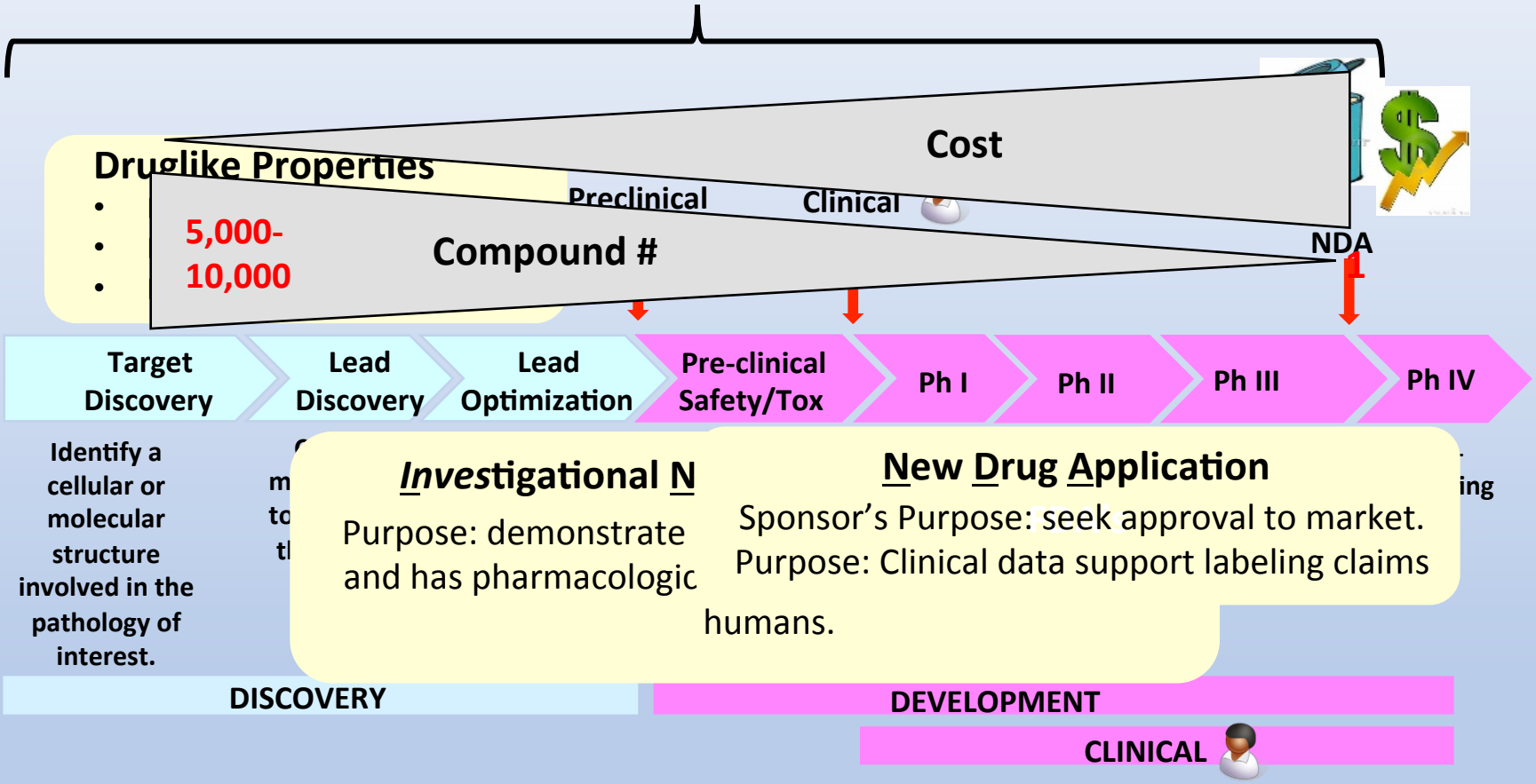
Pharma Industry is Challenged



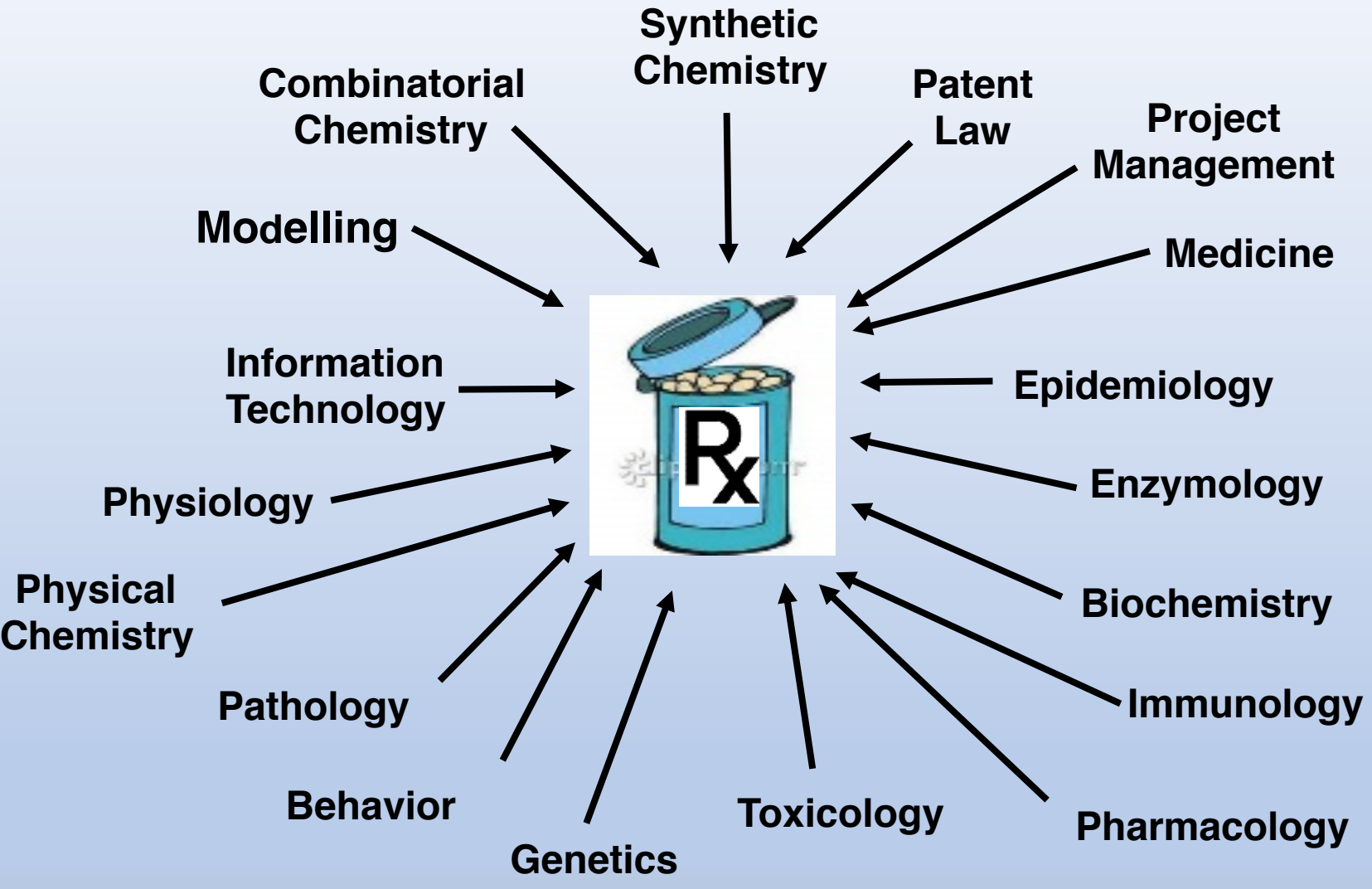
- Many analyses that probe and propose reasons for the decrease in R&D productivity.
- Consensus is that drug discovery needs to change to be able to deliver novel drugs in the current environment.

Drug Discovery and Development Process

Cost to bring a drug to market was $2.56 billion in 2013 dollars. (Tufts Center for the Study of Drug Development).



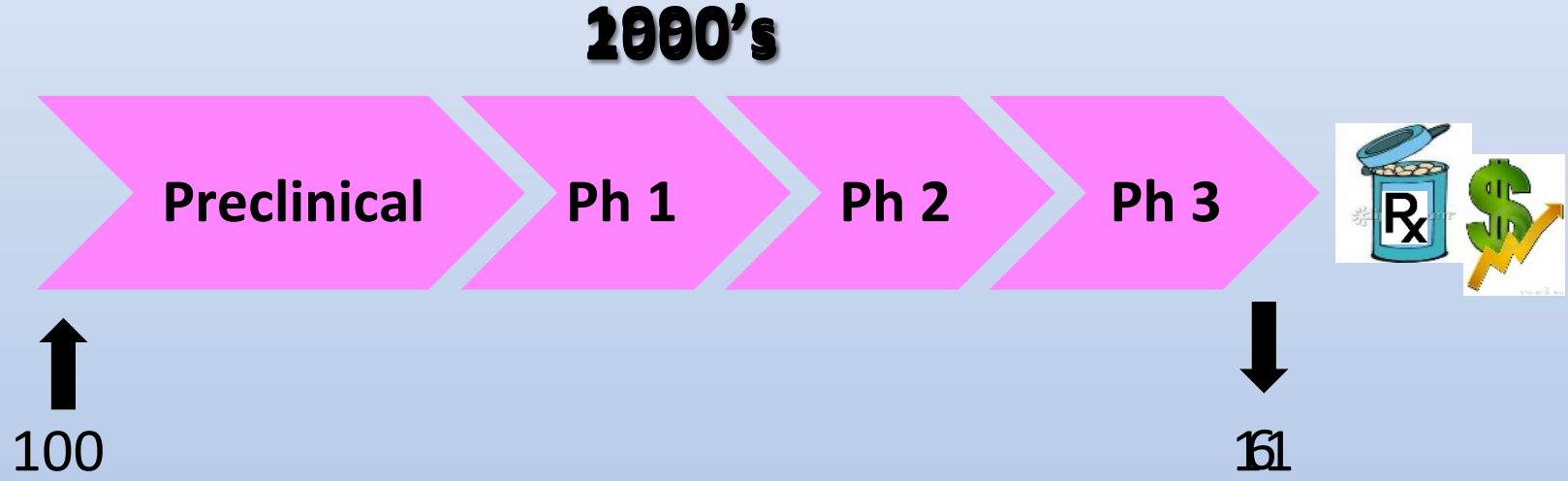
Drug Discovery—Convergence of Disciplines



What is the problem?

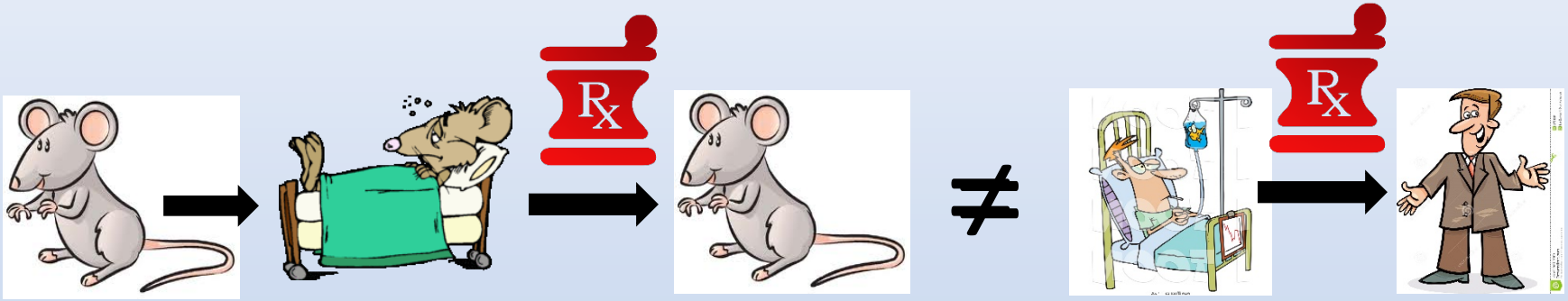
Problem: Drugs discovered in the Preclinical stage frequently fail to translate into clinical success (~10% overall success).

- 1991-2000 = 11% success rate (Nat. Rev. Drug Discov. 2004 Aug; 3(8):711-715.)
- 2005-2010 = 6% success rate (Nat. Rev. Drug Discov. 2014 Jun; 13(6):419-431.)



But why doesn't the preclinical work translate to humans?

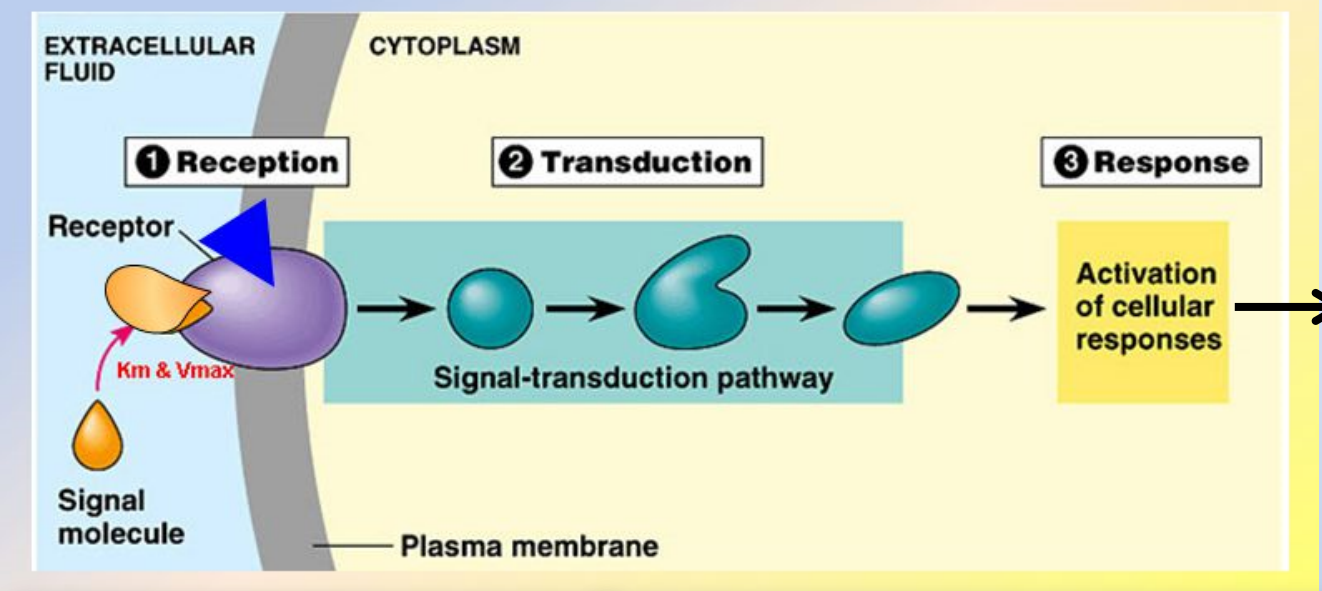
Animals ≠ Humans



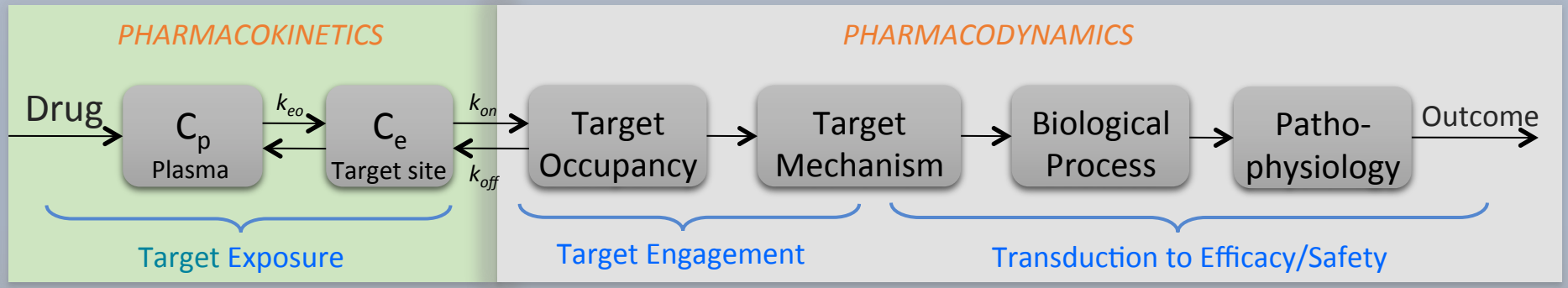
- Genetic
- Surgical Manipulation
- Mimic a chronic condition in an acute time-frame.
- Apply animal behavior to a human behavior.

- Effects in preclinical in vivo disease models are poor predictors of efficacy in the clinic.

Think about it Differently: What is a Drug Actually Doing



Biological Process → Pathological Process



Think about it Differently

1. An integrated and quantitative understanding of the PKPD relationships and how these translate to humans.

Human PK – can we get enough drug to where it needs to be?

Human Target Engagement – can we modulate the target with the right intensity and duration?

2. **Confidence in target-disease linkage**.

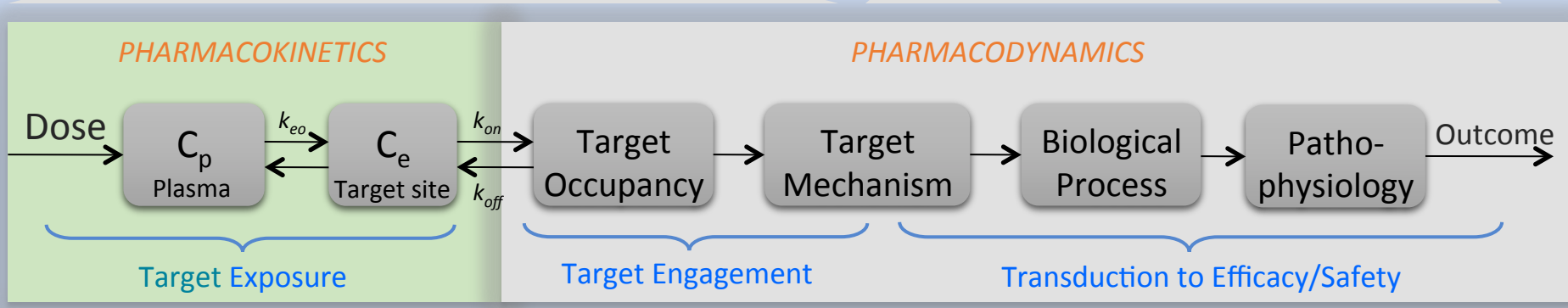
Human genetics

Validated preclinical model

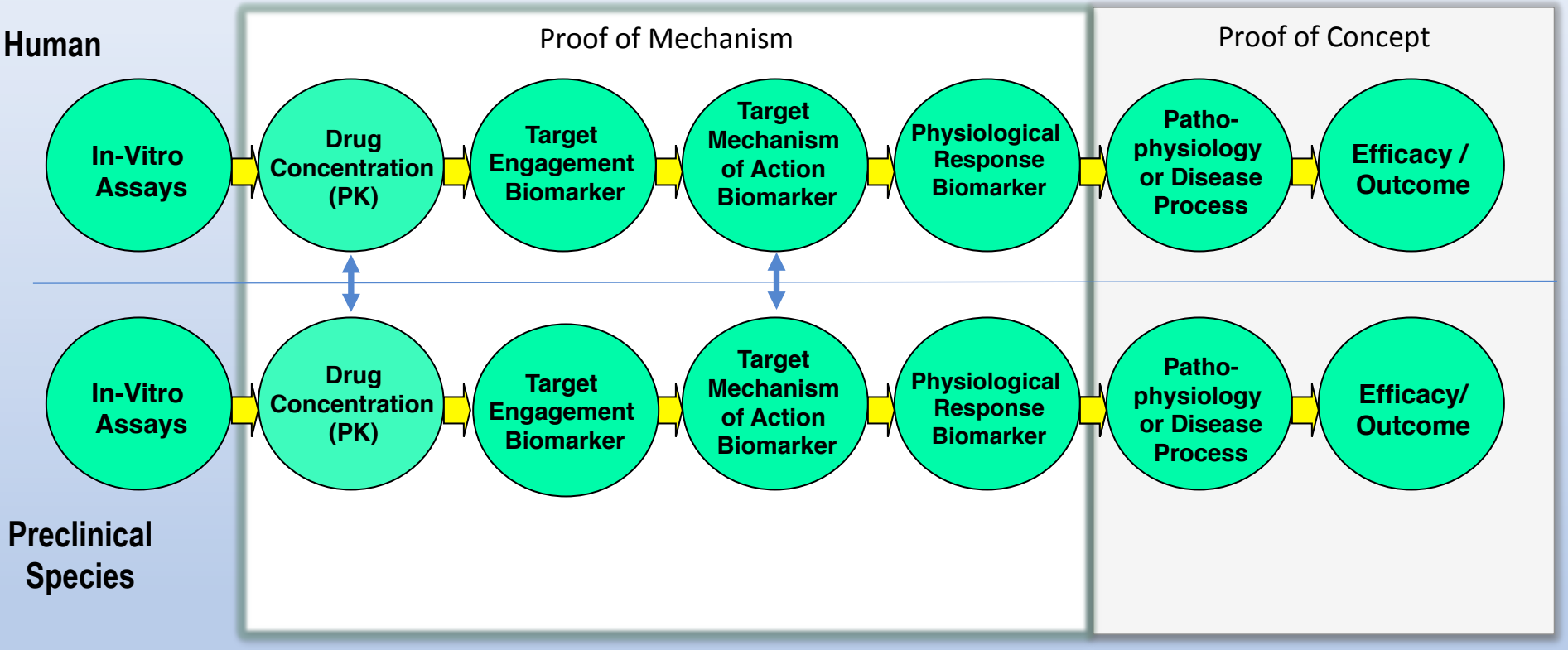
3. **Identify and test assumptions**

Integrate data to reduce assumptions

Identify critical assumptions and assess impact



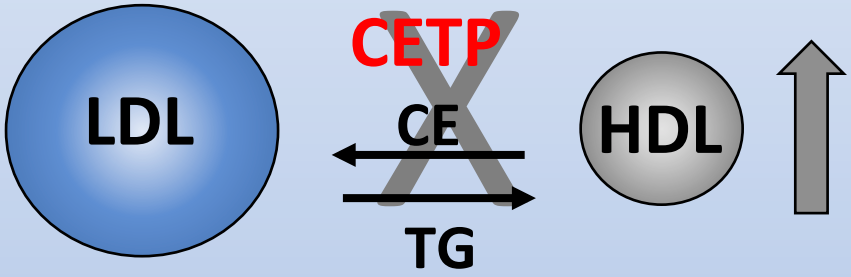
Translational Biomarker Bubble Diagram



Example : Respond to Data from a Clinical Trial

Lead-Optimization Drug Discovery Program for Cardiovascular Disease

Increase HDL → Protect from CVD



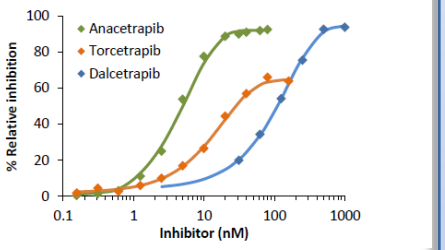
CETP Catalyzes the exchange of TG and CE between HDL and VLDL/LDL

Inhibit CETP → Increase HDL → Protect from CVD

What do we need to ask?/ What do we know? /What do we have?

1. What is the target?→ CETP
2. What do we want the drug to do?→ Inhibit CETP
3. What is the effect of inhibiting CETP?→ Increases HDL

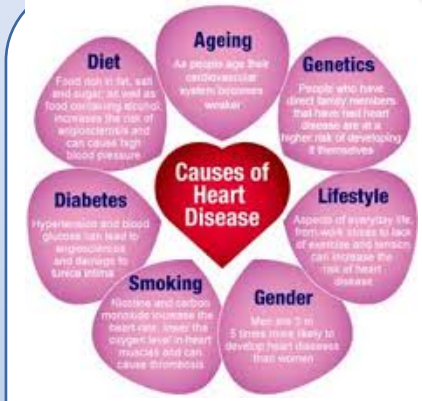
Commercial CETP Inhibitor Screening Kit



Human→ Yes
Blood→ Yes

Commercial HDL Screening Kit

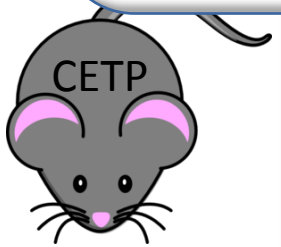
Human→ Yes
Blood→ Yes



Long time period

Measure of clinical effect = Decreased CVD related deaths

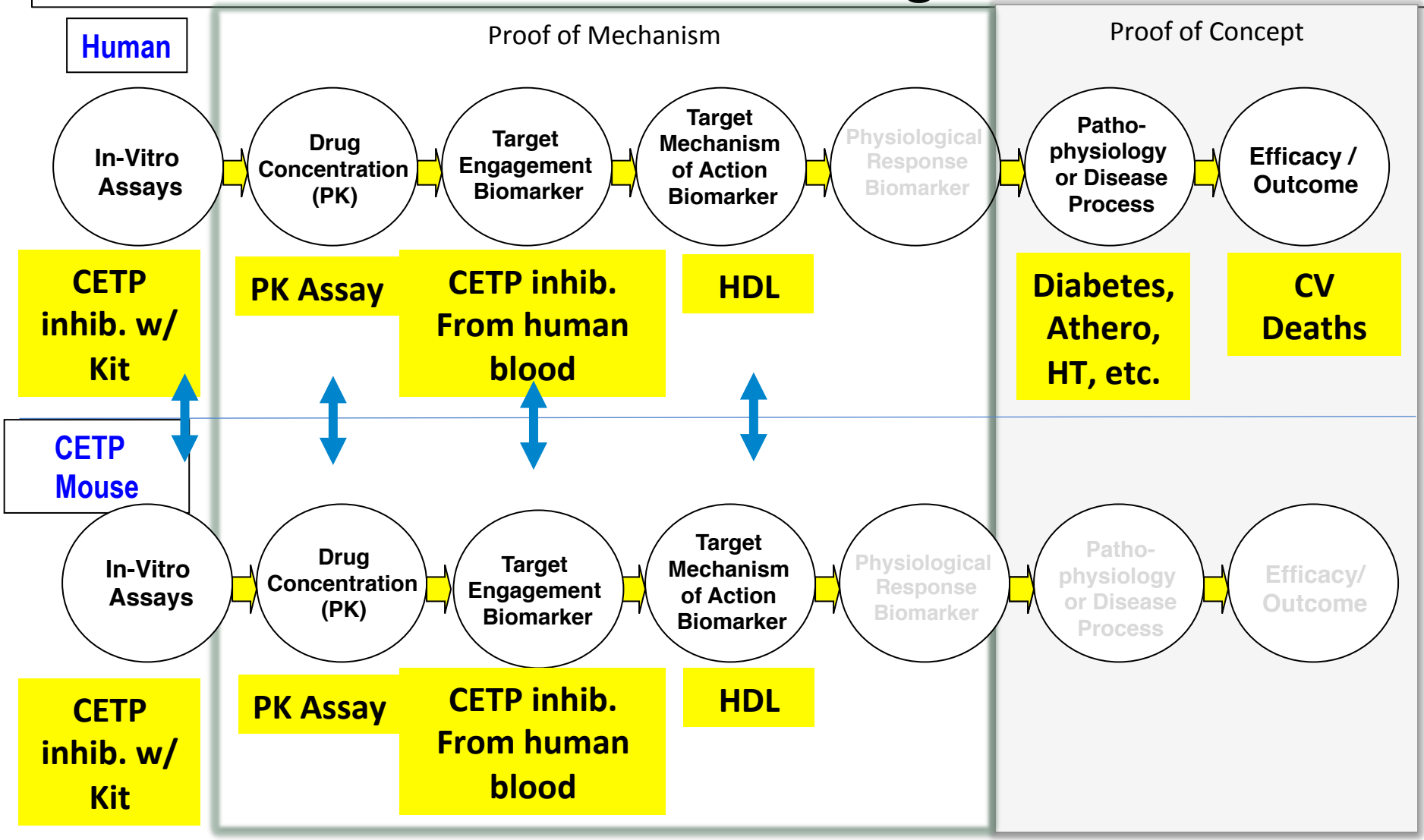
Able to measure drug levels in the circulation (Pharmacokinetics)



Human CETP Transgenic Mouse

- **Mice do not develop CVD naturally.**
- **Mice ≠Humans**

Translational Biomarker Bubble Diagram: CETP Inhibitor Program



Arrow = Can be measured both in preclinical experiments and in human clinical trials

Case Study

Case Study
Anti-Thrombotic Drug For Stroke and AFIB

What are the Main Cause and Effects of Thrombotic Events

1. Cause Atrial Fibrillation
2. Effect Stroke(s)

What is the Human cost?

1. Lives
2. Annually, Death rate is nearing 300,000 in the USA
3. More than 1,500,000 hospitalizations annually

What is the Financial cost?

1. Personal
2. Broad Economic losses (work related)
3. Forty Billion ($40,000,000) dollars!

Atrial Fibrillation - AFIB

Disease of the heart characterized by irregular and often faster heartbeat.

Causes of an Irregular Heartbeat

- Hypertension, Diabetes, Congestive heart failure, Dehydration, Hyperkalemia, Mitro-valve Prolapse, Poisoning, (cocaine, amphetamine, digitalis…), Anaphylaxis, hyper & hypo-thyroidism, Cardiomyopathy

Indications

- Abnormal electrical discharges (signals) that generate chaotically throughout the upper chambers of the heart (atria).
- Reduction in the Atria to pump blood into the ventricles
  - Response is the heart to beat too rapidly.
- AFIB causes turbulence of the blood which causes clot formation.
- https://youtu.be/fxUITWjrhhs
- Management: Rate Control, Maintenance of normal rhythm, stroke prevention

Cost

- Prevention: Pharmacological and/or surgical (Cardio conversion, Catheter Ablation, surgical ablation, atrial pacemaker)
- Annually more than **130,000** deaths in the USA.
- More than **750,000** hospitalizations occur annually.
- AFib costs the United States about $6 billion each year, diagnosis and treatment.

Strokes

Sudden death of brain cells from lack of oxygen.

- Caused by blockage of blood flow or rupture of an artery to the brain.
  - Ischemic stroke (part of the brain loses blood flow, bleeding from periphery)
  - Hemorrhagic stroke (brain bleed, Transient Ischemic Attack, TIA >24 hours)

Indications

- Sudden loss of speech, weakness, or paralysis of one side of the body can be symptoms.
- Confirmation by scanning the brain with special X-ray tests, such as CAT scans.

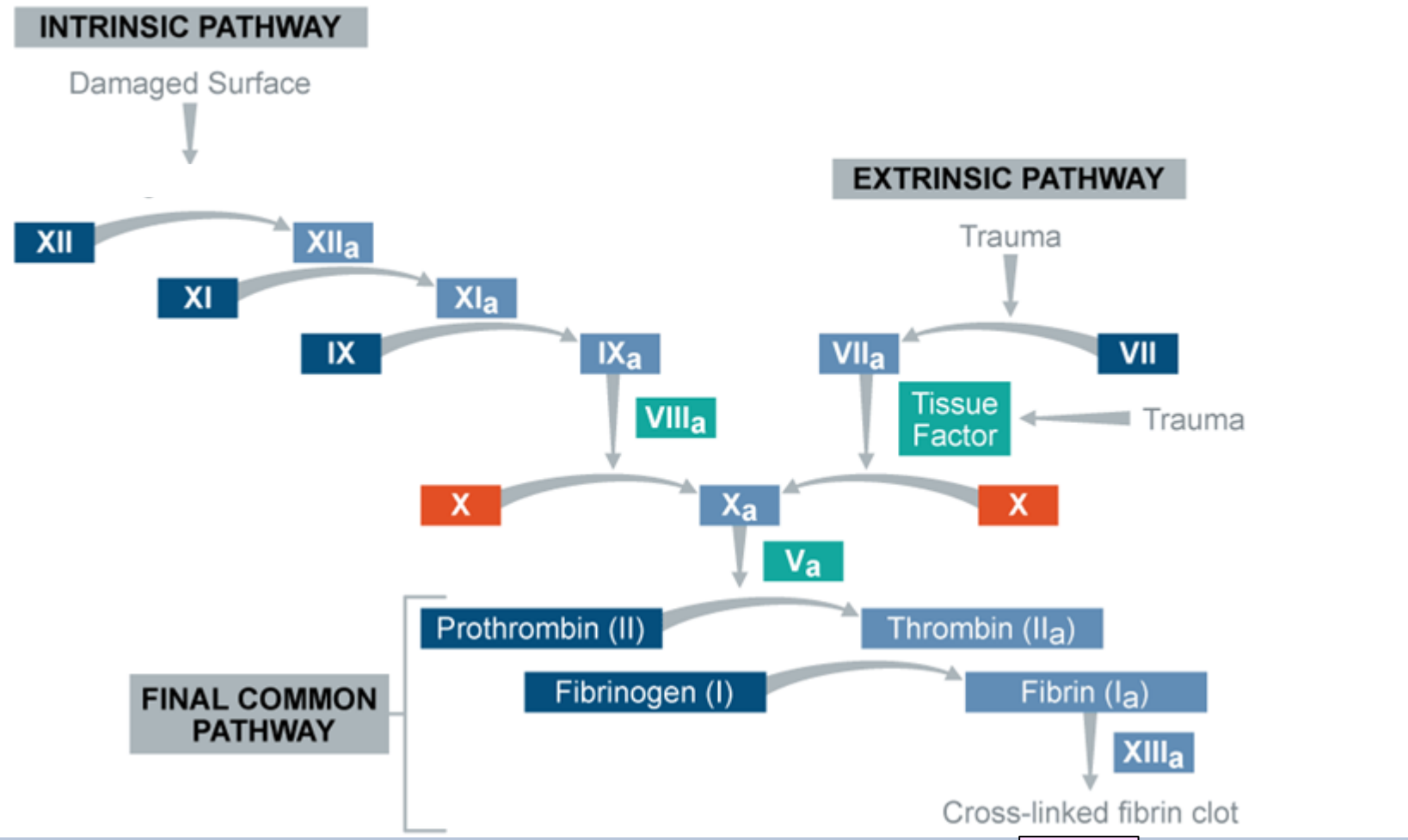
Costs

The death rate and level of disability resulting from strokes can be dramatically reduced by immediate and appropriate medical care.

- Prevention involves minimizing risk factors, such as controlling high blood pressure and diabetes.
- Stroke kills about **140,000** Americans each year—that's **1 out of every 20 de**aths.
- Annually**795,000 people** in the United States have a stroke. About 610,000 of these are first or new strokes
- About 87% of all strokes are ischemic strokes.
- Stroke costs the United States an estimated **$34 billion**

Animal Models: AV Shunt

Project A: Anti-Coagulant Drug Discovery Program: Intrinsic Pathway Inhibitor



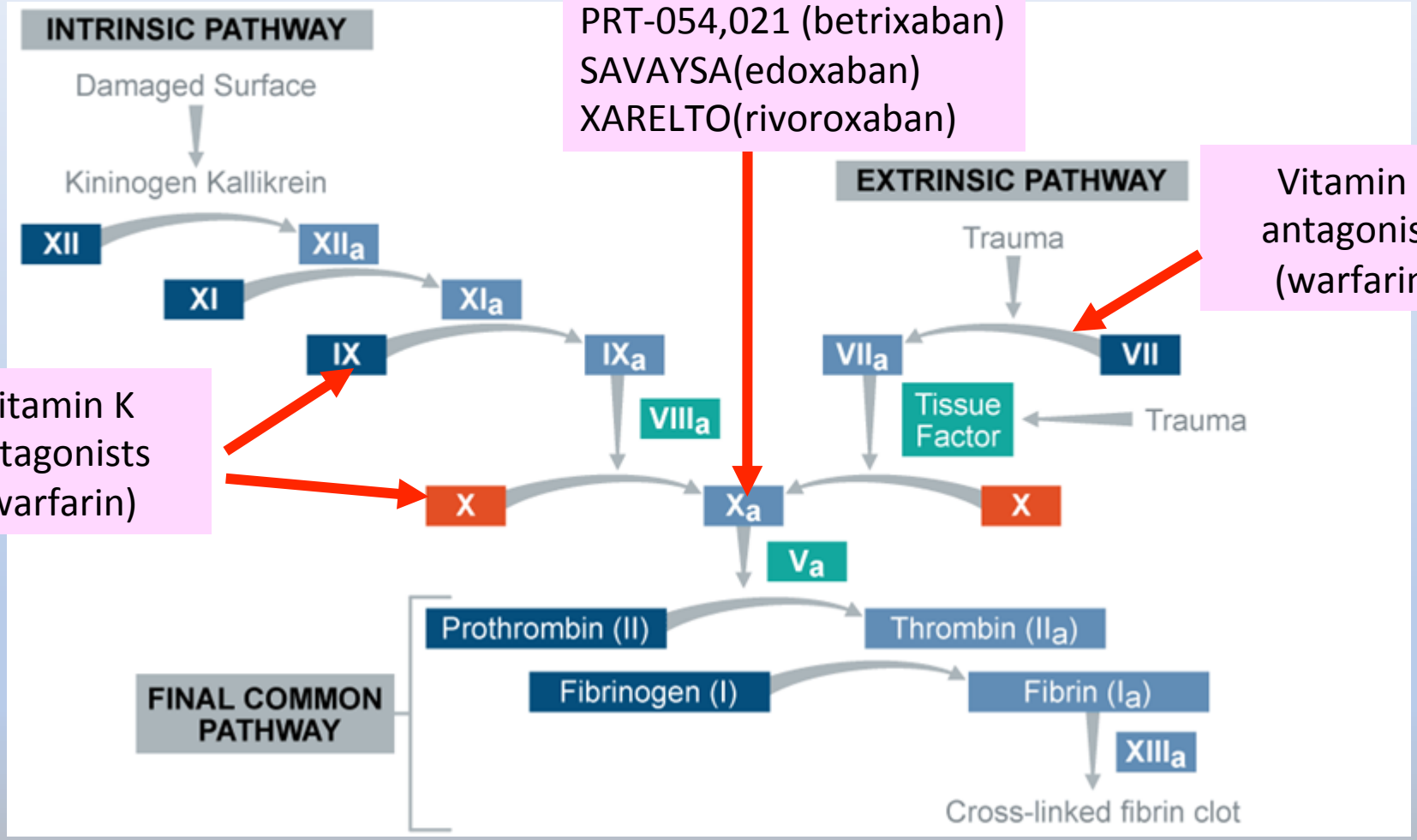
CLOT

Coagulation Factor Targets of Currently Approved SOC or Anti-Coagulant Drugs

ELIQUIS (apixaban)
PRT-054,021 (betrixaban)
SAVAYSA(edoxaban)
XARELTO(rivoroxaban)

Vitamin K antagonists (warfarin)

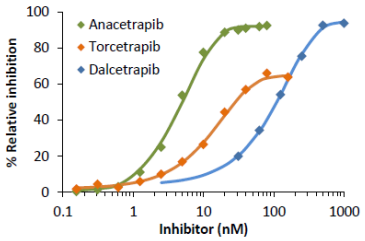
Vitamin K antagonists (warfarin)



What do we need to ask?/ What do we know? /What do we have?

1. What is the target?→ fIXa
2. What do we want the drug to do?→ Inhibit excess thrombotic activity
3. What is the effect of inhibiting factor 9?→ Decreased in thrombotic events

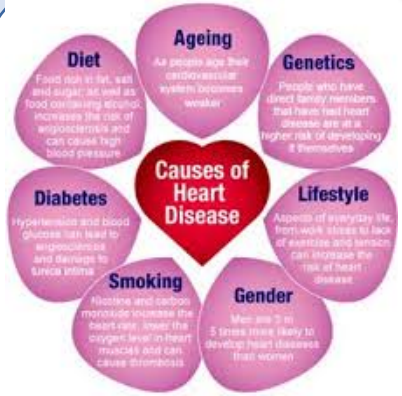
Commercial FIXa Inhibitor Screening Kit



Human→ Yes
Blood→ Yes

Commercial aPTT Screening Kit

Human→ Yes
Blood→ Yes



Long time period

Measure of clinical effect = Decreased CVD related deaths

[AVS](#)

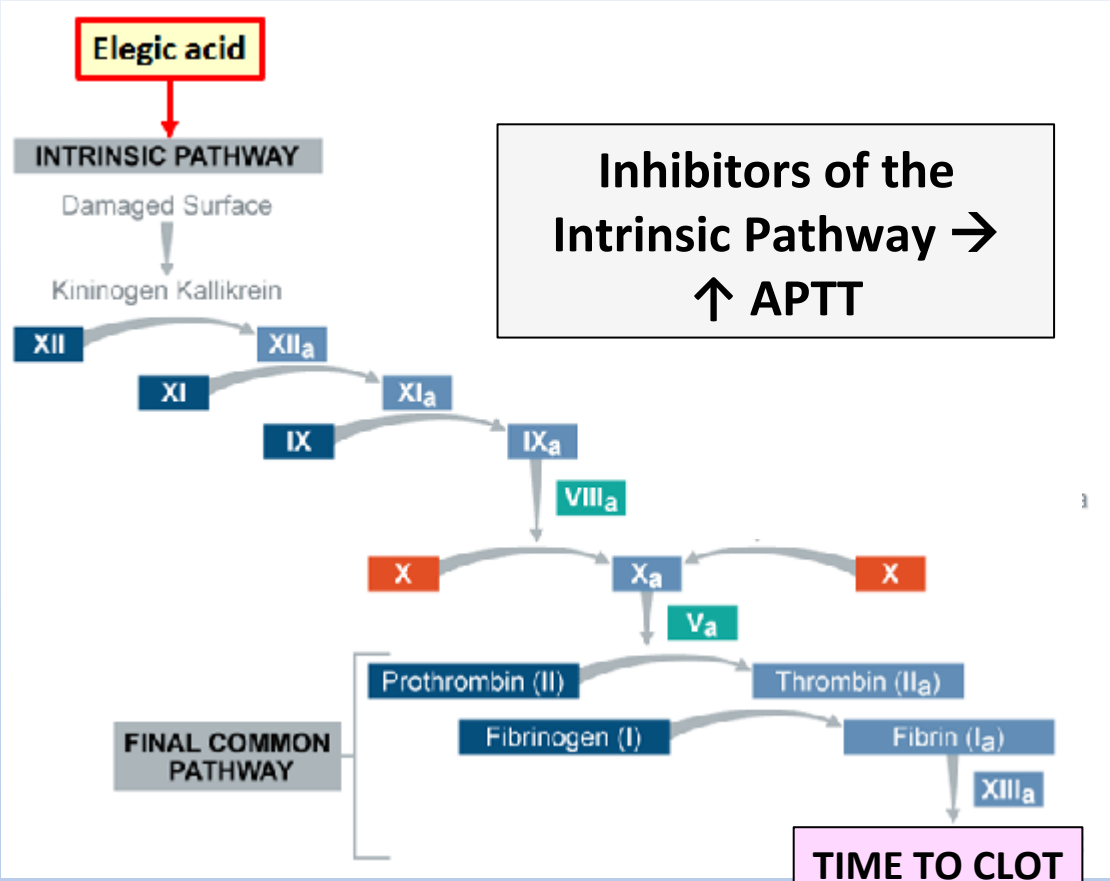
aPTT

Able to measure drug levels in the circulation (Pharmacokinetics)

AVS Model

- **Rabbits do not develop CVD naturally.**
- **Rabbits ≠ Humans**

aPTT: A Routine Clinical Test and a Biomarker of Intrinsic Pathway Coagulation

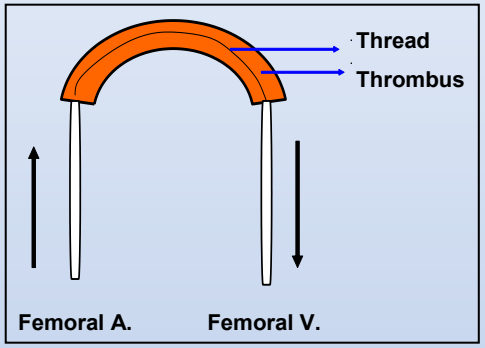


ACTIVATED PARTIAL THROMBOPLASTIN TIME (APTT)

Back

Arteriovenous (AV) Shunt in Rabbits : Model to assess anti-coagulation.

- Method:
  - Connect an artery and vein to a shunt.
  - A thrombogenic stimulus (e.g. thread) is inside the shunt .
  - As blood flows through the shunt → clot will form on the thread.
  - Weigh the clot.

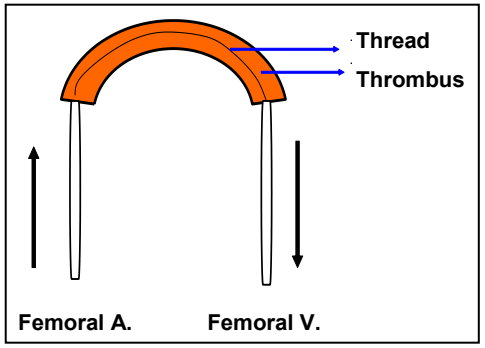


- **Anti-Coagulation** = clot weight, blood sampling
- **Issues:** AVS is a mixed arterial venous antithrombotic model.
- **Needs:** To enhance our confidence in the predictive value of our preclinical models, translational, or creating a plan to further characterize activity of SoC, define target engagement levels etc.

Back

Arteriovenous (AV) Shunt in Rats : Model to assess anti-coagulation.

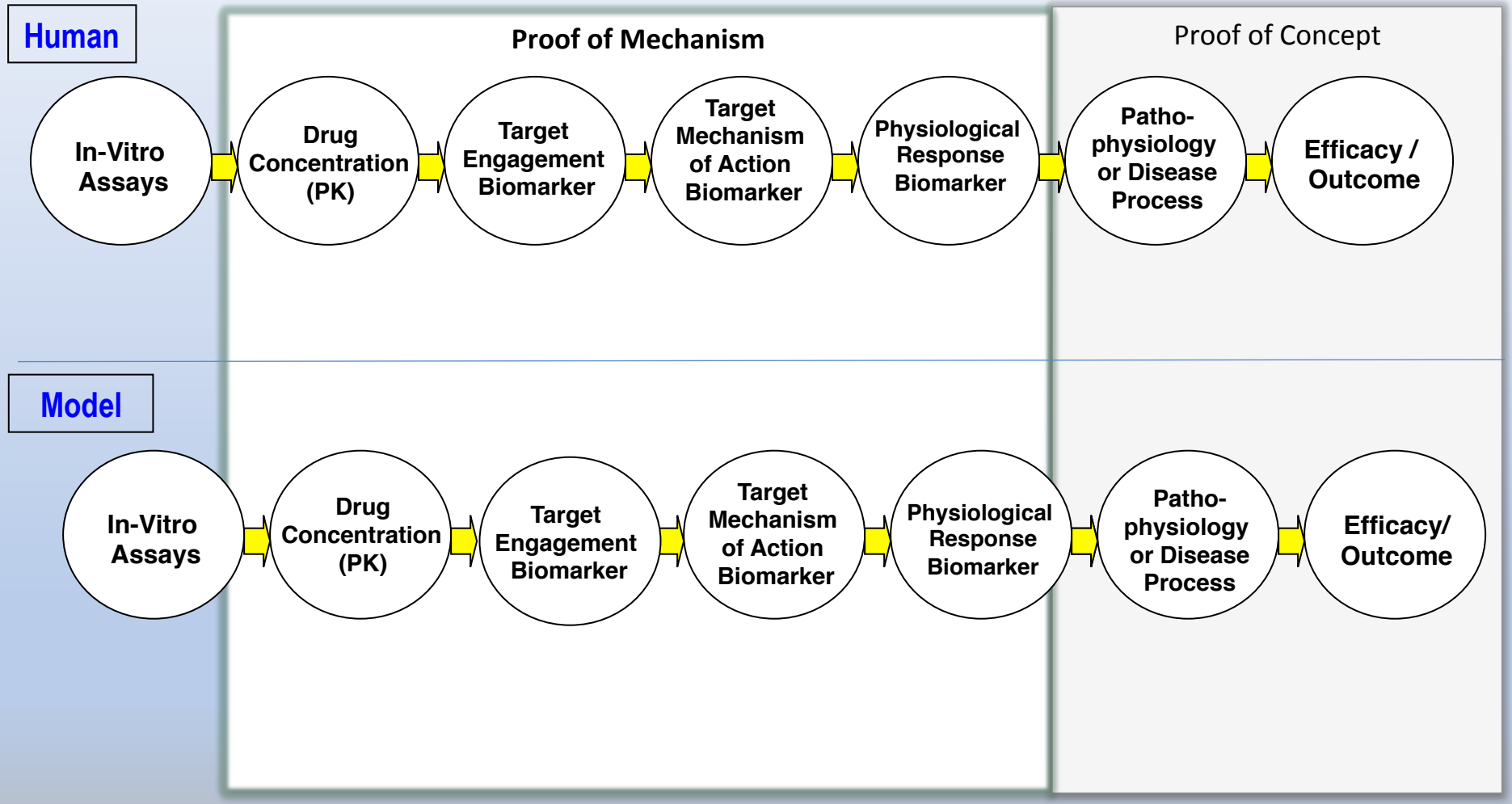
- Method:
  - Connect an artery and vein to a shunt.
  - A thrombogenic stimulus (e.g. thread) is inside the shunt .
  - As blood flows through the shunt → clot will form on the thread.
  - Weigh the clot.



- **Anti-Coagulation** = clot weight
- Can take blood samples from the AVS rats.

Work Sheet

Translational Biomarker Bubble Diagram:

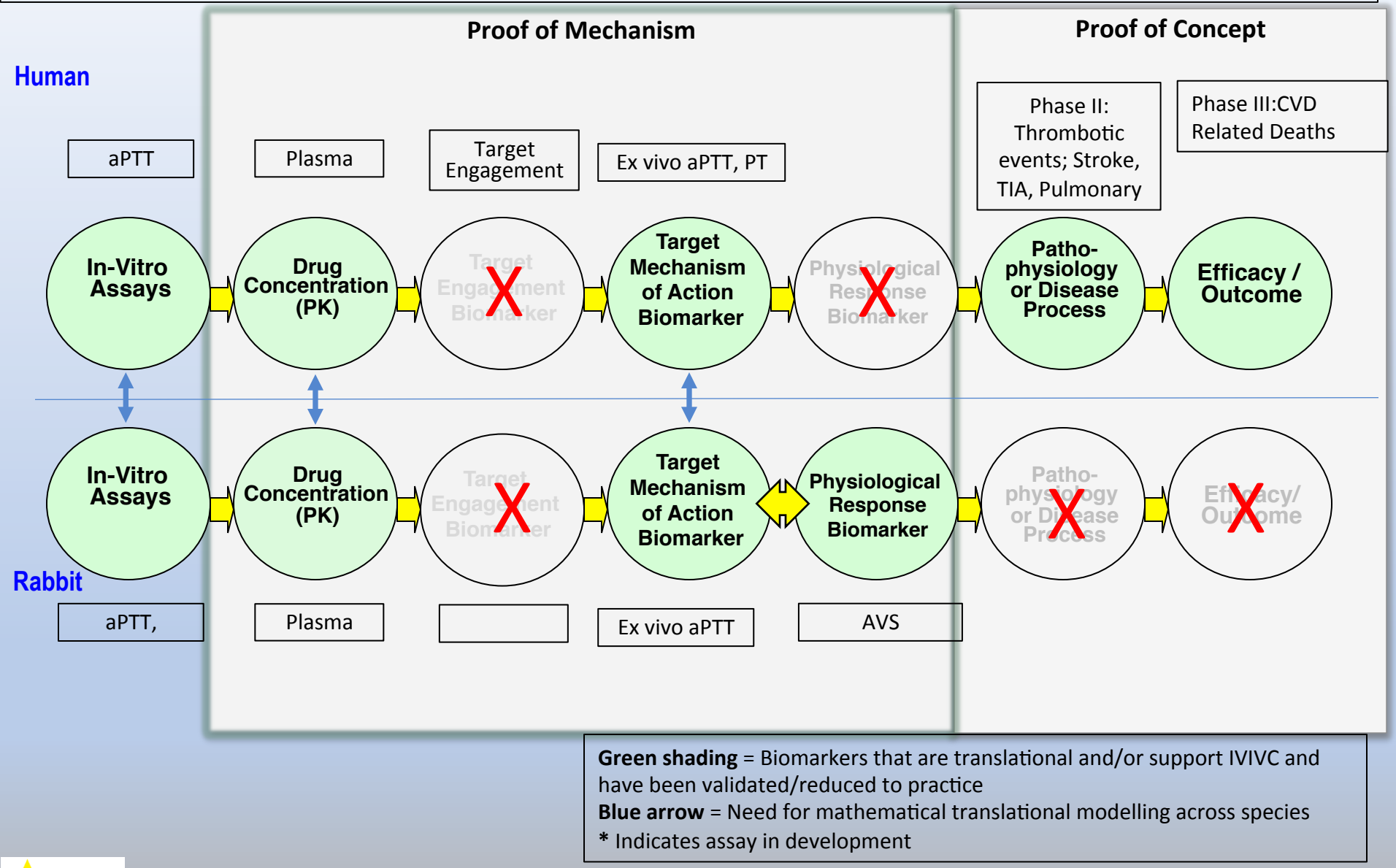


Arrow = Can be measured both in preclinical experiments and in human clinical trials

Explanation of Bubbles

In vitro assay: Measure of in vitro activity, such as potency or affinity
Drug concentration: The pharmacokinetics of the compound typically measured as unbound plasma concentrations and/or target site exposure
Target engagement biomarker: Measurement of compound binding to target, such as with PET or measuring antibody bound to antigen.
Target Mechanism of Action Biomarker: A proximal biochemical or proximal physiological (eg electrophysiological) response as a result of compound interaction with the target
Physiological Response Biomarker: A physiological or tissue response driven by compound activity at the target, but not directly linked to pathophysiology
Pathophysiology or Disease Process: A biochemical response involved in the disease process or activity in an animal model or on a clinical endpoint that serves as an index of the disease process
Efficacy/Outcome: Activity in an animal model of disease that has been demonstrated to predict clinical efficacy or positive effect on a clinical endpoint endorsed by regulators as sufficient for approval

Case Study: Translational Biomarker Bubble Diagram



Green shading = Biomarkers that are translational and/or support IVIVC and have been validated/reduced to practice
Blue arrow = Need for mathematical translational modelling across species
***** Indicates assay in development