



# ICT 2023

28th International  
Congress on Thrombosis

## The perspective of a basic / translational scientist

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# (Forward and reverse) Translational research

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“Facilitate the transition from basic in vitro studies and animal research to applications that improve the human health”... and viceversa... (reverse translation)

Reverse  
translational research



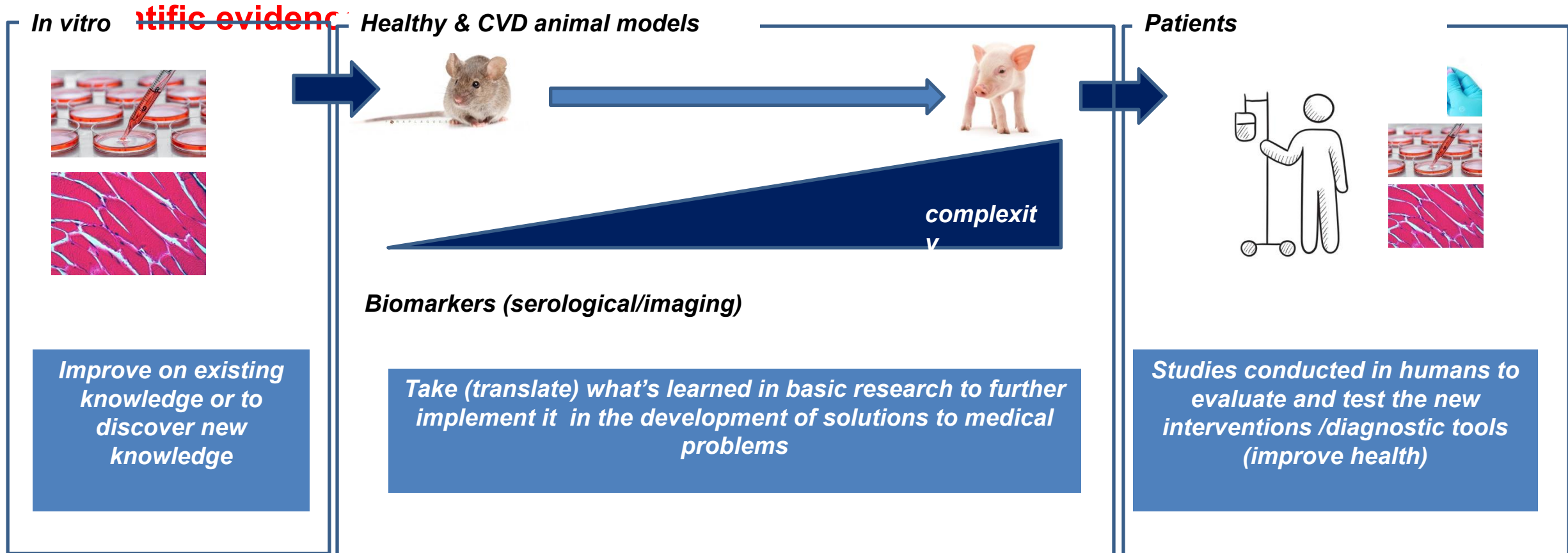
Forward  
translational research

# Types of research...

## Basic (Fundamental) Research

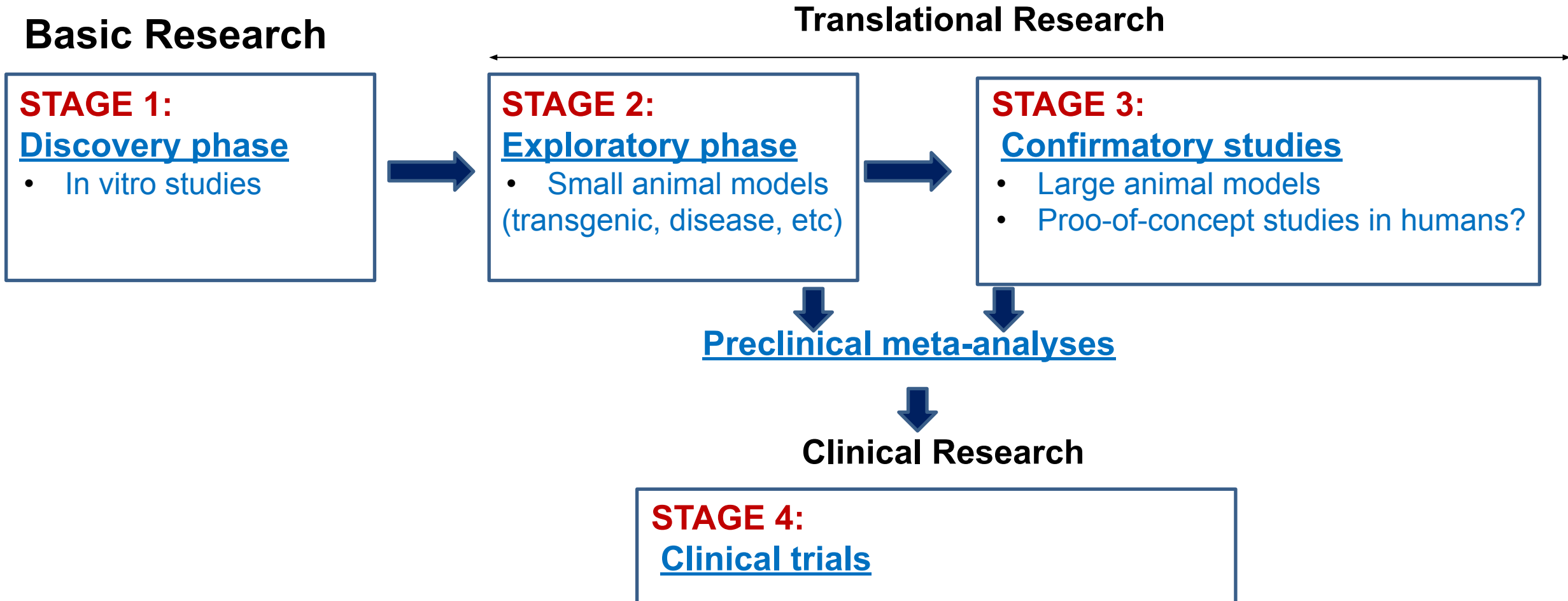
## Translational Research = = Clinical application?

## Clinical Research = Clinical confirmation



# The continuum of the research axis: stages and steps

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# Translational axis

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## STAGE 1: Discovery phase

### GOAL

**LS** UNDERSTAND THE BIOLOGY OF THE CELLS AND MECHANISMS OF DISEASE AND ITS PROGRESSION



**DISCOVER** PROMISING MOLECULE, GENE TARGET OR PATHWAY

**IDENTIFY** A VIABLE **THERAPEUTIC TARGET** or a

**BIOMARKER** and **TECHNIQUES MOST**

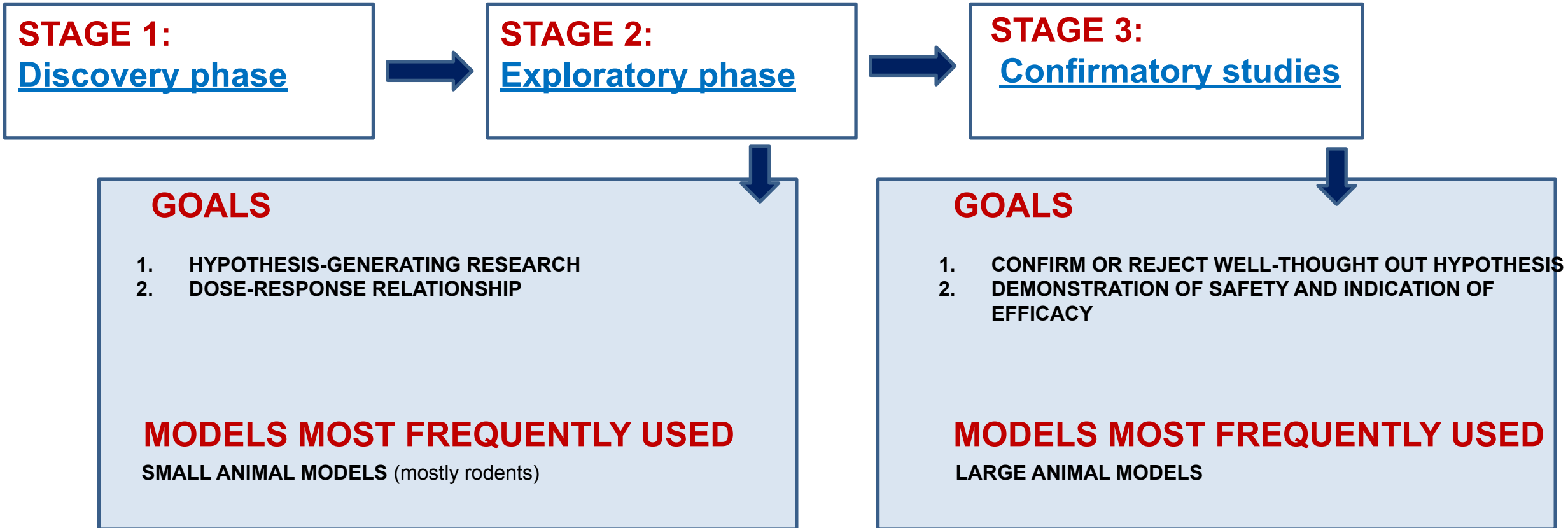
- FREQUENTLY USED**
1. STUDIES IN CELLS (SRVs, omics, etc)
  2. STUDIES IN BLOOD (biomarkers)

# STAGE 2 and 3: Exploratory and confirmatory phases

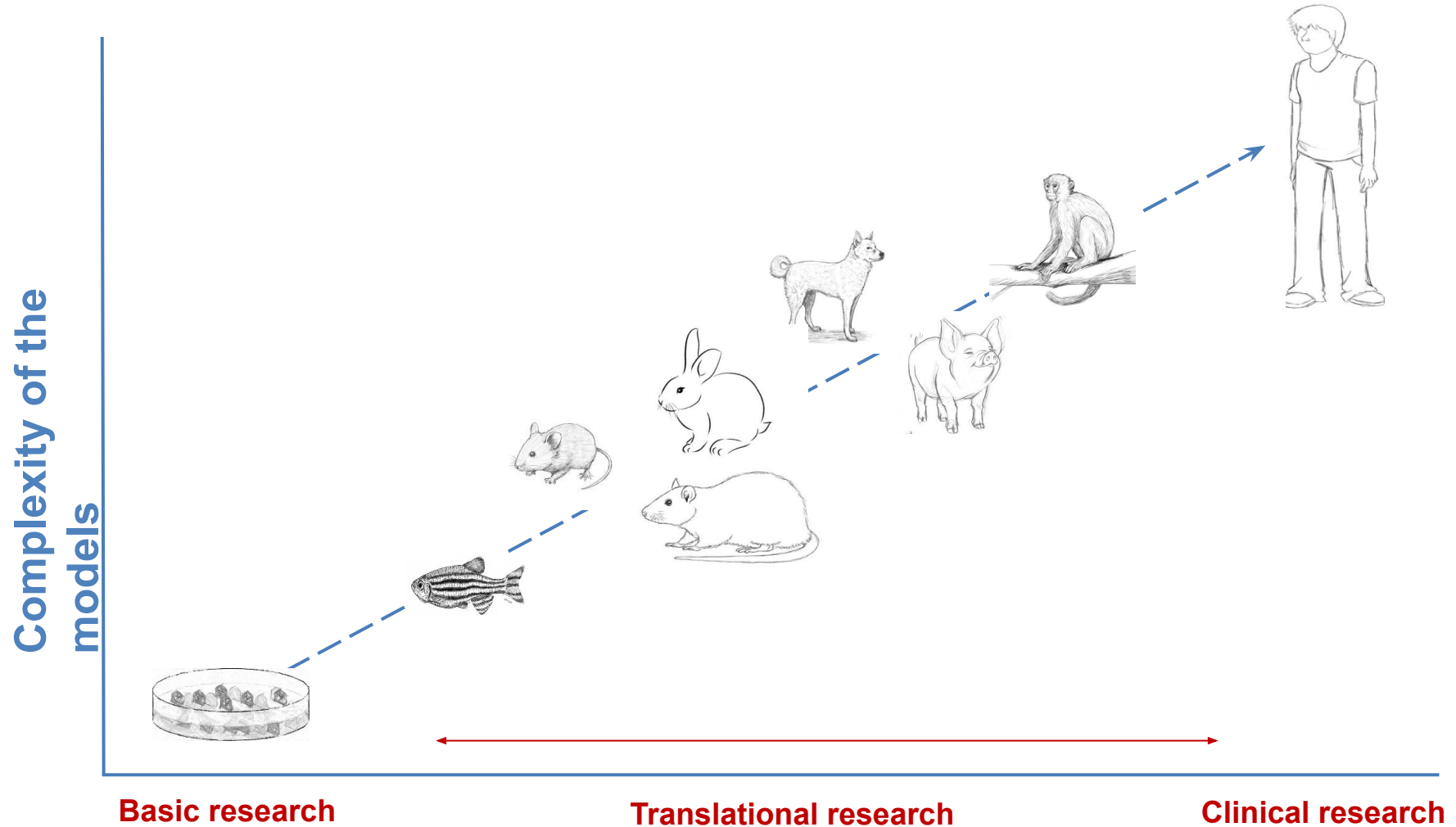
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## Basic Research

## Translational Research



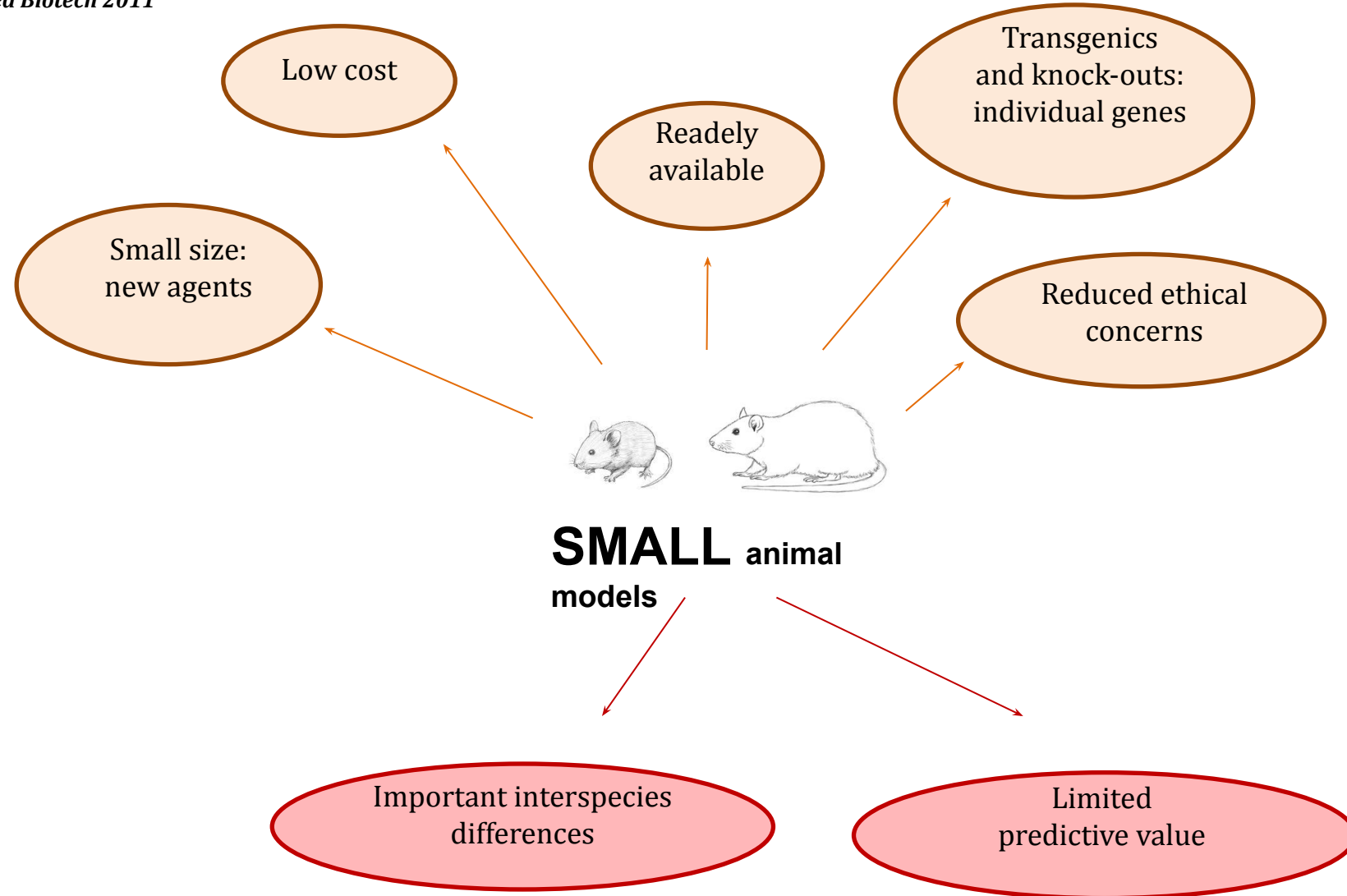
# STAGE 2 and 3: Complexity in the models



Applications of models during drug and biomarkers discovery

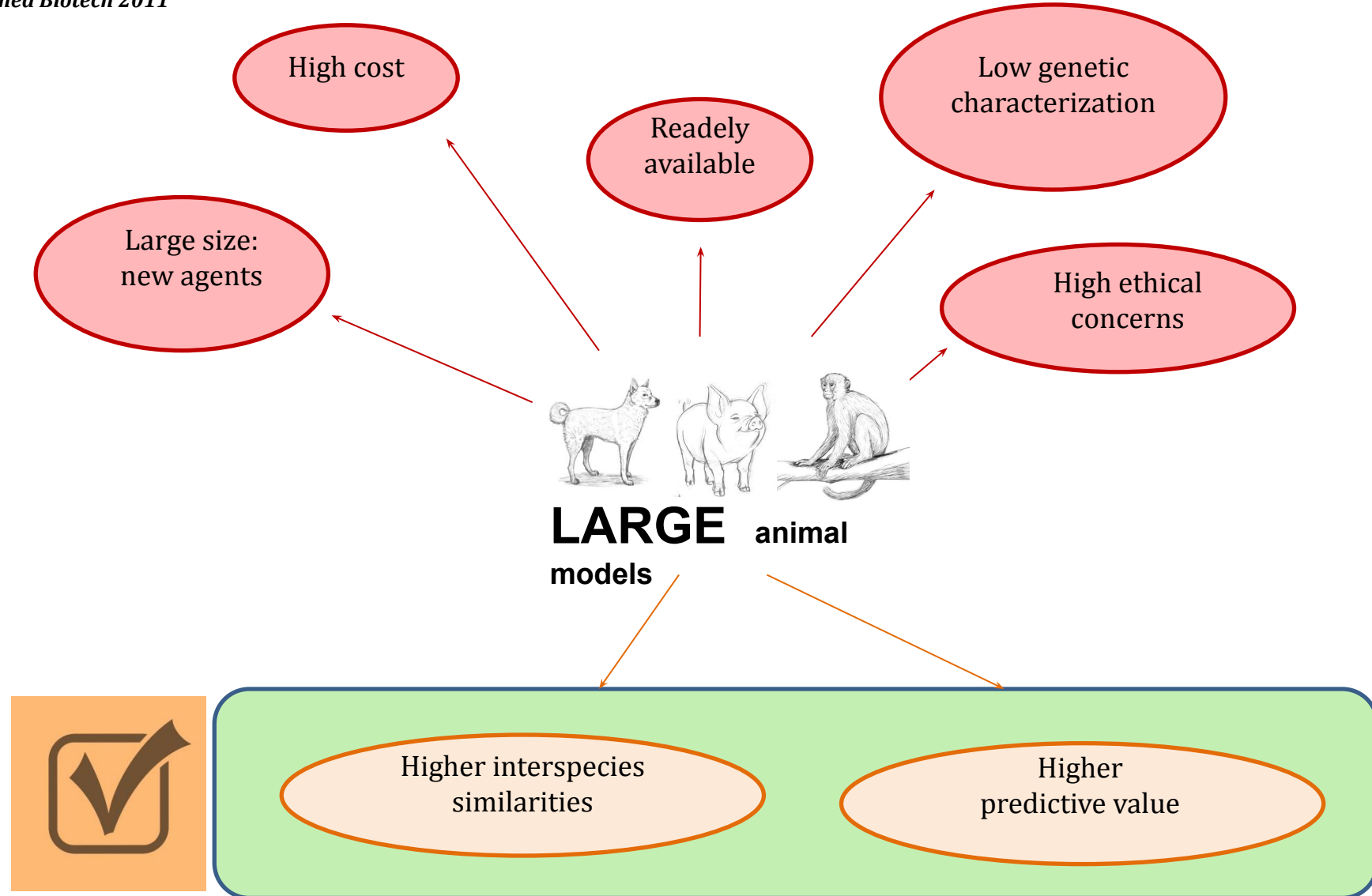
# Choice of the animal

Vilahur G, et al Badimon. *J Biomed Biotech* 2011



# Choice of the animal

Vilahur G, et al Badimon. *J Biomed Biotech* 2011



# Use the right model to address the right questions

Vilabru et al. *Badimon. Cardiovasc Thromb* 2018

## THROMBO



### Differences with humans

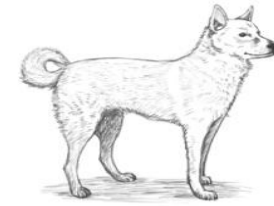
Platelets appear to play a greater role in thrombus formation than in humans

Different digestive metabolic pathways (antithrombotic agents)

- **Accelerated intrinsic cascade** activity because of higher levels of coagulation factors (IX, XI, XII)

- **Iron deficiency** is very frequent increasing erythrocyte rigidity

- GPIIb/IIIa platelet receptor



### Human similarities

**Vascular and platelet responsiveness to thromboxane** and endoperoxide analogues close to humans

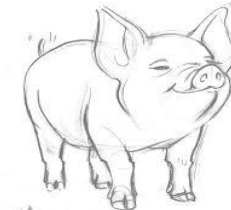
- **Platelet function, coagulation and fibrinolysis**

- Physiological hematologic values
- Flow hemodynamics



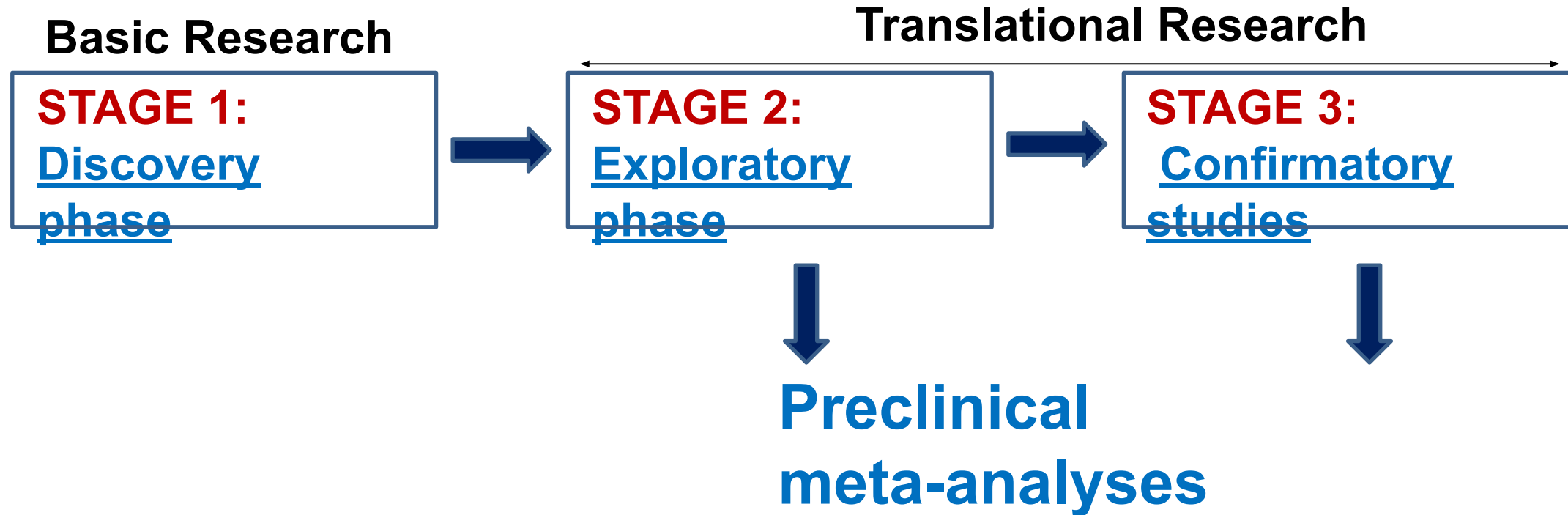
- **Platelet function**, extrinsic coagulation and fibrinolysis

- **Von Willebrand levels** close to humans
- Physiological hematologic values
- **Flow hemodynamics**
- **Low responders to aspirin**



# Translational axis

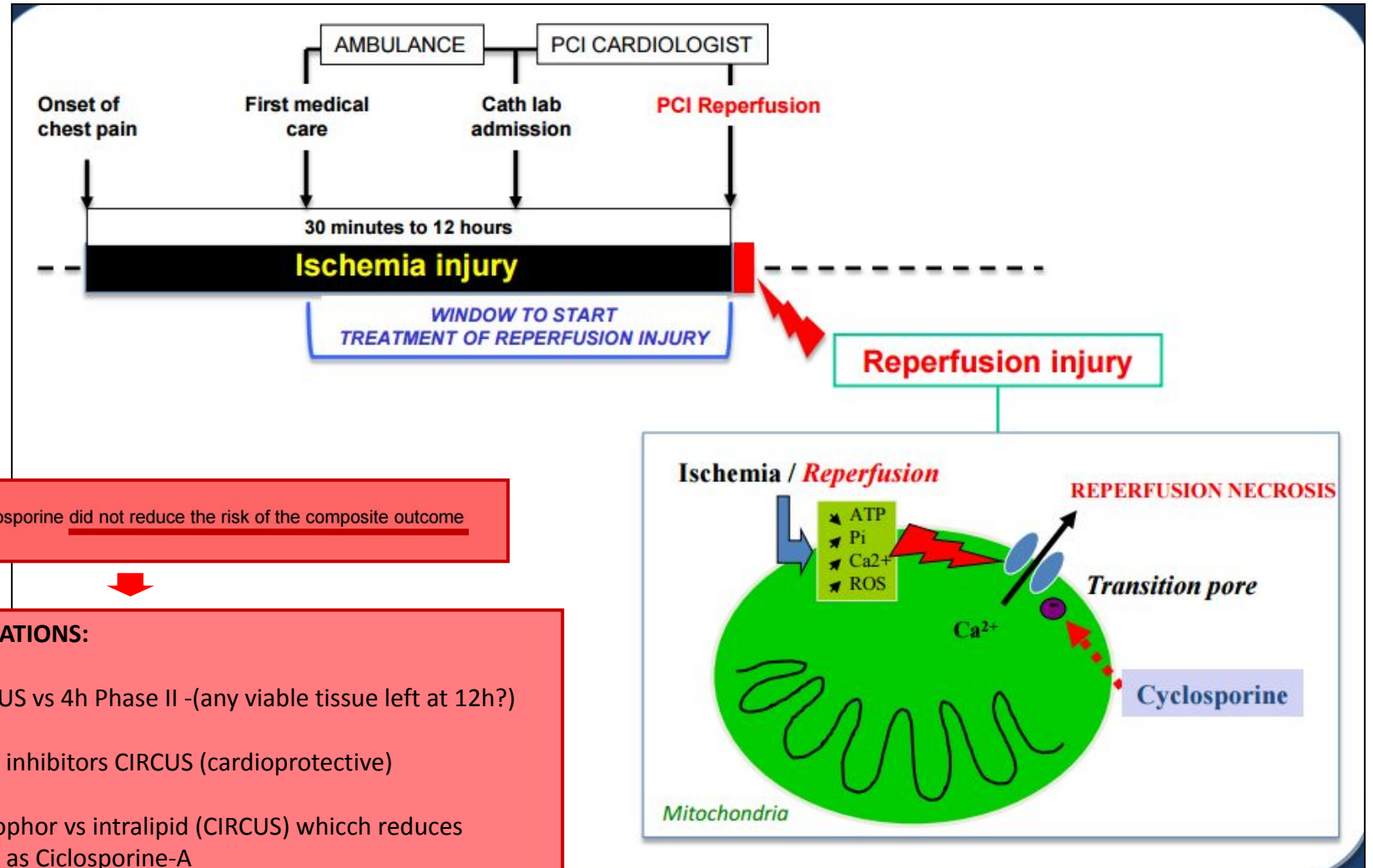
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# In CARDIOPROTECTION: The only PHASE III clinical trial ... NEUTRAL



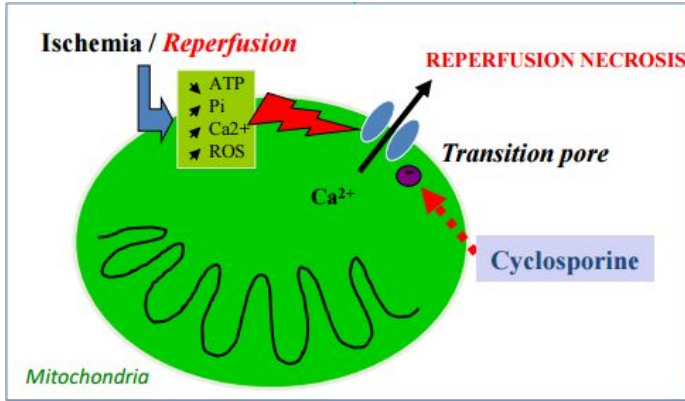
Michel OVIZE et al *N Eng J Med* 2015



In anterior STEMI, cyclosporine did not reduce the risk of the composite outcome

- POTENTIAL EXPLANATIONS:**
- 12h symptoms CIRCUS vs 4h Phase II -(any viable tissue left at 12h?)
  - Higher use of P2Y12 inhibitors CIRCUS (cardioprotective)
  - Vehicle used: cremophor vs intralipid (CIRCUS) which reduces infarct size as much as Cyclosporine-A

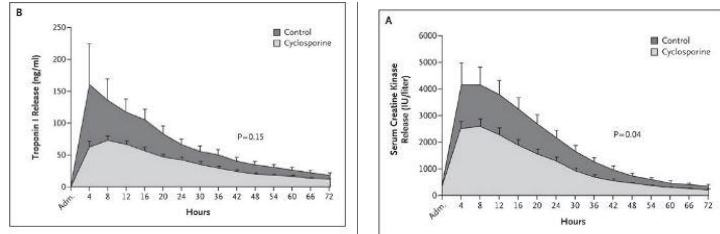
# CIRCUS: no consistent pre-clinical data



## CONSISTENT DATA



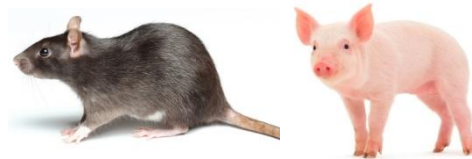
Argaud et al *J Mol Cell Cardiol* **2005**  
Lim et al *Cardiovasc Res* **2007**



Piot et al *N Eng J Med* **2008**



## INCONSISTENT DATA



Karlsson et al *J Cardiovasc Pharmacol Ther* **2010**  
Sheu et al *Int J Cardiol* **2011**



## INCONSISTENT DATA

*Cardiovasc Pharmacol Ther* **2012**  
De Paulis et al *Basic Res Cardiol* **2013**



**2012 - 2015**



**BJP** British Journal of Pharmacology

## REVIEW

**Cyclosporin variably and inconsistently reduces infarct size in experimental models of reperfused myocardial infarction: a systematic review and meta-analysis**

WY Lim<sup>1</sup>, CM Messow<sup>2</sup> and C Berry<sup>1</sup>

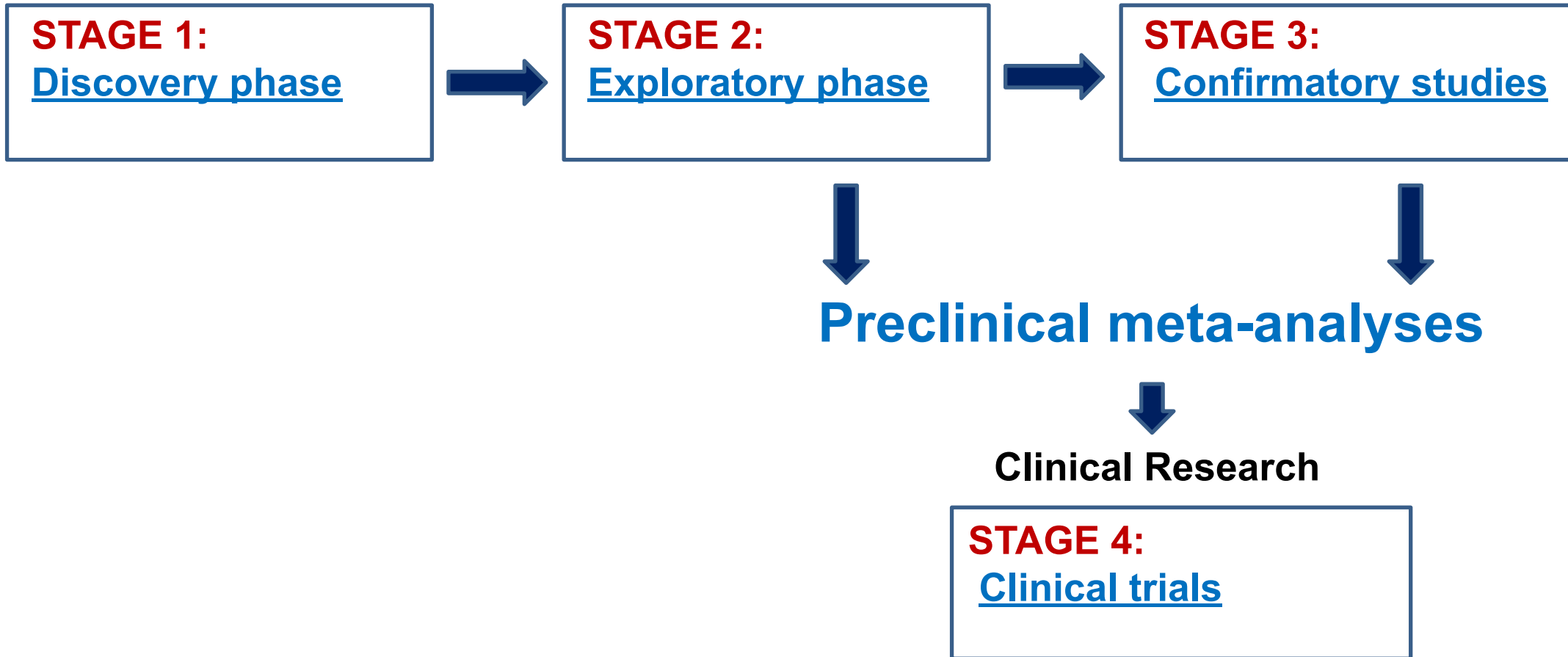
<sup>1</sup>BHF Glasgow Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK, and <sup>2</sup>Robertson Centre for Biostatistics, University of Glasgow, Glasgow, UK

*Brisith J Pharmacol* **2012**



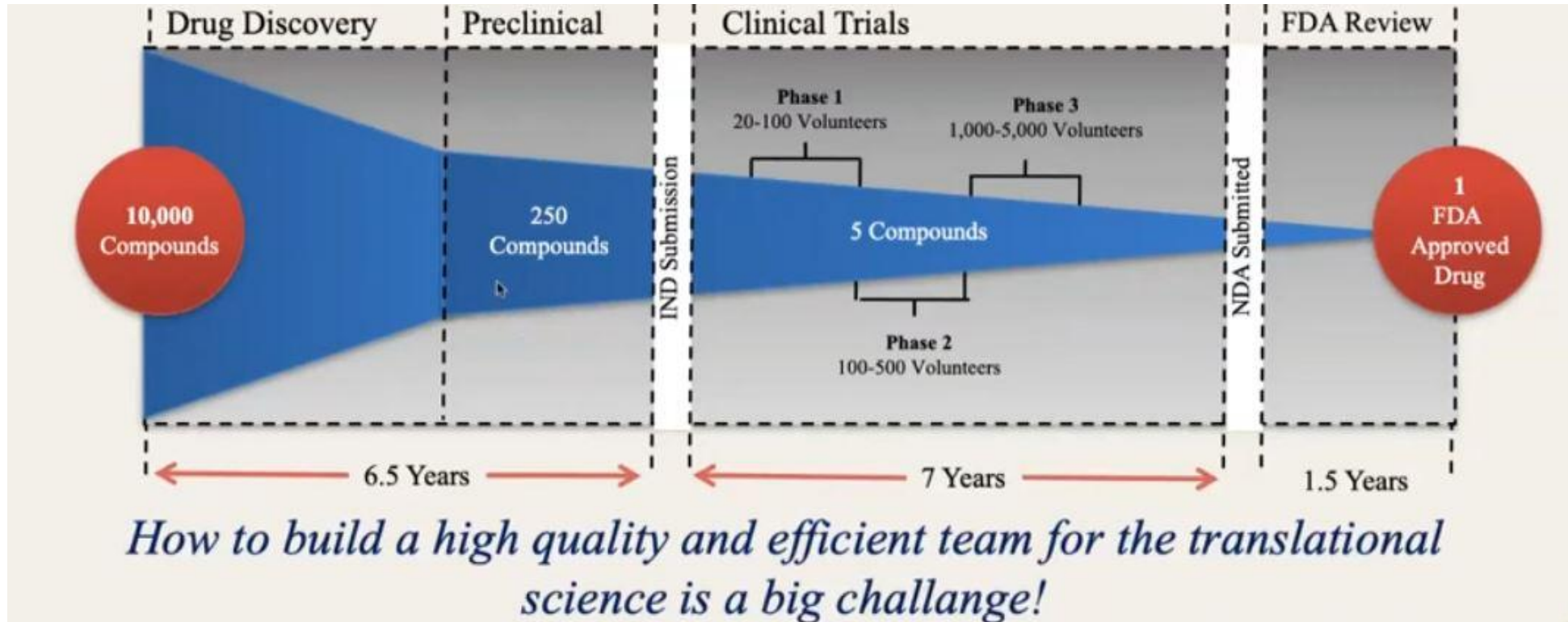
## Basic Research

## Translational Research



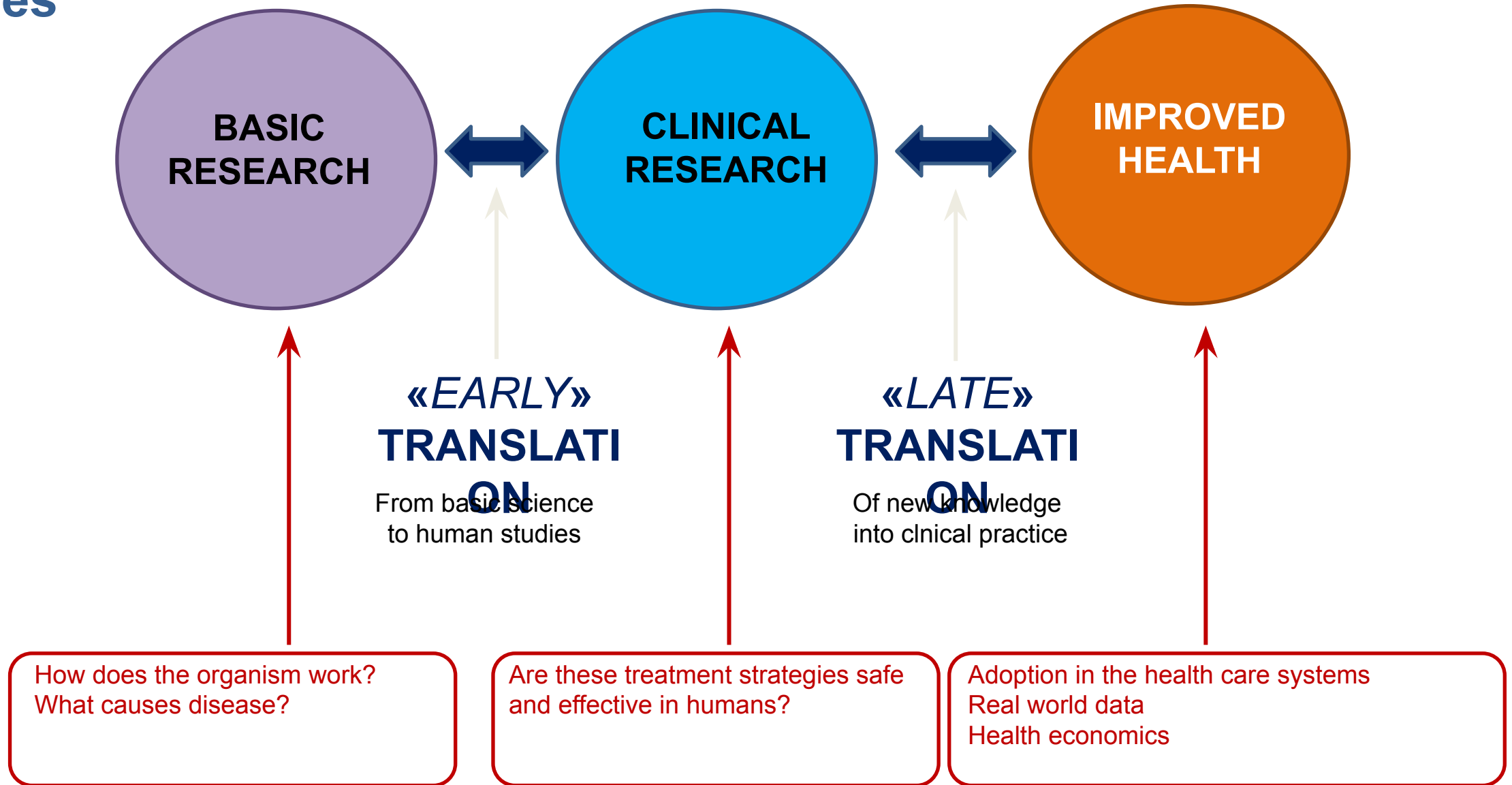
# Drug development is time consuming and money during process

Every 10,000 discovered compound it takes an estimated average of 15 years for only 1 compound to be FDA approved

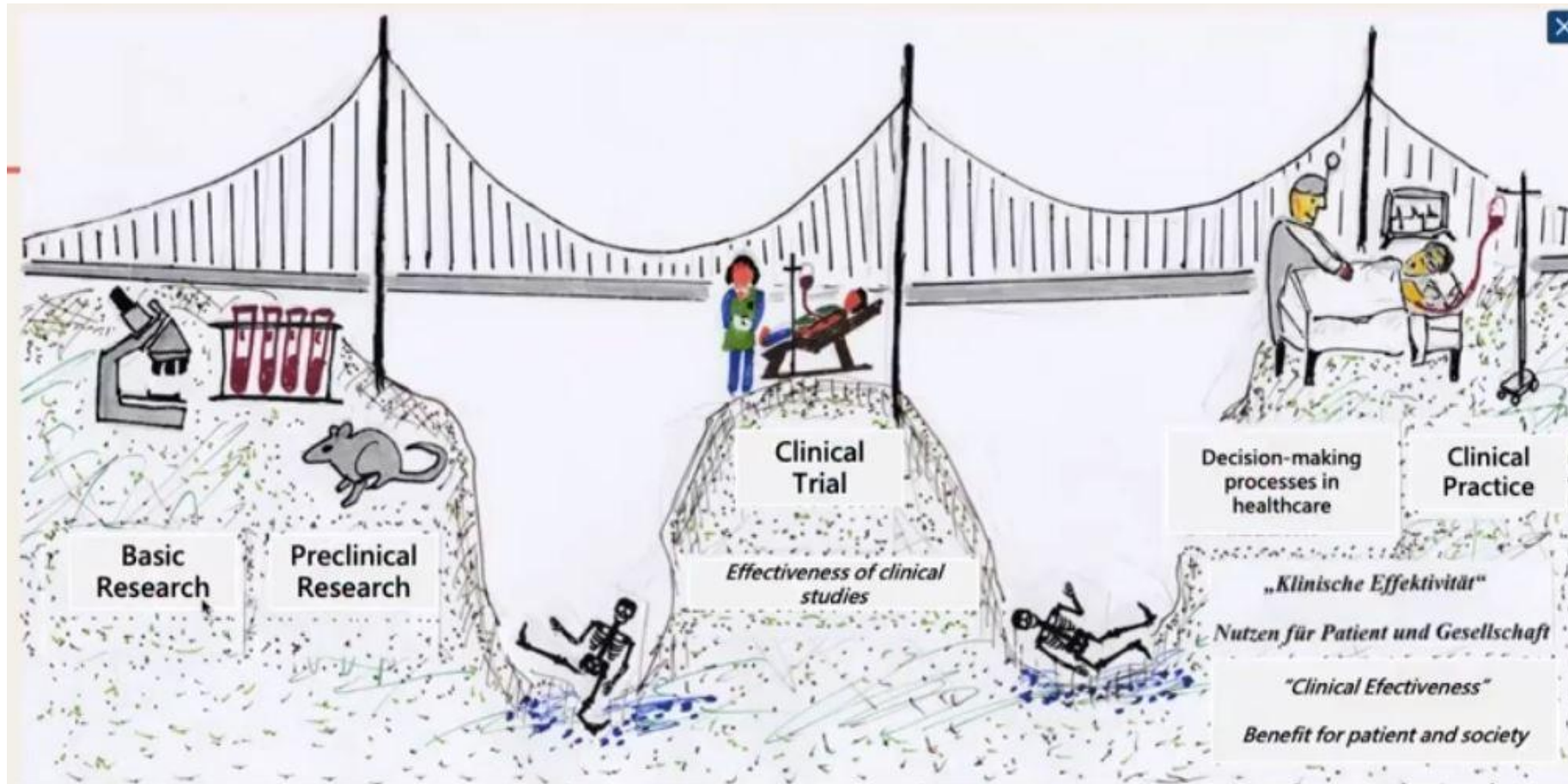


It takes an estimated average of 15 years for only 14% of new scientific discoveries to enter day-to-day clinical practice

# Translational research: *Early* and *Late* translation phases

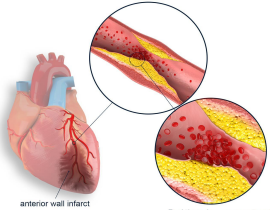


# Death valley in translational medicine

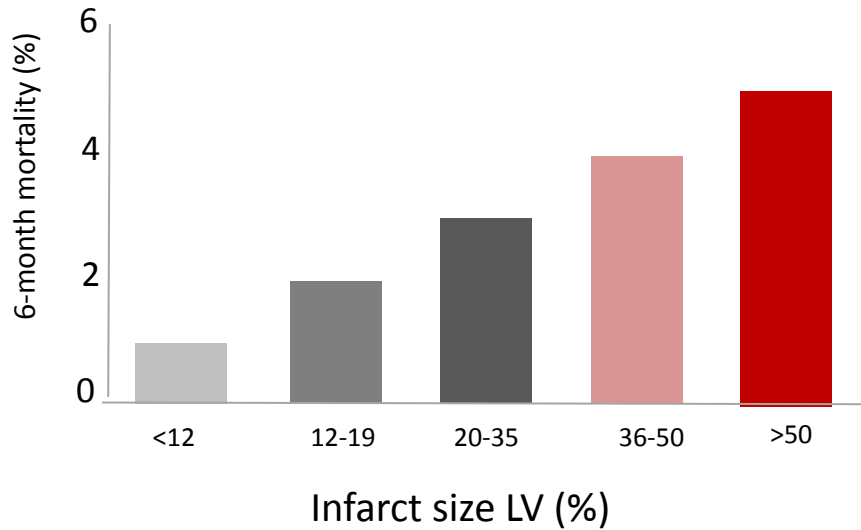


# My experience of a successful journey in translational medicine

**MEDICAL NEED: REDUCE DEATH**

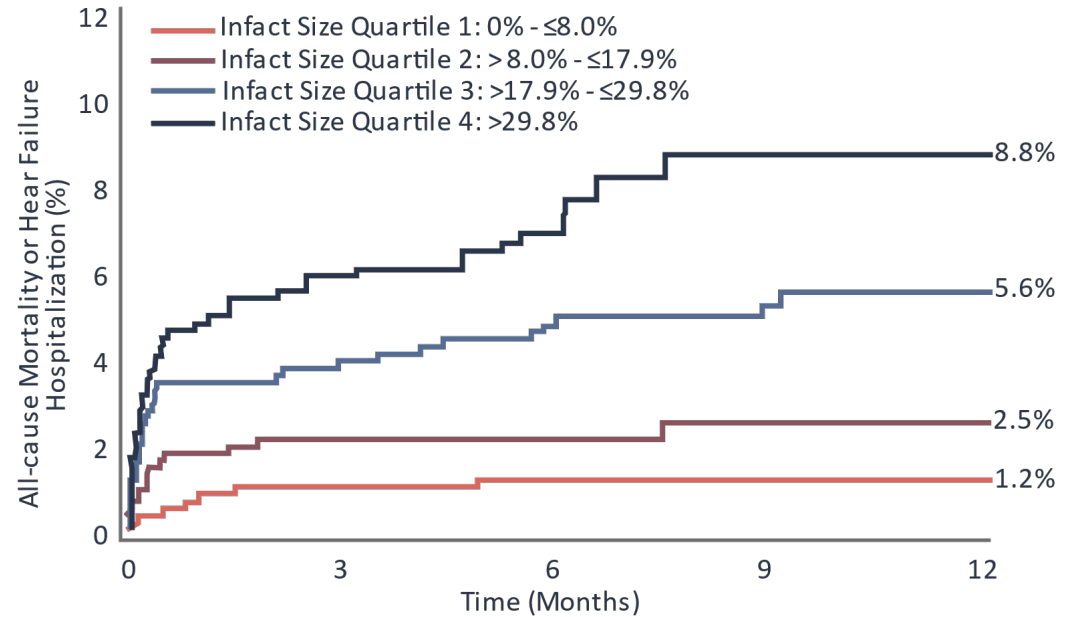


## Infarct size and Prognosis



Gibbons et al, *J Am Coll Cardiol* 2004

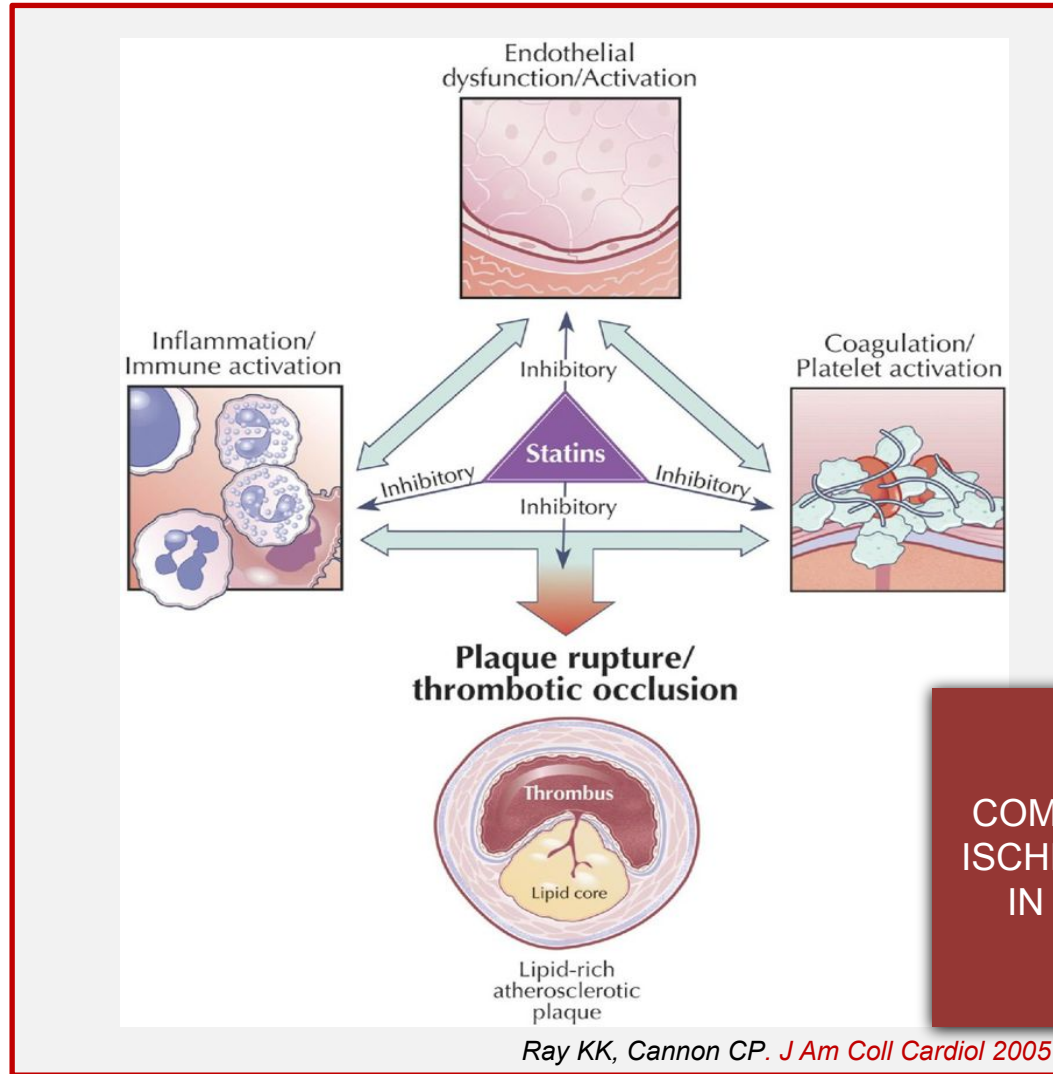
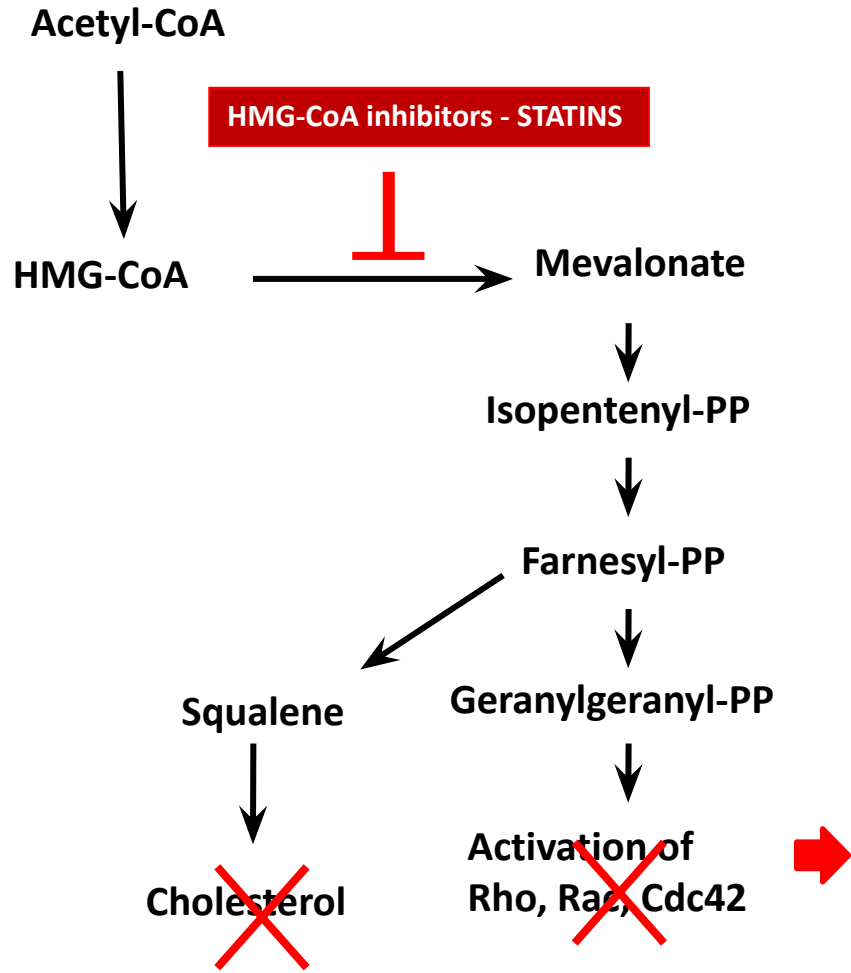
## Infarct size and Heart Failure Hospitalization



Stone et al *J Am Coll Cardiol* 2016

# My experience of a successful journey in translational medicine.

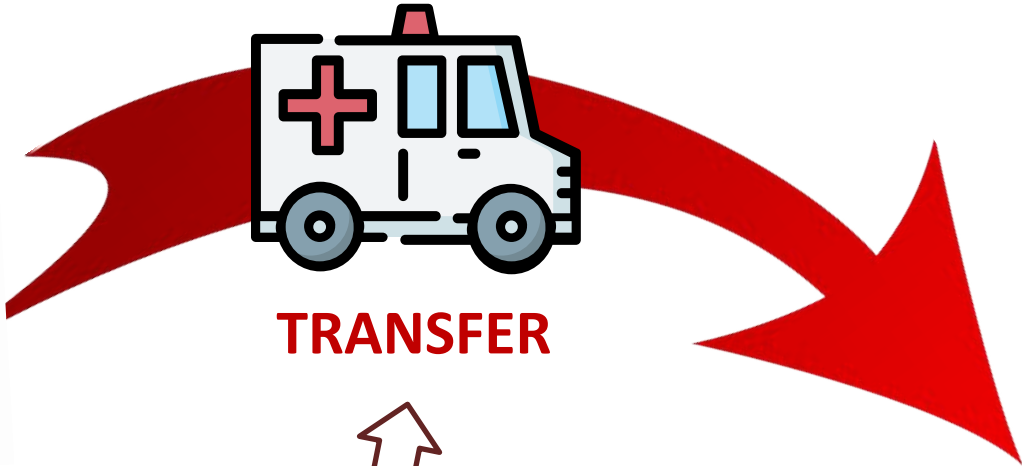
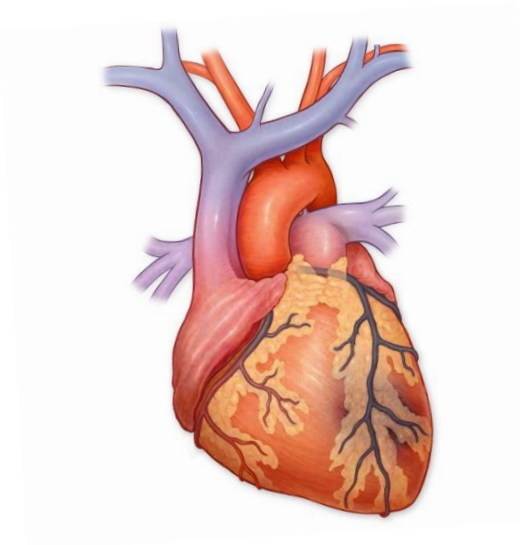
## BASIC KNOWLEDGE: THE POWER OF STATINS



*In vitro studies since 1998*

COMPONENTS INVOLVED IN ISCHEMIC CARDIAC DAMAGE IN THE SETTING OF ACS

# SHIELD4Heart: the new standard for the first line of ACS treatment



**TRANSFER**

**Cath lab for PCI**



**New formulation of statin (iv)  
Drug repositioning  
rapid onset of action**



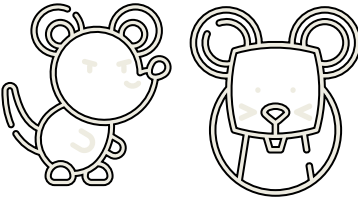


# Translational approach: from bench to bedside

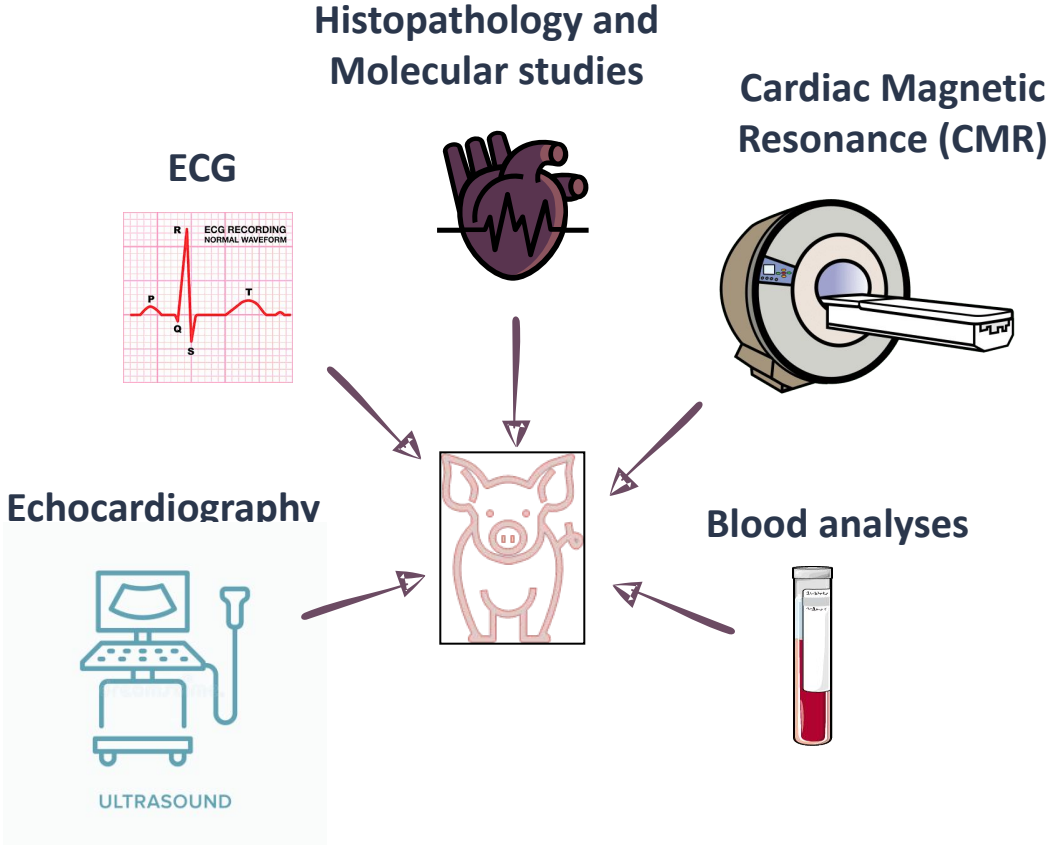
## Cell culture mechanistic studies



## Proof-of-concept studies



## Highly translational animal model



## Clinical testing (early 2024)



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*Casa del corazón - Madrid 25 Noviembre  
2022*