

Translational Safety in Drug Development – Innovations and Challenges

**A Joint Regional Chapter Meeting with SCCSOT and
the Critical Path Institute**



Accelerating Pathways to a Healthier World

Founded in 2004








Located in Tucson, Arizona, USA

The Critical Path Institute (C-Path) is an independent, non-profit public-private partnership with the Food and Drug Administration (FDA) created under the auspices of the FDA's Critical Path Initiative program.

The Critical Path Institute is a catalyst in the development of new approaches that advance medical innovation and regulatory science. We achieve this by leading teams that share data, knowledge, and expertise resulting in sound, consensus based science.

Critical Path Institute Consortia

Seven global consortia collaborating with 1,000+ scientists and 41 companies

 <p>CAMD CRITICAL PATH INSTITUTE</p>	<p>Coalition Against Major Diseases UNDERSTANDING DISEASES OF THE BRAIN</p>
 <p>CPTR</p>	<p>Critical Path to TB Drug Regimens TESTING DRUG COMBINATIONS</p>
 <p>CRITICAL PATH INSTITUTE MS National Multiple Sclerosis Society</p>	<p>Multiple Sclerosis Outcome Assessments Consortium DRUG EFFECTIVENESS IN MS</p>
 <p>PKD CONSORTIUM CRITICAL PATH INSTITUTE</p>	<p>Polycystic Kidney Disease Consortium NEW IMAGING BIOMARKERS</p>
 <p>PRO CONSORTIUM CRITICAL PATH INSTITUTE</p>	<p>Patient-Reported Outcome Consortium DRUG EFFECTIVENESS</p>
 <p>ePRO CONSORTIUM CRITICAL PATH INSTITUTE</p>	<p>Electronic Patient-Reported Outcome Consortium DRUG EFFECTIVENESS</p>
 <p>PSTC CRITICAL PATH INSTITUTE</p>	<p>Predictive Safety Testing Consortium DRUG SAFETY</p>



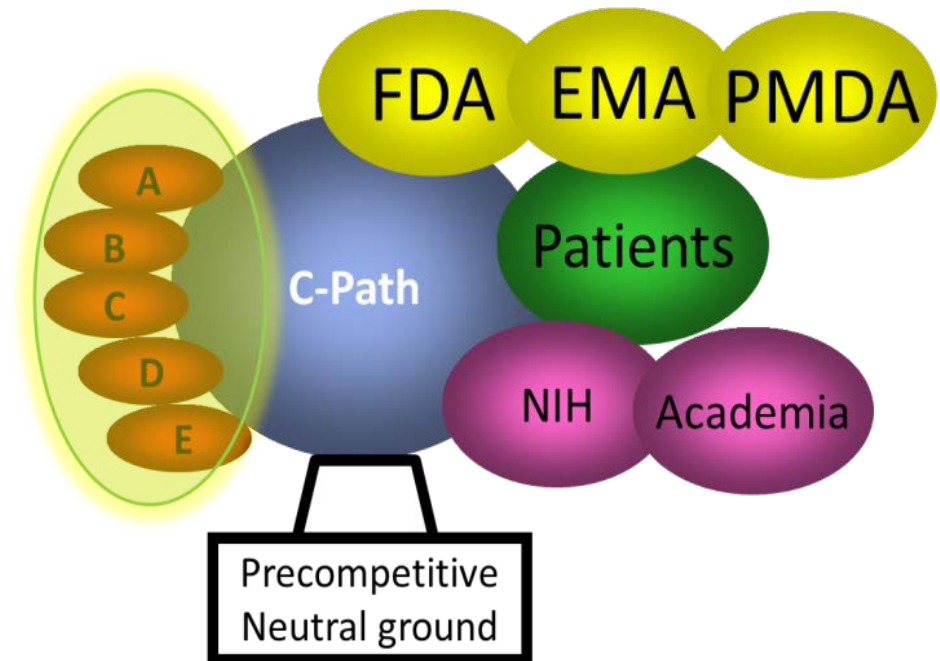
- ✓ Biomarkers
- ✓ Clinical Outcome Assessment Instruments
- ✓ Clinical Trial Simulation Tools
- ✓ Data Standards



Act as a trusted, neutral third party

Convene scientific consortia of industry, academia, and government for pre-competitive sharing of data/expertise

- The best science
- The broadest experience
- Active consensus building
- Shared risk and costs



Enable iterative EMA/FDA/PMDA participation in developing new methods to assess the safety and efficacy of medical products

- Official regulatory recognition through “qualification” of Novel Methodologies and Drug Development Tools and acceptance of data standards

Translational Safety in Drug Development

The role of safety biomarkers in predictive toxicology

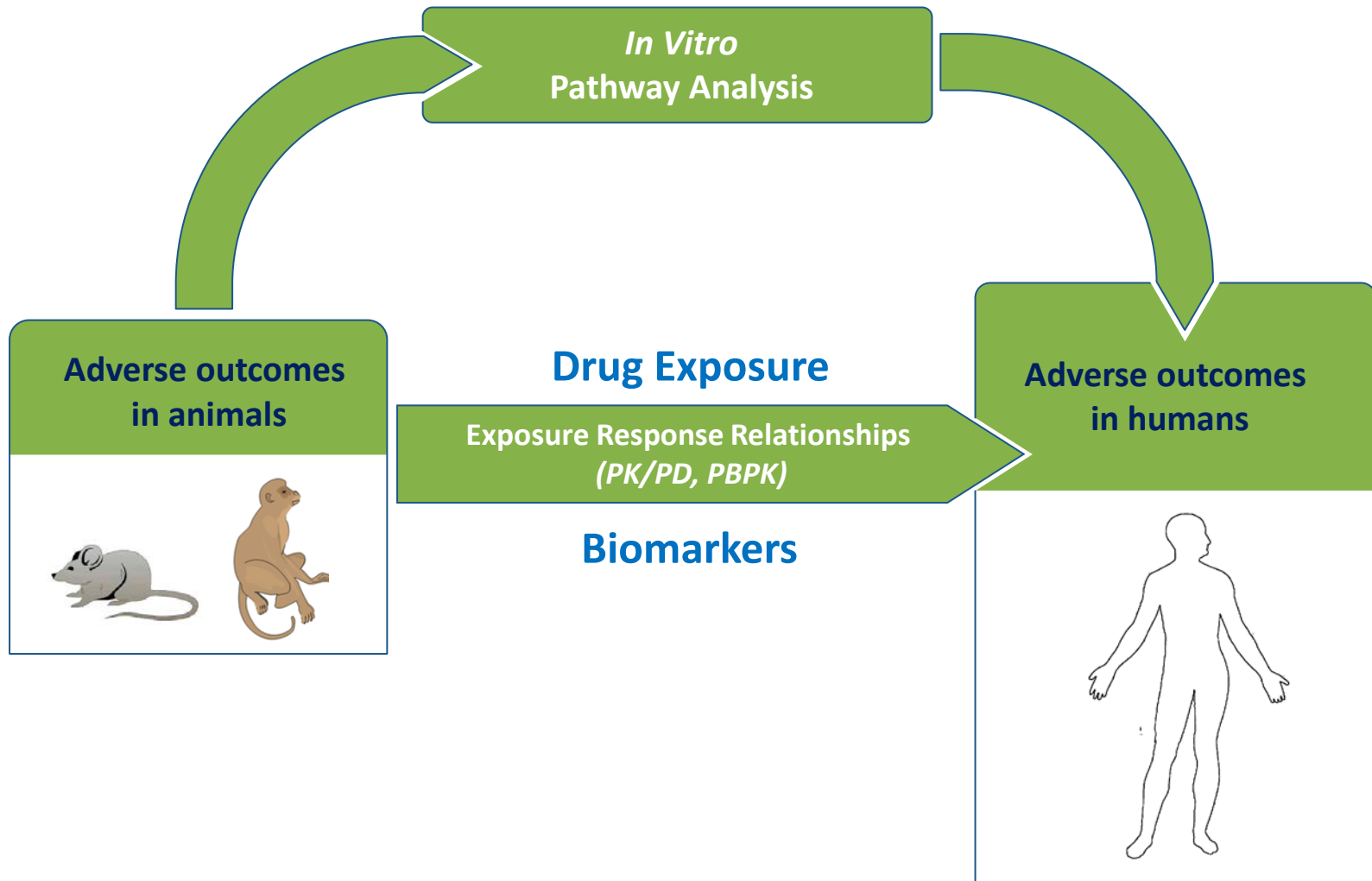
John-Michael Sauer, Ph.D.

Executive Director, Predictive Safety Testing Consortium
Critical Path Institute

Translational Safety:

- A sexy title for nonclinical and clinical safety assessment used to support drug discovery and development
- Is an overarching term encompassing the steps that must be taken to move (or translate) nonclinical safety findings into predicting adverse outcomes in humans

Translational Safety



Challenges

- For the last 4 decades our approach to safety assessment has not really changed
- It is “easy” to follow the regulatory guidance and move to the next milestone
- Regulations have resulted in the stagnation of the science for safety assessment

Innovations

- *In vitro* assay can be used to direct *in vivo* studies (hERG and genetic toxicology)
- There is a realization that we need to have a non-traditional approach to safety assessment
- Regulators have promoted alternative approaches to traditional safety assessment approaches

Idiosyncratic Toxicities:

- Unanticipated or unexplainable toxicity, are referred to as *idiosyncratic*.
- In nearly all cases, the failure of preclinical studies in animals to predict human toxicity can be attributed to interspecies differences that are either known or not yet characterized.
- Major distinction between unexpected toxicity that occurs in a large portion of patients versus toxicities that are rare.

Challenges in Translational Safety

Examples of where human safety issues were not anticipated from nonclinical studies:

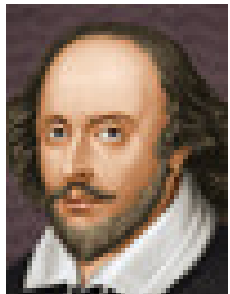
Toxic Drug	Disease	Mechanism of Action	Side Effect/Toxicity
cerivastatin	cardiovascular disease	HMG-CoA reductase inhibitor	rhabdomyolysis
trogliptazone	diabetes	PPAR _γ agonist	liver damage
astemizole	allergy	H ₁ receptor blocking drug	cardiac dysfunction
rofecoxib	inflammatory pain	COX-2 inhibitor	heart attack
dexfenfluramine	obesity	serotonin reuptake inhibitor	heart valve damage

Why are there safety prediction failures?

We lack the tools and understanding required to implement a true translational safety strategies in drug discovery and development.

The missing or incomplete tools in my toolbox:

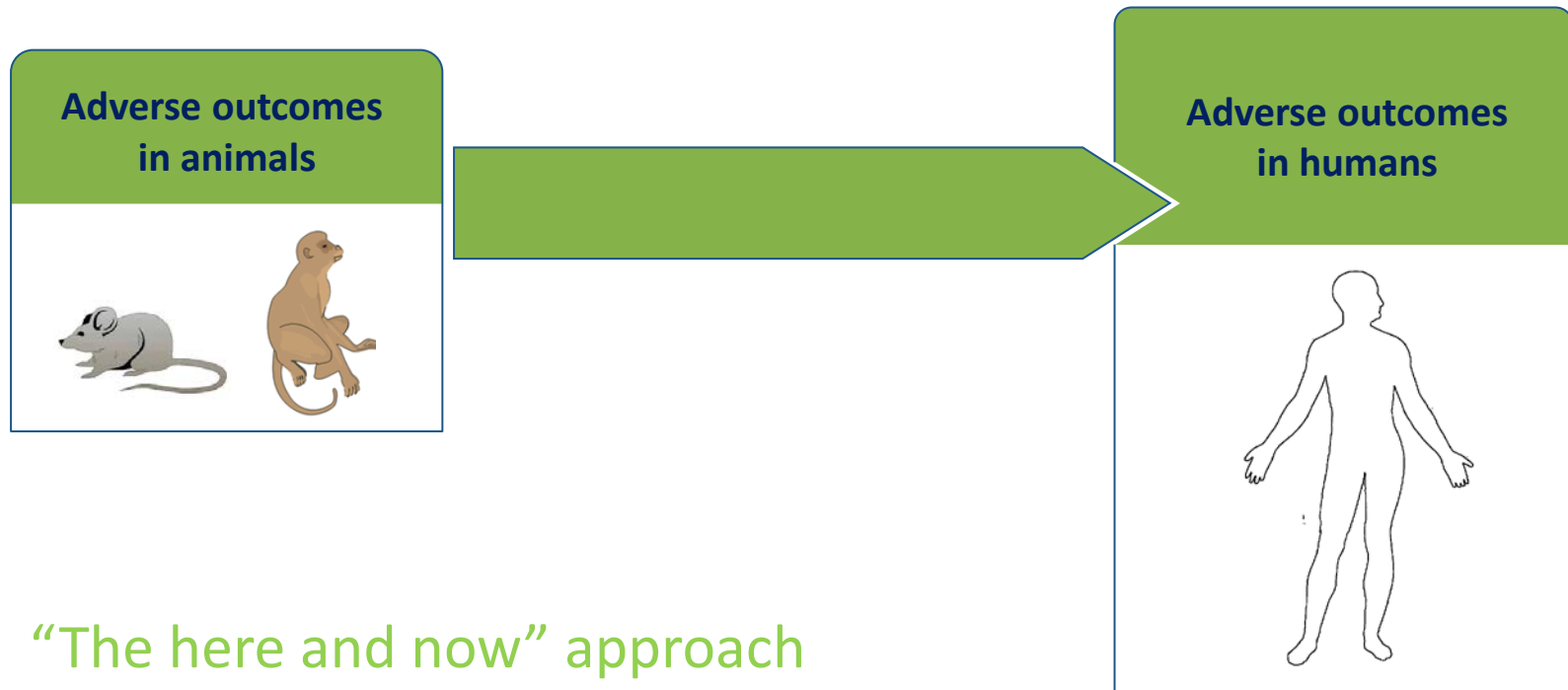
- *In vitro* assays to predict human safety
- Well characterized selective and sensitive safety biomarkers
- An integrated understanding of systems toxicology



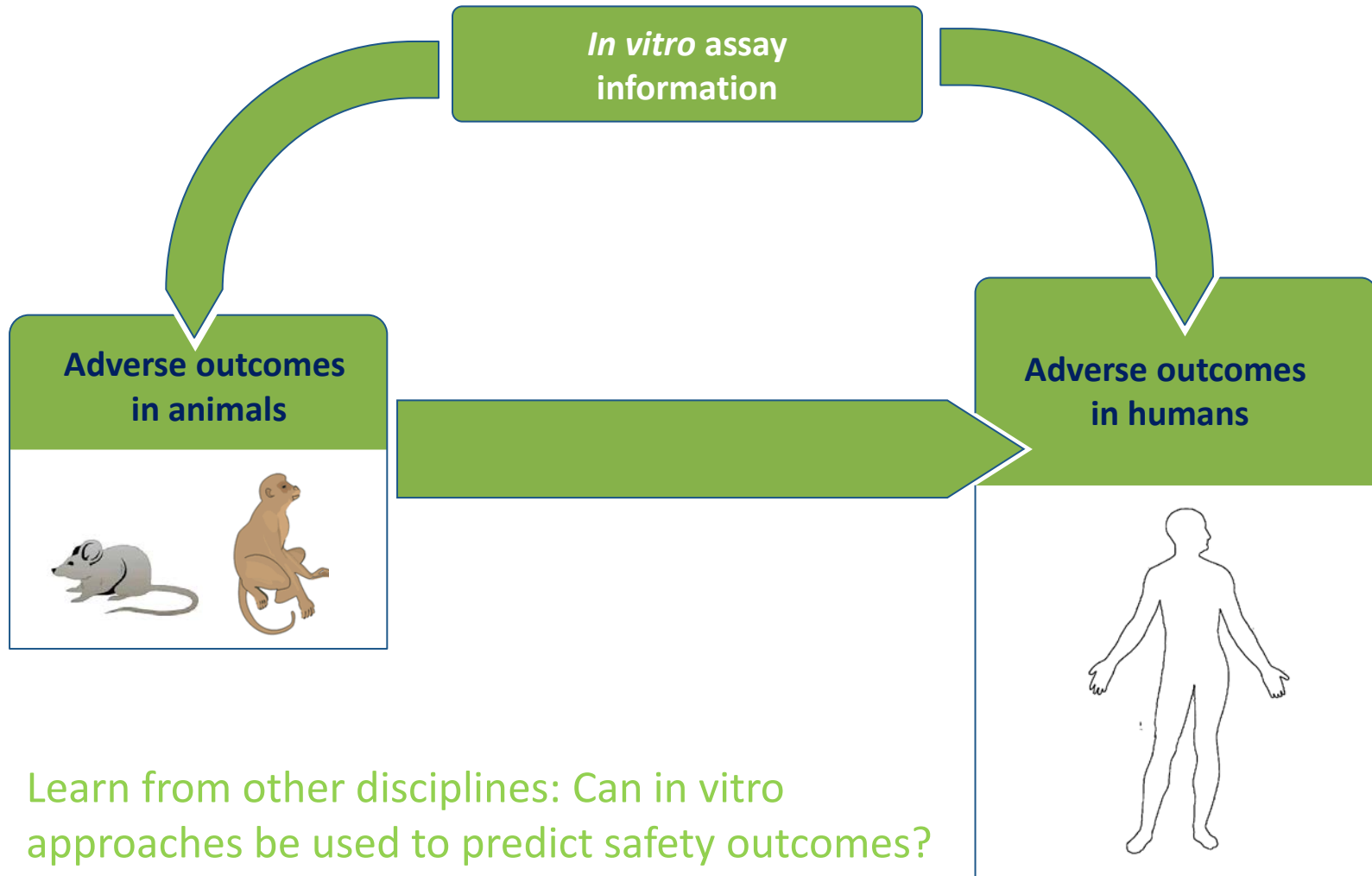
“The fault, dear Brutus, is not in our stars, but in ourselves.”
— *William Shakespeare, Julius Caesar*

What do we want to accomplish?

Improving our current approaches to safety assessment



Translational Safety: **In Vitro** Tools



Learn from other disciplines: Can in vitro approaches be used to predict safety outcomes?

In vitro toxicology systems

Hypothesis: Mechanistic human *in vitro* safety tools can increase our ability to predict human safety issues during drug development; and, these *in vitro* assays will eventually supplant the need for animal testing

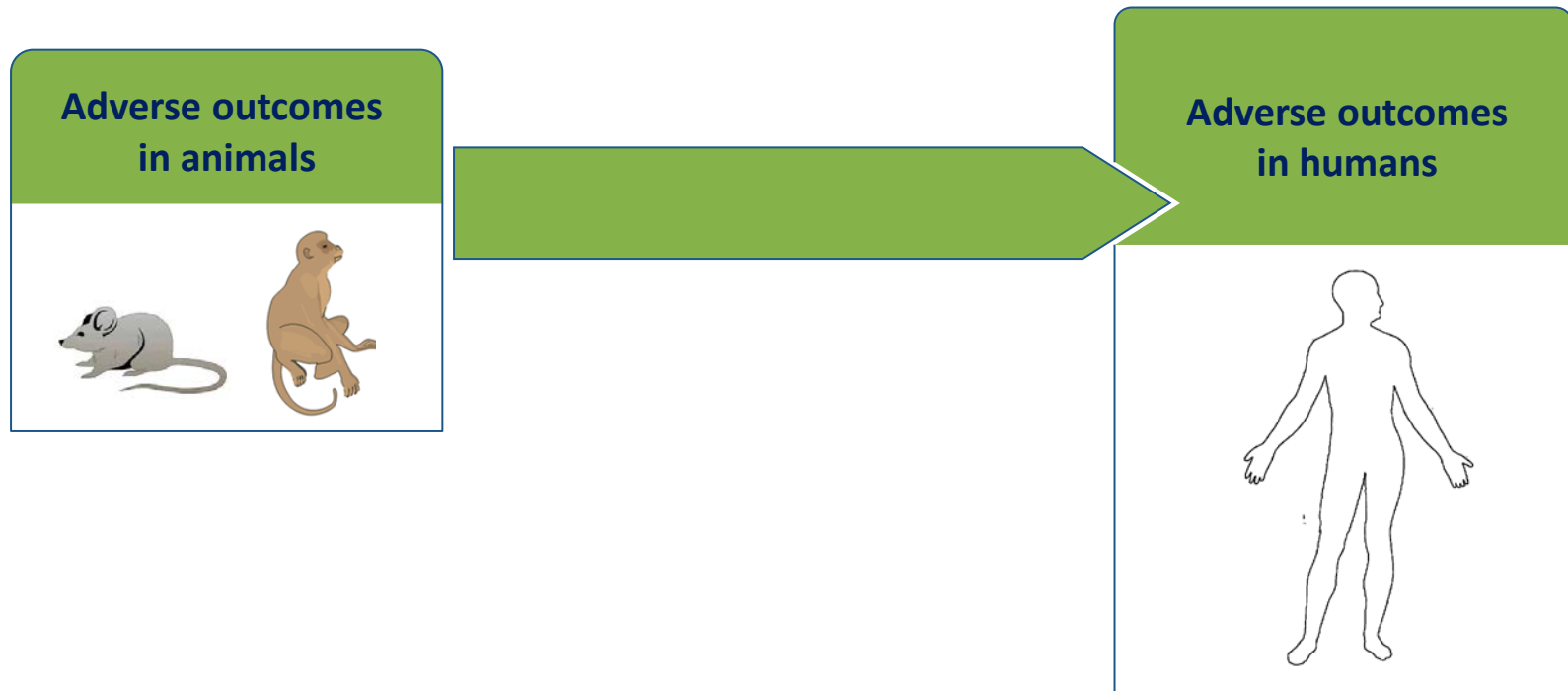
Two approaches to human biology based in vitro safety tools

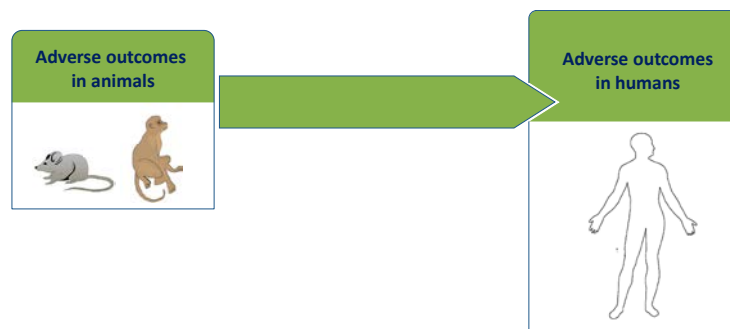
- Organ based tools such as organ on a chip (complex cultures)
- Pathway based tools that are organ agnostic but can predict outcomes across multiple organs

In vitro tool must be put in to perspective around other information (systems toxicology) likely utilizing computational approaches

- *Does the FDA agree that the introduction of these in vitro tools into the current safety assessment paradigm are meaningful steps towards the agency's goals to modernize toxicology and improve predictive safety tools?*

Systems Toxicology





Systems Toxicology

Integrated understanding of relationship of ALL safety and non-safety data

Pharmacology – ADME – Toxicology – Physiology

Systems toxicology

- The study of effects of toxicants on molecular/cellular networks, as defined in systems biology
- Systems toxicology also encompasses those related processes and pathways that contribute to toxicant exposure (i.e., fate, absorption, distribution, metabolism) and toxicant effects (beyond the cell – i.e., whole organisms and populations).

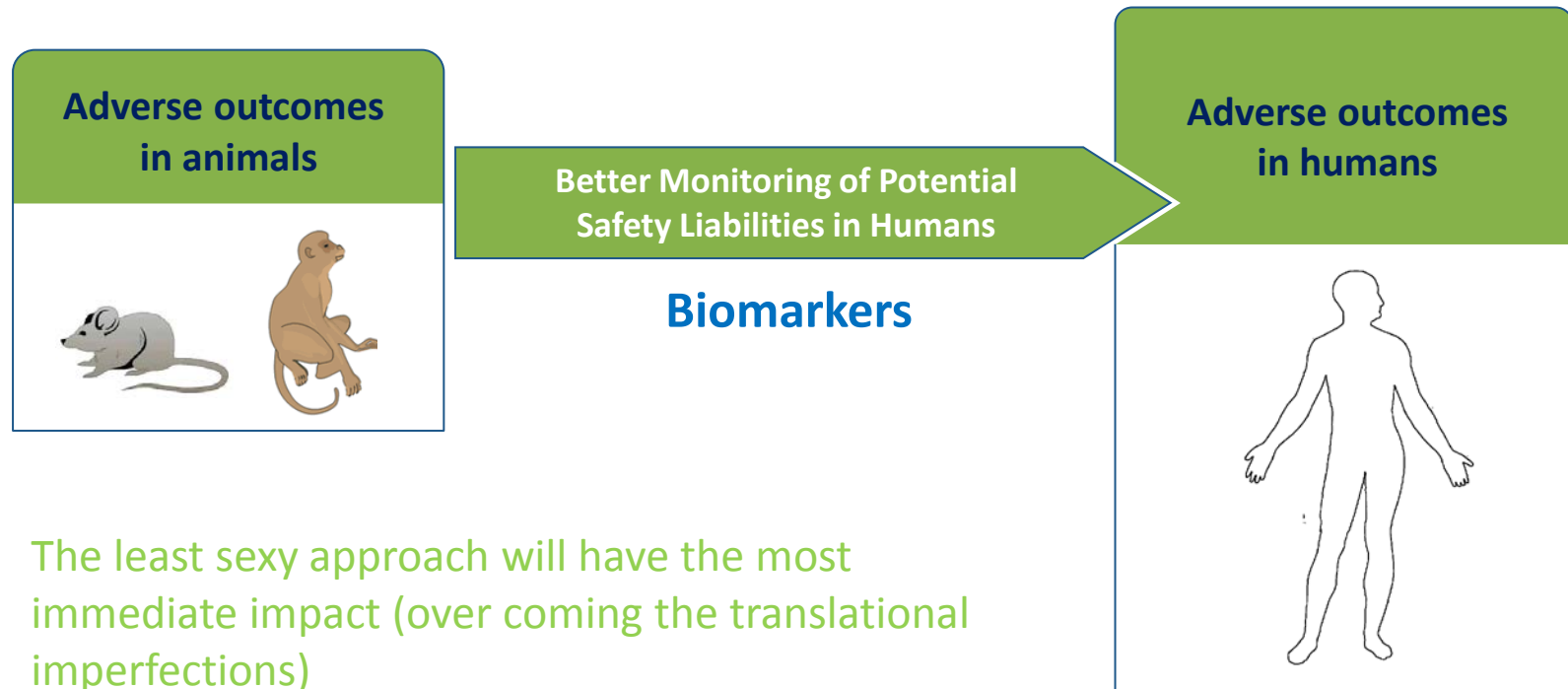
Integration

- Accordingly, systems toxicology involves the integrations of all aspects of toxicology into some coherent explanation or prediction of toxicity.

Data

- The strength of systems approach to understanding toxicology resides in the amount and integrity of the data used to model systems-level toxicity.

The role of biomarkers in translational (predictive) safety:



The least sexy approach will have the most immediate impact (over coming the translational imperfections)

Clinical Safety Biomarkers

Current biomarker standards do not exist or have significant limitations



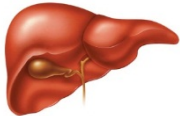
Nephrotoxicity:

Traditional safety biomarkers change only when 50 to 60 % of kidney function is lost



Skeletal Myopathy:

Current biomarkers are insensitive and nonspecific, as well as poorly predictive



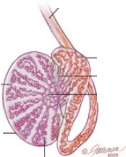
Hepatotoxicity:

Current biomarkers are not sufficiently sensitive and specific, and do not adequately discriminate adaptors from patients at high risk to develop liver failure



Vascular Injury:

No biomarkers are available for detecting drug-induced vascular injury in humans



Testicular Injury:

No circulating biomarkers for seminiferous tubule toxicity



Cardiac Hypertrophy:

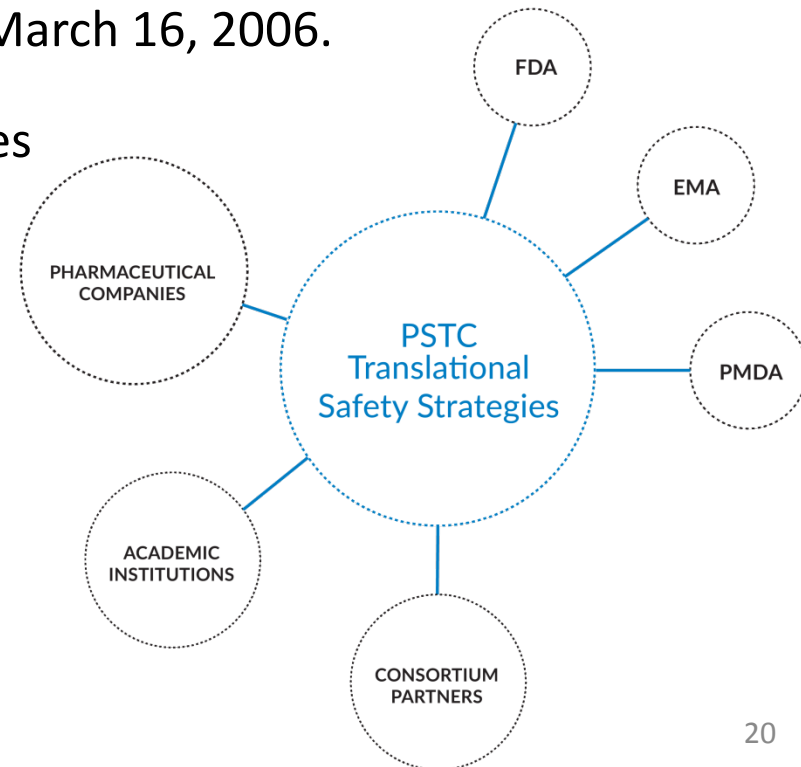
Currently no preclinical predictive markers for drug-induced hemodynamic stress leading to changes in cardiac mass

Predictive Safety Testing Consortium (PSTC)

PSTC was formed and officially announced on March 16, 2006.

PSTC brings together pharmaceutical companies to share and validate innovative safety testing methods under advisement of the FDA, EMA, and PMDA.

PSTC's nineteen corporate members have the same goal: to find improved safety testing approaches and methods.



PSTC Collaborators

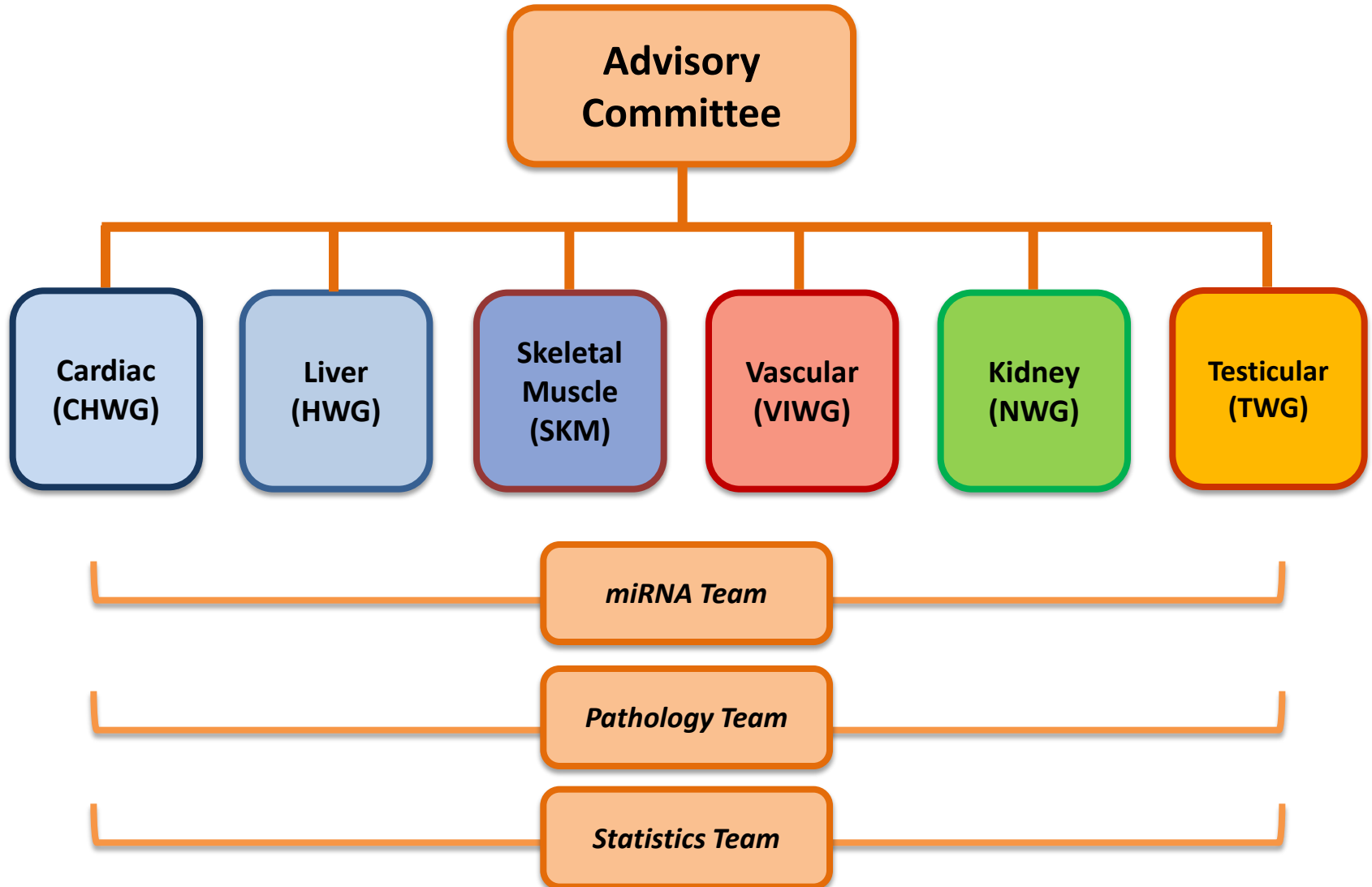
Consortia Members (19)



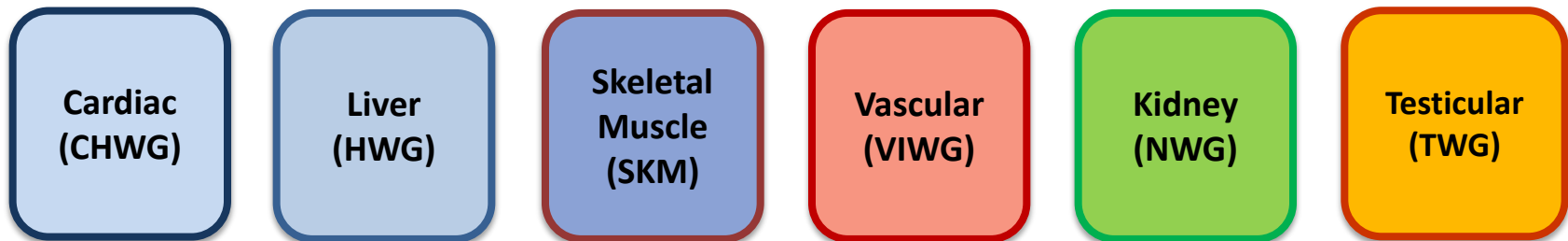
Partners (8)



Structure of PSTC



PSTC Working Groups



PSTC Work Groups are organized by target organ

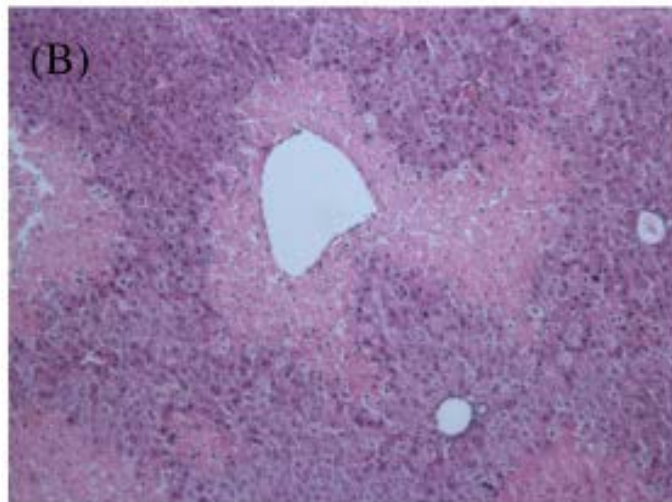
The primary goal of each working group is to define novel fluid based safety biomarkers for use in preclinical species and humans during drug development

Translational Safety Biomarkers:

- Fluid Based Biomarkers that are similar to routine clinical pathology (urine or blood)
- The objective is to define acceptable clinical biomarkers of tissue injury (regulatory and scientifically)
- Demonstrate the predictive certainty of the biomarker (Predictive Accuracy)

Translational Safety Biomarkers

Nearly all of PSTC's biomarker efforts are based on the relationship between the biomarker concentration and histopathological change in response to toxic insult.

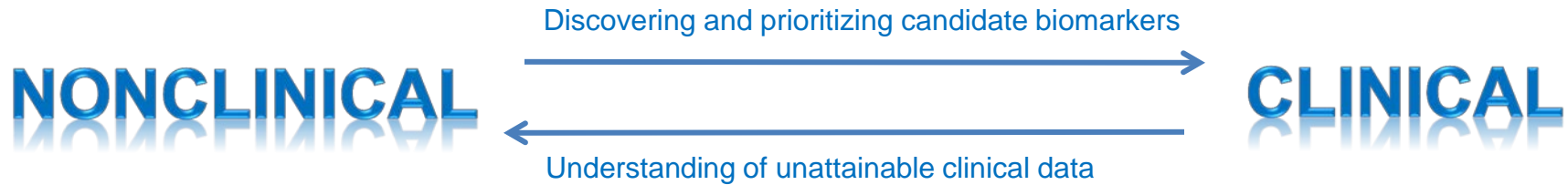


CCl_4

←→ [Biomarker]

The primary issue is that in early drug development we can characterize the pathology of drug induced injury in great detail in nonclinical species, but not in humans.

Moving Forward Using Translational Science

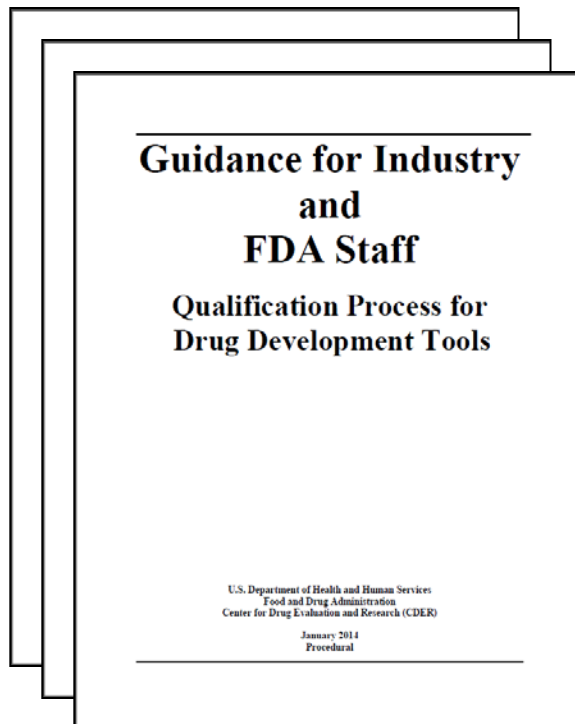


- How does the onset of injury (histopathology) correlate with appearance of biomarker?
- How does the resolution of injury (histopathology) correlate with normalization of the biomarker?
- How does onset and development of adaptation (resolution of histopathology) with continued dosing correlate with biomarker levels?
- What is the response of the biomarker when tissue function is reduced
- Is the performance similar with different drugs?
- How do confounding toxicities and health status affect biomarker performance?
 - Do preclinical species exhibit different metabolism, pathophysiology and biomarker behavior and performance ?

Translational Safety Biomarkers

Clinical Biomarker Qualification:

- Qualification is designed to enable the use of a biomarker to make decisions around clinical development studies (e.g. presence or lack of tissue injury, *etc.*)



This guidance describes the process for qualifying drug development tools intended for potential use, over time, in multiple drug development programs.

Once a biomarker has been qualified, CDER reviewers can feel confident of the application of the biomarker within the qualified COU and not have to re-confirm the biomarker utility.

Regulatory qualification of biomarkers will allow drug development sponsors to use these biomarker with confidence and an regulatory certainty.

Translational Safety Biomarkers

Nonclinical and Clinical Support of Clinical Biomarker Qualification

Rodent

- *Exploration/Conformation*
- *Support of Qualification*

Canine/Nonhuman Primate

- *Translational confirmation*
- *Support of Qualification*

Human

- *Biomarker baseline in NHVs, disease*
- *Explore biomarker response/Conformation*
- *Clinical Qualification*

Translational Safety Biomarkers

Nonclinical and Clinical Support of Clinical Biomarker Qualification

Rodent

- *Available assays/tools*
- *Low resource utilization*
- *Flexible study designs (histopath)*

Canine/Nonhuman Primate

- *Limited availability of assays/tools*
- *Resource intensive*
- *Limited study design (histopath)*

Human

- *Limited availability of assays/tools*
- *Very resource intensive*
- *Limited study design (no histopath)*

Further Defining PSTC's Vision

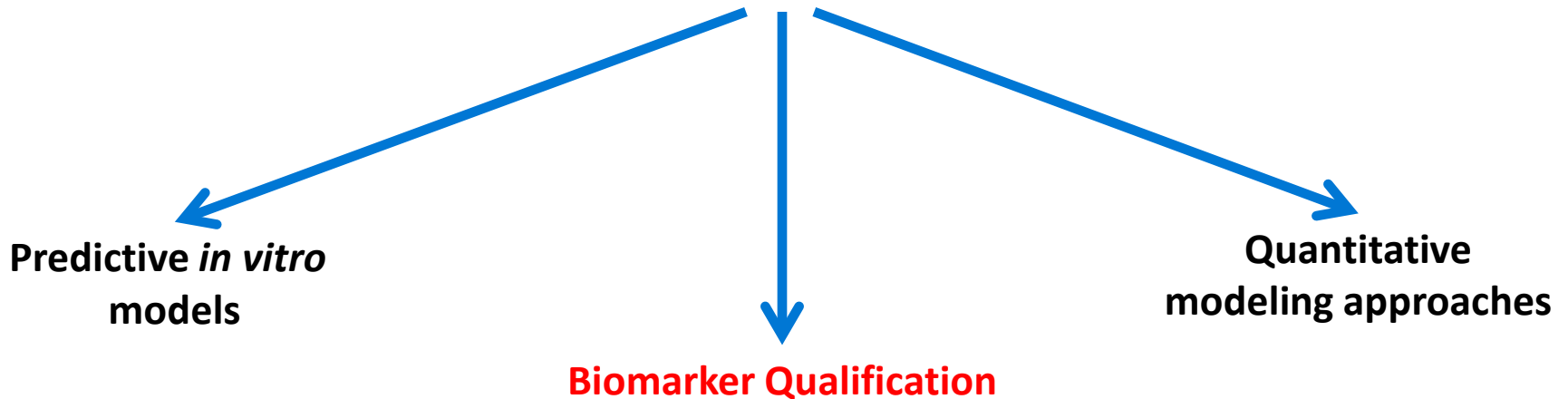


Translational Safety Strategies that Accelerate Drug Development

Is PSTC just about safety biomarkers?

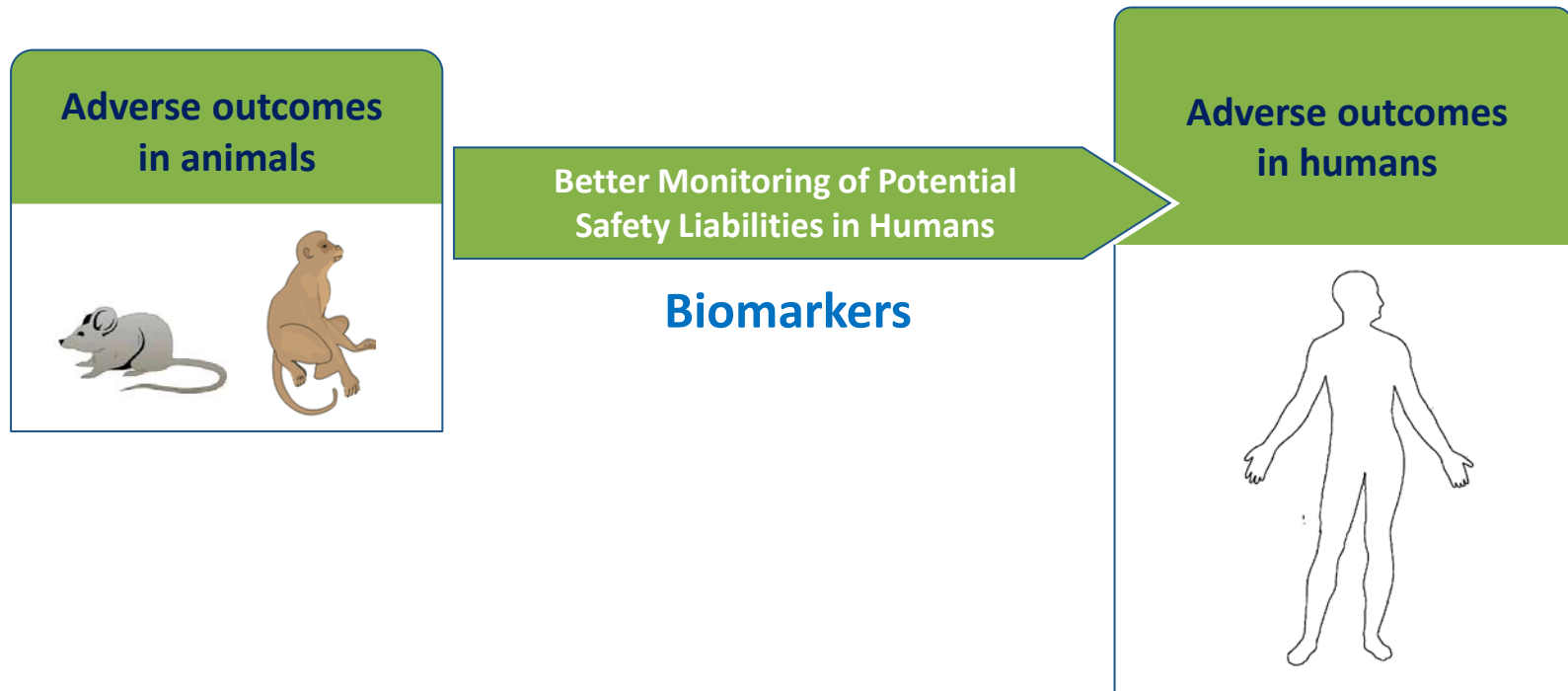
Further Defining PSTC's Vision

PSTC is helping to define translational safety strategies that accelerate drug development



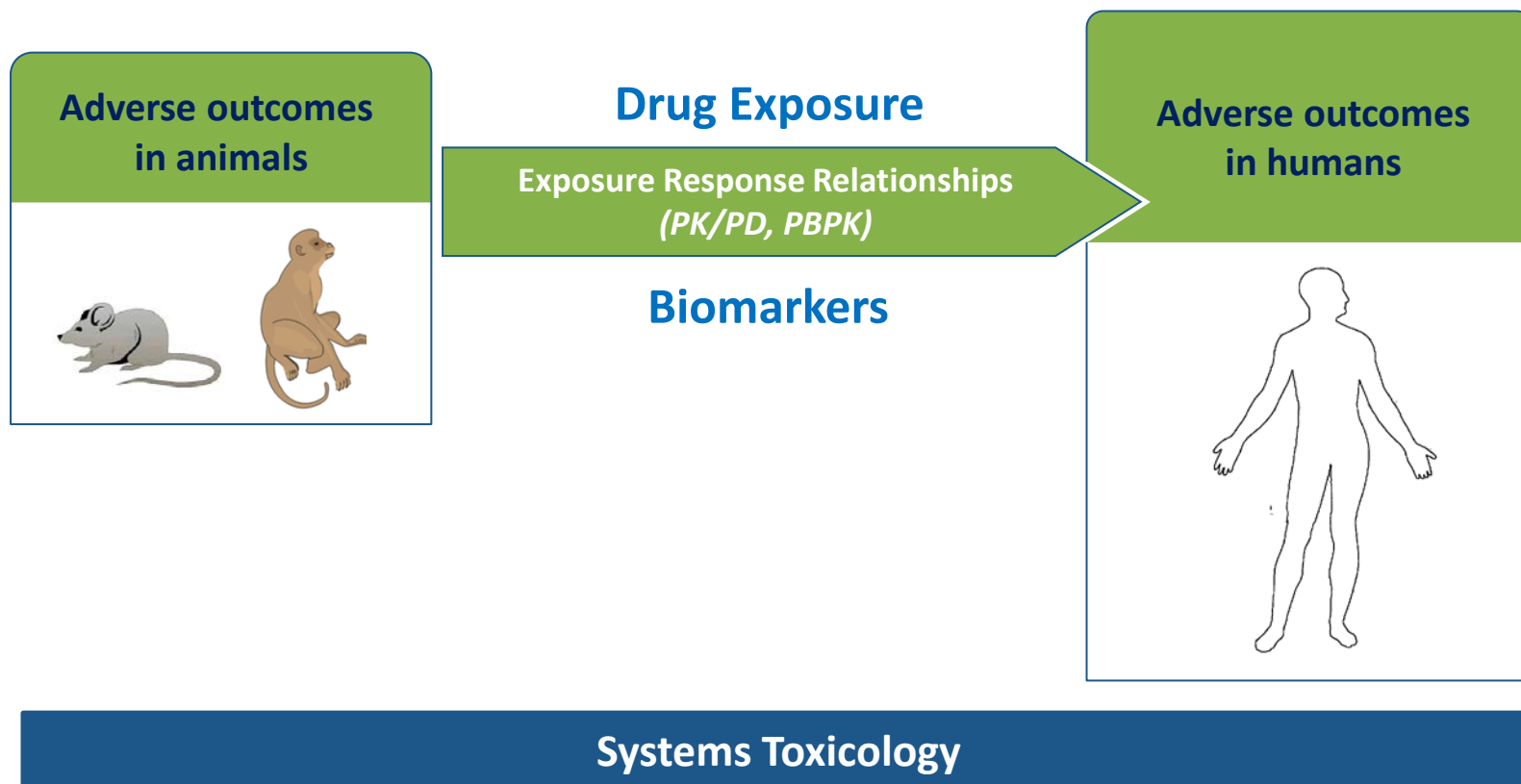
Building a Translational Safety Strategy

Accessible predictive (quantitative) biomarkers of tissue injury that can be used in preclinical animal models and humans



Building a Translational Safety Strategy

Accessible predictive (quantitative) biomarkers of tissue injury that can be used in preclinical animal models and humans



Quantitative Translational Safety = Toxicometrics

Can we steal a page from the quantitative pharmacologists (aka, PK/PD folks) playbook?

- Quantitative pharmacology = PK/PD = pharmacometrics
- Quantitative toxicology = PK/TD = toxicometrics

Toxicometrics: Quantitative Translational Safety



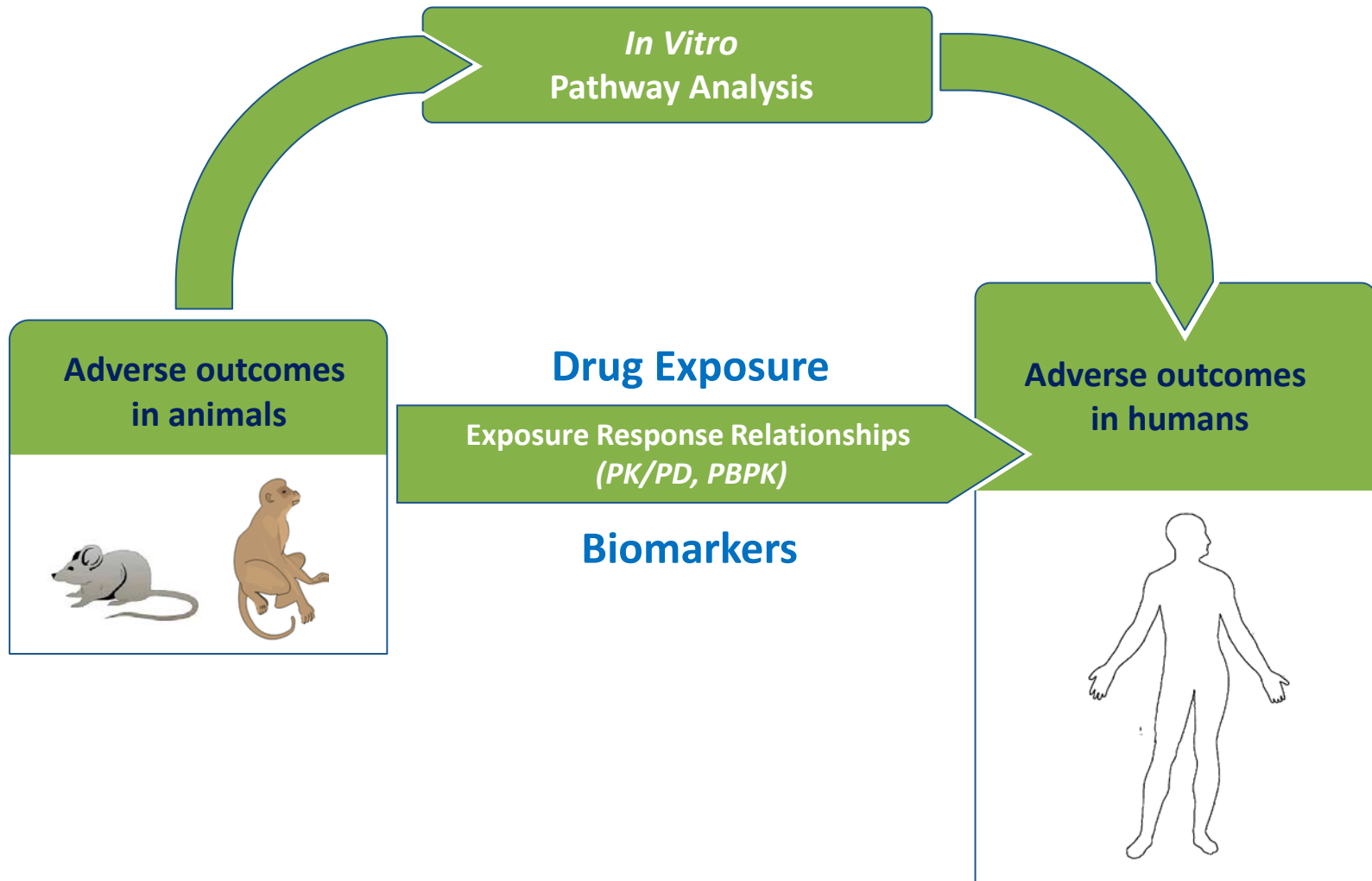
Toxicometrics uses models based on toxicology, physiology and individual susceptibility factors for quantitative analysis of interactions between drugs and patients. This involves pharmacokinetics, toxicodynamics, pharmacodynamics and individual subject factors with a focus on populations and variability,

Toxicometrics is defined as the science that quantifies drug, toxicity and clinical trial information to aid efficient drug development, regulatory decisions and rational drug treatment in patients.

Toxicometric-based drug models describe the relationship between exposure (pharmacokinetics), response (toxicodynamics and pharmacodynamics) for both desired and undesired effects.

A major focus of **toxicometrics** is to understand variability in drug safety. Variability may be predictable (e.g. due to differences in body weight or kidney function) or apparently unpredictable (a reflection of current lack of knowledge).

Quantitative Translational Safety



Translational Safety:

- Implementation of translational safety strategies will take years to complete and must be a progressive approach
- Health authorities will continue play a dual role (supporters of innovation and one of the causes of stagnation)
- Academic research needs to better support translational safety objectives
- Industry needs to embrace a more mechanistic approach to safety assessment
- In order for translational safety to have its full impact on drug development, quantitative approaches need to be implemented



Accelerating the Path to a Healthier World