Innovations in Early Clinical Trial Designs: Application to New Drug Development in Pharma

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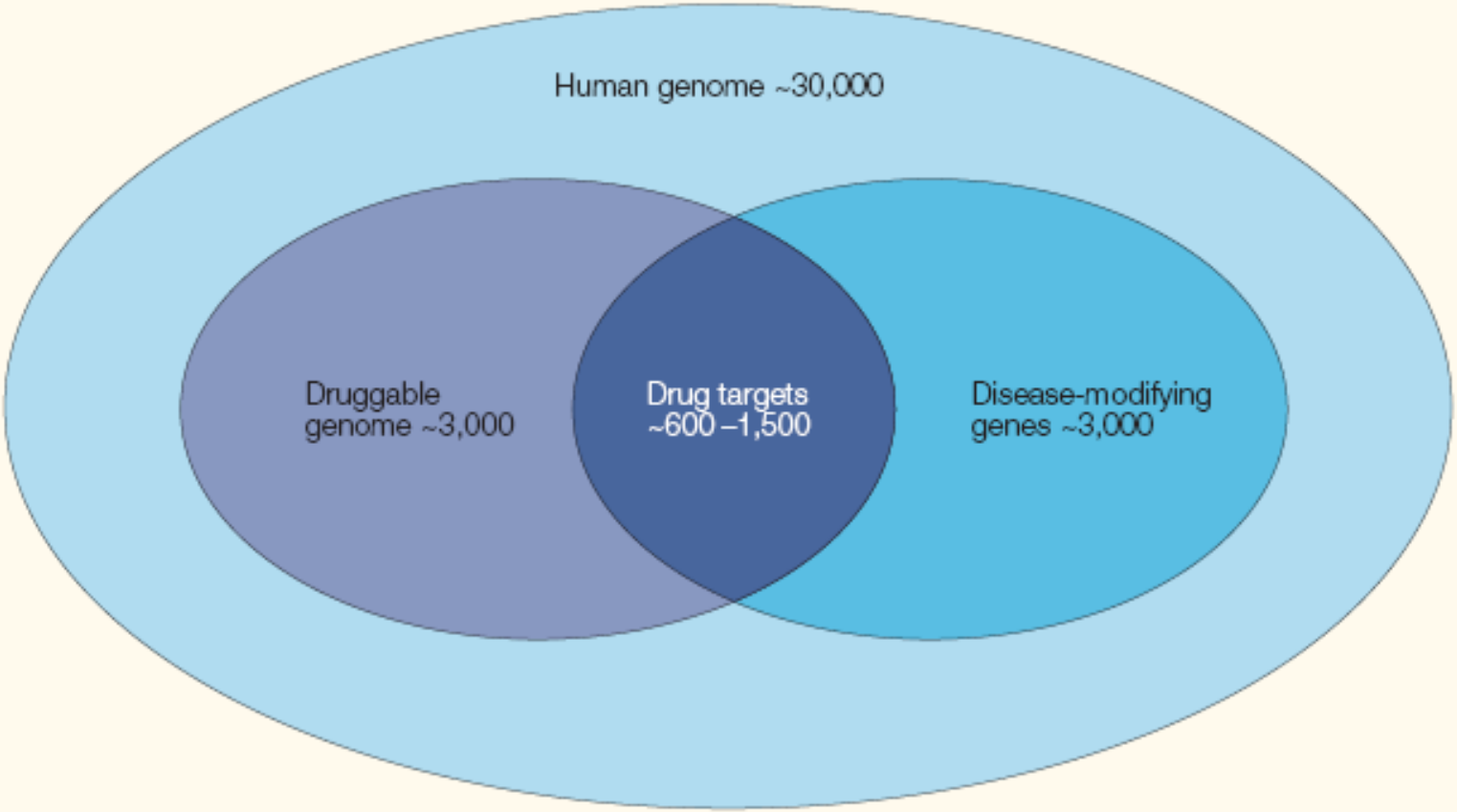
Disclaimer

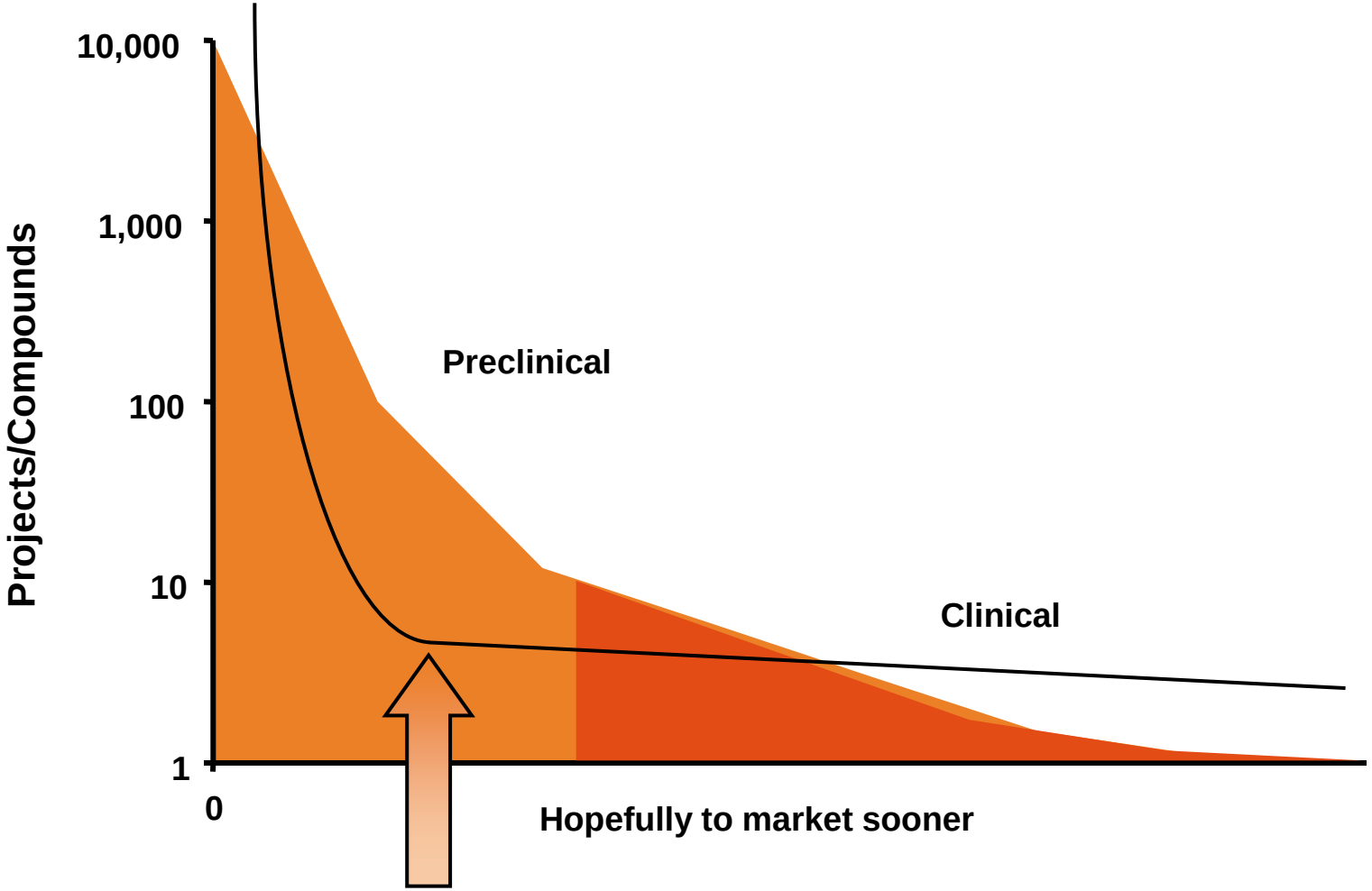
The views and opinions expressed in this presentation are my own and do not necessarily represent the official policy or position of Novartis.

Plenty of drug targets remain



Hopkins AL, Groom CR. The druggable genome. Nat Rev Drug Discov. 2002:727.

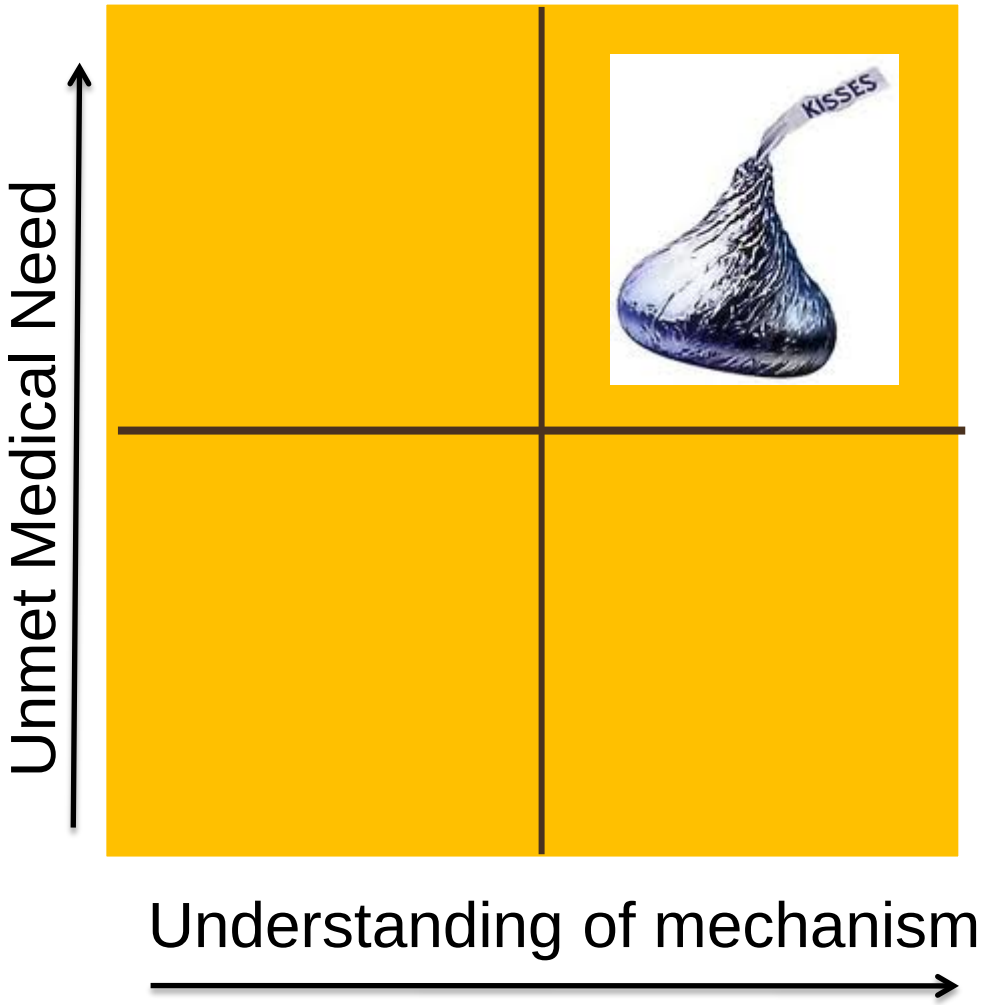
Compound attrition during pharmaceutical R&D



Mission

- **Bring medicines rapidly into the clinic:** Focus on tractable biological targets with excellent rationale for addressing unmet medical need
- **Establish a new grammar for drug discovery:** Increase access to genomic and chemical universe

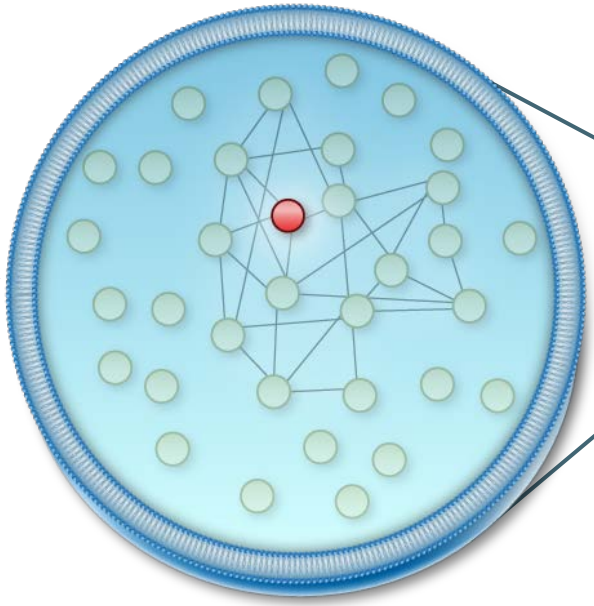
What diseases to pursue?

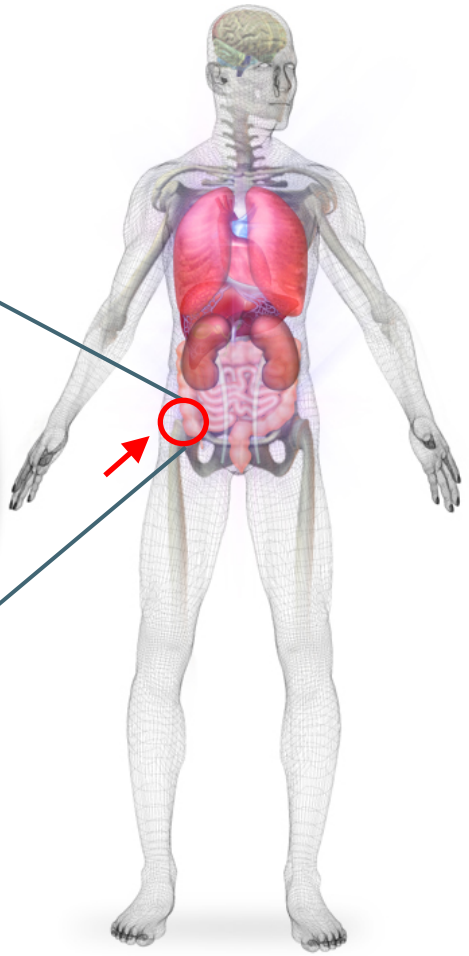


Translation of the genome to therapeutics

Defining the key druggable nodes within the network

Genome





Human Disease

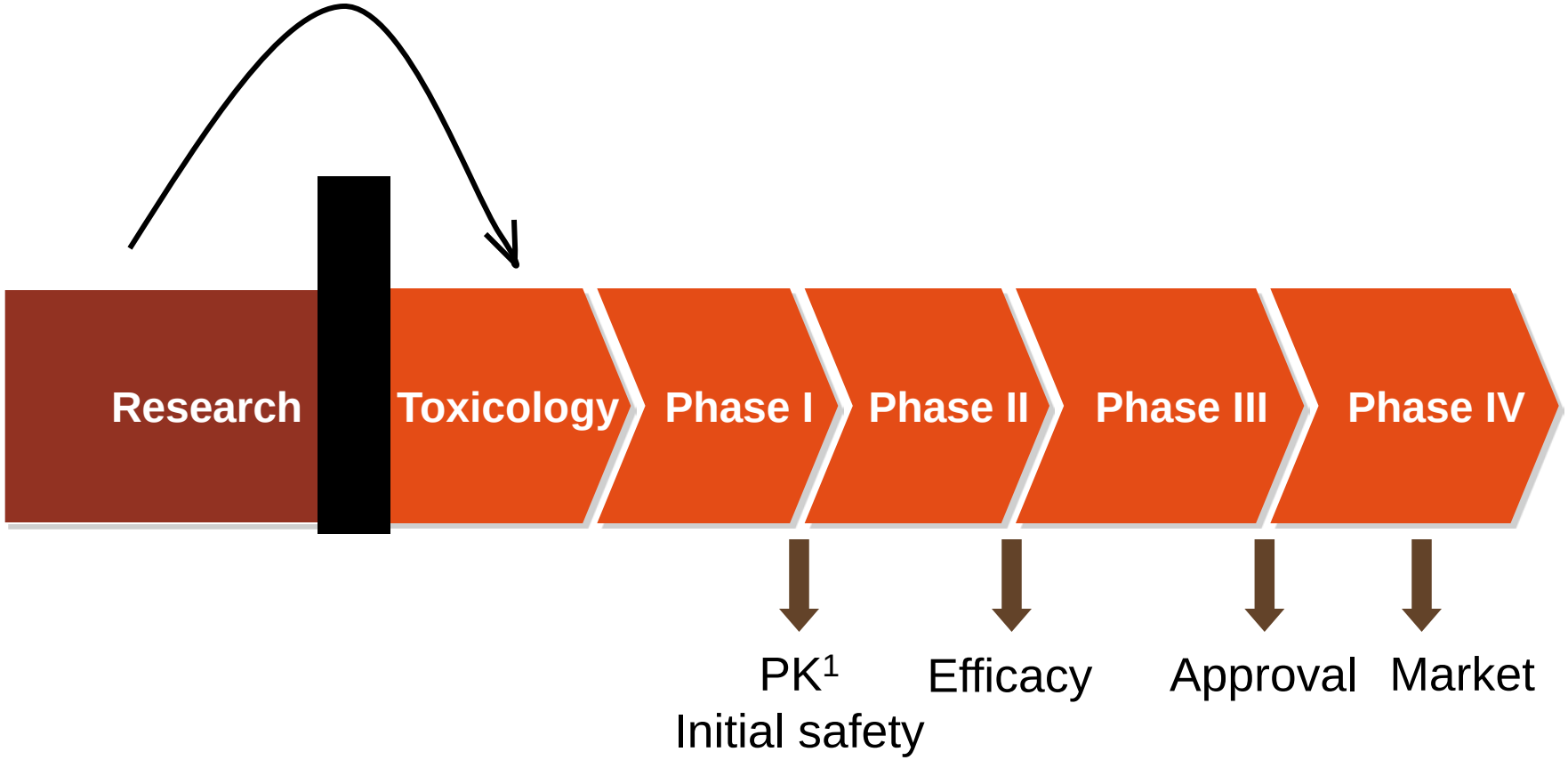
Selection of drugs to enter exploratory development

- High unmet medical need
  - Current treatment
- Well understood mechanism
- A path forward
  - Proposed proof of concept (PoC) study is feasible

and none of these guys...

The old paradigm

“Compounds tossed over the wall”



[1]Pharmacokinetics

The new paradigm: “tear down this wall”

Translational Medicine

Target discovery and validation → **PoC[1] clinical trials** → **Further clinical development**

Exploratory Phase | **Confirmatory Phase**

Target

PoC[1]

Efficacy

Approval

Market

[1]Proof-of-Concept

What does the exploratory phase look like?

- First in human
- De-risking studies
  - For example proving that a candidate drug has no clinically significant drug-drug interaction with the regimen with which it will be paired
- Proof of Concept (PoC)
  - It’s not just a good idea, it’s the LAW
  - The permissive step into full development

PoC: Subjects

- Subjects are typically the patient group of interest
  - Example: Muckle-Wells patients to measure efficacy of anti-IL-1β
- Many studies conducted in patients with rare disease
  - Currently >40 projects
  - Examples: medulloblastoma, Noonan's, pulmonary artery hypertension, lymphangioleiomyomatosis, Netherton's, hematopoietic stem cell transplantation, Gorlin's, Cushing's, etc.
- Attempt to genetically define patient population *a priori*
  - Commonly done with oncology/hematology studies
  - Examples: epigenetic features in Fragile X syndrome, K-RAS and B-RAF mutations in solid tumors

PoC: Design

- “20 subjects, 2 weeks, $2M”
- Typically short duration: 1-3 months
- Typically small N: 20-40
- 20-30% use a cross over design
- 30-40% have an active comparator group
- Biomarkers can be a key intermediate endpoint to de-risk the remainder of the trial. Drive a NO GO decision.
- Most studies have adaptive features, some are heavily adaptive

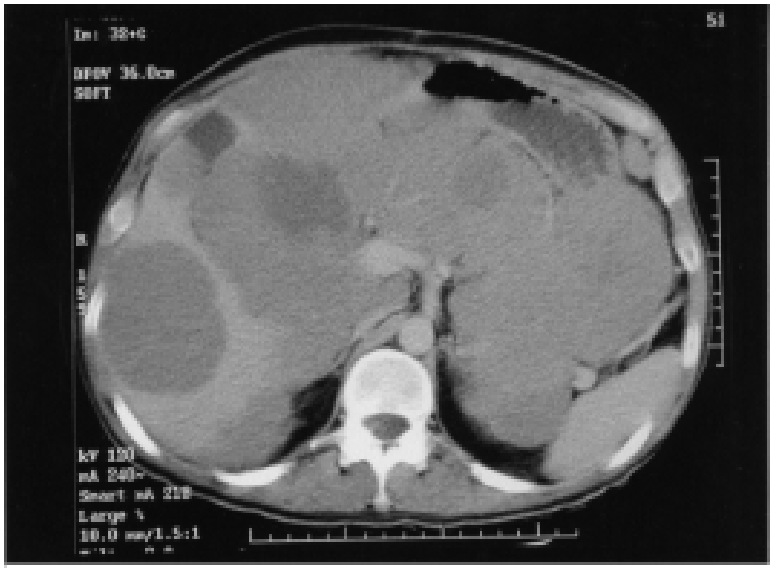
PoC: Study conduct

- Many are multicenter, multinational
  - Current record: 22 sites in 5 countries
- Continuous safety and activity data streaming to the study physician over the course of the study. Real time analysis using software such as Spotfire.
- Increasing interest in changing from “triple blind” to “double blind” exploratory approaches
  - Triple blind: subject, investigator, sponsor
  - Double blind: subject, investigator

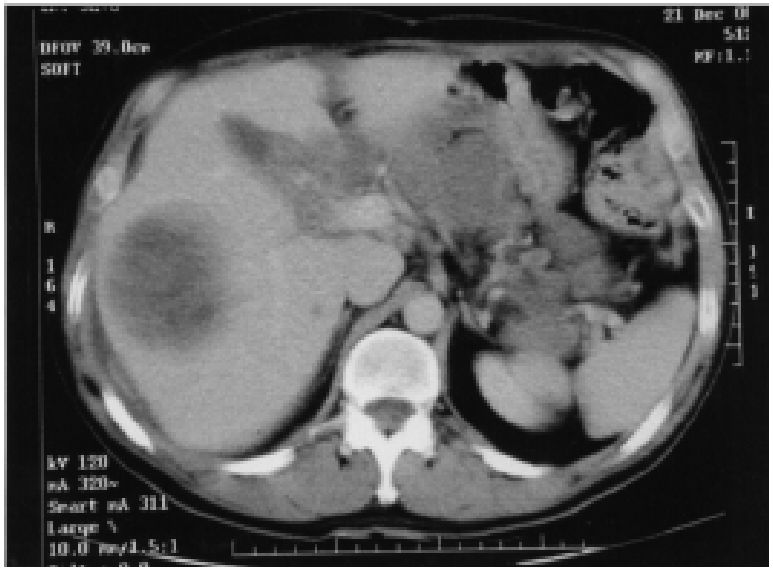
PoC: Analysis

- PoC Go and No Go criteria are defined and formally agreed upon *a priori*
- Primary end point is typically as close as possible to clinical activity
  - Examples: FEV1, cognitive battery, ventricular energetics, macular thickness, stand and walk time
- Go criteria typically tested using Bayesian statistics
  - Confidence level set at 60-70%
  - Cardinal Sin: false negative!
- Careful attention also to possible responder subsets
- Several “N of 1” studies conducted each year

“N of 1” Patient with Gastrointestinal stromal tumor



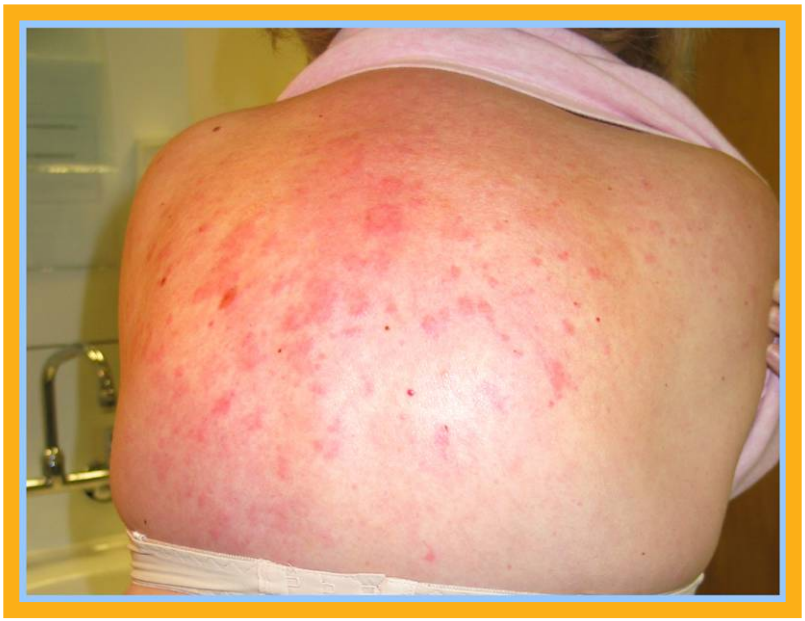
imatinib



Pre-treatment

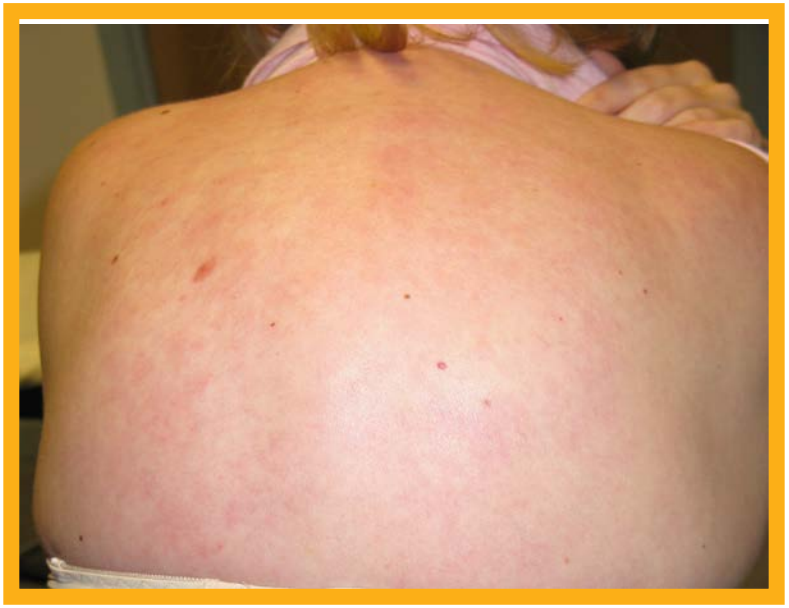
Post 3 months treatment

“N of 1” Patient with Muckle-Wells Syndrome



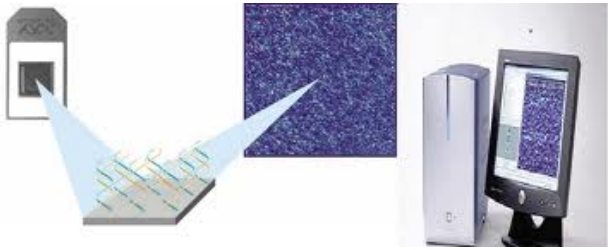
Pre-treatment

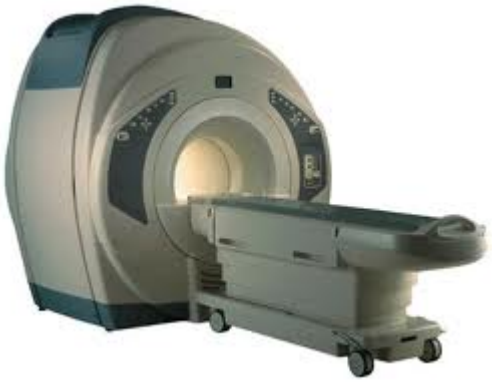
Anti-IL-1β

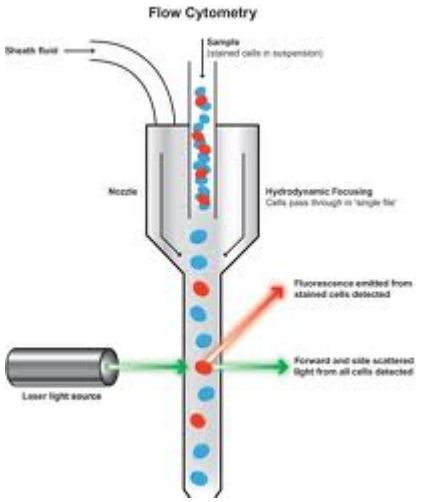


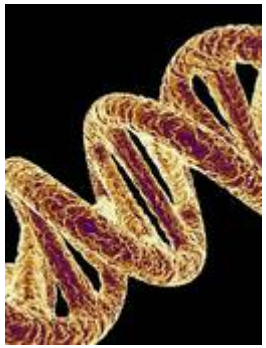
Single dose
at 24 hours

Biomarkers: Every PoC's got'em









Do you want PIE with that PoC?

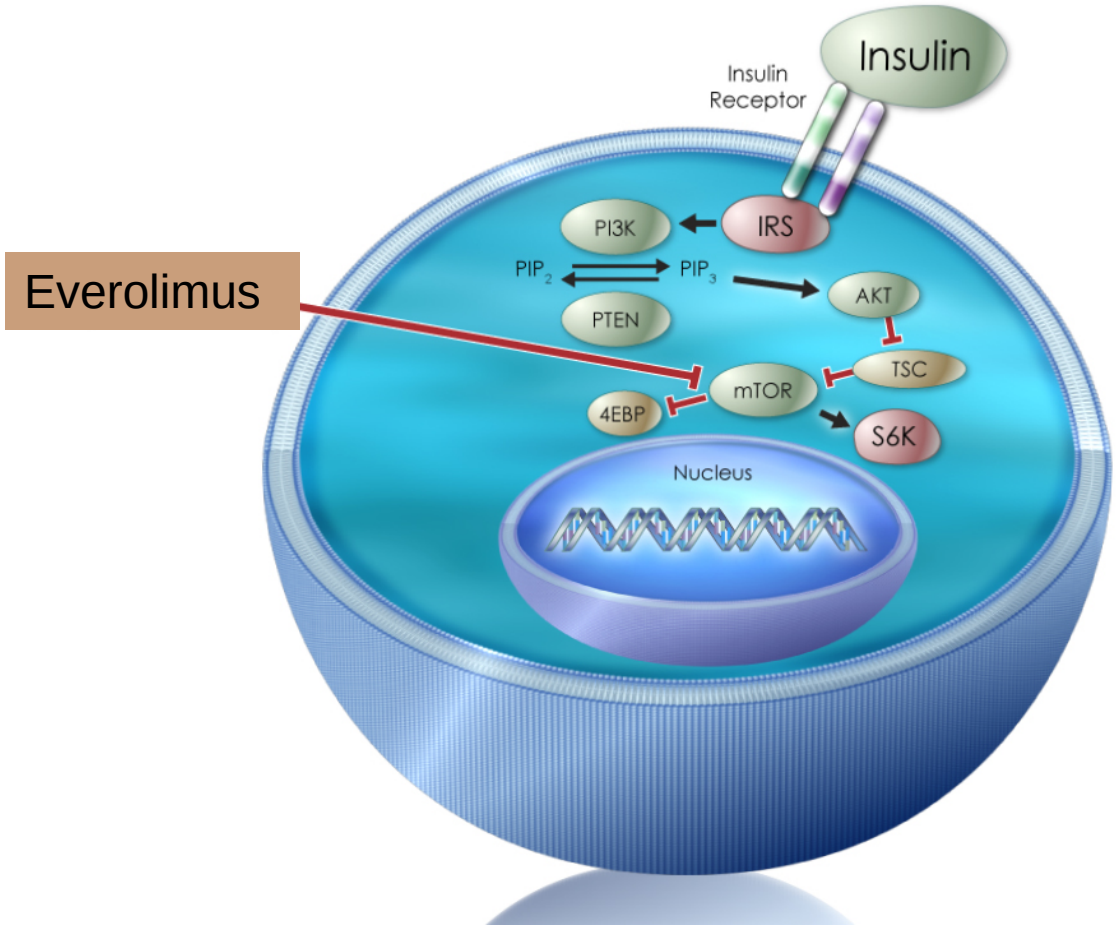
Q: What else does a PoC permit besides entry into full development

A: Parallel indications expansion (PIE)

- We follow the pathway
- If the pathway maps to other diseases of high unmet medical need, we will pursue those indications

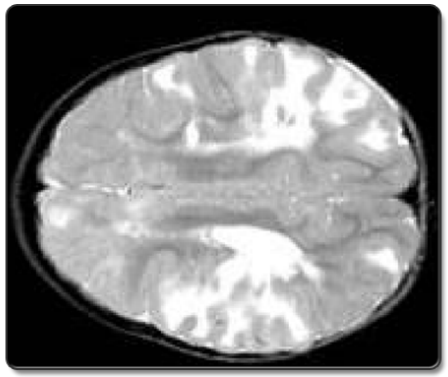
Two examples...mTOR inhibitor, anti-IL-17 mAb

Targeting Key Nodes to Develop New Drugs



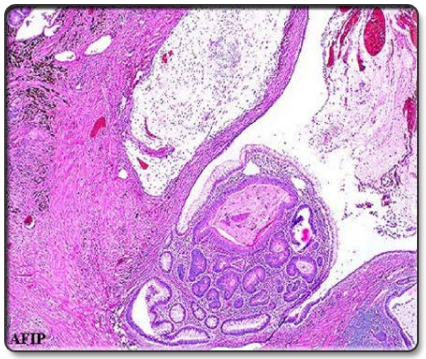
mTOR Pathway in Multiple Indications

Tuberous sclerosis

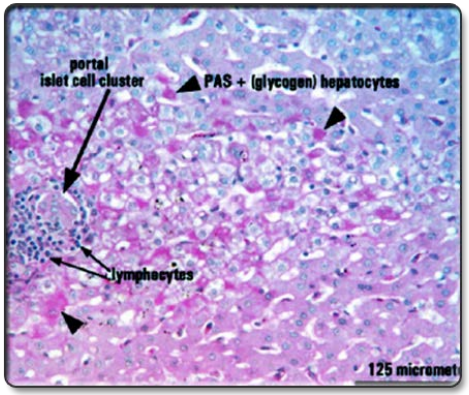


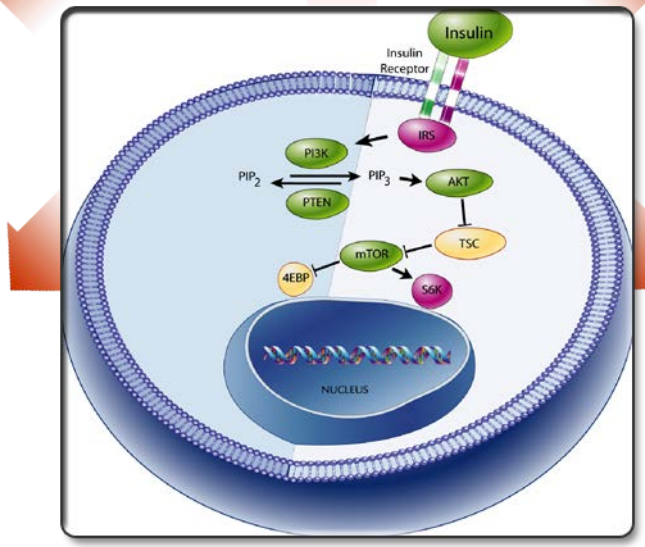
Retinitis pigmentosa

Cancer
(colon/breast/kidney)

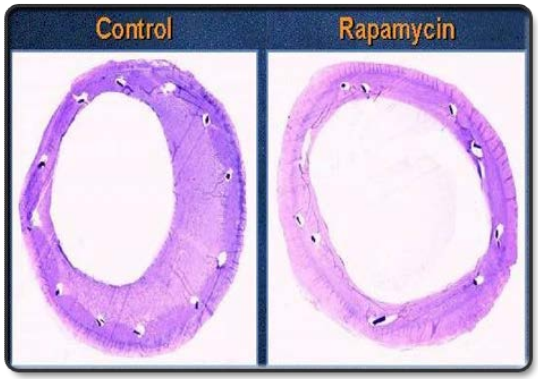


Immune diseases,
Tx rejection





Vascular proliferation
(stent implant)



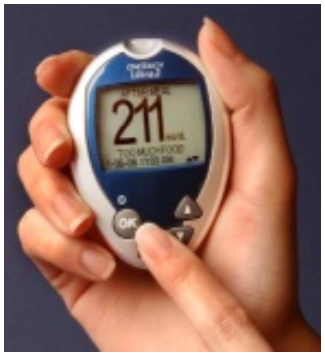
mTOR pathway

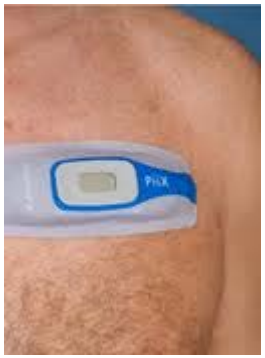
Rising complexity and burden of clinical research

	1999	2005	Percentage change
Unique Procedures per Trial Protocol (Median)	24	35	46%
Total Procedures per Trial Protocol (Median)	96	158	65%
Clinical-Trial Staff Work Burden (Measured in Work-effort Units)	21	35	67%
Length of Clinical Trial (Days)	460	780	70%
Clinical-Trial-Participant Enrollment Rate	75%	59%	-21%
Clinical-Trial-Participant Retention Rate	69%	48%	-30%

Source: Tufts Center for the Study of Drug Development, "Growing Protocol Design Complexity Stresses Investigators, Volunteers," *Impact Report, 2008*

Change is starting to happen: (2)





The most relevant species in drug development: *Homo sapiens*

Conclusions

- The PoC study can be a focus and driver of innovation
- These studies are the culmination of years of integrated chemical, biological, and medical efforts
- PoC studies have many moving parts and the organization, deployment, conduct and analysis of these studies can be challenging
- Trials of the Future: Bring the PoC study to the patient
- Exclusion of commercial and/or marketing input from early development could, in itself, be considered an innovation
- PoC studies both energize early development and de-risk late development

Questions

Multiple Choice Question 1

- What are some attributes of PoC studies (choose all that apply):
  - A) Typical size is 100-200 subjects
  - B) False positive result is “the worst sin”
  - C) Typically done only if the Net Present Value is positive
  - D) Provides confirmation of the patho-biologic pathway
  - E) Is powered to understand the safety of a new drug
  - F) Typically <6 months duration

Multiple Choice Question 2

- What is the value of Marketing / Commercial input in pathway based early development:
  - A) Allows building the “business case” to continue development
  - B) Provides free lunches at meetings
  - C) Helps to prioritize the business portfolio
  - D) There is minimal / no value of Marketing / Commercial input

Multiple Choice Question 3

- Which combination of attributes below defines the “sweet spot” of pathways based early drug development:
  - A) High Net Present Value (NPV) and high unmet medical need
  - B) Low NPV and high unmet medical need
  - C) High unmet medical need and clear understanding of the drug-disease mechanism
  - D) High NPV and clear understanding of the drug-disease mechanism
  - E) Clear understanding of the drug-disease mechanism and high NPV