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Key points of preclinical data in drug development

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Shanghai, China
November 2018

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Disclosures

1. **Employment:** Medical Director of the Institute for Applied Cancer Science and Associate Director for Translational Research of the Institute for Personalized Cancer Therapy at the University of Texas MD Anderson Cancer Center. Previous employee of the Institute of Cancer Research, London, UK
2. **Research support:** AstraZeneca, Bayer, Pfizer, Tesaro, Jounce, Eli Lilly, Seattle Genetics, Kyowa, Constellation, EMD Serono, Ipsen, Forbius (Formation Biologics), and Vertex Pharmaceuticals
3. **Scientific Advisory Board Member:** Pfizer, Atrin, Bayer, Cybrexa, and Seattle Genetics
4. **Consultancies:** Aduro, Almac, AstraZeneca, Atrin, Bayer, Bristol-Myers Squibb, Calithera, Clovis, Cybrexa, EMD Serono, Ignyta, Jansen, Merck, Pfizer, Roche, Seattle Genetics, and Vertex Pharmaceuticals
5. **Speaker Bureau:** AstraZeneca, Merck, Pfizer, and Tesaro

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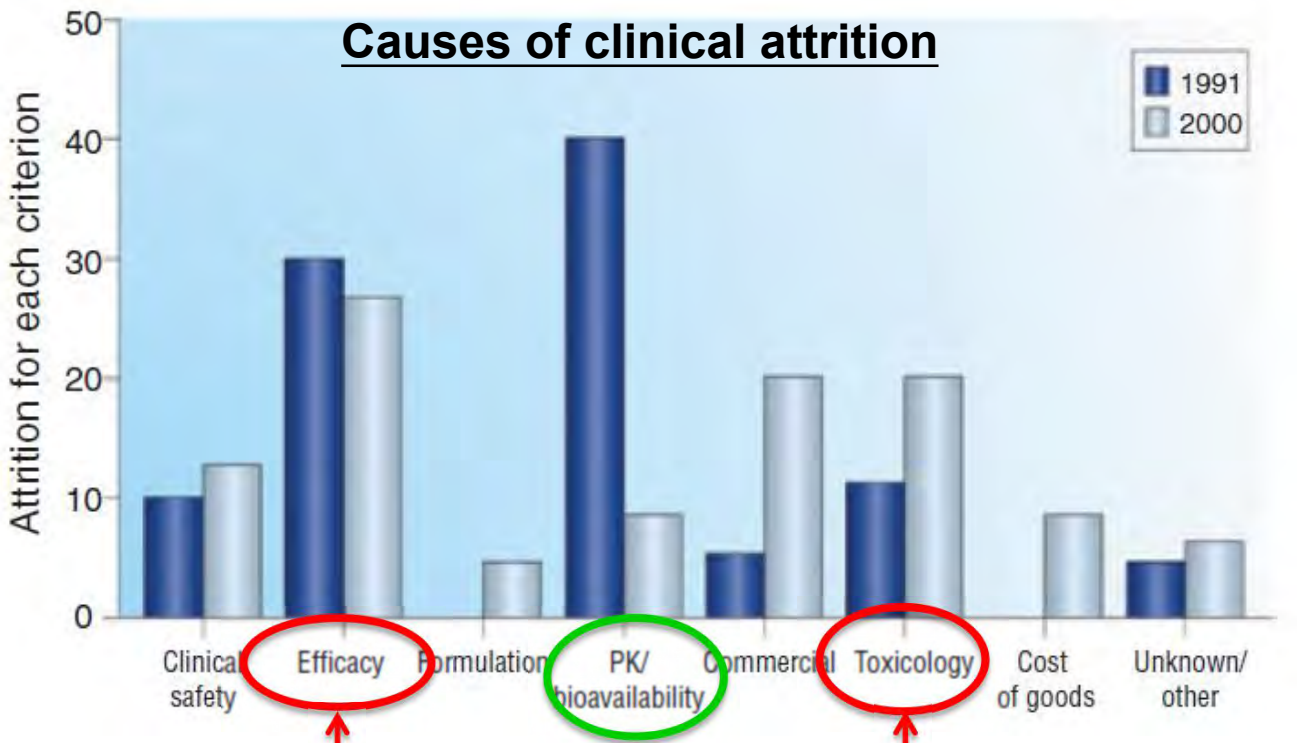
Multiple Reasons for Failure



- inadequate clinical activity at maximum tolerated dose
- lack of understanding of which patients to treat

- Improved drug candidate quality, reduced risk for suboptimal pharmacological properties

- adverse events
- drug-induced toxicity

Clin. Pharm. Ther. 2008, 83, 227

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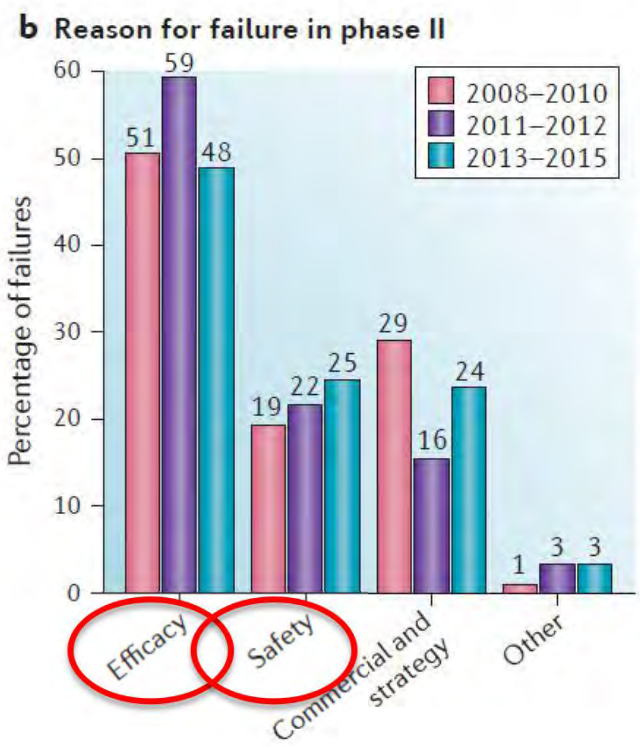

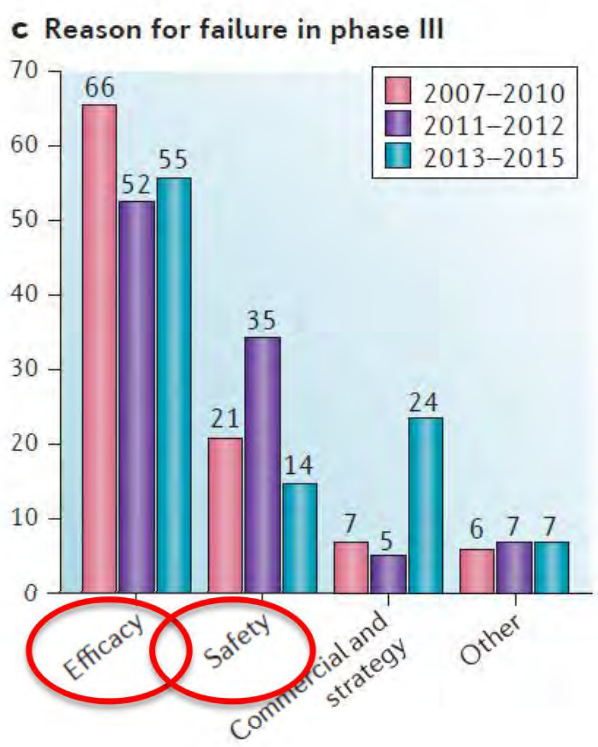

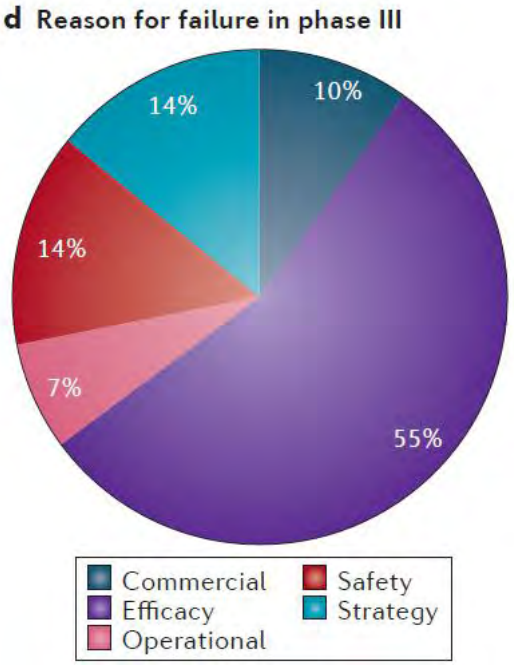

Nature Reviews – Drug Discovery, 2016, 15, 817

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What Does It Take to Have a Successful Drug ?

Efficacy — Demonstrated effectiveness

Safety — Benefits should out weigh risks

Quality — Consistent product performance

The label is the driver

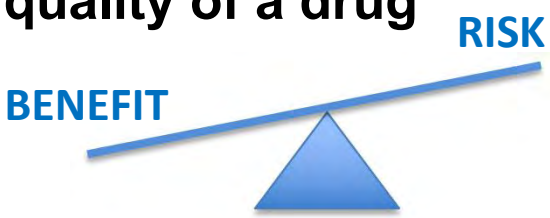
Demonstrate efficacy with acceptable safety in adequate and well controlled studies

Ability to generate product labeling that:

- Defines an appropriate patient population for treatment with the drug
- Provides adequate information to enable safe and effective use of the drug

FDA requirements to grant approval

- **Demonstrated safety, efficacy and quality of a drug**
- ***Acceptable risk-benefit profile***



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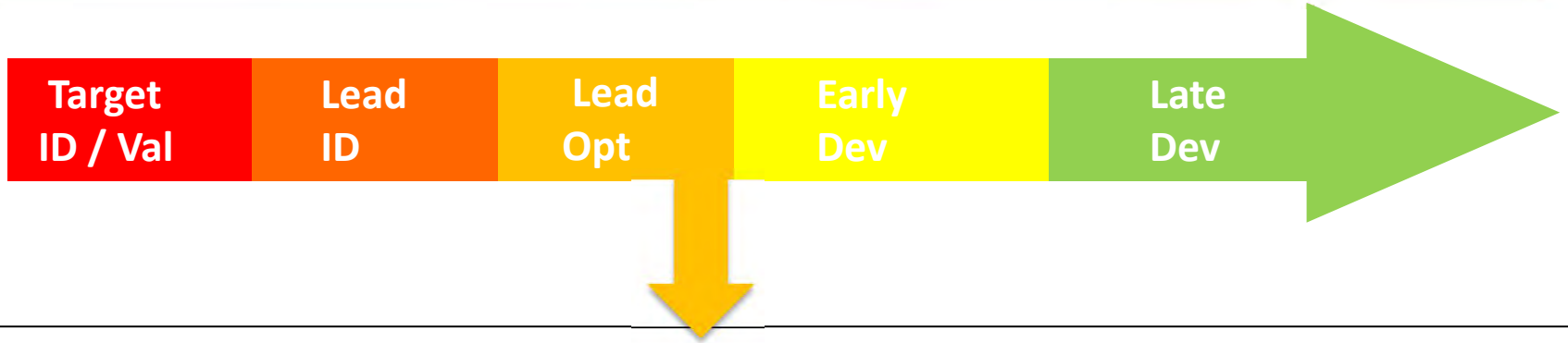
Target ID to Lead Optimization…



Identified a potential development candidate

installed all of the desired properties of a drug into a single compound …

- efficacious
- selective for target
- good pharmacokinetic profile
- well absorbed
- protected from metabolism
- well tolerated

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Focus of Today's Lecture

Translation / Early Development

Development Candidate Compound

Appropriate models

- **Efficacy**
- **Tolerability**
- **Drug Quality**

Impactful & Safe Drug

Specific responder patient population

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Outline

❑ Preclinical testing of EFFICACY

- Appropriate animal models
- PK / PD - Relationship between exposure and pharmacological effect
- In vivo target engagement, biomarkers of response

❑ Preclinical Safety and Toxicology Studies

- Regulatory aspects / Requirements for IND Filing
- Risk assessment in drug discovery and early development
- Therapeutic Window

❑ Biomarkers

- Parallel development of biomarker and drug
- Pharmacodynamic biomarkers
- Predictive biomarkers

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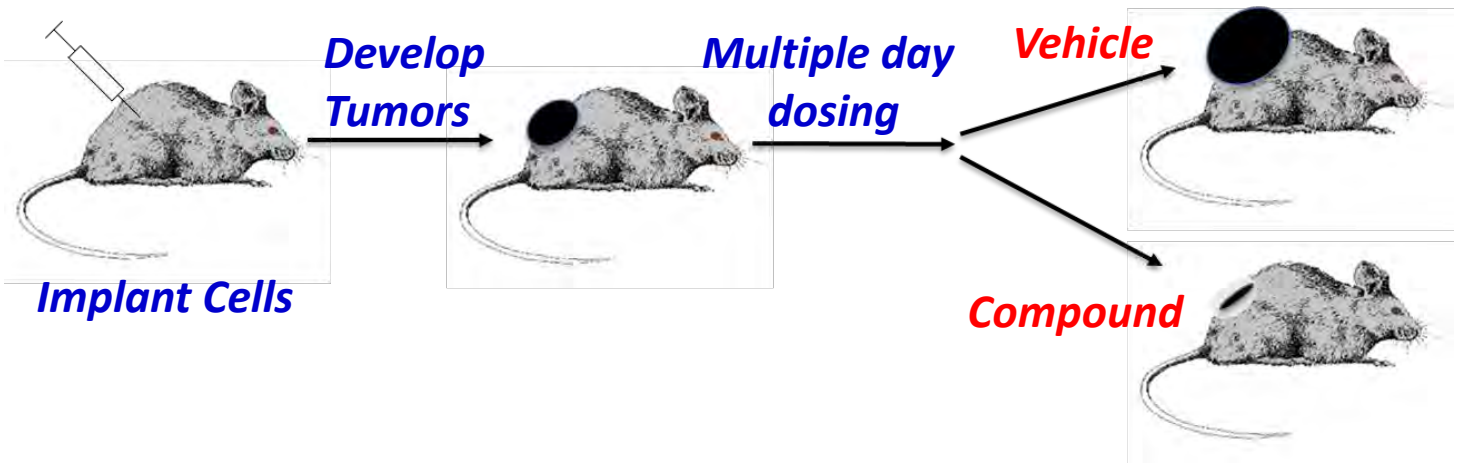
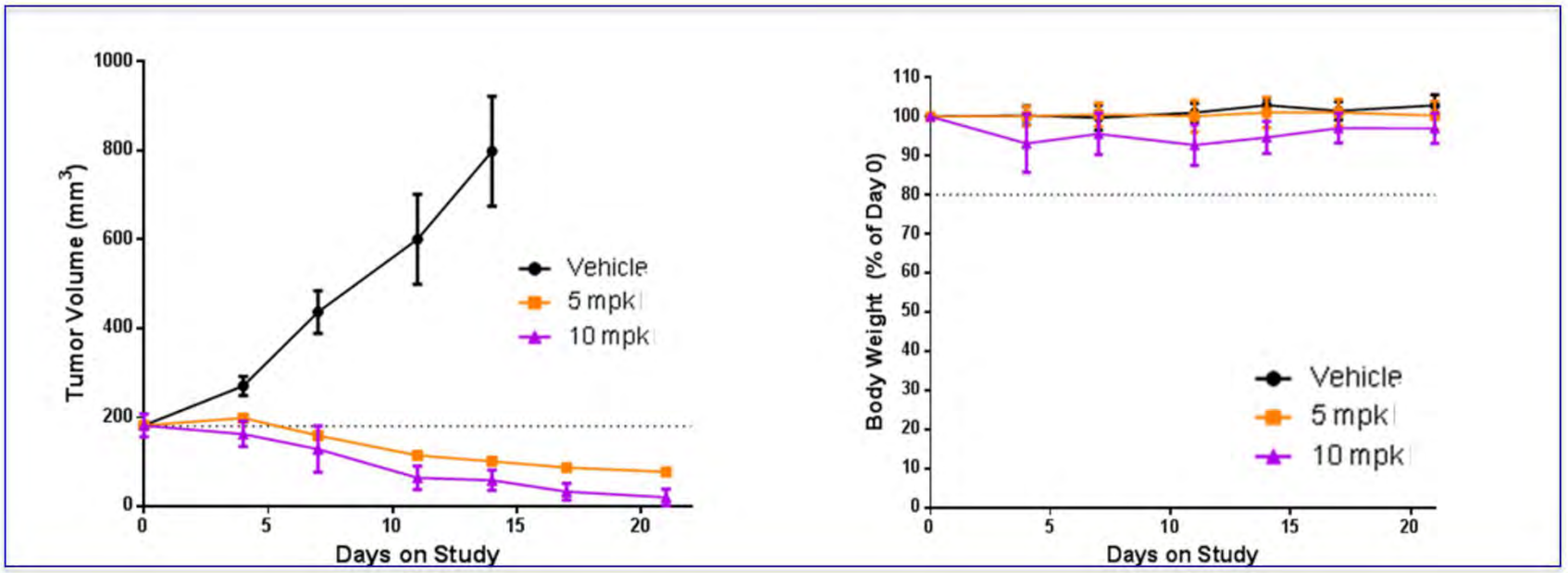
Tumor Xenograft Models Efficacy Experiments



End of Study

- tumor size
- body weight
- plasma conc.
- PD readout



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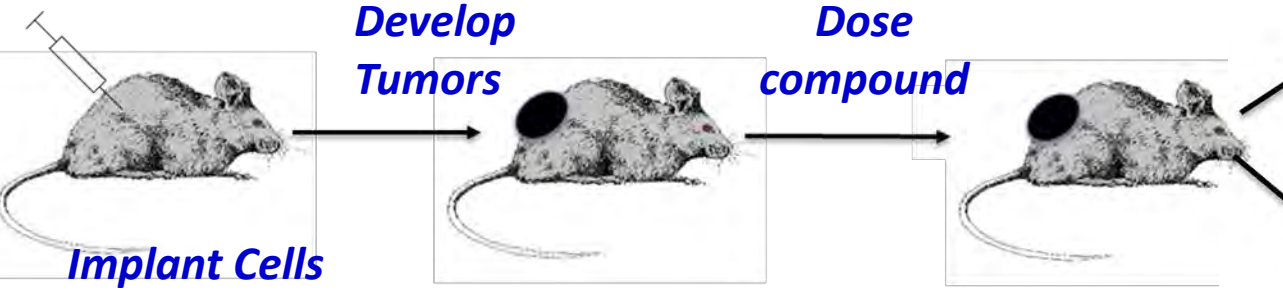
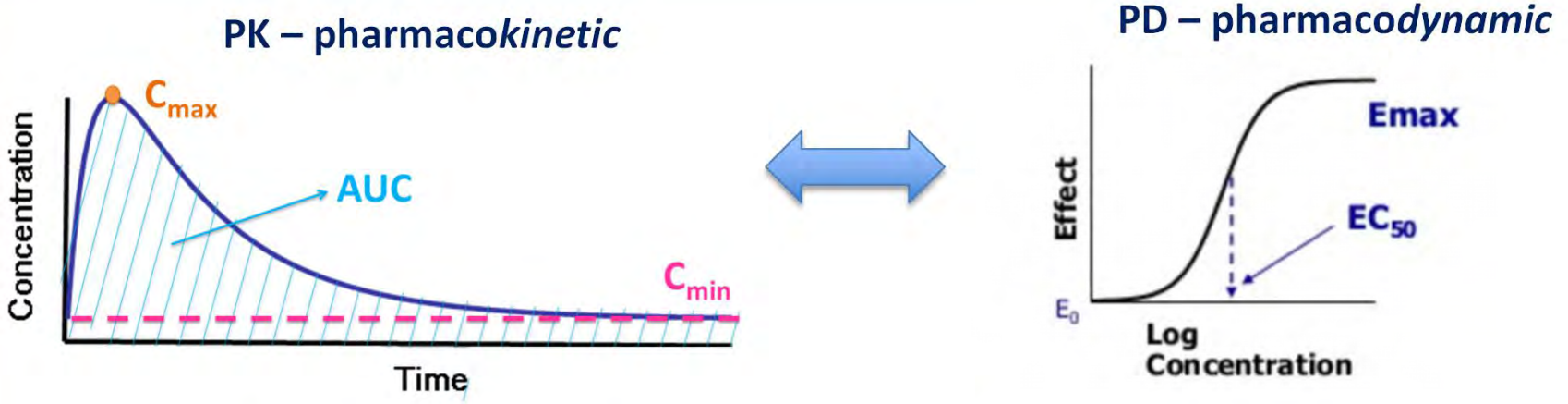
Tumor Xenograft Models
Acute PK/PD Experiments





Correlate drug concentration in plasma with pharmacological response

How much target inhibition do we need and for how long ?

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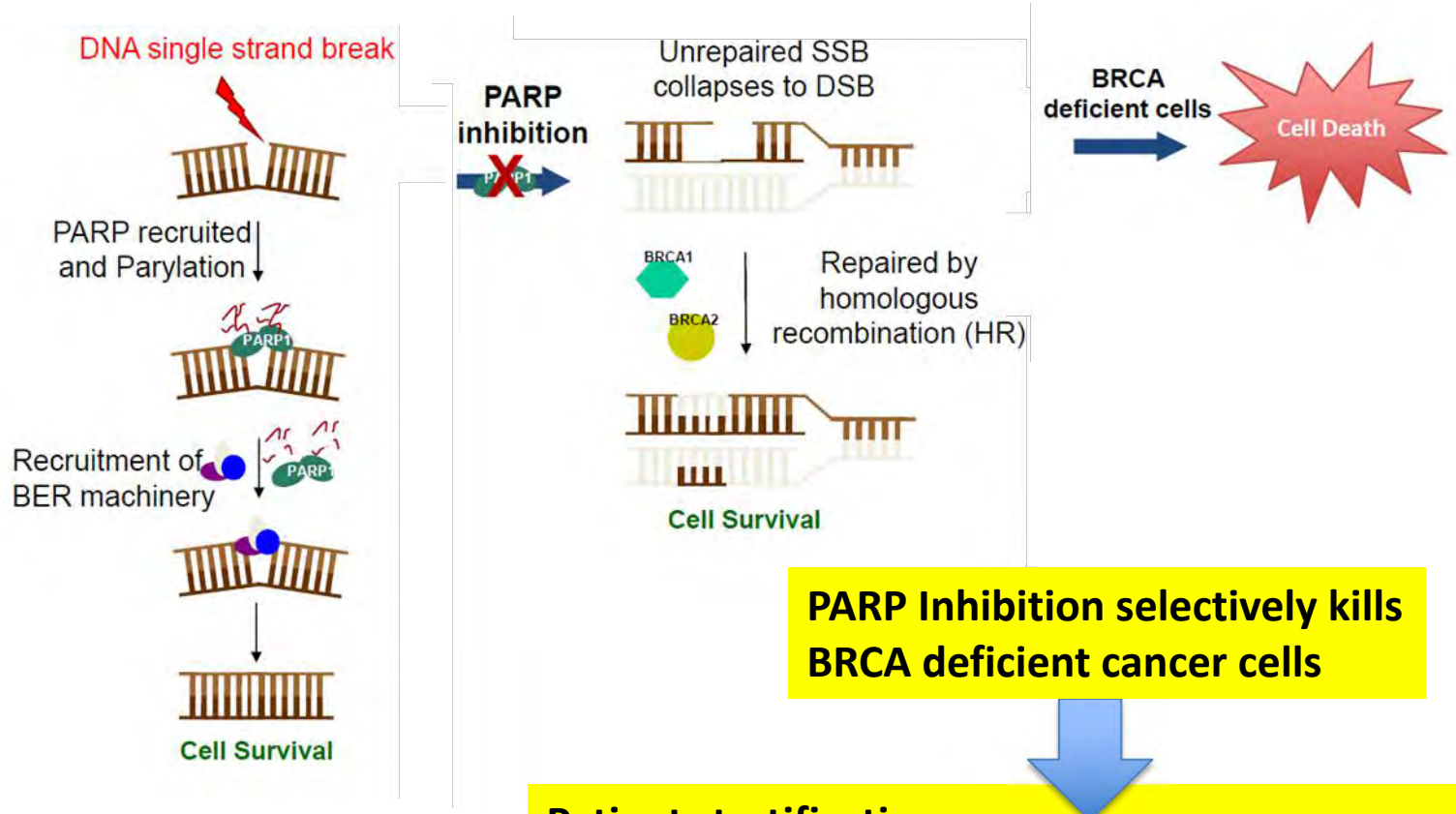
One Example: Niraparib PARP Inhibitor

PARP Inhibitors are Context-Specific Anti-Cancer Agents

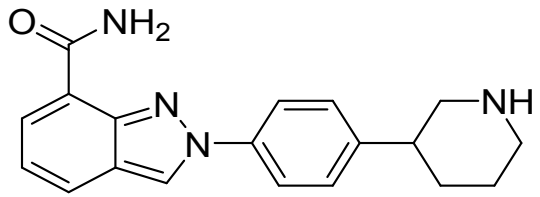


PARP Inhibition selectively kills BRCA deficient cancer cells

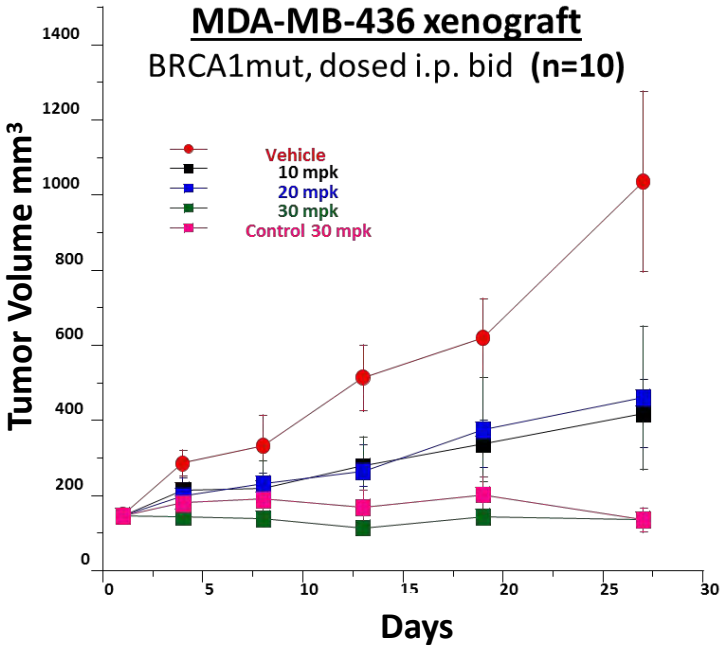
Patient stratification :
ovarian / breast cancer patients with BRCA-1 /-2 mutations

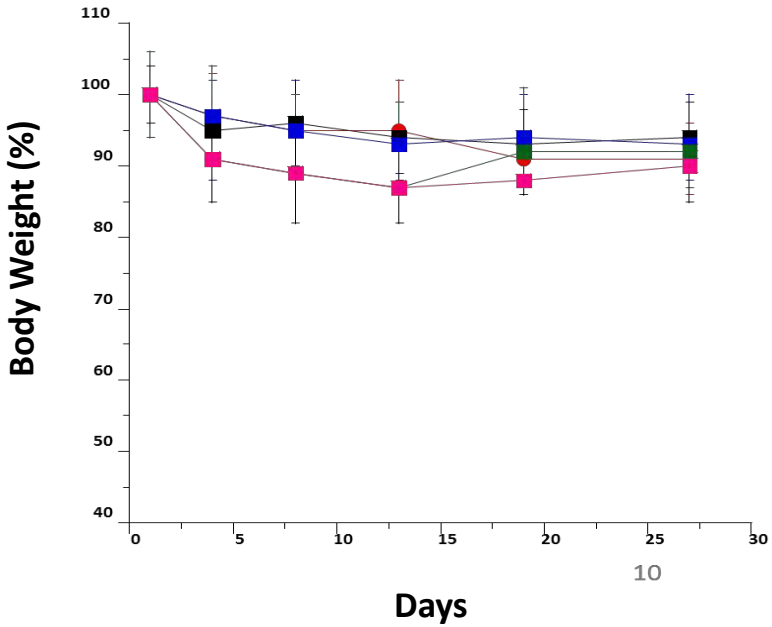
PARP = Poly(ADP-ribose) Polymerase

One Example: Niraparib PARP Inhibitor



	CC_{50}(nM)
MDA-MB-436 (BRCA1mut)	38
CAPAN-1 (BRCA2mut)	460





Jones et al, J. Med. Chem., 2015, 58, 3302

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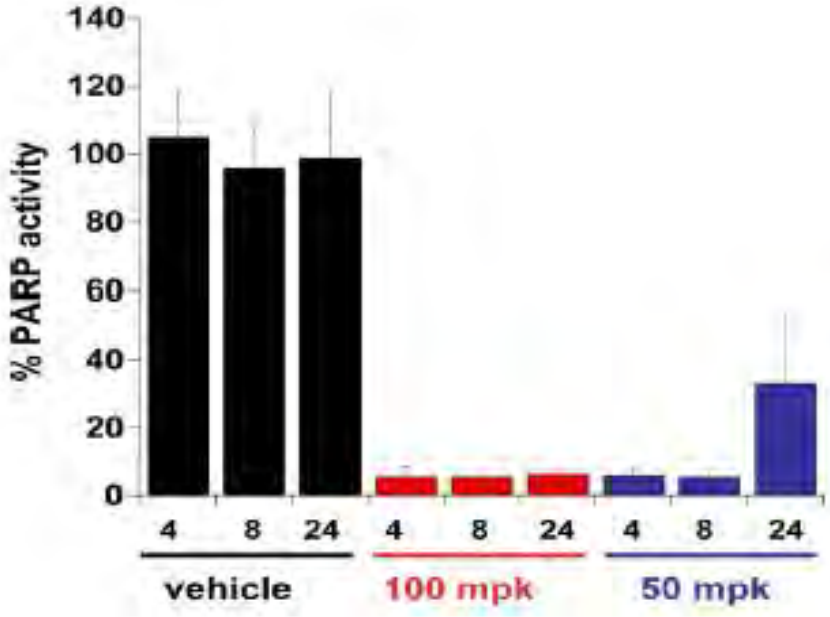
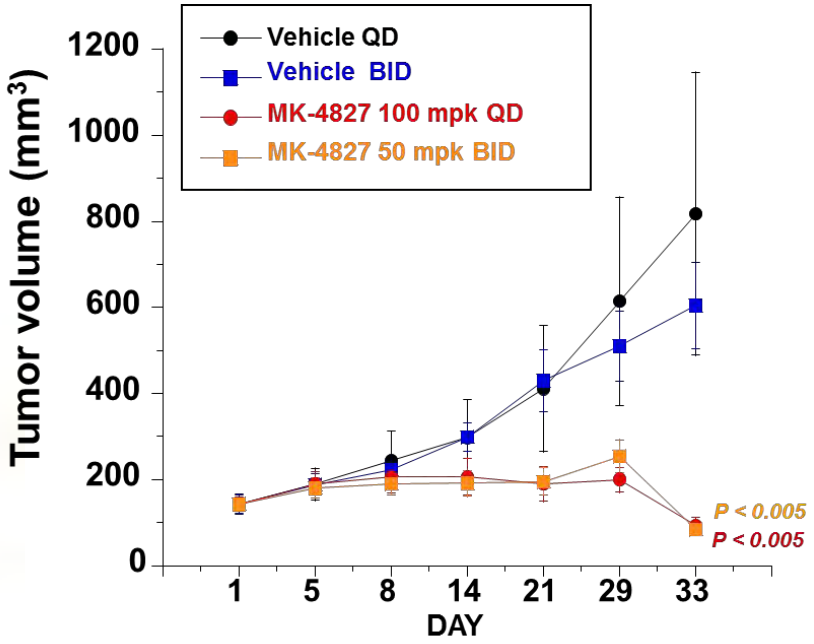
One Example
PARP Inhibitor Niraparib

Acute PK / PD experiment
– How much target inhibition do we need and for how long ?

Target Engagement in TUMOR TISSUE

Tumor Tissue homogenate → **Measure of PARP inhibition in Tumor Tissue**





Maximal efficacy seen with > 90% PARP inhibition in tumors 24 x 7

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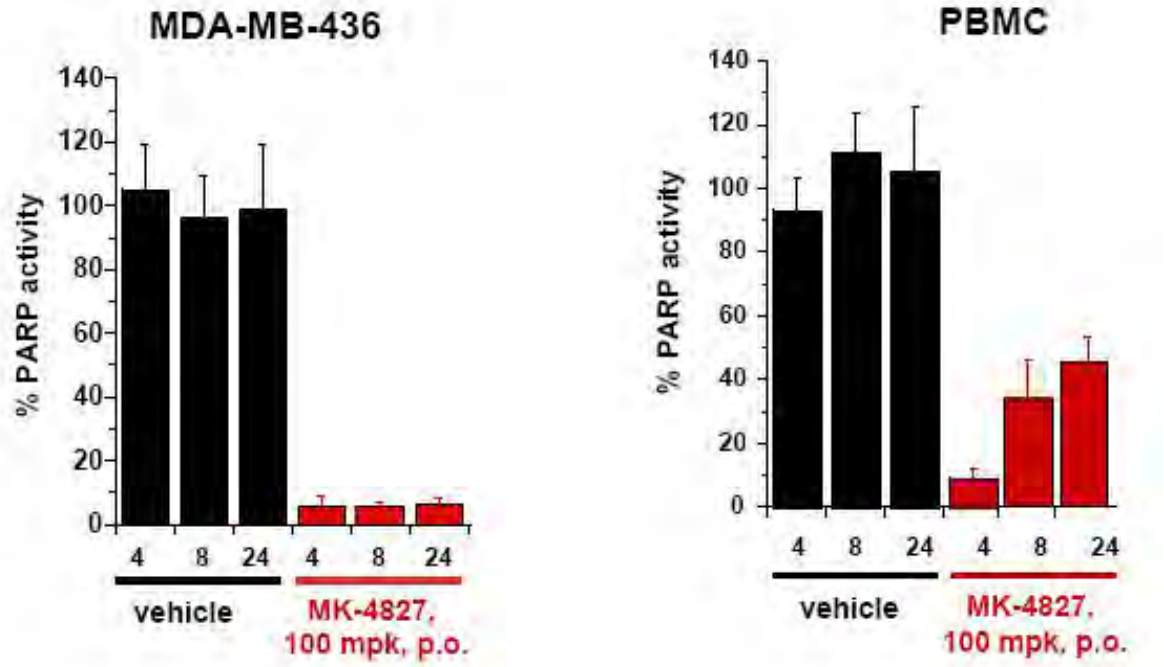
One Example
PARP Inhibitor Niraparib

Acute PK / PD experiment
– How much target inhibition do we need and for how long ?

Target Engagement in PERIPHERAL TISSUE –
peripheral blood mononuclear cells (**PBMCs**)



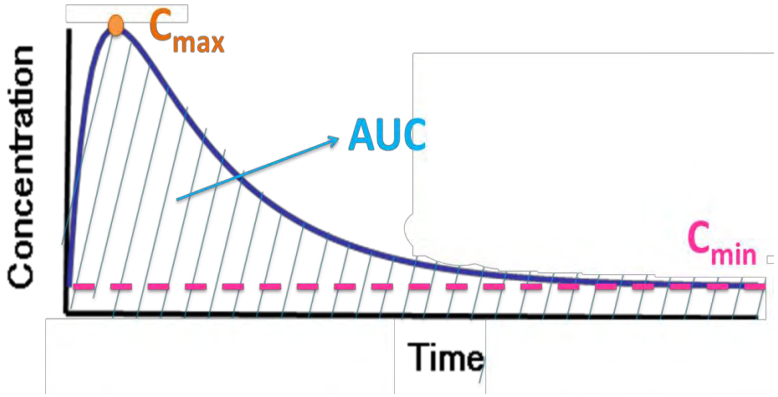
Maximal efficacy seen with > 50% PARP inhibition in PBMCs 24 x 7

Assay being used to support Phase I studies

From Efficacy Models to Clinic Translation of the PK / PD Relationships

- Establish solid PK / PD relationships
- Understand the "driver" for efficacy which PK target? C_{max}? C_{min}? AUC?

Predict dose & dosing regimen to achieve target drug exposure and elicit clinical response



Additional PK studies in RAT, DOG, MONKEY

Predict Human PK
e.g. allometric scaling

Use established PK /PD relationships

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Outline

- Preclinical testing of EFFICACY
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  - In vivo target engagement, biomarkers of response

- **Preclinical Safety and Toxicology Studies**
  - **Regulatory aspects / Requirements for IND Filing**
  - **Risk assessment in drug discovery and early development**
  - **Therapeutic Window**

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Toxicology

- **Definition**

The study of adverse effects produced by a potential therapeutic in an appropriate model

- **It's all about dose…..**

"All substances are poisons
and there is none which is not a poison.
Only the right dose differentiates
***poison from remedy*"**

- ***Paracelsus (***1493-1541 AD)
  The father of toxicology

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Toxicology Studies

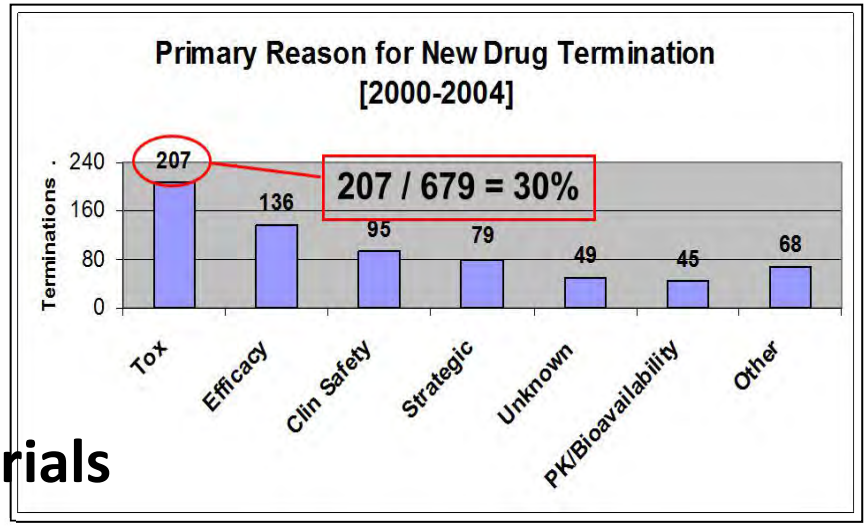
➢ Objectives

- **Define a safe entry dose for the first human exposure**
- **Understand the toxicological profile of a pharmaceutical**
  - identify the toxicity risks –target organs? reversibility?
  - dose response relationship – from safe to "adverse"

➢ Relevance

- ***estimate human risk***
- **Toxicology findings are *a major reason of failure* in clinical trials**
- ***And….Regulatory requirement !!***

see next slide



2005 Data - Centre for Medicines Research International

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Toxicology Testing Is Highly Regulated

- **Regulated by FDA & other national/regional governing bodies**

- **Major markets (USA, Europe, Asia) come together to form International Conference on Harmonization (ICH)**

  Guidance for worldwide development on safety, efficacy, quality of pharmaceuticals

  - ICH S9 - "Nonclinical evaluation for anticancer pharmaceuticals"
  - ICH S6 - "Preclinical safety evaluation of biotechnology pharmaceuticals".

- **BUT there is no typical toxicology program: *studies are designed to support a specific product for a specific clinical indication***

  - intended use (cancer therapeutic, chronic use...)

  - clinical plans (healthy volunteers, diseased patients)

  - route of administration, duration of dosing

  - previous finding with related agents....

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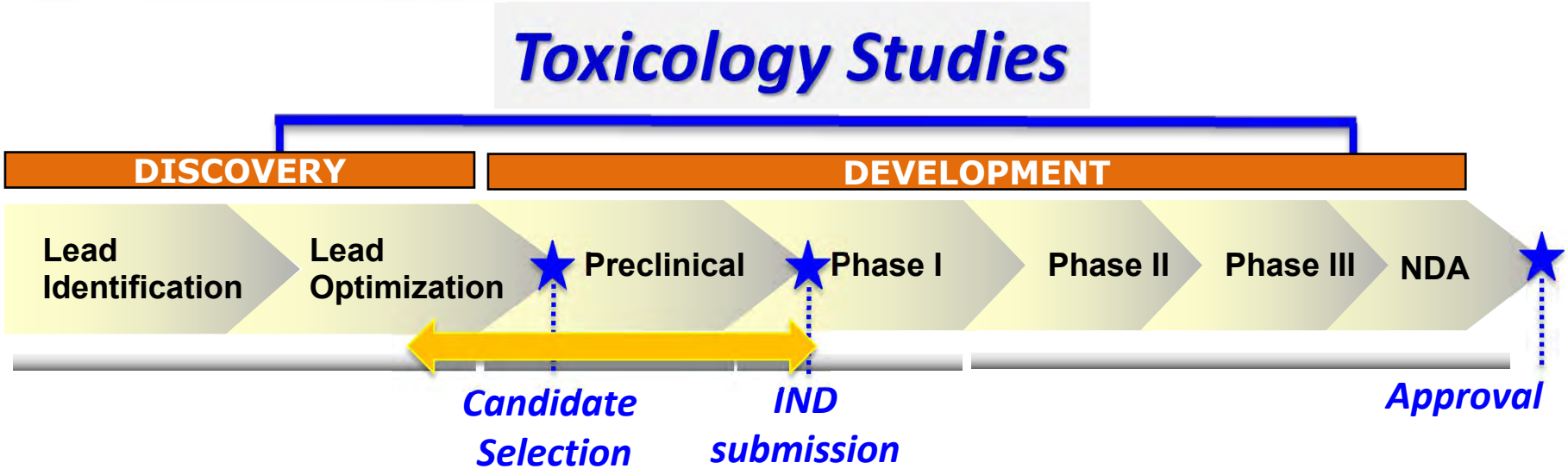
Safety Assessment in Drug Discovery and Development



Types of Toxicology Studies

- During drug discovery
- IND-enabling studies

} Today's focus

- Studies supporting clinical development/ marketing application (NDA)

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Some Definitions

➢ IND – Investigational New Drug (Application)

Goal: robust data package to allow safe administration to humans

- **Animal Pharmacology and Toxicology Studies**
  Efficacy, Toxicology Profile, Determine safe entry dose in humans

- **Chemistry and Manufacturing Information**
  Drug Substance: composition, stability, adequate production

- **Clinical Protocols and Investigator Information**
  Detailed protocols for proposed clinical studies

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Toxicology Studies During Drug Discovery
Exploratory Studies

GOAL: **Preliminary assessment *to identify & mitigate potential safety risks***

Help advance high quality drug candidates into development

Selectivity Screening
off-target pharmacology

Cardiovascular toxicity

Genetic toxicity

Metabolic activation

***In vivo* Tolerability**

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Toxicology Studies During Drug Discovery

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GOAL: **Preliminary assessment *to identify & mitigate potential safety risks***

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Selectivity Screening
off-target pharmacology

- panel of known receptors, transporters, enzymes
- binding or biochemical assays

CAUTION:

- *effect of binding/biochemical assay*
  does not necessarily correlate with functional effect
- off-target pharmacology does not predict for toxicity

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***In vivo* Tolerability**

- **rodent and non-rodent species – rat, dog**
- **escalating doses – single or repeated administration - *study design can vary***

One example:

3 dose levels + control - 10, 100, 750 mg/Kg + untreated
5 rats per group
7 days; necropsy at day 8;
endpoints: - ***Toxicokinetics (TK);*** physical signs;
serum chemistry; histophatology on organ and tissues

Advantages:

- **early read on tolerability and exposures**
- **dose-range finding: informs design of future GLP-studies**
- **reduced risk of failure to demonstrate toxicity**

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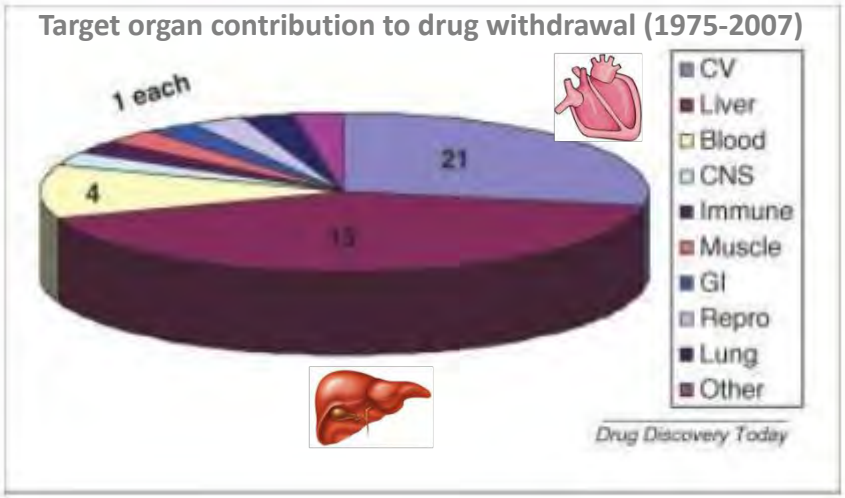
Cardiovascular Toxicity

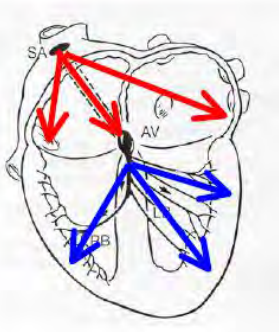
- **One of the leading cause of drug withdrawal**



- **>50 compounds removed from market due to risk of potentially *lethal ventricular tachycardia***
- ***Need to de-risk early !***

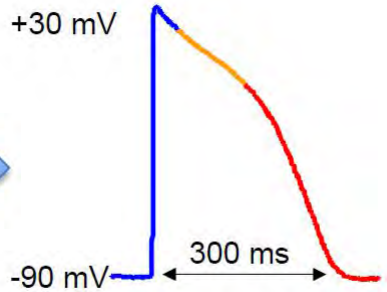
Biological Background

- **Heart beat: highly coordinated changes in cell membrane potential**
- **Ions' flux through protein channels modulates cell potential**



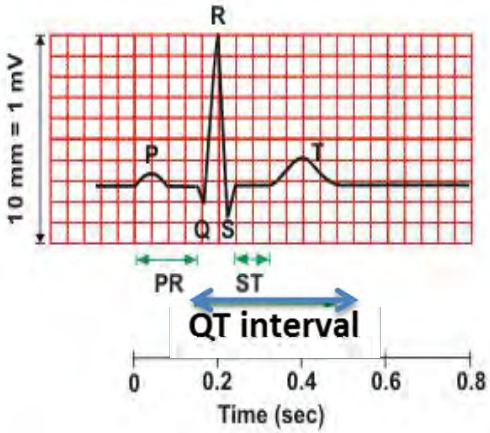
coordinated electrical impulses

open of voltage-gated ion channels



Na^+ influx Ca^{++} influx K^+ efflux

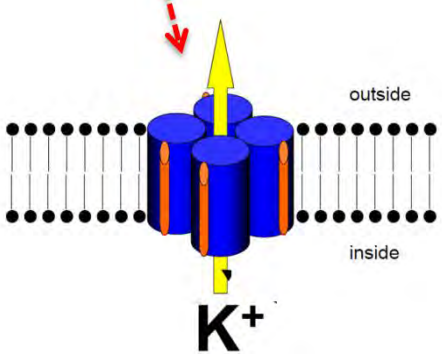
ECG records electrical activity



I_{kr} Channel

Encoded by hERG

Human-Ether-a-go-go Related Gene



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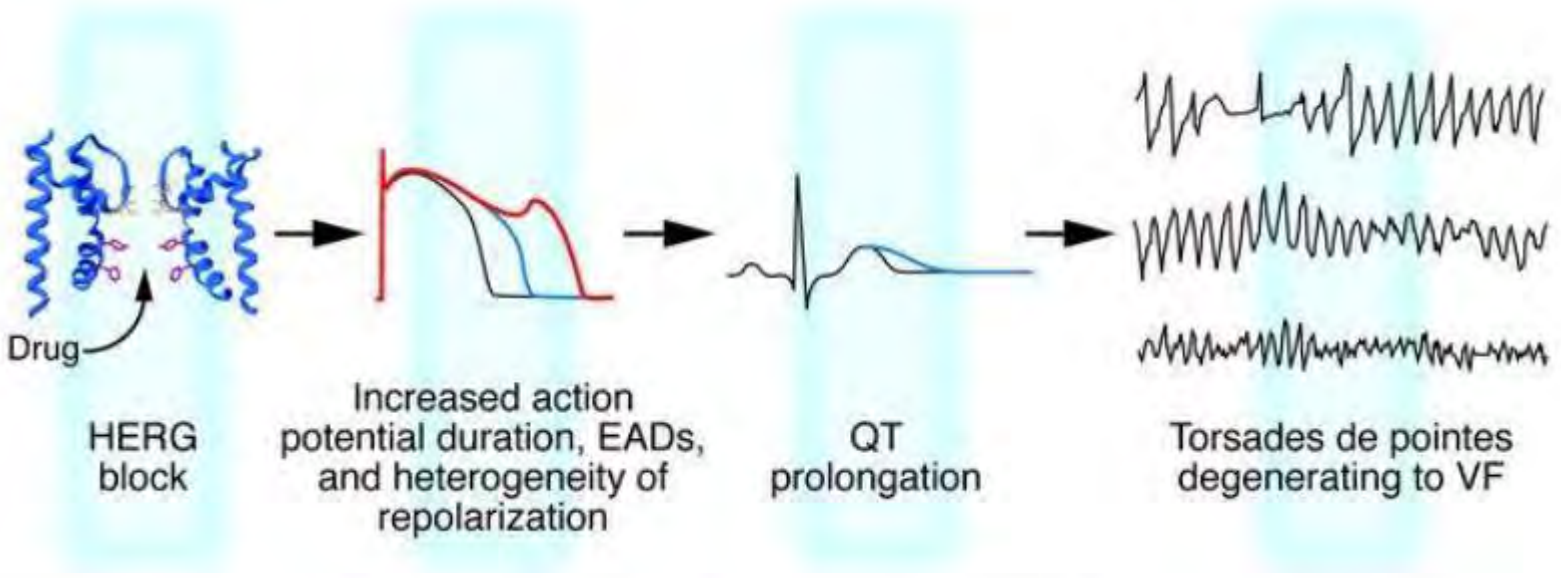
Cardiovascular Risks and hERG Channel

hERG block may results in slow repolarization, prolonged QT and fatal arythmia



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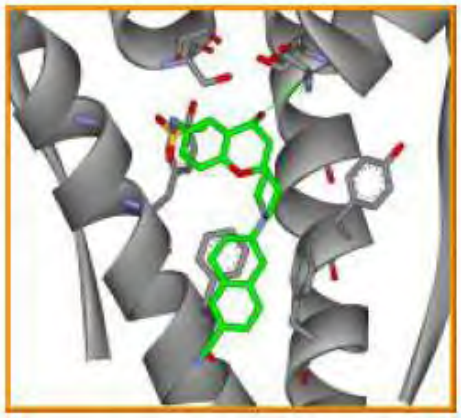
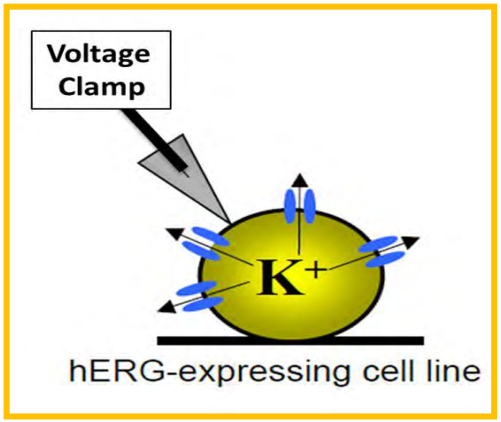
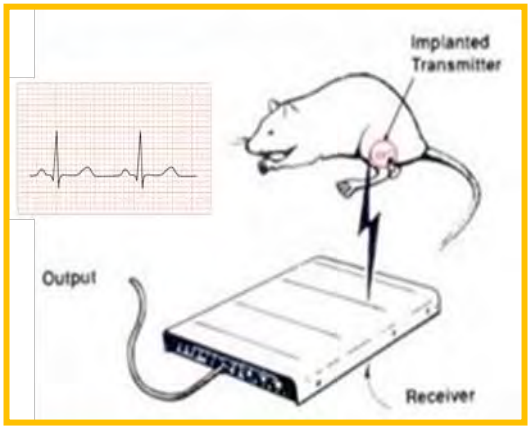
Assessing Cardiovascular Risk







receptor binding only → *functional assays* → *physiology of whole animal*

hERG Binding assay

- drug displaces a radio-labeled hERG ligand

"Patch-Clamp" assay

- direct measure of changes in K^+ hERG-current

Ion Channel Panel

- Na^+ and Ca^{++} current

In Vivo studies

- several models available: anesthetized Guinea Pig; conscious *telemeterized rat*, dog or monkey….

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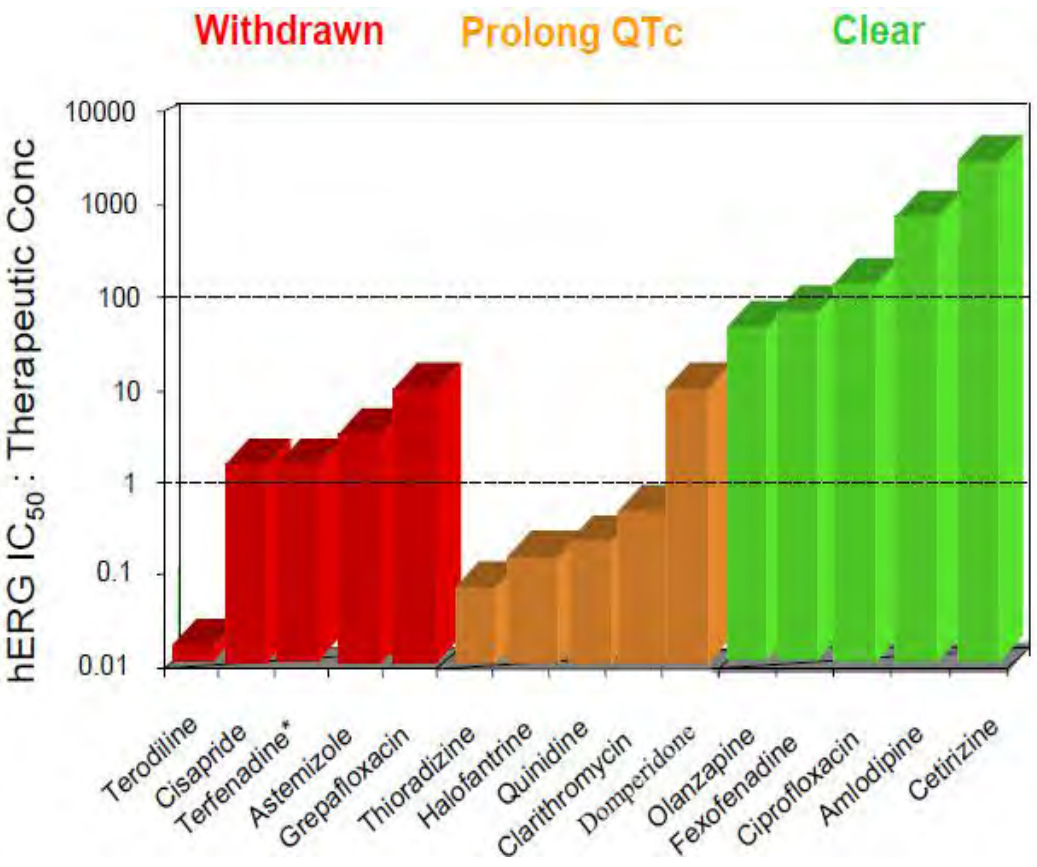
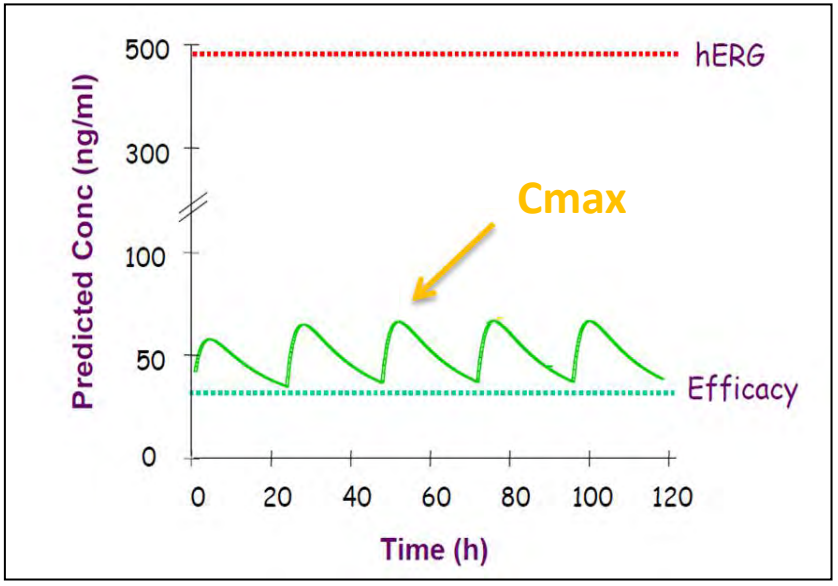
What Constitutes a Green Light To Enter Development

$$\text{hERG } IC_{50} \geq 30 \text{ uM} \quad \& \quad \frac{\text{hERG } IC_{50}}{\text{Projected Clinical } C_{max} \text{ free}} \geq 100$$





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Genetic Toxicology

Genotoxicity describes a deleterious action on a cell's genetic material affecting its integrity – (drug or radiation)

- **Many in-vitro mutagens are in vivo carcinogens**
- **Regulatory guidance: DNA reaction has *no safe effect level***
- ***Positive findings: typically No-GO for candidate development (non-oncology programs)***

- **Core battery of tests for risk assessment**

- Mutagenicity	(in bacterial strain)
- Chromosomal damage	(needs eukaryotic cells)
- in vitro	
- in vivo	(rat bone marrow)

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Toxicology Studies During Drug Discovery
Exploratory Studies

GOAL: **Preliminary assessment *to identify & mitigate potential safety risks***

Help advance high quality drug candidates into development

Selectivity Screening
off-target pharmacology

Cardiovascular toxicity

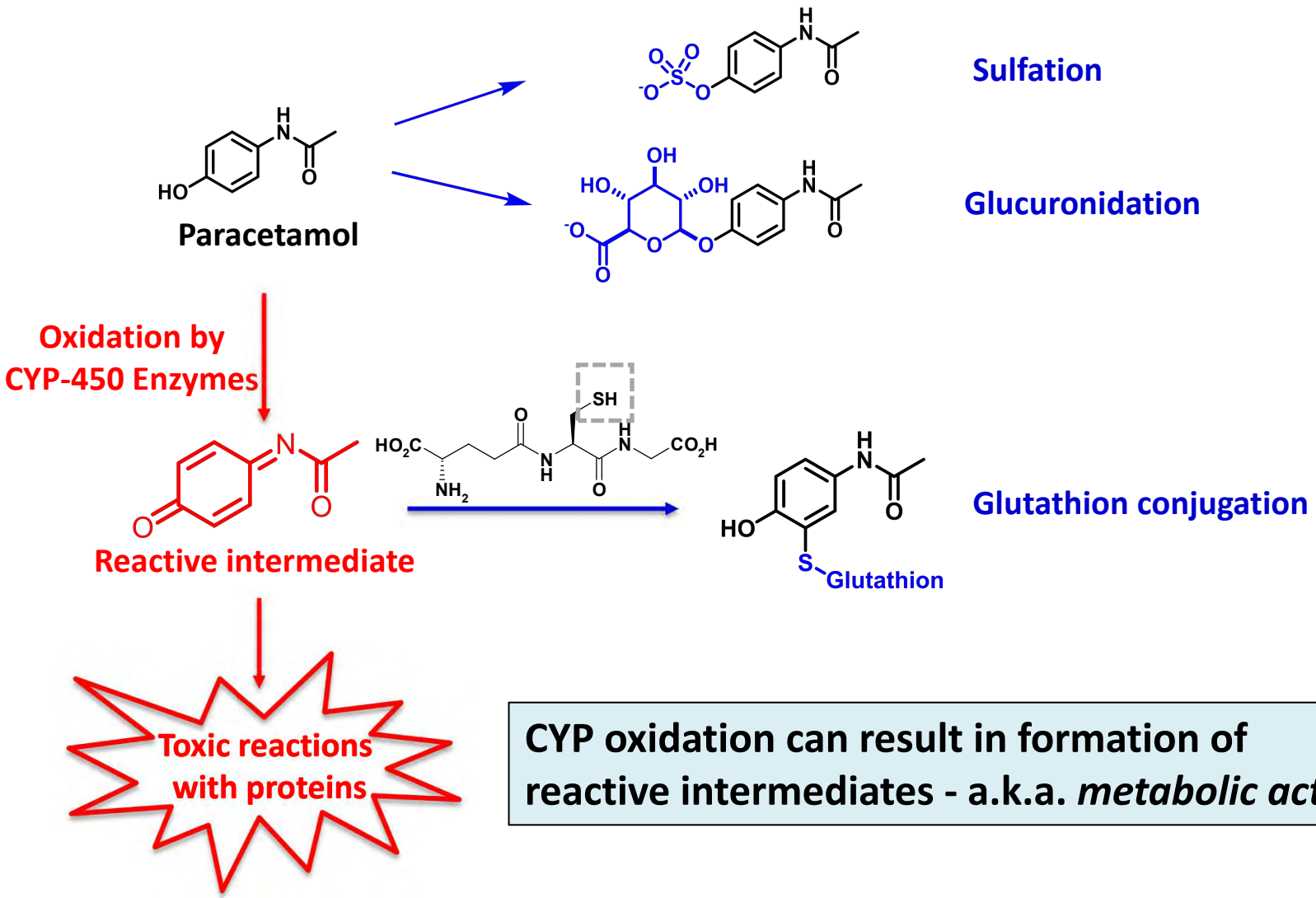
In vivo Tolerability

Genetic toxicity

Metabolic activation

Metabolic Activation

- One example: Liver metabolism of paracetamol



CYP oxidation can result in formation of reactive intermediates - a.k.a. *metabolic activation*

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Metabolic Activation and Its Toxicological Implications

➢ Hepatotoxicity – liver is main organ of metabolism!

➢ Risk of Drug-Drug-Interaction (DDI)

- reactive species can inactivate CYP_{450} itself
- metabolism of compound and co-administered drugs will be impaired, exposure will be higher, *toxicity risk*!!

NOTE – this is ONLY ONE of the way to have DDI….
much more to say, but not for today's lecture

➢ Idiosyncratic reactions

- serious / fatal **immune** mediated responses; small % of treated population;
- not predicted by animal toxicology
- not seen until Phase III and beyond

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Metabolic Activation and Its Toxicological Implications

What can we do to de-risk?

- **Select a good candidate for development!**
  - derived from a thorough Lead Optimization process
  - no structural alerts – see Lead Optimization lecture

- **Perform the right screens**
  - e.g. - Time-Dependent Inhibition of CYP_{450} isoforms
  - e.g. - Adducts with glutathione and other agent trapping agents

- **De-risk early with In vivo studies**
  - assess direct organ toxicity, such as liver toxicity

- **Strive for low dose**
  - protective mechanisms such as Glutathion conjugation are saturable
  - potency of therapeutic agent matters !

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Repeat Dosing GLP Toxicology Studies

- **Goals**: - Understand **toxicology profile** (target organ toxicity, is toxicity reversible?)
  - Estimate **therapeutic index**
  - ***Define entry level into the clinic***
    - » Maximum Tolerated Dose (MTD)
    - » **No Observed Adverse Effect Level (NOAEL)** ⟸
    - » No Observed Effect Level (NOEL)

- **How**: - **one rodent and one non-rodent species**
  Rat and Dog default - but pharmacological relevance of species is key!!
  - **mimic intended clinical route of administration**
  - **cover duration of clinical administration** (often 28 days)

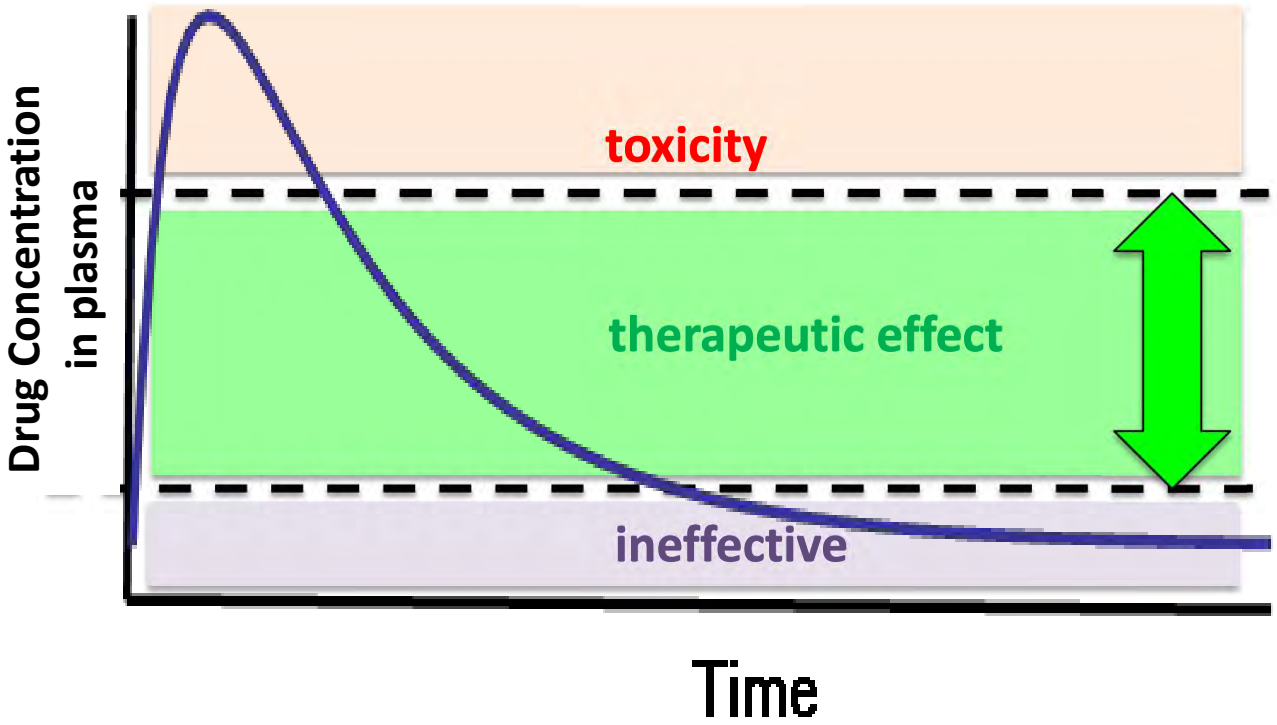
- **Studies expected to show toxicity, and understand if it is reversible**
  - Extra arms included to show reversibility or progression

Therapeutic Index TI

$$TI = \frac{\text{drug exposure level at NOAEL*}}{\text{drug exposure level required for efficacy**}}$$

* AUC, C_{min} and / or C_{max} at NOAEL as defined by general toxicity studies

**Minimal efficacious exposure as defined by efficacy studies AUC, C_{min} and / or C_{max}



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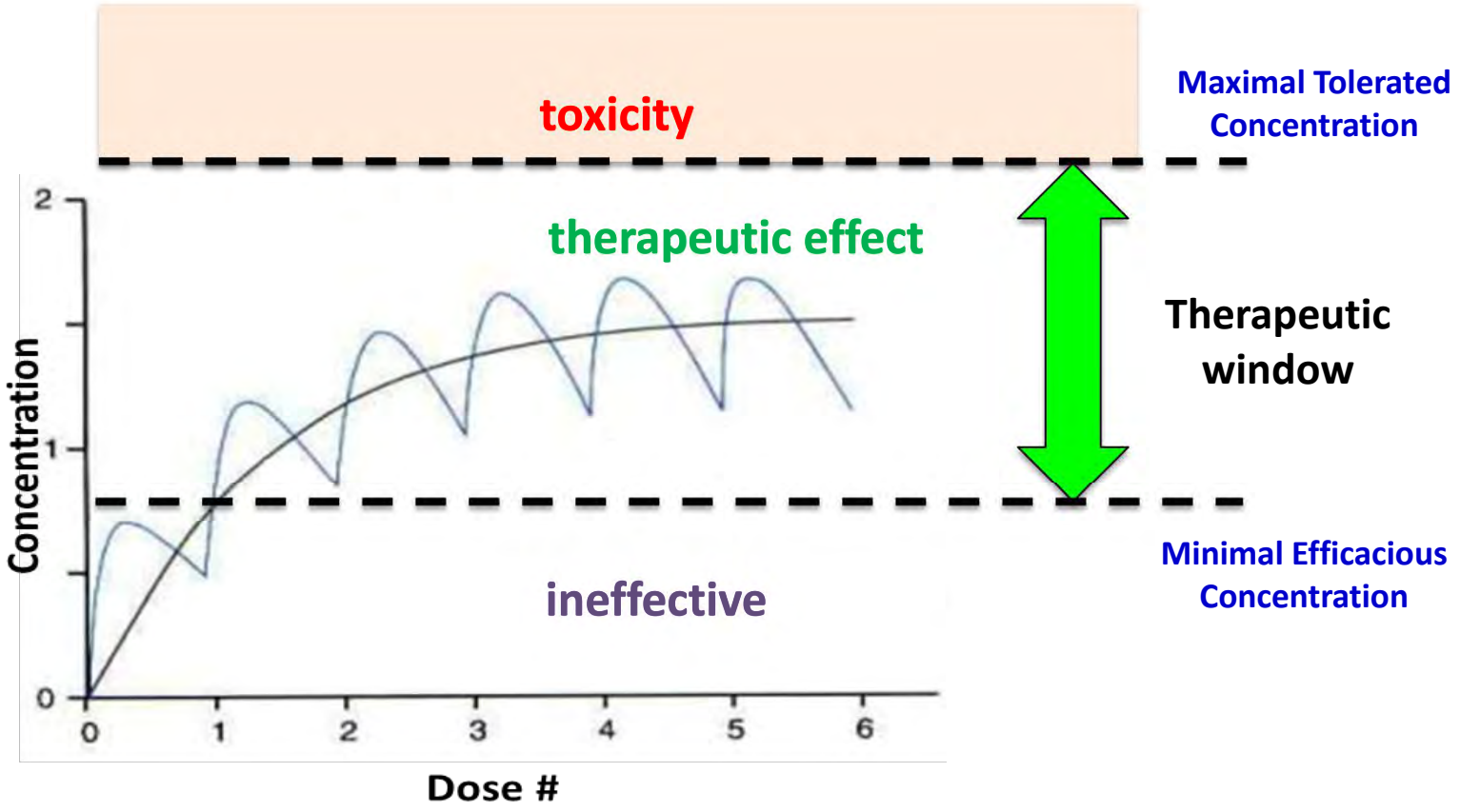
Therapeutic Window

Plasma exposure in the context of repeated dosing



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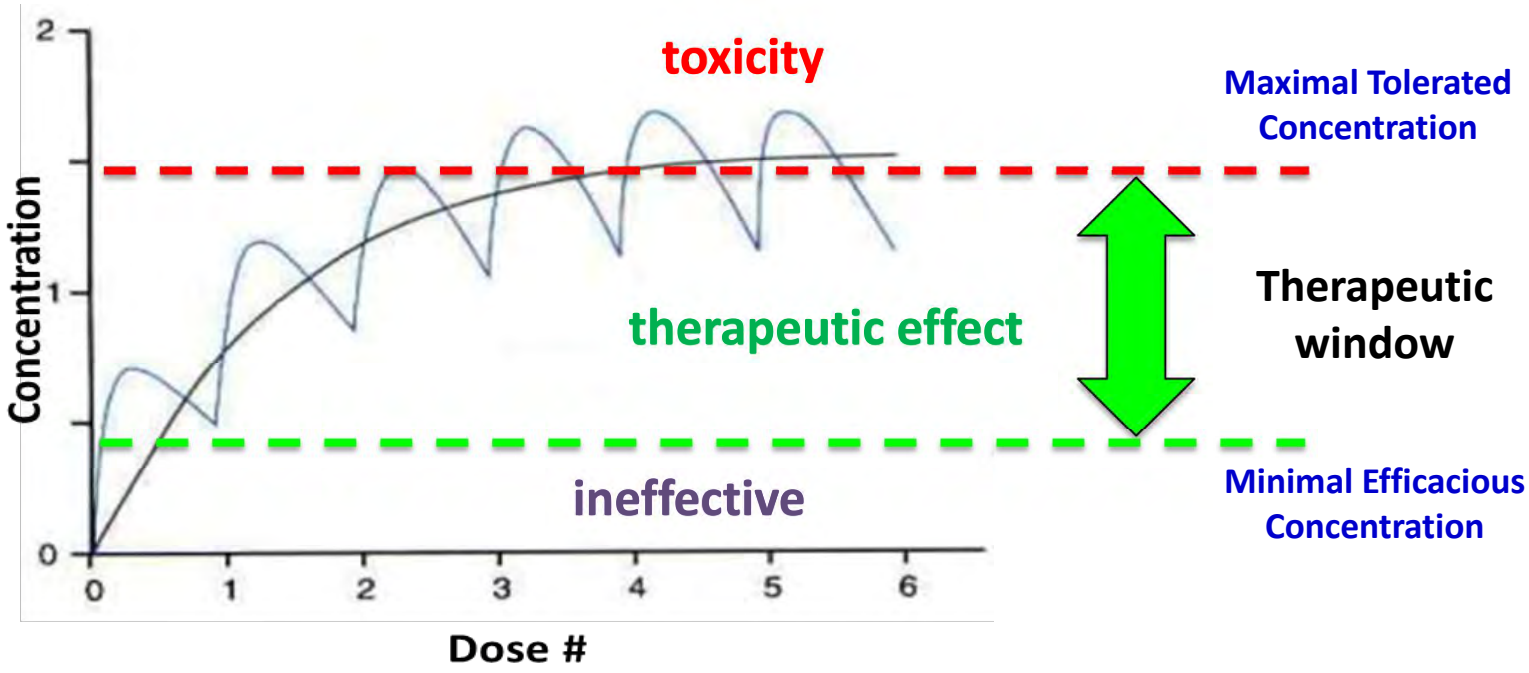
Therapeutic Window

Plasma exposure in the context of repeated dosing



- If limited therapeutic window, selecting the right dosing regimen can become a critical aspect of development

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Outline

- Preclinical testing of EFFICACY
  - Appropriate animal models
  - PK / PD - Relationship between exposure and efficacy
  - In vivo target engagement, biomarkers of response
- Preclinical Safety and Toxicology Studies
  - Regulatory aspects / Requirements for IND Filing
  - Risk assessment in drug discovery and early development
  - Therapeutic Window
- **Biomarkers**
  - **Parallel development of biomarker and drug**
  - **Pharmacodynamic biomarkers**
  - **Predictive biomarkers**

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Reiterative parallel development of drug and biomarker

- **PD biomarkers** (with PK)**:** "How much" and for "how long" modulating target and pathway; define the 'biologically effective dose range'
- **Predictive biomarkers of response**: for early antitumor signal searching

- **Preclinical:**
  - Validate "fit-for-purpose" biomarkers
    - Scientific validation – biologically relevant
    - Technical validation – robust and reproducible assay

- **Clinical:**
  - Incorporate biomarkers in phase I trial as exploratory endpoints to test biomarker
  - Reverse translation of data back to lab if necessary

Yap et al, Nature Reviews Cancer 2010

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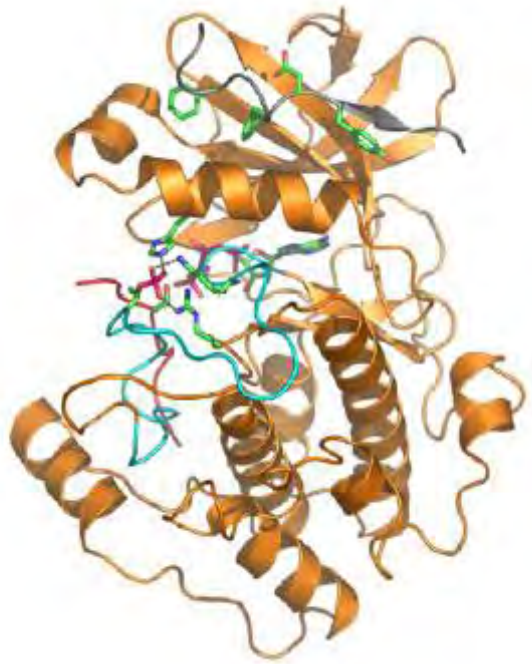
astex pharmaceuticals

ICR The Institute of Cancer Research

AKT inhibitor discovery program (2003)



Hit Generation

- High throughput Screen - AKT Kinase assay
  *Burns et al. (2006) J. Biomol. Screen, **11**, 822*
- Medicinal Chemistry on known kinase scaffold
  *Collins et al. (2006) Bioorg. Med. Chem. **14**:1255*
- Fragment-based screening - new scaffolds
  *Saxty et al. (2007) J. Med Chem. **50,** 2293*
  *Donald et al. (2007) J. Med. Chem. **50**, 2289*
- **Multiple chemical leads identified**
- **2 clinical candidates (AZD5363 and AT13148)**

David Barford – ICR

Yang et al, Nature Structural Biology 2002

FIH Phase I trial of novel AKT inhibitors
Assess PD effects to confirm target inhibition

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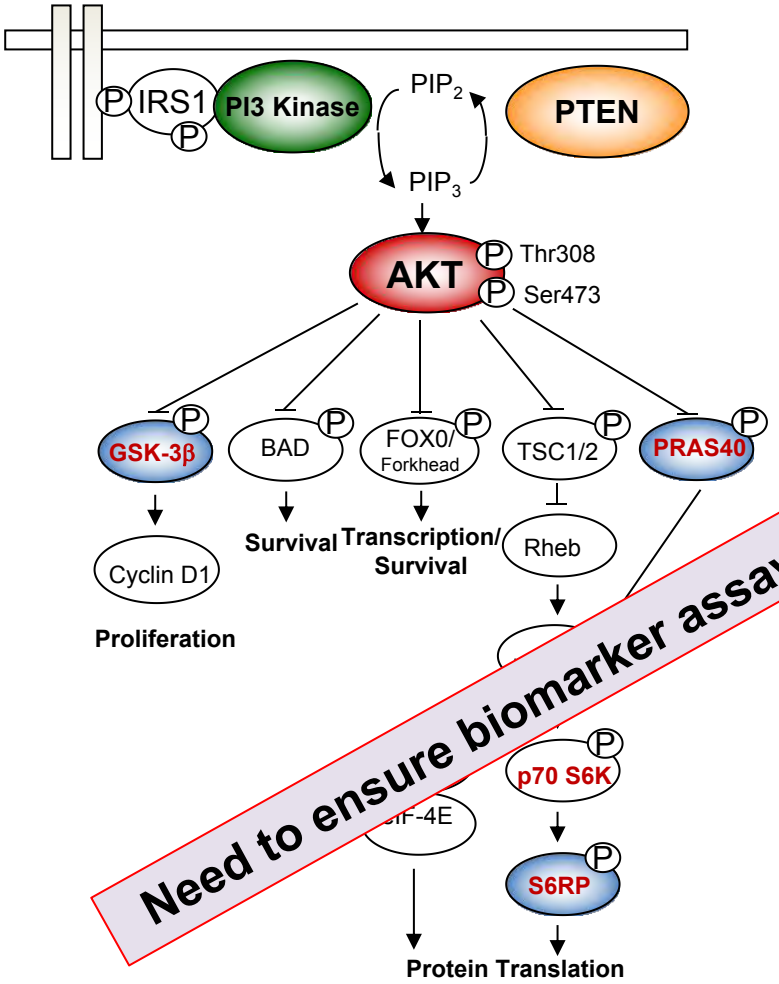
1. Pick biomarkers



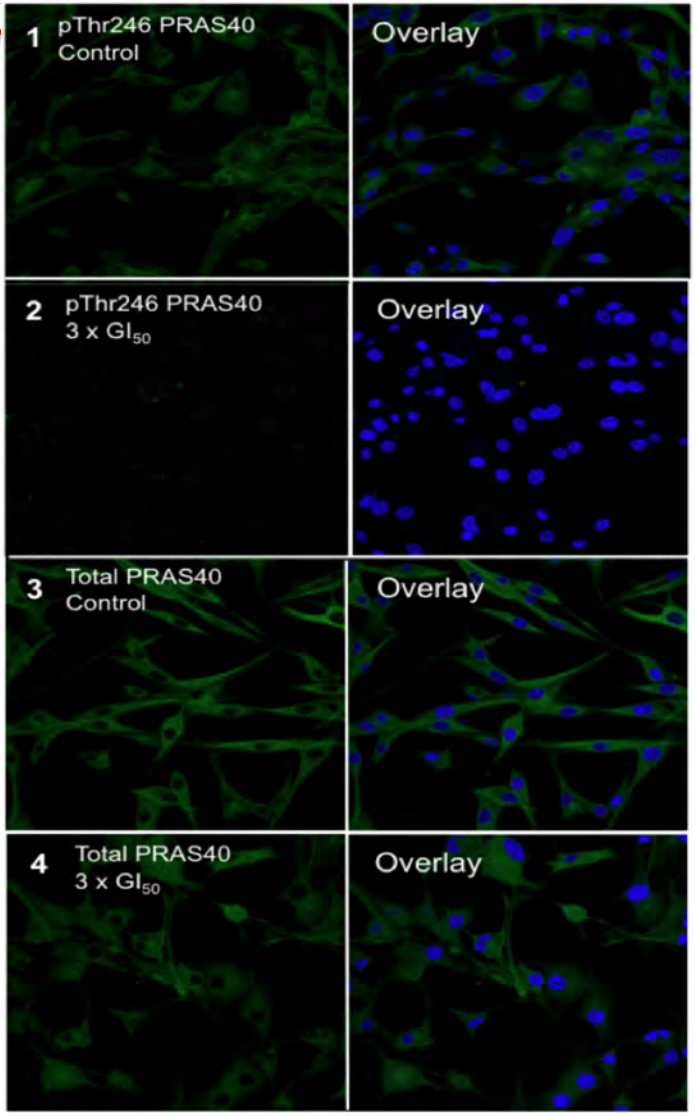
2. Pick tissue

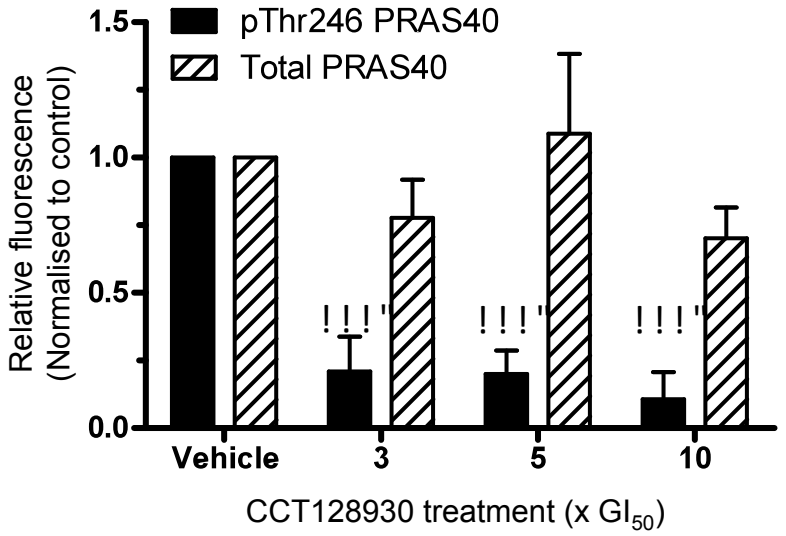
- **Tumor**
  - ELISA for phospho and total AKT, GSK3β, p70S6K and PRAS40
  - Only pre/post; not se… sampling (potential issues of intrap… variability); ***selected patients w… biopsiable disease (expansion)***
- **Blood – Platelet Rich Plasma (PRP)**
  - ELISA for phospho and total AKT, GSK3β, p70S6K and PRAS40
  - Serial sampling: multiple timepoints; ***all patients***
- **Hair follicles (eyebrows)**
  - Immunofluorescence for phospho and total PRAS40
  - Serial sampling: multiple hairs at each timepoint; multiple timepoints (minimize issues of intrapatient variability); ***all patients***

Need to ensure biomarker assay is analytically validated and fit for purpose

PRAS40 immunofluorescence studies ***in vitro***

PTEN-loss U87MG human glioblastoma cells



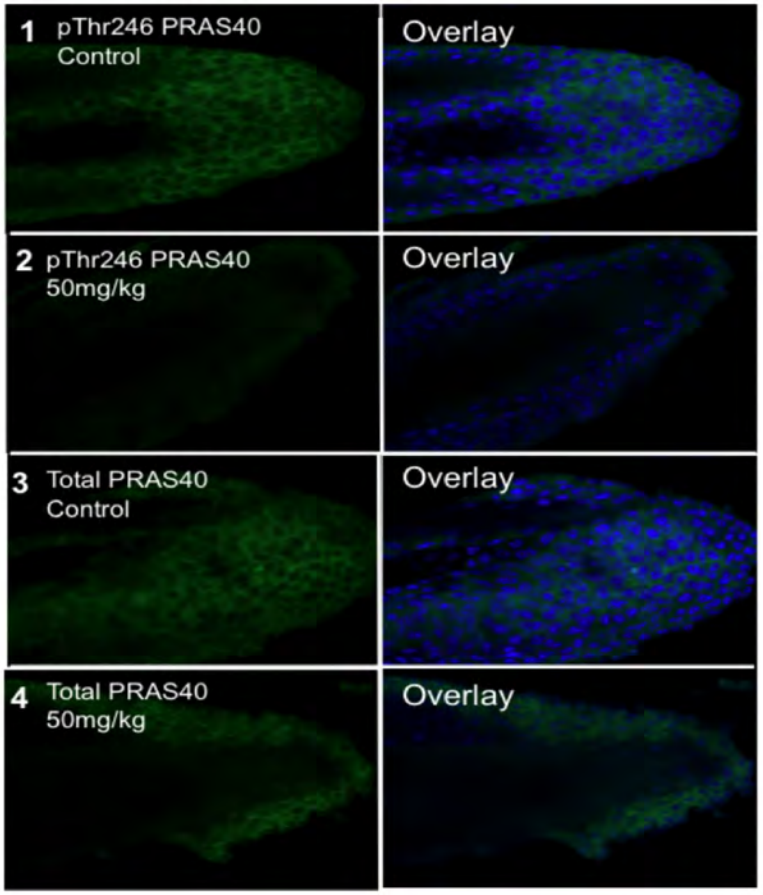


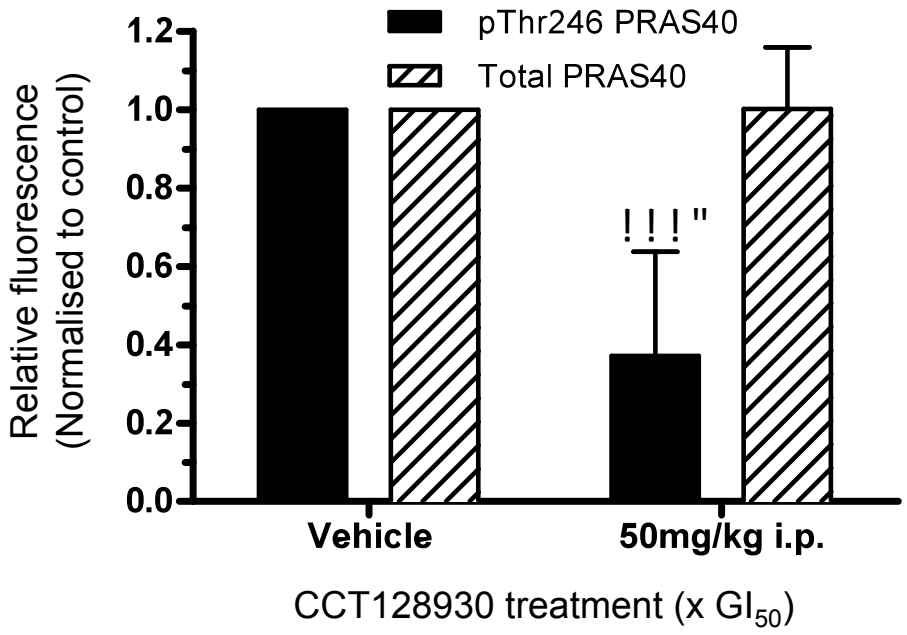
CCT128930 suppresses pThr246 PRAS40 immunofluorescence in vitro

Yap et al, Molecular Cancer Therapeutics 2011

PRAS40 immunofluorescence studies ***in vivo***

Whiskers from treated BALB/c mice





CCT128930 suppresses pThr246 PRAS40 immunofluorescence in vivo

Yap et al, Molecular Cancer Therapeutics 2011

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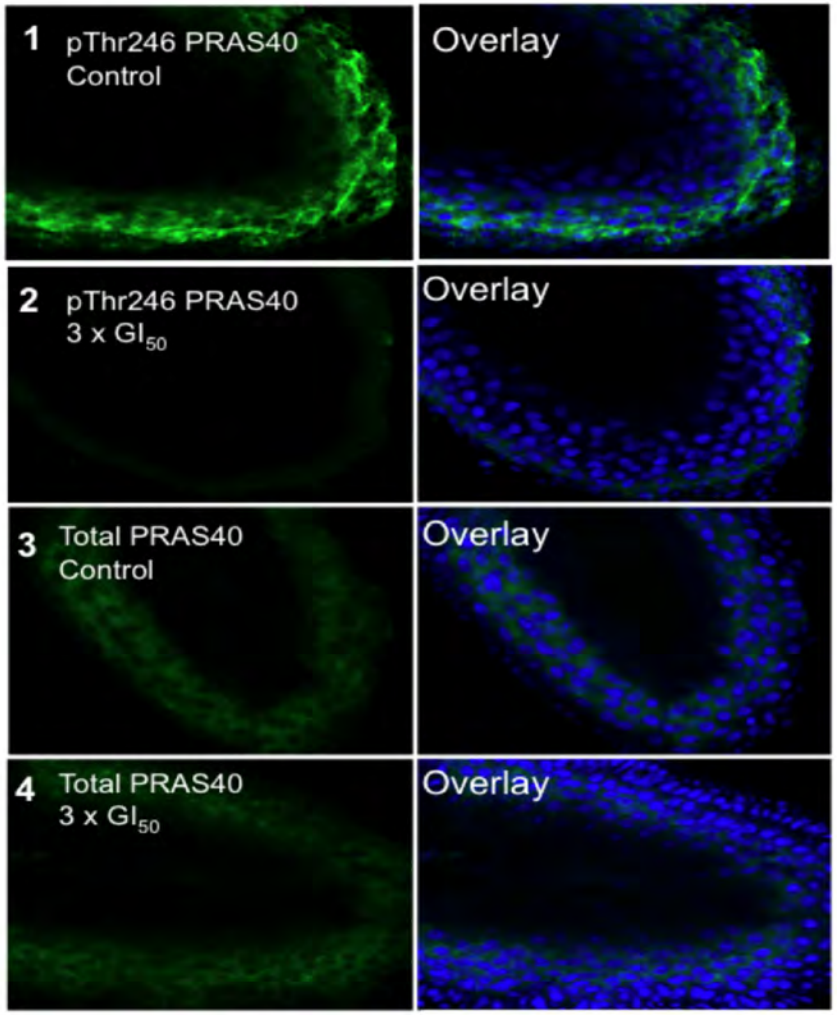
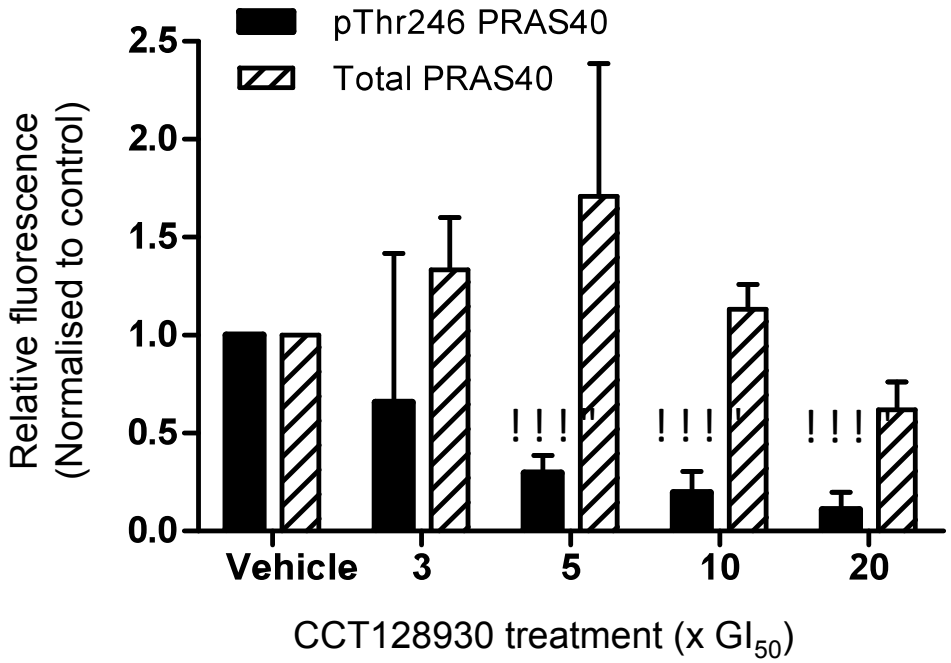
PRAS40 immunofluorescence studies ***ex vivo***

Hair follicles from human healthy volunteers





CCT128930 suppresses pThr246 PRAS40 immunofluorescence ex vivo

Yap et al, Molecular Cancer Therapeutics 2011

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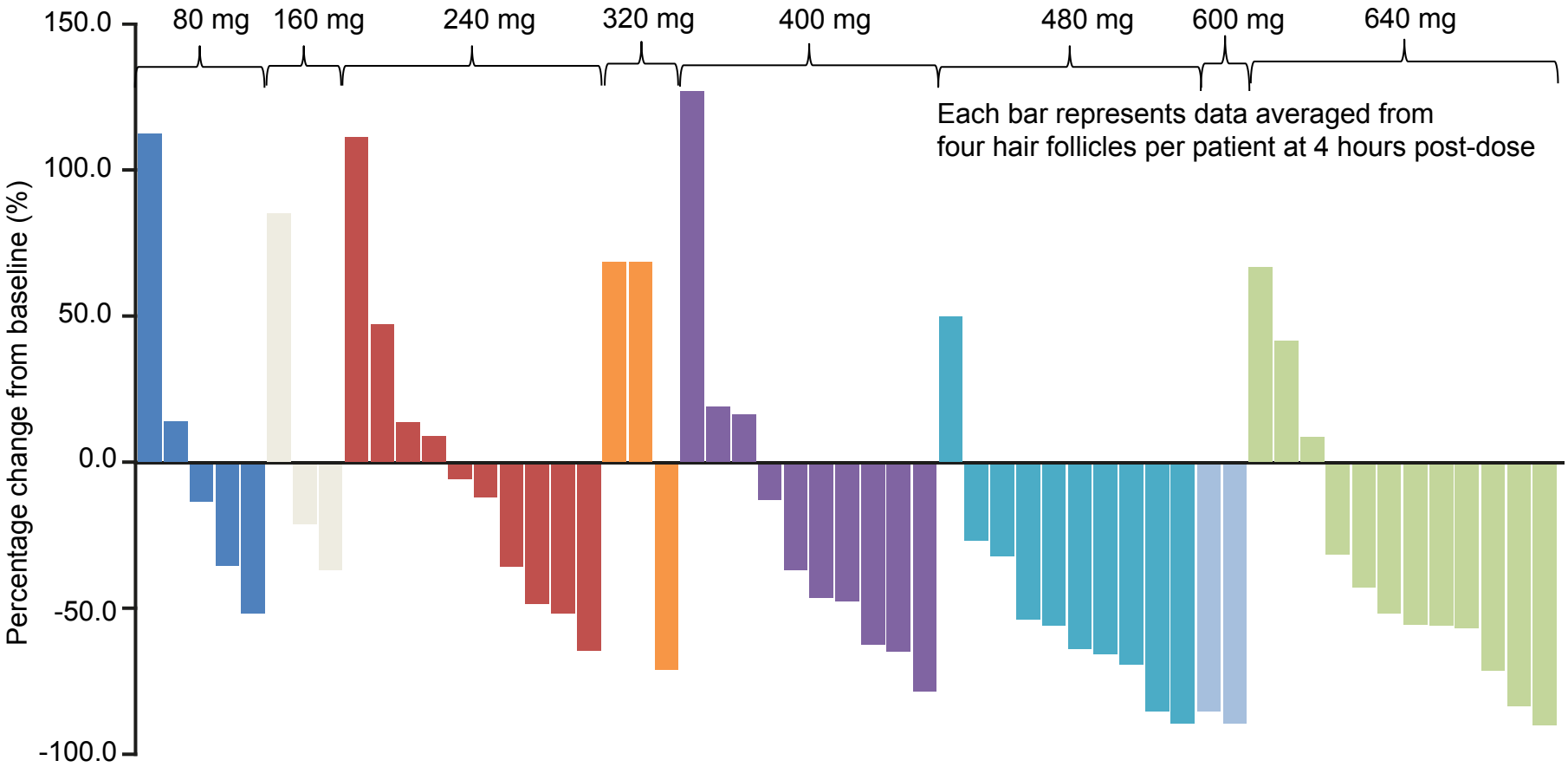
Phase I AZD5363 FIH Trial: all patients pPRAS40 inhibition in hair follicles



- Dose dependent activity: >50% inhibition at 400mg and above

AKT TARGET AND PATHWAY MODULATED

Banerji et al, ASCO 2015

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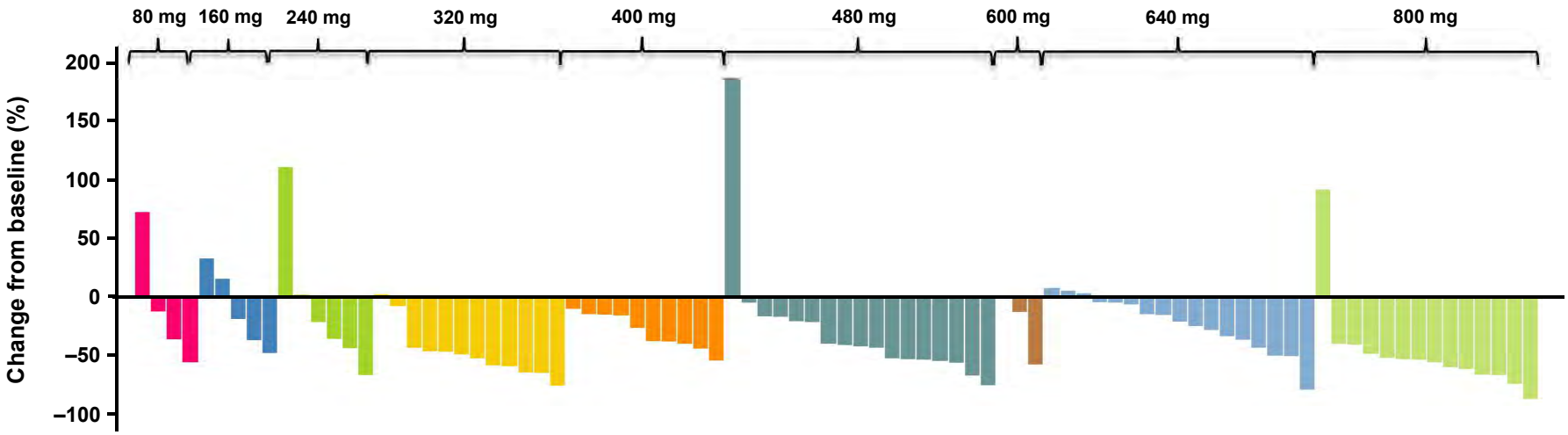
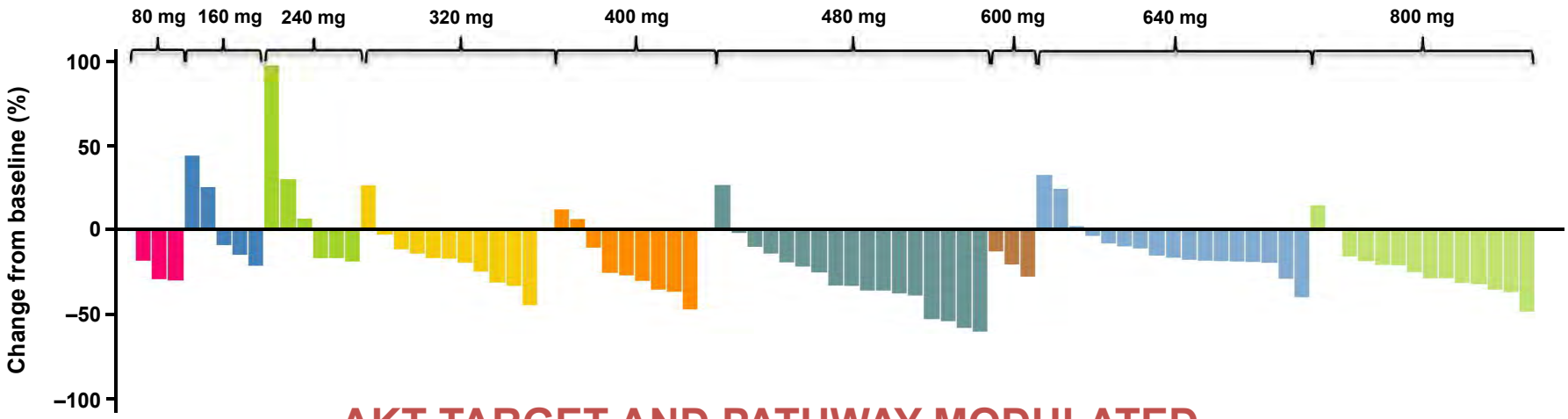
Phase I AZD5363 FIH Trial: all patients pGSK3β and pPRAS40 in platelet-rich plasma

pGSK3β in platelet-rich plasma at 4 hours



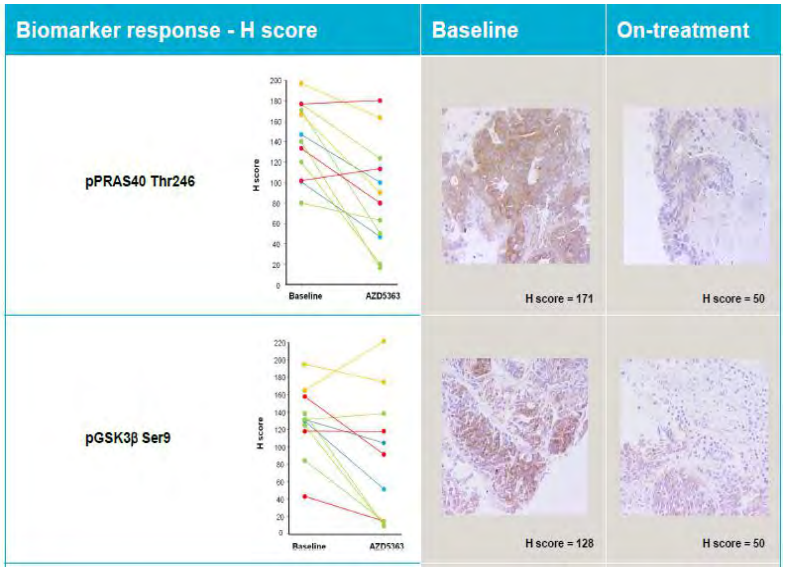
pPRAS40 in platelet-rich plasma at 4 hours

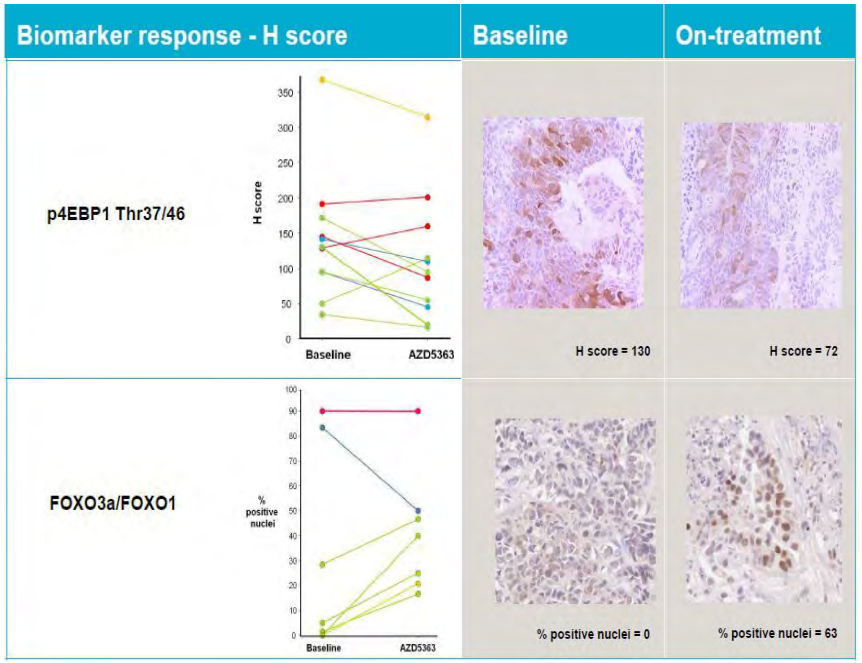


AKT TARGET AND PATHWAY MODULATED

Banerji et al, ASCO 2015

Phase I AZD5363 FIH Trial: selected patients
Paired tumor biopsies





Treatment with AZD5363:

- Inhibited phosphorylation of PRAS40, GSK3β and 4EBP1
- Resulted in translocation of FOXO transcription factors to the nucleus

AKT TARGET AND PATHWAY MODULATED

Banerji et al, ASCO 2015

Phase I MK-2206 AKT inhibitor FIH Trial: All patients

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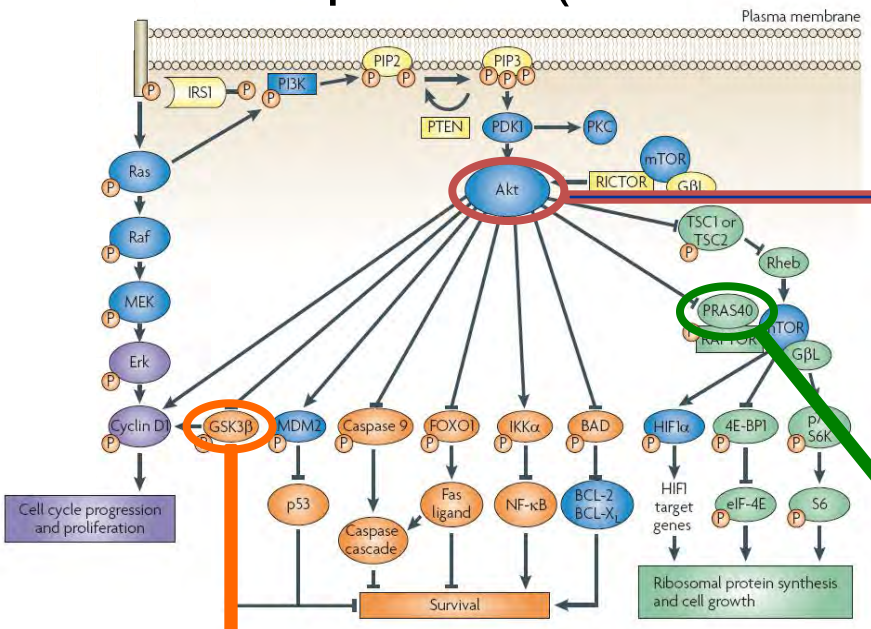
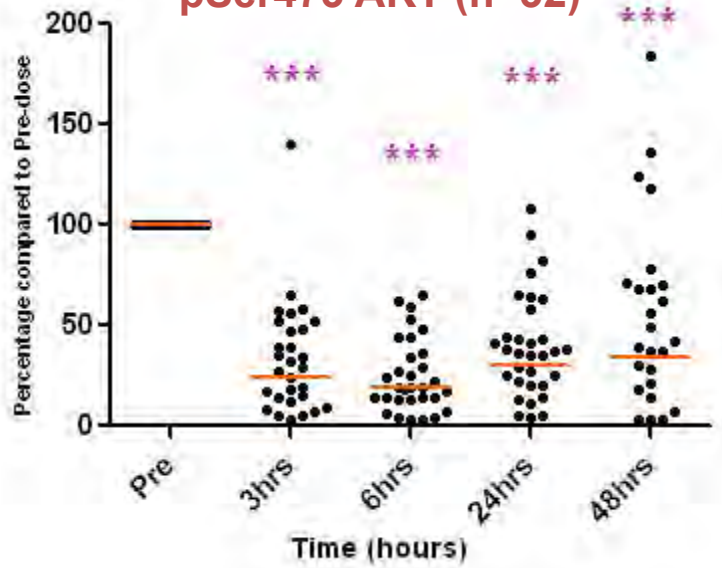
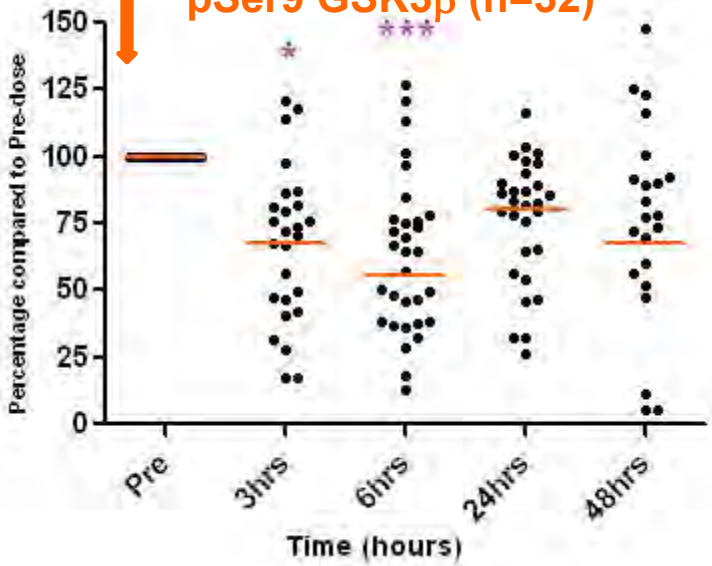
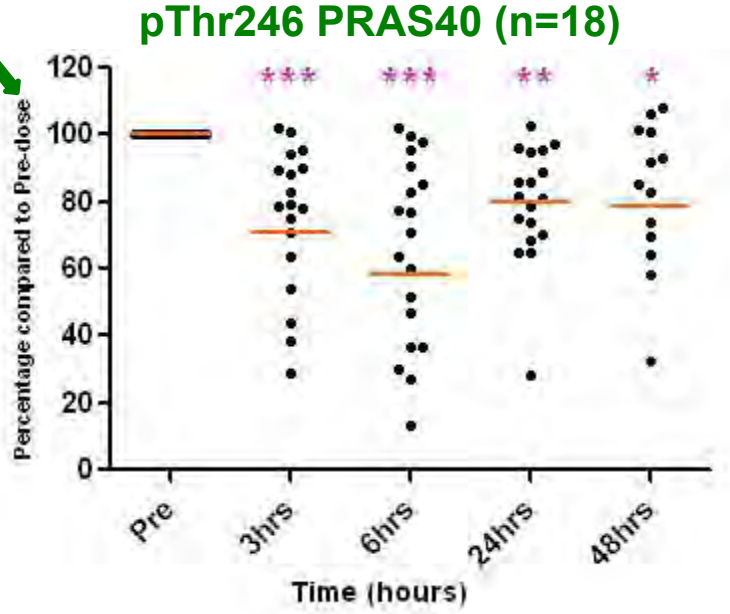
Platelet-rich plasma (MTD of MK-2206)









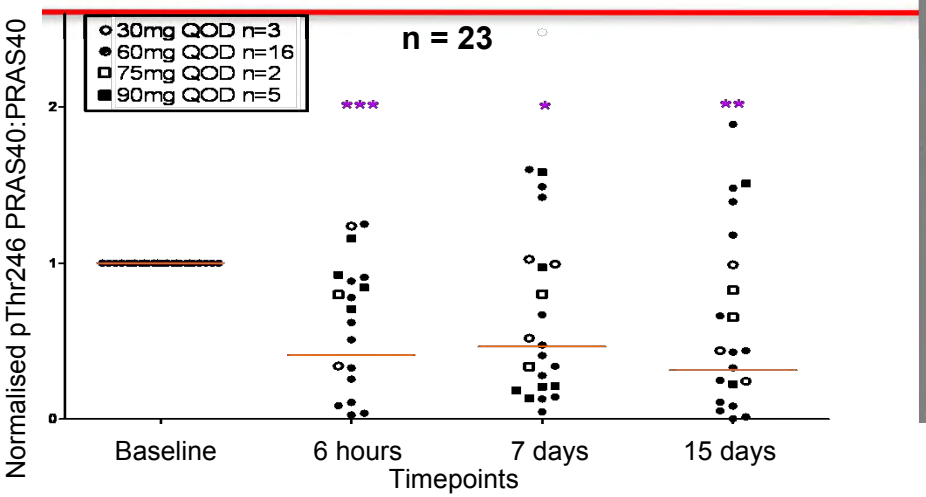
MSD® platform

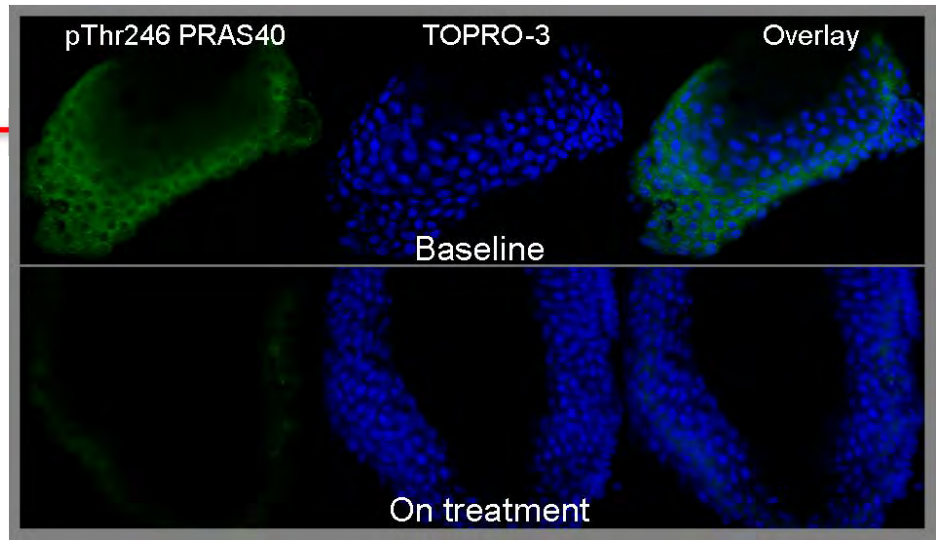
Paired t-test (predose vs treated) *p<0.05, **p<0.01, ***p<0.001

AKT TARGET AND PATHWAY MODULATED

Yap et al, CCR 2014

pThr246 PRAS40 in hair follicles

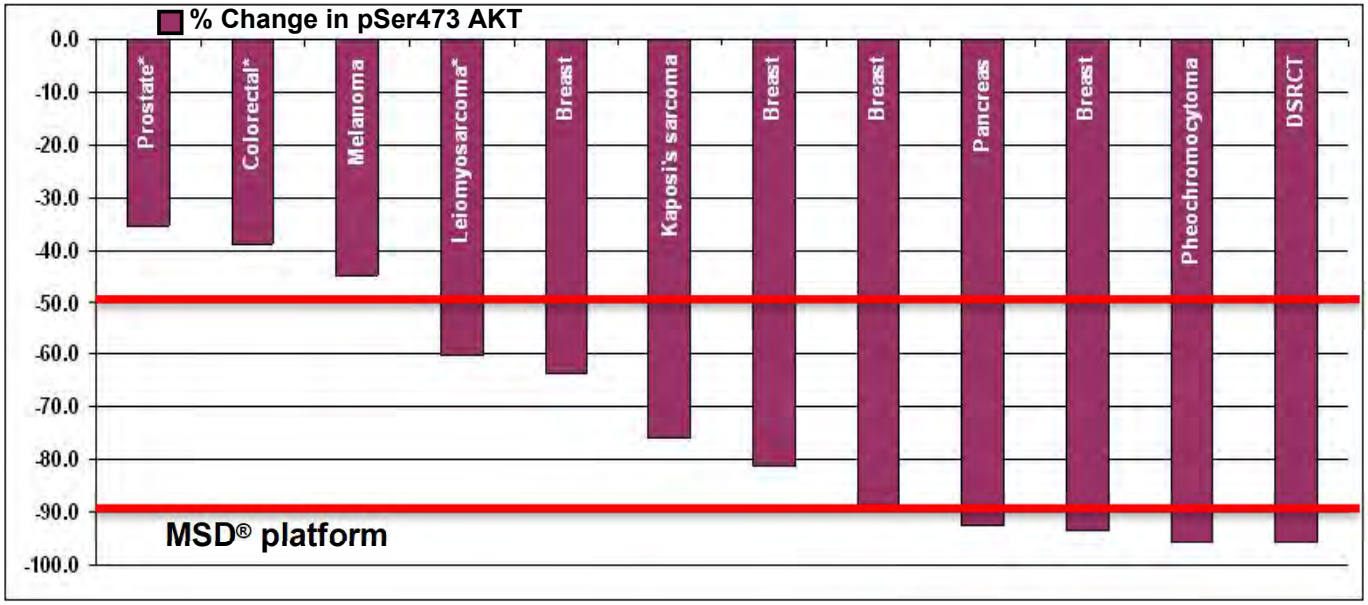




pThr246 PRAS40 immunofluorescence

pSer473 AKT in tumor

MTD expansion cohort
n = 12



AKT TARGET AND PATHWAY MODULATED

Paired t-test (predose vs treated)
*p<0.05, **p<0.01, ***p<0.001

Yap et al, JCO 2011; Yap et al, CCR 2014

Impressive PK-PD profile but limited antitumor responses

What have we learnt from "reverse translation" studies?

1. Not blocking target and pathway hard or long enough?
   - Dose limited by DLT of rash?

2. Compensatory escape mechanisms?
   - Crosstalk, feedback loops or other mechanisms (↑pERK; ↑IGF1R)
   - Need combinatorial approaches

3. Patient selection?
   - No validated 'predictive' biomarkers: Looking for a needle in a haystack
   - Intratumoral heterogeneity

Yap et al, JCO 2011; Yap et al, CCR 2014

AZD5363 phase I trial

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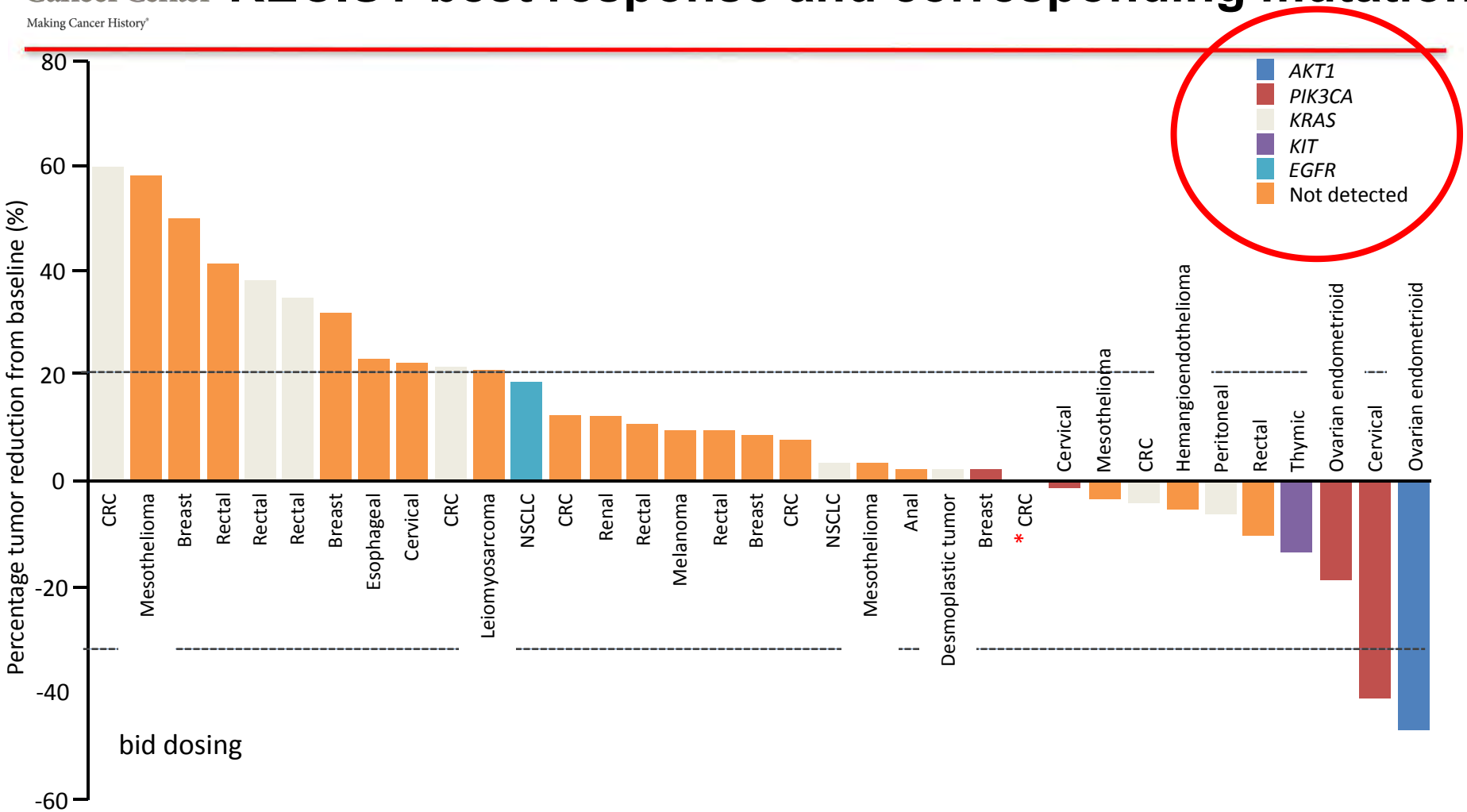
RECIST best response and corresponding mutation



- Not all patient samples tested due to lack of tissue availability
- Data shown are across whole dose range
- **3 patients with *PIK3CA* or *AKT1* mutations received AZD5363 ≥ 400 mg bid and all achieved tumour shrinkage**

Banerji et al, ASCO 2015

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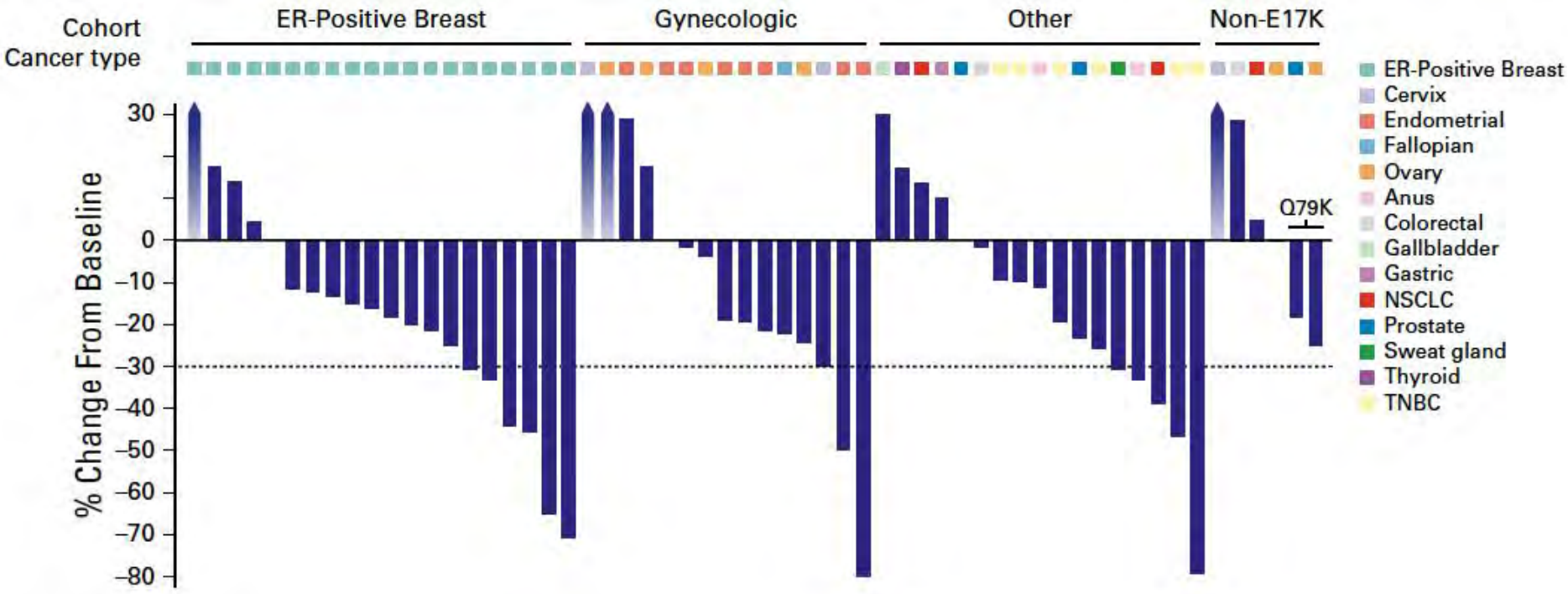
Phase I expansion cohort of 58 AKT1 mutant patients with advanced tumors



Hyman et al, JCO 2017

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Incorporating predictive biomarkers into phase I trials

How?

- Use multiplex NGS where available and appropriate for the question you are asking **(which should be based on *strong preclinical data*)**
- Enrich dose escalation population with predictive biomarker
  - Incorporate *a priori* provisions in protocol to add on patients of interest in each cohort
- Mandate cohort expansions with molecularly-driven tumors
  - Phase I expansions are the new single arm Phase II trials for early antitumor signal searching

Advantages?

- Allow early clinical testing/validation of biomarker assays
- Permit early hypothesis-testing/generating studies
- Optimize chance of early antitumor signals and decrease number of patients receiving ineffective treatments (***and avoid "drug development fatigue" for your compound***)
- May avoid late drug attrition and reduce costs

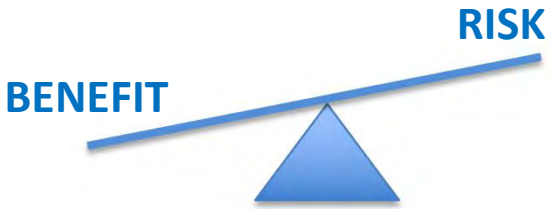
Ultimately, combinations will likely still be needed

Yap et al, Nature Reviews Cancer 2010

Summary

- **Drug development involves significant risk management**

- **Key Elements for a Success Drug Development Story**
  - **Efficacy**
  - **Safety**
  - **Biomarkers**
  - **Quality of drug agent**
  - **Well designed clinical trial with defined responder ID & patient population**



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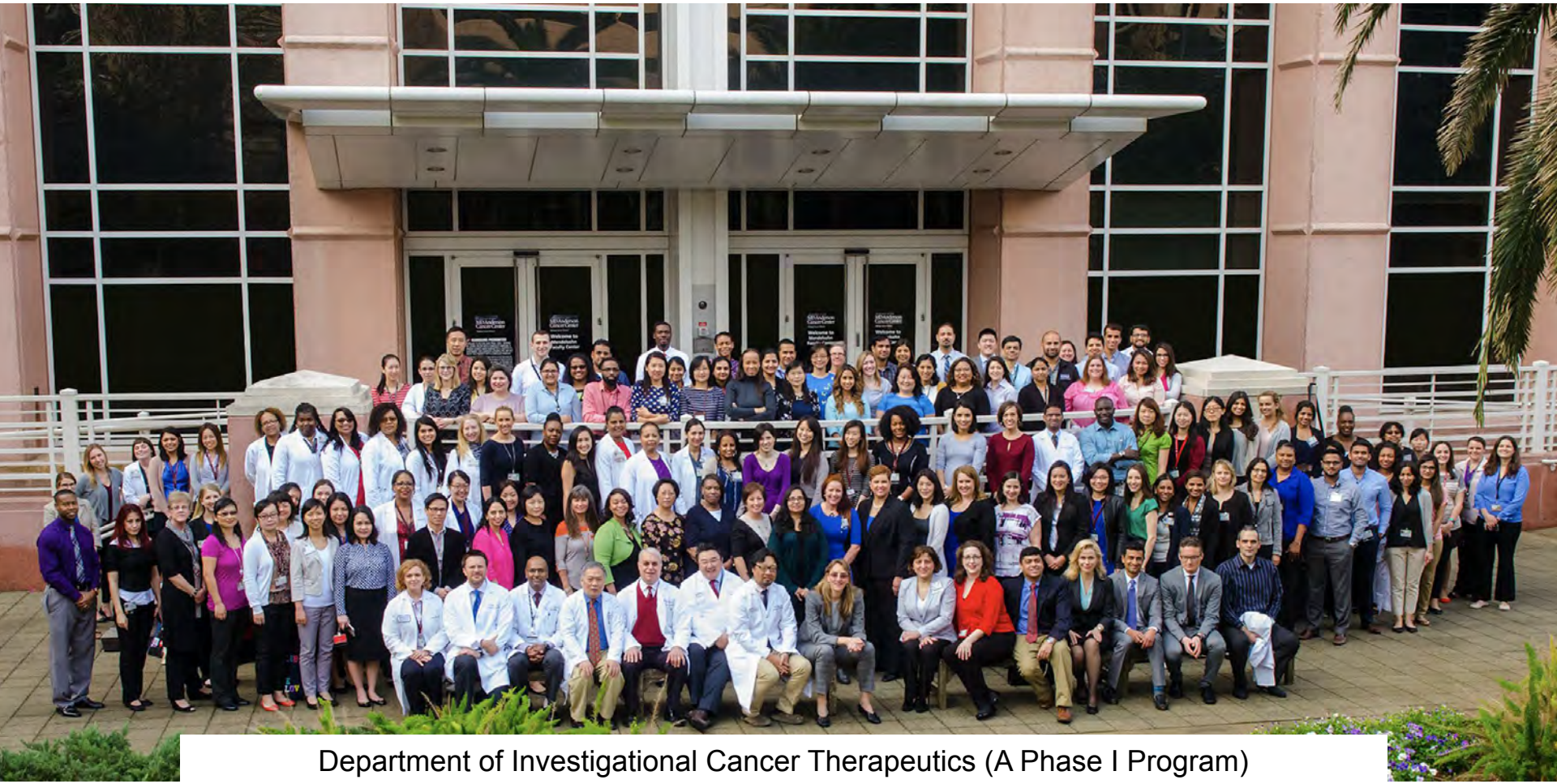
Thank you



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