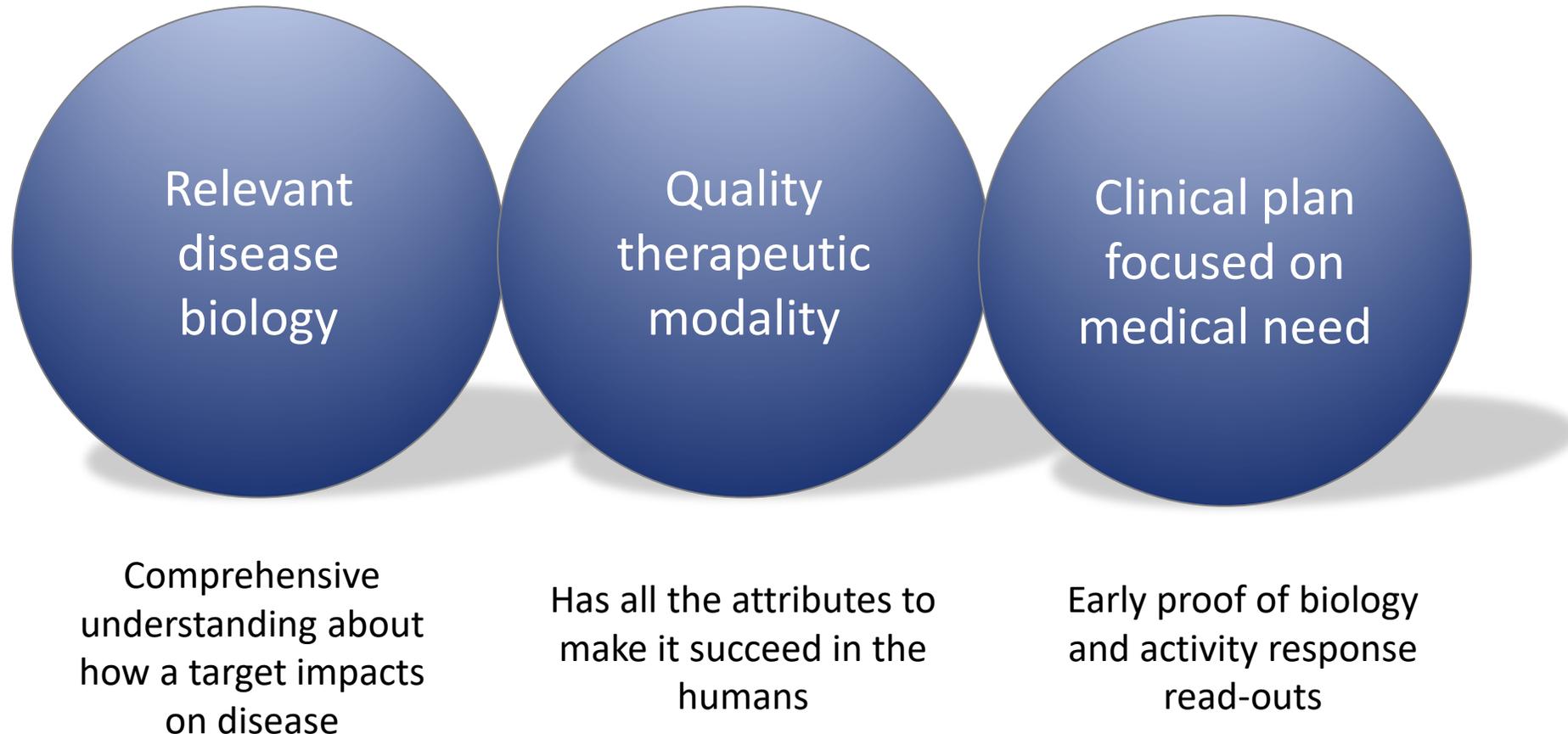

Key milestones in drug development and components of an IND-package

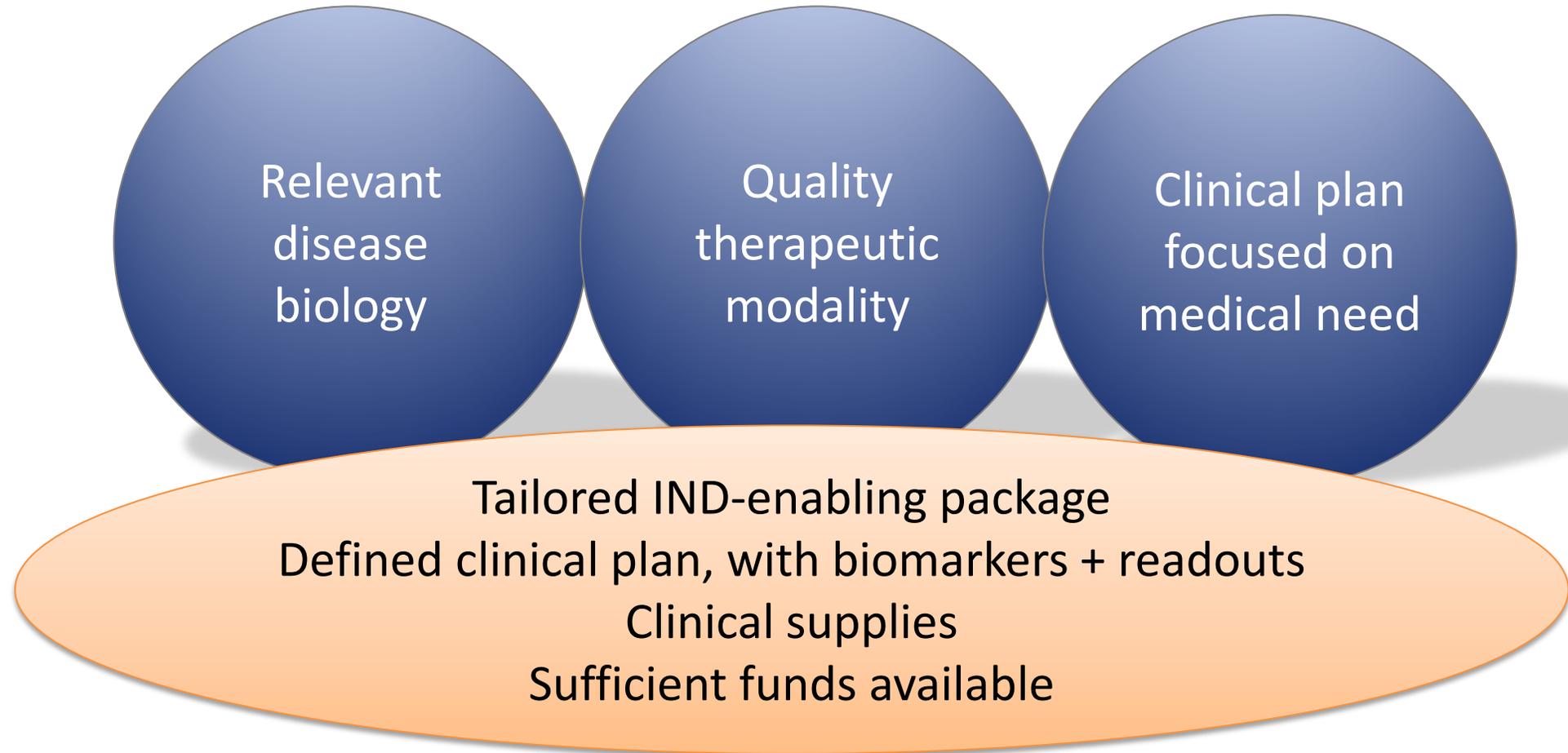
Philip Jones

VP for Therapeutics Discovery

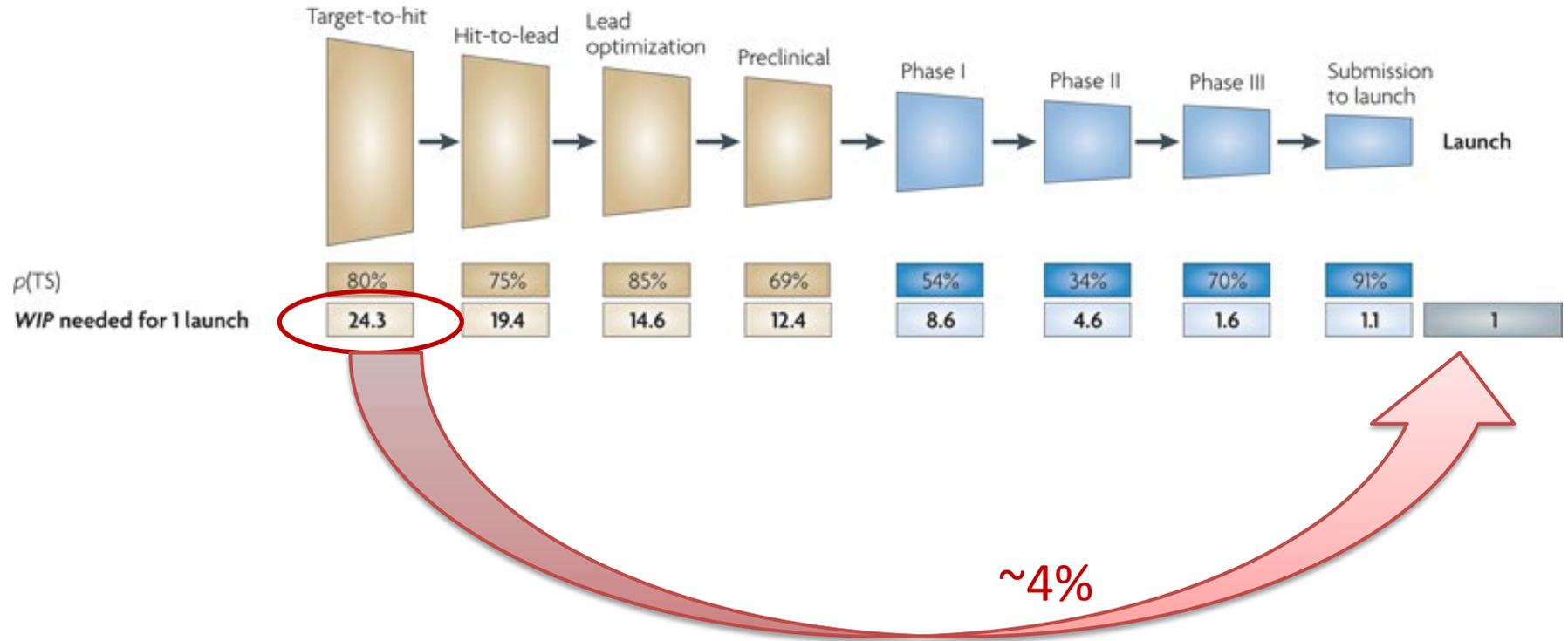
Behind every successful project there are three key pieces



Need preclinical development plan to get you successfully into clinic, & able to test hypothesis



Torturous path of drug discovery and development



Nature Reviews Drug Discovery 2010, 9, 209

Playing forward to clinical success

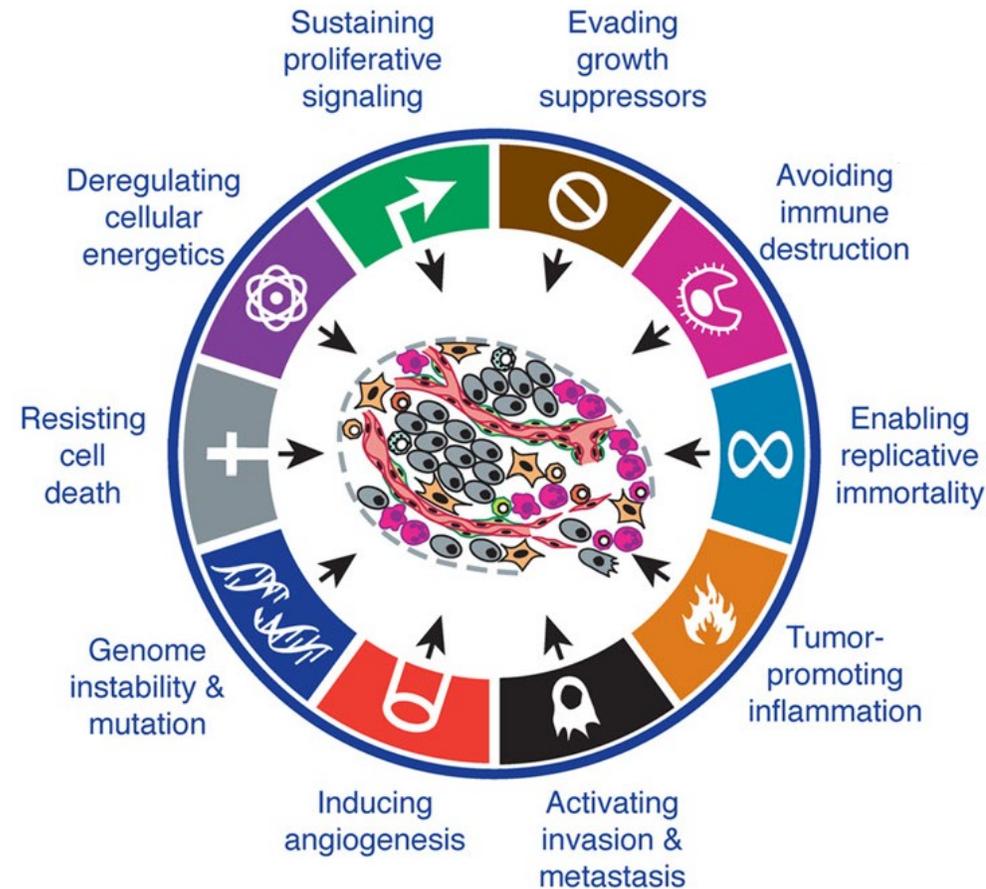
7. Clinical Indication: What is the unmet clinical need?
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2. Do I have a robust screening assay?
1. **Do I have a good target?**
 - a. **Novel, specific, characterized, assayable**
 - b. **Sufficiently validated with association to disease**

So what makes a good drug targets?

Answer: It depends....

Ideally something that has meaningful impact on the disease

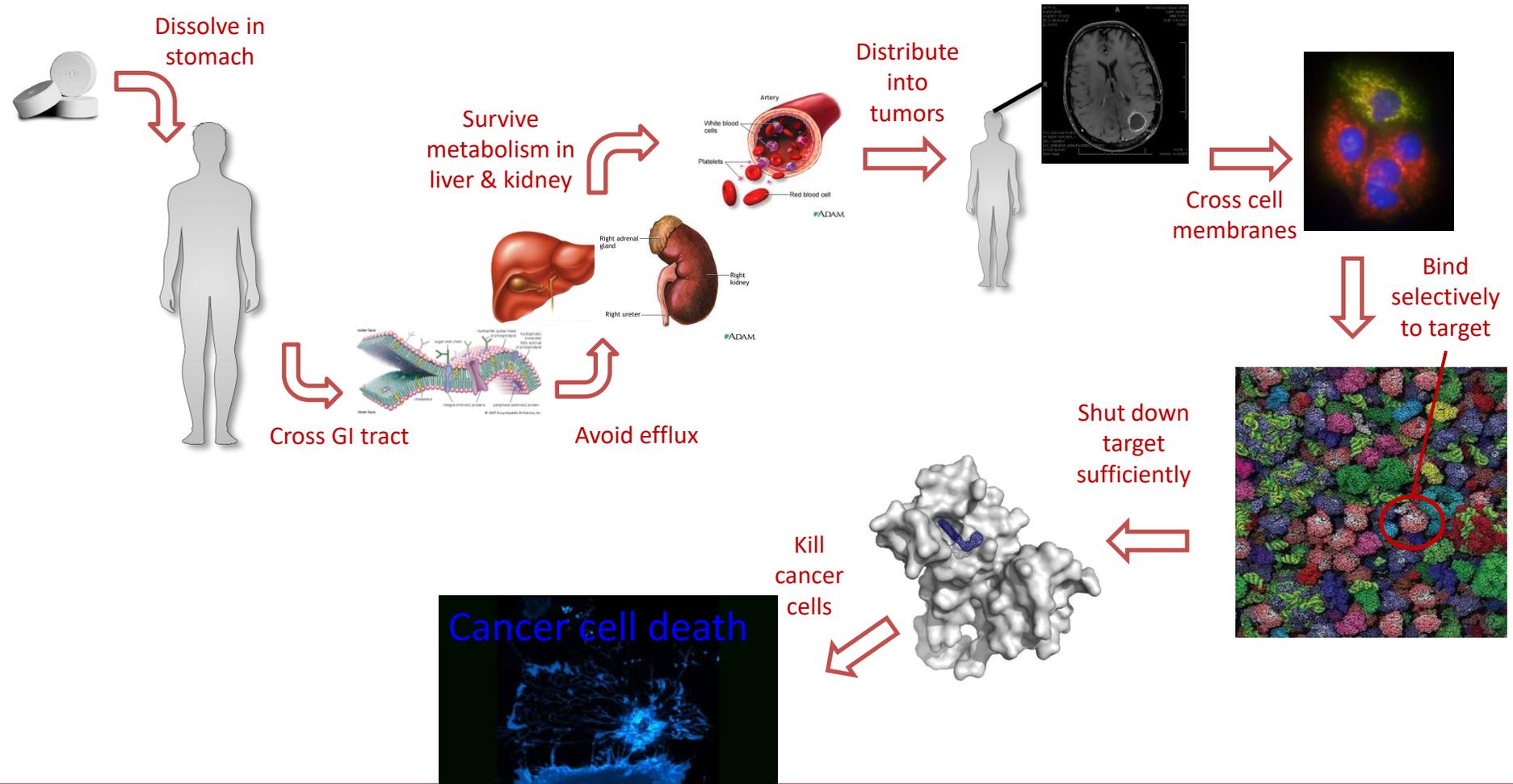
- Typically hits one of the Hallmarks of Cancer



Key considerations for any potential drug target

- Relevance
 - Biological activities of a target & its role in tumor maintenance/initiation
 - Supporting “omics” data, & cross species relevance
 - **Strong preclinical validation**
- Clinical development path
 - Clinical need
 - Clinicopathological validation - Try to define potential clinical indications
 - Biomarkers for stratification and pharmacodynamics
- Tractability
 - Druggability, viable screening cascade, appropriate preclinical models
- Issue Awareness
 - Therapeutic window, competition, intellectual property

Need to tune properties to ensure they are safe & effective in humans



- Need an agent that can effectively modulate the target in the desired manner in humans
- Need to think about:
 - Potency
 - Selectivity
 - PK profile
 - PK/PD/Efficacy relationship
 - How much target modulation is required, and for how long?
 - Safety/tolerability profile
 - Human dosage
 - Co-administered agents – Drug-Drug Interactions
 - And more....

Playing forward to clinical success

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Know at onset what you are trying to do – Target Product Profile (TPP)

	Clinical Candidate
Biochemical potency (IC ₅₀ nM)	≤ 50 nM

Does it modulate target in vitro

Does it modulate target in cells, & modulate the biology

Is it selective?
Does it have unwanted off-targets?

Does it have adequate PK properties?

Does it modulate the disease in preclinical in vivo models?
What dose and exposure?

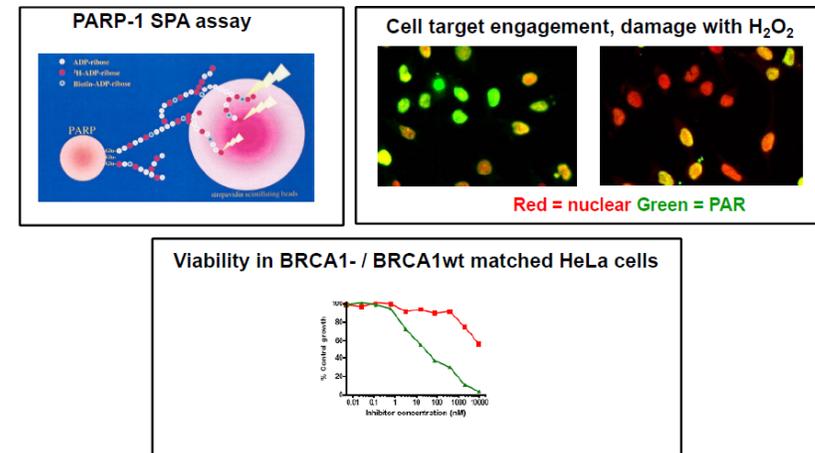
Is it safe?

Disease relevant screening funnel implemented



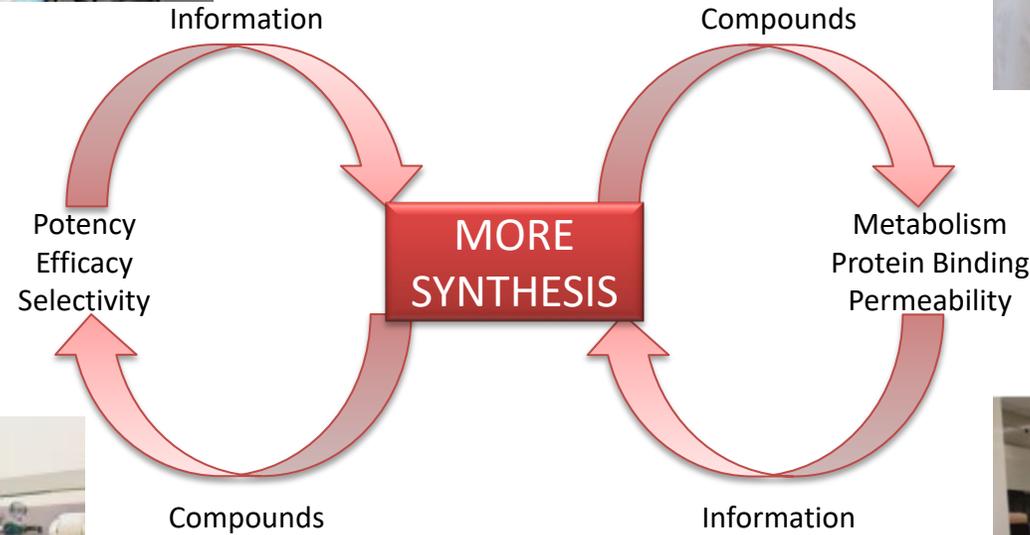
- Three key components
 - *In vitro* biochemical /binding
 - cellular target engagement assay
 - phenotypical assays
- Orthogonal biophysical assays, with different read outs
- Look for Up-assays (signal enhancement)

PARP screening funnel



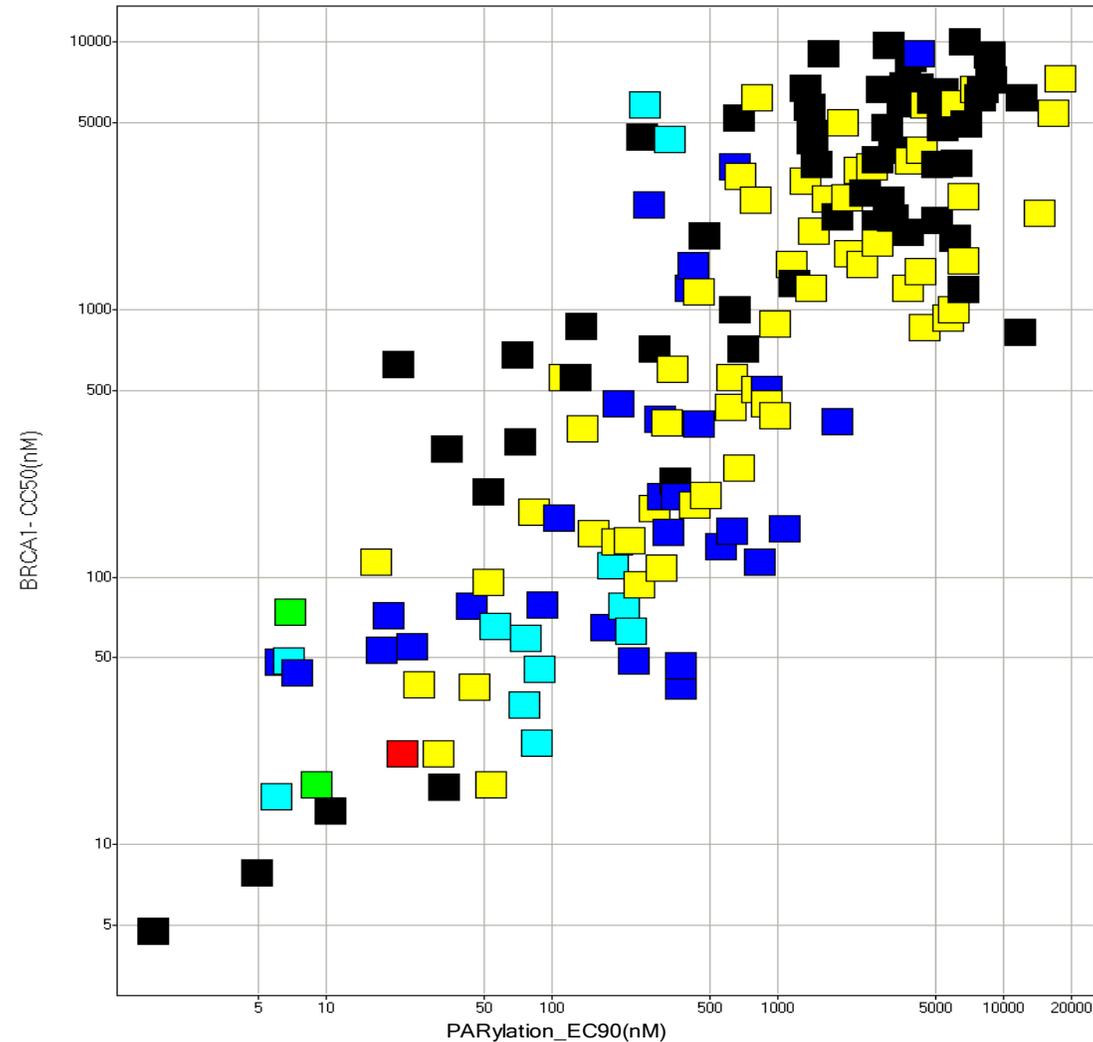
Pay attention to the quality of your reagents, Multiple examples of HTS screens conducted on impure protein – wasting millions of \$\$\$?

Weekly cycles of test and redesign, leveraging automation.



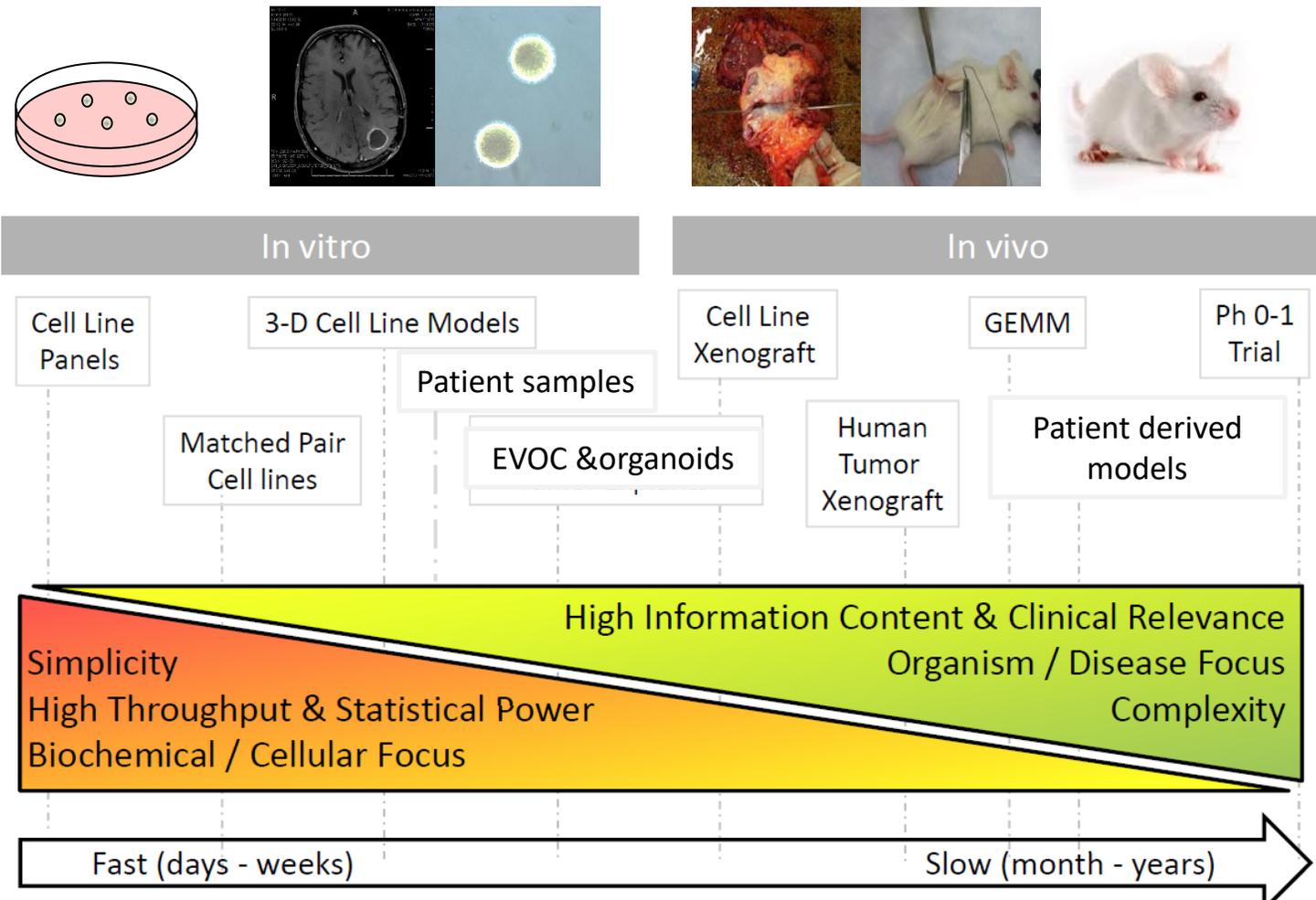
Expect to have strong correlation between target modulation and phenotype

Correlation of PARylation EC₉₀ vs. BRCA1- CC₅₀



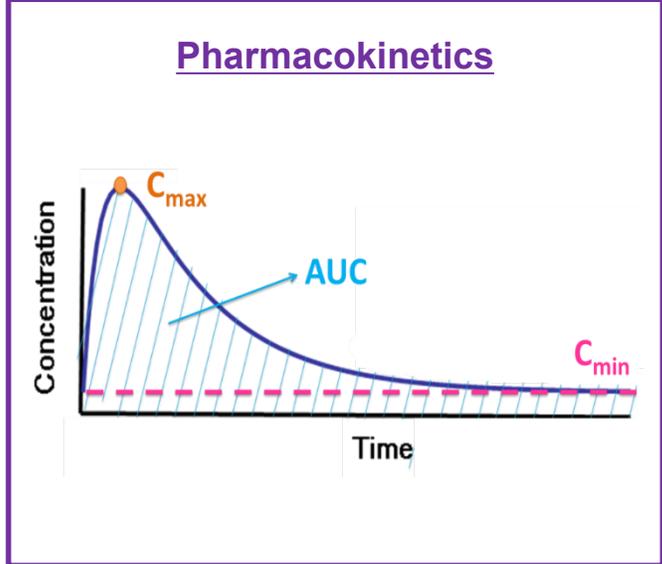
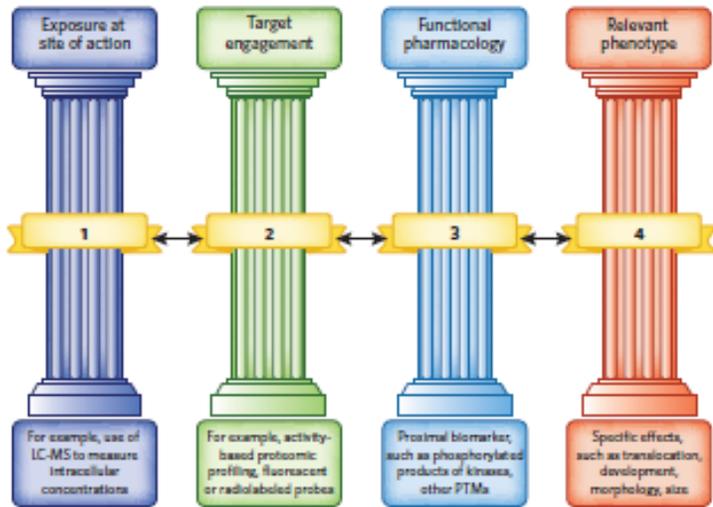
It works *in vitro*, does it work in a whole organism?

Disease modeling and drug testing: *Utilization of complementary model systems*

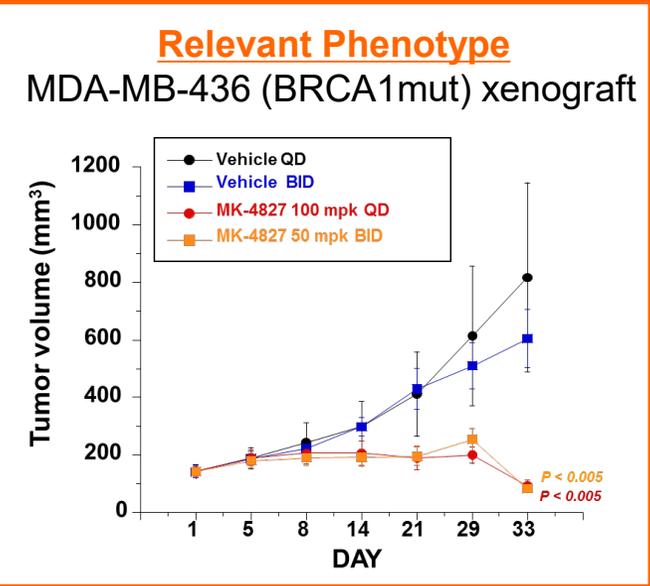
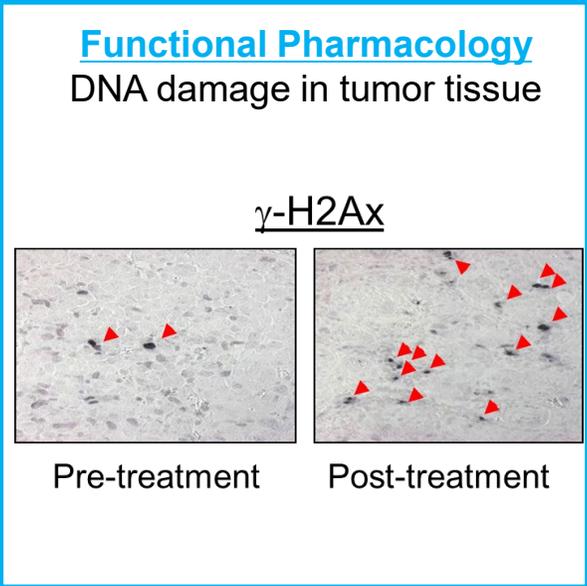
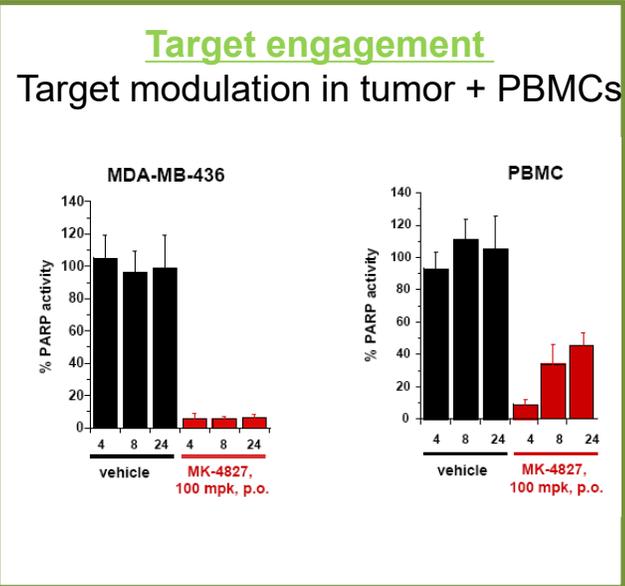


*No model is perfect.....no model is imperfect. **They are all surrogates.***

Pharmacological Audit Trail - Establish Pharmacokinetic-pharmacodynamic-efficacy relationships



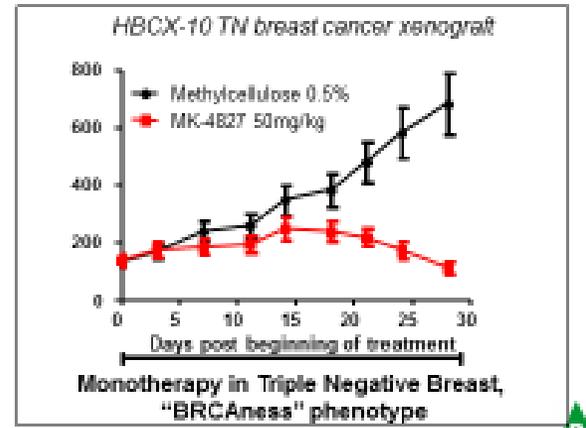
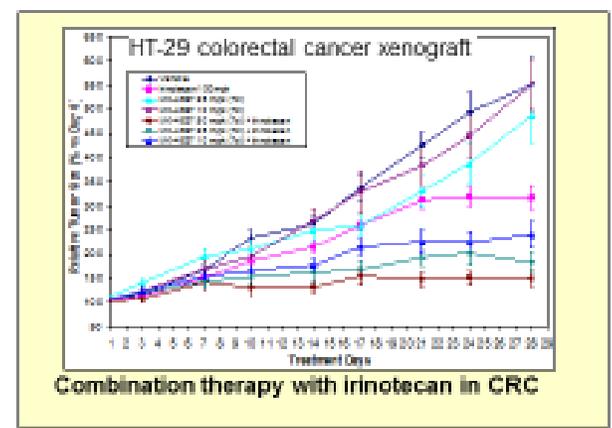
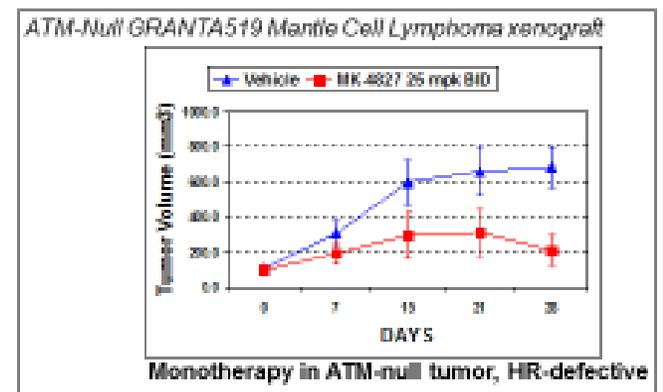
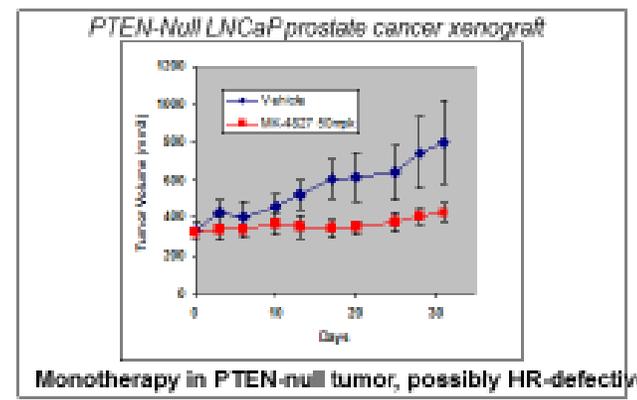
Bunnage, Piatnitski Chekler + Jones, *Nature Chemical Biology*, 2013, 9, 195



Ideally, you want to test in multiple models



Examples of “non-BRCA mutant” indications identified/validated by Post-PCC preclinical work



- And in independent labs



How much material do you need?

What is your human PK going to be like?

- Humans are not rodents, try to make a prediction of what your human PK will be like
- Do you need to be doing 10 mgs every day?
 - Or 2 grams three times a day? *Go back to drawing board*
- There are many ways to do so
 - Allometric scaling
 - In vitro – in vivo correlations

Pharmacokinetic Properties		Mouse	Rat	Dog	Monkey	Human
In Vitro	Liver Microsomes Cl _{int} (mL/min/Kg)	55	16	5	21	0
	Hepatocytes Cl _{int} (mL/min/Kg)	16	6	7	12	3
	PPB%	98.0	99.4	97.6	93.2	98.3
In Vivo 0.3 mpk IV / 3 mpk PO (mouse: 3 mpk IV / 100 mpk PO)	Cl _p (mL/min/kg)	4.1	0.31	0.59	8.0	0.30 <small>(predicted)</small>
	Vd _{ss} (L/Kg)	0.27	0.13	0.18	0.31	0.21 <small>(predicted)</small>
	t _{1/2} (h)	1.0	6.3	5.3	0.9	8.0 <small>(predicted)</small>
	F (%)	89%	70%	144%	72%	-

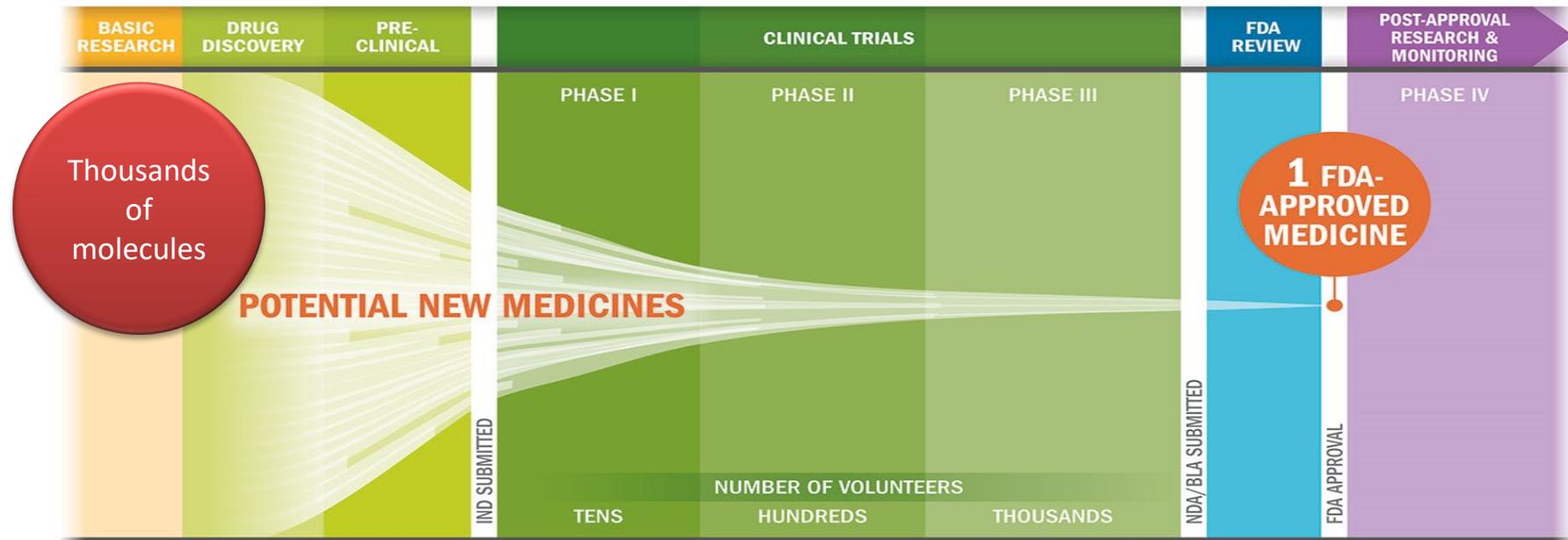
Predicted human dose (mg)*

$$\text{Dose (mg)} = \frac{C_{\min,ss} * V_{dss} * (k_a - k_e)}{(F * k_a * ((e^{-k_e \tau}) / (1 - e^{-k_e \tau})) - (e^{-k_s \tau} / (1 - e^{-k_s \tau})))}$$

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Its challenging..., but is life altering if we get it right



Key: IND: Investigational New Drug Application, NDA: New Drug Application, BLA: Biologics License Application

* The average R&D cost required to bring a new, FDA-approved medicine to patients is estimated to be \$2.6 billion over the past decade (in 2013 dollars), including the cost of the many potential medicines that do not make it through to FDA approval.

Source: PhRMA adaptation based on Tufts Center for the Study of Drug Development (CSDD) Briefing: "Cost of Developing a New Drug," Nov. 2014. Tufts CSDD & School of Medicine., and US FDA Infographic, "Drug Approval Process," <http://www.fda.gov/downloads/Drugs/ResourcesForYou/Consumers/UCM284393.pdf> (accessed Jan. 20, 2015).

Source: PhRMA

Therapeutics look their best the first time they are made

- They will pick up warts and baggage during development



- There is no such thing as the perfect drug
 - All have their flaws

Get it **Right**
First Time

It is going to take you ~3-4 years to show it works in the clinic.....

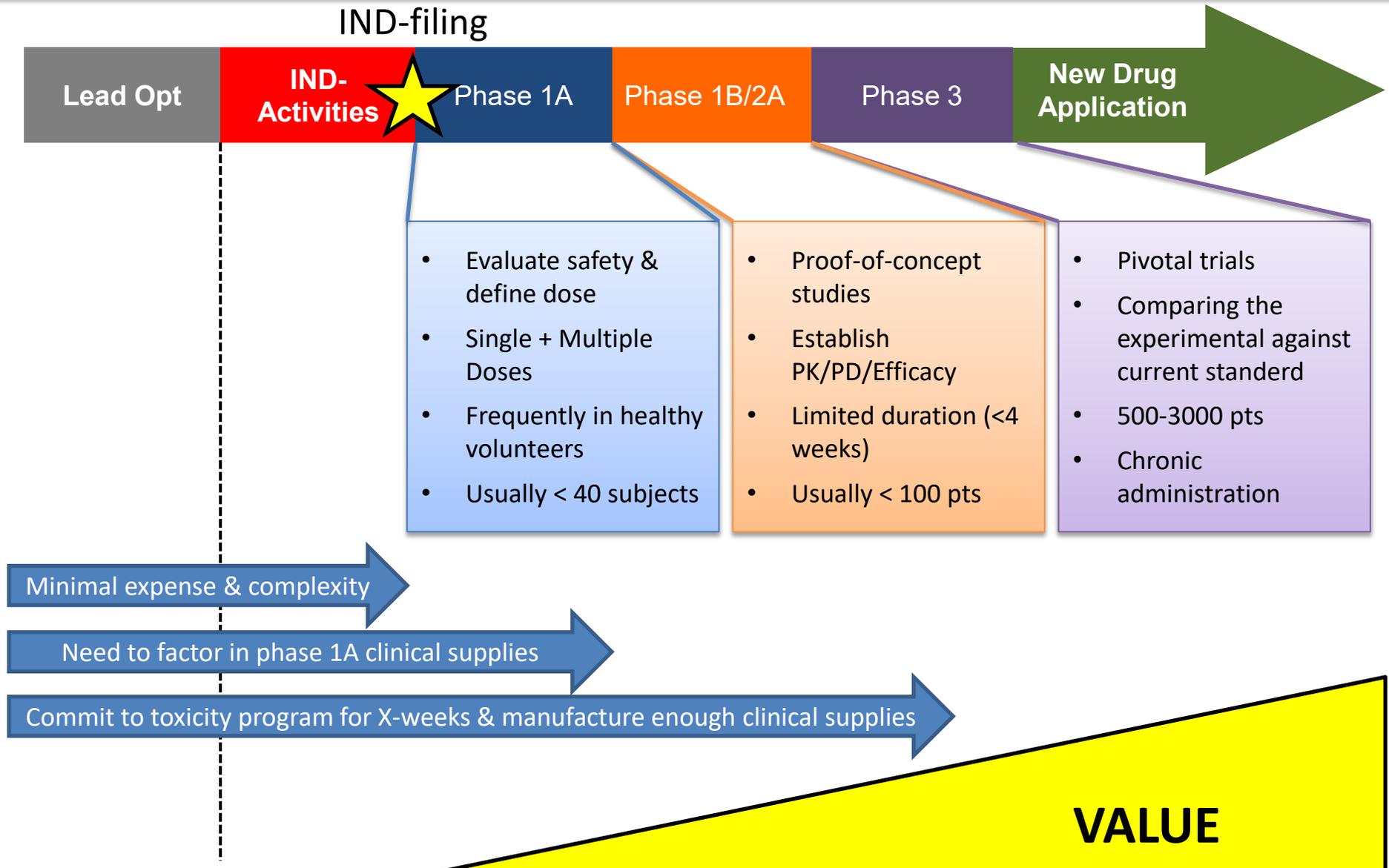
Take the time to optimize your therapeutic

Know examples were development candidate was 9th, & also 10,000th molecule!

Knowing where you have to get to, need to make sure your project has the legs to get there?



Define where you are heading



Preclinical Development

Consult FDA/EMA documents for specific requirements

- Clinical (modules 1, 2, 5)
 - General Investigation Plan (GIP) (m1.13)
 - Investigators Brochure (1.14)
 - Clinical Overview (2.5)
 - Protocol (m5)
- Non-clinical (module 2)
 - Intro (2.2)
 - Non-clinical overview (2.4)
 - Pharmacology (2.6.2, 2.6.3)
 - ADME/PK (2.6.4, 2.6.5)
 - Toxicology (2.6.6, 2.6.7)
- CMC (module 3)
 - Drug substance (3.2s)
 - Drug Product (3.2p)

Process is expensive

Candidate declaration to
IND-filing ~\$2-4 million!

Biologics cost even more

Pre-IND call should facilitate development

- FDA encourages sponsor to discuss products early in development
- Pre-IND call made whenever there is sufficient data to make a reasonable risk/benefit assessment
- Sponsor submits:
 - briefing document
 - non-clinical results/plan
 - clinical plan
 - highlights issues/controversial points
 - list of questions for FDA reviewers to consider
- Facilitates program advancement.
 - Learn what they expect
 - Your plans will be stronger as a result
 - May tell you what to watch out for

Playing forward to clinical success

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Drug Substance

Well defined, well characterized, stable & reproducible active pharmaceutical ingredient is critical

- Manufacture controlled by chemistry, manufacturing & controls (CMC)
 - full analytical characterization, with impurity profile
 - produced with full audit trail from regulatory starting materials (RSMs)
 - good lab practice (GLP)
 - good manufacturing practice (GMP)
- Define formulation & ensure desired exposure can be achieved
 - formulation for both preclinical & clinical work
 - stable to storage
 - non-toxic
 - acceptable dosing volumes
- Long and \$\$\$\$ process

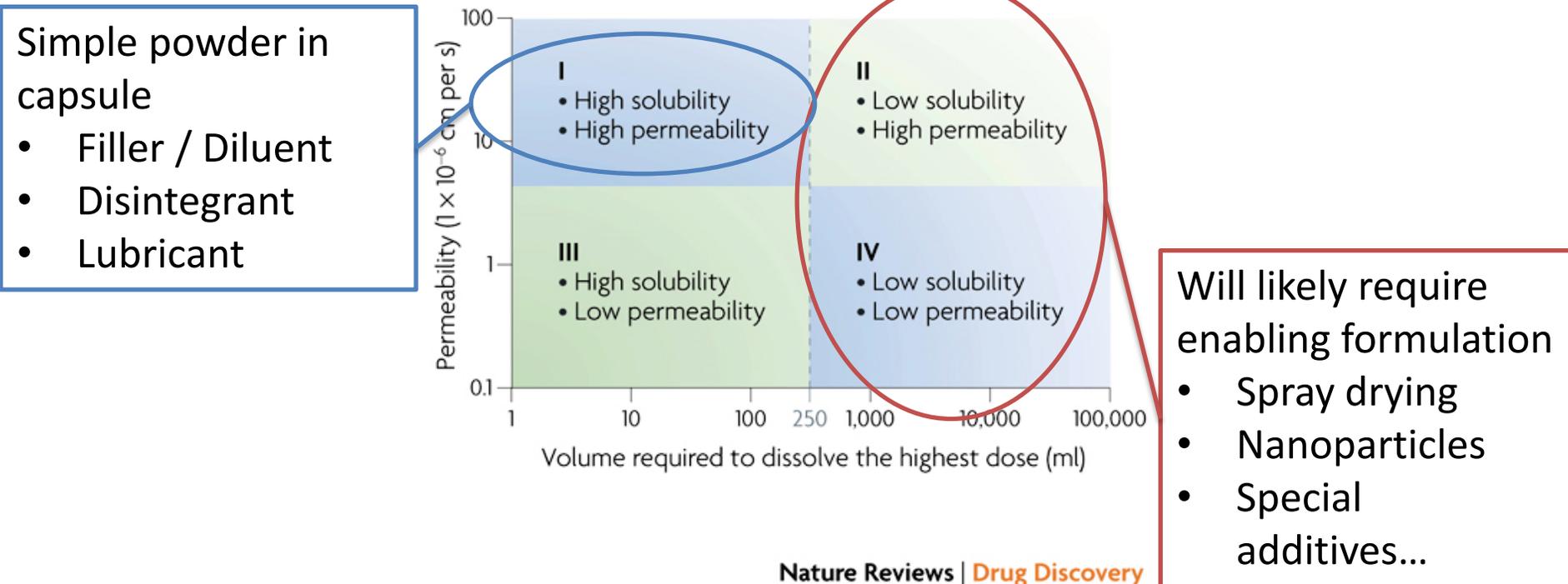


- Just because you can make 10's grams in the lab, doesn't mean you have the manufacturing routes
- Invest time and money in R+D to optimize the route
 - Try 3-4 routes & screen conditions at each steps (catalysts, bases, solvents)
- Seek convergent routes from defined building blocks
- High yielding chemistry, that is reproducible, and tolerant of subtle changes in conditions
- Purification by precipitation, washing, crystallization and slurring
- Good, robust analytical methods

Drug Product

Drug product is the dosage form given to human subjects

- Can be capsules, tablets, IV bolus
- Amount of complexity depends on route of administration and biopharmaceutical class



- Manufacture several strengths to enable clinical program
 - Decimal dosing – e.g. 1, 5 10 and 50 mgs; or 10, 50 & 100 mgs
- Need analytical methods
- Explore
 - Several prototypes
 - Test stability, % assay, & variability
 - Bridging PK?
 - Demo run
 - Pilot the equipment
 - Manufacture Clinical Trial Material
 - Thousands of units
 - Establish rolling stability program

Ingredient	Lot No. L394-01~					
	001		002		003	
	% w/w	mg /caps	% w/w	mg /caps	% w/w	mg /caps
IACS-xxxx	7.5	10.0	7.5	10.0	7.5	10.0
SMCC 90 HD	89.5	119.3	61.5	82.0	71.5	95.3
Dicalcium phosph. anh.	-	-	25.0	33.3	-	-
Pregel starch 1500	-	-	-	-	20.0	26.7
Sodium starch glycolate	2.0	2.7	-	-	-	-
Croscarmellose sodium	-	-	5.0	6.7	-	-
Magnesium stearate MF-2-V	1.0	1.3	1.0	1.3	-	-
Sodium stearyl fumarate	-	-	-	-	1.0	1.3
Total :	100	200	100	200	100	200
VcapsPlus, white opaque	Size 4	37.8	Size 4	37.8	Size 4	37.8

Project No.:	UTMD-20150908	Stability Protocol No.:	ST-NC0281-02, Revision 01			
Stability Sample /Lot No.:	Capsules 0.1 mg NC0281 Lot#1605FP1657-01	Stability Study Conditions:	25°C/60%RH,30°C/65%RH,40°C/75%RH			
Stability Start Date:	27-May-2016	Report No.:	RP-NC0281-17, revision 00			
Testing Item	Analytical Method	Acceptance Criteria	Initial		3 Months	
			Test date: 16-Jun-2016		Test date:01-Sep-2016	
Appearance	GM-036-AT	Hard Gelatin capsules, Size 3, white opaque cap, white opaque body. Upon opening the capsule, contents should confirm the presence of a white, to off white powder.	Hard Gelatin capsules, Size 3, white opaque cap, white opaque body. Upon opening the capsule, contents are white powder.		Hard Gelatin capsules, Size 3, white opaque cap, white opaque body. Upon opening the capsule, contents are white powder.	
Assay	AM-NC0281-01	Label claim: 90.0-110.0%	100.4%		99.7%	
Impurity	AM-NC0281-01	Individual unknown impurity: NMT 0.5%	ND		ND	
		Individual known impurity: NMT 1.0 % Total: No more than 3.0 %	ND		ND	
Dissolution	AM-NC0281-03	Report	Time(min)	Mean ± RSD (%)	Time(min)	Mean ± RSD (%)
			5	76.6±23.3	5	73.6 ± 22.3
			15	96.2±5.8	15	98.7± 3.1
			30	100.5±2.3	30	101.3± 2.0
			45	102.4±2.8	45	100.2±1.3
			60	102.3±3.7	60	101.4±1.6
90	101.5±2.2	90	99.4±2.3			
Water Content	GM-016-KFT	Report	5.1%		4.7%	

- Safety concerns may arise due to impurities
 - meet specs on purity, sterility, identity and potency
- Need reliable, reproducible & continuous supply
- Comparability testing must be undertaken - clinic lot conforms to those used in pharmacology/toxicity testing
 - "In general, the product that is used in the definitive pharmacology and toxicology studies should be comparable to the product proposed for the initial clinical studies"
- Changes may necessitate repeat toxicology studies !!

Biologics

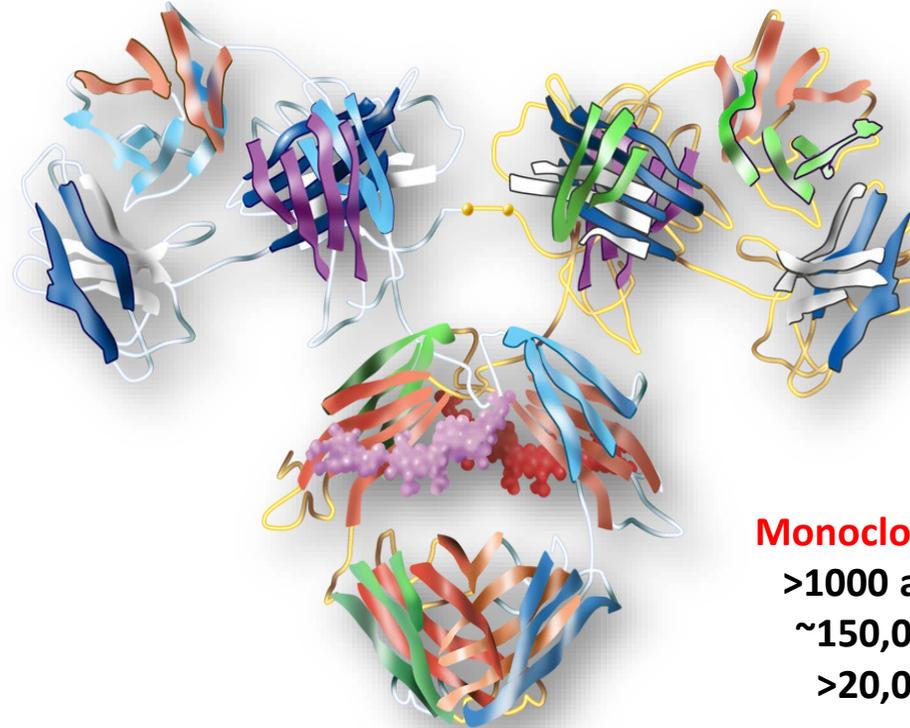
Slides courtesy of Jason Bock

Biologics' Inherent Complexity Requires a Different Approach to Development



Aspirin

~180 daltons
21 atoms



Monoclonal Antibody

>1000 amino acids
~150,000 daltons
>20,000 atoms

- Due to their large size and complicated structure, Biologics are produced in living cells
- The manufacturing processes used will affect the product profile
- Manufacturing is expensive and takes a long time

Biologics Manufacturing is Costly and Time Consuming

Commercial Example

Time

- Long Lead Times
- Long Manufacturing Processes



Packing a column with resin before starting to manufacture costs \$10M



Cost

- Up to \$15M in starting raw materials
- \$5M per batch

Arriving to Preclinical POC Requires More Effort Upfront but Enables Clear Path to Commercialization



TOOL

- Can provide preclinical proof of concept
- Research grade
- Example: mouse mAb, cheaper
- Requires humanization, optimization and re-development to GMP commercializable product



THERAPEUTIC

- Turns a concept into a developable product
- GMP grade and process that can be scaled
- Safety demonstrated
- Intellectual Property
- Example: human mAb, more expensive, requires special technology, high affinity

Antibody Sequence Selection/Engineering

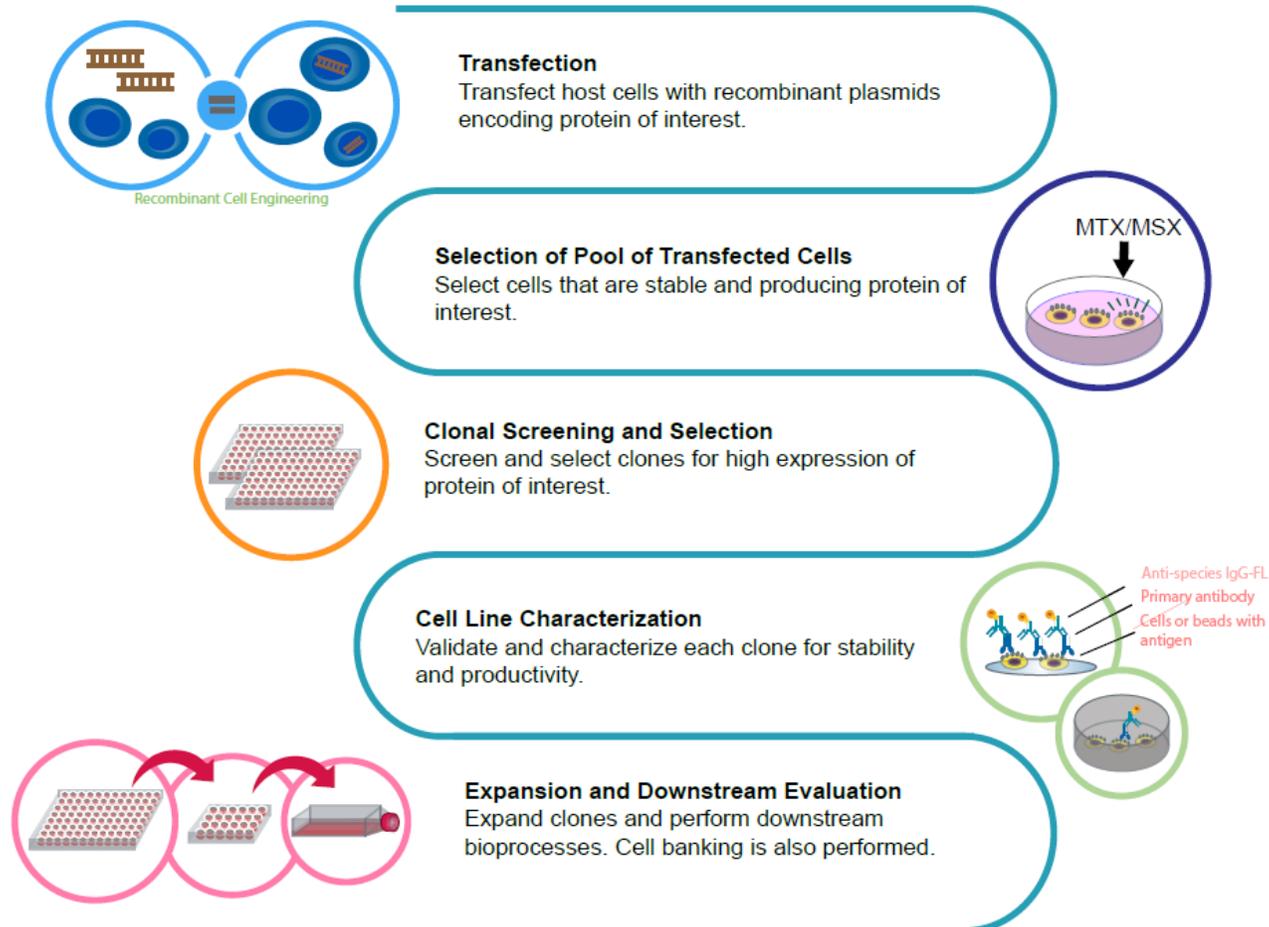
- Selectivity
- Affinity
- Epitope
- Species: Mouse as tool, Human as therapeutic
- Isotype:
 - IgG1 to engage effector function, esp for receptors on target cells
 - IgG2/4 to block binders, esp ligands and reduce toxicities
- Manufacturing considerations
 - Sites for post-translational modifications (glycosylation, deamidation, oxidation, etc)
 - Solubility including tendency to aggregate

The Path to a Biologics IND Has a Significant Tollgate

Stage	Time	Cost
Conversion from mouse to human (DNA sequence finalized)	6-12 months	\$0.2 – \$1.0M
Creation of final cell line (final clone that will be used from preclinical to commercial selected)	6-12 months	\$0.3 - \$0.8M
Creation of GMP master cell bank	~6 months	\$0.3M
Manufacturing process, analytical and formulation development	3-12 months	\$0.5M – \$2.0M
GMP drug substance production	~6 months	\$1.0 - \$3.0M
GMP drug product (vials)	3 months	\$0.3M
Clinical supply (labeling / packaging)		\$0.1M

Creation of a Clonal Cell Line

Cell Line Development for Recombinant Proteins



- Selection of parental host cell line
 - Finances
 - Regulatory familiarity
- Even though the DNA sequence is fixed, but clone selection is the next most critical decision
 - Titer
 - Glycosylation pattern
 - Other protein Quality attributes
 - Cell growth/doubling time
 - Expression Stability
- Need to assure clonality
- Will be used for life of product

<https://www.moleculardevices.com/applications/cell-line-development-workflow#ref>

Manufacture of Master Cell Bank-GMPs Begin

- Where GMP activities begin!
- Will be used for life of project
- 200-400 vials that can be used for each manufacturing batch and to produce a working cell bank
- Almost always outsourced to a few reputable CMOs (Bioreliance, Wuxi, Charles River)
- Extensive safety testing (viruses)

Product Development Work

- **Process Development**
 - Defining conditions to expand the cells and purify the product
- **Assay Development**
 - Analytical panel used for release, stability and characterization testing
- **Formulation Development**
 - Excipients added to final product to stabilize it for long shelf life (1.5 to 4 years)
- **There are mature platforms that work for the majority of mAbs**
 - Pick a reputable CDMO

Safety / Toxicology

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■ 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



Drug development involves significant risk management

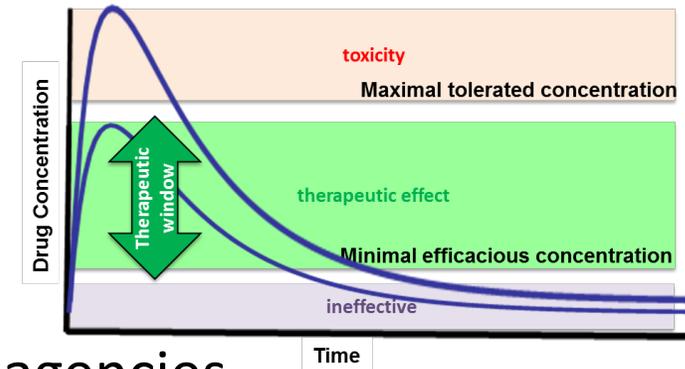
- Often call between clinical efficacy vs. potential harm to patients

- Therapeutic window/index =

$$\frac{\text{PK parameter (Cmax, and/or AUC) at NOAEL}}{\text{PK parameter for efficacy}}$$

- NOAEL = No adverse effect level
 - ideally want margin >10
 - for oncology this = 1, or even <1

- Remember every finding good or bad is reportable to agencies
 - erroneous result/finding doesn't go away
 - will take time & money to derisk finding
 - plan and execute every study carefully



- **Objectives**

- Define a safe entry dose for the first human exposure
- Understand the toxicological profile of a pharmaceutical
 - identify the toxicity risks: target organs; exposure-response relationships; and reversibility?
 - dose response relationship – from safe to “adverse”

- **Relevance**

- estimate human risk

- Regulated by FDA & other national/regional governing bodies

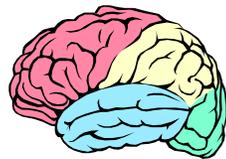


- International Conference on Harmonization (ICH) Guidance
 - ICH S2 – Genetic Toxicity
 - ICH S6 - Preclinical safety evaluation of biotechnology pharmaceuticals
 - ICH S7 - Safety Pharmacology
 - ICH S9 - Nonclinical evaluation for anticancer pharmaceuticals
- BUT there is no typical toxicology program: 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....

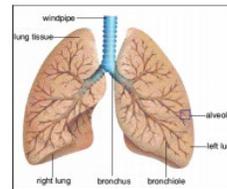
- **Safety pharmacology:**

- "An assessment of the pharmaceutical's effect on vital organ functions (including cardiovascular, respiratory and central nervous systems) should be available before the initiation of clinical studies... Detailed clinical observations following dosing and appropriate electrocardiographic measurements in non-rodents are generally considered sufficient."

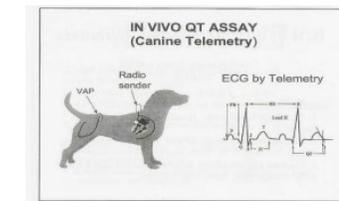
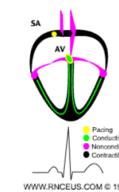
CNS Function (Rodents)
 Behavioral, motor activity...



Pulmonary Function (Rodents)
 Respiratory rate, volume...



Cardiovascular (NON Rodents)
 GLP hERG, Telemetrized dog



- **Ancillary pharmacology panel**

- receptor binding, transporter, channel and enzymatic assays

- Genotoxicity describes a deleterious action on a cell's genetic material affecting its integrity
 - 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
 - Mutagenicity (in bacteria) +/- metabolic activation
 - Chromosomal damage (eukaryotic cells)
 - in vitro
 - in vivo - rodent bone marrow

- **Include:**

- Exploratory toxicology range finding studies - limited animals, 5-7 days
- Definitive GLP toxicology studies typically 4 weeks + recovery period
- Rodent and non-rodent
- Mimic clinical route of administration

- **Goals:**

- target organ toxicity - **Agencies expect highest dose will induce toxicity**
- dose level/exposures necessary to elicit adverse reactions
- MTD - Maximum Tolerated Dose
- NOAEL - No Observed Adverse Effect Level
- NOEL - No Observed Effect Level
- Estimate therapeutic index

Exploratory study

- Preliminary assessment to identify & mitigate potential safety risks
- Define doses and toxicities for definitive GLP toxicology studies
- Rodent and non-rodent species
 - One example:
 - 3 dose levels (low, medium, high) + control; 5 rats per group
 - 7 days; necropsy at day 8;
 - Endpoints: toxicokinetics (TK); clinical chemistry; gross organ changes & histopathology on major organs

GLP study

- One rodent and one non-rodent species
 - pharmacological relevance of species is key (target conservation, metabolites...)
- Mimic intended clinical route of administration, cover duration of clinical administration
- Dose levels
 - Low dose - designed NOT to show toxicity – expected NOAEL - sets the clinical entry dose
 - Mid dose - potential NOAEL
 - High dose - designed to show toxicity & reversibility
- Larger studies, more animals, includes recovery groups
- Full characterization of effects

- Safety scaling factor is applied for starting dose in FIH study from MOST Sensitive toxicology species
- Non-oncology typically $<1/10^{\text{th}}$ NOAEL of most sensitive species
- Oncology lower margin acceptable
 - balance potential risk with consideration of providing efficacious therapy from first dose
- either:
 - STD10 (severely toxic dose for 10% rodents)
 - highest non-severely toxic dose for non-rodents. Dose converted to mg/m^2 , scaling factor $1/10^{\text{th}}$ or $1/6^{\text{th}}$ applied respectively

Playing forward to clinical success

7. Clinical Indication: What is the unmet clinical need?
6. Clinical Protocol: Patient population, dosing formulation, route, schedule, inclusion/exclusion
5. IND-ready Drug Product: Identity, Strength, Quality, Purity
4. Is the drug safety profile acceptable?
3. Is it a 'druggable' candidate?
2. Do I have a robust screening assay?
1. Do I have a good target?
 - a. Novel, specific, characterized, assayable
 - b. Sufficiently validated with association to disease

Eliminate as many variables as possible

- *Find motivated investigator who is vested in your concept*
- *Run trial in as few sites as possible*
- *Harmonize study population. If you've got a biomarker – use it!*
- *Stick to the plan, and don't compromise*

Submission

Submission of Investigational New Drug (IND) Application

- **Application for permission to proceed made to national regulatory agency, and await approval**
 - USA - IND application to FDA
- **Held by sponsor** (company, investigator or academic institution)
- **Contents:**
 - all pharmacology data accumulated in animal efficacy/toxicity studies
 - CMC on drug substance
 - drug disposition
 - proposed clinical trial protocol, & individuals responsible for each aspect
- **also contains:**
 - Investigator's Brochure (IB)
 - informed consent form (ICF)
- **Reviewed to verify if:**
 - selecting a **safe** starting dose
 - **and** to establish if it is likely **yield effective treatment**

Then wait 30-days
for FDA feedback....



We hope the Agency will approve moving ahead



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 128639

STUDY MAY PROCEED

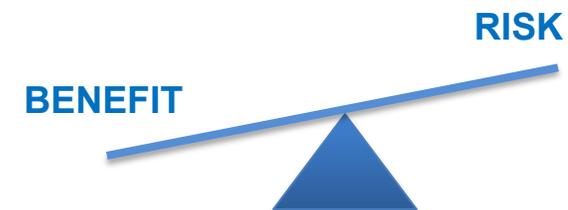
The University of Texas, MD Anderson Cancer Center
Attention: Aman Buzdar, MD
Vice President for Clinical Research Administration
1515 Holcombe Blvd., Unit 1636
Houston, TX 77030-4009

Dear Dr. Buzdar:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (FDCA) for IACS-010759.

We have completed our safety review of your application and have concluded that you may proceed with your proposed clinical investigation for acute myeloid leukemia (AML).

- Successful IND involves:
 - significant planning ahead & project management
 - Engagement in experts/consultants in their areas
- Key elements for success drug development:
 - Quality of Drug Agent
 - IND-package that enables clinical studies
 - Well designed clinical trial with defined goals, responder ID & testable hypothesis



NCI Drug Development Workshop: *How to Advance a Therapeutic Candidate from Bench to Bedside*

Session II. Pre-clinical Proof of Concept: Establishing Activity, Bioavailability, and Associated Effect, in Cancer Relevant Models

Session III. Non-clinical Toxicology

Session IV. Chemistry Manufacturing and Controls for Small Molecules

Session V. Development of Biological Products

Session VI. Regulatory Considerations

Session VII. Clinical Translation

Session VIII. Entrepreneurship: Partnering and Advancing

Session IX. NCI Translational Resources and Programs

Session X. Case Studies