Global Drug Development

Drug Discovery & Clinical Research

Medical Update Group - Mauritius

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Novartis South Africa
09 May, 2018

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Agenda

- Part 1:
  - Drug Discovery
  - Drug Development
- Part 2:
  - Introduction to PK & PD
  - Clinical Trial Design

PD: Pharmadynamics
PK: Pharmacokinetics
RCT: randomised controlled trial

Global Drug Development

Part 1

– **Drug Discovery**
– **Drug Development**

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Drug Discovery

Drug Discovery and Clinical Research:
Setting the Context

Drug Discovery and Development Overview:
Molecules and Targets into Clinical Research

Drug Discovery and Development:
Examples and Conclusions

Novartis is one of the world's most admired companies

FORTUNE WORLD'S MOST ADMIRED COMPANIES 2018

#3

Third-most admired company in the pharma sector – our 14th consecutive year among the top three

Dow Jones Sustainability Indexes

#4

In the 2017 Dow Jones Sustainability Index (DJSI) World (up from 7th in 2016)

2017 TOP 100 GLOBAL INNOVATOR Clarivate Analytics

4x

Named as a Clarivate Analytics (formerly Thomson Reuters) Top 100 Global Innovator 2014, 2015, 2016 and 2017

FORTUNE® CHANGE THE WORLD 2017

#4

Among companies that have a positive social impact through activities that are part of their core business strategy

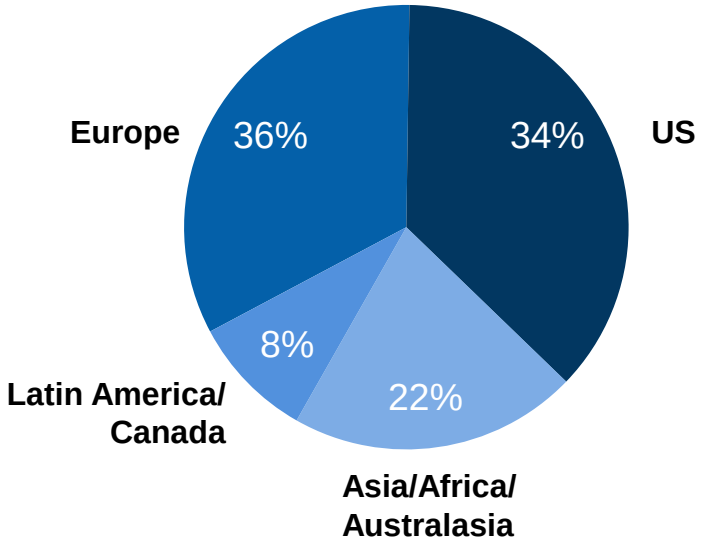
Novartis is one of the world's largest companies

2017

	USD billion
Net sales	49.1
Net income	7.7

People
126 000

Sales by region



Our mission and vision in challenging times

Our mission

Discover new ways to improve and extend people's lives

Our vision

Be a trusted leader in changing the practice of medicine

Our impact

In 2017, Novartis products reached nearly 1 billion patients

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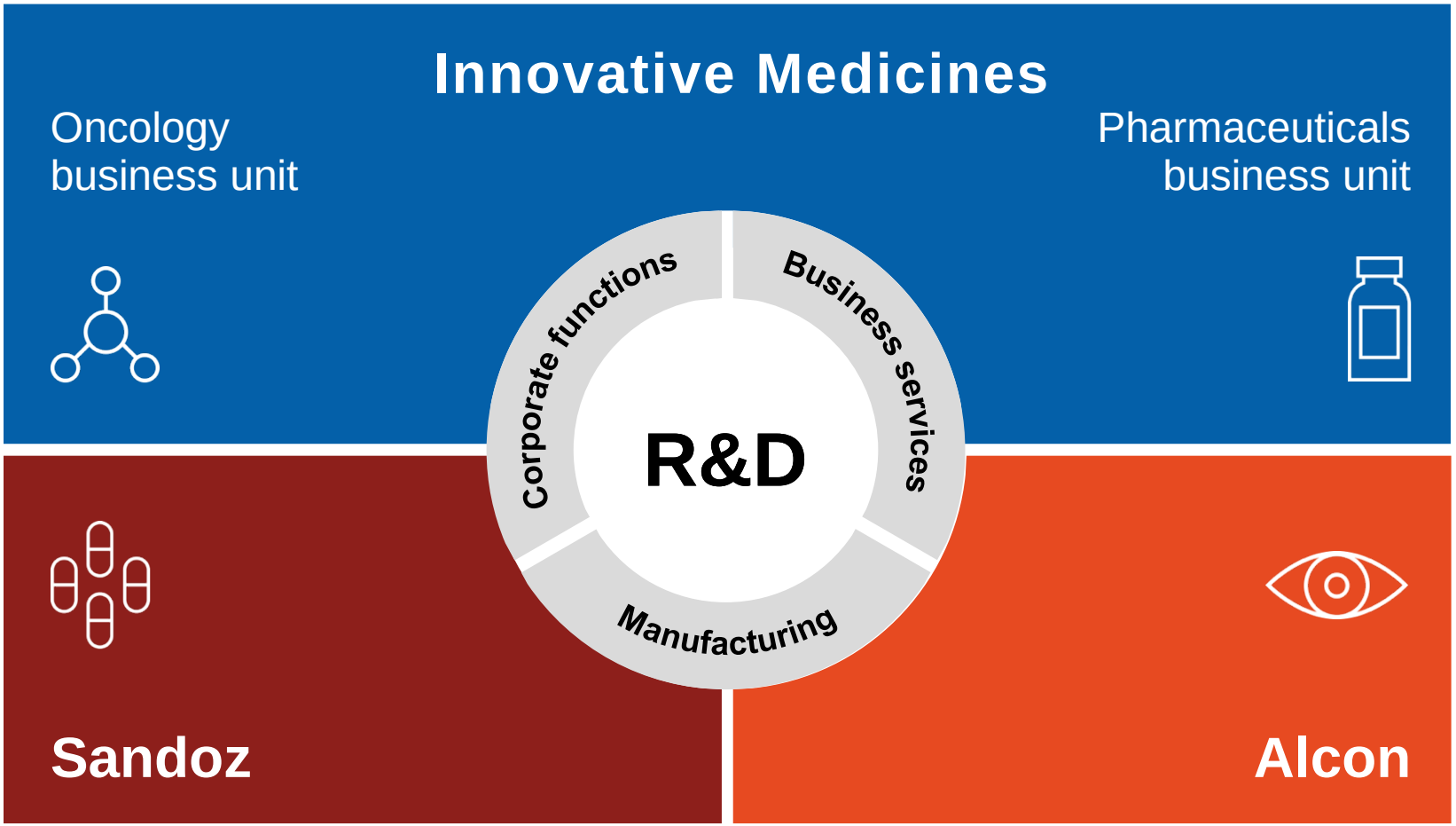
Focused businesses fueled by innovation and functional excellence



Drug Discovery & Clinical Research

NOVARTIS

Our innovation engine sustains an industry-leading pipeline

USD 9bn

Invested in research and development

200+

Projects in clinical development

23 000

People working in research and development worldwide

16

Major regulatory approvals in 2017 (US, EU and Japan)

All figures are for 2017

NOVARTIS

How we innovate

We work to create potential new treatments using visionary thinking and science-based innovation:

- **Regenerative medicine**
- **Personalized medicine**
- **Cellular therapies**
- **Biosimilars**

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Global Drug Development

Drug Discovery and Clinical Research

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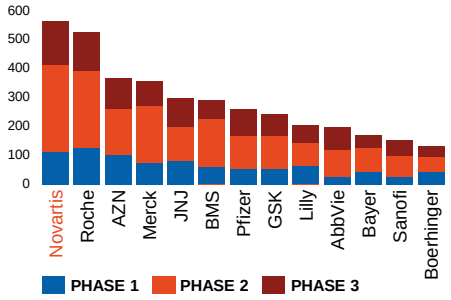
Novartis Institute for Biomedical Research (NIBR)
Drug discovery and early development

~6,000

scientists / 7 sites globally



>500

ongoing clinical trials

~400

research projects

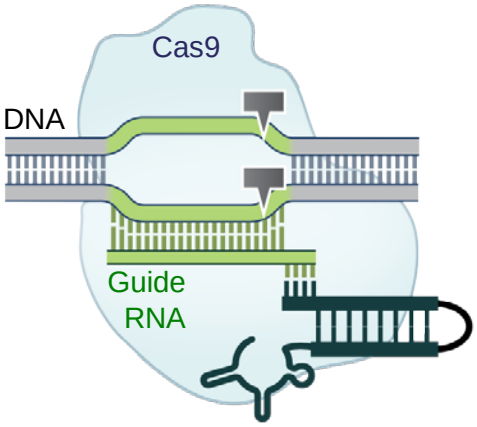
~90

new molecular entities

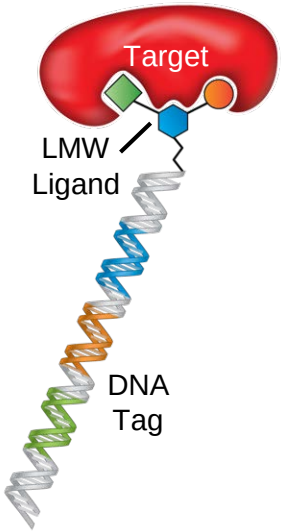
NIBR 2.0
The new science of therapeutics

https://www.youtube.com/watch?v=V9gpM8n6Ggg

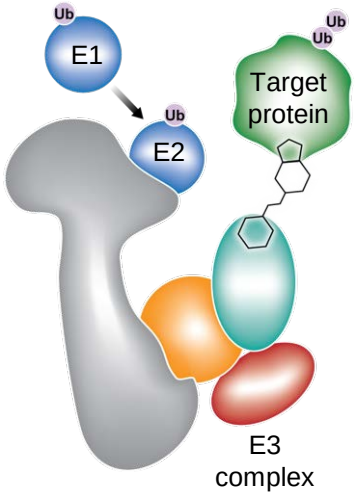
CRISPR Genome Editing



DNA-Encoded Libraries



Targeted Protein Degradation



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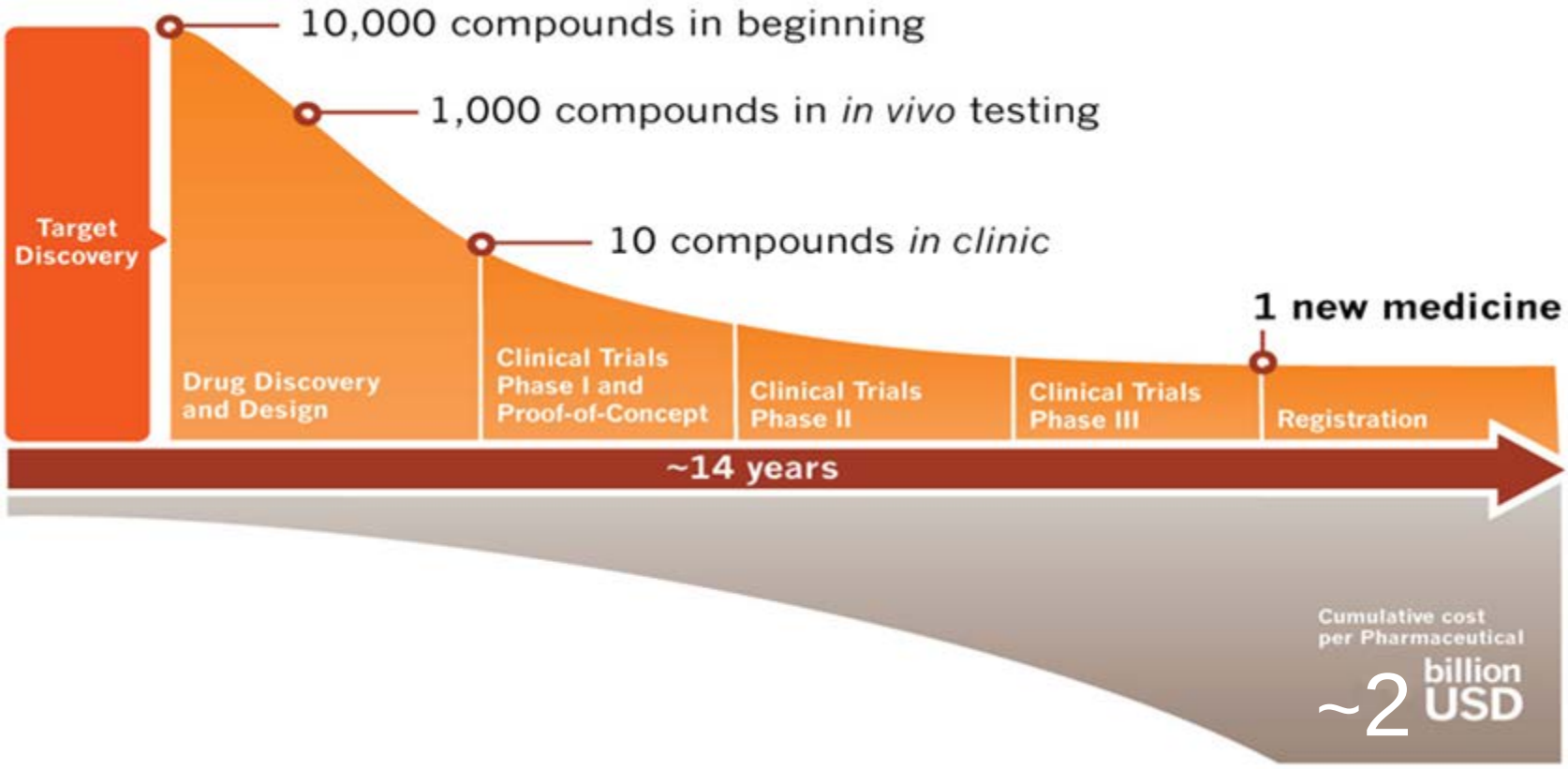
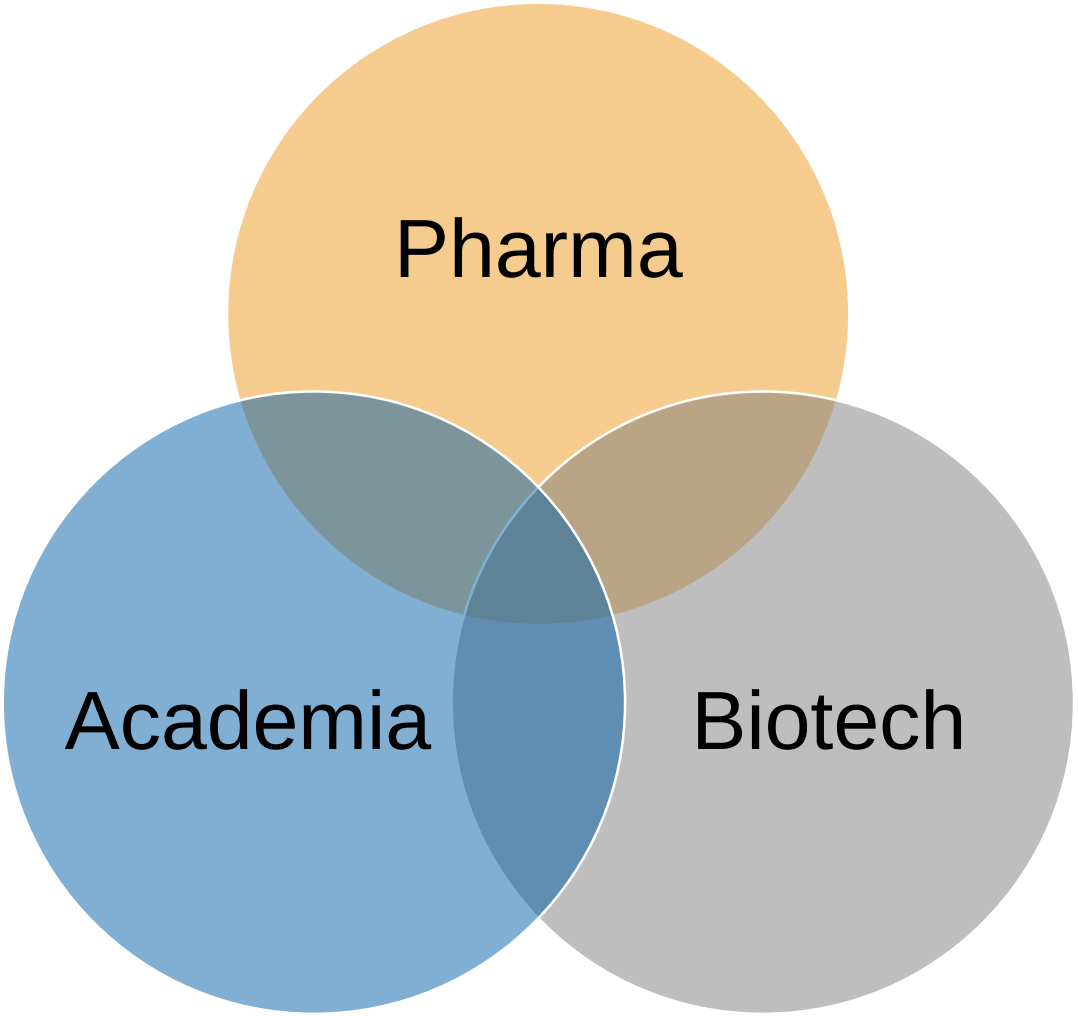
Drug Development Process Overview



http://www.novartis.com/innovation/research-development/drug-discovery-development-process/index.shtml

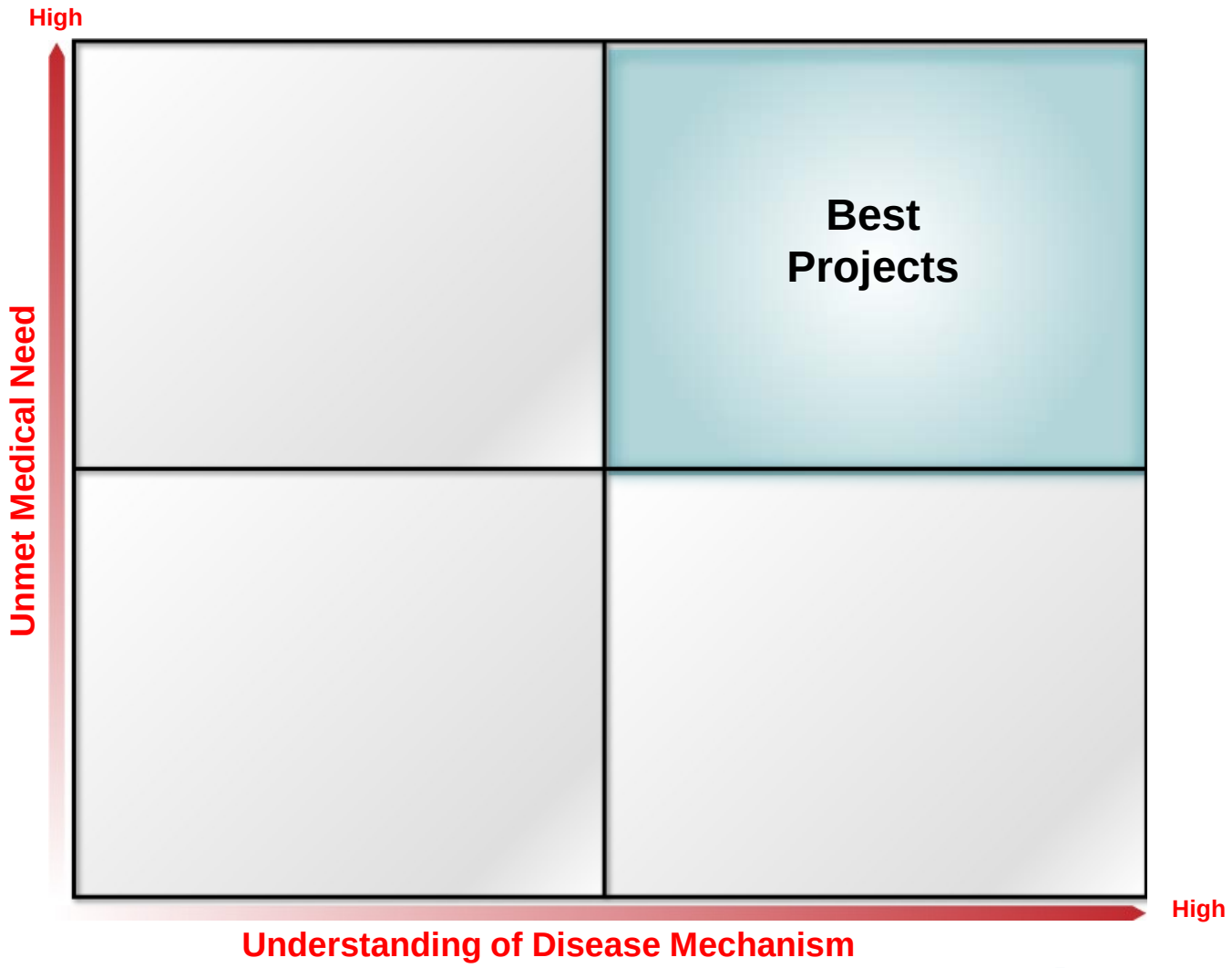
https://youtu.be/3Gl0gAcW8rw

General Concepts in Drug Discovery and Development are Universally Relevant

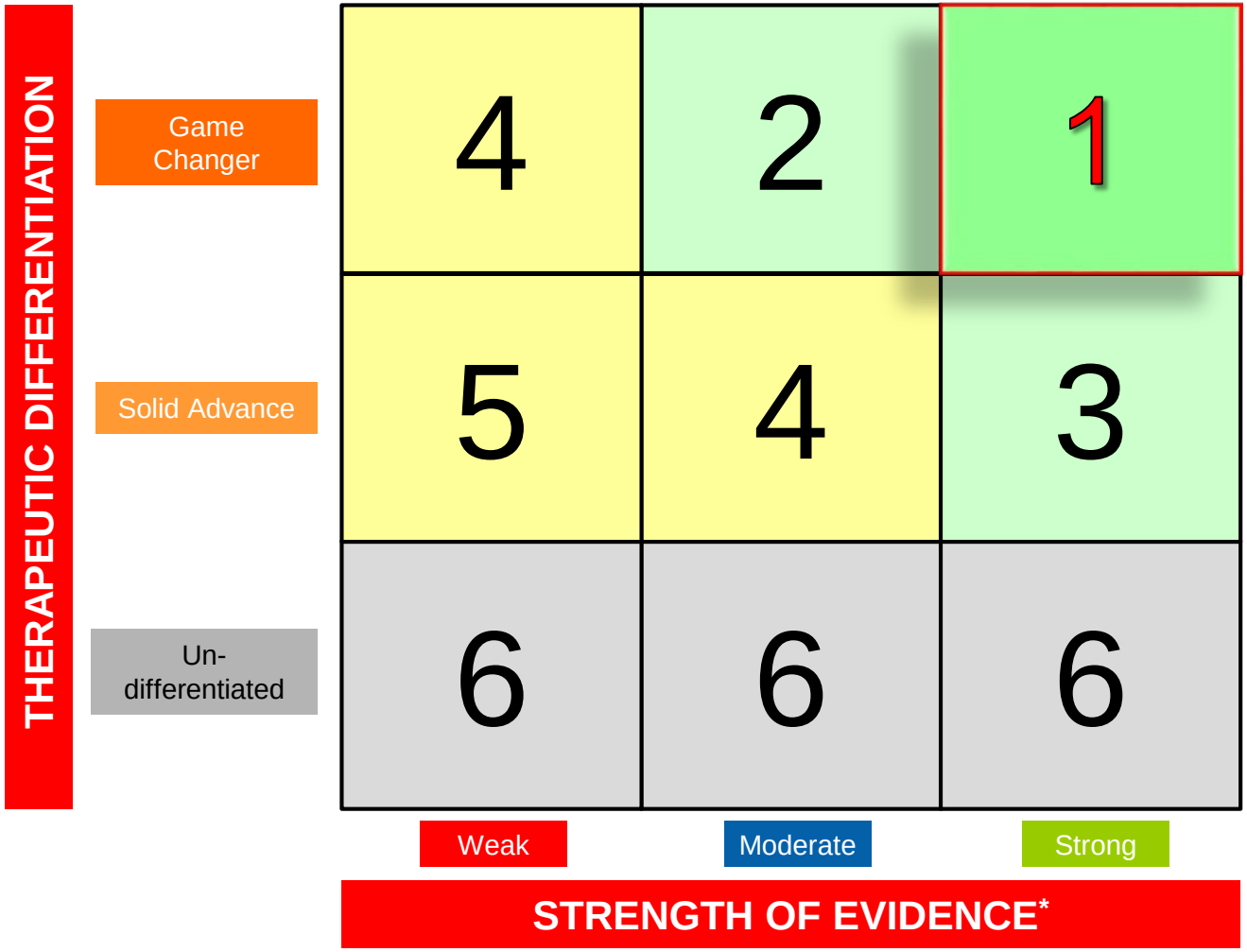


Research Strategy:

Mechanisms of disease and unmet medical need



Development Strategy:
Innovative solutions to unmet medical need



Development Priority

1 Highest Priority

6 Lowest Priority

**Strength of evidence adjusted to account for additional risk (e.g. regulatory, pharmaceutical science, intellectual property or dosing)*

Drug Discovery

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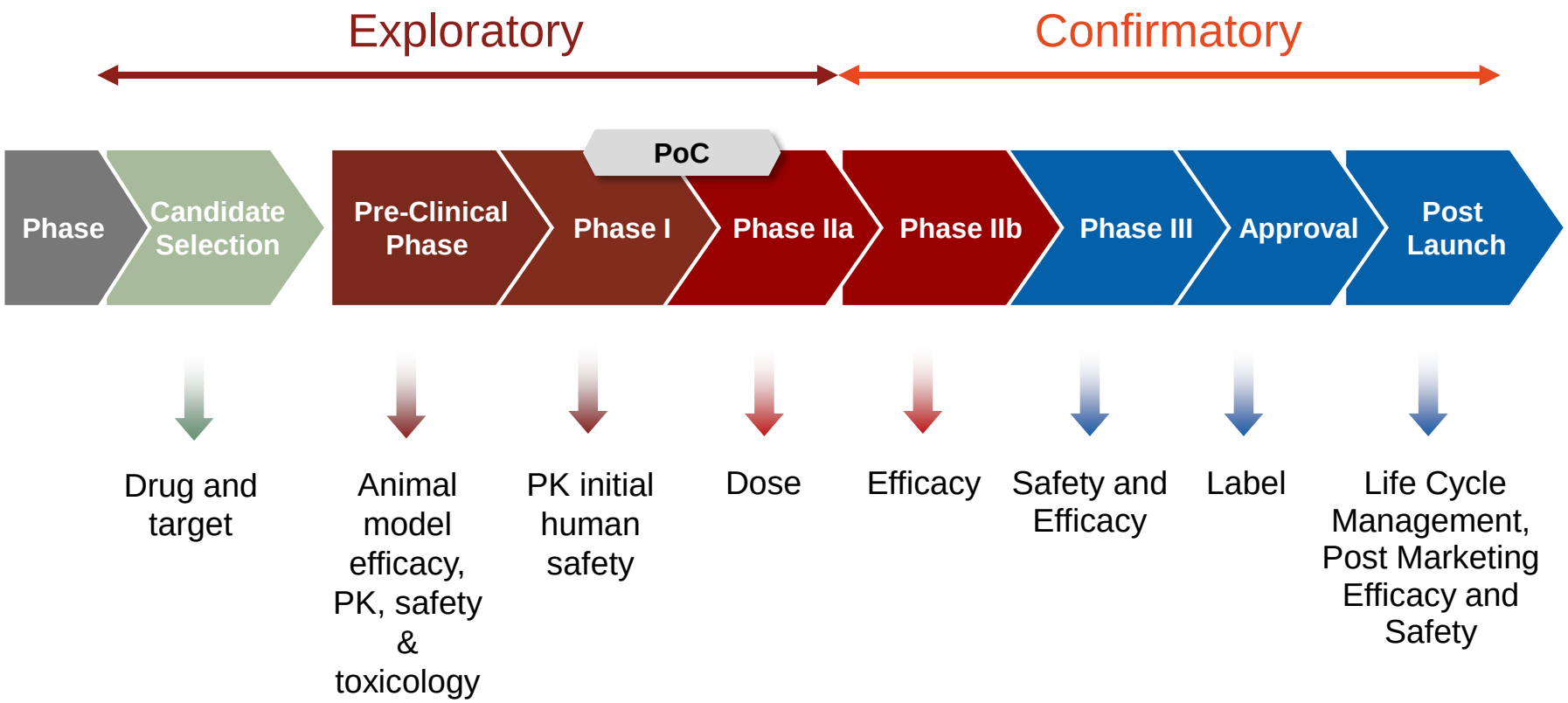
Examples and Conclusions

Pharmaceutical R&D
Multidisciplinary, Complex, Dynamic, Exciting



PK: pharmacokinetics
PoC: proof of concept
R&D: Research & Development

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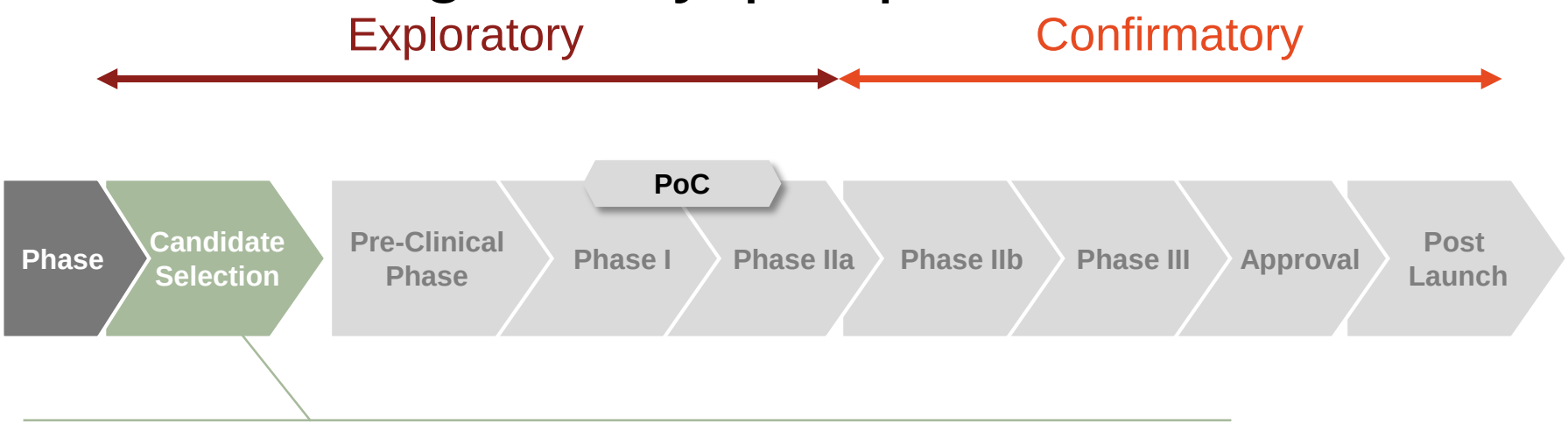
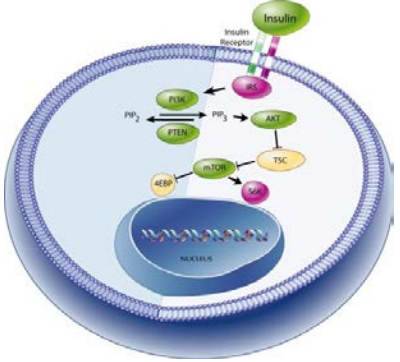
Candidates are selected by balancing many properties



- **Affinity** – specific interaction with the relevant target
- **Efficacy** – desired pharmacodynamic and clinical effect
- **Safety** – acceptable window between desired and undesired effects
- **Appropriate PK** – for Route of Administration, exposure etc
- **Developability** – possible formulation options
- **Competition** – advantage versus current and emerging therapies

PK: pharmacokinetics
PoC: proof of concept

“Pathways” and “Targets” are the beginning...



- **Pathways**

Networks of proteins in the cell describing a cascade of information and interactions which regulate cell and body processes

- **Targets**

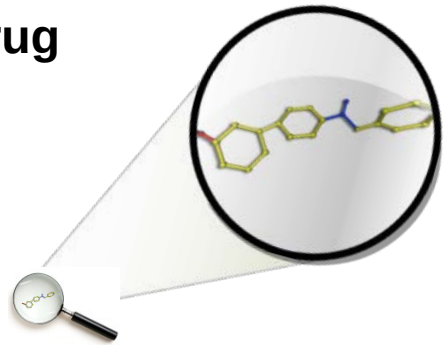
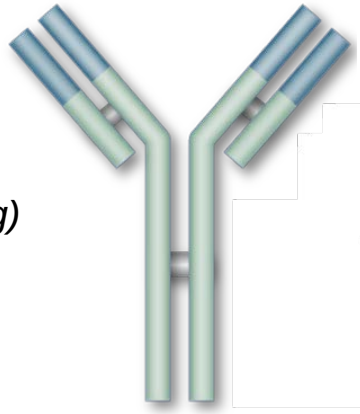
Individual proteins in a pathway. A drug target is a protein whose behaviour can be modulated by a drug and where this modulation has an effect on disease. Typical drug targets for therapeutic intervention are enzymes, receptors and ion channels

☞ Ideal Target

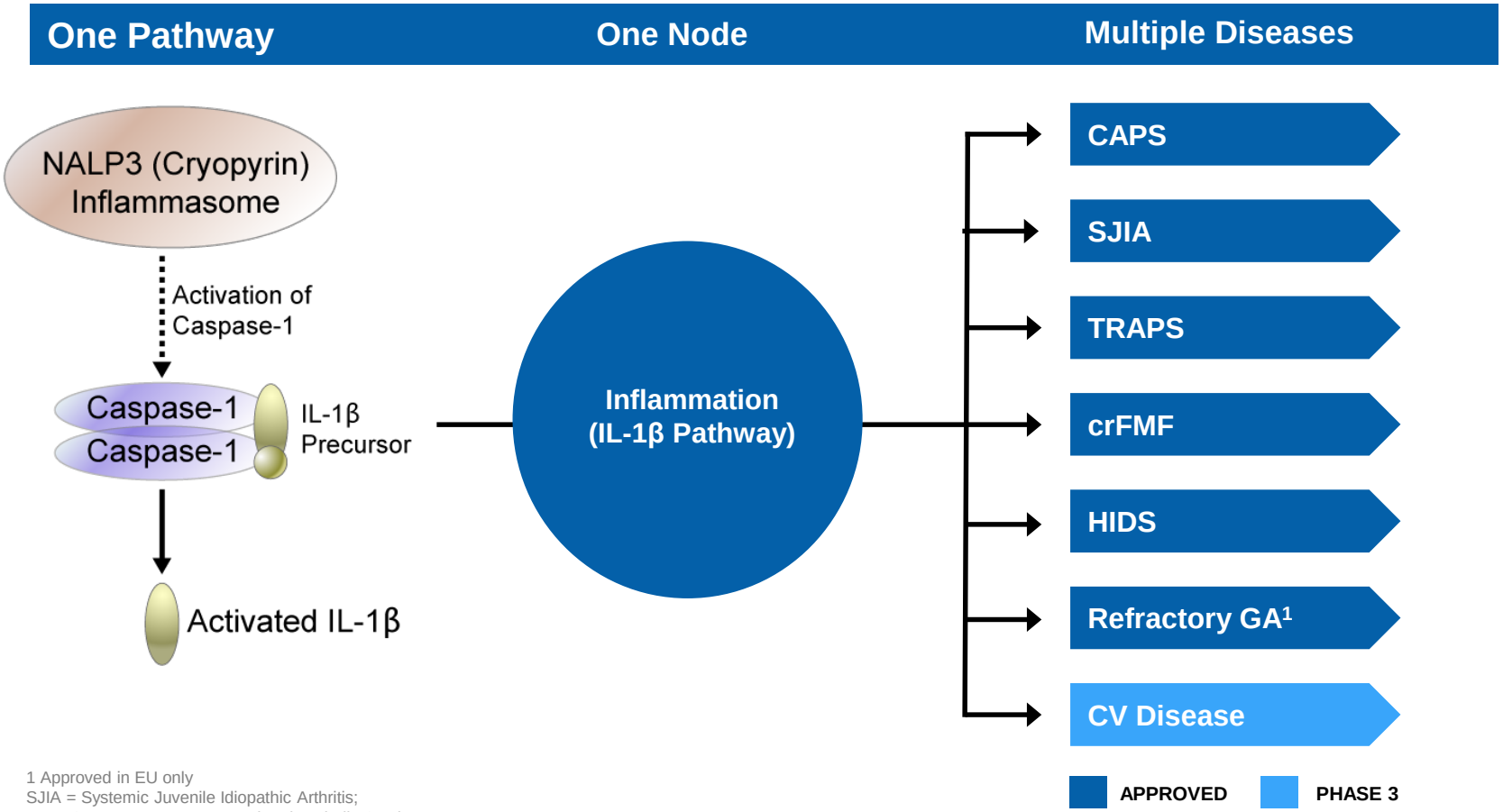
- Biological link to the unmet medical need
- Functionally or structurally characterized
- Druggable – not all targets can be modulated by ligands
- Quantified biological response
- Unique – selectivity over other members of their families
- Intellectual property – patentability of the compounds and/or target

Choosing a modality

Low Molecular Weight (LMW) drugs vs. Antibodies

	Drug Characteristics	Target	Side Effects
LMW Drug 	• Often orally administered • Dosed hourly to daily • Self administered	• Any druggable target • Enzymes, receptors, channels	• Less specific • Can inhibit multiple mechanisms
Antibody *(300x bigger than LMW drug)* 	• Parenteral administration • Dosed weekly-monthly • Physician administered	• Extracellular mechanisms • Protein-protein interactions	• Specific action • Low off target toxicity

Anti-IL-1β :One disease is only the start



1 Approved in EU only
SJIA = Systemic Juvenile Idiopathic Arthritis;
TRAPS = TNF Receptor Associated Periodic Syndrome;
crFMF = colchicine resistant Familial Mediterranean Fever;
HIDS = Hyperimmunoglobulinemia D with periodic fever syndrome;
Refractory GA = refractory Gouty Arthritis;
CV Disease = cardiovascular disease

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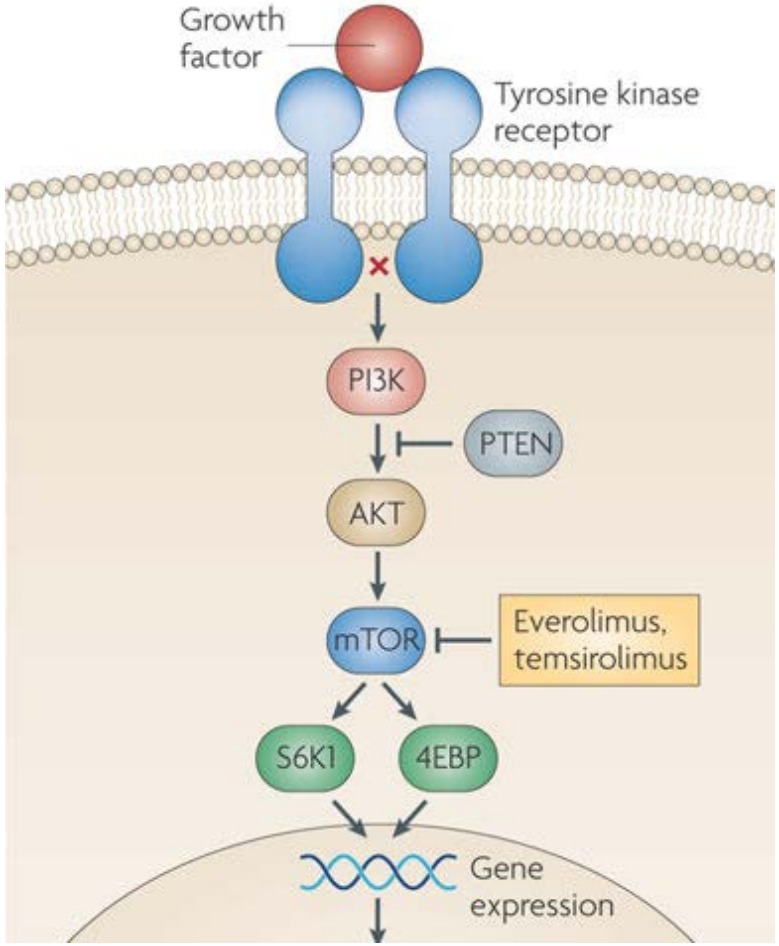
mTOR: a critical protein in the control of cell growth and proliferation



Nature Reviews Drug Discovery 8, 535-536 (July 2009)

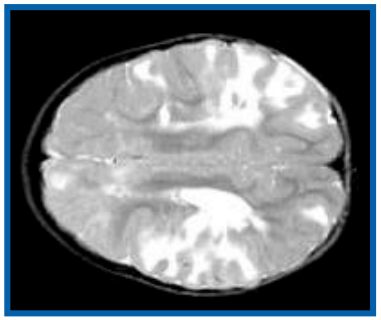
- mTOR = “mammalian Target of Rapamycin”: (2549 Aminoacids, MW 290’000), a key human kinase
- mTOR is a central controller of cell growth and thus, indirectly, of cell proliferation
- mTOR inhibition induces reduction of cell growth, cell metabolism and angiogenesis

Cell growth | Cell metabolism | Angiogenesis

Pathway Biology

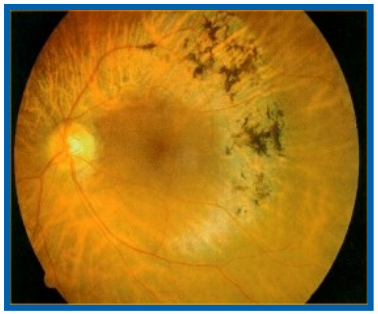
One mechanism, multiple diseases

Tuberous sclerosis

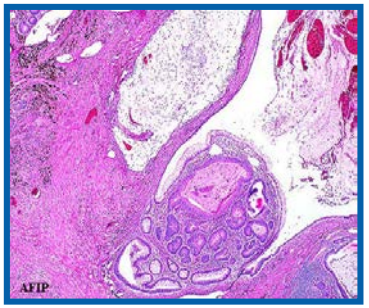


Votubia™ and Afinitor™

Retinitis pigmentosa

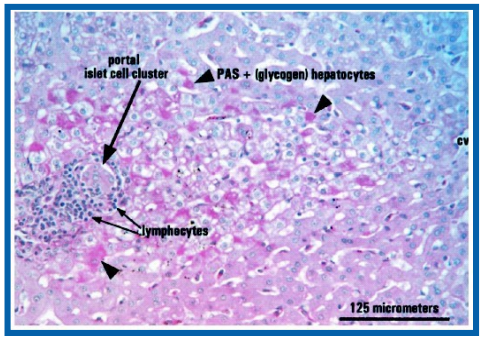


Cancer (kidney/breast)



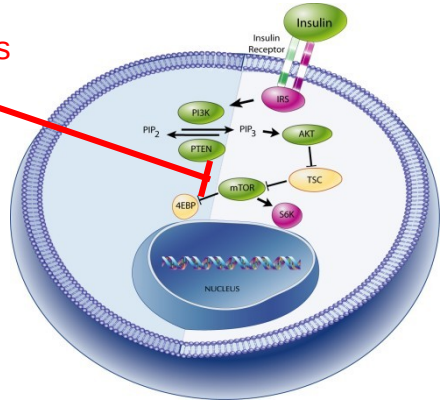
Afinitor™

Immune diseases, transplant rejection



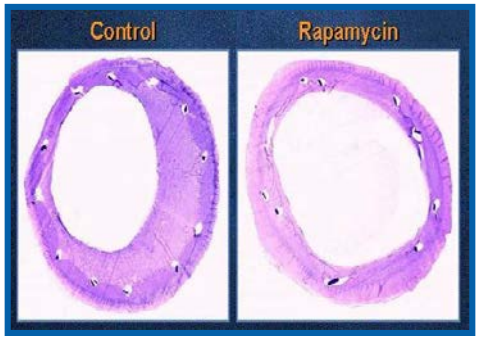
Certican™

Everolimus



mTOR pathway

Vascular proliferation (stent implant)



Xience™ Promus™

Drug Discovery & Clinical Research

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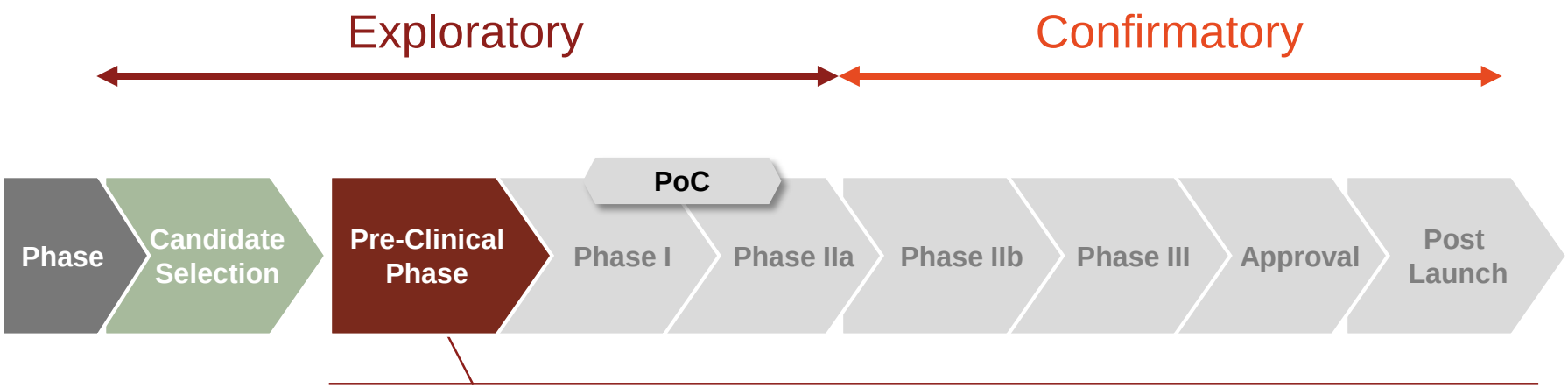
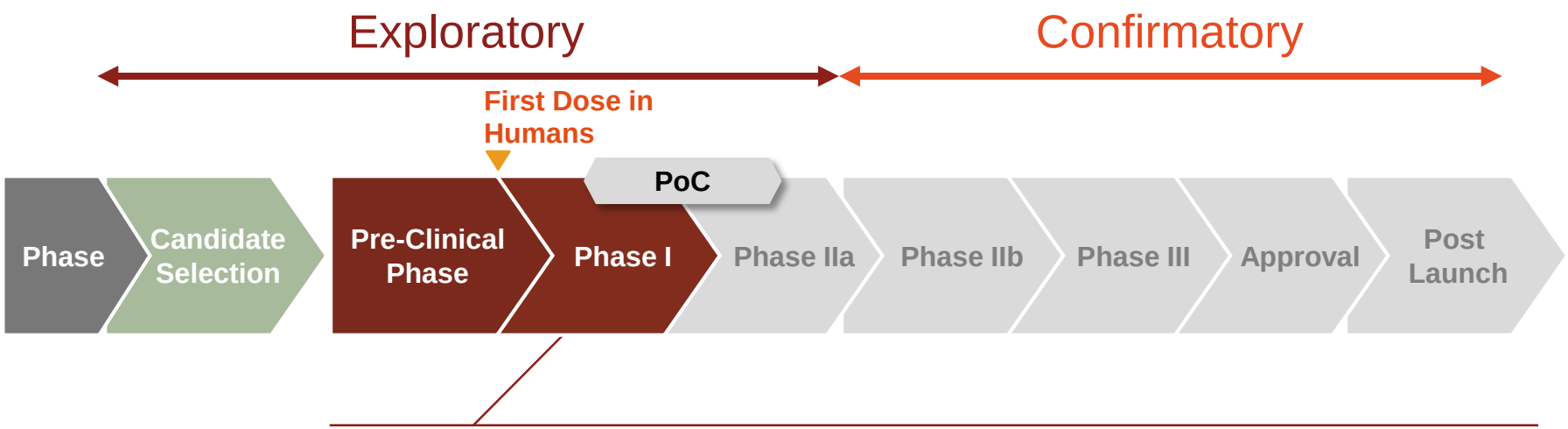
Pre-Clinical Phase concentrates on better understanding the candidate drug



- The pre-clinical phase investigates the candidate drug in more detail and determines a safe starting dose for humans
  - In-depth safety studies, including repeat dose animal toxicity studies, genotoxicity studies and others, based on target and indication
  - In-depth ADME studies
  - In-depth PK-PD studies
- Define the early clinical development plan, including protocols for the first trials
- Prepare sufficient compound for early clinical studies
- Apply for regulatory approval

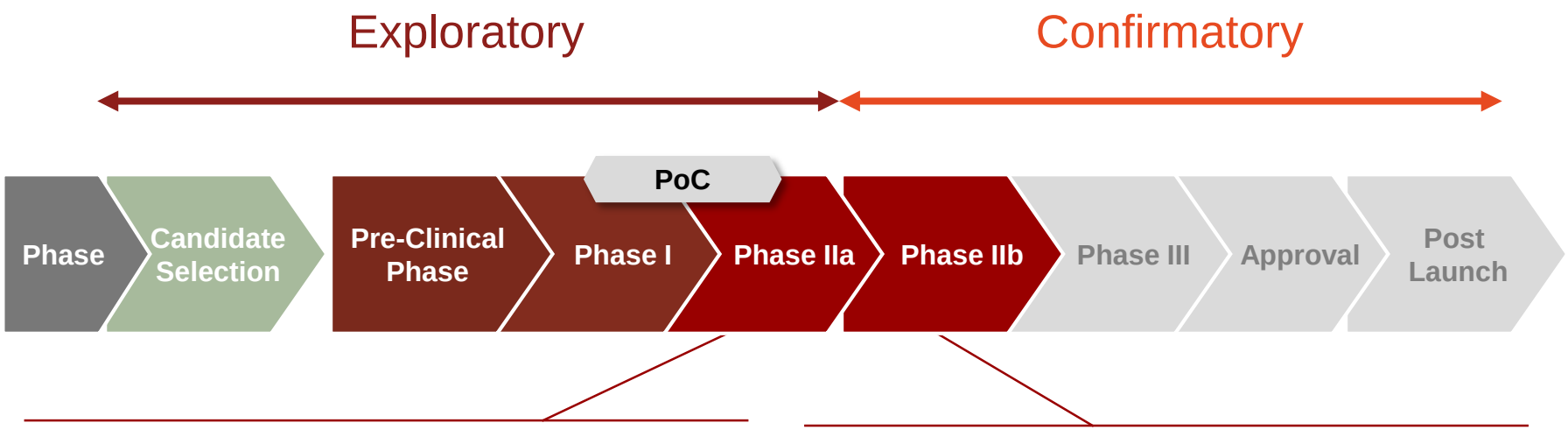
FIH* experience focused on Safety



- Phase I clinical trials assess safety & tolerability in a small number of people
  - Healthy volunteers usually, but patients in some cases
  - Often in an in-patient setting
- Conduct Proof of Concept study in the relevant population
- Evaluate PK & PD and metabolism in humans
- Refine formulation
- Conduct animal safety studies to support longer term treatment

*FIH: first in human

Efficacy assessed in Phase II studies to understand how well the drug works

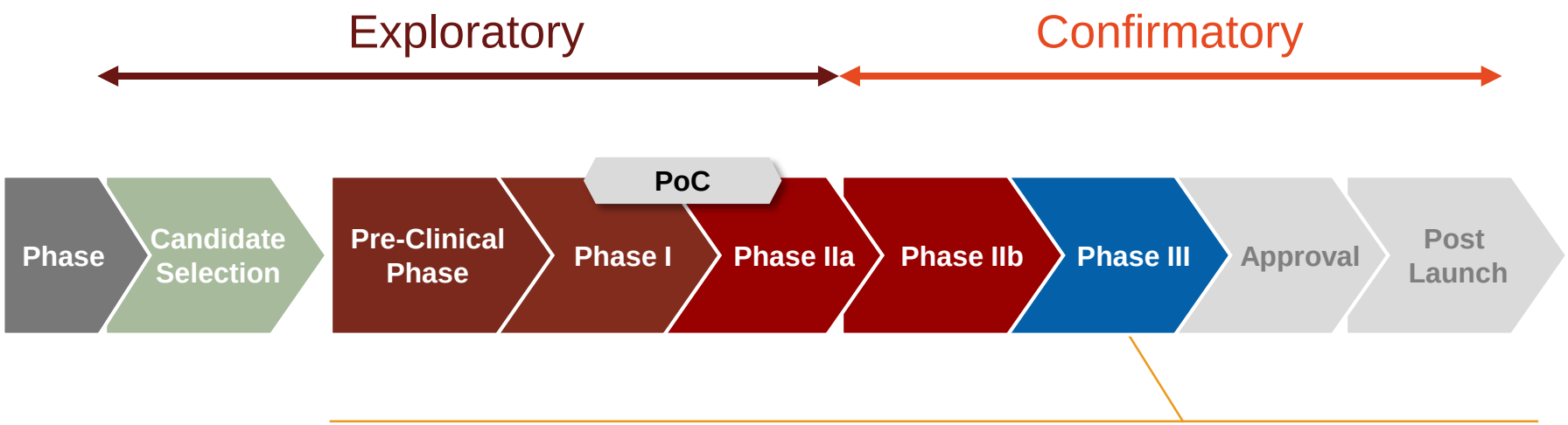


- Phase IIa clinical trials evaluate efficacy and safety
  - Focus is on effectiveness in a selected patient population
  - Typically controlled, double-blind, randomized trials
- Conduct Proof of Concept study in the relevant patient population

- Phase IIb clinical trials determine a dose for further development
  - Rigorous, multi-arm study designs
  - Establish Minimum Effective Dose (MED and Maximum Tolerated Dose (MTD) in patients
- Develop a market formulation

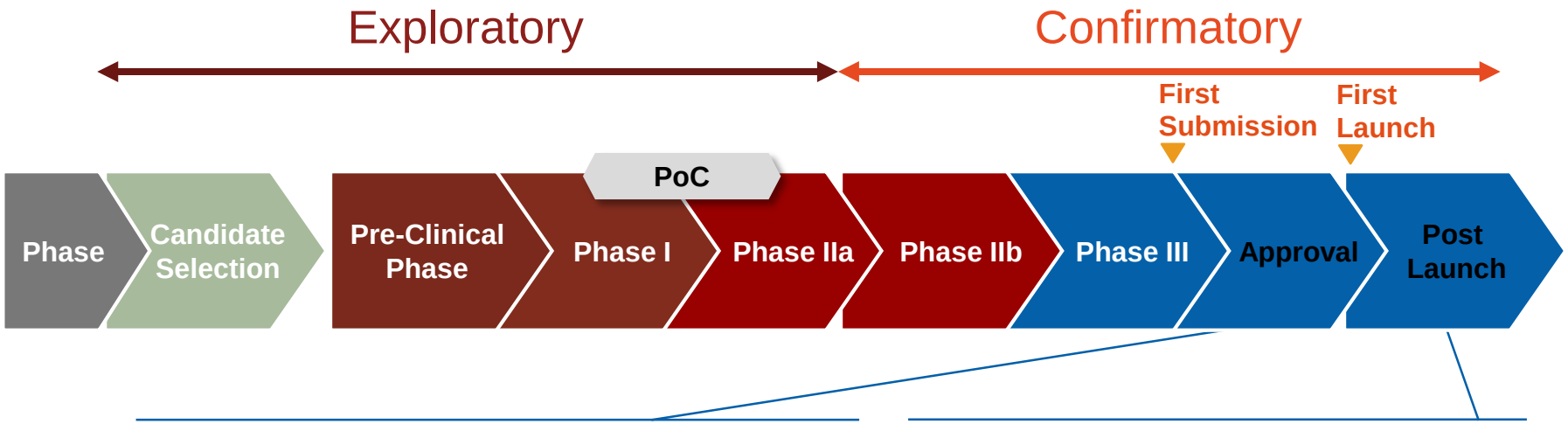
Further clinical profiling studies (technically PhI studies), such as drug-drug interaction, food effects and bioequivalence studies are often conducted in parallel to PhIIb and PhIII studies

Clinical Results, both Efficacy and Safety, confirmed in Phase III studies



- Phase III clinical trials definitively demonstrate the efficacy and safety of the product
  - Large, rigorous trials in thousands of patients
  - Trials typically include an active comparator or placebo control
  - Demonstrate adequate risk/benefit ratio
  - Provide much of the information needed for labeling
- Assess safety in special groups of patients, e.g. renal failure
- Assemble the registration dossier for submission
- Combination possibilities are investigated

Profiling continues in Phase IV studies as well as Safety Surveillance in 'real-life' patients



- Health authorities review the dossier
  - Requests for additional information are addressed
  - Additional studies may be needed
- Marketing authorization is granted
- Phase IV plans are developed and set in motion

- Phase IV studies are conducted
  - Continue to profile the efficacy and safety of the product
  - Comply with regulatory requirements
- Post-marketing surveillance studies are conducted
  - Primarily observational or non-experimental

Bringing Patient Focus to Drug Discovery
Mechanism-based medicine, and “niche” diseases

- Proof of concept trials first test the drug candidate’s efficacy and safety using small, homogeneous, well-defined populations. These well may be “niche” diseases
- The advantages of proof of concept studies include speed, quality of data, limitation of exposure, and scientific soundness
- Later trials can expand to different indications
- https://www.youtube.com/watch?v=3Gl0gAcW8rw

Global Drug Development

Part 2

–Introduction to PK & PD
–Clinical Trial Design

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Global Drug Development

Introduction to PK & PD

Exploratory Phase

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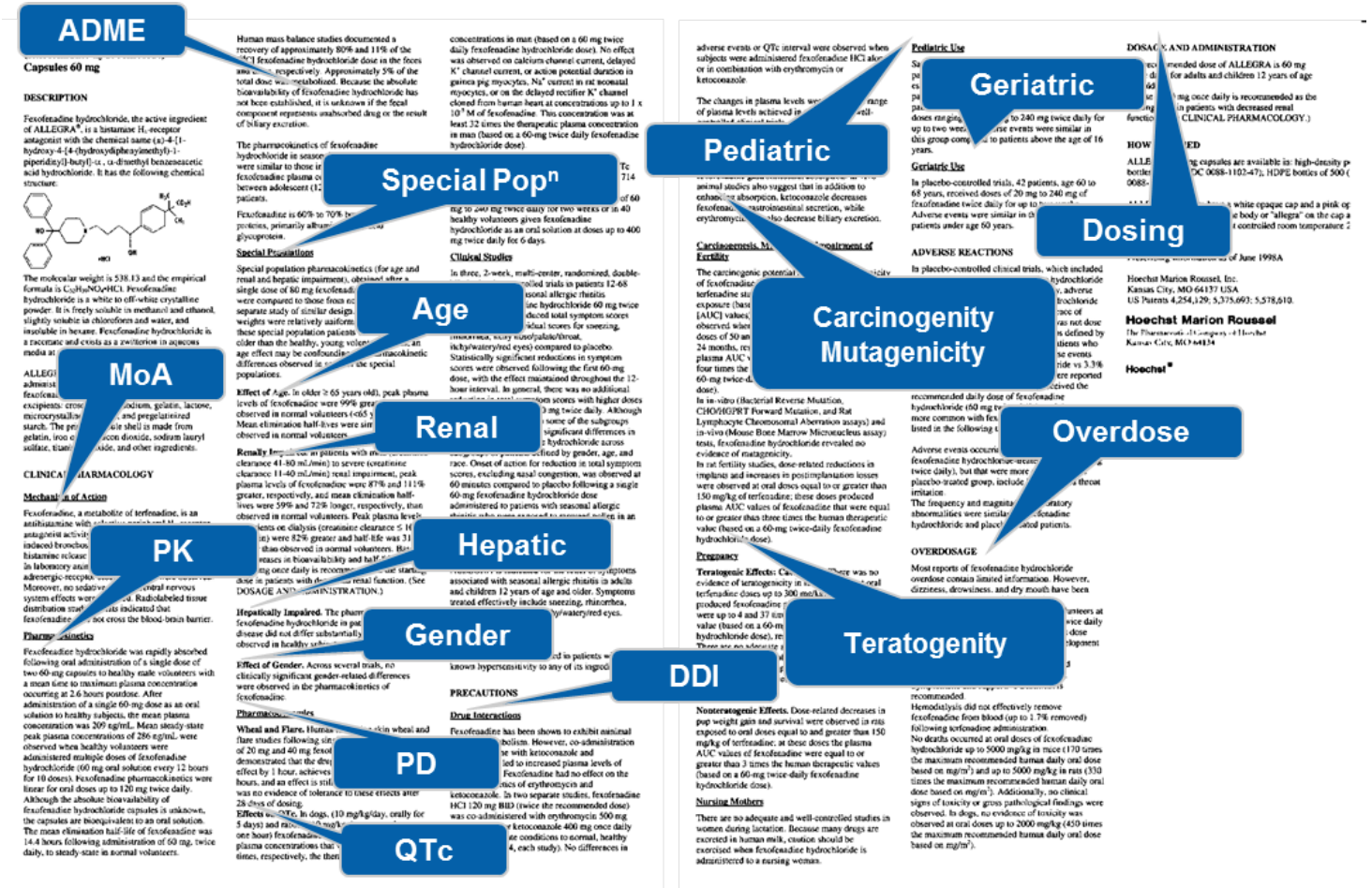
NIBR contribution to drug label



Definitions

- **PHARMACOKINETICS:**

The activity or fate of drugs in the body over a period of time, including the processes of absorption, distribution, localization in tissues, metabolism and excretion.

- **PHARMACODYNAMICS:**

The study of the biochemical and physiological effects of drugs and the mechanisms of their actions, including the correlation of action and effects of drugs with their chemical structure; also, the relationship between drug concentration and effect.

Ideal PK Properties of a Drug

1. Efficacious with once/day dosing
2. No dosing adjustments should be required
3. Should give consistent plasma concentrations in all patients from one dose.
4. No variability in metabolism
5. Excretion by both renal and hepatic mechanisms for those with liver or kidney problems

6. Rapid, predictable onset of action

7. Clearance high enough so compound is removed from body if any untoward side-effects are observed.

8. No accumulation

9. No interaction with co-administered drugs

Pharmacokinetics

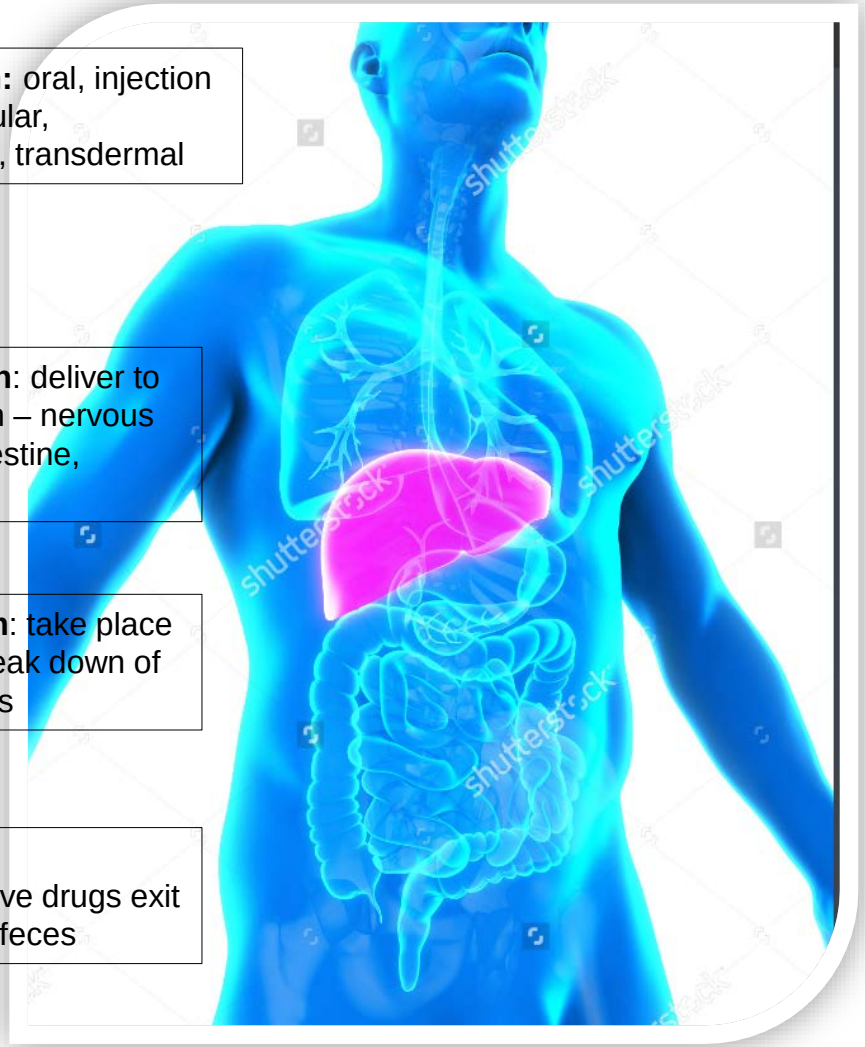
- **A**bsorption
- **D**istribution
- **M**etabolism
- **E**xcretion

Absorption: oral, injection –intramuscular, intravenous, transdermal

Distribution: deliver to target organ – nervous system, intestine, muscular

Metabolism: take place in liver – break down of the enzymes

Excretion: inactive/active drugs exit via urine or feces

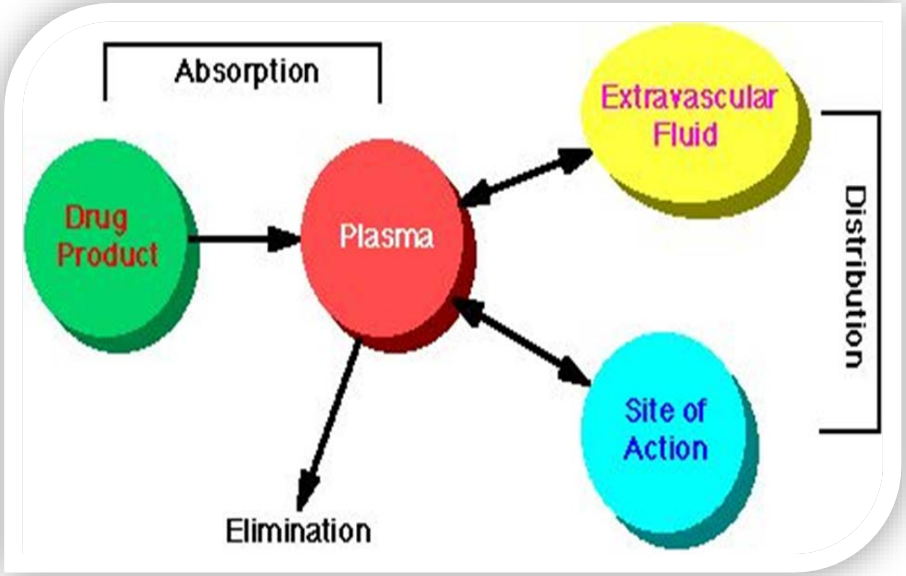


Absorption

- Absorption is the transfer of a drug into the blood after it is released from its dosage formulation.
- The body can absorb drugs in many ways, such as **oral** (swallowing a tablet), **intramuscular** (getting a flu shot in an arm muscle), **subcutaneous** (injecting insulin just under the skin), **intravenous** (receiving chemotherapy through a vein), or **transdermal** (wearing a skin patch).

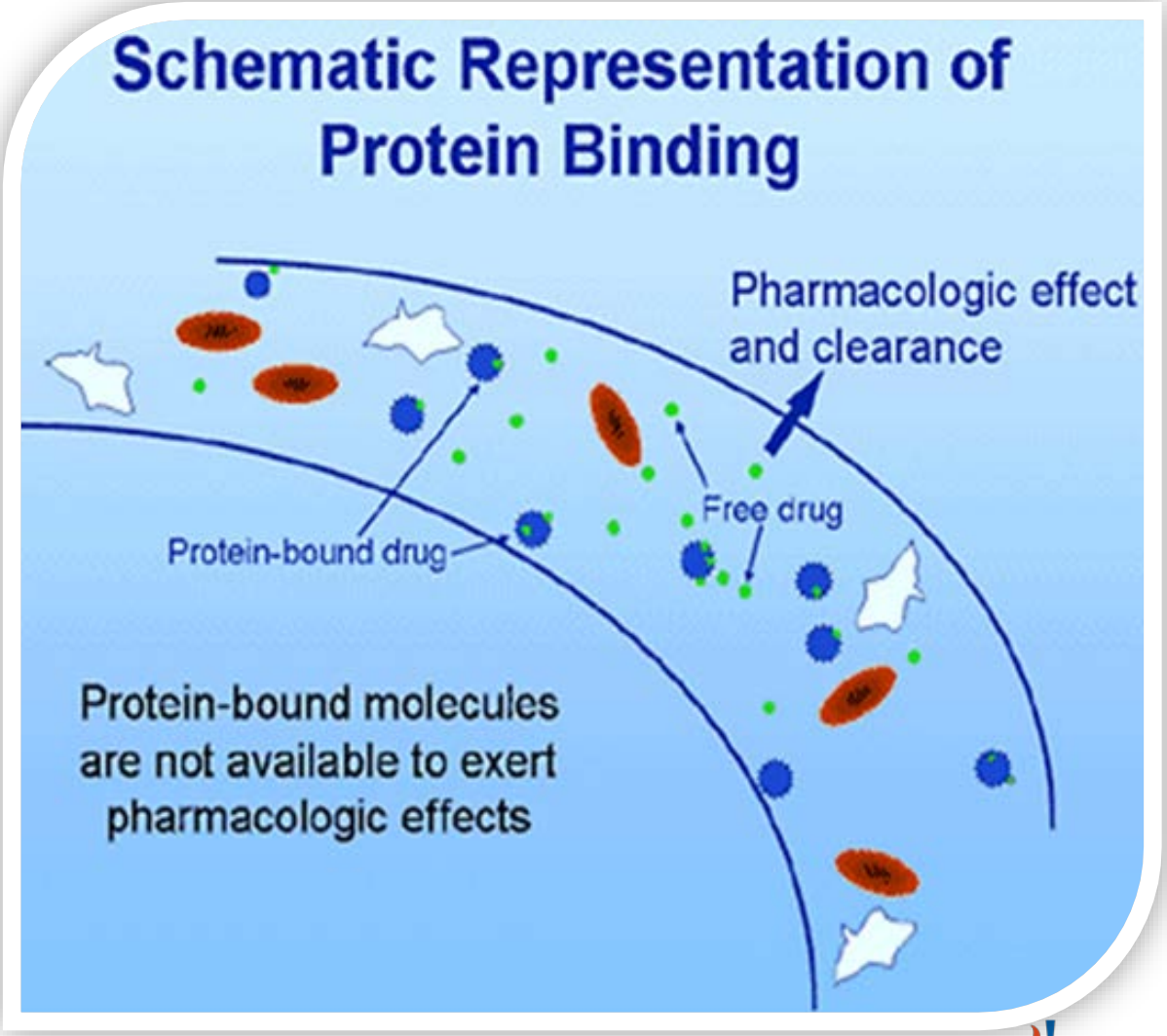
Distribution

- Distribution is the movement of a drug inside the body once the drug has reached the blood.
- Blood carries the drug throughout the body and also to its sites of action



Distribution

PROTEIN BINDING OF THE DRUG AFFECTS DISTRIBUTION



Metabolism

- Drug metabolism refers to the body's way of processing drugs.
- This drug that is being transformed inside the body is called a metabolite.
- Most metabolites are inactive molecules that are excreted but some are active and produce effects until they are further metabolized or excreted.
- The liver is the primary site of drug metabolism.
- The enzymes found inside the liver interact with drugs and change them into metabolites (CYP450).

Drug-drug Interactions

Drug-Drug Interactions

- Risks associated with CYP enzyme **Inhibition** or **Induction**

Inhibition of CYP enzymes

↓

Decreased degradation of co-medicated drugs

↓

Increased drug plasma concentrations

↓

Risk of increased side effects

Induction of CYP enzymes

↓

Increased degradation of co-medicated drugs

↓

Decreased drug plasma concentrations

↓

Loss of pharmacological effect

↓

Risk of lack of efficacy

Excretion

- Most drugs and their metabolites are excreted by the kidneys via the urine
- Some drugs combine with bile and enter the intestines. In the intestines the drug will join with the unabsorbed fraction of the administered dose and be eliminated in the stool.
- Some drugs are removed through the lungs in the expired breath e.g. alcohol, anaesthetics
- The rate of urinary excretion is much faster than that of faecal excretion.
- Drugs excreted through the urine take a couple of hours while drugs excreted through the faeces take a couple of days.

Pharmacodynamics

- **Bioavailability** : A measure for the proportion of the dose that reaches the systemic circulation i.e. how much needs to be given to deliver effect.
- **Clearance**: A measure of the elimination of a compound from the blood.
- **Unbound Fraction**: The fraction of drug not bound to proteins.
- **Half-Life** : A measure of the time it takes to decrease the concentration of the drug by 50% i.e. how often the patient needs to be dosed.

Global Drug Development

Clinical trial design

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Basics of Clinical Trial Design

OBSERVATIONAL

OBSERVATIONAL (NON-INTERVENTIONAL):

Treatment prescribed as per current practice

Primarily to evaluate long term safety outcomes

Also epidemiological studies

INTERVENTIONAL:

Participants are assigned to a treatment intervention which is then evaluated according to pre-defined outcomes

INTERVENTIONAL

What is an RCT?

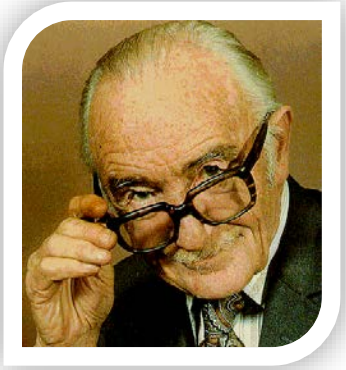
- The RCT is a study in which people are allocated at random to receive one of several clinical interventions and in which two or more interventions are compared and measured.
- One of the interventions is a standard of comparison / control.
- *RCTs are quantitative, comparative, controlled experiments in which a group of investigators studies two or more interventions in a series of individuals who receive them in random order*.

- RCT: randomised controlled trial

When was the first RCT?

- Credited to **Sir Austin Bradford Hill** (1897-1991)
  - English epidemiologist & statistician
  - 1940s: Streptomycin & TB – 1st RCT
  - 1950s: Case-control study in lung cancer patients (link with smoking)

- **Sir Archie Cochrane** (1909–1988)
  - "I knew that there was no real evidence that anything we had to offer had any effect on tuberculosis, and I was afraid that I shortened the lives of some of my friends by unnecessary intervention."
  - *Effectiveness and Efficiency: Random Reflections on Health Services, 1972* – led to development of the Cochrane Library – a database of systematic reviews and meta-analyses



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- RCT: randomised controlled trial

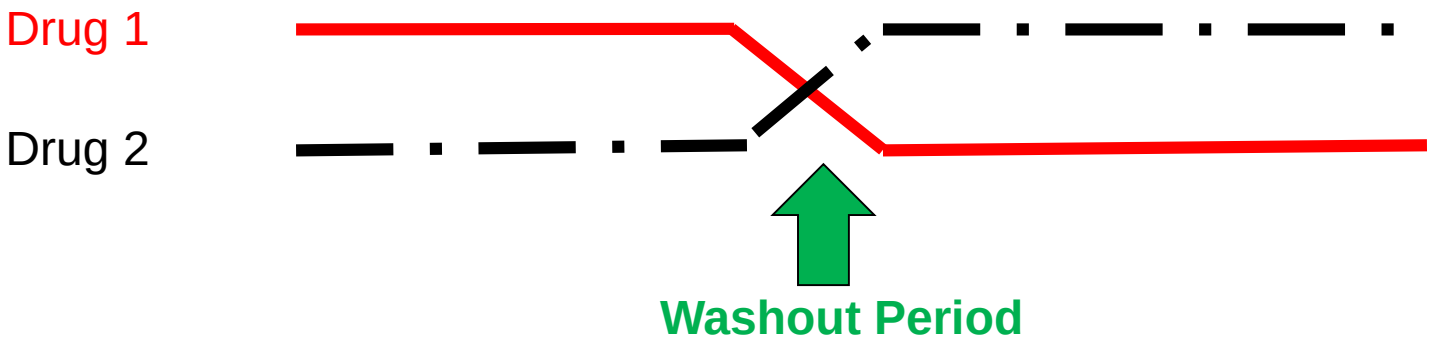
RCT Design

- Parallel group study

A

B

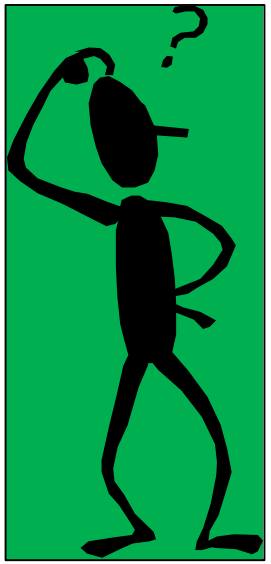
- Crossover study (a study design where all subjects receive all treatments but in different orders)



Can occur in higher order e.g. Double design

What is a Washout period?

- A period where drug treatment is suspended to allow patients to begin a study/new portion of a study, drug free
  - ➢This prevents treatment effects or side effects of the study drug from being confused with those of the previous drug



Mortality and Morbidity studies

- Hard outcomes
- Not surrogate markers
- Usually larger studies/mega trials
- Potentially change the way we practise medicine

Methodological Quality-Trial Check List

- Allocation Concealment
- Randomisation
- Blinding and whom
- Loss to follow up of less than 20%
- Intention to treat(I.T.T) analysis
- Table I must show that the 2 groups are the same

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Gold standard

Baseline Characteristics

- Must be the same in each treatment group

Randomisation

- Flip a coin
- Roll a die
- Envelope system
- Random number tables etc
- IVRS*
  - All participants have the same chance of being assigned to each of the study groups.
  - Thus the characteristics of the participants are likely to be similar across groups at the start of the study (baseline)
  - By keeping the groups similar at the start of the study investigators will be more able to isolate and quantify the impact of the interventions studied. Also allocation bias is reduced.

*IVRS: interactive voice response system

Blinding

- Blinding reduces observational bias
- A double-blind RCT is one where neither the patient nor the investigator knows which treatment they are receiving.

Trials where patients receive a placebo are known as double blind, randomised, placebo controlled trials.

In summary

- Pharmaceutical research and development is multi-disciplinary, complex, dynamic and exciting
- It takes strong teamwork from start to finish, to translate early research into a new drug for an unmet medical need
- Clinical trials are just one component in the long, complex, multi-phasic pharmaceutical R&D process

Thank you

NOVARTIS

Risk

- Risk is the probability of a disease occurring in a disease-free population during a specific time period.
- This is nothing other than INCIDENCE = % = probability

Divide the # new cases (n) in a specific period by the population at risk (P): **n/P**

➲ **EXAMPLE**

	No stroke	Stroke
Aspirin	95	5
Placebo	90	10

- Risk of stroke in aspirin group = 5/100 = 5%
- Risk of stroke in placebo group = 10/100 = 10%

* Patients not on aspirin have the double the risk of stroke

Odds

- Odds is the probability of a chosen outcome in a particular group
- Divide the # new cases (n) in a specific period by the # that did not have the outcome (P - n): **n/(P – n)**

➲ **EXAMPLE**

	No stroke	Stroke
Aspirin	95	5
Placebo	90	10

• odds of stroke in aspirin group = 5/100 - 5 = 5/95 = fraction

•odds of stroke in placebo group = 10/100 - 10 = 10/90 = fraction

➲ Rate

- Rate : relates the number of new cases not to population at risk but rather to person-time at risk (Y).

n/Y

- So in a defined population followed up for a period of time, we establish the total person years at risk.
- Eg incidence rate = 50/100 person years
- Note shown as %

➲ RRR vs ARR

- Relative risk (RRR) = ratio
  - x/y therefore 1 is the reference value
- Absolute risk (ARR) = difference, not ratio
  - x – y therefore 0 is the reference value

➲ ARR, RRR

- **AR (absolute risk)** = the number of events (good or bad) in treated or control groups, divided by the number of people in that group
  - **ARC** = the AR of events in the control group
  - **ART** = the AR of events in the treatment group
- **ARR (absolute risk reduction)** = ARC – ART
- **RR (relative risk)** = ART / ARC
- **RRR (relative risk reduction)** = (ARC-ART) / ARC

Examples –

AR and RR

	No stroke	Stroke
Aspirin	95	5
Placebo	90	10

- AR of stroke if treated with aspirin = 5/100 = 5%
- AR of stroke if not treated with aspirin = 10/100 = 10%

☞RR of having a stroke, aspirin vs placebo = 5/10 = 0.5 ie half as likely to have a stroke if taking aspirin; or double the risk if not

- AR: absolute risk
- RR : relative risk

RRR and ARR

	No stroke	Stroke
Aspirin	95	5
Placebo	90	10

- ARR = AR placebo – AR aspirin = 10% – 5% = 5% reduction with aspirin
- RRR of stroke = AR placebo – AR aspirin/AR placebo = 10%-5%/10% = 5/10 = 0.5

  ☞Therefore half as likely to have a stroke if on aspirin vs no aspirin

- ARR: absolute risk reduction
- RRR: relative risk reduction

Number Needed to Treat

NNT

- Very useful tool - measure of clinical significance
- = the number of patients who must be treated to prevent one of them having a bad outcome
- NNT= 1/ARR

There has to be statistical significance for this to be valid

Example

- NNT for aspirin = 1/0.05 = 20
  - For every 20 people treated with aspirin, you will see 1 fewer stroke
- If NNT = 100 for primary stroke prevention with aspirin for 1 year, means that for every 100 patient years of aspirin treatment, you will see 1 fewer stroke on average

Power

- Power is the probability of detecting
  a treatment difference if one truly exists.
- Sample size is determined by calculating how many patients are needed to determine the minimum clinically important difference.
- Large patient numbers are NOT necessary in certain trials while they are in others e.g. NAVIGATOR.
- Small sample size alone does NOT predict that a study is of good or poor quality.

P-values

- The P-value is the probability that the results found arose purely by chance.
- Basically convention states:
- P-value < 0.05 reject chance as an explanation
- P-value > 0.05 chance may explain the results

Confidence Intervals

- CI's are a measure of strength of evidence.
- 95% CI = the range of values within which we can be 95% certain that the population value lies.
- By convention 95% is most often used but sometimes we will see 90% or 99%.
- P-values <0.05 correlate with 95% confidence intervals.
- If the CI crosses 1 (for a relative measure) or 0 (for an absolute measure) the results could have favoured treatment or control.