Grand Challenges
African Drug Discovery Accelerator

Drug Discovery and Development Course

Introduction to Drug Discovery and Development
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Learning objectives

- Understand the overview of the drug discovery and development process
- Understand importance of working on the right biology
- Understand those properties that impact the chemical quality of a compound series

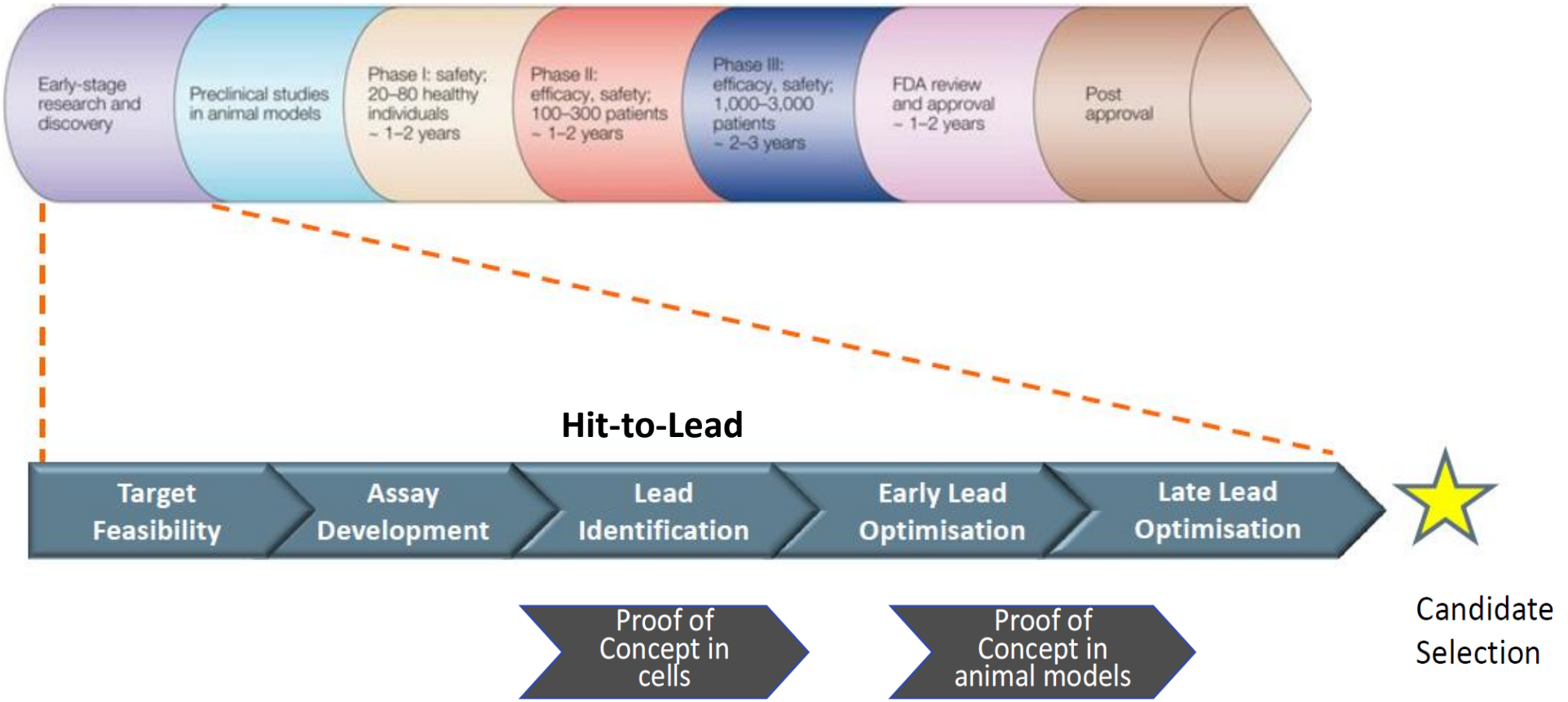
Drug Discovery Philosophy

- **Be curious – the best question is "why?"**
- **You will not understand everything outside your domains of expertise – ask questions!**
  - Do not pretend to be an expert in areas where you are not
  - Be responsible for understanding and delivering expertise in areas where you are expert – explain your thinking and interpretation of data to others
  - Ask, listen and learn from those who are experts outside your area
- **Focus on the goal of delivering a candidate drug**
  - Drug Discovery is not the same as doing basic science
  - Don't do something because you can do it, rather focus on answering the right questions
  - Gather data, define the issues, ruthlessly focus on solving the issues with chemistry, biology and pharmacokinetics
- **Collaboration and team-work are key**
  - It is not about "me" but the project and the project team
  - All need to learn the multi-disciplinary language of Drug Discovery

Drug Discovery – where to start?

- **Drug discovery is a misnomer**
  - “a wrong or inaccurate use of a name or term”
  - Except for some natural products – drugs are novel chemical entities that did not exist before they were made
    - Derived from imperfect starting compounds that have been extensively changed and optimized across many parameters
- **Drug discovery is a journey with various options**
  - New biology – need to find a disease indication
  - Defined disease – need to find the best approach
- **It is better to start from the end and define a route to get there!**
  - Target Product Profile (TPP)
  - TPP describes the profile of the medicine necessary to meet the goals of patients, care givers and payers

Drug Discovery Phases



Proof of Concept: Demonstration that the target/ compound series gives the desired response before studying in humans

What biological target to work on?

- **Critical to work on compounds having biology relevant for disease**
- **If not, even the best project team delivering the best candidate drug will deliver failure over years costing USD millions**
- **So biological target must be validated for the disease**
  - Many ways to confirm validation
  - Best to have evidence across several areas – genetic, phenotypic, disease model, chemical
- **Test cascade is the sequence of assays run to support optimisation**
- **Test cascade must also be validated and relevant for the disease**
  - *In vitro* biochemical, cellular phenotypic and *in vivo* efficacy assays are robust, validated with controls and deliver data that translate to patients
- **If not, even if working on the best target for the disease, the test cascade will lead the project team in the wrong direction**

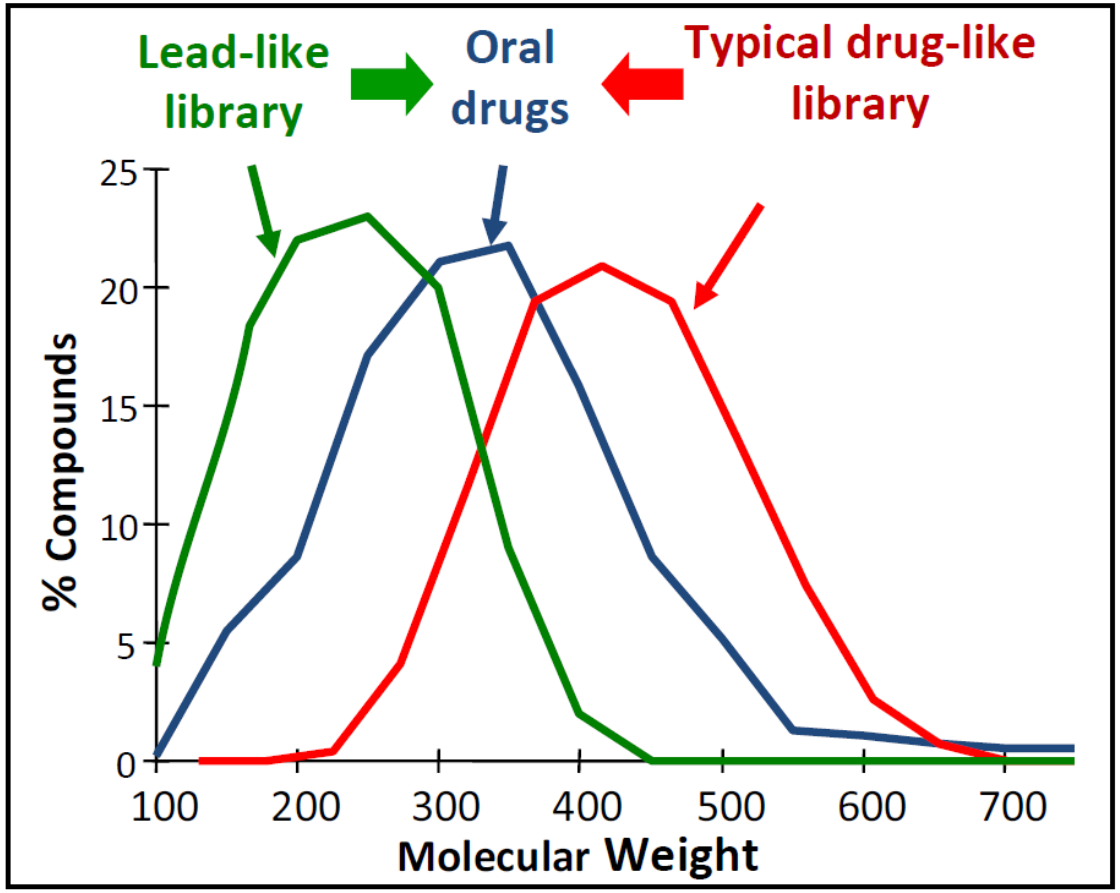
- **Right biology and right assays!**

Hit identification options

- **Target Based**
  - High Throughput Screening (HTS); often large compound numbers in low volume (384 / 1536 well)
- **Focused Screen (biased!)**
  - Subset of molecules based on target class / structural knowledge
- **Fragment Screen**
  - High concentration screen of small molecules - biophysical methods (MWt <250)
  - Crystallography often required for optimisation / confirmation of binding
- **Virtual Screen**
  - *In-silico* docking compound library into protein model (X-ray / AlphaFold)
- **Structure based design**
  - Exploit structural knowledge to design molecules
- **Phenotypic screen**
  - Seeking to see a desired response in cellular systems
  - Screening many targets
- **Literature – work from a known ligand, could be a back-up**

What happens during optimisation?

- Optimization often results in increasing Mol Wt and modulating lipophilicity (cLogP) to deliver a lead and candidate drug
- If a library is screened where the molecules have high Mol Wt then high potency compounds may be found – but they are hard to optimize
- Small Mol Wt “lead-like” molecules have a better chance of binding to a receptor than larger drug-like molecules and may have weaker potency – but they are easier to optimize
- Focus on a screening library or hits that are “Lead-like” will give a greater chance of success



Teague, S.J.; Davis, A.M.; Leeson, P.D.; Oprea, T. The Design of Leadlike Combinatorial Libraries. Angew. Chem. Int . Ed. 1999, 38, 3743-3748

What makes a good hit?

- **Potency and selectivity**
- **Drug-like properties including low Molecular Weight (MW) and low lipophilicity (LogP)**
- **Synthetic accessibility and versatility**
- **No undesirable groups**
- **Freedom to Operate (FTO) and Intellectual Property (IP) space**

Potency

- **Potency is the measure of compound activity and reflects the thermodynamics of a compound binding to a biological target**

- **Governed by $\Delta G=\Delta H-T\Delta S$**
  - **ΔH** enthalpy – bond breaking (i.e. desolvation) and bond forming (how well the drug binds to the target)
  - **ΔS** entropy – overall impact on disorder of the system

- **Most, but not all, drugs in the nM range**
  - Weaker compounds require higher concentrations to efficiently interact with target leading to increased chances of off-target effects
  - Potency impacts dose size
- **Potency is NOT the only game in town!**

Ligand Efficiency (LE) – A measure of "Fit"

- **Binding contribution per non-H atom**
  - "Goodness of fit"

$$LE = -\frac{RT\ln Ki}{HA}$$

HA = no. of Heavy atoms i.e. non-H atoms
R = Gas Constant ($0.001987 kcal K^{-1} mol^{-1}$)
T = Temperature in Kelvin
Ki = Potency in M

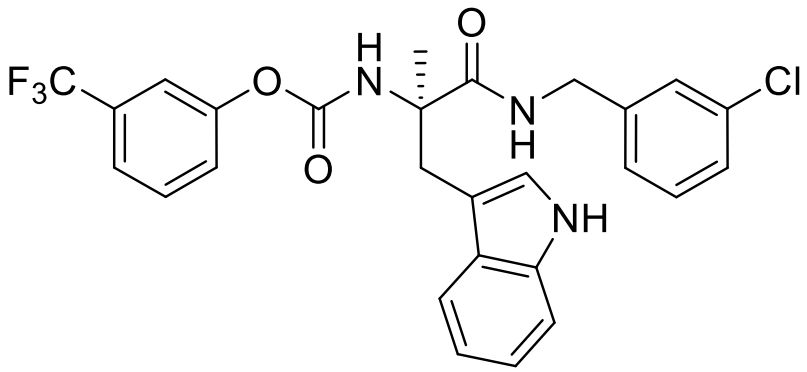
$LE = pIC_{50} * 1.37/HA$ [pIC_{50} is $-Log_{10}(IC_{50})$]

Has units kilocalories per mole per non-H atom

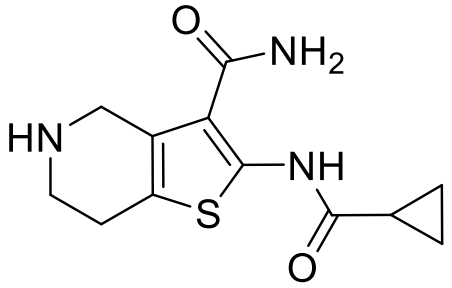
Lipophilicity Ligand Efficiency
LLE = pIC50 - LogD

- **Optimising a low LE hit has risks**
  - Poor, non-optimal fit to target; Potency gained by bulk and not specific interactions

Mentimeter:
Which molecule would you rather work on?

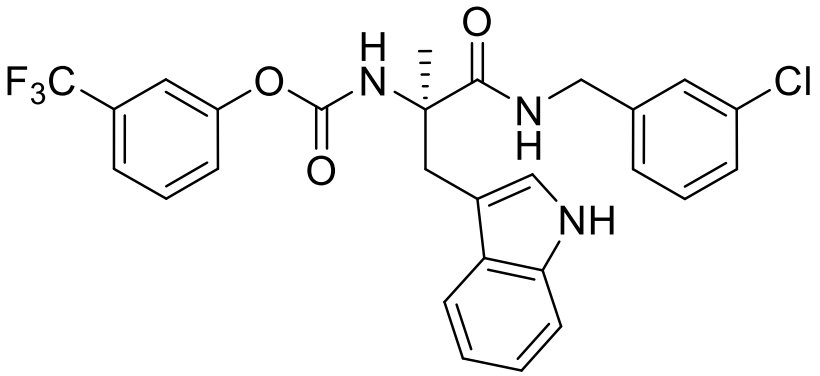


Ki = 100nM

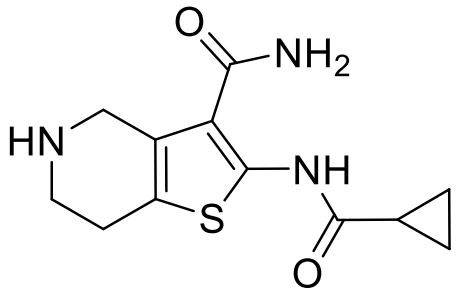


Ki = 10,000nM

Which molecule would you work on?



Ki = 100nM
Heavy atoms = 37
LE = 0.26



Ki = 10,000nM
Heavy atoms = 18
LE = 0.38

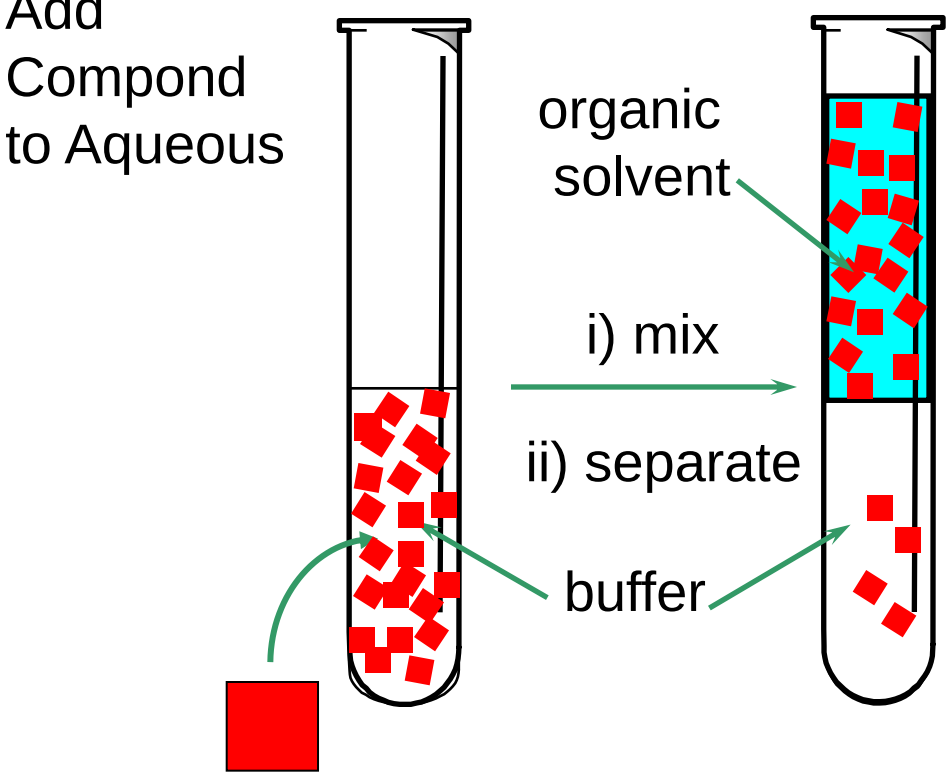
Selectivity

- **At Hit stage it is most critical to understand the selectivity over the most relevant off-targets**
  - Cellular selectivity >10 fold over cytotoxicity in hit
  - If biological target known, selectivity to closest human targets of concern, plus targets known to cause toxicity such as hERG
  - Helps to define the scale of the challenge for Hit-to-Lead
  - Selectivity can be altered with chemistry – so criteria increase with later phases

- **What selectivity window is needed ultimately?**
  - Depends on impact of non-selectivity!
  - Need to define what assays are used to define selectivity
  - At least 100-1000 fold selectivity typical goal for a candidate
  - hERG – 30 fold margin based on IC_{20} vs free Cmax at therapeutic dose

Lipophilicity (LogP)

- **Partition coefficient is called LogP**
- **Measure of lipophilicity or degree to which a compound will partition into 'fatty' tissue *vs* water**



Measure analyte in aqueous phase before and after shaking with organic solvent.

$$P = \frac{\text{conc in org}}{\text{conc in aqu}} = \frac{18}{2} = 9$$

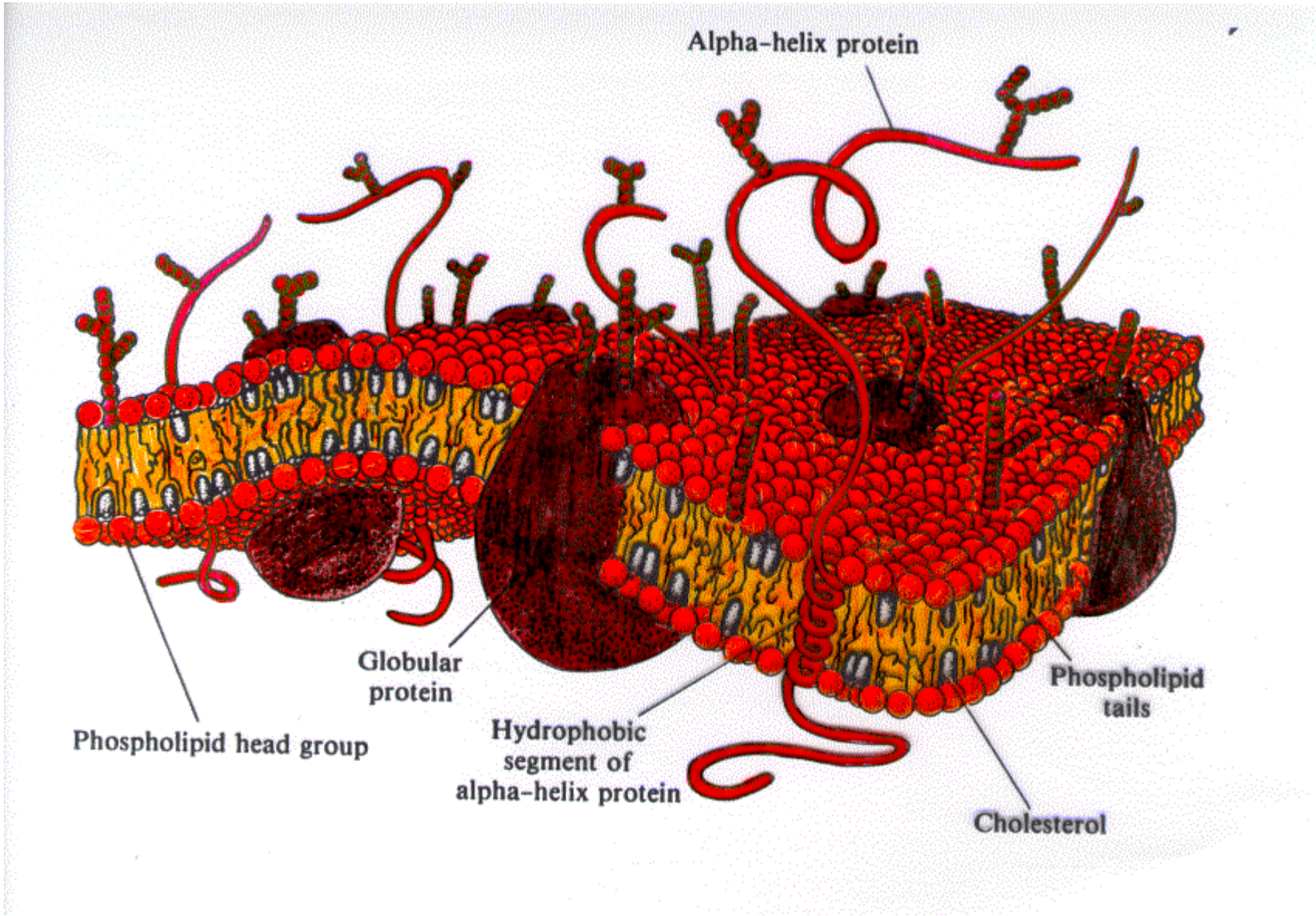
$$\text{LogP} = \text{Log}_{10}P = 0.954$$

clogP = calculated LogP

Solubility

- **Why is solubility important?**
  - Drugs must be in solution to be absorbed
- **What solubility do I need?**
  - Depends upon route of administration – e.g. oral versus IV
  - Related to dose size
  - Higher potency means lower solubility tolerated
- **Thermodynamic solubility measure is best, but kinetic OK for trends**
  - Remember that compound that resembled brick dust? Forget it!
- **A compound is more soluble as its partitioning into water increases i.e. lower logP the better**
  - If a compound is ionized to an acid or base – more soluble
  - LogD is distribution coefficient and corrects LogP for ionization
  - High melting point lowers solubility

Permeability

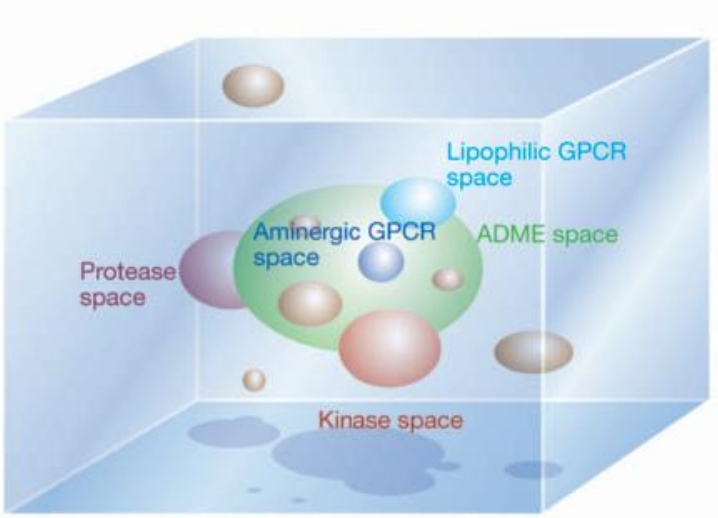


tPSA = Topological Surface Area

Lipinski's Rule of 5

- **Empirical rule, based on observation (marketed drugs) of physicochemical Assessment of orally bio-available drugs**

- **Poor absorption is likely when molecule has**
  - >5 Hydrogen-bond donors (NH, OH)
  - >10 H-bond acceptors (Heteroatoms)
  - cLogP >5
  - MW >500

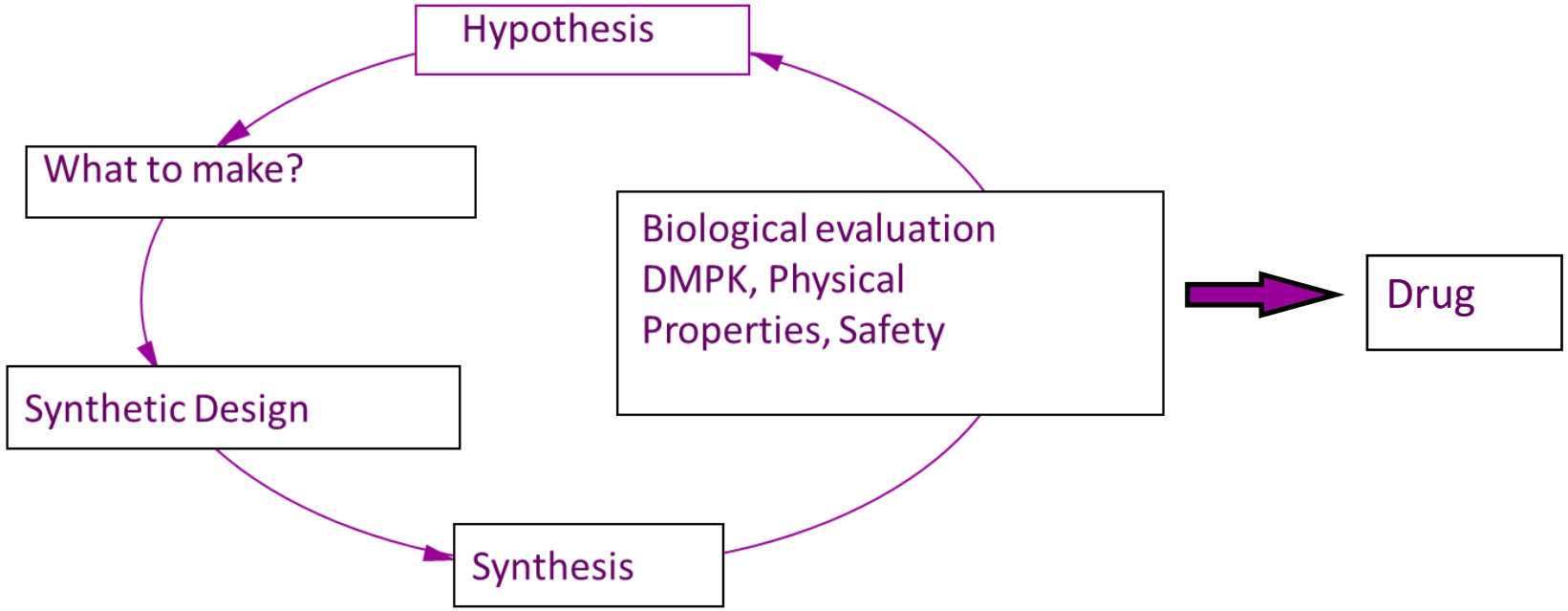


C. Lipinski and A. Hopkins, ***Nature,* 432**, 855-861, (2004)

- **Oral drugs need to be ADME compliant**
  - Absorption, Distribution, Metabolism, Elimination
  - Also called DMPK – Drug Metabolism, Pharmacokinetics

Synthetic accessibility and versatility

- **The central engine of a drug discovery project is the Hypothesis-design-make-test cycle**



- If a chemical series' synthesis is inaccessible the cycle cannot complete or is drastically slowed down
- Feasibility to modify the chemical structure at different points – synthetic versatility – important to explore scope of series

Undesirable groups and toxicophores

- **Includes groups known to:**
  - Be reactive
  - Be unstable
  - Be Toxic
  - Give rise to toxic species on metabolism
  - Lead to rapid metabolism and excretion
  - Have caused clinical candidates to fail

- **Such chemistry should be avoided or optimised out in Hit Generation**

Freedom to Operate and Intellectual Property

- **Important to know if a hit series has been published**
- **Chemical substructure searches of literature**
  - Provide information on novelty and known pharmacology of series
  - if not novel – information can help with synthesis, other biological activity and competition
- **If the project plan is to ultimately file a patent application, then the compounds patented must be novel and inventive**
  - No issue if series is novel from the outset – just need to keep confidential
  - If not novel, then chemistry will need to factor this in as an additional constraint
  - Must not publish or disclose novel chemical structures and data before patent application filed

Hit-to-Lead

- **Phase to drive project towards target product profile, addressing key issues along the way**
- **Aim is to validate chemical series as being able to deliver a compound meeting the profile by showing the series is:**
  - Potent and Selective
  - Drug-like (physicochemical)
  - Drug-like (DMPK/ADME)
  - Potential for acceptable safety
- **At lead stage the optimal profile does not have to exist in one compound, but each component should exist within the series**
- **Scope to deliver a candidate is believed to exist**

DMPK

- **DMPK = Drug Metabolism and Pharmacokinetics**
- **ADME = Absorption, Distribution, Metabolism and Elimination**
- **PD = Pharmacodynamics**

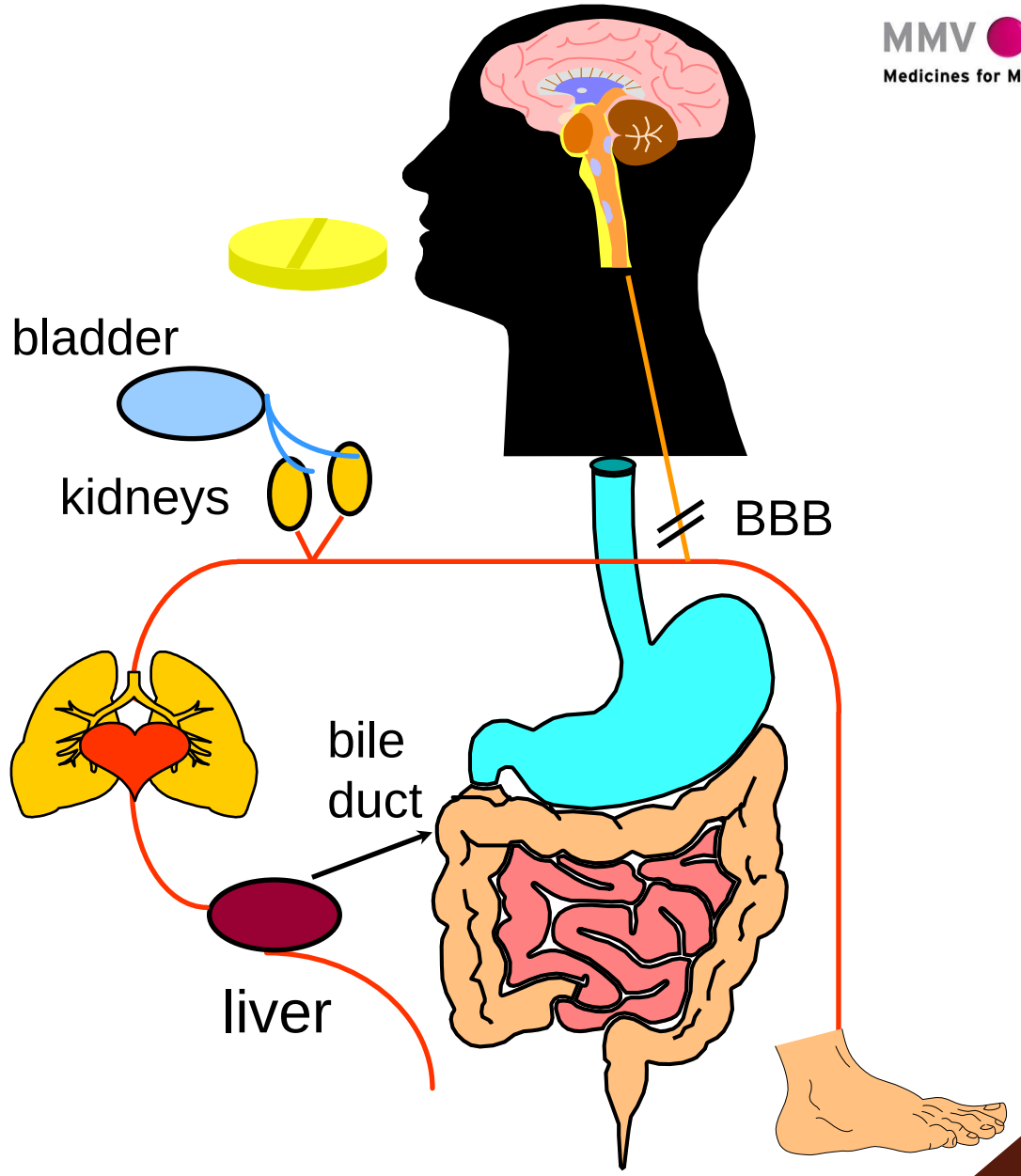
- **Pharmacokinetics is what the body does to a drug**
  - Want appropriate PK in animals (for efficacy and safety studies) and then to optimise, based on predicted human PK, to a candidate drug

- **Pharmacodynamics is what the drug does to the body**
  - Want to predict what drug concentration/ exposure results in efficacy
  - Demonstrate efficacy at those concentrations in disease model
  - Predicted human efficacious concentration defines human dose target

DMPK: Oral Dosing

To be active, oral drugs must:

- dissolve
- survive range of pH (1.5-8)
- survive intestinal flora/ fauna
- cross membranes
- survive liver (oxidation and conjugation)
- avoid active transport to bile
- avoid excretion by kidneys
- partition into appropriate place(s)



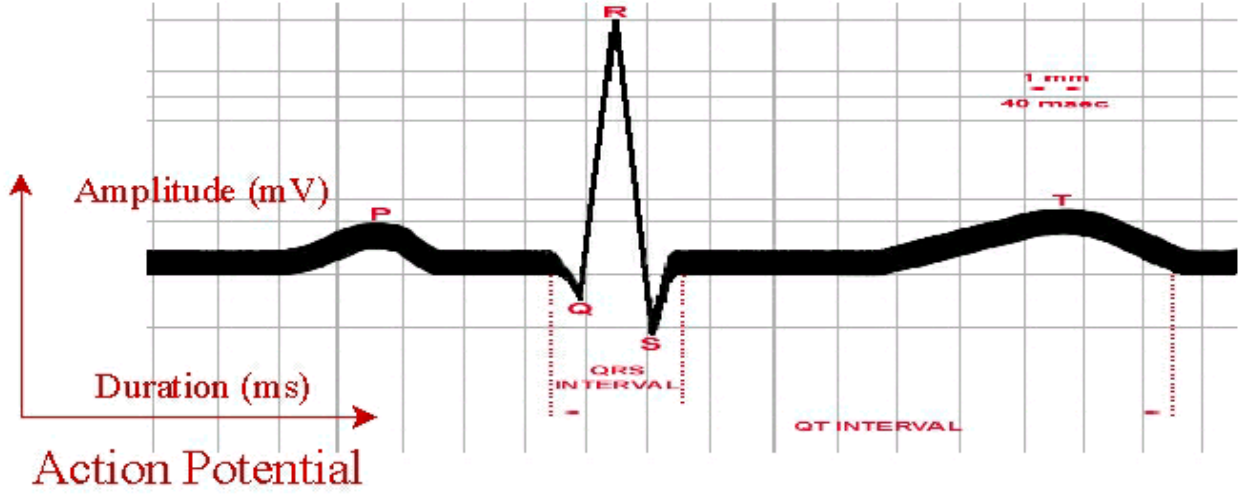
Lead Optimisation

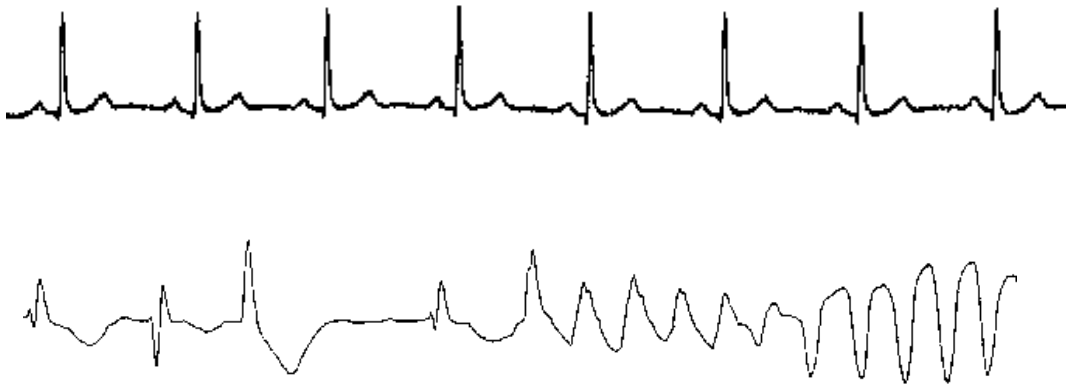
- **This phase fine tunes properties of the series such that the entire package is present in one or more compounds**
  - Optimisation of all properties, using the same or similar assays as used in Hit-to-Lead
  - Often requires synthesis and in-depth evaluation of a large number of related analogues
  - Can be expensive owing to the large number of complex studies required
  - These are usually built in at the latter stages owing to low through-put or high cost of such tests which limits numbers of compounds that can be tested

- **Candidate Criteria should be clearly defined**

Additional studies: QT effects & Genotoxicity

- **30% of post-marketing withdrawal of drugs has been attributed to QT prolongation**
  - Majority inhibit the IKr current mediated by hERG channels
  - IKr - 'rapid' delayed rectifier current that conducts potassium (K+) ions out of the muscle cells of the heart





- **Ames test used to assess the mutagenic potential of chemical compounds**
  - Uses well characterised bacterial strains

Additional studies: CMC (Chemistry Manufacturing and Control)

- **Cost of goods**
  - Criterion will depend on dose and therapy area
- **Chemical stability**
  - Check for decomposition in a range of situations to mimic the intestine
- **Shelf-life stability**
  - Compound subjected to humid conditions at elevated temperature to mimic accelerated shelf storage
- **Crystal form**
  - Salt selection (for acidic or basic drugs) or co-crystal
  - Potential look at polymorphic forms to find the most stable polymorph
  - Solubility and F% then measured with correct final form

Drug discovery into drug development

- **A candidate drug is an experimental “drug”**
- **Still a lot to do before it is a drug**
  - No direct evidence it is safe in animals let alone humans
  - No direct evidence it works in real patients
- **Clinical trials**
  - Long, expensive and littered with failure
- **Main causes of clinical failures are**
  - Efficacy – it doesn’t work! (~55%)
  - Safety – unexpected toxicity (~30%)
- **Safety and efficacy – risk/ benefit – assessed by independent stringent regulatory authority**

Non-clinical studies and Clinical trials in humans

- **Preclinical development – 12-24 months**
  - GLP rodent and non-rodent and other safety studies, GMP scale-up
- **Phase I – 3-9 months**
  - Healthy volunteers – safety, PK and maximum dose (20-80 male volunteers)
- **Phase IIa – 6-12 months**
  - Patients – safety and efficacy (100-200 patients)
- **Phase IIb – 12-24 months**
  - Patients – safety and efficacy (200-500 patients)
- **Phase III – 2-4 years**
  - Patients – safety efficacy (up to 3,000 patients)
- **Phase IV** – Post approval studies to monitor for safety

Summary

- **Drug Discovery is all about finding the ‘sweet spot’ where all properties necessary for a drug come together**
- **Candidate drug and target must be consistent with the TPP**
- **The principles and art of drug discovery are consistent regardless of biological target or disease**
  - Specific disease biology knowledge necessary
- **Regulators or patients do not care whether a drug was discovered in Pharma or Academia**
  - The data packages, compound/ science quality have to be the same
- **Drug discovery is multi-disciplinary and highly collaborative in nature**
  - Asking for help and advice is not a weakness

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Think with the end in mind: TPP

Work on the right biology

Many options to find chemistry – validation of series is key

Optimisation is not just about potency

DMPK and safety too determine whether you have a drug

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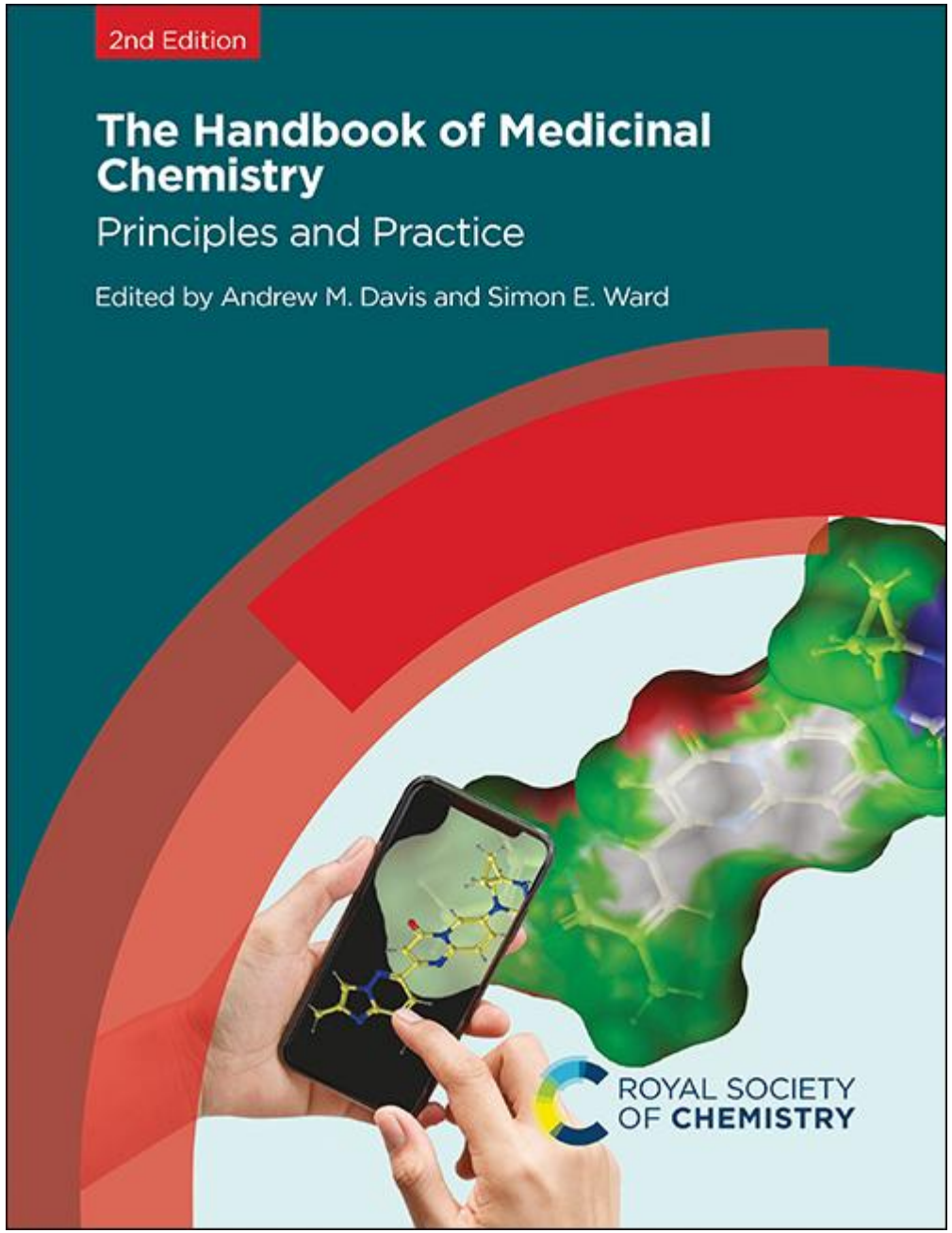
Practical lessons from a lifelong quest to discover medicines

- You need a thick skin: the science will beat you with a stick every day
- Stay humble
- And yet: you are constantly exposed to magic; the science is continually mind-blowing
- Helping make drugs that save people's lives: indescribable
- Stay positive
- Keep learning, try new things, think big, take chances
- Biology is what usually gets you
- Work hard, sweat the details, avoid unforced errors
- Structure can help you—and so can cellular phenotype
- Integrate everything: technologies, disciplines, hypotheses, mindsets,literature data, you name it
- Teams make drugs. Great teams behave in predictable ways and thrive in supportive environments. But teams are complex—and the interpersonal stuff is at least as important as the science
- Luck is a big factor in all our successes. Did I mention that you need to stay humble?
- Good fortune in our lives enables all we accomplish—pay it forward

Mark Murkco, Medicinal Chemistry Reviews, 2022, 57, 27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Abbreviations

- **Target:** biological molecule, usually a protein, whose function is to be modulated
- **Hit:** small molecule with promising activity in a primary screening assay
- **Lead:** molecule with suitable properties for optimization to give a drug candidate
- **Candidate:** molecule selected for development – no further optimisation
- **Asset:** a molecule or project with value associated with its stage in the pipeline
- **Pipeline:** an organisation's ensemble of projects at various stages
- **TPP:** Target Product Profile – description of the required drug
- **KO:** Genetic Knockout (usually mouse)
- **FTIH:** First Time in Human (aka Phase I Clinical Trial) – safety assessment in healthy volunteers
- **PoC:** Proof of Concept (aka Phase II Clinical Trial) – compound/mechanism gives desired clinical response
- **NOAEL:** No Observed Adverse Effect Level
- **MTD:** Maximum Tolerated Dose
- **MW/MWt:** Molecular Weight
- **MED:** Minimum Effective Dose
- **HTS:** High Throughput Screen
- **SAR:** Structure-Activity Relationship – relationship between the compound's structure and its activity
- **DMPK:** Drug Metabolism & Pharmacokinetics – how the drug is handled by the body
- **ADMET:** Absorption, Distribution, Metabolism, Elimination or Excretion, Toxicology
- **PD:** Pharmacodynamics – the activity of the drug in an animal or patient
- **DDI:** Drug-Drug Interaction – the effect of one drug on another, e.g. blocking or increasing metabolism
- **LO:** Lead Optimisation