Drug approvals by therapeutic area in 2018

~32% of approvals were for various cancers or related co-morbidities
16 new cancer treatments

- 64% small molecules (38)
- 20% antibodies (12)
- Enzyme (2)
- SiRNA (1)
- etc.

Source: https://www.bistrobiotech.com/biotechnologyrelated-links/
**Challenge of drug discovery**

Non-linear multi objective optimization ‘trajectory’ through multidimensional property space and integrated set of disciplines that work together to support the myriad activities needed to identify and validate targets (disease) until the selection of clinical candidates.

![Diagram](image)

Final pathway used to find clinical candidates, but several other possible!

*Nobody said this was easy!*
Pfizer lost virtually all of its market share after Norvasc’s patent expired in 2007

Calcium channel blocker (treatment of hypertension and coronary artery disease)
## WHY COMPOUNDS FAIL AND SLOW DOWN IN DEVELOPMENT

<table>
<thead>
<tr>
<th>Reasons for failure</th>
<th>Reasons for slowdown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxicity, 22%</td>
<td>Synthetic complexity</td>
</tr>
<tr>
<td>Lack of efficacy, 31%</td>
<td>Low potency</td>
</tr>
<tr>
<td>Market reasons, 6%</td>
<td>Ambiguous toxicity finding</td>
</tr>
<tr>
<td>Poor biopharmaceutical properties, 41%</td>
<td>Inherently time-intensive target indication</td>
</tr>
<tr>
<td></td>
<td>Poor biopharmaceutical properties</td>
</tr>
</tbody>
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Modern Drug Discovery
January/February 1999
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The rule of 5 (Ro5, Lipinski’s rule) is a simple set of easily in silico calculated physicochemical properties (guidelines) applied to drug discovery to prioritize compounds with an increased likelihood of high oral absorption.

Comparison of drug-like and non-drug-like compounds

Cut-off numbers of 5 or multiple of 5
Lipinski’s Ro5

Lipinski’s rule states that, in general, an orally active drug has no more than two violation of the following criteria:

2245 molecules of the Derwent World Drug Index (Phase II, oral)

- Not more than 5 hydrogen bond donors (nitrogen or oxygen atoms with one or more hydrogen atoms)

- Not more than 10 hydrogen bond acceptors (nitrogen or oxygen atoms)

- A molecular mass less than 500 daltons

- An octanol-water partition coefficient log P not greater than 5

If two or more properties are violated ⇒ high probability of lack of oral activity and bioavailability ⇒ Reduce the attrition due to unsatisfactory PKs but no guarantee that the molecule is druggable
Rule of 5 (Ro5, Lipinski’s rule)

Good *in vivo* drug absorption, distribution, metabolism, and excretion profile (eADME)

Does not predict if a compound is pharmacologically active

Disadvantage/advantage: ‘Simplicity’

Help medicinal chemists in proper selection of the drug and libraries of compounds
Different chemical spaces: Different criteria of druggability!
Compounds within the shaded region in (MW, logD) space were found to have a higher chance of achieving better outcomes for permeability and metabolic stability. This is a convenient visual rule-of-thumb for selecting compounds.

Golden Triangle' (Johson et al., 2009)

- Low solubility issue
- Low permeability (e.g. BBB)
- Permeability related to tPSA
- Limited side-effects
Beyond the Rule of Five (bRo5) chemical space

Target types
- Protein-Protein Interactions
- Class B GPCRs
- Proteases, Phosphatases
- Class A GPCRs, aminergic receptors
- Kinases
- Ion channels

Explore bRo5 space
- Macrocycles
- Natural products
- Peptides and mimetics

Native Proteins, Antibodies, RNAi, etc

Optimise in Ro5 space
- Right starting point
  - Better libraries
  - Fragments
- Will reduce compound risks

Small Molecule Drugs

Small Simple Molecules
Mw <600

Large Complex Molecules
Mw >10 000

Ligand Efficiency (LE)

Hits that confirmed by NMR were soaked into crystals of BTK
Artificial intelligence in drug development to accelerate R&D process and reduce costs by facilitating the rapid identification of compounds
AI in drug discovery and development
Partnerships between artificial intelligence (AI) and pharmaceutical companies and areas of collaboration in drug development

Source: DDT, 2018
Molecular Dynamic simulation

Docking of a competitive inhibitor in the active site of subtilisin, 10 ns of MD simulation in water to adapt the active site of the enzyme to the ligand

http://www.itqb.unl.pt/labs/protein-modelling/activities/upseknas