Introduction

Leiden Drug Development Symposium
Sep 19, 2024

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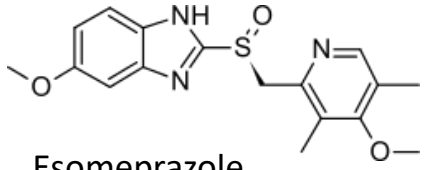
What is a drug?

drug
/drəg/

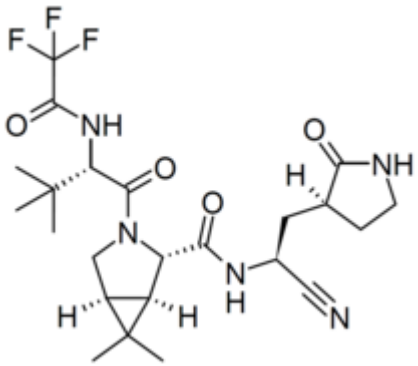
noun

1. a medicine or other substance which has a physiological effect when ingested or otherwise introduced into the body.
   "a new drug aimed at sufferers from Parkinson's disease"
   synonyms: medicine, medication, medicament, pharmaceutical; More

Small molecule



Esomeprazole
(Nexium)
(H+/K+ ATPase antagonist)

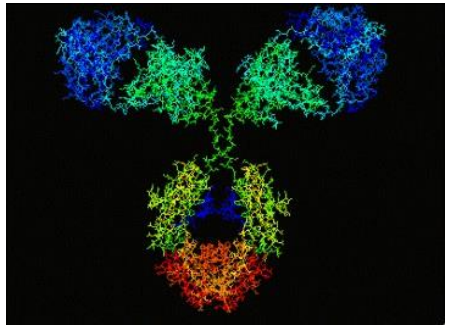


PF-07321332 (Paxlovid)
(Viral Coronavirus protease inhibitor)

MW ~ 500

Large molecule (aka: biologics)

Trastuzumab (Herceptin)
(erbB-2 antagonist)

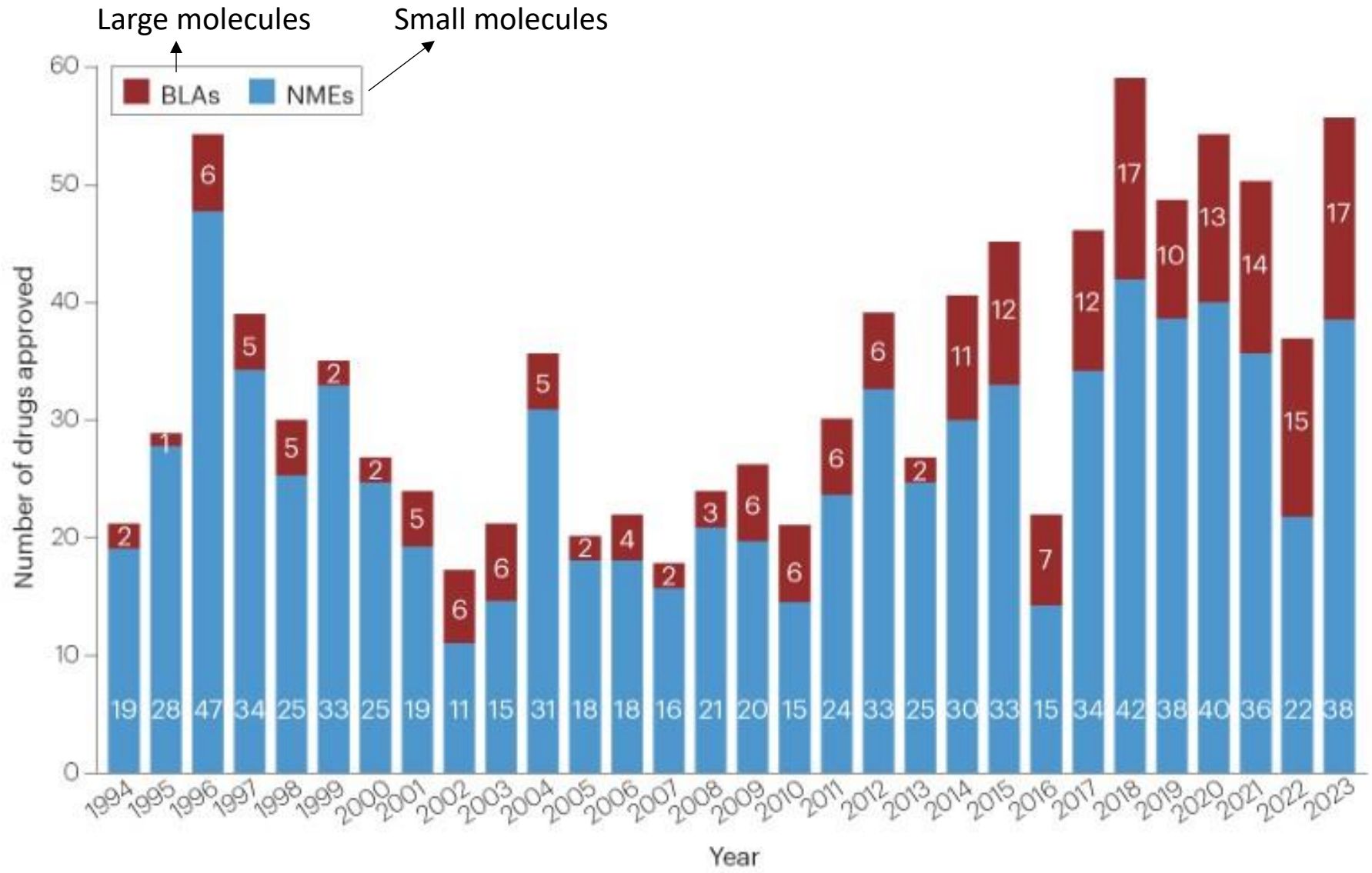


MW ~ 150,000

Other

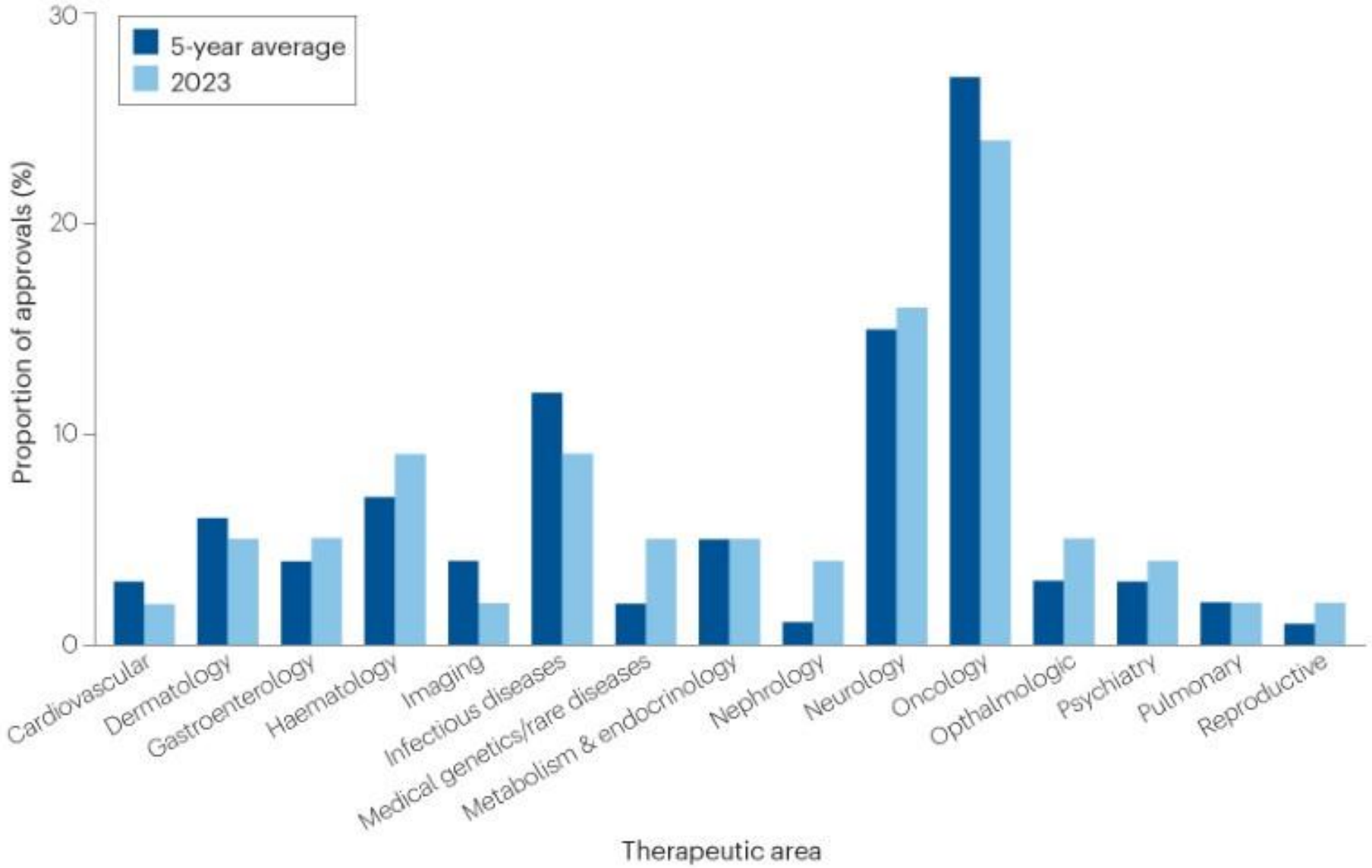
- Peptides
- Antibody-small molecule conjugates
- Polynucleotides
  - Antisense RNA
  - siRNA
  - Aptamers
- CAR-T cell therapy
- Gene therapy/editing
- …

New Drug Approvals: Numbers



Nature Reviews Drug Discovery 23:88 (2024)

New Drug Approvals: Therapeutic Areas



Nature Reviews Drug Discovery 23:88 (2024)

Machine Learning and Artificial Intelligence in Drug Discovery A hot topic

SPOTLIGHT · 30 MAY 2018

How artificial intelligence is changing drug discovery

Machine learning and other technologies are new pharmaceuticals quicker, cheaper and m

Nature **557**, S55-S57 (2018)

The rise of deep learning in drug discovery

JAMA Network Open

Research Letter | Health Policy

Use of Artificial Intelligence in Drug Development

Louise C. Druedahl, PhD; W. Nicholson Price II, JD, PhD; Timo Minssen, Dipl Jur, LLM, LLLic, LLD; Ameet Sarpatwari, PhD, JD

I in Drug Discovery: Challenges, Opportunities,

ílez [1,2,3], Alfonso Cabezón [1,2], Alejandro Seco-González [1,2], Daniel Conde-Torres [1,2], Ángel Piñeiro [2,*] and Rebeca Garcia-Fandino [1,*]

15 AI Startups Accelerating Drug R&D For Big Pharma

August 2, 2018

Artificial Intelligence | Client Intelligence | Expert Intelligence | Life Sciences/Healthcare

Discovery

How to Best Use AI & Machine Learning for Identifying and Optimizing Compounds and Drug Combinations

APRIL 12, 2019

Review article

Artificial intelligence for natural product drug discovery

nature reviews drug discovery

Artificial intelligence in drug discovery and develop

Debleena Paul[‡], Gaurav Sanap[‡], Snehal Sher
Dnyaneshwar Kalyane, Kiran Kalia and Rake

MIT News

ON CAMPUS AND AROUND THE WORLD

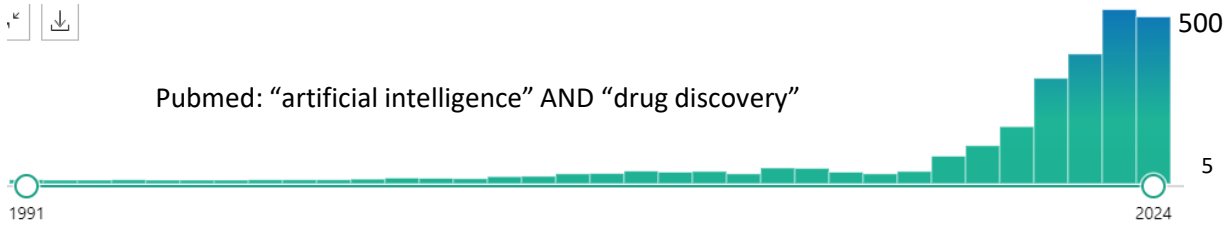
Applying machine learning to challenges in th pharmaceutical industry

MIT researchers and industry form new consortium to aid the drug discovery process

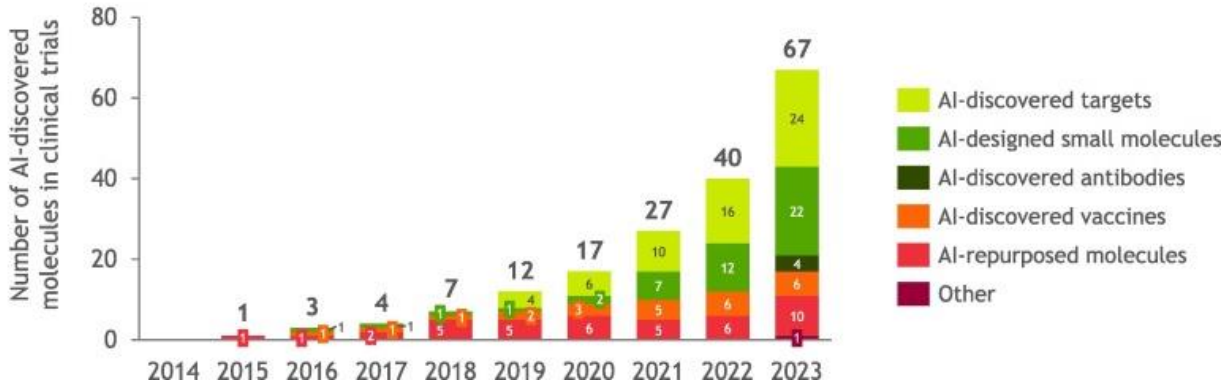
How A.I. Is Revolutionizing Drug Development

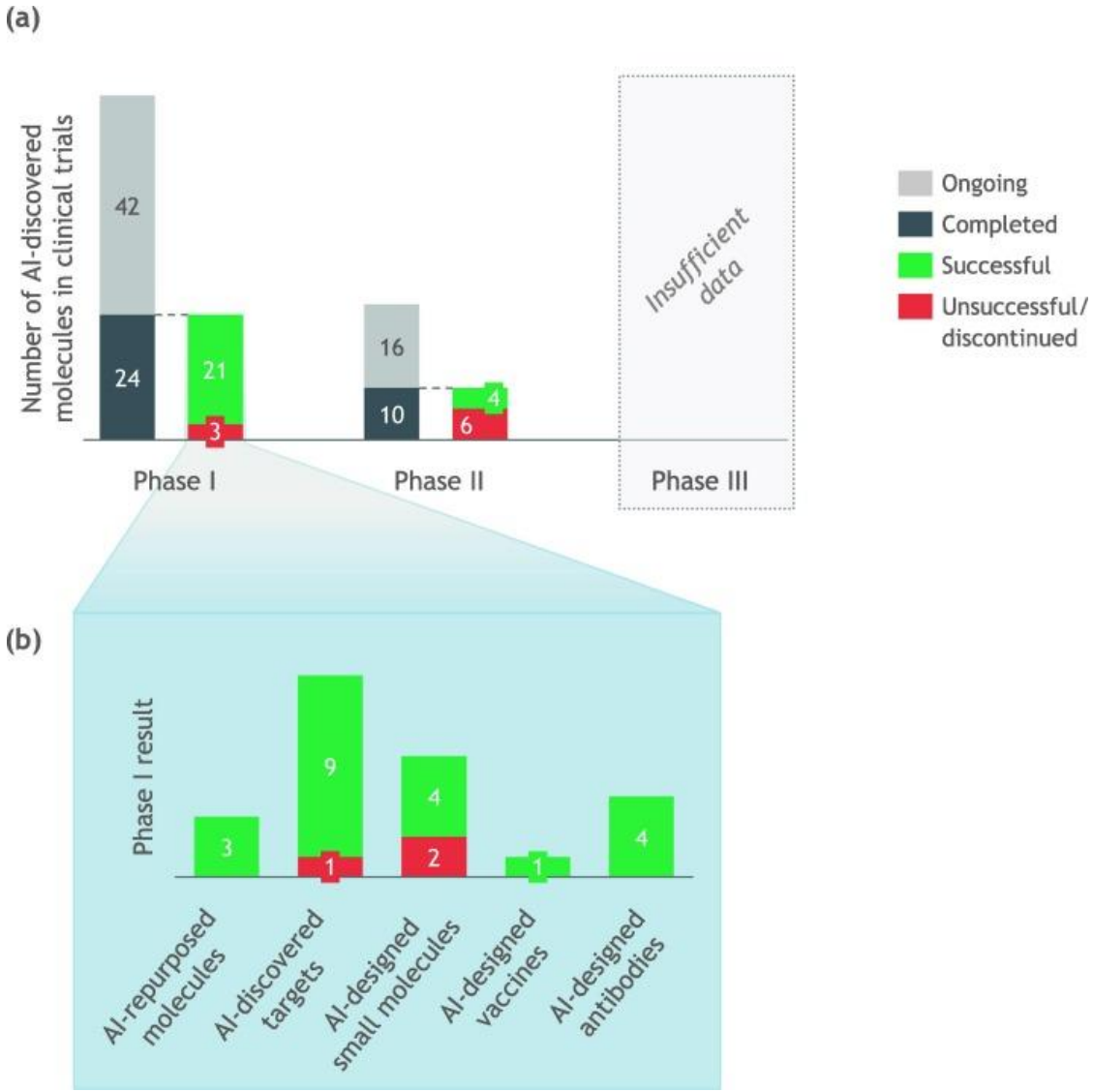
In high-tech labs, workers are generating data to train A.I. algorithms to design better medicine, faster. But the transformation is just getting underway.

AI for drug discovery is booming, but who owns the patents? nature biotechnology



AI Discovered drugs in clinical trials: A first analysis





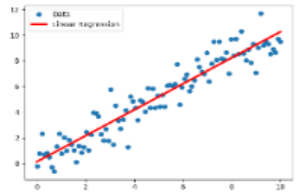
BUT:

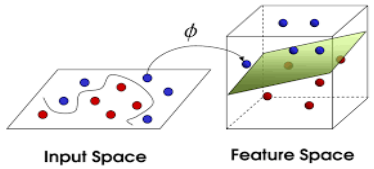
> OK, that's what I have from the table. I have linked to a relevant site for each drug candidate and then to a relevant site about the targets involved. The only one that I can't round up enough information to be sure about is ATH-63. What you will see is that in almost every case, these targets were *already known* to be implicated in the disease under investigation. In some of these examples, in fact there are several drugs already in the clinic targeting the same proteins, or even therapies that are already on the market working through the same mechanisms (*C. diff* toxin B, e.g.) I don't think any of these are bad targets, let me make that clear. There are some really interesting things on the list, but I do not see how any of them can be classified as "target discovered by AI". I really don't.

In the pipeline blog Derek Lowe, 13 May 2024

Jayatunga et al, Drug Discovery Today 29 (2024)

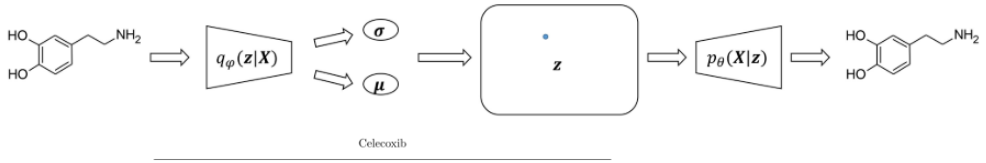
AI/ML in early discovery: Where does it make a difference?





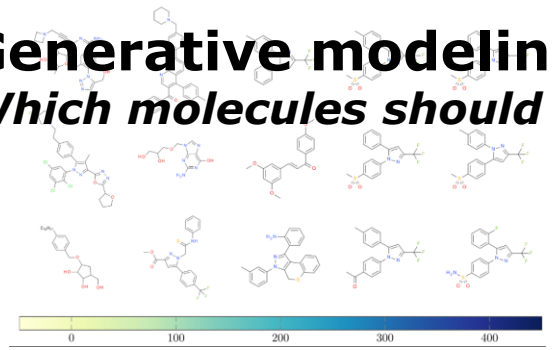
Improved activity and property modeling

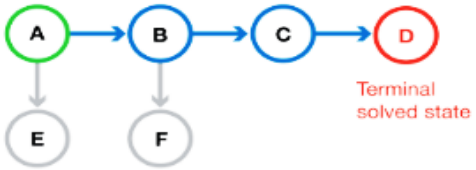
Computationally assess molecular properties



Generative modeling

Which molecules should we make?



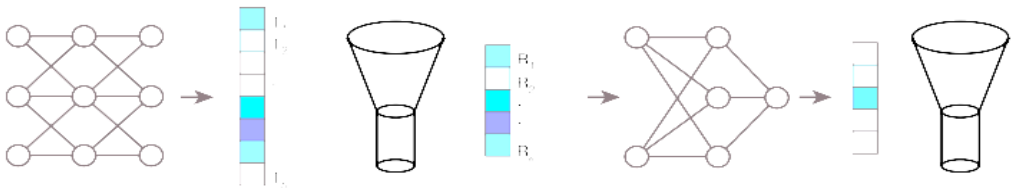


A= {1} B= {2,6} C= {3,6}
D= {4,5,6} E= {8,9} F= {6,7,8}

(Retro)synthesis Modeling

What is the best way to make this?

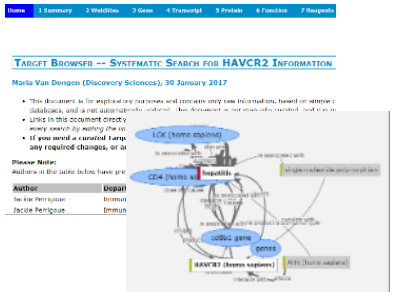
Which reactions are most likely to work?



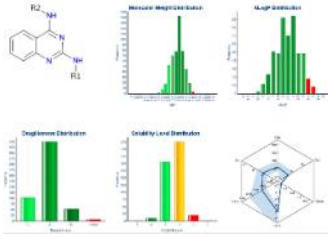
Computer-Aided Drug Design Across Discovery (small mol)

Target Identification | Hit Identification | Hit to Lead | Lead Optimization | Late Lead Optimization

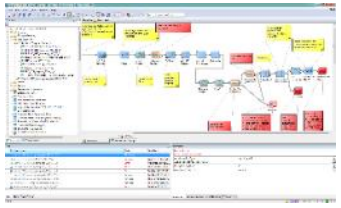
AI/ML



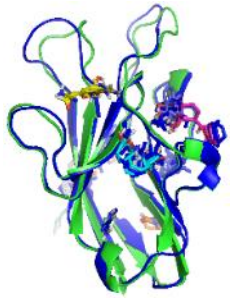
Information mining



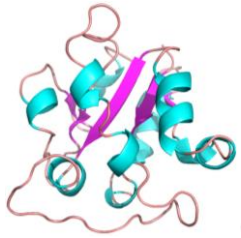
Library enrichment



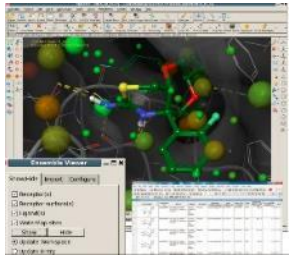
Hit triage



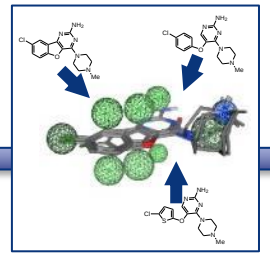
Ligandability assessment



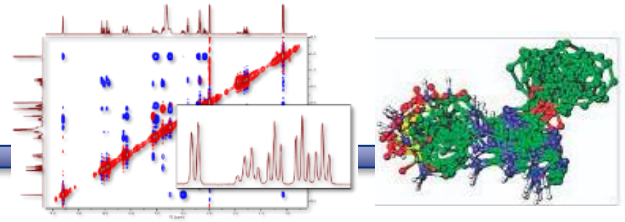
Structure prediction

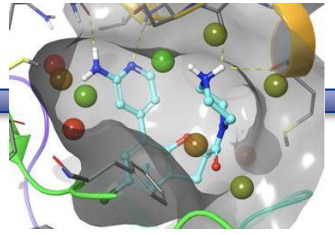


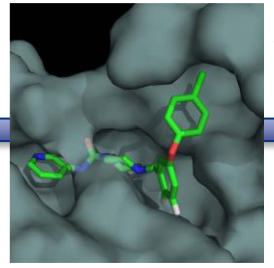
(uHT) Virtual screening



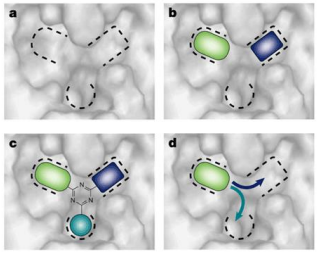
Ligand based design



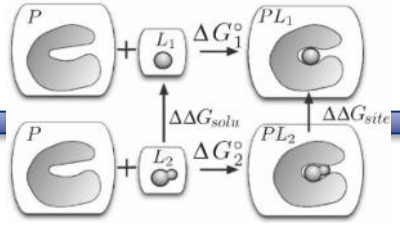




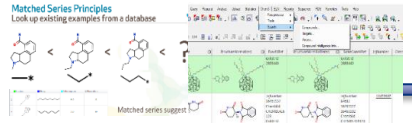
Structure-Based Design



FBLD



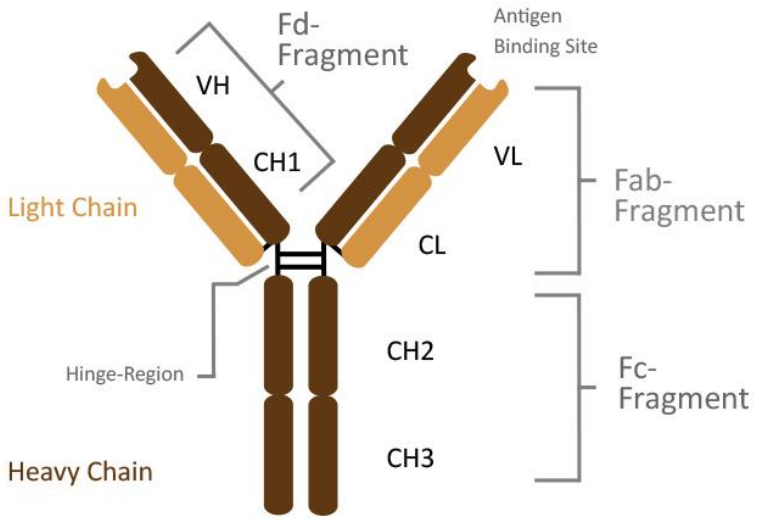
Free Energy of Binding

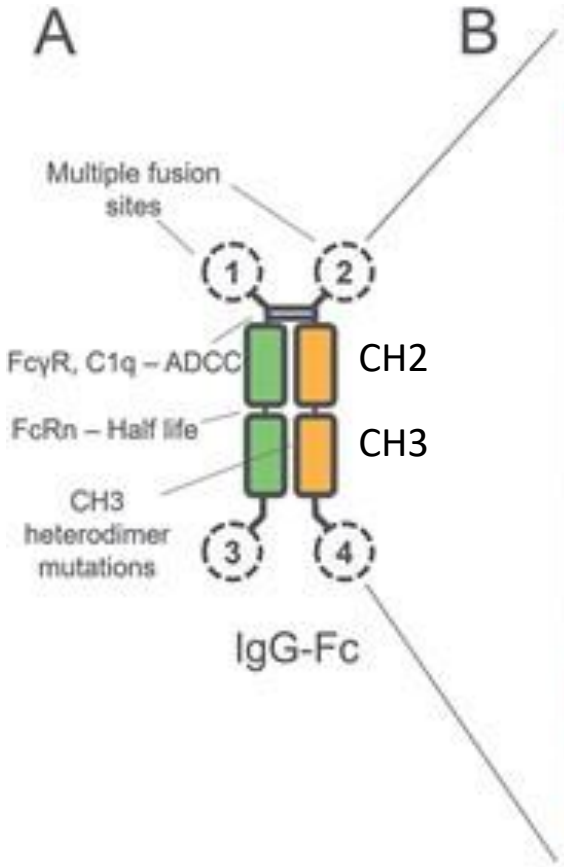


Cheminformatics

Antibodies: the main type of biologics

Standard antibody structure





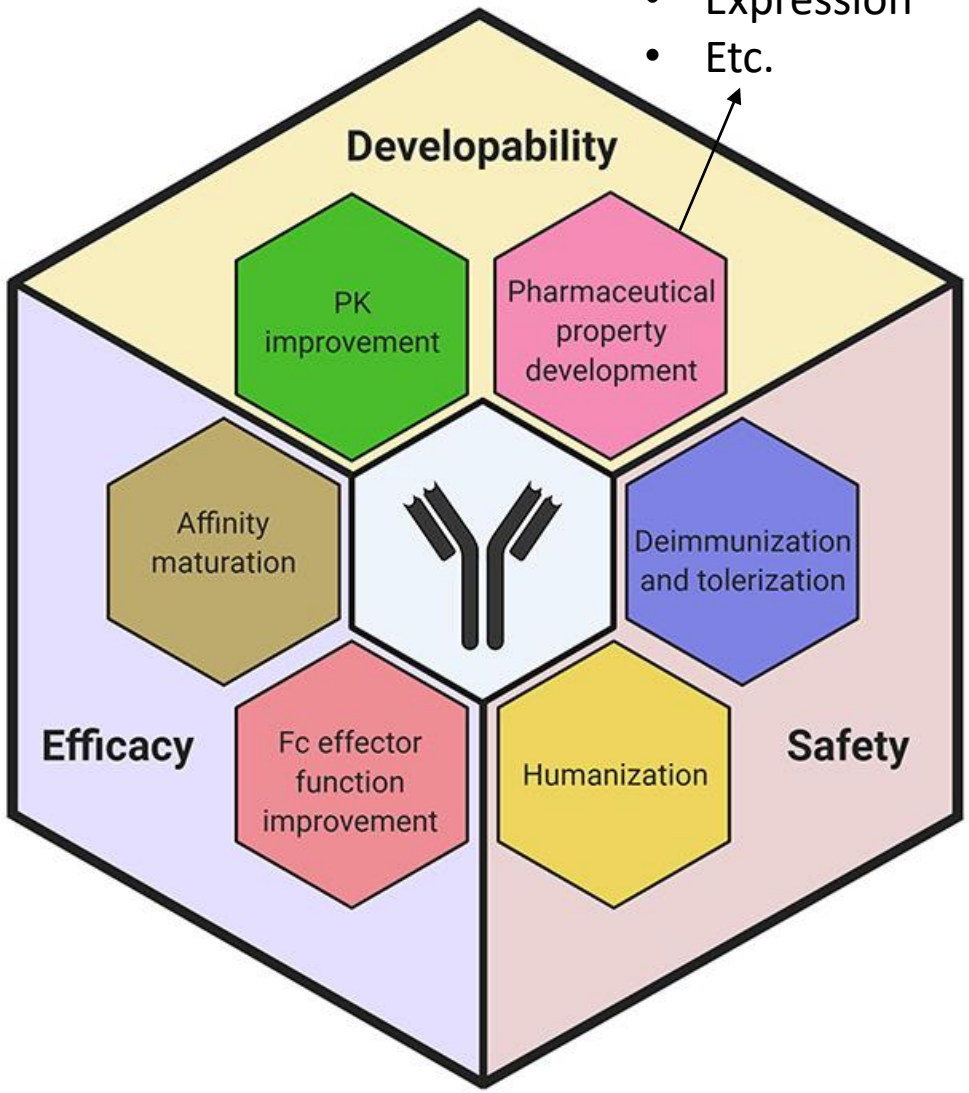
Large variety of genetically engineered antibodies

Building Blocks	Folding Domain	MW (kDa)	Binding SASA (Å²) / Total SASA (Å²)
Fab	Immunoglobulin	45-55	5-7%
scFv	Immunoglobulin	20-30	9-11%
VHH	Immunoglobulin	15-20	20-29%
Cytokine	IL2: Helical bundle IL18: β-trefoil fold IL23-p19: Helical bundle IL23-p40: Fibronectin type-III	10-30	19-56%
Miniprotein	DARPin: Ankyrin repeat Anticalin: β-barrel, attached helix Knottin: Cysteine knot	3-20	14-43%
De novo miniprotein	CTC-445.2: Alpha-beta motif IL7Rα Binder: Helical bundle HB1.6928.2.3: Alpha-beta motif	3-20	14-39%

Antibody Therapeutics, 7:37 (2024)

Property Optimization of biologics

- Thermostability
- Solubility
- Chemical stability
- Expression
- Etc.



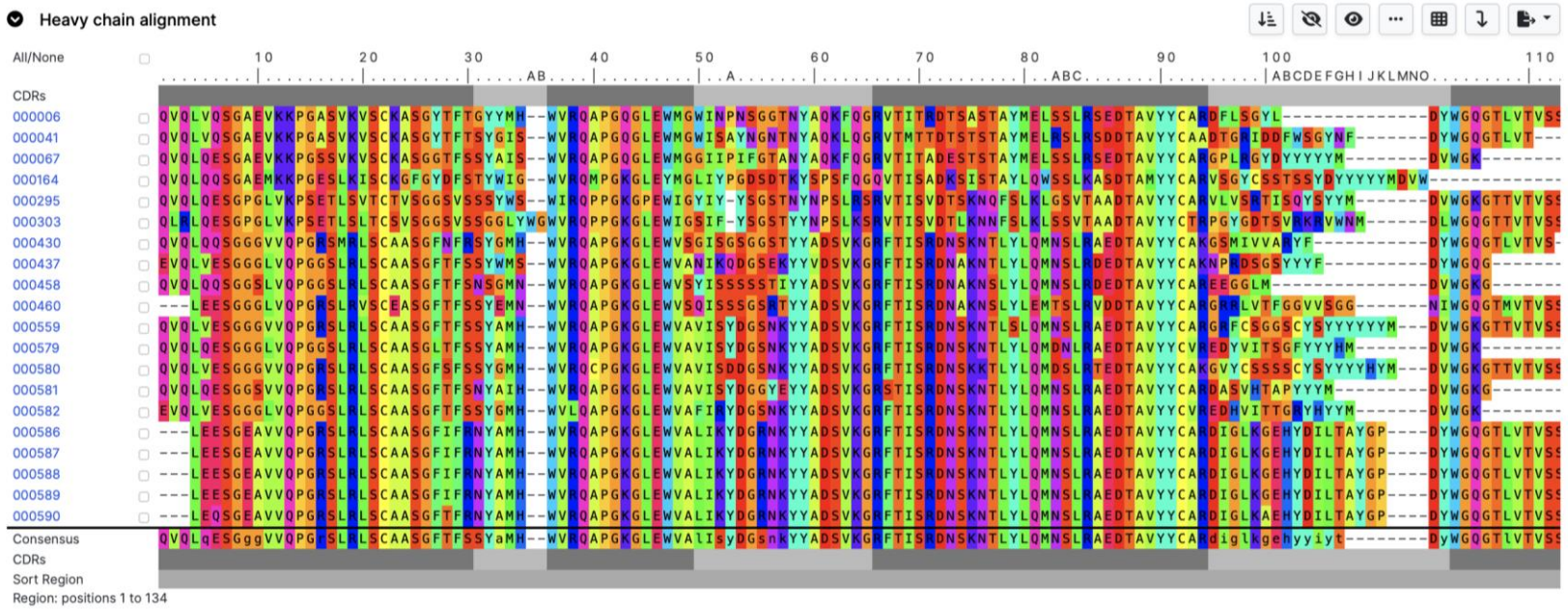
Antibody Therapeutics, 4: 45 (2021)

Large Language Models in molecular optimization

```
OC[C@H]1O[C@H]([C@H](O)[C@@H]1O)n2cnc3c2ncnc3CSc4ccccc4I
C#Cc1nc(nc2[nH]cnc12)Nc3cccc(c3)C(N)=O
O=[N+]([O-])c1cccc(c1)SCc2ncnc3c2ncn3[C@@H]4O[C@H](CO)[C@@H](O)[C@H]4O
CCN(CC)c1nc2c(nc(SCC(=O)NCCCN)n2CCc3c[nH]c4ccccc34)c(C)n1
O=C(O)CSCc1ncnc2c1ncn2[C@@H]3O[C@H](CO)[C@@H](O)[C@H]3O
C[C@]1(O)C(O[C@H](CO)[C@H]1O)n2cnc3c2ncnc3C(=N)N
OC[C@H]1O[C@H]([C@H](O)[C@@H]1O)n2cnc3c2ncnc3/C=C/N4CCOCC4
CCN(CC)c1nc2c(nc(SCC(=O)NCCCN)n2CCNc3nc(N)nc4[nH]cnc34)c(C)n1
COC(=O)c1ccc(cc1)SCc2ncnc3c2ncn3[C@@H]4O[C@H](CO)[C@@H](O)[C@H]4O
Cc1cc(C)c(SCc2ncnc3c2ncn3[C@@H]4O[C@H](CO)[C@@H](O)[C@H]4O)c(C)c1
CC(=O)OCCSC[C@H]1O[C@H]([C@H](OC(C)=O)[C@@H]1OC(C)=O)n2cnc3c2ncnc3C
C(#Cc1ncnc2c1ncn2C3CCOCC3)c4ccccc4
CCc1ccc(cc1)c2nc3c(nc(O)n3c4ccccc4OC)c(n2)C(N)=O
NS(=O)(=O)OC[C@H]1O[C@H]([C@H](O)[C@@H]1O)n2cnc3c2ncnc3C#Cc4ccccc4F
CCCCCCC#Cc1ncnc2c1ncn2C3O[C@H](CO)[C@@H](O)[C@H]3O
CCOc1ccccc1c2nc3c(nc(O)n3c4ccccc4)c(n2)C(N)=O
```

SMILES: language of small molecules

Amino acid sequence:
language of biologics



Thank you!