RNA and drug design

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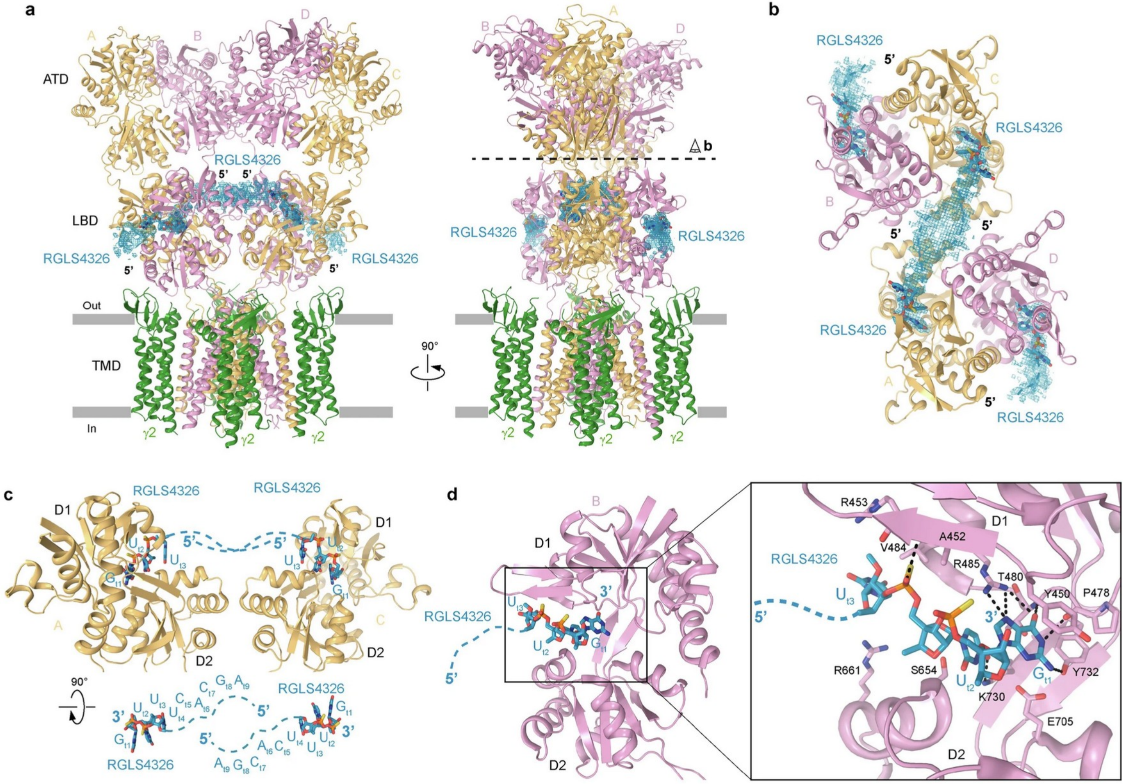
Outline

- RNA as a drug target
- Drug design pipeline and ML/AI impact
- Molecular aspects
- RNA again

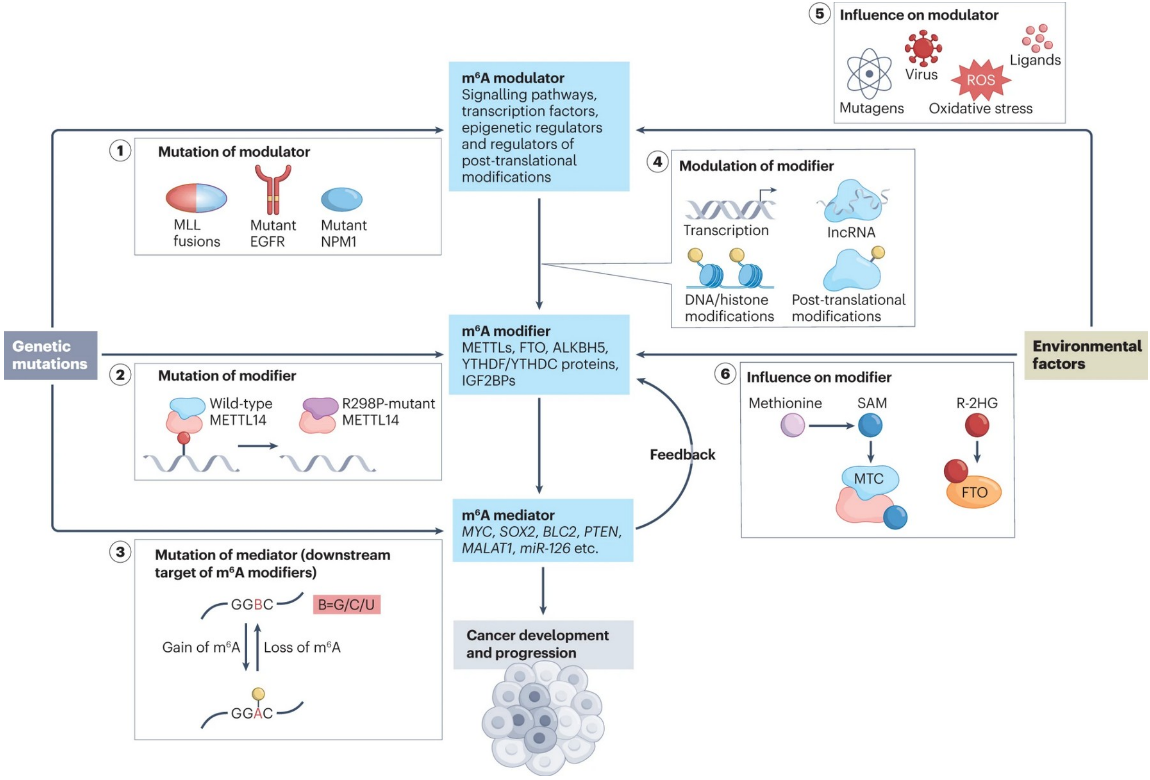
RNA and drug design

RNA as a drug



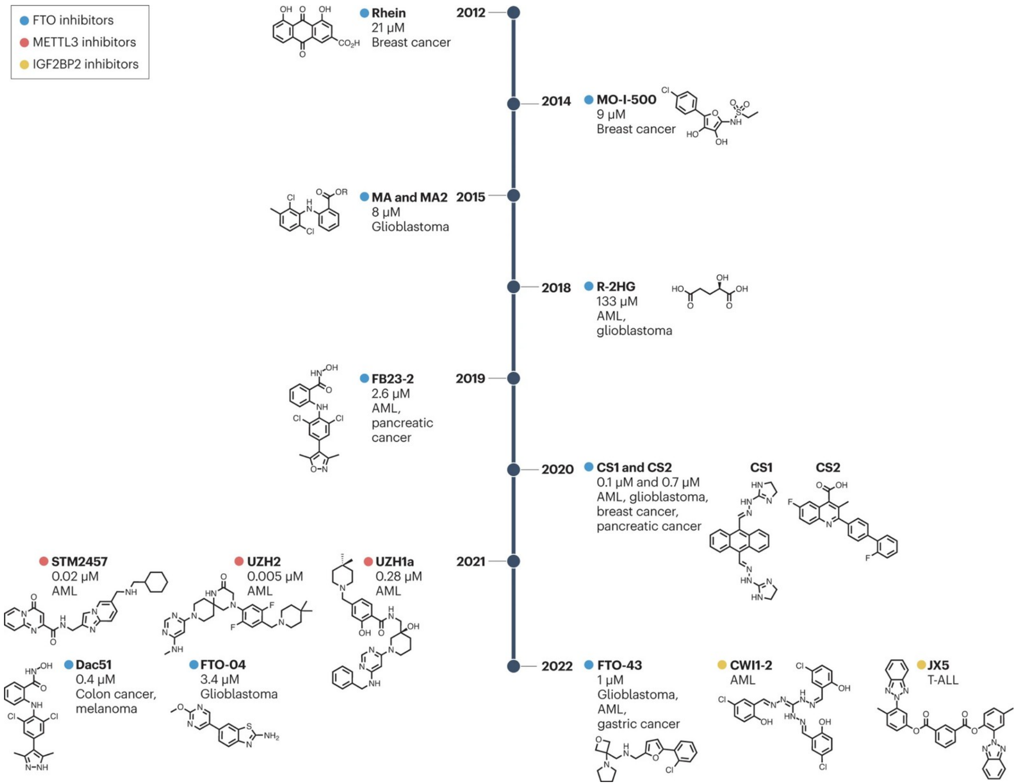
Valencia, T., Yen, L.Y., Berman, C. *et al.* The nucleobase guanine at the 3'-terminus of oligonucleotide RGLS4326 drives off-target AMPAR inhibition and CNS toxicity. *Nat Commun* 16, 10762 (2025). https://doi.org/10.1038/s41467-025-65799-5

RNA as a biomarker



Deng, X., Qing, Y., Horne, D., Huang, H., & Chen, J. (2023). The roles and implications of RNA m6A modification in cancer. *Nature Reviews Clinical Oncology*, *20*(8), 507-526.

Mechanisms underlying the dysregulation of RNA m6A modification and m6A-dependent processes in cancer.



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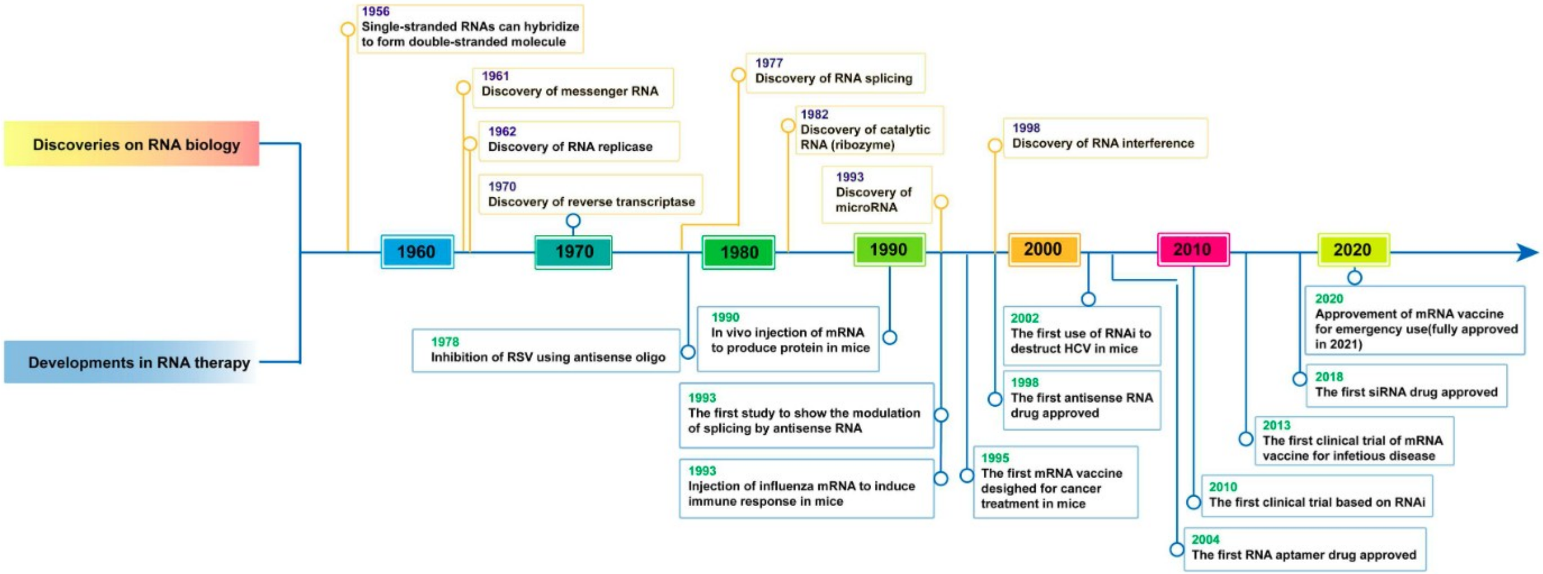
RNA therapeutics today



Cell Reports Medicine, 5(5). 2024

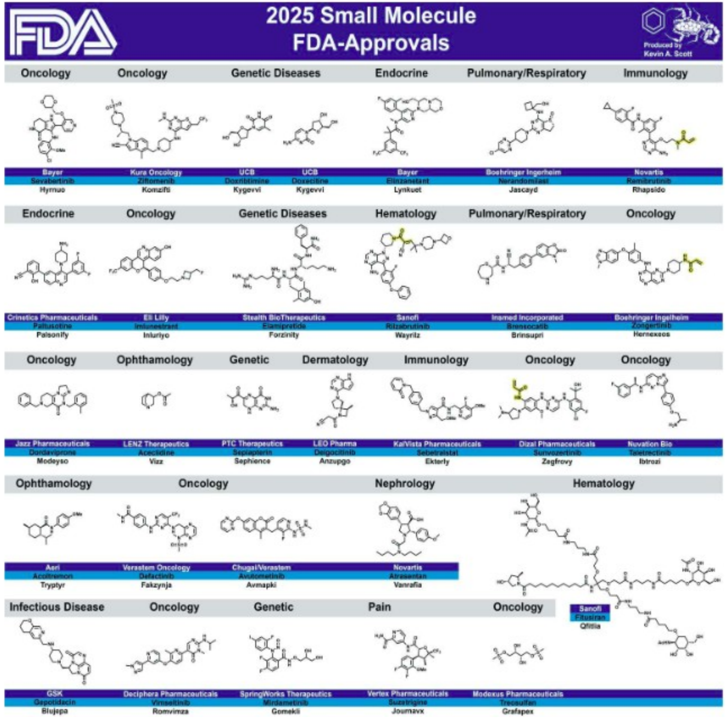
(from Michael slides)

Classes of RNA therapeutics

- messenger RNA (mRNA)
- small interfering RNA (siRNA/miRNA)
- antisense oligonucleotides (ASOs)
- CRISPR/Cas genome editing
- RNA aptamers
- **RNA-targeting small molecules**

RNA-targeting small molecules

- classical drugs interacting with structured RNA
- antibiotics, splice modulators, viral polymerase inhibitors
- includes nucleoside analogues used in antiviral therapy



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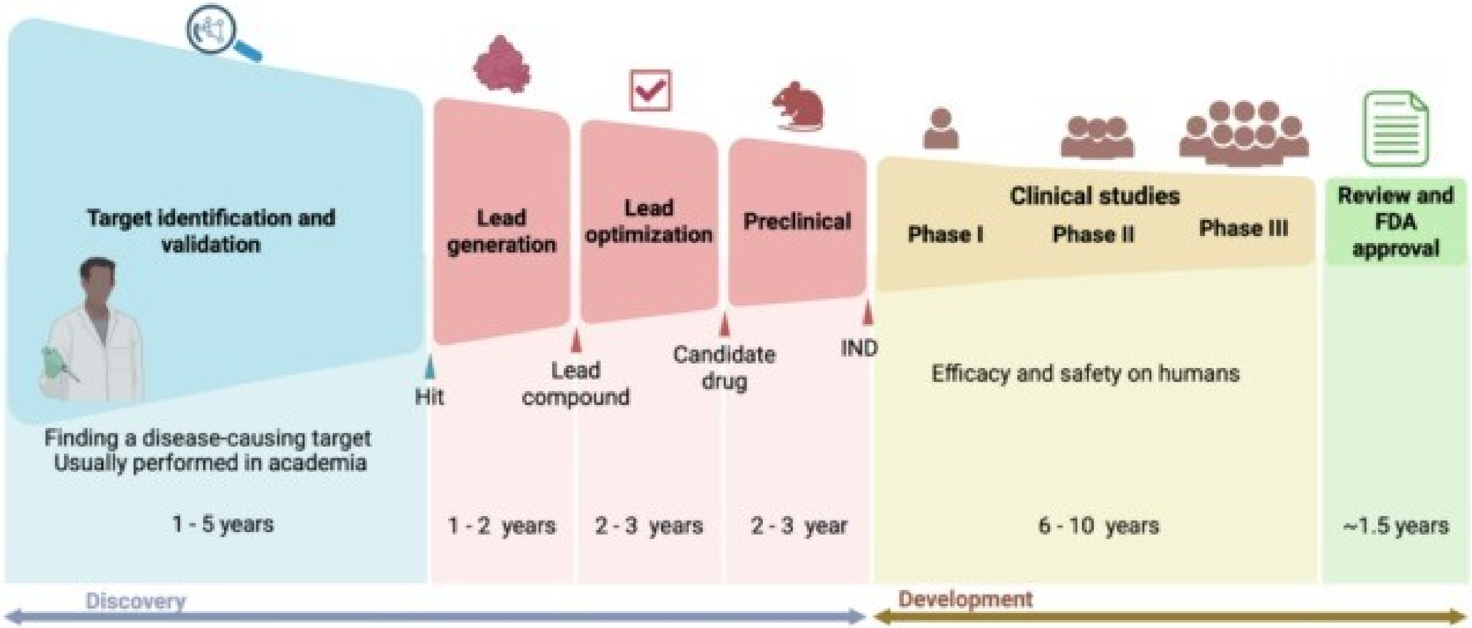
(from Michael slides)

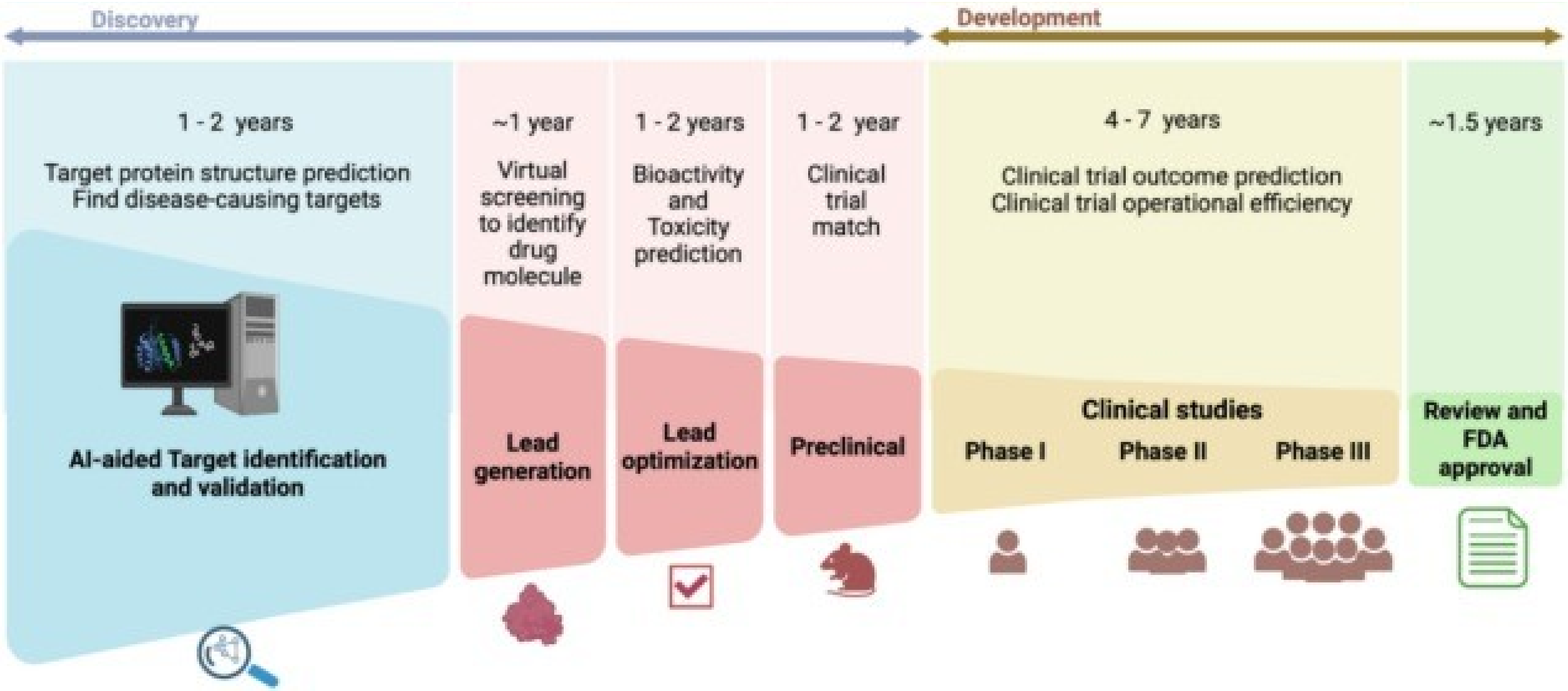
Drug design pipeline

Traditional pipeline



Jarallah, S. J., Almughem, F. A., Alhumaid, N. K., Fayez, N. A., Alradwan, I., Alsulami, K. A., ... & Alshehri, A. A. (2025). Artificial intelligence revolution in drug discovery: A paradigm shift in pharmaceutical innovation. *International Journal of Pharmaceutics*, 125789.

Advertised potential impact of ML/AI



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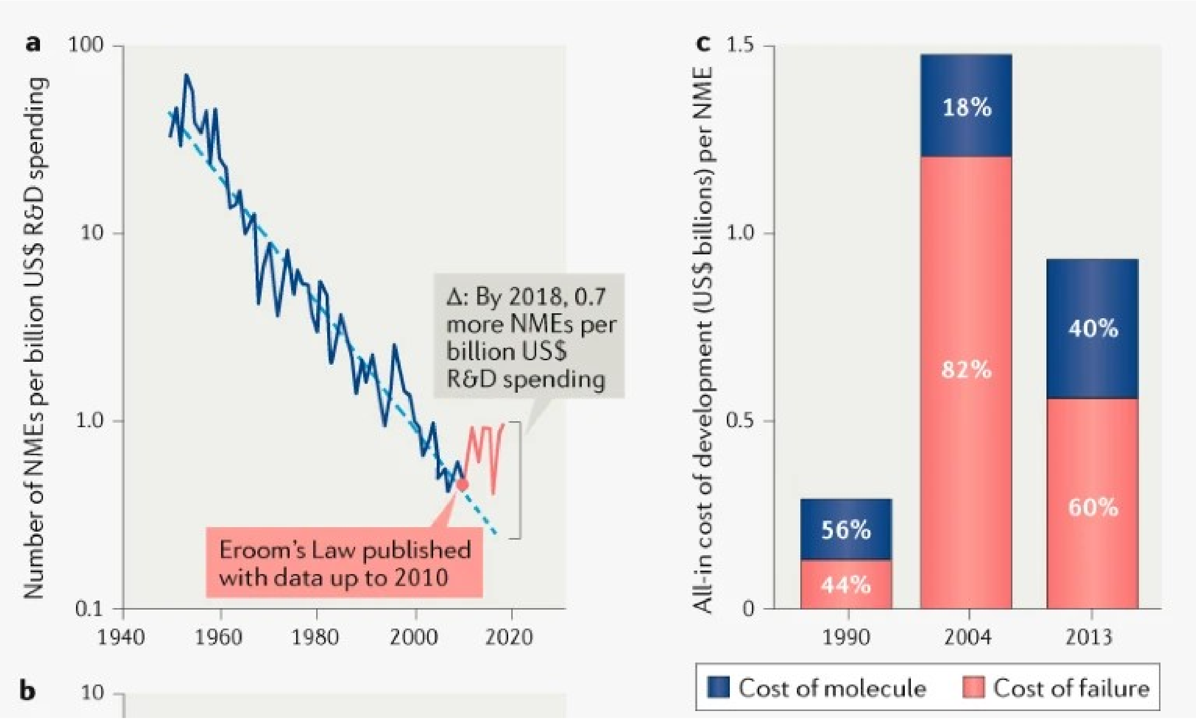
Where does the cost come from ?

Table 3. Nonclinical, Clinical, FDA Review, and Postapproval Costs as Percentage of Mean, Mean Expected, and Mean Expected Capitalized Total Cost[a]

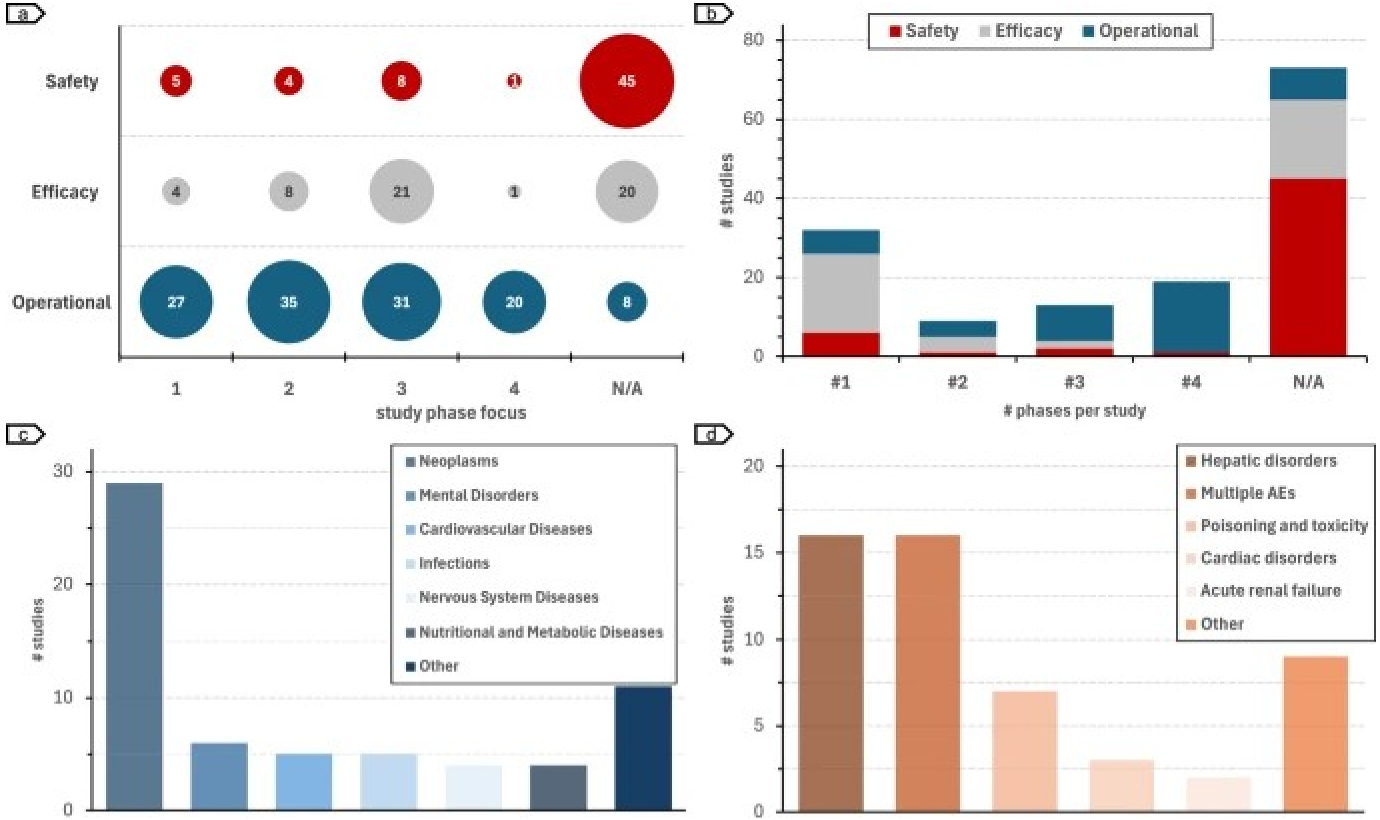
Therapeutic area and type of cost	Percentage of total cost (95% CI)			
	Nonclinical	Clinical	FDA review	Phase 4
All therapeutic areas				
Cost	6.8 (3.7-9.1)	68.0 (45.8-73.3)	1.5 (1.3-2.0)	23.7 (17.7-47.7)
Expected cost	27.0 (22.1-28.1)	60.5 (49.5-63.1)	4.6 (2.8-8.0)	7.9 (5.1-21.3)
Expected capitalized cost	40.2 (35.2-44.6)	53.0 (48.4-56.9)	2.9 (1.4-5.4)	4.0 (2.4-13.1)

Sertkaya A, Beleche T, Jessup A, Sommers BD. Costs of Drug Development and Research and Development Intensity in the US, 2000-2018. *JAMA Netw Open.* 2024;7(6):e2415445.

Where does the cost come from?

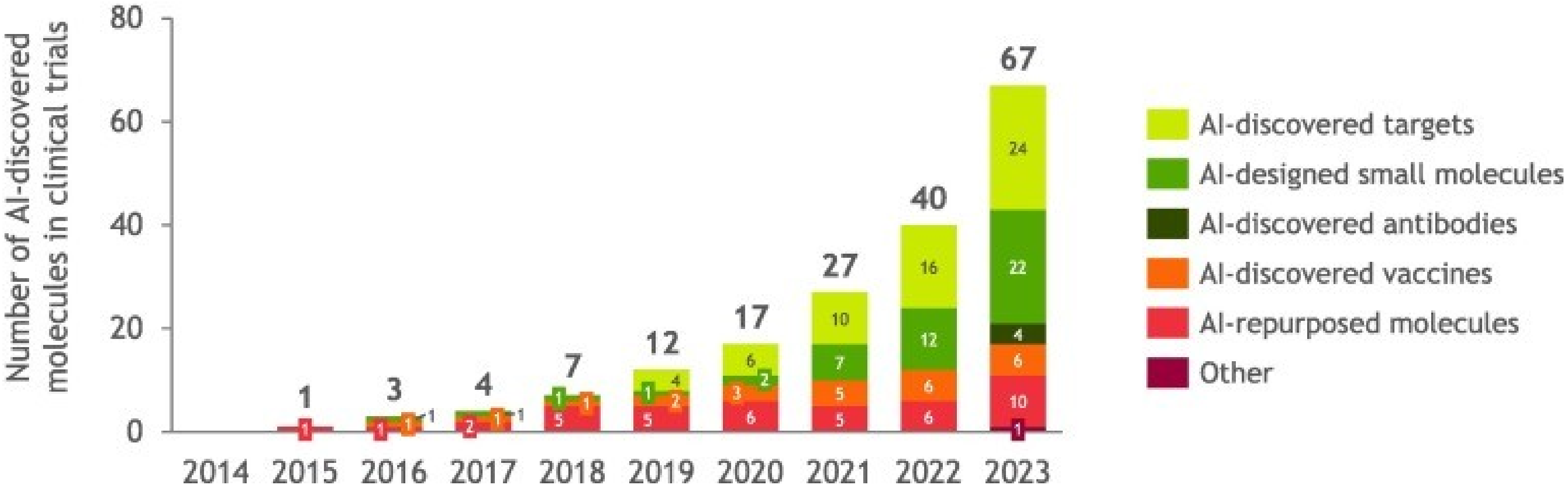


AI/ML in clinical trials risk management



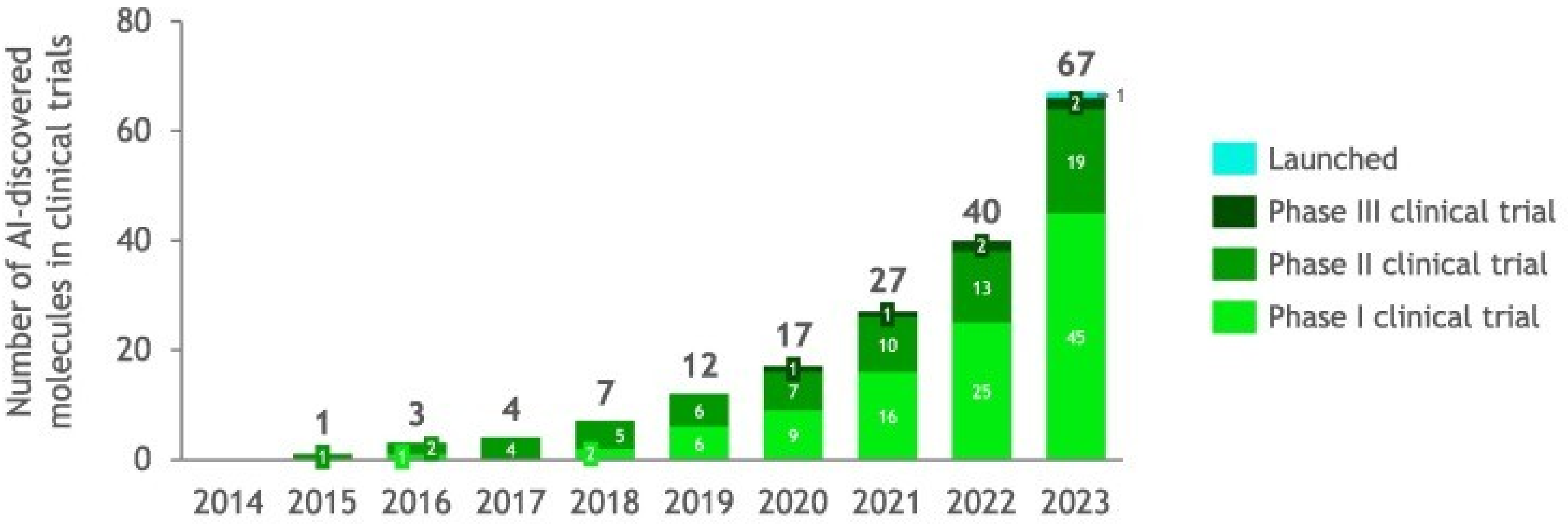
Teodoro, D., Naderi, N., Yazdani, A. *et al.* A scoping review of artificial intelligence applications in clinical trial risk assessment. *npj Digit. Med.* 8, 486 (2025)

How AI is used?



Jayatunga, M. K., Ayers, M., Bruens, L., Jayanth, D., & Meier, C. (2024). How successful are AI-discovered drugs in clinical trials? A first analysis and emerging lessons. *Drug discovery today*, *29*(6), 104009.

test phase of AI-discovered drugs



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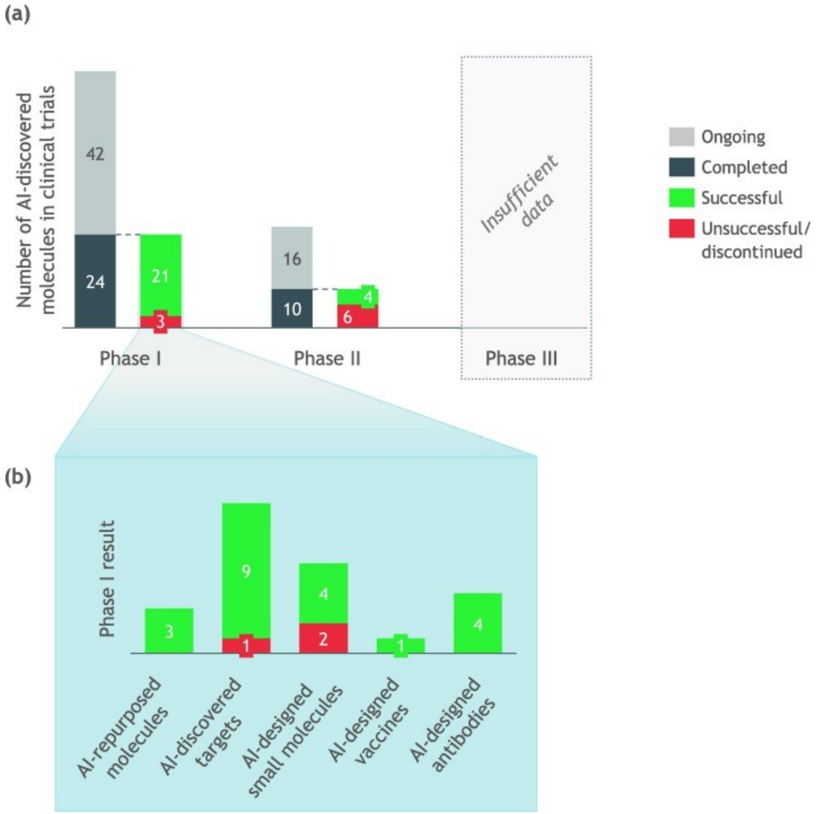
measure of the impact



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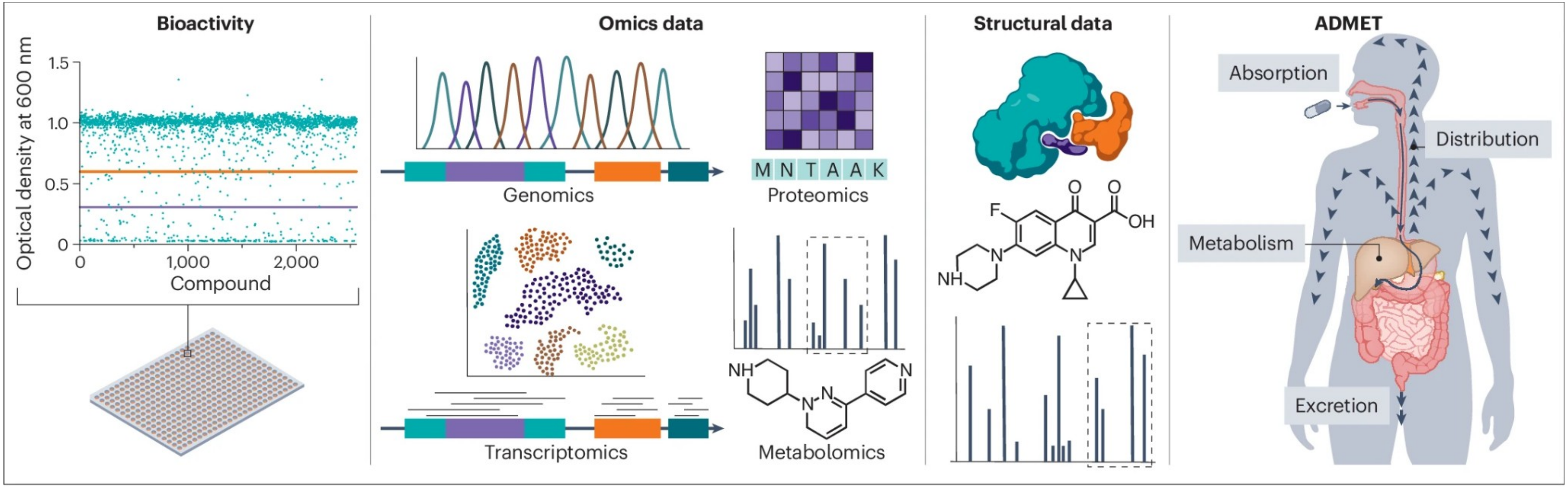
2025 update…

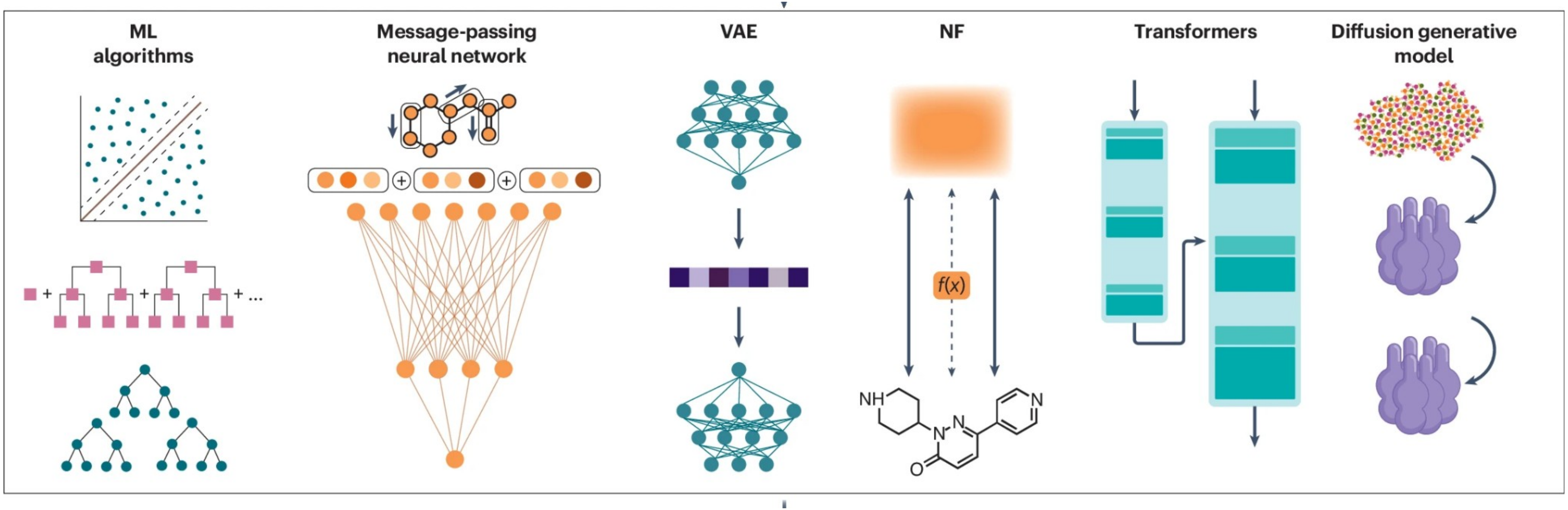
Overall, AI-designed molecules appear to have higher phase I success rates (~80%–90% vs ~52% industry average), likely reflecting better upfront filtering, but phase II outcomes (~30%–40% success) remain similar to traditional benchmarks.[380] These outcomes suggest that AI is indeed accelerating early-stage discovery and improving efficiency, but it has not yet overcome the fundamental biological hurdles of later-stage development. The mixed record highlights both progress and remaining challenges, underscoring the importance of rigorous validation.

Dharmasivam, M., Kaya, B., Akinware, A., Azad, M. G., & Richardson, D. R. (2025). Leading AI-driven drug discovery platforms: 2025 landscape and global outlook. *Pharmacological Reviews*, 100102.

Looking at the molecular scale



Catacutan, D.B., Alexander, J., Arnold, A. *et al.* Machine learning in preclinical drug discovery. *Nat Chem Biol* 20, 960–973 (2024).



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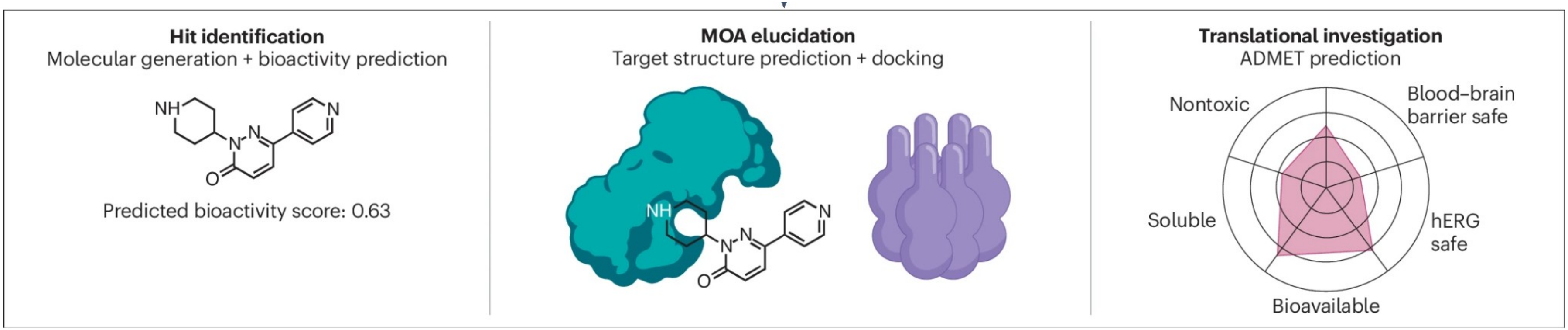

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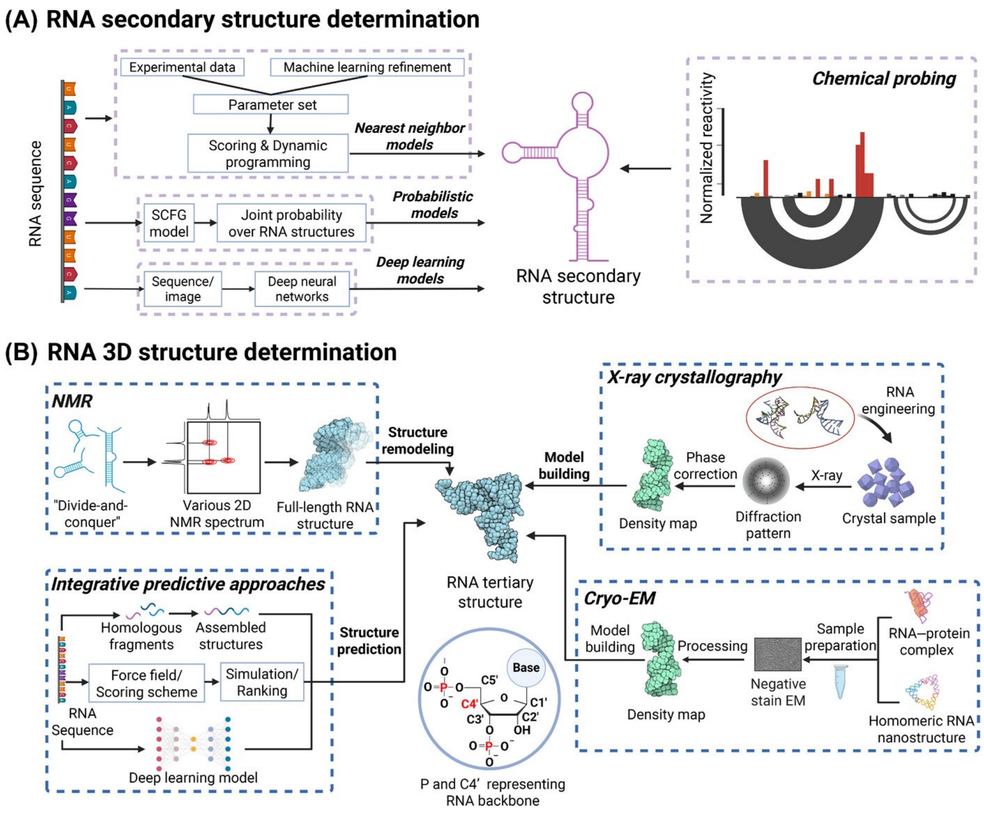
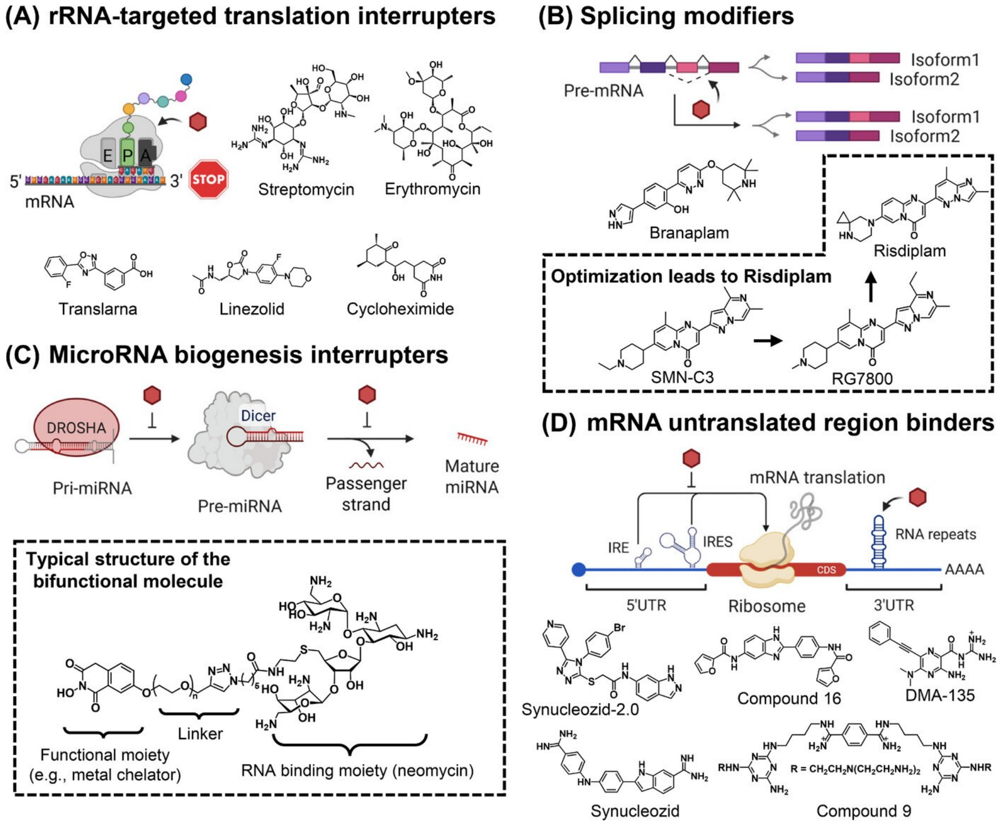
RNA is not protein

Getting help from experiments?



Cai, Z., Ma, H., Ye, F., Lei, D., Deng, Z., Li, Y., ... & Wen, H. (2025). Discovery of RNA-Targeting Small Molecules: Challenges and Future Directions. *MedComm*, *6*(9), e70342.

Strategies that can be used



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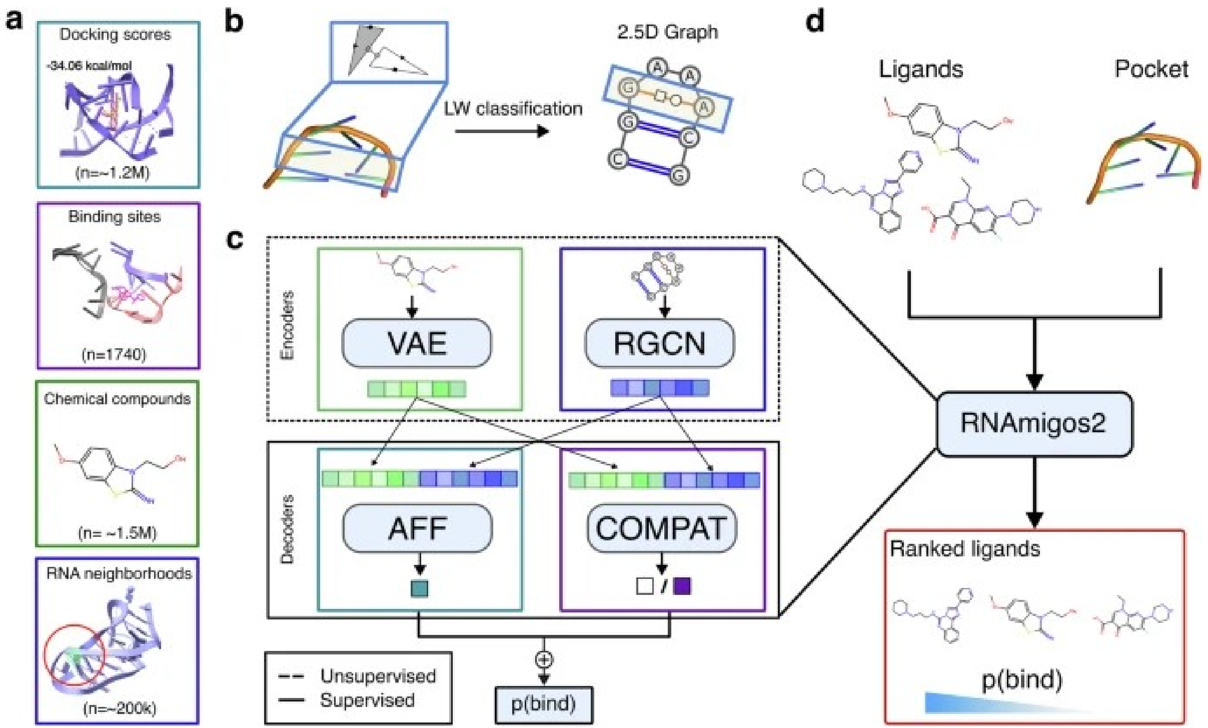
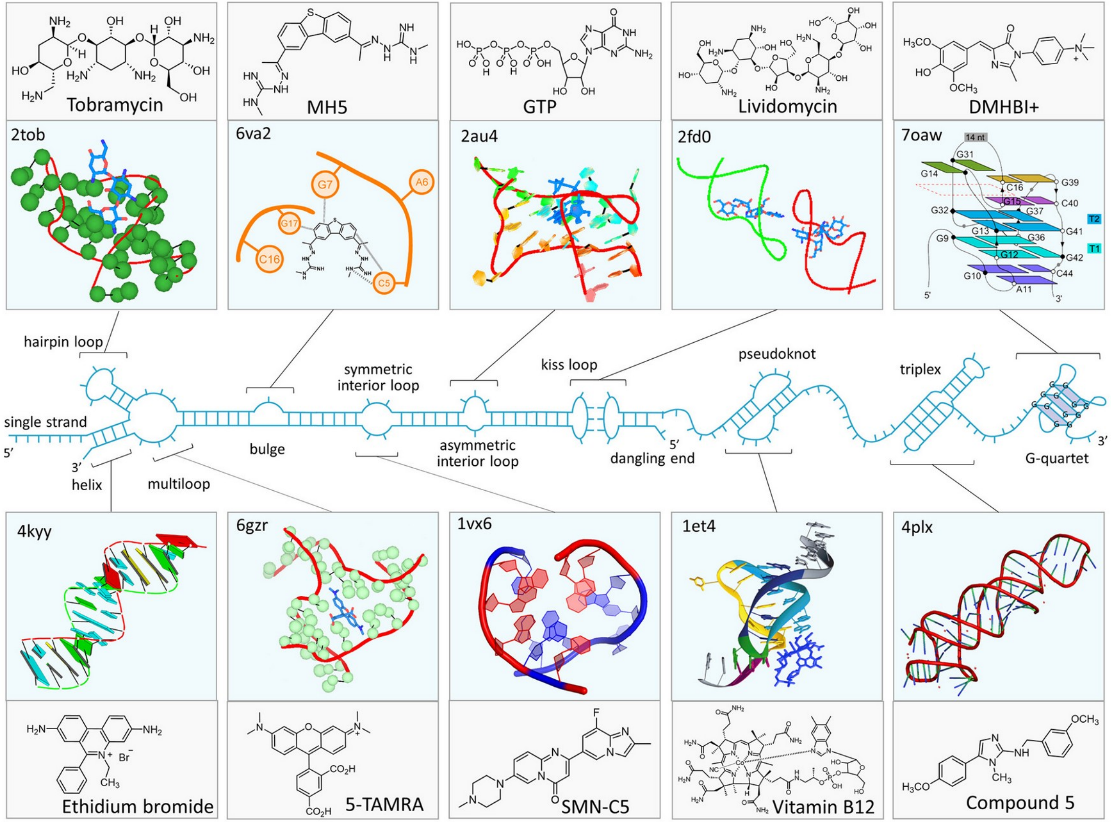
ML for screening of RNA-targeting molecules



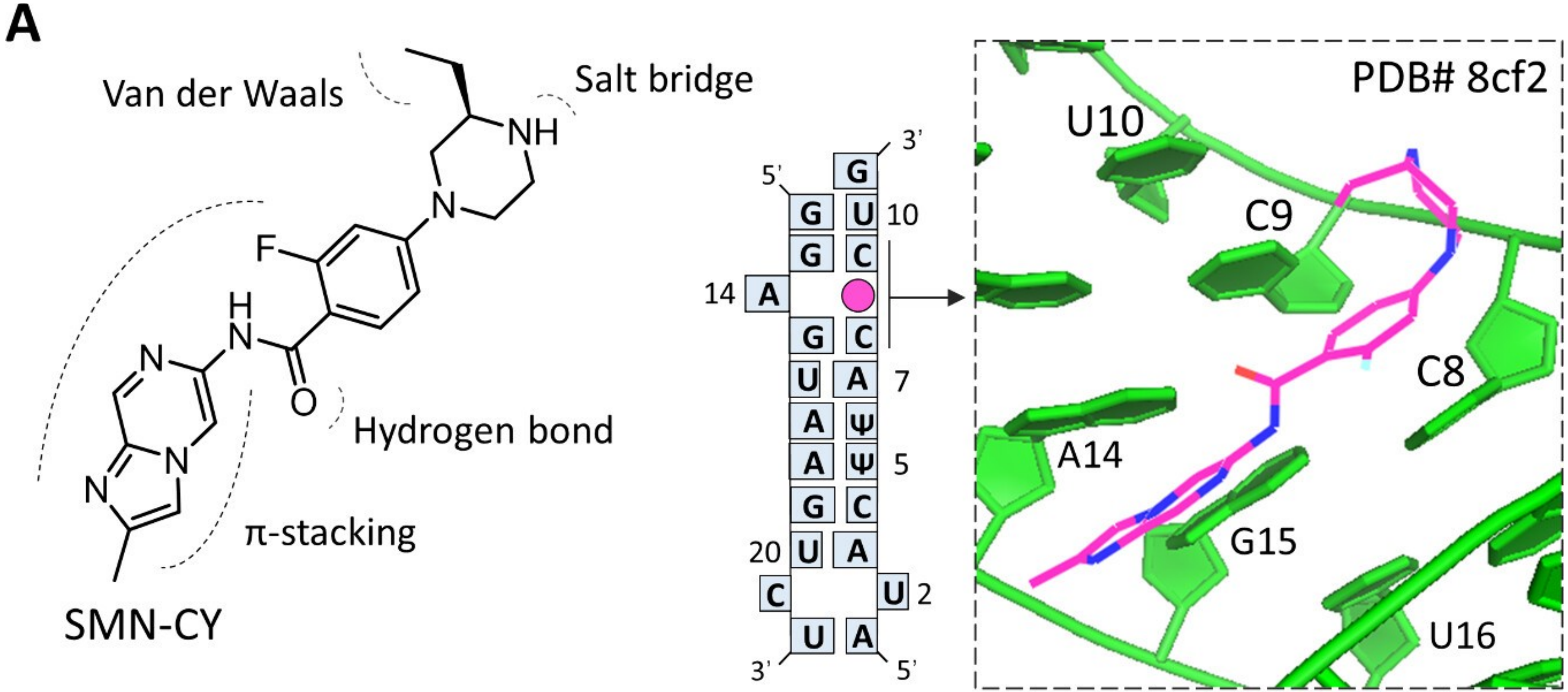
Carvajal-Patiño, J. G., Mallet, V., Becerra, D., Niño Vasquez, L. F., Oliver, C., & Waldispühl, J. (2025). RNAmigos2: accelerated structure-based RNA virtual screening with deep graph learning. *Nature Communications*, *16*(1), 1-12.

Various structural motifs can be targeted



Chen, S., Mao, Q., Cheng, H., & Tai, W. (2024). RNA-binding small molecules in drug discovery and delivery: an overview from fundamentals. *Journal of Medicinal Chemistry*, *67*(18), 16002-16017.

Interaction patterns



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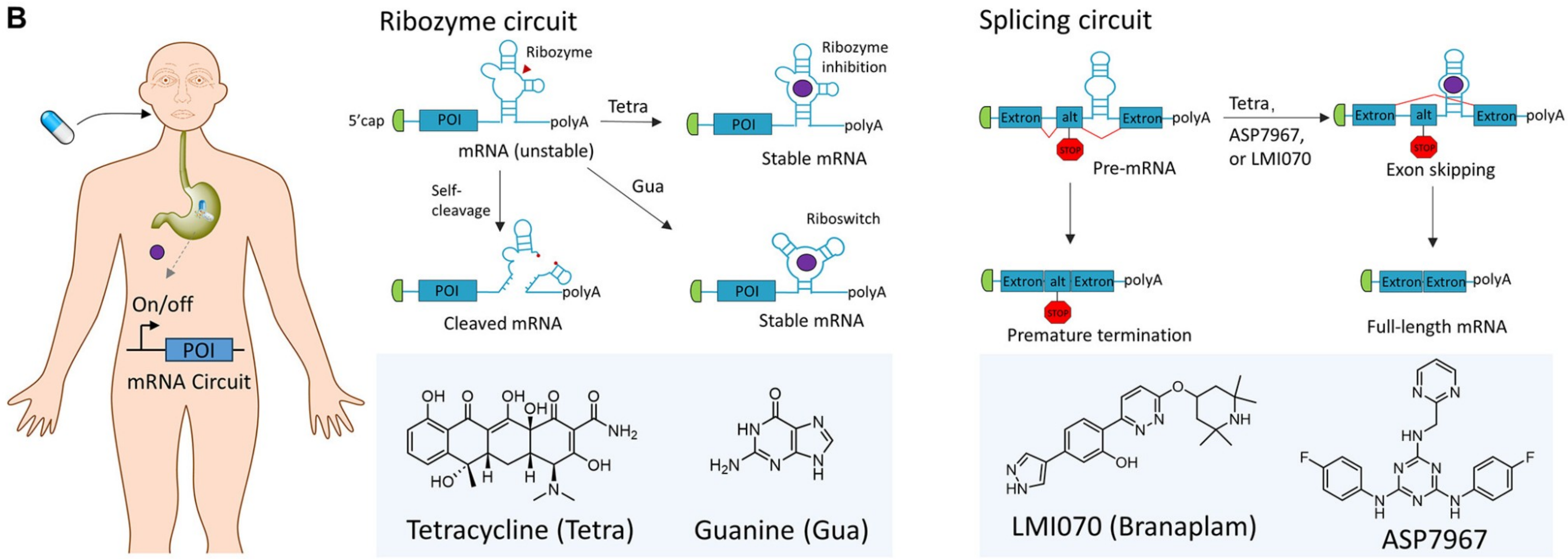
ADMET considerations



ADMET considerations