

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

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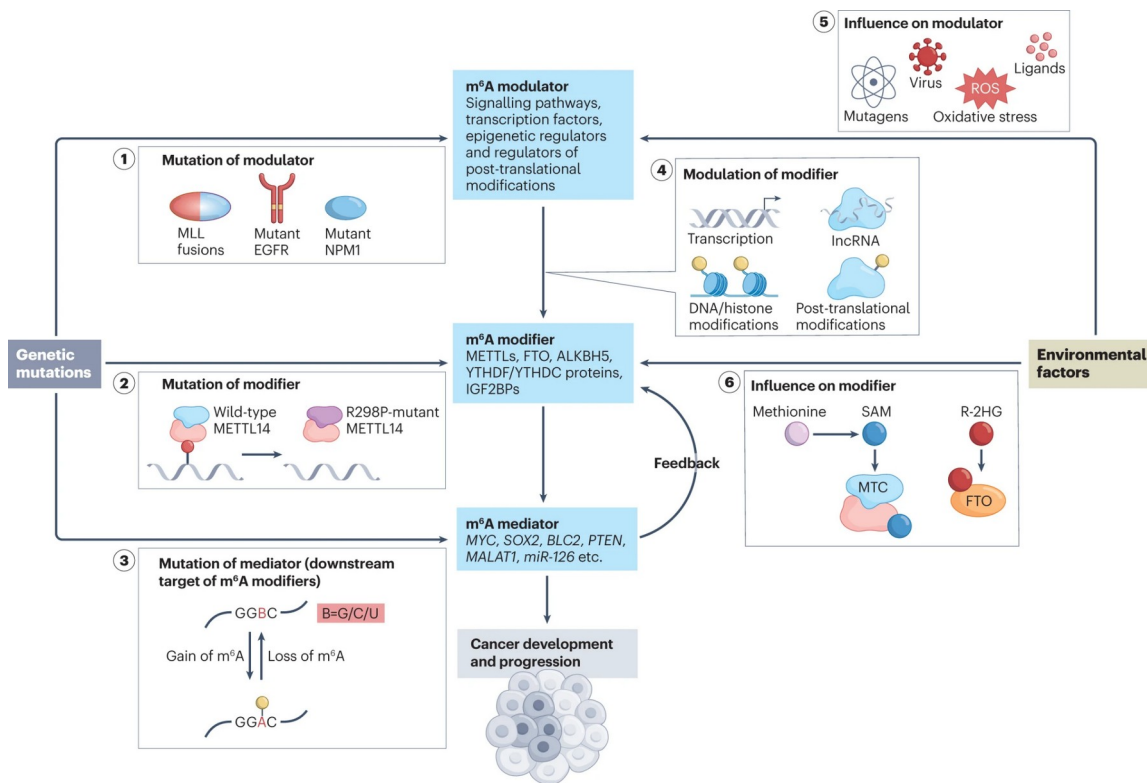
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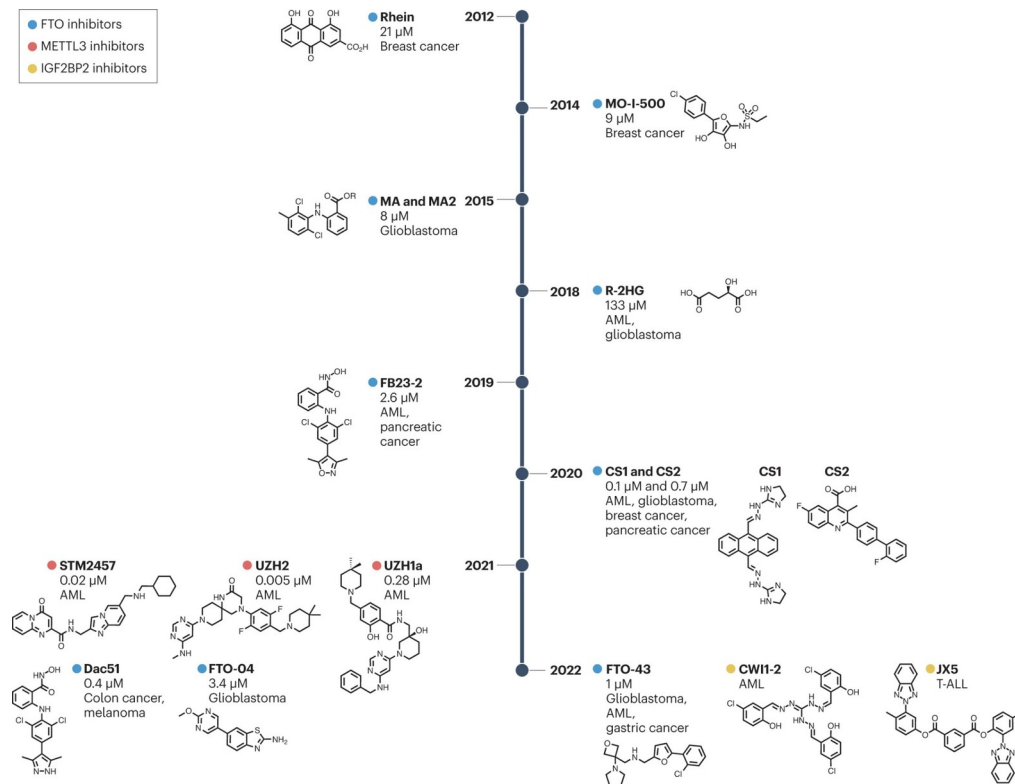
<https://doi.org/10.1038/s41467-025-65799-5>

RNA as a biomarker



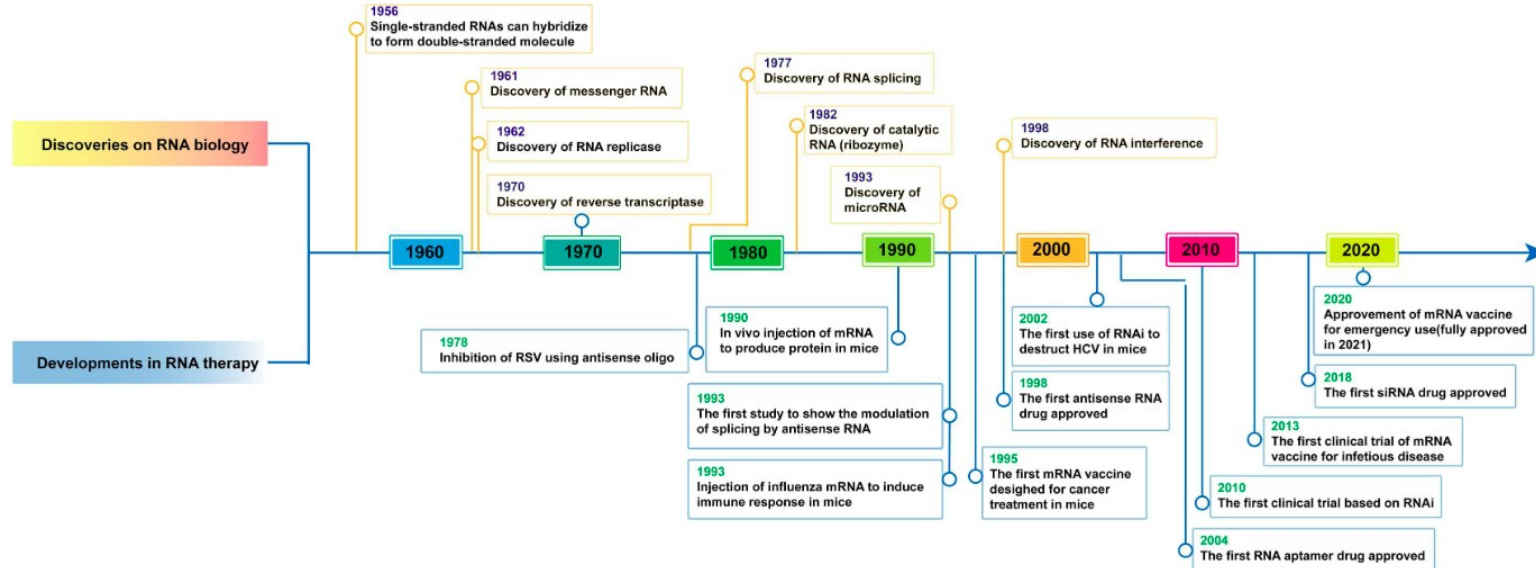
Deng, X., Qing, Y., Horne, D., Huang, H., & Chen, J. (2023). The roles and implications of RNA m⁶A modification in cancer. *Nature Reviews Clinical Oncology*, 20(8), 507-526.

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



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.

RNA therapeutics today




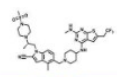
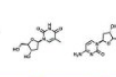
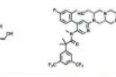
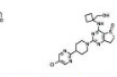
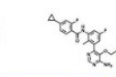

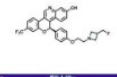
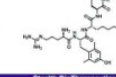
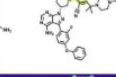
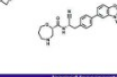
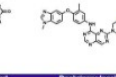

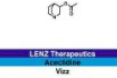

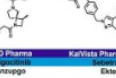
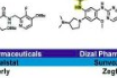
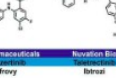


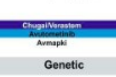

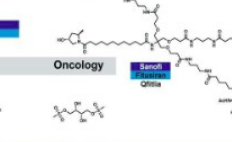







Classes of RNA therapeutics

- 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

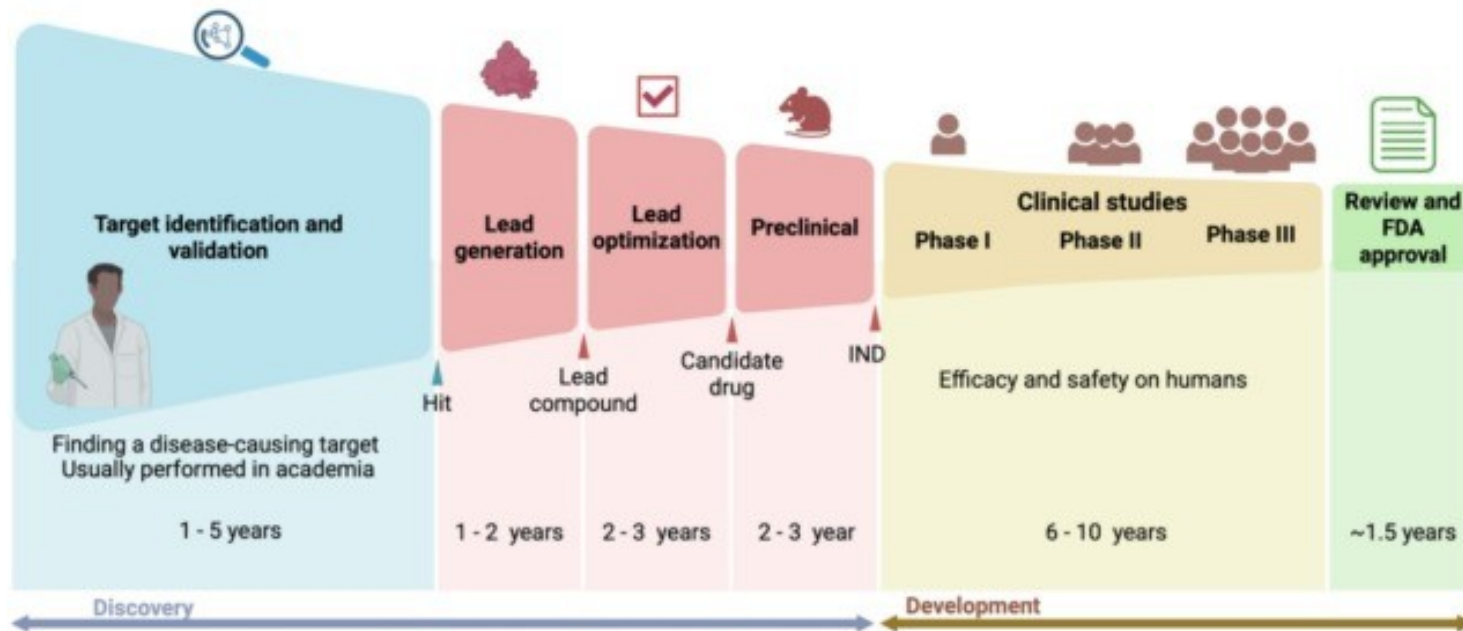
 2025 Small Molecule FDA-Approvals 					
Oncology	Oncology	Genetic Diseases	Endocrine	Pulmonary/Respiratory	Immunology
 Eysa Eysa Pharmaceuticals	 Karyo Karyo Pharmaceuticals	 UCB UCB	 Bayer Bayer	 Boehringer Ingelheim	 Novartis
Hyman	Romaflo	Kygerol	Lyfistat	Jascayd	Rhaparolo
Endocrine	Oncology	Genetic Diseases	Hematology	Pulmonary/Respiratory	Oncology
 Cytosine Cytosine Pharmaceuticals	 Eisai Eisai	 Shire Shire	 Sanofi Sanofi	 Hain Hain	 Boehringer Ingelheim
Palonitry	Inturilo	Porzinty	Wayritz	Braupit	Hemexeso
Oncology	Ophthalmology	Genetic	Dermatology	Immunology	Oncology
 Janssen	 Lenz	 PTC	 LEO	 Karyo	 Ozer
Modetso	Vux	Seprance	Anzago	Ektory	Zeghrovy
Ophthalmology	Oncology	Nephrology	Hematology		
 Auro	 Verastem	 Chugai	 Novartis	 Sanofi	
Academem	Fakerynle	Aumapki	Yamofia		
Infectious Disease	Oncology	Genetic	Pain	Oncology	
 GSK	 Genzyme	 Spring	 Vertex	 Moderna	
Enlogia	Rumvora	Geneti	Journeux	Grafepes	

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(from Michael slides)

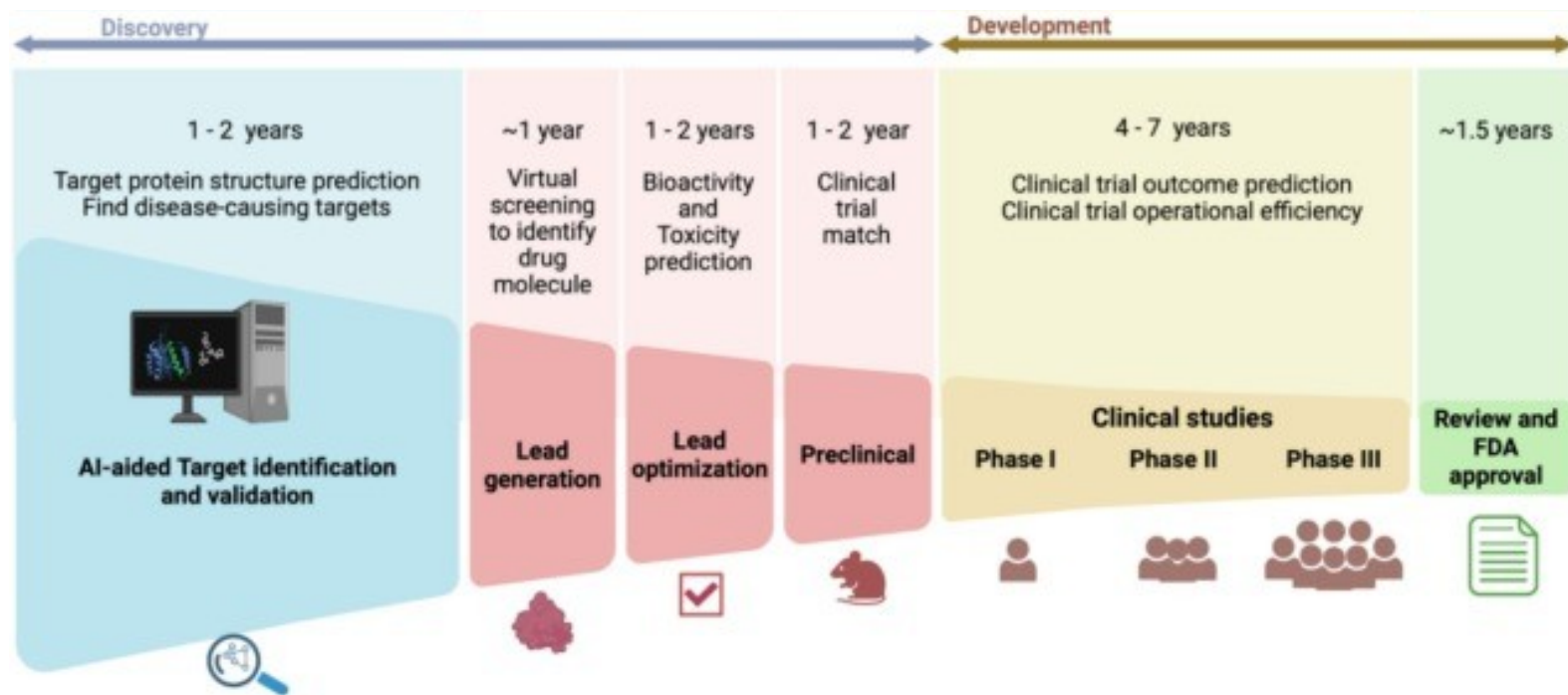
Drug design pipeline

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



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.

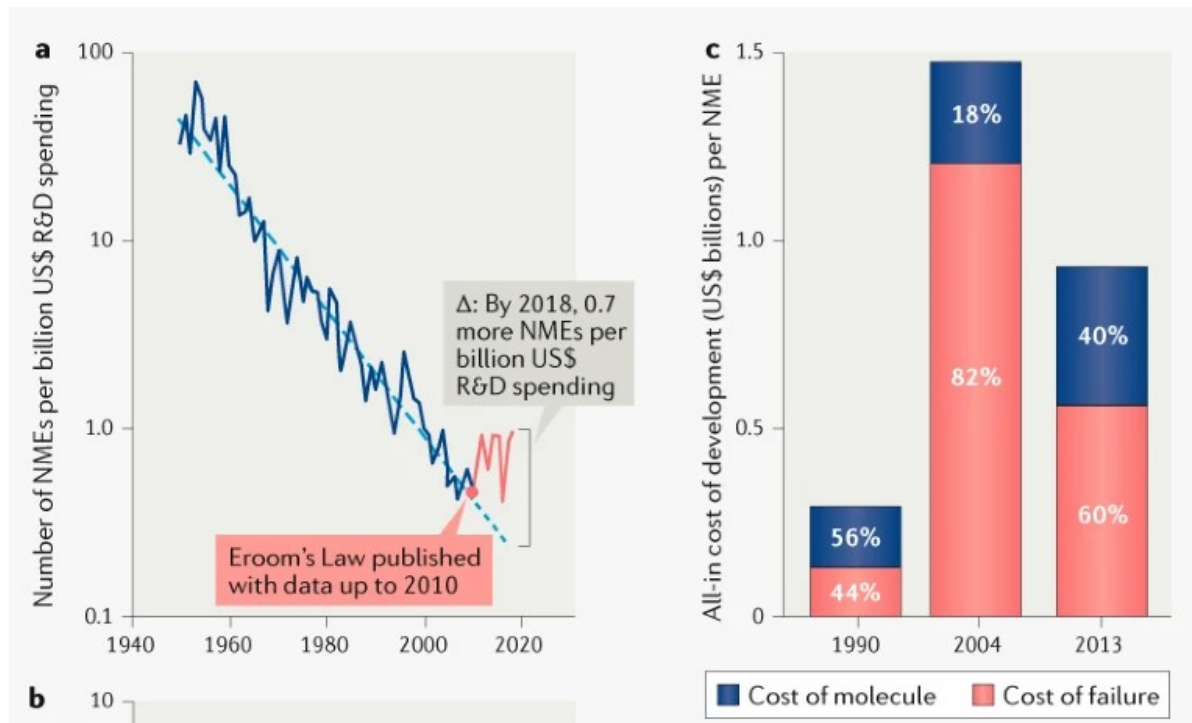
Where does the cost come from ?

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

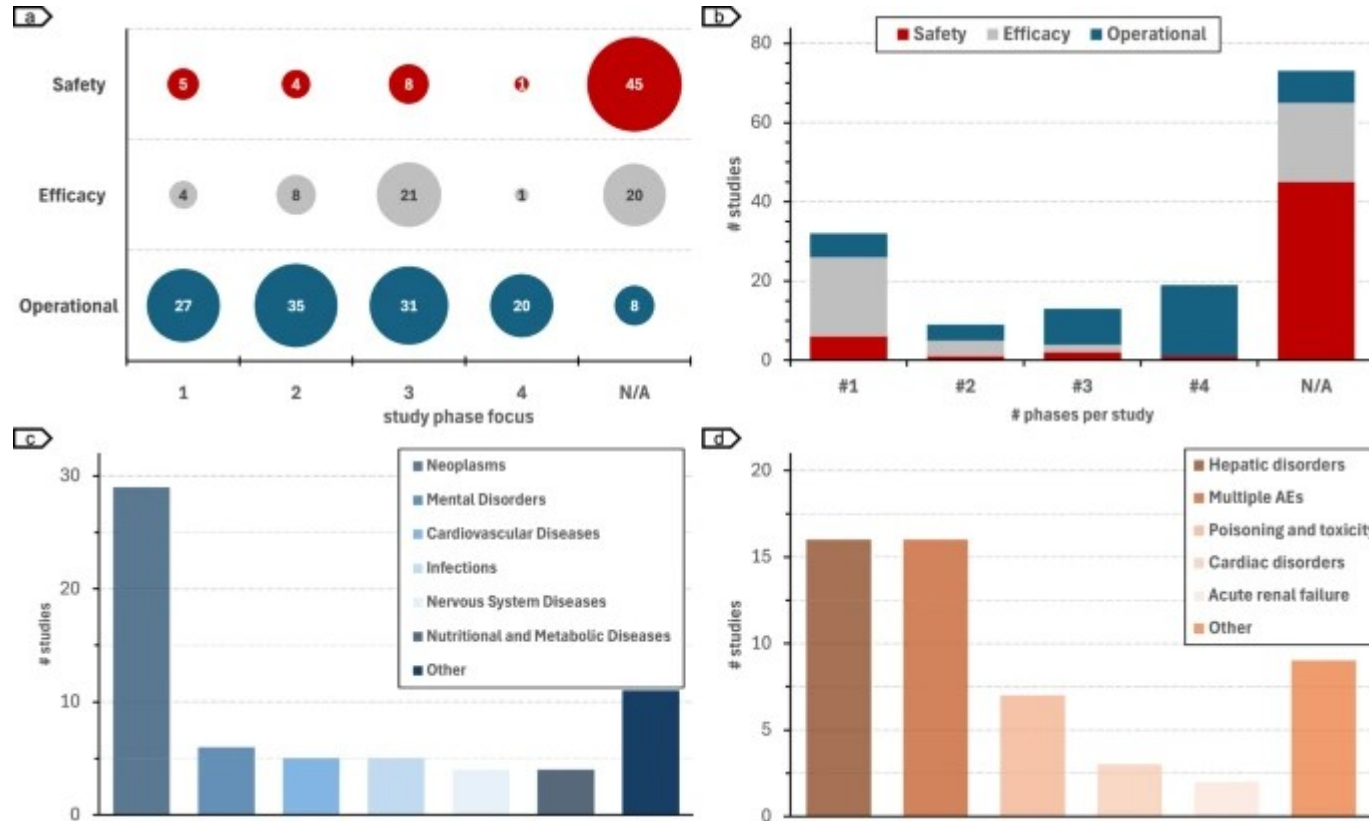
Therapeutic area and type of cost	Percentage of total cost (95% CI)			
	Nonclinical	Clinical	FDA review	Phase 4
All therapeutic areas				
Cost	6.8 (3.7-9.1)	68.0 (45.8-73.3)	1.5 (1.3-2.0)	23.7 (17.7-47.7)
Expected cost	27.0 (22.1-28.1)	60.5 (49.5-63.1)	4.6 (2.8-8.0)	7.9 (5.1-21.3)
Expected capitalized 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?

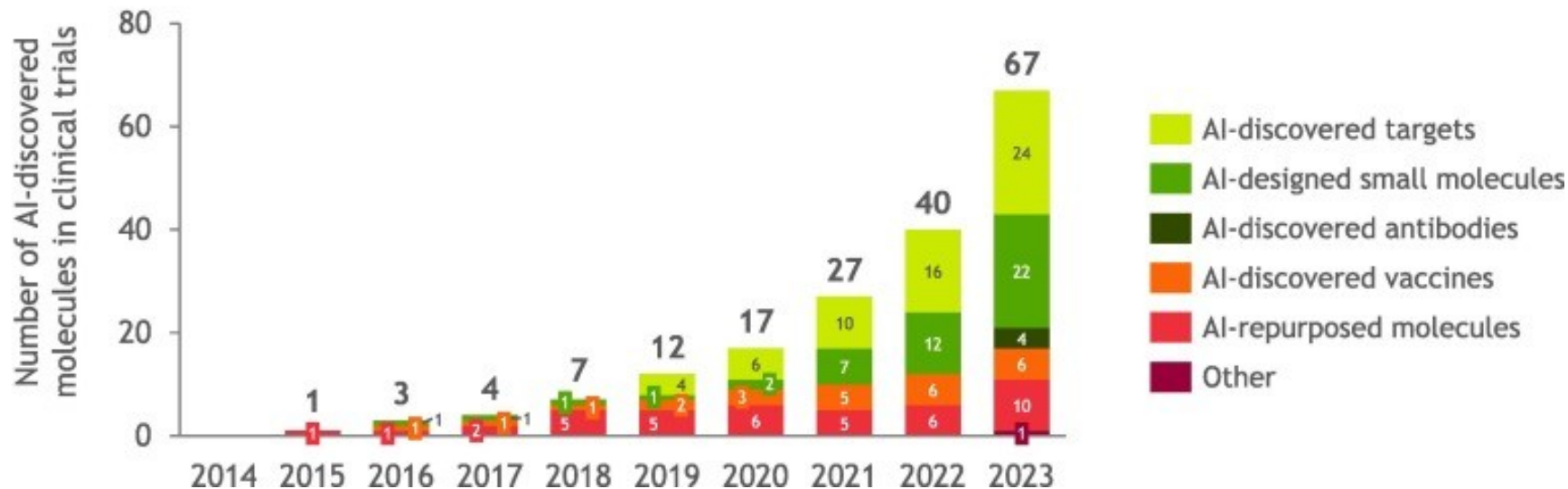


AI/ML in clinical trials risk management



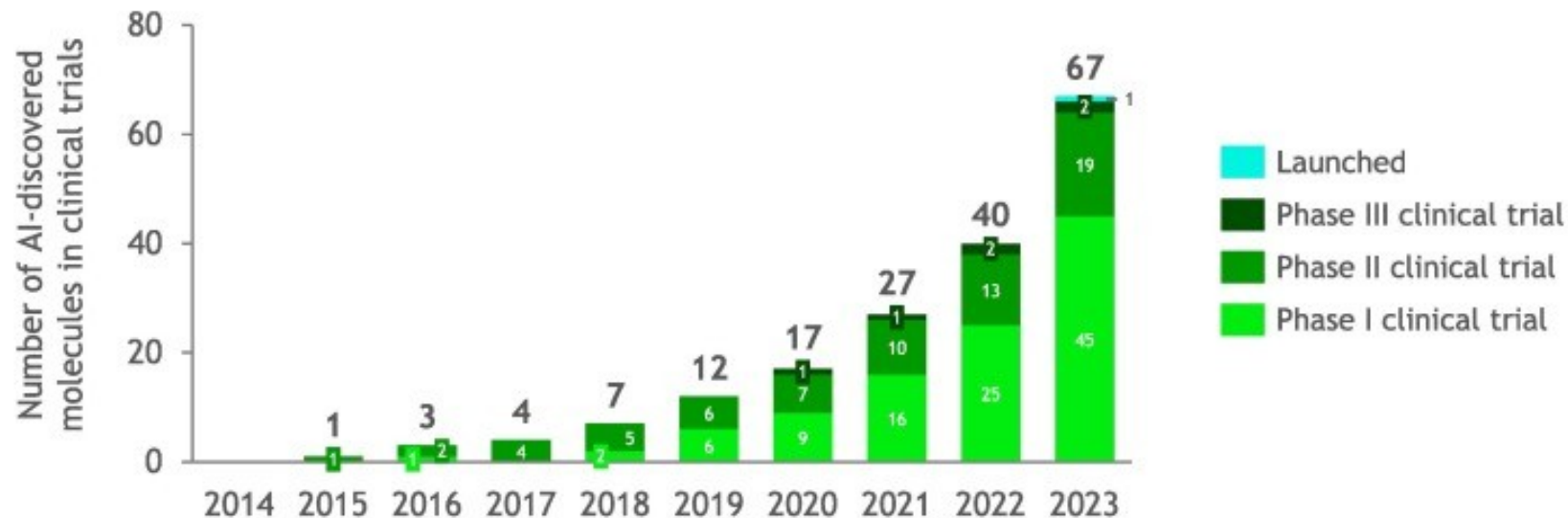
Teodoro, D., Naderi, N., Yazdani, A. *et al.* A scoping review of artificial intelligence applications in clinical trial risk assessment. *npj Digit. Med.* 8, 486 (2025)

How AI is used?



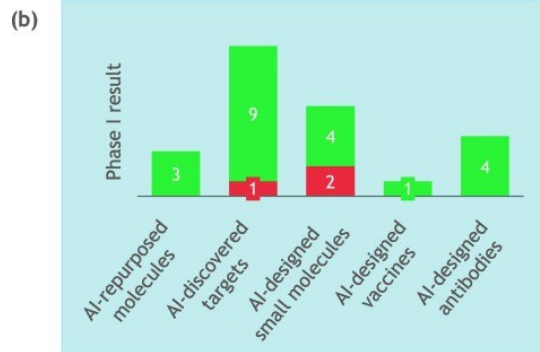
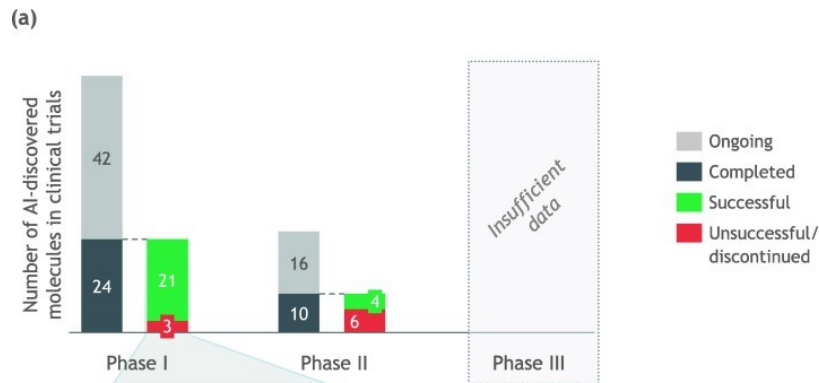
Jayatunga, M. K., Ayers, M., Bruens, L., Jayanth, D., & Meier, C. (2024). How successful are AI-discovered drugs in clinical trials? A first analysis and emerging lessons. *Drug discovery today*, 29(6), 104009.

test phase of AI-discovered drugs



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.

measure of the impact



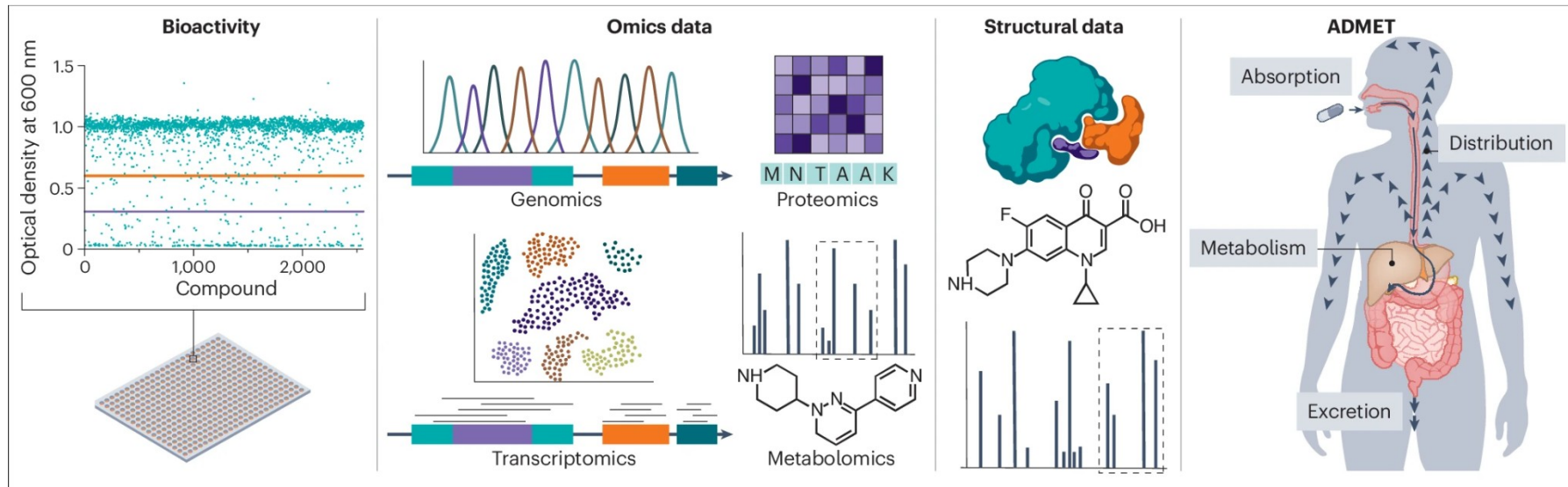
Jayatunga, M. K., Ayers, M., Bruens, L., Jayanth, D., & Meier, C. (2024). How successful are AI-discovered drugs in clinical trials? A first analysis and emerging lessons. *Drug discovery today*, 29(6), 104009.

2025 update...

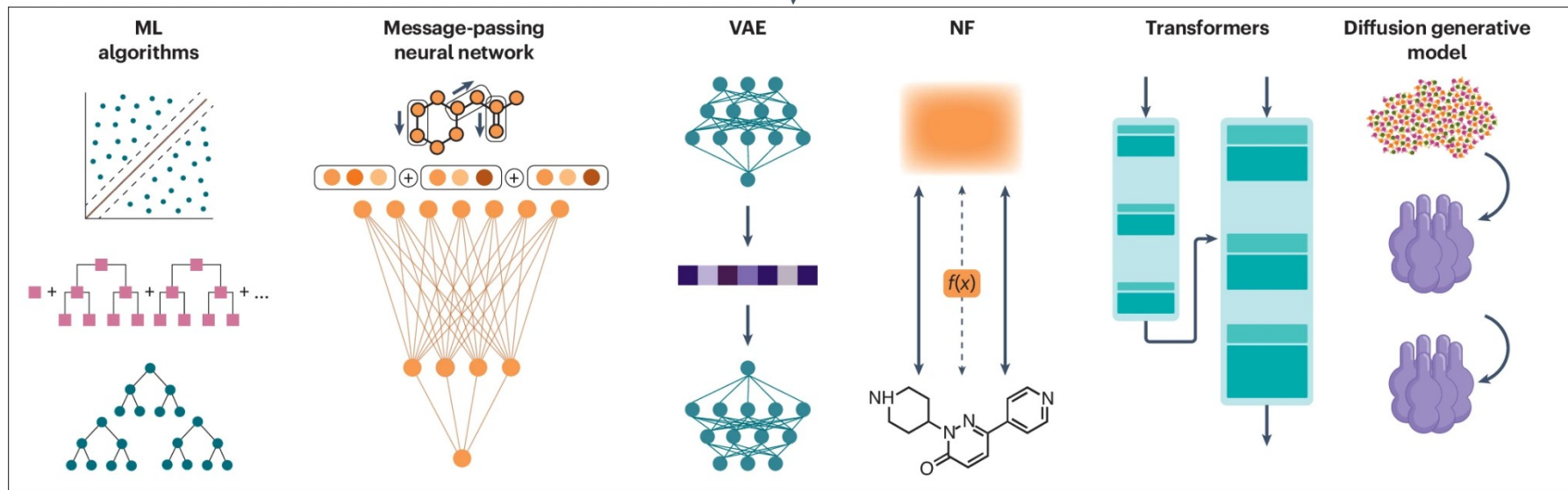
Overall, AI-designed molecules appear to have higher phase I success rates (~80%–90% vs ~52% industry average), likely reflecting better upfront filtering, but phase II outcomes (~30%–40% success) remain similar to traditional benchmarks.³⁸⁰ These outcomes suggest that AI is indeed accelerating early-stage 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.

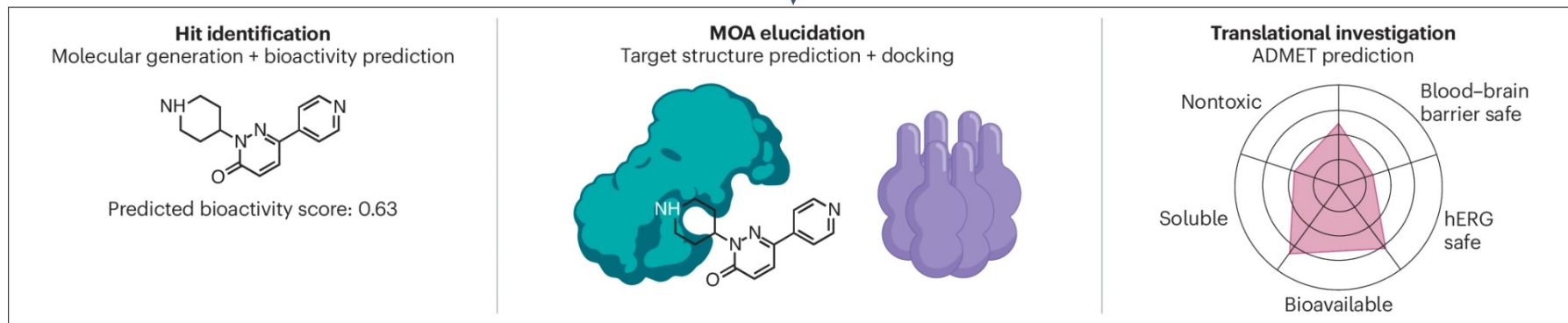
Looking at the molecular scale



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



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



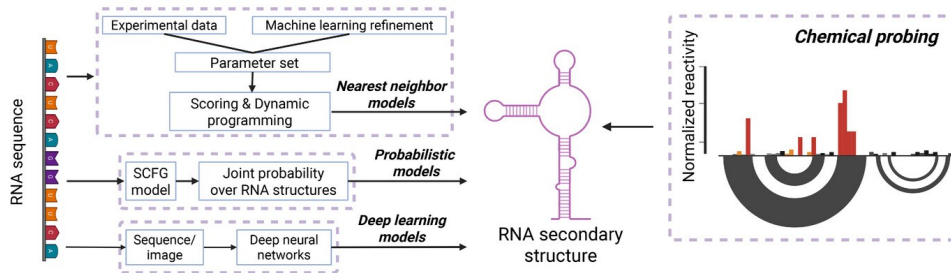
Catacutan, D.B., Alexander, J., Arnold, A. *et al.* Machine learning in preclinical drug discovery. *Nat Chem Biol* 20, 960–973 (2024).

RNA is not protein



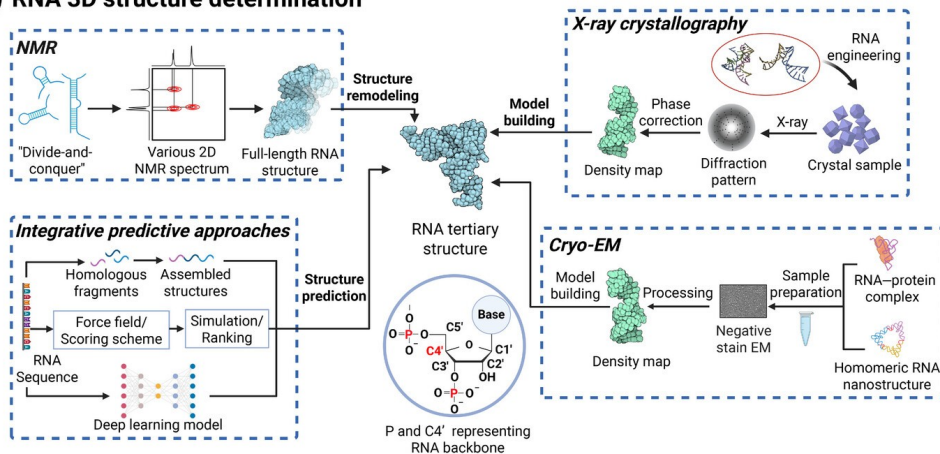
Getting help from experiments?

(A) RNA secondary structure determination



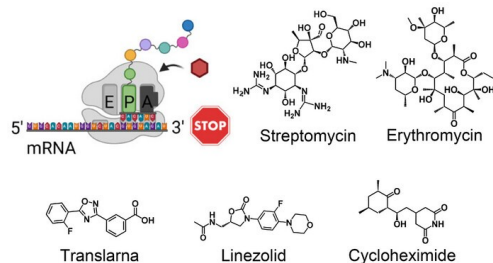
Cai, Z., Ma, H., Ye, F., Lei, D., Deng, Z., Li, Y., ... & Wen, H. (2025). Discovery of RNA-Targeting Small Molecules: Challenges and Future Directions. *MedComm*, 6(9), e70342.

(B) RNA 3D structure determination

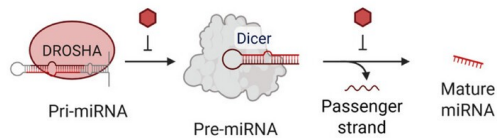


Strategies that can be used

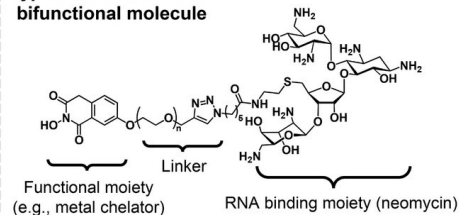
(A) rRNA-targeted translation interrupters



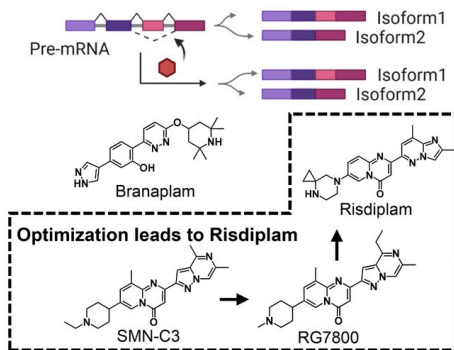
(C) MicroRNA biogenesis interrupters



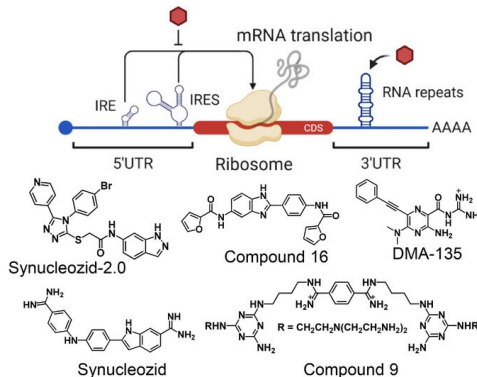
Typical structure of the bifunctional molecule



(B) Splicing modifiers

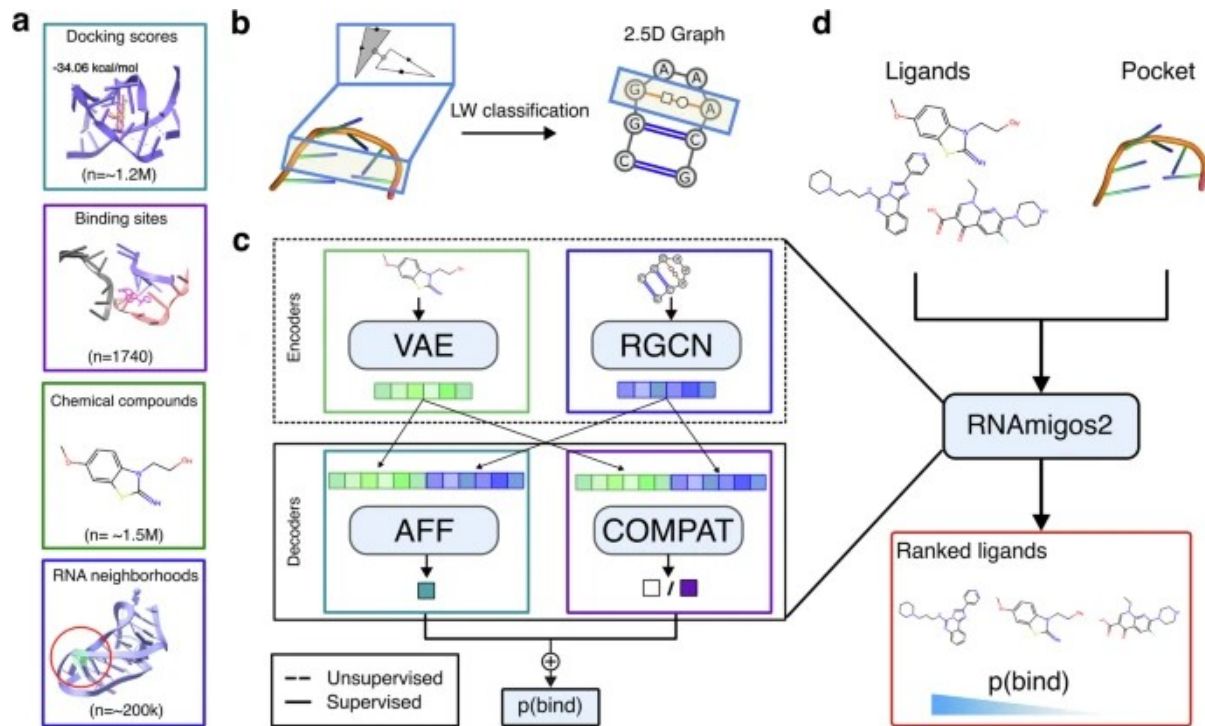


(D) mRNA untranslated region binders



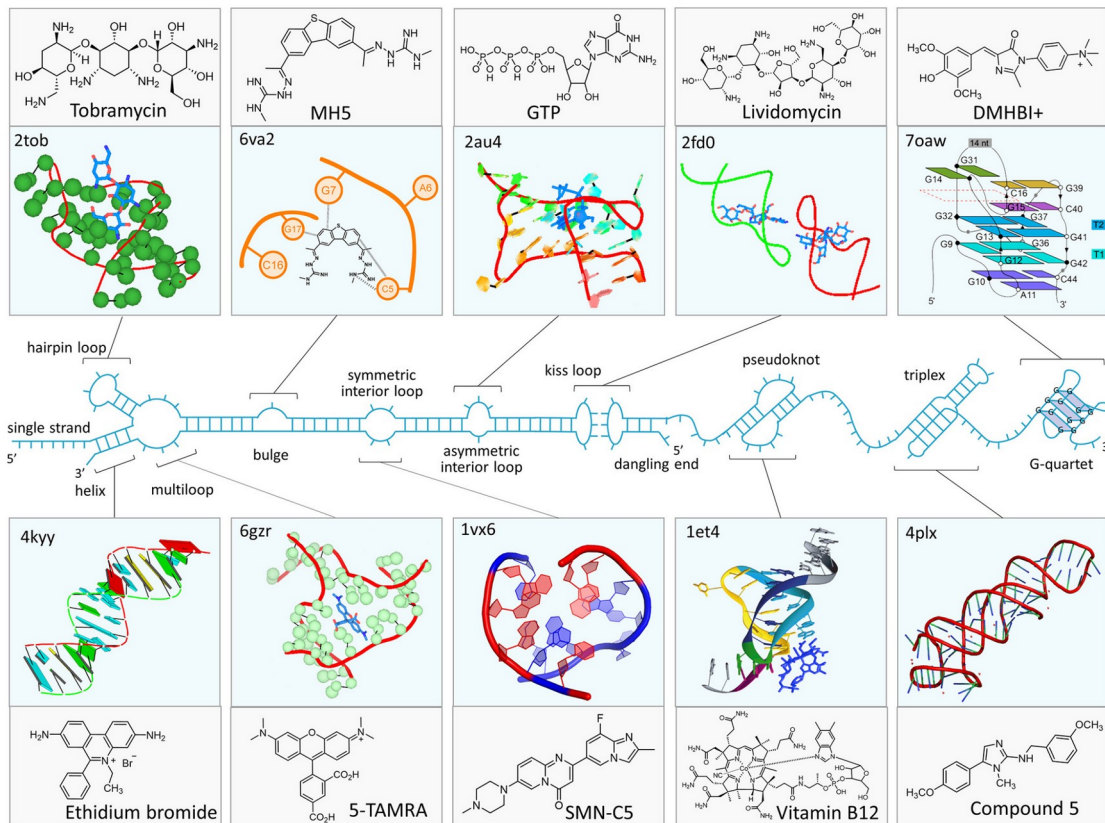
Cai, Z., Ma, H., Ye, F., Lei, D., Deng, Z., Li, Y., ... & Wen, H. (2025). Discovery of RNA-Targeting Small Molecules: Challenges and Future Directions. *MedComm*, 6(9), e70342.

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.

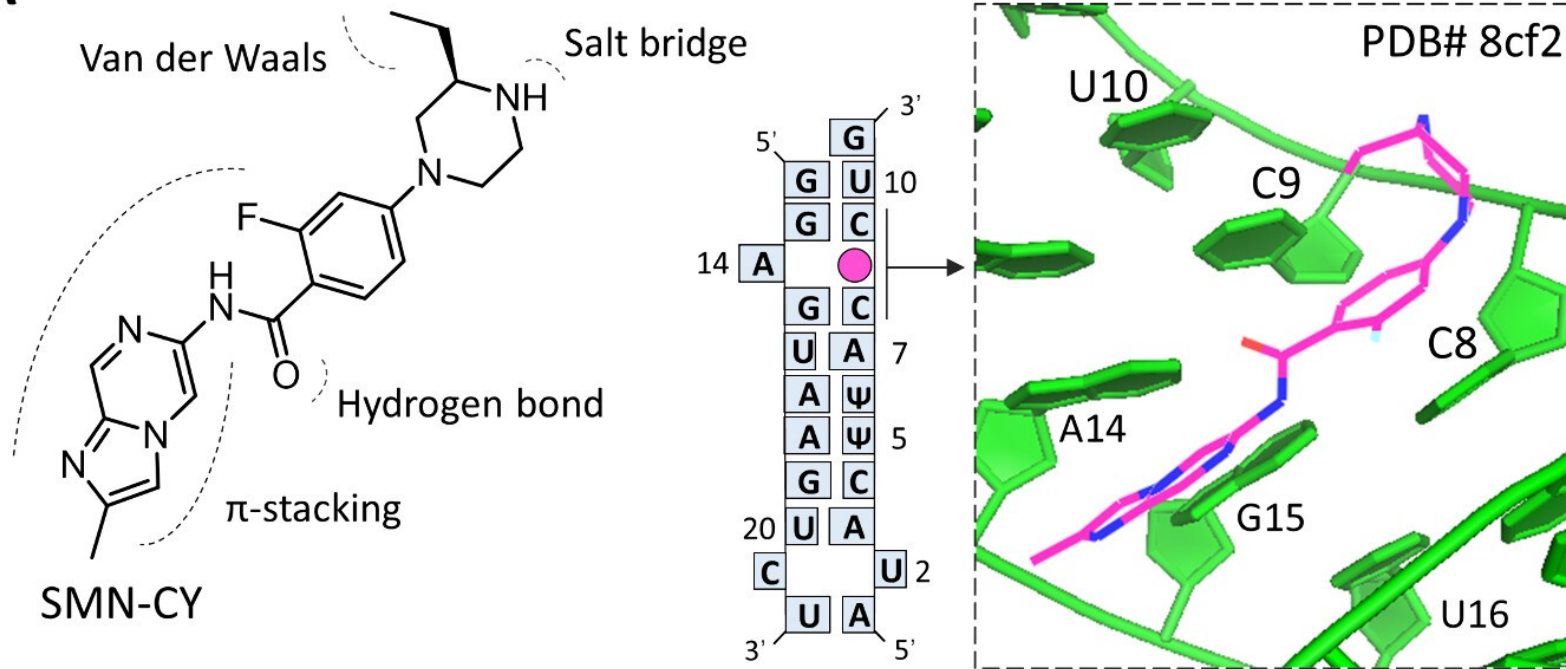
Various structural motifs can be targeted



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.

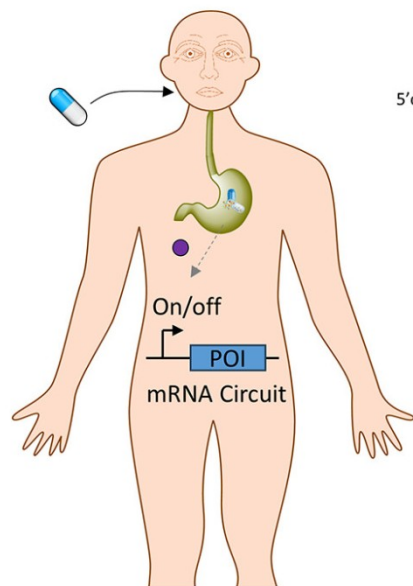
Interaction patterns

A

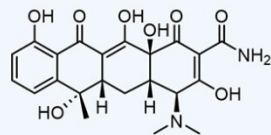
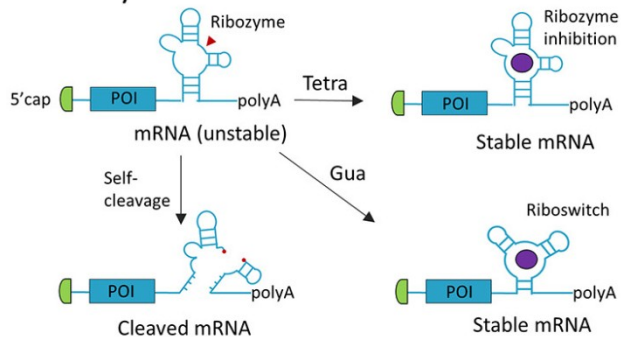


ADMET considerations

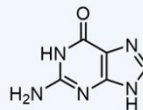
B



Ribozyme circuit

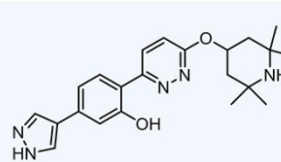
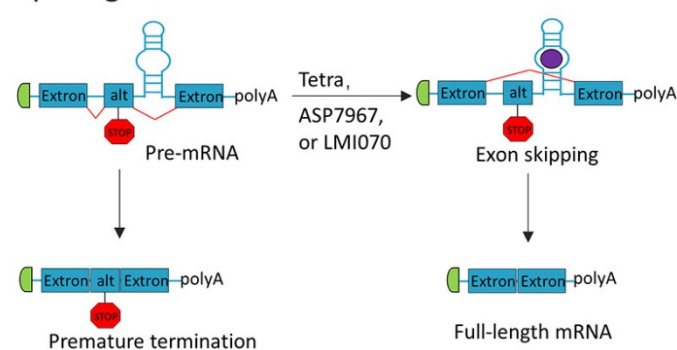


Tetracycline (Tetra)

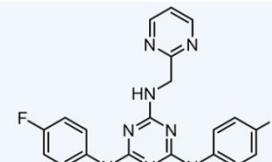


Guanine (Gua)

Splicing circuit



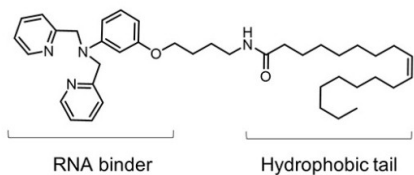
LMI070 (Branaplam)



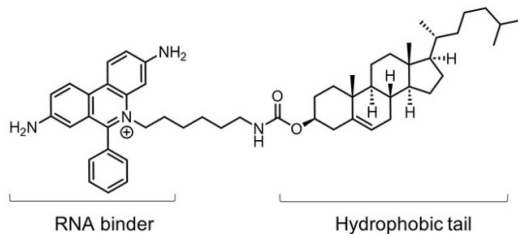
ASP7967

ADMET considerations

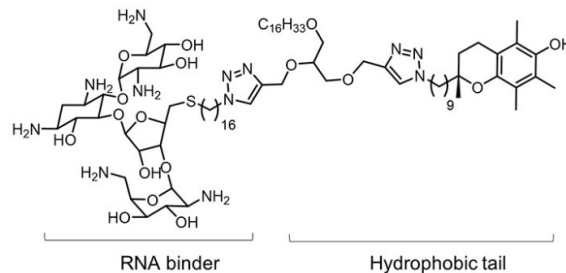
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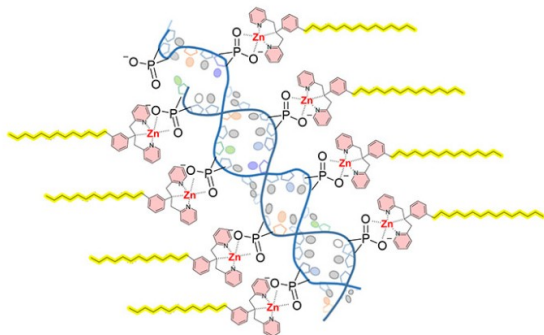
DPA-Oleo



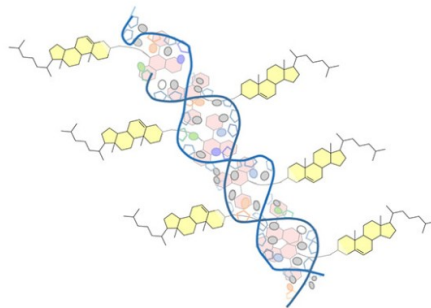
Ethidium-Cholesterol



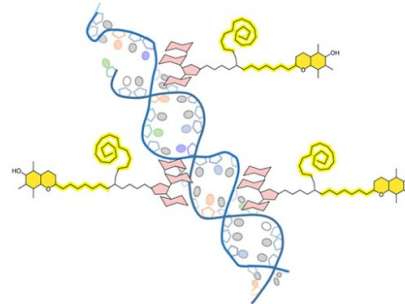
Neomycin-VE



Phosphate ion chelating mode



Interchain chelating mode



Groove binding mode