How multispecific medicines are transforming Amgen's pipeline

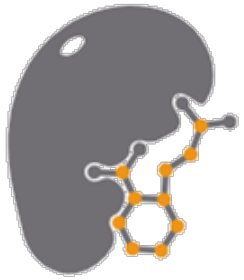
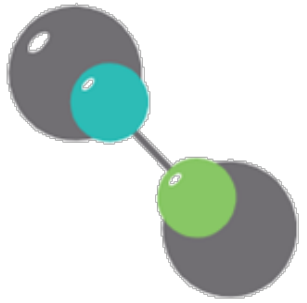
RAY DESHAIES, Senior Vice President, Amgen

Presentation to NASEM webinar series, "Advancing Drug Discovery"

18 September 2024

AMGEN

A Wave Of Transformative Innovation Is Sweeping Over The Biopharmaceutical Industry

c. 1900	1970s	1980s	Now
WAVE 1	WAVE 2	WAVE 3	WAVE 4
Advent of molecular drugs	**Rational drug design**	**Biotechnology revolution**	**Multispecific medicines**
			
Compounds with a known chemical structure but, at the time, unknown biology (how they work in the body)	Specific compounds with known molecular targets that play a role in disease	Recombinant DNA technology used to engineer cells to produce protein-based medicines (biologic medicine)	Multi-targeted compounds or biologic medicines to treat disease

Modified from Deshaies (2020) Nature, 580, 329–338

Biology Poses 4 Major Challenges to Drug Developers

1. Instability (low $t_{1/2}$): Many candidate drugs have too little persistence to have pharmacological impact
2. Redundancy: Biology is regulated by parallel/overlapping mechanisms
3. Therapeutic Index: Protein targets of drugs are expressed in multiple cell types
4. Druggability: We do not know how to modulate function of many of the proteins that drive disease

Multispecifics enable us to overcome these challenges

Multispecifics are the ladder that will enable us to reach the 'unharvested fruit'

Biotech Industry
1990-2000

Low-hanging fruit picked

Biotech Industry
2020s

Many remaining targets are redundant, have a challenging therapeutic index or are undruggable

INVESTING IN NEW TECHNOLOGIES WILL ENABLE US TO DRUG CHALLENGING TARGETS

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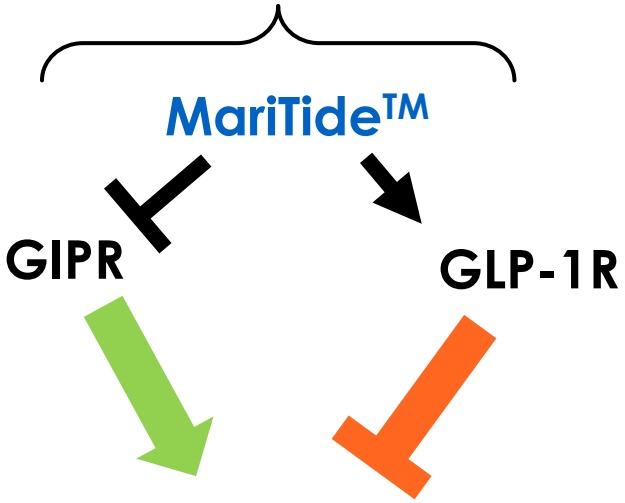
Four Major Classes of Multispecific Medicines @ Amgen

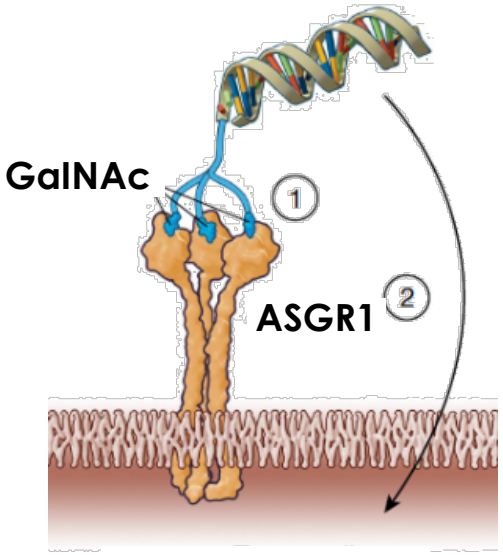
Multi-Actives
combat redundancy

Disease modulators



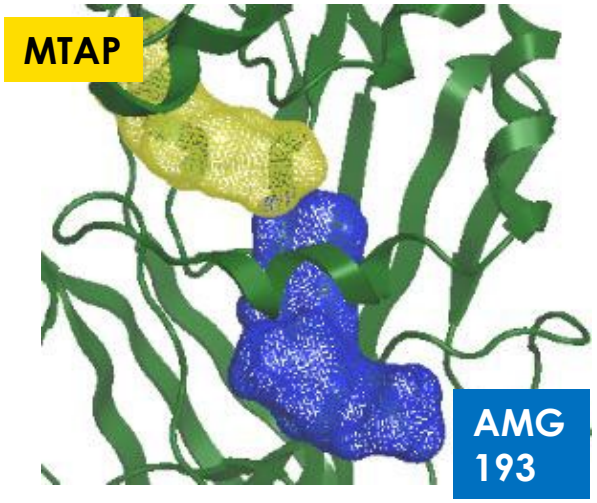
Target Obesity

'Tetherbodies'
enhance therapeutic index



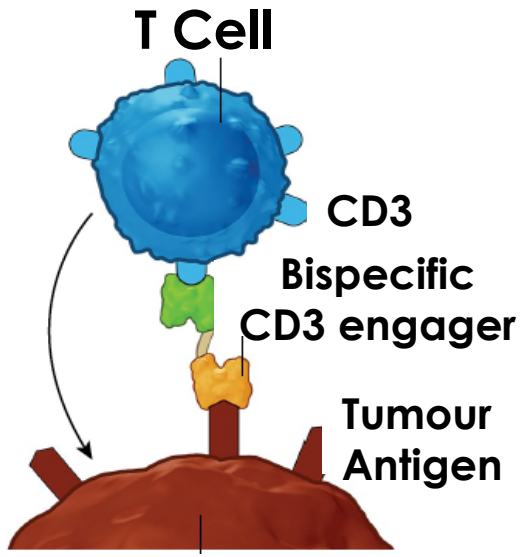
Target Lp(a)

'Conditionals'
enhance therapeutic index



Target PRMT5

'Matchmakers'
recruit help to drug difficult targets



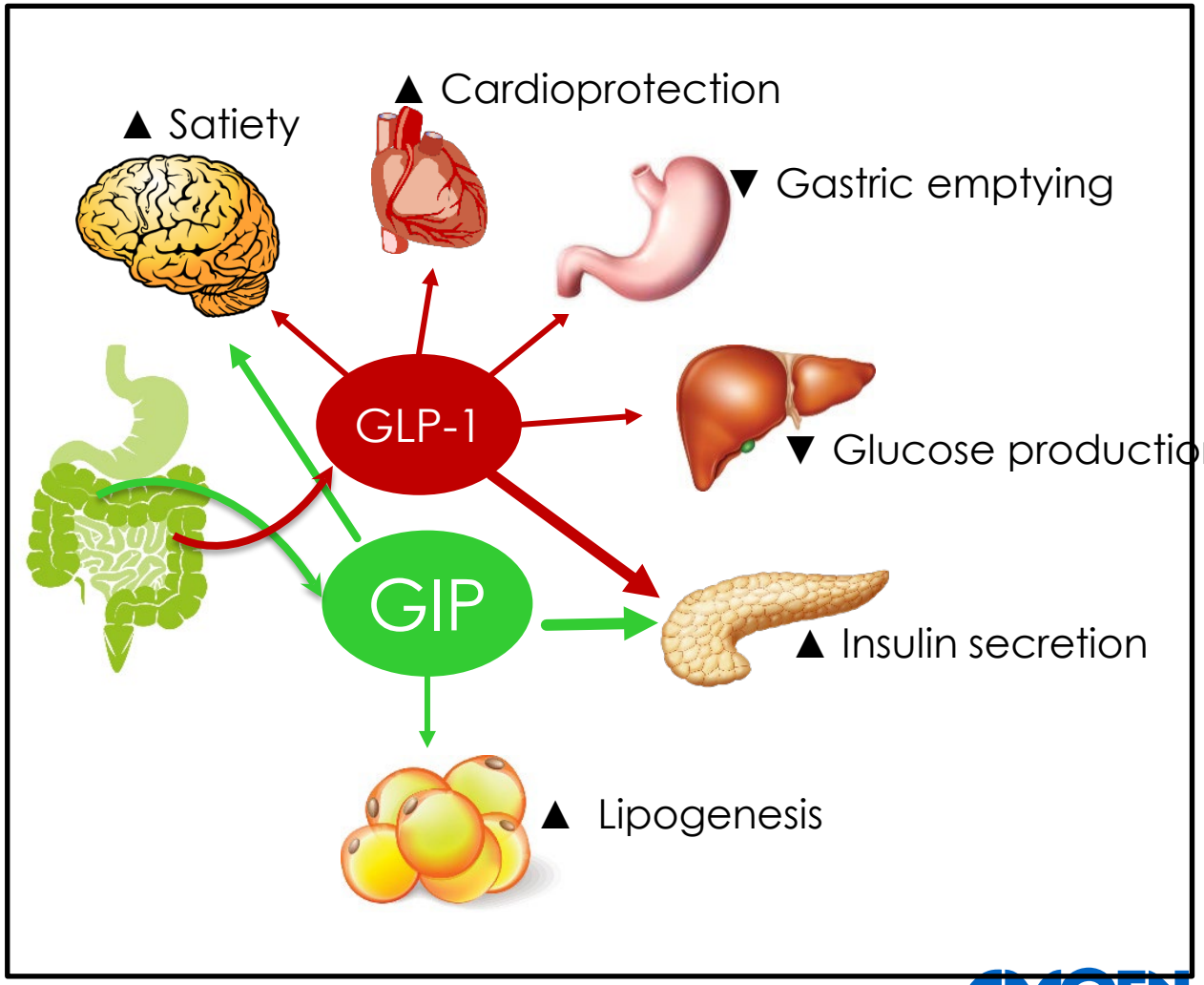
Target Tumor Cell

MULTISPECIFICS ENABLE US TO OVERCOME MAJOR CHALLENGES TO DRUG DEVELOPMENT

GLP-1 AND GIP ARE TWO INCRETIN HORMONES WITH NON-OVERLAPPING ROLES IN HUMAN PHYSIOLOGY

GLP-1

- **GLP-1 is released from the intestinal L cells after a meal and binds to GLP-1 receptor (GLP-1R)**
- **Analogs of GLP-1 are successfully marketed for type 2 diabetes and obesity**
  - Liraglutide, Dulaglutide and Semaglutide

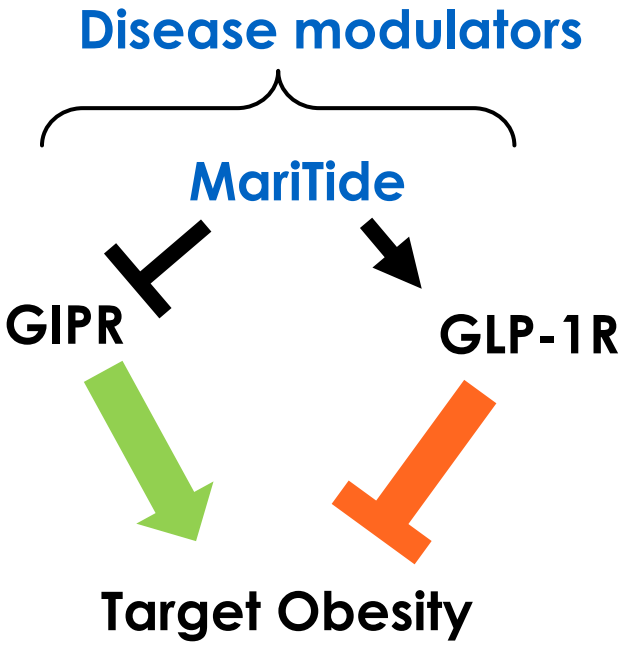


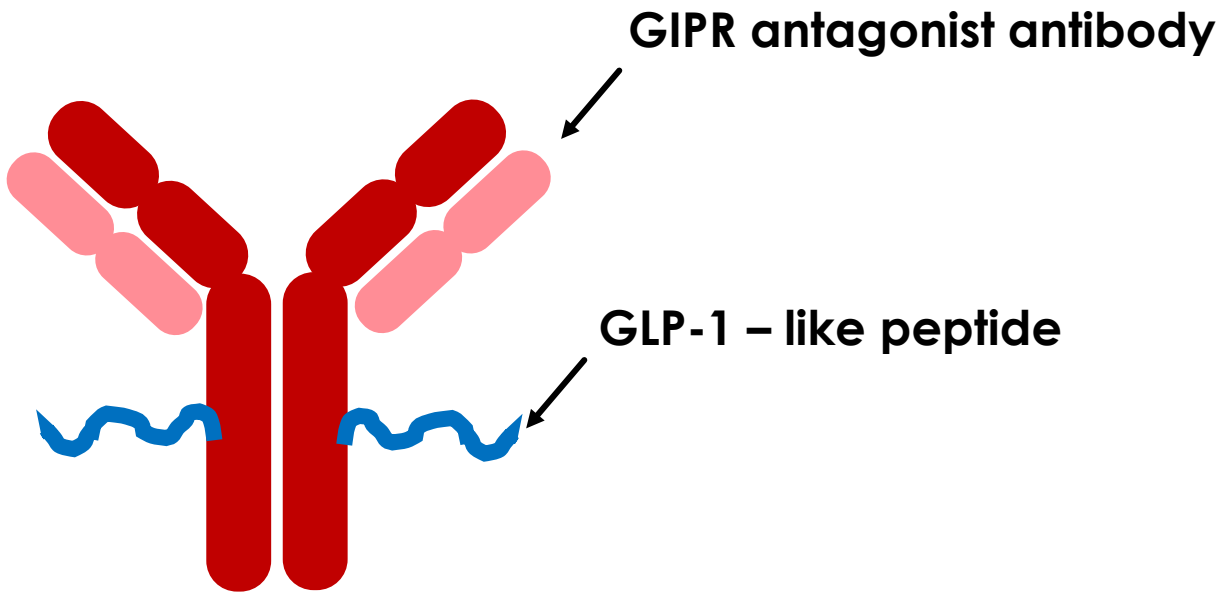
Modified from Campbell and Drucker, Cell Metabolism, 2013 17, 819-837

MariTide demonstrates the potential power of targeting multiple mechanisms simultaneously

Multi-Actives

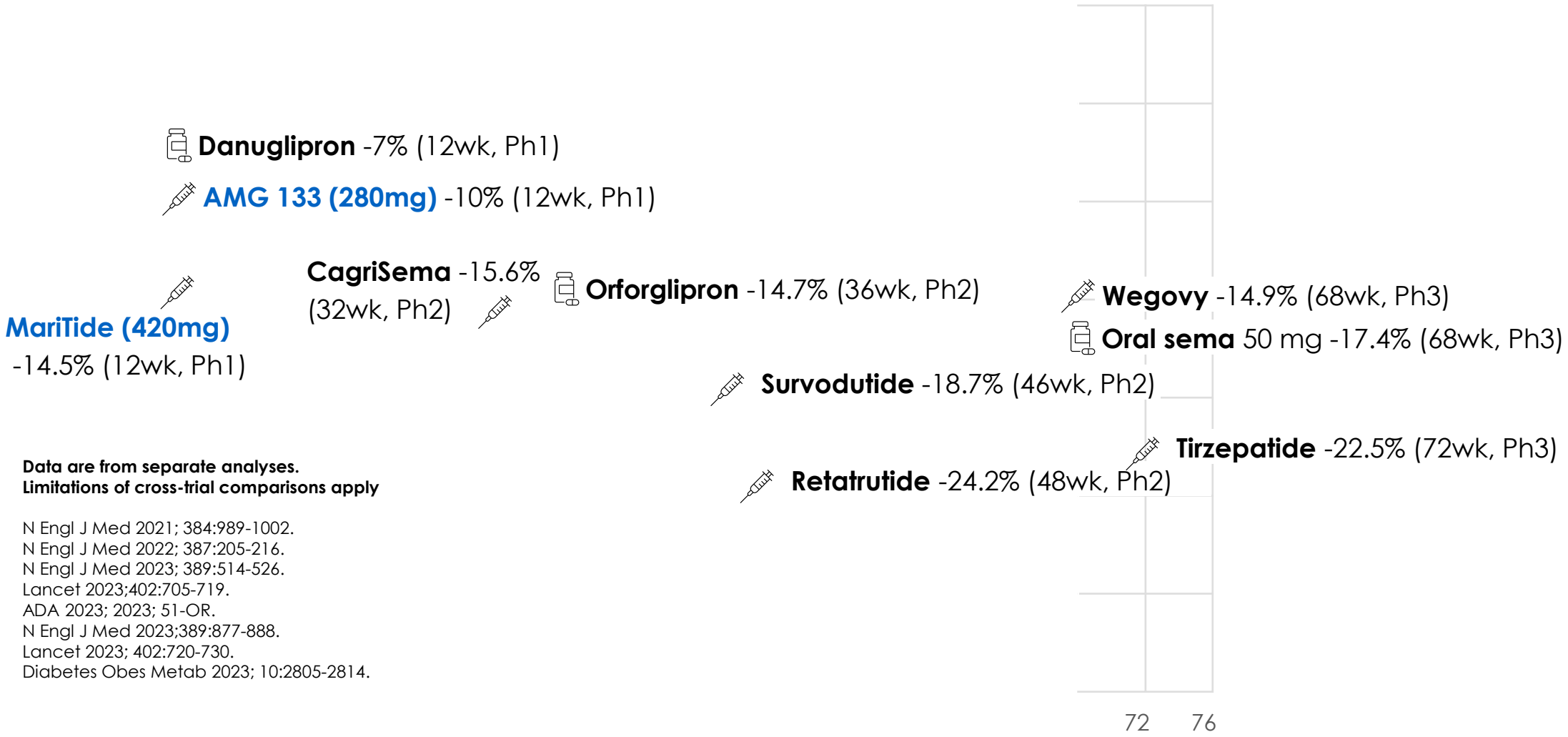
combat redundancy





MULTISPECIFICS ENABLE US TO OVERCOME MAJOR CHALLENGES TO DRUG DEVELOPMENT

MariTide Has Potential to Differentiate in Magnitude and Time to Weight Loss



Data are from separate analyses.
Limitations of cross-trial comparisons apply

N Engl J Med 2021; 384:989-1002.
N Engl J Med 2022; 387:205-216.
N Engl J Med 2023; 389:514-526.
Lancet 2023;402:705-719.
ADA 2023; 2023; 51-OR.
N Engl J Med 2023;389:877-888.
Lancet 2023; 402:720-730.
Diabetes Obes Metab 2023; 10:2805-2814.

Competitor data represents dose cohort with highest weight loss in obese patients

Olpasiran demonstrates the potential power of attaching a ‘zip code’ to a medicine

Multi-Actives

combat redundancy

Disease modulators

MariTide

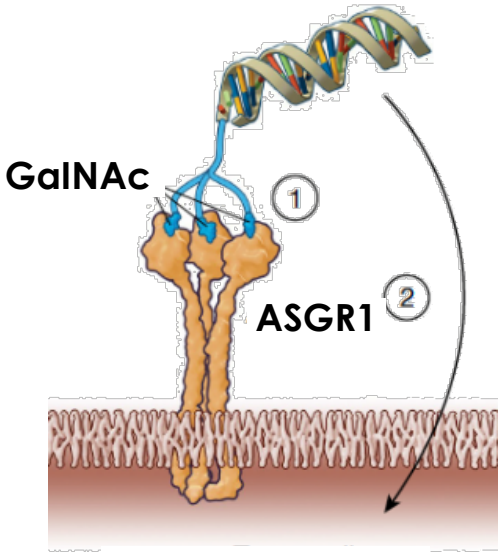
GIPR

GLP-1R

Target Obesity

‘Tetherbodies’

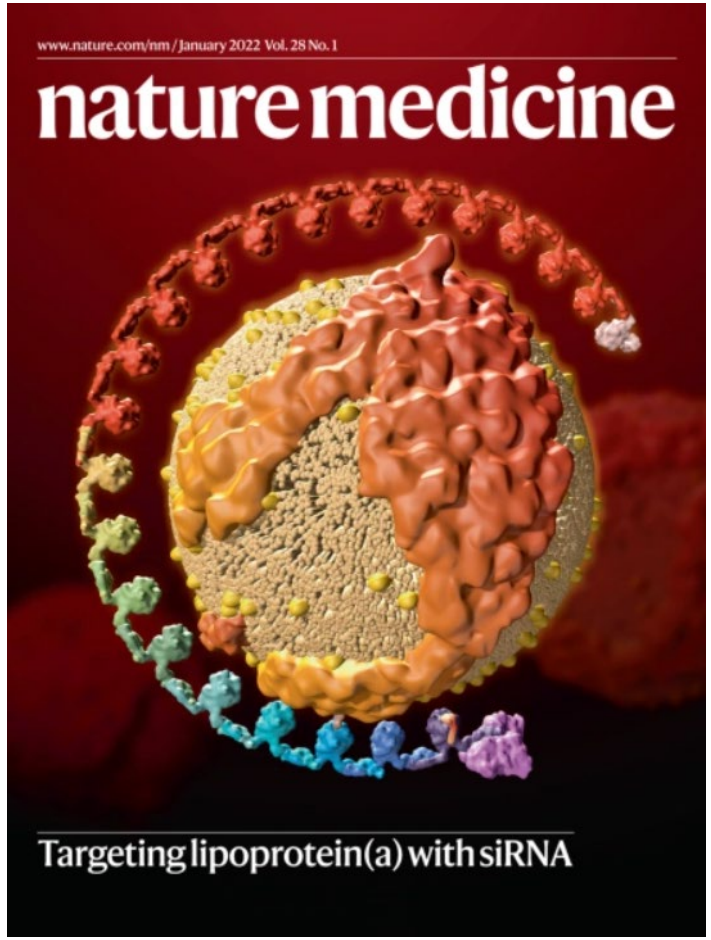
enhance therapeutic index



Target Lp(a)

MULTISPECIFICS ENABLE US TO OVERCOME MAJOR CHALLENGES TO DRUG DEVELOPMENT

Olpasiran: Seeking to Reduce Risk in High Lp(a) Population



The Washington Post

Friday January 7, 2022

Lipoprotein(a) is a type of 'bad' cholesterol you've probably never heard of. Some doctors are out to change that.

- Lp(a) expressed by liver and ~ 20% of people have increased Lp(a) levels
- Epidemiology and genetic studies show elevated Lp(a) is associated with CVD risk
- Levels are genetically determined and do not change with diet or exercise
- Approved drugs have no or minor effects on Lp(a) levels

Lp(a)= Lipoprotein(a); CVD= cardiovascular disease

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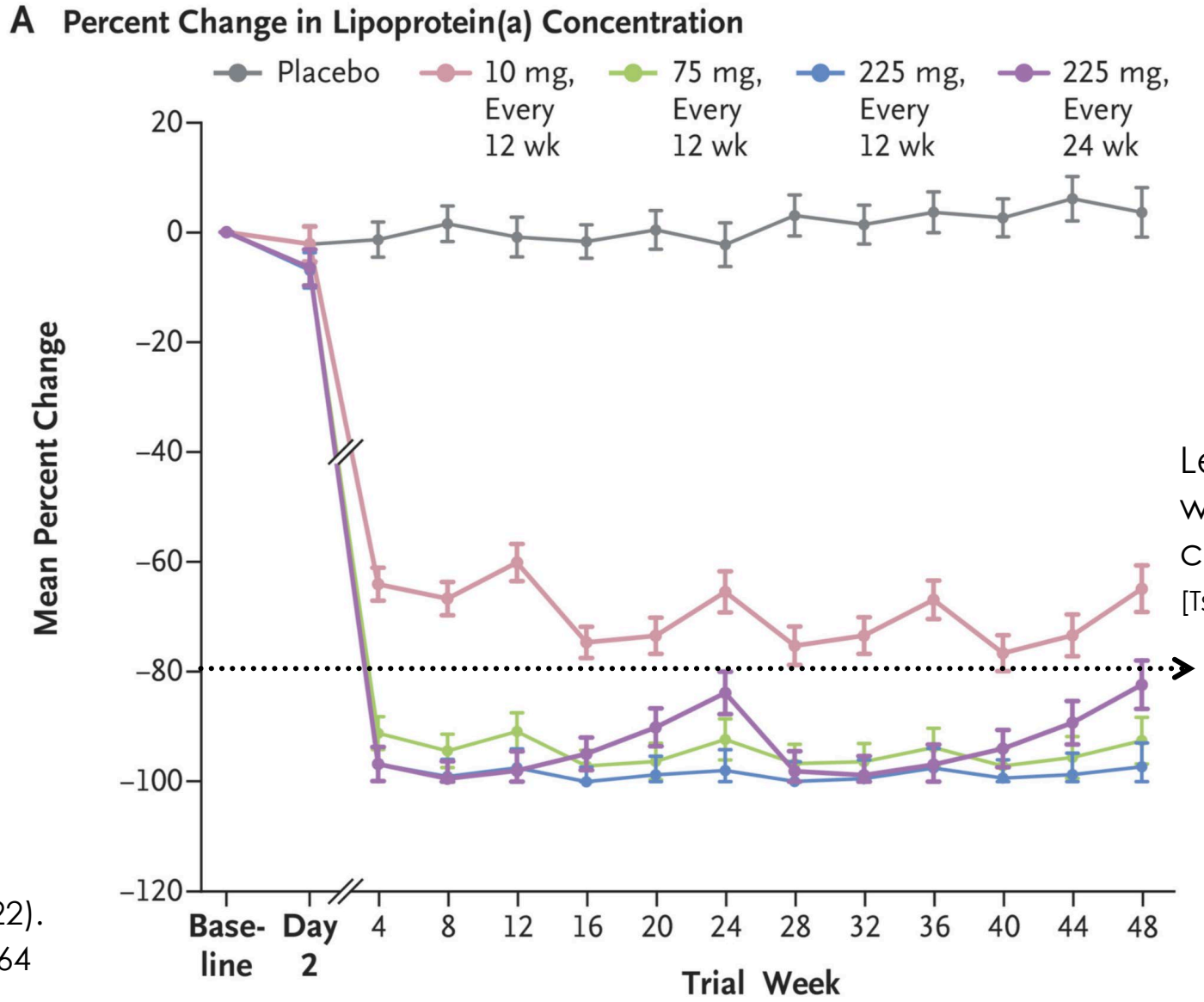
Profound Silencing of Lp(a) Expression with Olpasiran



Level of reduction achieved with WEEKLY dosing of competitor antisense

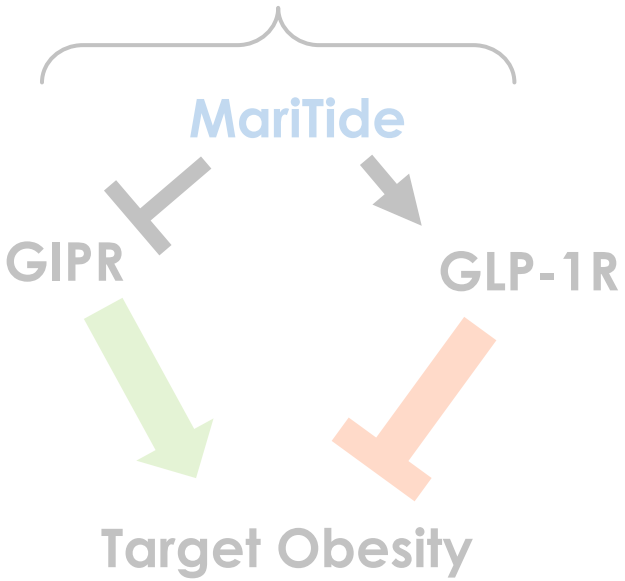
[Tsimikas et al (2020) NEJM 382, 244-55]

O'Donoghue et al. (2022). N Engl J Med 387:1855-64

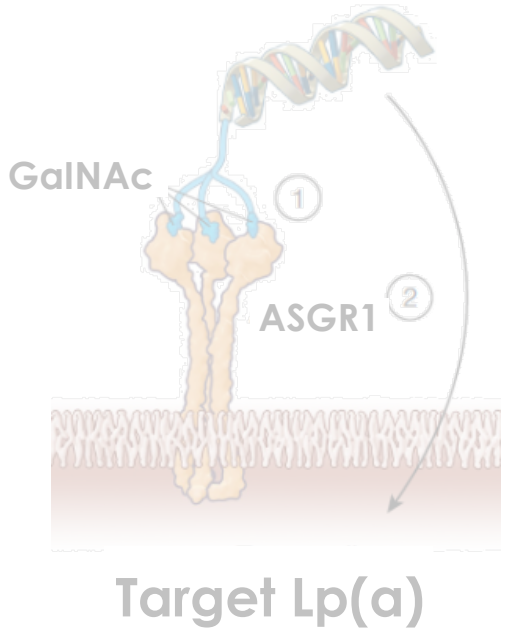
AMG 193 shows the potential power of a medicine that can only work in the presence of another factor

Multi-Actives
combat redundancy

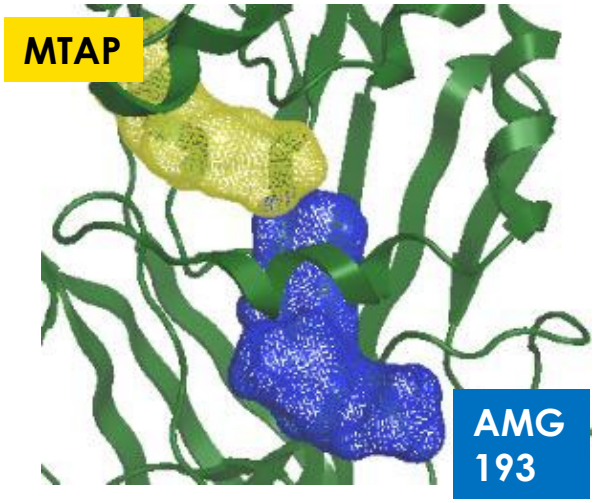
Disease modulators



'Tetherbodies'
enhance therapeutic index



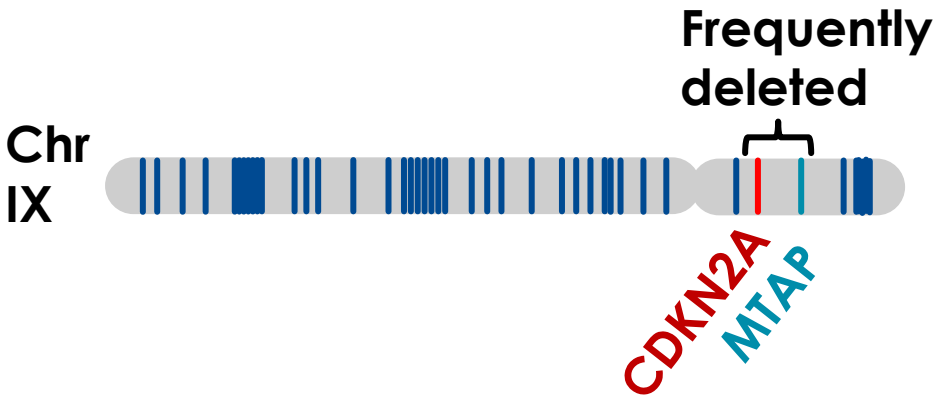
'Conditionals'
enhance therapeutic index

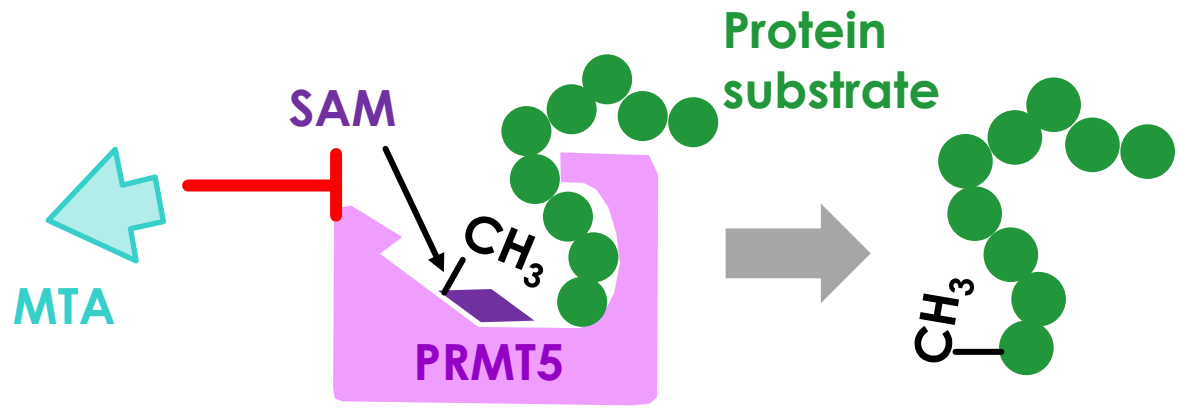


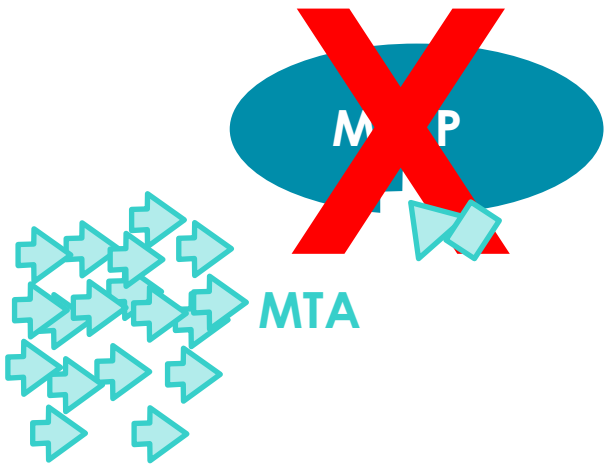
Target PRMT5

MULTISPECIFICS ENABLE US TO OVERCOME MAJOR CHALLENGES TO DRUG DEVELOPMENT

PRMT5: a candidate target in MTAP-deficient tumors



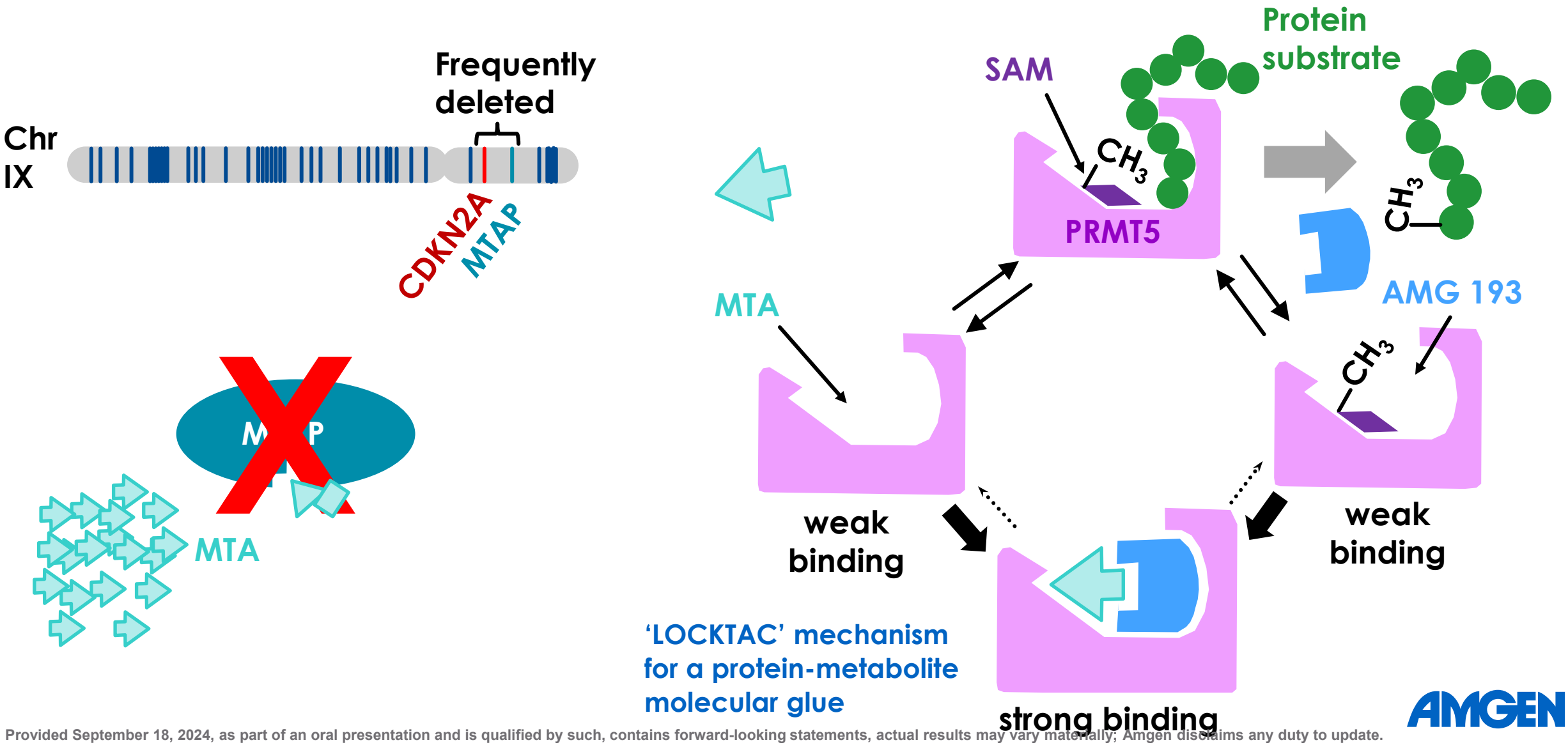




- PRMT5 is synthetic lethal with MTAP loss
- MTA is a weak, competitive inhibitor with SAM binding to PRMT5
- Global inhibition of PRMT5 has a small therapeutic index
- **Discovering a molecular glue that binds selectively to the inhibited PRMT5:MTA complex offers an opportunity to widen the therapeutic index**

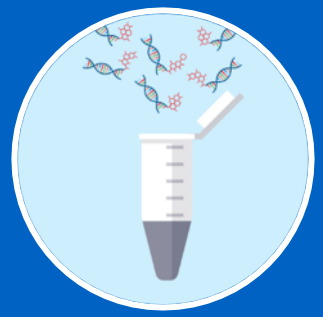
MTA = methylthioadenosine

PRMT5: a candidate target in MTAP-deficient tumors

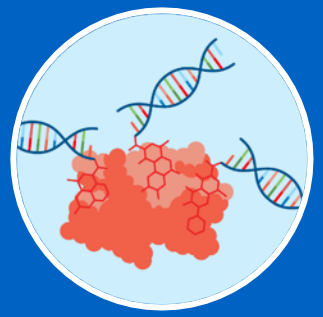


AMGEN's DNA-encoded Libraries Enable Screening Of Billions Of Compounds

Build DELs
from a massive library
of fragments



Billions of DNA-tagged small molecules, all in a single test tube



Enables us to screen for rare molecules that bind a target protein…

…whose identities are revealed by the sequence of the unique DNA barcode attached to each one

DEL= DNA encoded library

DNA ENCODED LIBRARIES ARE A CRITICAL TOOL FOR THE IDENTIFICATION OF NOVEL MULTISPECIFIC SMALL MOLECULE THERAPIES

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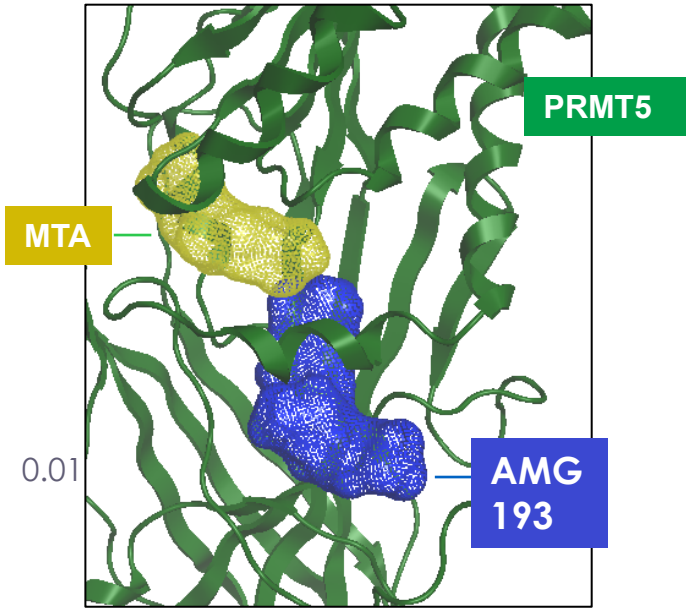
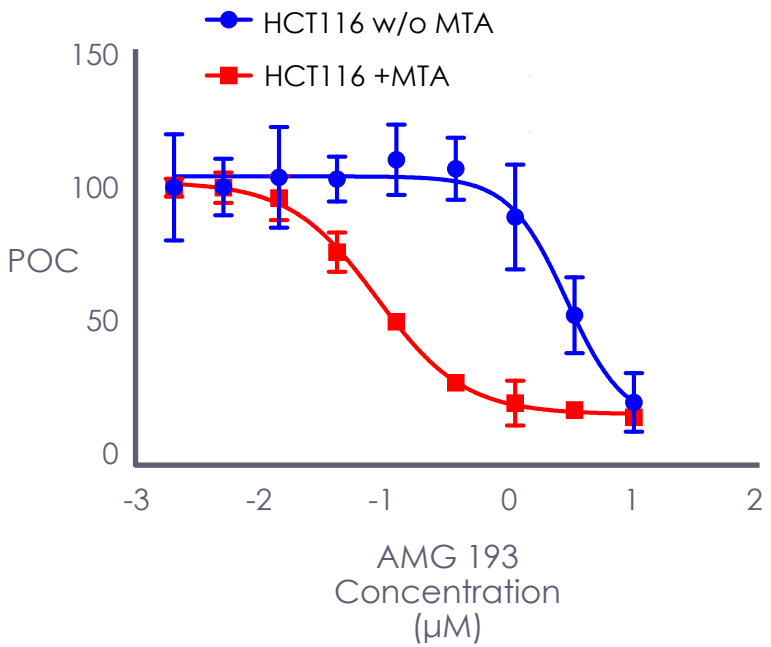
DNA Encoded Library Enabled Discovery Of A Multispecific That Selectively Targets PRMT5

Amgen PRMT5 inhibitors bind preferentially when MTA is present



AMG 193 has selective impact on viability in cells that accumulate MTA

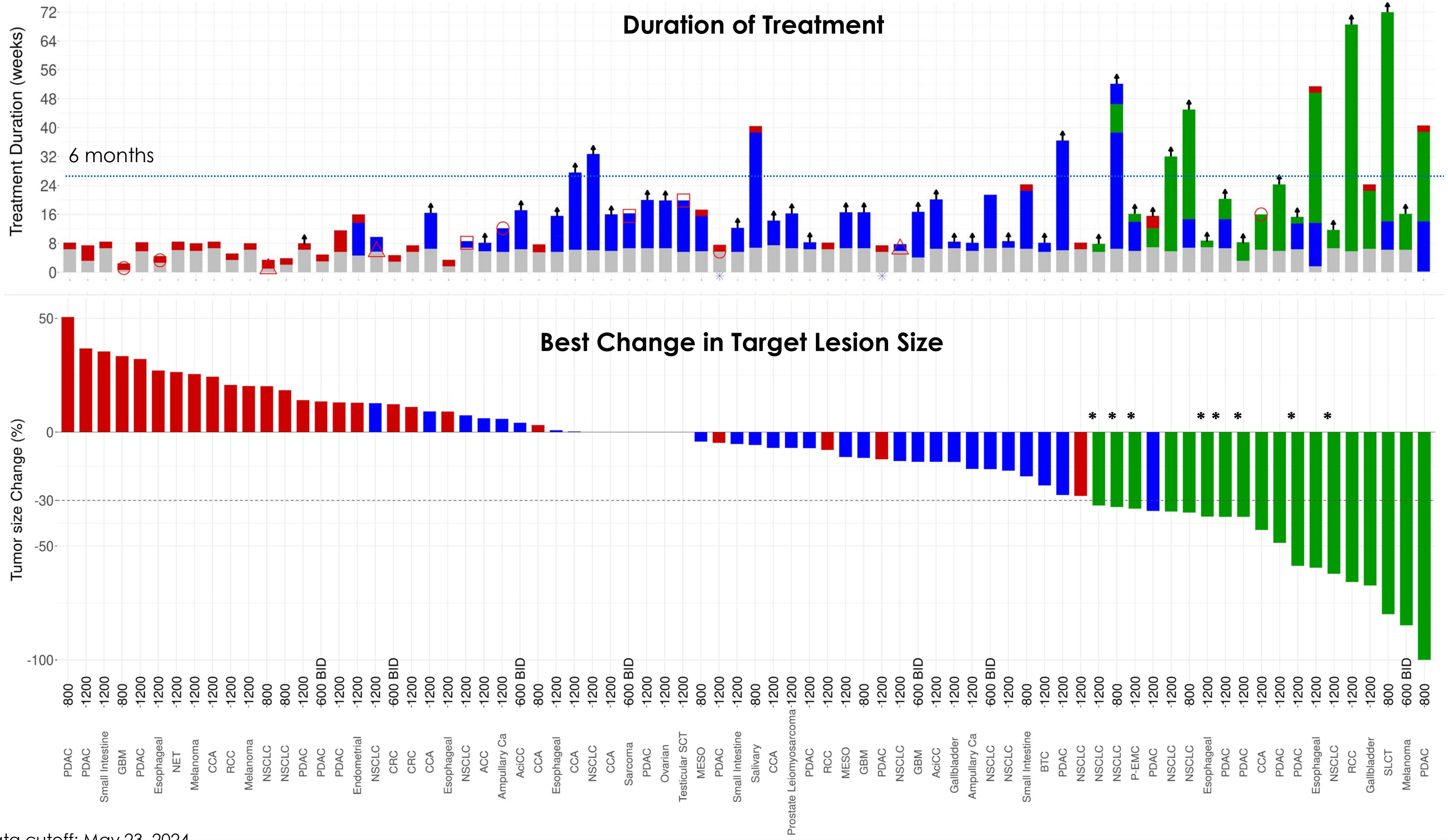


- Selectivity is critical
- First in clinic
- 10-20% of various solid tumors are MTA+

Cryo-EM Structure of PRMT5 bound to AMG PRMT5i and MTA
MTA = methylthioadenosine; PRMT5= protein arginine methyltransferase 5; WT= wild type

AMG 193: Change in Tumor Burden in Dose Exploration and Expansion at Active Doses

(800 mg QD, 1200 mg QD and 600 mg BID; N=76)



Best Overall Response in Dose Exploration and Expansion at Active Doses				
BOR	NSCLC (n = 17)	PDAC (n = 23)	BTC (n = 19)	E/G (n = 6)
CR	0	0	0	0
cPR	2	2	2	1
uPR	3	3	0	1
SD[a]	6	4	8	2
PD	3	8	3	2
NE[b]	3	6	6	0

* denotes unconfirmed PR with potential to confirm at time of data cutoff. Assessments were performed according to RECIST v1.1 based on local reads. [a] excluding 'uPR'. [b] includes 'not evaluable' scans and scans 'not done'. Median follow-up time (dose exploration and expansion at active doses): 4.5 months (95% CI: 4.0–5.5).

○ AE-related discontinuation
△ Patient withdrew
□ Clinical progression
→ Treatment Ongoing

Pre-scan
PR
SD
PD

Data cutoff: May 23, 2024

ACC, adenoid cystic carcinoma; AciCC, acinic cell carcinoma; AE, adverse event; BID, twice daily; BTC, biliary tract cancer; CCA, cholangiocarcinoma; CI, confidence interval; cPR, confirmed partial response; CR, complete response; CRC, colorectal cancer; E/G, esophageal/gastric tumors; GBM, glioblastoma multiforme; MESO, mesothelioma; NE, not evaluable; NET, neuroendocrine tumor; NSCLC, non-small cell lung cancer; PD, progressive disease; PDAC, pancreatic duct adenocarcinoma; P-EMC, pulmonary epithelial-myoepithelial carcinoma; QD, once daily. RCC, renal cell carcinoma; RECIST, Response Evaluation Criteria in Solid Tumors; SCT, Sertoli cell tumor; SD, stable disease; SLCT, Sertoli-Leydig cell tumor; uPR, unconfirmed partial response.

Blinatumomab shows the power of what a 'matchmaker' medicine can do

Multi-Actives
combat redundancy

Disease modulators

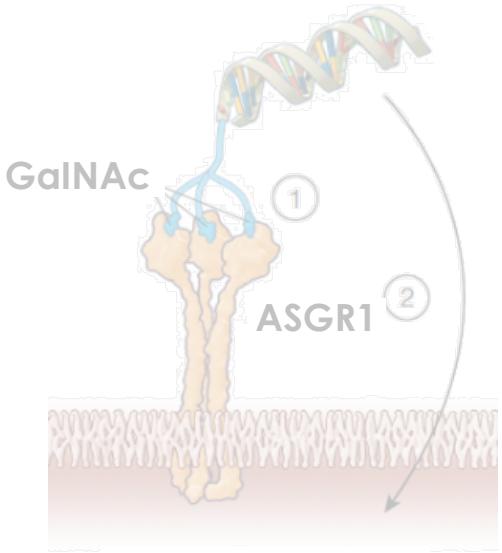
MariTide

GIPR

GLP-1R

Target Obesity

'Tetherbodies'
enhance therapeutic index



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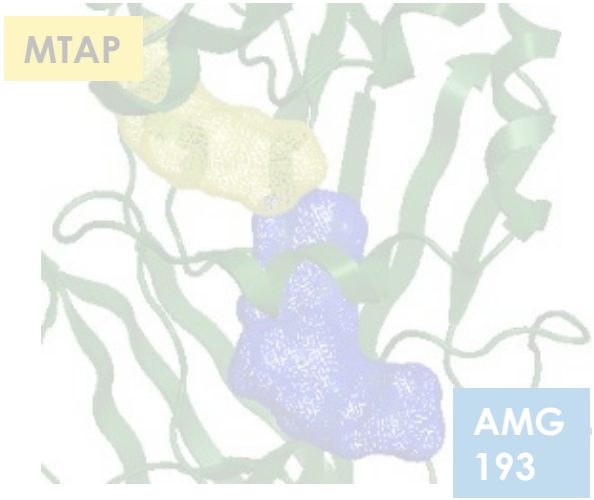
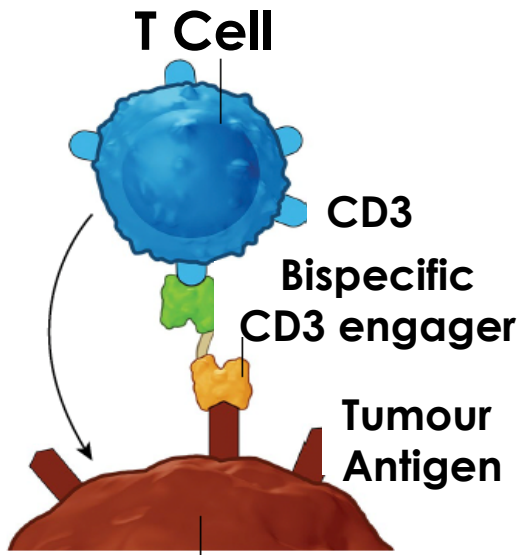


Target PRMT5

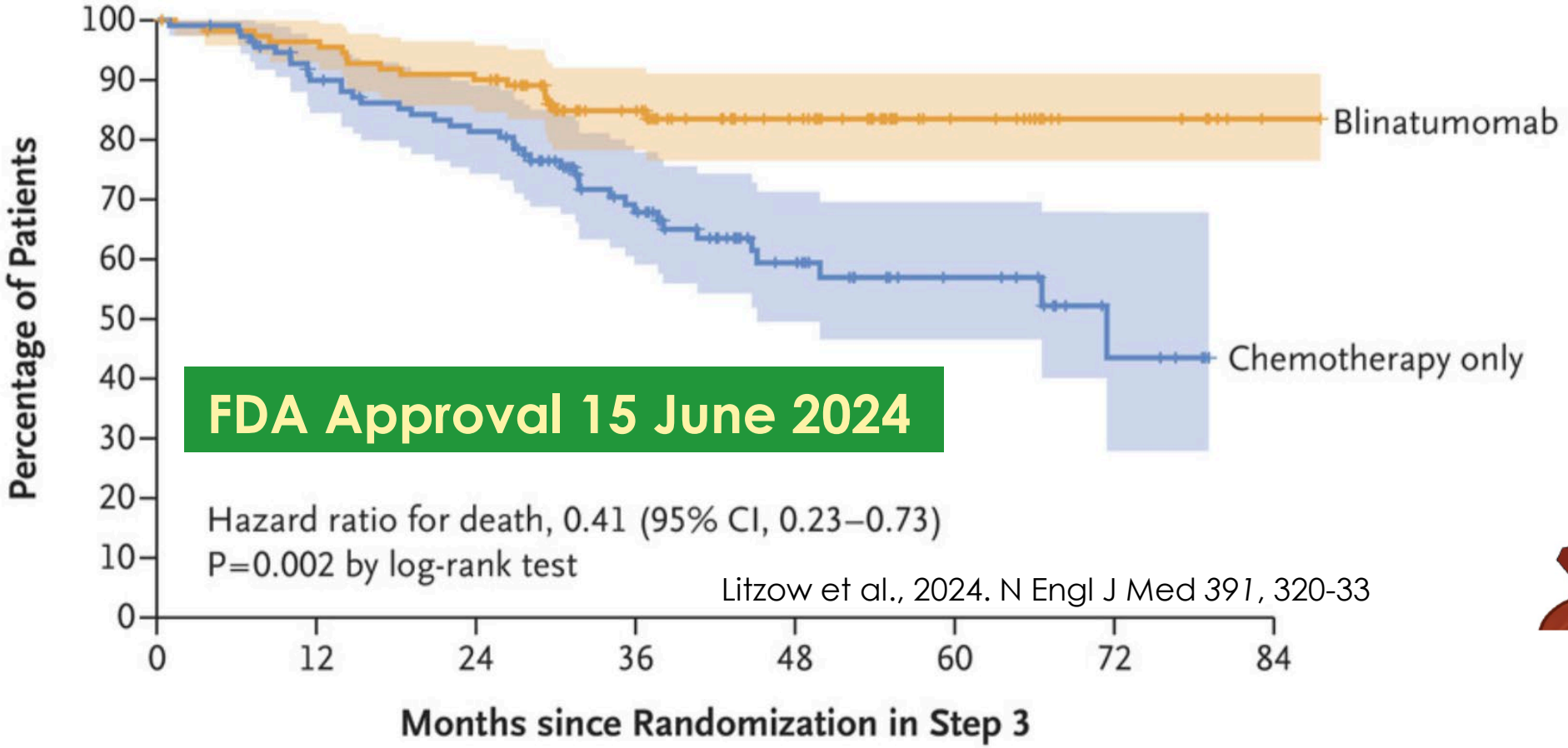
'Matchmakers'
recruit help to drug difficult targets

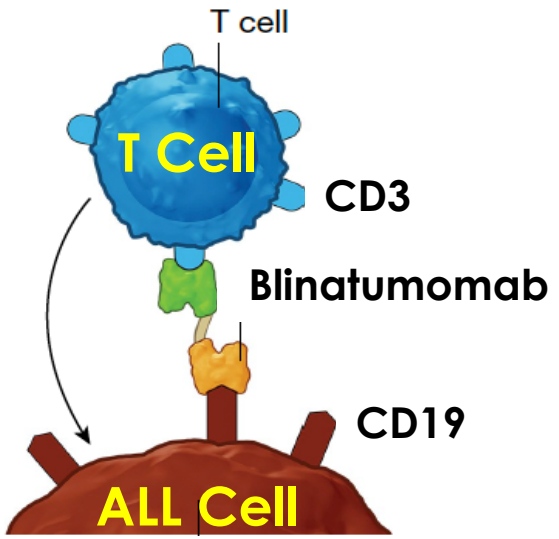


Target Tumor Cell

MULTISPECIFICS ENABLE US TO OVERCOME MAJOR CHALLENGES TO DRUG DEVELOPMENT

Survival Rate for MRD-negative ALL Patients Treated with 'Matchmaker' Blinatumomab as Consolidation Therapy





+FDA approval of BiTE® molecule IMDELLTRA™ tarlatamab-dlle for ES-SCLC on or after platinum-based chemo

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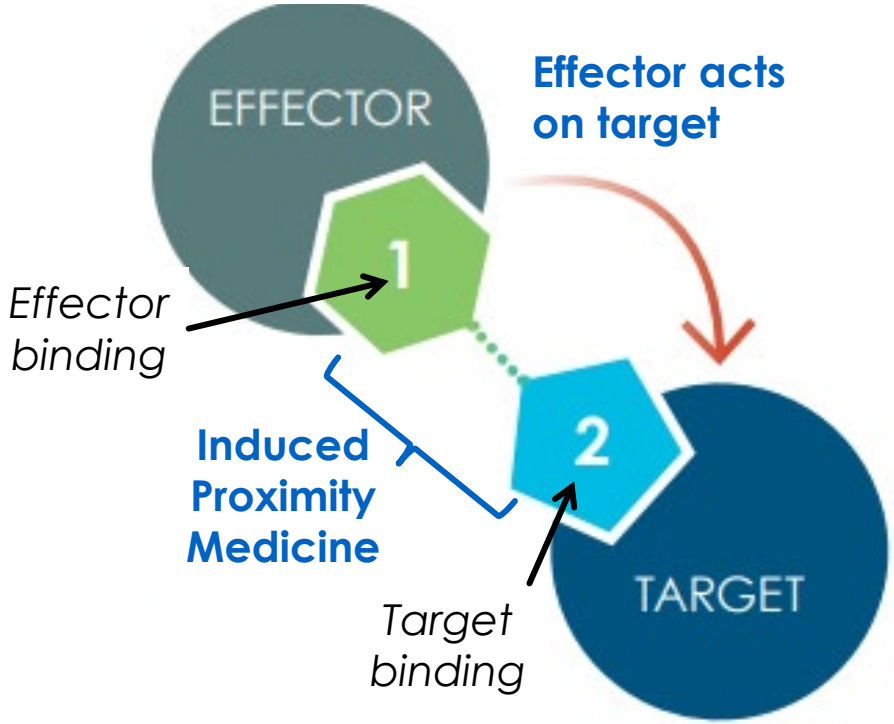
Induced Proximity: A General Approach to Drug Difficult Targets

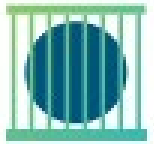
An **induced proximity matchmaker medicine** has **two parts**:



Target outcomes (depending on the nature of the **effector**):

Destruction
eg. Ligase, T cell

Activation
eg. Kinase



Inactivation
eg. Phosphatase

Relocalization
eg. Cytoskeleton

MULTISPECIFIC INDUCED PROXIMITY MOLECULES EXPAND THE DRUGGABLE GENOME BY LEVERAGING THE CELL'S NATURAL POWERFUL MACHINERY

How are we going to discover and engineer tomorrow's multispecific medicines?

AMGEN's DNA-encoded Libraries Enable Screening Of Billions Of Compounds

Build DELs
from a massive library
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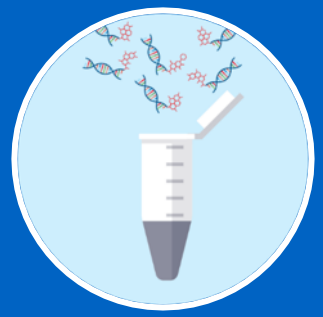
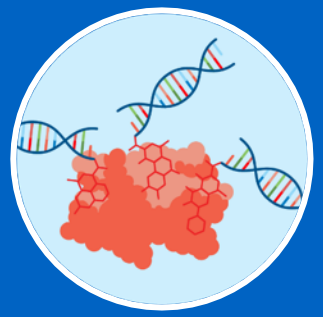


Billions of DNA-tagged small molecules, all in a single test tube



Enables us to screen for rare molecules that bind a target protein…

…whose identities are revealed by the sequence of the unique DNA barcode attached to each one

DEL= DNA encoded library

DNA ENCODED LIBRARIES ARE A CRITICAL TOOL FOR THE IDENTIFICATION OF NOVEL MULTISPECIFIC SMALL MOLECULE THERAPIES

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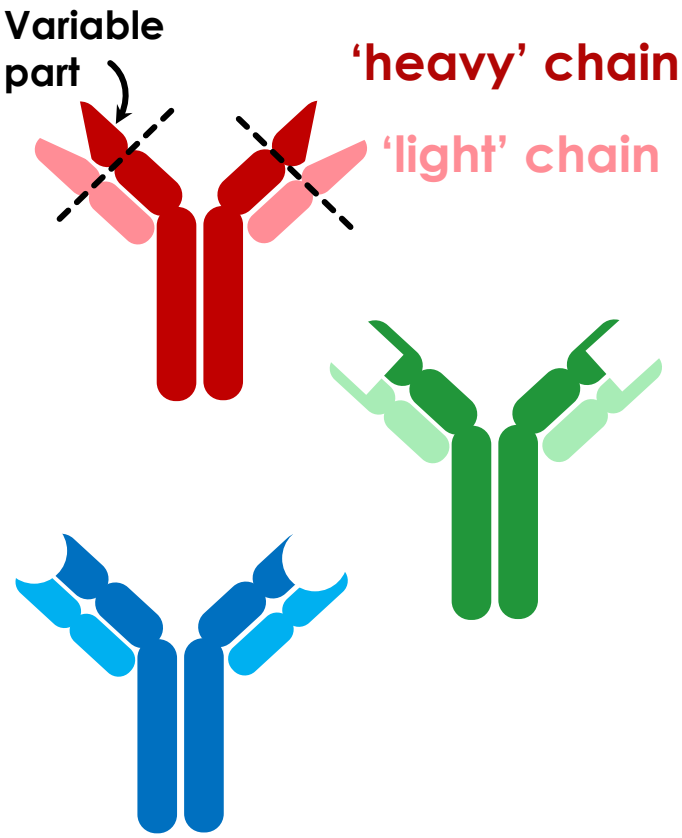
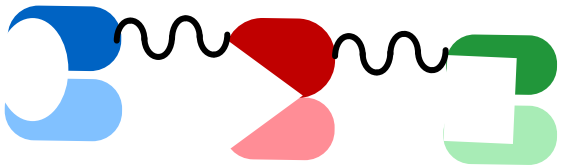
Generating Complex Multispecifics With UniDabs

Antibodies



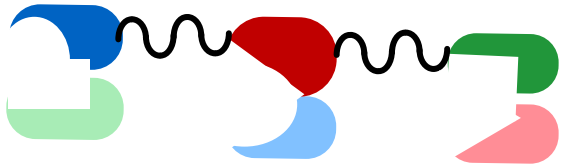
Antibodies bind shapes

What we'd like to do



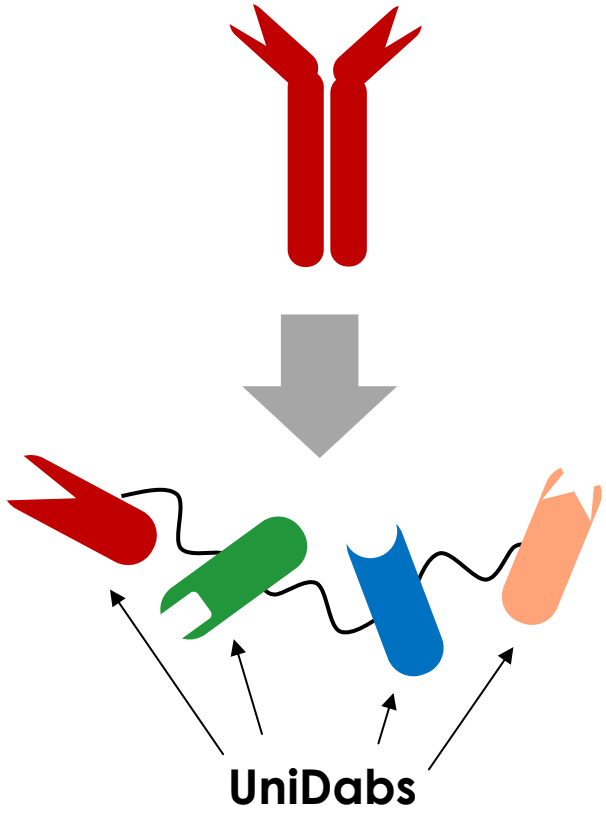
String together different shape-binders in their natural state to create multispecifics

What we'd end up with



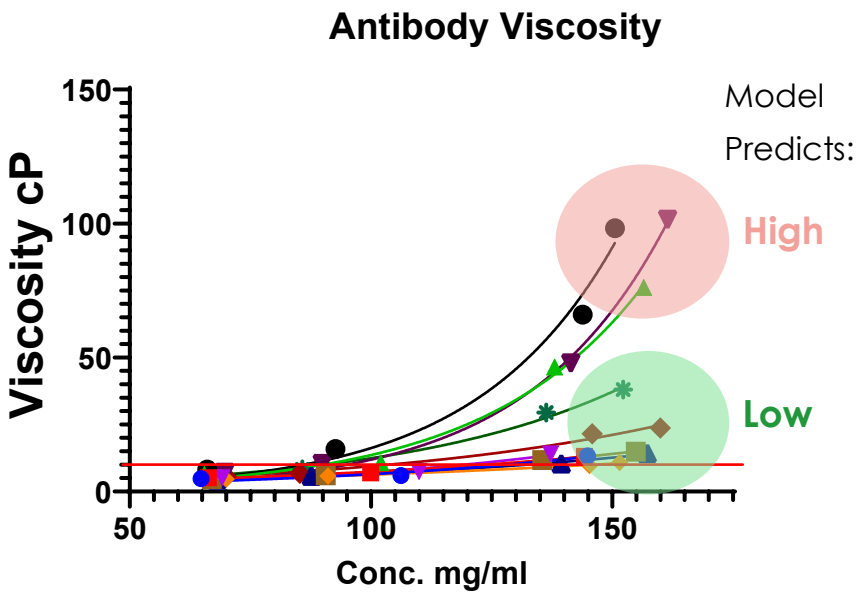
Light chains pair randomly with heavychains to yield a mess

Single (heavy) chain mAbs solve the problem



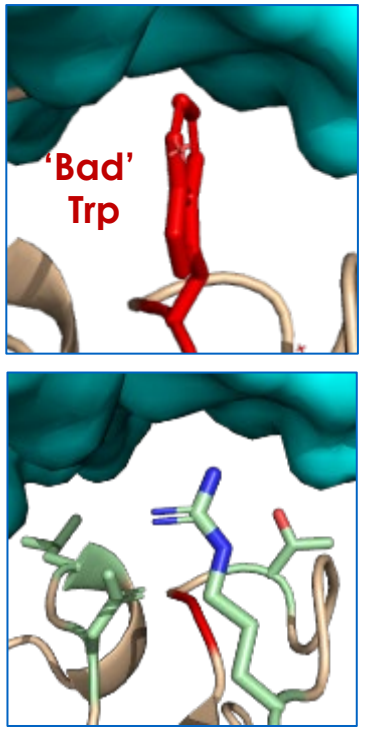
Machine Learning (ML) & Generative Artificial Intelligence (GenAI) are Enabling Discovery of Better Biologics, Faster

Machine learning predicts properties, enabling us to weed out undesirables efficiently



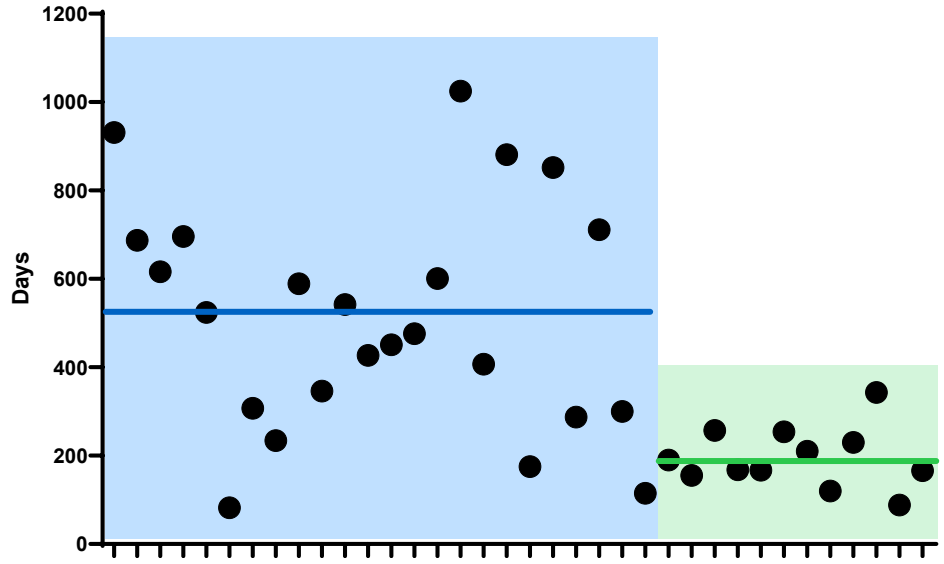
Viscosity: model vs. measure

GenAI gets us to molecules that humans can't



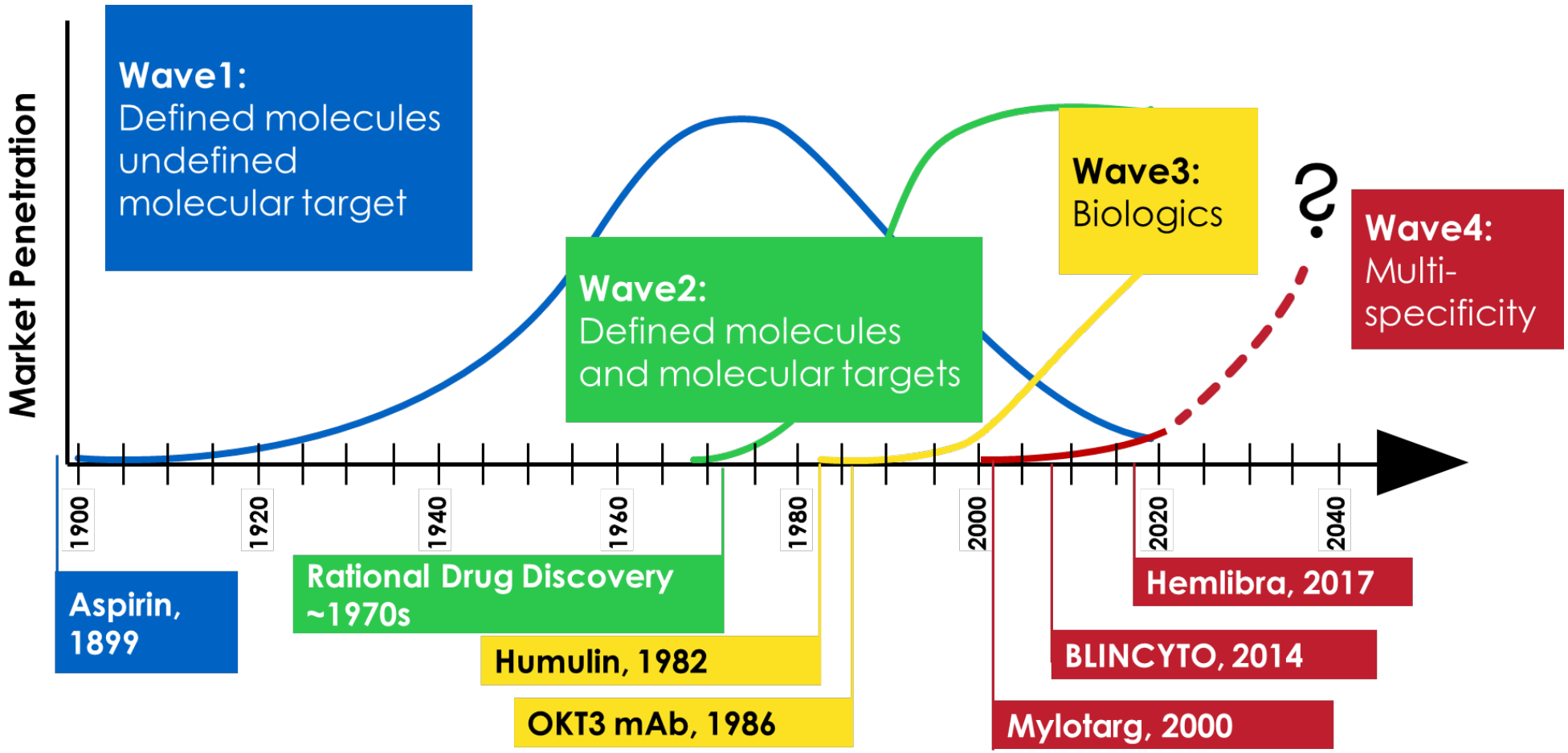
9 mutation interface redesign. Score: humans 5, GenAI 4. We're winning, but not for long!!!

Putting it together and adding special sauce (automation, process improvement)

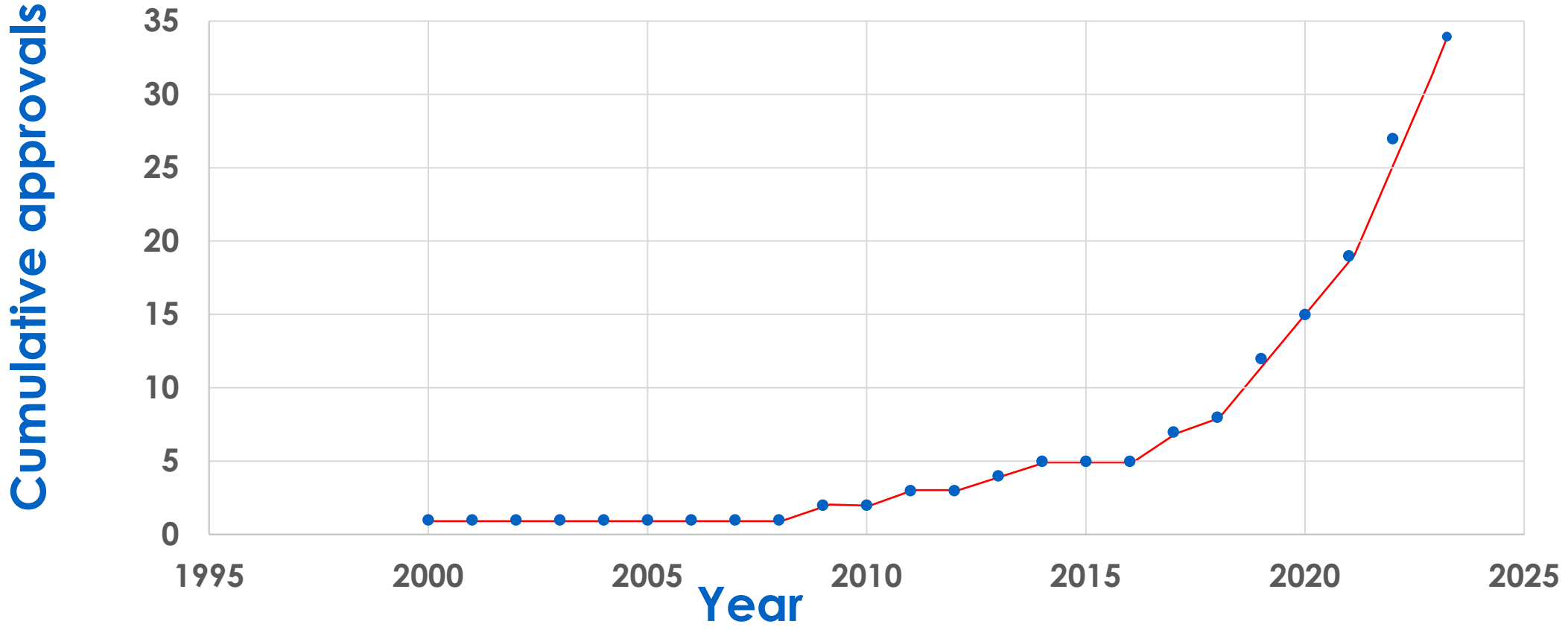


~3x faster to clinical candidate

What is the Status of the '4th Wave' of Biopharma Innovation?



The Fourth Wave of Transformative Biopharmaceutical Innovation – Multispecific Drugs – Is Cresting!



THE FUTURE IS HERE: 3 OF 105 NMEs IN 2017-18 WERE MULTISPECIFIC, BUT 8 OF 37 IN 2022!!!

Half of all multispecific approvals have happened since April 2021. 60% since 03/2020

Thank you!