Drug Discovery: Matching target biology with the right modality

September 2026

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Driven by innovation and curiosity, we create molecules that matter

The physics of our industry: long cycles, low probabilities, high capital intensity

10-15[1)]

years

from idea to market approval

~1 %[1)]

chance

for a project entering D1 to reach approval

$2.7 bn[3)]

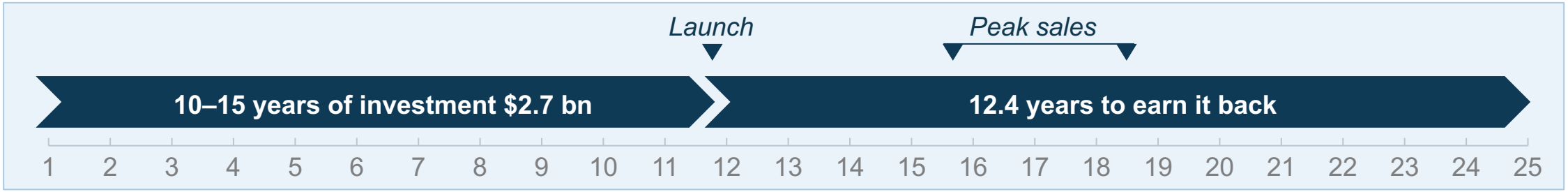
R&D spend

per approved drug from discovery to launch (incl. attrition)

12.4[4)]

years

average effective market exclusivity after launch



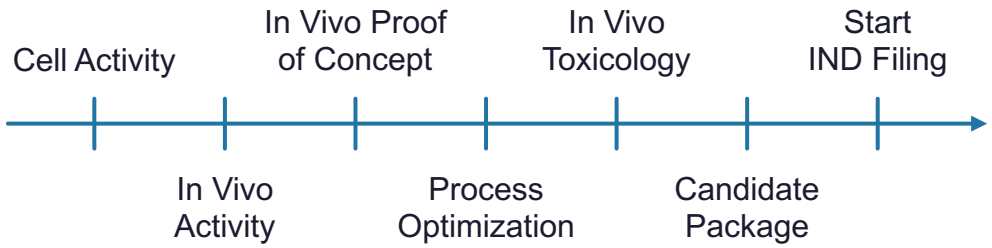
The question is not whether R&D output moved last year, but whether the innovation engine that produces output runs consistent and reliable

1) KMR industry benchmark from period 2023-25 from D1 to approval, 15 Ay. 2) KMR industry benchmark from period 2020-24 from D1 to approval. 3) Deloitte (05/2026) 'Measuring the return from pharmaceutical innovation'. 4) JAMA Intern. Med. 2015, 175, p. 635-638

Drug Discovery – what, like it's hard?

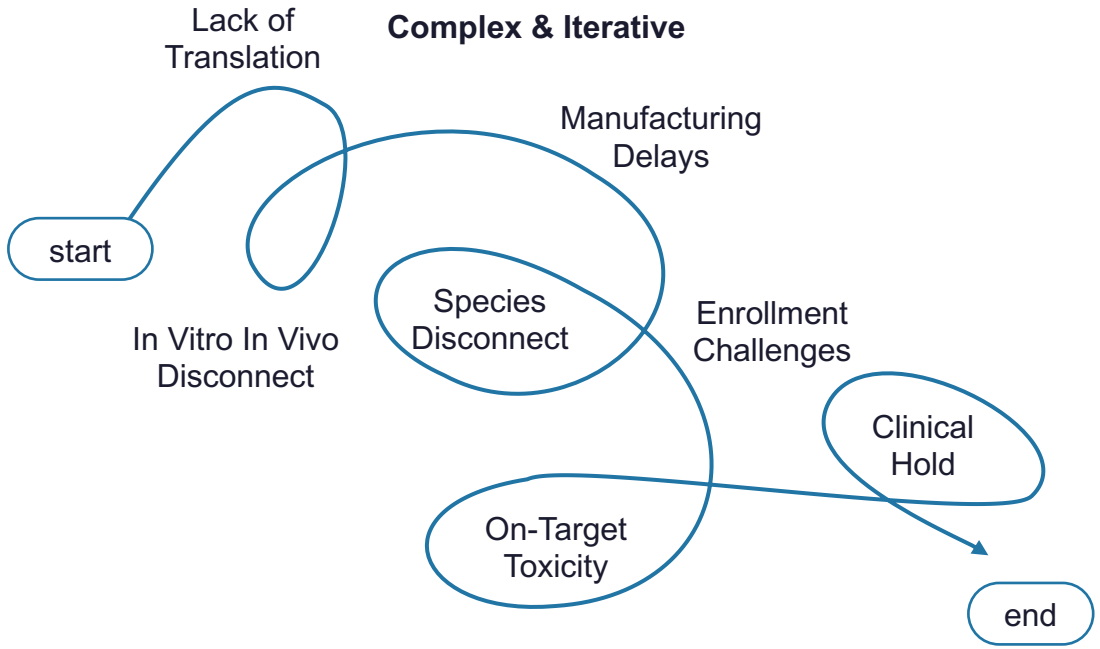
The Ideal Scenario

Linear & Predictable



The Reality

Complex & Iterative



Drug discovery is not guided by blueprints: it's driven by trial, error, and testing.

Our heritage:

- *Experience*
- *Expertise*
- *Evidence*

A history of ~165 years of innovation…



…and continuing

Kerendia® finerenon

NUBEQA® (darolutamide) 300 mg tablets

Xofigo® radium Ra 223 dichloride INJECTION

EYLEA® (aflibercept) Injection

Xarelto® Rivaroxaban

Next wave of innovation

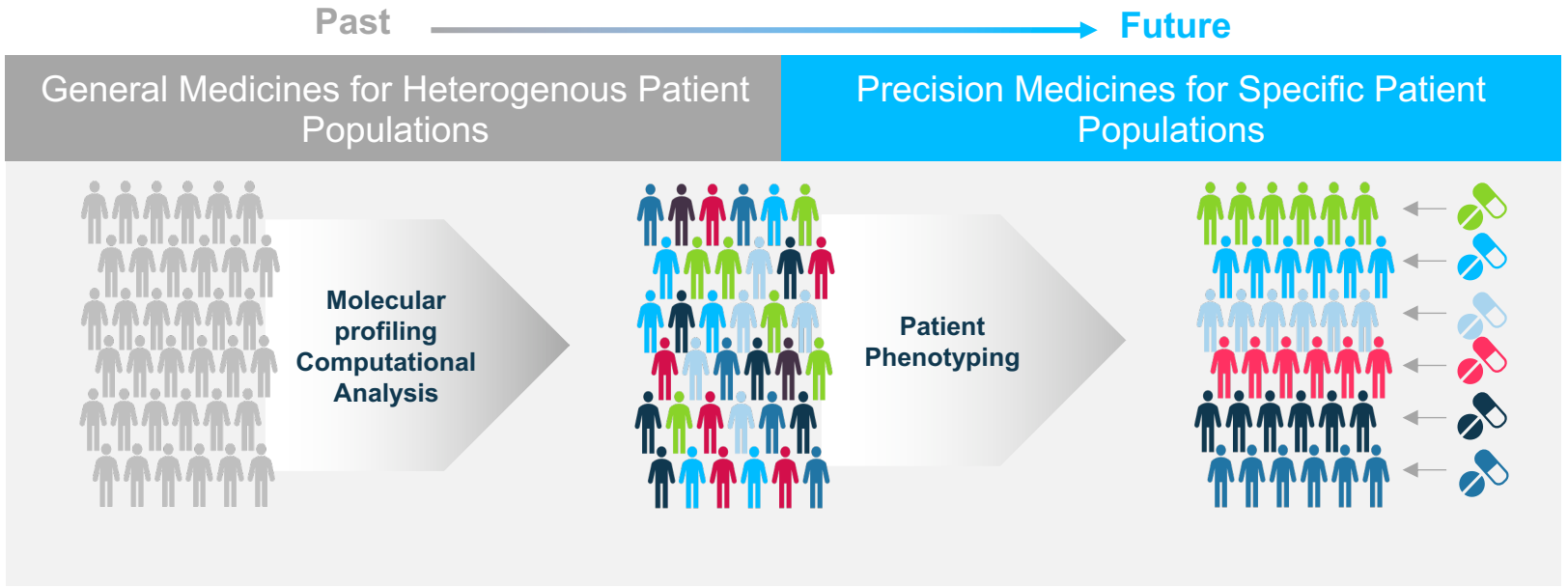
Through precision medicine, we meet the needs of patients and identify high impact and commercially viable programs

Precision medicine mandate

Delivering the **right treatment** at the **right time** to the **right patient**, addressing individual patient's needs to achieve optimal health

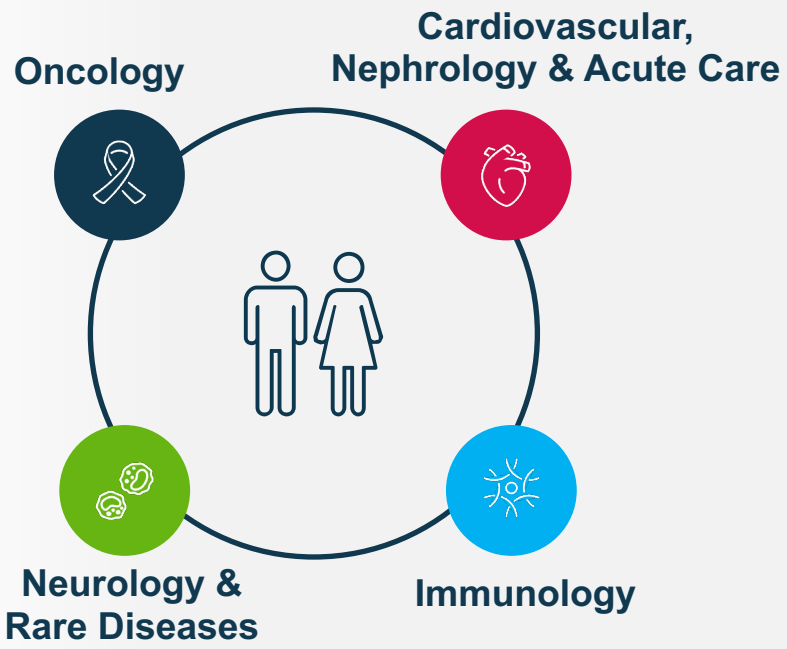
Precision medicine

Right Target + Biology + Defined patient + Measurable impact



Drug Discovery Sciences drives the creation of new medicines for patients

Focus areas for early innovation, with patient at the center…



Redefinition of diseases & changing treatment paradigms

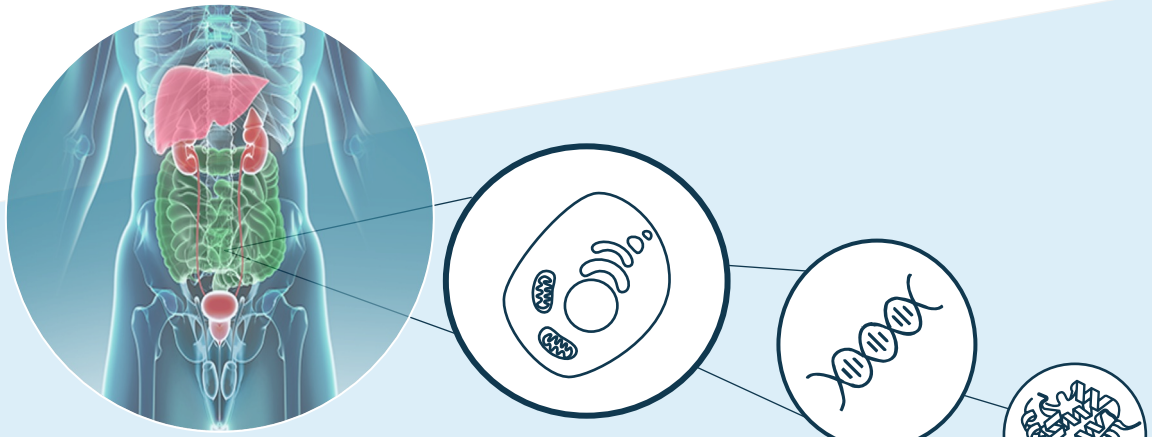
…to create molecules that matter



Image source: commons.wikimedia.org/wiki/File:202202_Protein_monochrome.svg

Starting point of research & development to tackling people's unmet medical needs





Small Molecules

Protein Therapeutics

Radio-therapies

Peptides

Cell Therapies

RNA Therapies

Gene Therapies

Digital Technologies

A dramatic shift in Drug Discovery

Leading us to new target space & molecular MoAs

From Traditional

Target space: Kinases, GPCRs, ion channels, nuclear receptors

Intervention: Small molecules & antibodies

Adempas riociguat · Adalat · NUBEQA (darolutamide) 300 mg tablets · Kerendia finerenone · Nexavar (sorafenib) tablets



To Expanding druggable Space

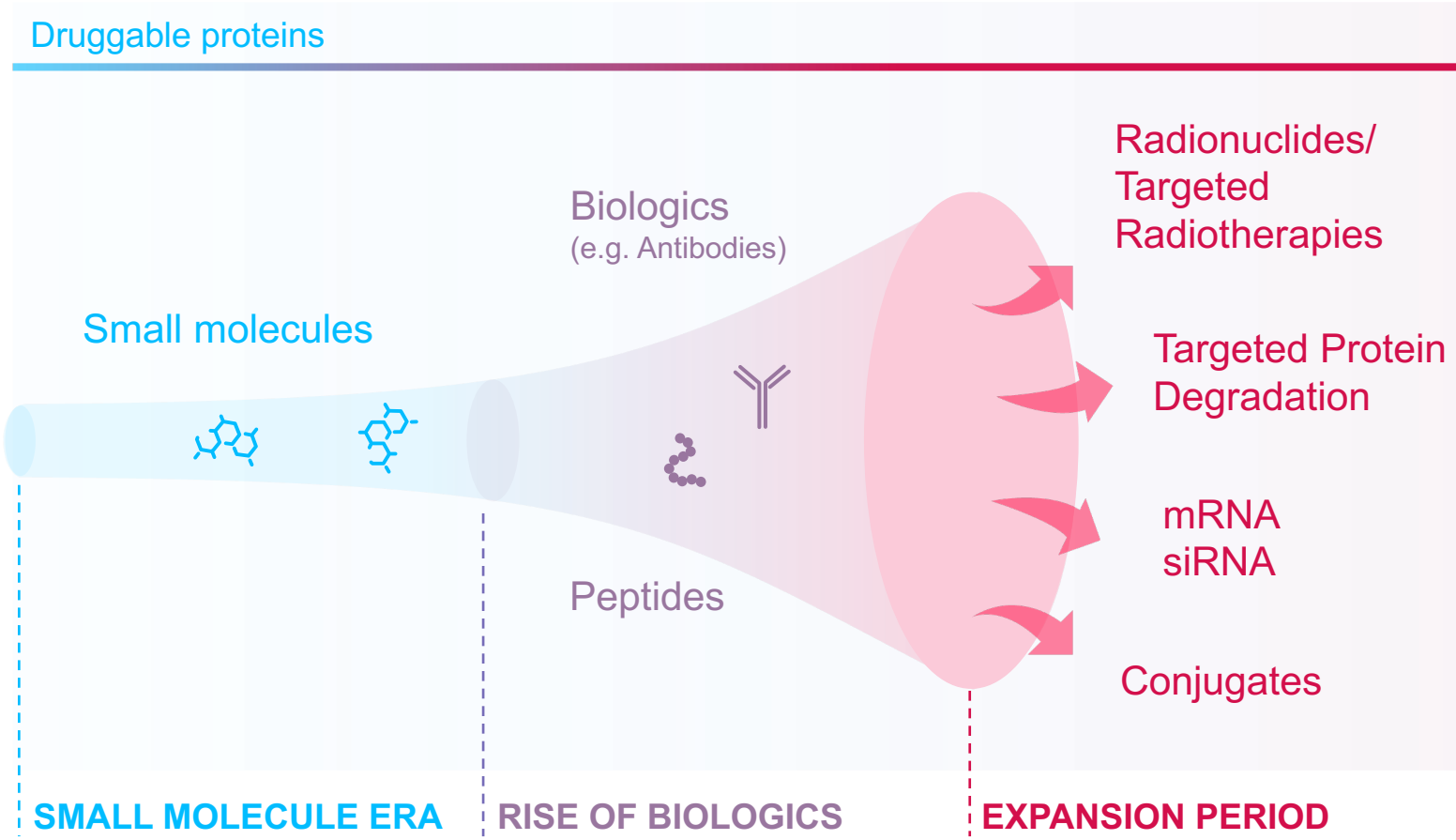
Target space: Transcription factors, scaffolding proteins, RNA & RNA-binding proteins, protein complexes

Intervention: Degraders, gene therapy, cell therapy, oligos

Image source: cbdm-01.zdv.uni-mainz.de/~galanisl/netbio/ (modified)

From Few to Many

What the modality revolution means for Drug Discovery



UNLOCKING UNDRUGGABLE BIOLOGY

- // Full target coverage – including previously inaccessible biological targets
- // Broad accessibility across all organs & tissues
- // Improved safety profiles – including for vulnerable & paediatric populations

DDS is driving innovation at four sites in Europe and the US





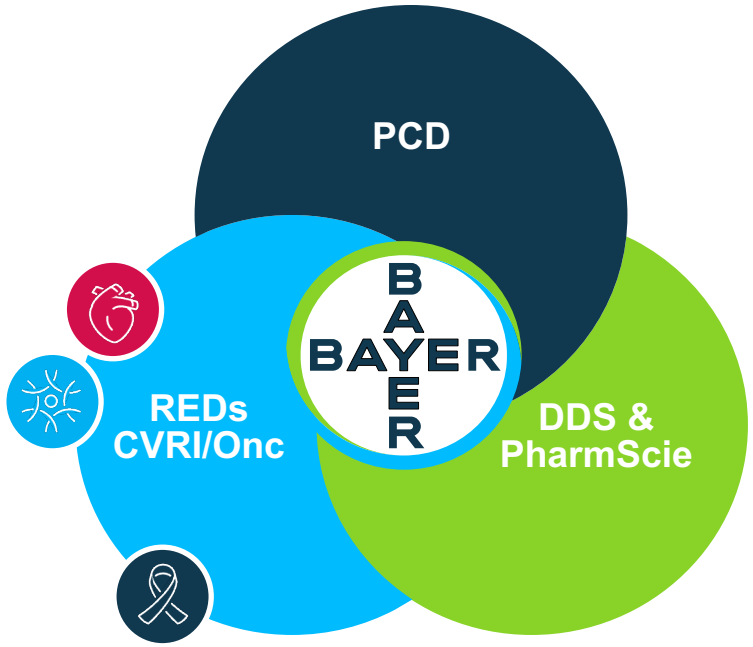




A strong innovation ecosystem, built on internal core capabilities, cutting-edge technology platforms, and external innovation

Overview Innovation Ecosystem

Internal innovation system

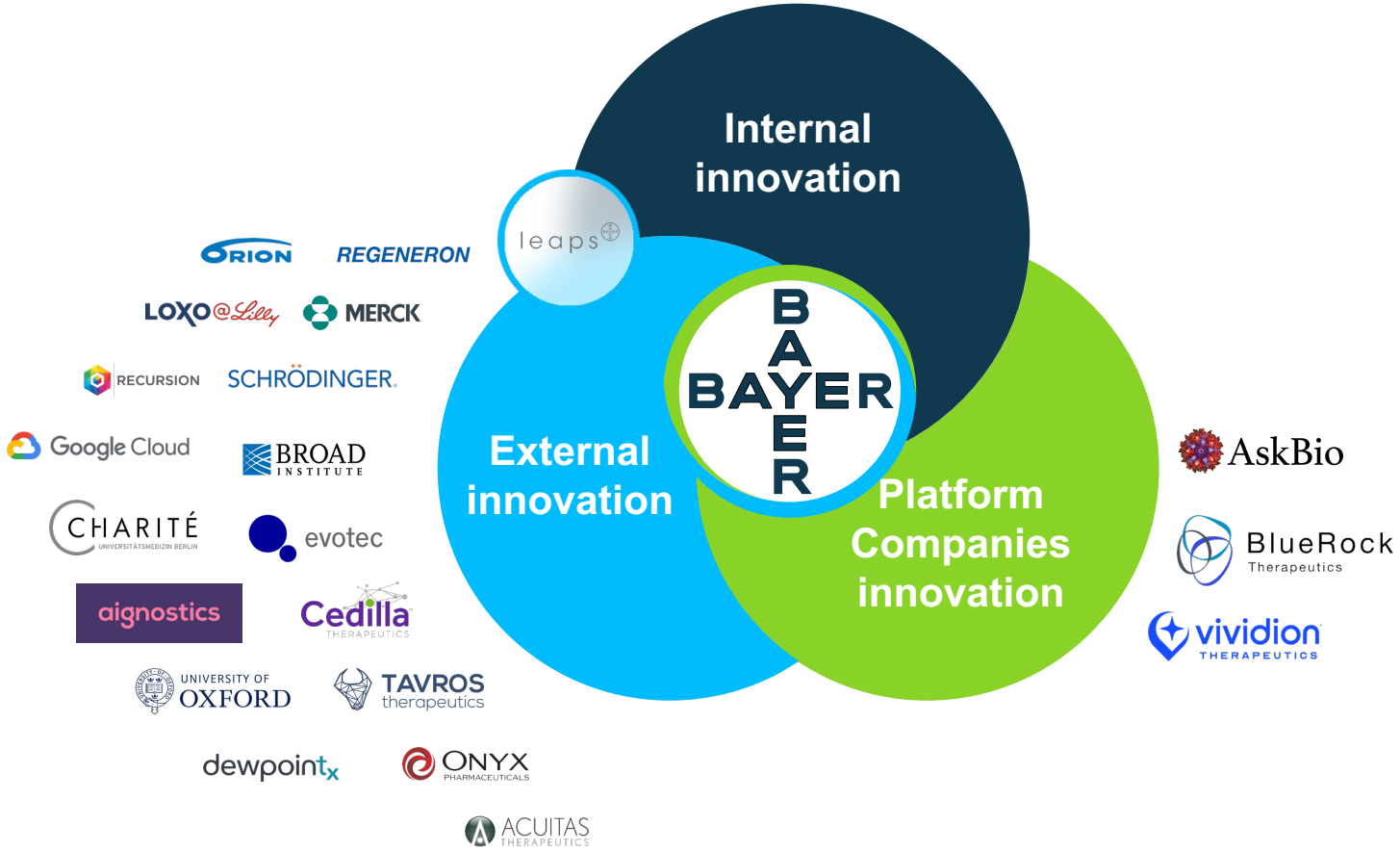


Key technology platforms *(non-exhaustive)*

RED	**Research & Early Development:** addressing the undruggable space
PCD	**Preclinical Development:** DMPK, toxicological profiling for all projects
DDS	**Drug Discovery Sciences:** In close collaboration with REDs discovery and characterization of molecules
PharmScie	**Pharmaceutical Sciences:** Early CMC starting prior to PCC in close collaboration with CMC Tech team in PS

Collaboration is a key lever to deliver on novel innovation and increases the chances of success significantly

Building on 160 years of innovation, we've significantly transformed our organization and shaped our strategy



- Revitalizing our internal innovation engines
- Most advanced cell & gene therapy capabilities
- Game-changing collaborations & partnerships
- Diverse and experienced new leadership team

What we do – and what we leave to others

What we do in industry

- Connect to patient early
- Discovery of therapeutic molecules
- Safe clinical development

What we leave to biotech and academia

- Very early research
- High-risk endeavours
- Next gen tech development

How we collaborate with academia & the biotech ecosystem

Co.Lab CONNECT

Lab space for start-ups in Berlin, Boston, Kobe, Shanghai

leaps by Bayer

Bayer's strategic investment unit funding disruptive innovations

CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN

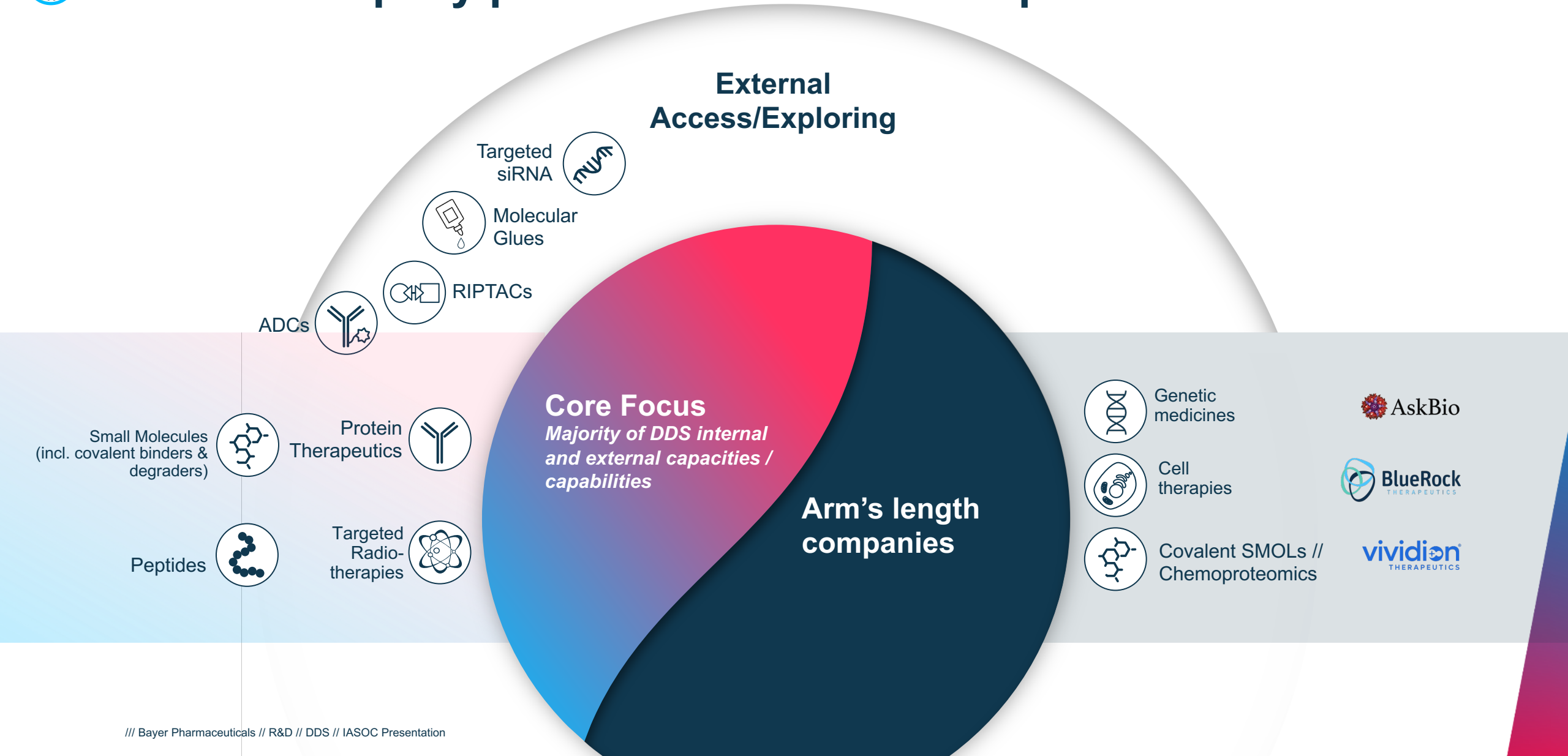
PEKING UNIVERSITY

Tsinghua University

BROAD INSTITUTE

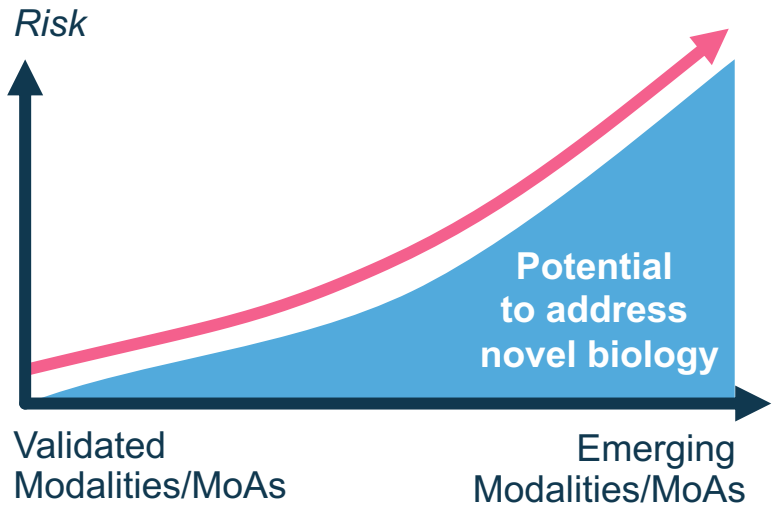
Academic Collaborations

We are uniquely positioned to deliver on patients' needs



While Novel Modalities & MoAs unlock undruggable biology, drug discovery undergoes a rapid evolution

New Modalities/MoAs



Unlocking undruggable biology



Evolving Drug Discovery Paradigm

Past

- Internal research silos
- Few modalities and targets
- Traditional screening methods
- Manual hypothesis generation

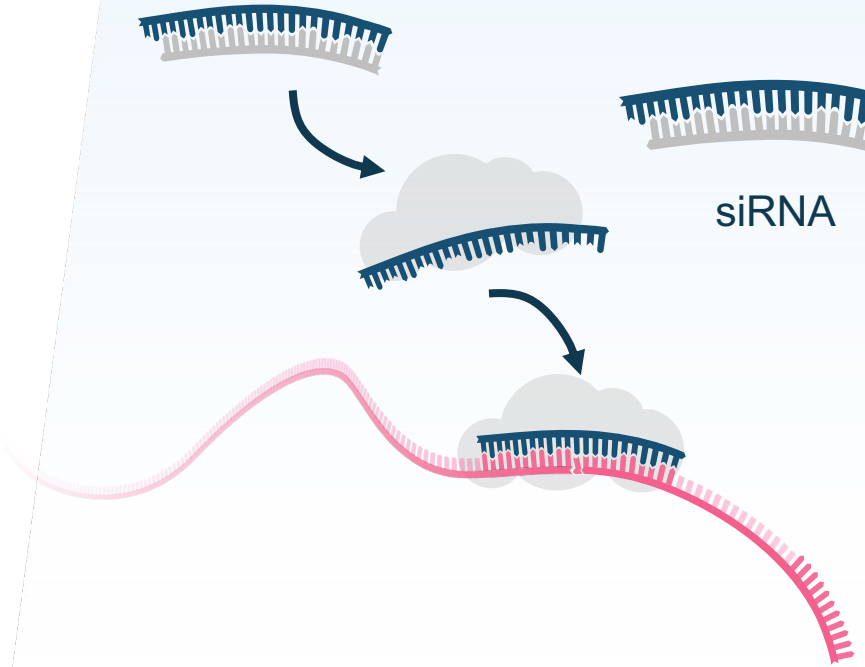
Future

- Co-creation across ecosystem
- AI-augmented drug discovery
- Data-rich, predictive platform
- Automated, model-informed hypotheses

What are targeted siRNAs and why we are excited about them?

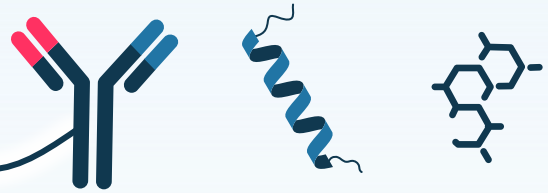
Advances in delivery are extending siRNA from liver-centric use to a multi-organ therapeutic platform

Therapeutic Effect

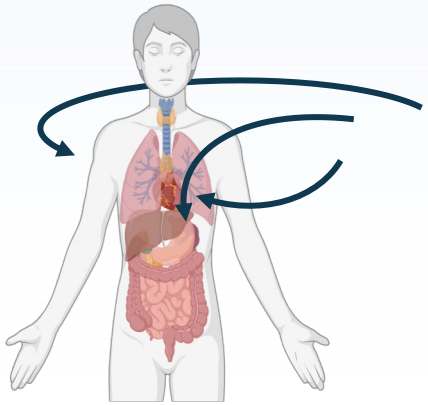


siRNA

Tissue Specificity



Antibody Peptide SMOL



Promise for Patients

- Cures for what was previously untreatable
- Kind medicines with established safety
- Less burden because of long-term activity

Image source: commons.wikimedia.org/wiki/File:MiRNA.svg (modified)

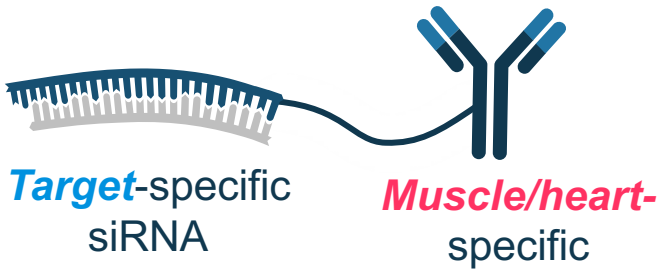
Precision siRNA to treat genetic dilated cardiomyopathy (DCM)

Genetic DCM patients need targeted therapy:

- High mortality with progressive heart failure and early loss of function
- Standard-of-Care only symptomatic treatment

World class CV organization… BAYER & SOUFFLÉ therapeutics ***…as partner of choice.***

- Deep cardiovascular disease expertise
- Global development & translational engine
- Scale, infrastructure & partnerships



- Precise delivery to heart/muscle
- Successful Proof-of-Concept in Cyno
- Own program progressing to clinical stage

Image source: commons.wikimedia.org/wiki/File:MiRNA.svg (modified)

CDK2: High selectivity overcomes liabilities of current assets in the clinic

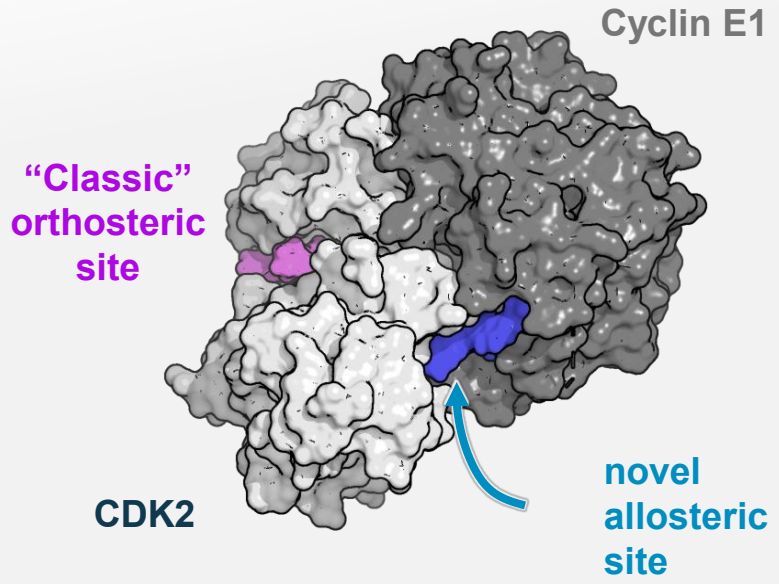
Our Opportunity

Mechanism
Inhibits the CCNE1/CDK2 complex with exquisite specificity, targeting CCNE1 amplified/ overexpressing tumours (e.g. ovarian) and CDK4/6 inhibitor emerging resistance (e.g. breast cancer)

Breakthrough potential
Highly selective CCNE1/CDK2 inhibitor with potential for best-in-class therapeutic window and combinability, supporting improved benefit and quality of life for cancer patients

Patient need
CCNE1 overexpression in ovarian cancer and acquired resistance to CDK4/6 class inhibitors in breast cancer result in limited overall survival for patients

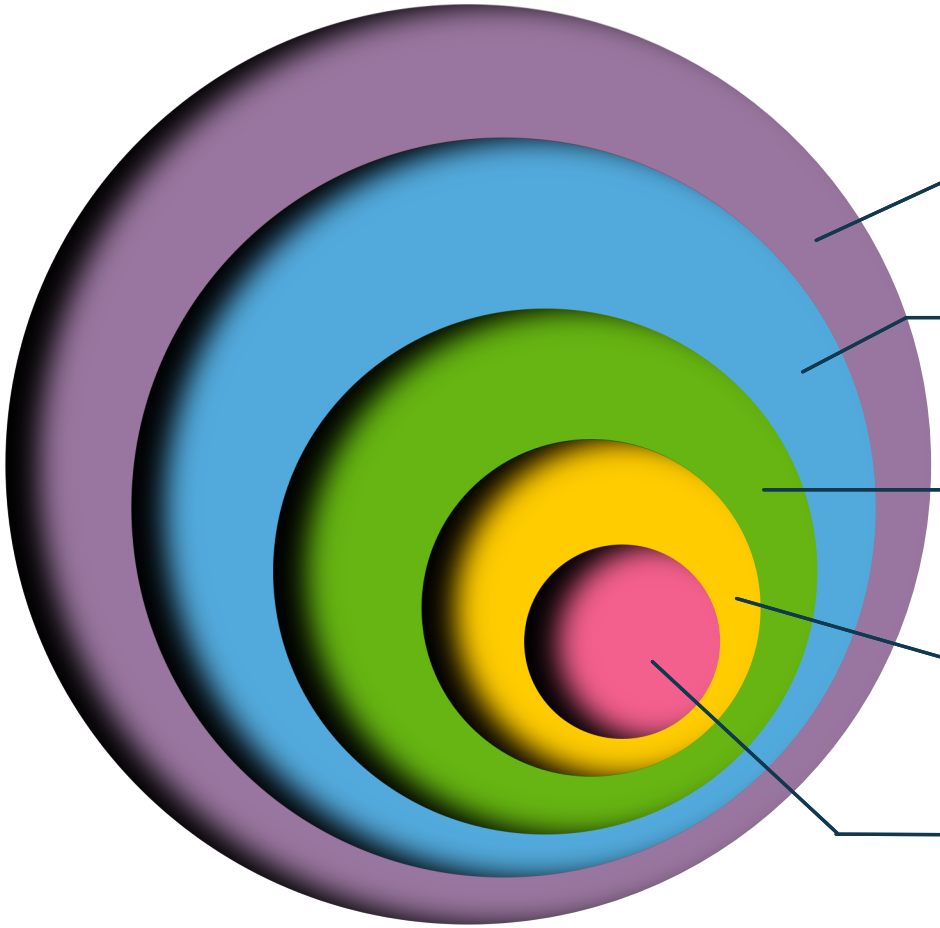
Our approach



A highly selective CDK2 inhibitor could improve efficacy and therapeutic window for deeper target inhibition, with less hematologic toxicity, and increased ability to combine with other medicines

1. Zhang Y, et al. Nature chemical biology, 2025 Mar;21(3):420-431. doi: 10.1038/s41589-024-01738-7. Epub 2024 Sep 18.

Modular Design of the Bayer compound collection



Full File Library
4,400,000 cmpds

Broadest chemical space – comprehensive HTS when the target is well assayable.

Next Gen Library
600,000 cmpds

Diversity-optimized subset – better physicochemical balance and novelty.

Diversity 10% Set
320,000 cmpds

Representative cover of major chemical space at a fraction of the screening load.

Diversity 1% Set
50,000 cmpds

Rapid, resource-efficient exploration – ideal for complex or low-throughput assays.

Specialty Sets
5,000-30,000 cmpds

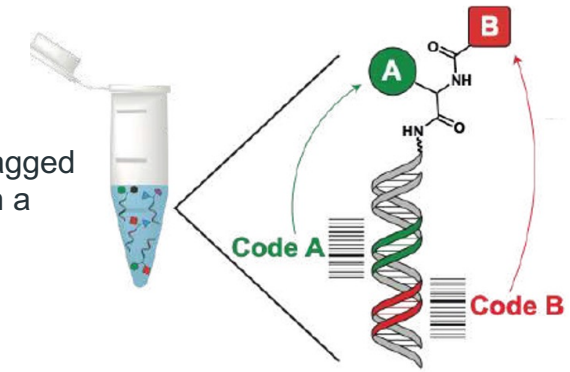
Focused sets per modality or mechanism: covalents, RNA binders, glue chemotypes, MoA tools.

Effective hit discovery is a selection decision:
Match the chemical space to the biological question, not the biggest file to every target.

Where DNA encoded libraries (DELs) open new druggable space

What is a DEL?

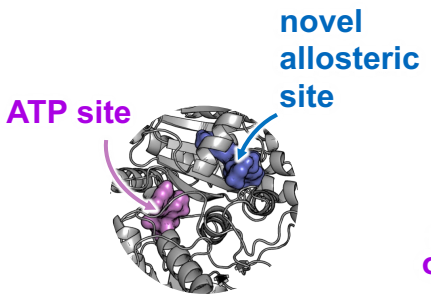
Large collections of compounds, each tagged with a DNA barcode; billions screened in a single tube.



Bassi, Neri, FEBS, 2018

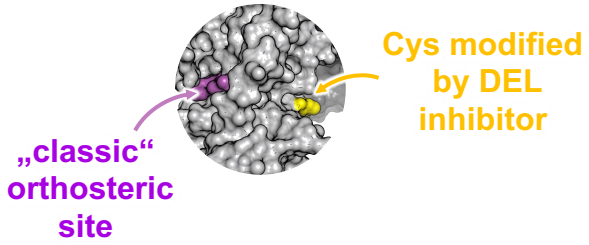
Opening new druggable space…

Cryptic pockets



Chromatin remodeler

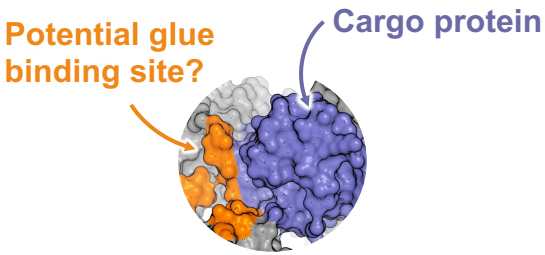
New modalities



Kinase complex

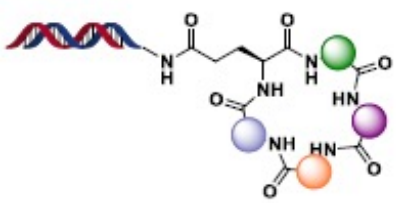
… and where DEL will help us in the future

Testing a starting hypothesis



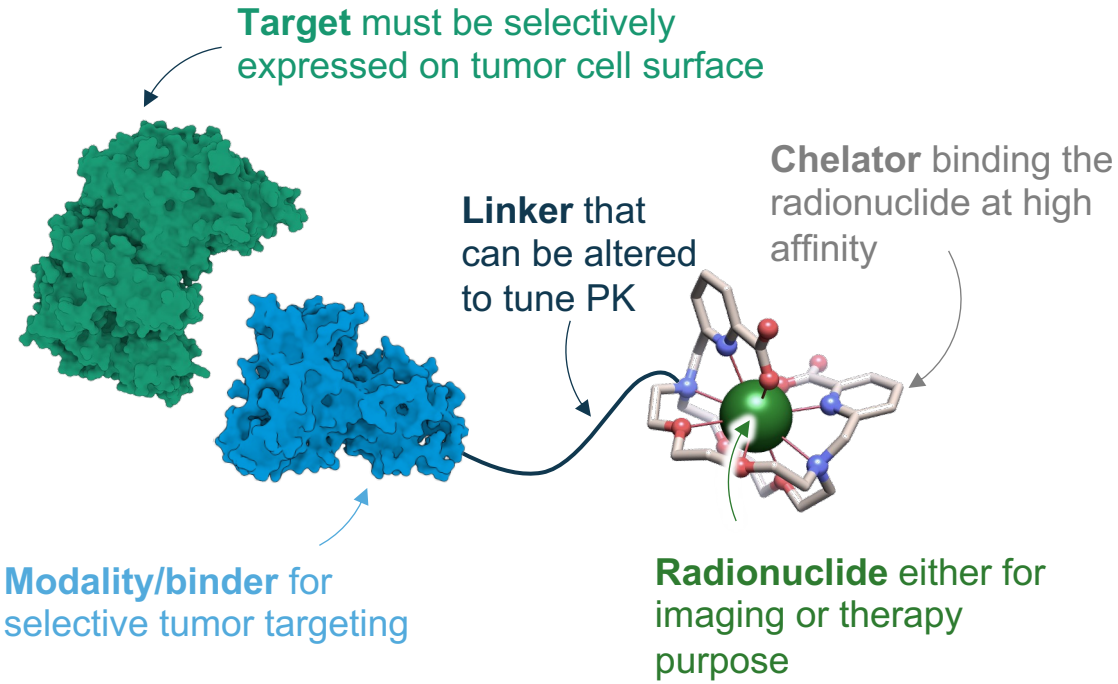
Nuclear transport chaperone

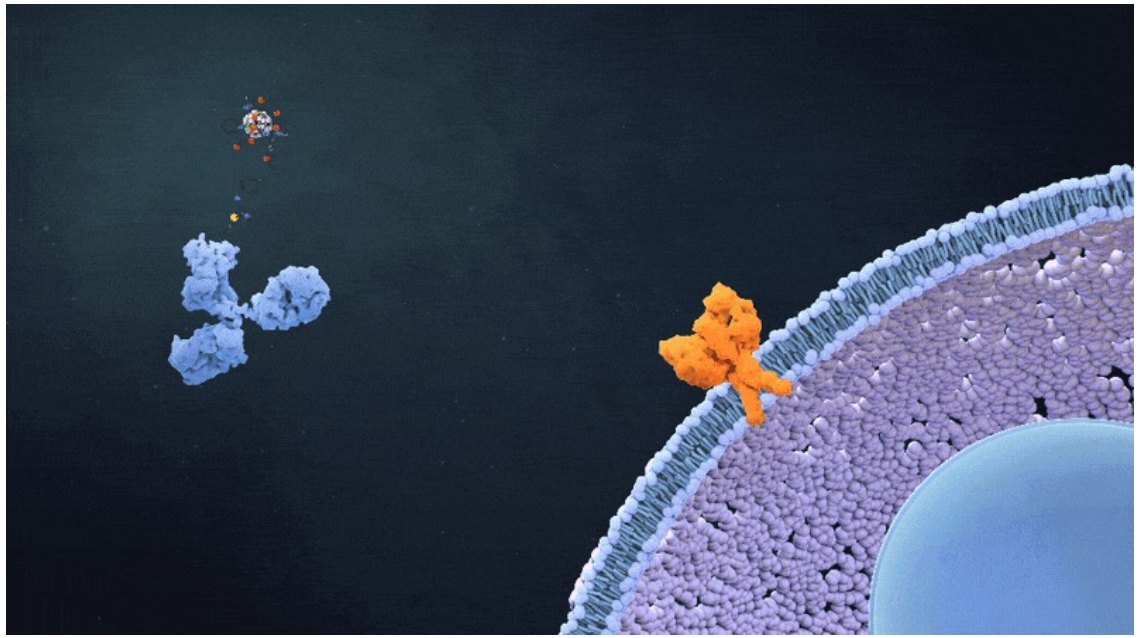
Macrocycle & peptide DELs



Target alpha therapy (TAT) delivers potent, localized tumor cell killing while sparing healthy tissue

TAT delivers localized high-energy particle radiation directly to tumor cells and their microenvironment

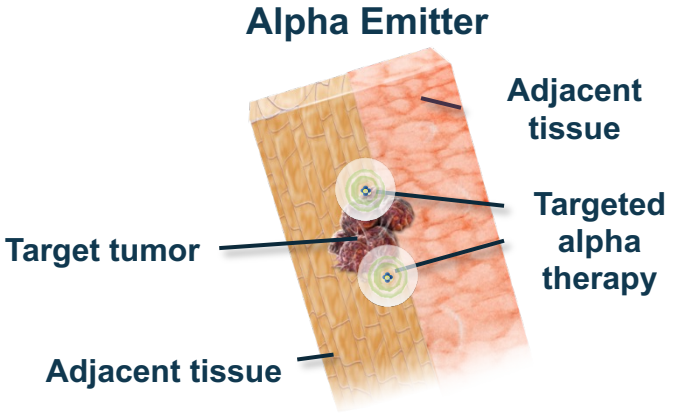


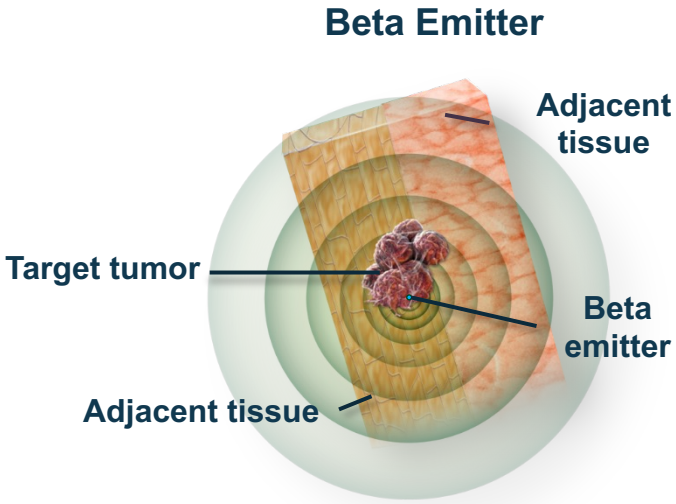


Ivanov et al, 2022: Elucidating the coordination chemistry of the radium ion for targeted alpha therapy
PDB: 1Z8L, 5YD3

Alpha and beta emitters have different radiophysical properties

Parameters	Alpha-emitter	Beta-emitter
Relative Mass / Charge	4 / +2	0.00055 / -1
Particle travel distance	< 0.1 mm	1–10 mm
Particle range in cell diameters	<10	20–100
Linear Energy Transfer	50 - 230 keV/µm	0.1 - 1.0 keV/µm
Type of DNA damage	Clustered difficult to repair DNA double-strand breaks	Isolated single-strand breaks
Hits required for cell killing	1 – 20 hits	~2000 hits
Examples	Radium-223/ Actinium-225	Lutetium-177

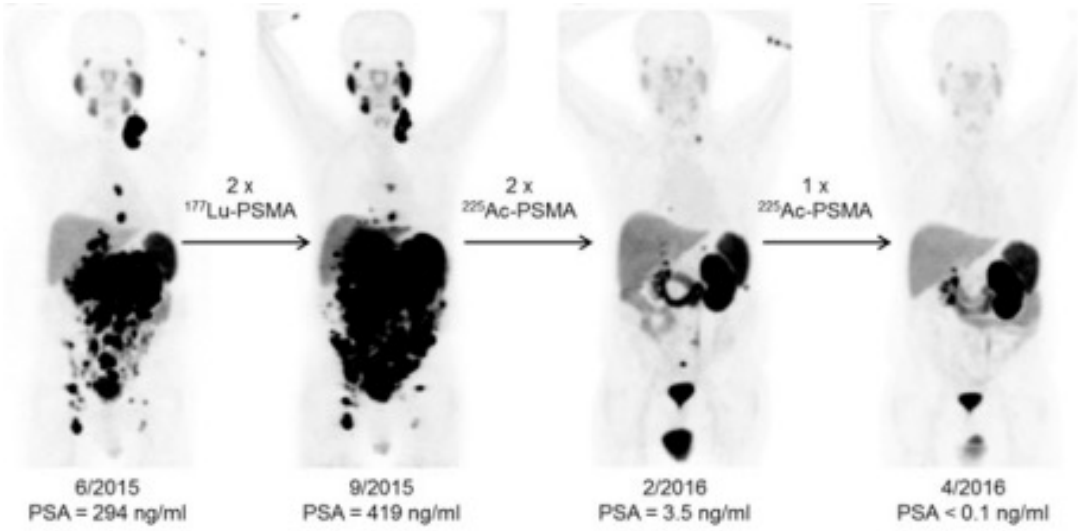




doi: 10.1080/14712598.2016.1185412; doi: 10.3389/fonc.2016.00273; doi: 10.3389/fonc.2013.00324; doi: 10.1039/B704726F

Prostate-specific membrane antigen (PSMA) is a validated target for TRT in prostate cancer

- PSMA is a 748 aa **cell surface expressed non-shed type II transmembrane internalizing glycoprotein**
- Significantly **overexpressed in >90% to 100%** of local prostate cancers and metastases which increases in advanced prostate cancer, including mCRPC, and upon androgen deprivation*
- 177Lu-PSMA-617 is an approved PSMA-targeted radiotherapy, yet patients eventually do progress and suffer from xerostomia**
- The alpha particle emitter 225Ac has been shown to be efficacious in patients progressing on 177Lu-PSMA-617
- Developing **an ^{225}Ac-PSMA-targeting asset designed to increase the efficacy & reducing side effects** e.g. xerostomia due to salivary gland accumulation offers an **opportunity for patients**



Kratochwil C: J Nucl Med 2016; 57:1941–1944

*mCRPC, metastatic castration-resistant prostate cancer; **,Sartor O:. N Engl J Med 2021; 385;1091-103

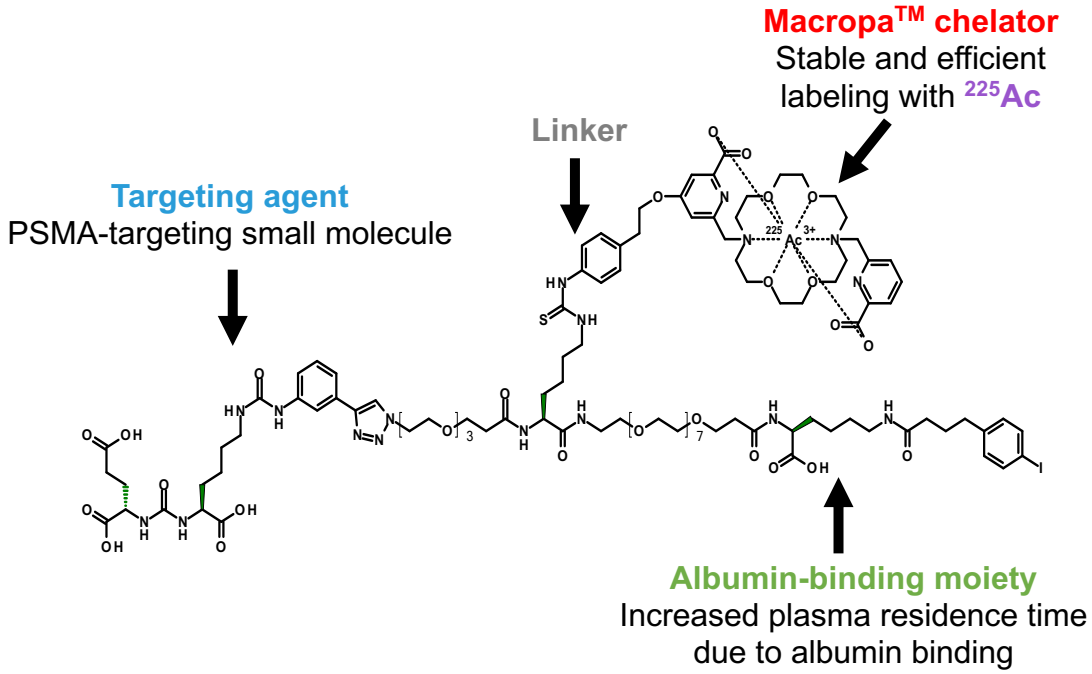
Background

The proven tolerability and efficacy of radium-223 and 177Lu-PSMA-617 in mCRPC provides a rationale for developing alpha-emitting PSMA-targeting agents

- ^{225}Ac emits alpha particles and ^{177}Lu emits beta particles[a]
- Compared with beta particles, alpha particles:[1,2]
  - Have significantly higher linear energy transfer
    - Thus, they **require fewer radiation events or "hits" to achieve a cytotoxic effect**
  - Have a shorter penetration range
    - This means there is **potentially less impact on nearby healthy tissues**

Presented here are the first clinical data for the trifunctional TrilliumTM and MacropaTM, a compound designed to increase efficacy and safety

^{225}Ac-PSMA-Trillium



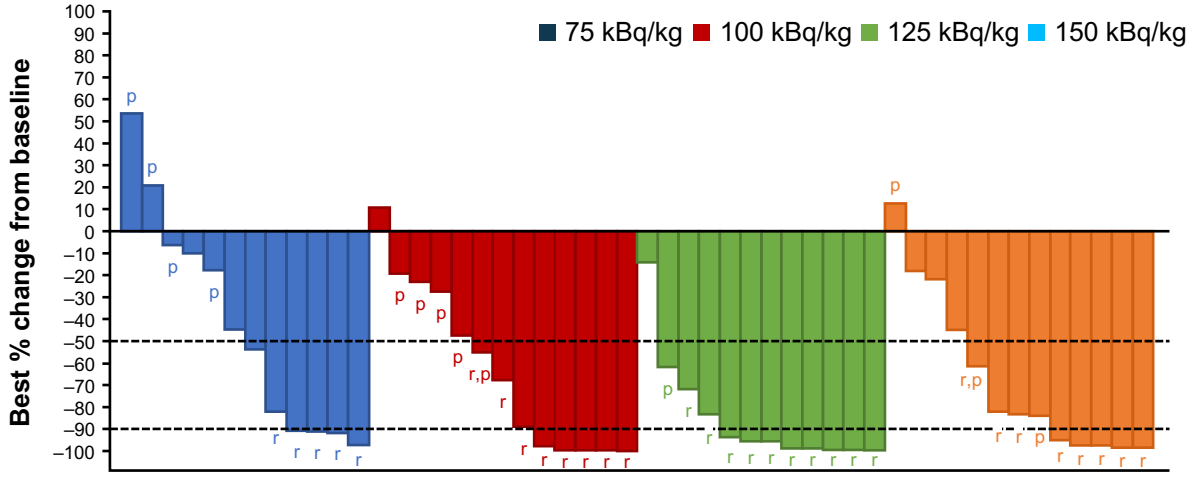
[a]The half-life for 225 Ac is 9.9 days compared with 6.7 days for ^{177}Lu[3,4]. TMBoth Trillium and Macropa are registered trademarks.

^{177}Lu, lutetium-177; ^{225}Ac, Actinium-225; mCRPC, metastatic castration-resistant prostate cancer; PSMA, prostate-specific membrane antigen.

1. Parker C, et al. JAMA Oncol. 2018;4:1765-1772. 2. Tafreshi NK, et al. Molecules. 2019;24(23):4314. 3. Pommé S, et al. Applied Radiation and Isotopes. 2012;70:2608–2614. 4. Mourtada F, et al. Brachytherapy. 2023;22:697–708.

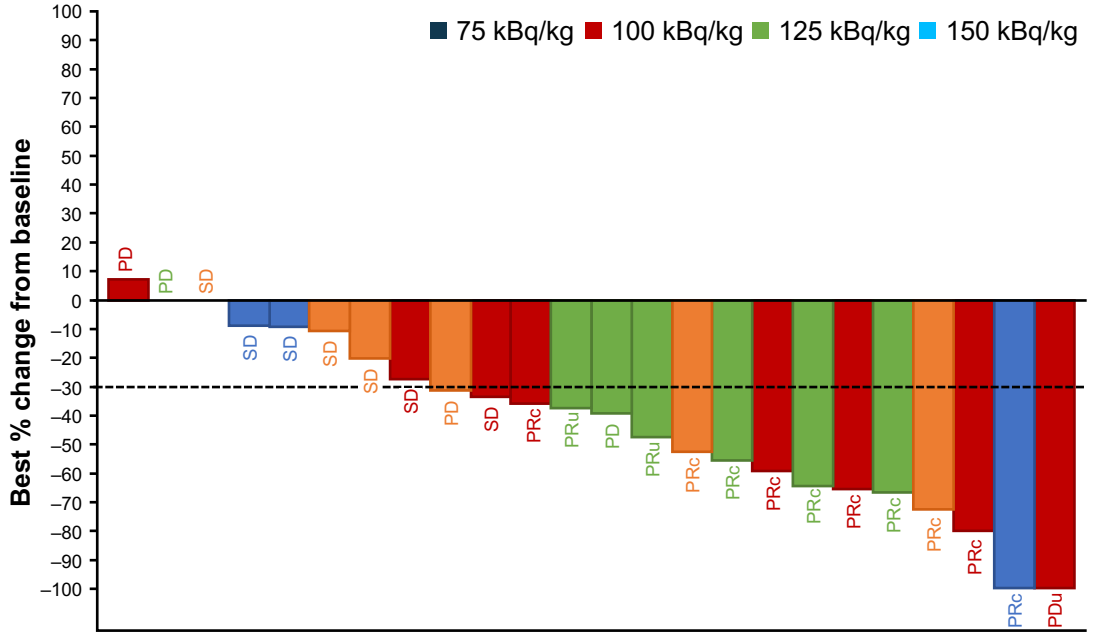
^{225}Ac-PSMA-Trillium demonstrates robust biochemical and radiographic responses in mCRPC patients

PSA response (N=50)



	All patients (N=50)	125 kBq/kg dose (N=12)
PSA50 response rate, %	62	83
PSA90 response rate, %	40	67
Overall response rate[a,c], %		
Confirmed responses only	42	43
Confirmed and unconfirmed	50	71
Disease control rate[a,c], %	79	71

Radiographic response (N=24)[a,b]



Based on the observed efficacy and safety data, the recommended dose for expansion was established as 125 kBq/kg

[a]Only patients with measurable disease at baseline. [b]Sum of diameters of all target lesions. Longest diameter for non-nodal target lesions and short-axis for nodal target lesions. [c]Per PCWG3 criteria; for all patients N=24; for 125kBq/kg dose n=7.

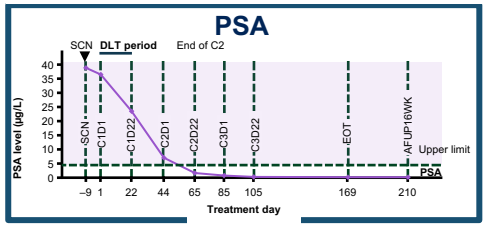
^{225}Ac, Actinium-225; mCRPC, metastatic castration-resistant prostate cancer; p, confirmed PSA progression; PCWG3, Prostate Cancer Working Group 3; PD, progressive disease; PDu, unconfirmed progressive disease; PRc, confirmed partial response; PRu, unconfirmed partial response; PSA, prostate-specific antigen; PSAx response, decline of x% from baseline in PSA; r, confirmed PSA response; r,p, confirmed PSA response and subsequent progression; SD, stable disease.

Durable radiographic and biochemical responses were seen with 125 kBq/kg ^{225}Ac-PSMA-Trillium treatment

PSMA PET

Screening





Post 2 Cycles



TTV: 471.3mL **(–83.2%)**
SUVmean: 4.7

PSMA PET

Screening



TTV: 77.5mL
SUVmean: 12.1

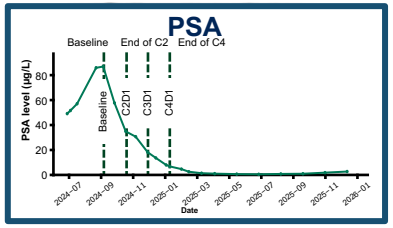
Cycle 2



TTV: 22.5mL **(–70.9%)**
SUVmean: 8.9

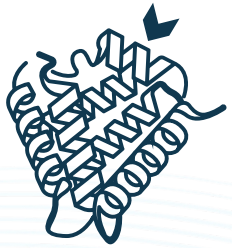
Cycle 4





^{225}Ac, Actinium-225; A-FU, active follow up; BOR, best overall response; C, cycle; D, day; DWI, diffusion-weighted imaging; EoT, end of treatment; G, grade; mCRPC, metastatic castration-resistant prostate cancer; mo, months; PCWG3, Prostate Cancer Working Group 3; PET, positron emission tomography; PR, partial response; PSA, prostate specific antigen; PSMA, prostate-specific membrane antigen; SUV, standardized uptake value; TEAE, treatment-emergent adverse event; TTV, total tumor volume.

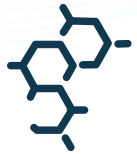
Where AI/ML already helps drive the drug discovery process



Find entry into druggability



Find the right MoA and modality



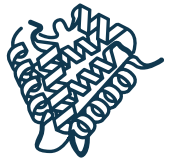
Create the right molecule

- Automated data capture to build our data-foundation
- High content imaging accelerating data analysis 15x
- AI enabled antibody optimization, saving months
- Building on Boltz, AF3, etc. for de-novo design of mini-proteins and beyond
- Advanced ADMET models asupport compound optimization - saving resources

STAMP: AI tools for biomolecular structure and binder design

Structural **T**arget **A**nalysis & **M**odality **P**rioritization

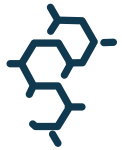
Find entry into druggability



Find the right MoA and modality



Create the right molecule



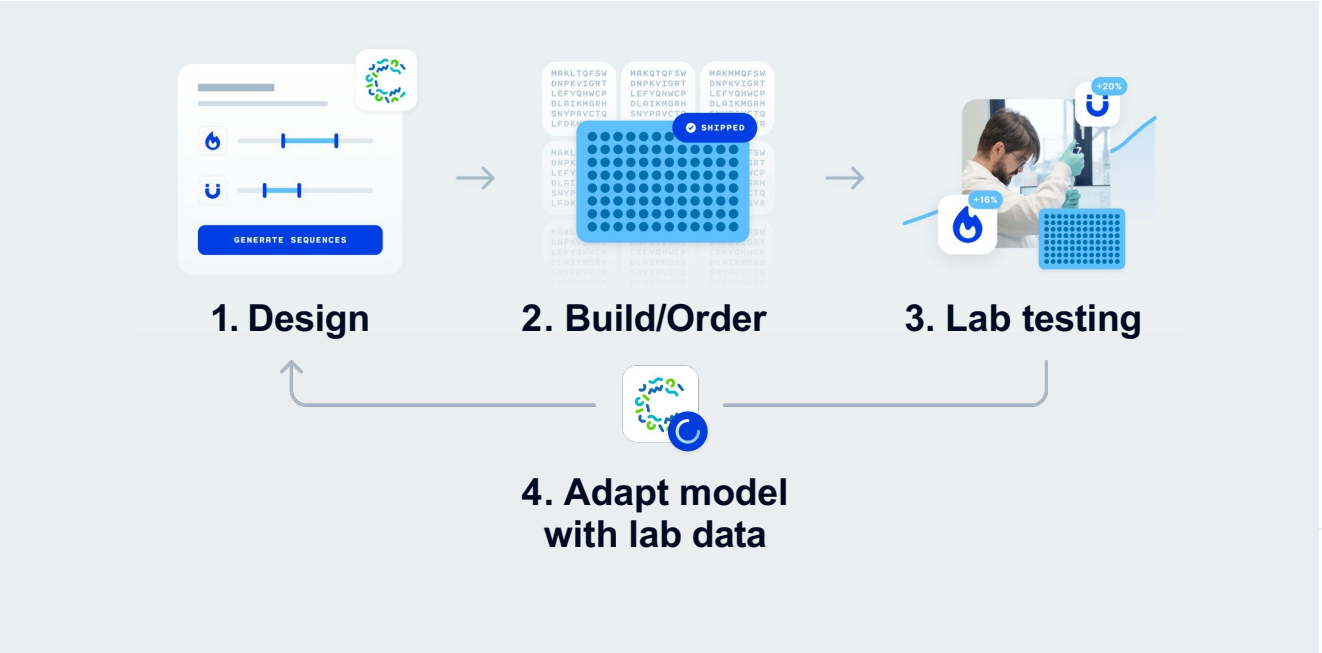
STAMP	// Structure & PPI insights // Proteome-wide druggability	// Binding motif detection // Tools to validate MoAs	// Co-folding + generative AI // De novo design (peptides)

PIPELINE IMPACT:

// Focus: mini-protein design – cell-expressible, high-affinity binders for user-defined epitopes
// Support challenging crystallization
// Derisking projects via MoA validation tools

2-35% Hit rates	~8 Weeks Cycle Time	<10 nM Affinity of binders

Bayer // Cradle collaboration for AI-based protein design



ENGLISH

“How are ____ doing today?”

The model fills the blank:

you

It learned grammar from billions of sentences.

PROTEINISH

EV__LESGGGL

The model fills the blank:

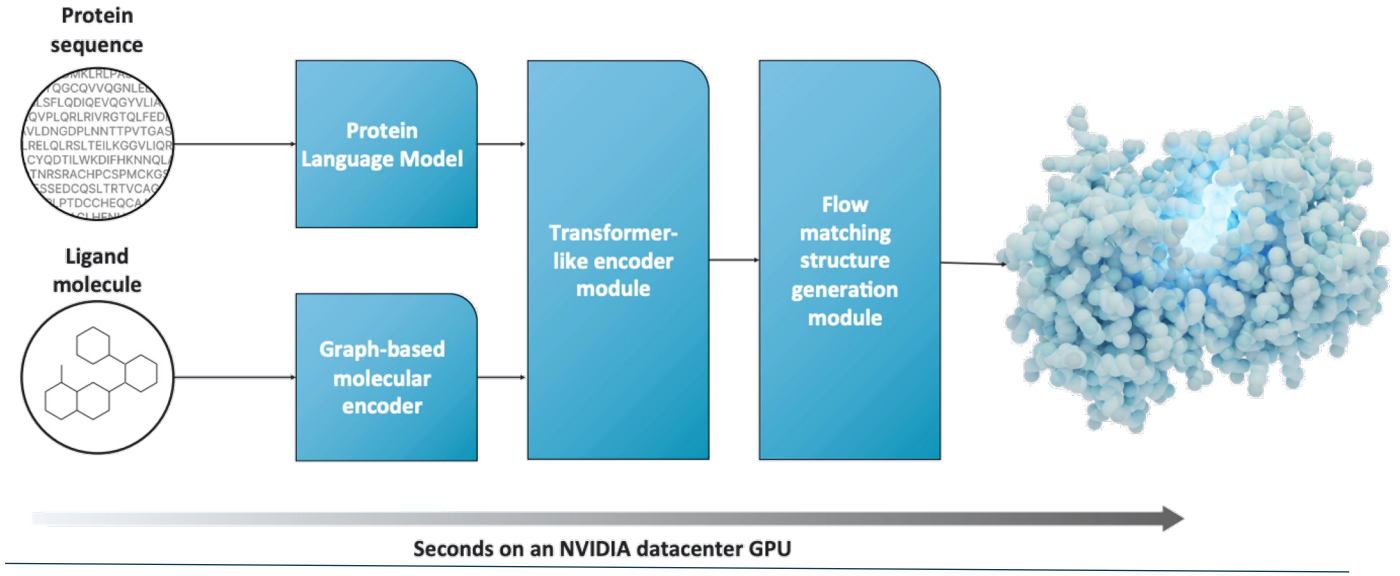
the right amino acids

It learned protein “grammar” from millions of sequences.

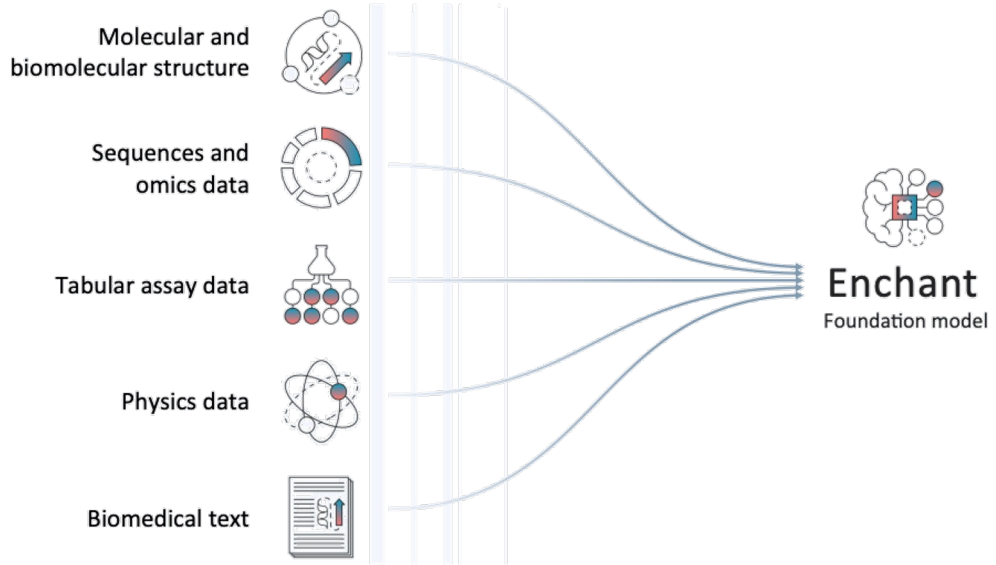
Source: Cradle (Bayer Science Conference Keynote, May 2026)

Iambic's AI-driven platform for small molecule research

NeuralPLexer



Enchant



Source: Iambic JPM Healthcare Conference 2026 Company Presentation

Health for all, Hunger for none



Thank you!

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