Radio-DARPin Therapy

Development of powerful targeting agents to treat cancer

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Christian Lizak, PhD:

- Employee of Molecular Partners
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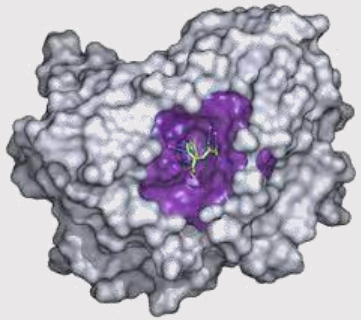
DARPins Expand the '*Ligandable*' Target Space

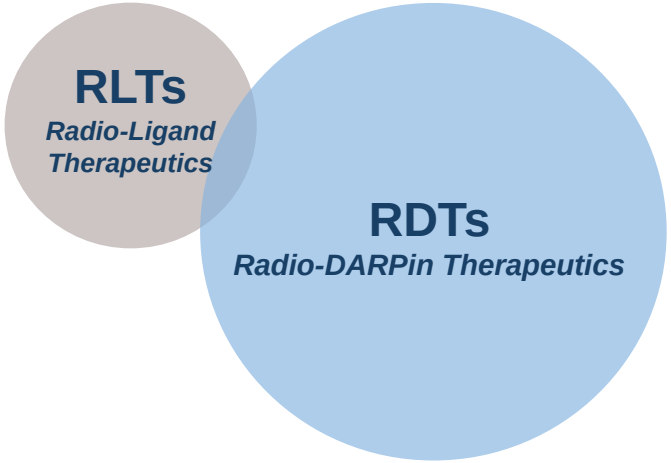
RLTs are suitable for

Targets where a small molecule ligand with high affinity & specificity can be generated



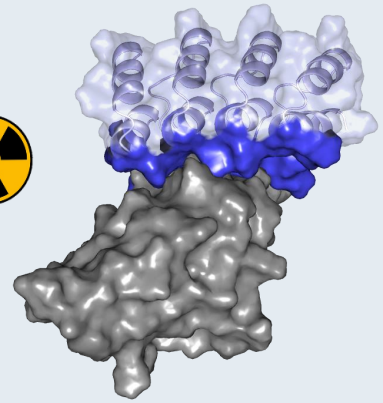
Examples:
PSMA, FAP, ...

TARGET SPACE



Focus with RDTs on

Targets that are challenging for peptides or small molecules to reach desired specificity & affinity



Examples:
Her2, DLL3, …

Target properties for Radiopharmaceuticals

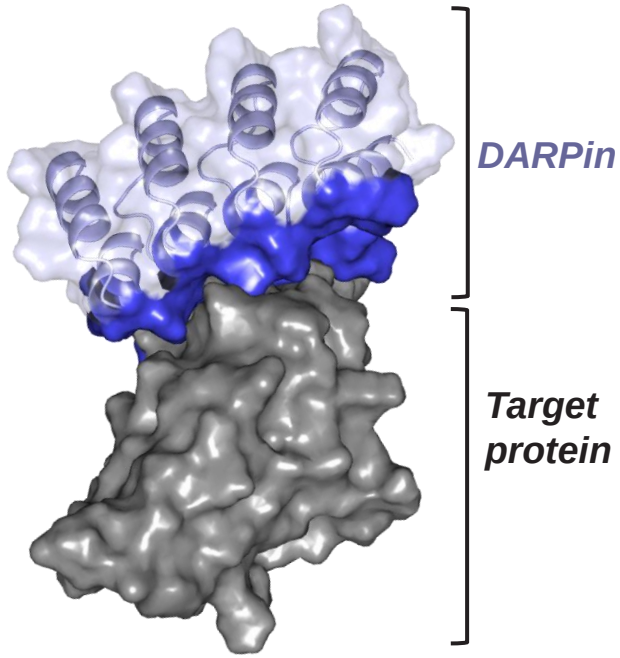
- Expressed on the cell surface and accessible for binding
- Expression limited to tumors (or high differential expression between tumors & healthy tissues)
- Relevant medical indications

PSMA (1Z8L)

CD33 (5IHB)

DARPin Modality: The Core of our Drug Engine

DARPins are derived from natural ankyrin repeat proteins



Key Properties of mono-DARPins

Small size (15 kDa)

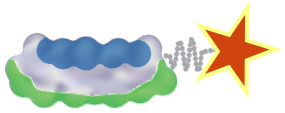
→ High tumor uptake

→ Fast clearance

Rigid protein scaffold

→ High affinity

→ High selectivity

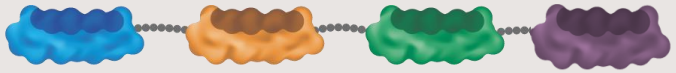


Robust architecture

→ Easy engineering

→ Simple conjugation & labelling

Multi-DARPin Therapeutics



- Clinically validated with 7 programs spanned from first-in-human up to regulatory submission
- +2500 patients safely dosed

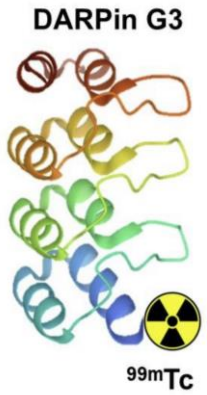
Radio-DARPin Therapeutics

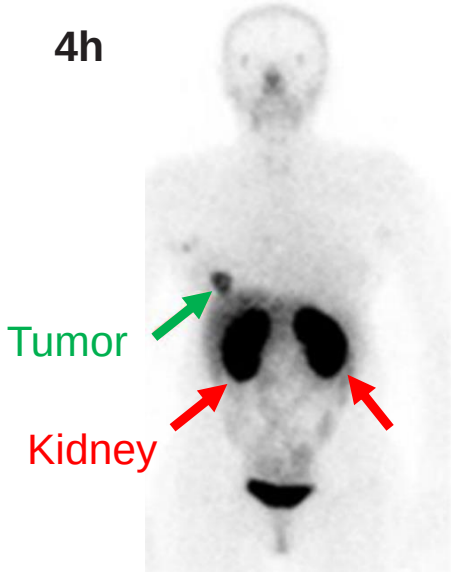
- Collaboration with external partners
- DLL3 selected as 1st in-house target

Rothenberger *et al.*, *Nature Biotech*, 2022
Fischer *et al.*, *JCO Precis Oncol*, 2022

Addressing the Key Limitation of Protein-based Delivery

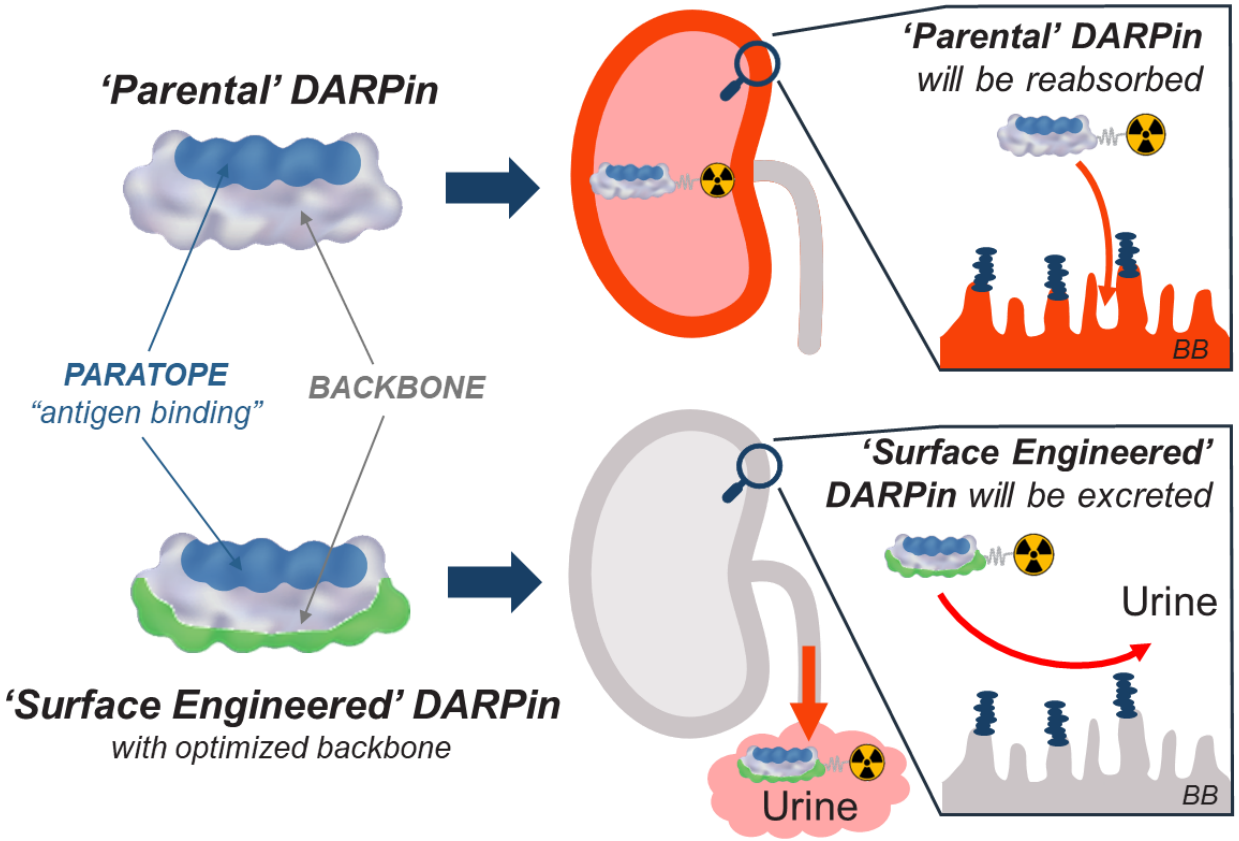
Polypeptides & proteins < 60 kDa are reabsorbed by kidneys





- → Strong kidney accumulation of residualizing radionuclides
- → Kidney toxicity with therapeutic radionuclides

Surface engineering of DARPins as a strategy to increase renal excretion



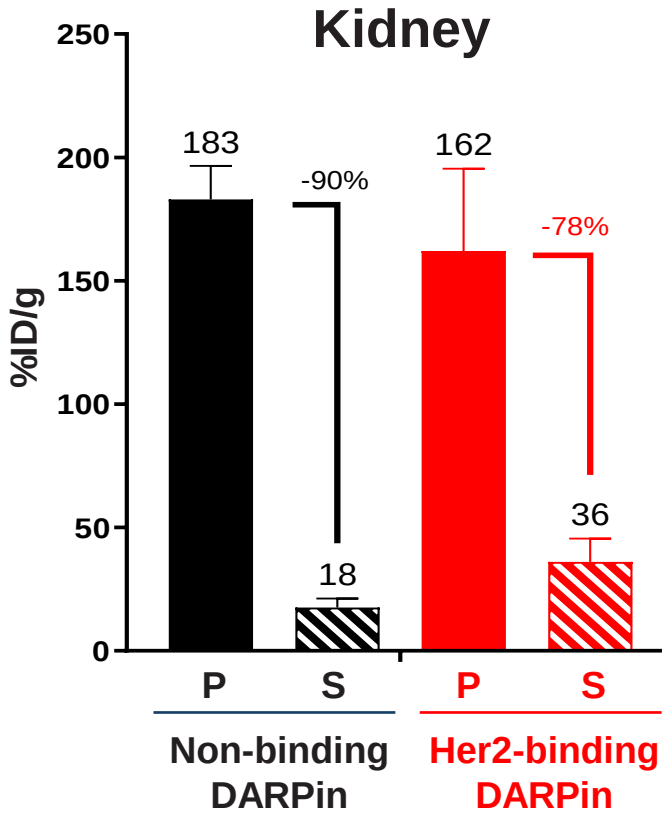
Bragina *et al., J Nuc Med*, 2021

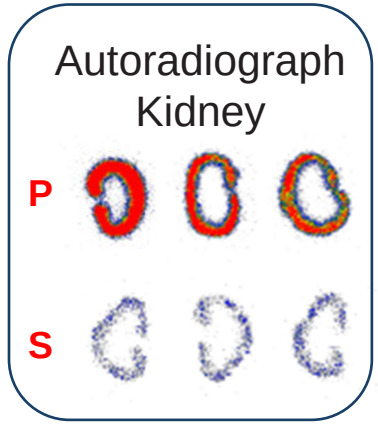
BB: Brush border of proximal tubular cells in the kidney with megalin/cubilin receptor complex

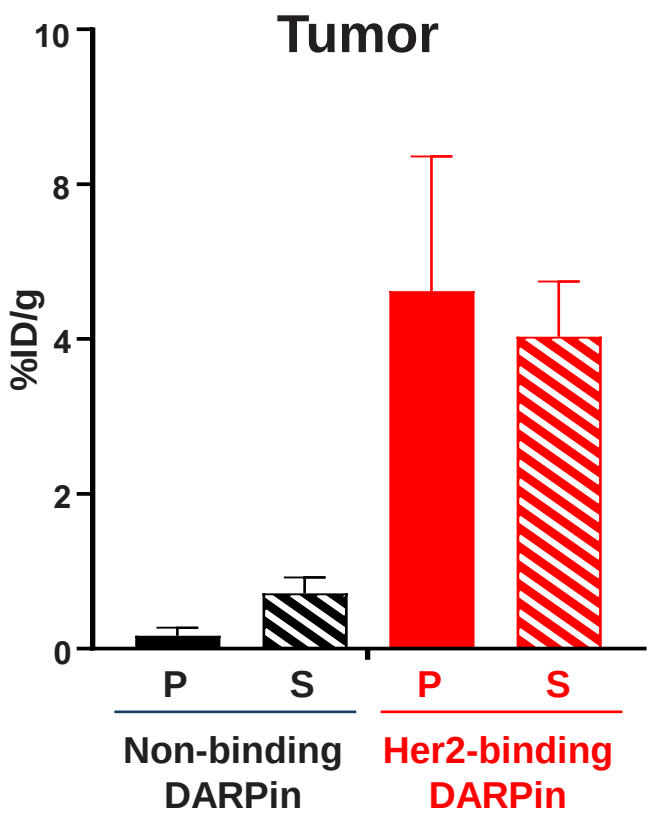
Surface Engineered Radio-DARPins Show Strongly Reduced Kidney Accumulation

P: Parental

S: Surface Engineered



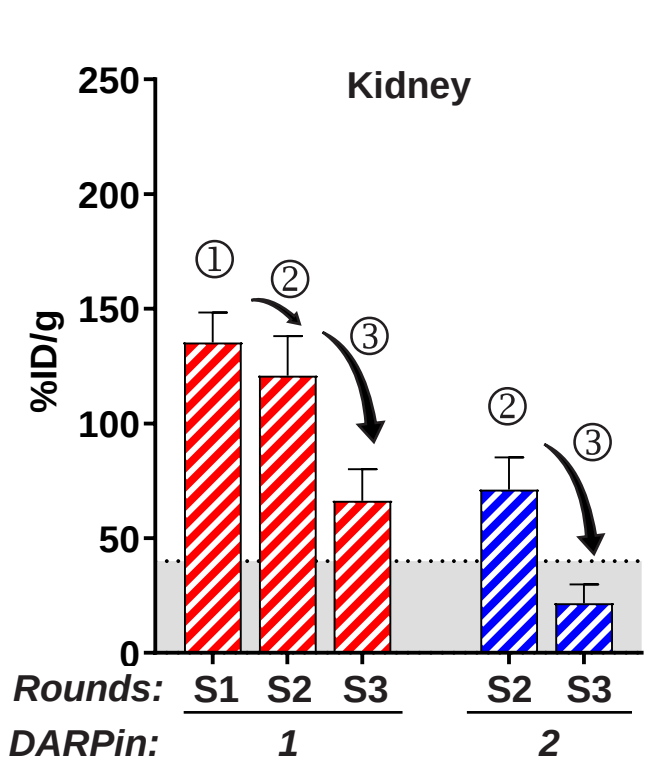




→ **Up to 90% reduction in kidney accumulation with maintained tumor uptake**

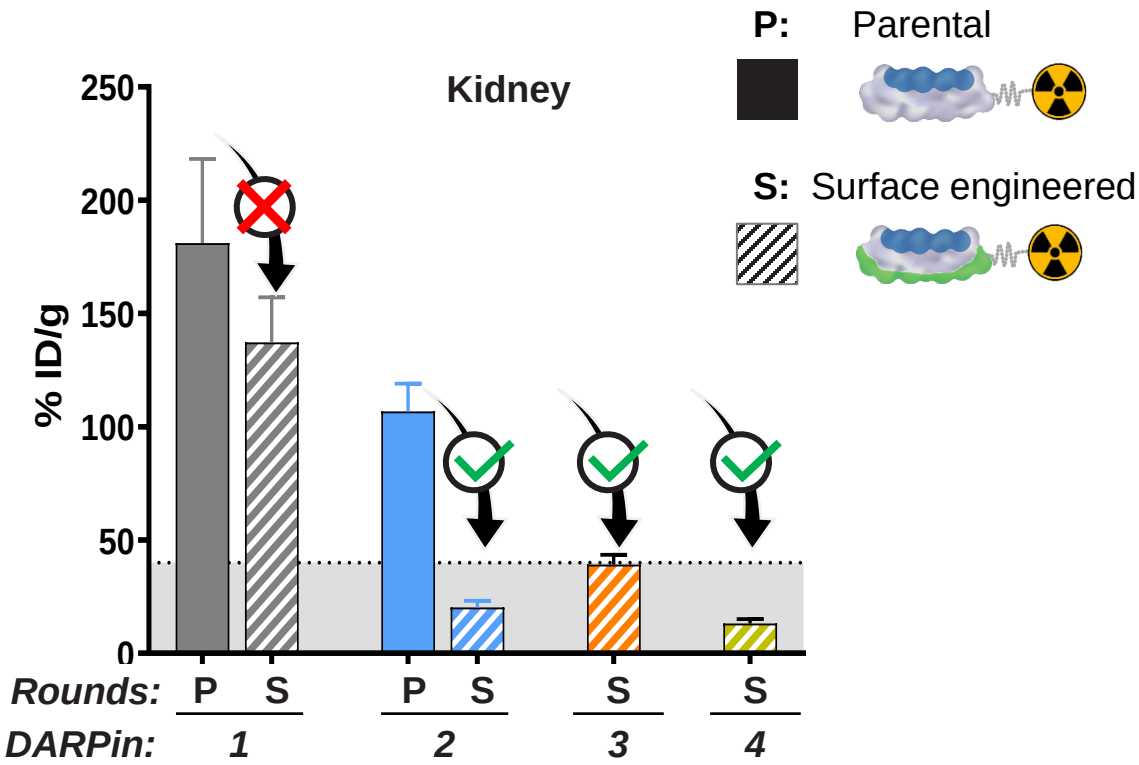
SKOV3 tumor mouse model,
111-In/DTPA labelled DARPin
4 h post injection

Kidney Protection via Surface Engineering is Applicable to Multiple Targets



Integration of learnings

across different TAAs and many DARPins



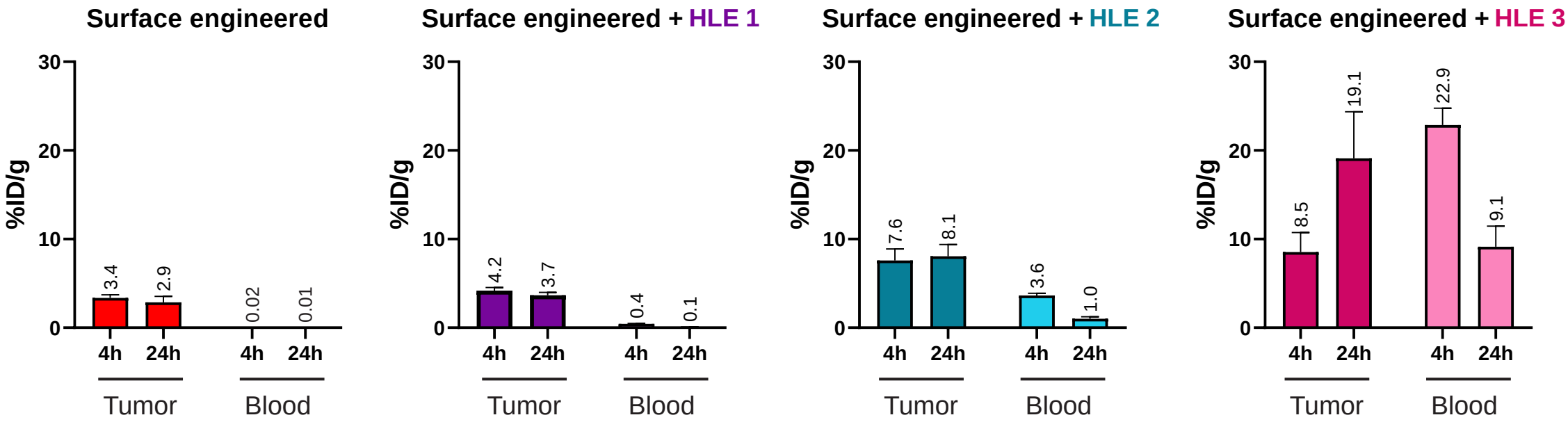
Learning phase: Iterative rounds of surface engineering needed to reach low kidney accumulation for many DARPins

Today: Low kidney values for most binders of new TAA in **single round of engineering**

TAA: tumor-associated antigen

4h timepoint in wt mice
DARPins conjugated to different chelators and labelled with different radioisotopes

Systemic Half-life Extension (HLE) Increases Tumor Uptake

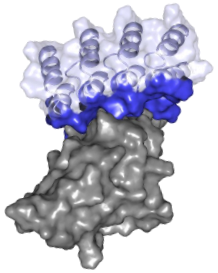


- Serum albumin binding results in increased blood levels that correlate with higher tumor uptake
- **HLE toolbox with different "strengths" allows RDT properties tailored to specific needs & payloads**

Our Goal: An Engine for Novel Radio-DARPin Therapeutics

Expanding the Target Space

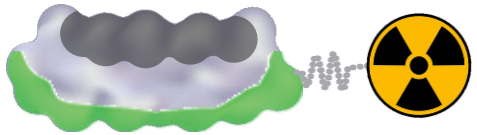
ESTABLISHED DARPin GENERATION



- DARPins against 50+ targets generated
- Binders available in ~ 4 months*
- Strong clinical validation

+

OPTIMIZED RDT PLATFORM



1) Low kidney accumulation
2) Optimized systemic half-life
3) High & durable tumor uptake
4) No uptake in healthy organs

→ ***Transferable from one target to the other***

RAPID CONVERSION TO RDT PRODUCT CANDIDATES

* *Starting from high-quality biotinylated target protein available for selections (without affinity maturation/engineering)*

Acknowledgments

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Thank you for your interest!

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