DARPin Platform

Development of powerful targeting agents for Radio-DARPin Therapy

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June 27th, 2023

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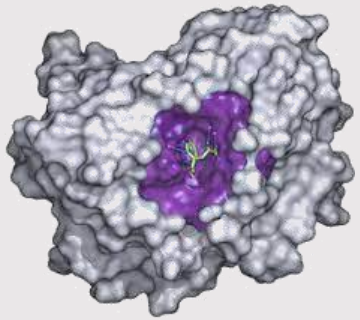
DARPins Expand the '*Ligandable*' Target Space

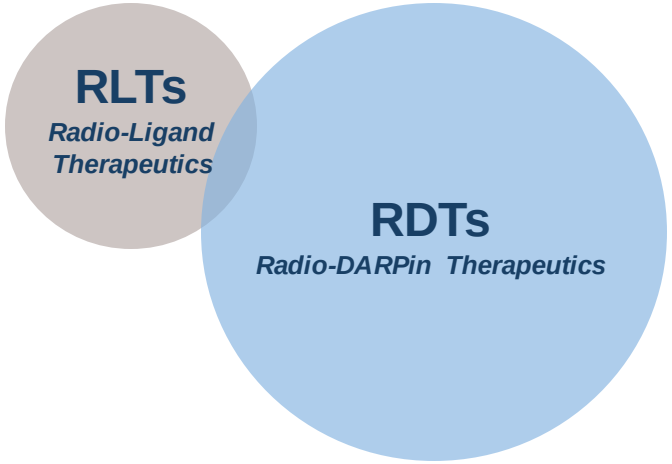
RLTs are suitable for

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



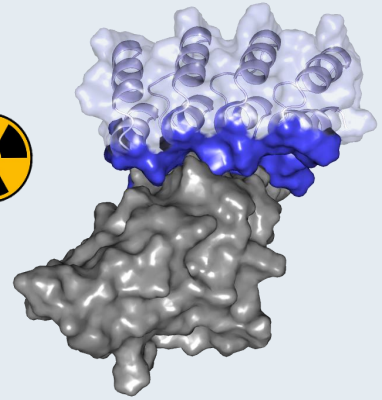
Examples:
PSMA, FAP, ...

TARGET SPACE



Focus with RDTs on

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



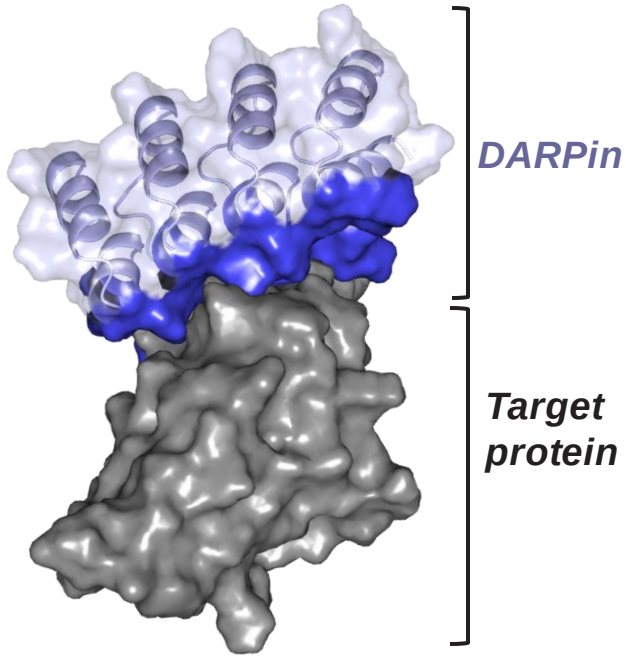
Examples:
Her2, DLL3, …

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

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)

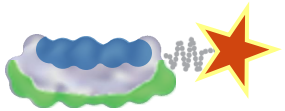
→ High tumor uptake

→ 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 FiH up to regulatory submission
- +2500 patients safely dosed

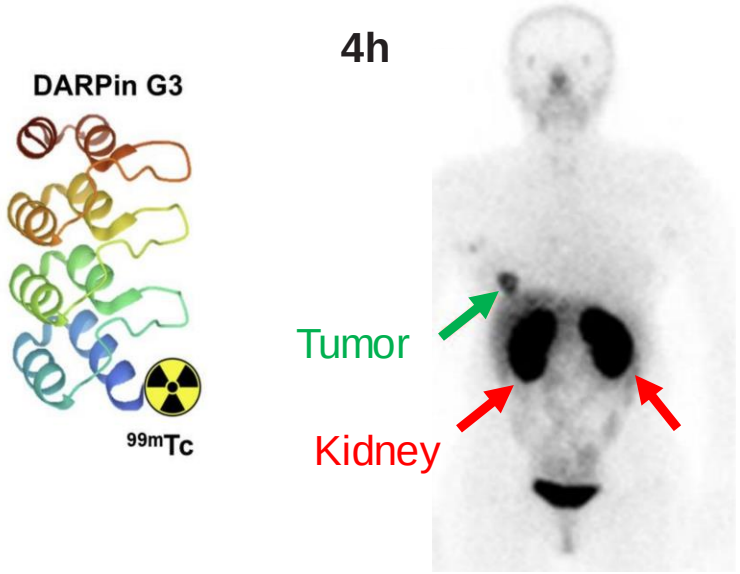
Radio-DARPin Therapeutics

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

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

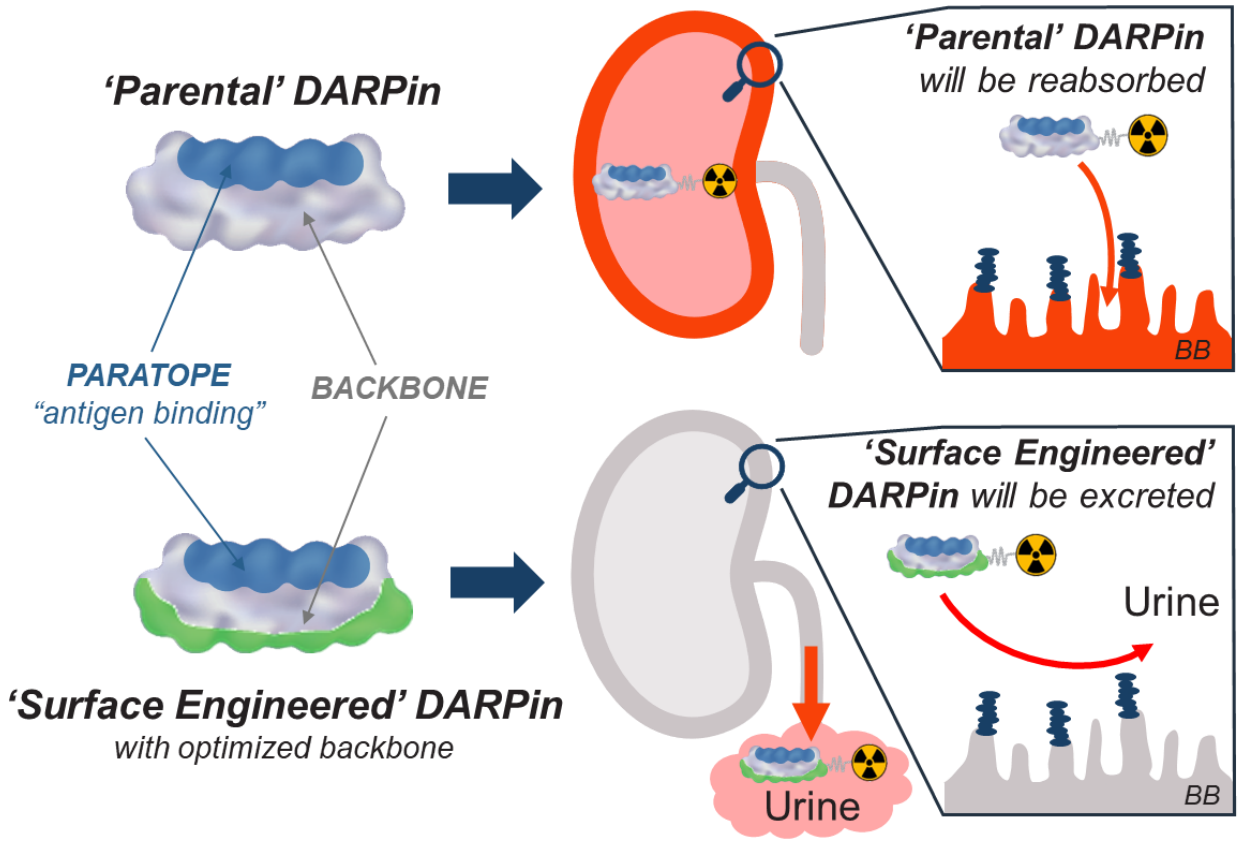
Addressing the Key Limitation of Protein-based Delivery

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



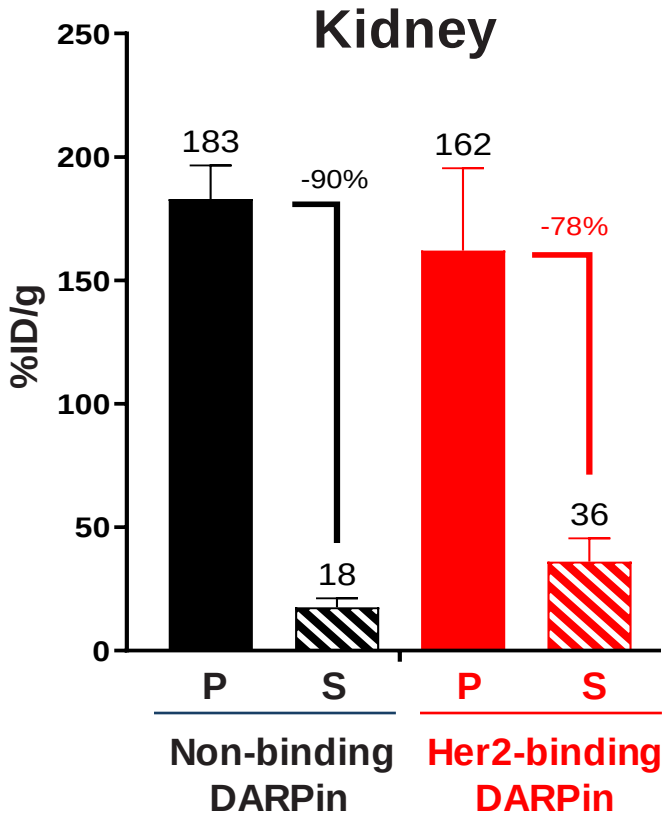
Bragina *et al., J Nuc Med*, 2021

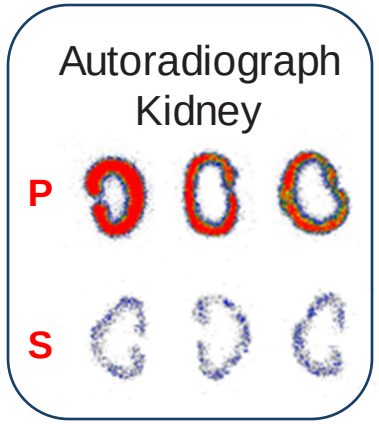
BB: Brush border of proximal tubular cells in the kidney with megalin/cubilin receptor complex

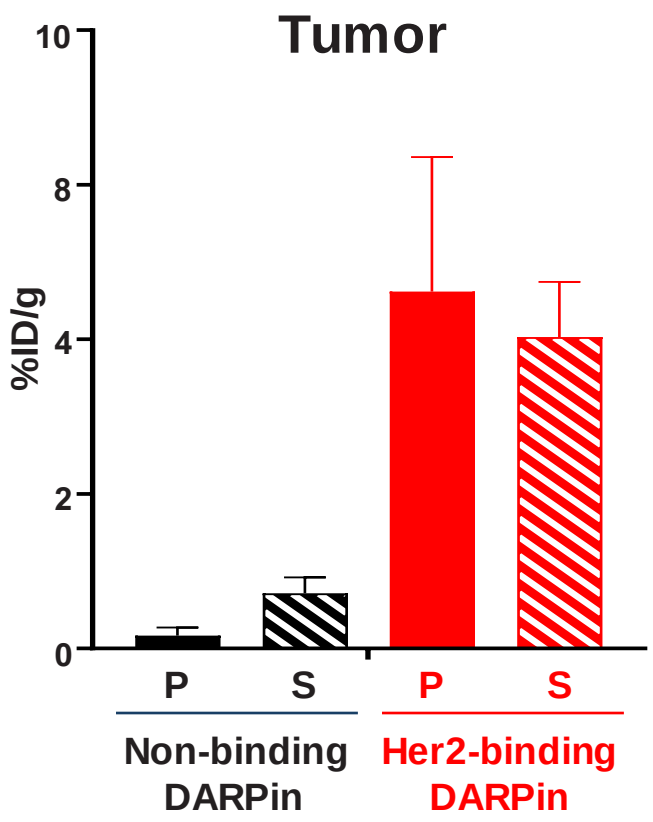
‘Surface Engineered’ Radio-DARPins Show Strongly Reduced Kidney Accumulation

P: Parental

S: Surface Engineered







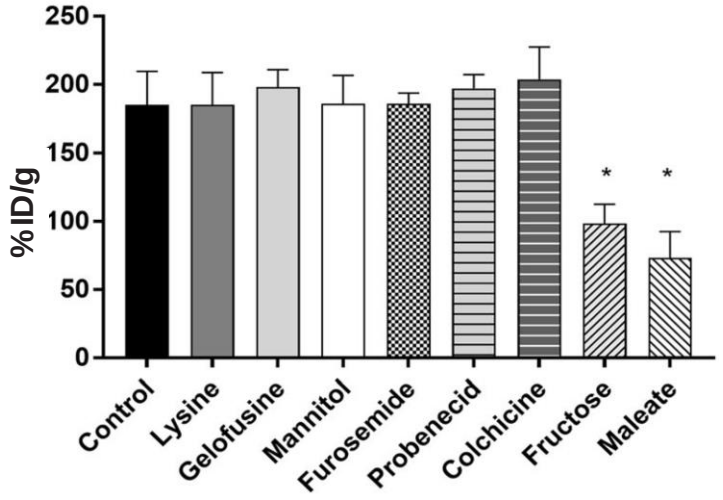
→ **Up to 90% reduction in kidney accumulation with maintained tumor uptake**

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

One Orthogonal Approach to Reduce Kidney Accumulation

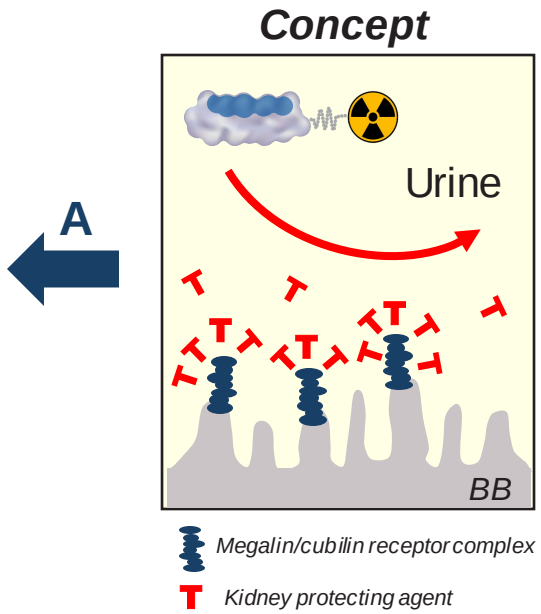
Prevent renal reabsorption of Radio-DARPins by administration of blocking or saturating agents

A: Conventional kidney protectants show limited effect on DARPins

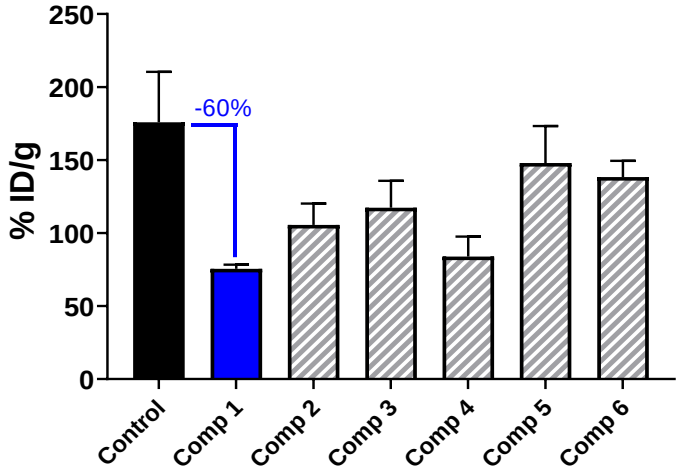


- **Most compounds have no effect**
- Fructose and Maleate only work at non-physiological conditions *

Concept



B: Identification of novel compounds with a strong effect on DARPins



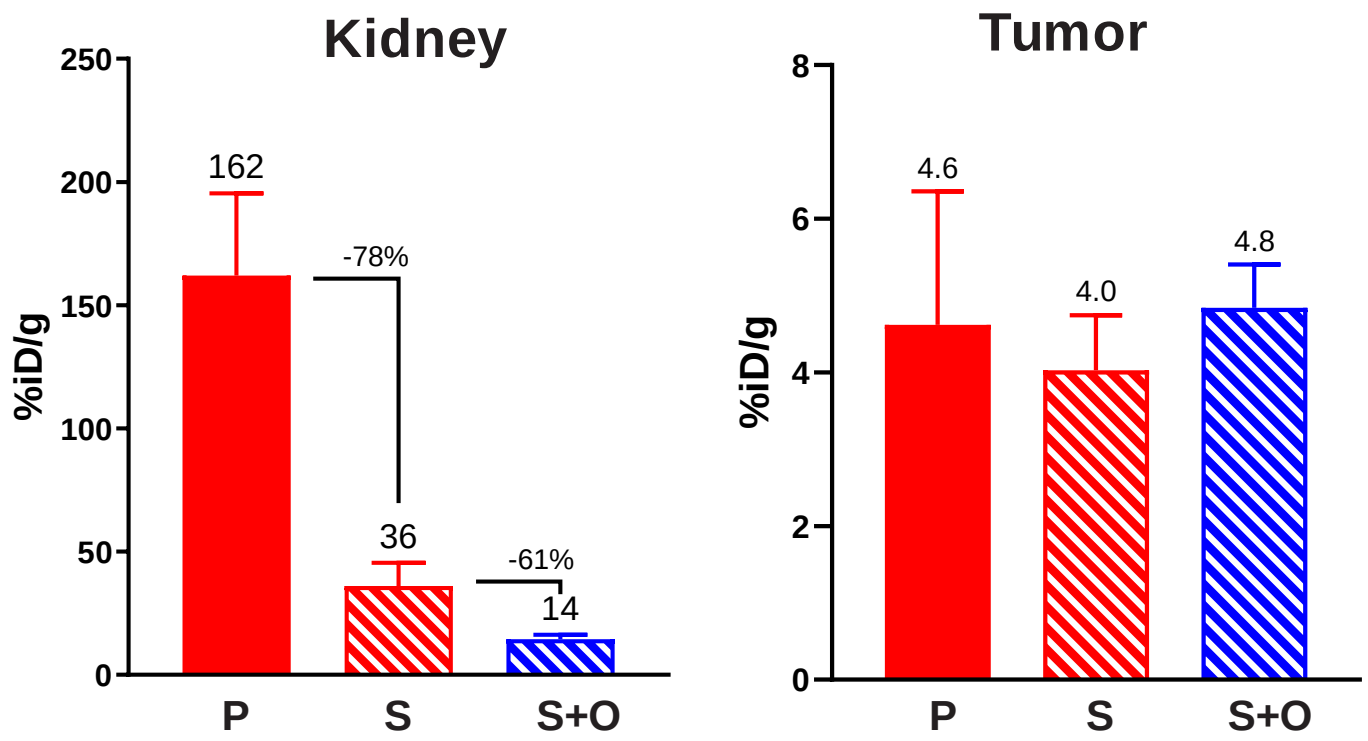
- **Up to 60% reduction of kidney accumulation** by newly identified compounds

Altai *et al.*, *EJNMMI Research*, 2020
* Fructose: 10.8 g/kg, (LD50 = 15 g/kg)
* Maleate: 480 mg/kg, (LD50 = 600 mg/kg)

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

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

Kidney Accumulation is Further Reduced by Combining 'Surface Engineering' with Orthogonal Approach



		T/K ratio*
P:	Parental	**1:35**
S:	Surface engineered	**1:9**
S+O:	Surface engineered + Orthogonal + **Comp 1**	**1:3**

**tumor-to-kidney ratio*

- Two independent Radio-DARPin platform optimizations result in **additive reduction of kidney accumulation**

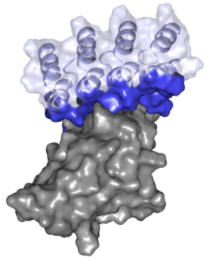
→ **Tumor-to-Kidney ratio of 1:3 for the combo approach**

- Optimization of both approaches and implementation of additional orthogonal methods is ongoing

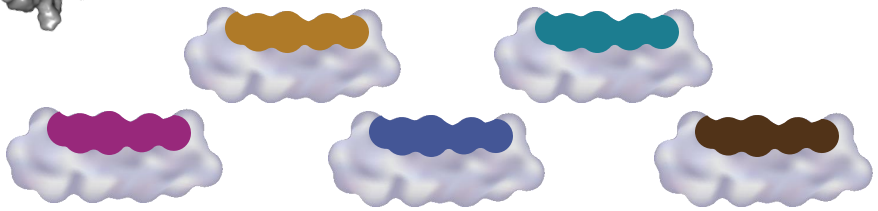
Our Goal: An Engine for Novel Radio-DARPin Therapeutics

Expanding the Target Space

ESTABLISHED DARPin GENERATION



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



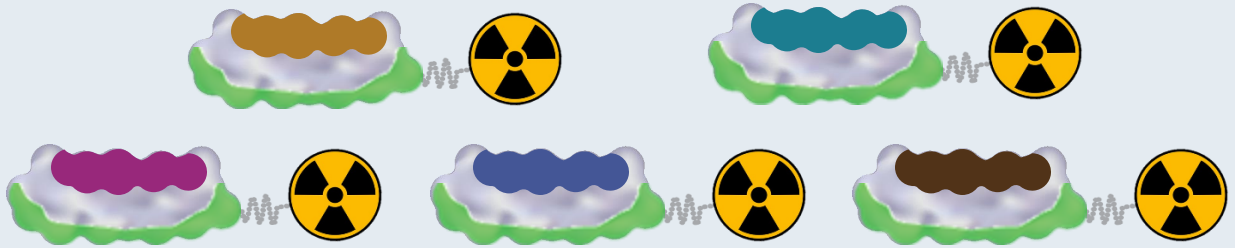
+

OPTIMIZED RDT PLATFORM

1) **Low kidney accumulation**
2) High & durable tumor uptake
3) Short systemic half-life
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 (no affinity maturation/engineering)*

Acknowledgments

Entire Team at Molecular Partners AG

Paul Scherrer Institute

Prof. Roger Schibli
Dr. Martin Behe
Alain Blanc
Tanja Chiorazzo
Stefan Imobersteg

Thank you for your interest!

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