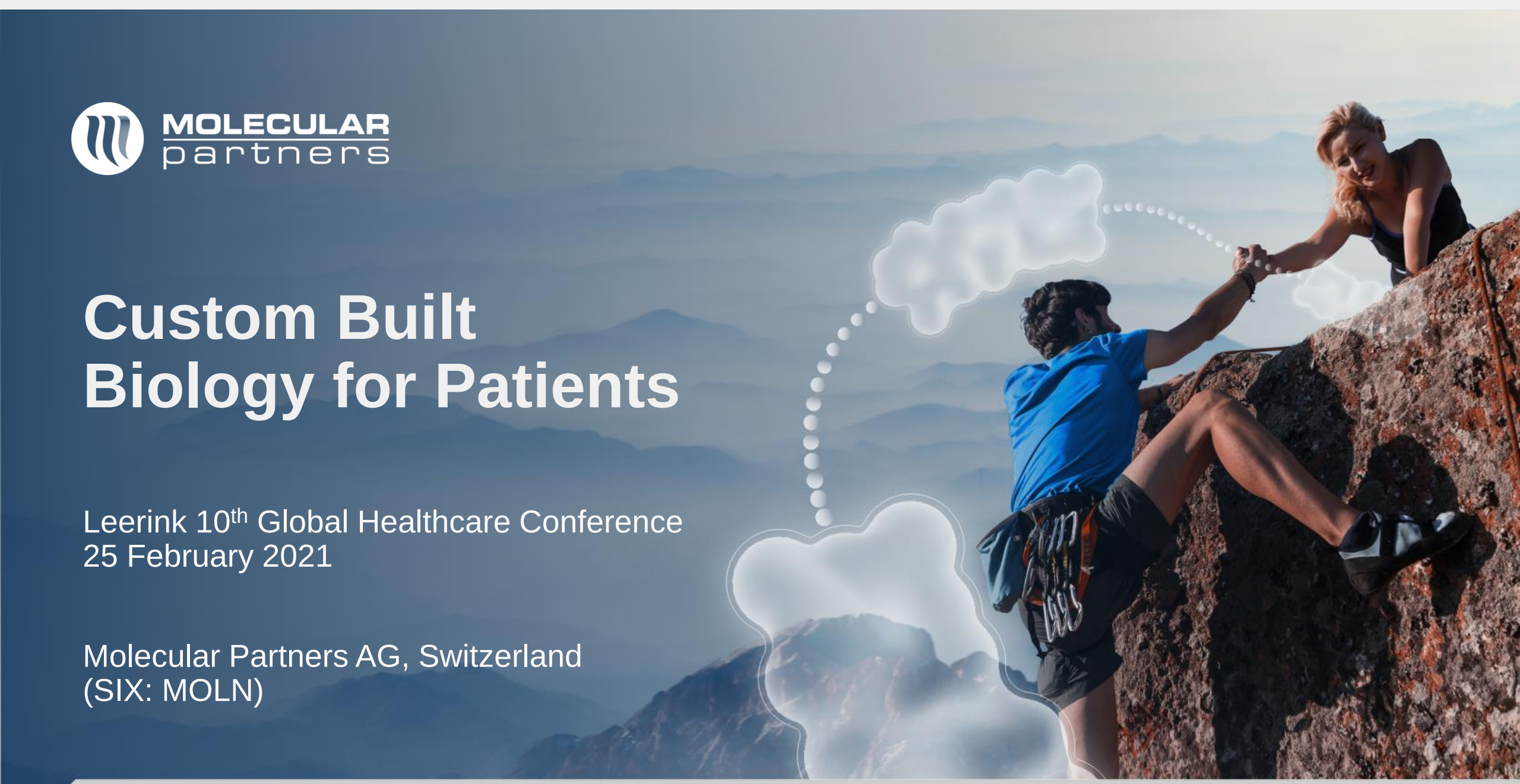
Custom Built Biology for Patients

Leerink 10th Global Healthcare Conference
25 February 2021

Molecular Partners AG, Switzerland
(SIX: MOLN)



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Pioneering DARPin® Solutions

We translate the unique properties of the **DARPin® drug class** into patient value

We build a **broad pipeline** of DARPin® therapeutics to address unmet medical need

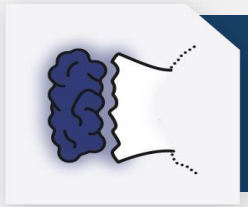
We aim to transform the lives of people with *serious diseases* by delivering truly innovative solutions

our purpose

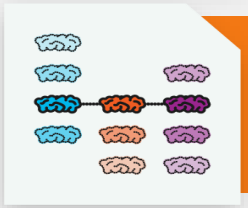
A global team united around a common purpose of making a positive impact in patients' lives

Innate Advantages Combined With Proprietary Approaches

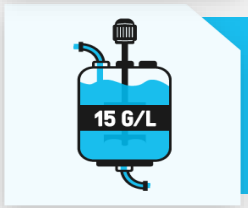
Unique DARPin® Features



Ideal binding properties
- Perfect fit
- High affinity
- Super specificity



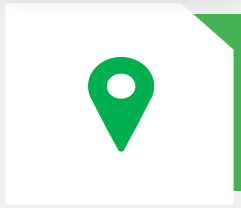
Turn-key multi-specifics
- Small size
- Uni-domain activity
- Up to 7 binders
- Open combinatorial space



Manufacturing & Storage
- High-yield microbial expression
- High stability

DARPin® Benefit

Tailored Grip
- Match disease requirements

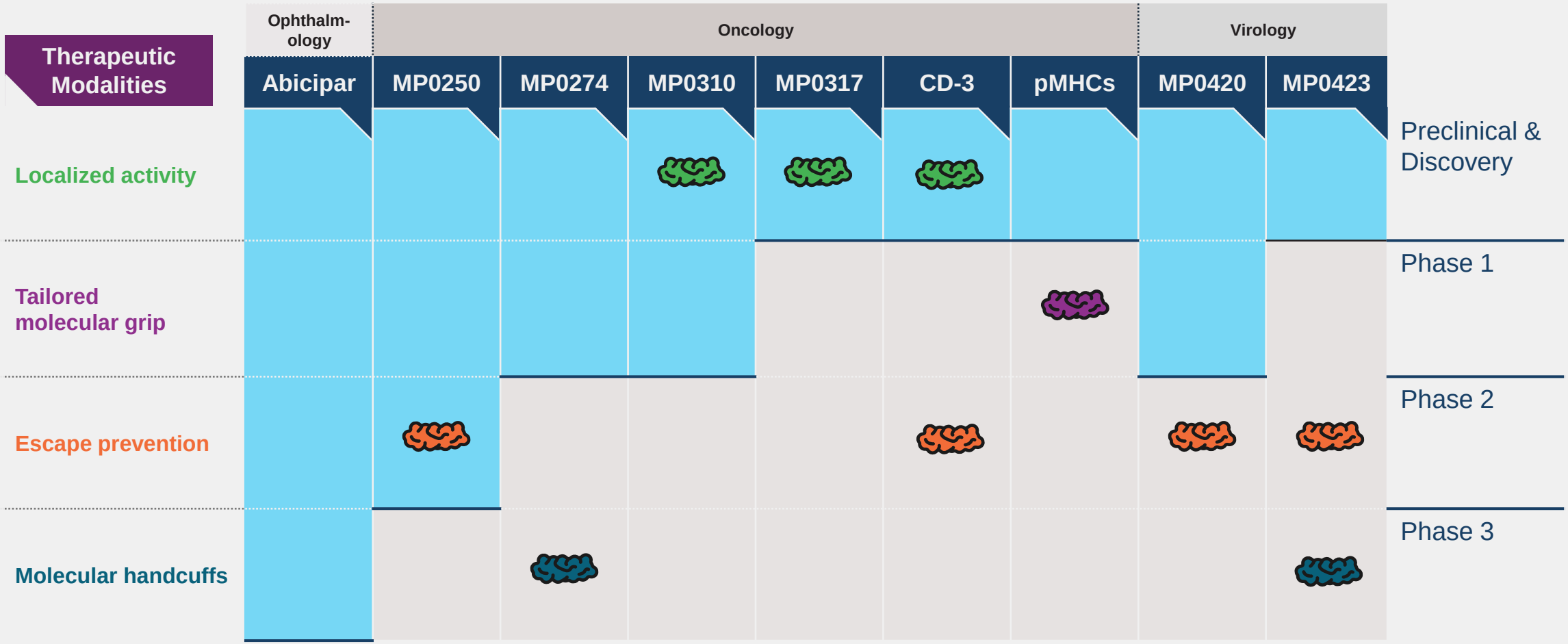


Localized Activity
- Local and temporal control of activity

Molecular Handcuff
- Full shut-down by conformational freeze

Multi-blocker to prevent escape
- Overcome escape pathways oncology / ID

A Portfolio Strategy Delivering Growth And Innovation



Synergistic Partnerships Built on a Versatile Drug Class

Ophthalmology

Therapeutic Area Deal

- Partnership for abicipar, two positive Phase 3 studies.
- Received $150m to date; $360m in potential milestones and teens royalty still possible
- CRL (June 2020): AbbVie evaluating next steps with agency

abbvie

Oncology

Product Combination Deal

- Partnership with Amgen to combine AMG 506 / MP0310 with BiTE® molecules
- Phase 1 conducted by MP and Amgen to develop for combination studies
- ~$500m in milestones and mid teen royalties

AMGEN®

Virology

Capability Deal

- Leverage production, global development and distribution of Sandoz Novartis for MP0420
- ~$165m milestone payment upon commercialization licensure
- 22% royalty on sales

NOVARTIS

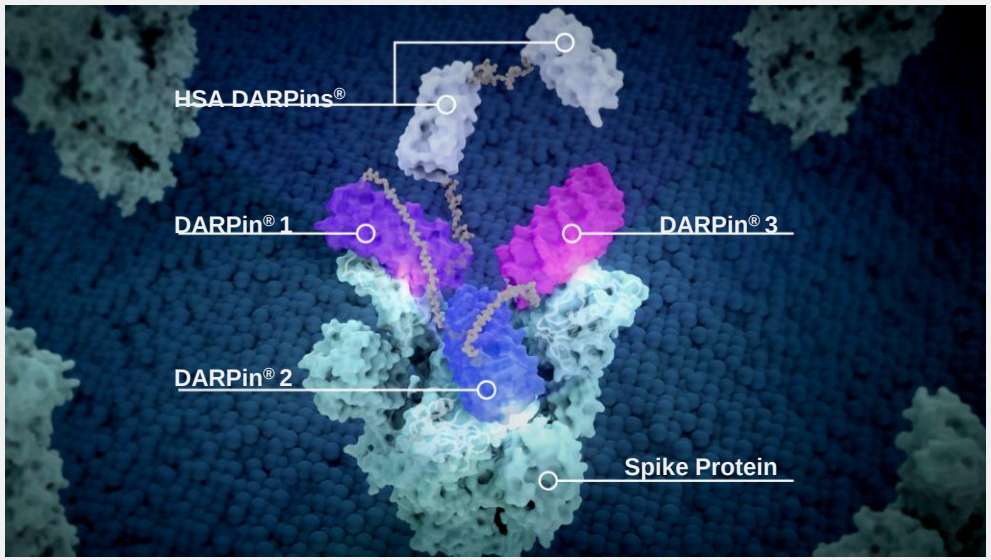
Over ~$1B in potential milestone across multiple programs

Clinical Program: Anti-COVID19

Our COVID-19 Program: Two Outstanding Candidates

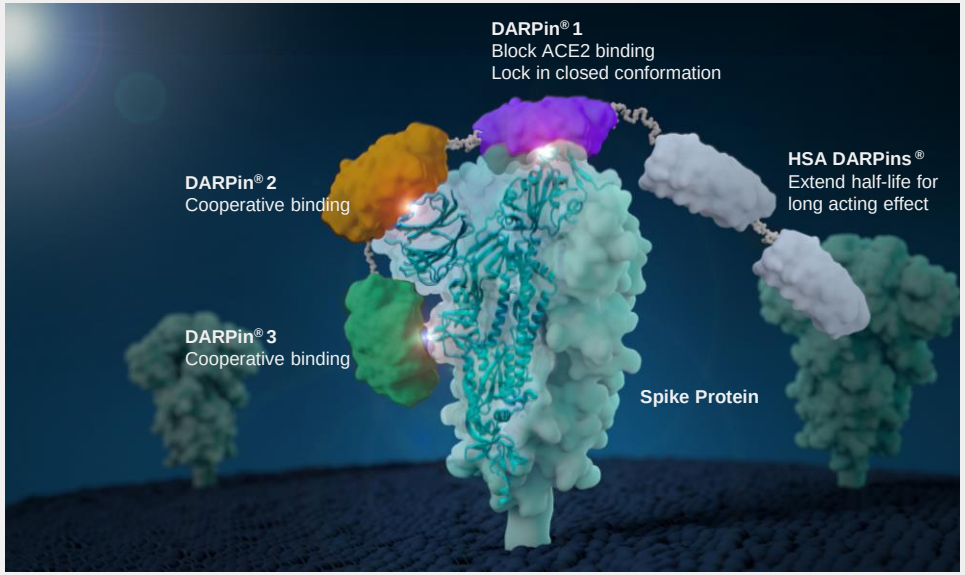
MP0420 (ensovibep)– best-in-class

- Tri-specific DARPin® antiviral targeting the RBD for highest potency & to prevent viral escape
- Long half-life (HSA DARPins) – single injection
- Low costs and high numbers of doses available
- Potential for bolus / s.c. injection – simple application



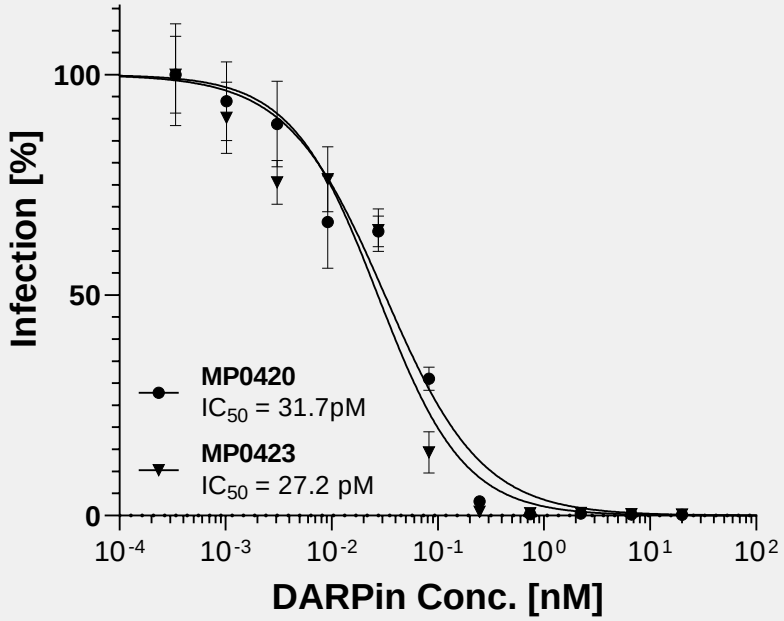
MP0423 – first-in-class

- 3 DARPins blocking different domains of the viral spike
- High activity even if RBD mutates heavily and escapes all vaccines and therapeutic antibodies
- All other benefits of MP0420



High Potency Inhibition Translates To *In Vivo* Prophylactic And Therapeutic Properties

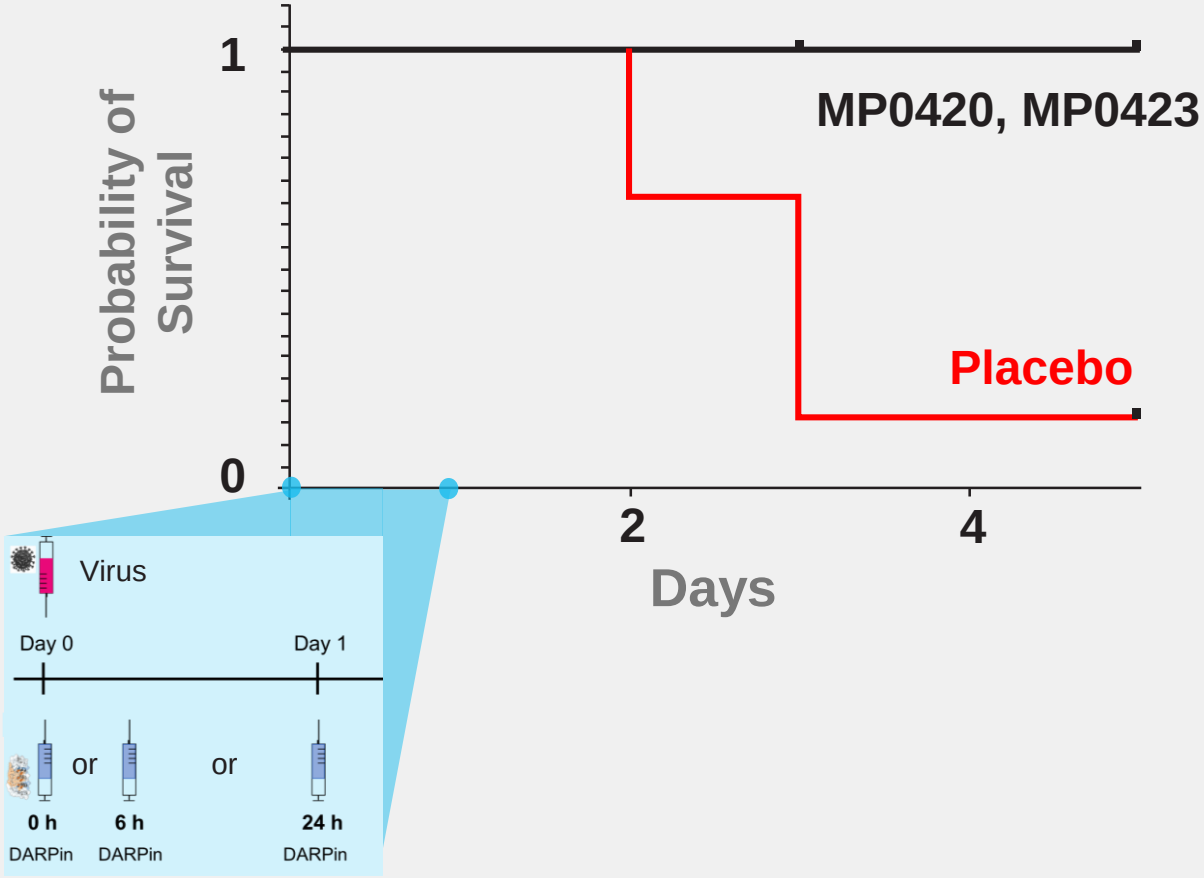
In vitro activity: Pseudotype Neutralization Assay



Highest potency

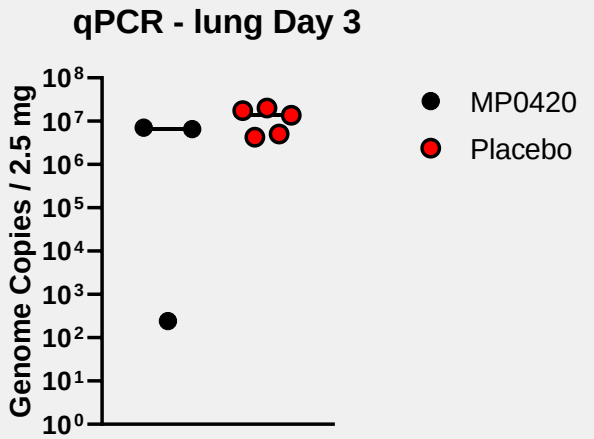
Tri-binding leads potency in the low pM range; likely at the assay limit

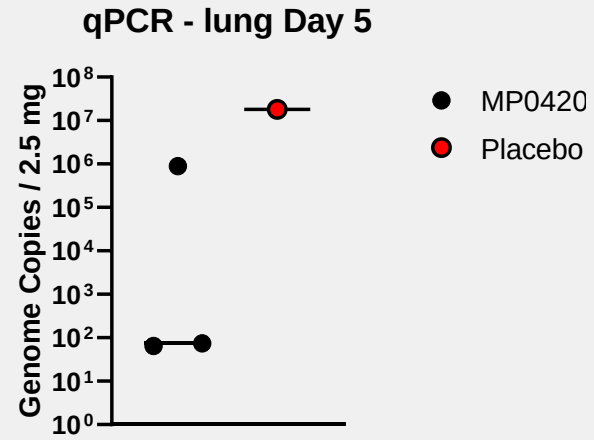
In vivo activity: Kaplan Meier Plot - Hamster Model (6 animals/group)



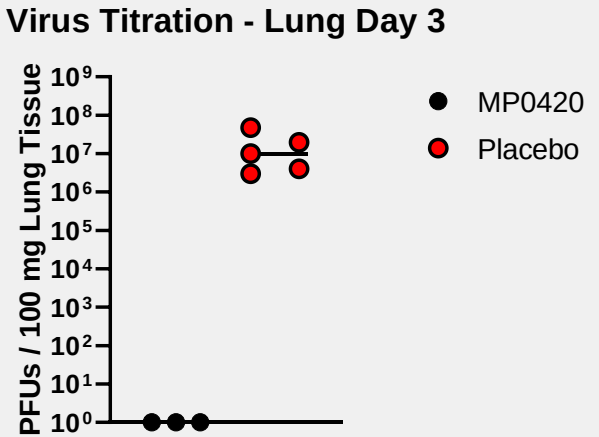
Ensovibep Blocks the Virus and Prevents Infection in the Lung

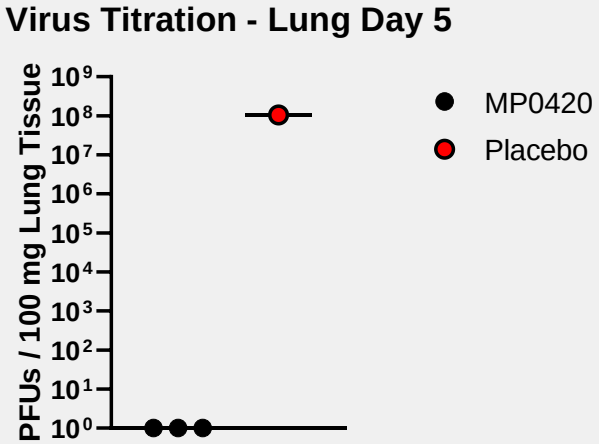
Viral titer in the lung





Viral infectivity in the lung

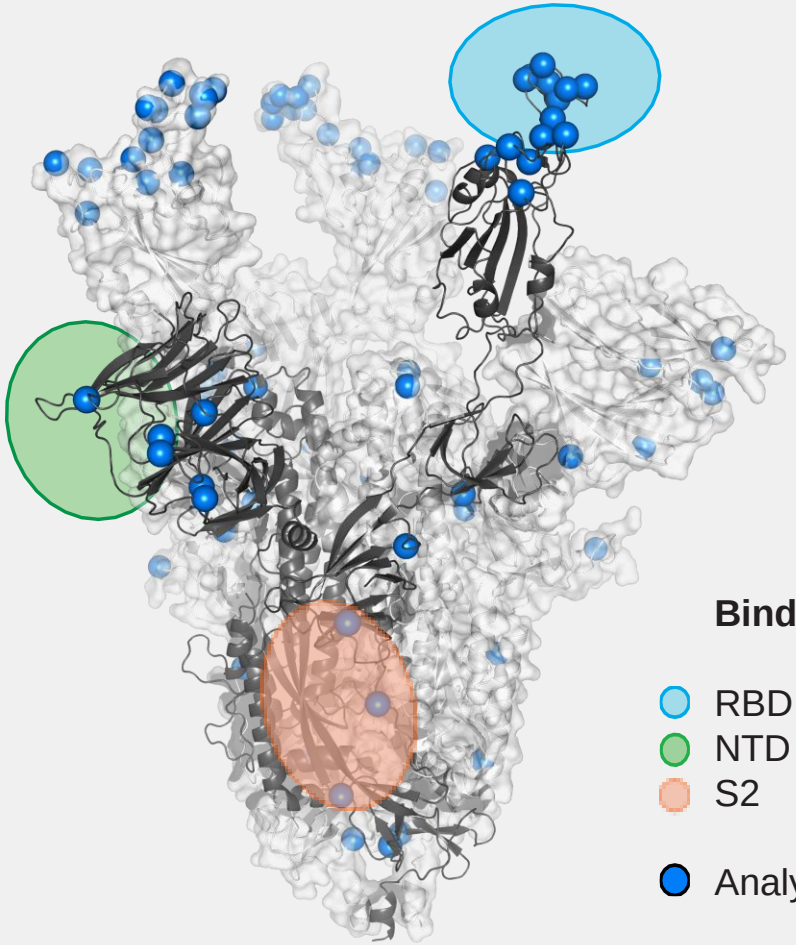




Ensovibep blocks viral infectivity completely

SARS-Cov2 Spike Protein: domains, mutations, variants

Spike Protein, Epitopes, Mutations

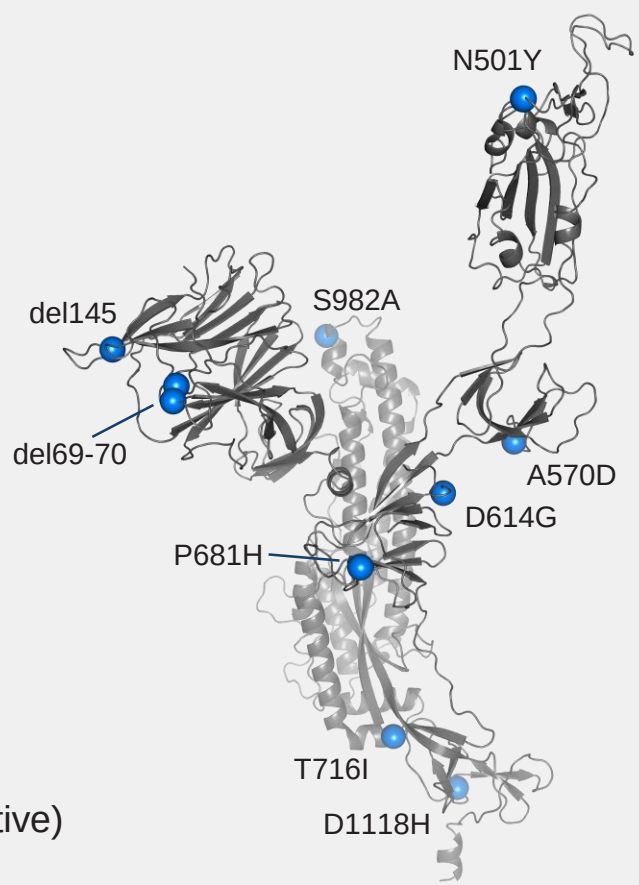


Binding regions:

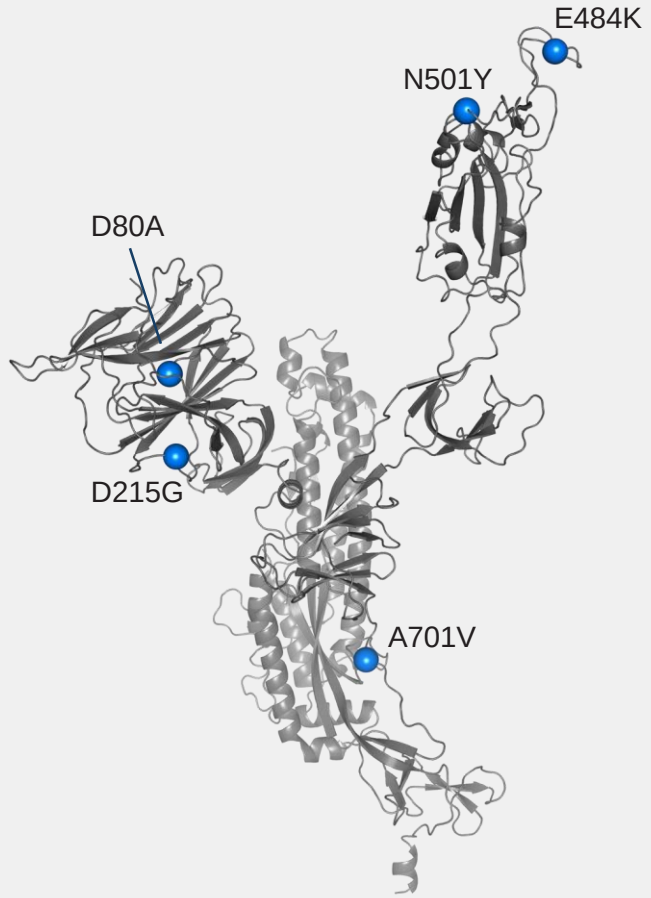
- RBD DARPin
- NTD DARPin
- S2 DARPin (putative)

- Analyzed mutations

UK and SA variant



UK Variant



South African Variant

Potency of our Candidates on viral mutants & variants

Variants	Rational	VSV Neutralizaiton Assay IC_{50} [ng/mL]			
		MP0420	MP0423	REGN 0933	REGN 10987
wild type	(Wuhan)	**1.0**	**3.1**	**3.9**	**6.1**
B.1.351	(SA, Δ5)*	**3.0**	**2.4**	**19.4**	**6.2**
B.1.1.7	(UK, Δ9)**	**1.7**	**70.1**	**2.4**	**3.5**
Individual Mutations: Residues in variants					
N501Y	in UK, SA, BRA variants; increases RBD/ACE2 interaction[1]	0.5	1.4	4.3	5.8
E484K	in SA, BRA variants; increases RBD/ACE2 interaction[1]	2.7	1.8	17	5.8
K417E	residue mutated to N/T in SA, BRA variants	0.5	1.2	>100	1.5
Y453F	key residue evolved in Danish mink farms variants	3.2	2	>100	11.8
Individual Mutations: Highly frequent mutations					
D614G	Wide global spread	2.4	2.8	n.d.	n.d.
S477N	Wide global spread	1.9	0.8	n.d.	n.d.
N439K	Wide spread in northern amerika, UK; increases RBD/ACE2 interaction[1]	1.3	2.5	2.8	30.1
A222V	Wide European spread	2.2	3.1	7	2.9
Individual Mutations: RBD epitope or reported resistance for other therapeutics					
G446V		1.7	1	1.5	>100
G476S		1.5	3.1	n.d.	n.d.
T478I		2.7	2.8	4	7
P479S		2.1	1.5	3.7	9.8
V483A		2.3	1.9	n.d.	n.d.
F486V	reduces RBD/ACE2 interaction non-fit virus[1]; key residue DARPin RBD binder[2]	>100	7.7	>100	4.4
Q493K		7.9	2.4	>100	10
F490S	Reduces RBD/ACE2 interaction[1]	3.8	1.6	3.1	9.2

Legend for the table

- n.d.: not determined
- Mutations (SA)*: D80A, D215G, E484K, N501Y, A701V
- Mutations (UK)**: del69-70, del145, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H
- Redish shade: IC50 values between >100 ng/mL (outside therapeutically active range)
- [1] Influence of residue mutations on spike protein binding to human ACE2 (Yi et al. 2020)
  - Increase: stronger ACE2 binding = fitter virus
  - Decrease: weaker ACE2 binding = unfit virus
- [2] Predicted interaction residue for DARPin RBD binder (Walser et al. 2020)

Cooperative binding – potency of the modules

Variants	Rational	VSV Neutralizaiton Assay IC_{50} [ng/mL]			
		MP0420	Mono-valent RBD Binders in MP0420		
			RBD-1	RBD-2	RBD-3
wild type	(Wuhan)	**1**	7.2	2.1	13.3
B.1.351	(SA, Δ5)*	**3.0**	76	26	>100
B.1.1.7	(UK, Δ9)**	**1.7**	4.6	5.4	11.7
Individual Mutations : Residues in variants					
N501Y	in UK, SA, BRA variants; increases RBD/ACE2 interaction[1]	**0.5**	9.1	4.8	27.8
E484K	in SA, BRA variants; increases RBD/ACE2 interaction[1]	**2.7**	64.2	10.2	>100
K417E	residue mutated to N/T in SA, BRA variants	**0.5**	1.8	1	3.6
Y453F	key residue evolved in Danish mink farms variants	**3.2**	10.9	5.9	3.3
Individual Mutations: Highly frequent mutations					
D614G	Wide global spread	**2.4**	11.9	6.2	23
S477N	Wide global spread	**1.9**	3	2	9
N439K	Wide spread in northern amerika, UK; increases RBD/ACE2 interaction[1]	**1.3**	7.3	5.3	12.9
A222V	Wide European spread	**2.2**	3.3	4.6	19.5
Individual Mutations: Within RBD epitope of DARPins or reported resistance mutation for other therapeutic					
G446V		**1.7**	0.7	1.8	2.3
G476S		**1.5**	2.3	3.7	29
T478I		**2.7**	11.2	3.1	16.7
P479S		**2.1**	7.2	2.3	27.6
V483A		**2.3**	21.8	8.4	21.3
F486V	reduces RBD/ACE2 interaction non-fit virus[1]; key residue DARPin RBD binder[2]	**>100**	>100	>100	>100
Q493K		**7.9**	30	28.2	45.8
F490S	Reduces RBD/ACE2 interaction[1]	**3.8**	2.3	1.7	8.1

MP0420 (ensovibep) Phase 1 Ongoing

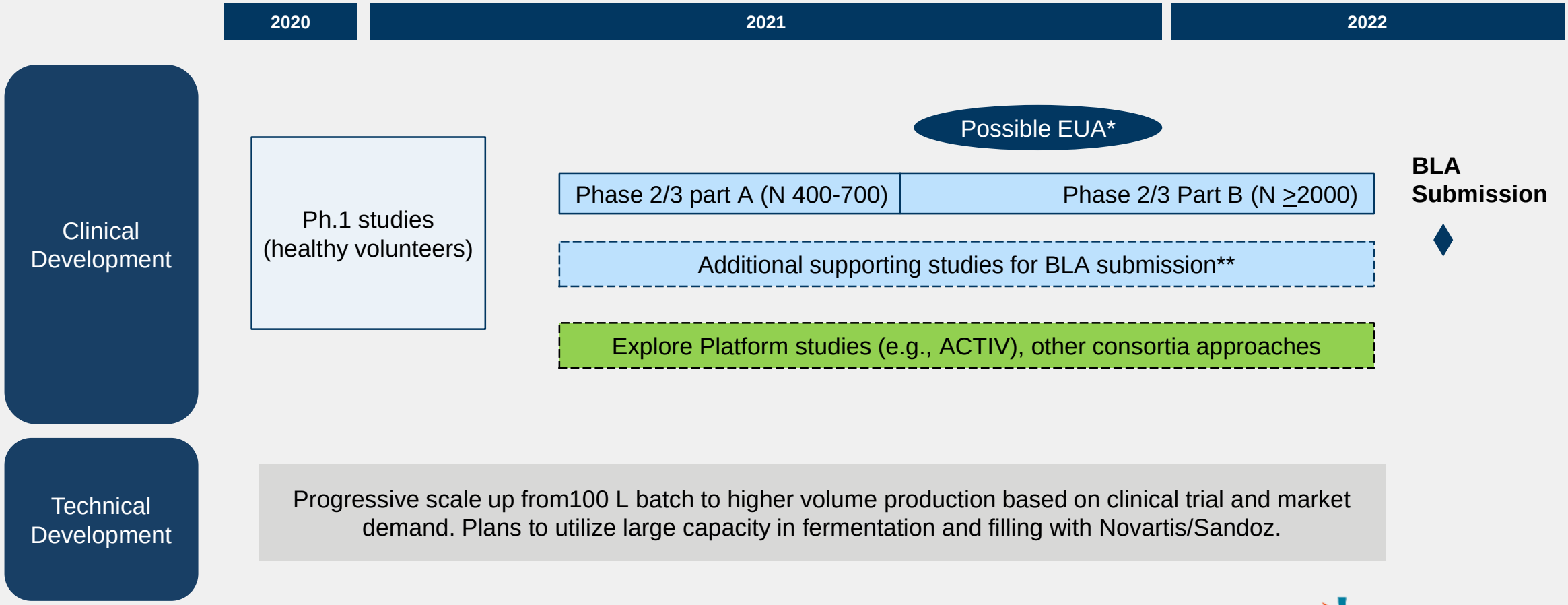
- Study initiated November 2020, first cohort fully enrolled
- Double-blind, placebo controlled trial exploring safety and PK.
  - IV administration
  - Up to 24 subjects total, stratified 3:1 (active: placebo)
  - Ages 18-65
- Dose range include 3 mg/kg (225 mg*), 9 mg/kg (675 mg) and 20 mg/kg (1.5 g)
- Endpoints: Safety, tolerability and pharmacokinetics (SAD)
- Status:1st cohort completed; 2nd cohort ongoing

Full data expected by Q1 2021

* Total amount in a person with 75 kg body weight

Novartis: Draft Development plan for MP0420

ALL DATES PRELIMINARY, SUBJECT TO HEALTH AUTHORITY INPUT



* Emergency Use Authorization submission, pending interim analysis of data is supportive of EUA
** Could involve additional dosing/ administration or treatment subtypes/ settings

NOVARTIS

Novartis Collaboration Highlights Strengths of Each Company

Novartis:
manufacturing, supply and logistics for global reach

Both parties commit to global access, aiming to make candidates available to all countries in need

Molecular Partners:
two multi-specific anti-COVID candidates

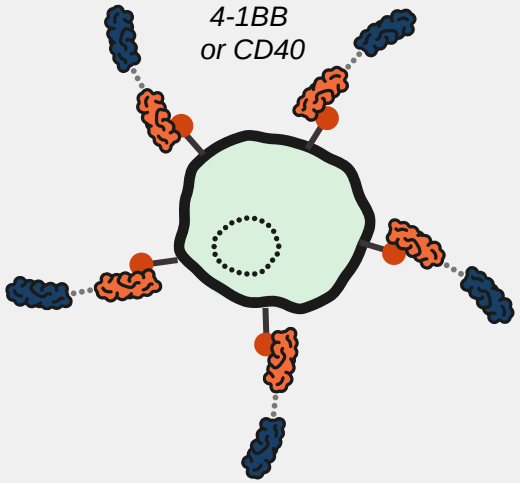
Novartis has the clinical expertise and capabilities fast development

Clinical Programs:
Tumor Localized Activators

Local Activation of Immune cells: Fibroblast Activation Protein (FAP) as a General Switch

BODY

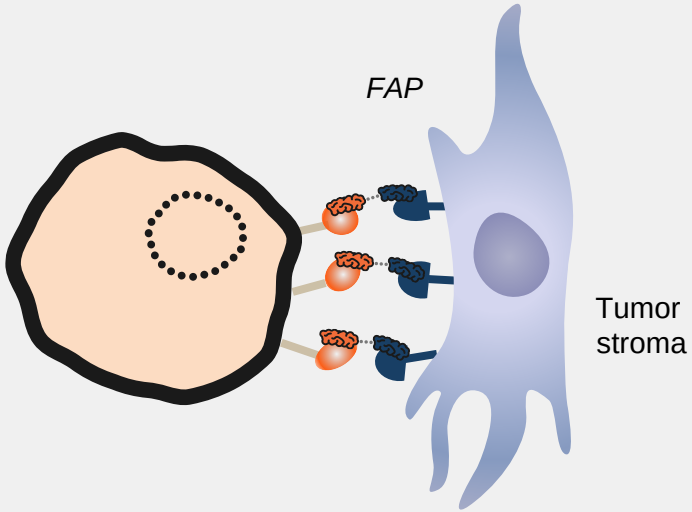
- In normal tissues, receptor is broadly distributed
- Immune cell remains inactive

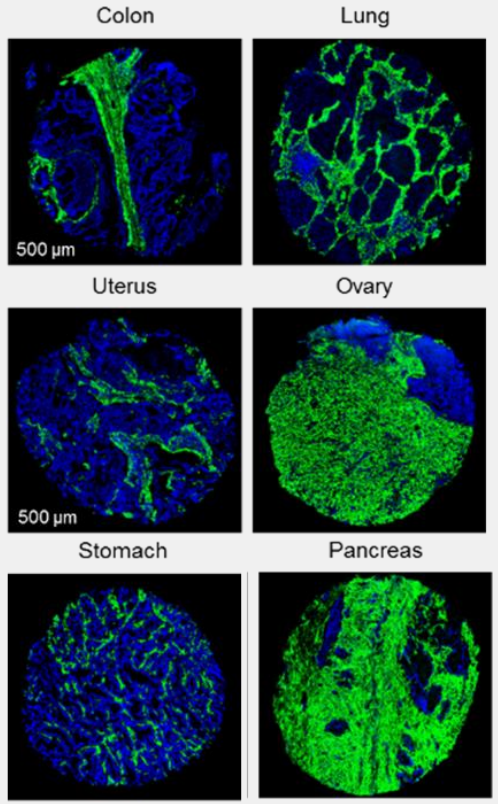


VS

TUMOR

- High FAP concentration near tumor clusters receptors
- Immune cell is activated





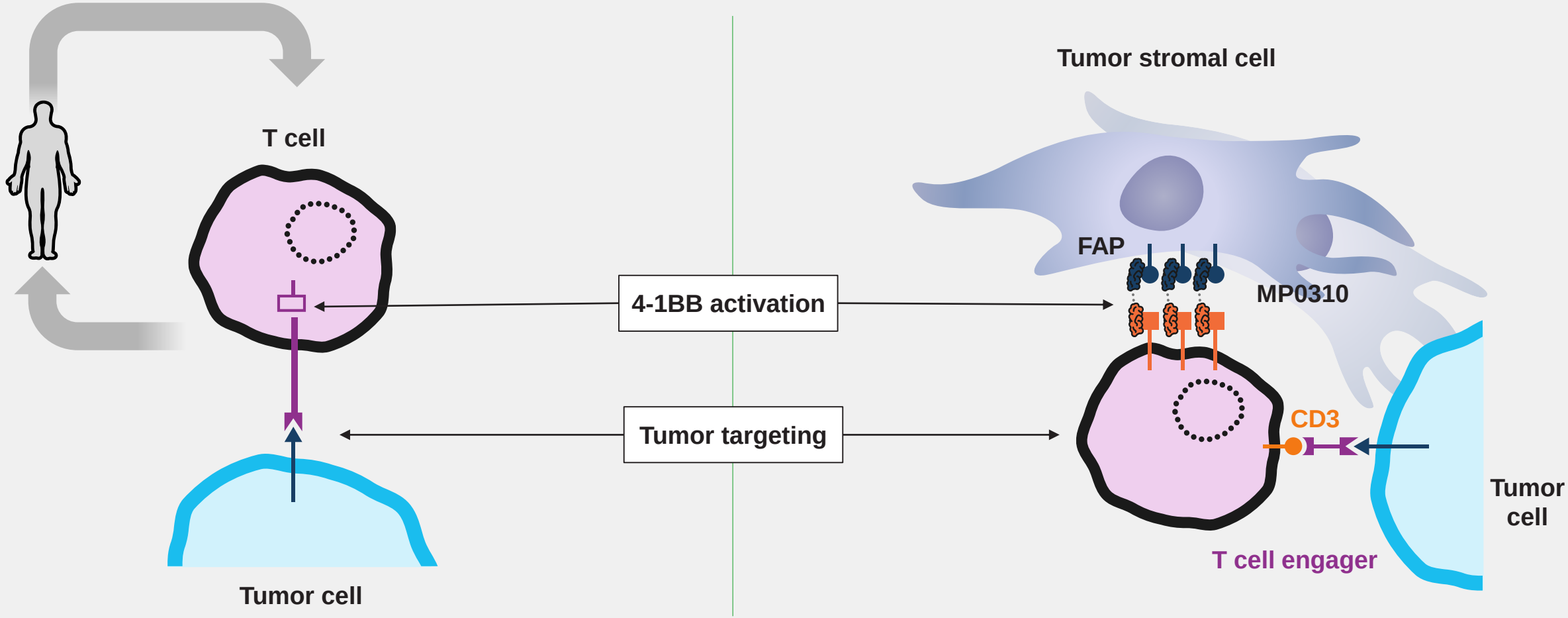
Human FAP, DAPI

- No activation by mono-binding of FAP or CD40/4-1BB
- Simultaneous binding leads to tumor-local immune activation

Application: Local T Cell Targeted Activation

Traditional CAR-T

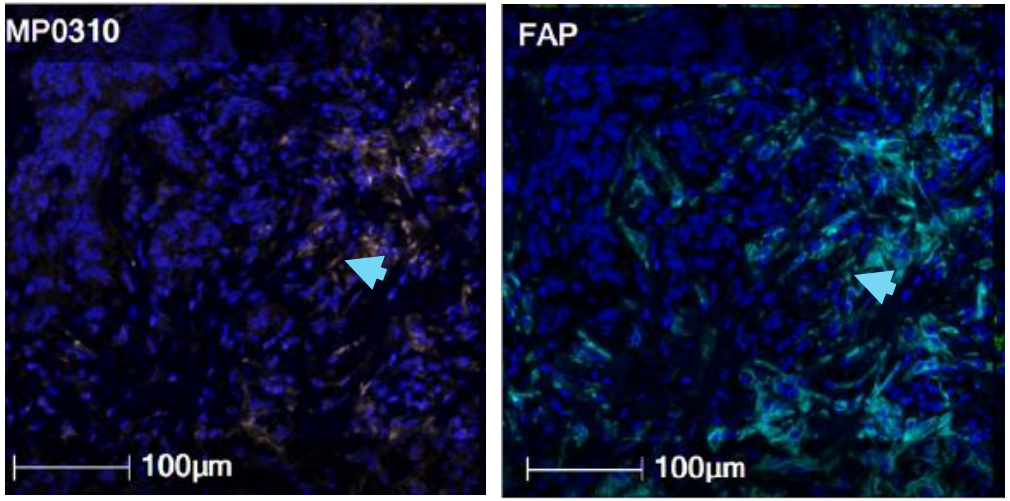
"CAR-T *in situ*"



AMG 506 / MP0310 Accumulates in Tumor Tissue in Dose Dependent Manner

MP0310 (0.5mg/kg) colocalizes with FAP

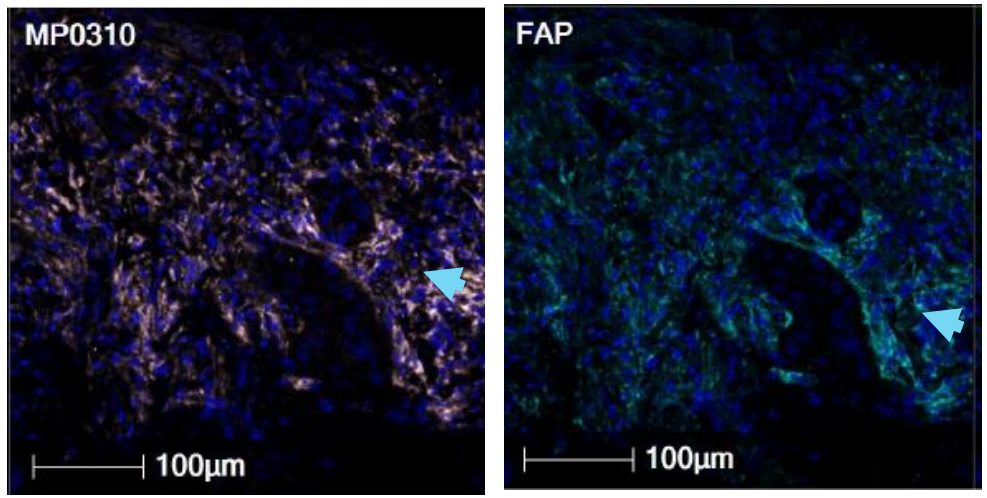
MP0310 < FAP



Endometrial carcinoma (Liver metastasis), C1D15

MP0310 (5mg/kg) saturates FAP

MP0310 > FAP



NSCLC (lung), C1D15

AMG 506 / MP0310 Dose Escalation Completed

- Executed on schedule through 2020
- 22 patients enrolled, 19 presently evaluable
- 7 dosing cohorts
  - Dosing: 0.015 mg/kg to 12 mg/kg
  - 8 patients with ≥4 cycles
- **No Dose limiting toxicities (DLTs)**
- 12 patients exhibited infusion related reactions (IRR) G2-3, out of 22 enrolled.
- No other AEs of special interest

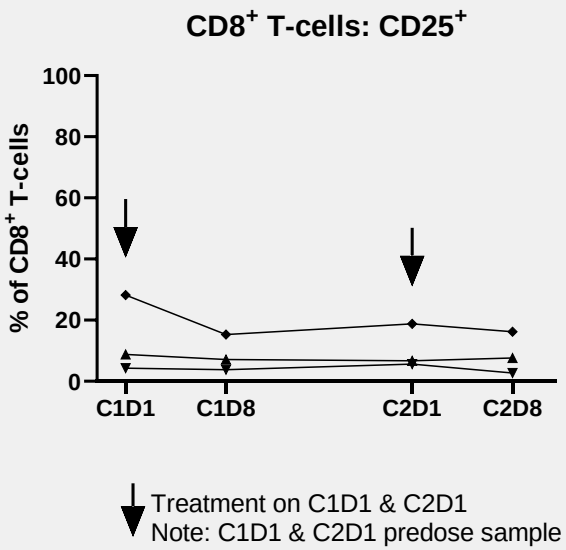
AESI	N affected pts. / N events	Max. grade
Infusion related reactions > G 1*	12 / 19	3
Cytokine release syndrome – any	0	-
Hepatitis – any	0	-
Pneumonitis – any	0	-
Respiratory distress – any	0	-
Colitis – any	0	-
Endocrinopathies > G 2	0	-
Skin Rash > G 2	0	-
Tumor lysis syndrome – any	0	-
Nephritis > G 1	0	-
Auto-immune disease > G 1	0	-

* Not included here: 1 IRR event G1;

Data as of 30 Nov 2020

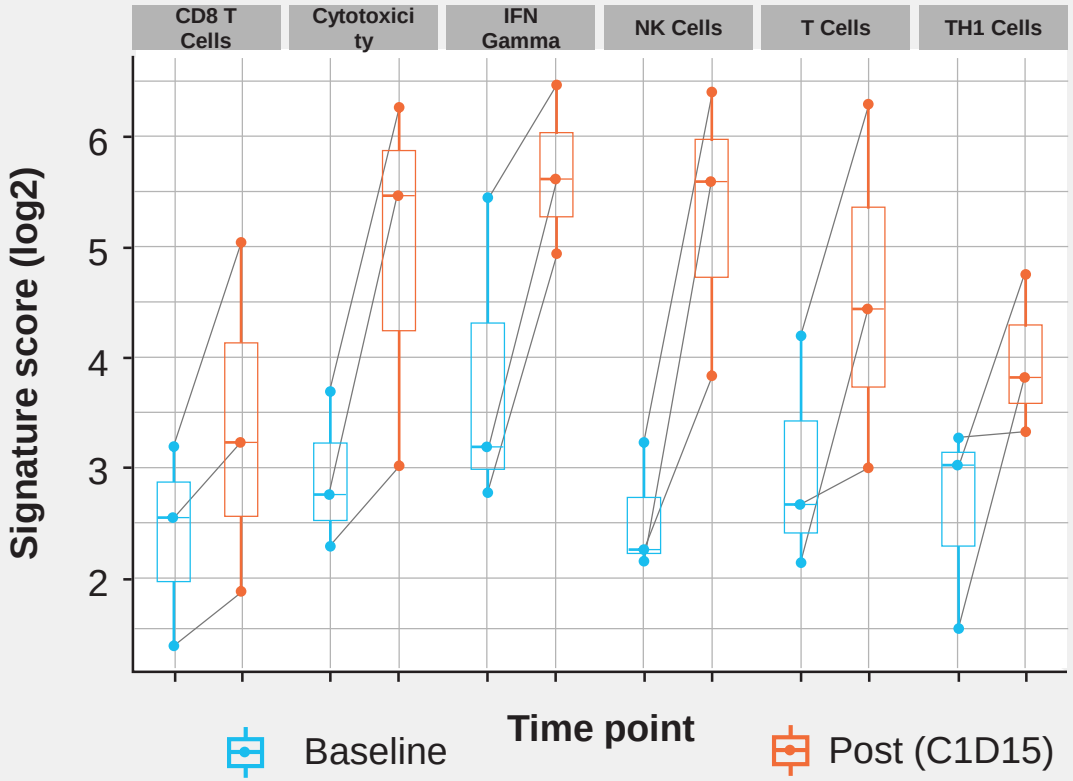
PD Activity in Paired Biopsies Supports AMG 506 / MP0310 MoA on 4-1BB Activation

BLOOD



- In the blood, immune cells remain inactive (CD8+ & CD4+ T-cells, Treg, NKT, B-cells, NK)

TUMOR



- In the tumor, T-cells and NK cells are activated

AMG 506 / MP0310 Dose Escalation Completed

- 22 patients enrolled
- 19 presently evaluable
- Typical Phase I population
  - heavily pretreated
  - with different cancer indications
- 8 patients with ≥4 cycles
- 9 patients with PD
- 9 patients with SD
- Cohort 7 not evaluable yet

Cohort	Patient ID	Cancer type	Cycles	Best Response
1	03-001	Mesothelioma	4	SD
0.015mg/kg	03-002	Cutaneous squamous cell	5	SD
	03-003	Mesothelioma	4	SD
2	02-001	Ovarian adenocc	4	PD
0.05mg/kg	01-001	Pancreatic adenocc	3	SD
	03-004	Pancreatic adenocc	2	PD
3	03-005	Endometrial adenocc	2	PD
0.15mg/kg	01-002	Pancreatic adenocc	2	PD
	02-003	Pancreatic adenocc	2	PD
4	03-006	Mesothelioma	5	SD
0.5mg/kg	02-004	Pancreatic adenocc	3	uPD
	01-003	Endometrial adenocc	2	PD
	02-005	Melanoma	5	SD
5	01-004	Adenocc colon	2	PD
1.5mg/kg	03-007	Mesothelioma	6	SD
	03-008	Mesothelioma	4	SD
6	03-009	NSCLC	2	SD
5mg/kg	01-006	Melanoma	2	PD
	02-006	H&N scq.cell cc	2	PD
7	01-007	Adenocc colon	2	Pending
12mg/kg	03-010	Mesothelioma	2	Pending
	02-007	Cervical	1	Pending

AMG 506 / MP0310 – Key Messages

1. **Good safety profile without major systemic toxicity**
    a. No liver toxicity, no systemic activation of immune cells
    b. IRRs frequent but manageable

2. **MP0310 is observed in tumor tissue**

3. **Tumor biopsies show tumor-localized immune response consistent with the MoA**

4. **Next step: investigate appropriate dosing schedule for sustained activity**

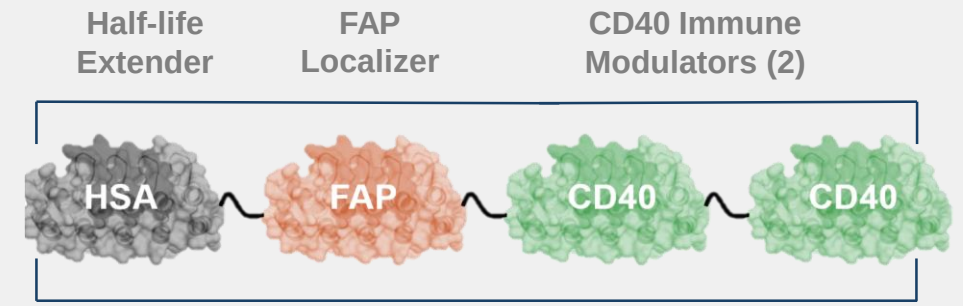
MP0317: Localized Activation of CD40

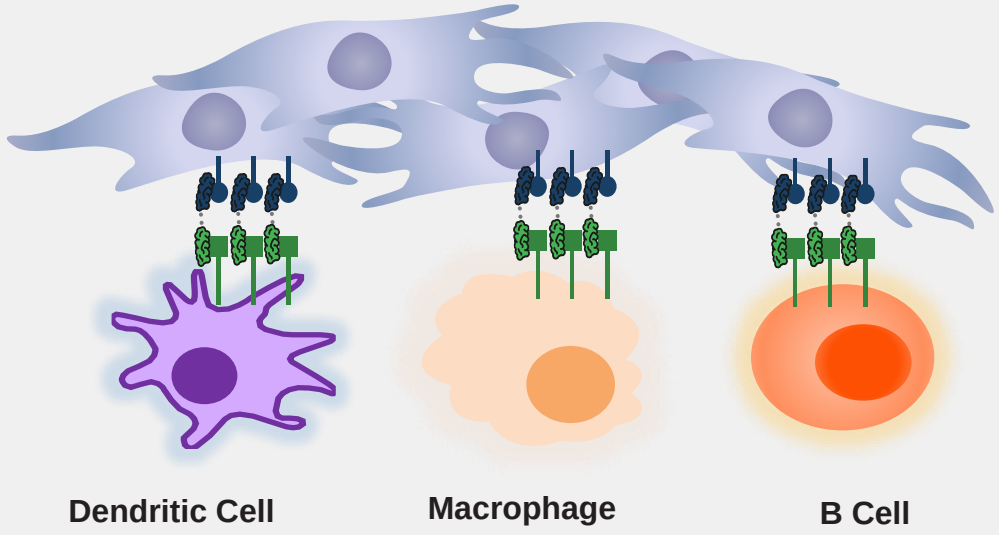
Current limitations and opportunity

- Rather low MTDs for systemic antibody agonists (< 1mg/kg)
- Likely need for combination therapy leading to additional risks for toxicity

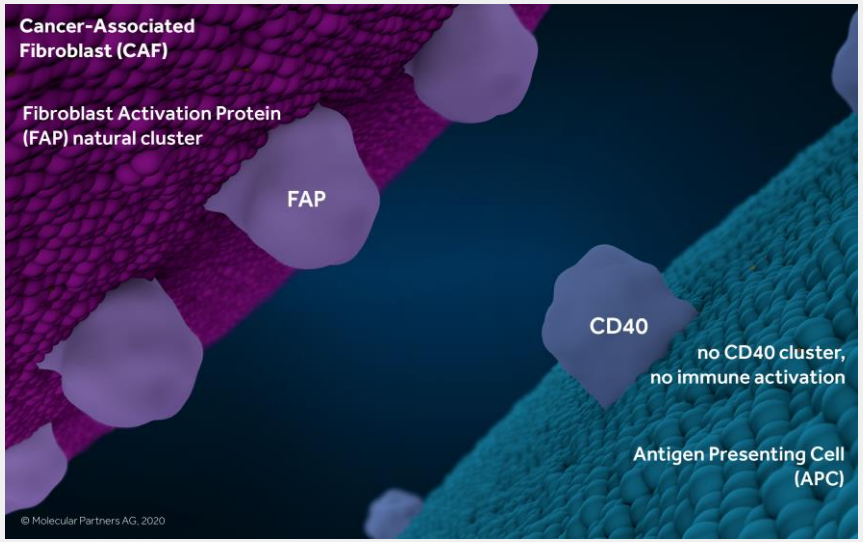
Opportunity

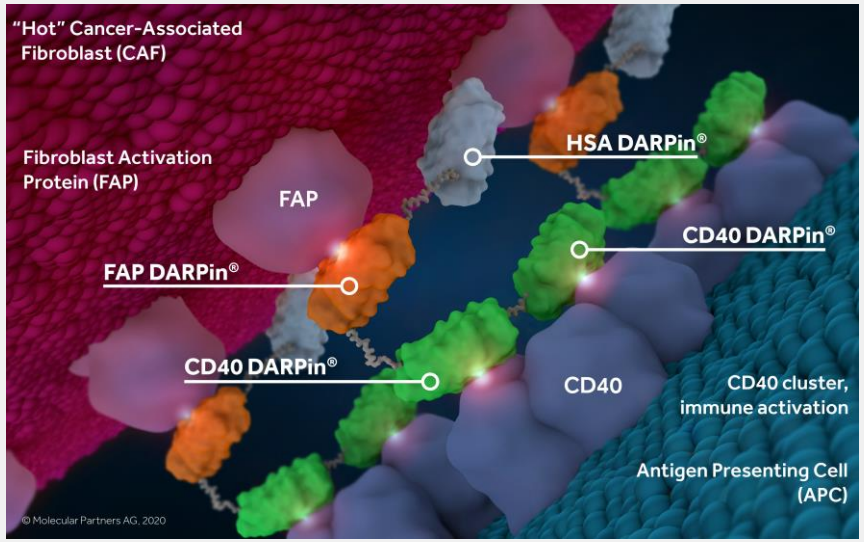
- Localized activation approach to limit systemic side effects and open a therapeutic window for combinations
- FIH H2 2021





CD40 requires clustering for activation

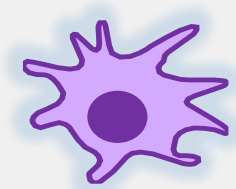




- Efficient signaling through CD40 requires high level of cross-linking
- **Our solution:** a FAP x CD40 bispecific molecule binding a densely expressed tumor associated antigen for clustering

MP0317: FAP-dependent Activation of Specific Immune Cells

A

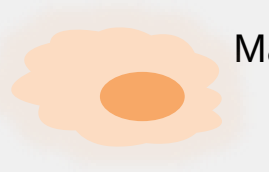


Dendritic cells:

CD86 ✓ IL-12 ✓

CD83 ✓ CD80 ✓

B



Macrophages:

TNFα ✓ IL-12 ✓

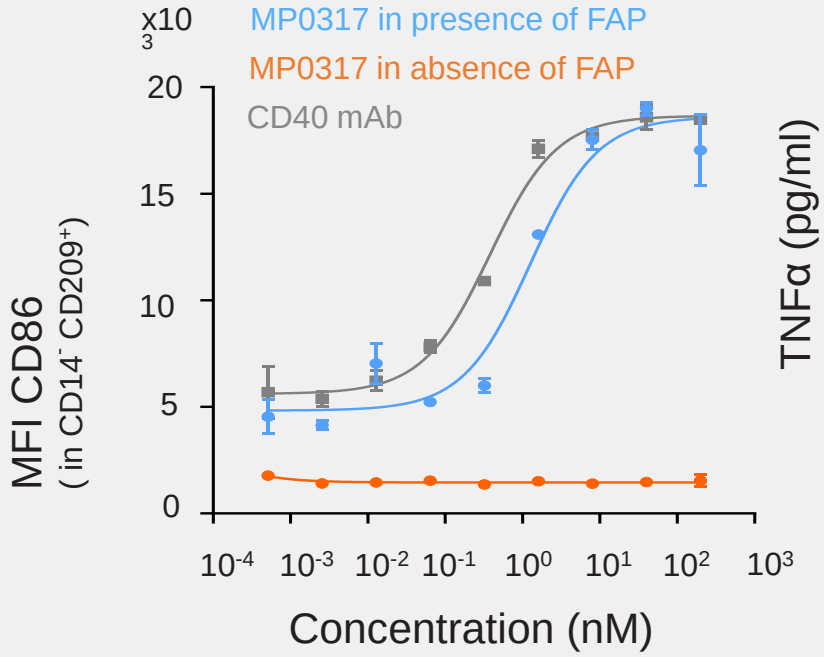
IL-6 ✓ CCL17 ✓

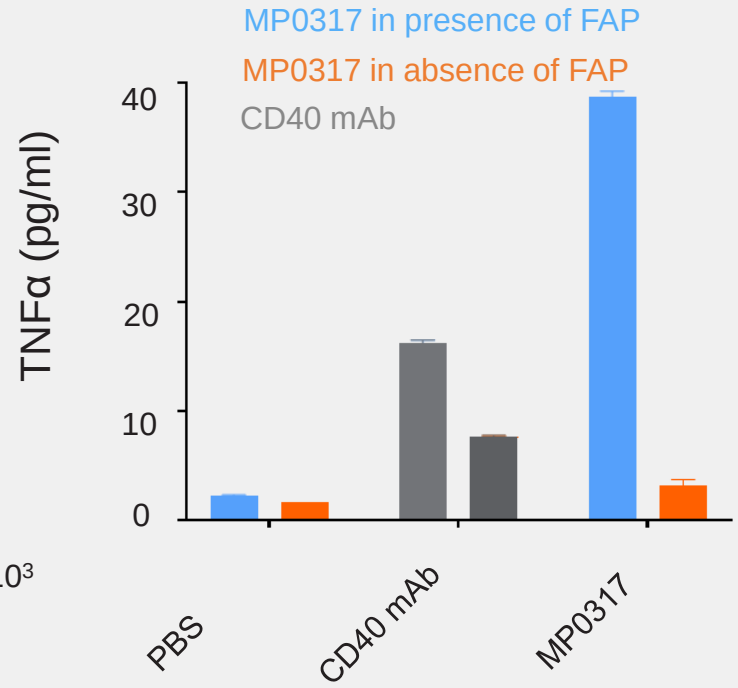
C

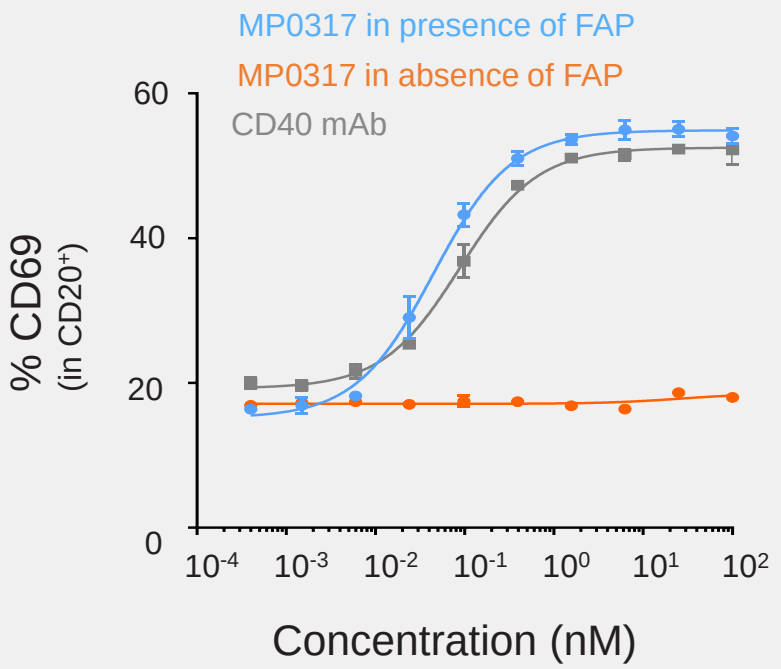
B cells:

CD69 ✓

CD86 ✓

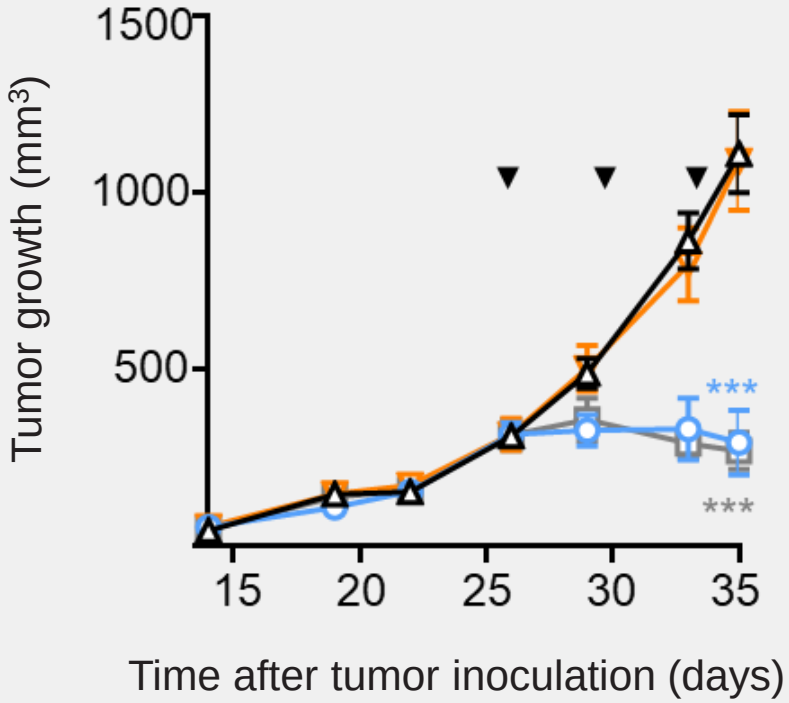


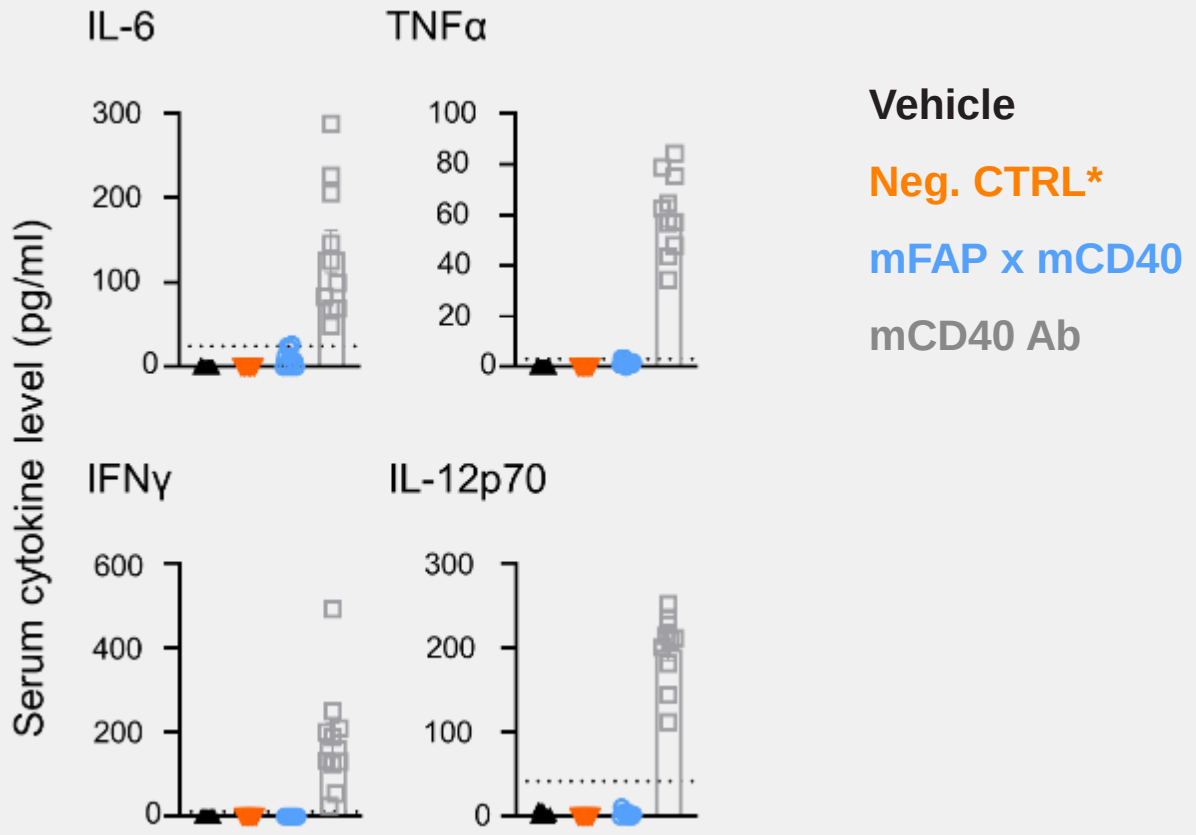




MP0317 Shows Full Activity with No Detectable Side-effects

FAP^{HIGH} TUMOR: MC38-FAP Colorectal cancer





MOLECULAR partners

New Therapeutic Platforms: Unlocked

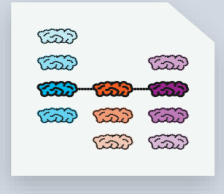
From DARPin® Features to Benefits

DARPin® Facts

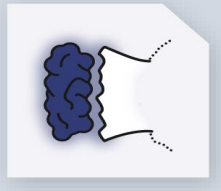
- Small (15 kDa) and simple
- High affinity and specificity
- High stability and solubility
- Well expressed in bacteria
- “Nature’s choice” for multi-specificity
- Tunable systemic half-life
- Safe & efficacious in clinic

Unique DARPin® Features

- **Turn-key Multispecifics:** multi-DARPin® formatting with up to 7 functionalities in one molecule



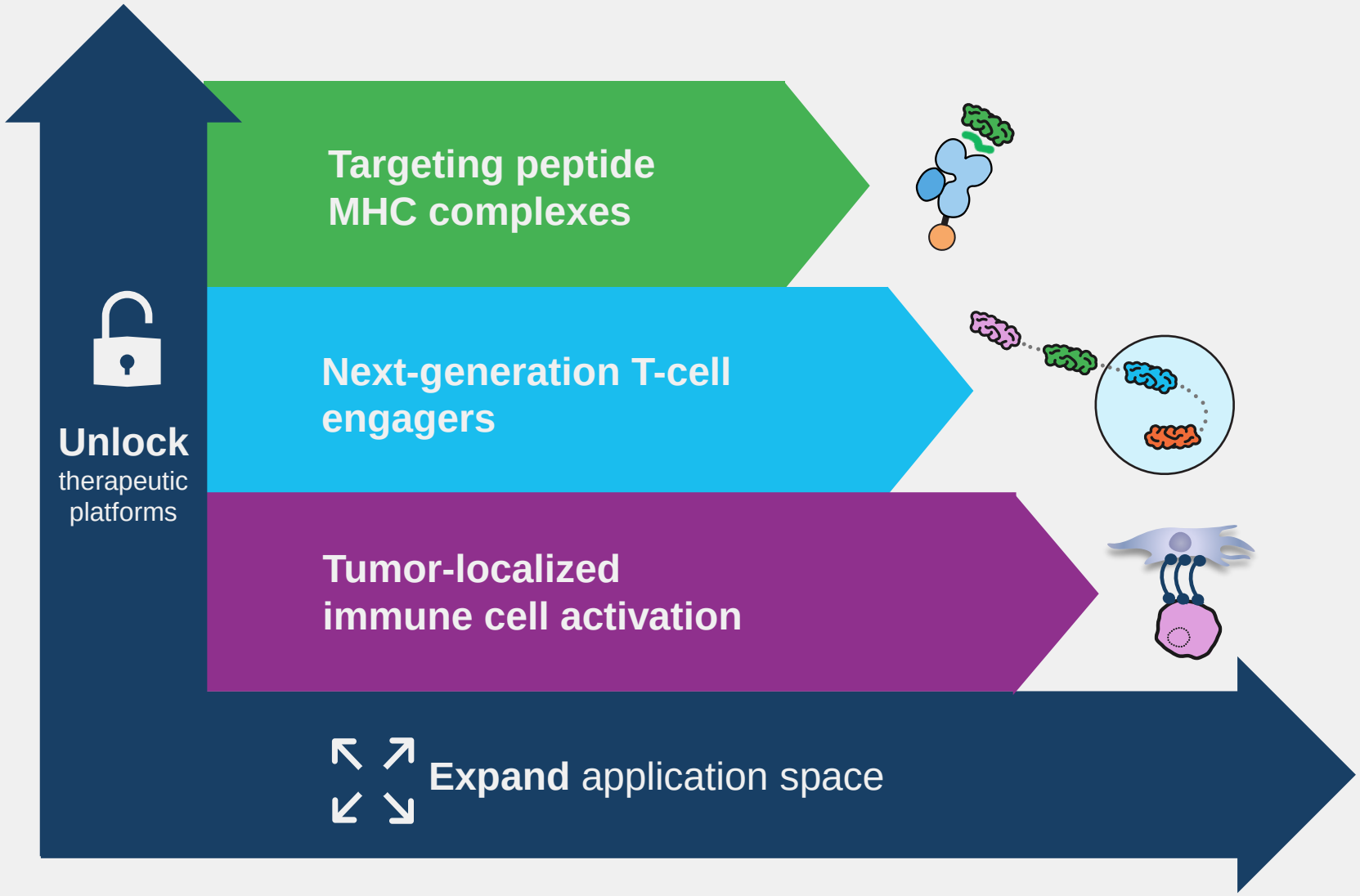
- **Super Specificity:** Based on structure of binding surface



DARPin® Benefit

- **Disease-localized activity** to open the therapeutic window
- **Multi-blocker** to prevent escape and resistance
- **Molecular handcuff** for complete inhibition
- **Tailored “grip”** on hard to bind targets (e.g. pMHC)
- **Broad potential** waiting to be unlocked

Unlock and Expand: Therapeutic Platforms



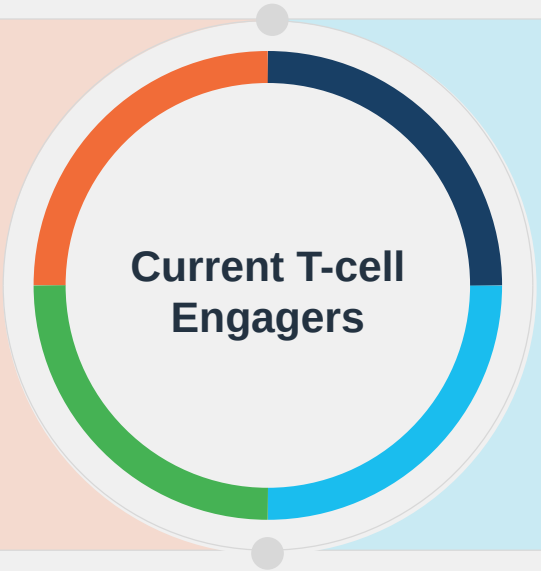
Challenges of T-cell Engagers in the Clinic

Safety

TOXICITY PROFILE LIMITS OPTIMAL DOSING

Attack on healthy tissues
(on-target off-tumor binding)

Hyper-immune stimulation:
CRS and neurotoxicity



Efficacy

LACKING LONG-LASTING AND DEEP RESPONSES

Tumor escape & relapse
(heterogeneity, target loss,
mutation or downregulation)

Lack of efficacy in solid tumors
(tissue penetration, suppressive
microenvironment, T-cell exhaustion…)

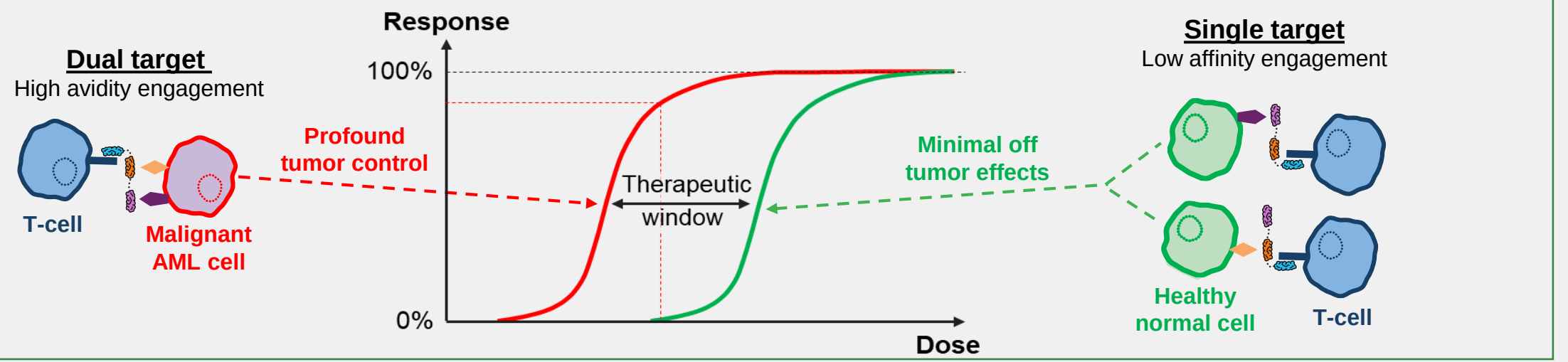
Multi-specific DARPin® T-cell Engager with Improved Benefit/Risk in AML

Medical problem

- **High medical need** and **high relapse rate** in AML with current therapies
- Single-target T-cell engagers show promising efficacy, but optimal biological dose level not reached due to **dose-limiting toxicities**

DARPin® solution

- **Multi-DARPin with enhanced tumor selectivity** to
  (i) reduce off tumor effects, (ii) achieve higher dose levels and ultimately, (iii) better efficacy



Multi-DARPin® Versatility Allows Screening for Function Sweet Spot

 # molecules

10^{12}
Library to generate binders against TAA1 / TAA2 / TAA3…

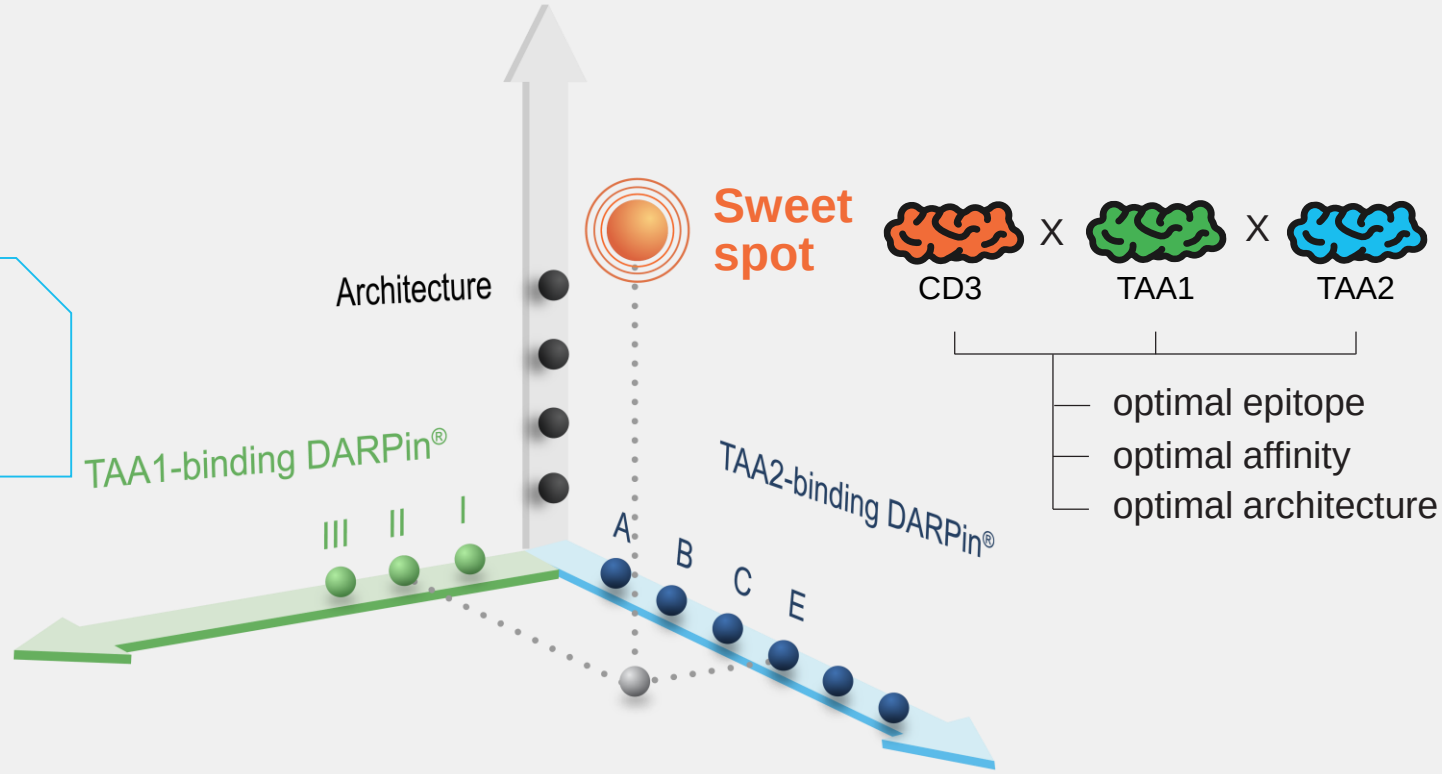
10s
Identified functional and well behaved DARPin® modules (for each target)

Recombination of DARPin® modules: **Fast & high throughput process: 2 weeks (start of cloning to purified proteins)**

1000s
Screening of multi-domain DARPin® space

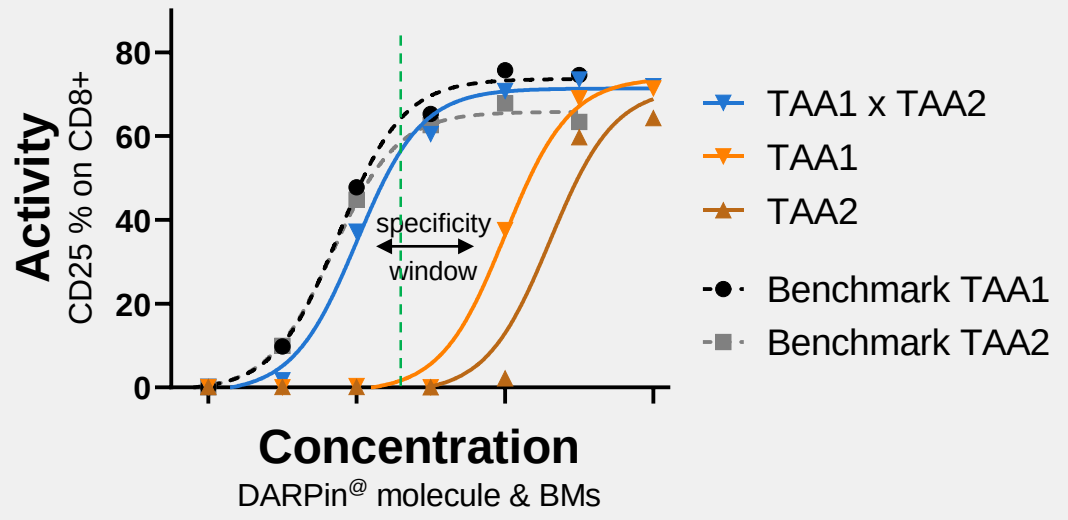
2-5
Multi-DARPin® product candidates

Multi-domain DARPin® space

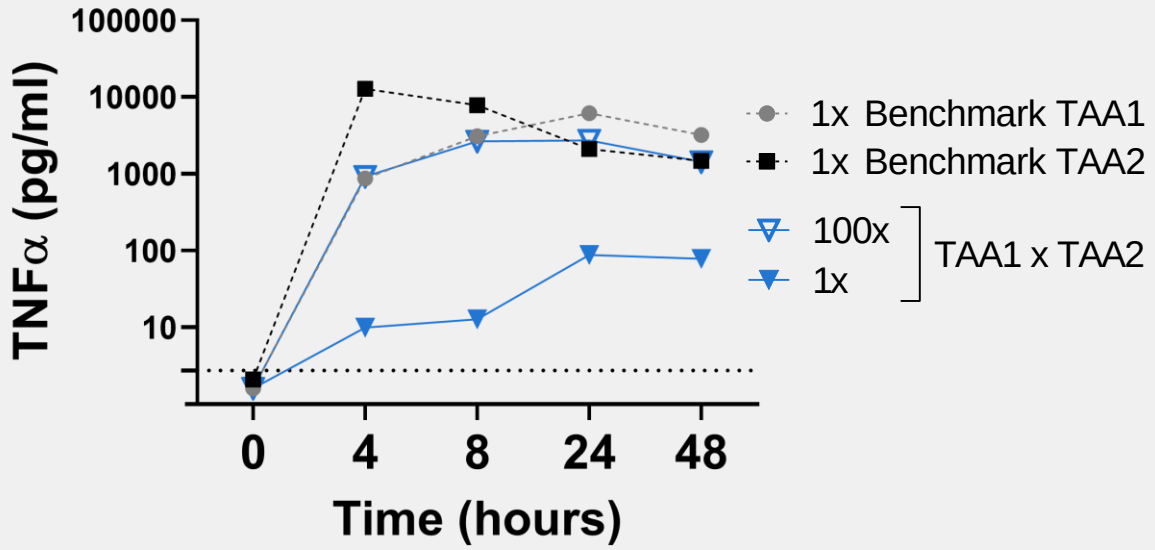


Multi-DARPins® for AML Show High Potency, Improved Selectivity and Potential for Reduced CRS

In-vitro potency and specificity assessment on AML cells



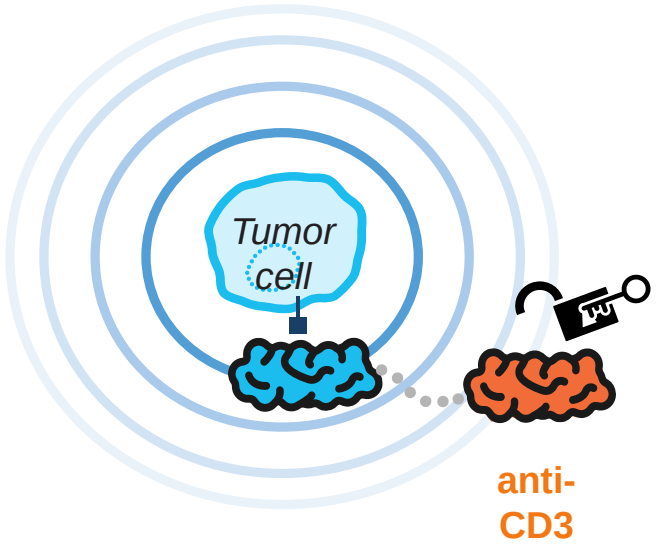
Ex-vivo cytokine release in healthy human whole blood



AACR 2021

Expand with Platform for Controlled Activation of CD3 Effector Function

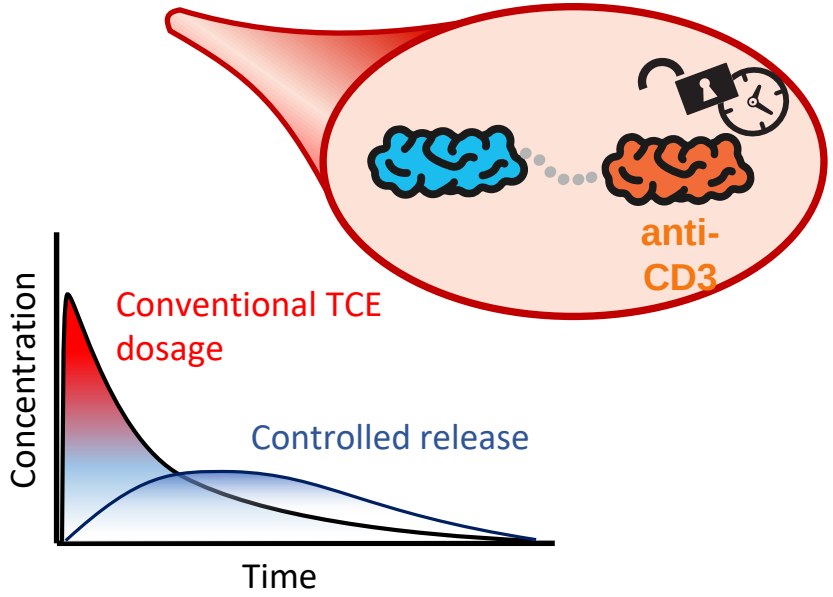
Where
Conditional activation locally in the TME



- Local activation for reduced on-target, off-tumor activity

Inactive at treatment start

When
Slow activation over time in circulation



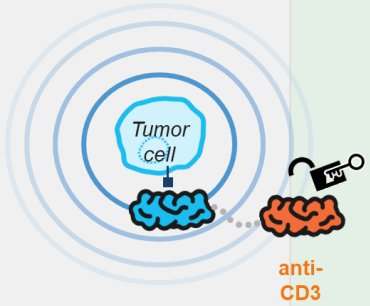
- Reduced C_{max} at treatment start, increasing bioactivity over time

AACR 2021

DARPin® solutions for improved benefit-risk profile of T-Cell Engagers

Safety

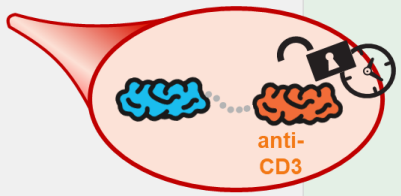
DECREASED TOXICITY FOR OPTIMAL DOSING



Multi-specific T-cell Engagers with increased selectivity

Decreased attack on healthy tissues

Controlled "conditional CD3 activation"



Controlled "slow CD3 activation"

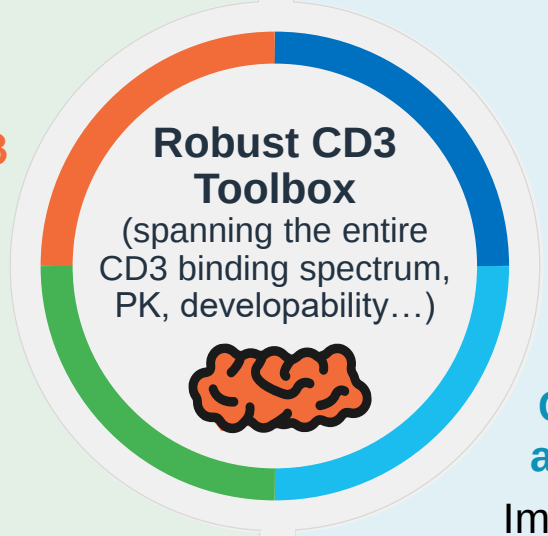
Reduced hyper-immune stimulation: CRS and neurotoxicity

Efficacy

LONG-LASTING AND DEEP RESPONSES

Multi-specific T-cell Engagers to cover heterogeneous tumors

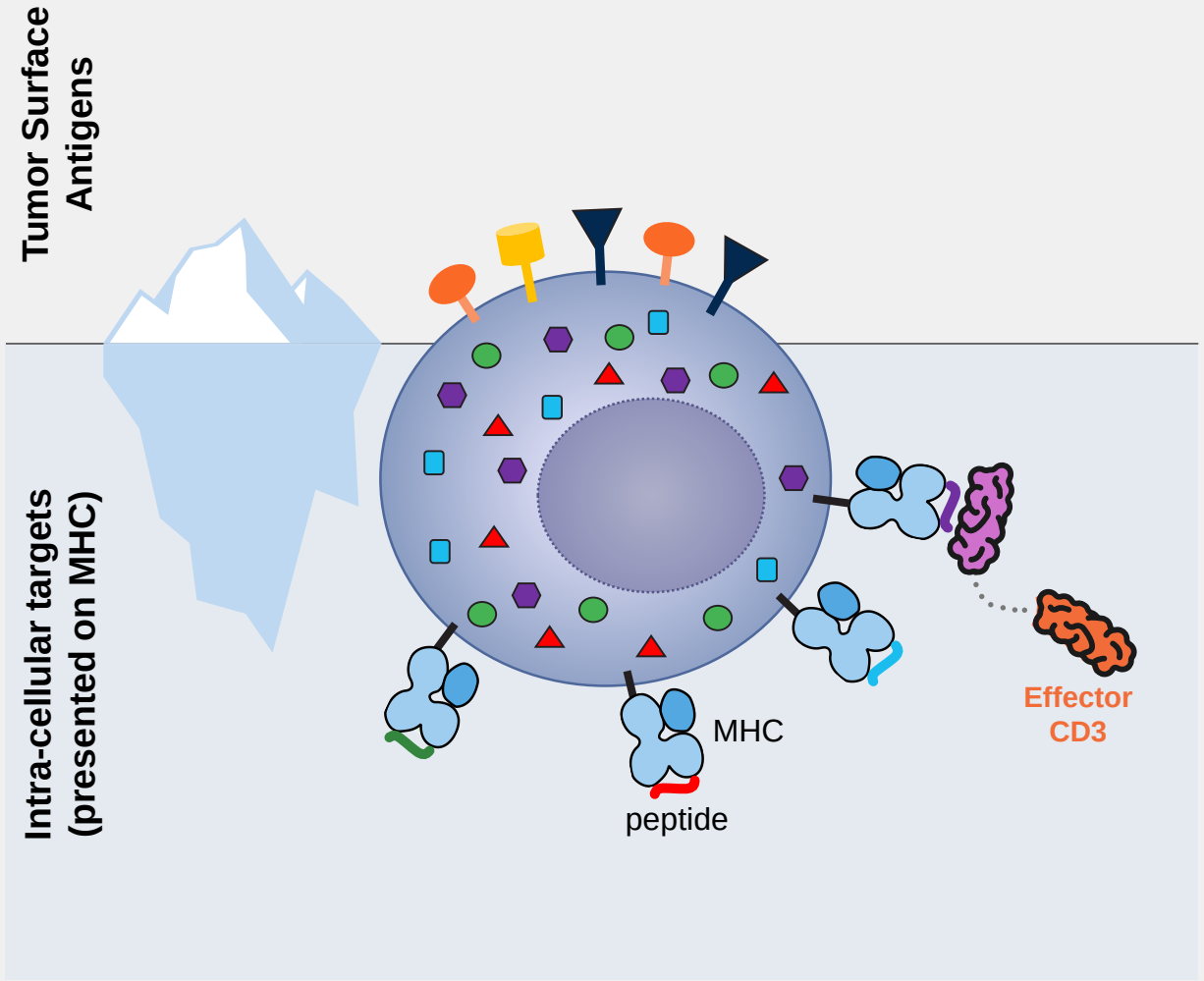
Circumvent tumor escape & relapse



Combination with localized agonist to deepen response

Improved efficacy in solid tumors

Peptide MHC Complexes: “Inaccessible” Intracellular Targets

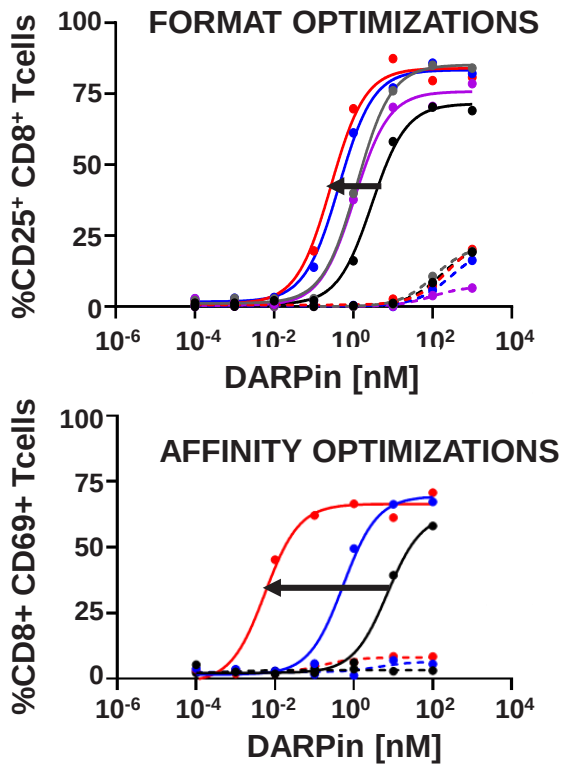


Challenges of the pMHC redirected T-Cell engager field:

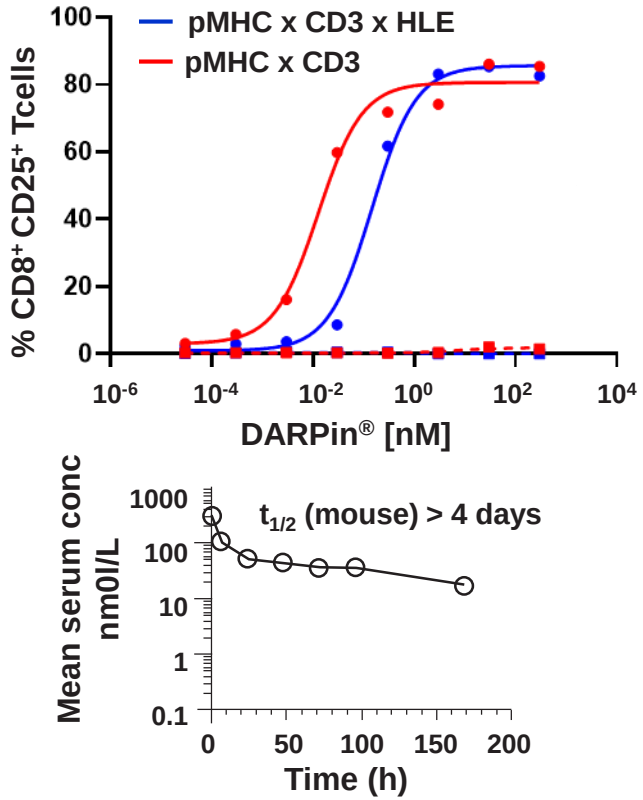
- Generation of binders with high selectivity and high potency
- High investment to generate binders
- Systemic half-life extension often leads to loss of potency
- Developability properties not ideal
- Target identification and validation
- Complex clinical development path

Multiple Technical pMHC Challenges: Solved

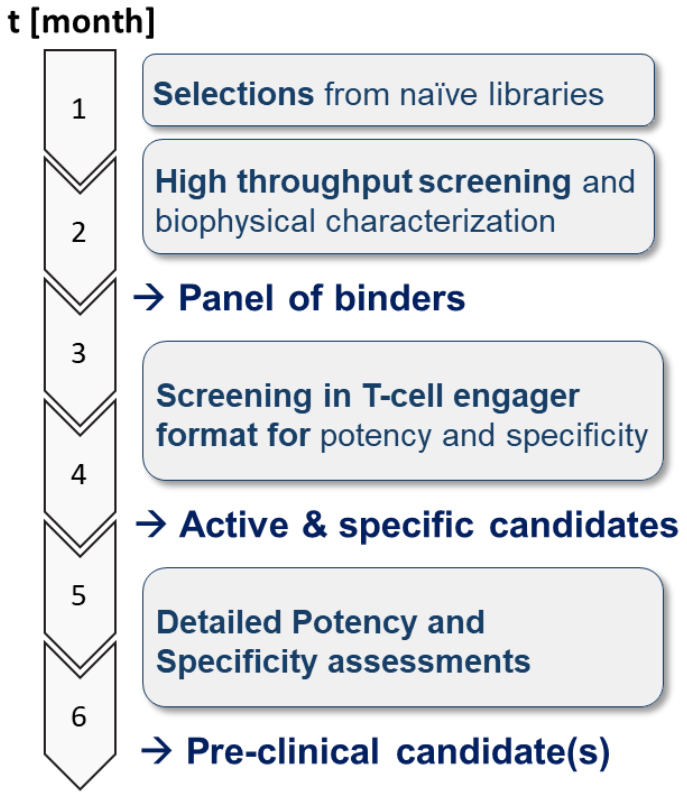
Gained several logs of potency while maintaining selectivity



Achieved good systemic exposure with limited impact on potency

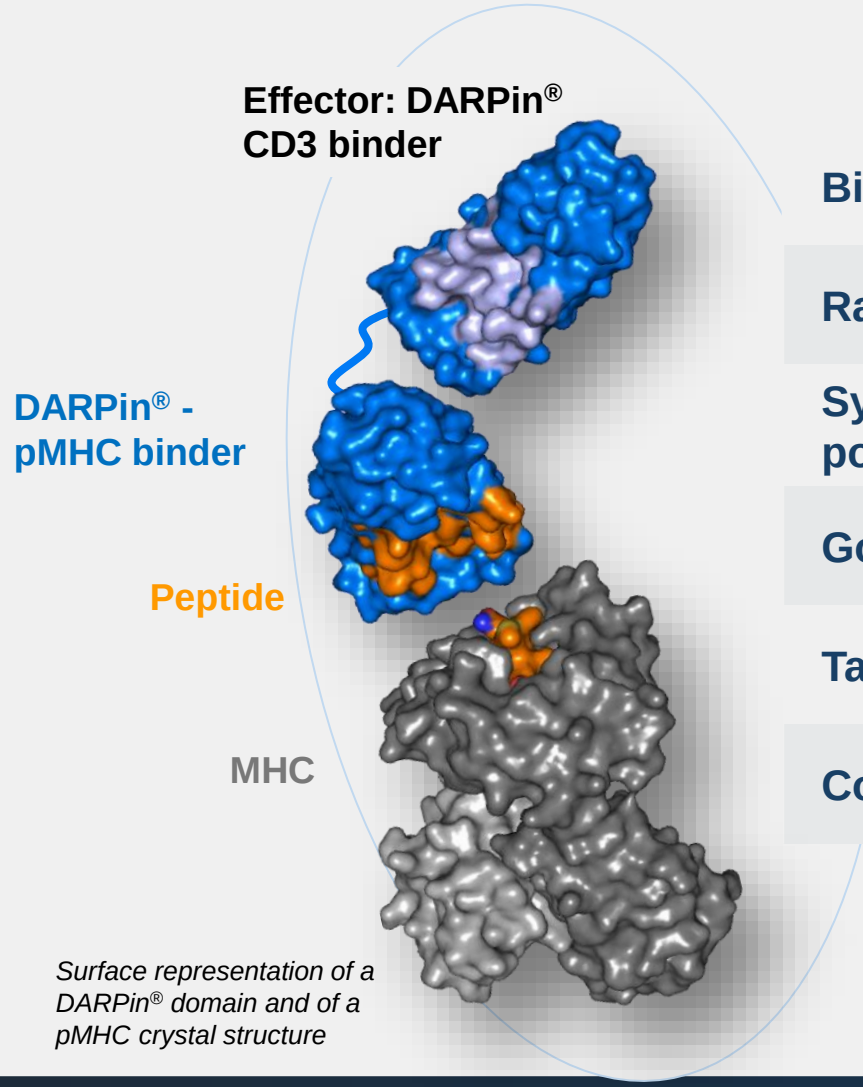


Candidate production for several pMHCs in parallel in less than six months



AACR 2021

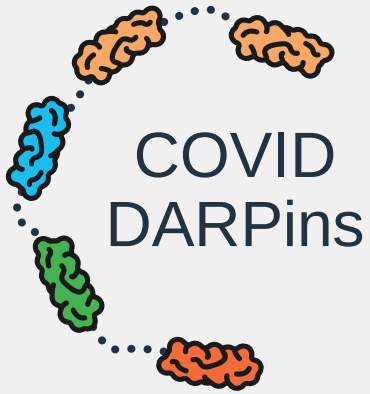
DARPin® Platform Especially well Suited to Address pMHC Targets



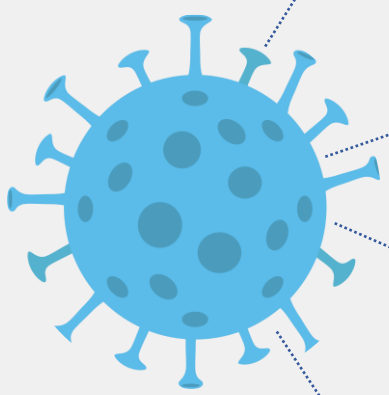
Surface representation of a DARPin® domain and of a pMHC crystal structure

Binders with high specificity and high potency	✓
Rapid and reliable generation of pMHC binders	✓
Systemic half-life extension with limited impact on potency	✓
Good developability properties	✓
Target identification and validation	○
Complex clinical development path	○

DARPin® Opportunities in Virology



- **Multi-valency** for superior potency
- **Multi-specificity** for mutation resistance
- **Speed of candidate generation**
- **High amount & low-cost production**
- **High stability and solubility** for simple administration and distribution



Respiratory Viruses
- RSV, influenza and others
- Benefits as per COVID DARPin®

Pandemic readiness
- Corona, influenza
- Early intervention to prevent spread

Viral reservoirs
- HIV, HBV, HCV
- Targeting pMHC

Low-income country viruses
- Example: dengue
- High stability
- Low costs

Summary

Financial Overview & Milestones:

- YE Cash 2020: ~174M CHF, no debt
  - Successful capital raise of CHF 80m, completed in early July 2020
- Additional funding from Novartis transaction (CHF 60m, received per end October 2020)
  - Funded into 2023, without consideration of future milestones
- ~$1B in potential milestones from R&D partners yet to be realized
  - $165m milestone from Novartis upon commercial licensure of COVID-DARPins
  - ~$500m in milestones from Amgen for AMG 506 / MP0310
  - >$360M in approval and commercial milestones associated with Abicipar
- Up to double-digit royalties outstanding with current R&D partners

Upcoming Catalysts Across The Portfolio in 2021

Antiviral portfolio	
Ensovibep (MP0420) MP0423	▪ POC with EUA/BLA and approval in 2021 ▪ Emergency Use Authorization and/or BLA submission possible in 2021 ▪ MP0423 FIH
Novel antivirals	▪ Develop novel DARPins for viral targets with first new target announced 2021
Immuno-oncology portfolio	
AMG 506 (MP0310)	▪ Identify ideal dosing regimen in ongoing Phase 1 (H1/2021) ▪ Amgen potential combination trials (H2/2021)
MP0317	▪ MP0317 FIH in H2 2021
T cell engagers	▪ 1st Candidate selected for development ▪ Follow-up pipeline established
pMHC	▪ Select Peptides for Candidate Selection – possibly with a partner

Funded into 2023

(Not incl. any future proceeds related to partnerships)

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