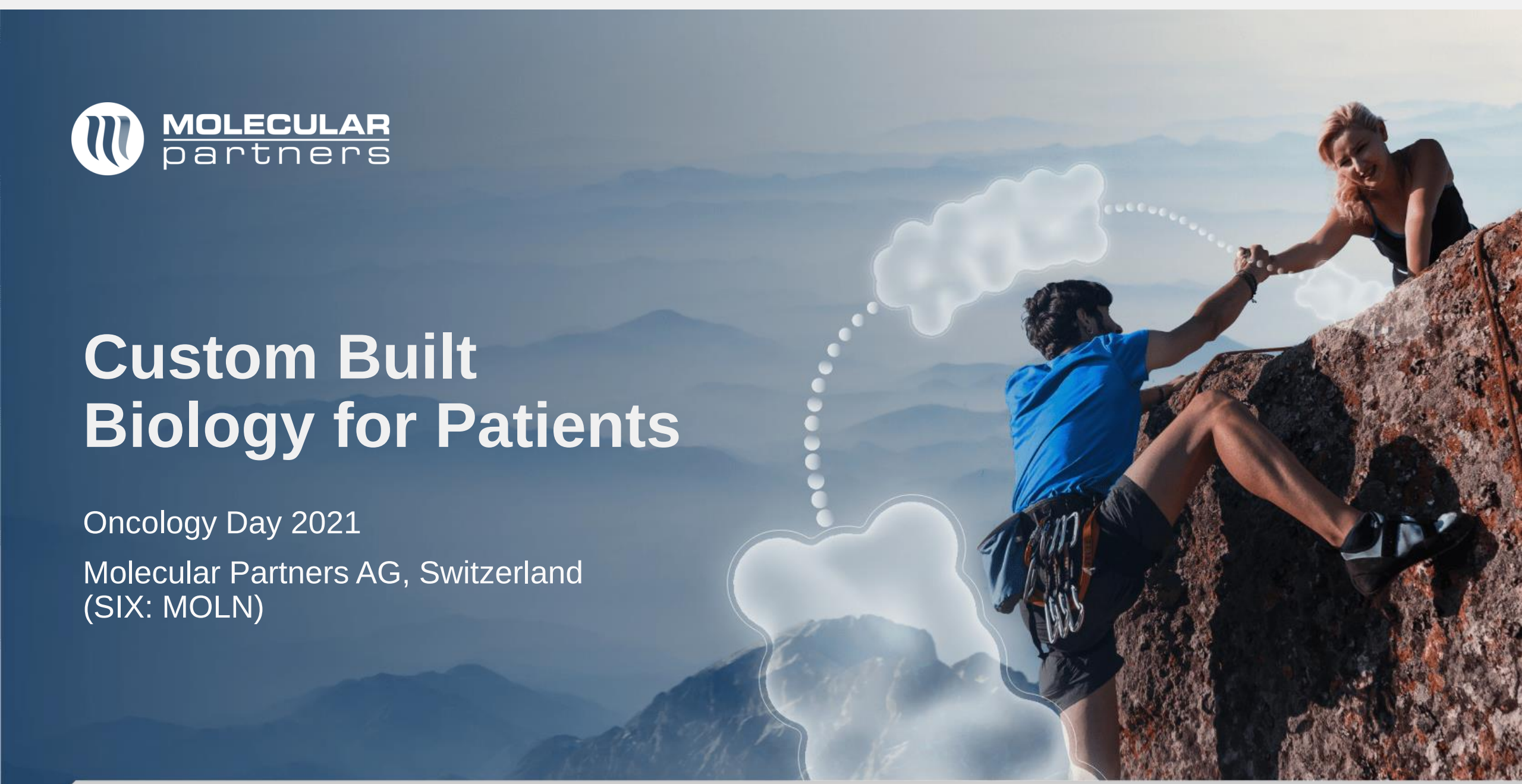
Custom Built Biology for Patients

Oncology Day 2021

Molecular Partners AG, Switzerland
(SIX: MOLN)



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R&D Day Speakers (and Intro to Agenda)

Patrick Amstutz, PhD
Chief Executive Officer, Molecular Partners

Michael Stumpp, PhD
Chief Operating Officer, Molecular Partners

Daniel Steiner, PhD
SVP Research, Molecular Partners

Nicolas Leupin, MD, PhD
Chief Medical Officer, Molecular Partners

Anne Goubier, DVM, PhD
VP Biology, Molecular Partners

Guest Speakers

Prof. Adrian Ochsenbein, MD
The University of Bern

Prof. Carsten Riether, PhD
The University of Bern

Pioneering DARPin Therapies to Transform Lives

Overview: Patrick Amstutz

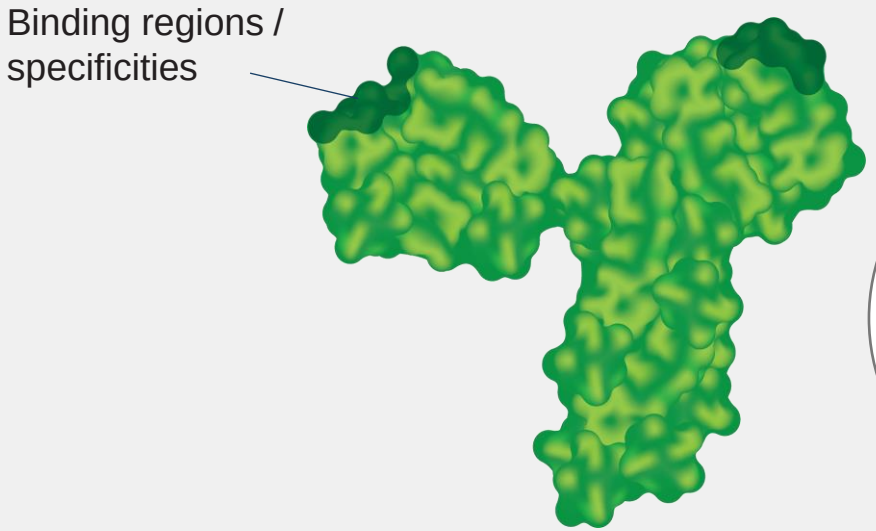
2021 in Review: Corporate & Portfolio Growth

Our ***purpose*** is to transform the lives of people with serious diseases

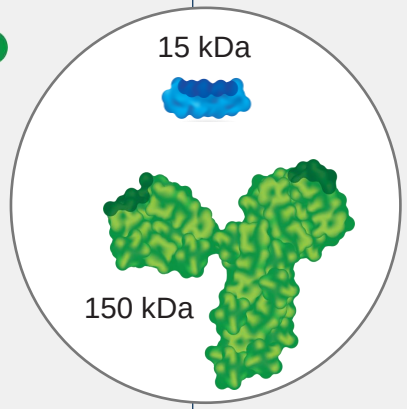
- Ensovibep (Covid) from Phase 1 to POC data imminent
  - Activity on all variants of concern, to date
- MP0317 (FAP x CD40) into Phase 1
  - Initial data anticipated in H2 2022
- Nomination of MP0533 for the treatment of AML
  - ASH poster; Bern collaboration; Phase 1 initiation in 2022
- Ongoing assessment of additional antiviral DARPins
  - Updates following ensovibep data in H1 2022
- Completion of NASDAQ Listing
  - Ensuring ability to fund pipeline and discovery

DARPins: A Unique Class of Biologics

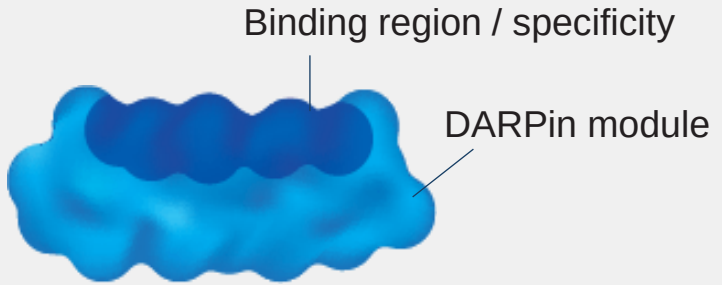
MONOCLONAL ANTIBODIES



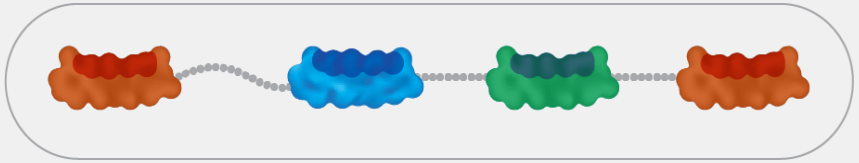
- High affinity and specificity
- Large size: 150 kDa
- Complex architecture; 4 proteins with 12 domains
- Long half-life
- Good safety & low immunogenic potential



MONO-DARPin



Multi-specific DARPin Candidate



- High affinity and specificity
- Small size: 15 kDa (1/10 of a monoclonal antibody)
- Simple architecture 1 protein with 1 domain
- Tunable half-life
- Good safety & low immunogenic potential

Pipeline

Infectious disease | Discovery Oncology | Oncology | Ophthalmology

Pipeline

CANDIDATE / FOCUS	RESEARCH	PRECLINICAL	PHASE 1	PHASE 2	PHASE 3	RIGHTS
Ensovibep – Covid	Covid ambulatory – Empathy					NOVARTIS
Next Gen Covid	Future VoC*					MOLECULAR partners
AMG506 / MP0310 FAP x 4-1BB	Solid tumors					AMGEN
MP0317 FAP x CD40	Solid tumors					MOLECULAR partners
MP0533 CD3 x CD33+CD70+CD123	AML					MOLECULAR partners
Abicipar VEGF	wet AMD – Cedar & Sequoia					MOLECULAR partners
Radio Ligand Therapy	Solid tumors					NOVARTIS

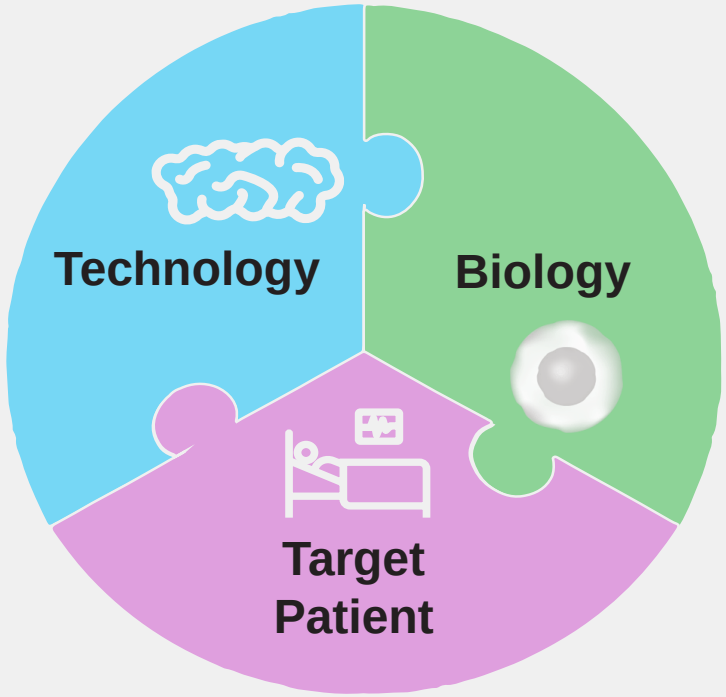
Platform Discovery

- Radical simplicity & Conditional Activation
- Additional Infectious Diseases

MOLECULAR partners

* VoC = Variant of Concern

MP Strategy – Building on our Strengths



TECHNOLOGY

We leverage the advantages of the **DARPin technology** to provide unique solutions to impact biology and bring value to patients

BIOLOGY

Our candidates' design aims to **directly change the course** of **disease biology** and allow testing in a model with **high translatable value**

TARGET PATIENTS

We aim to drive **true patient value** with **early clinical read-outs**

We strive to **collaborate** with the best scientists and clinicians in the field from ideation to clinical trials

Local Agonists in Oncology: **MP0310** (FAPx4-1BB) & **MP0317** (FAPxCD40)

TECHNOLOGY

- Multi-specific DARPin leading to clustering upon co-engagement

BIOLOGY

- Tumor local activation of immune cells

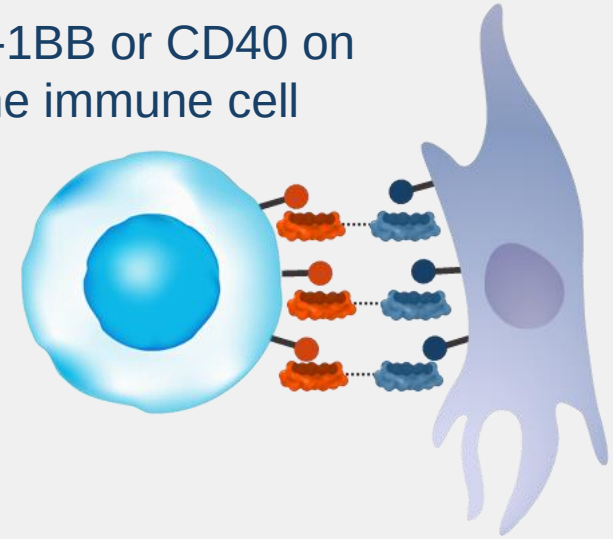
TARGET PATIENTS

- Wider therapeutic window for combinations

Early clinical read-out ✕

- **MP0310: Amgen, MP0317: not partnered**

4-1BB or CD40 on the immune cell



FAP on the tumor associated fibroblast

Targeting Leukemic Stem Cell in AML: **MP0533** (CD33+CD70+CD123 x CD3)

TECHNOLOGY

- Tri-specific T-Cell engager with optimized binding affinities and geometry

BIOLOGY

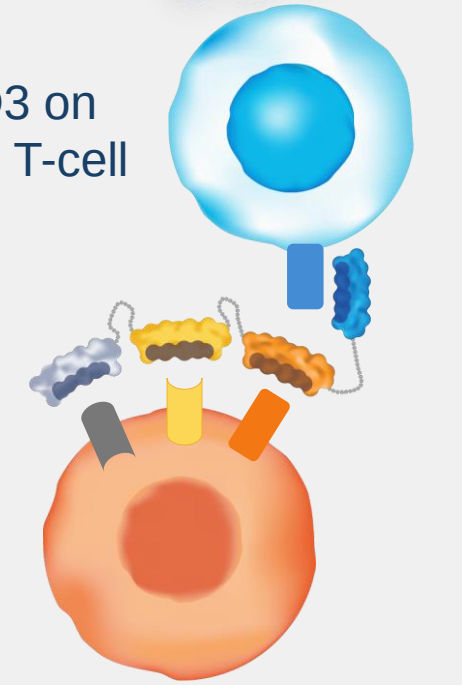
- Avidity driven targeting of leukemic stem cells

TARGET PATIENTS

- Long-term control of AML

Early clinical read-out ☑

- **University of Bern – Profs. Ochsenbein and Riether**



DARPin Radio-Ligand Therapy, DARPin-Drug-Conjugates

TECHNOLOGY

- Small sized DARPin with high affinity coupled to a highly toxic payload (radio ligand)

BIOLOGY

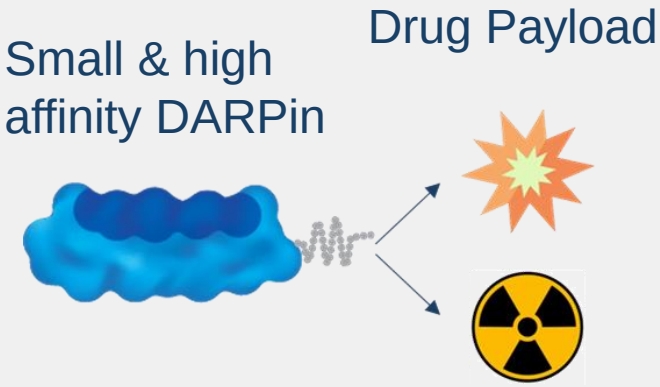
- Deep tumor penetration, low systemic exposure with high-tox payload

TARGET PATIENTS

- Deep response in hard-to-treat tumors

Early clinical read-out ☑

Novartis, a leader in the field of RLT:
US$ 20 mio up-front, US$ 560 mio MS, to dd royalties



NOVARTIS

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Radio Ligand Therapy	Solid tumors					NOVARTIS

Platform Discovery

Radical simplicity & Conditional Activation

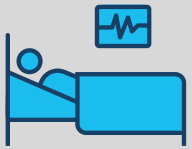
Additional Infectious Diseases

MOLECULAR partners

Abicipar – what's next?

Abicipar: Phase 3 Asset, Reviewing Data from AbbVie

Target Patient

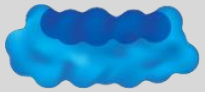


- Neovascular age related macular degeneration (nAMD) and diabetic macular edema (DME)
- nAMD - More than 200,000 cases/year in the US
- DME- Approximately 75,000 cases/year in the US

Disease Biology

- Growth/leakage of abnormal blood vessels beneath the retina
- VEGF-A has been found to be a key molecule in numerous retinal diseases
- VEGF-A inhibition has been established as a highly effective treatment for these diseases

DARPin Advantage

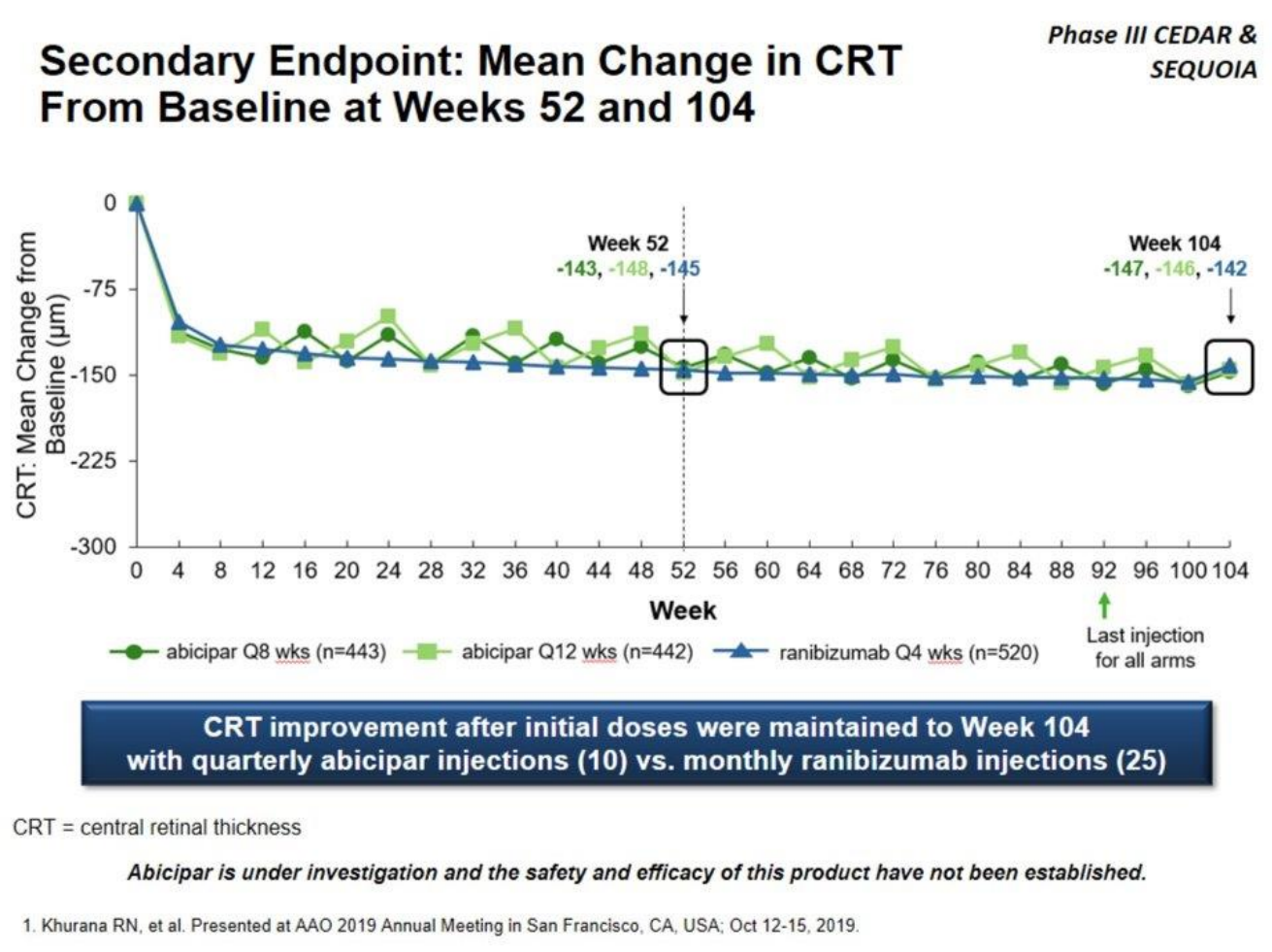


- Higher affinity and inhibition of VEGF-A
- Long half-life in the eye (PEGylated)
- Small – higher molarity per mg

Milestones

- AbbVie returned all rights to Molecular Partners in Aug. 2021
- Full data currently under review
- Meeting request with the FDA to discuss proposed path forward

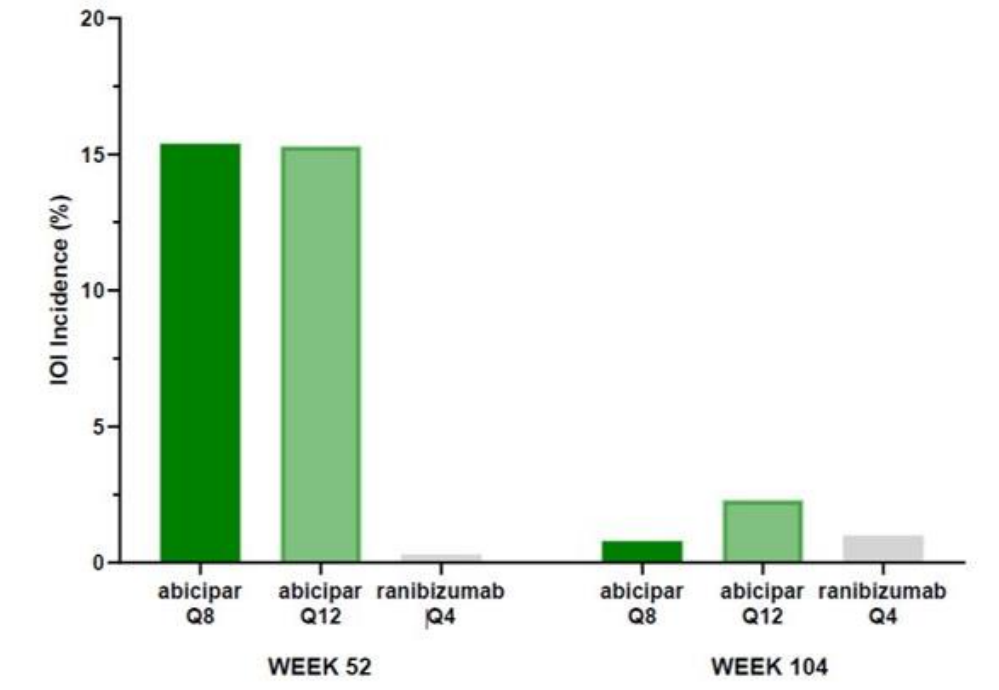
CEDAR & SEQUOIA Phase 3 using OCT as biomarker



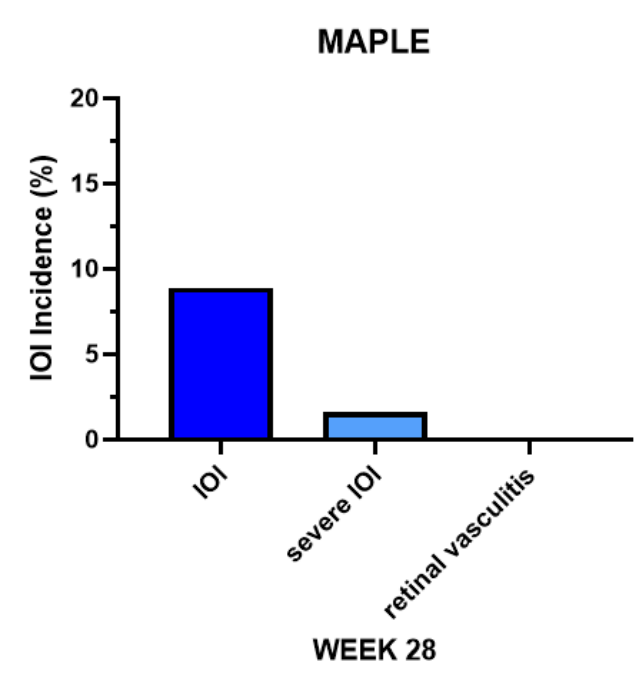
- Abicipar as effective as Lucentis
  - 10 injections instead of 25 (2 y)
- Fixed Q12w regimen proven
  - Potential to simplify visits
- OCT - ocular coherence tomography, a method to measure the thickness of the retina

Reducing Intraocular Inflammation (IOI)

- CEDAR/SEQUOIA (Phase 3)
  - Much less IOI in 2nd year (as Lucentis)



- MAPLE (Phase 2, improved purity)
  - lower severity of IOI reported



Type of Syringe Identified as Likely IOI Contributor *in vivo*

Drug Substance 301, Process 3B

AbbVie Lab Filled Drug Product → **Ophthalmic-use Syringe** — Developed for intraocular use

Commercial Scale Drug Product → **Vial+Syringe (used in Ph3)** — not developed for intraocular use

Each rabbit received 3 injections spaced 3 weeks apart

	Animal Numbers	150	151	152	153	154	155	156	157	158	159	160	161	162	250	251	252	253	254	255	256	257	258	259	260	261	262
	Overall IOI	2	0	0	1	0	0	1	1	0	0	2	0	0	4	3	0	4	0	0	1	0	4	0	0	0	2
Ocular Infiltates	Lymphoplasmacytic Cells	2	-	-	1	-	-	1	1	-	-	2	-	-	4	3	-	4	-	-	1	-	4	-	-	-	1
	Mixed Cells	-	-	-	-	-	-	-	1	-	-	-	-	-	-	3	-	-	-	-	-	-	1	-	-	-	-
	Mononuclear	2	-	-	-	-	-	-	1	-	-	2	-	-	2	3	-	2	-	-	-	-	2	-	-	-	2
Injection Tract	ILP Injection Tract	2	-	-	-	-	-	1	-	-	-	2	-	-	2	2	-	3	-	-	-	-	2	-	-	-	-
	Inf Mononuclear inj tract	-	-	-	-	-	-	-	-	1	-	-	-	-	-	3	-	2	-	-	1	1	-	-	-	-	1
	Vacuolated cells, inj tract	1	-	-	-	-	-	1	1	1	-	-	1	-	2	-	-	1	1	1	-	1	1	-	1	1	1
	Refractile material w/vacs	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	-	-	P	-	P
Vitreous, Retina and Optic Nerve Head	Hyalocytes / Macrophages	2	-	-	-	-	-	1	1	-	-	3	-	1	3	2	-	3	-	-	1	-	3	-	-	-	2
	Macrophage adhered retina	2	-	-	-	-	-	-	-	-	-	1	-	-	3	2	-	3	-	-	-	-	3	-	-	-	1
	Fibroplasia, retina or ONH	1	-	-	-	-	-	-	-	-	-	2	-	-	2	2	-	2	-	-	-	-	3	-	-	-	1
	Retinal Detach	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	1	-	-	-	-
	Vacuolated cells, retina	2	-	-	-	-	-	-	-	-	-	3	-	-	3	-	-	3	-	-	-	-	3	-	-	-	-

✓ **0/13 eyes had IOI**

✘ **4/13 eyes had IOI**

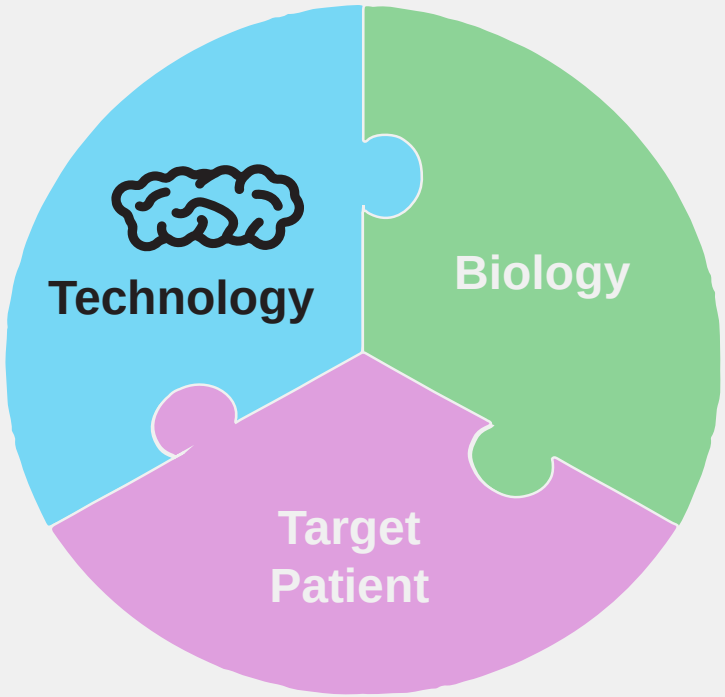
Abicipar Conclusions and Next Steps

- Increase benefit/risk ratio to address CRL
- Plan to discuss with FDA in Q1/2022
  - Establish precise need for additional clinical data/study
  - Further our understanding of potential timelines for re-submission
- If proposals are feasible, discuss partnerships and appropriate vehicle to enact clinical plan
- Acknowledging competitive landscape
  - Faricimab approval expected in Q1/22
- … and some set-backs in the field
  - Gene therapies
  - Brolucizumab
- Establishing future development plan
  - With experts in the field
  - Demonstrate value-add of abicipar
  - IP protection well into 2030's

Our Platform and future products

Daniel Steiner

MP Strategy – building on our Strengths



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We leverage the advantages of the **DARPin technology** to provide unique solutions to impact biology and bring value to patients

BIOLOGY

Our candidates' design aims to **directly change the course** of **disease biology** and allow testing in a model with **high translatable value**

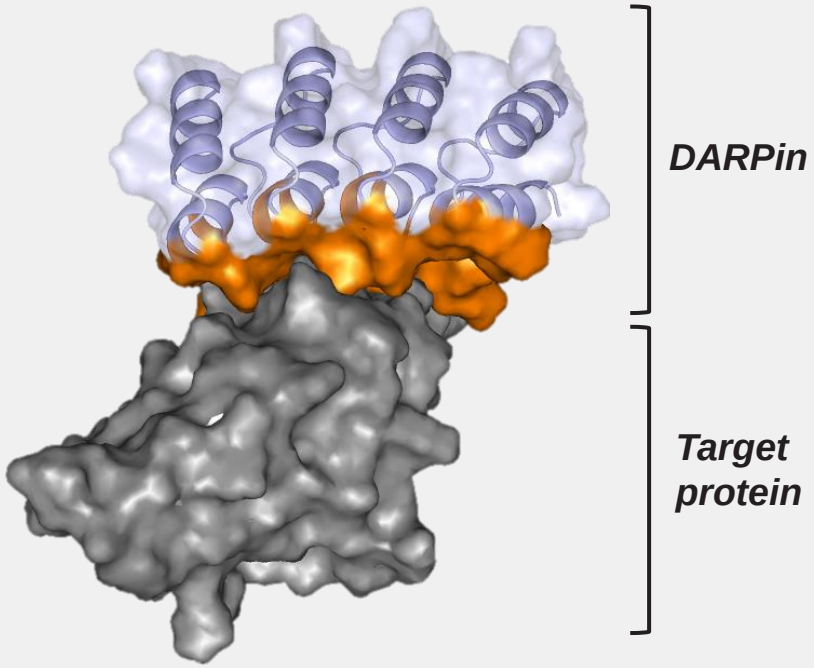
TARGET PATIENTS

We aim to drive **true patient value** with **early clinical read-outs**

We strive to **collaborate** with the best scientists and clinicians in the field from ideation to clinical trials

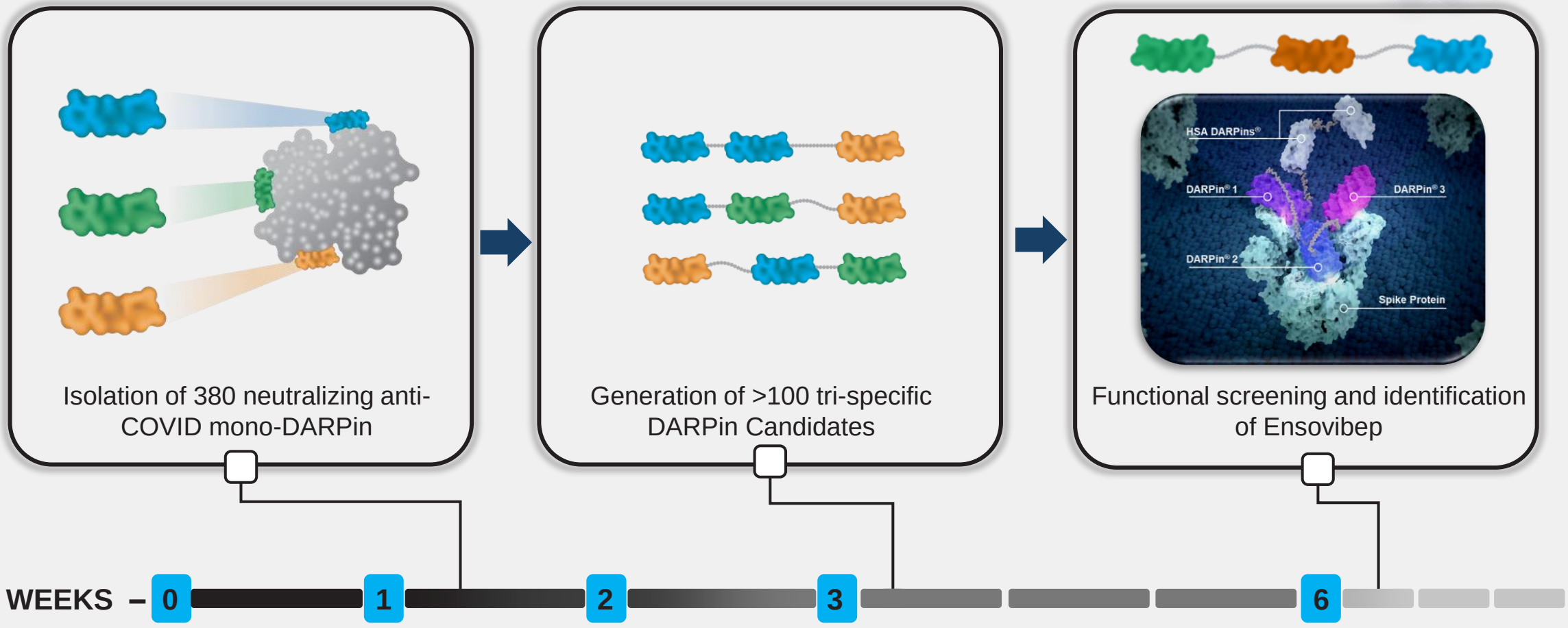
DARPins: The Core of our Drug Engine

DARPins are binding proteins derived from natural ankyrin repeat proteins

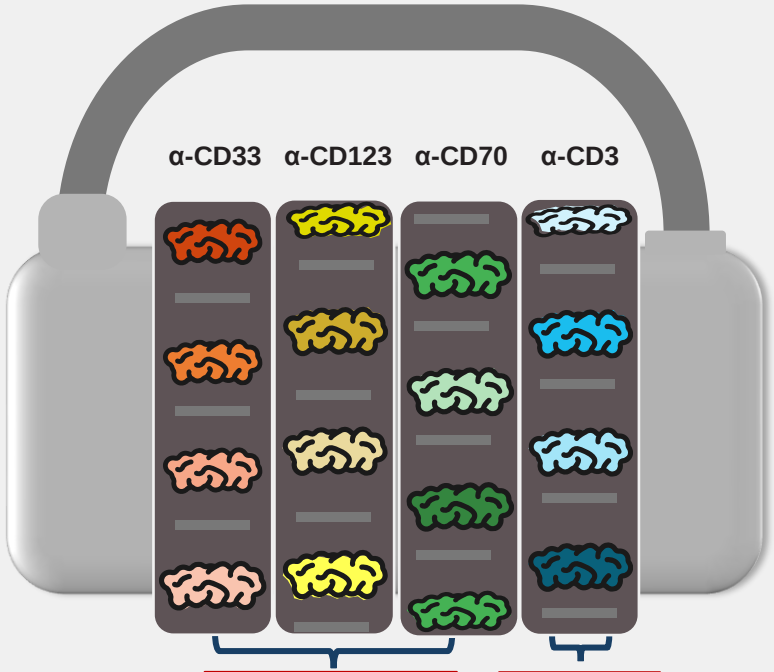


DARPin **KEY PROPERTIES**	DARPin **ADVANTAGE**
Small size (15 kDa)	➢ Deep tissue penetration ➢ High molar concentration
Rigid protein scaffold	➢ Ultra-high binding affinity and selectivity
Simple & robust architecture	➢ Turn-key multispecifics ➢ Easy coupling of payloads

Our Platform in Action: Creating Ensovibep

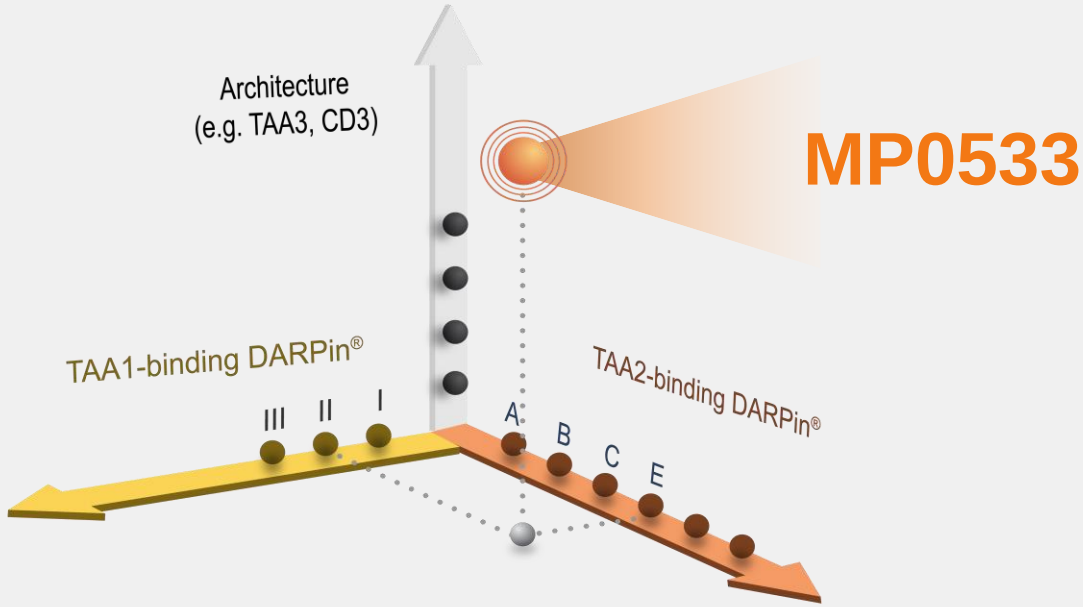


Creating MP0533: Unique Avidity-Driven Tumor Selectivity



Optimal affinity	Optimal epitope	Optimal spacing	Optimal orientation

- **The problem:** Address AML tumor heterogeneity and reduce impact on healthy cells
- **The solution:** DARPin platform allows to rapidly screen & iterate 100s of tri-specific T cell engagers to find the potency – selectivity – heterogeneity sweet spot



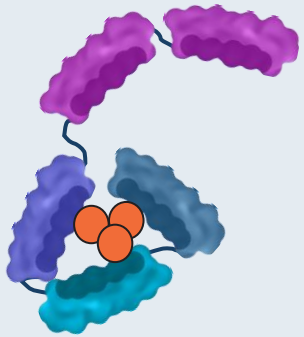
Multi-DARPins are Offering a Broad Spectrum of Unique Solutions

Multispecificity enabled possibilities

Conditional activation

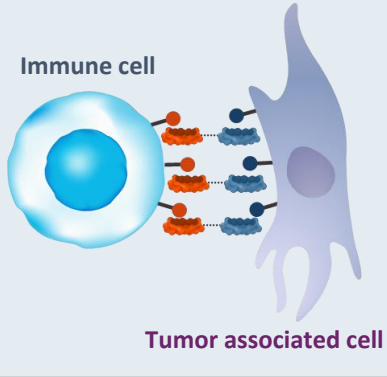
Ensovibep

High affinity for deep SARS-Cov-2 inhibition and prevention of escape



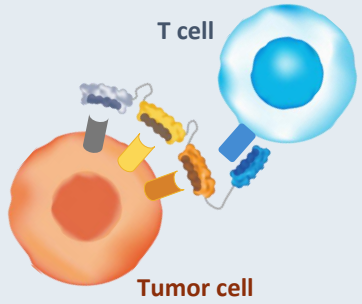
MP0310 & MP0317

Tumor localized clustering to activate effector cells in tumor only



MP0533

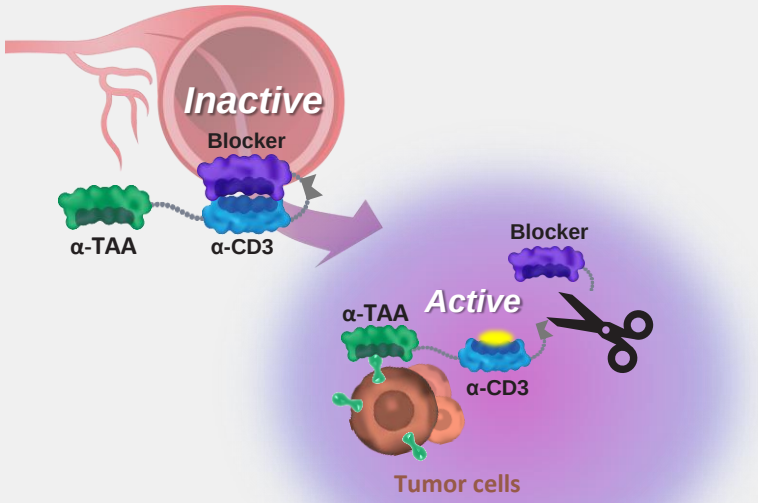
Avidity driven TCE for tumor-specificity and control of tumor heterogeneity



Conditional Activation to Unlock full Potential of Potent Effectors

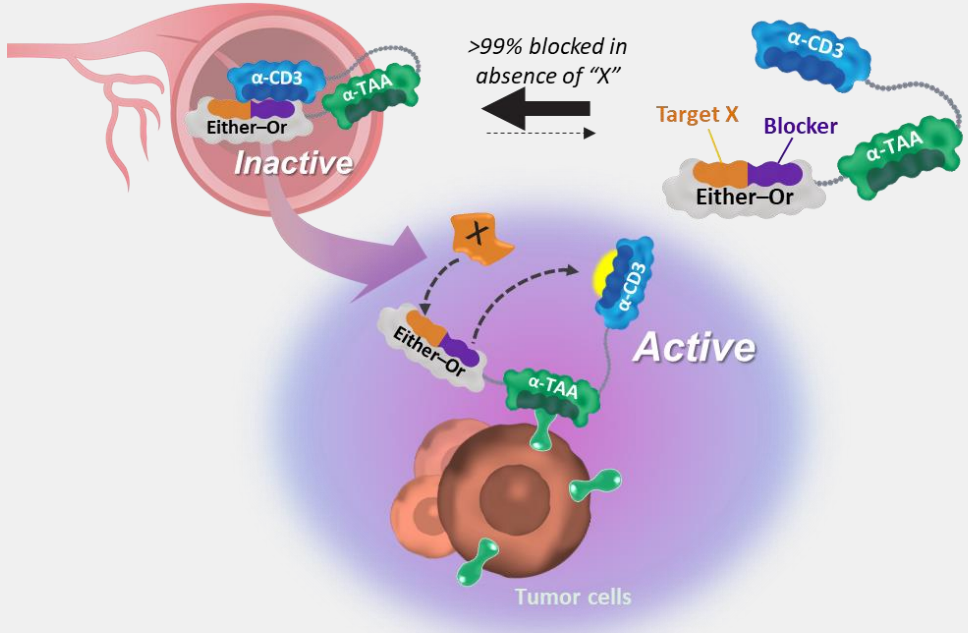
Tumor protease-activated ProDrug
T-cell engager

AACR 2021



- **Local activation via protease cleavage**
- **Key challenge: protease heterogeneity**

Target binding activated Switch DARPin
T-cell engager



- **Local activation via target "X" binding**
- **No need for protease cleavage**

Expanding Multi-DARPins by Programming of Highly Potent Effectors

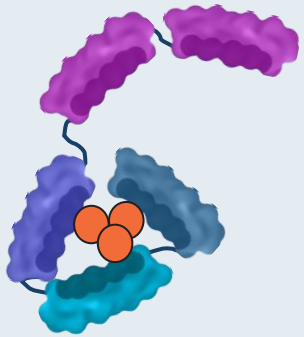
Delivery Vectors "radical simplicity"

Multispecificity enabled possibilities

Conditional activation

Ensovibep

High affinity for deep SARS-Cov-2 inhibition and prevention of escape



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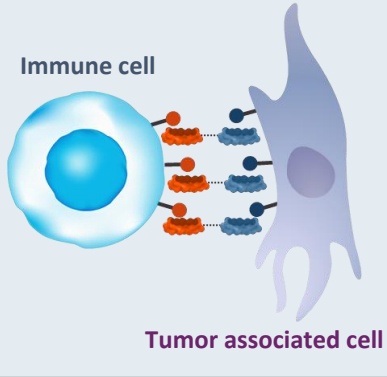
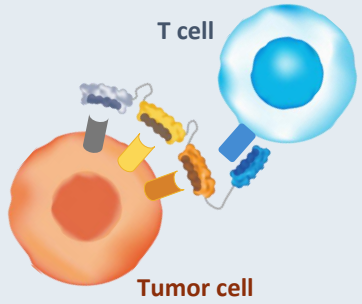


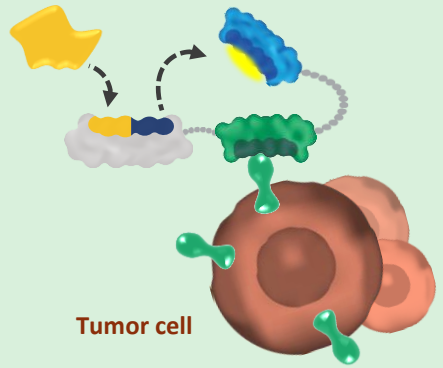
MP0533

Avidity driven TCE for tumor-specificity and control of tumor heterogeneity

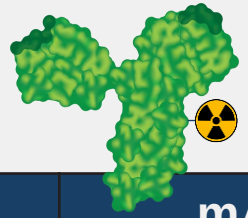


SWITCH

Programming highly potent effectors to omit off-tumor activity



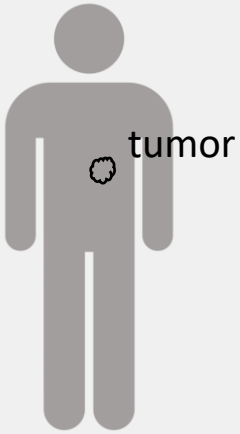
Challenges of Standard Delivery Vectors of Potent Payloads



	mAB	Peptide
Size	150 kDa	1-2 kDa
Affinity	high (bivalent)	low
Specificity	high	limited
High tumor load ➢ concentration at site of action	+	+
Deep tumor penetration ➢ access site of action	-	+
Long tumor retention ➢ maintenance at site of action	+	-
Limited normal tissue exposure ➢ improved safety profile	-	+

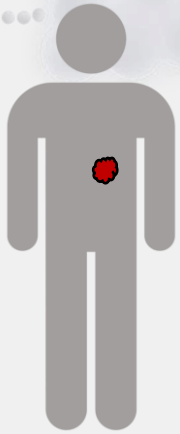
Mono-DARPins as Ideal Delivery Vectors for Potent Payloads

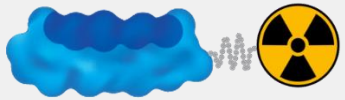
Efficient tumor targeting with limited systemic exposure



Drug infusion

Infusion stopped





Small size (15 kDa)
fast extravasation &
deep tumor penetration

Homogeneous **access to tumor cells** for killing

Small size (15 kDa)
rapid systemic
clearance

Limited normal tissue exposure for **improved safety**

High affinity (< 50 pM)
long tumor retention

Maintenance on tumor for **complete local killing**

Applying our DARPin Advantages to Address Disease Biology

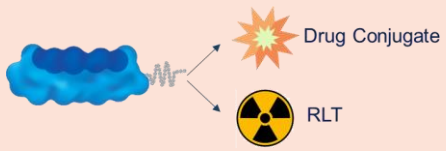
Delivery Vectors "radical simplicity"

Multispecificity enabled possibilities

Conditional activation

RLT & DDC

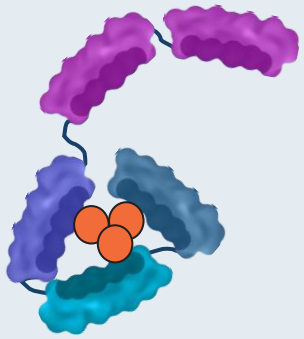
Small size – ultra high affinity for efficient delivery with limited systemic exposure



New / Collaborations

Ensovibep

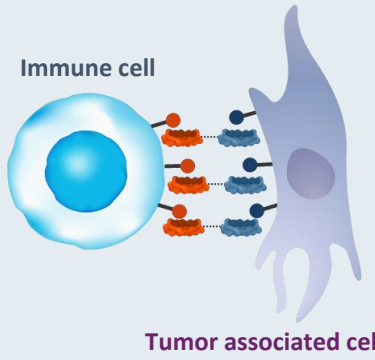
High affinity for deep SARS-Cov-2 inhibition and prevention of escape



New infectious disease

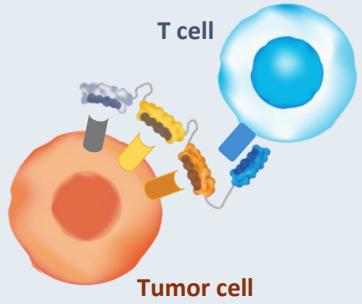
MP0310 & MP0317

Tumor localized clustering to activate effector cells in tumor only



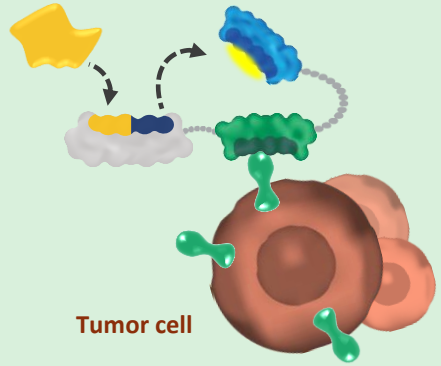
MP0533

Avidity driven TCE for tumor-specificity and control of tumor heterogeneity



SWITCH

Programming highly potent effectors to omit off-tumor activity



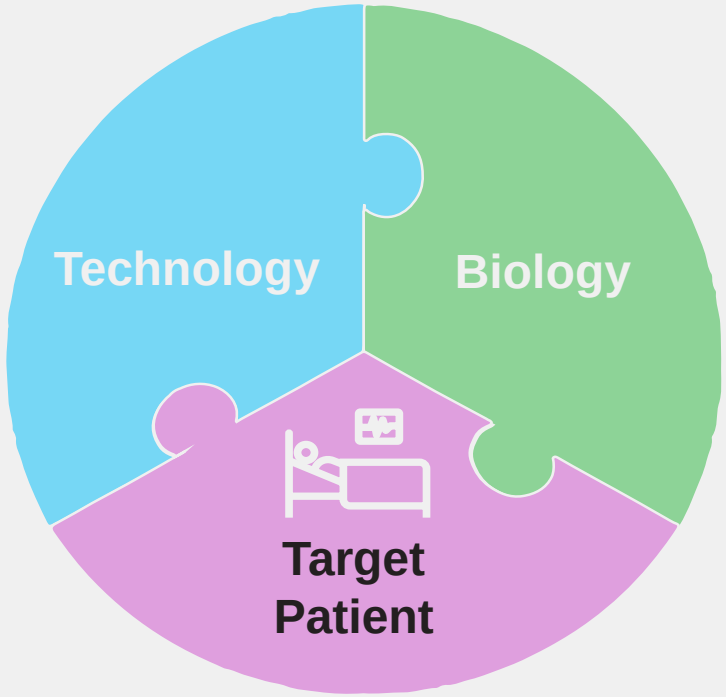
New

Clinical Progress

MP0310 & MP0317

Nicolas Leupin

MP Strategy – Building on our Strengths



TECHNOLOGY

We leverage the advantages of the **DARPin technology** to provide unique solutions to impact biology and bring value to patients

BIOLOGY

Our candidates' design aims to **directly change the course** of **disease biology** and allow testing in a model with **high translatable value**

TARGET PATIENTS

We aim to drive **true patient value** with **early clinical read-outs**

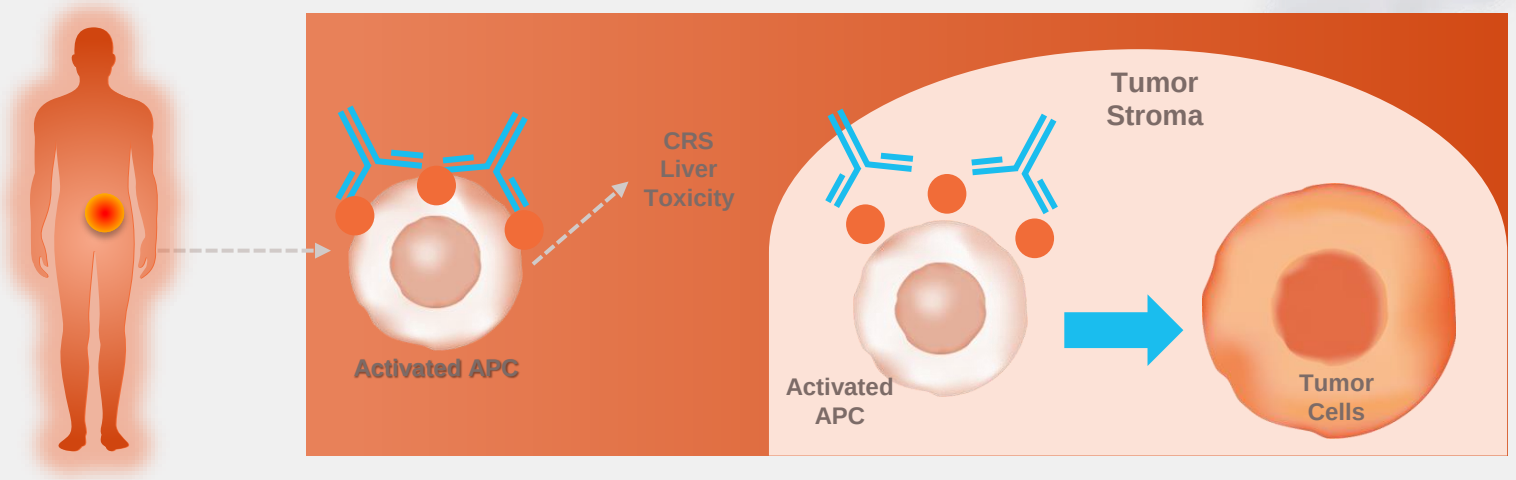
We strive to **collaborate** with the best scientists and clinicians in the field from ideation to clinical trials

What We Achieved in 2021 – a Very Challenging & Successful Year @MP

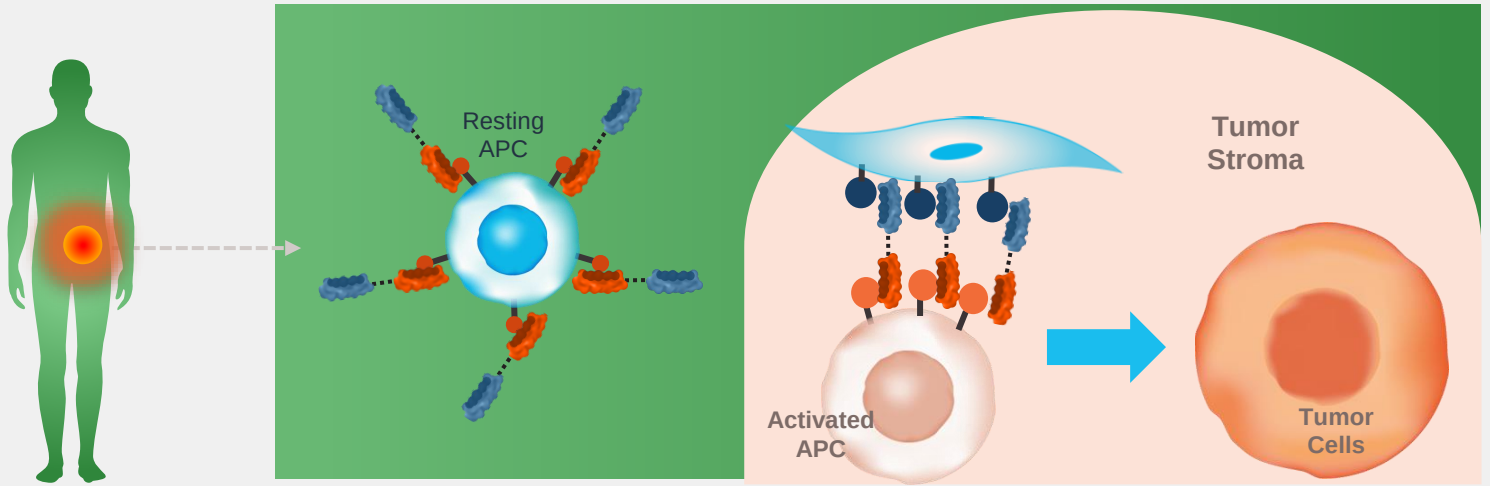
- **>900 patients dosed across all clinical programs, a new "record" for MP**
  - Ensovibep, MP0310, and MP0317 all progressing well
- **Thousands of clinical samples analyzed, despite logistical challenges**
  - Both in house and at external providers
- **~15 clinical batches produced at various scales (up to >10'000 L)**
  - Yielding hundreds of thousands of doses for clinical studies
- **Countless hours spent in video calls**
  - Learnt how to say "you are on mute" politely

Toxicity of 4-1BB & CD40 Antibodies Has So Far Limited Their Activity

Systemic activation of immune cells
leads to **toxicity that limit treatment option**



DARPin advantage: Increasing therapeutic window via a tumor-localized approach



AMG 506 / MP0310: Localized Activation of 4-1BB

Target Patient

- Patients with solid tumors, low T-cell tumor penetration and positive FAP expression
- Patient populations where there are T-cell engagers in development, that can be boosted

Disease Biology

- Many solid tumors are surrounded by dense stromal tissue in which FAP expression is high
- 4-1BB activation is a strong recruiter of T cells

DARPin Advantage

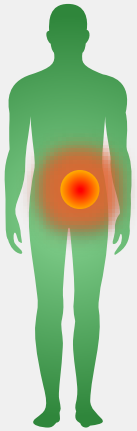
- Systemic administration of MP0310, with localized activation at site of disease
- MP0310 is observed in tumor tissue, with no liver toxicity or systemic activation of immune cells
- Tumor biopsies show tumor-localized immune response consistent with the MoA

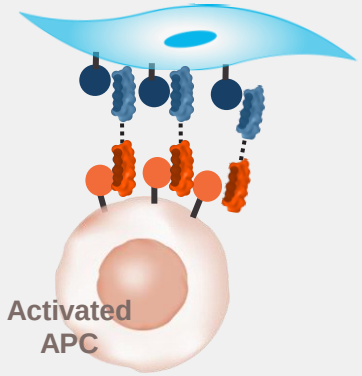
Expected Milestones

- Analyze data from ongoing phase 1 study, exploring weekly dosing.
- Determine appropriate next steps

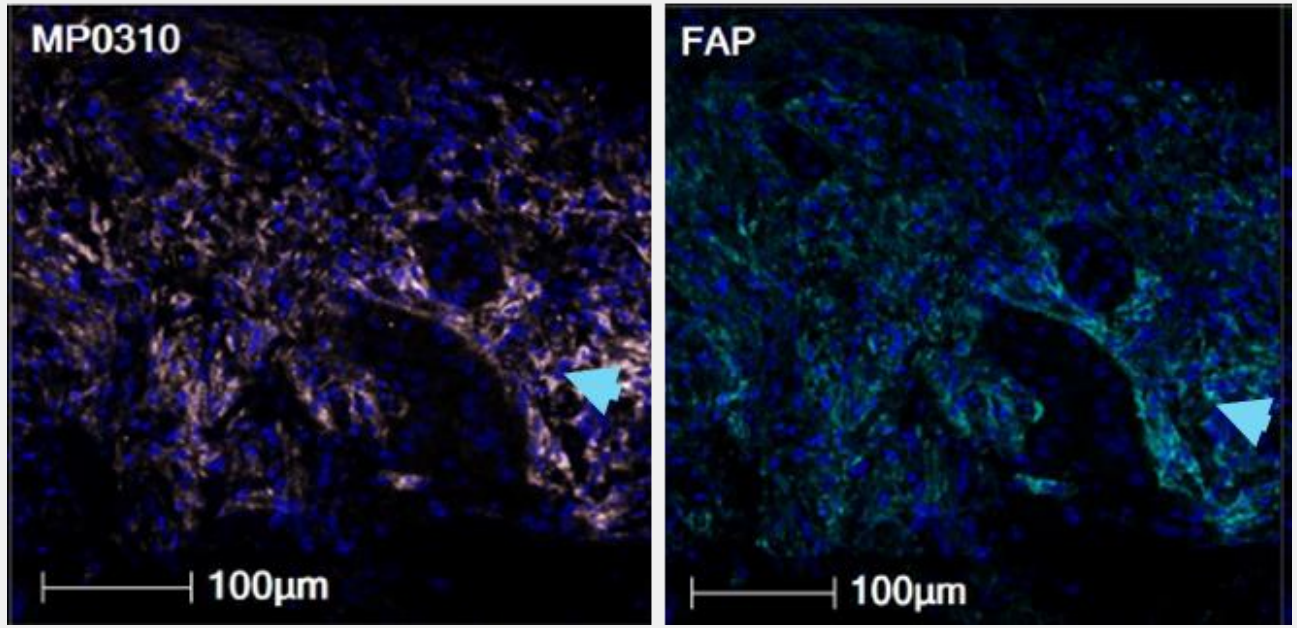
FAP – an Ideal Target for Tumor-localized Activity

- FAP is expressed on **activated cancer associated fibroblasts (CAFs)**
- **Overexpression** in the stroma of **many solid tumors**
- Limited expression in normal adult tissues





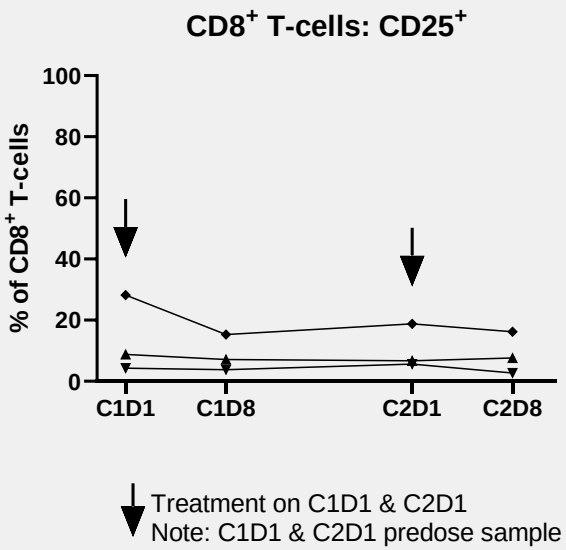
MP0310 (FAP-4-1BB) Phase 1 human biopsy samples



FAP is a clinically validated target for tumor-localization

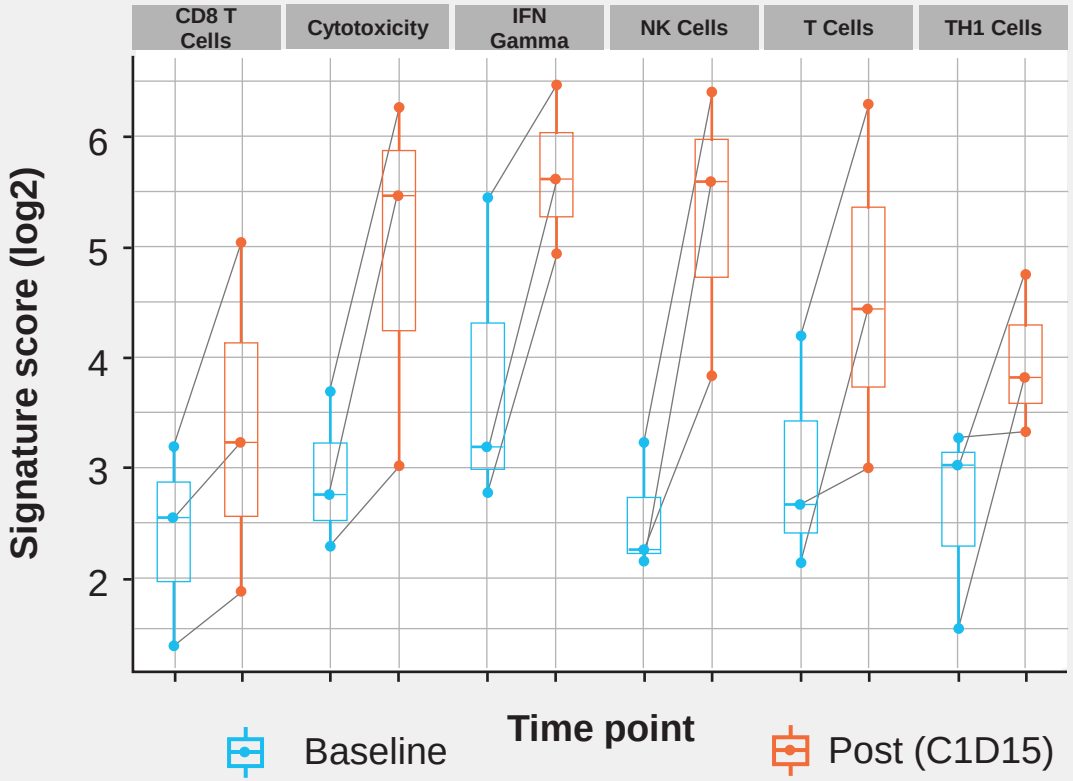
PD Activity in Paired Biopsies Supports AMG 506 / MP0310 MoA on 4-1BB Activation

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

Objectives of MP0310-CP101 Study

Primary Objectives

- To define the safety and tolerability of MP0310 as monotherapy (with or without rituximab pre-treatment) in patients with advanced solid tumors
- To determine the maximum tolerated dose (MTD) AND recommended expansion dose (RED) for MP0310 as monotherapy, based on biomarkers from biopsies
- **Cohorts (1-7):** 0.015-12 mg/kg, completed to plan

Data to date:

Best clinical response:

- Part A: 1/21 pts PR (Pt 03-010); 10/21 pts SD; 10/21 pts PD;
- Part B & C: Ongoing
  - 6 patients enrolled, analysis pending

Drug safety: no DLT or SAEs; IRRs (mostly G2) in 28% of infusions => incomplete infusions in 10% of cases; clinically manageable

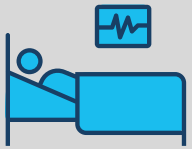
- Peripheral cytokines: increased levels of CXCL9 and CXCL10 at DL3-6 (0.15-5 mg/kg) suggest enhanced IFN_{γ} signaling
- Peripheral immune cells: no activation observed

MOLECULAR partners

MP0317

MP0317: Localized Activation of CD40

Target Patient

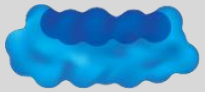


- Solid tumor patients with positive FAP expression
- Many patients still fail to benefit from current immunotherapy options, or relapse

Disease Biology

- CD40 is a potent activator of dendritic cells, macrophages, and B cells, and has long been considered an attractive immunotherapy target
- Prior attempts at targeting CD40 have shown anti-tumor activity but remain hampered by toxicity issues

DARPin Advantage

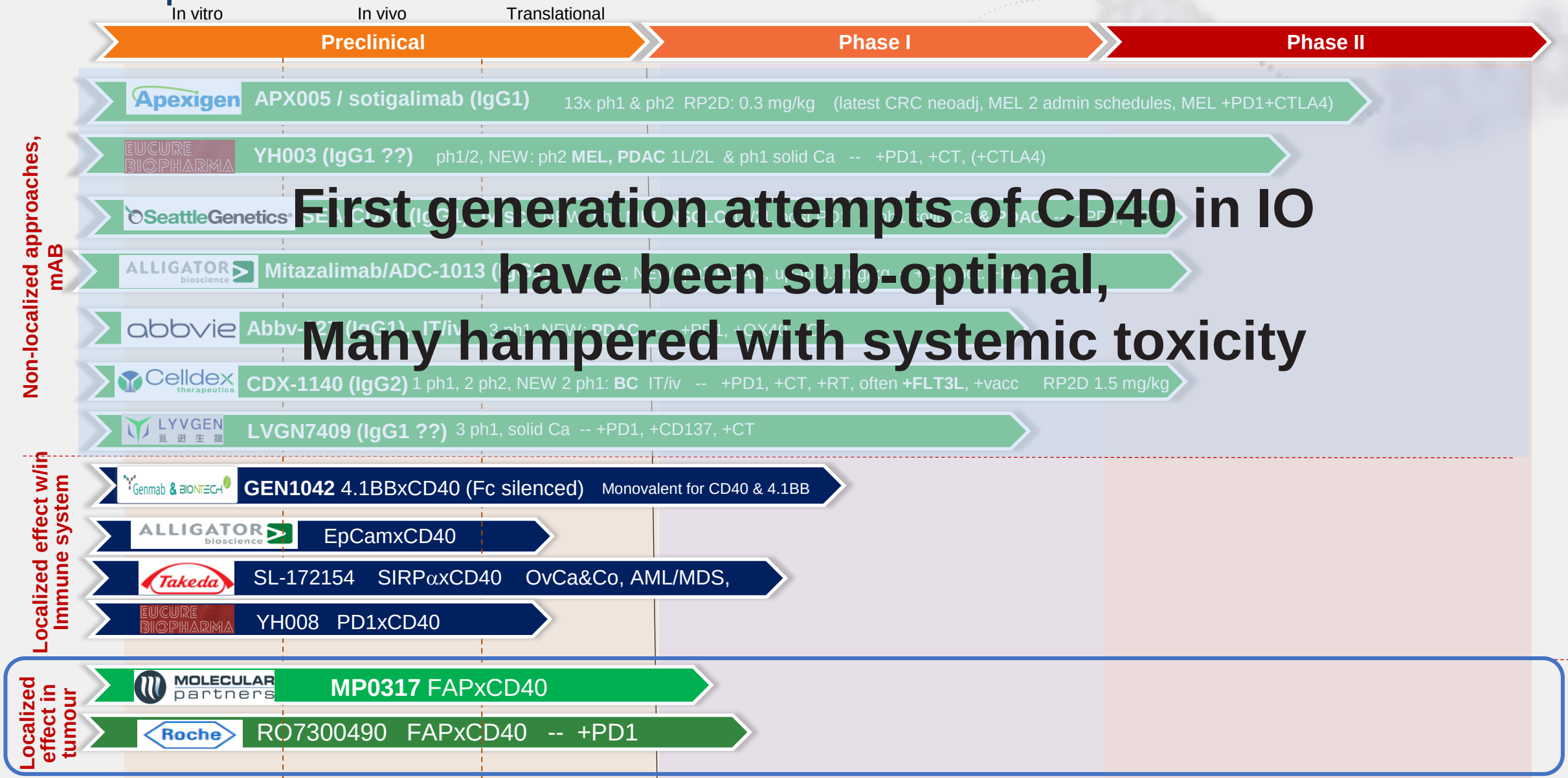


- MP0317 is designed to activate CD40 in a context dependent manner, by anchoring to FAP and activating via clustering
- Preclinical data show local activation of immune cells while limiting off target toxicity

Expected Milestones

- FIH studies initiated in Q4 2021
- Initial data in H2 2022
- Rapidly explore expansion arms in phase 1b

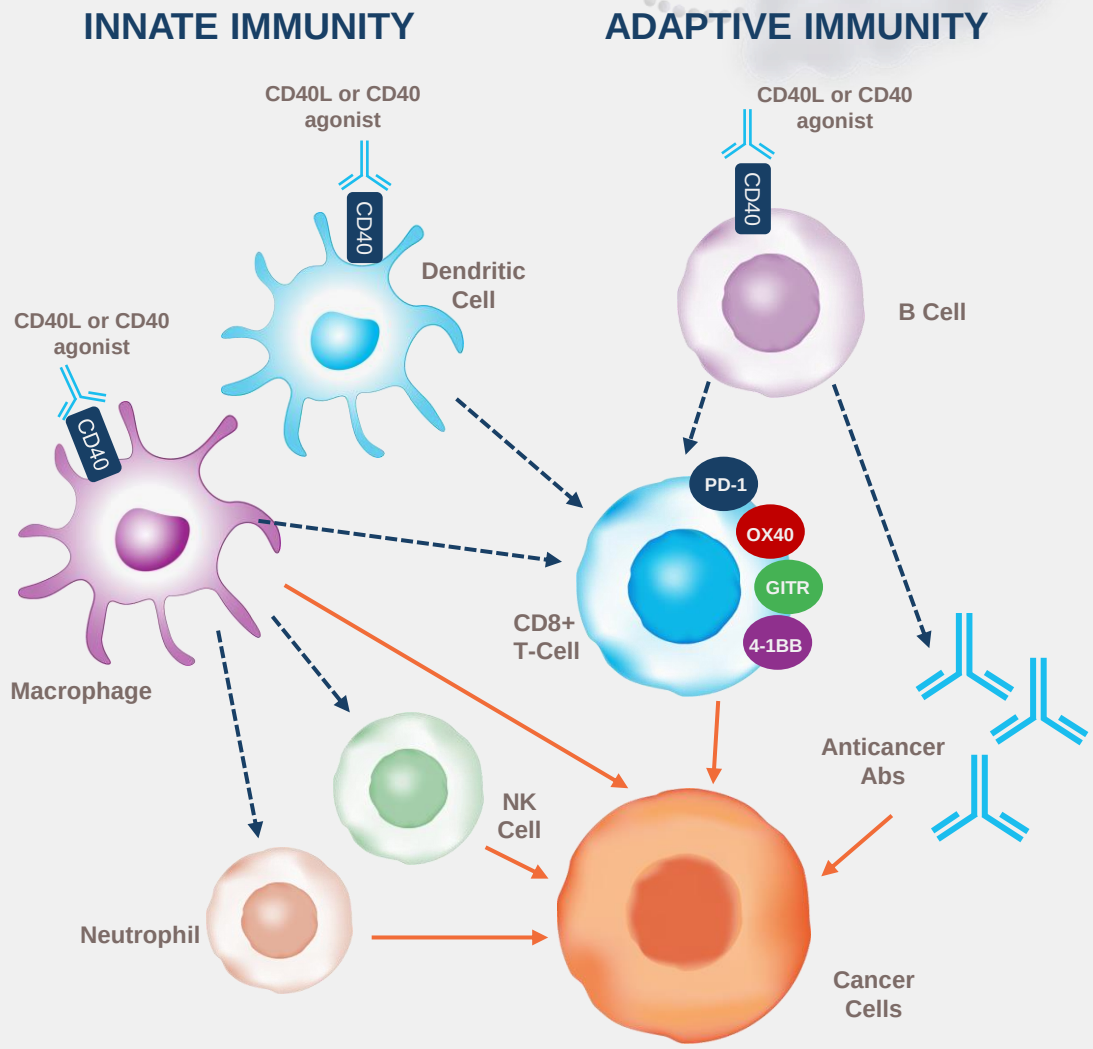
Competitive Environment is Favorable for MP0317



First generation attempts of CD40 in IO have been sub-optimal, Many hampered with systemic toxicity

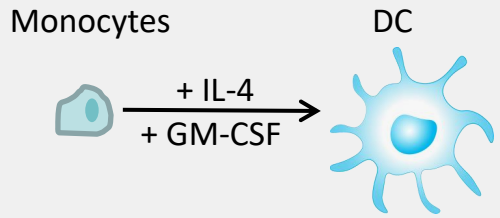
CD40 Biology and Therapeutic Potential

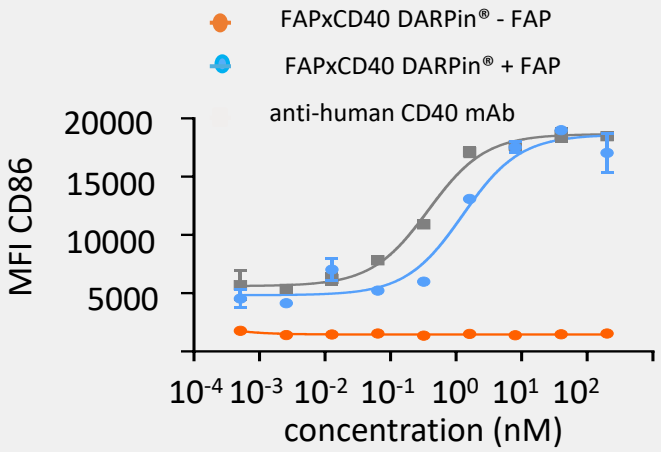
- **Cell surface** receptor member of the TNFRSF
- **Expressed broadly on Antigen Presenting Cells** (B cells, DC and macrophages) as well as many non-immune cells and a range of tumors
- CD40 is a **central regulator** of **multiple pathways** of both the innate and adaptive immune system
  → reduce the risk of immune escape
- Potential for therapeutic activity in cold tumors by targeting the **myeloid compartment**
  → Ccomplementarity with T cell directed therapies



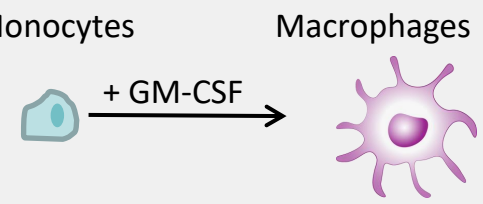
MP0317 Activates all APCs in a FAP-dependent Manner in vitro

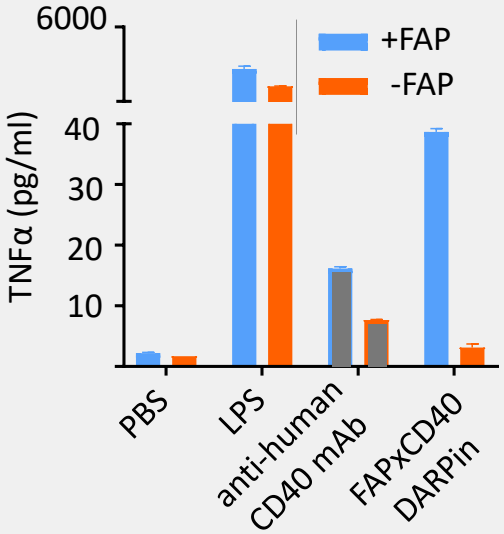
1 Dendritic cells:



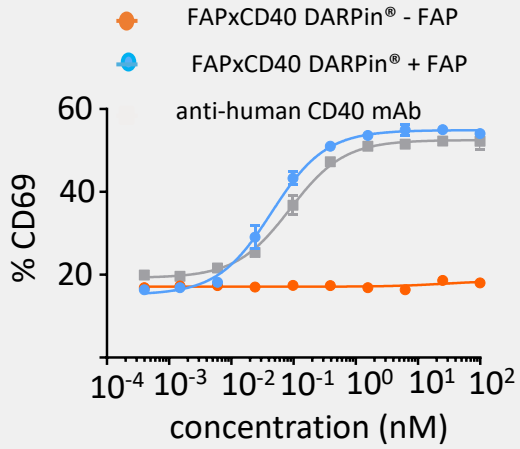


2 Macrophages:





3 B cells:



Surrogate molecule mFAPxmCD40 with similar properties:

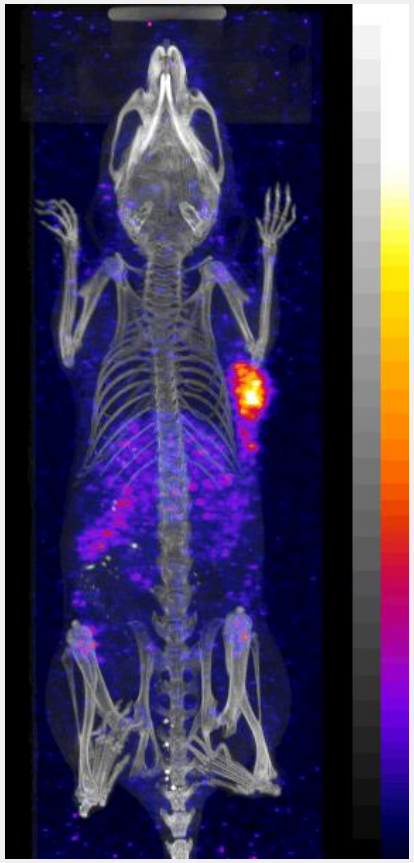
✓ **DC activation**
FAP-specific

✓ **Mφ activation**
FAP-specific

✓ **B cell activation**
FAP-specific

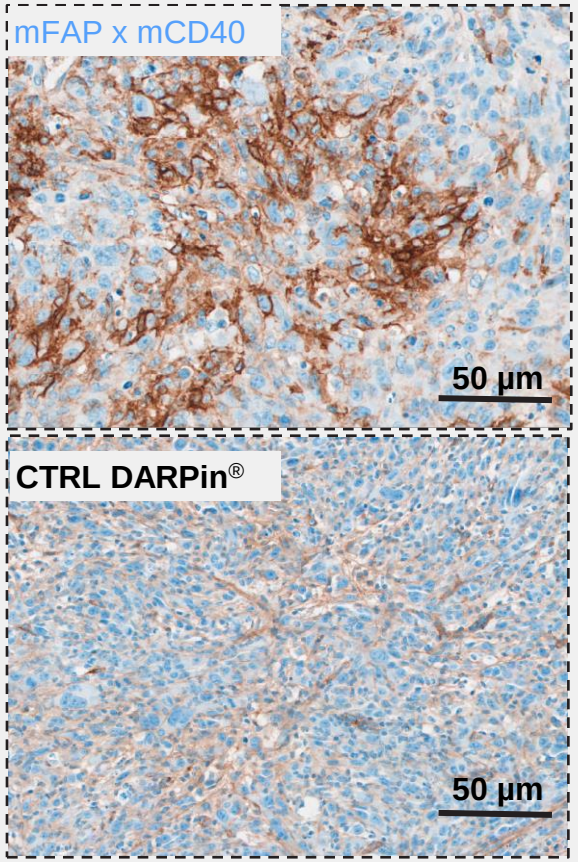
MP0317: Localizes to MC38-FAP Tumors

SPECT-CT study



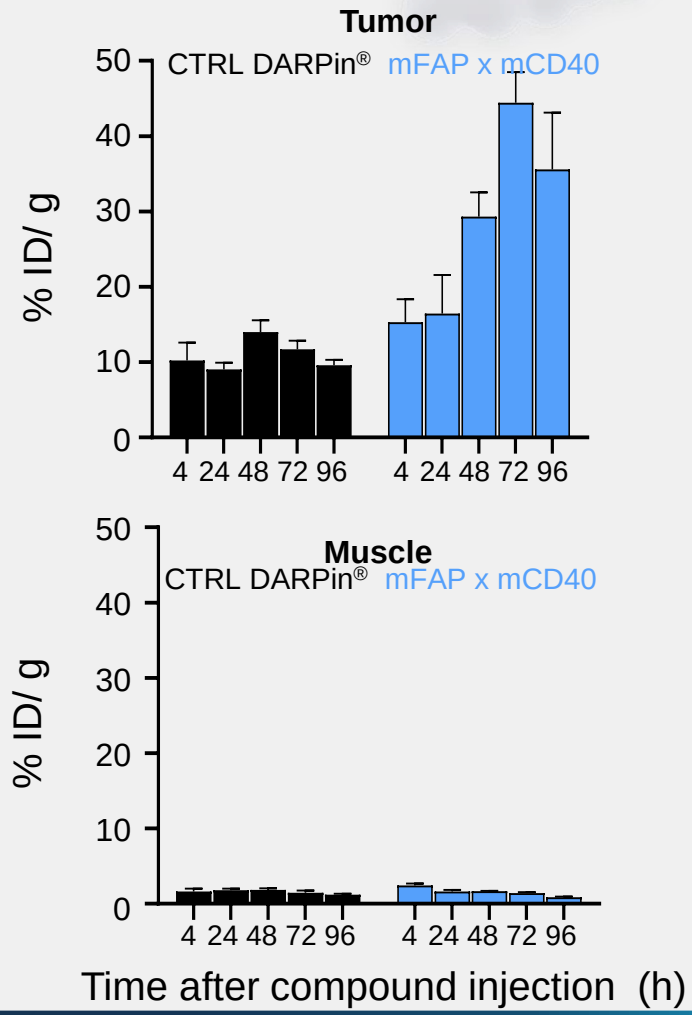
mFAP x mCD40

DARPin detection in the tumor by IHC



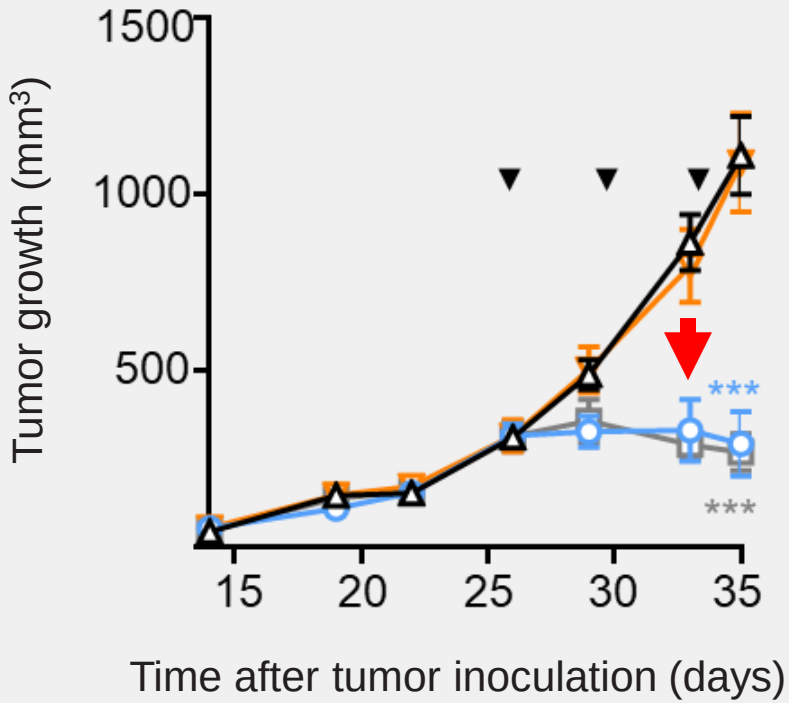
CTR DARPin
Binding HSA but not FAP and CD40

Biodistribution study

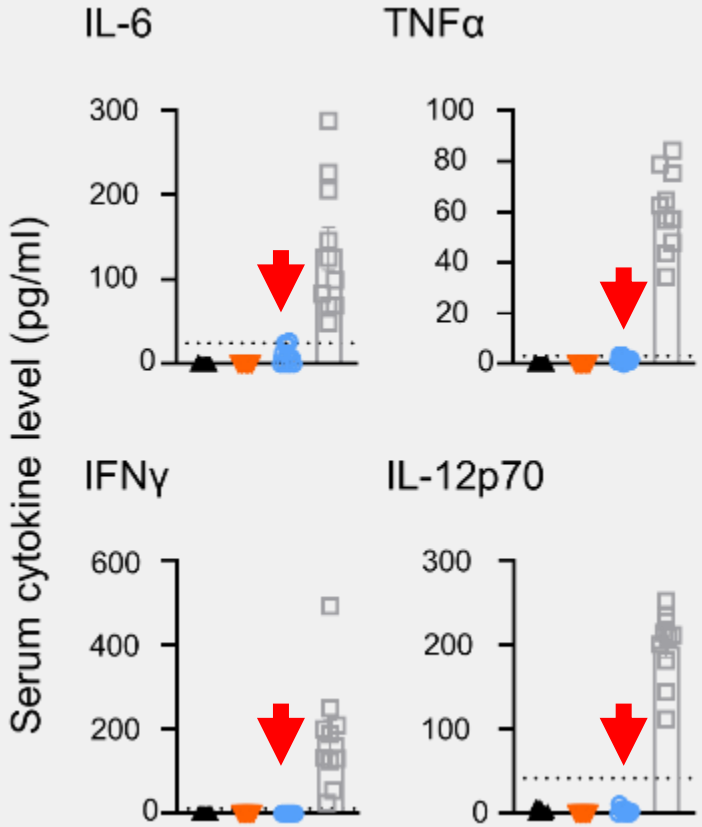


MP0317 Shows Therapeutic Activity without Cytokine Release

Efficacy



Peripheral cytokine release



Vehicle

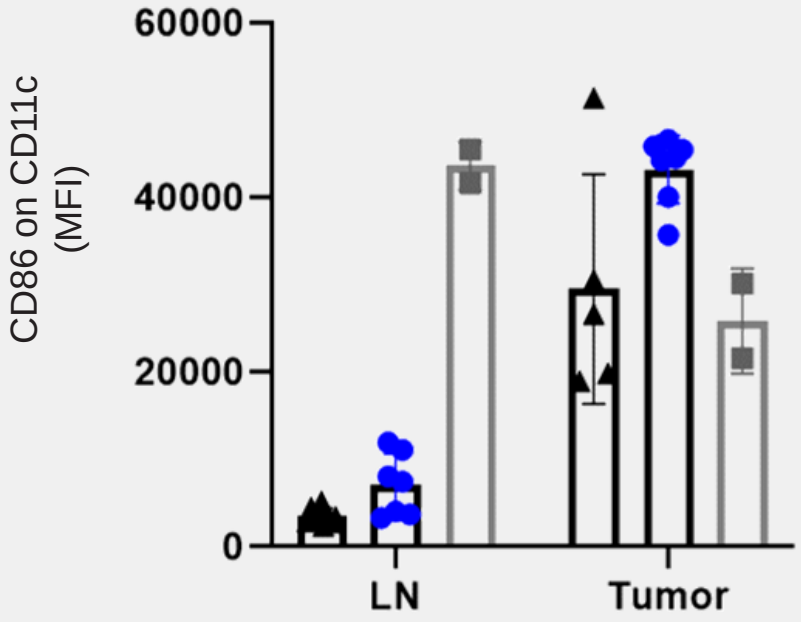
Neg. CTRL*

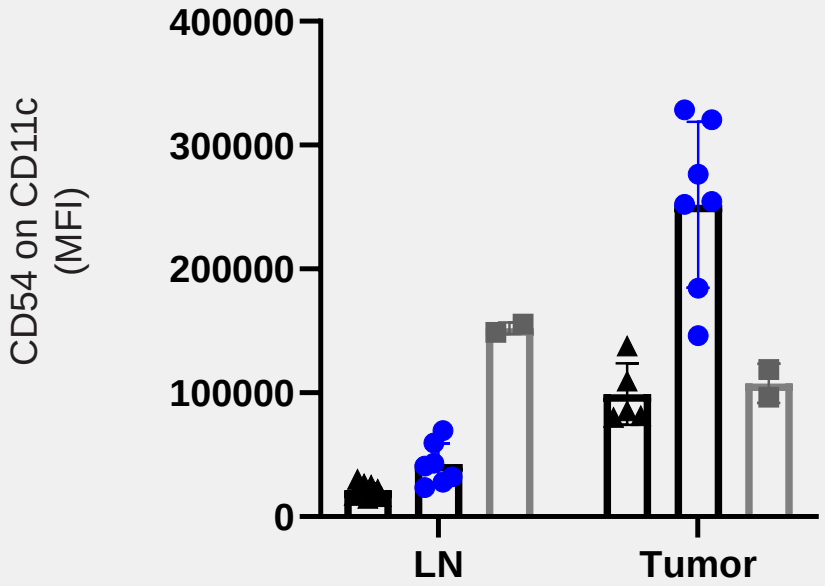
mFAP x mCD40

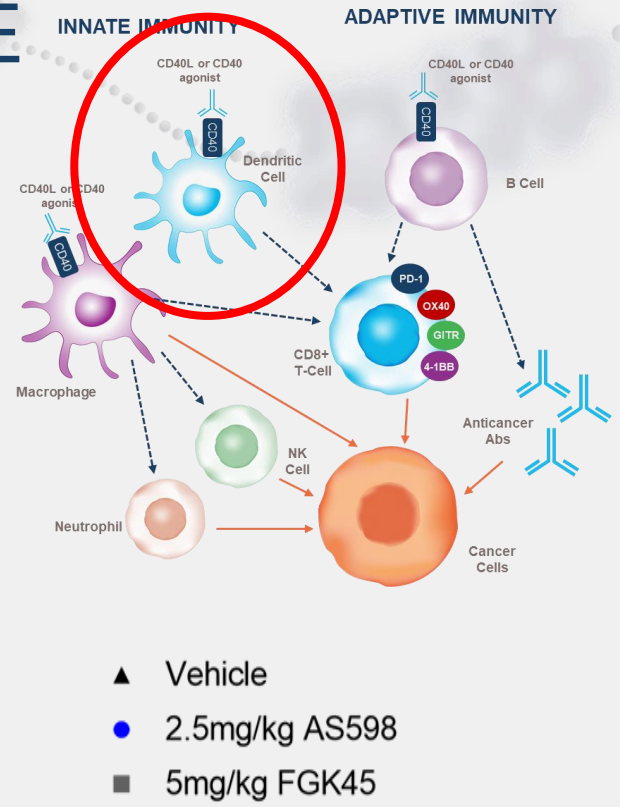
mCD40 Ab

MC38-FAP
Colorectal cancer

ex-vivo: mFAPxCD40 Activates DC in the TME

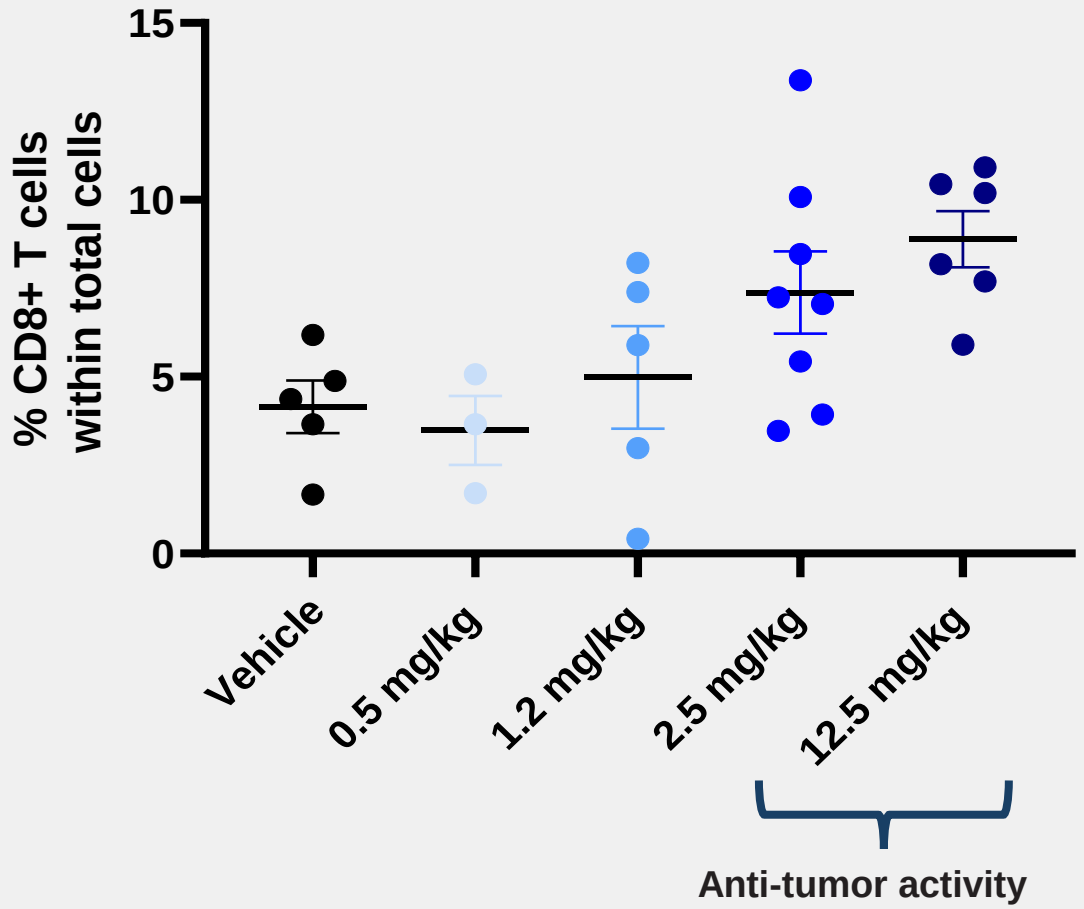


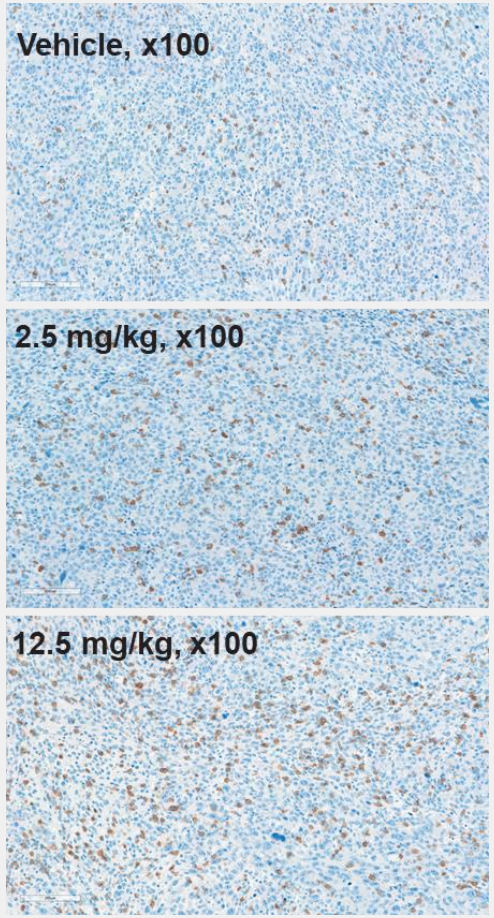


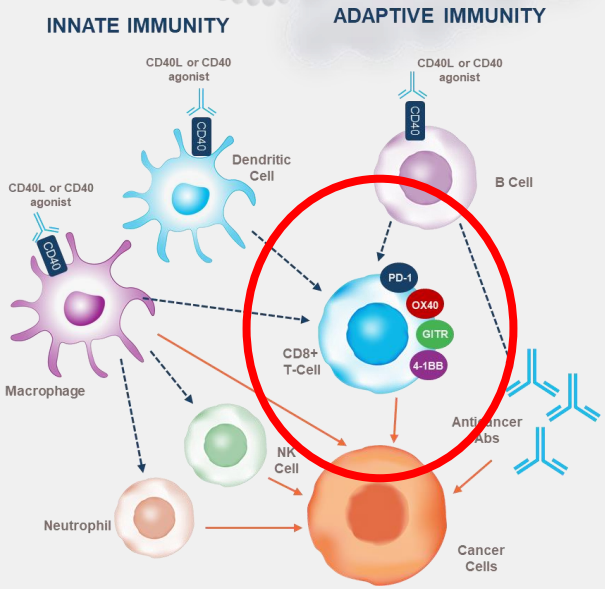


- Upregulation of co-stimulatory molecules on tumor Dendritic cells → potential for better T cell activation
- Higher activity in Tumor vs LN, in contrast to aCD40

mFAPxCD40 Increased CD8 T cell Infiltrate in the TME

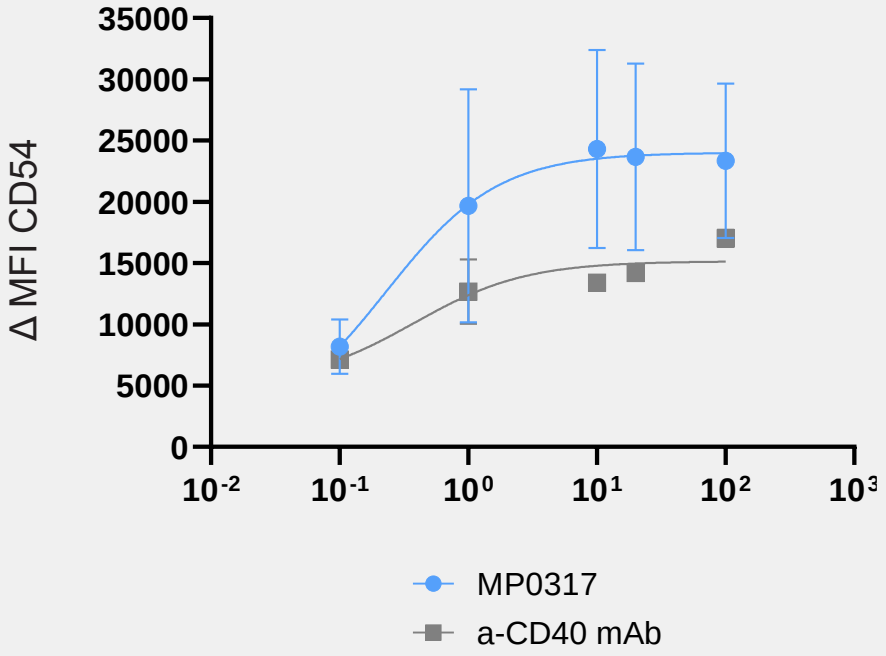




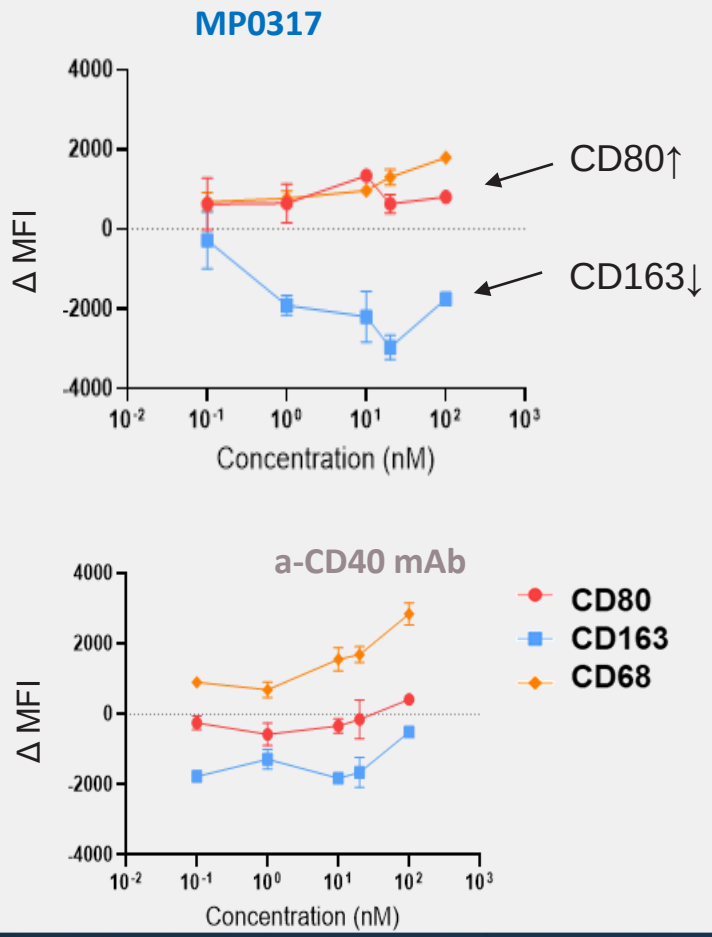


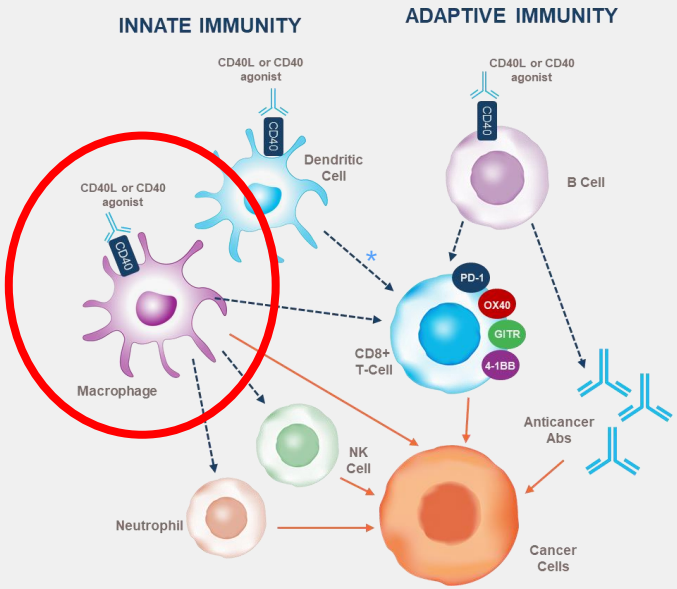
FAP Expression in Human Tumor Allows CD40 Mediated Immune Activation

B cell activation - CD54



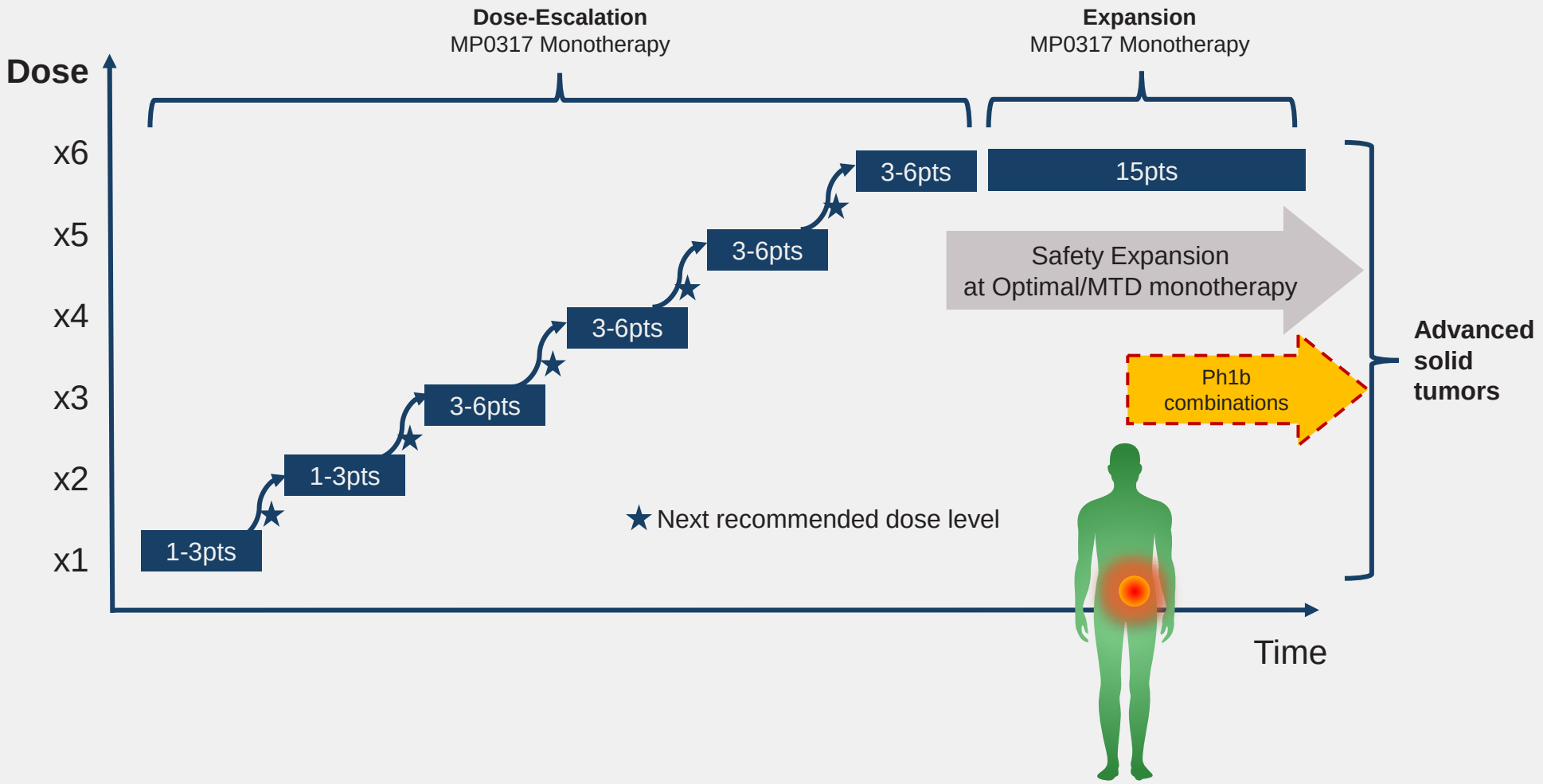
Macrophage repolarisation – inflammatory phenotype (CD80hi CD163lo)





- ✓ Macrophage repolarization is further supported by in vitro data

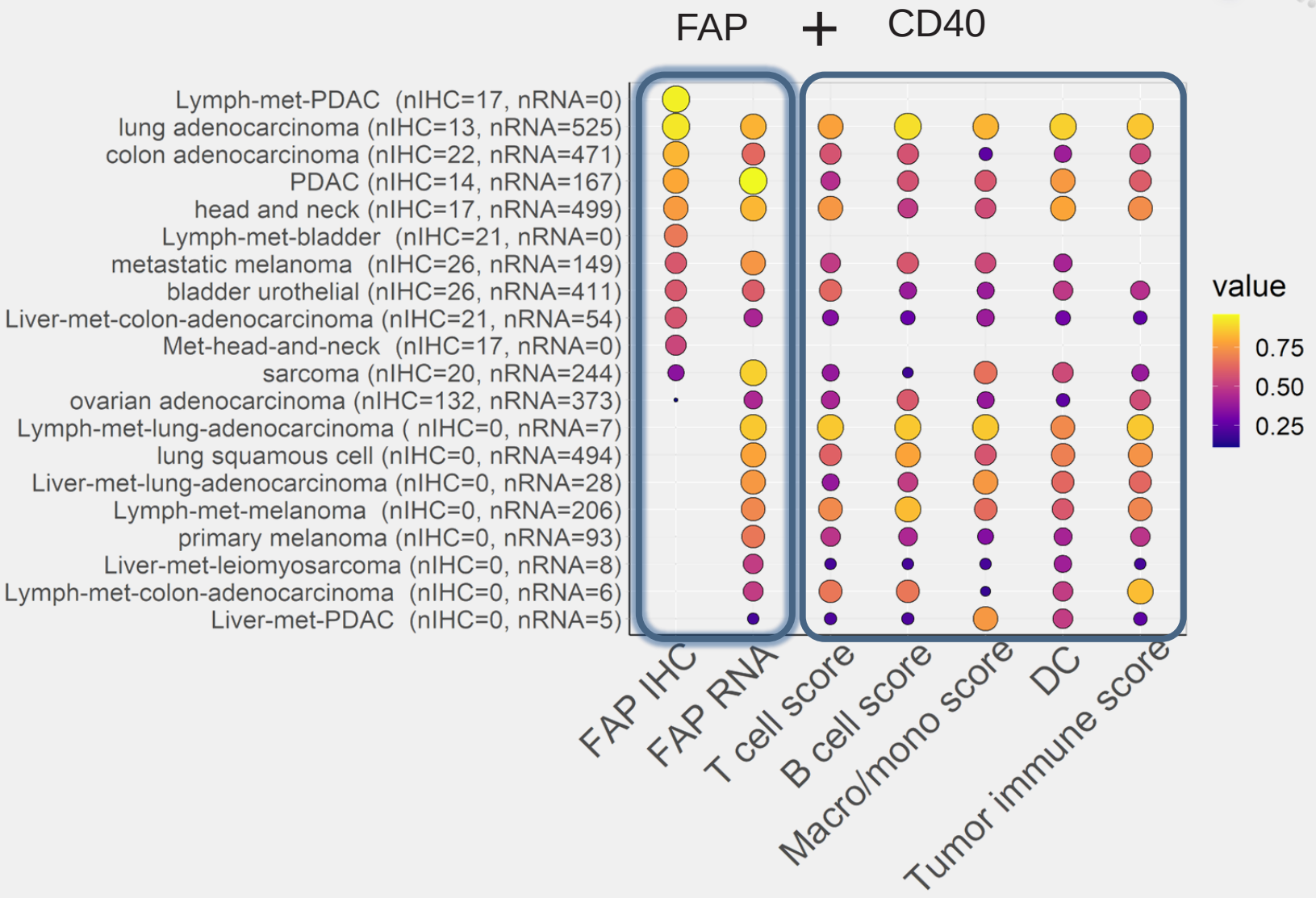
MP0317-CP101 Biomarker and Safety Trial Design



Objectives:

- Safety
- Local activity
- No systemic reactivity

Identification and Screening of Potential Tumor Targets from MP0317

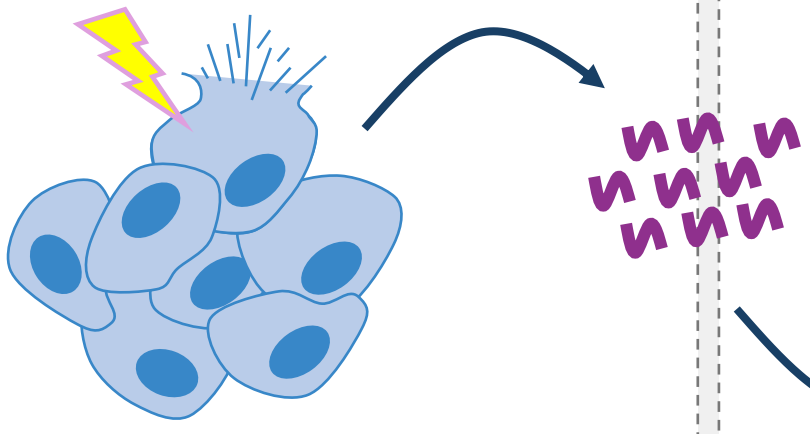


- The tumor immune score is correlated to response to aPD1. The FAP threshold is 20% > 2/3 score.

CD40 Open for Multiple Combination (IO or Other)

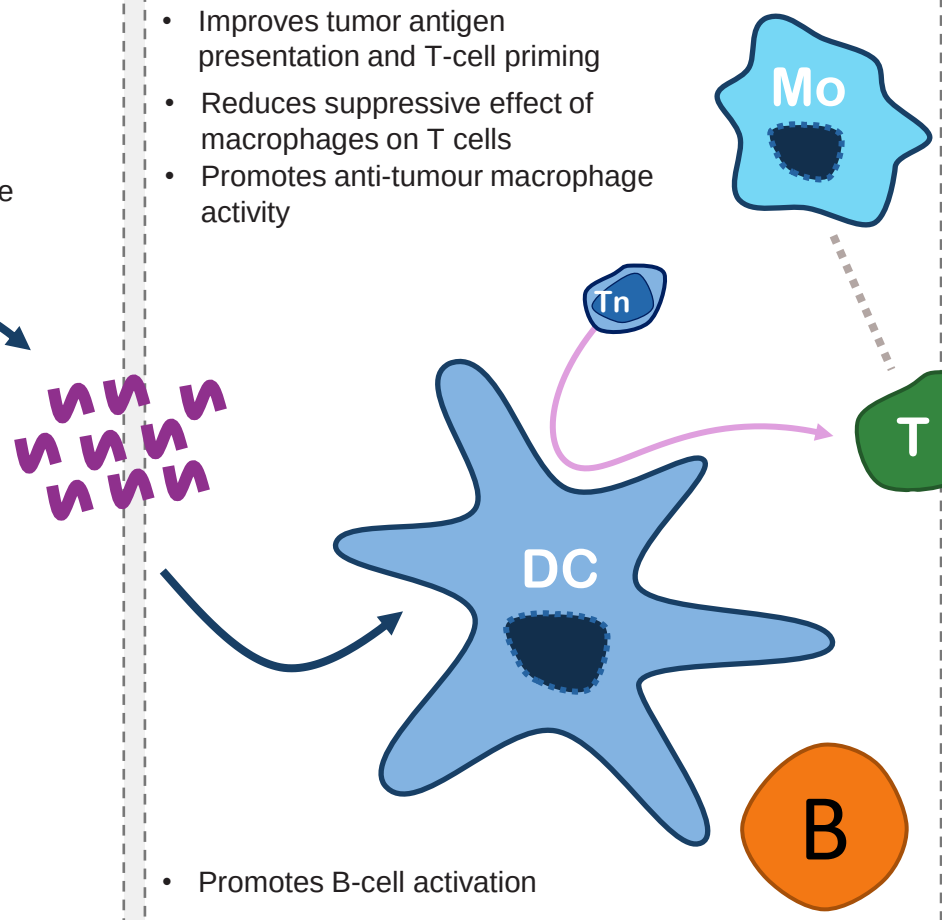
Chemo / Radio Therapy

- Direct tumor killing
- Release of tumor antigens
- Debulking aids immune cell access
- Timing with immunotherapy is important because immune cells can also be damaged



CD40

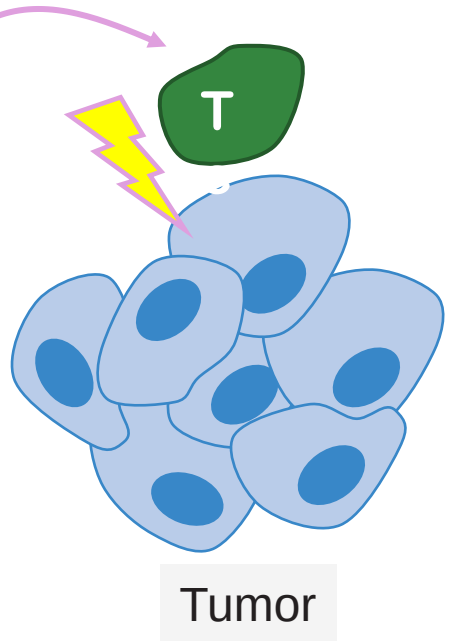
- Improves tumor antigen presentation and T-cell priming
- Reduces suppressive effect of macrophages on T cells
- Promotes anti-tumour macrophage activity



- Promotes B-cell activation

PD-1 or other IO Therapy

- Removes suppression of T-cell responses by PD-L1 in the tumor



Conclusions: Highly Differentiated Multi-Specific IO Assets

- Localized activity achieved with **MP0310/AMG 506**
  - No systemic immune activation observed
  - Tumor local immune stimulation confirmed after 1st dose
  - **FAP "validated" as target in the TME of many solid tumors for DARPin IO agonists**
  - Clinical work to establish optimal dosing regimen ongoing
  - H1 2022 data for review with MP and Amgen

- **MP0317** is at the intersection of the innate and adaptive immune system
  - Additional combination strategies possible with CD40
  - Ongoing Phase 1 will provide critical information re: dosing, safety, and immune activation
  - Initial data in H2 2022

AML & MP0533

Prof. Adrian Ochsenbein, University Hospital Bern
Prof. Carsten Riether, University Hospital Bern
Dr. Anne Goubier, Molecular Partners

Prof. Adrian Ochsenbein, MD, EMBA

Director
Department Medical Oncology, Inselspital, University Hospital Bern

- Trained in Experimental Oncology in the lab of Prof. Zinkernagel, University of Zürich
- Translational Research in the lab of Prof. Greenberg, FHCRC, Seattle, USA
- Research on Cancer Stem cells in the lab of Prof. Reya, UCSD, USA
- Research focus on anti-tumoral immunity, interaction of immune cells with cancer (leukemia) stem cells, CD70/CD27

Prof. Carsten Riether, PhD

Head of Research
Department Medical Oncology, Inselspital, University Hospital Bern

- PhD in Immunology, ETH Zurich
- Post-doc in Tumorimmunology in the lab of Prof. A. F. Ochsenbein, University of Bern
- Research focus on the identification of molecular and cellular mechanisms by which cells of the tumor microenvironment regulate cancer stem cells in leukemia and solid tumors.

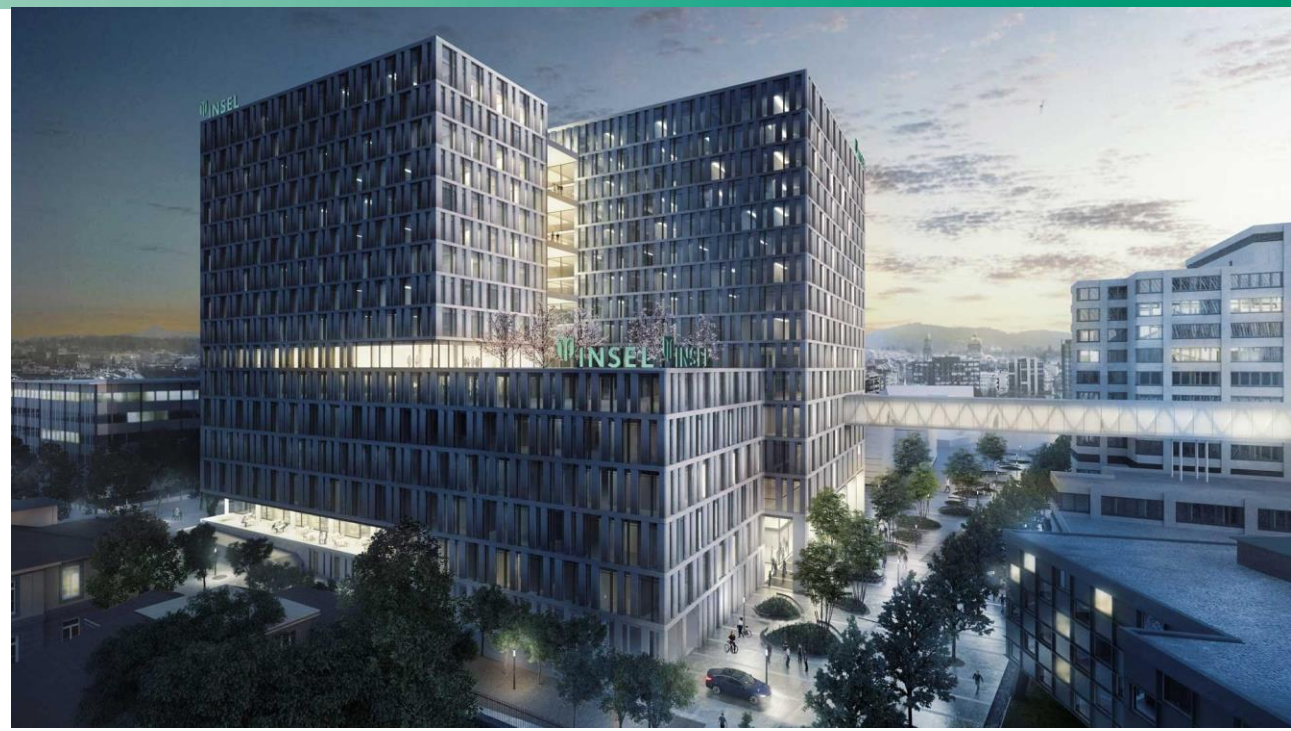
Anne Goubier DVM, PhD

VP Biology, Molecular Partners

- Doctorate in Veterinary Medicine, Ecole Vétérinaire de Nantes
- PhD in Immunology, Université Claude Bernard Lyon 1
- Former CSO, Black Belt Therapeutics
- VP Immunology, Tusk Therapeutics

RD Day Molecular Partners

INSELSPITAL
UNIVERSITÄTSSPITAL BERN
HOPITAL UNIVERSITAIRE DE BERNE
BERN UNIVERSITY HOSPITAL



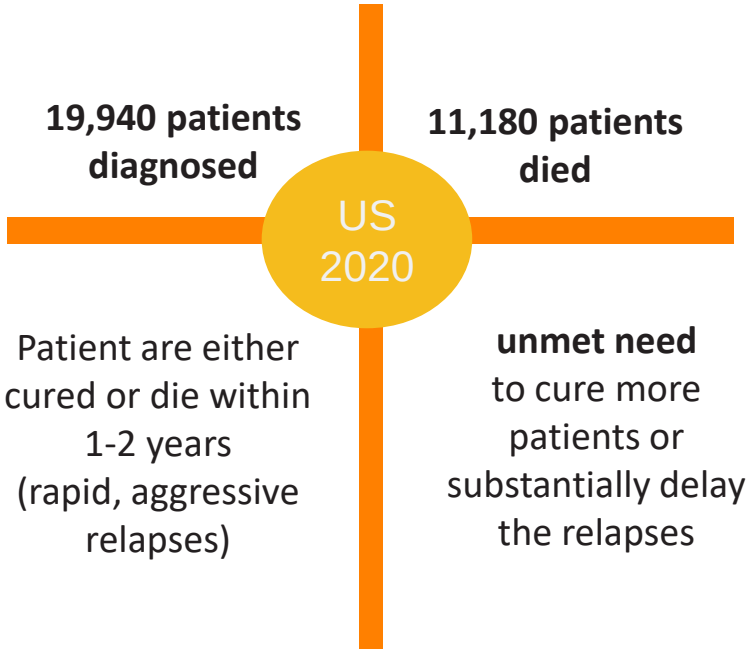
Adrian Ochsenbein / Carsten Riether

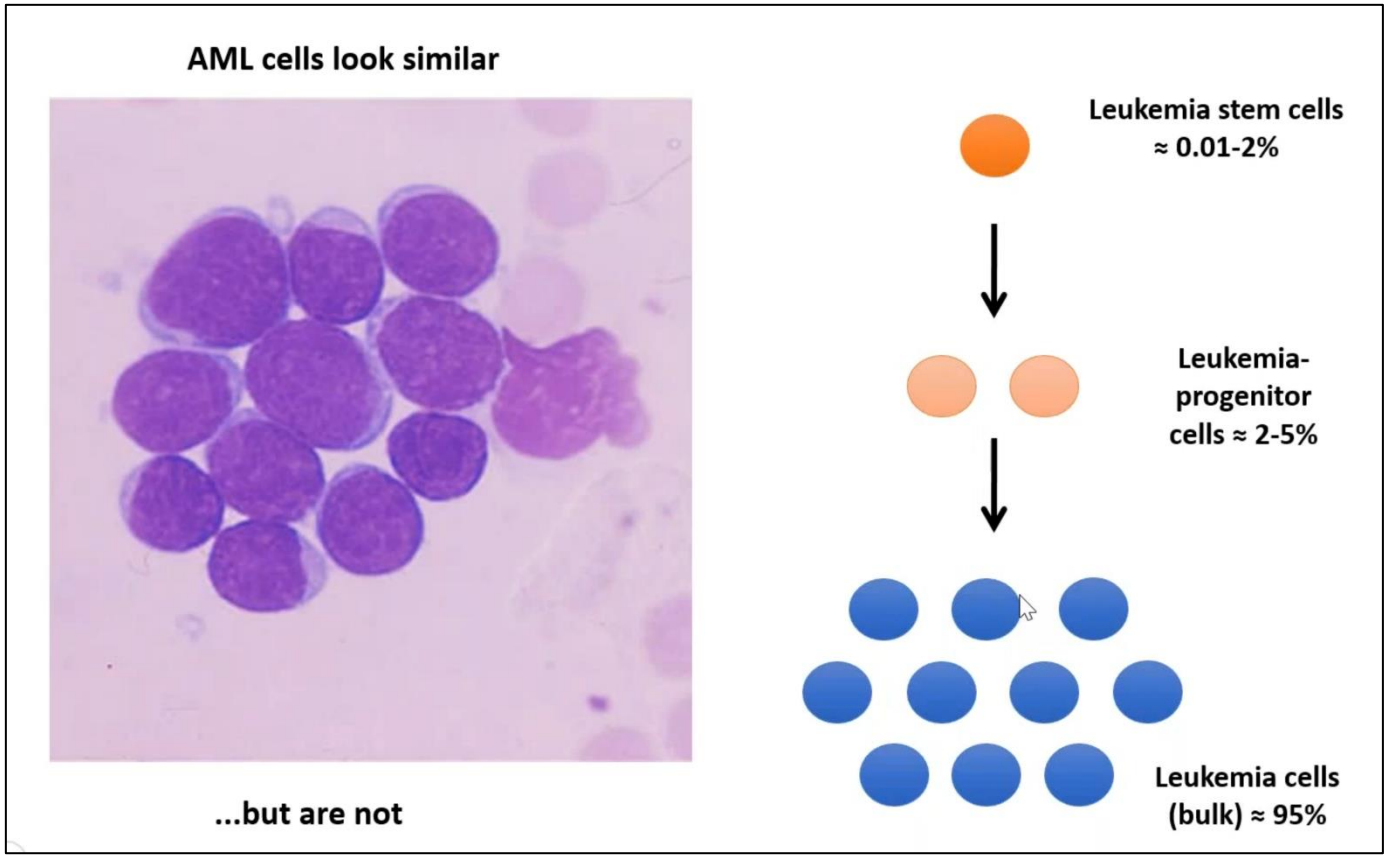
Disclosures

Molecular Partners: consultancy

Argenx: research funding, consultancy, royalties

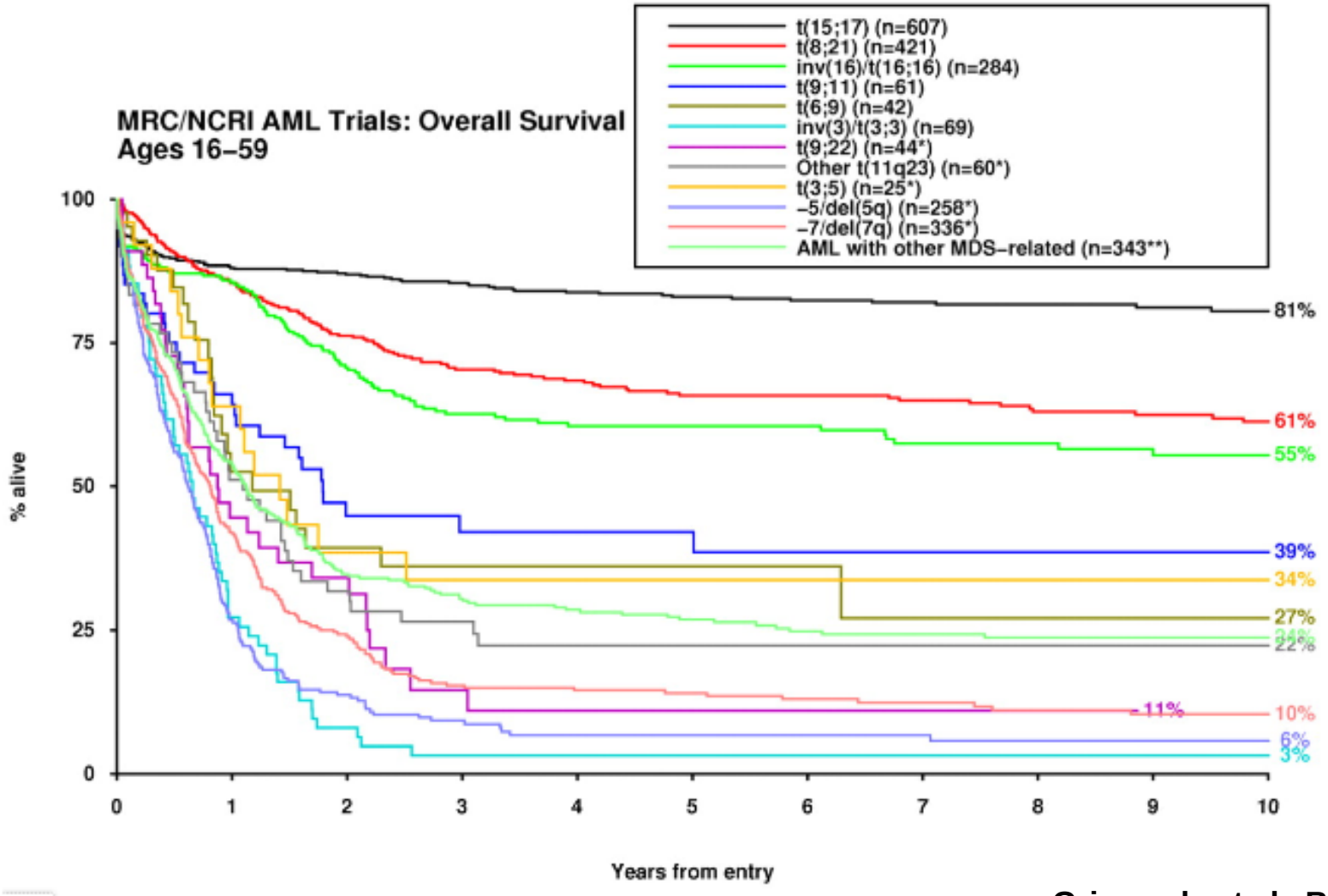
AML: Deadly Disease for About Half of the Patients





MRD+ is driver of relapse (only partial eradication of leukemic stem cells)
→ for curative intent LSCs need to be fully eradicated, while leaving HSCs untouched

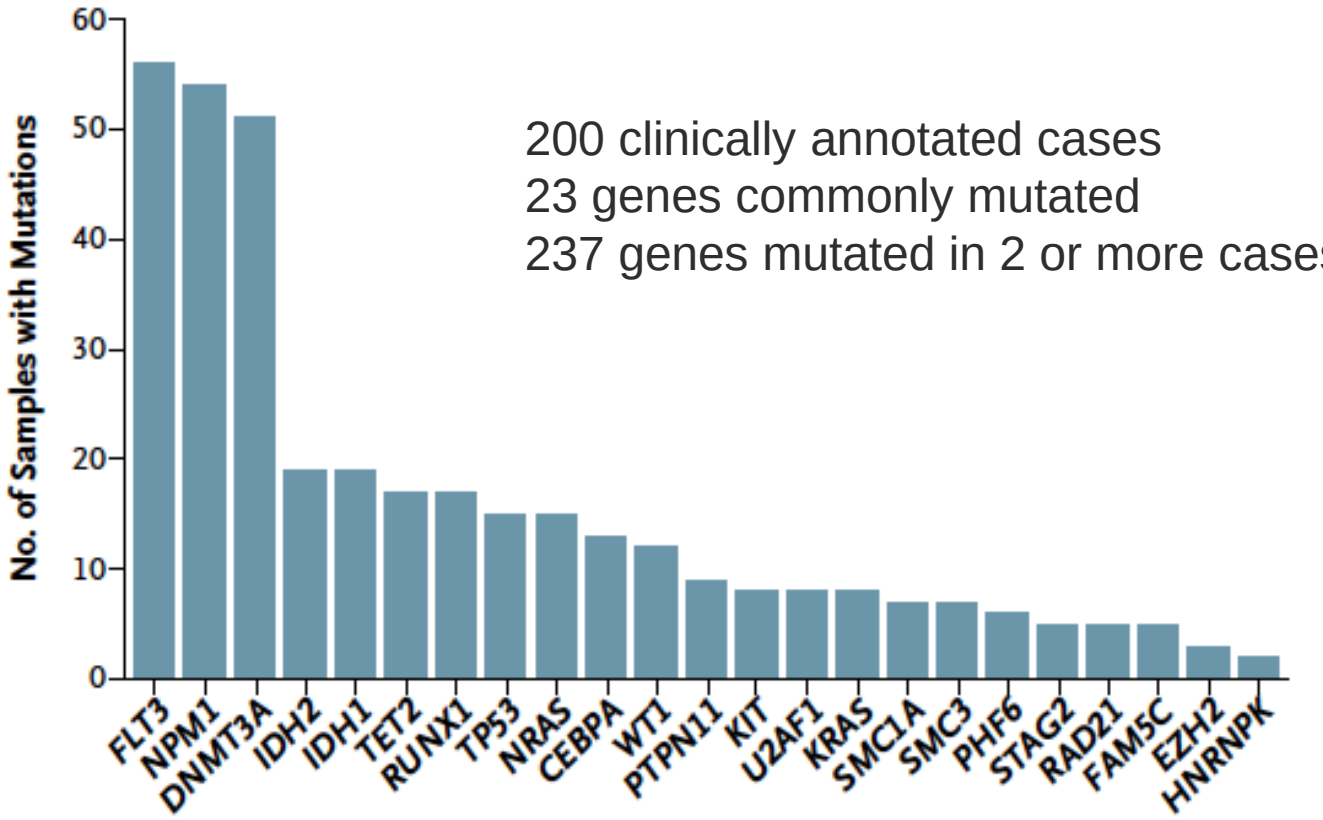
AML is a Heterogeneous Disease



Grimwade et al., Blood 2010

Pathogenesis and Biology of AML

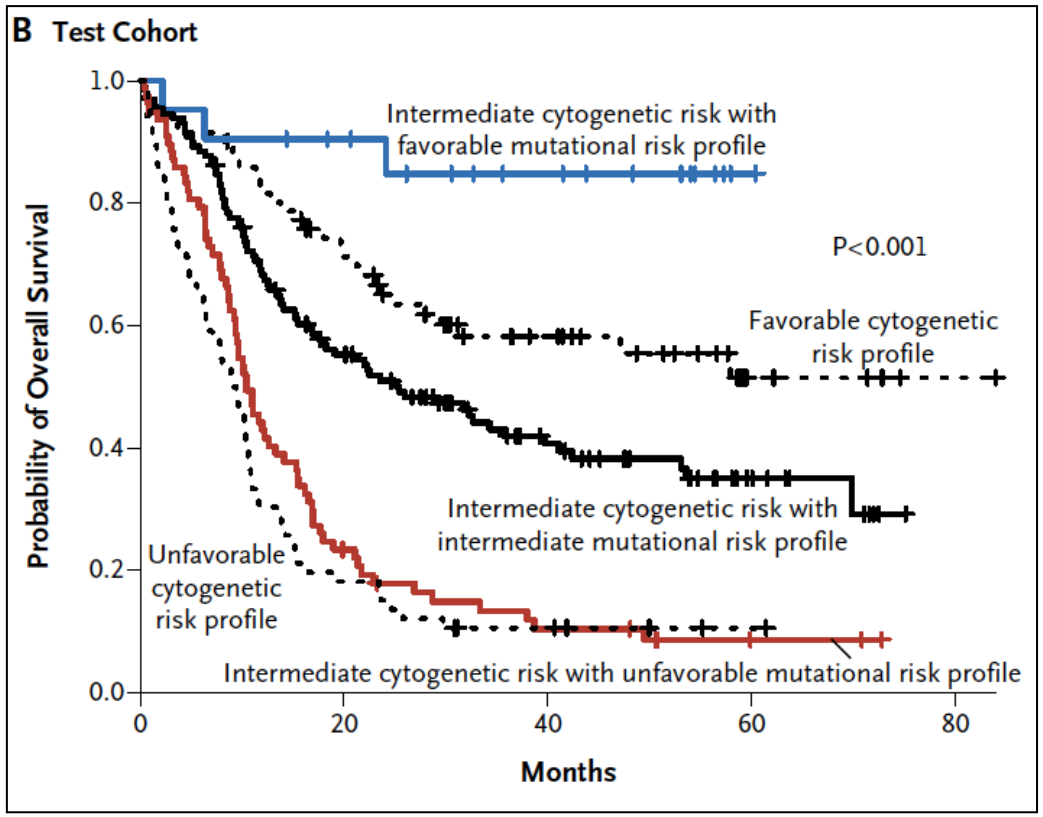
Gene	Overall Frequency (%)
FLT3 (ITD, TKD)	37 (30, 7)
NPM1	29
DNMT3A	23
NRAS	10
CEBPA	9
TET2	8
WT1	8
IDH2	8
IDH1	7
KIT	6
RUNX1	5
MLL-PTD	5
ASXL1	3
PHF6	3
KRAS	2
PTEN	2
TP53	2



200 clinically annotated cases
23 genes commonly mutated
237 genes mutated in 2 or more cases

Patel, et al., NEJM 2012; TCGA NEJM 2013.

2017 European Leukemia Net Stratification by Genetics



Revised Risk Stratification of Patients with AML on the Basis of Integrated Genetic Analysis

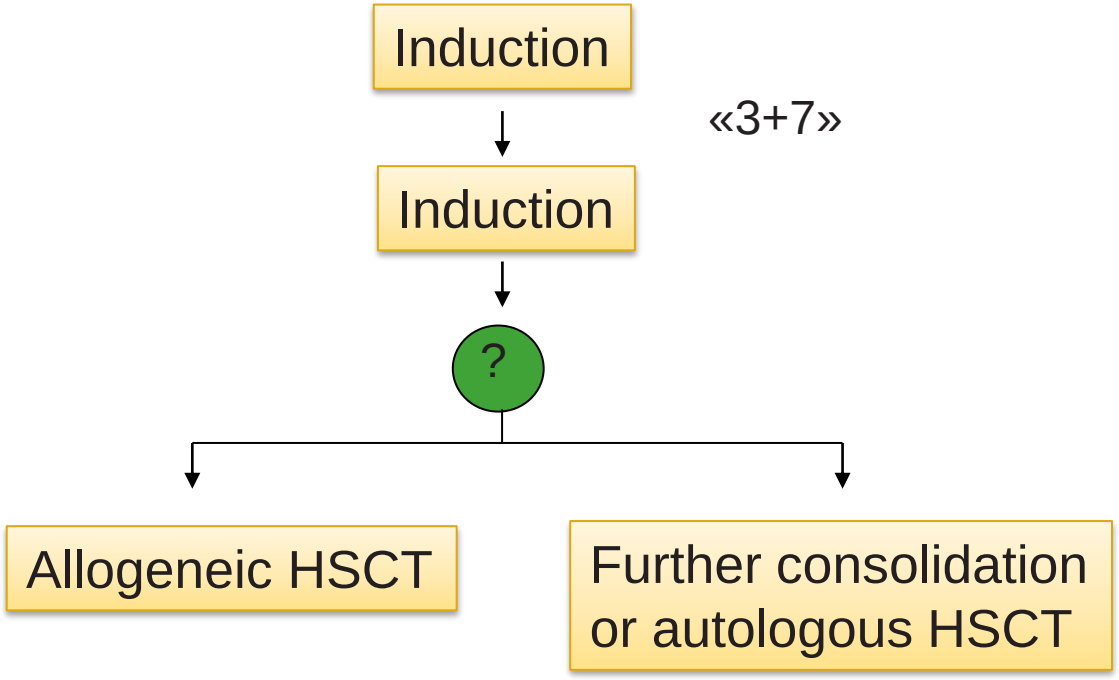
Genetic Risk Group	Subset
Favorable	• t(8;21)(q22;q22); RUNX1-RUNX1T1 • inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11 • Mutated NPM1 without FLT3-ITD (normal karyotype) • Biallelic mutated CEBPA (normal karyotype)
Intermediate	• Mutated NPM1 and FLT3-ITD^{high} (normal karyotype) • Wild-type NPM1 without FLT3-ITD or FLT3-ITD^{low} (normal karyotype) • t(9;11)(p22;q23); MLLT3-MLL • Any cytogenetics not classified as favorable or adverse
Adverse	• inv(3)(q21q26.2) or t(3;3)(q21;q26.2); GATA2.MECOM(EVI1) • t(6;9)(p23;q34); DEK-NUP214 • t(v;11)(v;q23); KMT2Arearranged • Monosomy 5 or del(5q); monosomy 7; -17p; complex karyotype (≥3 abnormalities) • Mutated RUNX1 • Mutated ASXL1 • Mutated TP53

Patel et al. NEJM 2012 March 22; 366(12):1079-89.

Döhner et al. Blood 2017;129:424-447.

Treatment for AML patients

curative intention



palliative intention

- hypomethylating agents (HMA)
- + BCL 2 inhibitor venetoclax

Treatment for AML patients

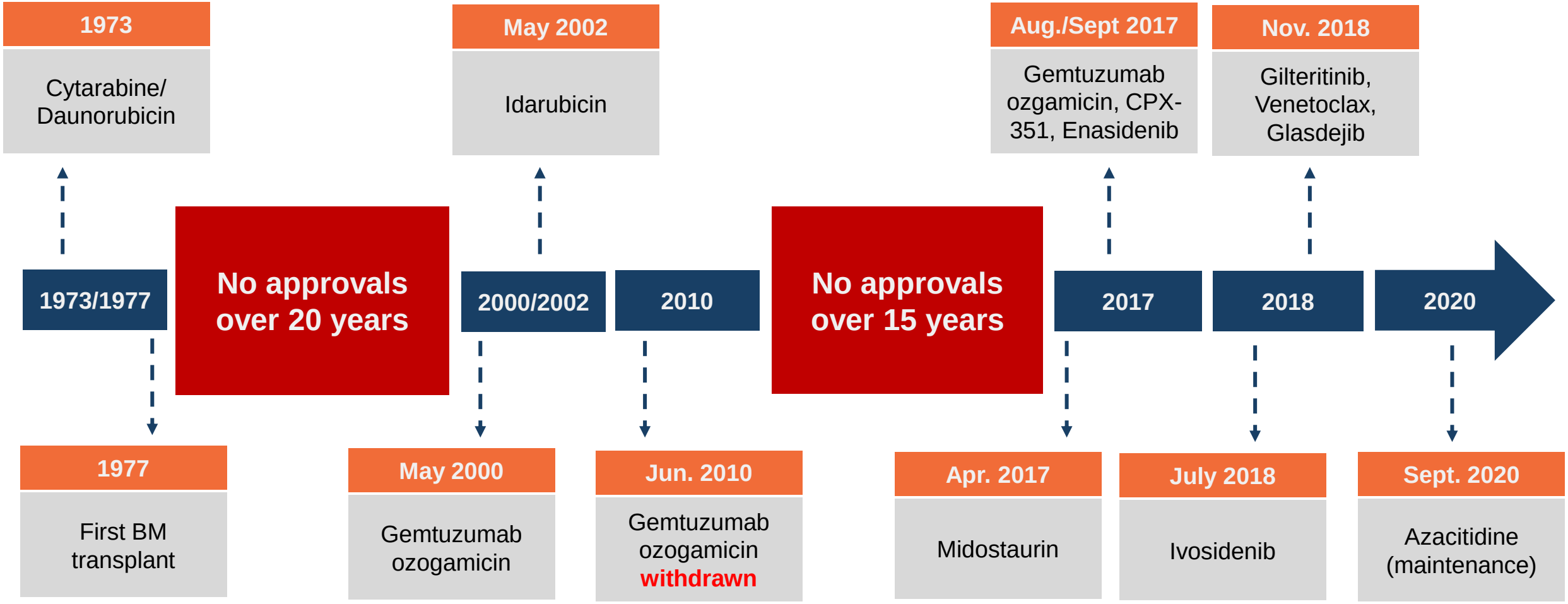
curative intention

palliative intention

thylating agents (HMA)
inhibitor venetoclax

Allogeneic HSCT

History of FDA approved AML therapy



CD33 and CD123 as single therapeutic targets in AML

CD33

Expression:

- on blasts and LSCs > 90% patients
- on virtually all healthy myeloid and progenitor cells

Treatment approaches:

- **Gemtuzumab ozogamicin** (GO, Mylotarg): CD33-targeting antibody-drug conjugate; approved treatment in combination with daunorubicin and cytarabine for newly diagnosed CD33-positive AML
- **AMG330, AMG 673 and AMV564**: BiTE molecules. Ongoing Phase I/II studies (NCT02520427, NCT03224819, NCT03144245)

Toxicity:

- The on-target off-leukemia toxicity is a major side effect observed in the clinical practice and in clinical trials investigating CD33-targeting therapies

Alternatives:

- **Combination of CD33 with other antigens.** Dual CD33-CLL1 CAR-T Therapy in R/R AML (NCT05016063)
- **Gene editing:** A first-in-human trial will be initiated that combines an alloHSCT utilizing genetically modified, CD33-negative HSCs with CD33-directed CAR-T cells

CD123

Expression:

- on blasts and LSCs > 90% patients
- on virtually all healthy myeloid and progenitor cells, megakaryocytes, B cell subsets as well as endothelial cells.

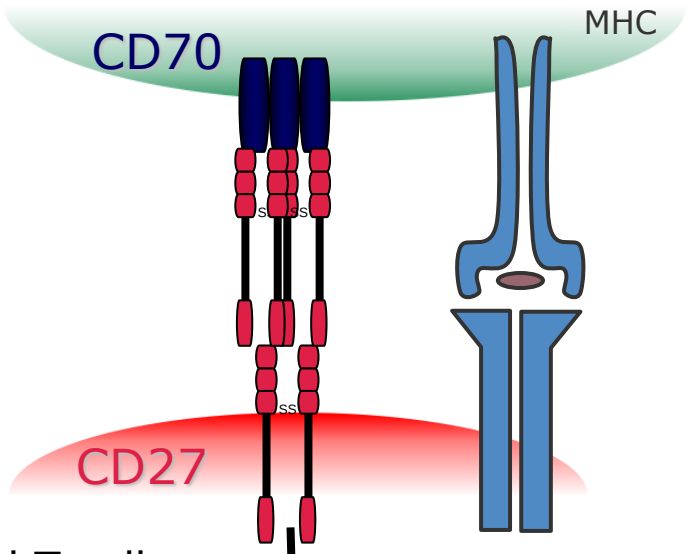
Treatment approaches:

- **Flotetuzumab**: humanized BiTE; FDA-orphan drug. ongoing phase I/II clinical trials (NCT02152956), (NCT04158739).
- **Other CD123 x CD3 bispecific antibodies in early-phase**: Vibecotamab (XmAb 14045, NCT02730312), SAR440334 (NCT03594955), APVO436 (NCT03647800), and JNJ63709178 (NCT02715011)
- **IMGN632,** CD123-targeting antibody-drug conjugate, **:** phase Ib/II in combination with standard of care (Ven/Aza) or monotherapy MRD+ AML (NCT04086264)
- **CD123-targeting CAR T cells**: Autologous CD123-specific CAR-T cells are under investigation (NCT02159495) for R/R AML. Few reports using CD123 CAR T cells have shown muted effectiveness in patients compared to pre-clinical models.

Toxicity:

- Cytokine-release syndrome
- on-target off-leukemia toxicity: CAR T cell infusion was accompanied by serious adverse events; CRS

activated lymphocytes
dendritic cells



B and T cells
HSCs

- *proliferation*
- *anti-apoptotic signals*
- *effector function*
- *memory function*

CD70/CD27 signaling .....

.. induces T cell expansion and differentiation of effector cells *Hendriks J. Nat Immunol. 2003*

.. improves secondary expansion of effector cells and CTL memory
Matter M. EJM, 2005, Matter M. EJM 2008

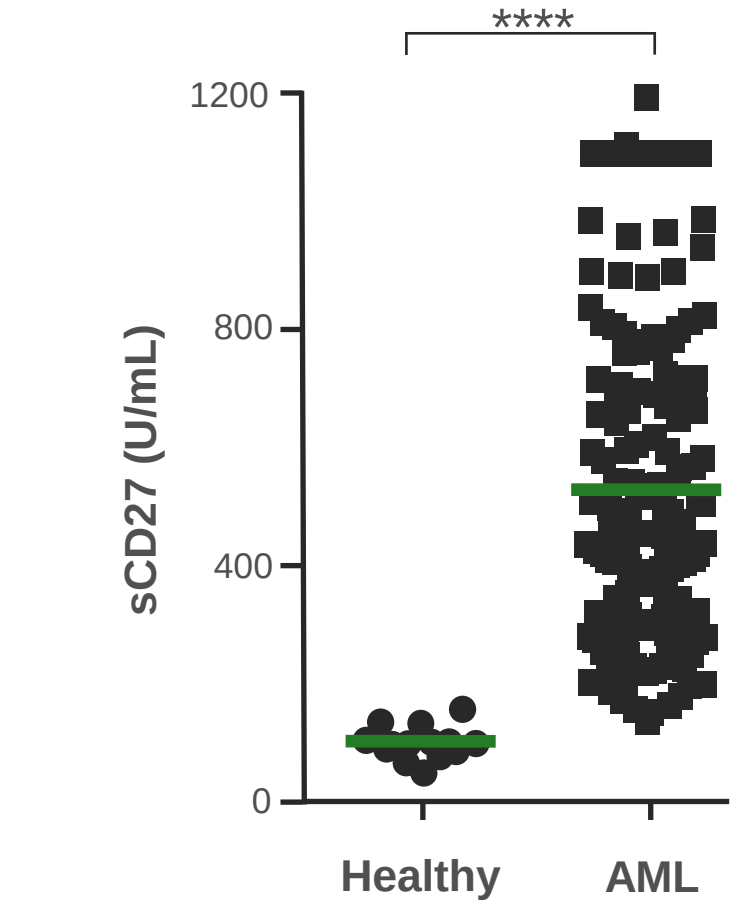
.. increases resistence of HIV specific CTL to exhaustion
Ochsenbein AF 2004. J Exp. Med.

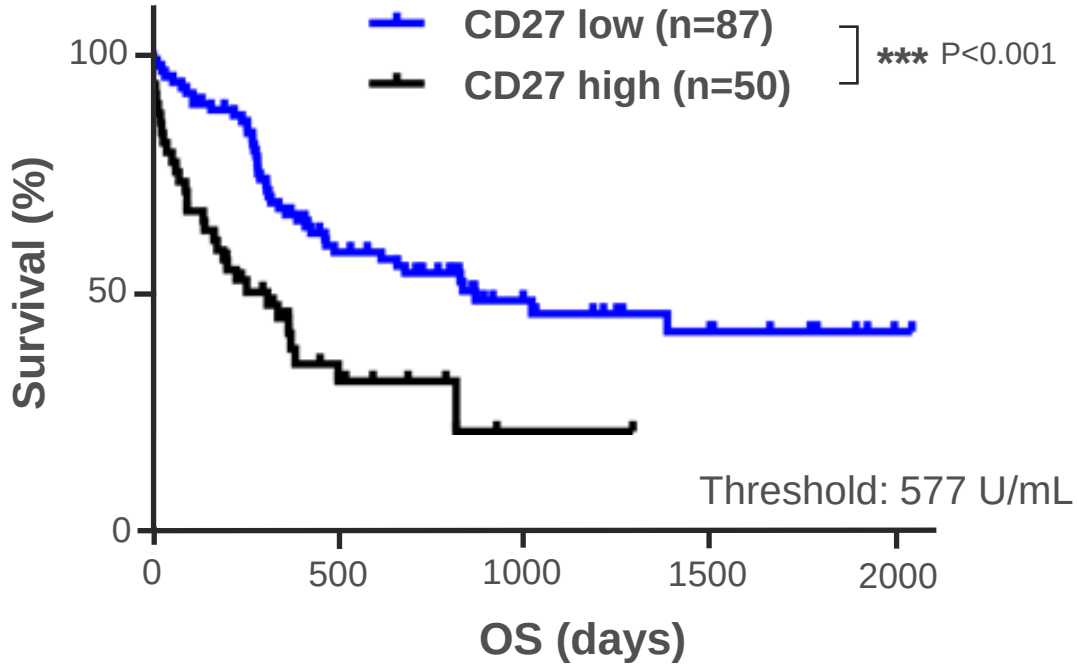
.. induces immunopathology and aquired immuno-deficiency in chronic LCMV infection
Matter M. 2006. J Exp Med.

… induces regulatroy T cells and promotes tumor progression
Claus C. 2012. Cancer Research

… provides a negative feedback signal to leukocyte differentiation during immune activation
Nolte M. 2010. Nat. Immunol.

Elevated levels of soluble CD27 correlate with poor prognosis in AML

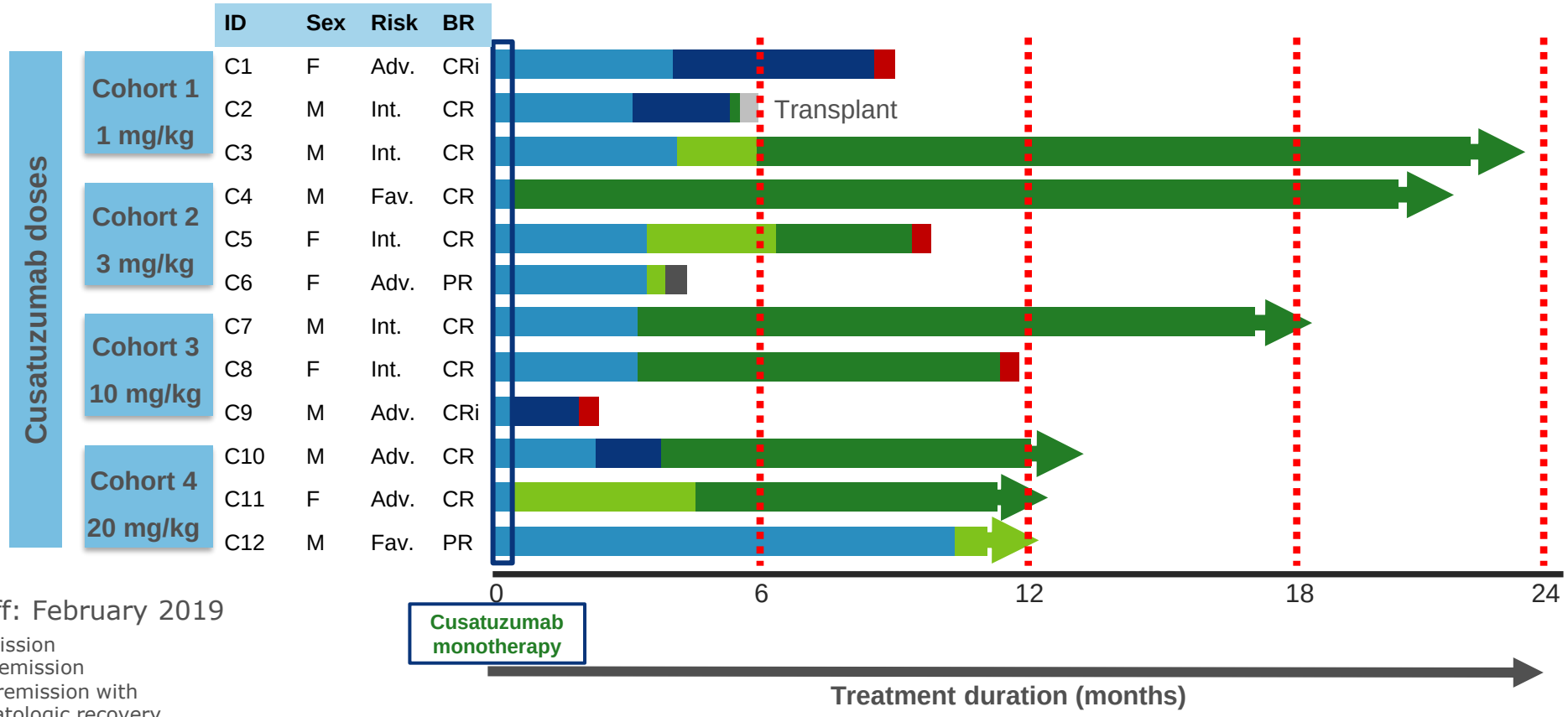




Parameter	HR (95% CI)	P-value
sCD27	2.17 (1.34–3.50)	0.0016
Risk group	1.69 (1.29–2.38)	0.0024
Age	1.03 (1.01–1.05)	0.0050

Riether et al, J Exp Med 2017; 214:359–80

Cusatuzumab: Swimmer plot



* Data cut-off: February 2019

PR = partial remission
CR = complete remission
CRi = complete remission with incomplete hematologic recovery
EOT = end of treatment
PD = progression of disease
AE = adverse event

NCT03030612

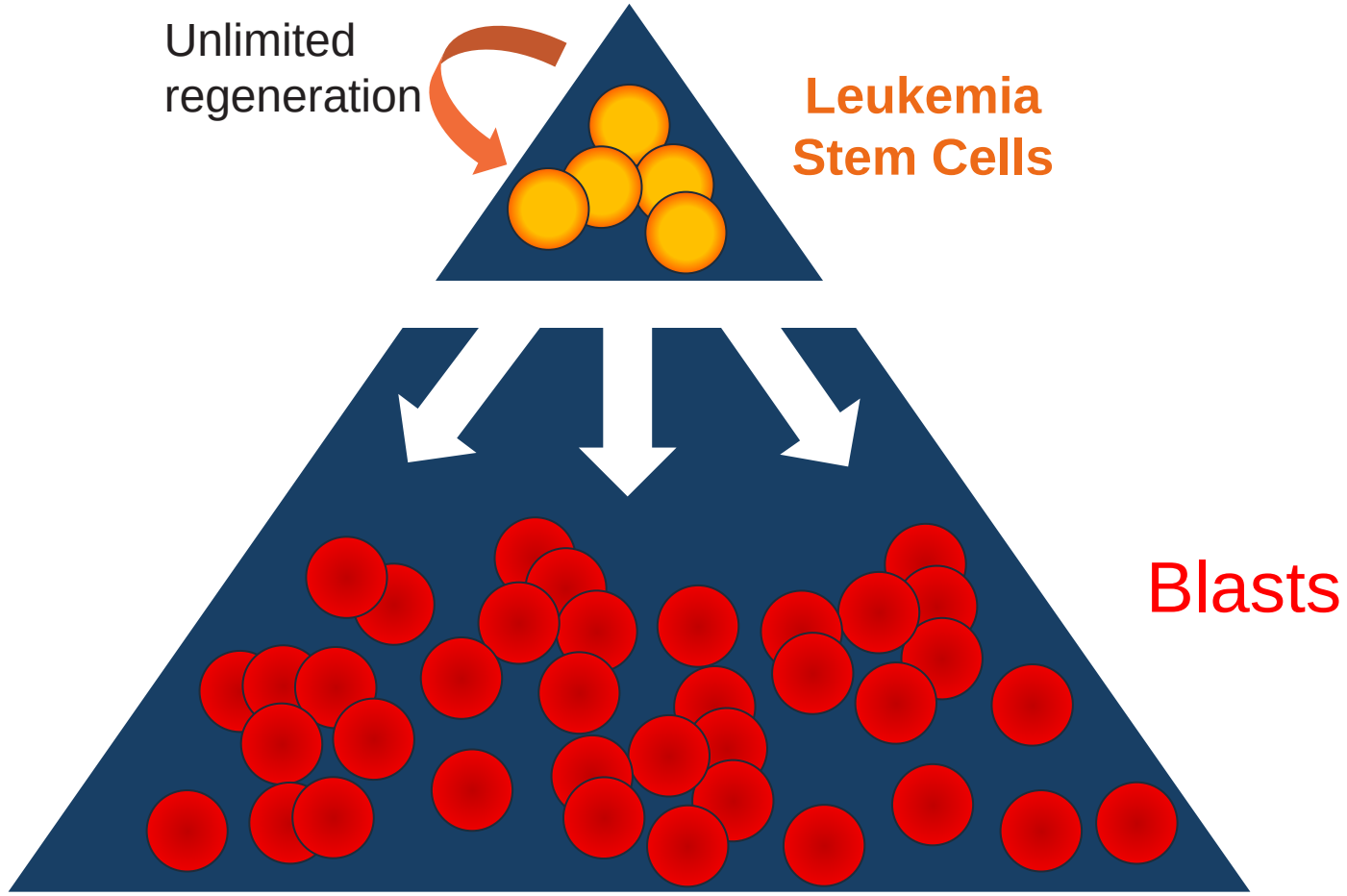
Riether et al, Nat. Med. 2020; 26; 1459-1467

Summary I

- CD70 has a unique expression pattern on activated immune cells and on AML LSCs
- Blocking the CD70/CD27 signaling pathway eliminates LSCs
- Treatment with HMA upregulates CD70 on LSCs
- cusatuzumab monotherapy reduces AML blasts and LSCs within 2 weeks of therapy
- Different strategies to target CD70 are currently under investigation: CAR-T cells; bi- (tri-) specific antibodies
- Although cusatuzumab reduced LSCs, all patients in the phase Ib/II trial relapsed

Leukemia: a Paradigmatic Stem Cell Disease

- Self-renewing
- Therapy-resistant
- Quiescent

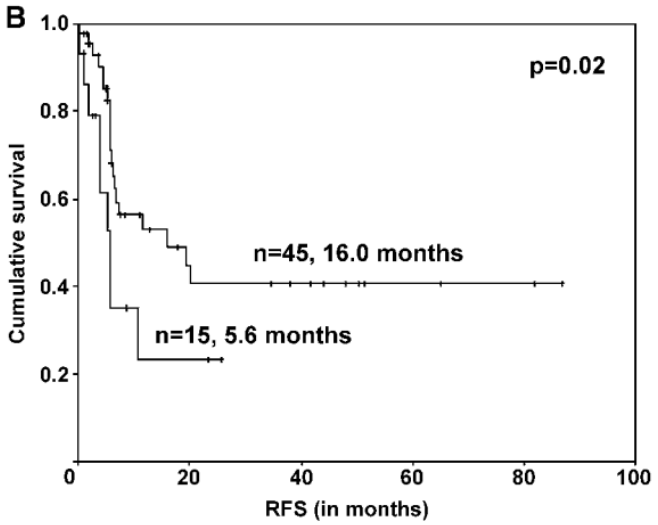


Bonnet et al. Nature Medicine 1997; 3, 730 - 737

Leukemic SC Numbers and Stem Cell Signatures are negative Predictors for Survival in AML

High Stem Cell Frequency in Acute Myeloid Leukemia at Diagnosis Predicts High Minimal Residual Disease and Poor Survival

Anna van Rhenen,[1] Nicole Feller,[1] Angèle Kelder,[1] August H. Westra,[1] Elwin Rombouts,[2] Sonja Zweegman,[1] Marjolein A. van der Pol,[1] Quinten Waisfisz,[1] Gert J. Ossenkoppele,[1] and Gerrit Jan Schuurhuis[1]

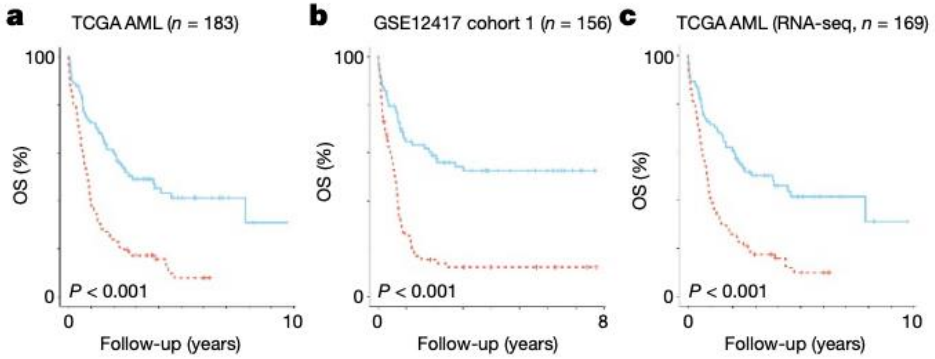


LETTER

doi:10.1038/nature20598

A 17-gene stemness score for rapid determination of risk in acute leukaemia

Stanley W. K. Ng[1]*, Amanda Mitchell[2]*, James A. Kennedy[2,3,4]*, Weihsu C. Chen[2], Jessica McLeod[2], Narmin Ibrahimova[2], Andrea Arruda[2], Andreea Popescu[2], Vikas Gupta[2,3,4], Aaron D. Schimmer[2,3,4,5], Andre C. Schuh[2,3,4], Karen W. Yee[2,3,4], Lars Bullinger[6], Tobias Herold[7,8], Dennis Görlich[9], Thomas Büchner[10]‡, Wolfgang Hiddemann[7,8], Wolfgang E. Berdel[10], Bernhard Wörmann[11], Meyling Cheok[12], Claude Preudhomme[13], Hervé Dombret[14], Klaus Metzeler[7,8], Christian Buske[15], Bob Löwenberg[16], Peter J. M. Valk[16], Peter W. Zandstra[1], Mark D. Minden[2,3,4,5]§, John E. Dick[2,17]§ & Jean C. Y. Wang[2,3,4]§



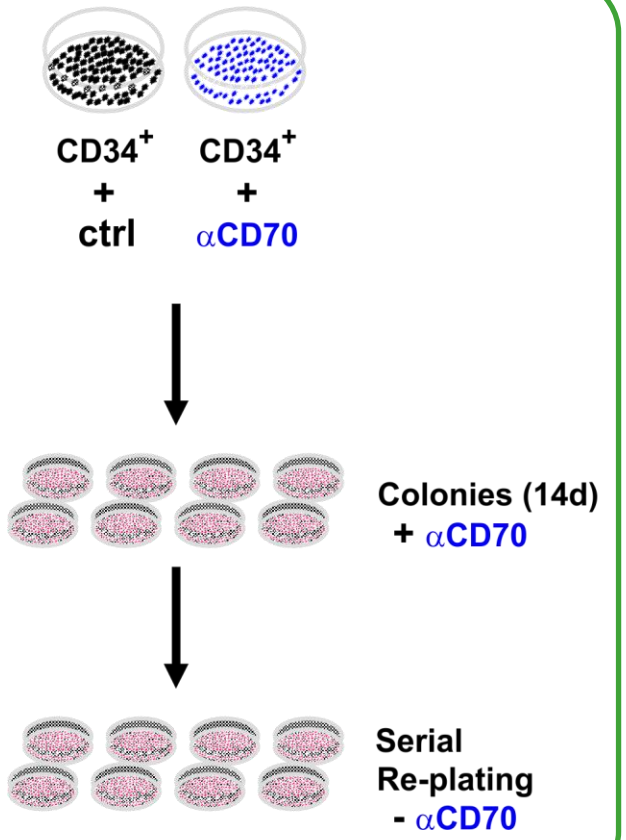
van Rhenen et al. Clin. Cancer Research 2005; 11:6520–6527
Pearce et al. Blood 2006; 107:1166–1173.
Gentles et al. JAMA 2010; 304:2706–2715.
Eppert et al. Nature Medicine 2011; 17:1086–1093
Stanley et al. Nature 2016; 540(7633):433-437

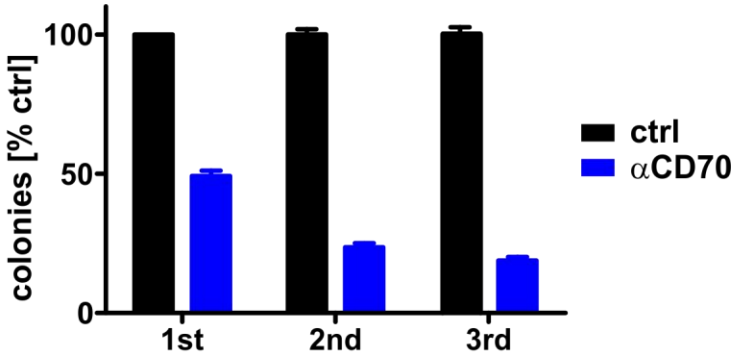
How Can We Study the Effect of a Treatment on LSCs?

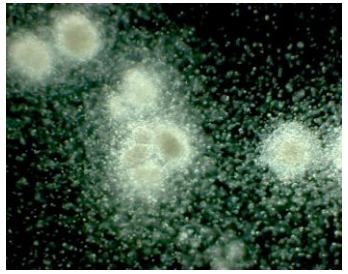
1. Colony formation assay (ex vivo)
2. Re-platings assays (ex vivo)
3. Gold-standard: Patient-derived xenograft model
4. Next-generation RNA sequencing analysis

Blockade of CD70/CD27 Signaling reduces Stem Cell Function

αCD70 = Fc-diminished blocking version of cusatuzumab without ADCC potential

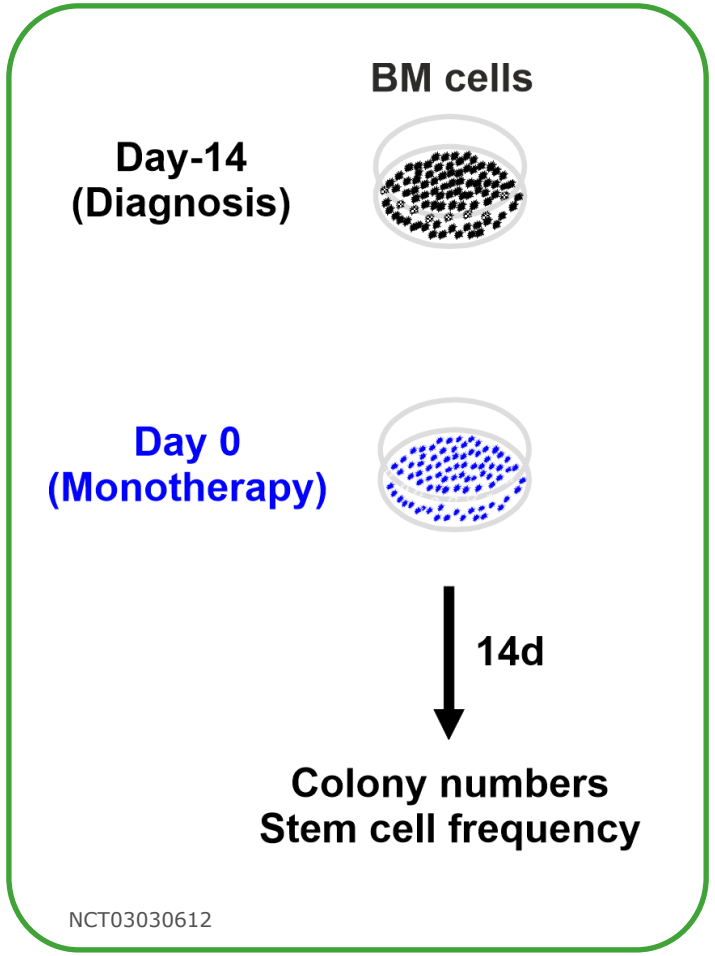


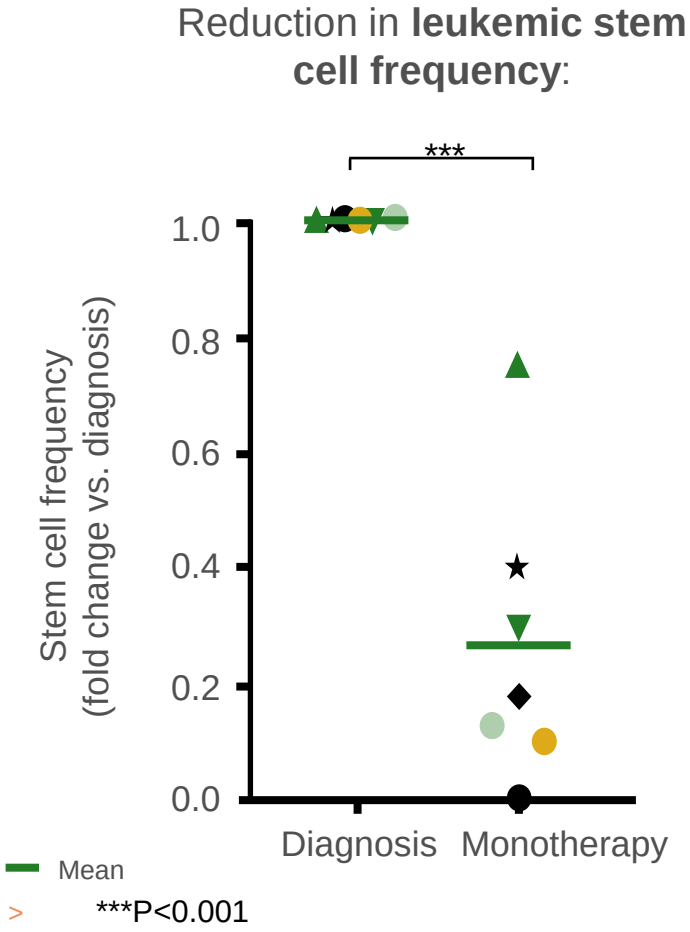




Riether et al. J Exp Med; 214, 359-380

Cusatuzumab kills leukemic stem cells





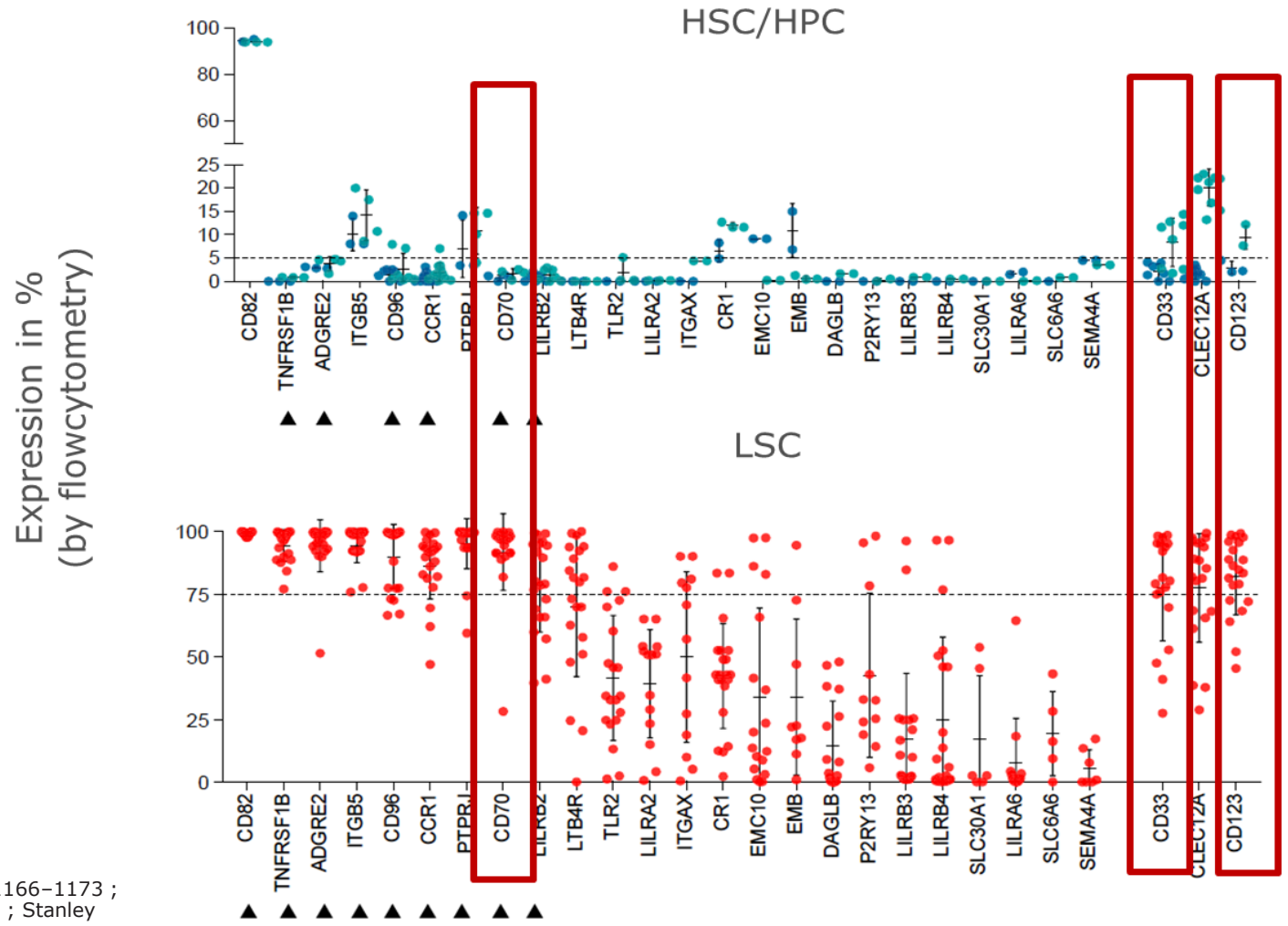
Riether et al. Nat Med 2020; 26, 1459 - 1467

Identification of Targets for the Treatment of AML Patients

New therapies must aim at the elimination of leukemia stem cells

Targeting various surface proteins simultaneoulsy may increase specificity

Commercial		In development	
IDH1	IDH2	CD70	CD33
FLT3	BCL2	CD123	CD47
		HDAC	



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CD33 and CD123 as single therapeutic targets in AML

CD33

Expression:
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- on virtually all healthy myeloid and progenitor cells

Treatment approaches:
- **Gemtuzumab ozogamicin** (GO, Mylotarg): CD33-targeting antibody-drug conjugate; approved treatment in combination with daunorubicin and cytarabine for newly diagnosed CD33-positive AML
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Alternatives:
- **Combination of CD33 with other antigens.** Dual CD33-CLL1 CAR-T Therapy in R/R AML (NCT05016063)
- **Gene editing:** A first-in-human trial will be initiated that combines an alloHSCT utilizing genetically modified, CD33-negative HSCs with CD33-directed CAR-T cells

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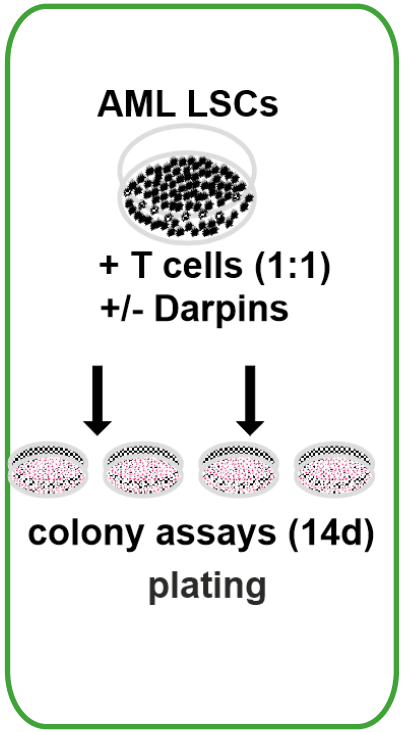
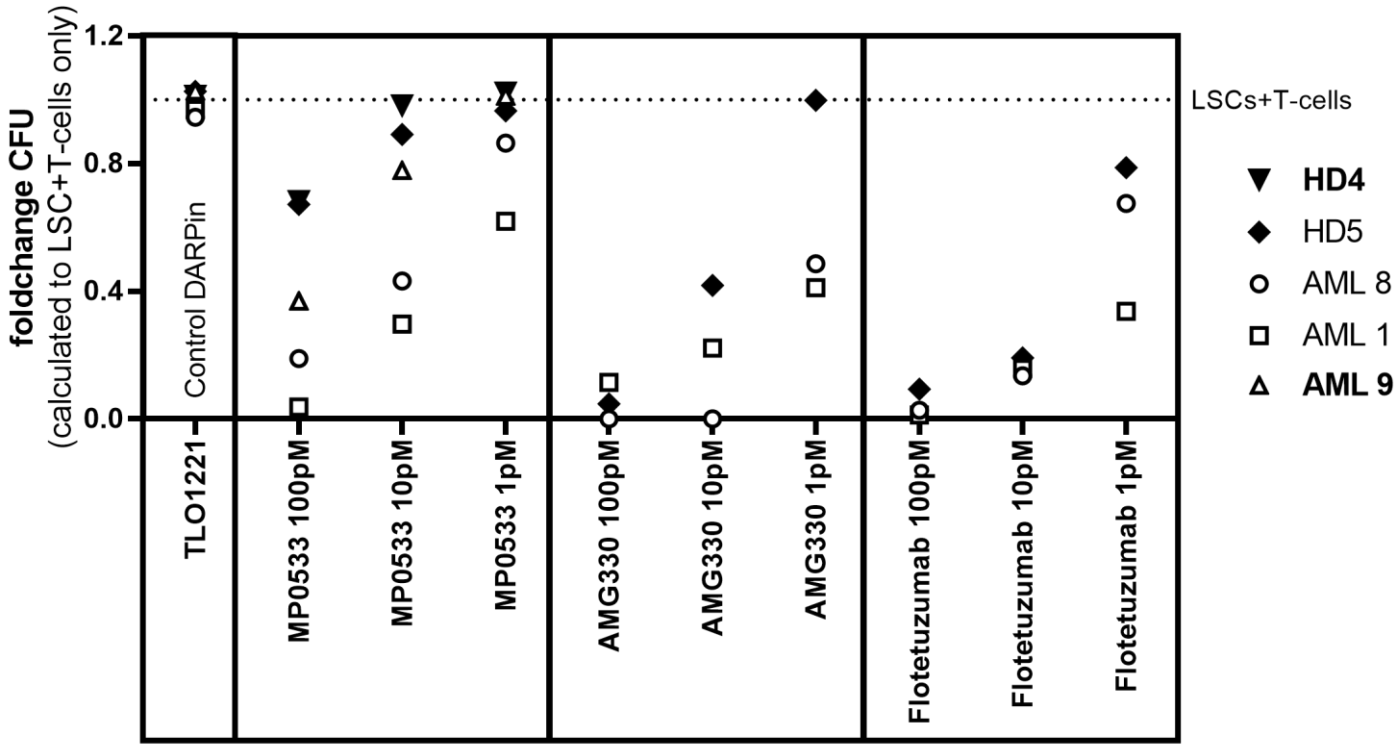
Toxicity:
- Cytokine-release syndrome
- on-target off-leukemia toxicity: CAR T cell infusion was accompanied by serious adverse events

MP0533 Reduces Colony Formation of Primary Human LSCs ex vivo





Summary II

- Various targetable surface antigens in AML have been identified (e.g. CD33, CD123, CLL-1, CD70).
- Therapeutic approaches targeting most of these antigens have been shown to reduce leukemia burden and induce remission in a fraction but not all patients.
- Major problem: on-target off-leukemia toxicity is a major side effect observed in the clinical practice.
- Potential solution: Targeting several tumor antigens to induce specificity and reduce side-effects.
- Ongoing collaboration work:
  - Assessment killing of SOC-resistant/refractory LSCs
  - Combination with SOC and assessment of LSC and HSC killing

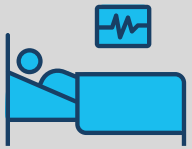
MOLECULAR partners

MP0533

Anne Goubier

MP0533: Tri-specific T-cell Engager for AML

Target Patient

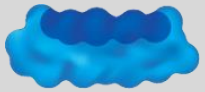


- ~20,000 people are diagnosed with AML every year
- Over 50% of patients die in the first year
- High relapse rates

Disease Biology

- **Persistence of LSCs is the driver of relapse**
- “MRD+ status” refers to low level disease and can be detected by immunophenotypic or molecular markers
- Current T-cell engager approaches are limited by on-target toxicity (not clean targets)

DARPin Advantage



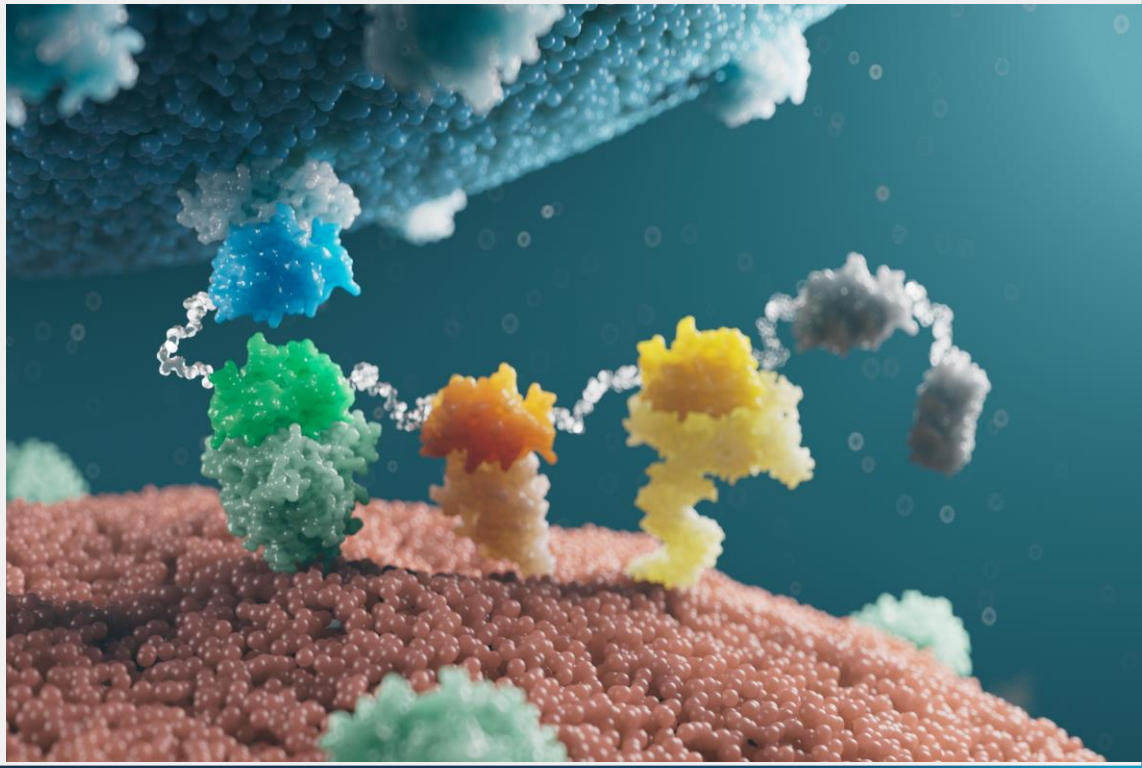
- Avidity driven multispecific DARPin, targeting 3 TAA's, engaging CD3
- T cell are activated only when 2 or more TAA's are bound
- Should allow for broader therapeutic index with reduced safety issues

Expected Milestones

- FIH clinical studies in 2022

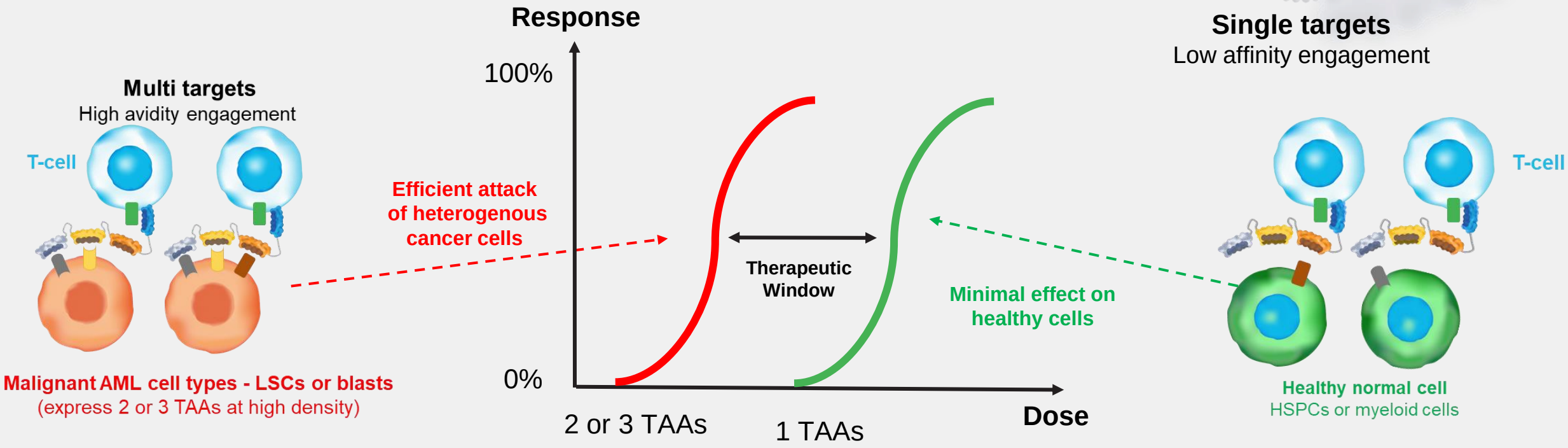
Requisites for an Ideal AML Therapeutic Solution

- **An ideal AML therapeutic solution should:**
  - Achieve control of the disease by eliminating LSCs
  - Cover tumor heterogeneity by targeting multiple antigens
  - Increase the therapeutic window: optimal dose levels with limited side effects
    - Limited killing of healthy HSCs
    - Reduced CRS



The DARPin Solution: a Trispecific CD3 Engager DARPin

For Specific killing of all LSCs and blasts via avidity-driven T cell engagement

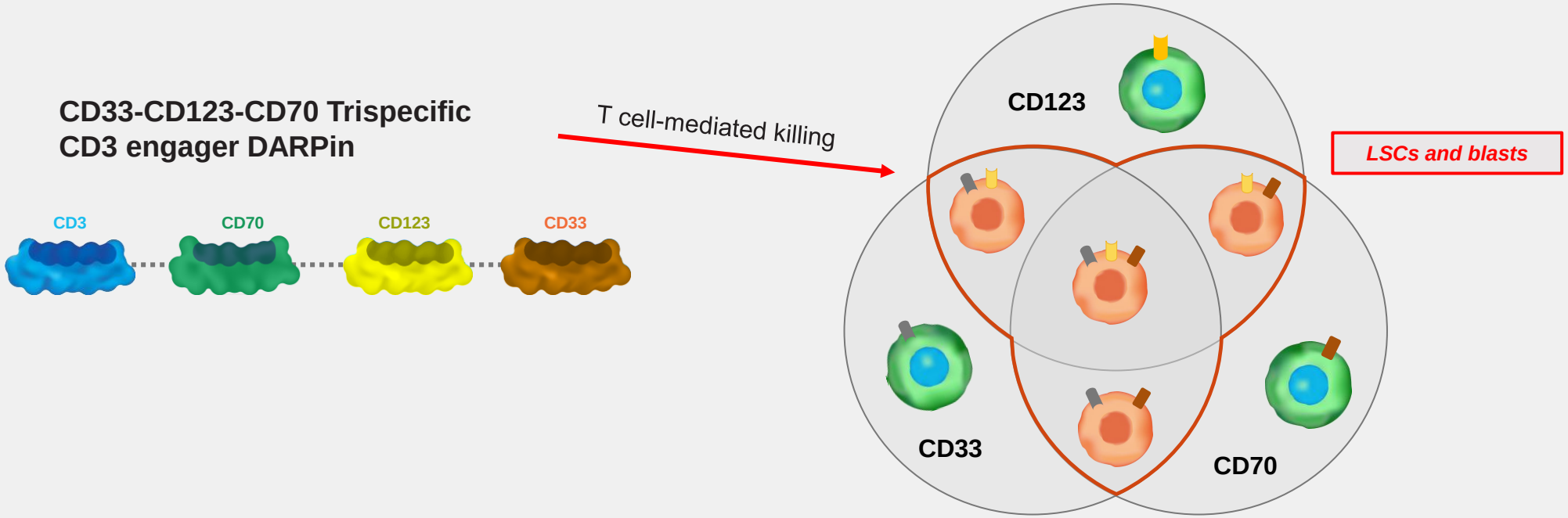


CD3 engager: demonstrated potency in hematological malignancies
Targeting 3 TAA in order to:

- Ensure tumor-specificity via avidity-driven T cell activation
- Control tumor heterogeneity

CD33, CD123 & CD70: Optimal Targets to Maximize Efficacy and Selectivity

- Clinically validated targets
- Co-expression pattern of CD70, CD33 and CD123 on LSCs and AML blasts
  - Differentiates LSCs and AML blasts from healthy cells → **optimal selectivity**
  - Covers tumor heterogeneity → **optimal efficacy**



CD123/CD70/CD33 co-expression differentiates LSCs and AML Blasts

Allowing for or avidity-driven specific T cell killing of LSCs and blasts

	LSCs	Blasts	HSC	Lymphocytes	Inflamed EC	Myeloid cells	pDCs	Basophiles
CD70	Low	Low	Neg /Low	Variable	Neg	Neg	Neg	Neg
CD123	High	High	Low	Neg	Medium	Low/ Medium	High	High
CD33	High	High	Medium	Neg	Neg	High/ Medium	Low	Medium
Theoretical Avidity-based killing*	**Yes**	**Yes**	Limited	**No**	**No**	Limited	Limited	Likely

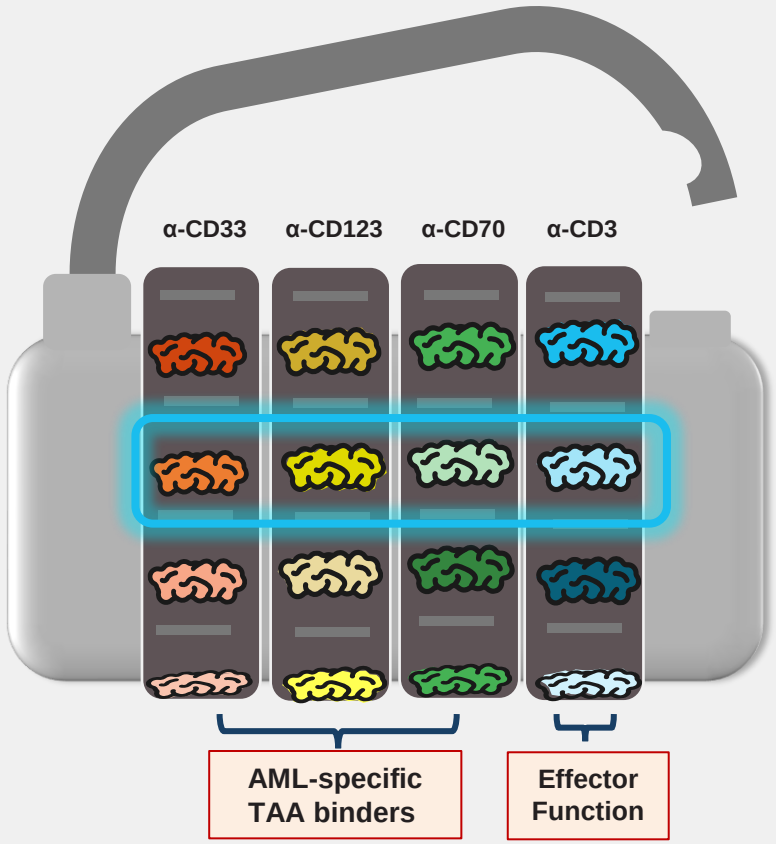
* Assuming equivalent affinity for CD33, CD123 and CD70

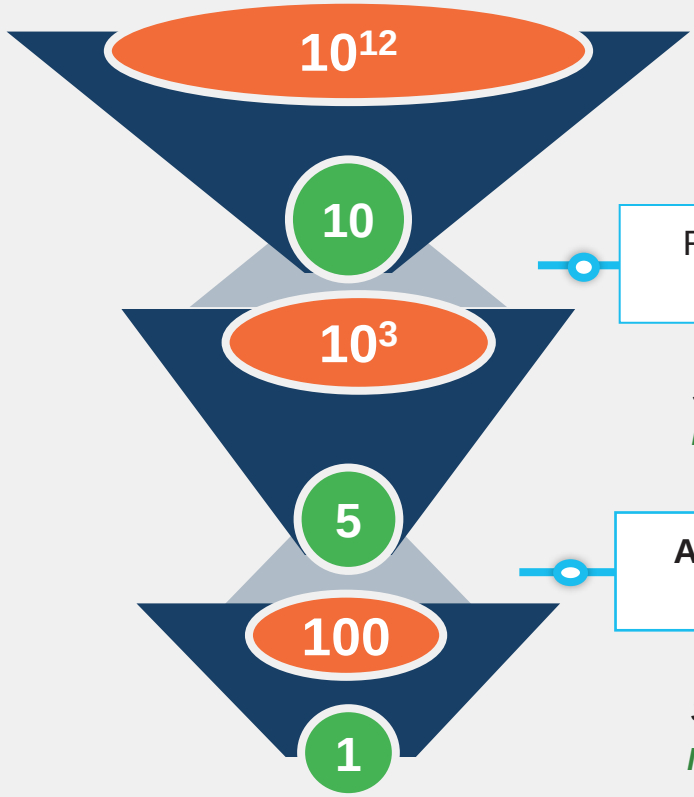
Eliminating LSC and Blast through avidity-driven selective targeting should be doable and will allow

- Treating frail patients thanks to a higher safety profile
- Increasing dose and thus deepening responses for long term control of the disease

From the Idea to MP0533: Exploiting DARPin Platform Versatility

Allows Screening for Function Sweet Spot





Library used to generate binders against TAAs

Identified functional DARPin modules to each TAA

Recombination of DARPin modules:
TAA1 x TAA2 x TAA3 x CD3

Screening of multi-domain DARPins

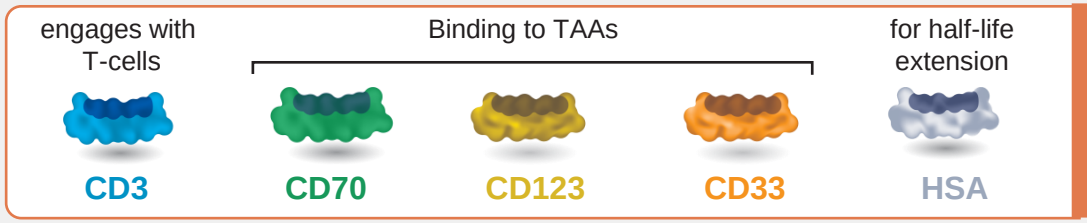
Functional Multi-DARPin candidates

Affinity & **format** & **half-life optimization**
Recombination of DARPin modules

Screening of multi-domain DARPins

Multi-DARPin lead molecule

Multiple Iterations

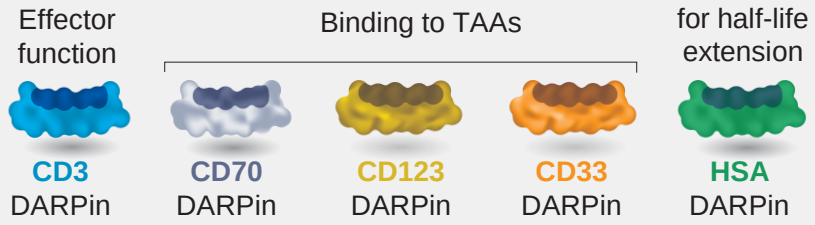


MP0533:
a multi-domain, multi-specific, half-life extended DARPin

MP0533: a DARPin Solution for AML Patients?

1. Validation of the **avidity-driven T cell mediated killing concept**
   - Can MP0533 induce killing of cells expressing 2 or 3 TAA while sparing cells with 1 TAA?
2. Demonstration of **MP0533 efficacy against AML**
   - Is the level of TAA expressed by AML blasts sufficient for MP0533-induced killing?
   - Are patient T cells fit and numerous enough for MP0533 to induce AML blasts killing?
   - Is MP0533 also potent in vivo?
3. Demonstration of **MP0533 enhanced therapeutic window**
   - Can MP0533 induce LSCs killing while sparing HSCs?
   - Can MP0533 preserve healthy blood cells and show reduce cytokine release?

MP0533



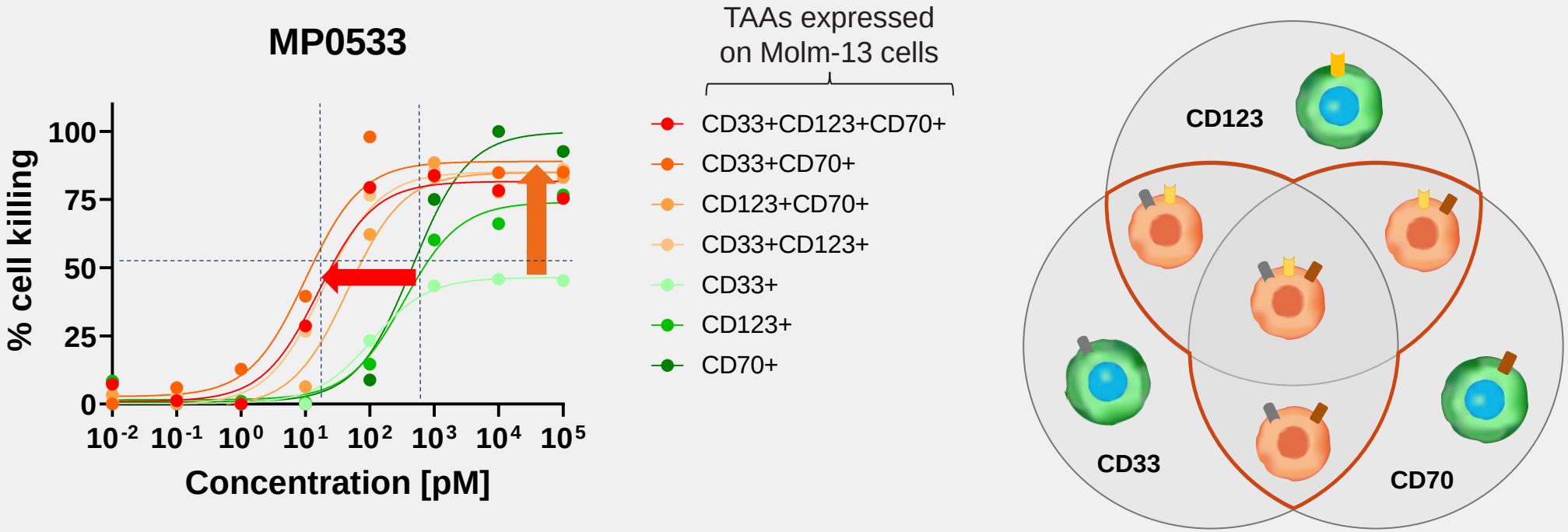
MP0533 Induces Specific Killing of AML Cells Expressing 2 or 3 TAAs

MOLM-13 cells WT
or KO for CD70, CD33 and/or CD123
+ Healthy donor T cells (E:T = 5:1)

MP0533 or controls

48 hours

Tumor cell killing
T cell activation



MP0553 Induces Potent T-Cell Mediated Killing of AML Blasts

As compared to CD123-DART and CD33-Bite

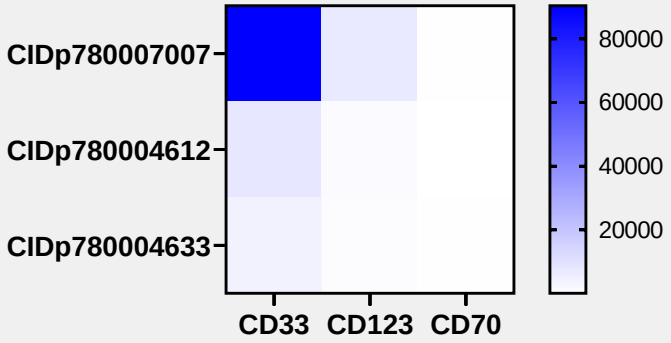
Primary AML samples +
Healthy donor T cells (E:T = 4:1)

MP0533 or controls

48 hours

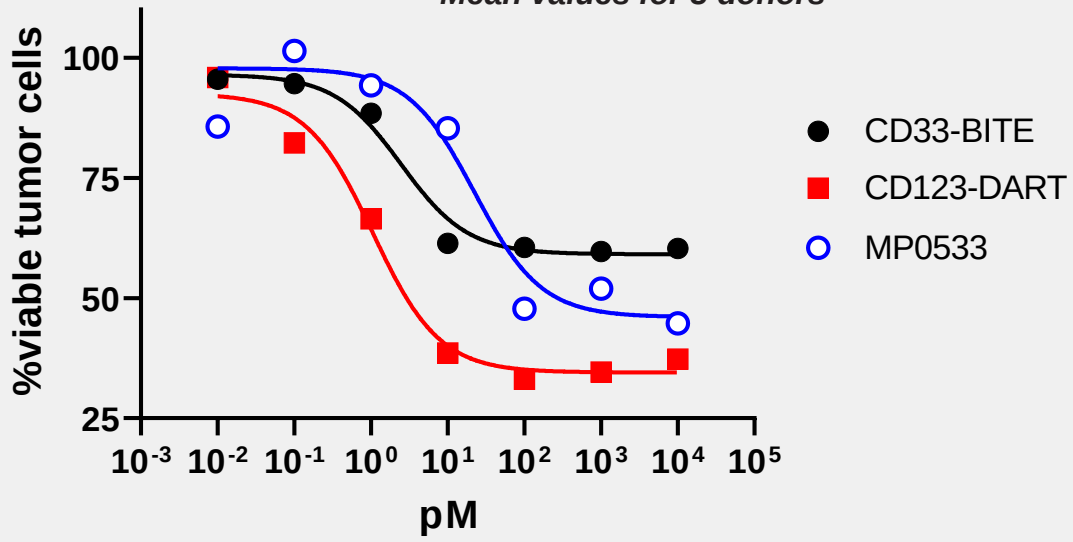
Tumor cell killing
T cell activation

BMMC AML - TAA expression



BMMC AML – Tumor killing

Mean values for 3 donors



MP0533 Induces AML Killing by Patients' Own T Cells

Despite lower frequency and expected lower quality of T cells

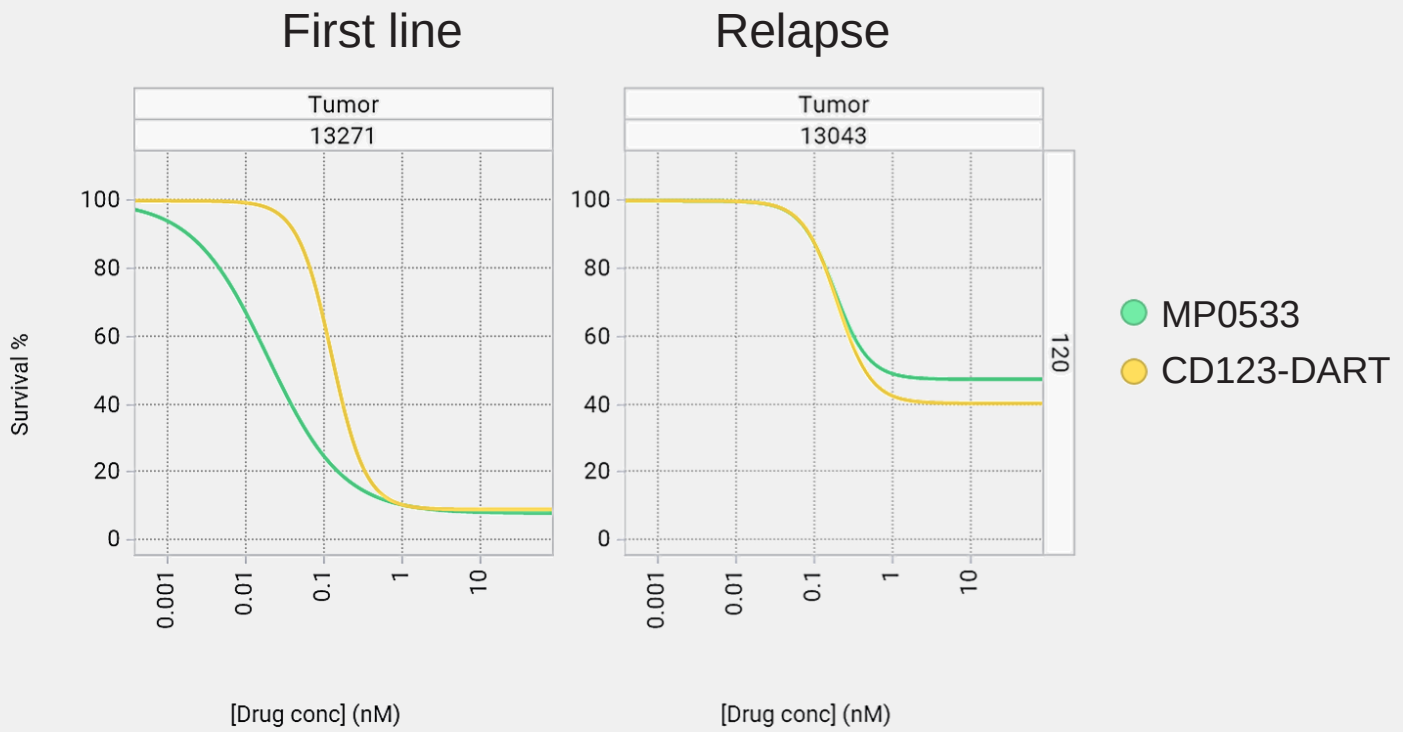
Primary AML samples
(no addition of healthy T cells)

MP0533 or controls

120 hours

Tumor cell killing

TREATMENT_LINE	SID	E:T ratio
FIRST LINE	13045	1:82
	13271	1:49
	15131	1:27
RELAPSE	13043	1:84
	13272	1:132



*No unspecific killing with NB-CD3 control (not shown)

MP0533 Shows in vivo Efficacy Against Established MOLM-13 Tumors

As compared to CD33-Bite

HuPBMCs — Day -2

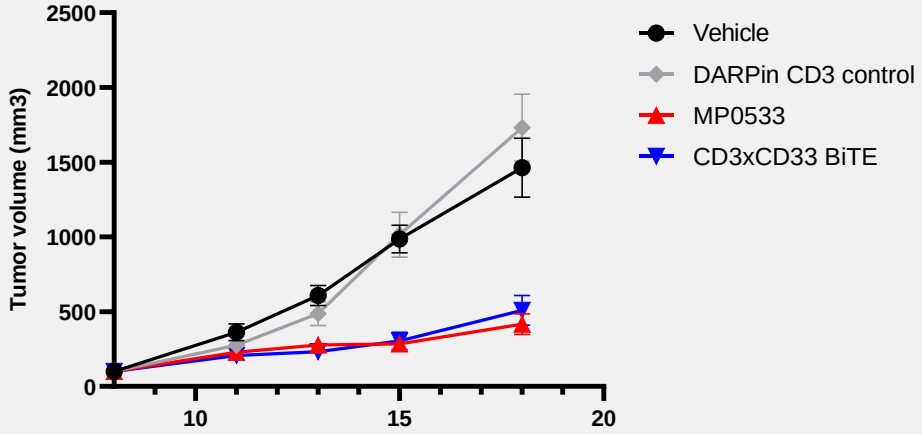
MOLM-13 — Day 0

Treatment Start — Day 8

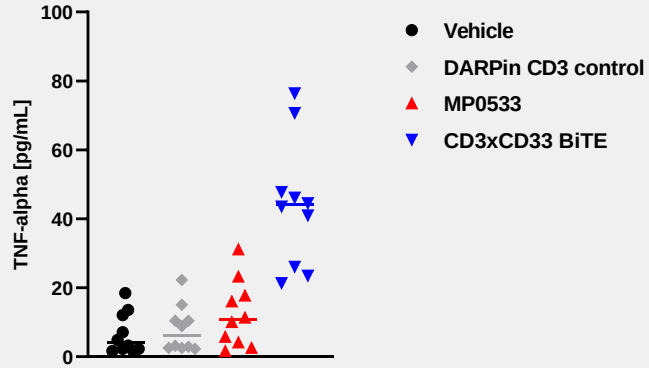
MP0533 3 times per week for 2 weeks (6 injections)

CD33-bite or vehicle daily for 2 weeks (14 injections)

MOLM-13 tumor growth



TNFα in serum



Efficacy

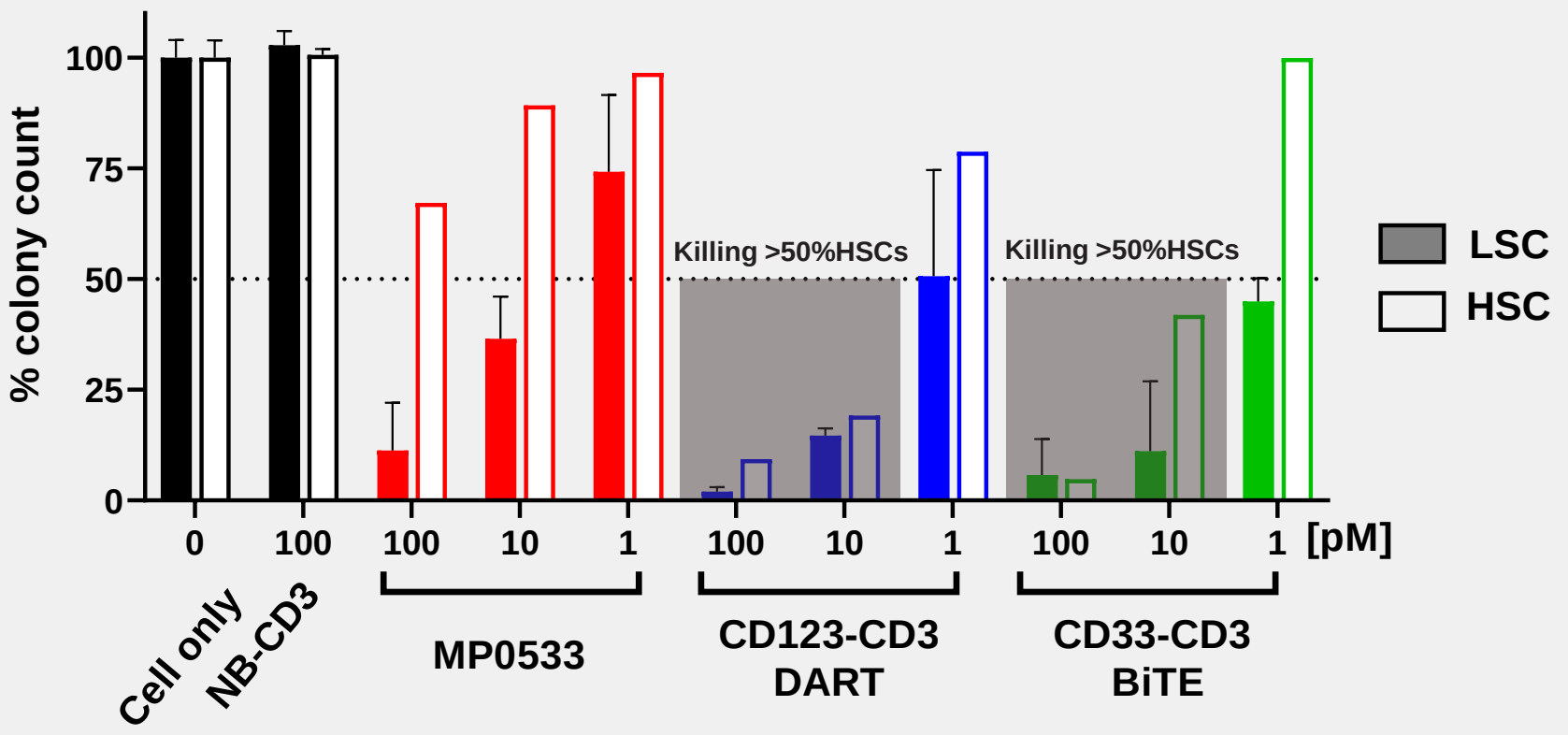
Safety

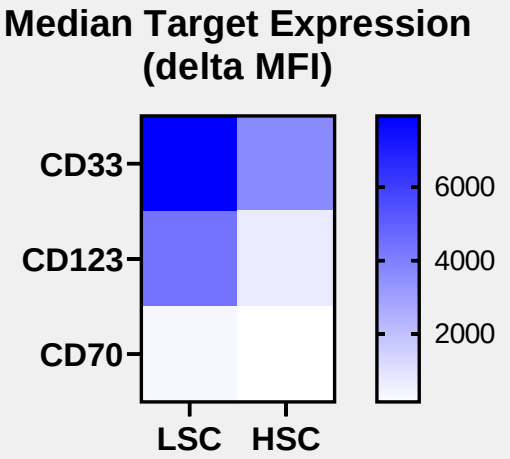
MP0533 Shows Preferential Killing of CD34+ LSCs over HSC

Larger therapeutic window as compared to CD123-DART and CD33-bite

Killing of sorted CD34+ LSC or HSC by colony formation assay

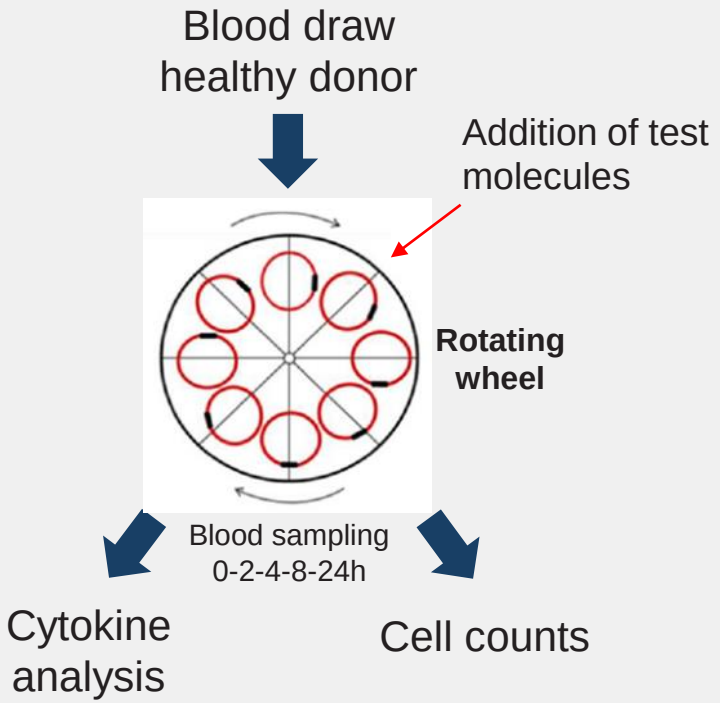
using allogenic T-cells (E:T of 1:1, 4 d) / CFU counted after 2 weeks semi-solid media

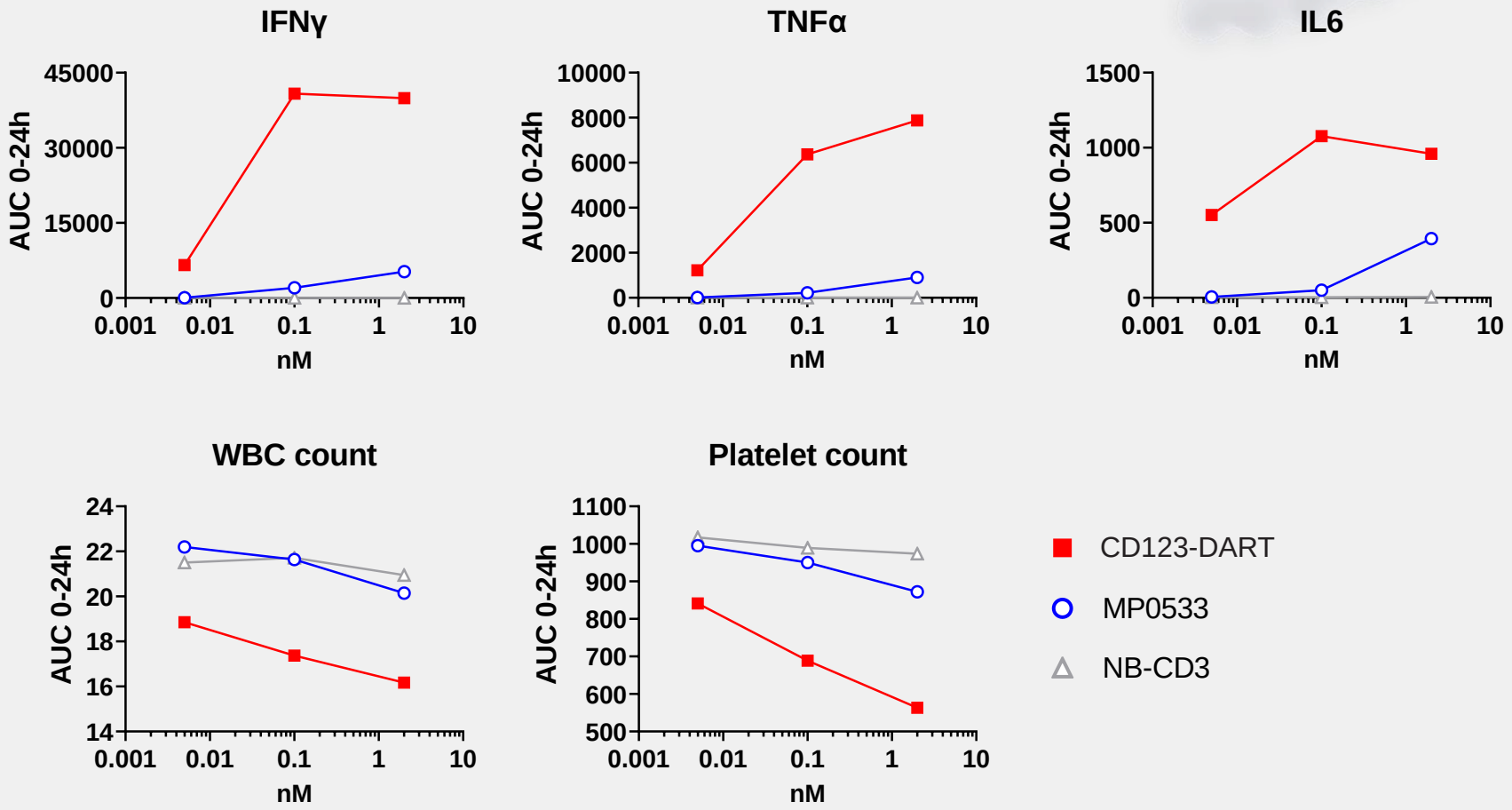




MP0533 Demonstrates Reduced Cytokine Release and Hemotoxicity

As compared to CD123-DART





*NB = Non-Binding to TAAs

MP0533: a DARPin Solution for AML Patients

1. Validation of the **avidity-driven T cell mediated killing concept** ✓
   - Can MP0533 induce killing of cells expressing 2 or 3 TAA while sparing cells with 1 TAA?
2. Demonstration of **MP0533 efficacy against AML** ✓
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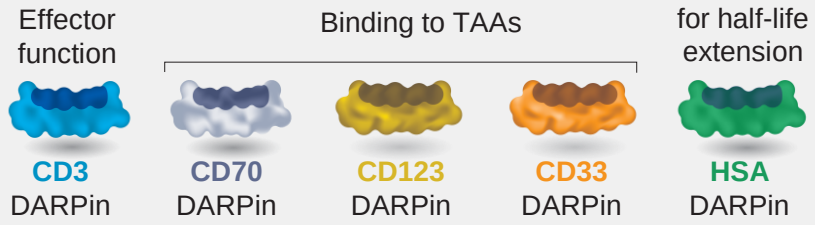
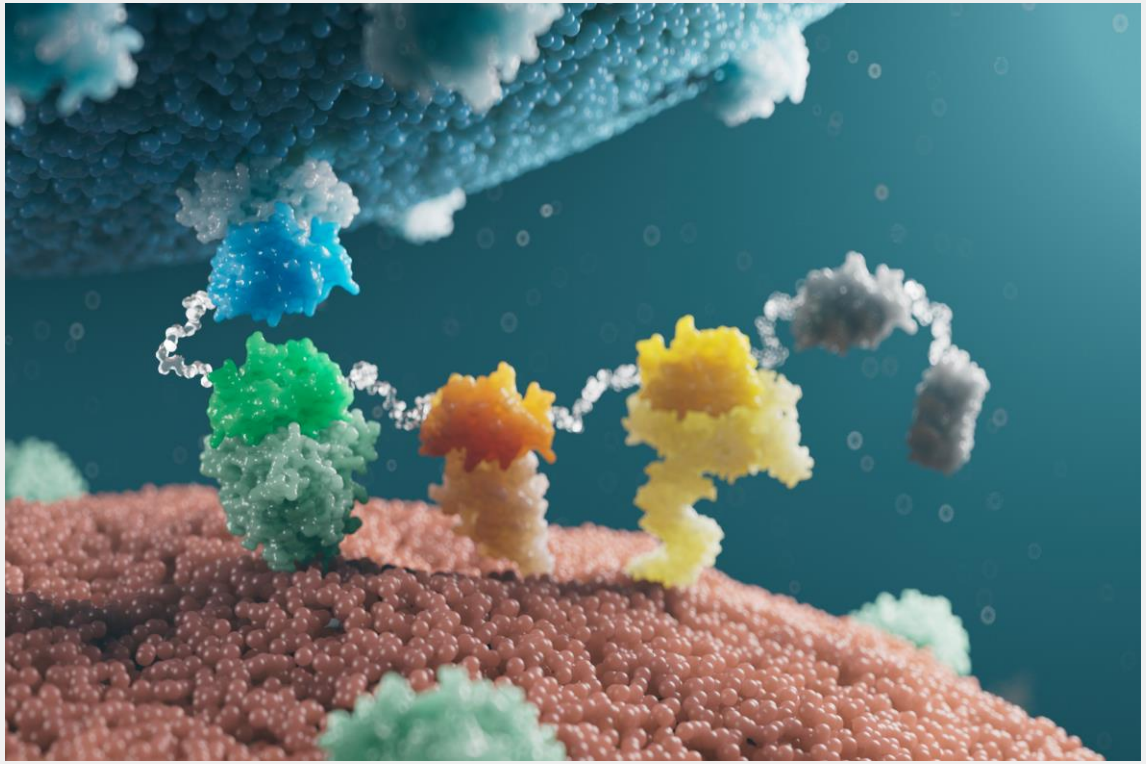
MP0533



MP0533: a Unique DARPin Solution for AML Patients

- **An ideal AML therapeutic solution should:**
  - Ensure long term control of the disease by eliminating LSCs ✓
  - Control tumor heterogeneity by targeting multiple Ag ✓
  - Increase the therapeutic window: optimal dose levels for efficacy with limited side effect
    - Limited killing of healthy HSCs ✓
    - Reduced CRS ✓

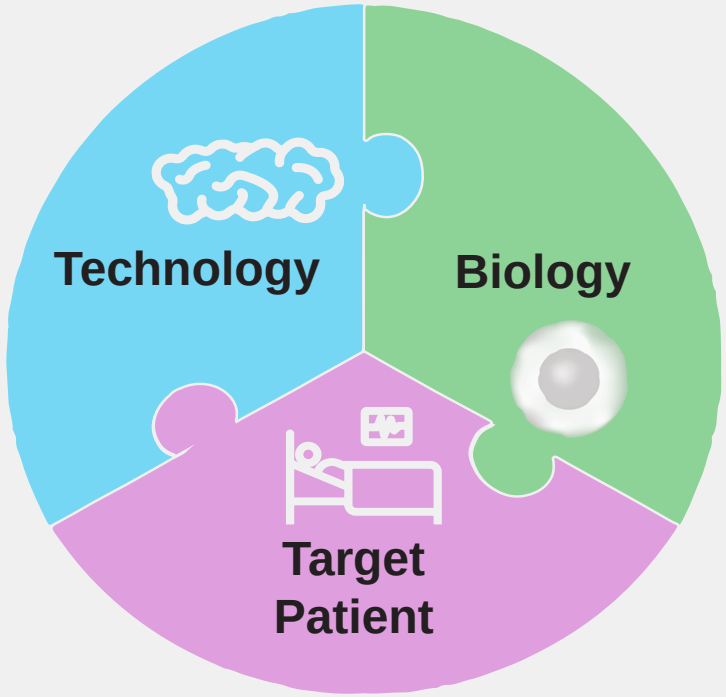


Phase 1 clinical trial initiation H2 2022

Conclusions

Patrick Amstutz

MP Strategy – Building on our Strengths



TECHNOLOGY

We leverage the advantages of the **DARPin technology** to provide unique solutions to impact biology and bring value to patients

BIOLOGY

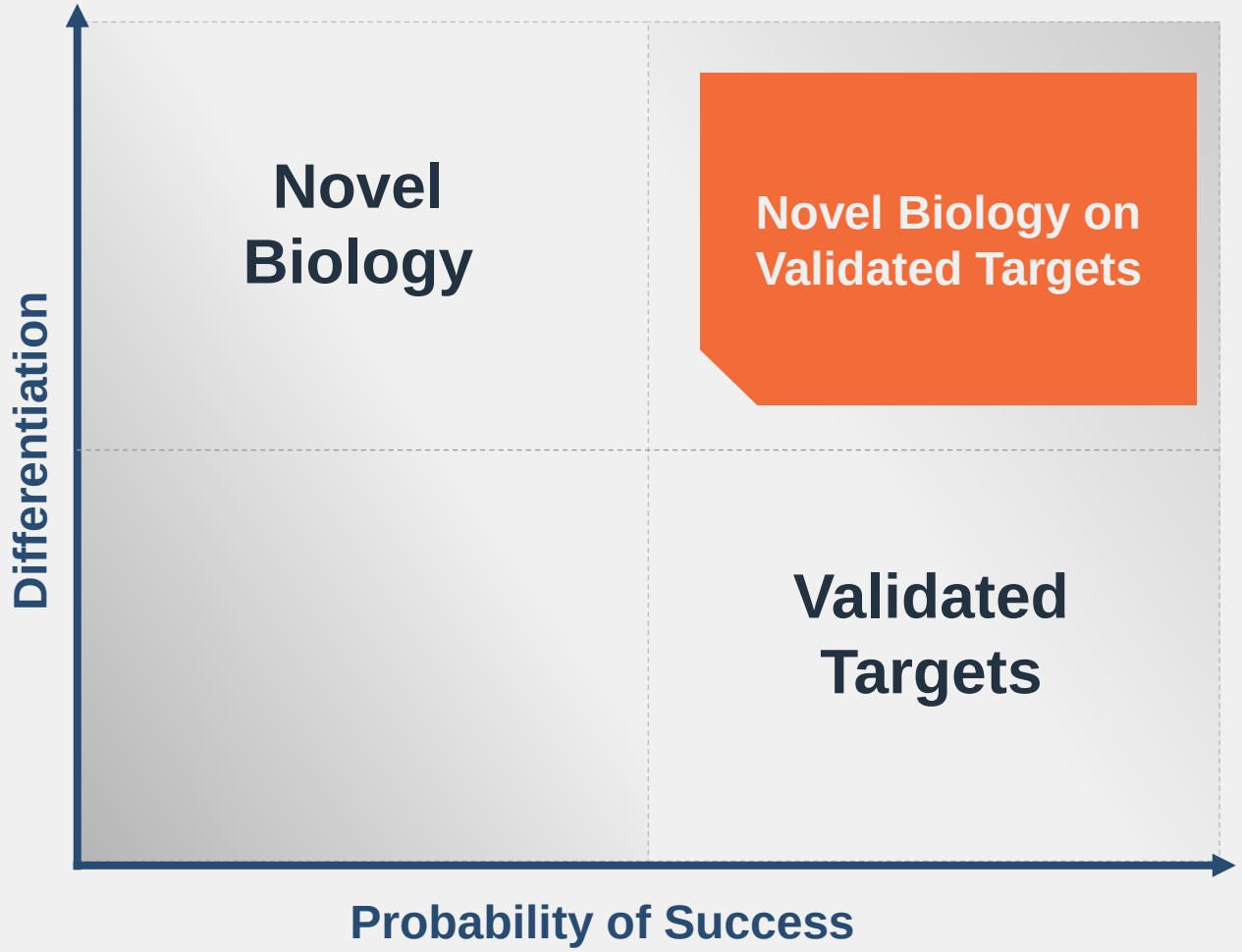
Our candidates' design aims to **directly change the course** of **disease biology** and allow testing in a model with **high translatable value**

TARGET PATIENTS

We aim to drive **true patient value** with **early clinical read-outs**

We strive to **collaborate** with the best scientists and clinicians in the field from ideation to clinical trials

How we Select Targets for Optimized Risk/Reward



OUR PURPOSE:

Transform the lives of people with cancer by delivering truly innovative therapies

Putting our Strategy into Action: Slide from our R&D Day Webcast 2019

Pipeline Inflection Points

Infectious disease | Discovery Oncology | Oncology | Ophthalmology

Pipeline

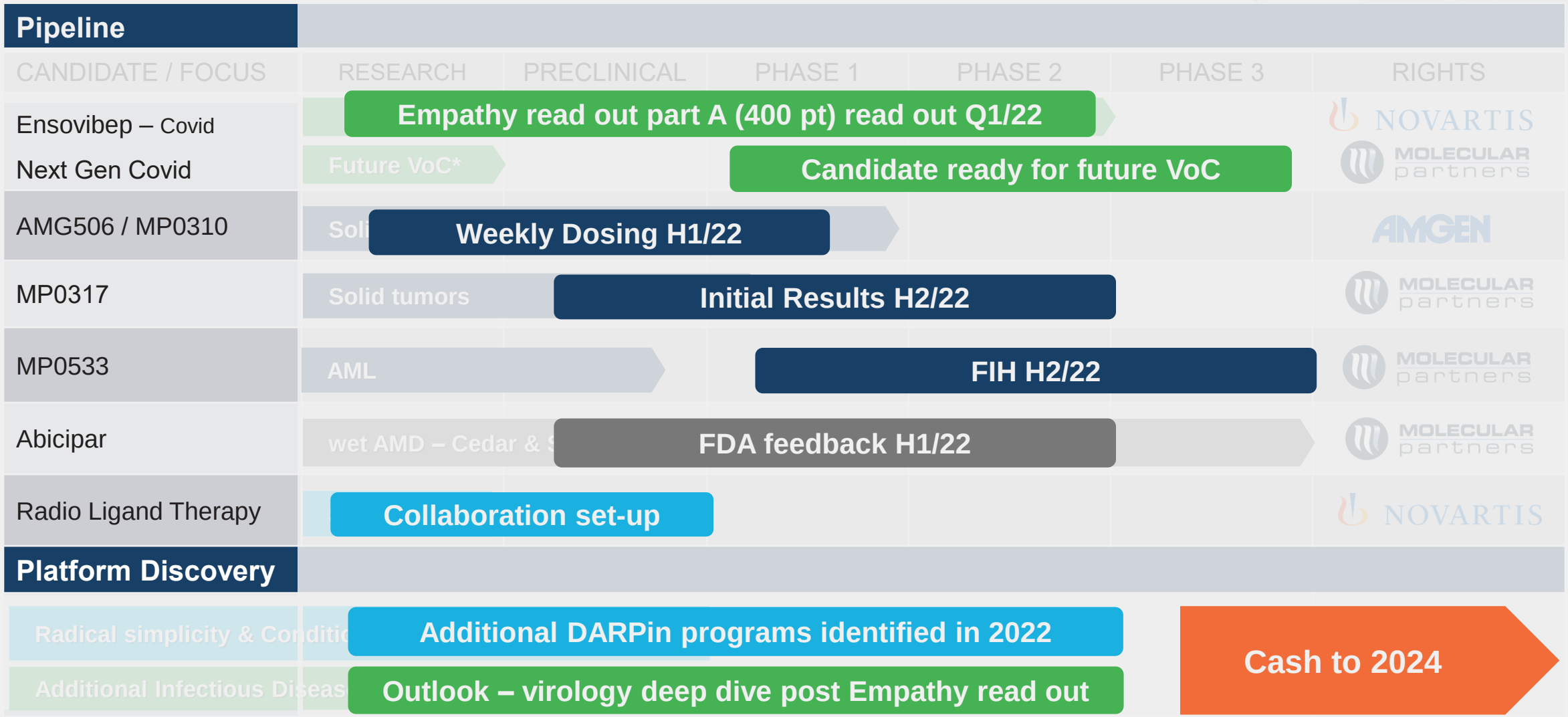
CANDIDATE / FOCUS	RESEARCH	PRECLINICAL	PHASE 1	PHASE 2	PHASE 3	RIGHTS
Ensovibep – Covid	Covid ambulatory – Empathy					NOVARTIS
Next Gen Covid	Future VoC*					MOLECULAR partners
AMG506 / MP0310 FAP x 4-1BB	Solid tumors					AMGEN
MP0317 FAP x CD40	Solid tumors					MOLECULAR partners
MP0533 CD3 x CD33+CD70+CD123	AML					MOLECULAR partners
Abicipar VEGF	wet AMD – Cedar & Sequoia					MOLECULAR partners
Radio Ligand Therapy	Solid tumors					NOVARTIS

Platform Discovery

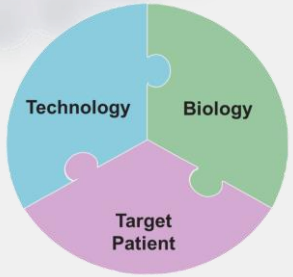
Radical simplicity & Conditional Activation	MOLECULAR partners
Additional Infectious Diseases	

* VoC = Variant of Concern

Pipeline Inflection Points



My Key Takeaways



- DARPin leadership and Product Strategy in place
- Strong cross-functional execution: Technology & Biology & Medical
- Continued collaboration to leverage outside expertise

AND

- Creation of molecules where we control our full destiny:

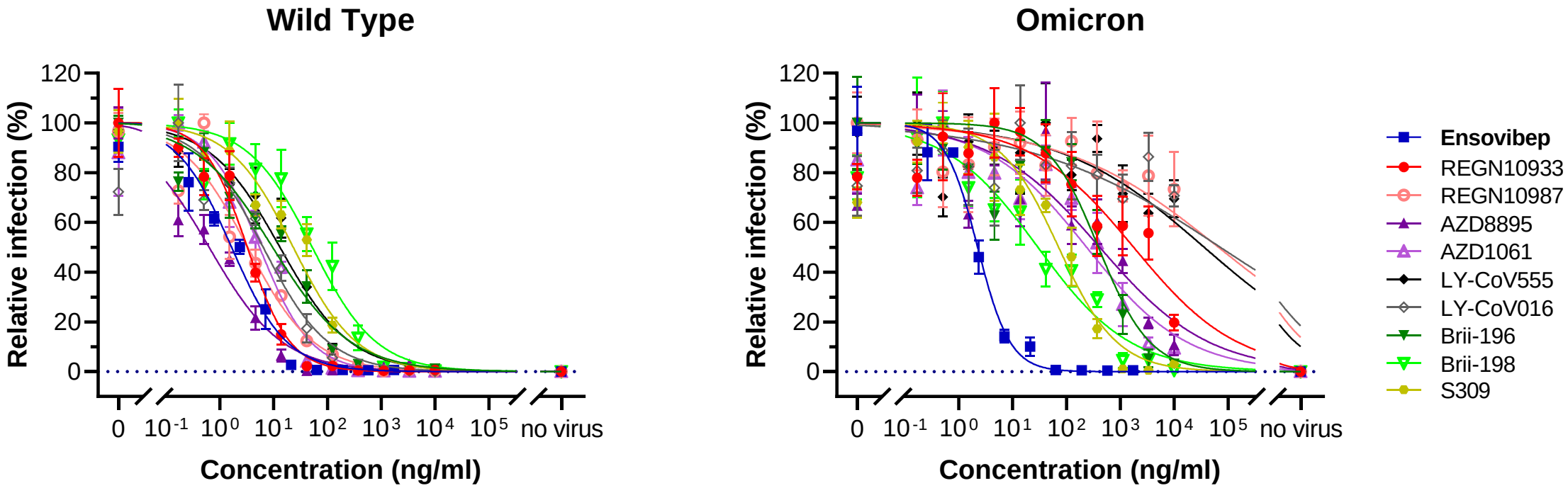
➢ MP0533 = first DARPin with real potential to generate clinical data for POC in-house (ideally registrational)


THANK YOU
MOLECULAR
partners

Molecular Partners AG
Wagistrasse 14
8952 Zürich-Schlieren
Switzerland
www.molecularpartners.com
T +41 44 755 77 00

Ensovibep Protects Against Omicron

Covid Pseudotype Inhibition – From Wilde-Type to Omicron



Ensovibep Remains Fully Active Against Omicron Pseudotype

Neutralization of ensovibep and a panel of monoclonal antibodies in VSV-pseudotype assays containing the Omicron variant spike protein with >30 substitutions.			
	Wild Type	**Omicron[1]**	
Compound	IC_{50} (ng/mL)	IC_{50} (ng/mL)	fold change to wt
ensovibep	1.6	2.2	1.4
REGN10933	3.2	>1000	>100
REGN10987	3.3	>1000	>100
LY-CoV555	13	>1000	>100
LY-CoV016	6.4	>1000	>100
S309	23	72	3.1
AZD8895	0.6	415	>100
AZD1061	5.5	237	43
Brii-196	9.5	392	41
Brii-198	52	30	0.6

IC_{50}: *green: <10 ng/mL; orange: 10-100 ng/mL; dark orange: 100-1000 ng/mL; red: >1000 ng/mL*
fold change to wt: *green: <10-fold; orange: 10-100-fold; red: >100-fold*

[1] Set of mutations: A67V, Δ69-70, T95I, G142D, Δ143-145, Δ211, L212I, ins214EPE, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, N969K, L981F.

DARPin – Radio-Ligand Therapeutics

New collaboration with Novartis

Radio-Ligand Therapeutics Collaboration

- NIBR established as world leader in the RLT field
- RLTs - the potential to deliver targeted radiation to tumor cells anywhere in the body
- DARPins – small size and high specificity & affinity may offer an advantage in RLT's, which often require a highly specific delivery vehicle
- Both parties to collaborate on the discovery and optimization of the therapeutic candidates
- Novartis would be responsible for all clinical development and commercialization activities
- $20 million upfront to Molecular Partners, total potential milestone payments of up to $560 million, and up to low double-digit percent of royalties.