Avacta LIFE SCIENCES

FAP-Activated Drugs and Drug-Conjugates

Immunotherapy World Congress – November 2021

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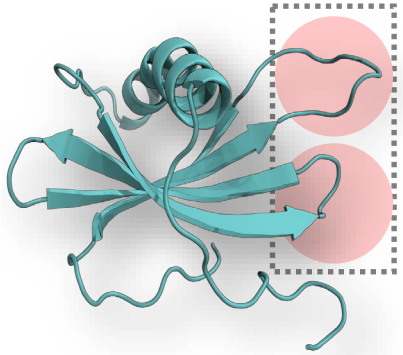
Our Therapeutic Strategy - Targeting Cold Tumours

Affimer
Antibody Mimetic

100aa (14kd) single domain antibody mimetic with superior biophysical properties

heat and solvent stable, highly soluble (>400mg/ml) and easily deployed across multiple fusion protein and chemical conjugation formats



Multi-specific Biologics

Enable tumour localization and single infusion/injection to reduce drug administration complexities and limitations of combinatorial therapies

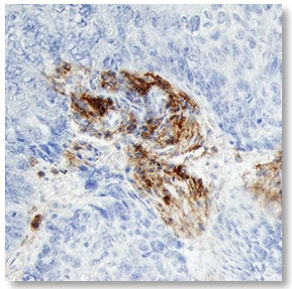
- **PD-L1 Inhibitory Affimer x Cytokine Fusion proteins**
- **Bispecifics targeting both Checkpoint and EMT Signals**
- **Generation of "Af-Mab" bispecifics**

preCISION
FAPα-activated Prodrugs

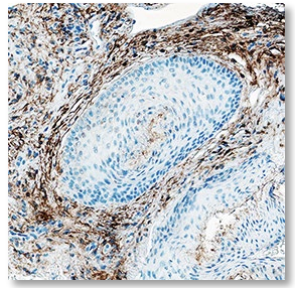
Small Molecule Prodrugs Selectively Activated by FAP upregulation in Tumour Microenvironment

Exploits the extracellular upregulation of Fibroblast Activation Protein (FAP) on the cell surface of human tumours and tumour stromal cells.

FAP ↑ in Squamous Cell Carcinoma.



FAP ↑ in Basal Cell Carcinoma.



Extracellular activation creates cell permeable active drug or enables receptor binding

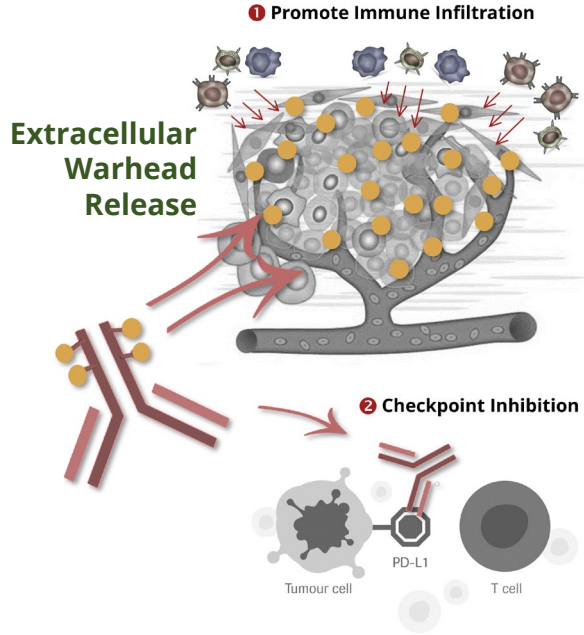
Increase intratumoural exposure and therapeutic index and expand eligible patient populations

TMAC
FAPα-activated Affimer/Antibody Conjugates

Macromolecular-Drug Conjugates Selectively Activated by FAP in Tumour Microenvironment

Adapted pre|CISION substrate in drug conjugate linkers to generate FAP-activated ADCs and AfDCs that

- Provides serum half-life extension
- Extracellular drug release in tumour
  - ✓ **Warhead can Target Stroma and Immune Cells**
- Add IO activity (such as checkpoint inhibition)



Fibroblast Activation Protein-α (FAPα) as a Tumor Target

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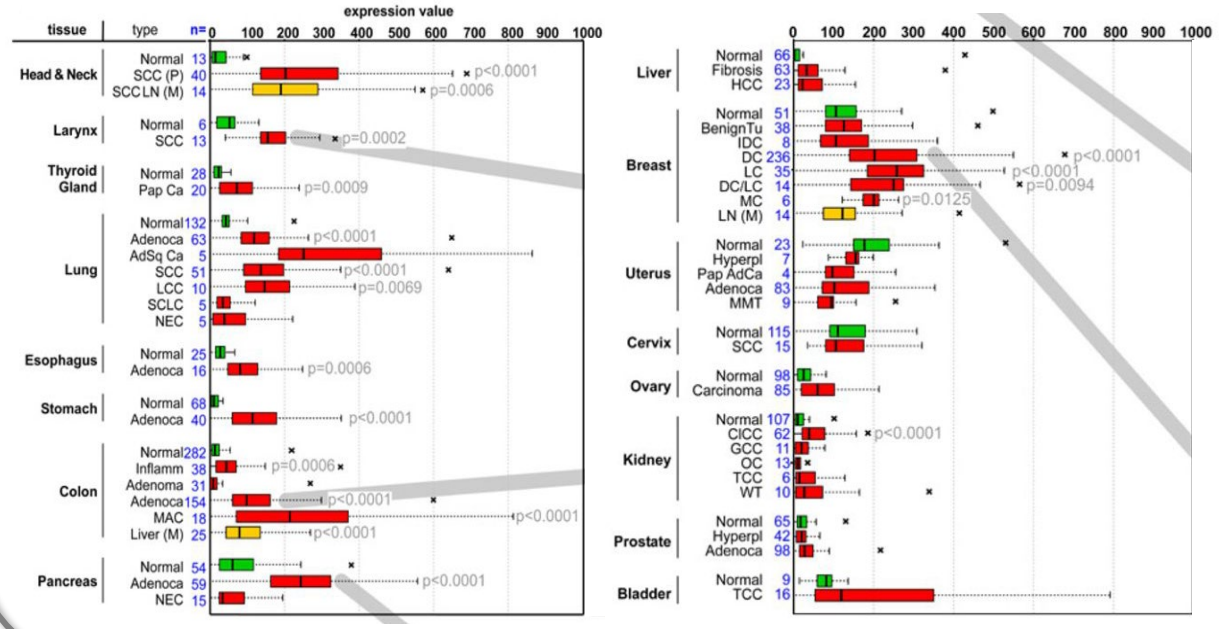
FAPα is selectively overexpressed and FAPα enzymatic activity is elevated in the tumour microenvironment of most solid tumours

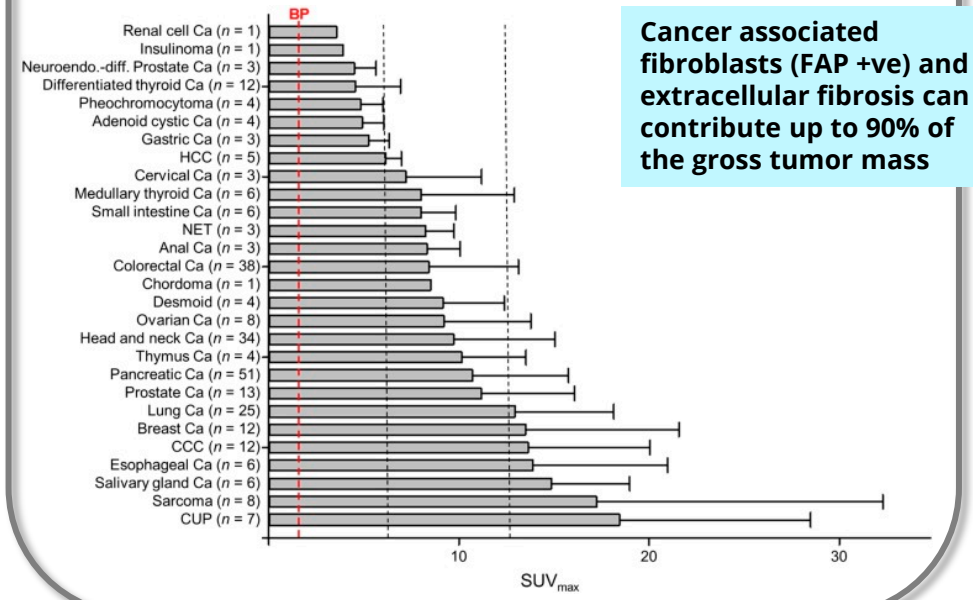
Expression profiles of FAPα in normal and malignant human epithelial tissues



Whisker-box plots for normal (green), malignant (red), and malignant metastatic lesions (orange); the number of samples for each tissue is given. The bold lines in each box indicate median values, and box limits represent the first and third quartiles; the whiskers extend to 1.5 times this interquartile range. The highest value in each cohort outside the whiskers is marked by the letter "x." For significant upregulation of FAPα in cancers *versus* matched normal tissues, the *P*-values in Student's *t*-tests are shown.

Adapted from Dolznig et al. Cancer Immun 2005 5:10

^{68}Ga-FAPI-04 Tracer uptake in tumous – defines "FAP High" tumours



Cancer associated fibroblasts (FAP +ve) and extracellular fibrosis can contribute up to 90% of the gross tumor mass

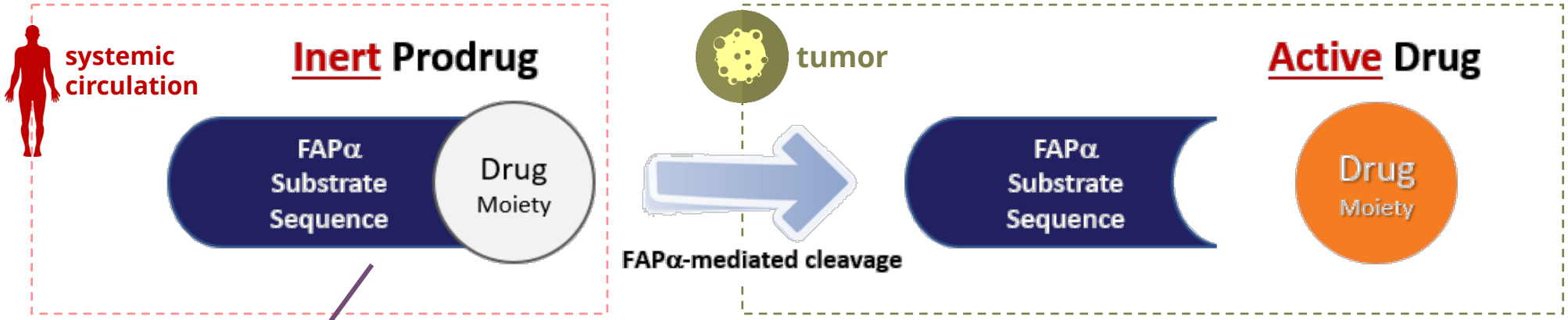
A FAP PET imaging study assessed the FAP expression of 28 different kinds of cancer by using PET/CT imaging to detect the amount of 68Ga-FAPI tracer uptake by each type of cancer. The results are expressed as Standardized Uptake Values (SUV).

Kratochwil et al. J Nucl Med. 2019 60(6): 801–805

FAP Activated pre|CISION and TMAC Prodrugs

Proprietary Prodrug Platform Relies on Extracellular FAPα Enzyme Activity

The **overexpression of FAPα on the surface stromal cells of human tumors** (relative to normal tissue) provides the premise for the development of **prodrugs that remain inert until specifically activated by the enzymatic activity of FAPα** to the active drug moiety **inside the tumor** microenvironment.



Covalently linked FAP Substrate Sequence inhibits mechanism of action – such as by rendering prodrug cell impermeable or by inhibiting interaction with target/receptor

Intended to produce Increased Maximum Tumor Exposure (MTE) of Active Drug and Improved Therapeutic Index (TI)

preCISION
FAPα-activated Prodrugs

AVA6000 – FAPα-Activated Doxorubicin pre|CISION Prodrug

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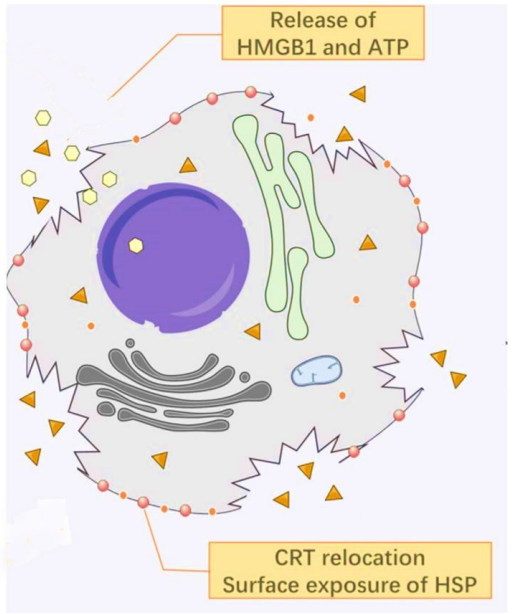
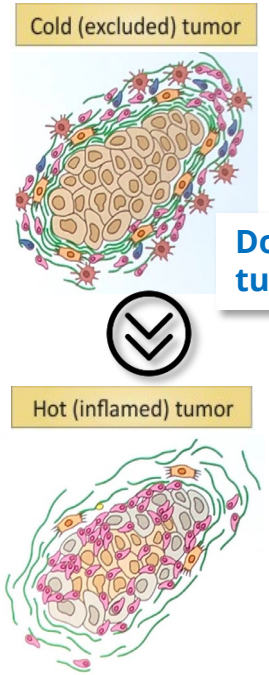
Why start with Doxorubicin?
Because of its Effects Beyond Direct Toxicity to Cancer Cells
pivotal contribution of both innate and adaptive immunity

In practice, cardiotoxicity creates limits to patient exposure below maximum effective concentration

Induces Immunogenic Cell Death of Tumour Cells



Disrupts Tumour Stroma & Promotes Immune Cell Infiltration



Doxorubicin targets tumor stroma

- **MDSC** (Myeloid-derived Suppressor Cell) **Causes MDSC depletion and impairs MDSC immunosuppression activity**
- **Promotes tumour infiltration of IL-17-producing γδ T lymphocytes**
- **Promotes tumor infiltration of activated, IFN-γ–producing CD8 T cells**
- **Tumor antigen cross-presentation**
- **Granzyme B and IFN-γ production by effector T and NK cells**

Anticipates synergies with cancer immunotherapies, including checkpoint inhibitors and costimulatory agonists, and preconditioning ahead of CAR-T therapies

For DOX effects, see for example, clinical and non-clinical data discussed in Kepp et al. (2019) OncoImmunology, 8:10; Alizadeh et al. (2014) Cancer Res. 74(1): 104–118; Mattarollo et al. (2011) Cancer Res 71(14): 4809-4820; Shurin et al. (2009) J Immunol. 183(1): 137–144; Ma et al. (2011) J Exp Med. 208:491–503

Begins with A Proprietary and Selective FAPα Substrate Moiety

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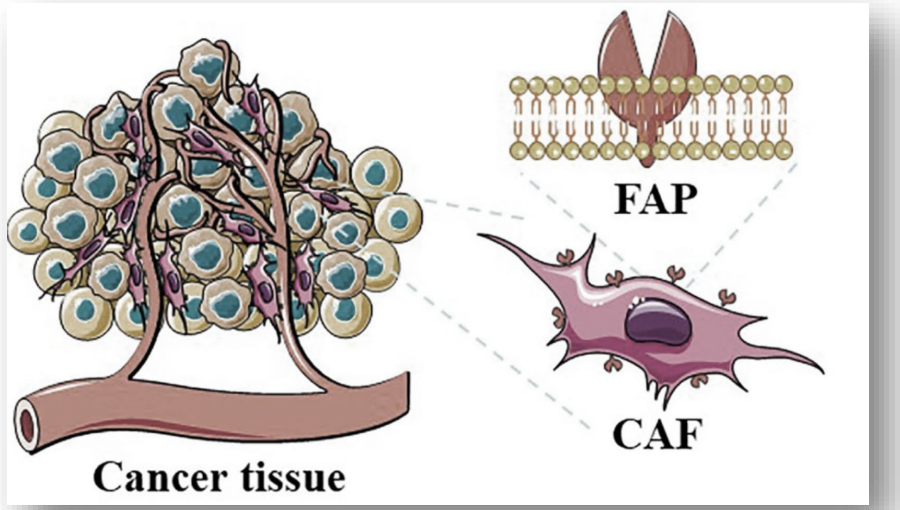
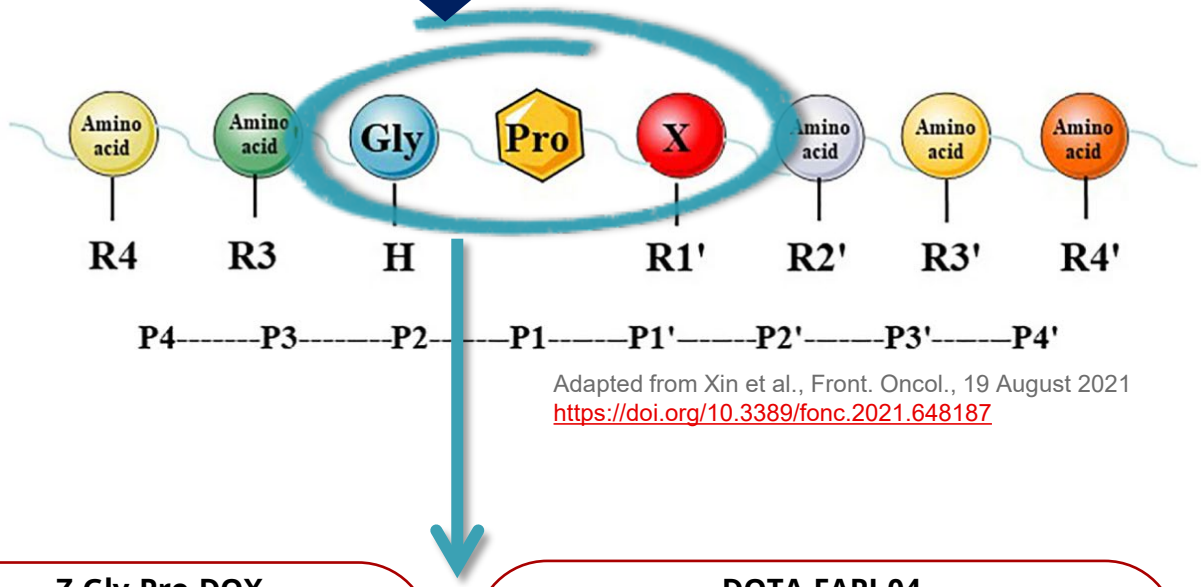
FAP is a cell surface protein, meaning its protease activity is located in the extracellular space of the tumor



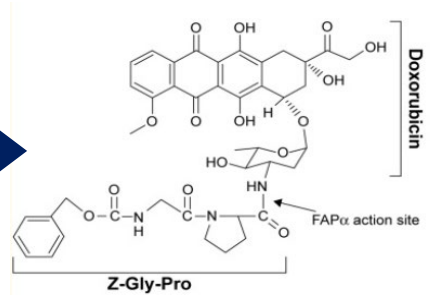
Based on natural substrate specificity, the field has focused on Gly-Pro for creating FAP-targeting and FAP-activated prodrugs



Adapted from Xin et al., Front. Oncol., 19 August 2021
https://doi.org/10.3389/fonc.2021.648187

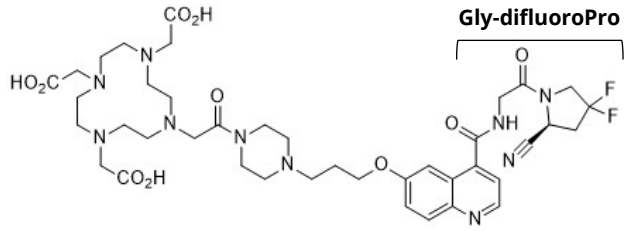
BUT –
Gly-Pro has overlapping substrate specificity with PREP and other Enzymes

Z-Gly-Pro-DOX



See Huang et al. J Drug Target. 2011;19(7):487–496

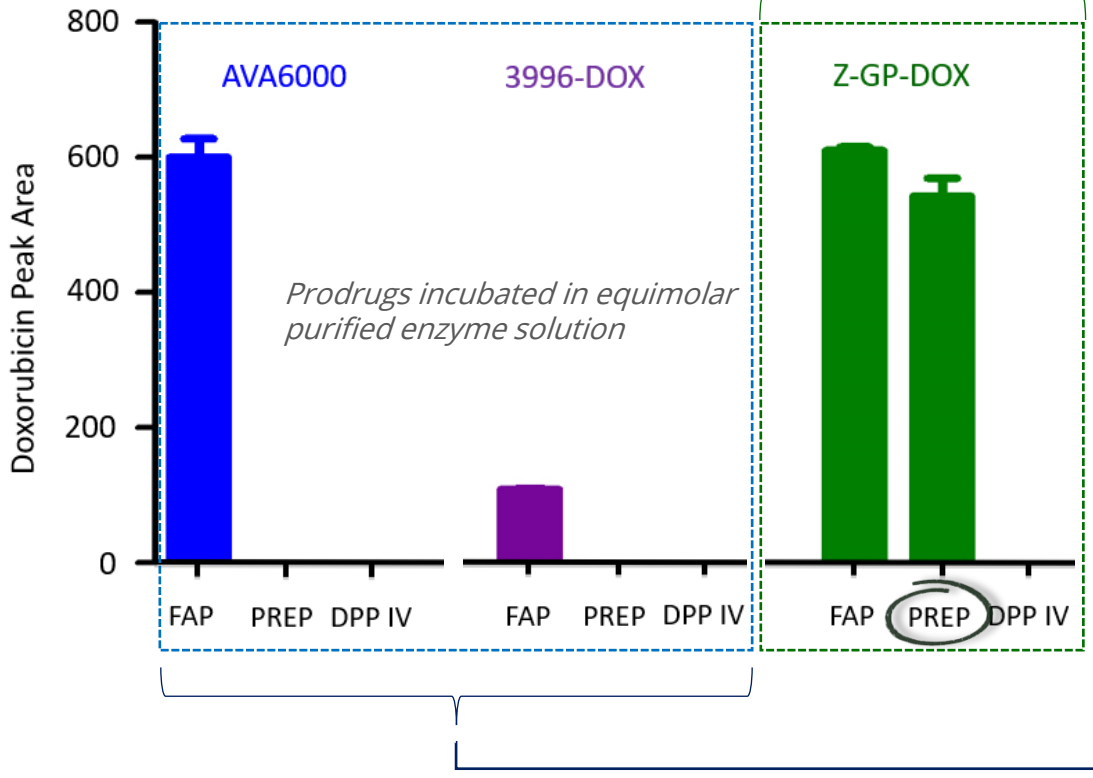
DOTA-FAPI-04

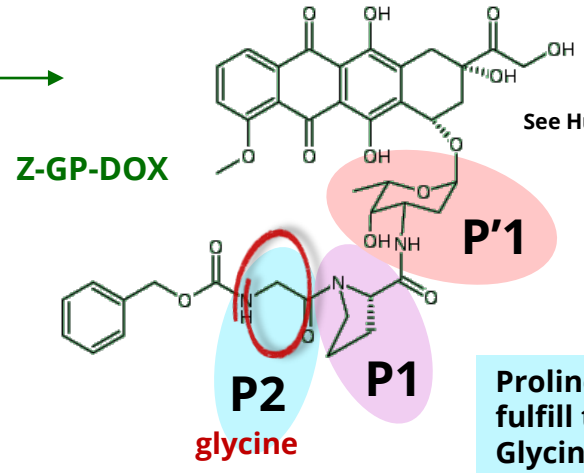


See Kratochwil et al. J Nucl Med 2019; 60(6):801-805

Proprietary FAPa Substrate is key to pre|CISION prodrugs and TMAC

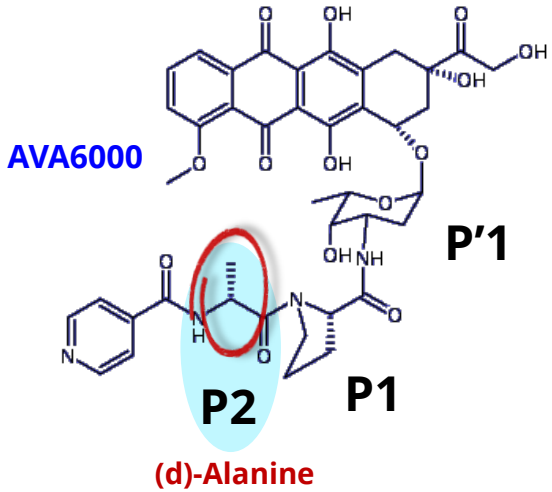
Post-Proline Cleaving Enzymes

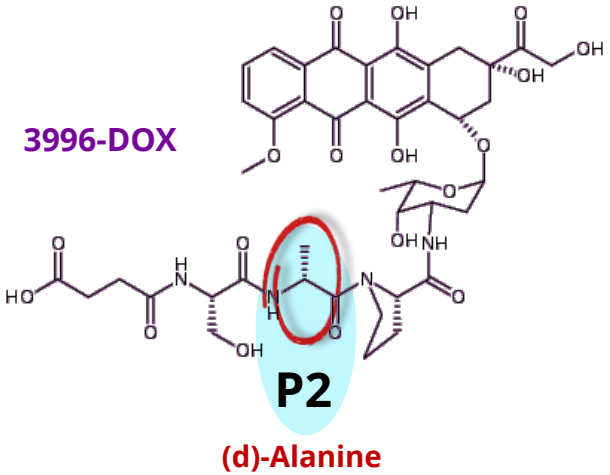




See Huang et al. J Drug Target. 2011;19(7):487–496c

Proline and daunosamine (D) ring of DOX fulfill the P1 and P'1 specificity of FAP - <u>but</u> Glycine in P2 position is not specific to FAP

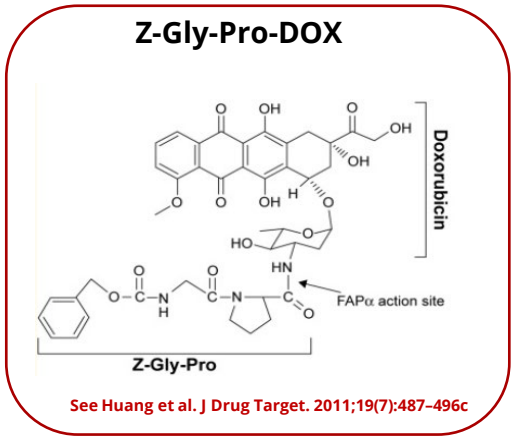


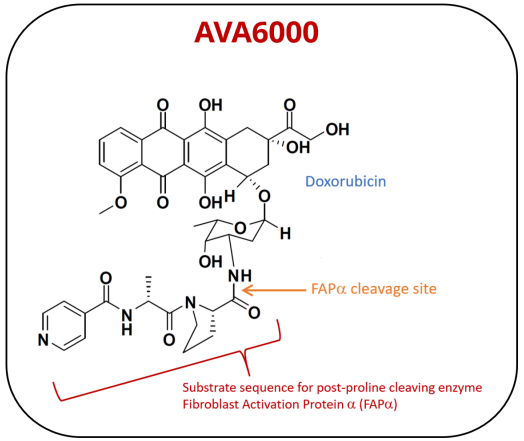


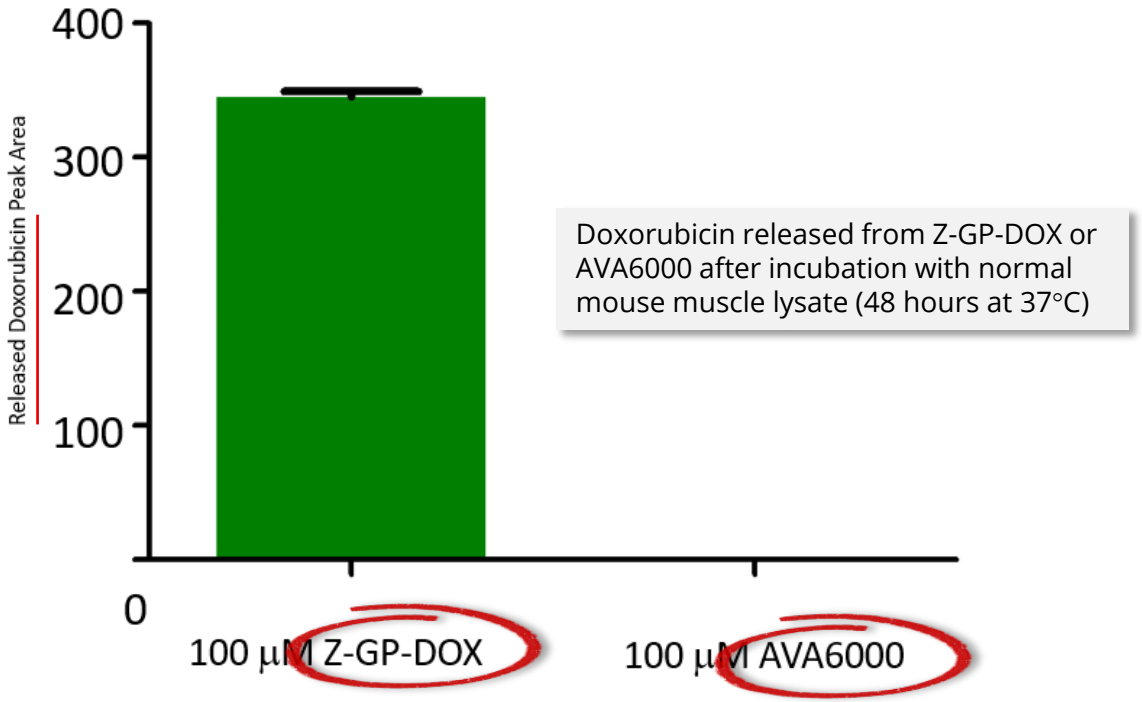
Cleavage of pre|CISION Substrate is Very Tightly Controlled for FAPα-selective Activation

Normal mouse muscle lysate catalyzes the release of doxorubicin from Z-GP-DOX, *but not from AVA6000*

Indicates some enzyme(s) beyond FAPα activate Z-GP-DOX but not AVA6000



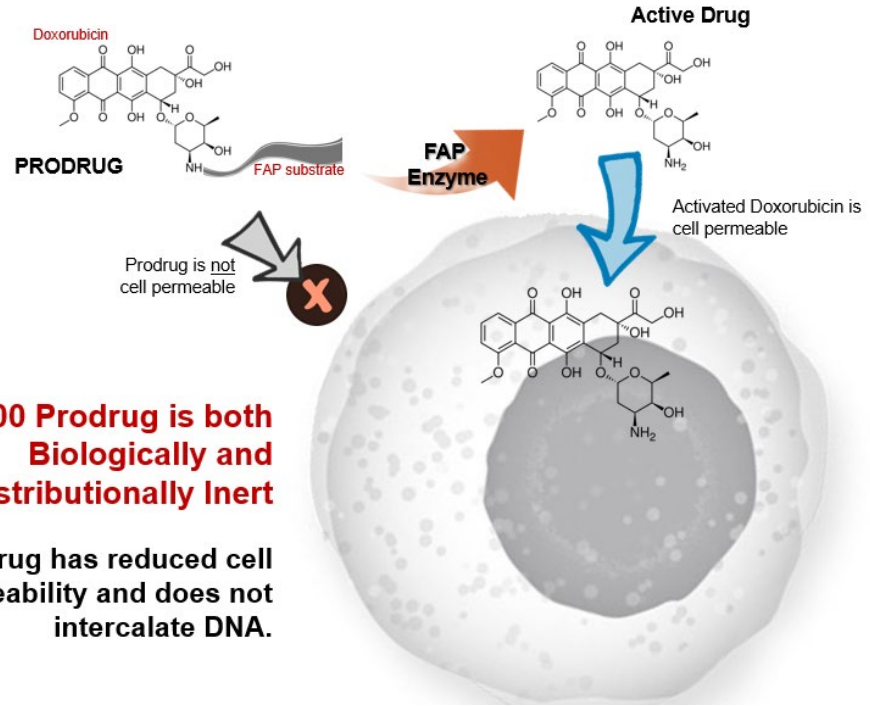




Doxorubicin released from Z-GP-DOX or AVA6000 after incubation with normal mouse muscle lysate (48 hours at 37°C)

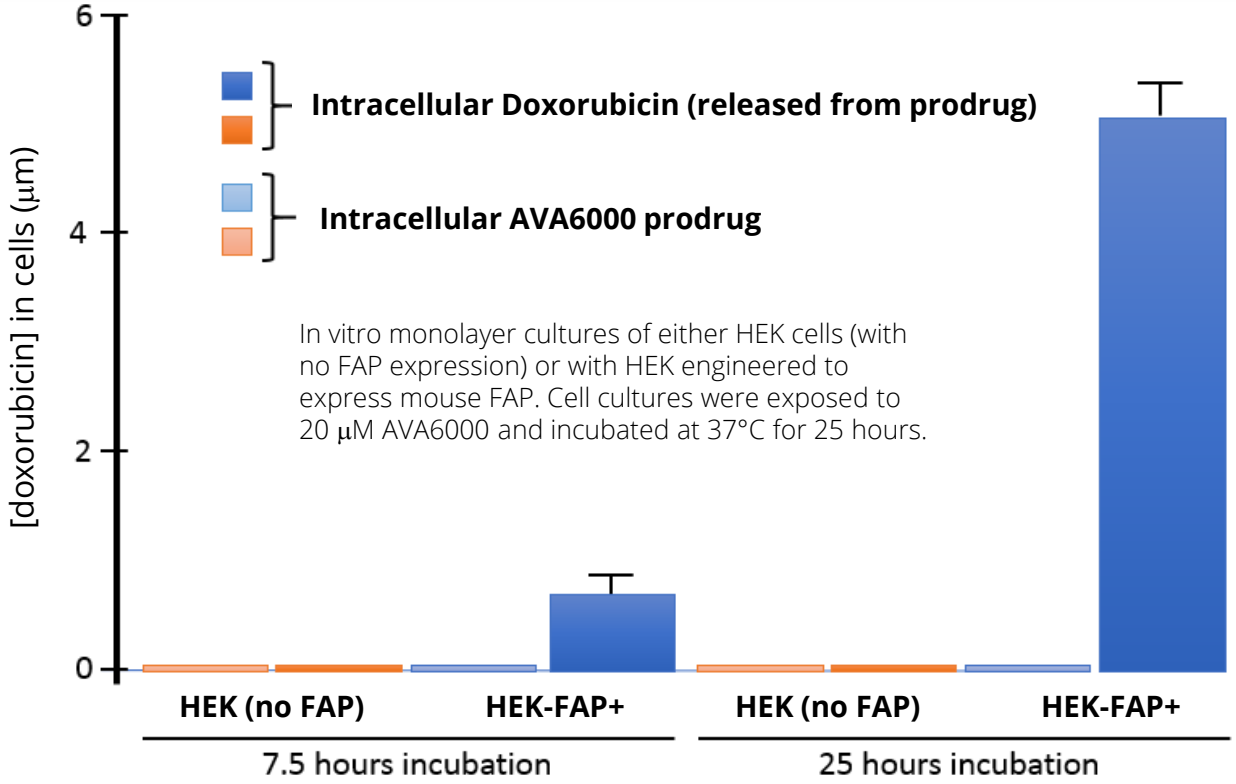
Summary of Early Safety Information - *Non-clinical Studies*

AVA6000 Prodrug is Not Cell Permeable so is Excluded from the MOA site of Doxorubicin



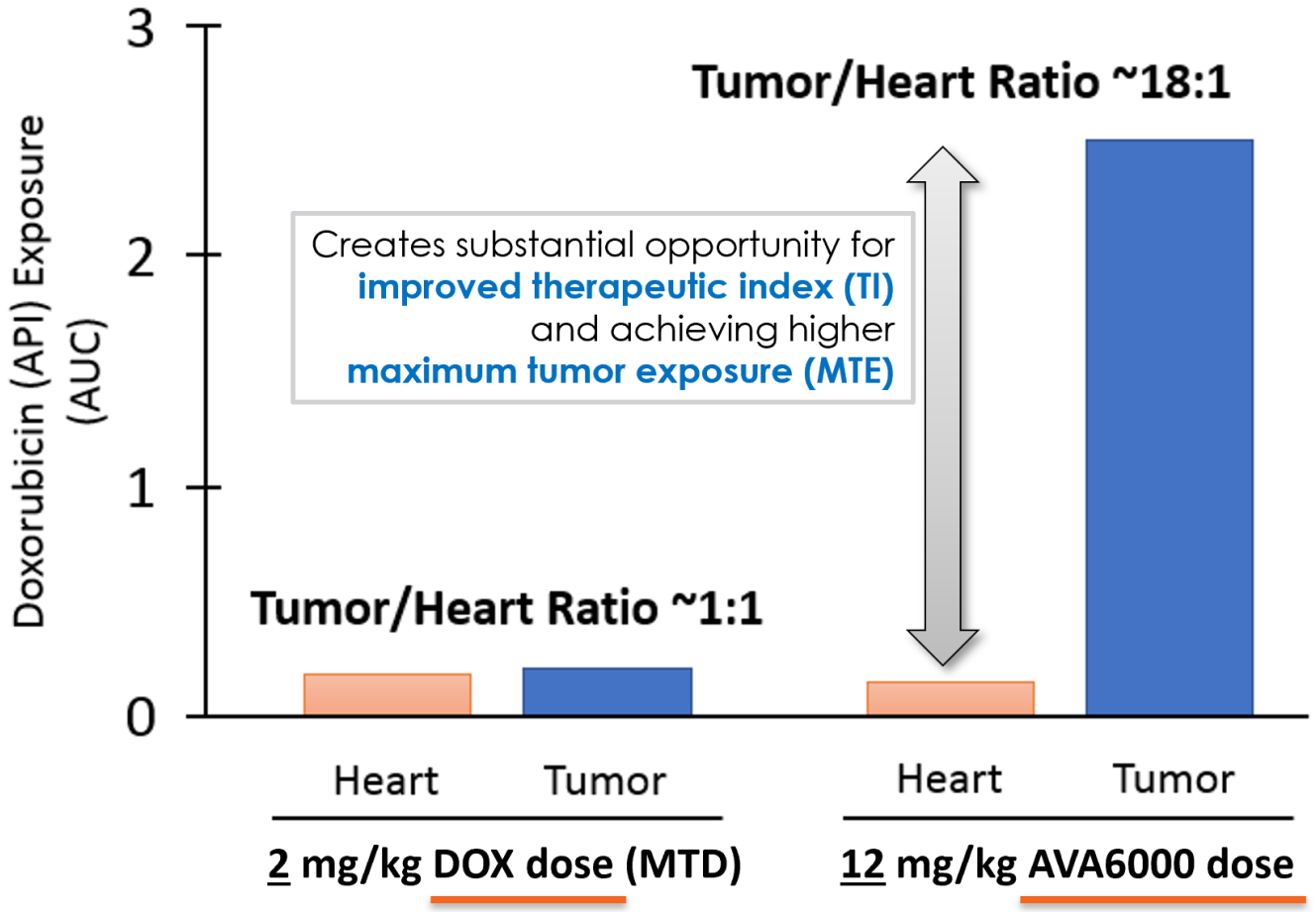
AVA6000 Prodrug is both Biologically and Distributionally Inert

Prodrug has reduced cell permeability and does not intercalate DNA.



Cell permeability of doxorubicin is dependent on FAPα release from the prodrug: Lack of distribution of prodrug into cells helps to create the substantial improvement in therapeutic index

AVA6000 - Doxorubicin Selectively Delivered to Tumour Relative to Cardiac Tissue



Tissue levels ($AUC_{15\text{-}45\ mins}$) of doxorubicin in HEK-mFAP-tumor bearing mice following a single intravenous dose of doxorubicin or AVA6000

Metastatic Sites Also Overexpress FAPα Relative to Site Tissue

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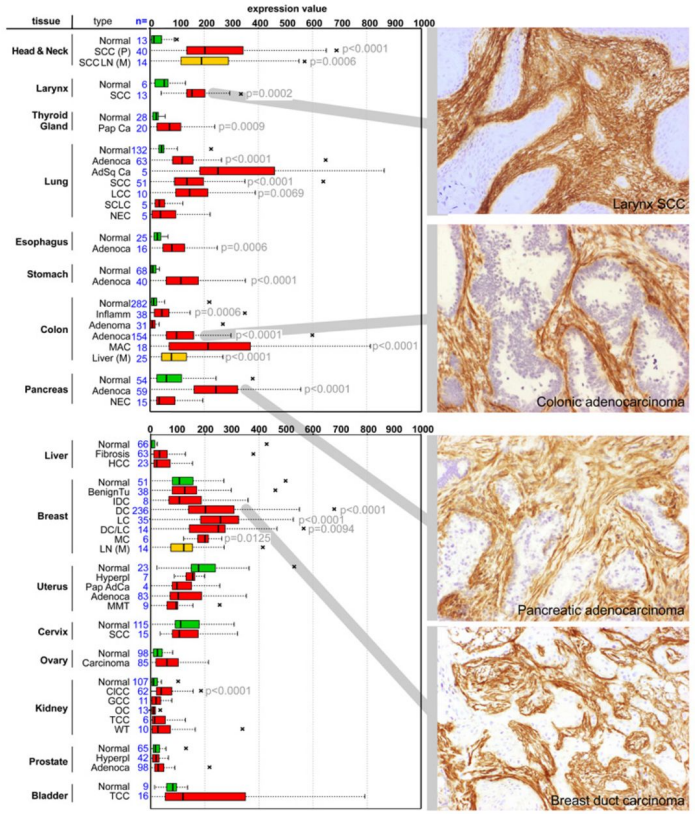
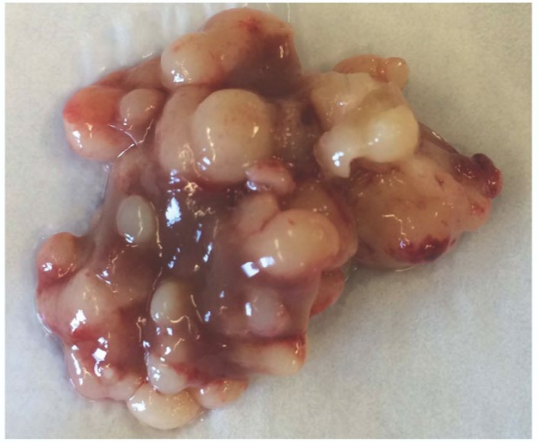
Expression profiles of FAPα in normal and malignant human epithelial tissues.

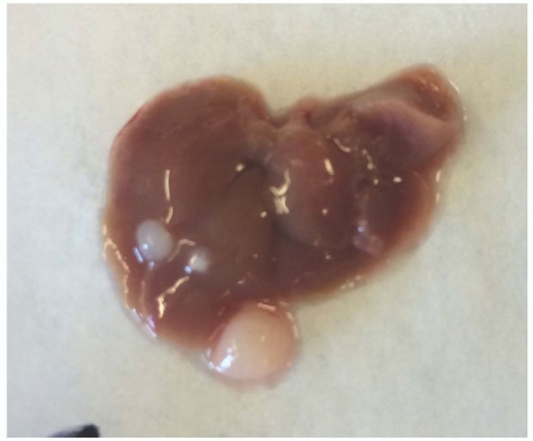
Normal (green), malignant (red), and malignant metastatic lesions (orange)



AVA6000 Reduces Colorectal Cancer (CRC) Liver Metastasis



Vehicle



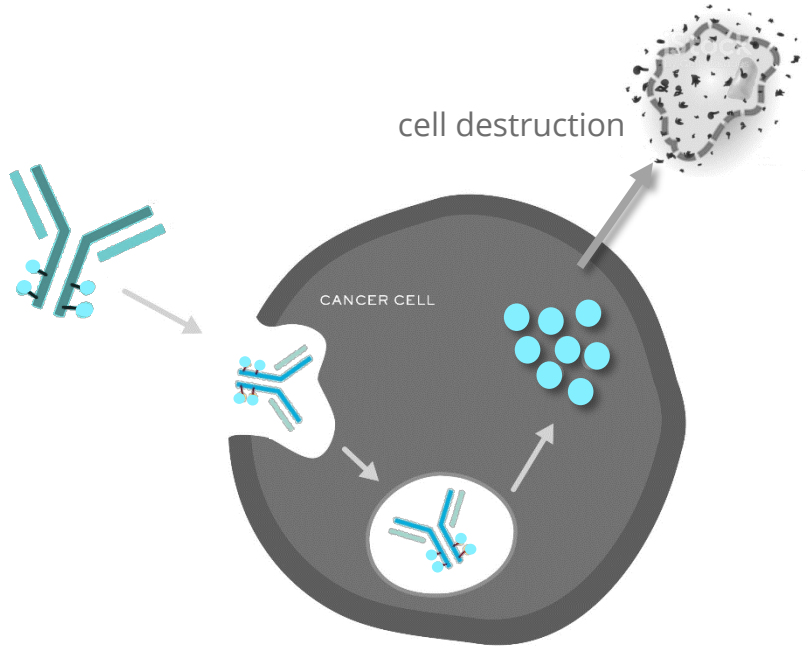
AVA6000

- Tumour cells derived from genetically engineered (*Apc*$^{flox/flox}$ *Kras*^{G12D} *p53*$^{flox/flox}$) mice were implanted in spleens
- Immune competent B6 mice, splenic injection of 500,000 tumour cells
- AVA6000 administered i.v. at 12 mg/kg at week 2, 3, 4, 5; 7 mice treated with AVA6000, 7 mice treated with vehicle
- Animals sacrificed at week 6

Adapted from Dolznig et al. Cancer Immun January 1 2005 (5): 10

TME-Activated Drug Conjugates

Traditional ADCs



Traditional Antibody-Drug Conjugates (ADCs) utilize cathepsin-sensitive linker that require the antibody bind the target cell and be internalized in order to release the toxin payload inside the cell.

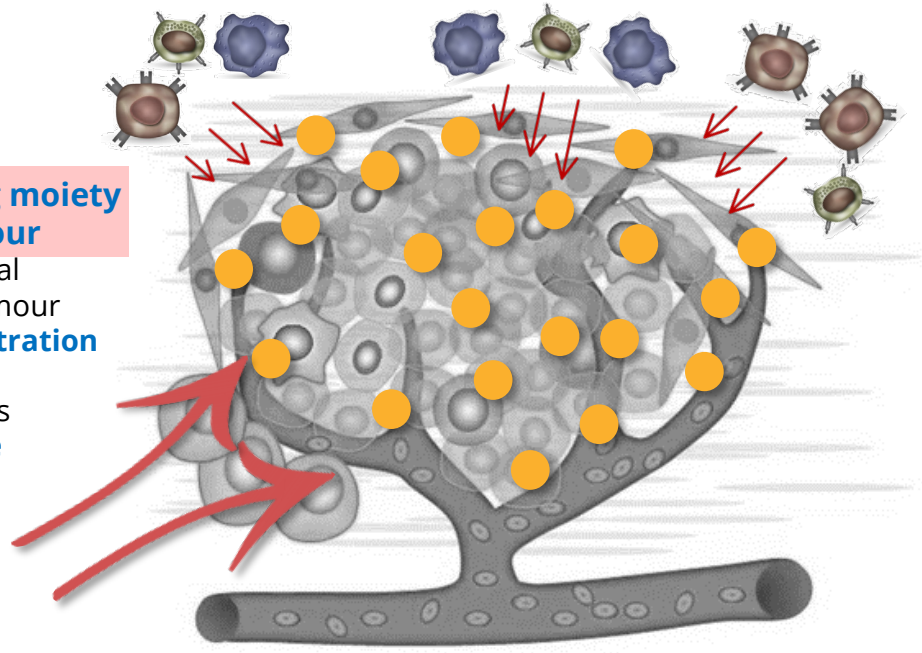
- Toxin payload is selected to be potently toxic to cells.
- Any cell that internalizes the ADC will be killed, leading to toxicity issues with ADCs.

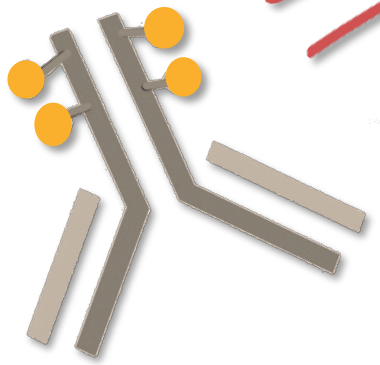
TMAC

FAP-selective linker releases drug moiety in the extracellular space of tumour

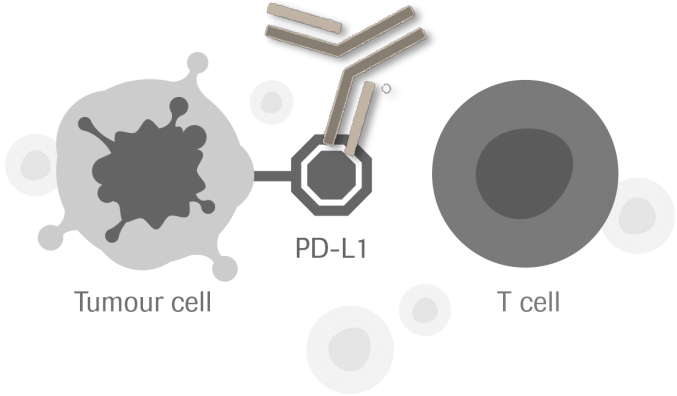
- Drug moiety is selected to create local inflammatory response, degrade tumour stroma, **promote immune cell infiltration** and/or kill tumour cells
- Preferred Drug Moieties are Inducers of Innate Immune Response – **cause local inflammatory signals**

1 Promote Immune Infiltration





2 Checkpoint Inhibition



Checkpoint Targeting Antibody/Affimers

- Such as PD-(L)1 and CTLA-4 inhibitors
- Designed to promote adaptive immune response and synergize with drug moiety

Modular Design Enabled : Exemplars

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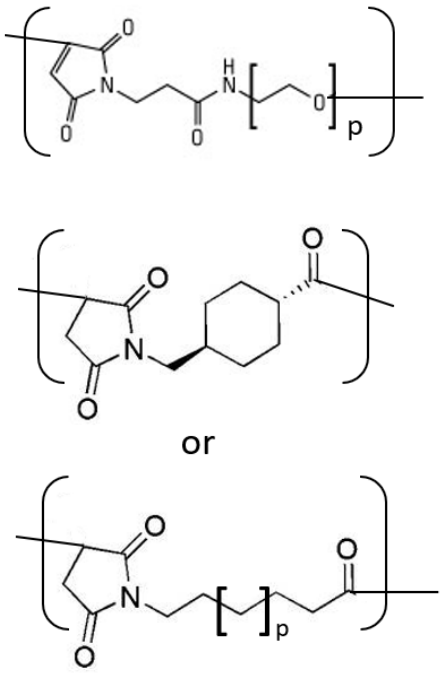
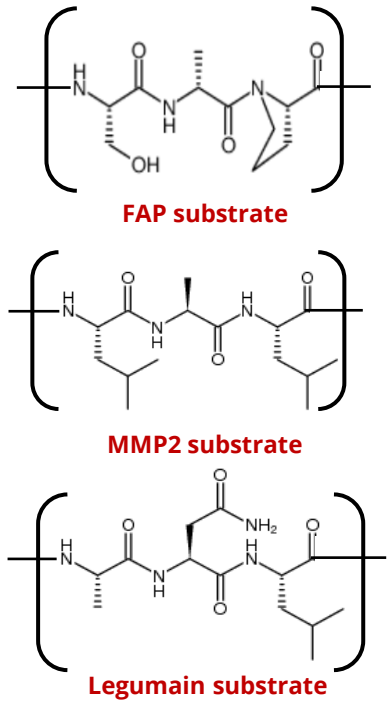
Linking Chemistry + Spacer



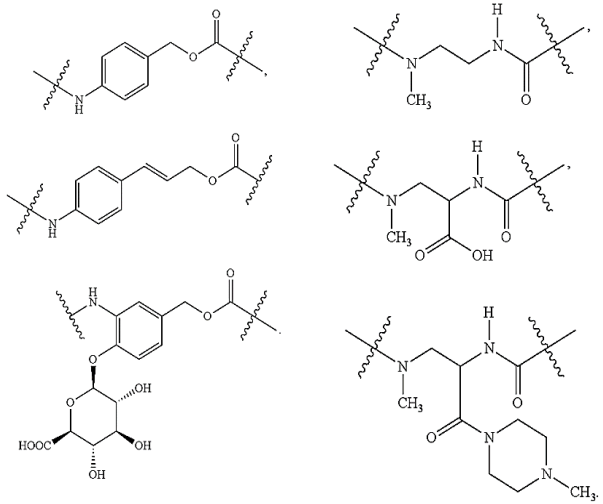
- Hydrocarbon to polyethers (like PEG) for spacing and solubility
- Wide range of protein cross-linking chemistries

Enzyme Cleavage Site



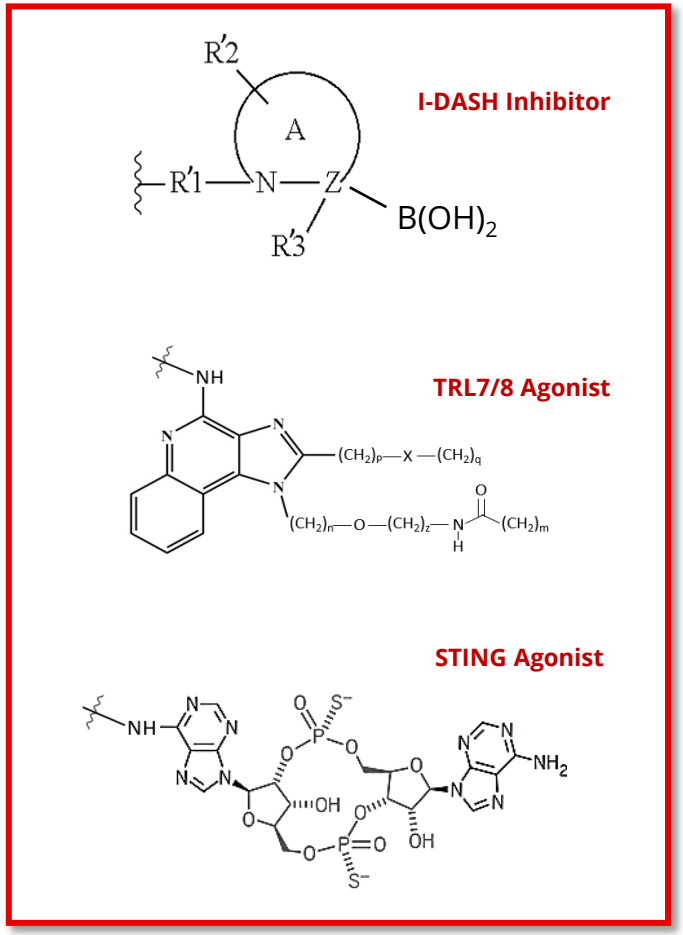
- Extracellular Enzyme Substrate Recognition Sequence

Optional: self immolative linker



- Can serve as P'1 specificity for Cleaving Enzyme
- Can permit attachment to a range of functional groups on drug moiety (i.e., beyond free amines)

Drug Moiety

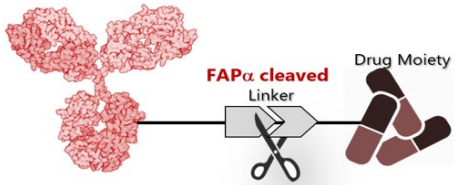


Broad range of drug moieties enabled by combination with binder targeting and enzyme cleavage site combinations

TMAC
FAPα-activated
Affimer/Antibody Conjugates

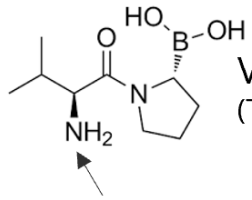
I-DASH Inhibitors - Induce Broad T-cell Activation and Enhance Recruitment of Elements of the Innate Immune System.

PD-L1 Checkpoint Inhibitor
Induction/Maintenance of
Adaptive Immune Response



I-DASH Inhibitor
Induction of localized
Innate Immune Response

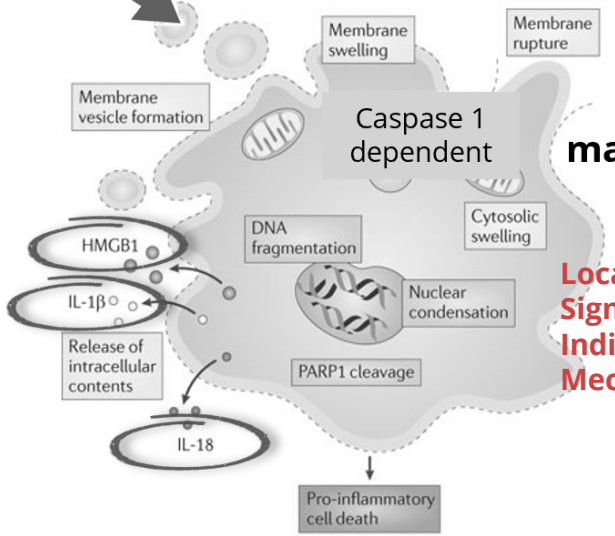
Initial TMAC Candidates Utilize FAP-activated I-DASH Conjugates



Val-boroPro
(Talabostat)

site of linker conjugation

I-DASH inhibitor Selectively Induces Macrophage Pyroptosis



Localized Inflammatory Signals Promote Direct and Indirect Anti-tumour Mechanisms

Synergizes with Checkpoint Inhibitors

- Promotes expansion and survival of effector cells including NK, γδ T, and CD8+ T cells
- Augments expansion of effector cells in the presence of immune checkpoint antibodies
- Reduces proportion of regulatory T cells.

I-DASH Inhibitors Direct and Indirect Effects*

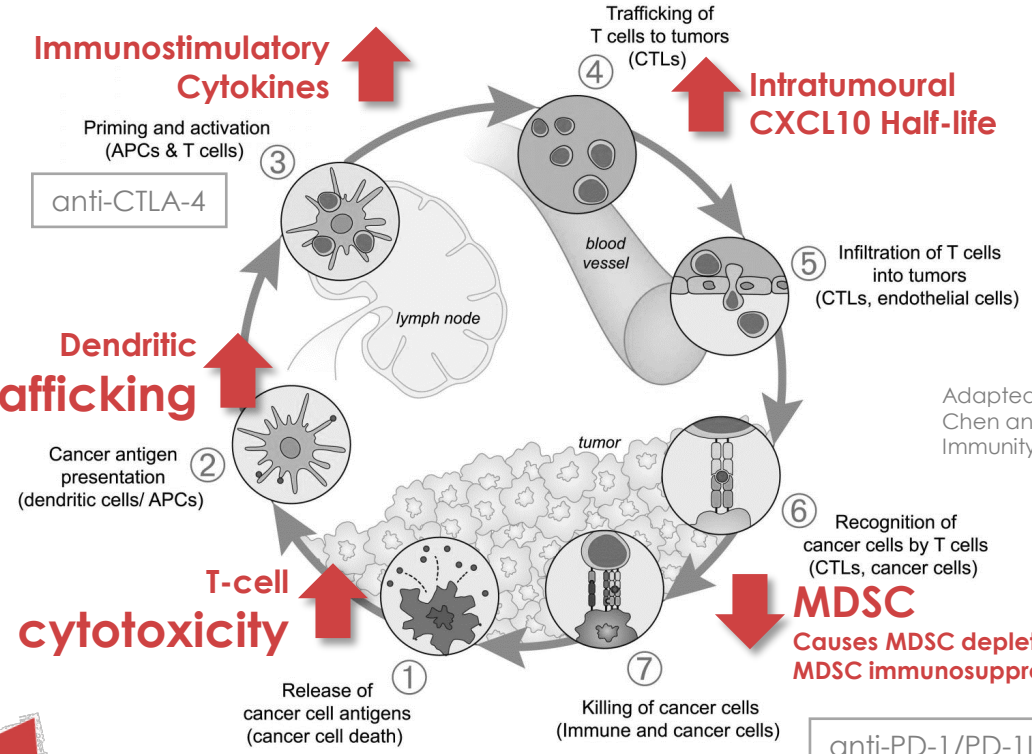
Immunostimulatory Cytokines

Intratumoural CXCL10 Half-life

Dendritic Cell Trafficking

T-cell cytotoxicity

MDSC
Causes MDSC depletion and impairs MDSC immunosuppression activity



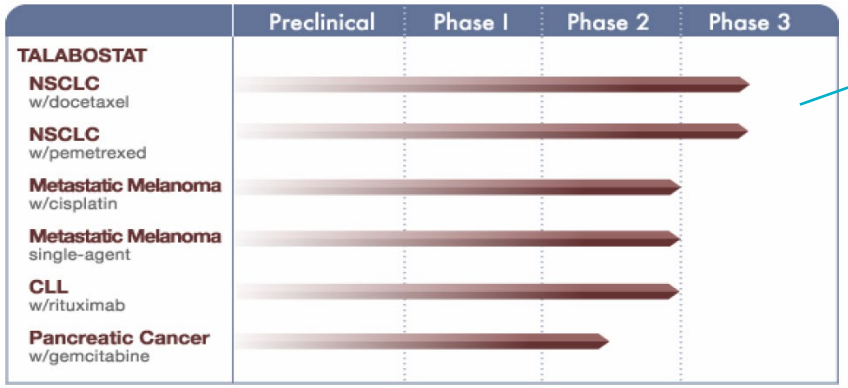
Adapted from
Chen and Mellman 2013,
Immunity 39(1):1-10

Data Presentation Available Upon Request

Through collaborations with

Tufts University School of Medicine
National Cancer Institute

Drafting on Clinical Experiences… Solving for Systemic Toxicity that produce the DLTs



Point Therapeutics brought Talabostat (Val-boroPro) to Phase 3 for oncology indications without understanding the true MOA (macrophage pyroptosis) – and without understanding the true IO potential of the I-DASH inhibitors, did not understand how to manage dose limiting toxicities or how to deploy in an IO clinical strategy

Both Phase 3 Trials were put on clinical hold (May 2007) following Interim Analysis.

- Interim analysis indicated tumors were not shrinking fast enough to meet response rate objective & treatment cohort experienced more severe edema and pleural effusion
- Investigators were reluctant to continue subjecting patients to the increased risks from AE's when there did not appear to be a chance for a benefit.

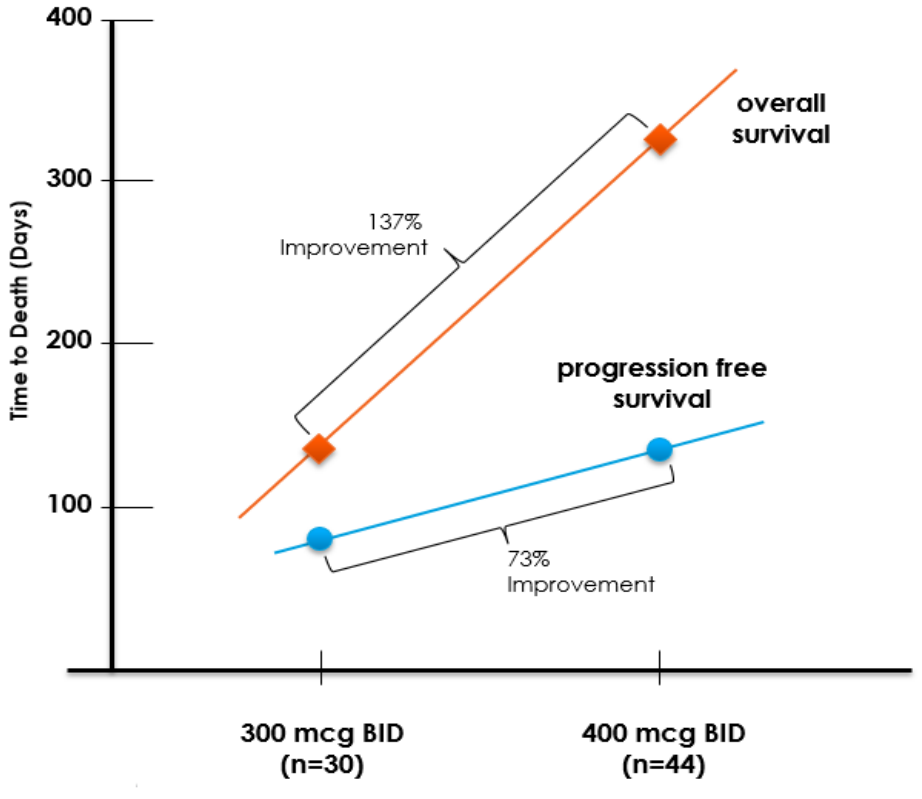
This is a repeating story for innate immune activators, including TLR7/8 agonists and STING agonists

→ **on-target/off-tumor induction of inflammation** produces acute toxicity which requires dose de-escalation below the intratumoral EC50 for the drug's anti-tumor activity in order to reduce systemic activation of inflammation.

STING and TLR7/8 agonists are now injected intratumorally in an effort to solve this problem

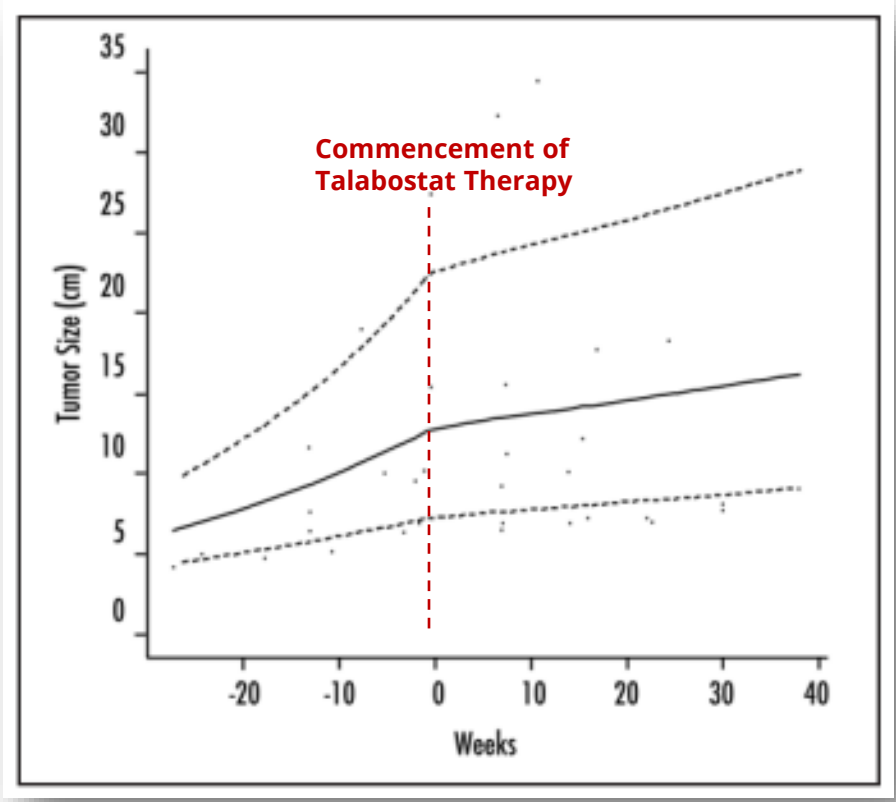
Talabostat turns out to have been a near miss …. due to dose de-escalation after Phase 1

Phase II assessment of Talabostat and cisplatin in second-line stage IV melanoma



Phase II, open label, single arm study was conducted to evaluate the safety and efficacy of 75–100 mg/m2 cisplatin combined with 300–400 mcg Talabostat bid for 6, 21-day cycles. **The primary endpoint was overall response. The rate of complete responses, duration of overall objective response, progression-free survival (PFS), and overall survival were the secondary endpoints**

Phase II assessment of Talabostat in metastatic colorectal cancer



Attenuation of tumor growth with treatment. Radiographic tumor measurements before and during Val-boroPro treatment were calculated using RECIST criteria. Mean value (solid line) with 95% C.I. (dotted lines) are shown.

Talabostat turns out to have been a near miss …. due to dose de-escalation after Phase 1

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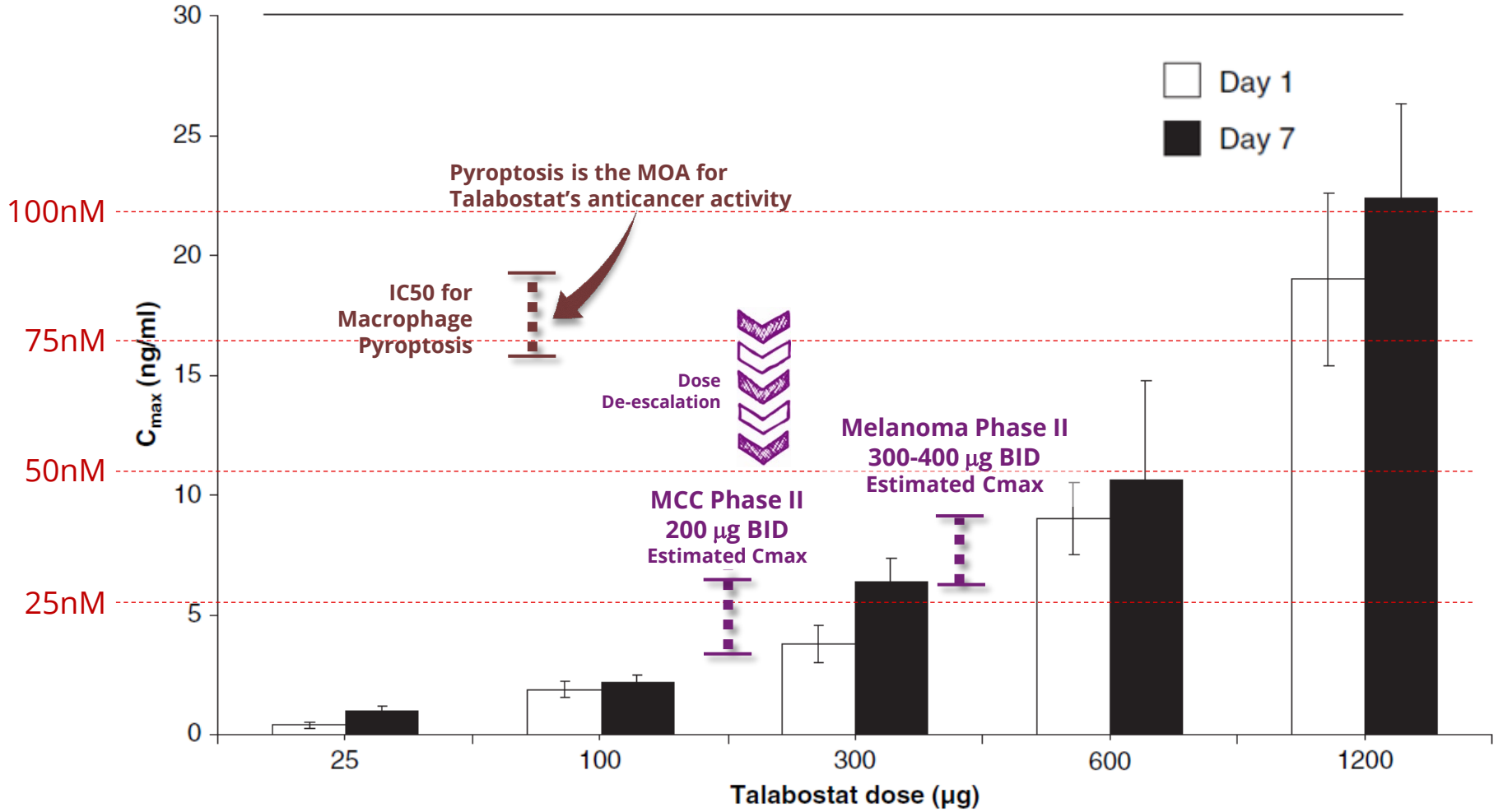
Phase I

Figure 3. Maximal dose tolerance study in healthy talabostat plasma levels on subjects: days 1 and 7.
There were six subjects per group. For talabostat 600 μg, n = 5 as 1 subject was not dosed on day 7. C_{max}: Maximal plasma concentration.



In FAP+ tumor burdened models, various FAP-activated TMAC formats can achieve intratumoral concentrations greater than 100nM Val-boroPro while maintaining low systemic exposure levels

"Talabostat was rapidly absorbed, with a median time to maximum concentration (Tmax) of ≤ 2 h. Maximum observed plasma concentration (Cmax) values appeared to be dose proportional and increased with higher doses, as shown in ***Figure 3*** *. Once peak plasma concentrations were reached, plasma elimination of talabostat was slow. It is thought that talabostat binds irreversibly to plasma proteins and that this binding is responsible for the long half-life. Urinary excretion and renal clearance increase with dose. Plasma levels of talabostat in the multiple-dose study suggested a multi-compartmental distribution."*

Adapted from, Charles Casey Cunningham (2007) Expert Opinion on Investigational Drugs, 16:9, 1459-1465

TMAC Conjugates Selectively Deliver Activated Drug Moiety to Tumour
with Low Systemic Exposure and for Sustained Periods of Time

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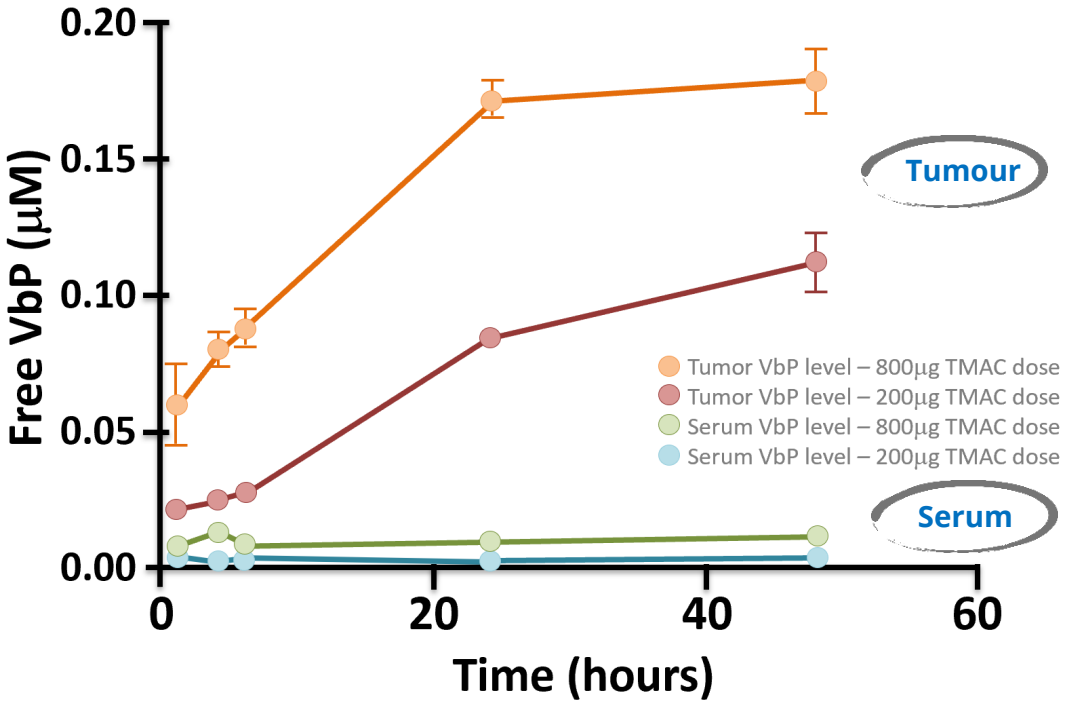
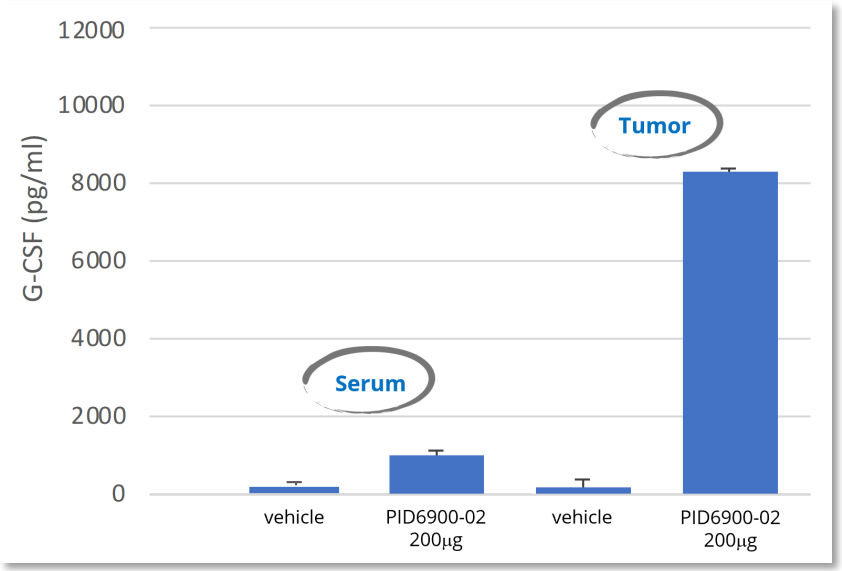
Note: Val-boroPro is the active ingredient in Talabostat, and selectively induces macrophage pyroptosis, which in the tumor causes induction of both innate and adaptive responses

PK Study: Tumour and Serum Concentrations of "free" Val-boroPro released from TMAC

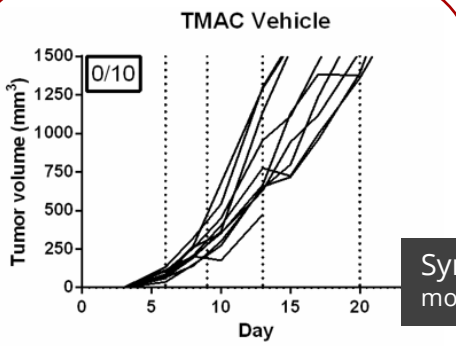


PK/PD Experiments Demonstrate Preferential Intratumoural Cytokine Activation
(correlates with increased efficacy and decreased toxicity)

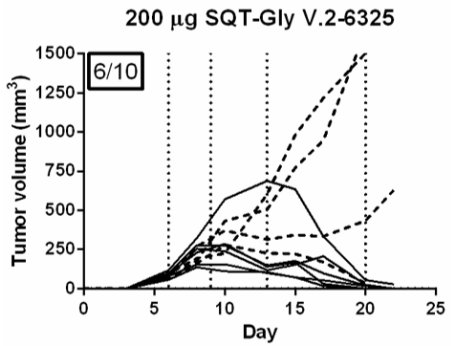


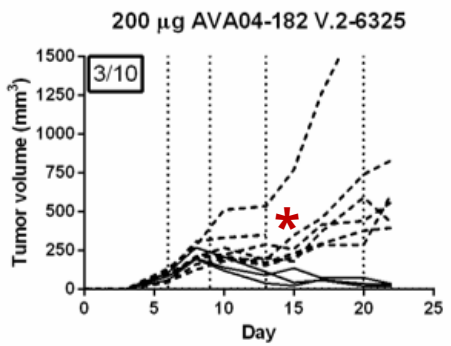
Syngeneic Model: CT26 – mFAP+
mouse colon carcinoma – hFAPα gene knock-in

TMAC Conjugate Has Pronounced Safety Improvement over Talabostat



Syngeneic Model: CT26 – mFAP+
mouse colon carcinoma – **FAPα gene knock-in**



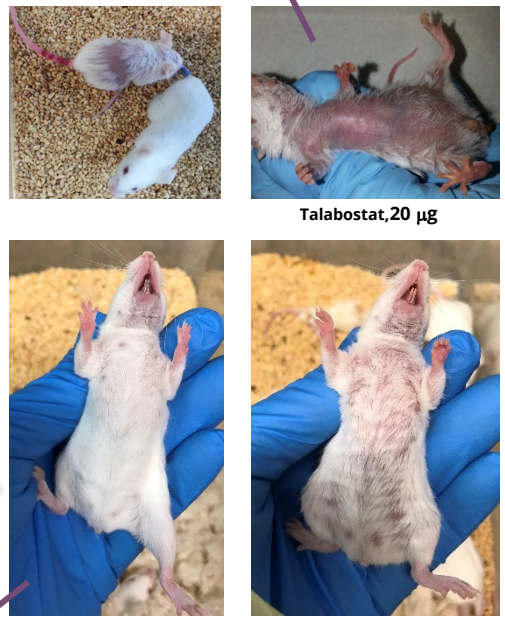


* Note, this is a human protein in mouse – escape from activity is consistent with eventual immune response to construct

This dose of Parent Drug produces inhibition of tumor growth in ~50% of mice, but not full regression

This dose of TMAC produces full regression and immunity to rechallenge in >50% of mice

Val-boroPro TMAC format is better tolerated than Talabostat



Talabostat, 20 µg

PID6900-02
200 µg

Talabostat
10 µg

The amount of Val-boroPro present in the conjugate is less than 2µg

Thank-you