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TMAC Affimer Drug Conjugates

A novel and proprietary class of immuno-oncology active, dual mode of action drug conjugates

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Immune-checkpoint Therapies: Improving Patient Response Rates

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- Despite great progress and excitement surrounding immune-checkpoint targeting therapies, the fact remains that overall response rates across the patient population are low.
- What approaches can be used to improve the response rate?

1. Hitting more than one immune-checkpoint at once through combination therapies, bispecific and trispecific molecules.
2. Combining immune-checkpoint therapies with chemotherapy, viral vaccines, radiotherapy, and others
3. Targeting chemotherapy using drug conjugates
4. Harnessing the power of agonists

Avacta is actively addressing the opportunities for Affimers to create novel, safe and effective multispecific immune check point inhibitors and drug conjugates.

This document provides an introduction to drug conjugates and to Avacta's proprietary TMAC (Tissue Microenvironment-Activated Conjugates) platform, a novel and proprietary class of immuno-oncology active, dual mode of action drug conjugates

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What is a drug conjugate?

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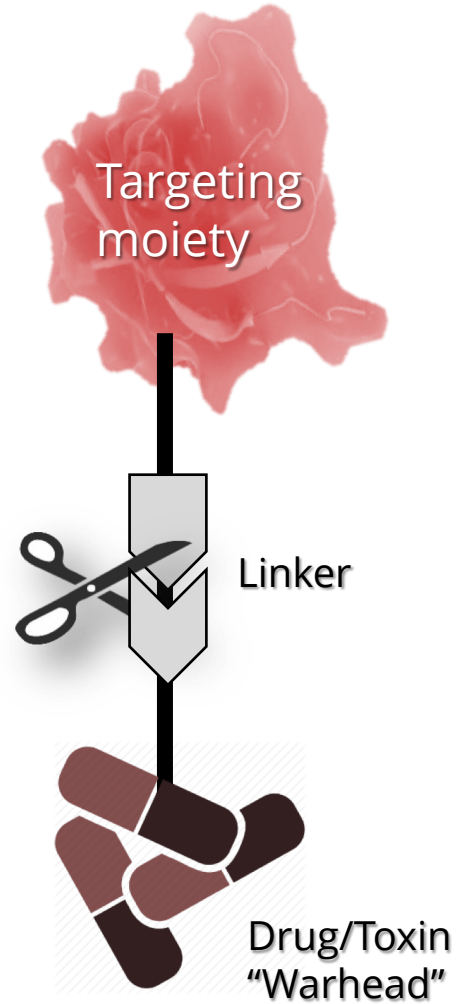
- Biopharmaceutical targeted therapies consisting of:

  A targeting moiety: can be an antibody or an Affimer the role of which is to localise the conjugate to the tumour to deliver the drug payload specifically to cancer cells.

  A linker: which attaches the drug/toxin to the targeting moiety and can be cut (by enzymes) specifically at the site of action (typically inside a cancer cell) to release the active warhead.

  A drug/toxin warhead: inactive when conjugated to the targeting moiety, but has a cytotoxic activity (usually cell killing) when released.



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Introducing Affimer-TMAC technology

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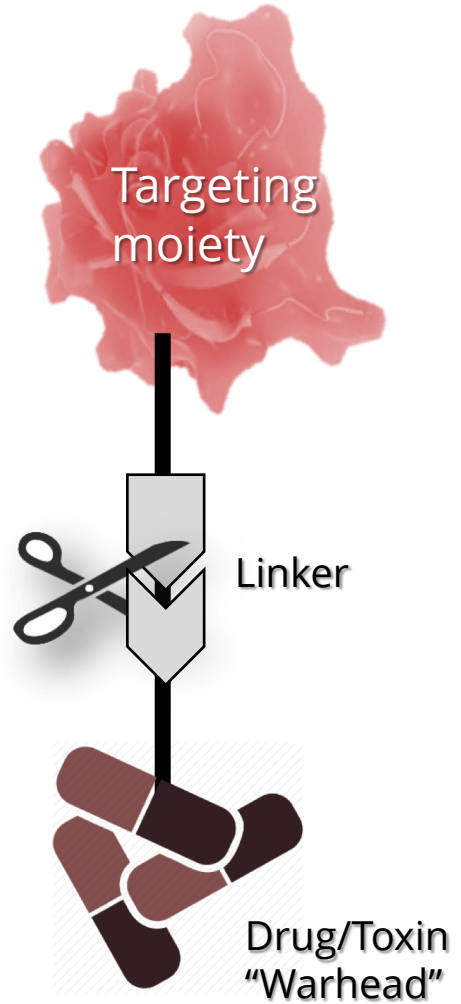
	Traditional ADC	TMAC
Targeting moiety	Needs to be tumour specific AND internalised.	Needs to be overexpressed in tumour cells and can have its own biological activity. Does not need to be internalised.
Linker	Cut by enzymes after the conjugate is internalised to release toxin inside the cell.	Cut in the tumour microenvironment to release the drug around the cancer cells.
Drug warhead	Very potent toxin, killing the cell when released inside the cytoplasm.	Different classes of drugs and mechanism of action possible, acting either on the cancer cells or on the immune response to the tumour.



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Benefits of TMACs

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- Molecules such as inhibitors of immune checkpoint (PD-L1 for instance) that have a biological activity but are not internalized quickly enough can be chosen as a targeting moiety and synergize with the payload they deliver (combination therapy).
- A key differentiating feature of TMACs is the novel linker which is cleaved by enzymes that are only upregulated in the in the tumour microenvironment and not in healthy tissue which provides an additional mechanism to enhance specificity and safety.
- Since the payload doesn't need to be internalised to be activated, it opens up many mechanism of action possibilities, including activation of local inflammation events, turning tumours from 'cold' to 'hot' which attracts the immune system.

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Example of TMAC Affimer

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- Targeting moiety: PD-L1

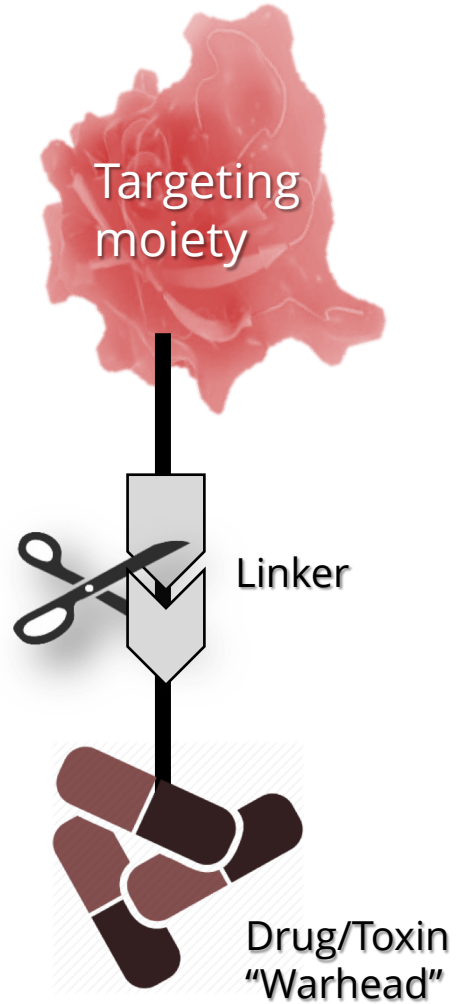
  Expressed on the surface of tumour cells causing accumulation of the conjugate while at the same time overcoming resistance to the immune response.

- Linker: FAPα

  Specifically cleaved by fibrobroblast activation protein, an enzyme which is overproduced by many tumour types including pancreatic, bladder and ovarian.

- Drug warhead: i-DASH inhibitor

  Activating innate immunity and inducing a local inflammatory response turning ‘cold’ tumours into ‘hot” tumours and synergising with I/O checkpoint inhibitors such as PDL-1.



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Collaboration with Bach Biosciences/Tufts University School of Medicine

The TMAC drug conjugate concept is a joint invention between Avacta and Tufts University School of Medicine.

Avacta has agreed a co-development partnership with Bach BioSciences, a company commercialising the research of William Bachovchin, Professor of Developmental, Chemical and Molecular Biology at Tufts University School of Medicine, Boston, to develop a new class of Affimer drug conjugate therapies called "TMAC" with a novel mode of action that combine Avacta's Affimer technology with drug conjugates developed at Tufts.

Avacta has sole commercial rights to the TMAC platform.

About Bach Biosciences LLP

Bach Biosciences LLP is the mission-driven development company associated with Dr. William Bachovchin's laboratory at Tufts University School of Medicine. Bach Biosciences is accelerating breakthrough discoveries into therapeutics for patients, from its own drug development pipeline or by working in partnership with other life science companies. The company and its founders have established strategic partnerships with contract research organizations, investors, and pharmaceutical partners to support technology development. Dr. Bachovchin is the inventor on 46 issued US patents, including reach-through patents covering the field of DPP-IV inhibitors for treating diabetes, a $10B market. This patent has been licensed by Merck, Novartis, Bristol-Myers Squibb and Boehringer Ingelheim. In addition three drugs first designed, synthesized and characterized in Dr. Bachovchin's laboratory at Tufts University School of Medicine have been advanced into human clinical trials.

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TMAC: Technical Details

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TMAC Affimer : Avacta's First Programme

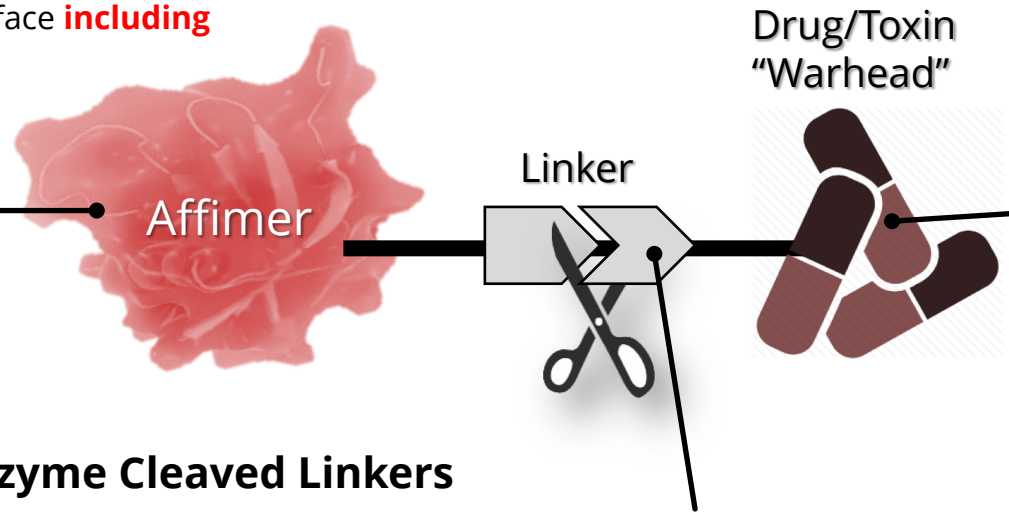
Immune Checkpoint Targeting

Targeting immune checkpoints (ICP) expressed in the tumour microenvironment causes accumulation of Affimer drug conjugates (AfDC) in checkpoint over-expressing tumours and leads to **induction/maintenance of adaptive immune response overcoming immune evasion.**

Use of a TME active warhead permits targeting of ICP not rapidly internalized from cell surface **including bispecific formats**.

First Programme

- PD-L1 (monomeric or dimeric)



Drug/Toxin "Warhead"

Utilisation of **"I/O Active" warheads** targeting "bystander" cells, including macrophage, NK cells, etc. and supporting tumor stroma (CAFs).

Induction of localized **innate immune response** potently primes tumor antigen-specific CD8+ T-cell responses.

Warhead inert when linked improving safety profile.

First Programme

- I-DASH Inhibitor targeting tumour associated macrophage.
- The effects include potent priming of tumour antigen-specific CD8+ T-cell responses, enhanced trafficking of key effector immunocytes to the tumour, increased levels of dendritic cells and activated NK cells and accelerated expansion of tumour specific T-cells.

TME Enzyme Cleaved Linkers

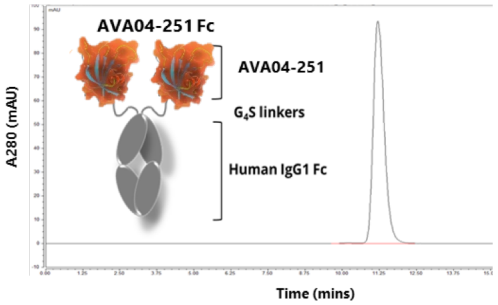
Linker is only cleaved by **enzymes that are upregulated in the tumour microenvironment** (TME).

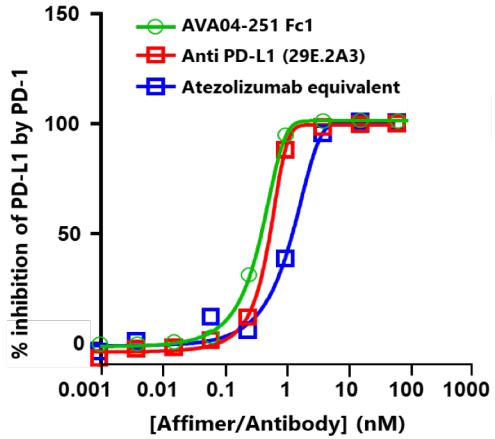
TME enzyme requirement provides **secondary targeting mechanism**, and a basis for a biomarker supporting breakthrough designation.

First Programme

- Fibroblast Activation Protein (FAPα)

Affimer PD-L1 Inhibitors: Targeting a Key Immune Checkpoint Pathway



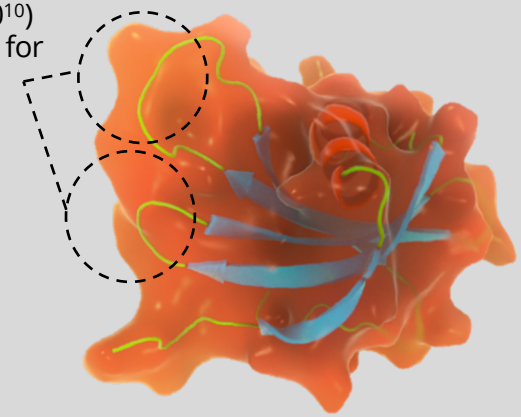


Clone	IC_{50} (nM)
AVA04-251 Fc1	0.4
29E.2A3 mAb	0.5
Atezolizumab”	1.2

What is an Affimer?

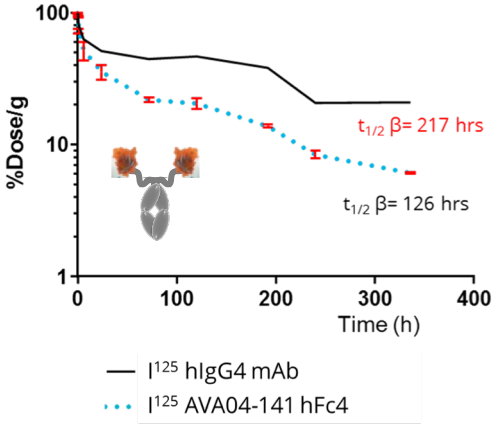
- Based on a **naturally occurring protein** and engineered to **behave like an antibody**.
- Its **binding surface** is created by loops which can be altered to **capture different targets**.

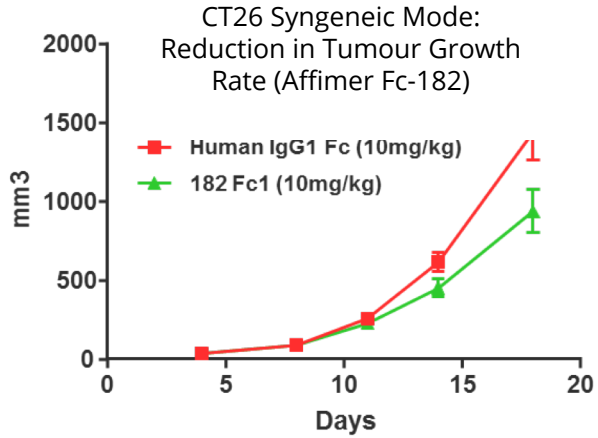
Affimer Libraries:
Variable loop regions allow very large (10^{10}) libraries to be built for phage selections.



Key Benefits

- **Proprietary and unencumbered IP**.
- **Freedom to operate** where there is antibody IPR.
- **Security of supply**.
- **Cheaper to produce (*E.coli*)**.
- **Smaller**, **simpler**, **more robust** than antibodies.
- **High affinity** Affimers generated for new targets in a matter of weeks, **much quicker** than antibodies.
- **Very specific** to the target of interest – no cross reactivity.
- **Easily modified** and **easily manufactured**.
- **Non-immunogenic**.





PD-L1 Binding Affimers, and Uses Related Thereto. UK Patent Application Serial Number 805963.4

I-DASH Inhibitor: Exploits Macrophage-Selective Cell Death Pathway

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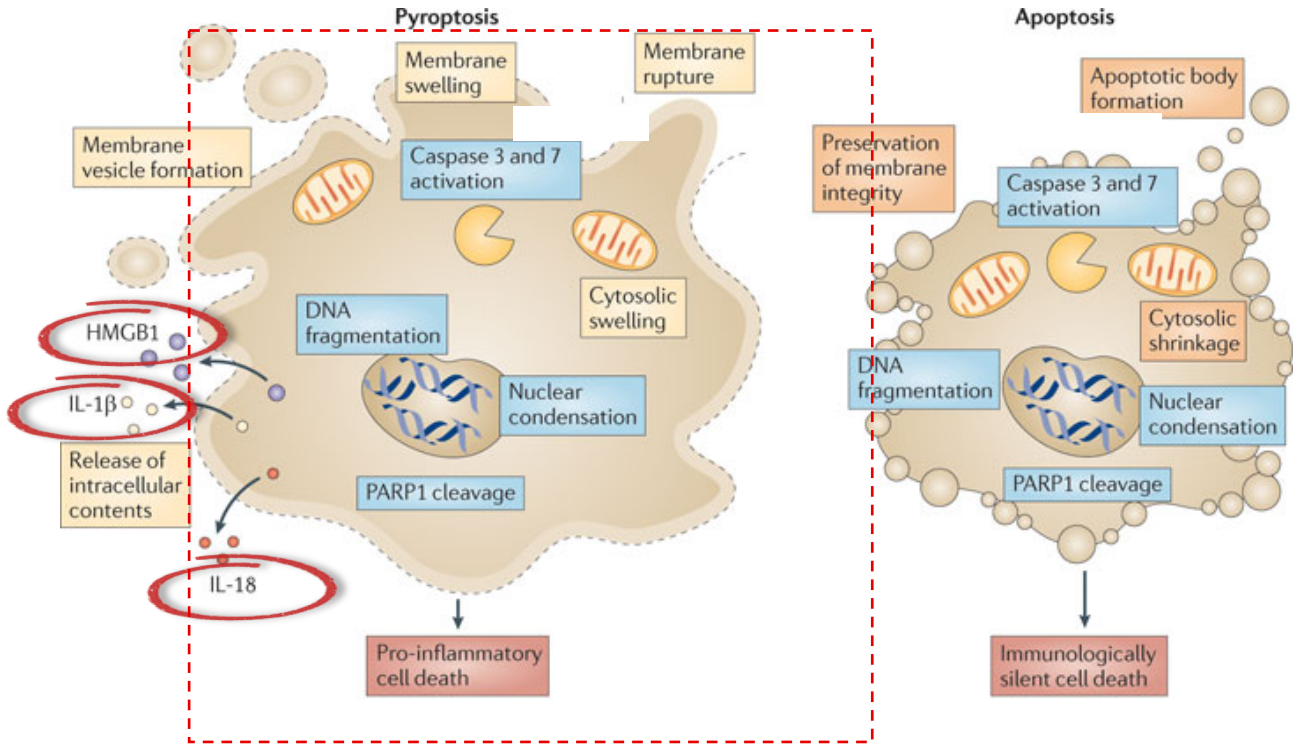
I-DASH induced pyroptosis leads to "inflammatory cell death"

Distinct differences between **pyroptosis** and **apoptosis**

- I-DASH induced pyroptosis is not universal – limited to macrophage (and AML cells)

Induces innate immune responses
Enhances adaptive immunity



Pyroptosis of MΦ results in the release of proinflammatory cytokines IL-1β, IL-18 and other antitumor immune signals.

Released cytokines consistent with promoting expansion and survival of effector cells including NK, γδ T, and CD8+ T cells, augmenting expansion of effector cells in the presence of immune checkpoint antibodies, and reducing proportion of regulatory T cells.

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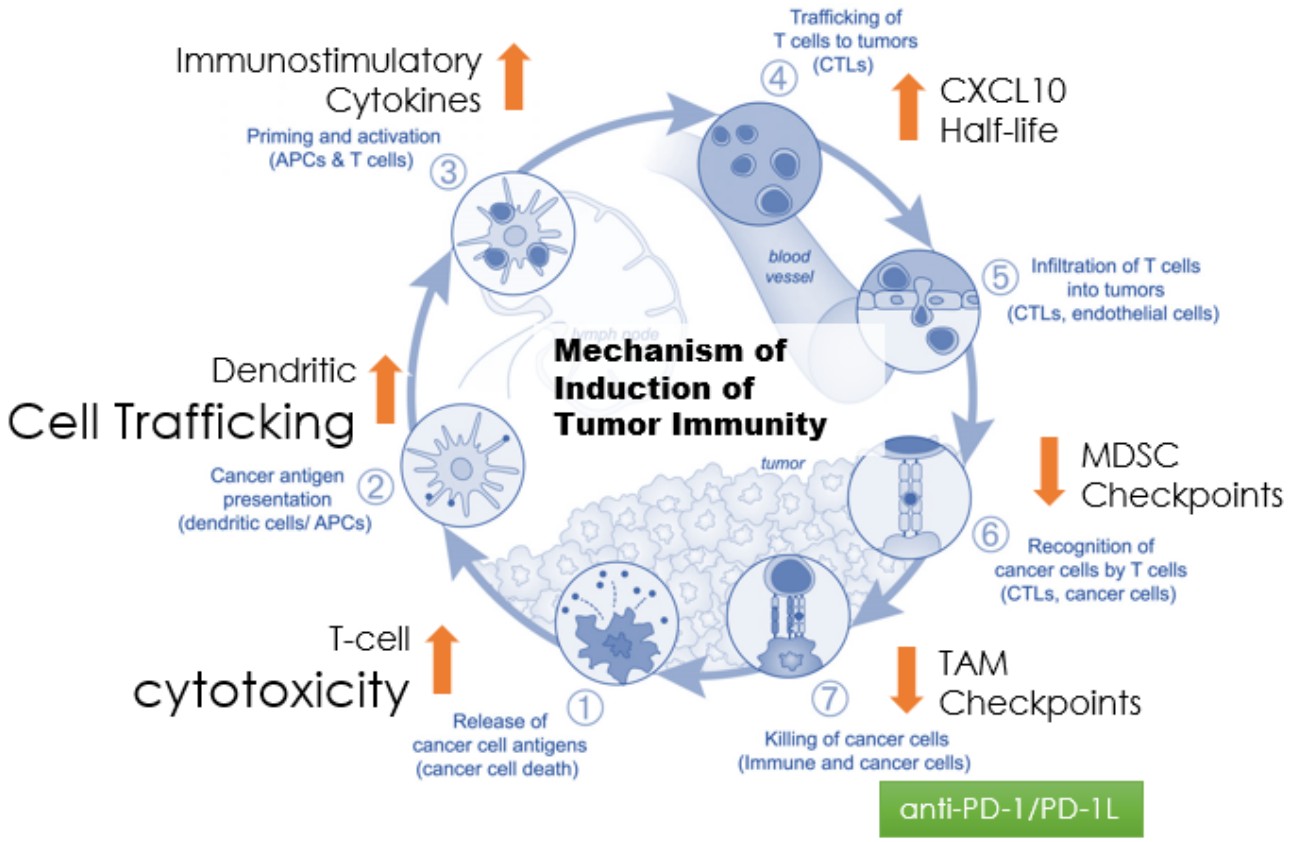
I-DASH Inhibitor: Direct and Indirect Effects



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

MDSC = Myeloid-derived Suppressor Cell
TAM = Tumor Associated Macrophage

* Orange arrows denote changes caused by AVA-100 treatment

Demonstrated Effects:

- Programmed cell death selectively in macrophages
- Reduced monocytic MDSCs in tumor
- Reduced T-cell suppressive activity of granulocytic MDSCs
- Enhanced trafficking of key effector immunocytes
- Increased levels of dendritic cells and activated NK cells
- Accelerated expansion of tumor specific T-cells
- Sensitization of carcinoma cells to CTL killing
- Induction of immunostimulatory cytokines and chemokines

Observed effects are consistent with I-DASH inhibitors being able to induce broad T-cell activation and enhance recruitment of elements of the innate immune system

TMAC Linkers: Linkers Cleaved by Enzymes in the TME

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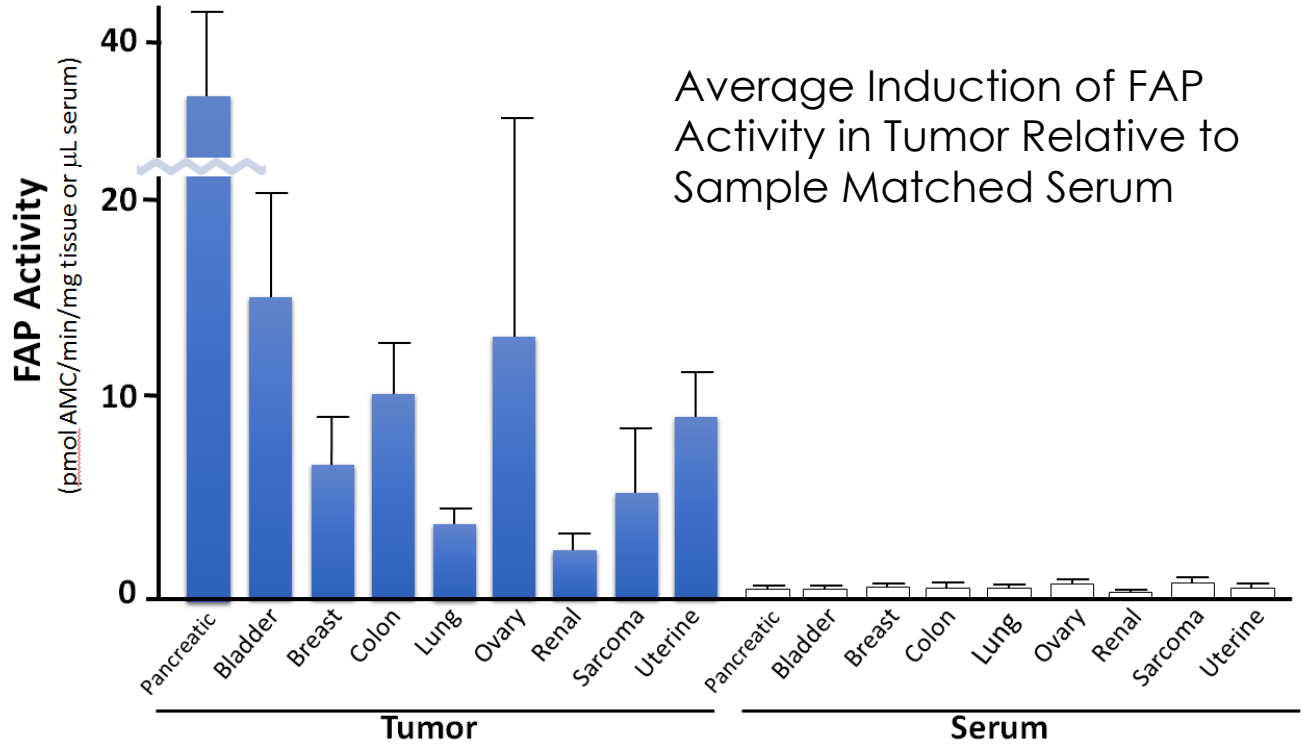
Fibroblast activation protein (FAPα) activity is elevated in human tumor samples relative to matched serum samples which exhibit only low activity.

ARI-3144 is a linker that shows differential enzymatic activity as a substrate for FAP in tumor microenvironment relative to serum.



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Potential Future Programmes: Exploiting a Range of ICP Targeting, Linkers and Warheads

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Range of targeting:

- Other immune-checkpoints and costimulatory receptors
- Bispecific targeting (e.g. PD-L1/LAG-3)

Range of linkers cleaved by tumour specific enzymes such as:

- MMP2, MMP9, MMP14
- Matriptase
- Legumain

Range of toxins that could synergise with the immune-checkpoint targeting:

- STING Agonist
- TLR7/8 Agonist
- Doxorubicin
- Proteasome Inhibitors
- AKT Inhibitors
- CDK Inhibitors

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Intellectual Property

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Two Prong Patent Strategy – Broad Monopolistic coverage of platform but with product-focused patent coverage to intended pipeline

- Targeted moieties: Claims cover, for example, checkpoints and costimulatory receptors, disease tissue types (i.e., tumor, inflammation), etc.
- Targeting moieties: Affimers and other scaffolded binders, antibodies and fragments, peptides, receptor traps, etc.
  - Includes claims to particular Affimer sequences as well humanized antibodies.
  - Includes bispecifics, etc.
- Linkers: Claims cover a range of enzyme substrate sensitivities, as well as a variety of spacer and self-immolative moieties as optional additions.
- Drug moieties: Broadly claimed, with sub-genus and species claims to classes such as innate inducers of immunity, chemotherapeutics, epigenetic agents, immunomodulators, etc.

Initial embodiment being developed based on PD-L1/I-DASH with FAP cleavable linker

Tumor Microenvironment – Activated Drug-Binder Conjugates, and Uses Related Thereto. US Patent Application Serial Number 62/680,300

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