AdAlta

i-body platform - superior versatility and tunability relative to classic scFv domains for CAR cell therapies

TIM OLDHAM
CEO
t.oldham@adalta.com.au

Disclaimer

Investment in AdAlta is subject to investment risk, including possible loss of income and capital invested. AdAlta does not guarantee any particular rate of return or performance, nor do they guarantee the repayment of capital.

This presentation is not an offer or invitation for subscription or purchase of or a recommendation of securities. It does not take into account the investment objectives, financial situation and particular needs of the investor. Before making any investment in AdAlta, the investor or prospective investor should consider whether such an investment is appropriate to their particular investment needs, objectives and financial circumstances and consult an investment advisor if necessary.

This presentation may contain forward-looking statements regarding the potential of the Company's projects and interests and the development and therapeutic potential of the company's research and development. Any statement describing a goal, expectation, intention or belief of the company is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercialising drugs that are safe and effective for use as human therapeutics and the financing of such activities.

There is no guarantee that the Company's research and development projects and interests (where applicable) will receive regulatory approvals or prove to be commercially successful in the future. Actual results of further research could differ from those projected or detailed in this presentation. As a result, you are cautioned not to rely on forward-looking statements. Consideration should be given to these and other risks concerning research and development programs referred to in this presentation.

Your small format alternative to scFv with greater versatility and tunability

Technology: AdAlta i-body Platform

Description: AdAlta i-bodies mimic the properties of natural single domain antibodies on human protein scaffolds. The small format (half the size of the traditional CAR binding domain) with long binding loops offers unique tumor antigen access, greater tunability of the immune synapse, and efficient multifunctional CAR cell creation. i-bodies may target antigens which are considered difficult or intractable for traditional antibodies and CAR constructs. *In vitro* proof of principle has been established.

Applications:

- CARs against novel targets (e.g. GPCRs)
- Dual and bi-specific CARs
- Antibody secreting CARs for tumor micro-environment modulation
- Example: [STRUGGLINGPROGRAM] under development by [COMPANYNAME] by [SCIENTIST].

i-bodies: sdAB-like molecules with engineered binding loops conferring unique binding properties

1

AdAlta **i-bodies** are combination of a human protein with unique long loop binding sites that mimic the structural features of the shark single domain antibody system

Human protein scaffold

Engineered target specific binding loops

2

AdAlta **i-body library** contains 10^{10} unique i-bodies. Each unique i-body has different binding loops

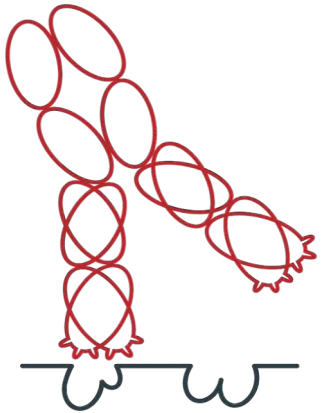
12-15kDa protein
90% smaller than MAb
50% smaller than scFv

i-bodies allow for high affinity, high specificity binding to targets that are intractable for traditional antibodies

Small Molecules

i-bodies have high specificity, avoiding off-target issues of small molecules

Antibodies



i-bodies are ~10% the size of human antibodies, capable of engaging sterically hindered cell membrane receptors

i-bodies

The i-body CDR structure confers unique binding capabilities, enabling unique epitope engagement and tunable pharmacology

Flexible, modular formats

CAR cell therapy

ADC/ radiotherapeutic

Bi-specific

Fc-fusion

PEGylation

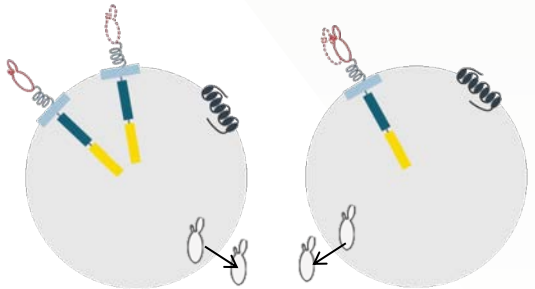
Naked i-body

i-bodies enable optimized CAR constructs (i-CARs)

Feature	Benefit
Small size	• Increased CAR gene cassette/vector capacity, efficient multi-functional CAR cell creation
Long CDR3 binding domain	• Access to unique tumor antigens/epitopes and TME modulating proteins in cancer tissue
Tunable binding	• Control of immune synapse (length + strength)
Robust conformation	• Natural stability delivers robust CAR binding domain and stable secreted molecules

Superior i-CAR products

- CARs against novel tumor antigens
- Dual and bi-specific CARs for enhanced specificity, reduced tumor escape and logic gated CARs
- Secreted antibodies to modulate TME

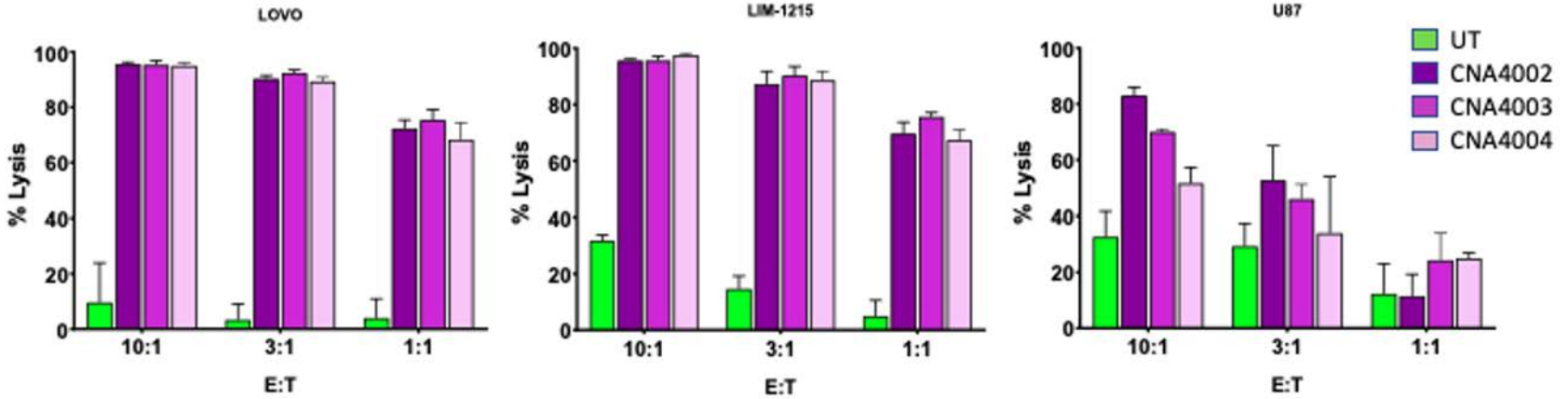


i-body-like sdAb CAR-T therapies are an emerging, validated approach

Group	Year	Stage	sdAb CAR Target	Available Results
AdAlta Ltd/Carina Biotech	***2022***	***Proof of principle (in vitro)***	***Undisclosed***	
Johnson and Johnson[1] Legend Biotech	2022	Market	anti-BCMA CAR-T (biepitopic)	P3 results for n=97 patients • ORR: 97.9%; sCR 78.4% • PFS: 77% (at 12 months) • Overall survival: 89%
Shenzhen Pregene Biopharma[2]	2021	Phase 1 (complete)	anti-BCMA CAR-T	P1 results for n=34 patients: • ORR: 88.2%; sCR/CR: 55.9% • PFS(at 12 months): 53.7%; Median PFS: 12.1 months • Overall survival at 12 months: 78.8%
PersonGen BioTherapeutics[3]	2020	Phase 1 (ongoing)	CD7	P1 results for n=3 patients: • All patients had increased IL-6 • PFS observed in 3/3; remission observed in 2/3 patients
PersonGen BioTherapeutics[4]	2022	Phase 1 (ongoing)	CD19	Not yet available
Legend Biotech[5]	2020	Phase 1 (ongoing)	Claudin 18.2	Not yet available
National Cancer Institute (USA)[6]	2022	Preclinical (mouse)	PD-L1	*In vitro* lysis of breast and liver tumor cells *In vivo* regression of liver tumor cells
Boston Children's Hospital[7]	2019, 2020	Preclinical (mouse)	PD-L1 EIIIB fibronectin	*In vivo* reduction of tumor growth and increased survival Improved activity of CAR-Ts secreting anti-CD47, anti-PD-L1 and anti-CTLA4 nanobodies

[1]https://www.clinicaltrialsarena.com/projects/carvykti-ciltacabtagene-autoleucel/
[2]https://ascopubs.org/doi/abs/10.1200/JCO.2021.39.15_suppl.8025
[3]https://ascopubs.org/doi/10.1200/JCO.2020.38.15_suppl.3026
[4]https://clinicaltrials.gov/ct2/show/NCT04691349?term=car-t+single+domain+antibody&draw=2&rank=1
[5]https://clinicaltrials.gov/ct2/show/NCT04467853
[6]https://www.cell.com/molecular-therapy-family/oncolytics/fulltext/S2372-7705(22)00032-8#secsectitle0020
[7]https://www.pnas.org/doi/10.1073/pnas.1817147116; https://pubmed.ncbi.nlm.nih.gov/32019780/

And we have done it: i-body enabled CAR-T (i-CAR-T) cells demonstrate *in vitro* cell killing[1]



Experimental details

- Cell lines: colorectal cancer (LOVO and LIM1215); glioblastoma (U87)
- CAR-T constructs: CNA4002/CNA4003/CNA4004 incorporate an i-body against a single target “X” and variable linker lengths
- Control: unmodified T cell (UT) that does not result in significant killing (lysis) of these cell lines
- i-CAR-T cells manufactured with 97% transduction (i-body CAR insertion) efficiency
- i-CAR-T cells included 60-70% CD4+ (helper) and 20-30% CD8+ (cytotoxic – killer) T cells

1. ASX Release 29 November 2021

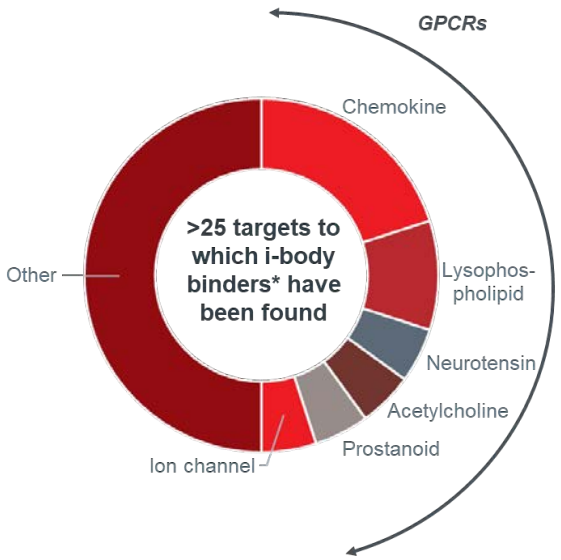
i-bodies can address multiple targets of interest for solid tumour CAR cell therapy

GPCRs are implicated in multiple cancer types, poorly addressed by antibody drugs

- ***i-bodies identified against at >10 GPCRs from >5 classes***

Other soluble and membrane bound targets are implicated in cancer or influence the tumour micro-environment

- ***i-bodies identified against >25 membrane bound and soluble protein targets including proteases, growth factor receptors, peptides, ECM proteins***



Example cancers where GPCRs are upregulated

Colorectal	Breast
HCC(liver)	Prostate
Pancreatic	Myeloma
Stomach	Melanoma
Bone	NSCLC/SCLC
Esophageal	Glioma
HNSCC	Cervical
Thyroid	Synovial
Ovarian	Neuroendocrine

Example GPCR families implicated in cancer

Adhesion	Glycoprotein hormone
Adreno	Lysophospholipid
Angiotensin	Orphan (many)
Calcitonin	Prostanoid
Chemokine	Proteinase activated
Frizzled	Somatostatin

Example other cancer relevant target classes

Upregulated	*TME modulating*
IGFR	PD-1
EGFR	PD-L1
MUC	CTLA-4
NKGD2	CD47

Experienced leadership from discovery through manufacturing, clinical and commercialisation

Board

Dr Paul MacLeman
Chair

Liddy McCall
Director (alt: Dr James Williams)

Tim Oldham, PhD
CEO & Managing Director

Dr Robert Peach
Independent Director

Dr David Fuller
Independent Director

Executive

Tim Oldham, PhD
CEO & Managing Director

Dallas Hartman, PhD
Chief Operating Officer

Claudia Gregorio-King, PhD *VP Clinical Product Development*

Mick Foley, PhD
Founding Chief Scientist

Michael Rasmussen
Consultant Medical Expert

Scientific Advisory Board

Brian Richardson
Drug discovery and development expert

Steve Felstead
Clinical development

John Westwick
Pulmonary drug discovery and development

Development team

12 staff (10 PhD's)

Skills in protein chemistry, i-body discovery, product development, pre-clinical development, clinical development

Your small format alternative to scFv with greater versatility and tunability

Technology: AdAlta i-body Platform

Description: AdAlta i-bodies mimic the properties of natural single domain antibodies on human protein scaffolds. The small format (half the size of the traditional CAR binding domain) with long binding loops offers unique tumor antigen access, greater tunability of the immune synapse, and efficient multifunctional CAR cell creation. i-bodies may target antigens which are considered difficult or intractable for traditional antibodies and CAR constructs. *In vitro* proof of principle is established.

Applications:

- CARs against novel targets (e.g. GPCRs)
- Dual and bi-specific CARs
- Antibody secreting CARs for tumor micro-environment modulation

AdAlta is currently fielding a number of active conversations.
Please contact t.oldham@adalta.com.au to confirm your next step with us.

AdAlta
next generation protein therapeutics

Contact:

Tim Oldham, CEO and Managing Director
enquiries@adalta.com.au
www.adalta.com.au

AdAlta

Appendix

Benefits of i-bodies over scFV for CAR targeting

	i-body	scFV
Natural monomer	+++	-
Stable - conformation	+++	+/-
Stable – thermal stability	++	++
Small size	12-15 kDa	25-30 kDa
Multivalent targeting	+++	-
Tuned affinity	+++	++
Tuned linkers	+++	+
Clinically validated	++	+++
Soluble – TME modifying	+++	+

AdAlta-Carina collaboration synergies

By joining forces, AdAlta and Carina access complimentary expertise to create a toolbox to address three main challenges facing solid tumour CAR-T therapies. AdAlta expands its pipeline and further validates the i-body platform.

Precision

Limited tumour-specific antigens – healthy tissue can be damaged

Incomplete expression of tumour-antigens – tumour can escape

AdAlta

i-bodies specifically designed to enable access to new, difficult antigens

Small size confers greater design flexibility, enabling bi-specific and dual CARs to enhance specificity

Performance

Tumour mass hard to penetrate for immune cells

carina biotech

Engineered Chemokine Receptor Platform directs CAR-T cells to and into solid tumours

Persistence

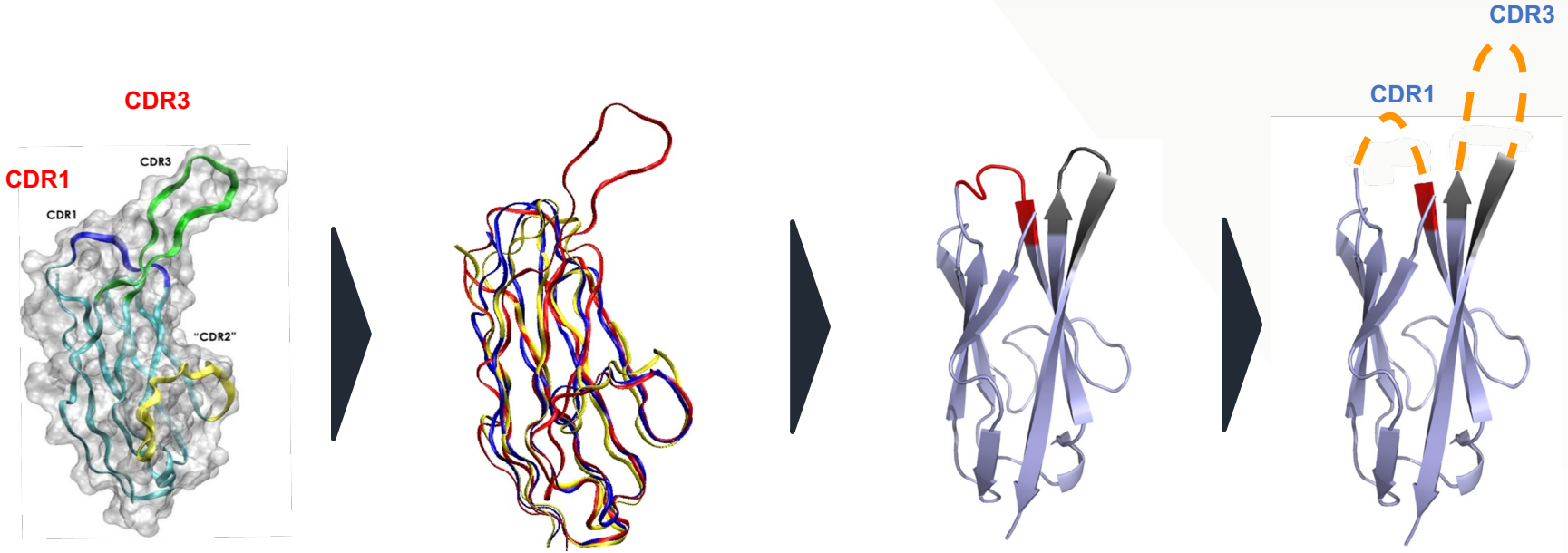
Tumour secretes molecules that suppress immune cell activity

carina biotech

Best practice manufacturing process (9 days, 90% efficiency) and Chemokine Receptor Platform make more robust, resilient CAR-T cells

Invention of i-bodies

i-bodies are built from a human NCAM domain 1 scaffold and randomized synthetic shark VNAR-like binding loops



Shark VNAR

Basic research on unique shark immune system …

Ribbon overlay*

… led to discovery that the i-set family of human proteins have the same scaffold structure …

hNCAM Domain 1

… leading to the choice of human NCAM domain 1 for the current scaffold …

i-body library

… and invention and patenting of i-bodies by adding randomized synthetic VNAR-like binding loops to NCAM-1

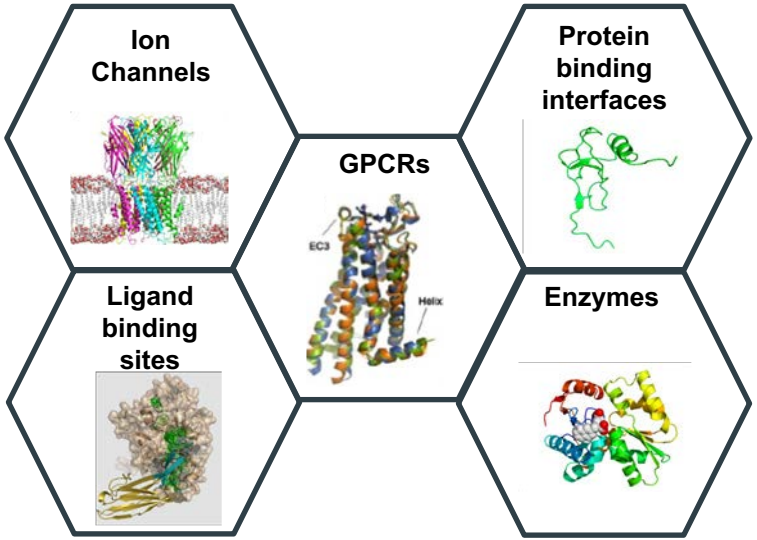
* Shark VNAR (red); human i-set immunoglobulins (yellow and blue)

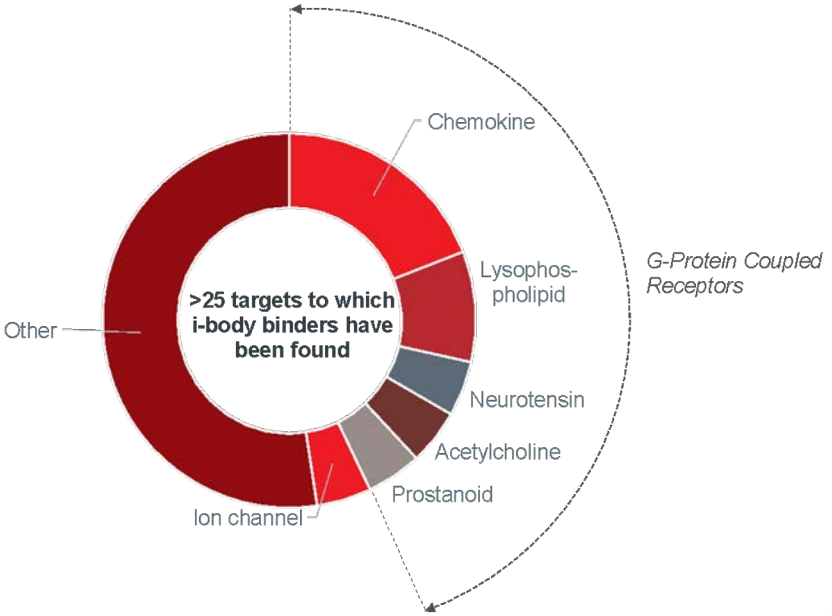
An immensely powerful drug discovery platform

i-body technology can enable a wide range of therapeutic and diagnostic products

Wide range of target classes

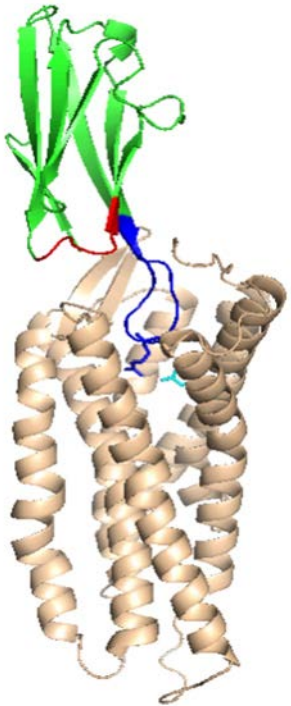
Small size, long loop of i-body can access unique epitopes

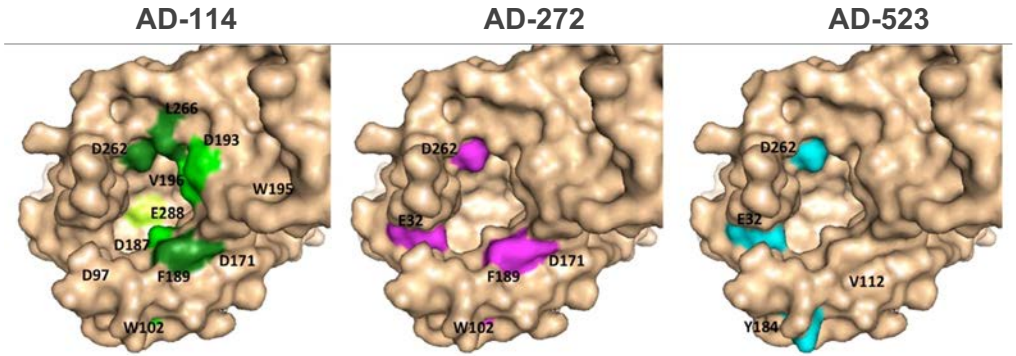




CXCR4 i-bodies demonstrate tunable pharmacology and functional biology

Three i-bodies with high affinity to CXCR4 and differing by only 2-3 amino acids have distinct epitope binding, different signaling and *in vitro* functional readouts





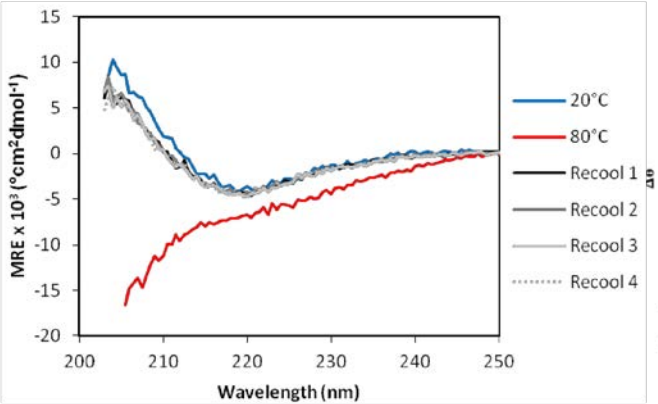
Affinity to CXCR4 (K_D/nM)	4.2	1.8	9.2
Inhibition of β-arrestin (IC_{50}/mM)	1.18	1.38	2.94
Inhibition of cAMP (IC_{50}/nM)	99	300	225
Inhibition of HIV entry (IC_{50}/nM)	131	838	349
Reduction of leaking and fibrosis in mouse laser CNV model	YES		NO

Griffiths et al, 2016; Fletcher et al, 2021 unpublished data (mouse laser CNV results)

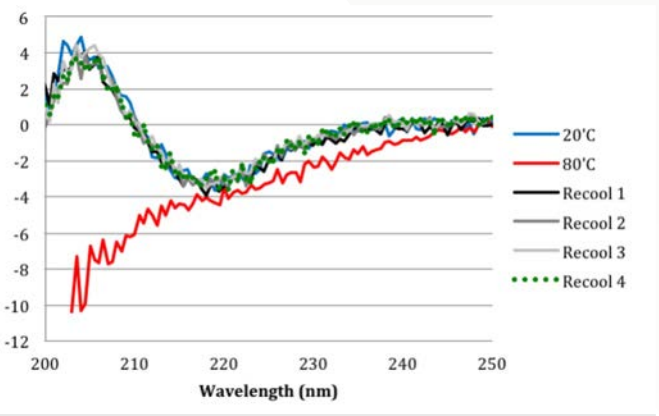
i-body stability: temperature cycling

i-body and shark IgNAR refolding (measured by circular dichroism) has been demonstrated following repeated temperature cycling to 80°C.

IgNAR



i-body



- **The i-body and IgNAR unfolds and then re-folds upon heating when measured by circular dichroism (CD) spectroscopy**
- At 20°C the secondary structure of the i-body and IgNAR is predominantly β-strand
- When heated to 80°C a predominantly random coil structure at the high temperature is present (red lines for both i-body and IgNAR) consistent with unfolding of the scaffolds
- Upon re-cooling to 20°C the i-body and IgNAR adopted a similar profile to that obtained prior to heating. Repeated heating-cooling cycles resulted in reproducible results, suggesting the proteins are very resistant to high temperatures and are able to refold following thermal denaturation

Griffiths et al, 2013 (IgNAR); AdAlta unpublished data (i-body)

Indicative i-body screening campaign