

**5 April 2022**

**ASX Announcement**

**ADALTA TO PRESENT AT INAUGURAL PAC PARTNERS HEALTHCARE CONFERENCE**

**MELBOURNE Australia, 5 April 2022:** AdAlta Limited (ASX:1AD) the clinical stage biotechnology company developing novel therapeutic products from its i-body platform is pleased to be presenting at the Inaugural PAC Partners Healthcare Conference, to be held in Sydney on 6 April 2022.

Dr Tim Oldham, CEO and Managing Director, will deliver a presentation entitled “Developing high value drugs for challenging diseases” that will showcase four human health needs that AdAlta’s i-body platform and product pipeline is addressing today:

- Traditional antibodies cannot address all diseases – AdAlta’s i-bodies are a differentiated drug discovery platform for difficult diseases;
- Idiopathic pulmonary fibrosis is a degenerative and fatal disease with no good treatment today – AdAlta’s lead product AD-214 could meet a desperate need for new approaches to this debilitating disease;
- Immuno-oncology drugs are revolutionising cancer outcomes, however not all patients respond – AdAlta and GE Healthcare’s granzyme B iPET imaging agent could help identify responders and non-responders early; and
- CAR-T cell therapy is providing new hope for patients with blood cancers who have exhausted all other options – AdAlta and Carina Biotech’s iCAR-T cell therapies aim to offer the same hope to patients with solid tumours.

The presentation will also set out experimental and other milestones for the remainder of 2022.

A copy of the presentation, together with an appendix containing previously announced supporting technical data is attached.

Authorised for lodgement by:

**Tim Oldham**

**CEO and Managing Director**

**April 2022**

## Notes to Editors

### About AdAlta

AdAlta Limited is a clinical stage drug development company headquartered in Melbourne, Australia. The Company is using its proprietary i-body technology platform to solve challenging drug targeting problems and generate a promising new class of single domain antibody protein therapeutics with the potential to treat some of today's most challenging medical conditions.

The i-body technology mimics the shape and stability of a unique and versatile antigen binding domain that was discovered initially in sharks and then developed as a human protein. The result is a range of unique proteins capable of interacting with high selectivity, specificity and affinity with previously difficult to access targets such as G-protein coupled receptors (GPCRs) that are implicated in many serious diseases. i-bodies are the first fully human single domain antibody scaffold and the first based on the shark motif to reach clinical trials.

AdAlta has completed Phase I clinical studies for its lead i-body candidate, AD-214, that is being developed for the treatment of Idiopathic Pulmonary Fibrosis (IPF) and other human fibrotic diseases for which current therapies are sub-optimal and there is a high unmet medical need. AdAlta has a second target in discovery research, also in the field of fibrosis and inflammation.

The Company is also entering collaborative partnerships to advance the development of its i-body platform. It has an agreement with GE Healthcare to co-develop i-bodies as diagnostic imaging agents against Granzyme B, a biomarker of response to immunooncology drugs, a program now in preclinical development. It also has a collaboration with Carina Biotech to co-develop precision engineered, i-body enabled CAR-T cell therapies to bring new hope to patients with cancer.

AdAlta's strategy is to maximise the products developed using its next generation i-body platform by internally discovering and developing selected i-body enabled product candidates against GPCRs implicated in fibrosis, inflammation and cancer and partnering with other biopharmaceutical companies to develop product candidates against other classes of receptor, in other indications, and in other product formats.

Further information can be found at: <https://adalta.com.au>

### For more information, please contact:

#### Investors

Tim Oldham, CEO & Managing Director  
Tel: +61 403 446 665  
E: [t.oldham@adalta.com.au](mailto:t.oldham@adalta.com.au)

#### Media

IR Department  
Tel: +61 411 117 774  
E: [jane.lowe@irdepartment.com.au](mailto:jane.lowe@irdepartment.com.au)

# Developing high value drugs for challenging diseases

*Tim Oldham PhD, CEO and Managing Director*  
Inaugural PAC Partners Healthcare Conference, 6 April 2022

## 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.

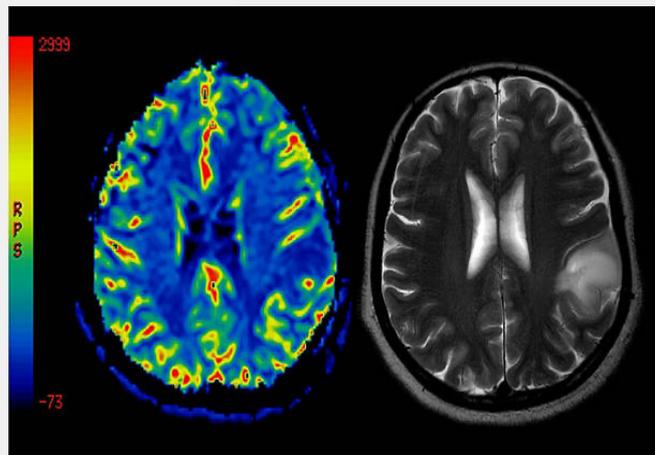
There is no guarantee that the Company's research and development projects and interests (where applicable) will receive regulatory approvals or prove to be commercially successful in the future. Actual results of further research could differ from those projected or detailed in this presentation. As 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.

## AdAlta at a glance

AdAlta's i-body platform is enabling a high-value product pipeline in two therapeutic areas of significant unmet medical need



A wholly owned fibrosis and inflammation pipeline



A co-developed immuno-oncology pipeline

## Four human health needs AdAlta is addressing today



### **Antibodies cannot do everything!**

*AdAlta's i-bodies are a differentiated drug discovery platform for difficult diseases*



### **Idiopathic Pulmonary Fibrosis: degenerative, fatal**

*AdAlta's AD-214 could meet a desperate need for new approaches for a debilitating disease*



### **Immuno-oncology drugs revolutionising cancer treatment ... for some**

*AdAlta and GE Healthcare's GZMB iPET imaging agent could identify responders early*



### **CAR-T cell therapy providing new hope ... for blood cancer patients**

*AdAlta and Carina's iCAR-T cells could offer same hope for patients with solid tumours*

Lead program: AD-214

## About | Idiopathic Pulmonary Fibrosis (IPF)

Scarring and stiffening of the lungs progressively and irreversibly reduces lung function

>300,000 people living with IPF; 40,000 people die from IPF every year

Only 3.8 years median survival after diagnosis

Two current therapies sell for \$3b per year ...

... despite having limited effectiveness and serious side effects

Burden of fibrotic lung disease following COVID-19 likely to be high

“Long COVID” is a developing issue – further increasing the need for better anti-fibrotic drugs.\*

\* PM George, et al, “Pulmonary fibrosis and COVID-19: the potential role for antifibrotic therapy”, Lancet published online May 15, 2020.



## AD-214 | Completed Phase I, preparing superior inhalation format for Phase II

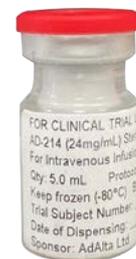
### Phase I intravenous (iv) clinical study successfully completed<sup>1</sup>

- AD-214 (iv) is well tolerated in single and multiple doses
- Target (CXCR4) binding observed well beyond clearance from blood
- Preclinical animal data supports potential iv efficacy

### Direct lung delivery (inhalation) of AD-214 could be a superior format for IPF<sup>3</sup>

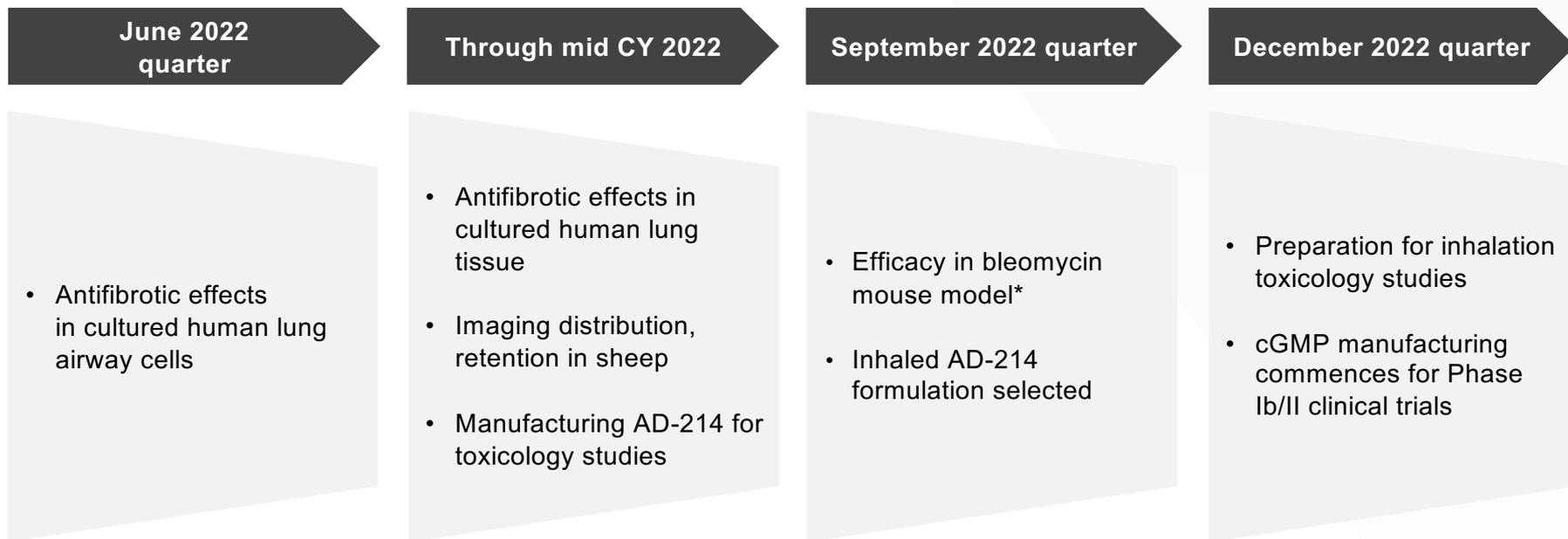
- PET imaging shows rapid liver distribution (reduced bioavailability) – direct lung delivery could significantly reduce dose, costs
- At home inhalation far more flexible and convenient than iv infusions in clinic
- Preclinical development of inhaled formulation well advanced

Drug substance manufacturing secured for next clinical studies<sup>2</sup> – delivery mid 2023



Next clinical studies to commence second half 2023

## Inhaled AD-214 | Milestones and opportunities in 2022

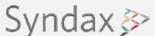


### Aim of pre-clinical studies

1. Demonstrate nebulised AD-214 can reach lower airways of sheep lungs (similar to human)
2. Demonstrate that AD-214 reaching the lower airways is retained in fibrotic tissue (bleomycin mice, sheep, cultured lung tissue)
3. Demonstrate AD-214 delivered to fibrotic tissue can moderate disease progression (bleomycin mice, cultured lung tissues and cells)

**Preclinical success anticipated to accelerate existing partnering discussions**

## AD-214 | Valuable IPF partnering options as early as Phase I

Date	Licensee	Licensor	Transaction Terms	Clinical Phase
Nov-21			US\$254m Upfront	2 (Ready)
Nov-21			€320m Milestones	2 (Ready)
Sep-21			US\$152m Upfront +US\$602m Milestones	2 (Ready)
Nov-19			US\$390m Upfront +US\$1b Milestones	2
Feb-21			US\$517.5m Milestones	1
Jul-19			€45m Upfront +€1.1b Milestones	1

## AD-214 | Multiple indication extension options in other forms of fibrosis

- Preclinical tissue and animal models show that AD-214 may improve fibrosis across a range of fibrotic diseases and cancer
- **Unique formulations for different indications enable multiple potential partnering deals**
- **Each additional indication could address multiple markets with US\$ billion potential**



### Lung

IPF/ILD

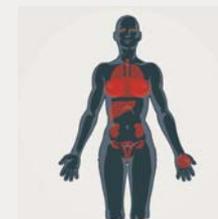
>US\$3b



### Eye

Wet-AMD

>US\$15b



### Cancer

23 different cancers, I/O

>US\$1b ea



### Kidney

RENAL FIBROSIS

>US\$10b



### Liver

NASH & CIRRHOSIS



### Skin

SCLERODERMA

\* Subject to development of a satisfactory, improved intravenous formulation.

## Co-developed immuno-oncology assets

## About | Immuno-oncology (I/O) PET imaging

Immuno-oncology (I/O) drug market is worth US\$95 billion<sup>1</sup> ...

... but only 20-40% of patients respond<sup>2</sup> to therapy

Granzyme B (GZMB) is produced by immune cells to kill cancer: potential biomarker of I/O drug activation of the immune system

PET imaging GZMB could help identify early who will – and won't – respond to I/O drugs

The PET imaging agent market is valued at US\$6.4billion<sup>3</sup>

Largest products >US\$400m<sup>4</sup>

## GZMB iPET imaging asset | GE Healthcare co-development collaboration

**AdAlta and GE are co-developing a GZMB i-body PET imaging (iPET) asset to evaluate the effectiveness of immuno-oncology drugs**

### Revenue generative pipeline asset

- AdAlta earns research fees, development and sales milestone payments and royalties on product sales
- A\$2.27 million revenue\* earned to December 2021
- GZMB iPET asset could generate royalty revenue sooner than a therapeutic due to shorter diagnostic development timelines

### Current status

- Panel of GZMB specific i-bodies identified
- Pre-clinical proof of concept studies underway
- Manufacturing development underway



**Co-developed iPET imaging immuno-oncology asset.**

## About | CAR-T therapies

CAR-T therapies are providing new hope for patients with cancer who have failed all other options

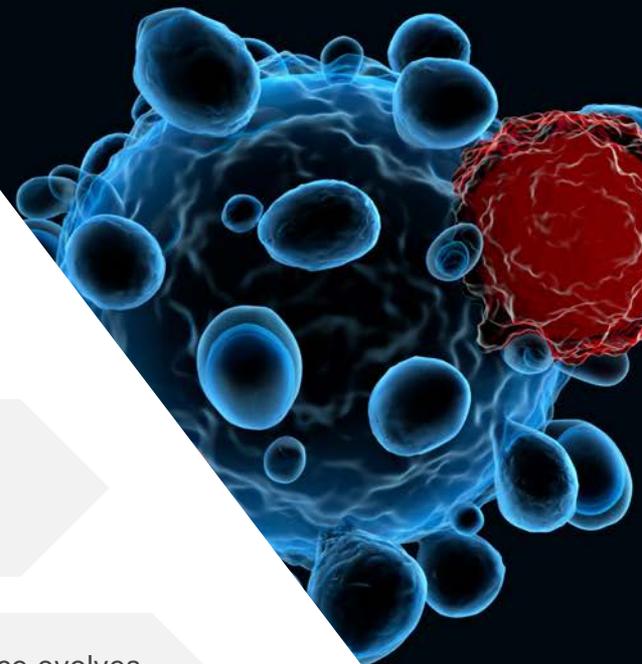
Therapy involves removing immune cells from blood and re-engineering them so they “see” cancer as a pathogen

Already 6 FDA-approved CAR-T therapies ... but so far only for blood cancers

>\$US1 billion earned by CAR-T therapy products in 2020

\$US20.3 billion<sup>1</sup> revenue forecast for 2028 as more products are commercialised, science evolves

Solid tumours to account for >50% of CAR-T revenues by 2030<sup>2</sup>



## iCAR-T assets | Carina co-development collaboration

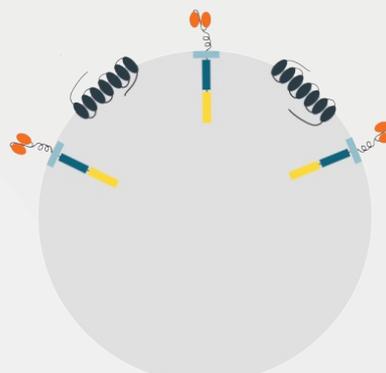
AdAlta and Carina are combining i-bodies and a world class CAR-T platform to create iCAR-Ts that could offer improved precision, performance and persistence

Further expands AdAlta's pipeline in an attractive deal space

- Collaborating on up to five tumour targets
- Sharing costs to pre-clinical proof of concept (in mice)
- Jointly own resulting products: ready for partnering or further development

### Current status

- i-body enabled CAR-T (iCAR-T) cells have been successfully generated by Carina and demonstrate *in vitro* cell killing (lysis)<sup>1</sup>
- First target A selected, iCAR-T cells incorporating i-bodies against Target A being built



The diagram shows a circular cell surface with several receptors. Each receptor consists of a blue stem and a yellow tip. Some receptors have orange structures attached to their tips, while others have black, coiled structures. This represents the interaction of i-bodies with a CAR-T platform.

 AdAlta  
next generation protein therapeutics

 carina  
biotech

**Co-developed iCAR-T  
immuno-oncology asset**

1. .ASX release 29 November 2021

## I/O assets | Milestones and opportunities in 2022



Through mid CY  
2022

Through mid CY  
2022

September 2022  
quarter

December 2022  
quarter

- GZMB iPET imaging agent preclinical proof of concept

- Initial *in vitro* cancer cell killing screening assays completed for iCAR-T target A

- iCAR-T targets B and C selected

- iCAR-T Target A
- *in vitro* cancer cell killing assays complete
  - *in vivo* proof of concept studies commenced

## Corporate snapshot

### Key financial details (31 March 2022)

ASX code	1AD
<b>Market capitalisation</b>	<b>A\$22.94m</b>
Share price (12 month closing range)	A\$0.073 (\$0.071 - 0.183)
12 month return	(52)%
Ordinary Shares (daily volume)	314,184,746 (308,506)
Unlisted Options	14,184,060
<b>Cash (31 Mar 2022)</b>	<b>A\$10.54m</b>

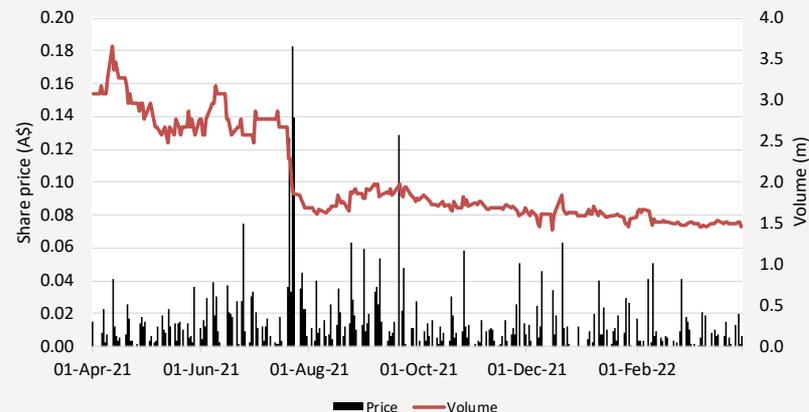
### Major shareholders (31 March 2022)

	%
Yuuwa Capital LP	17.2
Platinum Asset Management	15.7
Meurs Holdings Pty Ltd	6.4
Radiata Super Pty Ltd	3.5
Sacavic Pty Ltd	3.1
<i>Other (1,567 total holders)</i>	<i>54.1</i>
<b>Total</b>	<b>100%</b>

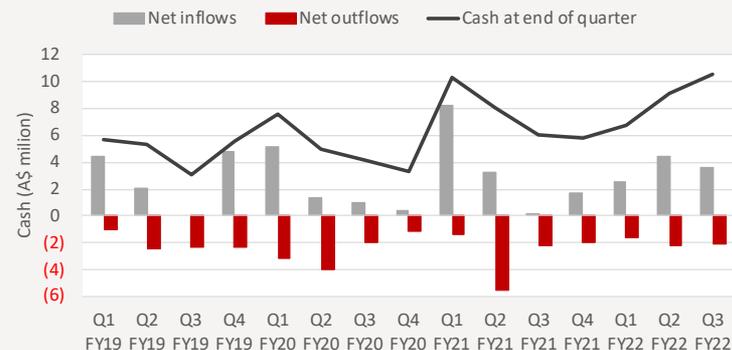
### Analyst Coverage

Pitt Street Research
Lodge Partners (pending)

### Share price performance (last 12 months)



### Quarterly cash flows (A\$ million)



# Investment proposition



**i-body platform to create value**



**Fibrosis/inflammation**  
**Lead asset advancing to Phase II**  
 >\$3b market potential in first indication<sup>1</sup>

**Discovery initiated on 2<sup>nd</sup> target**



**Immuno-oncology**  
**2 x co-development collaborations to leverage platform**

- ✓ GE Healthcare: \$6b PET market<sup>2</sup>
- ✓ Carina Biotech: \$20b CAR-T market<sup>3</sup>



**Leading expertise**



**Clear vision for growth through pipeline expansion**



**Regular near-term news flow**

1. GlobalData, Idiopathic Pulmonary Fibrosis Opportunity Analysis and Forecasts to 2029, November 2020 2. 2027 forecast by Global Industry Analysts, Imaging Agents: Global Market Trajectory and Analytics, April 2021 3. 2028 forecast by Grandview Research, "T-cell Therapy Market Size, Share & Trends Analysis" Feb 2021

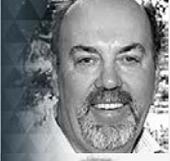
**Contact:**

Tim Oldham, CEO and Managing Director  
[enquiries@adalta.com.au](mailto:enquiries@adalta.com.au)  
[www.adalta.com.au](http://www.adalta.com.au)

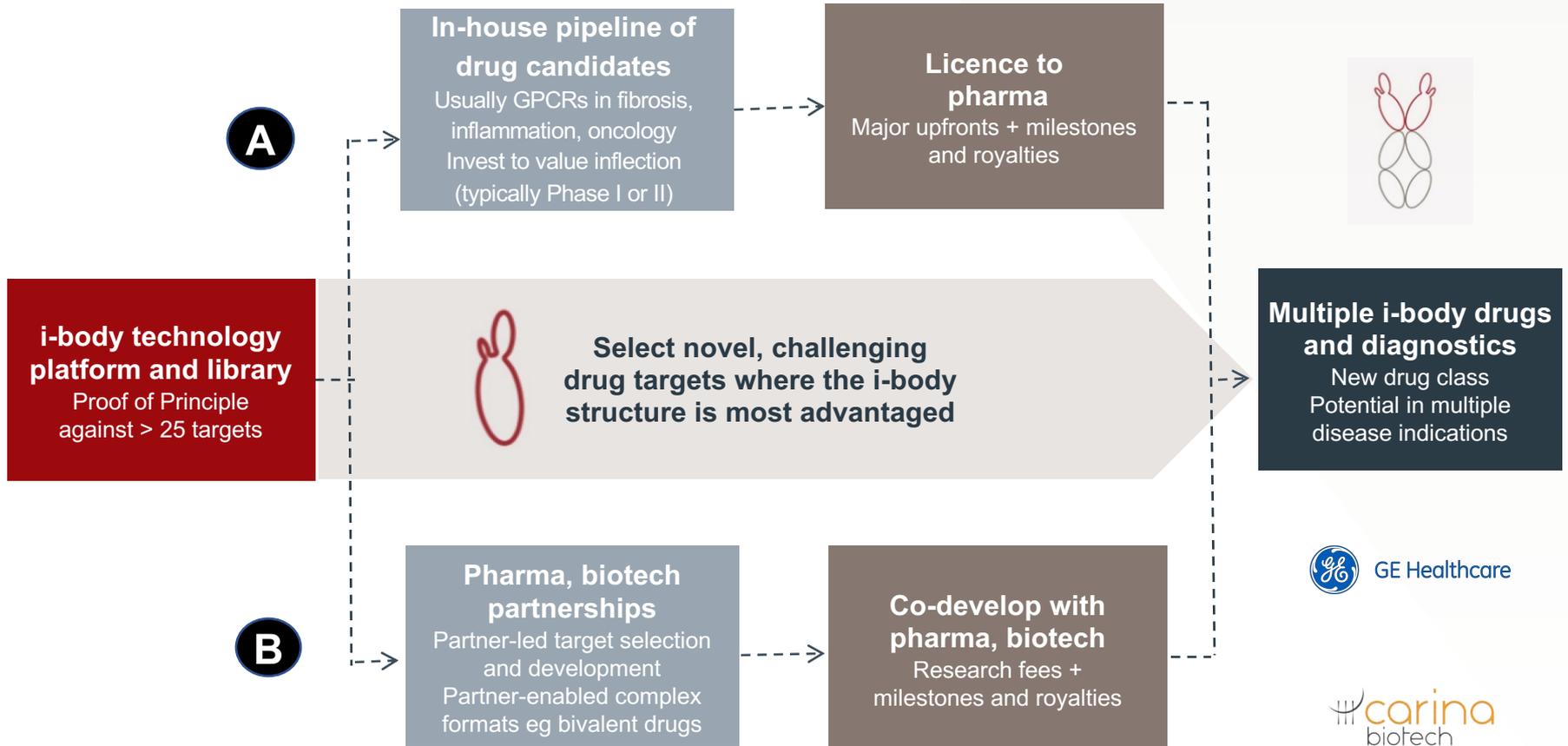
# Appendix: Company overview

## Industry experienced leadership and advisors

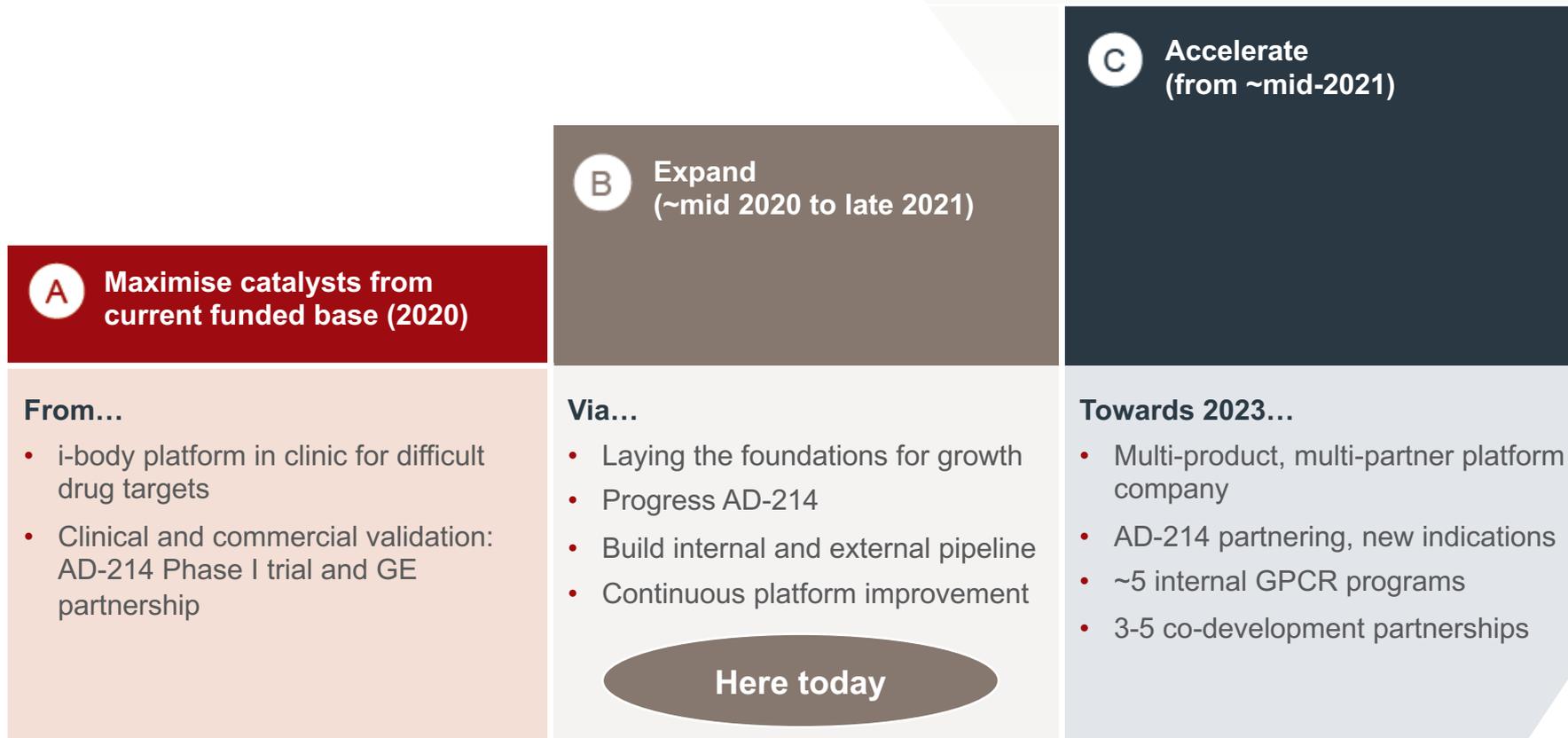
Team with experience from discovery through manufacturing, clinical and commercialisation

Board	Executive	Scientific Advisory Board
 <p><b>Dr Paul MacLeman</b> <i>Chair</i></p>  	 <p><b>Tim Oldham, PhD</b> <i>CEO &amp; Managing Director</i></p>  	 <p><b>Brian Richardson</b> <i>Drug discovery and development expert</i></p> 
 <p><b>Liddy McCall</b> <i>Director (alt: Dr James Williams)</i></p>  	 <p><b>Dallas Hartman, PhD</b> <i>Chief Operating Officer</i></p>  	 <p><b>Steve Felstead</b> <i>Clinical development</i></p> 
 <p><b>Tim Oldham, PhD</b> <i>CEO &amp; Managing Director</i></p>  	 <p><b>Claudia Gregorio-King, PhD</b> <i>VP Clinical Product Development</i></p>  	 <p><b>John Westwick</b> <i>Pulmonary drug discovery and development</i></p> 
 <p><b>Dr Robert Peach</b> <i>Independent Director</i></p> 	 <p><b>Mick Foley, PhD</b> <i>Founding Chief Scientist</i></p>  	<p><b>Development team</b></p>
 <p><b>Dr David Fuller</b> <i>Independent Director</i></p>  	 <p><b>Michael Rasmussen</b> <i>Consultant Medical Expert</i></p>  	<p>13 staff (10 PhD's)</p> <p>Skills in protein chemistry, i-body discovery, product development, pre-clinical development, clinical development</p>

# Our strategy



# AdAlta has successfully transitioned to the expansion phase of our growth plan\*



\* March 2020 strategy

## Summary: our platform and programs



**Building out pipeline** with additional internal and external programs: targeting 10 by 2023



### Immuno-oncology: two co-development collaborations



1. GZMB PET imaging agent with **GE Healthcare**: US\$6.4b PET imaging agent market
2. i-body enabled CAR-T with **Carina Biotech**: US\$20b market by 2028



### Fibrosis/inflammation:

1. **Lead asset AD-214** preparing for Phase II clinical trial
2. Second target in discovery



**i-body platform:** powerful drug discovery tool for creating drugs against challenging diseases underserved by traditional antibodies

# An expanding pipeline of i-body enabled products



\* Target #3 may be replaced by third Carina target, delivering shorter time to proof of concept

# Appendix: i-bodies

## i-bodies: next generation protein therapeutics

i-bodies are built on human protein scaffolds to mimic the properties of single domain antibodies

### Generation of the i-body

1



**Shark** antibody binding domain with unique long loop

2

Two binding loops are engineered onto the human protein. These enable tight binding to the drug target and have a therapeutic effect



A **human** protein that is structurally equivalent to the shark single domain antibody is the backbone or scaffold protein of the i-body

3



Each unique i-body has different binding loops. AdAlta's i-body library has  $10^{10}$  unique i-bodies

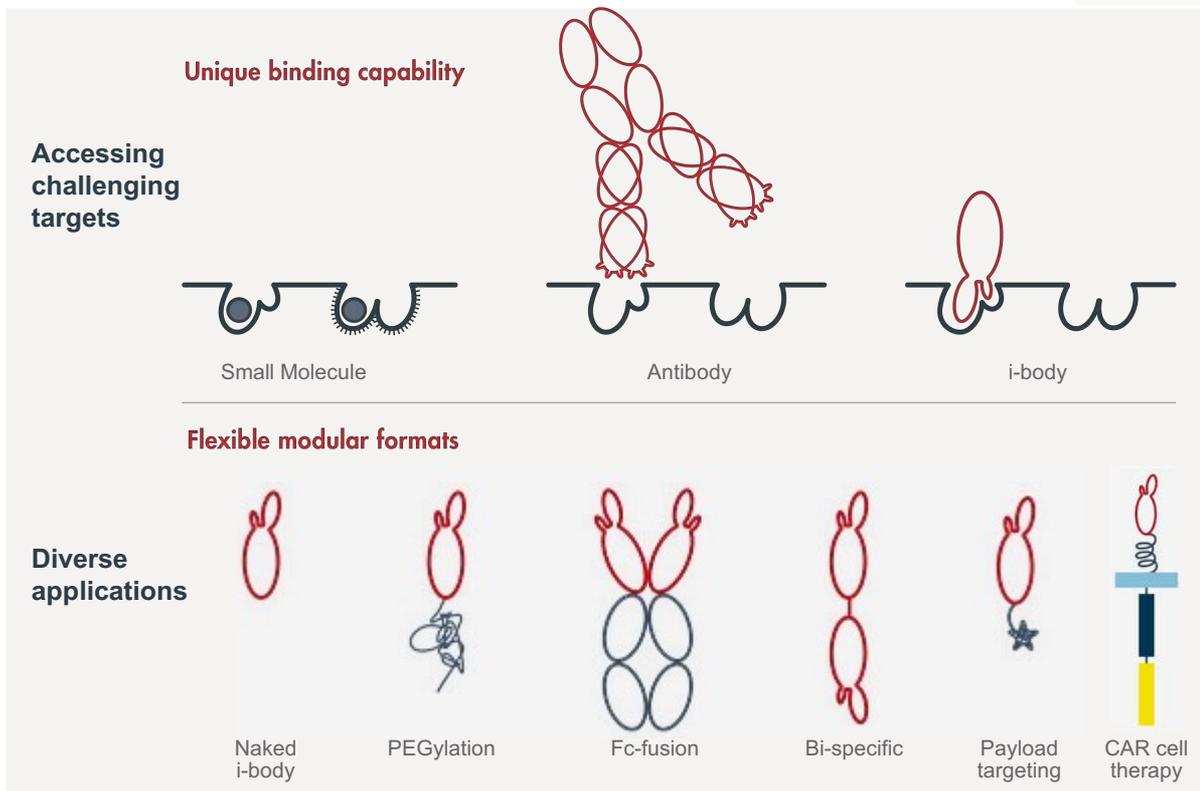
**AdAlta i-body** is the combination of a human protein that mimics the structural features of the shark antibody with unique long loop binding sites

The long CDR3 loop of the i-body confers exceptional targeting and binding properties, providing therapeutic access to drug targets that have evaded traditional monoclonal antibodies

Drug targets include G-protein-coupled receptors (GPCRs), currently the most heavily investigated class of drug targets in the body

## What is the i-body advantage?

All the selectivity and specificity of antibodies with greater versatility and tunability



### Small size, flexible binding domain

Confers unique binding capability for targets challenging traditional antibodies; enables modular drug design across diverse applications

### Minimising off-target side effects

Unique binding capability potentially allows greater selectivity and specificity, tunable affinity

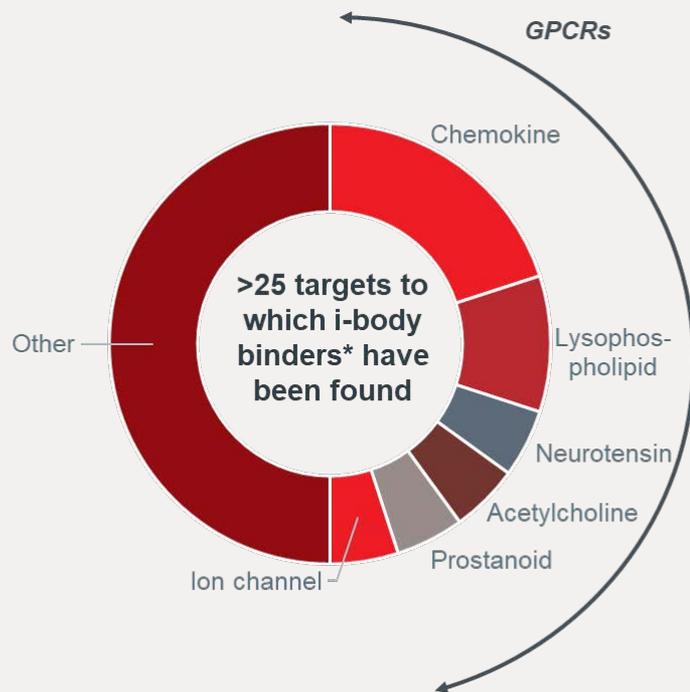
### Multiple drug administration routes

Amenable to multiple administration routes (e.g. injection, inhalation and topical)

### Robust

Resilient to pH and temperature cycling

## An immensely powerful drug development platform



### Demonstrated i-body platform capability

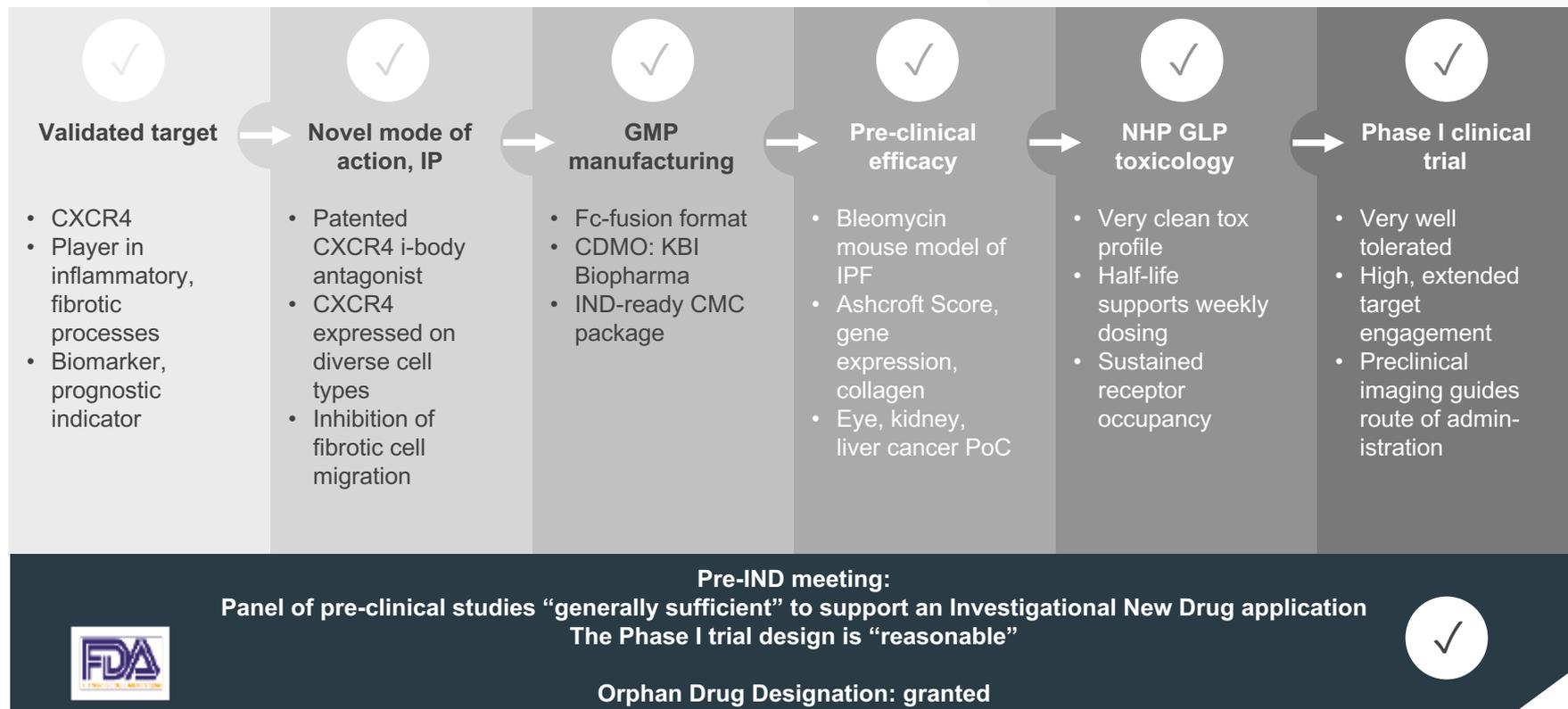
- G-protein coupled receptors (GPCRs)
  - Fibrosis, inflammation, oncology
- Diagnostics (PET tracers; cancer imaging)
  - Chimeric antigen receptor (CAR) cell therapy

**GPCRs are the most heavily investigated class of drug today and 80% of GPCR targets are yet to be effectively exploited**

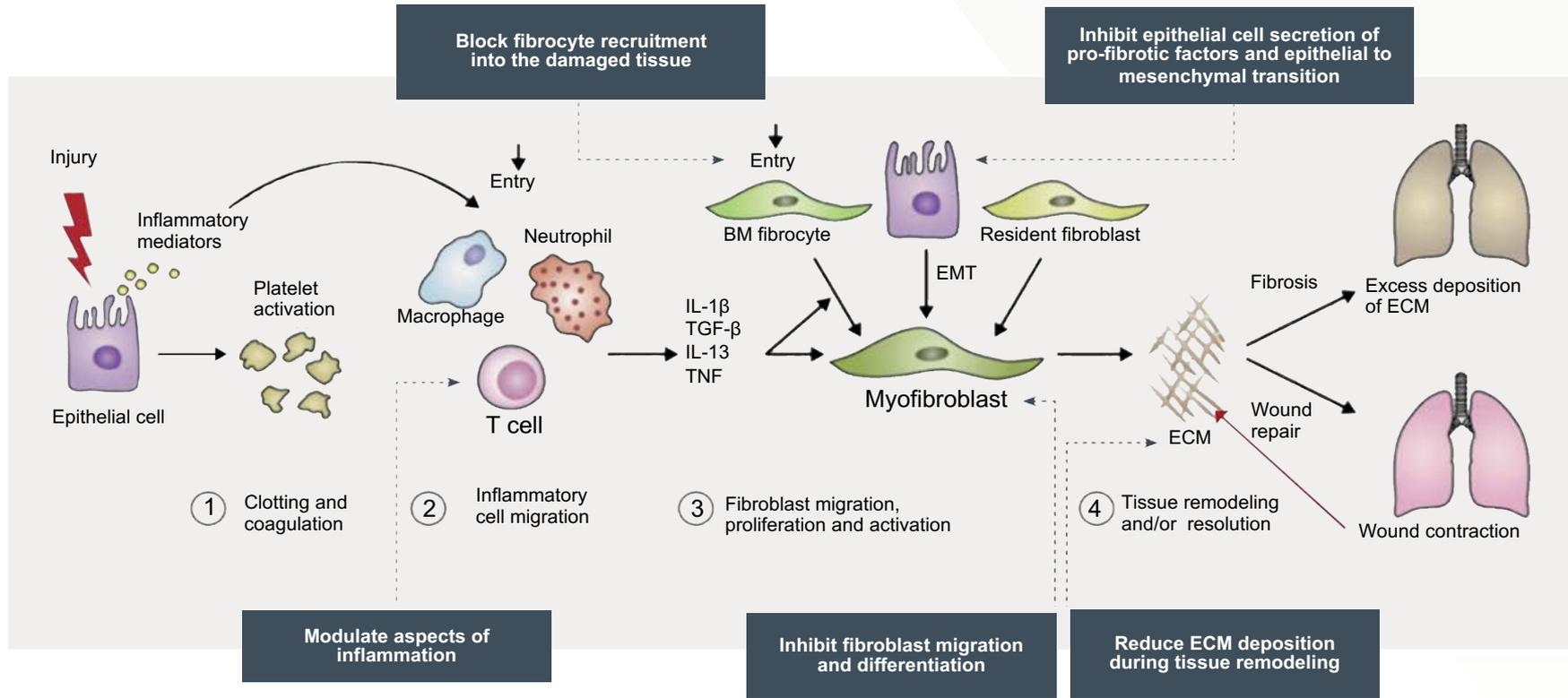
\*Includes both i-body and VNAR/IgNAR formats

# Appendix: AD-214

## AD-214: development summary



# AD-214 inhibits key features of the fibrogenic pathway with novel MOA



# AD-214: first in class treatment for fibrosis

AD-214's initial focus is IPF

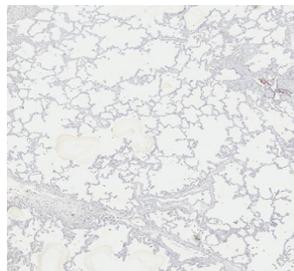
**First-in-class** (novel mode of action) treatment

Targets a receptor called **CXCR4**

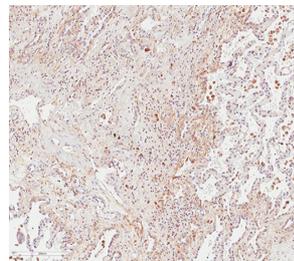
Initial focus is **Idiopathic Pulmonary Fibrosis (IPF)**, one of a group of **Interstitial Lung Diseases (ILDs)**

**Blocking CXCR4 reduces fibrosis** in animal models

**Human Lung Tissue**



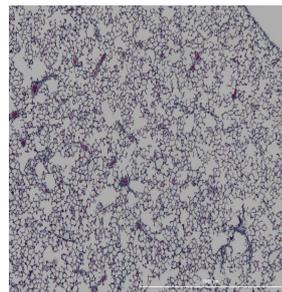
Normal



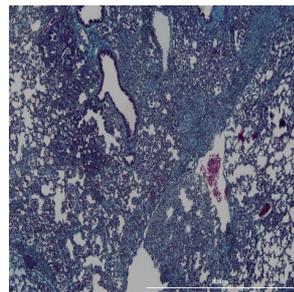
Diseased

*Brown stain shows increased amount of CXCR4 in fibrotic lung tissue*

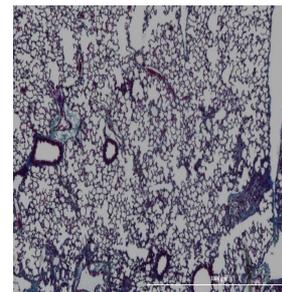
**Mouse model of lung fibrosis**



Normal mouse lung tissue



IPF mouse lung tissue\*

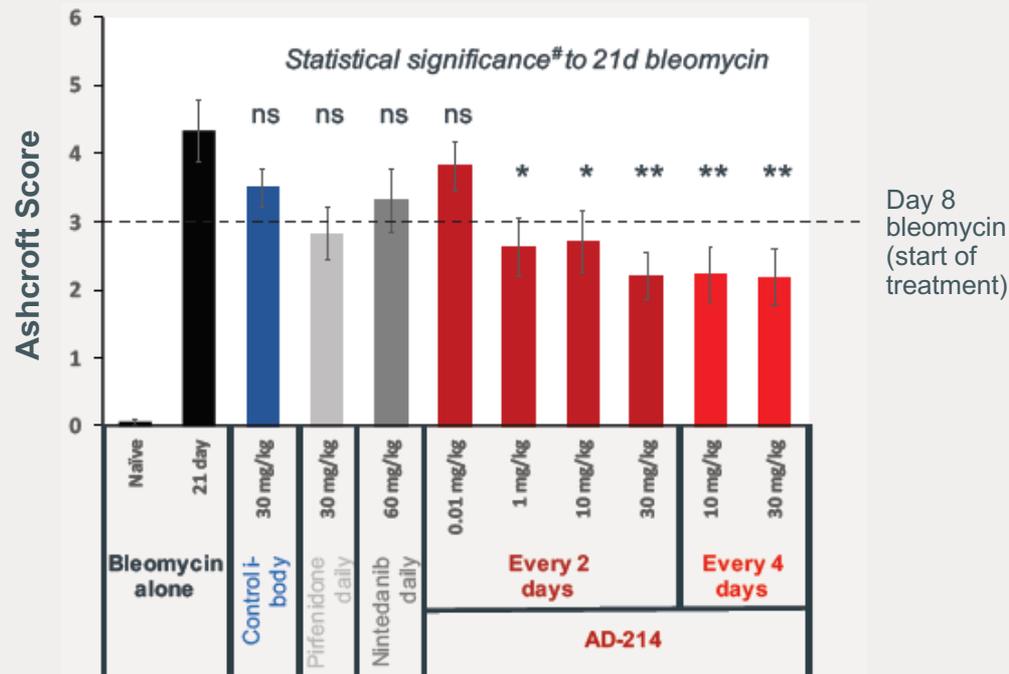


IPF mouse lung tissue + AD-214\*

*Purple stain shows amount of collagen (fibrosis)*

\* IPF tissue images taken 21 days after bleomycin (BLM) was administered to induce fibrosis; mouse treated with AD-214 received 10 mg/kg AD-214 every 4 days from day 8 after bleomycin administration.

## AD-214 induced reduction in progression of fibrosis in mouse bleomycin model



**AD-214 reduced Ashcroft Score with statistical significance compared to bleomycin treated mice at:**

- 1-30mg/kg every second day
- 10-30mg/kg every fourth day

**Wide range of dosing regimens can be used to test efficacy**

- 10mg/kg every second day exhibited effectiveness by most study parameters
  - Human equivalent dose: 1mg/kg (estimated)

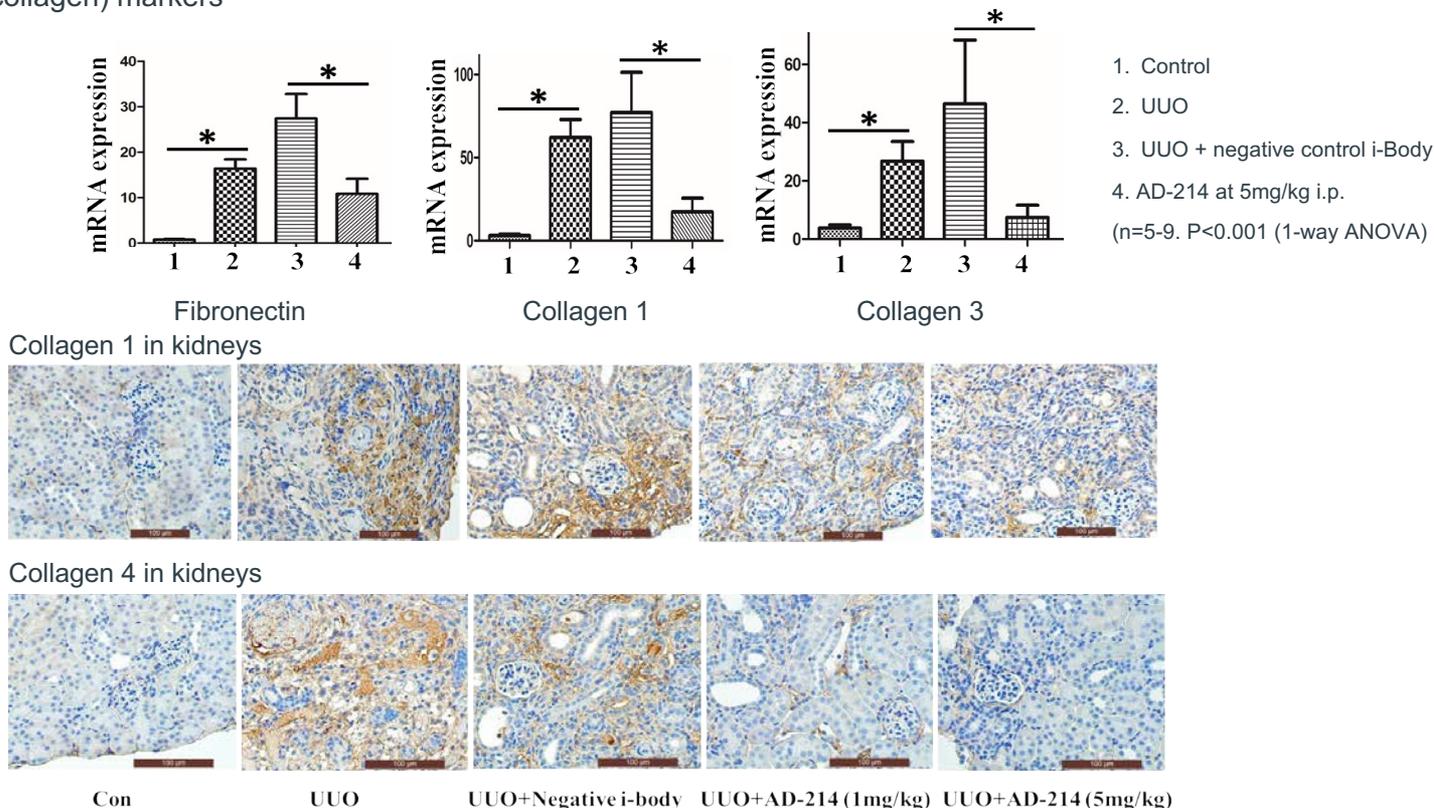
**AD-214 efficacy demonstrated in gold standard IPF disease model**

**Supportive of potential human therapeutic window beginning as low as 1mg/kg**

## AD-214 attenuates renal damage induced by unilateral ureteral obstruction

UUO induces an increase in Fibronectin, Col1 and Col3 gene expression and protein deposition in murine kidneys.

1 and 5mg/kg AD-214 by intraperitoneal injection every two days for 14 days to mice with UUO decreases gene expression of key extracellular matrix (collagen) markers



## NHP GLP toxicology: AD-214 safe

### 3 non-human primate studies completed Good Laboratory Practice (GLP) study to evaluate safety and toxicology

10mg/kg, 30mg/kg and 100mg/kg multiple doses over four weeks plus recovery (human equivalent dose 32mg/kg)

AD-214 well tolerated with no deaths, no AD-214-related clinical signs, no changes in a panel of clinical observations:

- body weight
- ophthalmoscopy
- blood pressure
- electrocardiography
- respiratory function
- neurological function
- coagulation
- urinalysis
- organ weight
- macroscopic and microscopic findings

Minor, transient, completely reversible increase in total white cell and circulating CD34+ cells

Small, transient, completely reversible decrease in serum total protein and albumin at highest dose only (100 mg/kg)

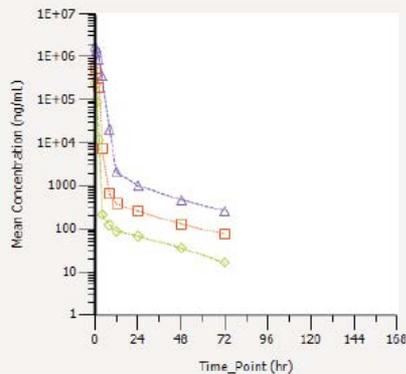
**Tox study results were in line with expectations and in keeping with previous studies**

**No major organ toxicity has been observed on repeat dosing at high doses  
No suggestion of off-target toxicities**

# Non-human primate GLP toxicology: Phase I dose justification

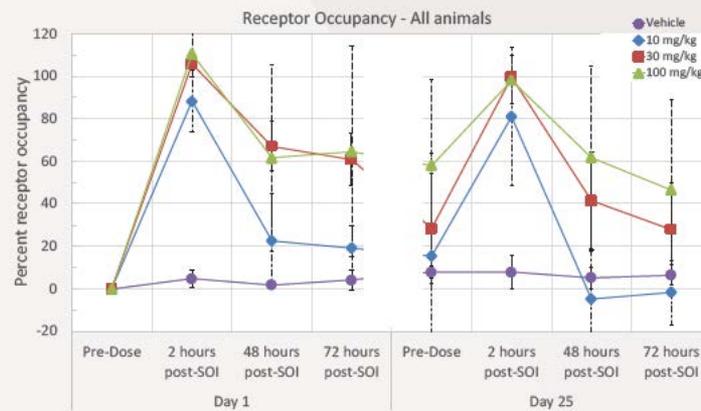
## Pharmacokinetics

- Elimination half-life 22-29h
- Human equivalent: ~71h (estimate)
- AD-214 available for >3 days



## Pharmacodynamics

- >60% receptor occupancy\* for 72h at >30mg/kg
- Human equivalent: ~10mg/kg (estimate)
- High receptor binding for >3 days



Supportive of human therapeutic dose window including 10mg/kg intravenously, weekly or every second week

# Intravenous AD-214 Phase 1 clinical and pre-clinical imaging programs

The Phase 1 program has demonstrated the safety and target engagement of intravenous AD-214 in healthy volunteers

## Phase 1 protocol in healthy volunteers - COMPLETE

<p><b>Part A</b></p> <p><b>Single iv dose, healthy volunteers (HV SAD)</b></p> <p>42 participants, 7 cohorts 0.01-20 mg/kg dose</p> 	<p><b>Part B</b></p> <p><b>Multiple ascending iv dose, healthy volunteers (HV MAD)</b></p> <p>8 participants 3 x 5 mg/kg (every 2 weeks)</p> 	<p><b>Objectives of Phase 1 Part A and B:</b></p> <ul style="list-style-type: none"> <li>• Top-line safety data</li> <li>• Explore optimal dosing intervals</li> <li>• Support FDA IND applications for further studies in all CXCR4 indications</li> </ul>
<p><b>PET imaging*</b></p>		

### Pre-clinical

**Development of RL-AD-214 for PET imaging – complete**

#### Distribution and efficacy studies

Intravenous and inhaled administration  
Healthy and IPF disease models (mouse and large animal)

### Clinical (future)

**Single and multi-dose in fibrotic diseases**

Open label with standard of care\*\*



### Objectives of PET imaging program:

- Effect of elevated lung CXCR4 on distribution of AD-214
- Correlation of AD-214 distribution with efficacy
- Explore CXCR4 expression as potential biomarker
- Safety of AD-214 in combination with standard of care\*\*

\* Supported by a Biomedical Translational Bridge grant from Medical Research Future Fund and MTPConnect

\*\* Includes pirfenidone, nintedanib or non-pharmacologic intervention.

## Intravenous AD-214 Phase I healthy volunteer results

Intravenous AD-214 is well tolerated in single doses to 20 mg/kg and multiple doses to 5 mg/kg\*

### AD-214 molecule is well tolerated in single and multiple iv doses (see Appendix for more detail)\*

- No dose limiting toxicities or adverse events of clinical concern in single doses to 20 mg/kg
- Moderate infusion related reactions (IRRs) in 3 participants (2 drug, 1 placebo) receiving multiple 5mg/kg doses
  - Rapidly resolved at end of infusion
  - *Appear formulation related*
- No concerning clinical laboratory results, no adverse liver or other organ function detected
- *HREC approved progressing to 10 mg/kg*

### AD-214 clearly engages the target CXCR4 receptor *in vivo*\*

- Dose dependent changes in biomarkers of CXCR4 engagement observed
- High and extended duration of receptor occupancy on circulating T cells
- *Biomarker response consistent across multiple doses at 5 mg/kg – no evidence of tolerance*

### AD-214 iv pharmacokinetics are dose proportionate\*

- Peak and total AD-214 exposure increases in a dose proportionate or more manner to 20 mg/kg, consistent across multiple doses at 5 mg/kg
- Elimination half-life  $44 \pm 15$  hours at 20 mg/kg
- *No evidence of tolerance or drug induced clearance*
- *Rapid distribution from plasma observed at all doses, consistent with rapid increase/saturation of receptor occupancy and preclinical imaging*

\* Multiple dose data subject to database lock and full statistical analysis; receptor occupancy data only available to 4 hours after end of third infusion; antidrug antibody data only available to 14 days after second infusion (pre third infusion)

## Intravenous AD-214 Phase I healthy volunteer study: safety findings

### Single iv doses to 20 mg/kg (42 participants)

- **No dose limiting adverse events**
- **No serious adverse events**
- **No concerning clinical laboratory results**
- **Dose escalation steps completed without concern**
- **Adverse events (AEs) were non-concerning**
  - Predominantly mild
  - Three Grade 2 (moderate) AEs

### Multiple iv doses 5 mg/kg (8 participants)

- **No dose limiting adverse events**
  - Safety Management Committee and Human Research Ethics Committee approved progression to 10 mg/kg
- **No serious adverse events**
- **No concerning clinical laboratory results**
- **Adverse events (AEs) profile supports safety of AD-214 molecule**
  - Predominantly mild
  - Three Grade 2 (moderate) treatment related AEs
  - Infusion related reactions (IRRs) reported in three participants – resolved rapidly when infusion ended
- **IRRs linked to formulation**
  - Observed in participants receiving both AD-214 (2) and placebo (1)
  - Trended to increasing intensity and frequency with subsequent doses
  - Not associated with changes in vital signs, clinical, physical or cytokines
  - Protocol amended to include standard antihistamine and corticosteroid treatment options

## Intravenous AD-214 Phase I healthy volunteer study: immune response findings

### Single iv doses to 20 mg/kg (42 participants)

- **Isolated instances of minor cytokine elevation**
  - Transient and primarily low level of elevation of IL-6 and IL-8 in some participants (including placebos)
- **No clinically significant cytokine release**
- **Antidrug antibodies: detected in 11 participants**
  - Predominantly low titre
  - Characterisation pending
- **No clinical symptoms related to immune response observed**

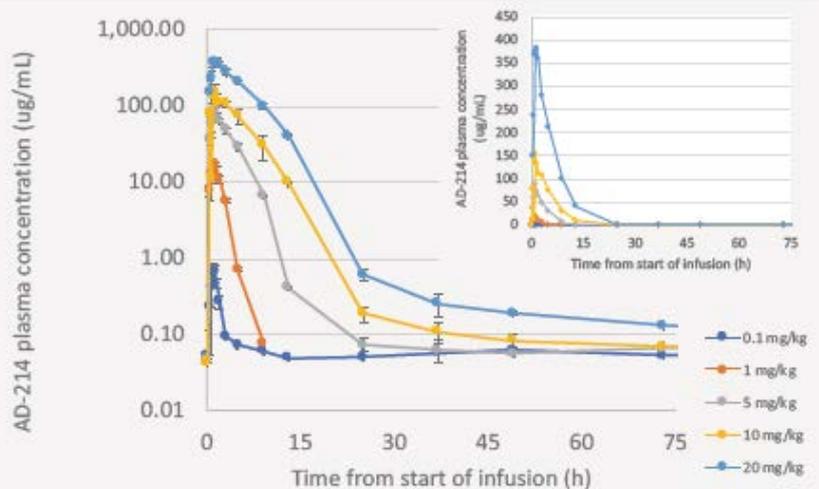
### Multiple iv doses 5 mg/kg (8 participants)

- **Sporadic and primarily low level elevation of cytokines IL-6 and IL-8, sporadic increases in TNF- $\alpha$  and IFN- $\gamma$** 
  - No clear association with IRRs or antidrug antibodies
  - Low level increases in IL-6 in many participants 24-48h post infusion
- **No clinically significant cytokine response and no link to IRRs or ADAs**
- **Antidrug antibodies: detected in three participants after second dose**
  - All low titre
  - One also reported IRR (association unlikely)
  - Characterisation pending
  - Third dose data pending

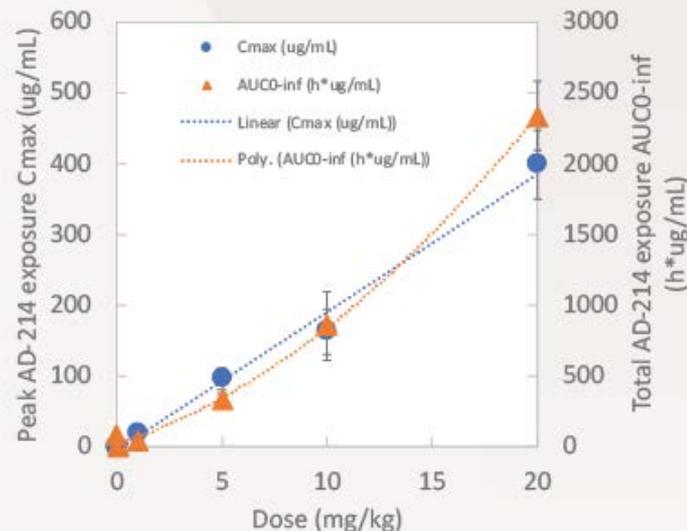
## Intravenous AD-214 pharmacokinetics increase proportionally with dose (single doses)

- Maximum exposure, C<sub>max</sub>, increases in a dose proportional manner
- Total exposure, AUC<sub>0-inf</sub>, increases in a more than dose proportional manner
- Elimination half-life t<sub>1/2</sub> ~40h

AD-214 plasma concentrations (log and linear scale)



Maximum and total plasma exposure

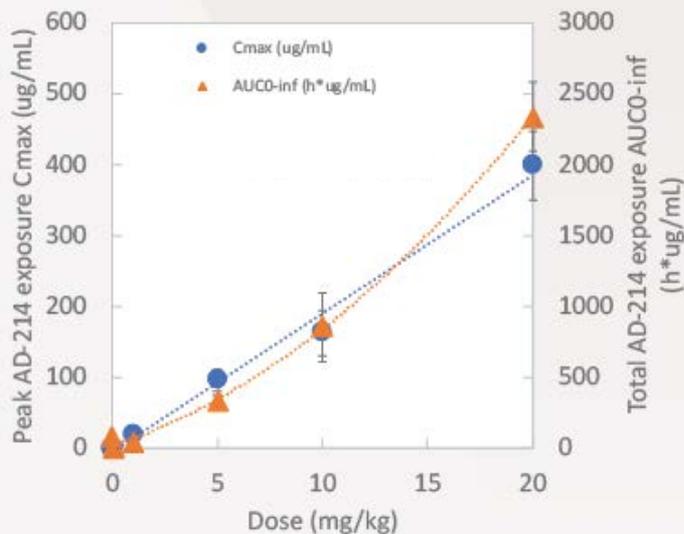


\* Single ascending dose data presented as mean ± std dev

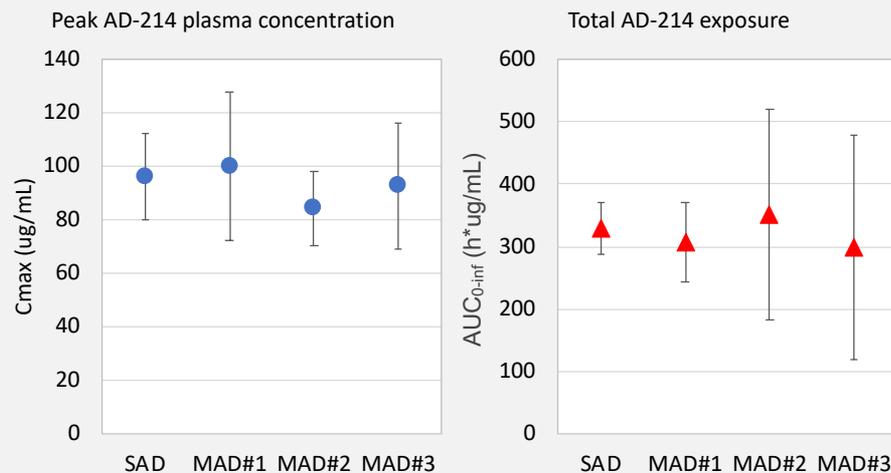
## Intravenous AD-214 pharmacokinetics

Maximum exposure,  $C_{max}$ , and total exposure,  $AUC_{0-inf}$ , increase in a dose proportionate manner and are consistent across multiple doses of AD-214 at 5 mg/kg, supporting absence of drug induced tolerance or clearance

### Maximum and total plasma exposure - SAD



### Maximum and total plasma exposure – 5 mg/kg



### Pharmacokinetic profile

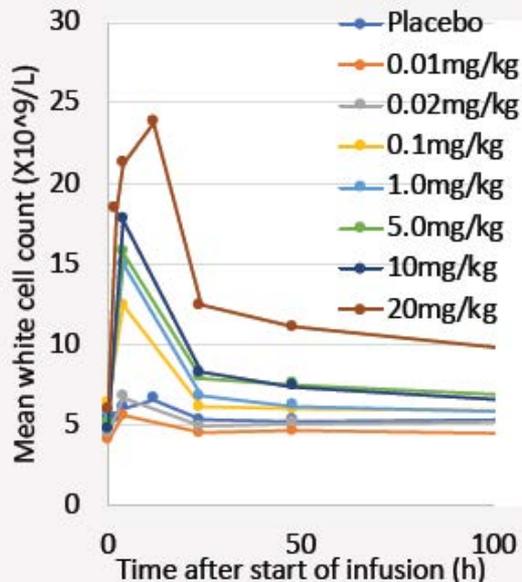
- Rapid distribution from plasma (consistent with rapid and high CXCR4 receptor occupancy and PET imaging distribution studies)
- Elimination half-life  $44 \pm 15$  h at 20 mg/kg

# Transient white blood cell and blood stem cell increases indicate CXCR4 engagement

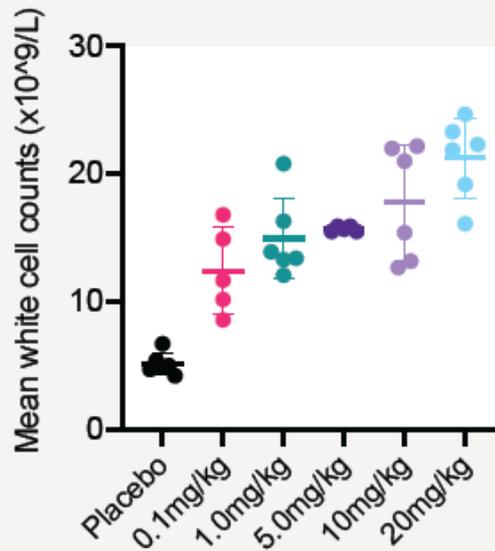
Observed in Phase I HV SAD\*

Transient, dose dependent, increase in WCC and CD34+ counts at 4-12 hours consistent with CXCR4 blockade

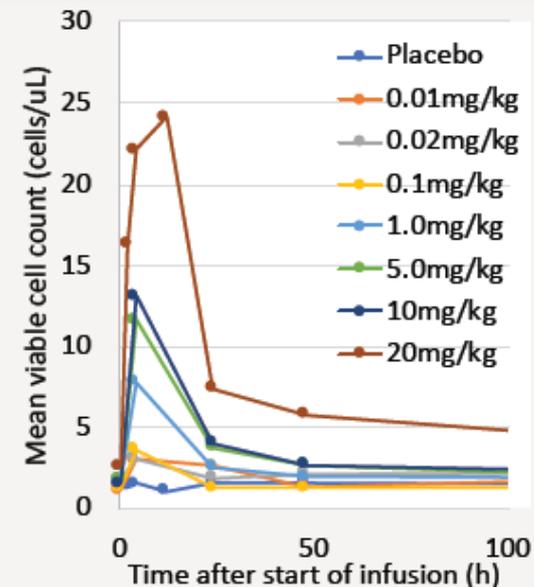
WCC counts



WCC counts at 4h



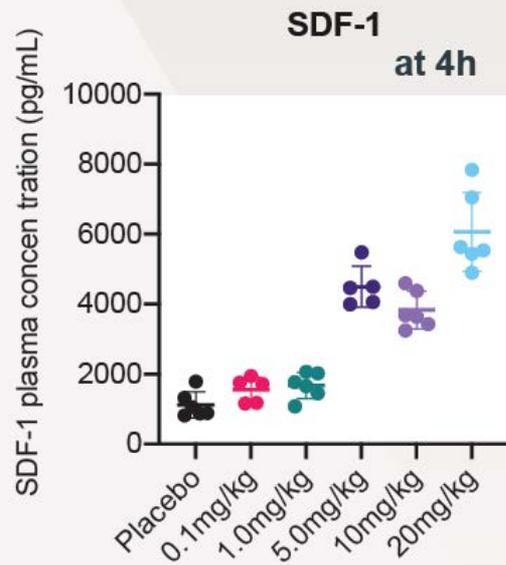
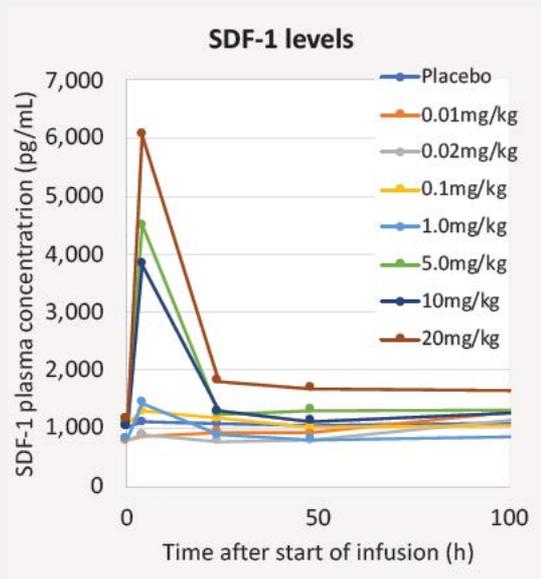
CD34+ cell counts



\* Single ascending dose data presented as mean ± std dev

## Transient increase in SDF-1 (natural ligand of CXCR4) consistent with CXCR4 engagement

Transient increases in SDF-1 levels at 4 hours in some participants, returning to baseline at 24h consistent with CXCR4 blockade



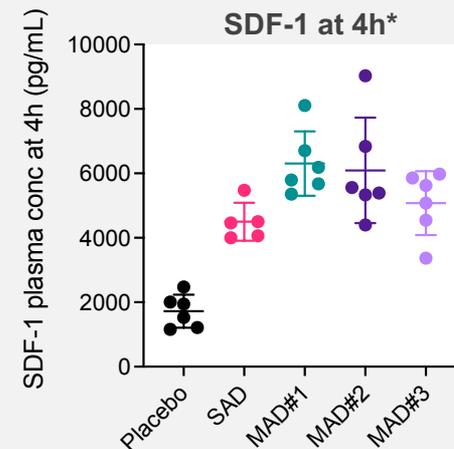
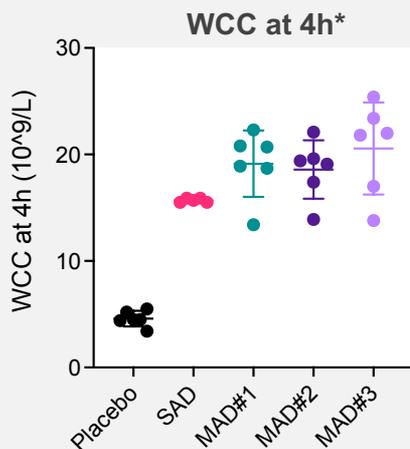
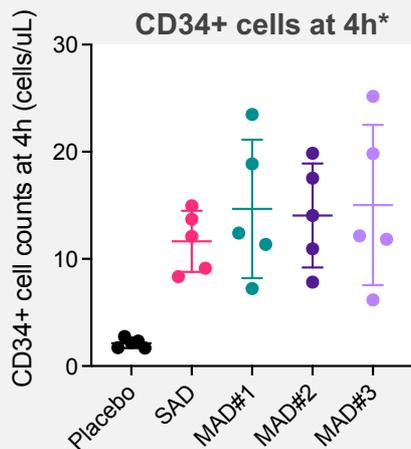
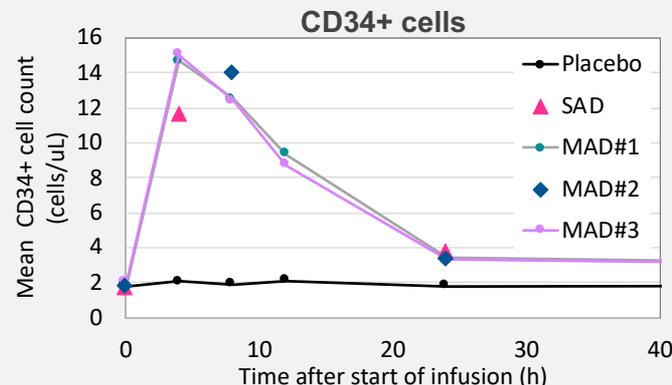
\* Single ascending dose data presented as mean  $\pm$  std dev

## Biomarkers of CXCR4 receptor engagement at 5 mg/kg

Transient increases in blood biomarkers demonstrate consistent engagement of the target receptor, CXCR4 across multiple AD-214 doses

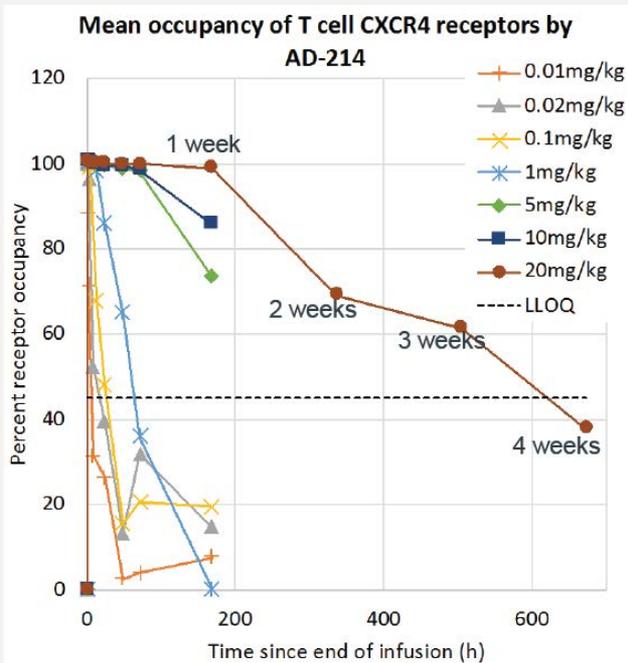
**Biomarker data confirm single dose findings, consistent across multiple doses: no drug induced tolerance or accumulation**

- ▶ White blood cell counts (WCC), haematopoietic stem cell (CD34+) counts and concentration of SDF-1 are biomarkers of CXCR4 engagement by AD-214
- ▶ Profile of biomarkers is consistent across multiple doses at 5 mg/kg\*
- ▶ 100% T cell CXCR4 receptor occupancy achieved for at least 24h (data not shown, maximum duration analysis pending)



\* SAD = single dose at 5mg/kg; MAD#1/MAD#2/MAD#3 are first, second and third multiple doses at 5 mg/kg; CD34+ and WCC data is shown at 8h for MAD#2

## Sustained high levels of CXCR4 receptor occupancy on T cells



White blood cells naturally express CXCR4 in healthy individuals, providing an accessible surrogate for AD-214 target engagement or receptor occupancy (RO)

Understanding duration of RO is critical to inform dosing

### Primary

- >70% CXCR4 RO at 7 days after 5-10 mg/kg infusion
- >60% CXCR4 RO at 21 days after 20 mg/kg infusion\*
- **Duration of RO is considerably longer than PK profile**

If replicated on CXCR4 receptors in fibrotic tissues, result supports extended dosing intervals despite relatively rapid clearance from circulation

\* Receptor occupancy was monitored for one week at all dose levels except 20 mg/kg (4 weeks)

## PET imaging studies\* inform dosing and route of administration

PET imaging with radiolabelled AD-214 supports early transition to inhaled route of administration

### Rapid liver distribution and clearance reduces bioavailability

- ▶ Consistent with pharmacokinetic profile and a first pass clearance mechanism
- ▶ More than half administered dose not available to target site of action

### CXCR4 binding capability retained, supportive of potential efficacy

- ▶ Consistent with observed biomarker, receptor occupancy and bleomycin mouse efficacy data

### Liver distribution does not appear to affect safety profile

- ▶ No localization in hepatocytes (responsible for metabolic activity in liver)
- ▶ Consistent with lack of observed changes in liver function or toxicity in toxicology and clinical studies

**Direct lung delivery of AD-214 could achieve a therapeutic dose at lower levels than intravenous delivery**



**Radiolabelled AD-214 will continue to be a useful development tool**  
**Alternate intravenous formulations to be evaluated to improve bioavailability**

\* These studies were part supported by a Biomedical Translational Bridge grant, a program of Australia's Medical Research Future Fund administered by MTPConnect and supported by UniQuest

## Phase II planned with inhaled formulation

Delivery of AD-214 by inhalation has potential to improve bioavailability, be more convenient for patients, be more cost effective, and improve partnering flexibility\*



<b>Improved bioavailability</b>	<ul style="list-style-type: none"> <li>• AD-214 delivered direct to fibrotic areas</li> <li>• First pass liver clearance avoided</li> <li>• Dosing schedule flexibility to optimise receptor coverage</li> </ul>
<b>Greater patient convenience</b>	<ul style="list-style-type: none"> <li>• Self administration (no scheduled clinic visits; freedom of movement)</li> <li>• Less invasive</li> </ul>
<b>Enhanced cost effectiveness</b>	<ul style="list-style-type: none"> <li>• Lower drug dose means lower cost of goods</li> <li>• Lower healthcare costs for administration</li> </ul>
<b>Diversified partnering options</b>	<ul style="list-style-type: none"> <li>• Potential to partner AD-214 by indication using different routes of administration - broadens potential long term options</li> </ul>

\* Development is part supported by a Biomedical Translational Bridge grant, a program of Australia's Medical Research Future Fund administered by MTPConnect and supported by UniQuest

## Inhalation in IPF

Numerous drugs have been formulated for inhalation in IPF and respiratory disease, a substantial number of biologics are in development for inhalation and off-the-shelf devices are available for rapid translation from intravenous route

### Inhalation used regularly in IPF and other respiratory diseases

4 inhaled IPF therapeutics in development



(Phase III)



(Phase IIb)



(Phase I/II)



(Pre-clinical, biologic)

- IPF patients routinely inhale salbutamol and steroids for symptom relief
- Inhaled therapeutics also marketed for asthma, COPD, cystic fibrosis

### Substantial number of biologics in development for inhalation\*

- 2 marketed inhaled biologics
- 19 clinical stage inhaled biologics including
  - Several fragment antibodies
  - 1 single domain antibody (nanobody)
- Majority sized between 15-80 kDa (AD-214 73 kDa, single i-bodies 15 kDa)
- Majority via solution for inhalation

### Off-the-shelf devices for nebulization of liquid formulations

OMRON

PHILIPS



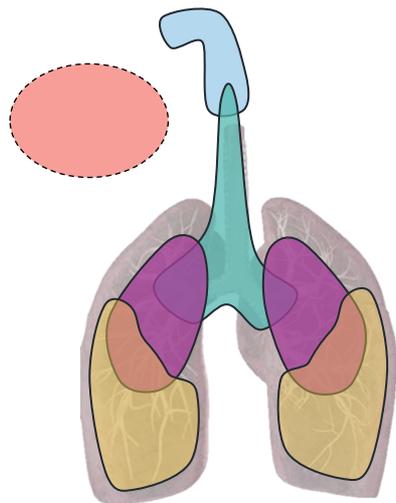
- Smart mesh nebulisers assist compliance, accuracy, drug efficiency
- Low shear forces designed for biologics
- Liquid formulations: potential to utilize AD-214 intravenous formulation with minimal modification



\* W Liang *et al*, Pulmonary delivery of biological drugs, *Pharmaceuticals* 2020, 12, 1025

## Predicted regional deposition of AD-214 in human lungs

The ICRP66<sup>1</sup> model predicts that 17-46% of AD-214 delivered from commercial nebulisers will be delivered to the smallest (alveolar/interstitial) airways of the lungs where most IPF is found



- Exhaled fraction
- Extra thoracic fraction
- Tracheobronchial fraction
- Bronchiolar fraction
- Alveolar/interstitial fraction

	Device A	Device B
<b>Aerosol particle size</b> (volume mean diameter)	4.8 $\mu\text{m}$	4.4 $\mu\text{m}$
<b>Fine particle fraction</b> (% particles $\leq 5 \mu\text{m}$ )	55%	60%
<b>Deposition fraction</b>		
<b>Extra thoracic</b>	17%	23%
<b>Tracheobronchial</b>	8%	11%
<b>Bronchiolar</b>	15%	11%
<b>Alveolar / interstitial</b>	<b>46%</b>	<b>17%</b>
<b>Total lung (BB, bb, AI)</b>	<b>69%</b>	<b>38%</b>
<b>Exhaled</b>	14%	38%

1. International Commission for Radiation Protection

## A clinician's perspective on AD-214 results so far

- **Un-met need in IPF/ILD remains – need to progress new therapies**
- **Research at The Alfred suggests if targeting CXCR4 works in IPF it may work in other ILD's**
- **AD-214 is well tolerated and ready to move forward into multi-dose studies in healthy volunteers and patients**
- **The data is supportive of extending dosing interval to two weekly at least**
- **AdAlta approach is methodical and appropriate**
  - PET imaging strategy is particularly important as an innovative way to explore target engagement and mode of action in diseased tissue
- **Key insights anticipated from multidose and early patient studies (in addition to safety):**
  - CXCR4 receptor engagement in tissue
  - Nature of the anti-drug antibodies that are expected with a biologic
  - Further characterisation of biomarker responses: CD34+, white cells, SDF-1a



**Prof Glen Westall**  
leading respiratory and  
lung fibrosis specialist

AdAlta Investor Briefing  
10 March 2021

## IPF late-stage clinical landscape: a narrow development field

AdAlta's novel mode of action and Orphan Drug Designation expected to be attractive to partners as an alternative to, and in combination with other therapies

Company	Drug	Mode of action	Phase	Orphan Drug Designation
	PRM-151	Endogenous human protein that directs the immune cells called macrophages to turn off and reverse fibrotic processes	Phase 3 (Mono or combination therapy)	YES
	Pamrevlumab	Human monoclonal antibody (mAb) that inhibits the activity of connective tissue growth factor (CTGF) to inhibit myofibroblast activation, collagen deposition and other pro-fibrotic factors	Phase 3 (Monotherapy)	YES
	Inhaled Treprostinil	Small molecule analogue of prostacyclin that reduces pulmonary artery pressure through direct vasodilation of the pulmonary and systemic arterial vascular beds	Phase 3 (Supportive care/ symptom reduction)	YES
	AD-214	<i>i-body-Fc fusion protein blocking CXCR4 to inhibit inflammatory cell migration, epithelial to mesenchymal transition and fibrotic growth factor production, and deposition of collagen</i>	Phase I	YES

## Current IPF clinical development landscape: a narrow development field

AdAlta's novel mode of action expected to be attractive to partners

COMPANY	DRUG	MODE OF ACTION	CURRENT PHASE	ORPHAN DRUG DESIGNATION
 United Therapeutics	Inhaled Treprostinil	Reduction in pulmonary artery pressure through direct vasodilation of the pulmonary and systemic arterial vascular beds	Phase 3	Yes
 Roche	PRM-151	Recombinant human serum amyloid P/pentraxin 2	Phase 3	Yes
 FibroGen	Pamrevlumab	Fully human recombinant monoclonal antibody against connective tissue growth factor (CTGF)	Phase 3	Yes
 Galecto	GB0139	Small molecule galectin-3 inhibitor	Phase 2	Yes
 Boehringer Ingelheim	BI-1015550	Small molecule phosphodiesterase 4b inhibitor.	Phase 2	No
 Nitto	ND-L02-s0201	Lipid nanoparticle encapsulating an siRNA which inhibits expression of heat shock protein 47 (HSP47), a collagen-specific chaperone.	Phase 2	No
 Bristol Myers Squibb	BMS-986278	Small molecule LPA1 antagonist	Phase 2	No
 Celgene	CC-90001	Small molecule of c-Jun N-terminal kinase (JNK) inhibitor	Phase 2	No
 Avalyn	AP01	Poorly understood. Believed to interfere with profibrotic TGF- $\beta$ production.	Phase 2	No

## IPF partnering: valuable options as early as Phase I

IPF assets have recently yielded attractive deal terms at early stages of development

Date	Licensee	Licensor	Transaction Terms	Asset/Mode of Action	Clinical Phase	Additional Comments
Nov-21			<b>US\$254m Upfront</b>	Cudetaxestat Autotaxin inhibitor	2 (Ready)	SPAC merger; Deal includes cudetaxestat (lead product) + calpain inhibitor products
Nov-21			<b>€320m Milestones</b>	OATD-01 Chitotriosidase/acidic mammalian chitinase (CHIT1/AMCase) inhibitor	2 (Ready)	Single product license
Sep-21			<b>US\$152m Upfront +US\$602m Milestones</b>	Axatilimab CSF-1R inhibitor	2 (Ready)	Lead indication cGVHD
Nov-19			<b>US\$390m Upfront +US\$1b Milestones</b>	PRM-151 Recombinant form of human pentraxin-2 (PTX-2) protein.	2	Deal includes PRM-151 (IPF lead asset) + multiple assets for fibrotic diseases
Feb-21			<b>US\$517.5m Milestones</b>	TDI01 Rho containing protein kinase 2 (ROCK2) inhibitor	1	Single product license
Jul-19			<b>€45m Upfront +€1.1b Milestones</b>	BBT-877 Autotaxin inhibitor	1	Single product license

## IPF partnering: valuable options as early as Phase I

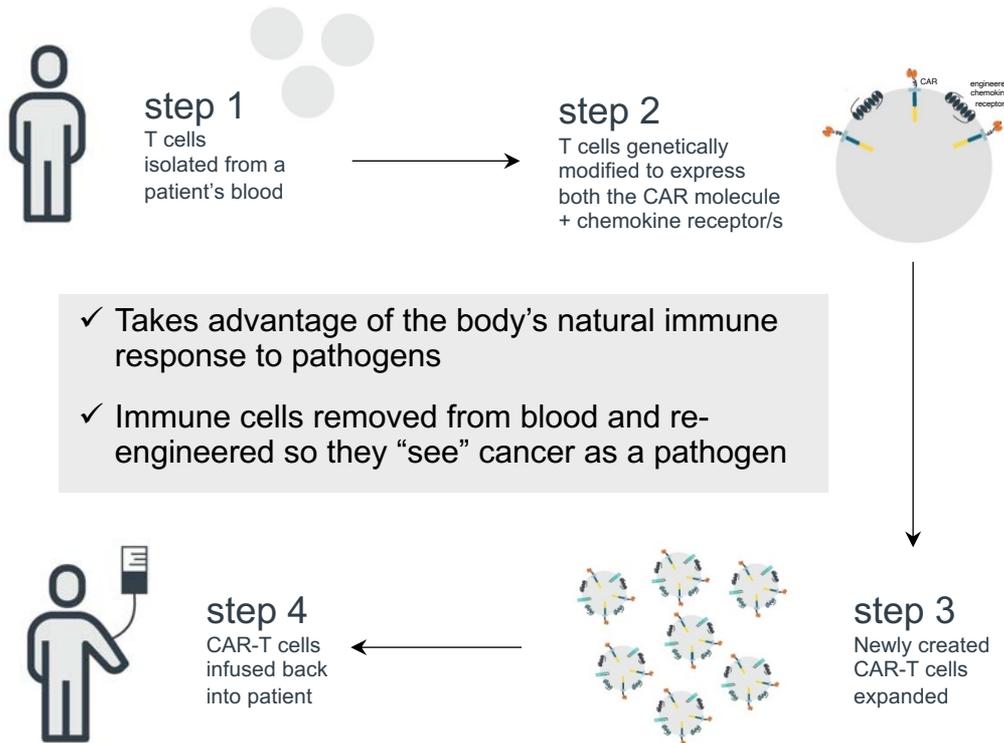
IPF assets have recently yielded attractive deal terms at early stages of development

Date	Licensee	Licensor	Transaction Terms	Asset/Mode of Action	Clinical Phase	Additional Comments
Mar-22	 bridgebio	 CELLION BIOMED	US\$0.4m upfront +24m milestones	<i>BBT-301</i> <i>Ion channel modulator</i>	Preclinical	Option-to license
Aug-20	 Redx	AstraZeneca 	US\$17m upfront +US\$360m milestones	RXC006 <i>Porcupine inhibitor</i>	Preclinical	Single product license
Jan-20	 ENLEOFEN	 Boehringer Ingelheim	Upfront undisclosed +US\$1b milestones	Multi-asset platform <i>Interleukin-11 inhibitor for</i> <i>fibro-inflammatory disease</i>	Preclinical	Platform for multiple fibrotic disorders
Jul-19	 Recursion	 BAYER	US\$30m upfront +\$US1.03b milestones	<i>AI drug discovery platform for</i> <i>fibrotic disease</i>	Preclinical	

# Appendix: CAR-T

# CAR-T therapies are revolutionising cancer treatment

Reprogramming a patient's own immune system to fight cancer is a fast growing market at the cutting edge of medicine



- ✓ Takes advantage of the body's natural immune response to pathogens
- ✓ Immune cells removed from blood and re-engineered so they "see" cancer as a pathogen

**>US\$1b** earned by CAR-T therapy products in 2020<sup>3</sup>

**2m** addressable patient population within next 10 years<sup>1</sup>

**US\$20.3b** revenue forecast for 2028<sup>1</sup>

**50%** solid tumour share of revenues by 2030<sup>2</sup>

1. Grandview Research, "T-cell Therapy Market Size, Share & Trends Analysis" Feb 2021

2. Polaris Market Research, "CAR-T Cell Therapy Market Share, Size Trends, Industry Analysis Report", June 2021

3. Yescarta and Kymriah market size estimates calculated from various publicly available sources. Estimates vary and different analyses may give different results.

## Current approved CAR-T products

Six FDA approved CAR-T products for blood cancers generate strong revenues and are in high demand

<b>Manufacturer</b>				
<b>Product</b>		 	 	
<b>Notable CAR-T transactions</b>	UPenn and Novartis alliance Aug 2012 <sup>2</sup>	Gilead acquired Kite Aug 2017 US\$11.9b <sup>1</sup>	Celgene acquired Juno Jan 2018 US\$9b; BMS acquired Celgene Jan 2019 US\$74b <sup>3</sup>	Janssen – Legend Biotech collaboration and license agreement Dec 2017 Upfront US\$350m, US\$200m prior to approval <sup>5</sup>
<b>FDA approval</b>	<b>August 2017</b> (acute lymphoblastic leukemia, large B cell lymphoma)	<b>October 2017</b> (large B cell lymphoma) <b>July 2020</b> (mantle cell lymphoma)	<b>February 2021</b> (large B cell lymphoma) <b>March 2021</b> (multiple myeloma)	<b>February 2022</b> (multiple myeloma)
<b>Revenue 2020<sup>4</sup></b>	<b>US\$474m</b>	<b>US\$563m</b> <b>US\$44m</b>	<b>N/A</b> <b>N/A</b>	<b>N/A</b>

- <https://www.businesswire.com/news/home/20210204006011/en/Gilead-Sciences-Announces-Fourth-Quarter-and-Full-Year-2020-Financial-Results>
- <https://www.novartis.com/>
- <https://www.celgene.com/newsroom/cellular-immunotherapies/celgene-corporation-to-acquire-juno-therapeutics-inc/>
- [businesswire.com/news/home/20210204006011/en/Gilead-Sciences-Announces-Fourth-Quarter-and-Full-Year-2020-Financial-Results](https://www.businesswire.com/news/home/20210204006011/en/Gilead-Sciences-Announces-Fourth-Quarter-and-Full-Year-2020-Financial-Results), [novartis.com](https://www.novartis.com/), [celgene.com/newsroom/cellular-immunotherapies/celgene-corporation-to-acquire-juno-therapeutics-inc/](https://www.celgene.com/newsroom/cellular-immunotherapies/celgene-corporation-to-acquire-juno-therapeutics-inc/)
- <https://www.fiercepharma.com/pharma/jpm-2022-j-j-legend-hope-to-avoid-supply-challenges-have-ailed-abecma-as-cilta-cel-nears-fda>

## Advantages of CAR-T therapy

For patients, CAR-T therapies offer a potentially curative, single shot therapy that is precision engineered to find and kill cancer



### Can be curative

Even in patients whose cancers have returned after multiple prior standard therapies



### Long lasting

Living therapy: a single treatment can attack cancer over months and then remain in the immune system long term to fight cancer cells that return

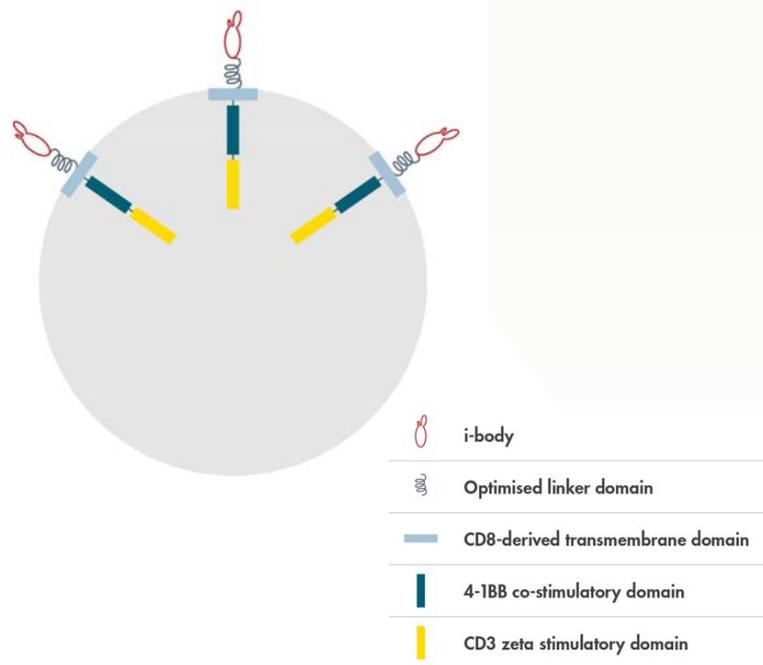


### Highly targeted

Precision engineered to engage with tumour cells and to minimise healthy tissue damage

## i-bodies in CAR-T format

- **i-bodies are approximately half the size of the traditional CAR binding domain**
  - Enables greater flexibility in CAR design
  - Ideally suited to bispecific CARs
- **i-bodies are specifically designed to target antigens considered difficult or intractable for traditional antibodies and CAR constructs**
- ***In vitro* proof of principle established for i-bodies in a CAR-T platform (in collaboration with Carina Biotech)**

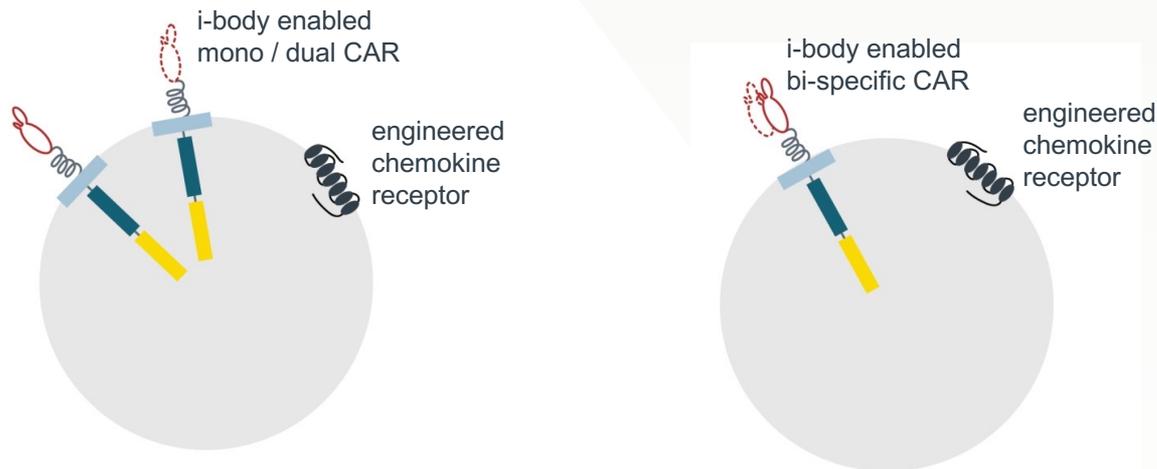


## Advantages of i-body enabled CAR-T

i-body enabled CAR-T cells may demonstrate improved precision, performance and persistence, particularly in bi-specific and dual CAR-T cells

### Delivering precision to difficult to treat cancers: bi-specific and dual-specific CAR-T cells

- ✓ Targets 2 antigens on cancer cells
- ✓ Reduces opportunity for tumour cells to be missed
- ✓ Reduces chance of damaging healthy tissue



## Carina collaboration details

AdAlta and Carina will jointly develop up to 5 targets to create CAR-T, bi-specific CAR-T and dual CAR-T cell therapy products

### Up to 5 targets

- **Proof of principle already achieved** (*in vitro*)
- Targets not yet disclosed
- **Combine targets for bi-specific and dual-targeted CARs**



### Significant new, shared IP

- Share costs, research to *in vivo* proof of concept
- AdAlta + Carina will **jointly own collaboration IP**



### Post proof of concept commercialisation options

- Can continue to develop products together, progress independently or out license
- **Products** emerge from the collaboration at proof of concept



### Attractive deal space

- Biotech and immuno-oncology segment: very attractive deal space
- **Large biotech and pharma companies are actively sourcing CAR-T products**



## 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



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



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



### Persistence

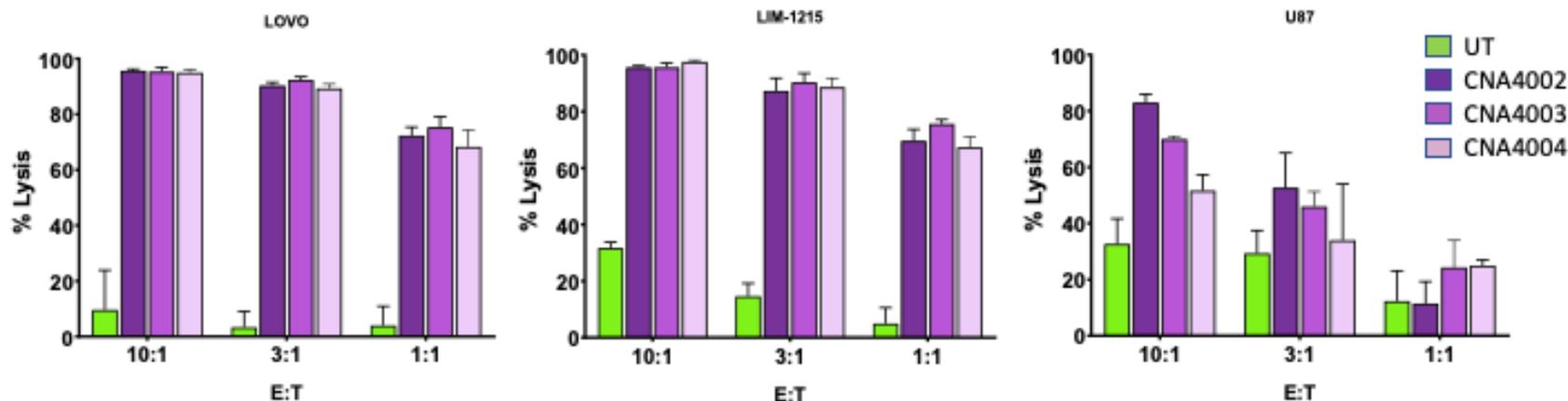
Tumour secretes molecules that suppress immune cell activity



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

## Building the first iCAR-T cell therapy: proof of principle results

i-body enabled CAR-T (iCAR-T) cells have been successfully generated by Carina and demonstrate *in vitro* cell killing (lysis)<sup>1</sup>



### Experimental details

- LOVO and LIM1215 are colorectal cancer cell lines; U87 is a glioblastoma cell line
- 3 different Carina CAR-T constructs incorporating i-body against a single target “X” (CNA4002/CNA4003/CNA4004)
- UT is an unmodified T-cell 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