ASX Release

AdAlta investor and analyst briefing presentation material

MELBOURNE Australia, 31 January 2019: AdAlta Limited (ASX: 1AD), the biotechnology company advancing its lead i-body candidate towards clinical development, is pleased to release material to be presented in Melbourne today at a special briefing for investors and analysts.

The theme of the briefing is "Pathway to the clinic". Presentations will focus on the process required to manufacture an Fc-Fusion protein (including an update on manufacturing of AD-214, further to the Company's announcement on 29 January) and the idiopathic pulmonary fibrosis (IPF) treatment and clinical trial landscape. The briefing will include perspectives from AdAlta's Scientific Advisory Board member, an IPF clinician and an IPF patient and will conclude with an update from AdAlta CEO Sam Cobb.

Speakers and topics on the agenda at the symposium include:

- Hugh MacNally, Chairman and Founder of Private Portfolio Managers
    - *Investing in biotech, what does it take? Hugh is the founder of PPM and will provide an overview of what it takes to invest in the biotech sector and what 2019 holds for investors.*
- Dr Robert Peach, AdAlta Non-Executive Board Member
    - *Therapeutic Fc-Fusion Proteins: What are they? Robert will give an overview of the various Fc Fusions he has developed including Orencia, currently sold by BMS with $US2.5 billion in sales in 2017.*
- Dr Dallas Hartman, Chief Operating Officer AdAlta Limited
    - *Manufacturing of AD-214: Dallas will provide an overview of where AdAlta is up to manufacturing its Fc-Fusion protein AD-214.*
- Steve Felstead, Clinician and Member of Scientific Advisory Board
    - *The IPF landscape: Steve will provide an overview of the IPF clinical landscape.*

- Glen Westall, IPF Clinician, Alfred Health
    - *An IPF clinician's perspective: Glen will provide an overview of what IPF is, how it is treated and an update on his recent findings as a clinician*.
- Bill Van Nierop, IPF patient
    - *An IPF patient's perspective: Bill will discuss what IPF means to him as a patient diagnosed in 2015 and his experiences including the Long Kayak For Lungs Journey.*
- A panel discussion including Dr Steve Felstead, Dr Brian Richardson, Dr John Westwick and Dr Robert Peach will discuss what a good drug looks like.
    - *The panel includes a number of drug development experts who have significant experience taking a drug from the research bench, through the clinic and providing it to patients.*
    - *The panel will discuss what it takes to get a drug to the clinic. What a good drug looks like in terms of clinical development and in order to get a commercialisation deal across the line.*
- Sam Cobb, CEO and Managing Director AdAlta
    - *Sam will provide investors an update on AdAlta's achievements and progress towards advancing AD-214 to the clinic in January 2020.*

Highlights from the symposium will be made available during the coming weeks.

To find out more about AdAlta, contact Sam Cobb, CEO, Tel: (03) 9479 5159 or email enquiries@adalta.com.au.

Notes to editors

AdAlta Limited is an Australian based drug development company headquartered in Melbourne. The Company is focused on using its proprietary technology platform to generate i-bodies, a new class of protein therapeutics, with applications as therapeutic drugs to treat disease.

I-bodies are a promising, novel class of drugs that offer a new and more effective approach to treating a wide range of human diseases. They are identified and developed using our proprietary technology platform.

We have pioneered a technology that mimics the shape and stability of a crucial antigen-binding domain, that was discovered initially in sharks and then developed as a human protein. The result is a range of unique compounds, now known as i-bodies, for use in treating serious diseases.

AdAlta is developing its lead i-body candidate, AD-214, 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.

AD-214 is an Fc-fusion protein that contains two i-body molecules that bind with high affinity to the human target CXCR4. At the back end of AD-214 is the Fc fragment, or tail region, of a traditional monoclonal antibody that will extend the drug's half-life. As AD-214 is made using Fc-fusion technology, it requires an alternate manufacturing process to the original drug, AD-114.

The Company also plans to continue further drug discovery and development directed towards other drug targets and diseases with its i-body technology platform.

Further information can be found at: www.adalta.com.au.

AdAlta

next generation protein therapeutics

Analyst and investor briefing

The pathway to the clinic

January 2019

ASX: 1AD

Analyst & Investor Briefing

- AdAlta's 2019 Special Investor/Analyst Briefing will focus on the drug development process and getting to the clinic.
- Hugh MacNally will kick off the day with an overview of what it takes to invest in Biotech.
- Manufacturing of antibodies is a major hurdle when advancing a biologic to the clinic.
  - AdAlta Non-Executive Director Robert Peach has developed several biologic products and will outline what is required to take a biologic to market.
  - AdAlta Chief Operating Officer Dallas Hartman will further elaborate on how AdAlta is taking AD-214 through this process.

Analyst & Investor Briefing

- Idiopathic Pulmonary Fibrosis (IPF) represents a large unmet clinical need globally
  - No current clinically satisfactory approach to treatment.
  - IPF landscape is evolving with a number of Phase II clinical trials completed in the last 12 months.
  - What this means to the clinician, patient and companies developing new therapeutics, such as AdAlta, will be discussed.
- What does a good drug look like and how do you know you have one?
  - AdAlta's world class Scientific Advisory Board: Steve Felstead, John Westwick and Brian Richardson and AdAlta's non-executive Director Robert Peach
  - Each will give an example of a product in which they were involved and answer questions about what it takes to get a fibrosis drug to the clinic and a deal.
- Sam Cobb will then provide an update on the progress of AD-214 to the clinic

Agenda






Hugh MacNally	**Investing in Biotech, what does it take?** Hugh is the founder of Private Portfolio Managers (PPM) and will give us an insight into what he is investing in 2019 in the biotech sector and what it takes.
Robert Peach	**Therapeutic Fc Fusion Proteins** What are they? Robert will give an overview of the various Fc Fusions he has developed including Orencia, currently sold by BMS with $2.5billion sales in 2017.
Dallas Hartman	**Manufacturing of AD-214** Dallas will provide an overview of where AdAlta is up to manufacturing its Fc-Fusion protein AD-214.
Glen Westall	**An IPF clinician's perspective** Glen will provide an overview of what IPF is, how it is treated and an update on his recent findings as a clinician.
Steve Felstead	**The IPF Landscape** Steve will provide an overview of the IPF clinical landscape of the clinical landscape for Idiopathic Pulmonary Fibrosis (IPF.)
Bill Van Nierop	**An IPF patient's perspective** Bill will discuss what IPF means to him as a patient diagnosed in 2015 and his experiences including the LungKayakForLungs Journey.

Agenda

PANEL DISCUSSION:
Steve Felstead
Brian Richardson
John Westwick
Robert Peach

What does a good drug look like?

The panel includes a number of drug development experts who have significant experience taking a drug from the research bench, through the clinic and providing it to patients.

The panel will discuss what it takes to get a drug to the clinic. What a good drug looks like in terms of clinical development and in order to get a deal across the line.

Sam Cobb

AdAlta Investor Update

Sam will provide investors an update on AdAlta's achievements and progress towards advancing AD-214 to the clinic in January 2020

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Investing in Biotech, what does it take?

Hugh McNally

Private Portfolio Managers

Hugh MacNally

- Chair and Founder of PPM.
- PPM is a boutique investment manager founded in 1995. It is managed and majority owned by its employees and founding shareholders.
- Hugh has been the CIO since the company was founded in 1995 and is responsible for management of both the global and domestic equities portfolios.
- Prior to founding PPM, Hugh held various analytical and management roles at Australian institutions from 1984.
- Hugh is a graduate of the University of NSW and the Owner President Management course at Harvard Business School (2010–12).

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Therapeutic Fc Fusion Proteins

Robert Peach

AdAlta Non-Executive Director

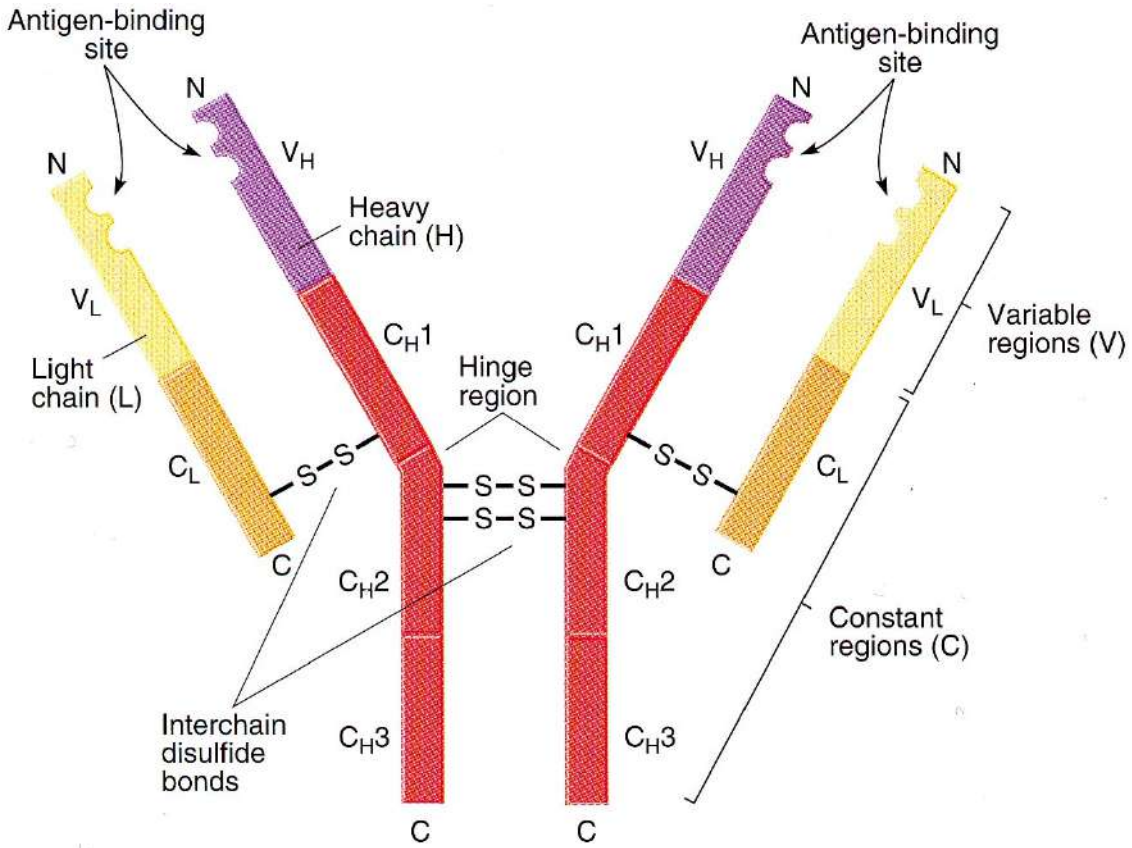
Robert Peach

- Dr Peach has over 25 years of drug discovery and development experience in the pharmaceutical and biotechnology industry.
- In 2009 he co-founded Receptos, becoming Chief Scientific Officer and raising US$59M in venture capital and US$800M in an IPO and three subsequent follow-on offerings. In August 2015, Receptos was acquired by Celgene for US$7.8B.
- His extensive drug discovery and development experience in autoimmune and inflammatory diseases and cancer has resulted in multiple drugs entering clinical trials and 3 registered drugs.
- He currently serves on the Board of Directors of Innate Immunotherapeutics and Avalia Immunotherapies and is a consultant for several other biotechnology companies.
- Robert is the co-author of 70 scientific publications and book chapters, and 17 patents. He was educated at the University of Canterbury and the University of Otago, New Zealand.

PRESENTATION OVERVIEW

- What is an Fc Fusion protein?
- Why utilize the Fc construct as a therapeutic modality?
  - Extend circulatory half-life
  - Dial in/out effector functions
  - Ease of manufacture
- Personal experience with Fc Fusion proteins
  - Abatacept, Belatacept
- Marketed therapeutic Fc Fusion proteins

Typical IgG Antibody Structure



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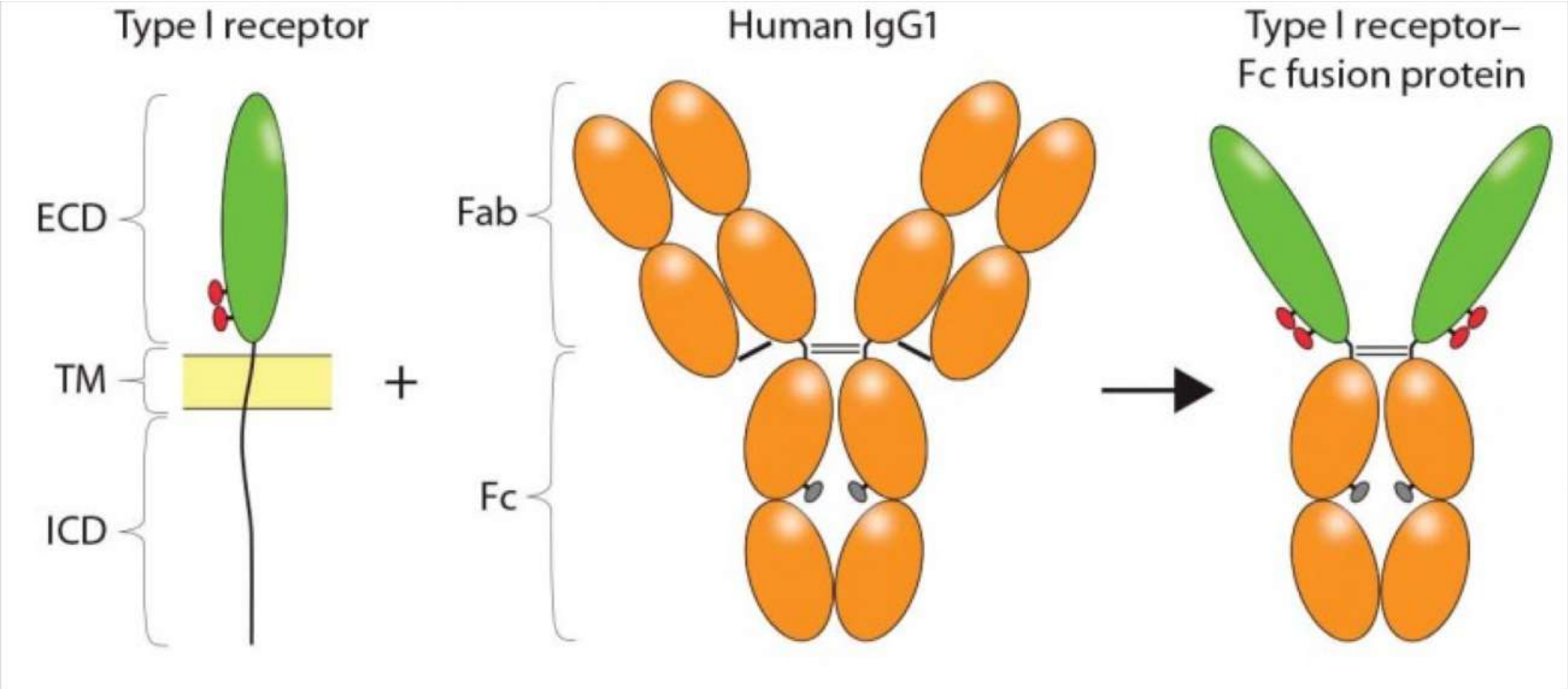
What is an Fc Fusion Protein?



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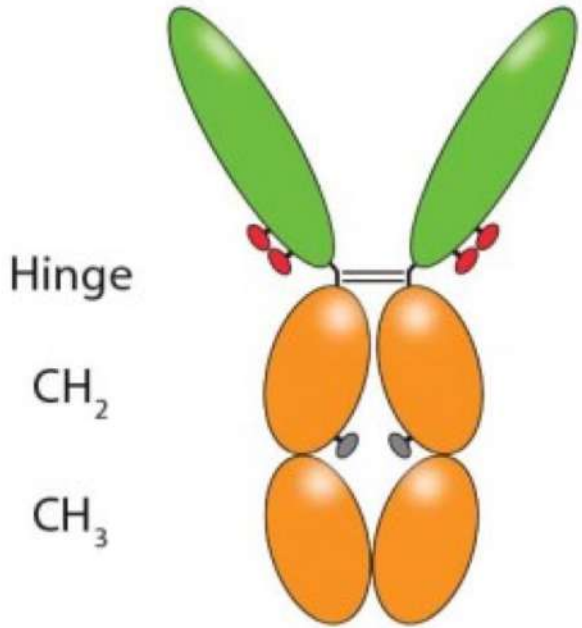
Fc Fusion Protein Structure and Function



Protein of interest

Receptor extracellular domain
Cytokine
Enzyme
Peptide

Fc region

FcγR binding → ADCC
C1q binding → CDC
FcRn binding → Half-life

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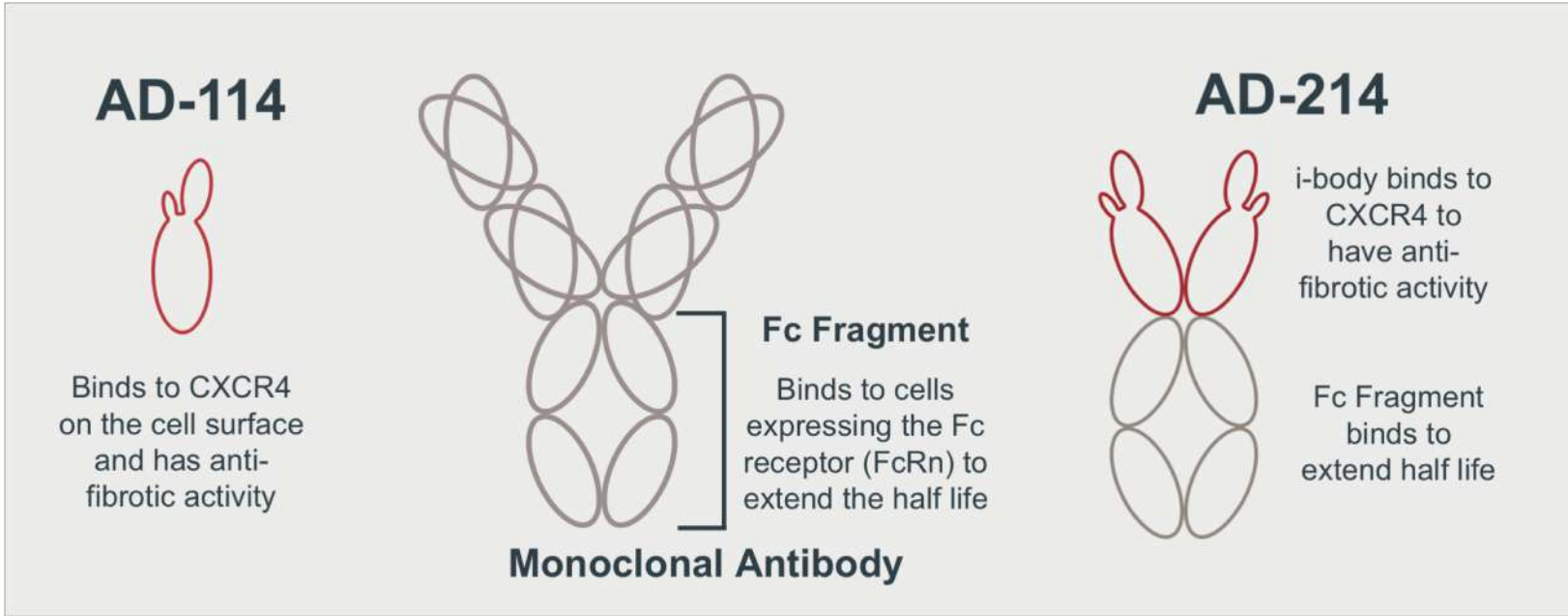
AdAlta's lead i-body AD-214 is an Fc-Fusion Protein



AD-214 is a superior drug candidate

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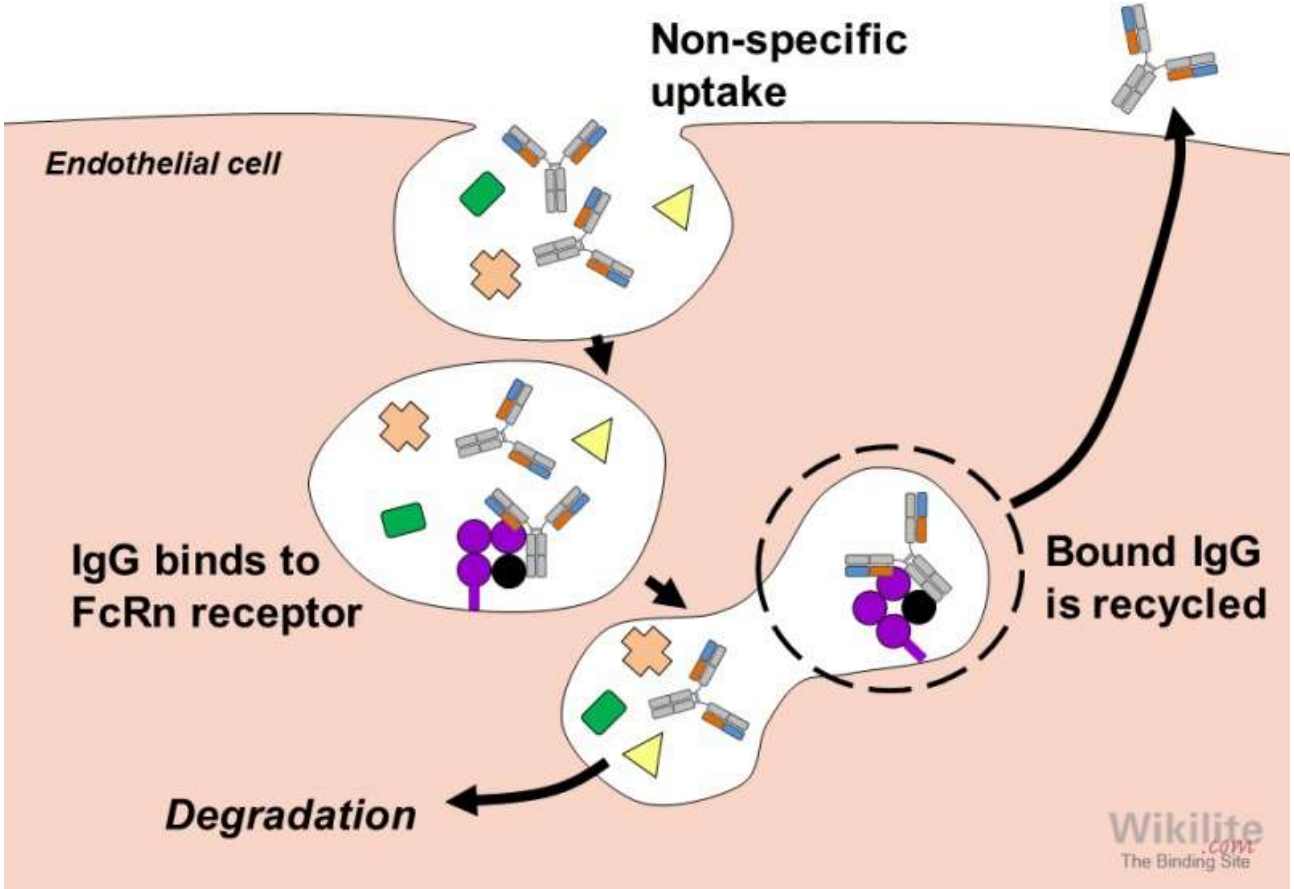
Binding to FcRn Extends Half-life



The neonatal Fc receptor for IgG (**FcRn**) is expressed by endothelial cells and circulating monocytes. These cells internalize serum IgG, which binds to **FcRn** in an acidic endosomal compartment. **FcRn** hen recycles IgG back into circulation, thus extending its serum half-life.

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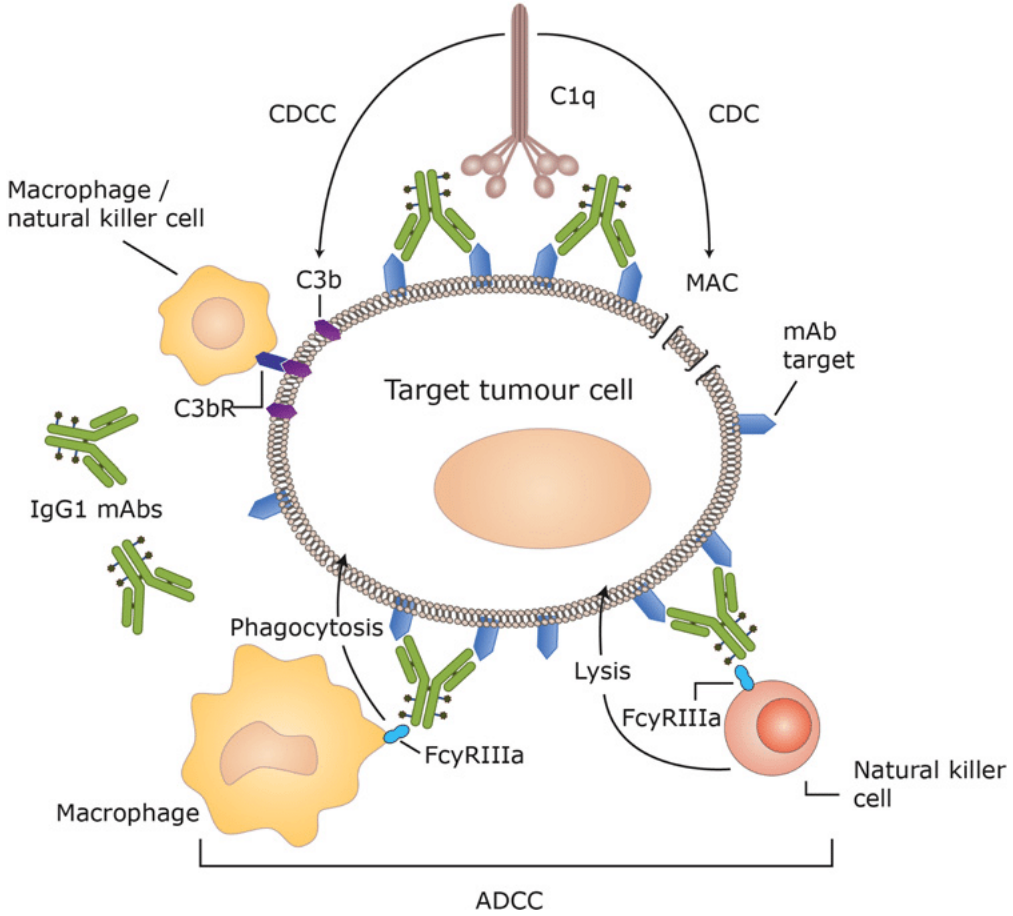
Fc Region Effector Functions



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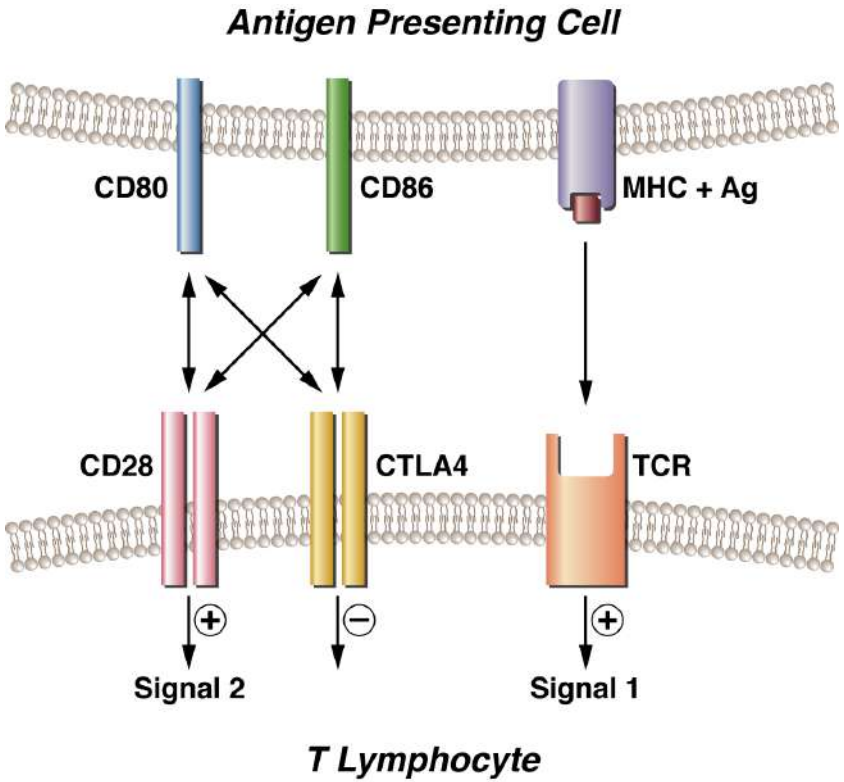
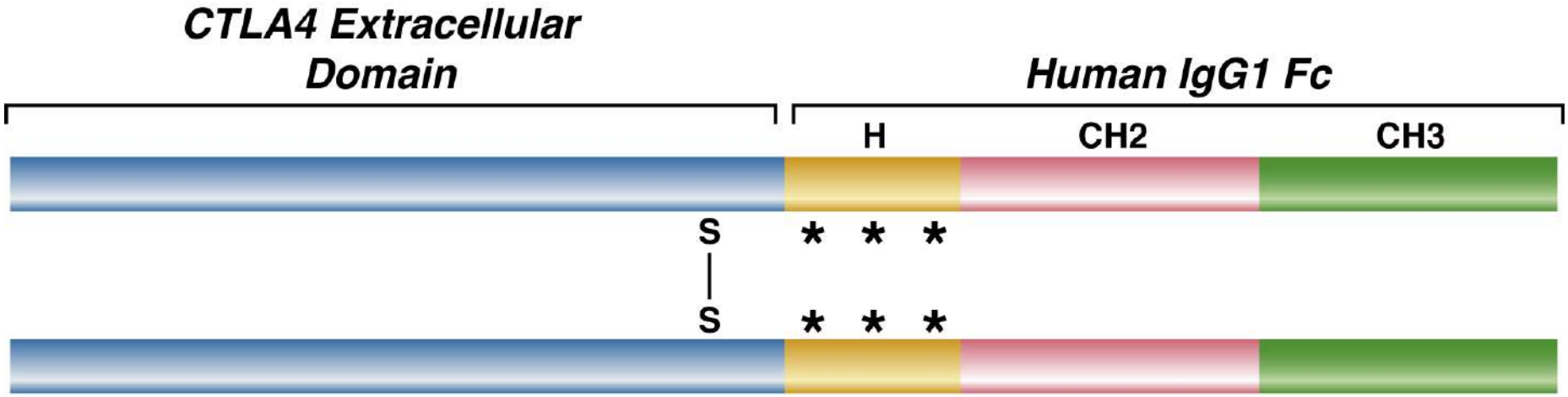
T Lymphocyte Activation



CTLA4Ig: An Fc Fusion Protein Construct



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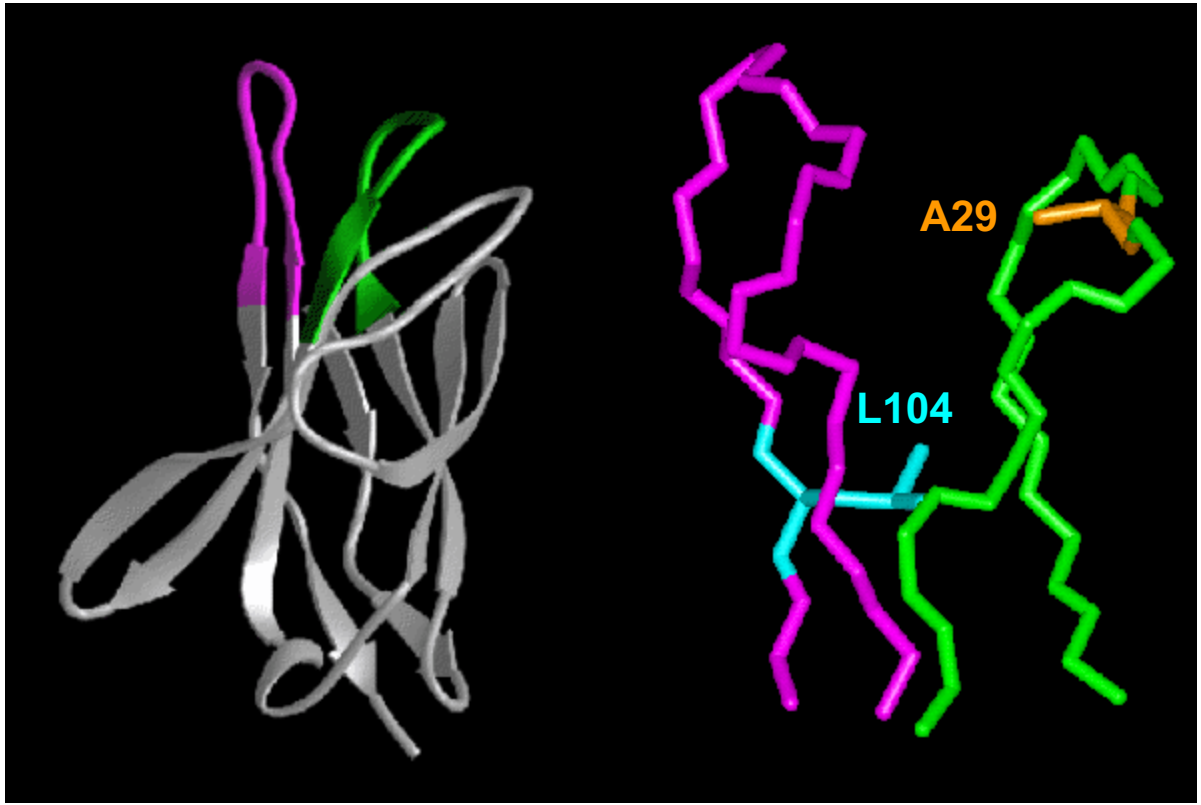
CTLA4Ig: A Therapeutic Fc Fusion Protein

- Also called Abatacept and marketed as Orencia
  - T1/2 ~14 days in humans (5-7 days in monkeys)
- Indicated to treat:
  - Moderate to severe rheumatoid arthritis
    - USA 2005; Europe 2007
  - Juvenile idiopathic arthritis
    - USA 2008, Europe 2010
- 2017 worldwide sales ~$2.6B US

Ongoing Orencia Clinical Studies

- Relapsing-remitting multiple sclerosis
- Ulcerative colitis, Crohn's disease
- SLE, lupus nephritis
- Uveitis
- Psoriatic arthritis
- Giant cell arteritis, Takayasu's arteritis
- Urticaria
- Acute GVHD
- Sarcoidosis
- Wegener's granulomatosis
- Scleroderma
- Polymyositis, Dermatomyositis
- ANCA-associated vasculitis
- Type 1 diabetes mellitus
- Ankylosing spondylitis
- Atopic asthma
- Relapsing polychondritis
- Alopecia totalis

LEA29Y



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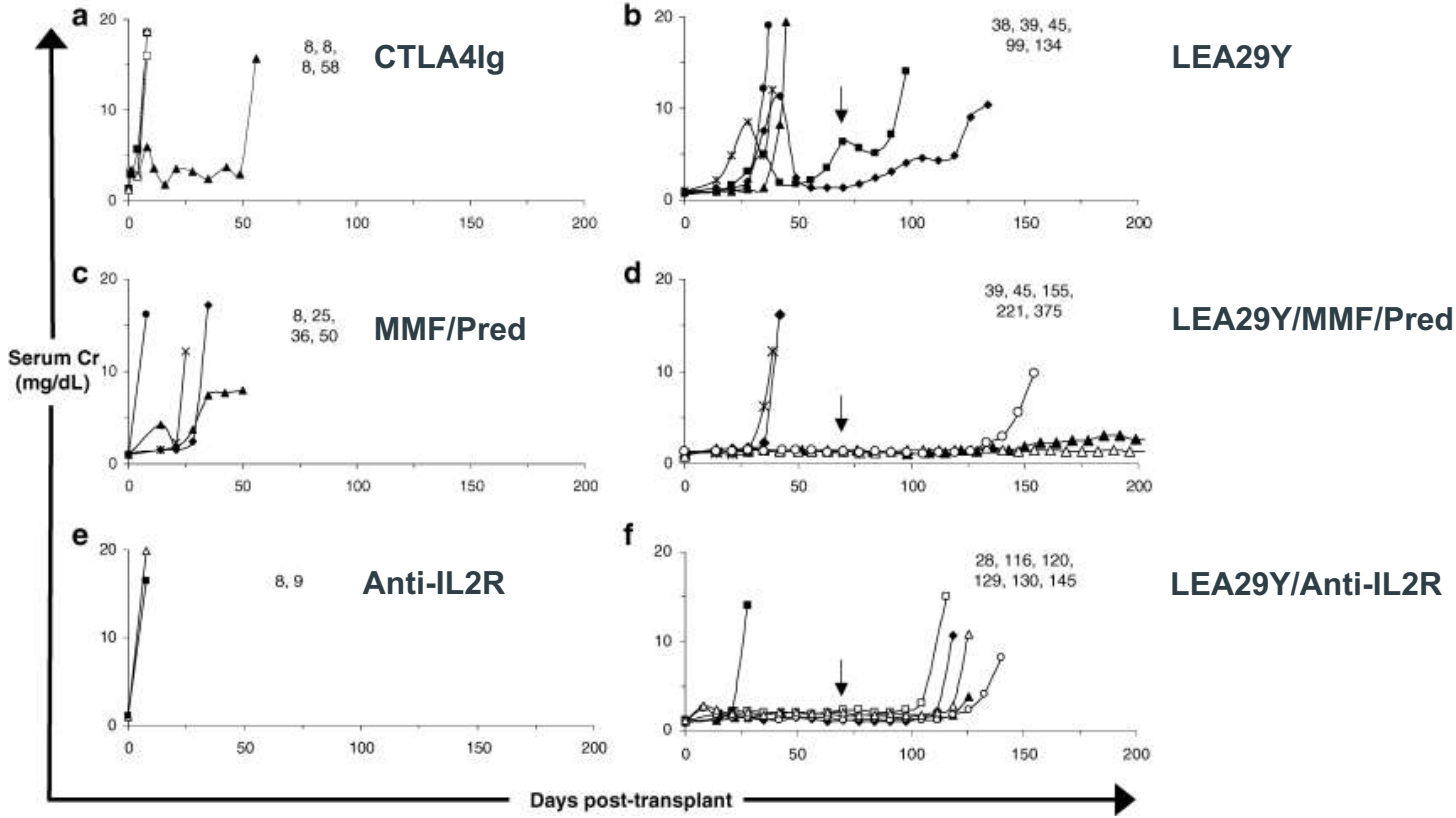
Primate Allogeneic Renal Transplantation



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LEA29Y (Nulojix): A Therapeutic Fc Fusion Protein

- Indicated to treat adult patients receiving kidney transplants
  - USA and Europe, 2011
- T1/2 ~8-10 days in humans (5.6-9 days in monkeys)

2017 Sales of Marketed Fc Fusion Proteins

Enbrel
(TNFRII), 1998, rheumatoid arthritis
$8.25B

Amevive
(LFA-3), 2003, plaque psoriasis

Orencia
(CTLA-4), 2005, rheumatoid arthritis
$2.6B

Arcalyst
(IL-1R/accessory protein), 2008, plaque psoriasis

Nplate
(TPO peptide mimetic), 2008, thrombocytopenia

Nulojix
(CTLA-4), 2011, kidney transplant

Eylea
(VEGFR1,2), 2011, wet AMD
$6.3B

Zaltrap
(VEGF1,2), 2012, colorectal cancer

Eloctate
(FVIII), 2014, hemophilia A

Alprolix
(FIX), 2014, hemophilia B

Trulicity
(GLP-1 peptide analog), 2014, type 2 diabetes
$2.2B

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Manufacturing of AD-214

January 2019

Dallas Hartman

AdAlta Chief Operating Officer

Dallas Hartman

- Over 15 years experience in the biotechnology industry
- Previously Vice President of Product Development at Nexvet where he was responsible for scalable bioprocess development, formulation, stability, analytical characterisation and cell line development
- Worked at CSL for 14 years in several roles including director of Analytical Biochemistry
- Completed postdoctoral research at the University of Texas Southwestern Medical Central and the University of Melbourne

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.

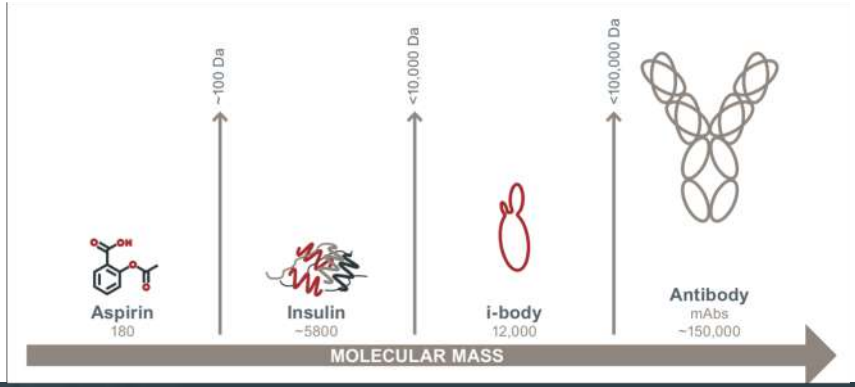
This presentation may contain forward-looking statements regarding the potential of the Company's projects and interests and the development and therapeutic potential of the company's research and development. Any statement describing a goal, expectation, intention or belief of the company is a forward-looking 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.

Why is manufacturing so important?

- Regulatory
  - Materials that are going to be given to humans as potential treatments need to meet certain standards set by government regulatory agencies
  - The process for manufacturing biologics defines the final product
  - The pathway for the development of biologics manufacturing takes 12-18 months – sometimes longer
- Safety
  - A defined process is required to produce biologics materials in order to begin clinical trials in humans
- Creating a commercial product
  - Investing time in manufacturing is critical for the success of a biologics program
  - The manufacturing process forms an integral part of a due diligence package for the potential partnering of a biologics product

Manufacturing biologics

Small Molecules	Biologics
Produced by chemical synthesis	Produced by living host cells
Low molecular weight	High molecular weight
Single molecular entity	Heterogeneous mix of similar molecules
Well defined modifications	Many modifications possible
Stable	Sensitive to many conditions
Purification relatively easy	Relatively complex purification process
Low specificity; off-target effect	High specificity



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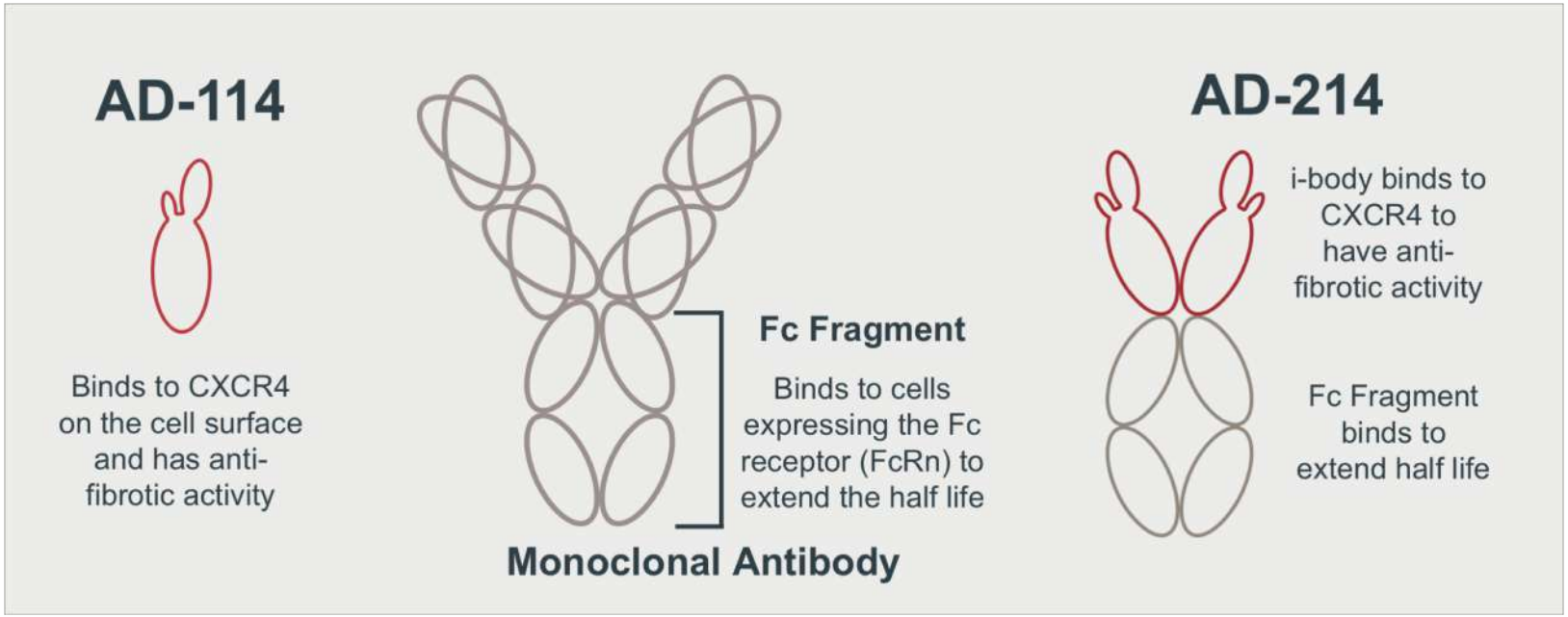
What is an Fc-Fusion?

AdAlta's lead i-body AD-214 is an Fc-Fusion



AD-214 is a superior drug candidate

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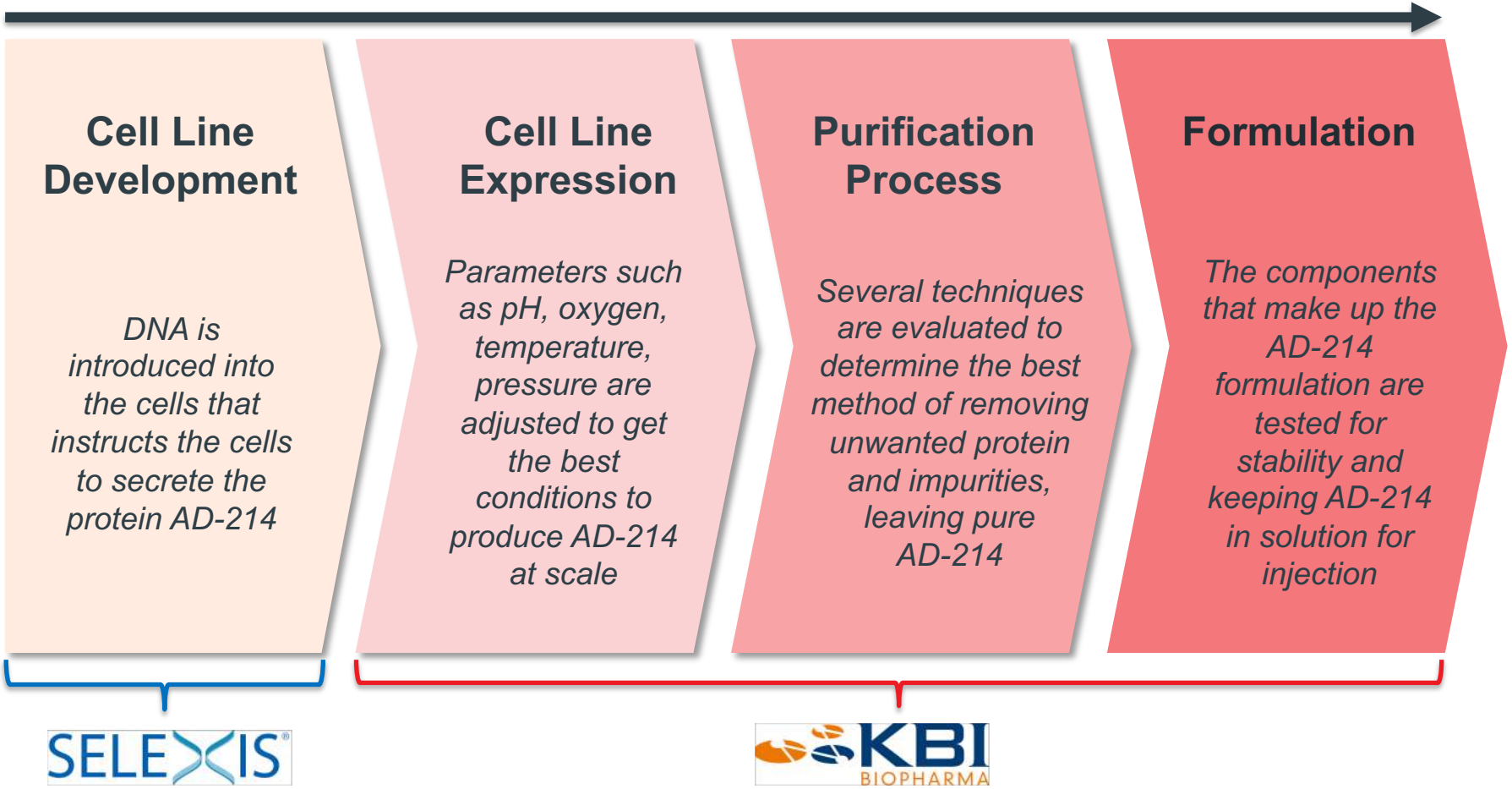
Developing AD-214 manufacturing process



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Why Selexis?

R&D & Clinical Pipeline Based on the SURE*technology*TM Platform

	PRECLINICAL	IND FILING	PHASE I	PHASE II	PHASE III	MARKET
AUTOIMMUNE/INFLAMMATORY DISEASES	23			1	3	2
BLOOD DISORDERS		1	3		1	
CANCER	20	1	15	8	1	1
METABOLIC/INFLAMMATORY DISORDERS	2	1	1	1		
DERMATOLOGY/EYE DISORDERS	1			1		
UNDISCLOSED	7					

94 CLINICAL DRUG CANDIDATES

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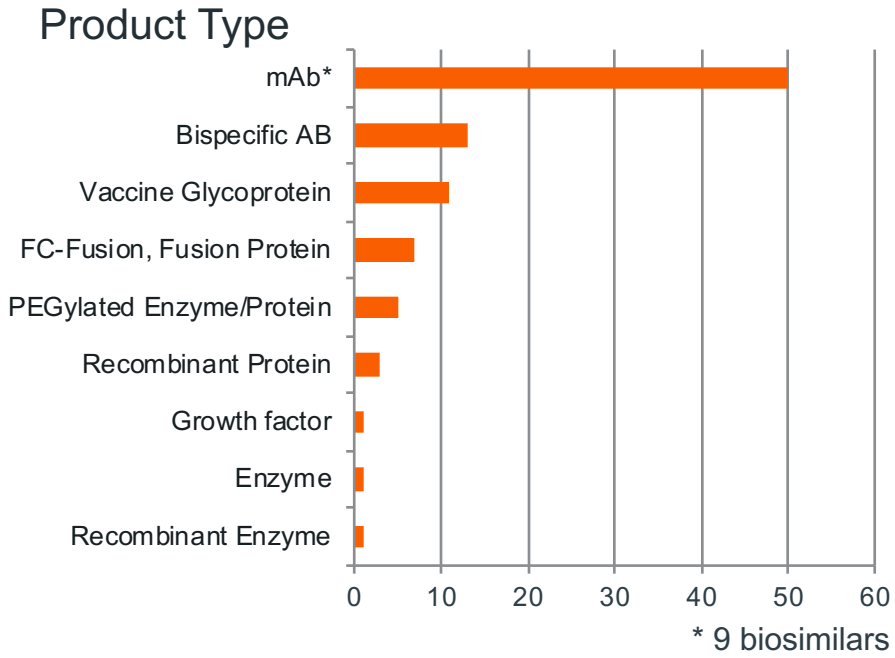
Why KBI?

Mammalian Process Development: >90 Projects



50+ programs & 12 client INDs supported per year

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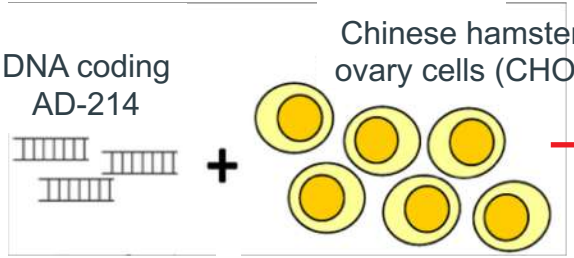
Selexis & KBI together

KBI has performed Process and Analytical Development using over 20 Selexis cell lines

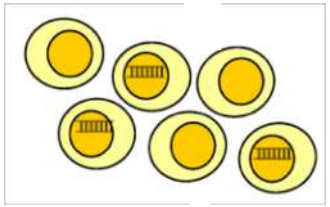
Project	Type of Molecule	Clone stage	Titer Range (g/L)
A	mAb	Final clone	4.5 - 8.5*
B	Bispecific mAb	Final clone	3.5 - 4.5
C	Fusion protein	Lead clones	2.2 - 2.8
D	Bispecific mAb	Lead clones	2.1 - 2.7
E	Bispecific mAb	Lead clones	2.0 - 2.4
F	Bispecific mAb	Lead clones	4.2 - 4.8
AdAlta	Fc- Fusion	Lead clones	2.7 - 3.3

* Example of titer improvement from first-in-human to commercial production

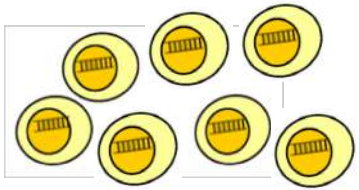
What is a clone?



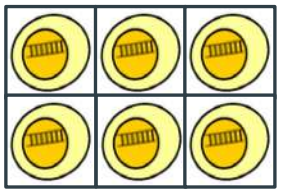
Introduce AD-214 DNA into cells



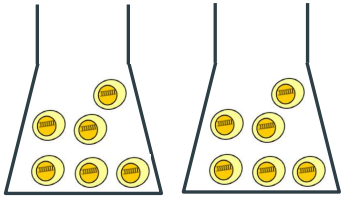
Only some cells integrate the DNA from AD-214 The cells with integrated AD-214 DNA are individual clones



Clones with only AD-214 are then selected and further evaluated



Separate individual clones are tested for production levels of AD-214



Grow highest producers at larger scale and test with more conditions

Lead clones
- Check that they are stable
- Check they are isolated from a single cell

Cell line for GMP production

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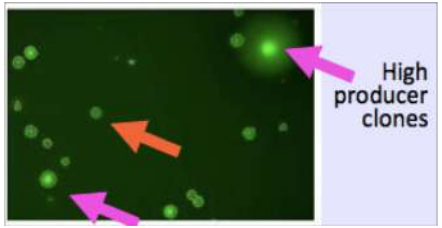
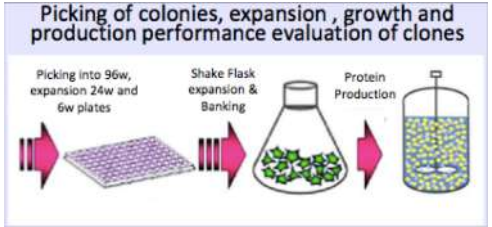
Cell line development (Selexis)

- Selexis completed the following cell line development activities:
  - Generated research cell banks (RCB) for the four lead AD-214 clones
  - Confirmed sequences of all lead clones
  - Determined copy number for all lead clones
  - Demonstrated monoclonality for all lead clones
- Cell line stability is ongoing; completion due late February
- ICH complaint documentation near complete





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Cell line expression (KBI)

- Performed for clone selection and process optimization
- Process optimization focused on product levels and quality
- Process optimization performed in scalable mini bioreactors
- Examine nutrient, media feed strategies, temperature shifts, pH, oxygen content and metabolite levels
- All four lead clones produce approximately 3g/L

Small-scale bioreactor

Lead clones

	ProA Titer (g/L)						
Days	R1	R2	R3	R4	R5	R6	R7
6	0.7	0.8	0.8	0.8	0.8	0.8	0.9
8	1.3	1.4	1.3	1.3	1.3	1.3	1.5
10	2.1	2.3	2.0	2.0	2.0	2.0	2.0
12	2.4	2.7	2.6	2.5	2.4	2.5	2.6
14	2.7	2.7	3.0	3.0	3.0	3.1	3.2
Harvest	2.4	2.5	2.9	3.0	3.0	3.1	3.1
	Clone 1		Clone 2		Clone 3		Clone 4

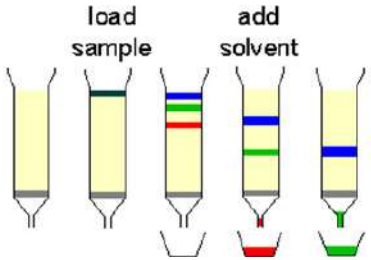
Different conditions for Clone 1

	ProA Titer (g/L)						
Days	R13	R14	R20	R21	R22	R23	R24
6	0.7	0.8	0.8	0.6	0.7	0.7	0.7
8	1.3	1.4	1.5	1.0	1.1	1.4	1.4
10	2.1	2.3	2.4	1.8	2.0	2.4	1.9
12	2.4	2.7	3.0	2.5	2.5	2.6	1.6
14	2.7	2.7	3.3	2.8	2.6	3.0	1.6
Harvest	2.4	2.5	2.9	2.5	2.4	2.7	1.5

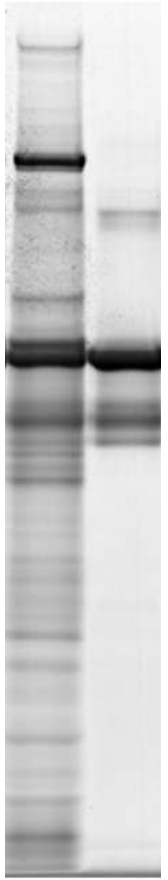
Product purification (KBI)

- Cell culture media contains the product plus contaminants that need to be removed
- Product is purified by chromatography

Add cell culture media which includes i- body AD-214, host cell proteins and other contaminants



Collect purified i- body AD-214



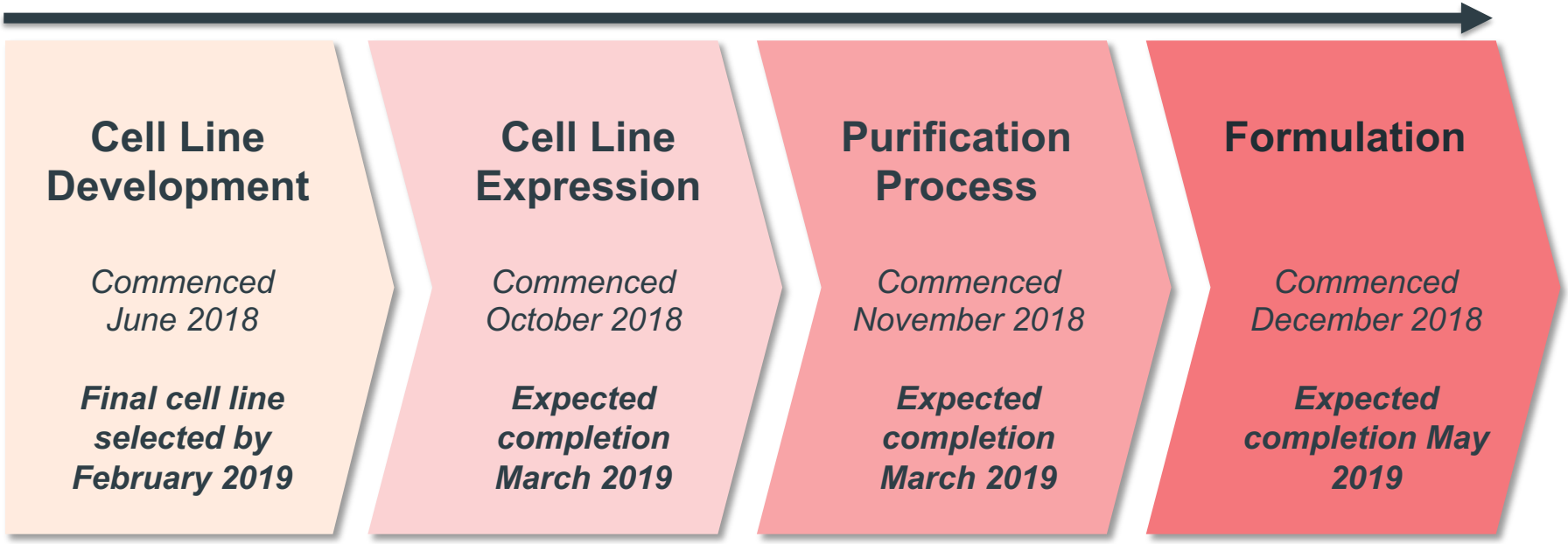
- A standard 3-step purification is being developed by KBI
  - Capture
  - Intermediate polishing
  - Final polishing
- A chromatography resin for each step has shown promising results and will be incorporated into a complete process

AdAlta

Product formulation (KBI)

- Proteins can be very sensitive to their environment
- AD-214 need to be in a solution that keeps it stable and active over long periods of time
- Screen different additives (excipients) to determine most appropriate formulation solution
- Early screening of additives has been completed

AD-214 manufacturing progress



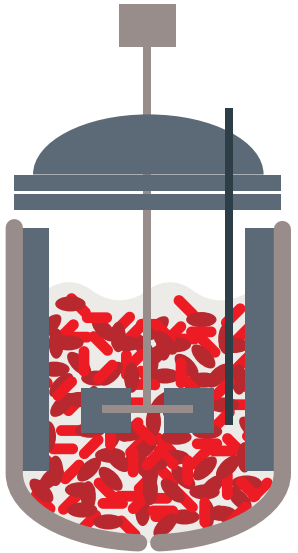
SELEXIS®

KBI BIOPHARMA

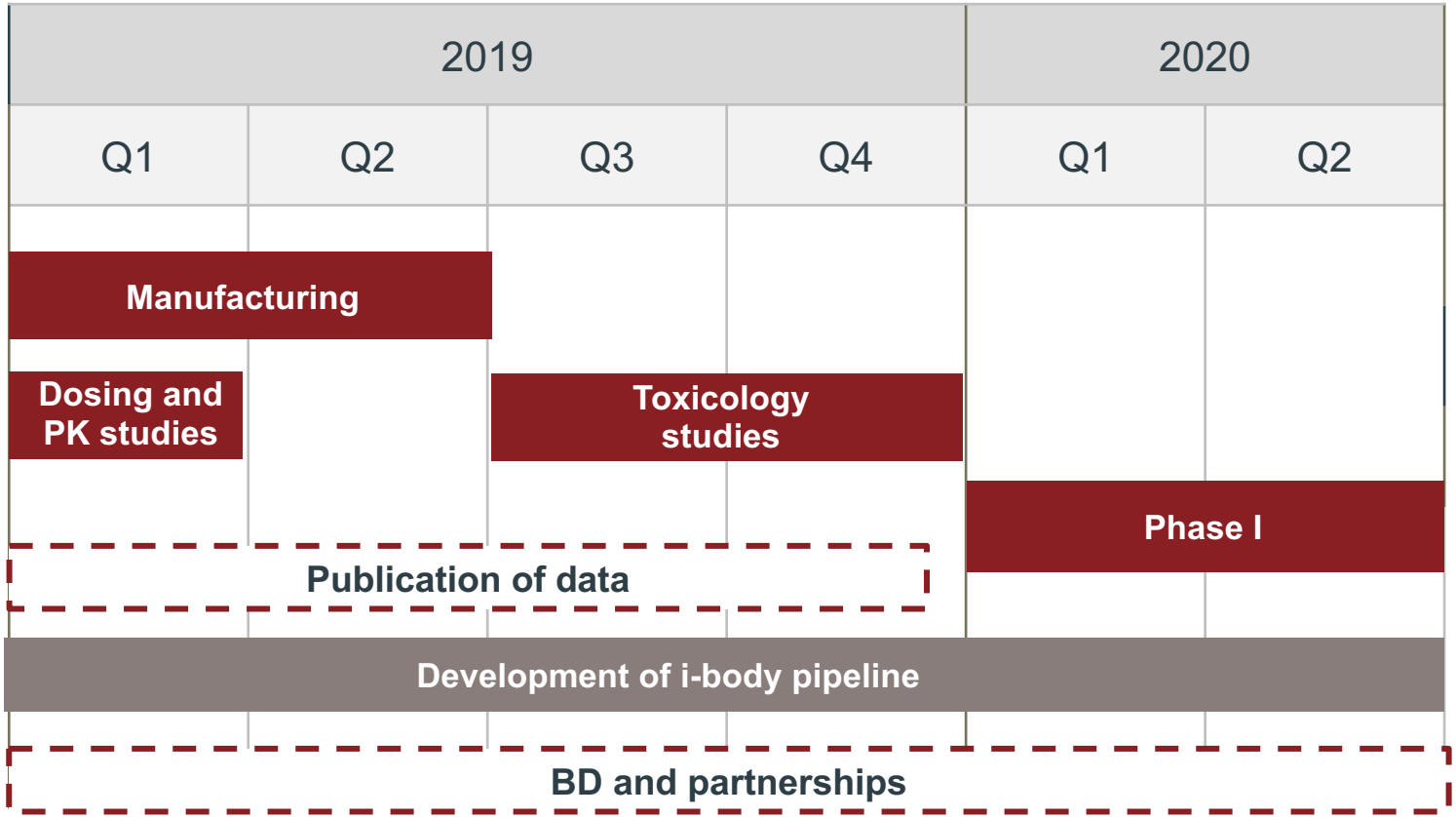
AdAlta

Manufacturing Milestones

Milestone	Expected Date
Cell line development	February 2019 ✓
Optimisation of process development and formulation	March 2019
AD-214 material available for toxicity studies	June 2019
AD-214 material available for Phase I clinical study	December 2019



AD-214 development: key milestones



AdAlta

AD-214 manufacturing summary

- AD-214 has significant pre-clinical validation demonstrating broad anti-fibrotic and anti-inflammatory effects as well as safety
- Cell line development results are now ahead of expectations at 3 grams per litre (3g/L), up from the 1g/L reported in October 2018
- On track to deliver non-Good Manufacturing Practice (non-GMP) material for its four-week non-human primate toxicology study to commence in July 2019
- On track to deliver Good Manufacturing Practice (GMP) material for its Phase 1 human study which is expected to commence in January 2020

AdAlta working successfully with Selexis and KBI to provide materials for progression of AD-214 to the clinic

AdAlta

next generation protein therapeutics

Pulmonary fibrosis – current state of play in Idiopathic Pulmonary Fibrosis

A/Prof Glen Westall

Lung Fibrosis Service, Alfred Hospital

NHMRC Centre of Research Excellence: Lung Fibrosis

Glen Westall

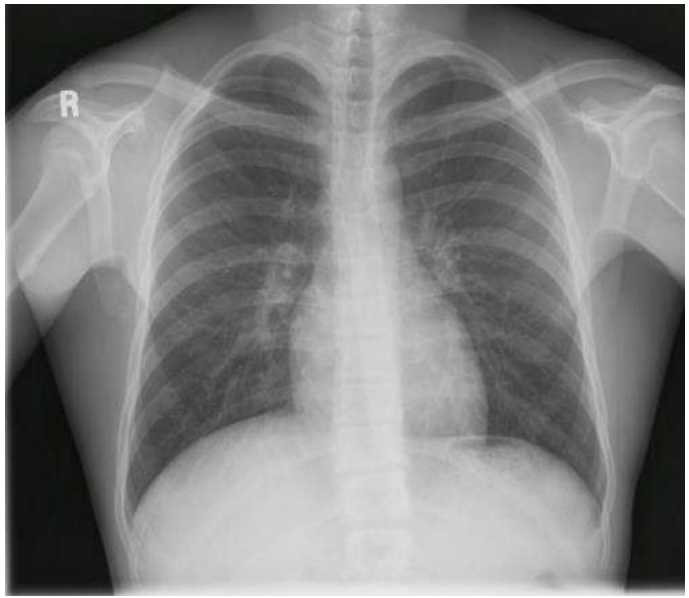
- Completed undergraduate medical training at King's College Medical School in London, UK, before
- Training in general and respiratory medicine at the Royal Brompton Hospital in London and the Alfred Hospital in Melbourne.
- Clinical interests include advanced lung disease, bronchoscopy and lung transplantation
  - Physician-in-charge of the Paediatric Lung Transplant program at the Alfred.
- Research interests parallel his clinical expertise in advanced lung disease and lung transplantation.
  - Wider interest into how activation of the innate immune system early post-lung transplant influences clinical outcomes.
  - Establishing a research platform in pulmonary xenotransplantation has resulted in the award of an internationally competitive Career Development Award
  - principal and co-investigator on numerous studies in lung transplantation and bronchoscopic lung volume reduction.

Lung Fibrosis

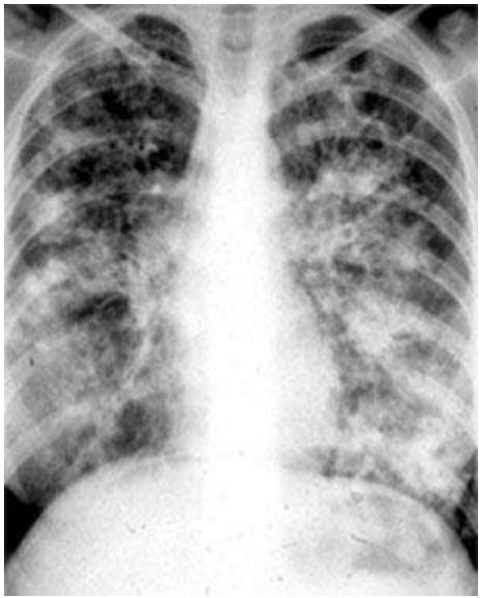
Scaring of the Lung

Lungs become stiff

Lungs shrink in size

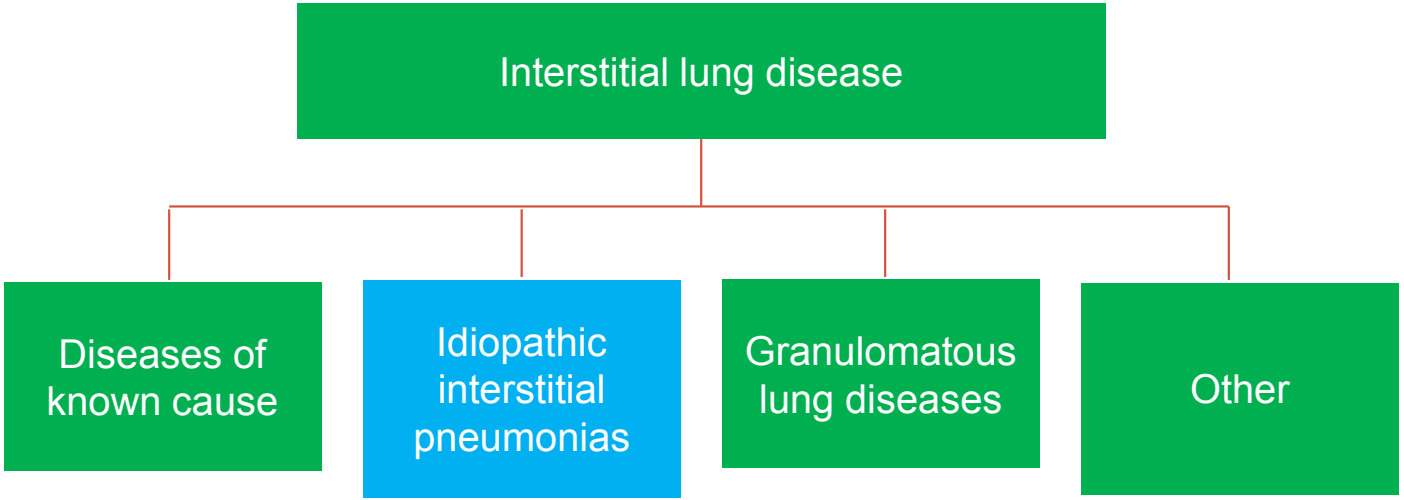


Normal CXR



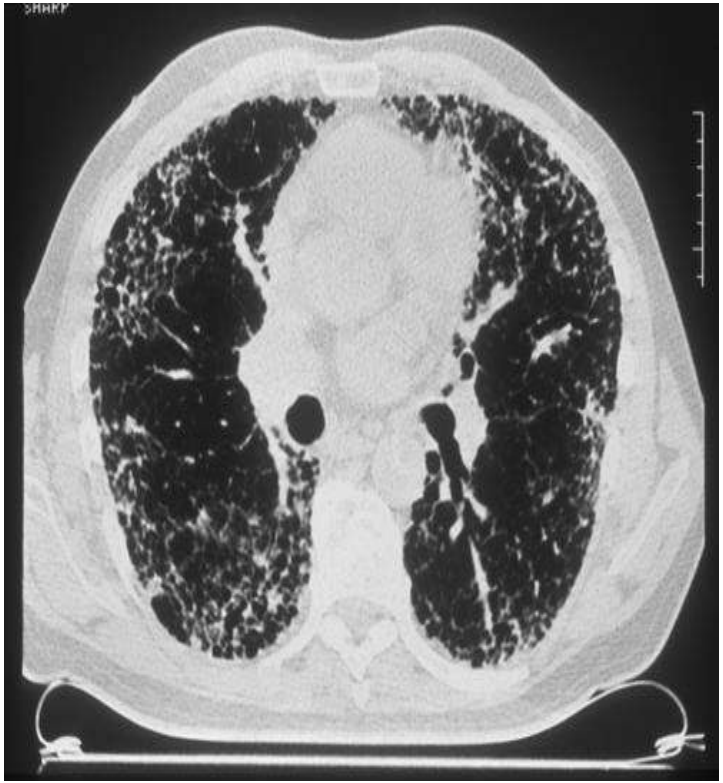
Lung Fibrosis

Interstitial lung disease (ILD) classification



Multiple subtypes – over 200 types of disorder in total!

Idiopathic Pulmonary Fibrosis (IPF)



Represents 50% of all Fibrotic Lung Conditions

Male:Female	1.5:1
Age of Presentation	66 yrs
Smoking history	70%
Australian IPF Cases	5000-10,000

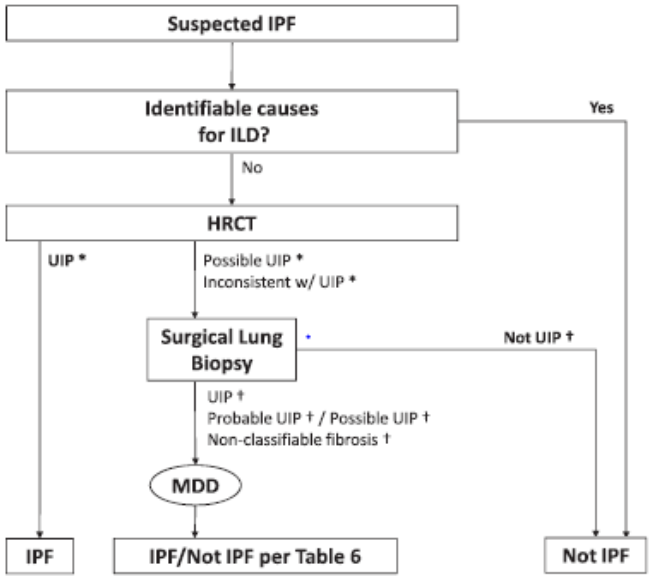
Diagnosed by MDT Meeting

Lungs deteriorate over time

AdAlta

IPF Diagnosis: Multi-Disciplinary Team (MDT) meeting

- Communication between clinician, radiologist and when appropriate pathologist
- Clinical data
  - Presentation, Exposures, Smoking status, Associated disease, Lung function and Radiologic findings



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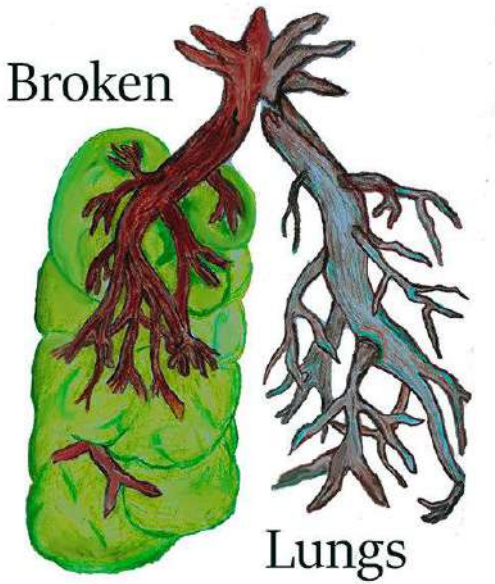
Traditional Therapy for IPF: historical view

- Uncontrolled Chronic Inflammation
  - Corticosteroids
  - Cyclophosphamide
  - Azathioprine

  - N-acetylcysteine (NAC)



2011 Evidence Based Guidelines: Treatment recommendations

Agent	For	Against
Corticosteroids		**Strong +**
Colchicine		**Strong +**
Cyclosporine A		**Strong +**
Corticosteroid and imm-mod		**Strong ++**
Interferon gamma		**Strong ++++**
Bosentan		**Strong +++**
Etanercept		**Strong +++**
NAC, predisolone, azathioprine		**Weak ++**
NAC monotherapy		**Weak ++**
Anticoagulation		**Weak +**
Pirfenidone		**Weak ++**

Raghu et al. Am J Respir Crit Care Med Vol 183. pp 788–824, 2011

2011 Evidence Based Guidelines: Treatment recommendations

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Corticosteroids		**Strong +**
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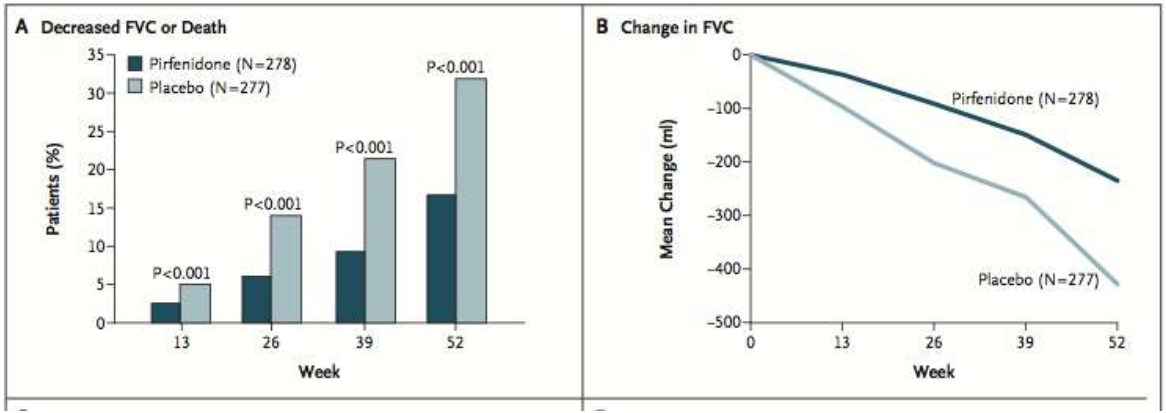
Etanercept		**Strong +++**
NAC, predisolone, azathioprine		**Weak ++**
NAC monotherapy		**Weak ++**
Anticoagulation		**Weak +**
Pirfenidone		**Weak ++**

Raghu et al. Am J Respir Crit Care Med Vol 183. pp 788–824, 2011

2014: A big year for lung fibrosis!

Pirfenidone approved by FDA

Reduction in mortality and decreased FVC



47% reduction in proportion of patients with a decline in FVC

Pooled data: Ascend & Capacity studies

All cause mortality ↓ 48%

IPF deaths ↓ 68%

NEJM 2014; 370: 2083

Adverse Events

Table 3. Adverse Events.*

Adverse Event	Pirfenidone (N=278)	Placebo (N=277)
	no. of patients (%)	
Cough	70 (25.2)	82 (29.6)
Nausea	100 (36.0)	37 (13.4)
Headache	72 (25.9)	64 (23.1)
Diarrhea	62 (22.3)	60 (21.7)
Upper respiratory tract infection	61 (21.9)	56 (20.2)
Fatigue	58 (20.9)	48 (17.3)
Rash	78 (28.1)	24 (8.7)
Dyspnea	41 (14.7)	49 (17.7)
Dizziness	49 (17.6)	36 (13.0)
Idiopathic pulmonary fibrosis†	26 (9.4)	50 (18.1)
Bronchitis	39 (14.0)	36 (13.0)
Constipation	32 (11.5)	38 (13.7)
Back pain	30 (10.8)	37 (13.4)
Dyspepsia	49 (17.6)	17 (6.1)
Nasopharyngitis	33 (11.9)	30 (10.8)
Anorexia	44 (15.8)	18 (6.5)
Vomiting	36 (12.9)	24 (8.7)
Decrease in weight	35 (12.6)	22 (7.9)
Gastroesophageal reflux	33 (11.9)	18 (6.5)
Insomnia	31 (11.2)	18 (6.5)

2014: A big year for lung fibrosis!

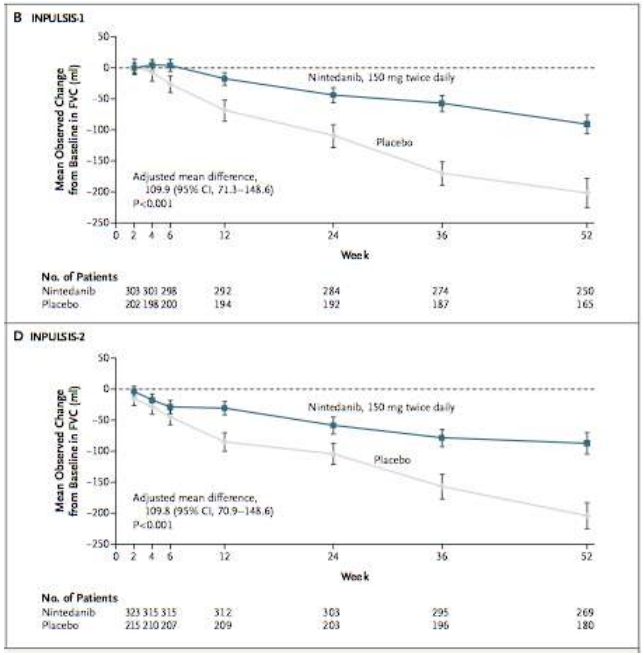
Nintedanib approved by FDA

Reduction in mortality and decreased FVC

Intracellular inhibitor of multiple tyrosine kinases

NB: Not curative

Secondary end points not achieved



Adverse Events

Table 3. Adverse Events.

Event	INPULSIS-1		INPULSIS-2	
	Nintedanib (N=309)	Placebo (N=204)	Nintedanib (N=329)	Placebo (N=219)
	number of patients (percent)			
Any adverse event	298 (96.4)	181 (88.7)	311 (94.5)	198 (90.4)
Any adverse event, excluding progression of idiopathic pulmonary fibrosis*	296 (95.8)	179 (87.7)	311 (94.5)	197 (90.0)
Most frequent adverse events†				
Diarrhea	190 (61.5)	38 (18.6)	208 (63.2)	40 (18.3)
Nausea	70 (22.7)	12 (5.9)	86 (26.1)	16 (7.3)
Nasopharyngitis	39 (12.6)	34 (16.7)	48 (14.6)	34 (15.5)
Cough	47 (15.2)	26 (12.7)	38 (11.6)	31 (14.2)
Progression of idiopathic pulmonary fibrosis*	31 (10.0)	21 (10.3)	33 (10.0)	40 (18.3)
Bronchitis	36 (11.7)	28 (13.7)	31 (9.4)	17 (7.8)
Upper respiratory tract infection	28 (9.1)	18 (8.8)	30 (9.1)	24 (11.0)
Dyspnea	22 (7.1)	23 (11.3)	27 (8.2)	25 (11.4)
Decreased appetite	26 (8.4)	14 (6.9)	42 (12.8)	10 (4.6)
Vomiting	40 (12.9)	4 (2.0)	34 (10.3)	7 (3.2)
Weight loss	25 (8.1)	13 (6.4)	37 (11.2)	2 (0.9)
Severe adverse events‡	81 (26.2)	37 (18.1)	93 (28.3)	62 (28.3)
Serious adverse events‡	96 (31.1)	55 (27.0)	98 (29.8)	72 (32.9)
Fatal adverse events	12 (3.9)	10 (4.9)	25 (7.6)	21 (9.6)
Adverse events leading to treatment discontinuation§	65 (21.0)	22 (10.8)	58 (17.6)	33 (15.1)
Gastrointestinal disorders	26 (8.4)	3 (1.5)	21 (6.4)	2 (0.9)
Respiratory, thoracic, and mediastinal disorders	12 (3.9)	10 (4.9)	8 (2.4)	18 (8.2)
Investigation results¶	10 (3.2)	1 (0.5)	8 (2.4)	1 (0.5)
Cardiac disorders	5 (1.6)	4 (2.0)	2 (0.6)	3 (1.4)
General disorders and conditions involving site of study-drug administration‖	8 (2.6)	3 (1.5)	2 (0.6)	1 (0.5)

Study discontinuation 5%

Treatment era for IPF

- Anti-fibrotics approved in 2014 by FDA
- Change in FVC does not equate to improved quality of life (QOL) or survival
- No IPF studies will be powered to show survival advantage
- QOL important as 61.5% develop diarrhoea with Nintedanib and 36% develop nausea with pirfenidone

EDITORIAL

Clinical Trials in Idiopathic Pulmonary Fibrosis in the "Posttreatment Era"

Kevin F. Gibson, MD; Daniel J. Kass, MD

The "treatment era" for idiopathic pulmonary fibrosis (IPF) in the United States and other countries was inaugurated in November 2014 following the Food and Drug Administration's (FDA's) approval of pirfenidone and nintedanib as treatments for IPF.[1] Even the most optimistic pulmonologists may have doubted that such a day would ever arrive, let alone a day when a practicing clinician would have not 1, but 2 medications to treat IPF. The FDA approved pirfenidone and nintedanib on the basis of published studies that showed these therapies slowed the rate of deterioration of forced vital capacity (FVC).[2,3]

Related article page 2299

The change in FVC, referred to as a clinically meaningful end point in IPF,[4,5] is used as a surrogate for the ultimate question in IPF—does therapy stop progression and improve survival? The clinician prescribing these medications is left with the unsatisfying published results that neither nintedanib nor pirfenidone convincingly enhance survival or improve quality of life. However, the pirfenidone and nintedanib studies were not powered to detect changes in mortality,[6] and it is unlikely that any IPF trial will ever focus on mortality.[7] How to design IPF clinical studies has often been debated.[4,5] Nevertheless and aside from the academic debates over IPF trial design, the concerns about adverse effects in older patients, combined with uncertain therapeutic outcomes, give many clinicians pause when considering prescribing these new drugs. Diarrhea occurred in 61.5% of patients treated with nintedanib, and nausea occurred in 36% of pirfenidone-treated patients.[2,3]

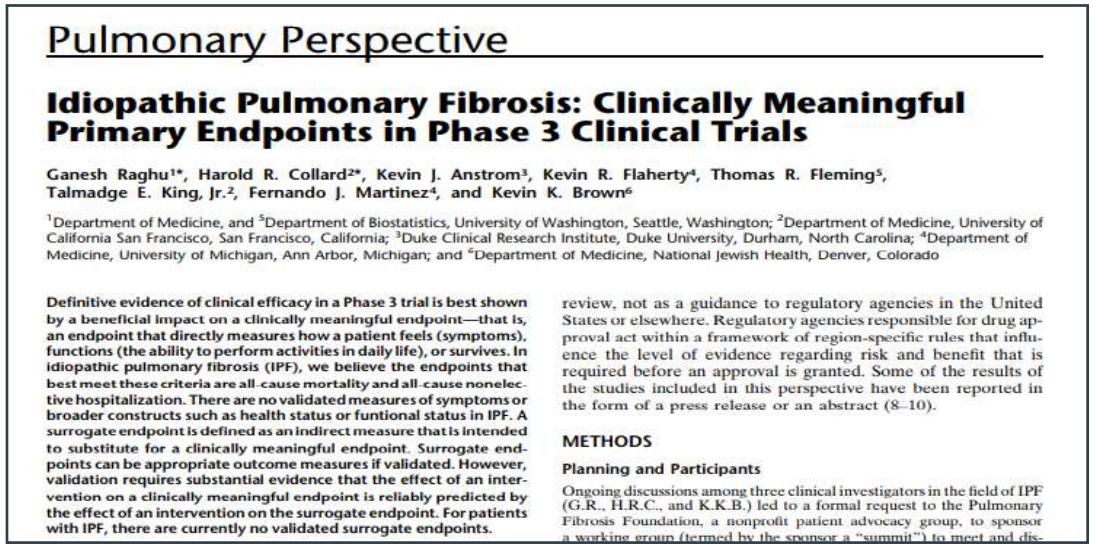
In this issue of *JAMA*, Raghu and colleagues[8] report the results of a phase 2 randomized clinical trial that tested recombinant human pentraxin 2 (also known as PRM-151) vs placebo in patients with IPF. A smaller clinical trial (reported in 2016) showed that treatment with recombinant human pentraxin 2 was relatively safe, increased plasma levels of pentraxin 2, and was associated with a nonsignificant (and very modest) improvement in FVC and 6-minute walk distance.[9]

In the study by Raghu et al,[8] 117 patients with a clinical diagnosis of IPF, based on 2011 guidelines,[10] were included if they had FVC between 50% and 90% and diffusing capacity for carbon monoxide (DLCO) between 25% and 90% predicted. Concurrent therapy with current FDA-approved medications was permitted if the dosing was stable for 3 months. Following a 4-week screening period, patients were then randomized to receive 4 intravenous infusions of drug (10 mg/kg) every 4 weeks or placebo. Patients were followed up for 24 weeks. The primary outcome was mean change in FVC (% predicted value) from baseline to week 28. Secondary end points included volumetric analysis using high-resolution computed tomographic scanning and change in 6-minute walk distance.

At week 28, the change in FVC (% predicted value) among patients treated with placebo was −4.8 compared with −2.5 among patients treated with recombinant human pentraxin 2 (mean difference, 2.3 [90% CI, 1.1-3.5]; $P = .001$). Among secondary end points, the change in 6-minute walk distance was −0.5 m among patients treated with recombinant human pentraxin 2 compared with −31.8 m in patients treated with placebo (difference, 31.3 m [90% CI, 17.4-45.1]; $P < .001$). The study showed that the rate of deterioration of FVC percentage of predicted value was significantly slower in the recombinant human pentraxin 2 group vs the placebo group. The authors noted the rate of adverse events was similar between the placebo group and drug treatment group. Cough was observed more frequently among patients in the recombinant human pentraxin 2 group (18%) than the placebo group (5%).

The findings reported by Raghu et al[8] are cause for optimism. A strong body of mechanistic evidence supports the potential efficacy of the drug. Pentraxin 2 knockout mice developed exaggerated bleomycin-induced pulmonary fibrosis.[11] In a murine model of kidney fibrosis, recombinant human pentraxin 2 was associated with decreased kidney failure, improved histology, and improved survival.[12] Collectively, the experimental research has elucidated both a potential receptor and signaling pathway. In macrophages and epithelial cells, recombinant human pentraxin 2 attenuated activator protein-1 signaling activity.[12] In the lung, stimulation of a novel putative receptor for pentraxin 2, DC-SIGN (dendritic cell–specific intercellular adhesion molecule-3-grabbing nonintegrin), which is present on monocytes and neutrophils, attenuated fibrocyte differentiation and collagen deposition in bleomycin-injured mice.[13] However, further mechanistic studies[14] are needed to help determine ways that the parent compound can be enhanced for therapeutic efficacy. In the case of pirfenidone and nintedanib, comparable mechanistic data are lacking.[14] A bedside-to-bench approach could leverage the results of clinical trials to guide basic science researchers to study mechanisms that clearly affect clinical phenotypes.

Despite the impressive results of this phase 2 trial reported by Raghu et al,[8] the next step is for recombinant human pentraxin 2 to proceed to phase 3. The investigators are experienced IPF trialists who recognize the need for further research and present a balanced discussion that illustrates restrained excitement. Success in phase 2 studies of agents with strong biological rationale does not necessarily portend success in phase 3 trials. Accepting



Pulmonary Perspective

Idiopathic Pulmonary Fibrosis: Clinically Meaningful Primary Endpoints in Phase 3 Clinical Trials

Ganesh Raghu[1*], Harold R. Collard[2*], Kevin J. Anstrom[3], Kevin R. Flaherty[4], Thomas R. Fleming[5], Talmadge E. King, Jr.[2], Fernando J. Martinez[4], and Kevin K. Brown[6]

[1]Department of Medicine, and [5]Department of Biostatistics, University of Washington, Seattle, Washington; [2]Department of Medicine, University of California San Francisco, San Francisco, California; [3]Duke Clinical Research Institute, Duke University, Durham, North Carolina; [4]Department of Medicine, University of Michigan, Ann Arbor, Michigan; and [6]Department of Medicine, National Jewish Health, Denver, Colorado

Definitive evidence of clinical efficacy in a Phase 3 trial is best shown by a beneficial impact on a clinically meaningful endpoint—that is, an endpoint that directly measures how a patient feels (symptoms), functions (the ability to perform activities in daily life), or survives. In idiopathic pulmonary fibrosis (IPF), we believe the endpoints that best meet these criteria are all-cause mortality and all-cause nonelective hospitalization. There are no validated measures of symptoms or broader constructs such as health status or funtional status in IPF. A surrogate endpoint is defined as an indirect measure that is intended to substitute for a clinically meaningful endpoint. Surrogate endpoints can be appropriate outcome measures if validated. However, validation requires substantial evidence that the effect of an intervention on a clinically meaningful endpoint is reliably predicted by the effect of an intervention on the surrogate endpoint. For patients with IPF, there are currently no validated surrogate endpoints.

review, not as a guidance to regulatory agencies in the United States or elsewhere. Regulatory agencies responsible for drug approval act within a framework of region-specific rules that influence the level of evidence regarding risk and benefit that is required before an approval is granted. Some of the results of the studies included in this perspective have been reported in the form of a press release or an abstract (8–10).

METHODS

Planning and Participants

Ongoing discussions among three clinical investigators in the field of IPF (G.R., H.R.C., and K.K.B.) led to a formal request to the Pulmonary Fibrosis Foundation, a nonprofit patient advocacy group, to sponsor a working group (termed by the sponsor a "summit") to meet and dis-

AJRCCM 2012

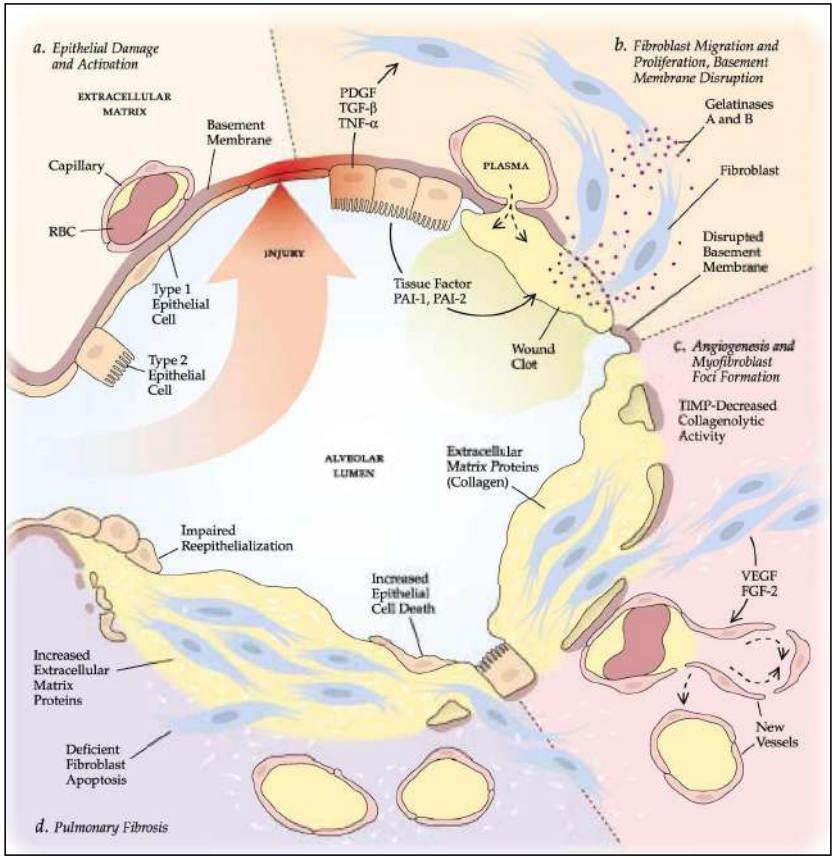
- Survival
- Hospitalisation
- (acute exacerbation)
- (functional status – 6MWT)

Clinical meaningful endpoints – reflect how a patient feels, functions or survives

AdAlta

Unmet clinical need: drugs in development

- Current drugs have limited efficacy and substantial side effects
- Other anti-fibrotic and anti-angiogenic agents currently in development with multiple targets
  - Inhaled Pirfenidone
  - WNT signaling
  - FG-3019
  - Zileutin
  - ACE inhibitors
  - Anti-vβ6 integrin
  - Imatanib
  - LOXL-2
  - CXCR4



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Clinical trials

Phase I	
PharmAkea	PharmAkea have demonstrated safety for PAT-1251 currently in trials for several fibrotic conditions.
Vicore Pharma	Phase I trial completed and a Phase II trial planned for lead fibrosis candidate C21.
Aeolus Pharmaceuticals	Currently completing Phase I for AEOL-10150 which has been grated FDA Orphan Drug Designation.
GalxoSmithKline	GSK-3008348 have completed Phase I and a Phase II trial is planned.
Other companies currently completing Phase I studies in IPF include:	Samumed (SM-04646), ZAI Lab (ZL-2102), Moerae Matrix (MMI-0100) and Pharmaxis (PXS-5338K)

Phase II	
Kadmon	Top line results of Phase II trial for KD025 released, currently completing trial expansion.
Biogen Inc	Biogen have completed a small Phase II trial for BG-00011 in IPF patients and have plans to initiate a second larger Phase II trial in 2018.
Galapagos	Galapagos have recently begun recruiting a Phase II trial for an additional IPF therapeutic, GLPG1205
Bristol Myers Squibb	BMS is completing a Phase II trial for BMS-986263, an RNAi compound licensed from Nitto BioPharma Inc. BMS have also obtained exclusive rights to acquire PRM-151 from Promedior following the completion of Phase II trials.
Galecto Biotech	Galecto Biotech have completed a small Phase IIa trial for TD-139 in IPF patients that demonstrated safety but efficacy is yet to be determined.
Other companies currently completing Phase II studies in IPF include:	MediciNova (tipelukast), Kasiak Research (Refacell-IPF), Celgene Corporation (CC-90001), Merck & Co (gefapixant), Novartis (VAY-736) and Taiho Pharmaceutical (TAS-115)

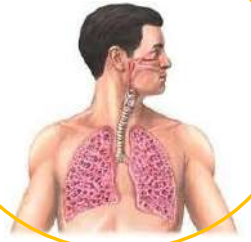
Phase III	
Galapagos	Began recruitment for the first of two Phase III studies for GLPG1690 in December 2018, recruiting a total of 1500 IPF patients.
Fibrogen	Phase III trial announced for Pamrevlumab, recruitment of 500 IPF patients to commence in January 2019.
ProMetic Life Sciences	Clinical trial design for Phase III study of PBI-4050 announced, yet to commence recruitment.
Promedior	Phase III study for PRM-151 announced following successful Phase II, aim to commence recruitment in 2019.

Drug Discovery and translational research

In-vitro science

Animal model

Human IPF Tissue



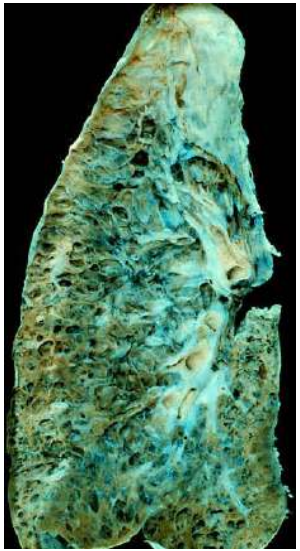
Clinical Trials

Assessment of human IPF tissue provides additional evidence of efficacy prior to clinical trials

AdAlta

Alfred Tissue Bank

- National resource
- Collaborations (Academic and Commercial entity)
- Creation of pilot data
- Conduit: Alfred Lung Transplant Program (n=100)

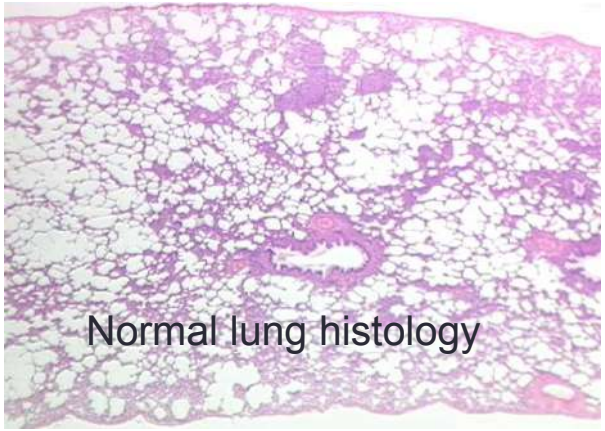


ILD Explant Lungs

Normal Lungs donated for research (Donate Life)

CXCR4 Role in IPF

Very limited expression in normal or non-diseased tissues



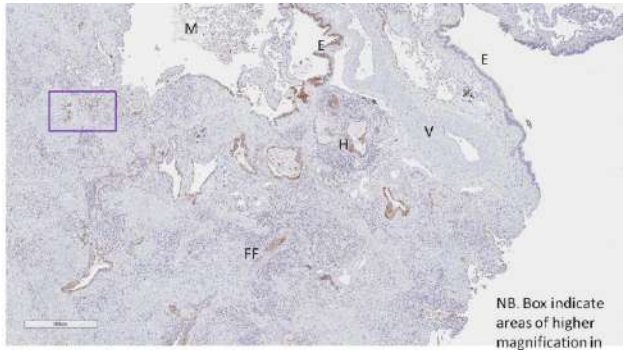
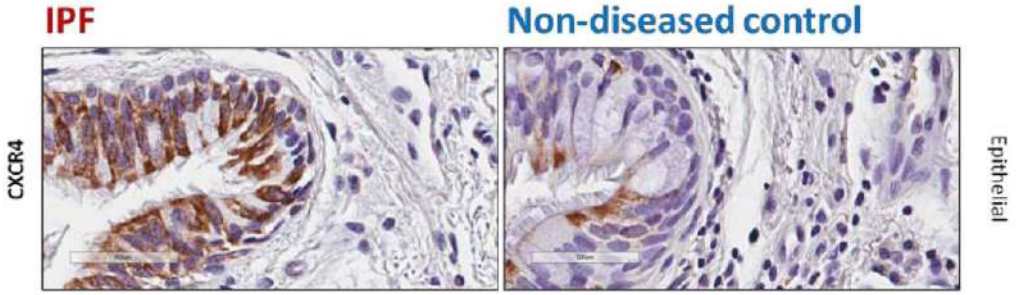


Figure 5. Immunohistochemical staining of IPF lung tissue for CXCR4 (brown). 8x magnification, scale bars are 500 µm.

CXCR4 is upregulated in IPF tissue



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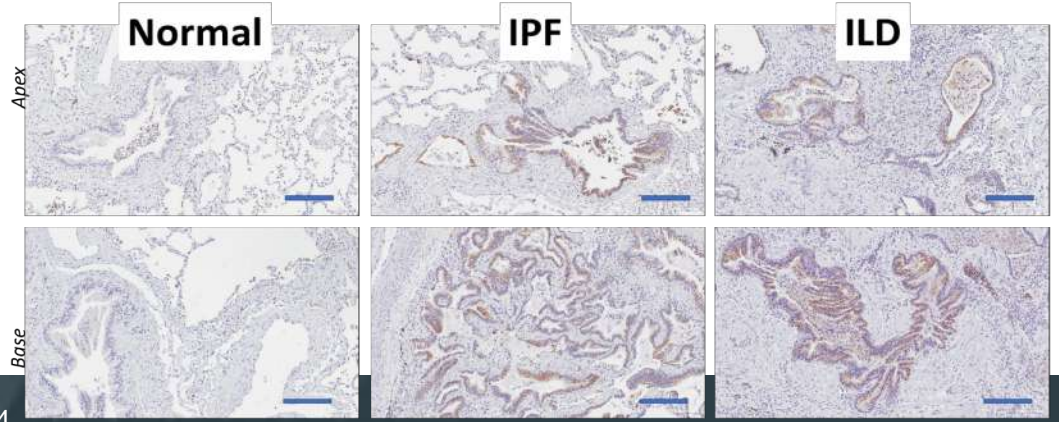
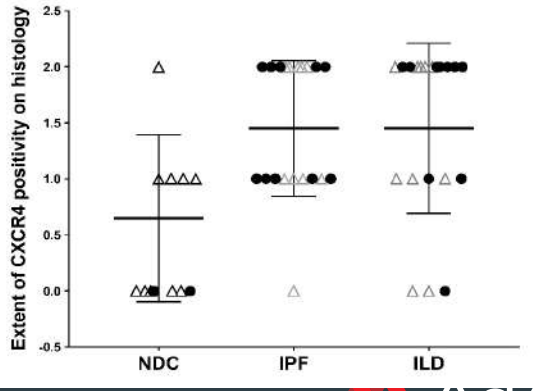
CXCR4 abundantly expressed in both IPF and ILD patient lung tissue

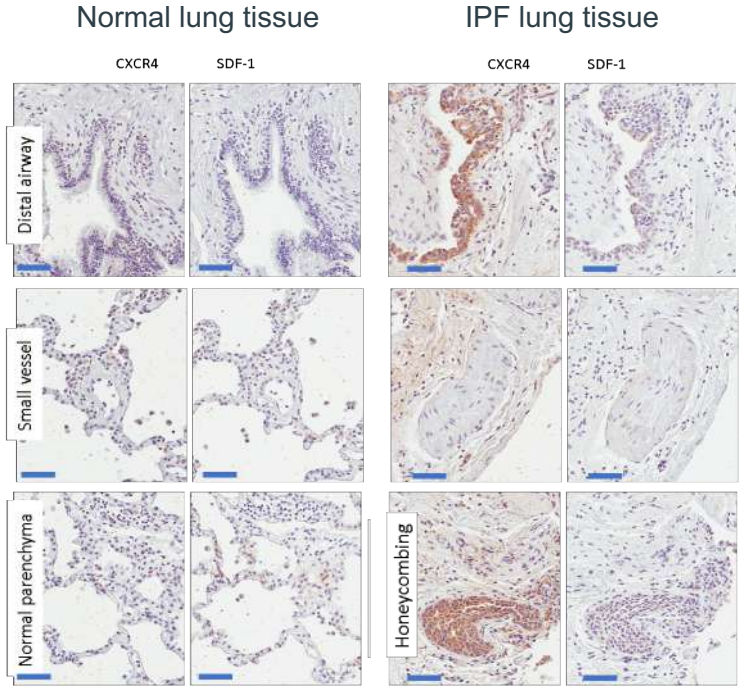
- Lung tissue was sampled from lung apex (∆) and lung bases (•) of patients with IPF, ILD and donors with no lung disease (NDC) and stained immunohistochemically for CXCR4 expression
- CXCR4 was abundantly expressed in both IPF and ILF donors compared with non-diseased controls, with only 3 patients with non-IPF ILD and 1 patient with IPF having no CXCR4 (n=40)
- CXCR4 expression is not exclusively limited to circulating immune cells and we have demonstrated that CXCR4 is significantly upregulated in the **fibrotic airway epithelium** of patients with IPF and other fibrotic ILDs
- CXCR4 is elevated in honeycombing seen largely in the lung bases of patients with IPF
- Significant CXCR4 expression was also observed in the distal airways of the lung





CXCR4 is expressed in honeycomb cysts, vessels and distal airways

- CXCR4 expressed in distal airways, small vessels and honeycombing
- Immunostaining of serial sections of lung tissue for CXCR4 and SDF-1 demonstrated heterogeneity in the expression of both molecules amongst patients with IPF and largely negative expression in normal donors
- In normal tissue, CXCR4 and SDF-1 expression was homogenous



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Summary

- Increasing understanding of the pathophysiology
- Treatments (albeit limited)
- Many Lung Fibrosis services/clinics

Need better therapies for a terminal disease!!

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The IPF Landscape

Dr Steve Felstead

Clinician and Member of AdAlta Scientific Advisory Board

Steve Felstead

- Retired in 2014 from the position of Vice President, Head of Clinical Research, Pharmatherapeutics Division, Pfizer Inc
- Joined Pfizer in 1989, having qualified in Medicine at Leeds University UK in 1982.
- Appointed Head of Clinical Research in January 2009 responsible for Clinical Development and Pharmacology, Translational and Molecular Medicine, Preclinical and Clinical Statistics.
  - responsible for research projects up to Proof of Concept (Phase 2a) in the following Therapeutic Areas: Neuroscience, Cardiovascular and Metabolic Disease, Anti-Infectives, Pain and Regenerative Medicine.
  - roles at Pfizer included Zithromax (azithromycin) clinical project manager in Europe, head of clinical development in Sandwich, Viagra (sildenafil) development team leader, Vfend (voriconazole) development team leader and Groton/New London development site head.
  - led the Viagra (sildenafil) team when the first pulmonary hypertension study was being designed, which led to the successful Revatio development program.
  - From 2003-2007 he led the Celsentri/Selzentry (maraviroc) team through to successful transatlantic registration of this novel anti-retroviral medicine.
- Since retirement Steve consults widely on various programmes for VC, Biotech, and Pharma.
- Member of Innovate UK, Biomedical Catalyst Late Stage Award committee and a member of Tweed Renaissance Investment Capital Group, which invests in emerging businesses.

Current Targeted Pharmacotherapy for IPF

Pirfenidone (Esbriet)

- US Approval October 15th 2014 – previous rejection in 2010 (albeit positive advisory committee vote) with FDA requiring an additional study.
  - Sales 1st 9 months of 2018 CHF739MM approximately same in US$
  - 16% increase on 1st 9 months of 2017.
  - On course to sell $1BN in 2018 full year.

Nintedanib (Ofev)

- US Approval October 15th 2014
  - Sales 1st half of 2018 $620MM
  - 35% increase on 1st 6 months of 2017
  - On course for > $1BN sales in 2018 full year

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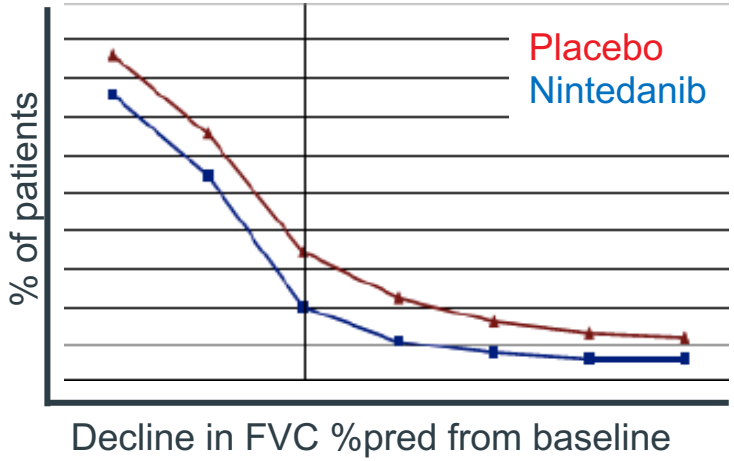
Pirfenidone Background

- Long regulatory history, approval in Japan and then EU, pre-dating US approval. Three efficacy studies were eventually required for FDA.
- The mechanism of action of pirfenidone is described as unknown in the Package Insert (PI). Publications suggest that the mechanistic pathway is via inhibition of the TGF-Beta phosphorylation.
- Dosing is an oral tablet three times per day with a 2 weekly titration period of 801mg (total/day) 1 week, to 1602mg 1 week, to 2403mg per day as a maintenance dose.
- Drug-drug interactions are noted with CYP1A2 inhibitors and inducers, as pirfenidone is a substrate (victim). Fluvoxamine (anti-depressant) should be discontinued with use, and smokers will experience reduced exposure to drug.

Pirfenidone Efficacy

- Patients had confirmed IPF by HRCT, and had FVC (lung capacity) measurements >50% of predicted but less than 90%.
- (Note NICE have supported the use of pirfenidone in IPF patients with FVC 50%-80% predicted, treatment may continue unless decline of 10% or greater is seen within 12 months).



- Efficacy studies 2/3 showed statistically significant slowing of disease progression
  - FVC %predicted placebo corrected difference of 4.4% (193ml), 2.9% (157ml) and 0.6% (not calculated)
  - American Thoracic Society consensus as to clinically meaningful difference is 10%. Proportions of patients declining by more than 10% was 17% and 20% after 52 weeks pirfenidone therapy in the 2 positive studies versus 32% and 35% on placebo. (Source Chowdhury FDA review)
  - From the package insert presentation it can be seen in one study 90% of placebo patients' FVC declined but 77% declined on drug.
  - All Cause Mortality across the program was numerically in favour of drug therapy
- Study sizes for Phase 3 were typically 350-550 randomised 1:1

Pirfenidone Safety

Esbriet® pirfenidone

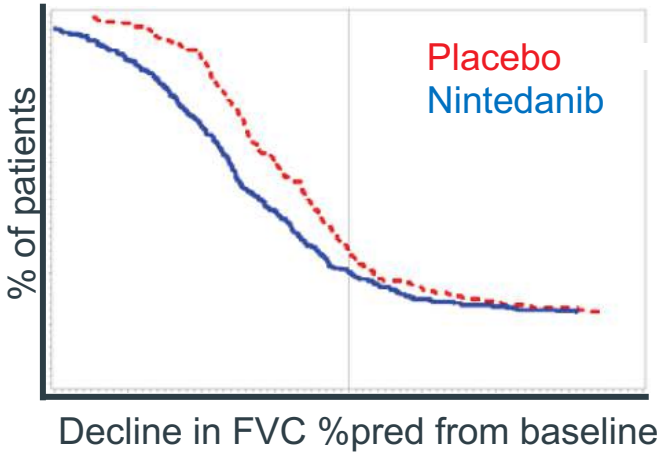
- Key safety issues identified are:
  - Drug Induced Liver Injury – Hy's law cases noted within the program, but no deaths or liver transplants reported
    - Liver function test monitoring is recommended monthly for 6 months then 3 monthly. Dose suspension or discontinuation may be required. Elevated enzymes were reported in 3.7% of patients.
  - Photosensitivity reactions and rash
    - Patients are advised to avoid sunlight and wear sunblock and protective clothing. Reactions were noted in 9% of subjects.
  - Gastrointestinal disorders
    - GI disorders are frequent with pirfenidone, and this is the reason for dose titration and dosing with food recommendations. 18.5% required dose reduction or interruption. The pattern included nausea, vomiting, weight loss etc
- Generally patients stayed on drug, with 15.6% discontinuing (source Noble et al ERS 2016)

Nintedanib Background

- Nintedanib had a conventional development pathway. A dose response study over 52 weeks to determine optimal dose (and provide supportive efficacy data) followed by 2 Phase 3 studies.
- The mechanism of action is known – a multiple receptor tyrosine kinase inhibitor, PDGFR (alpha beta), FGFR 1-3, VEGFR 1-3, which have been implicated in IPF and FLT3. A few other kinases are also inhibited.
- Dosing is 150mg bid with a step down to 100mg bid to manage adverse events eg LFT elevations or GI disorders.
- Drug interactions are possible as nintedanib in broken down using P-gp and CYP3A4 of which other drugs interact also, but only interacting drugs that reduce exposure are recommended to be avoided.
- As a VEGFR inhibitor it may interact with anti-coagulants.

Nintedanib Efficacy

- Efficacy based upon a Phase 2 dose ranging, followed by 2 phase 3 studies. Studies enrolled patients with FVC > 50% predicted in much the same way as pirfenidone. (Note that NICE recommends the use of nintedanib for the same patients as pirfenidone).
- The Phase 2 study over 52 weeks showed a clear dose response (c85 patients/5 dose groups) for efficacy and safety, allowing 150mg bid selection with a dose reduction to 100mg bid.



- Two Phase 3 studies (3:2) randomization with 500-550 patients showed a statistically significant slowing of disease progression as measured by FVC
  - Phase 3 study placebo corrected differences were 125ml/52 weeks and 94ml/52 weeks, but no percentages are given in FDA regulatory review
  - Taking 10% decline as the threshold for clinical difference, then 29% declined on drug versus 43% on placebo (Study 1) and 30% versus 36% in the second study.
  - Both studies adjudicated IPF exacerbations and showed numerical benefit, and this was supported by a trend in favour of drug for all cause mortality.

Nintedanib Safety

- Key safety issues identified are:
  - Liver related adverse events. Elevated ALT/AST were seen in 3-4% of patients, but no Hy's law cases were defined.
    - Liver function test monitoring is required monthly for 3 months and then 3 monthly.
    - Note: drug-induced liver injury noted in post-market surveillance
  - Gastro-intestinal disorders
    - Diarrhoea is very frequently reported with nintedanib (>60%), with nausea, vomiting also frequently reported. In addition GI perforation has been reported
  - Arterial Thromboembolic events and bleeding risk
    - A slight excess of ATE of 2.5% has been noted.
- Discontinuation rates on drug exceeded placebo 25% vs 18%, mainly driven by adverse events. (*Richeldi et al 2014 NEJM*)

Combination Therapy?

INJOURNEY Phase 4 trial compared nintedanib + pirfenidone vs nintedanib alone in 104 patients over 12 weeks.

Described as a safety and PK trial.

Open label, no formal statistical analysis of efficacy.

- Primary endpoint GI toleration over 8 weeks.
- Combination therapy led to 70% with GI Adverse events versus 53% on nintedanib alone
- Discontinuations 34/53 (7 stopped combination, 12 stopped pirfenidone alone) versus 42/51
- pirfenidone had no effect on nintedanib PK
- FVC mean changes were -13.3 combination vs -40.9ml on single therapy

Conclusions: many questions unanswered (Source Vancheri C et al AJRCCM 2018).

What's next?

	FibroGen	Promedior	Galápagos	Prometic.	Kadmon
	Pamrevlumab	**PRM-151**	**GLPG-1690**	**PBI-4050**	**KD025**
Molecule Type	Monoclonal Antibody to CTGF	Recombinant Protein, Serum Amyloid A	Small molecule to Autotaxin	Small Molecule to CTGF	Small molecule to ROCK2
Phase II Trial Design	103 patients 48 weeks No background therapy	116 patients 24 weeks Background of pirfenidone and nintedanib	23 patients 12 weeks No background therapy	41 patients 12 weeks Background of pirfenidone and nintedanib	39 patients 24 weeks No background therapy
Phase II Trial Results	Change in FVC FG3019: -126mL Placebo: -308mL	FVC %pred PRM-151: -2.5% Placebo: -4.8%	Change in FVC GLPG: +8mL Placebo: -87mL	Change in FVC PBI-4050: -12mL PBI + Nin: +2mL PBI + Perf: -102mL	Change in FVC KD025: -48mL SOC: -175mL
Phase III Trial Design	500 patients No background therapy Primary endpoint FVC from baseline	Primary outcome is FVC Secondary outcome is 6 minute walk distance On top of standard of care	1500 patients On top of standard of care At least 52 weeks Two dose levels Primary endpoint is FVC at 52 weeks	Nintedanib only 52 weeks interim analysis at 26 weeks Two dose levels Primary endpoint is annual rate of decline in FVC	No Phase III trial design released as of January 2019
Phase III Progress	Enrolment planned January 2019	Aim to commence recruitment in 2019	First patient dosed December 2018	No details released	No details released

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Conclusions 1

- Landmark decade for treatments for IPF, approval of pirfenidone and nintedanib
- Definite effects on FVC and other lung function biomarkers maybe a trend to improved mortality
- Can/should we use in combination? – as yet unknown
- Neither are optimal therapies, the disease process is slowed not reversed
- Will we see another agent approved before the 10th anniversary of FDA pirfenidone and nintedanib approval?
  - Probability is high
- The pathway to Phase 3 studies is diverse:
  - open label, dose escalation, 12 week, 24 week, 52 week Phase1b/2a studies and double blind Phase 2b, vs placebo, with or without background therapy, all being deployed
  - Galapagos approval for Phase 3 – probably not a precedent
  - IV dosing, SC dosing and oral dosing all being utilised

Conclusions 2

- The approval of nintedanib and pirfenidone has led to greater confidence in the development of drugs for IPF
- The Phase 3 pathway and database is reasonably established (2 studies FVC based 52 weeks, 600 on drug)
- Phase 2 pathway more varied, but dose response work or MTD on stratified placebo/active background therapy over 24 weeks probably optimal to reduce Phase 3 failure risk
- Phase 3b/4 studies in (pulmonary) fibrosis secondary to other diseases present a significant upside opportunity
- Increased treatment options and probable survival benefit in IPF, will lead to an effective increase in prevalence, such that more patients will be seeking therapy
- There is a significant opportunity for multiple classes of drug to be clinically valuable and commercially successful for the management of IPF patients

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An IPF patient's perspective

Bill Van Nierop

IPF patient and advocate

Bill Van Nierop

- Diagnosed with Idiopathic Pulmonary Fibrosis in 2015, and found a lack of community awareness and understanding around IPF and other lung diseases.
- With his diagnosis, Bill has become determined to work with Lung Foundation Australia to raise awareness of this devastating disease as well as symptoms of lung disease so that people can be diagnosed and treated earlier.
  - At least 1500 Australians are diagnosed with IPF each year. IPF has no cure and only one fifth of patients diagnosed survive 5 years.
- In 2018 Bill set himself a challenge to kayak 2,200km from Albury to the mouth of the Murray Mouth over 42 days
  - in doing so raised awareness of IPF and close to $100K for the Australian Lung Foundation.
- Bill lives in Brisbane, working for AGnVET Services. Bill is married to Lesley with 3 children and 5 grand kids, who Bill would like to see grow up.


THE LONG KAYAK FOR LUNGS
WHEN YOU CAN'T BREATHE,
NOTHING ELSE MATTERS.
Lung Foundation Australia
when you can't breathe... nothing else matters®

Lung Foundation Australia
when you can't breathe... nothing else matters®

THE LONG KAYAK FOR LUNGS

Today

- IPF- Diagnosis that changed my life
- Early days - A 'Private Strategy'
- Living with IPF
- Why do what I do?
- The future

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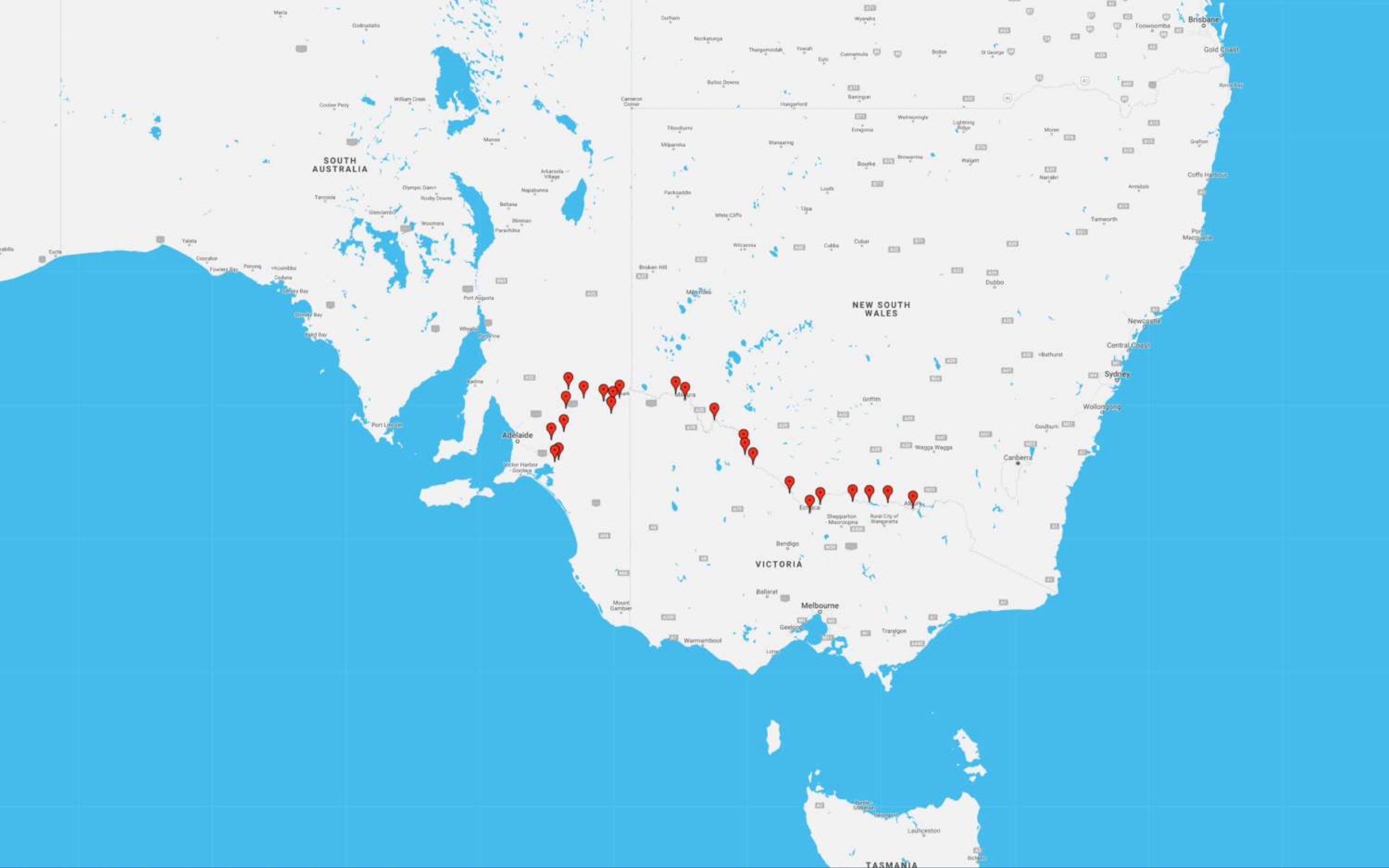

SOUTH AUSTRALIA
NEW SOUTH WALES
VICTORIA
TASMANIA
Brisbane
Gold Coast
Toowoomba
Coffs Harbour
Tamworth
Port Macquarie
Dubbo
Newcastle
Central Coast
Sydney
Wollongong
Goulburn
Canberra
Wagga Wagga
Griffith
Bourke
Cobar
Broken Hill
Mildura
Adelaide
Port Augusta
Port Pirie
Port Lincoln
Victor Harbor - Goolwa
Mount Gambier
Bendigo
Ballarat
Melbourne
Geelong
Warrnambool
Traralgon
Echuca
Albury
Shepparton - Mooroopna
Launceston
Coober Pedy

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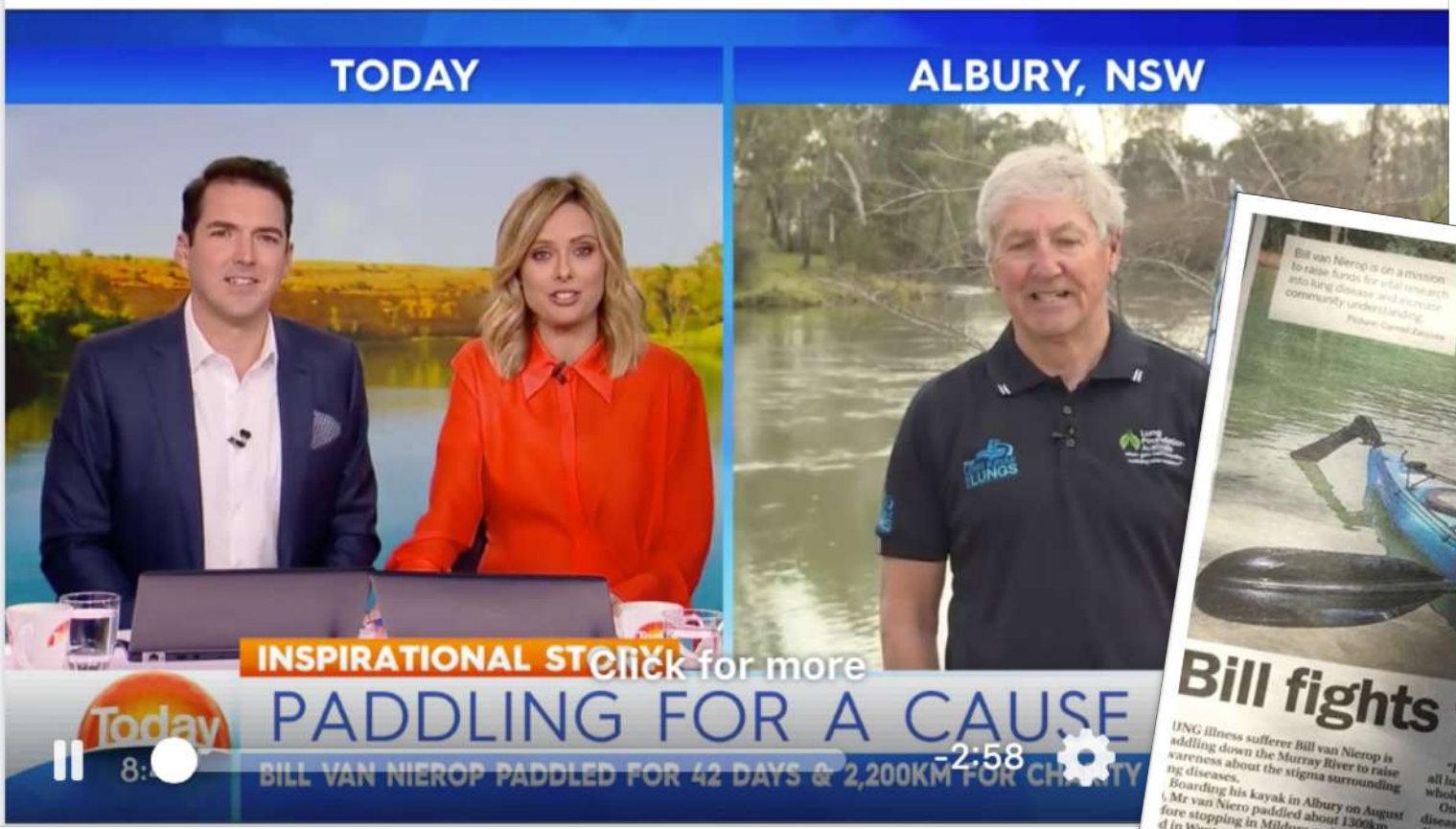
TODAY
ALBURY, NSW
INSPIRATIONAL STORY
Click for more
PADDLING FOR A CAUSE
BILL VAN NIEROP PADDLED FOR 42 DAYS & 2,200KM FOR CHARITY
Today
8:
-2:58


Bill van Nierop is on a mission to raise funds for vital research into lung disease and increase community understanding.
Picture: Carmel Falzone
Bill fights with every brea
UNG illness sufferer Bill van Nierop is addling down the Murray River to raise vareness about the stigma surrounding ng diseases.
Boarding his kayak in Albury on August , Mr van Nierop paddled about 1300km fore stopping in Mildura on Monday d in Wentworth yesterday.
During his 2200km journey, the -year-old Queenslander is raising funds research into lung disease, a "highly gmatised" illness.
"Lung disease is associated only with oking, so if I tell someone I have only f of lung function, they think I'm a oker straight away," he said.
I know a number of people who have al sense of guilt because they have a disease and that's unfair.
"However, smoking is not the cause of all lung diseases – it is a contributor to a whole host of diseases, not only lungs."
One in seven deaths is a result of lung disease, yet the stigma surrounding lung disease is a major barrier to research, funding and support, according to Lung Foundation Australia.
With only 50 per cent lung function, Mr van Nierop suffers a debilitating and terminal lung condition called idiopathic pulmonary fibrosis, whose cause remains unknown.
Paddling at an average speed of 8km/h, he said the effort required as much mentally as physically.
"Kayaking is highly aerobic, which means the impact of the disease is much greater," he said.
"In the afternoon it's all I struggle to breathe but m stubborn and I will finish t
His message is one of em understanding, as it is estim than 12,000 Australians die eases each year.
"Nobody talks about it an Foundation Australia] is the have – so I'm doing my bit th
"I think it's unfair that peo disease are treated as though be ashamed of what they've g
Mr van Nierop's initiative ha raised nearly $55,000, with th reach $100,000 following his journey, expected to end in We September 20.
– Mari

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Lung Foundation Australia
when you can't breathe... nothing else matters®

THE LONG KAYAK FOR LUNGS

Live your Life

Remember, when it gets a bit tough:

"Don't wait for the storm to pass, learn to dance in the rain"


News

BILL'S BATTLE

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I have IPF-
I'm up for the fight!

Bill Van Nierop My Journey with IPF

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Panel Discussion:

What does a good drug look like?

Dr Steve Felstead

Dr Brian Richardson

Dr John Westwick

Dr Robert Peach

Brian Richardson

- Member of The Leadership Team Global Head of Musculoskeletal Disease Therapeutic Area at The Novartis Institutes for Biomedical Research having
- Held several senior positions in a 42 year career in the pharmaceutical industry.
- Research conducted in Brian's laboratories led to the introduction of several new therapies.

John Westwick

- Over 14 years at Novartis Institutes for Biomedical Research
- Responsible for all aspects of drug discovery and early development in the respiratory area
- Included severe asthma, Chronic Obstructive Pulmonary Disease (COPD), cystic fibrosis, pulmonary arterial hypertension, and pulmonary fibrosis.
- 13 positive proof of concepts including a number monoclonal antibodies which are now in phase III clinical trials.

Steve Felstead

- Retired in 2014 from Head of Clinical Research, Pharmatherapeutics Division, Pfizer Inc
- Joined Pfizer in 1989, having qualified in Medicine at Leeds University UK in 1982.
- Consults widely on various programmes for VC, Biotech, and Pharma.
- Member of Innovate UK, Biomedical Catalyst Late Stage Award committee
- Member of Tweed Renaissance Investment Capital Group, which invests in emerging businesses.

Robert Peach

- Over 25 years of drug discovery and development experience.
- In 2009 co-founded Receptos, becoming Chief Scientific Officer and raising $59M in venture capital and $800M in an IPO and three subsequent follow-on offerings.
- August 2015 Receptos was acquired by Celgene for $7.8B.
- 3 registered drugs and multiple in Phase III trials
- Extensive drug discovery and development experience in autoimmune and inflammatory diseases and cancer


NOVARTIS
GILENYA
(fingolimod)
capsules
0.5 mg


Pfizer
Revatio® 20 mg
film-coated tablets
Sildenafil


ViiV Healthcare
Celsentri® 150 mg
Maraviroc


NOVARTIS
CERTICAN® 0,5 mg
everolimus


ultibro
breezhaler
NOVARTIS


ILARIS
(canakinumab)
For injection
180 mg sterile powder for reconstitution/vial
For Subcutaneous Use
NOVARTIS


VIAGRA
CONNECT
4 Tablets


ORENCIA®
(abatacept)
Injection
125 mg/mL
Single-Dose Prefilled Syringe
FOR SUBCUTANEOUS USE ONLY


TOBI® Podhaler®
(tobramycin inhalation powder)

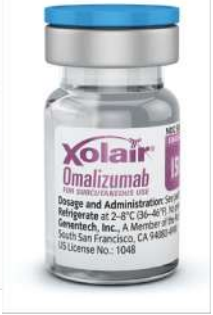

NOVARTIS
Simulect® 20 mg
Basiliximab


Pfizer
ZITHROMAX
azithromycin
250 mg
6 CAPSULES


NOVARTIS
Navoban®
Tropisetron
5 mg


onbrez
breezhaler

Selzentry
300 mg
Pfizer Labs


Xolair
Omalizumab
Dosage and Administration: See package insert
Refrigerate at 2-8°C (36-46°F)
Genentech, Inc., A Member of the Roche Group
South San Francisco, CA 94080-4990
US License No.: 1048


Cosentyx® 150 mg
solution for injection in pre-filled pen
secukinumab
Subcutaneous use
2 pre-filled Sensoready pens


Pfizer
VFEND
VORICONAZOLE
200mg


seebri
breezhaler
NOVARTIS

What does a good drug look like?

- What drugs have you specifically been involved in developing?
- What does a good drug look like and how do you know you have one?
- What do Pharma look for when partnering? Is it the same criteria?

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next generation protein therapeutics

AD-214: a novel treatment for IPF

January 2019

Sam Cobb, CEO and Managing Director

AdAlta Limited (ASX:1AD)

s.cobb@adalta.com.au

Sam Cobb

- Sam is the founding CEO of AdAlta and has over fifteen years' experience in business development and commercialisation of early-stage scientific technologies.
- Prior to AdAlta, Sam was the Business Development Director at the Co-operative Research Centre for Diagnostics. Sam has also worked for the biotech start-up companies, Sensologix Inc and Nephrogenix Pty Ltd and at the University of Queensland's technology commercialisation companies, Uniquest Pty Ltd and IMBcom Pty Ltd.
- Sam has a Bachelor of Science, a Masters of Intellectual Property Law and has completed the Australian Institute of Company Directors course.

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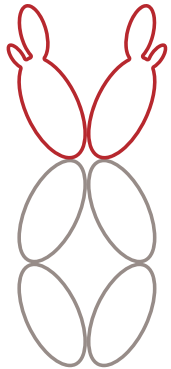
AdAlta (1AD) investment summary



- AdAlta Limited (ASX:1AD) is an Australian listed drug discovery and development company using its powerful technology platform to generate a promising new class of protein therapeutics, known as i-bodies, for treating a wide range of human diseases.

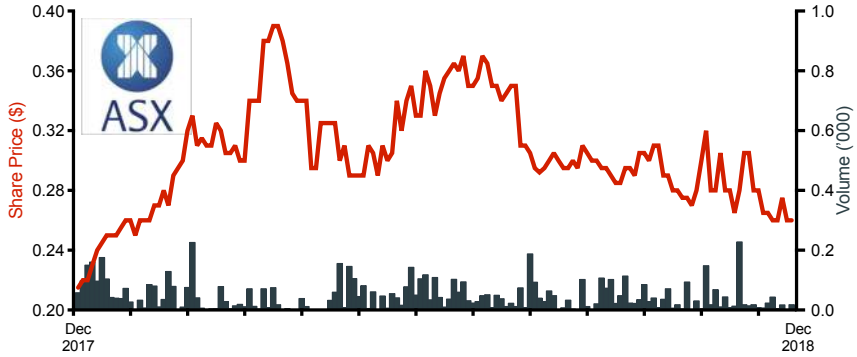
- **Investment highlights**
  - Initial focus on treating fibrosis – high unmet medical need
  - Advanced lead fibrosis drug candidate AD-214 with significant pre-clinical validation
  - Orphan drug designation for IPF granted with USA FDA
  - Early commercialisation potential
  - Developing i-body pipeline to further expand opportunities for partnering of novel i-body platform
  - Experienced team with proven track record of drug development and ability to deliver
  - Cash balance of AU$5.3m and strong support from institutional investors

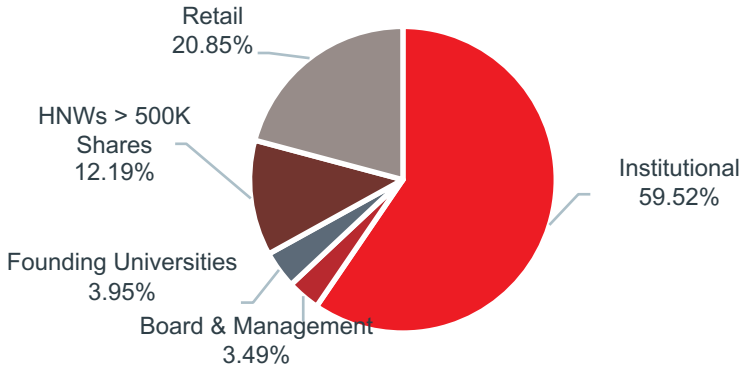
Financial position

Key financial details	
ASX code	1AD
Share price (29 January 2019)	AU$0.27
Market capitalisation	AU$31.75m
Shares on issue	117,604,523
Options on issue	4,109,472
Current cash (31 December 2018)	AU$5.36m
Trading range (last 12 months)	AU$0.20 to $0.40
Average daily volume	47,747

Major shareholders	%
Yuuwa Capital LP	45.97
Platinum Asset Management	9.77
Citycastle Pty Ltd	4.56
National Nominees Limited	3.79
Meurs Holdings Pty Ltd	2.83
Other shareholders	33.08
Total	100%

Share price performance (last 12 months)





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Extensive support from institutional investors and HNWs

- Top 20 shareholders ~80%
- 60% institutional shareholders
- 12% HNWs with >500K shares each
- 4% founding academic institutions
- 3.5% Board, SAB and Management and 4,109,472 Options issued from $0.17-$1 under Employee Share Option Plan

YUUWA CAPITAL
reach for the sky

Australian-based venture capital $40m fund

Platinum
ASSET MANAGEMENT

$27b under management, global equities investor

PPM
PRIVATE PORTFOLIO MANAGERS

Australian and international equities investor

Management and Board in place to deliver strategy

Sam Cobb: Founding CEO and Director

Extensive experience in raising equity, contract and grant funding

15 years of commercialisation and management experience

Dr Paul MacLeman: Chairman

Chairman of Livac and a Non-Executive Director of Sypharma Pty Limited

Founded biologics companies, experienced ASX-listed executive

Dr Robert Peach: Independent Director

Founder and CSO of Receptos Inc, acquired by Celgene Corporation in 2015 for US$7.8bn

Deep experience in research and drug development

Dr John Chiplin: Independent Director

CEO of investment company, NewStar Ventures

Managing Director of acquired antibody company Arana Therapeutics (acquired by Cephalon Inc. for US$200 million)

Liddy McCall & Dr James Williams: Yuuwa Capital Directors

Founders and investment Directors of Yuuwa Capital

Founders of iCeutica Inc (acquired 2011) and Dimerix Limited

Directors of several Australian biotech and Agritech companies

Multiple FDA, CE Mark and TGA approvals

AdAlta

Scientific Advisory Board

Internationally recognised with proven track record of drug development

Dr Mick Foley, AdAlta CSO

Expert in phage display

NIH, NHMRC, ARC, Gates funding and over 70 scientific publications

Brian Richardson: drug discovery and development expert

Ex-Sandoz and Novartis (40+ years), including Head of Pre-clinical Research

Over 60 original peer reviewed research papers

Steve Felstead: clinical advisor

Ex-Pfizer (25 years), including Head of Clinical Research, Pharmatherapeutics Division

Developed Zithromax, Vfend, Celsentri, Viagra

John Westwick: pulmonary drug discovery and development

Over 14 years experience at Novartis, head of respiratory drug discovery

Five product launches and 13 positive proof of concepts in respiratory, including a number of antibodies which are now in phase III.

David McGibney: pre-clinical and clinical advisor

20 years with Pfizer, including Head of European R&D

Ex Pfizer Ltd board member

Developed Viagra, and 10+ blockbuster drugs

Market opportunity for IPF

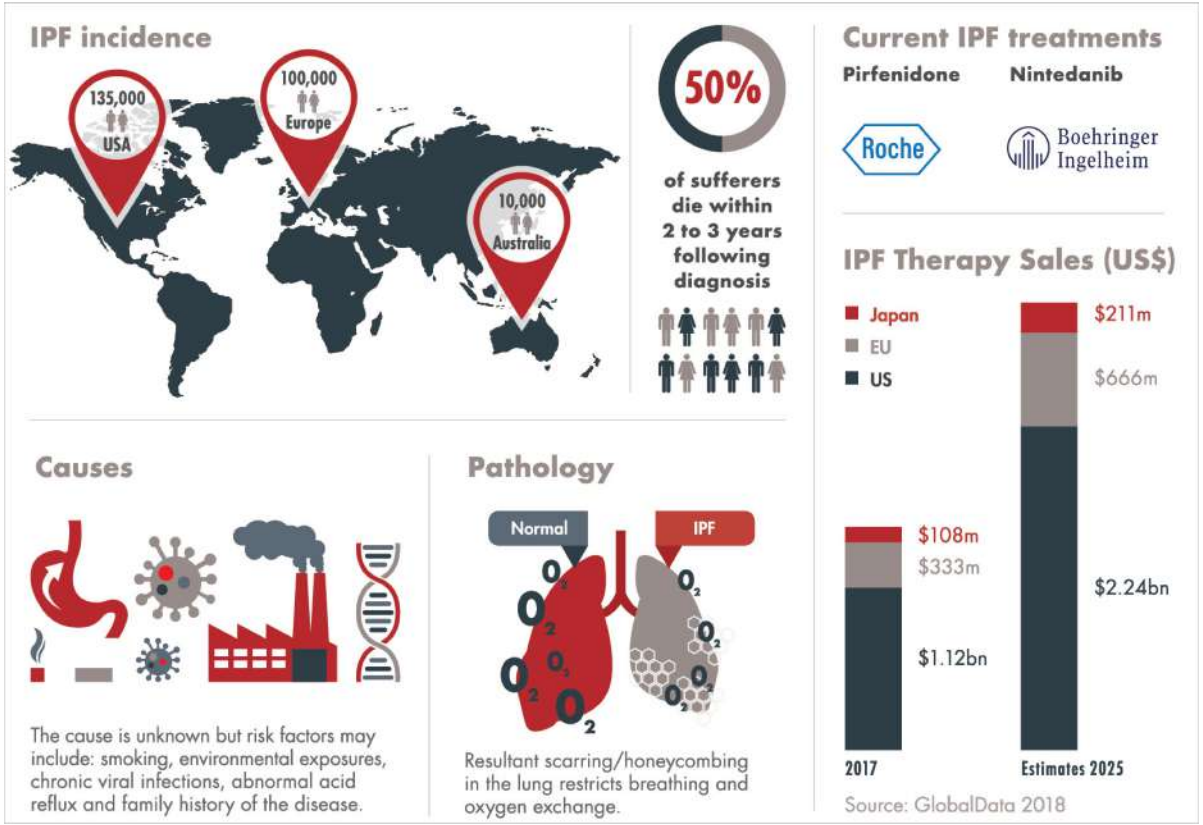
Idiopathic Pulmonary Fibrosis (IPF) is an irreversible, unpredictable and incurable disease

THE STATISTICS

People living with IPF
300,000

People die from IPF every year
40,000

Median length of survival after IPF diagnosis
3.8 years



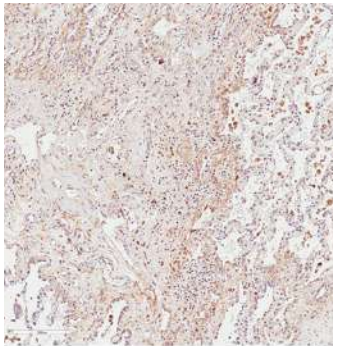
AdAlta

CXCR4 novel target for treatment of IPF

- Significant literature to support hypothesis of the involvement of CXCR4 in fibrosis
- IPF diseased lung tissue has increased CXCR4 expression compared with normal lung tissues
- AD-214 has unique activity compared to other CXCR4 binders
- AD-214 has been granted orphan drug status by US FDA
- Data recently published in ***Scientific Reports (2018) 8:3212*** supports anti-CXCR4 i-body treatment of fibrosis

Normal human lung tissue

Diseased IPF lung tissue



SCIENTIFIC REPORTS

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Anti-fibrotic Effects of CXCR4-Targeting i-body AD-114 in Preclinical Models of Pulmonary Fibrosis

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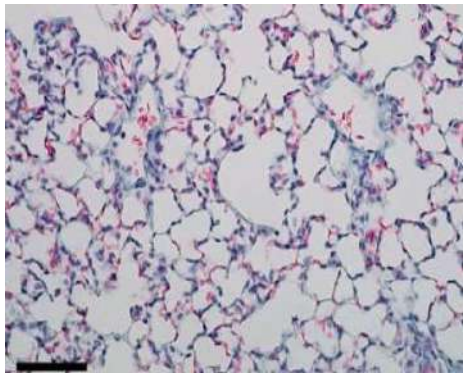
K. Griffiths[1,2], D. M. Habiel[3], J. Jaffar[4], U. Binder[5], W. G. Darby[1,2], C. G. Hosking[1,2], A. Skerra[5], G. P. Westall[4], C. M. Hogaboam[3] & M. Foley[1,2]

AdAlta

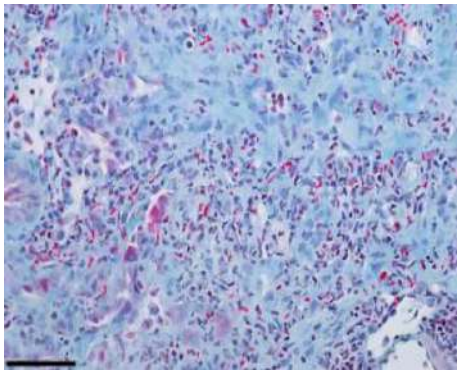
AD-214 novel treatment for fibrosis

AdAlta's lead i-body has demonstrated in vivo activity in the Bleomycin mouse model

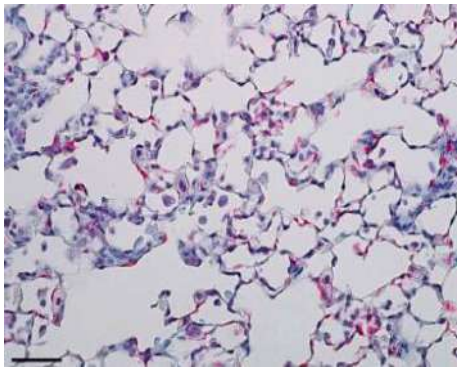
AdAlta's i-body reduces collagen content and inflammatory cell infiltration and demonstrates a similar architecture to that of the normal lung



Normal lung tissue



IPF lung tissue
(lung disease mouse model)



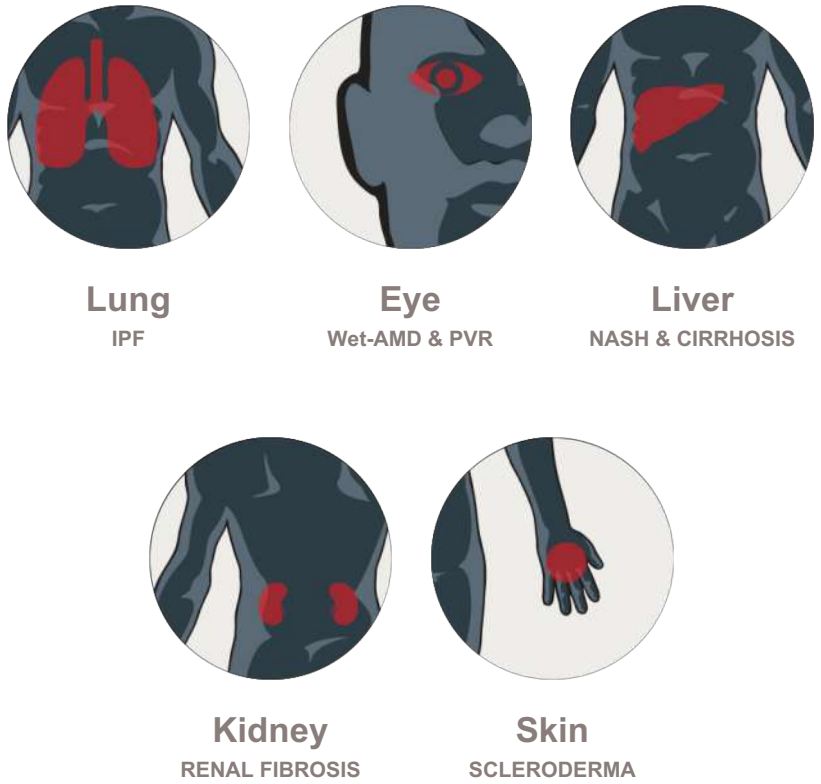
IPF lung tissue + AdAlta anti-CXCR4 i-body dosed for 21 days
(lung disease mouse model)

AD-214 has broad application in treating fibrosis

AdAlta data shows that AD-214 can improve fibrosis across a range of fibrotic diseases

- **LUNG:** Idiopathic Pulmonary Fibrosis
- **EYE:** Wet-Age Related Macular Degeneration
- **LIVER:** NASH
- **SKIN:** Hypertrophic scar
- **KIDNEY:** Chronic kidney disease

AdAlta has demonstrated broad anti-fibrotic and anti-inflammatory effects in several animal models of disease and with human tissues with its lead i-body candidate.



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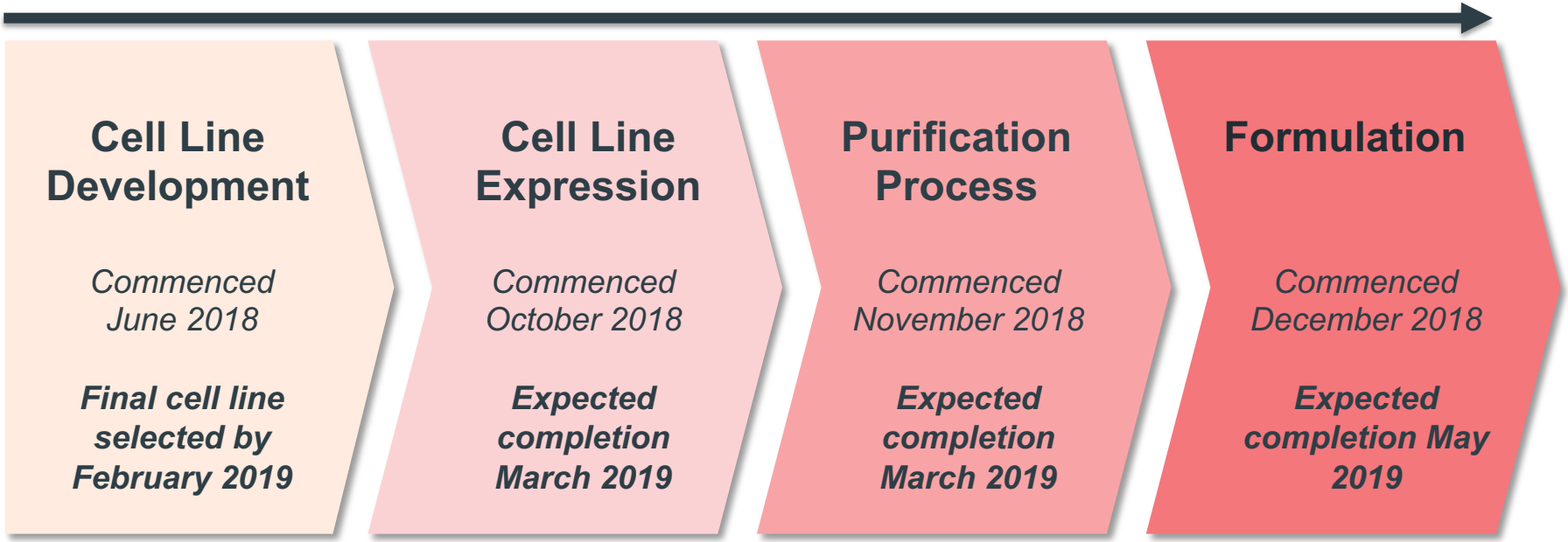
Global market interest in fibrosis treatments

Fibrosis assets acquired at an early stage – typically based on Phase I results

Date	Company	Target	Acquired by	Deal value (US$)	Deal commentary
Sep-18	Samumed	SM04646	United Therapeutics	$10m upfront, plus $340m milestones	Undergoing Phase I, USA rights only
Sep-15	Adheron Therapeutics	SDP051	Roche	$105m upfront, plus $475m in milestones	SDP-51 at end of Phase I for IPF
Aug-15	Promedior	PRM-151	BMS	$150m upfront + $1.25B	Phase II IPF and myelofibrosis
Nov-14	Galecto Biotech AB	TD139	BMS	$444m	Option to acquire at end of clinical POC (no later than 60 days following Ph 1b for IPF completion)
Aug-14	Intermune	Esbriet / Pirfenidone	Roche	$8.3b	Approval in Europe / Japan, phase III in the US
Jun-13	MicroDose Therapeutx	MMI0100	Teva Pharmaceuticals	$40m upfront $125m milestones	MMI0100 was in pre-clinical development
Mar-12	Stromedix	STX100	Biogen Idec	$75m upfront $487.5m milestones	End of phase I for IPF
Jul-11	Amira / BMS	BMS-986020	BMS	$325m upfront $150m milestones	End of phase I for IPF

Source: GlobalData (all IPF deals since 2011)

AD-214 manufacturing progress



SELEXIS®

KBI BIOPHARMA

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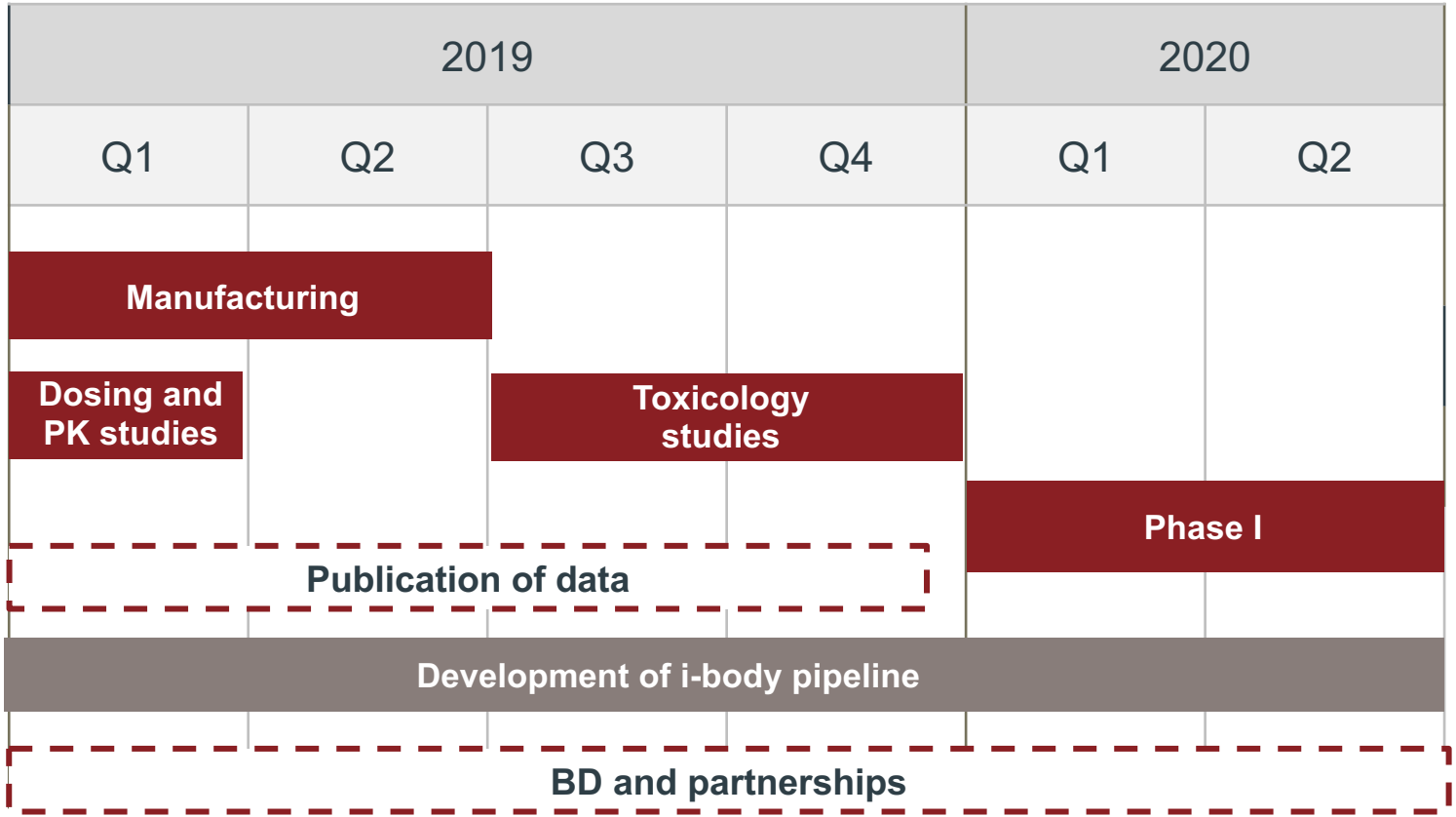
AD-214 development: key milestones



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2018: significant achievements

- ✓ Orphan Drug Designation (US FDA) of AdAlta i-body for treatment of IPF
- ✓ Completion of additional pre-clinical animal models in diseases of the lung, kidney, skin; strengthening broad anti-fibrotic data package of anti-CXCR4 i-body
- ✓ Publication of key data in *Scientific Reports* (a *Nature* publication)
- ✓ Completion of several non-human primate studies demonstrating safety of CXCR4 i-body but also safety of platform
- ✓ Key AU patent granted covering AD-214
- ✓ Successfully completed AD-214 cell-line development process

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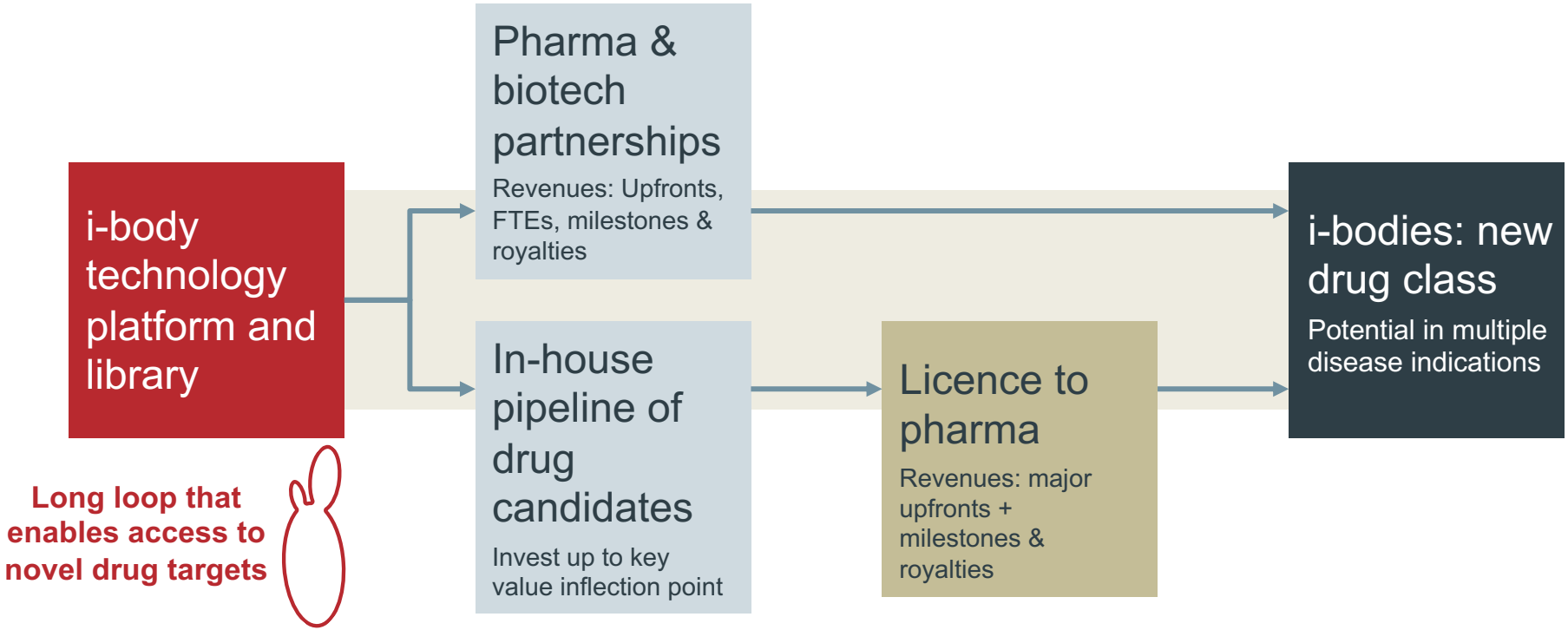
AdAlta business model – strategy to create value



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Market benchmarks

Fibrosis lead AD-214	Sep-15 acquired by Roche $105m + $475m milestones phase I asset	Aug-15 acquired by BMS $150m + $1.25b milestones phase IIa asset	Nov-14 acquired by BMS $444m phase I asset
Next-gen antibodies	April-16 with Abbvie $40m upfront + $645m milestones & royalties	May -17 with AZ $58m upfront + $2.1b milestones & royalties	July-17 with Sanofi €31m upfront + €2.4b milestones & royalties
GPCRs	Acquired Feb-15 by Sosei $400m Phase Ib asset + 7 pre-clinical leads	Acquired by Celgene July-15 $8b Ph III, Ph II and GPCR platform	April-16 with Boehringer €8m payment for Ph1 GPCR nanobody + €125m milestones & royalties

Expected news flow

H1 2018	✓	Publication of AD-114 data in *Scientific Reports* demonstrating i-body application of pulmonary fibrosis with human tissue and animal model data
	✓	Investor and analyst briefing detailing application of the i-body for the undruggable targets such as G Protein Coupled Receptors (GPCRs) and ion channels
	✓	Commence manufacturing of AD-214 with Selexis and KBI
H2 2018	✓	Manufacturing update on cell line development
	✓	Expected R&D tax return of ~$2m
H1 2019	▶	Complete manufacturing including materials for tox program
	▶	Update on i-body pipeline development
	▶	Publish i-body ½ life and eye fibrosis data
	▶	Preliminary non-human primate data with AD-214
H2 2019	▶	4 week NHP toxicology study
	▶	Regulatory discussions with US FDA
H1 2020	▶	Phase I SAD/MAD study with AD-214

AdAlta Limited (ASX:1AD) summary

- December 2018 cash position of $5.3m with strong support from existing institutional investors
- AD-214 has significant pre-clinical validation demonstrating broad anti-fibrotic and anti-inflammatory effects as well as safety
- Initial focus on treating Idiopathic Pulmonary Fibrosis (IPF) and other fibrotic diseases - high unmet clinical need
- Manufacturing on track with AD-214 set to be in clinic by Q1 2020
- Platform technology for pipeline expansion and partnerships

Experienced management and Board to drive AD-214 development and secure technology platform partnerships / product licensing deals

AdAlta Limited

ASX: 1AD

Sam Cobb, CEO and Managing Director

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