IDIOPATHIC PULMONARY FIBROSIS

AdAlta's i-body approach

AdAlta
next generation protein therapeutics

What is Idiopathic Pulmonary Fibrosis?

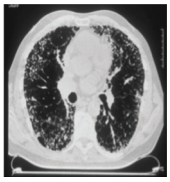
Idiopathic pulmonary fibrosis (IPF) is a rare lung disease, with approximately 1,500 new cases diagnosed each year. It is a progressive lung disease associated with scarring of the lung, causing the tissue to stiffen and making it hard to breathe. It is almost always fatal.

The term 'idiopathic' literally means 'of no known cause' but certain environmental factors have been shown to increase the risk of being diagnosed with IPF. Smoking is the most common of these factors that also include occupational exposure to irritants such as dust, coal, silica and agricultural products. After repeated exposure to the irritant the lung loses the ability to properly repair itself, causing scarring and stiffening of the tissue. IPF has no cure and only one fifth of patients survive five years from diagnosis.

Symptoms, Diagnosis and Prognosis

The most common indications of IPF are shortness of breath, a persistent cough and a crackling "Velcro-like" sound when breathing.

IPF is challenging to diagnose and is performed by a multi-disciplinary team which reviews the patient's clinical data including physical examination, lung function tests, blood tests and appearance of the lung in a CT scan (see figure to the right). The course of the disease varies greatly, ranging from a lengthy progression over several years to a series of acute exacerbations that are likely to lead to death. However, a decline in lung function and increased reliance on supplemental oxygen is common to all patients diagnosed with IPF.



CT scan from an IPF patient

IPF incidence

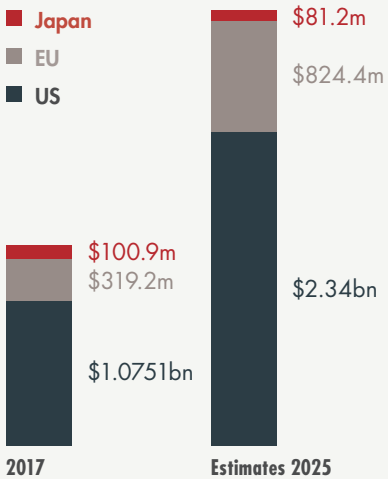
of sufferers die within 2 to 3 years following diagnosis

Current IPF treatments

Pirfenidone — Roche

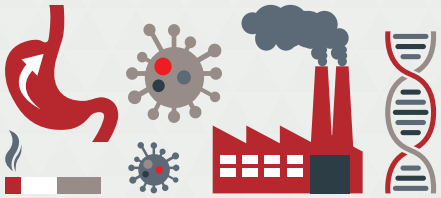
Nintedanib — Boehringer Ingelheim

IPF Therapy Sales (US$)



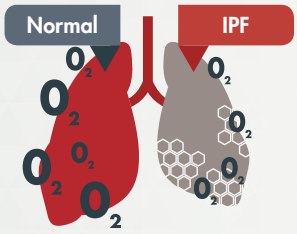
Source: GlobalData

Causes



The cause is unknown but risk factors may include: smoking, environmental exposures, chronic viral infections, abnormal acid reflux and family history of the disease.

Pathology



Resultant scarring/honeycombing in the lung restricts breathing and oxygen exchange.

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Version 2

Current IPF treatment options

Two treatments for IPF were approved by the US Food and Drug Administration in 2014 – Pirfenidone (Esbriet®) and Nintedanib (Ofev®). Despite differing modes of action, the anti-fibrotic agents Pirfenidone and Nintedanib are deemed by respiratory clinicians to be equally effective, with both compounds slowing the reduction in lung volume that is characteristic in IPF patients. However, these compounds only delay the progression of the disease, they do not act as a cure and cannot halt or reverse the decline in lung function.

Despite their benefits, Pirfenidone and Nintedanib are also associated with significant side effects. Treatment with Pirfenidone can result in rash, nausea and increased sensitivity to sunlight. Nintedanib also has significant gastro-intestinal side effects that include nausea and diarrhoea.

Living with IPF

Bill Van Nierop lives in Brisbane, Australia and was diagnosed with IPF in 2015. Bill has received both existing treatments, initially Nintedanib and now Pirfenidone.

Bill describes some of his experiences living with IPF and his treatments below:

On the symptoms of IPF: "I have 53% lung function …you get breathless with exertion"

On dealing with the bad days: "on a scale of 1–10, about 18, …usually being active gets me through it. Not today, had to live with it"

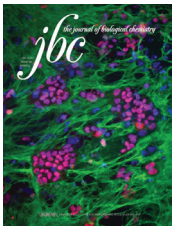
On the beast that is IPF: "this disease …it sneaks into your body like a coward …it has two clear objectives: …to start to take over your air sacs and …move you into dependence on others and artificial oxygen"

The need for better IPF therapies

The poor prognosis for IPF patients, even with existing treatments, combined with the unpleasant side effects of those treatments, highlights the urgent need for better treatment options. While no new treatments have been approved over the past few years, there are a number of products progressing through clinical trials.

Currently, four compounds are preparing for Phase III studies, there are several compounds completing Phase II trials to demonstrate effectiveness as well as compounds in Phase I trials which aim to evaluate drug safety. These are outlined in the table right.

AdAlta's unique approach



AdAlta has developed an i-body (see box on page 3 for further information) that binds specifically to CXCR4 and blocks activation of the receptor. These results have been published in the peer-reviewed *Journal of Biological Chemistry* (June 2016) *(right)*.

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.

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)

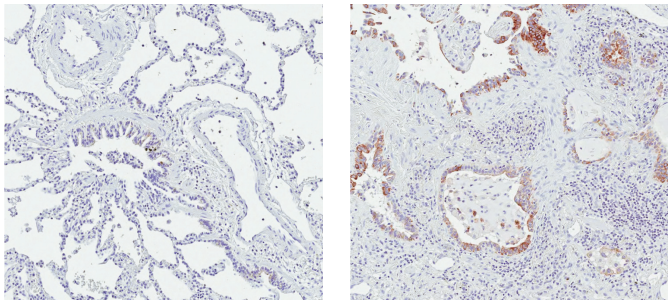
Phase I	
PharmAkea	PharmAkea have demonstrated safety for PAT-1251 currently in trials for several fibrotic conditions.
Vicore Pharma	Phase I trial completed and a Phase II trial planned for lead fibrosis candidate C21.
Aeolus Pharmaceuticals	Currently completing Phase I for AEOL-10150 which has been 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)

A novel target for the treatment of IPF

There has been increasing evidence that levels of the chemokine receptor CXCR4 are increased in Idiopathic Pulmonary Fibrosis patients compared to healthy patients, suggesting the involvement of this receptor in the disease's progression.

Studies completed by AdAlta in collaboration with Alfred Health have shown significantly increased expression of CXCR4 in IPF lung tissue compared to normal lung tissue (see below). The levels of CXCR4 were highest in the fibrotic 'honeycomb' areas of the lung that are characteristic of IPF.

CXCR4 has also been identified as a negative prognostic factor; patients exhibiting a greater amount of CXCR4-expressing inflammatory cells (fibrocytes) have poorer average survival *(Moeller et al, Am J Res Crit Med, Vol 179, 2009)*. The therapeutic value derived by targetting CXCR4 has also been established by AdAlta collaborator Cory Hogaboam, Professor of Medicine at Cedars Sinai Medical Centre, using a humanised mouse model that utilises lung cells from IPF patients *(Habiel et al, Am J Path, Vol 188, 2018)*.



CXCR expression healthy (left) and diseased IPF human lung tissue (brown staining)

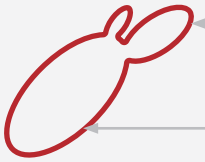
By targetting CXCR4, the i-body binds exclusively to diseased lung tissue from IPF patients who have increased expression of CXCR4. It does not bind to healthy tissue due to the absence of CXCR4. Extensive pre-clinical experiments have been performed in the lab *(in vitro)* and in animal models *(in vivo)*, showing both the anti-inflammatory and anti-fibrotic activity of the i-body that targets CXCR4. This work was published in February 2018 in the peer-reviewed journal Scientific Reports.

In April 2018, AdAlta announced an improved version of AD-114, its first-generation CXCR4 i-body, renaming it AD-214 (see below). This modification has significantly increased its potency by combining two i-bodies at the front end of the molecule, which have anti-fibrotic activity. The half-life, or the time the drug stays in the body, has also improved, through the addition of the Fc Fragment at the back end. The increased potency and half-life of AD-214 is expected to result in less frequent patient dosing, providing benefits for both patients and clinicians and making AD-214 more valuable to potential pharmaceutical partners.

CXCR4 is a novel disease target pathway in IPF, and, if approved, the i-body targetting CXCR4, AD-214, would be a "first in class" drug for what is an orphan indication. The FDA classes an indication as orphan if it affects fewer than 200,000 patients in the US. AdAlta was granted FDA orphan drug designation for the CXCR4- i-body in January 2017, which allows potential R&D tax credits, fee waivers, fast track to market and a seven-year period of exclusivity once the drug is on the market.

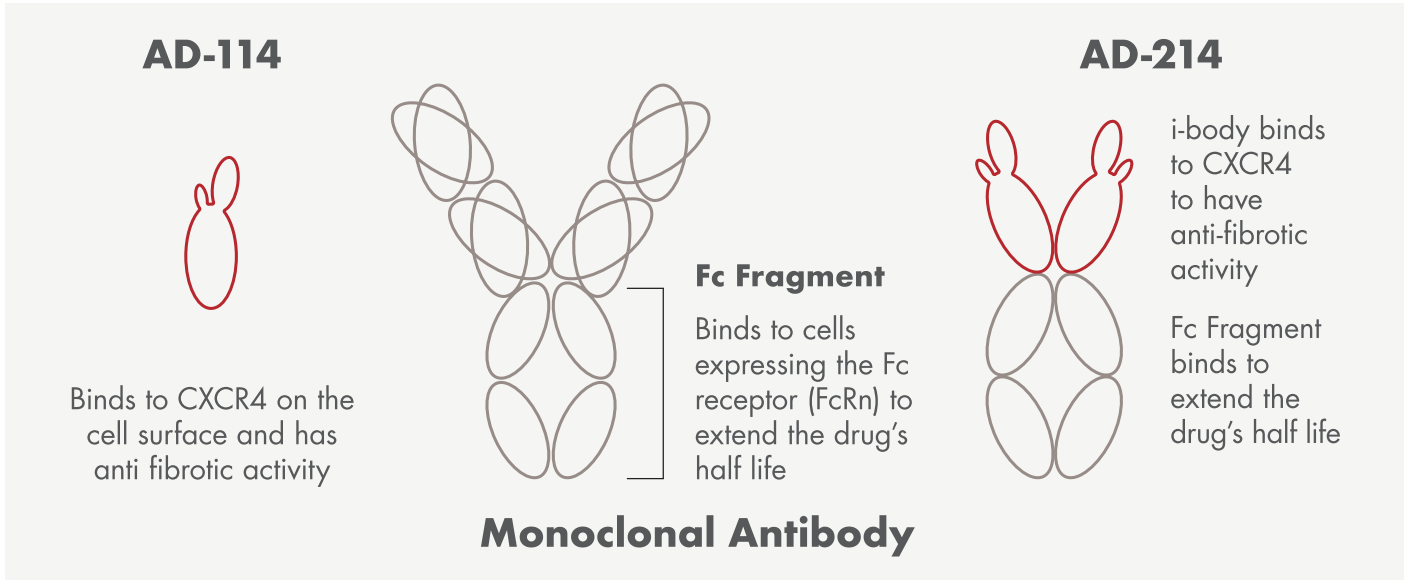
What is an i-body?

An i-body is a unique human protein that combines the advantages of small molecules (for stability) and antibodies (with a high affinity and specificity for treating certain illnesses) in one powerful treatment.



The i-body has a unique long loop that can bind to a diverse range of targets meaning that it has wide applicability across many diseases.

AdAlta's AD-214 represents a UNIQUE approach not currently addressed by approved drugs or other candidates in the clinic.

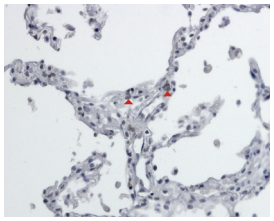


AD-214 makes progress to the clinic

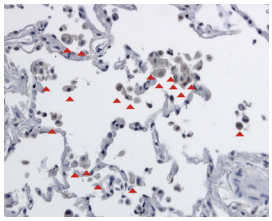
- ✓ AdAlta's CXCR4-targetting i-body binds more specifically to diseased human IPF tissue than normal lung tissue
- ✓ i-body has different results from existing approved IPF therapies Nintedanib and Pirfenidone
- ✓ In an animal model of IPF, the i-body targetting CXCR4 reduced key measures of fibrosis
- ✓ US FDA grants AdAlta Orphan Drug status for the treatment of IPF in January 2017
- ✓ Key preclinical data published in Scientific Reports February 2018
- ✓ AD-214, an Fc-fusion version of CXCR4 i-body, demonstrates increased potency and half-life
- ✓ AdAlta signs key manufacturing partners for AD-214
- ✓ AdAlta manufacturing AD-214 with commercial yields
- Toxicology studies to demonstrate safety of AD-214
- First in man Phase I studies

Images of normal and fibrotic lung

A. Normal lung tissue



B. IPF diseased human lung tissue



The red arrows indicate binding of CXCR4 i-body to IPF diseased human lung (B) with limited binding to normal lung tissue (A). These studies confirm the significant binding of the i-body to diseased tissue.

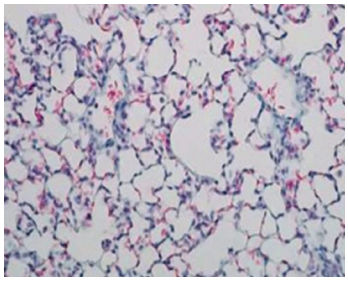
***In vitro* Migration Assay Results**

Test Agent	No effect on normal fibroblasts	Inhibition of IPF progressor fibroblasts
CXCR4 i-body	✓	✓
Nintedanib (Boehringer)	×	✓
Pirfenidone (Roche)	✓	×

CXCR4 i-body AD-114 shows anti-fibrotic effects in samples from IPF patients

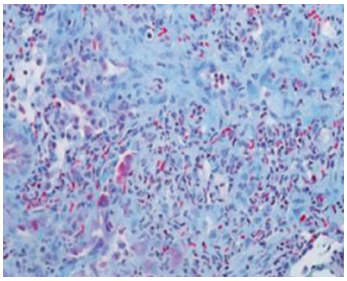
Effect of CXCR4 i-body on lung tissue of an IPF mouse model

A. Normal lung tissue



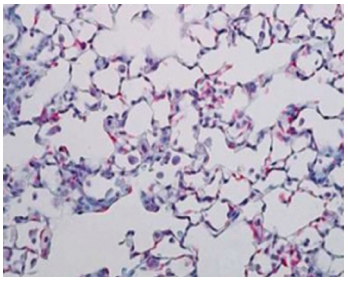
This picture of a normal healthy lung has been stained to show collagen which appears in blue. Compared to Figure B there is little blue staining.

B. IPF diseased lung tissue



This picture shows the mouse lung after treatment with Bleomycin, a toxin that is used to simulate the effects of IPF in this model. The Bleomycin is administered at day 0 and at 21 days post administration the lung tissue collagen content is analysed. The Bleomycin treated mouse lung shows extensive collagen deposition (blue staining) typical of fibrosis.

C. IPF disease diseased lung tissue treated with CXCR4 i-body



This picture shows the lungs of a mouse given Bleomycin and then treated with the CXCR4 i-body daily for 21 days. The lungs are now observed to have a similar architecture to that of the normal lung. The CXCR4 i-body decreased total collagen content in the lungs demonstrating the anti-fibrotic effect of the i-body in vivo. It shows very little collagen staining similar to the normal lung tissue as in Figure A.

AdAlta exciting collaboration with The Alfred Hospital, Melbourne

TheAlfred

AdAlta has fostered a highly successful collaboration with The Alfred Hospital and the clinical research team led by Dr Glen Westall, an expert in lung fibrosis and IPF. Dr Westall is a consultant at the Interstitial Lung Disease Clinic managing both the diagnosis and treatment of patients with IPF.

"We are excited to continue working with AdAlta to further understand this complex fibrotic disease and how the Company's novel i-body may play a role in the treatment of IPF, for which there is currently no cure."
Dr Glen Westall, Respiratory Physician at The Alfred hospital.

Dr Glen Westall provides an overview of IPF, current treatments and unmet medical need in the AdAlta Fibrosis Briefing video series available on the AdAlta website http://adalta.com.au/fibrosis-symposium-video-material.

Further Information

The following resources provide further information on IPF:

Lung Foundation Australia Fact Sheet

https://lungfoundation.com.au/wp-content/uploads/2018/09/Factsheet-IPF-Feb2018.pdf

IPF Registry Information

https://lungfoundation.com.au/research/our-research/australian-ipf-registry

Introduction Video to IPF

https://youtu.be/7nemp1f0YF4