Idiopathic Pulmonary Fibrosis - a degenerative disease in need of a regenerative solution

Dan Chambers

Queensland Lung Transplant Service, The Prince Charles Hospital
School of Medicine, The University of Queensland

innovation and collaboration
ISCT Speaker Declaration

• The presented clinical data and findings are the result of experimental trial(s) and/or in accordance with Article 37 in the 2013 Helsinki Declaration amendment. In both cases the procedures were performed with the approval of all required regulatory authorities and with signed informed consent of all patients following principles as described in the current World Medical Association Declaration of Helsinki.
Overview

• What is idiopathic pulmonary fibrosis (IPF)?
• What evidence is there that IPF is a degenerative disease?
• MSC therapy for IPF
  – Preclinical data
  – Results of first-in-man trials
What is Idiopathic Pulmonary Fibrosis (IPF) ?

- Relentlessly progressive fibrosing lung disease
- Median survival < 3 years
- Few treatment options
IPF deaths compared to cancer

Adapted from Cancer Research UK, Cancer incidence and mortality (2011), 2014
IPF survival compared to common cancers

5-year survival (%)

Testis, Melanoma, Breast, Hodgkin’s Lymphoma, Prostate, Leukaemia, Myeloma, Ovary, IPF, Stomach, Brain, Oesophagus, Lung, Pancreas
IPF survival over the last decade

Strongman, Kauser, Bogman and Maher, BTS 2013
IPF treatment - are we there yet?

Inflammation → Fibrosis

Anti-inflammatory agents
IPF treatment - are we there yet?

Inflammation → Fibrosis

Anti-inflammatory agents

Anti-fibrotics
pirfenidone &
nintedanib

innovation and collaboration
IPF treatment - are we there yet?

Degeneration → Fibrosis

Regenerative agents, cells, molecules, vesicles

Anti-fibrotics: pirfenidone & nintedanib
IPF – a disease of ageing

B

Narrow Case Definition

Rate per 100,000

0 0.8 2.2 10.8 18.7 50.0 87.9
0.9 5.9 11.3 23.3 29.3 48.4
18-34 35-44 45-54 55-64 65-74 75+

Age, years

Men
Women

Raghu et al AJRCCM 2006
Cellular and molecular hallmarks of ageing

- Altered intercellular communication
- Genomic instability
- Stem cell exhaustion
- Telomere attrition
- Cellular senescence
- Epigenetic alterations
- Mitochondrial dysfunction
- Loss of proteostasis
- Deregulated nutrient-sensing

López-Otín Cell 2013
Mrs RC

• 45 years
• Referred ? lung transplantation
• 8 year history
  – Arthralgia
  – Macrocytosis (MCV 113)
    • B12, folate, BM biopsy * 3 all normal
  – Mild thrombocytopaenia (100)
  – Ongoing immunologic review ? diagnosis
    • Multiple immunosuppressants
  – Mildly raised LFTs – no alcohol
Mrs RC

- US/S abdomen - noted increase echo signal at lung base
- Mild SOB, mild dry cough
- Never smoked
- FHx - sister ? scleroderma with lung involvement
- No industrial dust exposure
- No significant environmental exposures
What test would you do?

- Mild clubbing
- No CTD signs
- Velcro crackles
- Restrictive physiology
Mrs RC

- Telomere length < 1st centile
- TERT sequencing
  - alanine to aspartic acid at position 678
The end replication problem
PF – the most common phenotype in humans with telomerase mutations
Mrs RC

- PF exacerbation
- Respiratory failure
- Transplanted emergently
- Dialysis-dependent acute kidney injury, bone marrow failure, cirrhosis\(^1\)
- Now well 3 years post-transplant with normal graft and kidney function

\(^1\)Silhan et al ERJ 2014
Explant histology - indistinguishable from IPF
But what can these rare mutations tell us about IPF pathogenesis?

2. Snetselaar et al Chest 2015
Telomere length *independently* predicts survival in sporadic IPF

Stuart *et al* Lancet Resp Med 2014
Dai *et al* Respirol 2015
What can the epidemiology tell us?

- Short telomeres ↑ risk of sporadic IPF
  - Dose:response - shorter telomeres = worse survival
- TERT mRNA is markedly reduced in IPF tissue\(^1\)
- Germline loss of function TERT mutations cause a human disease identical to IPF
- TERT protects stem and stem-like cells from senescence
- Stem cell senescence/dysfunction is a central and early event in IPF pathogenesis
In the end it’s a replication problem.
... but lung is a low turnover tissue....

- Mitochondrial function is intimately linked to stemness in quiescent tissues
- Accumulation of dysfunctional mitochondria in IPF
MSCs as mitochondrial donors?

Mitochondrial transfer from bone-marrow–derived stromal cells to pulmonary alveoli protects against acute lung injury

Mohammad Naimul Islam, Shonit R Das, Memet T Emin, Michelle Wei, Li Sun, Kristin Westphalen, David J Rowlands, Sadiqa K Quadri, Sunita Bhattacharya & Jahaar Bhattacharya
Cell therapy in IPF - getting to the bedside
# MSC in PF – preclinical data

<table>
<thead>
<tr>
<th>Author</th>
<th>Intervention</th>
<th>Model</th>
<th>Outcome</th>
<th>Engraftment?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ortiz¹</td>
<td>Allogeneic 5*10⁵ BM-MSC @0,7 days via jugular vein</td>
<td>Mouse bleomycin</td>
<td>↓ hydroxyproline – not significant with day 7 infusion</td>
<td>Yes, increased in fibrotic areas</td>
</tr>
<tr>
<td>Cui²</td>
<td>BM-MSC @ 1,7 days via tail vein</td>
<td>Rat bleomycin</td>
<td>↓ hydroxyproline and lung fibrotic score – more pronounced with day 1 infusion</td>
<td>Yes</td>
</tr>
<tr>
<td>Zhao³</td>
<td>5*10⁶ BM-MSC @ 12 hours via tail vein</td>
<td>Rat bleomycin</td>
<td>↓ hydroxyproline and pro-fibrotic cytokines</td>
<td>Yes</td>
</tr>
<tr>
<td>Moodley⁴</td>
<td>Xenogeneic umbilical cord-derived MSC 1*10⁶ @ 1 day</td>
<td>Mouse bleomycin</td>
<td>↓ hydroxyproline, collagen and pro-fibrotic cytokines</td>
<td>Yes, only in fibrotic areas</td>
</tr>
<tr>
<td>Bitencourt⁵</td>
<td>Autologous MSC engraftment encouraged by hyaluronidase</td>
<td>Mouse belomycin</td>
<td>↓ collagen content and fibrotic score</td>
<td>Yes</td>
</tr>
<tr>
<td>Choi⁶</td>
<td>Xenogeneic BM-MSC 2*10⁵ IV or microvesicles @ 12 &amp; 14 weeks</td>
<td>Mouse silica</td>
<td>↓ collagen content and fibrotic score, more pronounced with MSC</td>
<td>Yes + ATII differentiation</td>
</tr>
<tr>
<td>Yan⁷</td>
<td>Isogeneic BM-MSC 2*10⁵ IV @ 0, 60, 120 days</td>
<td>Mouse radiation</td>
<td>↑ fibrosis with late delivery</td>
<td>Yes</td>
</tr>
<tr>
<td>Jun⁸</td>
<td>Isogeneic Lung MSC (Hoechst) 2.5*10⁵ IV day 0</td>
<td>Mouse bleomycin</td>
<td>Bleomycin causes lung MSC depletion with repletion attenuating fibrosis</td>
<td>No - ?rescue of lung resident MSC</td>
</tr>
</tbody>
</table>

---

2. *Zhonghua Jie He He Hu Xi Za Zhi* 2007
5. *Fibrogenesis Tissue Repair* 2011
8. *Jun Stem Cells* 2011
The lung – an attractive target for intravenous somatic cell therapy

• ‘First pass effect’ makes delivery to other organs problematic, but is an advantage in lung
ORIGINAL ARTICLE

A phase 1b study of placenta-derived mesenchymal stromal cells in patients with idiopathic pulmonary fibrosis

Daniel C. Chambers,1,2 Debra Enever,1 Nina Illic,3 Lisa Sparks,4 Kylie Whitelaw,1 John Ayres,5 Stephanie T. Yerkovich,1,2 Dalia Khalil,6 Kerry M. Atkinson7,8 and Peter M.A. Hopkins1,2
The ‘bedside’ - MSCs for human IPF

- Phase Ib, open-label, single centre, non-randomized, dose-escalation study
- 1 (n=4) & 2 x 10^6 (n=4) MSC/kg delivered IV
- MSC from term placenta (elective Caesarean)
  - Easily obtained and abundant source of MSC
  - Cell surface phenotype and *in vitro* behaviour comparable to that of bone marrow derived MSC
- NCT01385644

1. Chambers *et al* Respirol 2014
2. Barlow Stem Cells Dev 2008
Objectives

• Primary endpoint safety, particularly:
  – Acute peri-infusion toxicity
  – Pro-fibrosis over the medium term

• Secondary endpoints:
  – Lung function (FVC, DLCO)
  – 6MWD
  – Lung fibrosis score (assessed by HRCT chest at 0, 3, 6 months)\(^1\)

1. Best Radiology 2008
Results – Baseline data

• 8 subjects
  – 4 female
  – Aged 63.5 years (57-75)
  – FVC 60% (52.5-74.5) (ASCEND 68%; INPULSIS 80%)
  – DLCO 34.5% (29.5-40) (ASCEND 40%; INPULSIS 47%)
  – 6MWD 460m (375.5-540) (ASCEND 406m)
  – Fibrosis score 14.8% (12.9-17.05)
Results – Acute haemodynamics / gas exchange

![Graphs showing changes in MAP, SaO2, and HR over time during infusion.](image-url)
Results – Lung function, 6MWD, Fibrosis Score

Chambers Respirol 2014
Conclusions

• IV infusion of up to $2 \times 10^6$ placental MSCs is associated with a satisfactory medium-term (6 months) safety profile in human IPF

• Key safety data for future human trials
A Phase I Trial
to Evaluate the Safety, Tolerability, and Potential Efficacy of
Human Mesenchymal Stem Cell Infusion
in patients with
Idiopathic Pulmonary Fibrosis
AETHER (Glassberg et al)

- IPF patients, very similar to Chambers et al
- BM-MSC IV
- 3 dosing cohorts (20*10^6, 100*10^6, 200*10^6 cells), n=3 / cohort
- Primary outcome feasibility amnd safety
  - No treatment related adverse events were reported
  - Most common adverse event was bronchitis (22% subjects)
Results – FVC decline

All Cohorts (N=7)
Average Absolute Decline – Baseline = -3.0%

Baseline 12 24 36 48 60

% Predicted FVC

ClinicalTrials.gov Identifier: NCT02013700; IND 15205, unpublished AETHER study data
Results – 6 minute walk distance

6-MWT Distance over Time
(N=7)

ClinicalTrials.gov Identifier: NCT02013700; IND 15205, unpublished AETHER study data
Mean Absolute DLCO Decline Post Infusion minus Baseline Averaged below 15%

All Cohorts: % Predicted DLCO over time
Average Absolute Decline to Baseline...

All Cohorts: Data Normalized to Baseline Average Relative Decline to Baseline...

Cohort 2+3: Data Normalized to Baseline Average Relative Decline to Baseline
42%, Absolute Decline = ...

Cohort 1: Data Normalized to Baseline Average Relative Decline to Baseline...

Cohort 2: Data Normalized to Baseline Average Relative Decline to Baseline...

Cohort 3: Data Normalized to Baseline Average Relative Improvement to Baseline...
Conclusions

• Developmental pathway to regenerative strategies for IPF becoming clearer
  – Rapid advances in understanding pathogenesis, on a background of long appreciated epidemiology
  – Safety of cellular approaches to regeneration confirmed
  – Biomarkers, potency assays to assist with dosing, dose ranging now within sight
Thank you
<table>
<thead>
<tr>
<th>PRODUCT</th>
<th>Intravenous Adult Human Mesenchymal Stem Cells (MSCs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAIN CRITERIA FOR INCLUSION</td>
<td>Confirmed Idiopathic Pulmonary Fibrosis (IPF)</td>
</tr>
<tr>
<td>STUDY OBJECTIVES</td>
<td>To demonstrate the safety of bone marrow derived MSCs in patients with IPF and to explore treatment efficacy (decline of lung function, frequency of acute exacerbations, change in symptom related quality of life, and survival).</td>
</tr>
<tr>
<td>STUDY DESIGN</td>
<td>Phase I, randomized, double-blind, placebo-controlled.</td>
</tr>
<tr>
<td>TREATMENT REGIMEN</td>
<td>MSCs or matched placebo administered at a dose of 20,000,000, 100,000,000 or 200,000,000 cells.</td>
</tr>
<tr>
<td>ROUTE OF ADMINISTRATION</td>
<td>Intravenous</td>
</tr>
<tr>
<td>DURATION OF STUDY PARTICIPATION</td>
<td>60 weeks</td>
</tr>
<tr>
<td>NUMBER OF SUBJECTS</td>
<td>9 patient pilot safety completed enrollment October 2014</td>
</tr>
</tbody>
</table>

**PRIMARY Endpoint (SAFETY)**

Incidence (at week 4 post infusion) of any treatment-emergent serious adverse events, defined as the composite of:
- death,
- non-fatal pulmonary embolism,
- stroke,
- hospitalization for worsening dyspnea,
- clinically significant laboratory test abnormalities.

**SECONDARY Endpoint (EFFICACY)**

1) Difference in rate of decline of lung function: difference in absolute decline of FVC percent predicted, difference in absolute decline of DLCO.
2) Difference in frequency of acute exacerbations of IPF defined as: new or worsened dyspnea (<30 days), new ground glass opacities on HRCT superimposed on chronic findings, new or worsened hypoxemia in the absence of other identifiable causes.
3) Difference in subject reported dyspnea and quality of life assessment.
4) Death from any cause.