A Decade of IPF Research What Have We Learned?

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The Curious Case of Benjamin Button

How did I get involved?

- 1999 – Saw RN for the first time
  - Driver of a cleanup truck on the Big Dig
  - Rode Harley's
  - Optimistic, engaging personality
  - Had tried conventional therapy with no success
- Read Ziesche's article in NEJM
  - Enquired about availability of gamma interferon
  - Compelled by RN to apply to be involved in study
  - RN got gamma off label – lung function improved, lived for 4 more years, rode Rte 66 from Kingman, AZ to LA with O2 welded to his bike

When did the story start?

- 1975 – Liebow
  - Idiopathic interstitial pneumonias
    - UIP, GIP, BOOP, DIP
- 1991 – Raghu publishes the first paper reporting successful treatment of IPF (27 patients)

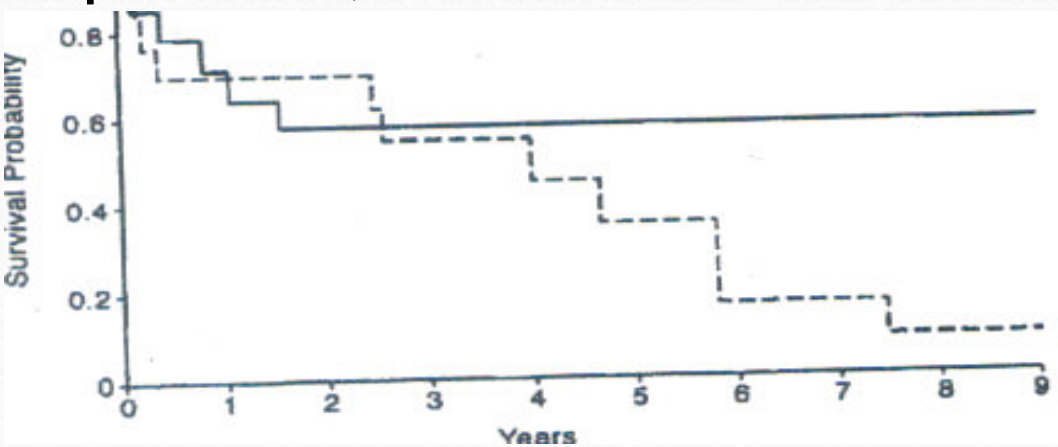
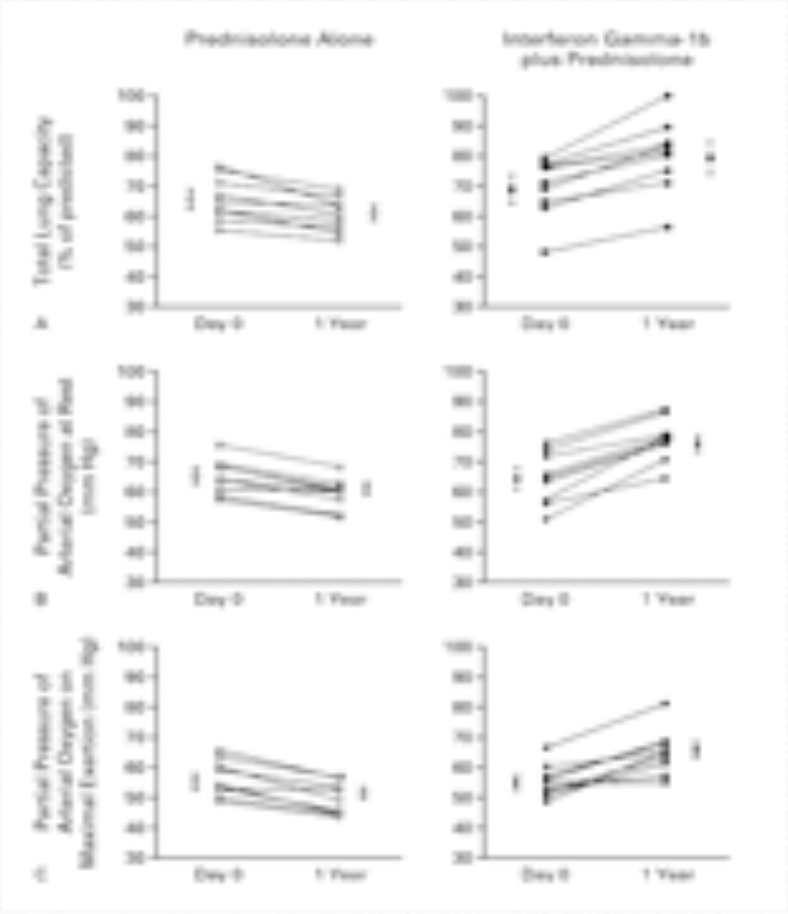


Fig. 1. Survival curves of patients in Group 1 (prednisone plus placebo) and Group 2 (prednisone plus azathioprine). Age adjusted analysis shows a significant survival advantage in the patients treated with combined prednisone plus azathioprine ($p = 0.02$, see text). Solid line = prednisone + azathioprine; dotted line = prednisone + placebo.

Gamma Interferon – 1999

- In a preliminary study, 12 months of treatment with interferon gamma-1b plus prednisolone was associated with substantial improvements in the condition of patients with idiopathic pulmonary fibrosis who had had no response to glucocorticoids alone.



A Preliminary Study of Long-Term Treatment with Interferon Gamma-1b and Low-Dose Prednisolone in Patients with Idiopathic Pulmonary Fibrosis
Ziesche R, Hofbauer E, Wittmann K, Petkov V, Block UH
N Engl J Med 341:1264, October 21, 1999 *Original Article*

Current Therapy for PF

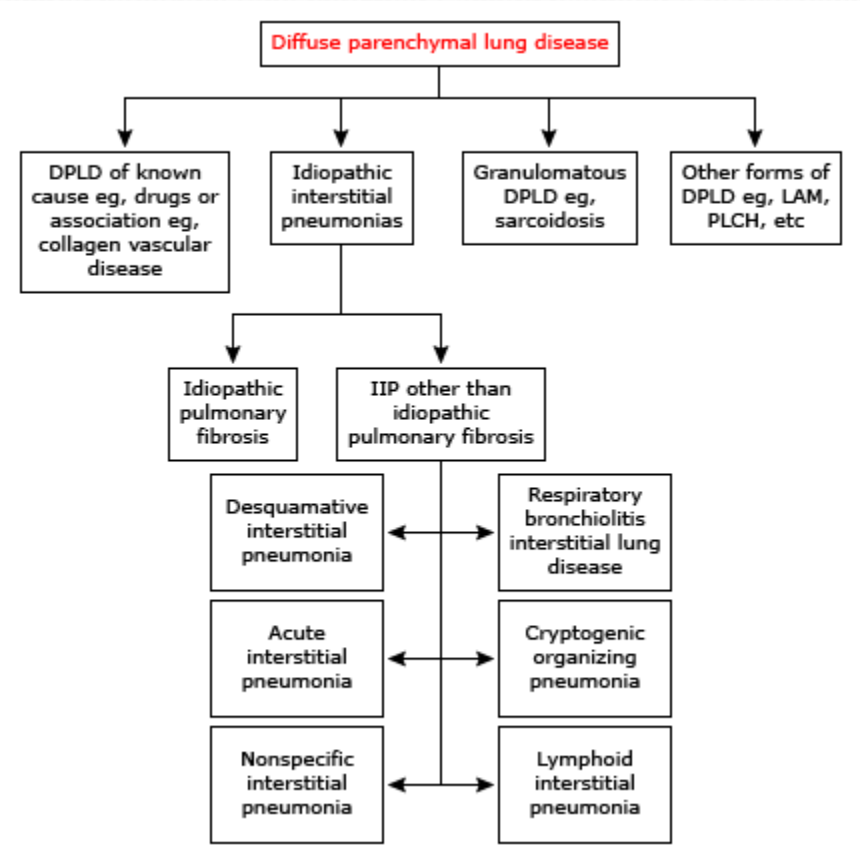
- "No data exist that adequately document that any of the current treatment approaches improves survival or the quality of life for patients with IPF

- The committee suggests that therapy is not indicated for all patients with IPF. If therapy is recommended to a patient, it should be started at the first identification of clinical or physiological evidence of impairment or documentation of decline in lung function"

International consensus statement on idiopathic pulmonary fibrosis

Eur Respir J 2001; 17: 163–167

ATS/ERS Consensus Conference on Classification



What is a Clinical Trial

- Trial of a new agent or device compared to either placebo or standard therapy
- At the onset, investigators are uncertain if therapy is better than no therapy or the conventional therapy
- Best studies are randomized, double blind
  - Neither investigator or patient knows who is in “control” group
  - Sufficient patients are entered to allow for a statistically significant result

Clinical Trials- 2

- All clinical trials are reviewed by a "Human Subjects" committee or IRB
  - Composed of doctors, lawyers, religious leaders, lay persons
  - Cannot begin study procedures until approved
- Clinical trials are monitored by:
  - Sponsoring institutions
  - Pharmaceutical company
  - Federal regulators
    - Investigators are subject to regular and unannounced review
    - Are criminally libel for misconduct

Gamma Interferon

- Multiple large studies – a first
  - Biologic plausibility – TGF-beta
- Initial optimism in select populations
  - FVC > 50%
  - DLCO > 35%
- Very large trial (INSPIRE)
  - No clear survival advantage or alteration in rate of decline of lung function

CAPACITY – Pirfenidone

- CAPACITY 2 demonstrated a statistically significant treatment effect on progression free suvival and rate of decline in lung function
- CAPACITY 1 did not
- FDA concerned about the disparity in outcomes between CAPACITY 1 and 2
- FDA did not consider the Japanese Study in their deliberations because they did not have access to primary data
- FDA asked for a tie breaker

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Phase III Clinical Trials

- Pirfenidone – ASCEND
  - Inclusion Criteria
    - Age 40–80 inclusive
    - Confident diagnosis of IPF by biopsy or CT
    - FVC $\geq$ 50 and $\leq$90 % predicted
    - DLCO $\geq$30 and $\leq$90% predicted
    - Symptoms for > 12 mos
    - Duration of IPF diagnosis at least 6 mos and no greater than 48 mos prior to enrollment
    - No evidence of any connective tissue disease
    - No history of asthma or COPD

Phase III Clinical Trials

- PANTHER
  - NIH Multicenter Trial
    - Prednisone, Azathioprine, N-Acetyl Cysteine
    - Three Arms
  - Over 300 patients enrolled
  - Inclusions
    - Confident diagnosis of IPF – CT/Lung Biopsy within 48 months of enrollment
      - Central adjudication
    - Age 35-85
    - FVC >50%, DLCO >30%
  - Enormously valuable multidimensional database

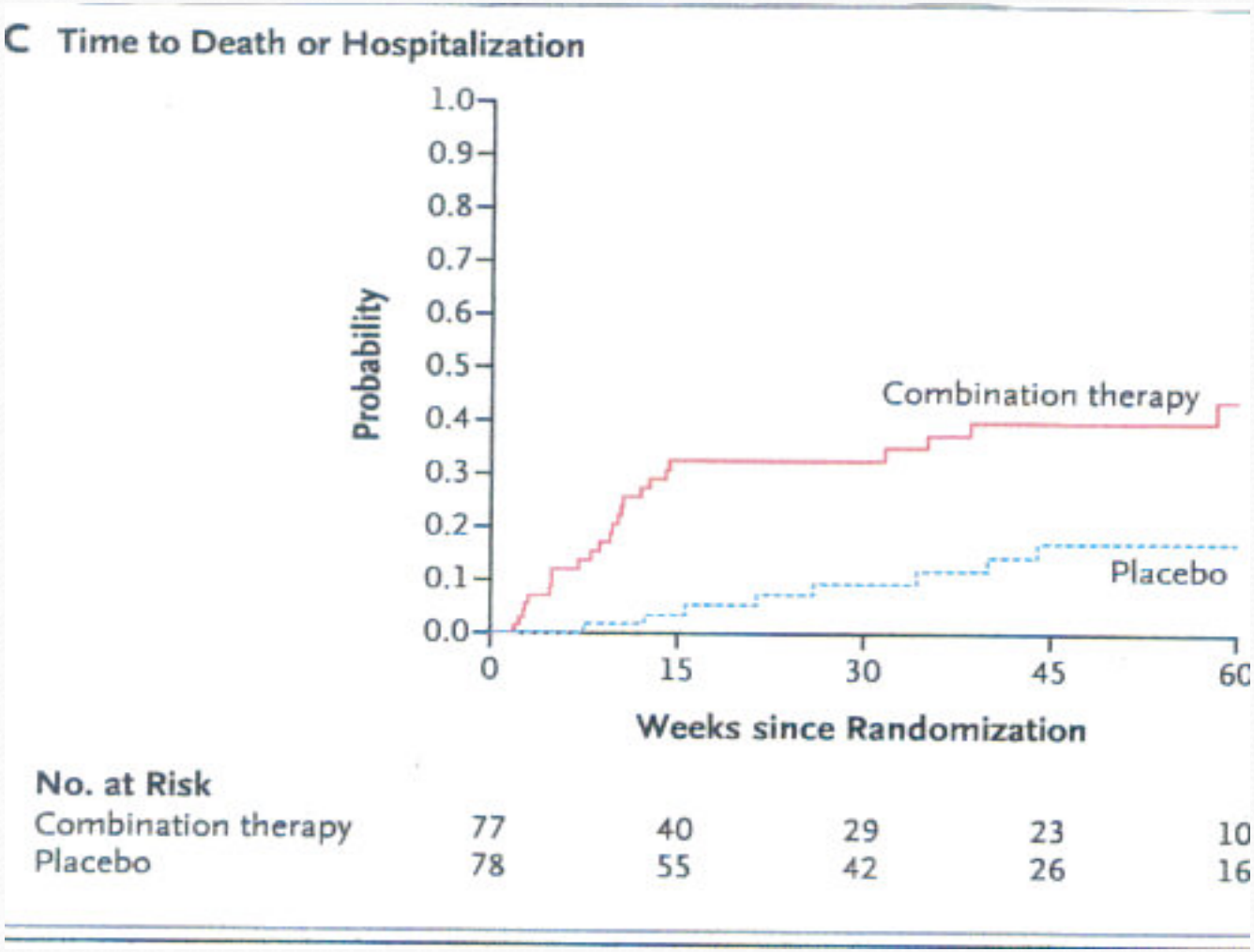
Panther Results

Table 2. **Safety End Points.***

End Point	Combination Therapy (N=77)	Placebo (N=78)	Hazard Ratio	P Valu
Death — no. (%)				
From any cause	8 (10)	1 (1)		0.01
From respiratory causes	7 (9)	1 (1)		0.02
Hospitalization for any cause — no. (%)	23 (30)	7 (9)		<0.001
Acute exacerbation — no. (%)	5 (6)	0		0.03
Serious adverse event — no. (%)	24 (31)	8 (10)		0.001
Based on Kaplan–Meier estimate at 60 wk — % (95% CI)				
Death from any cause	19.8 (9.9–37.2)	2.0 (0.3–13.6)	9.26 (1.16–74.1)	0.01
Death from any cause or hospitalization	43.6 (30.7–59.0)	16.9 (8.7–31.5)	3.74 (1.68–8.34)	<0.001
Death from any cause or ≥10% decline in FVC	36.3 (23.7–53.0)	32.4 (19.7–50.3)	1.46 (0.70–3.05)	0.30

FVC denotes forced vital capacity.

Panther Results



Why is this so hard

- Oncology – cancer
  - Unregulated cell growth
    - Numerous successes with combination therapy
- Cardiology – atherosclerosis
  - Obstruction of arteries with plaque
    - Statins/Antiplatelet Agents/Stents
- Infectious Diseases – retroviruses (HIV)
  - Immunodeficiency states
    - HAART Therapy
    - Vaccine
- Pulmonary – IPF
  - Scarring, senescence
    - Reverse the Aging Process!

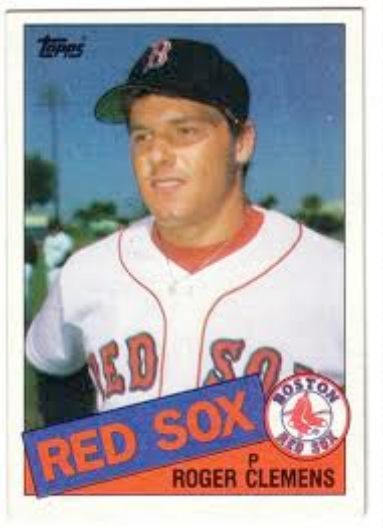
Clinical trials take a long time

- Design
- Approval of protocol
  - FDA
  - IRB
- Recruitment
- Study period
- Analysis
- Approval
- Production of product

Surface Area of Lung

Possible Etiology

- Largest interface with the environment
- Bombarded with toxins over a lifetime
- Constantly being injured and requiring repair
  - Genetic factors determine repair capabilities



Possible Etiologic Factors

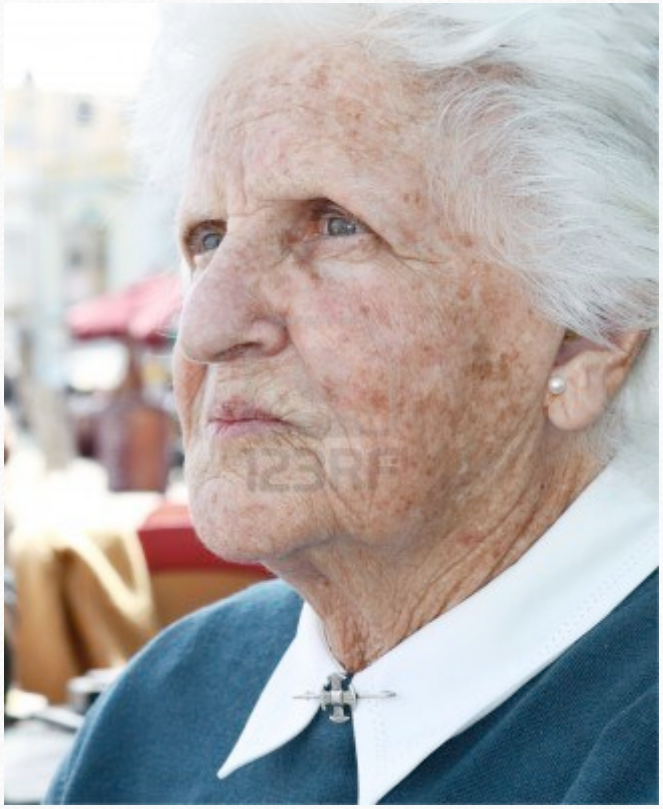
- GERD
- Short telomere syndrome
- Abnormal intracellular protein accumulation
  - Endoplasmic Reticulum Stress
- Imbalance between repair and scarring cytokines
- Greater frequency in older people
- More aggressive in certain populations
  - Air pollution?
  - Cigarette Smoke
  - Industrial Toxins

Loss of lung function

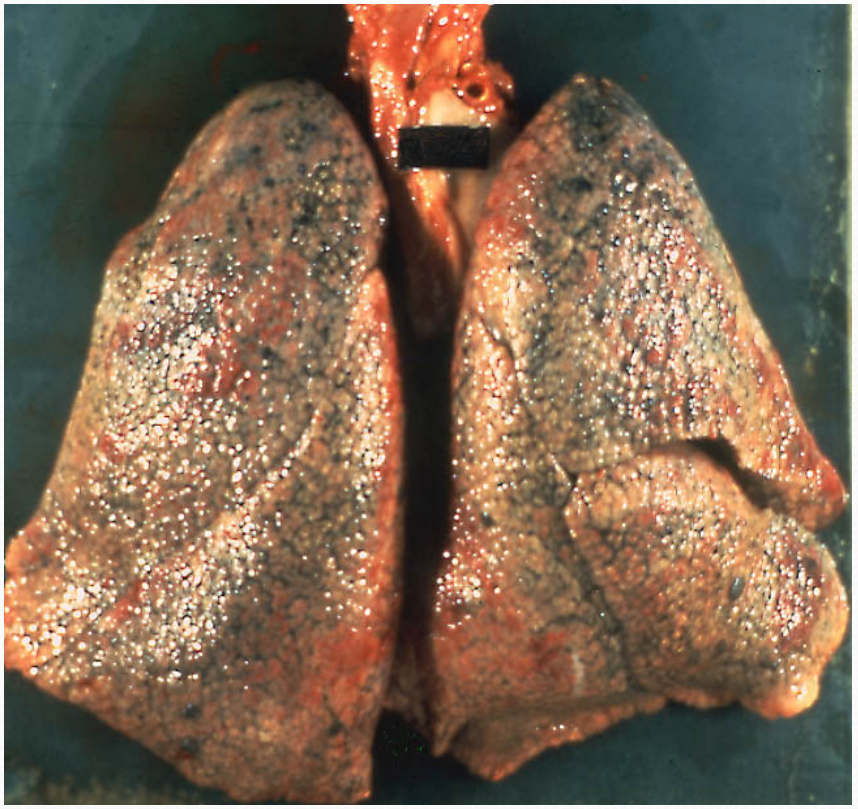
- Every person loses lung function over time
- We report “lung age” on PFT’s
- 120 year (pulmonary) limit on longevity

Living in a dangerous environment?

Scarring/Sun Damage



IPF Lungs



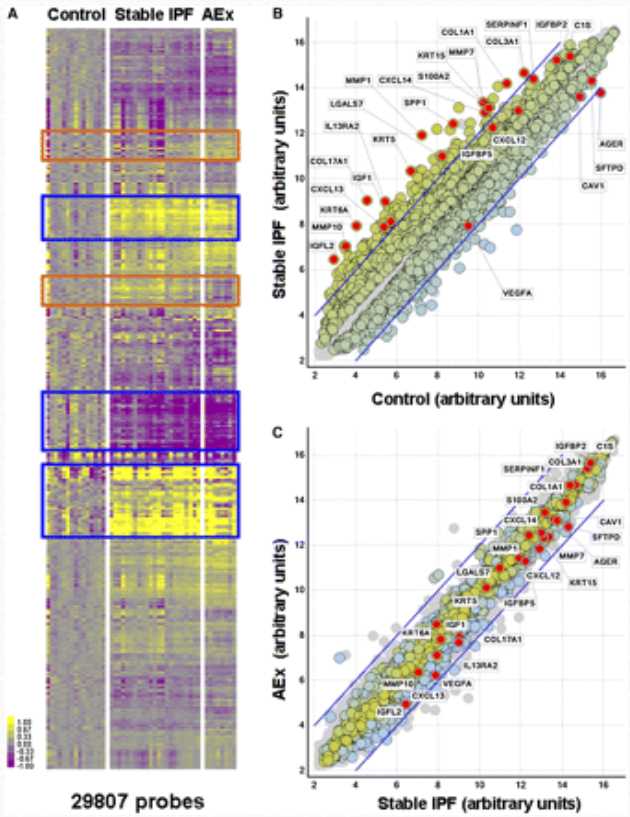
Can we re-set the ageing process?

Young Benjamin Button

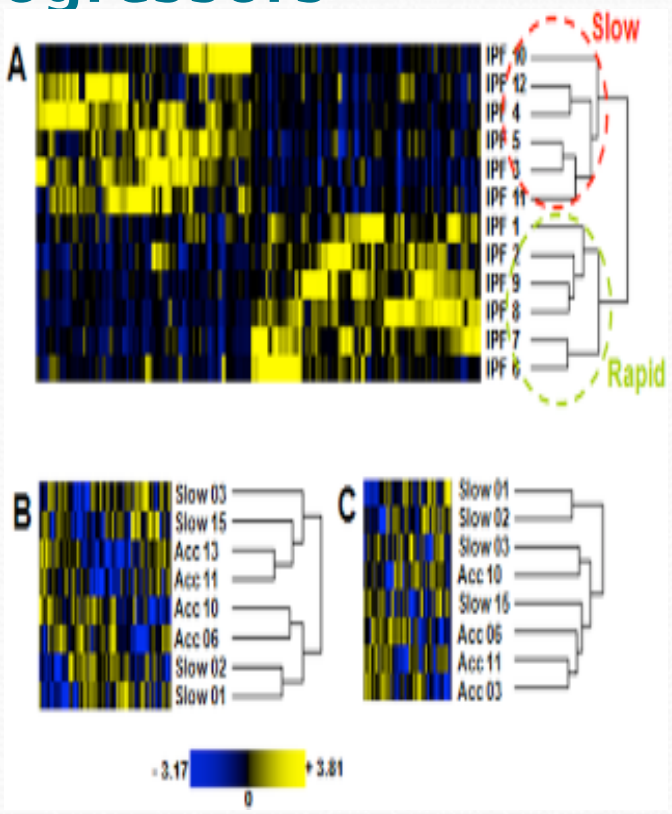
Old Benjamin Button

Genetic heat mapping – clues to effective therapies?

Control vs IPF vs IPF Exacerbation



Rapid vs Slow Progressors



Advances

- We know many agents that do not work
- We have identified disease markers and genes that put people at risk
- GERD was under recognized and may play a role in perpetuating the disease
- We have studied 1000's of people in clinical studies
- CT Scanning has simplified diagnosis
- The scientific understanding of the disease has led to the development of many exciting new agents that in the early testing stages

What do we do – 2012

- Avoid potentially harmful agents
- Protect the lung from injury
  - Treat GERD aggressively
  - Be vigilant about infection
  - Consider using an anti-oxidant (NAC)
  - Avoid poor air quality, toxic exposures
- Maintain optimal oxygenation
- Continue to exercise
- Early evaluation for transplantation
- Search out well designed clinical trials

Conclusions

- IPF is not going to be licked with a single agent!
- Multidrug approach
  - Just like the other complicated diseases I presented
- It isn't going to happen quickly
  - We need approved agents to proceed
- We need your help and participation
  - More shots on goal – more likely to win the game

Boston IPF Collaborative

- Access to trials of the most promising therapies
  - Participation in ASCEND
  - Low Dose CO in IPF is an exciting therapy
  - STX 100 and QAX576 in Phase II trials promise to expand our knowledge of the pathophysiology of IPF
  - Velcade/Roflumilast
  - Lung Transplantation
- Support Group for IPF patients
- A commitment to improving quality of life and survival for all our IPF patients