Scleroderma Research Update 2015

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Broad View of Scleroderma Research

• Introduction/Concepts
• Genetics
  – Genome wide studies
  – GRASP study
• Clinical Studies
  – Epidemiological
    • Importance of “phenotype”
    • Prediction of progression
  – Clinical Trials
    • Pulmonary fibrosis
    • Pulmonary hypertension
    • Diffuse skin disease
Types of Research

Basic, laboratory based research

• Understand fundamental biologic processes, both normal and disease

• Examples
  – Cells in culture and manipulating them
  – Animal models of disease
  – Cell signaling (how cells talk to each other and get things done)
Types of Research

Clinical and Epidemiologic

• Describe human disease and identify risks, patterns (phenotypes) and outcomes

• Examples:
  – Identify subsets of patients and how they differ
  – Examine risk factors for developing a disease or for progression of a disease
Types of Research

Translational

• “Bench to Bedside”; using patient materials in the lab
• Examples:
  – Human serum samples and identify markers that predict outcomes
  – Extract cells from biopsy specimens and see how they behave
  – Samples collected from clinical trials to assess treatment response
  – DNA from patient groups and look at genes that modify risk or prognosis
Types of Research

Clinical Trials

• Investigate new treatments for particular diseases

• Types
  – **Phase 1**: First in human of new drug; assess safety, drug properties
  – **Phase 2**: First study in disease; safety, tolerability, dose finding, proof of concept
  – **Phase 3**: The gold standard clinical trial for showing efficacy; typically blinded and controlled
  – **Phase 4**: Post approval follow up for safety and efficacy measures
Collaborative Efforts

• Ties all of these things together
• Basic/clinical/translational

Our patients hold the key to understanding and eventually curing scleroderma
Scleroderma And Genetics
Scleroderma Research: Translational
The story of the GWAS

• GWAS = Genome Wide Association Study

• Investigates genes across the entire genome for ones that are different between people with and without a condition

• Requires large numbers of patients
Scleroderma GWAS

Radstake, T. Nature Genetics, 2010
The Next Phase

BRIEF REPORT

Clinical and epidemiological research

EXTENDED REPORT

IRF5 polymorphism predicts prognosis in patients with systemic sclerosis

EXTENDED REPORT

Novel identification of the IRF7 region as an anticentromere autoantibody propensity locus in systemic sclerosis association with systemic sclerosis-related pulmonary fibrosis
Importance of racial background

US population is represented on black, German on blue, Dutch on green and Spanish on orange.  
Radstake, T. Nature Genetics, 2010
GRASP

Genome Research in African American Scleroderma Patients
GRASP Study Investigate Variations of Gene Sequence Across the Entire Genome to Discover why African American Patients Tend to Have Worse Scleroderma

Old Genome Studies

- Test small DNA segments
- Test only candidate genes
- Test some variations (polymorphisms)

Whole Genome Sequencing

- Test all the DNA
- Test ALL the genes
- Test most variations (mutation, polymorphisms, duplications)
African American patients with scleroderma have worse disease burden compared to other ethnic groups (earlier onset, more aggressive course)

Published Genome-Wide Association Studies (GWAS) have not investigated specific genetic markers for scleroderma susceptibility in African Americans

The GRASP project was established to:
1) Assemble a large cohort of clinically well characterized African American scleroderma patients from all over the country
2) Use the most advance technology (next generation DNA sequencing) to capture genetic variations extensively across the genome that would confer susceptibility for scleroderma and its manifestations

The National Institute of Health (National Human Genome Research Institute) has accepted to become partner in this critical study
### GRASP Centers

Johns Hopkins University  
University of Texas-Houston  
University of Michigan  
University of Pittsburgh  
Rutgers University  
University of Pennsylvania  
Georgetown University  
Northwestern University  
University of Alabama  
Hospital for Special Surgery  
Medical University of South Carolina  
George Washington  
Tulane University  
Emory University  
UCSF  
University of Miami  
New York University  
Stanford  
University of Chicago
GRASP

Genome Research in African American Scleroderma Patients

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Clinical/Epidemiology

Studies of the variability of a condition
The Scleroderma disease process (like other rheumatic diseases) is complex

- The disease is rare (15 new cases per million per year)
- Wide variation in expression
- Involves multiple organ systems
- Involves multiple pathologies
  - Immune system
  - Vascular system
  - Fibrosis (scar)
The importance of phenotype

- **Phenotype = an observable characteristic**
  - Based on skin subtype: limited or diffuse
  - Based on organ dysfunction: how much lung fibrosis
  - Based on antibody type

- **If you can sufficiently phenotype you can correlate this with:**
  - How well someone does
  - Who responds to medications
  - Who is at higher risk for complications

- **If you combine phenotype with other measures (genotype, molecular markers, biomarkers) you will get meaningful answers**
Scleroderma Antibodies

- Centromere
- Muscle PM–Scl
- Fibrillarin B23 Th/To
- Topoisomerase-1 (Scl-70)
- PAH
- Lung Fibrosis
- Diffuse Skin
- U3 RNP
- C.R.E.S.T.
- Centromere
- MCTD
- UI RNP
- Diffuse Skin
- Lung Fibrosis
- PH
- Kidney
- Diffuse skin
- RNA Polymerase I/III

# Phenotypes

<table>
<thead>
<tr>
<th>Duration</th>
<th>Skin Subtype</th>
<th>Antibody</th>
<th>Lung Severity</th>
<th>Raynaud Severity</th>
<th>Biomarker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short</td>
<td>Limited</td>
<td>Centromere</td>
<td>Mild</td>
<td>Severe</td>
<td>High</td>
</tr>
<tr>
<td>Long</td>
<td>Diffuse</td>
<td>Topo</td>
<td>Moderate</td>
<td>Mild</td>
<td>Low</td>
</tr>
<tr>
<td>Short</td>
<td>Limited</td>
<td>None</td>
<td>Severe</td>
<td>Mild</td>
<td>High</td>
</tr>
<tr>
<td>Long</td>
<td>Diffuse</td>
<td>RNAPol</td>
<td>Mild</td>
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Impact of skin score trajectory

A. Change in skin score over 3 years in the LTM subgroups

B. Survival in the LTM subgroups
Inherent Trajectories?
Layer Clinical Data (antibody)
Layer Treatment Data
Scleroderma Lung Disease
Epidemiology of ILD in Scleroderma

• Depends on the definition
  – PFT
  – XRAY, CT scan
  – Pathology
• 25–90% of scleroderma patients have lung involvement
• Only ~15% will progress
• Lung disease is leading cause of mortality
Who is at risk?

• Diffuse disease > Limited disease
• Autoantibodies
  – Topoisomerase-1
• Early disease
  – Majority of decline in first 2 years
• Racial/ethnic background
• Lung function testing
• Lung inflammation?
• Degree of fibrosis on CT

Negative Predictors

• Normal CT at baseline
  – 84% will have normal CT at 5 years

• Antibodies
  – Centromere
  – RNA polymerase III

Launay D et al. J Rheumatol 2006; 33: 1789-1801
How to best use this data

Define risk/outcome
- Outcome
- Organ disease presence
- Progression
- Regression

Inform clinical trials
- Who to include
- High risk groups
- What expected is
Clinical Trials
Pulmonary Hypertension

- Narrowing of pulmonary artery
- Enlarged right ventricle

- Aorta
- Pulmonary valve
- Right atrium
- Tricuspid valve
- Mitral valve
- Left atrium
- Aortic valve
- Left ventricle
- Right ventricle
- Ventricular septum
Approved Therapies for PAH

• Endothelin receptor antagonists
  – Bosentan (Tracleer): A+B
  – Ambrisentan (Letairis): A–selective
  – Macinintentan (Opsumit): Tissue targeting

• Prostenoids
  – IV Epoprostenol (Flolan, Valetri)
  – SQ/IV Treprostinil (Remodulin)
  – Inhaled Iloprost (Ventavis)
  – Inhaled Treprostinil (Tyvaso)
  – Oral Treprostinil (Orenitram)

• Phosphodiesterase inhibitors
  – Sildenafil (Revatio)
  – Tadalafil (Adcirca)

• Soluble guanylate cyclase stimulants
  – Riociguat (Adempas)
Future Therapies

• Combination of existing therapies
• Next generation of existing therapies
  – New selective ERA antagonists
  – Tissue targeting ERA antagonists
  – Vardenafil
• New targets
  – Tyrosine kinase inhibitors (imatinib)
  – Soluble guanylate cyclase inhibitors
  – Rituximab
• New patient groups
  – PH related to left heart disease
  – PH along with interstitial lung disease
Combination Therapy

• AMBITION TRIAL
  – Combination ambrisentan/tadalafil vs. monotherapy with either
  – 500 patients randomized 2:1:1
  – First line therapy
  – 50% reduction in clinical events

<table>
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<tr>
<th>Outcome</th>
<th>Combination (n = 253)</th>
<th>Monotherapy (n = 247)</th>
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<tbody>
<tr>
<td>All-cause deaths (%)</td>
<td>3.6</td>
<td>3.2</td>
</tr>
<tr>
<td>Hospitalization (%)</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>Improvement in 6-minute walking (m)</td>
<td>49.0</td>
<td>23.8</td>
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Presented at European Respiratory Society (ERS) International Congress 2014
Early Detection: Impact

Scleroderma Lung Disease
Frequency distribution of $\Delta$ FVC % pred from baseline by treatment group

(p<0.01; Fisher’s Exact)
Scleroderma Lung Study II

- 24 month study
- Patients with early scleroderma (7 years) with evidence of active lung disease
- Patients are randomized to receive:
  - Cytoxan for 12 months + placebo; then placebo + placebo for 12 months
  - Cellcept for 24 months + placebo
- Study is has completed enrollment
Early Results from SLS II

Treatment – Rationale

TRIGGER

INFLAMMATION

SIGNAL (CYTOKINES)

SCAR FIBROSIS

TGF-β, INTERFERON, ENDOTHELIN INTERLEUKINS

FIBROBLAST
Clinical Trials

- Immunomodulating/Immune suppressing
  - IVIG
  - Rituximab
  - Stem Cell Transplant
  - Abatacept
  - Tocilizumab

- Anti-fibrotic/other therapy
  - Nintedanib
  - Perfenidone
  - Fat derived stem cells
  - Cannaboid agonist
  - Abatizumab
Conclusion

• Significant progress continues to occur for our understanding of the pathology and nature of the disease
• Exciting new treatments are being evaluated and there is significant progress in several areas
• Many centers and consortiums in place to better evaluate potential therapy