The National Institute of Arthritis and Musculoskeletal and Skin Diseases

Reducing Chronic, Common, and Costly Conditions through Research

Stephen I. Katz, M.D., Ph.D.
Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases

National Institute of Arthritis and Musculoskeletal and Skin Diseases
The 27 Institutes and Centers of the NIH
Shared Interest in Bone Diseases
Shared Interest in Autoimmune Diseases
Shared Interest in the Muscular Dystrophies
Overview

• Trans-NIH efforts
• Multi-center clinical studies
• Basic and translational research
Study of Osteoporosis (SOF) and Mr. OS

• Bone mineral density of the hip
  – One of the best predictors of fracture

• Factors influencing bone mineral density
  – Diet
  – Body weight
  – Family history
  – Physical activity
  – Smoking
  – Medications

• Other factors influencing fracture development
  – Visual acuity
  – Clutter
  – Medications
Hip Fractures Among Women Aged ≥65 Years, United States

Year


Incidence per 100,000 Population

1991 – Increased funding for osteoporosis research

1994 – The NIH Osteoporosis and Related Bone Diseases ~ National Resource Center – Consensus conference on Optimal Calcium Intake

1995 – Study of Osteoporotic Fractures

1996 – Bisphosphonates

1996 – Bisphosphonates

2000 – Consensus conference on Osteoporosis Prevention, Diagnosis, and Therapy

The Bone and Joint Decade

2003 – Findings re: combination therapy

2004 – Surgeon General’s Report

2005 – Mr. OS findings – Meeting on Bone Quality: What Is It and Can We Measure It?

Brauer CA et al, JAMA 2009
Foundation for NIH (FNIH) Biomarkers Consortium Bone Quality Project

• Advance the qualification of biomarkers for drug development and patient management
  – Qualify imaging and biochemical markers from clinical trials

• Goal
  – Improve ability to predict fracture

• Project team
  – NIH
  – U.S. Food and Drug Administration
  – Academic researchers
  – Pharmaceutical industry (Amgen, Eli Lilly, Merck)
  – American Society for Bone and Mineral Research
  – The Dairy Research Institute®
Osteoarthritis (OA)

- Degenerative joint disease resulting in breakdown of cartilage and loss of joint function
- Often develops in weight-bearing joints
  - Injury can trigger OA development
- Most common type of arthritis
  - Affects an estimated 27 million adults in the United States
The Osteoarthritis Initiative
A Research Resource for Biomarker Validation

• Need
  – Objective and measurable standards for osteoarthritis (OA) onset and progression by which new drugs can be evaluated

• Goal
  – Create research resources to aid in identification and evaluation of biomarkers as candidates for surrogate endpoints for OA

• Mechanism
  – Develop a prospective, natural history cohort
    ▪ ~ 5,000 people, most of whom have or are at high risk of developing OA
    ▪ ~ 20% minority enrollment
The Osteoarthritis Initiative Consortium

University of California, San Francisco (data coordinating center)
Memorial Hospital of Rhode Island, Pawtucket
The Ohio State University, Columbus
University of Maryland School of Medicine, Baltimore
University of Pittsburgh

Private sector sponsors
- GlaxoSmithKline*
- Merck Research Laboratories*
- Novartis Pharmaceuticals Corporation
- Pfizer, Inc.

NIH Sponsors
- NIAMS
- NIBIB
- NIMHD
- NIA
- NCCAM
- ORWH
- NIDCR*

NIH Management
- Project Officer
- Contracting Officer
- Institute Directors
  - NIAMS
  - NIA

OAI Steering Committee
- OAI institutions
- Private sector sponsors
- NIH sponsors
- Liaison from the Food and Drug Administration
- Liaisons from other interested entities

Observational Safety and Monitoring Board

* GlaxoSmithKline, Merck Research Laboratories, and NIDCR participated between 2001 and 2009 only.
Osteoarthritis (OA)

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Recent Findings from OAI Data

• **Results published**
  – 158 OAI-based publications as of September 2013

• **Analytic methods developed**
  – Facilitate longitudinal comparison of images

• **Predictive markers identified**

MRI markers predictive of symptomatic OA

- Cartilage defect
- Bone marrow lesions
- Meniscal extrusion
Ongoing Efforts

• FNIH Biomarkers Consortium
  – Goal: Discover imaging and biochemical biomarkers of OA progression

• NIAMS-funded contracts focused on OAI data / image analysis
  – Pivotal Osteoarthritis Initiative Magnetic Resonance Imaging Analyses
  – Hip Morphology and Limb Specific Risk Factors for Radiographic Hip OA
  – Efficacy of Complementary Alternative Medical Treatments for OA of the Knee on Patient-Centered Outcomes

• Basis for investigator-initiated research projects
• **Patient Reported Outcomes Measurement Information System (PROMIS)**
  – Large item bank measuring patient-reported outcomes
  – Computerized adaptive testing system
  – Relevant to a wide range of chronic diseases

• **NIH Common Fund Initiative**
  – Begun in 2004
  – Transitioning to institute support
**PROMIS Self-Reported Health Domains**
*(Patient Response)*

- **Physical Health**
  - Pain
  - Fatigue
  - Symptoms
  - Function

- **Mental Health**
  - Behavior
  - Cognition
  - Emotion
  - Anxiety
  - Depression
  - Anger / aggression
  - Substance abuse

- **Social Health**
  - Role Participation
  - Social Support

- **Activities of daily living**
  - Lower extremities / mobility
  - Upper extremities / dexterity

... and more
PROMIS Resources

**Informatics**
Assessment Center
Supports >600 active studies in past year alone

**Advancing Knowledge**
>240 Peer-Reviewed publications in 116 different journals

**Cooperative Group**
12 Research Sites
3 Centers
150+ Scientists

**Tools**
40 Adult Measures
20 Pediatric Measures

**Translations**
All item banks → Spanish
(Over 40 other languages)

**NIH funding** (>100M)
Numerous RFAs and supplements since 2004 to support Center & Sites
Engaging Federal Partners

• Food and Drug Administration / Interagency Clinical Outcomes Assessment Working Group
  – Moving PROMIS into the FDA qualification process and assessing whether it may substitute for the SF-36

• Centers for Medicare and Medicaid / Centers for Clinical Standards and Quality
  – Discussing PROMIS instruments as quality performance measures

• Patient Centered Outcomes Research Institute (PCORI) / NIH-PCORI Task Force
  – Involved in PCORI’s Patient-reported Outcomes (PRO) Infrastructure Workshop (November 2013)

• Department of Defense (DoD)
  – Working with PROMIS to implement Pain Assessment Screening Tool and Outcomes Registry (PASTOR)
Overview

• Trans-NIH efforts
• Multi-center clinical studies
• Basic and translational research
Spine Patient Outcomes Research Trial (SPORT)

• Begun in 1999
  – Is surgery better than non-operative treatments such as physical therapy and medication?
  – Does conservative treatment that delayed surgery harm patients?

• Three common causes of surgery for low back pain
  - Intervertebral disc herniation
  - Degenerative spondylolisthesis
  - Spinal stenosis
# SPORT: Robust Cohorts Leading to Many Publications

<table>
<thead>
<tr>
<th>Condition</th>
<th># of Participants</th>
<th>Key Publications</th>
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<td>RCT</td>
<td>Obs.</td>
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<td>Intervertebral disc herniation</td>
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SPORT Results for All Groups

- At 2 and 4 years, surgical patients had better function and were more satisfied with their progress than those who did not have surgery
  - Similar results observed 8-years post treatment for intervertebral disc herniation
  - 8-year data will be available soon for spinal stenosis and degenerative spondylolisthesis
- Surgery remains an option for patients with worsening symptoms or who did not improve with conservative treatment
  - People are not subjecting themselves to further harm if they adopt a “wait-and-see” approach before committing to surgery
SPORT Back Pain Treatment Calculator Guides Decisions

• Rich database led to treatment calculator showing possible patient results after surgical or non-surgical treatment for low back pain
  – Website: http://caligari.dartmouth.edu/SpinalOutcomes/
  – Answer questions about
    ▪ Diagnosis
    ▪ Age and sex
    ▪ Activity level
    ▪ Pain
    ▪ Overall health

• Next step: Refine calculator to include
  – Individual patient characteristics
  – longer-term outcomes data from SPORT
  – Information about complications following surgery or the need to have a second procedure
  – Results from other related studies
Bracing in Adolescent Idiopathic Scoliosis Trial (BrAIST)

• Scoliosis
  – Curvature of the spine
  – More common in girls than in boys
  – Treatments: waiting, bracing, surgery

• Multi-center clinical trial
  – Led by Dr. Stuart Weinstein at University of Iowa
  – Begun in 2006
  – 383 patients (155 randomized cohort, 228 observation cohort)

• Monitoring patients who have mild curves in the spine
  – Do curves get worse?
  – Do braces help?
Bracing Significantly Reduces Risk of Curve Progression and Need for Surgery


Before and after bracing x-rays of a girl with adolescent idiopathic scoliosis.

Images courtesy of Lori Dolan, University of Iowa / BrAIST database
More Hours of Brace Wear Associated with Higher Success Rates

**Successful treatment** = reaching skeletal maturity without a curve progressing to 50 degrees (the point at which surgery is recommended)
• **Childhood Arthritis and Rheumatology Research Alliance (CARRA)**
  - Self-actuated network
  - More than 390 pediatric rheumatologists and researchers
  - Over 92 institutions in North America

• **CARRA Registry**
  - More than 9250 patients
  - Basis for more than 30 research projects
    - Standards of care for juvenile dermatomyositis
    - Early, aggressive therapy for juvenile idiopathic arthritis
    - Trial of rilonacept for systemic juvenile idiopathic arthritis
    - Atherosclerosis prevention in pediatric lupus erythematosus
Atherosclerosis Prevention in Pediatric Lupus Erythematosus (APPLE)

A collaborative effort between NIAMS and the Childhood Arthritis and Rheumatology Research Alliance (CARRA) to study the effects of a common cholesterol drug (atorvastatin) against artery fat buildup in children with lupus.
APPLE Conclusions

- Preclinical atherosclerosis starts in children and adolescents with systemic lupus erythematosus
- Statins should not be routinely prescribed to children with lupus
  - Finding will spare children the cost and potential side effects of a drug that is not proven to be beneficial
  - Low dose, intermediate duration statin therapy was safe in this population
  - Statins may benefit patient subgroups with severe disease
- A well-functioning network can successfully complete a complex trial in a rare pediatric disease

Overview

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Proposed Mechanism of Marfan Syndrome

Consortium for Translational Research in Marfan Syndrome P01 AR049698 (FY ‘02-14)

Excess TGF-beta activation

1. Latent complex
   - Normal
   - Microfibrils

2. TGF-beta
   - Marfan syndrome
   - LAP
   - LTBP

Excess TGF-beta signaling

3. Cytoplasm
   - R-Smad
   - Smad4
   - Cytoplasm

Phenotypic consequences

- Emphysema
- Mitral valve prolapse
- Aortic aneurysm
- Myopathy
- Others?

Losartan, an angiotensin II receptor inhibitor

Ramirez and Dietz, Curr Opin Genet Dev 2007
Recessive dystrophic epidermolysis bullosa (RDEB) –
Severe inherited blistering skin disease caused by absence of a protein known as type VII collagen
Patients develop large, severely painful blisters and open wounds from minor trauma to their skin
Patients often die in late-teens or early-20s from metastatic skin cancer originating in chronically scarred skin

Gene Transfer for RDEB
Phase I clinical trial
Create a graft from the patient's own skin cells that have been genetically engineered to express this missing protein
Lack of Type VII Collagen Changes Skin Structure

**Normal skin**
- Keratinocytes synthesize type VII collagen molecules (red), which assemble into anchoring fibrils
- Fibrils entrap the interstitial collagen fibers in the dermis, securing the stable association at the dermal-epidermal junction

**RDEB**
- There are only a few rudimentary anchoring fibrils, allowing formation of blisters below the lamina densa as a result of minor trauma

Recessive dystrophic epidermolysis bullosa (RDEB) – Severe inherited blistering skin disease caused by absence of a protein known as type VII collagen – Patients develop large, severely painful blisters and open wounds from minor trauma to their skin – Patients often die in late-teens or early-20s from metastatic skin cancer originating in chronically scarred skin

Gene Transfer for RDEB – Phase I clinical trial – Create a graft from the patient's own skin cells that have been genetically engineered to express this missing protein
Gene Transfer for Recessive Dystrophic Epidermolysis Bullosa

Preliminary Results

OR Post-Prep  OR Post-Graft  Day +28

Images courtesy of Alfred Lane, Stanford Univ. School of Medicine
Recombinant Type VII Collagen (rC7) on Normal and RDEB Mouse Skin

Topical rC7 Accelerates Wound Closure on Normal Mouse Skin

Topical rC7 Forms Anchoring Fibrils (AF) in RDEB Mouse Skin

Wang et al, *Molecular Therapy* 2013
Rheumatoid Arthritis (RA)

• Causes pain, swelling, stiffness, and loss of joint function

• Occurs when the immune system attacks the synovial membrane that lines the joint
  – Inflamed synovium invades and destroys cartilage and bone within a joint
  – Muscles, ligaments, and tendons that stabilize the joint weaken

• Affects approximately 1.5 million adults in the United States
Gut Microbiome Implicated in RA

Relative abundance of gut microbiota changes with RA onset.

People who have new-onset RA have a significant increase in *Prevotellaceae* (red) and a concomitant decrease in *Bacteroidaceae* (blue).

Scher et al, *eLife* 2013
Microbiome and Mucosal Inflammation as Extra-Articular Triggers for RA

• Periodontitis
• *P. gingivalis*
• Peptidyl arginine deiminase activity

• Smoking
• Lung disease
• Peptidyl arginine deiminase activity

• Gut microbiome
• Antibiotics

Brusca et al, *Curr Opin Rheumatol* 2014
Autoinflammatory Diseases

The Expanding Spectrum

IL-1β activation disorders

- Pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA)
- Familial Mediterranean fever (FMF)
- Hyperimmunoglobulinemia D with periodic fever syndrome (HIDS)
- Neonatal-onset multisystem inflammatory disease (NOMID)
- Deficiency of the interleukin-1 receptor antagonist (DIRA)

Meet Alex—
Before and After an NIH Clinical Trial

NOMID patient and clinical trial participant Alex (then and now) with NIAMS researcher Dr. Goldbach-Mansky
Deficiency of the Interleukin-1 Receptor Antagonist (DIRA)

Inflammatory Skin and Bone Manifestations in Patients with DIRA


Jacob Whelan (center) with his parents, and Raphaela Goldbach-Mansky, M.D. who, along with her team at NIAMS, discovered DIRA, for which Jacob has been undergoing treatment.
Jak Inhibitors – an 18-year Journey from Bench to Bedside

- **1994:** Cloning of JAK3 and identification as a mediator of IL-2 signaling
- **1995:** Discovery of Jak3 mutations in SCID
Type I/II cytokines signal via Janus kinases and STATs

- ~200 “cytokines” in the human genome
- ~60 signal via Jak-Stat pathway
- Diverse roles in cell growth, differentiation, host defense and inflammation
- Four Jaks: Jak1, Jak2, Tyk2 – broad functions
- Function of Jak3?
Jak Inhibitors – an 18-year Journey from Bench to Bedside

- 1994: Cloning of JAK3 and identification as a mediator of IL-2 signaling
- 1995: Discovery of Jak3 mutations in SCID
- 1995-2000: Development of small molecule JAK3 inhibitors (NIH-Pfizer)
- 2005: Demonstration that lead compound (CP-690,550) prevents allograft rejection
- 2008: Efficacy of CP-690,550 in animal models of RA
- 2008-2011: Phase II/III clinical trials of CP-690,550/Tofacitinib in Rheumatoid Arthritis: Efficacy comparable to TNF inhibitors, slows erosions
- 2012: At least 7 JAK inhibitors in trials, FDA approved JAK1/2 inhibitor for myelodysplastic syndrome (ruxolitinib)
- May 9, 2012: FDA advisory panel recommends approval of tofacitinib for treatment of RA