Updates on Lupus 2017

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Outline

• Research at UR
• What’s new in diagnosis?
• Pathogenesis (leads to treatment)
• Treatment
Research in Lupus

The more that is known about clinical outcomes and immune abnormalities associated with lupus, the better equipped we are to fight the disease!
What we’re doing at the U of R:

• NIH funded networks
  • Accelerating Medicines Partnership

• Clinical Cohorts/Consortiums
  • LuCIN (Lupus Clinical Investigators Network- LRI/ALR collaboration, repurposing drugs)

• Clinical Trials

• Outcomes research and new patient centered care delivery models
Episode 408:
“You don’t want to know” %
It is lupus! %
How do we diagnose lupus?:
American College of Rheumatology (ACR) criteria

<table>
<thead>
<tr>
<th>Skin criteria</th>
<th>Systemic criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Malar rash</td>
<td>5. Arthritis</td>
</tr>
<tr>
<td>2. Discoid Rash</td>
<td>6. Serositis</td>
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Lab criteria
- 9. Anti-nuclear antibody
- 10. Immunologic
- 11. Hematologic

For the purpose of identifying patients in clinical studies, a person shall be said to have SLE if any 4 or more of the 11 criteria are present, serially or simultaneously, during any interval of observation.
Autoantibodies precede diagnosis

- Identifying ‘at risk’ individuals

The Future of Diagnosis

- Identify and detect more lupus specific autoantibodies - Next generation proteomics
  - Stanford silicon chip with thousands of histone related proteins
  - Rochester collaboration with CDI-19,000 human proteins on a single microscope slide
- Highly sensitive detection of interferon

Duffy and Yanick Crow, J Exp Med 2017
Cause/Pathogenesis

- Genetics
- Hormones
- Environment

The 'exposome'
Genetics

- Polygenic- each single gene contribution is very small
- Genetic burden
Genetics: ‘Cumulative hits hypothesis for autoimmune disease’

- Largest multi-ethnic lupus genetics study (>27,000 subjects) to date recently identified many new genetic markers using ImmunoChip, a genotyping technology designed specifically for autoimmune disease.
- Some of the markers were specific to individual ethnic groups and others that are shared across ethnicities.
- Many of the genetic markers associated with lupus are shared across numerous autoimmune diseases.
- As the number of genetic risk variants a person has increases, the risk for lupus increases exponentially.

Langefeld Nature Communications 2017
Regular exercise and stress make a big difference in lupus.

• Mouse model of lupus:
  • **moderate exercise** (45 minutes of treadmill walking per day) significantly decreased inflammatory damage to the kidneys
  • Animal model of psychological **stress** -- daily encounters with a stronger "bully" mouse. The results were almost exactly the opposite -- inflammatory markers shot up, which caused substantial kidney damage in the mice.

• Stress Moderation Impacting Lupus with Exercise (SMILE) study:
  Daily tai chi program for SLE patients focused on both moderate exercise and stress reduction. Initial results show a significant decrease in some of the same inflammatory biomarkers identified in the mouse

Saba et al. Frontiers in Physiology 2017
SLE pathogenesis and treatment targets

Stages of autoimmunity

- Loss of tolerance
- Innate and adaptive dysregulation
- End organ targeting

Sle1, CD22, C1q, BANK, BAFF  
Sle2 (B), Sle3 (T, DC), PTPN22  
FcR, ITGAM

Autoantibodies  
Immune complex

Proteasome inhibitors  
antibodies  
TLR inhibitors  
IFNα blockade

Antibodies

BAFF inhibitors

mBAFF  
IFNα

mDC  
B7.1/2

CTLA4-Ig Abatacept

Lymphocyte signaling small molecule inhibitors

pDC  
IFNα

N

B

pDC  
IFNα

TNFα  
IL-1β  
IL-6  
IL-17

TNF blockade

IL-6 blockade
B cells behaving badly

B-cell → Plasma cell

(Auto)-antibody production

SLE Controlled

SLE Active

CD27

IgD

Protective (B cell functions)

Pathogenic (B cell functions)

Anolik et al. AR 2007
Palanichamy et al. JI 2010
Wei, Anolik, Sanz, 2017 in preparation
A subset of B cells called ‘Age-associated B cells’ (ABCs) may drive lupus. A transcription factor called T-bet drives the development of these B cells. These investigators deleted T-bet inside B cells, and mice prone to develop autoimmune disease remained healthy.
Why do we need new treatments?

• The more that is known about clinical outcomes and immune abnormalities associated with lupus, the better equipped we are to fight the disease!

• Current treatments do not always work

• Current treatments can have toxicity

• We have no cure for lupus
Identifying new treatment targets and biomarkers

**Accelerating Medicines Partnership (AMP) Initiative**

First-of-its-kind partnership and study

**Goal:** To evaluate the molecular pathways and relevant drug targets of autoimmune diseases to help develop new therapies

Learn more: fnih.org/AMP-RA-Lupus
Boosting Success by Improving Efficacy: Phase II Clinical Trials

Current targets
- Animal models
- Cell lines

AMP targets
- Emerging Technologies
  - DNA sequencing
  - Proteomics
  - Single-cell analysis
  - Bioengineered cells
  - Imaging
- Extensive Human Data
  - Tissue/blood samples
  - Clinical information
  - Demographics
- Big Data Tools

Adapted from: Arrowsmith J, Miller P. Nat. Rev. Drug Discov. 12, 569, August 2013
Origin of AMP: Pharma R&D Leaders and NIH Director Meet To Address A Central Challenge in Drug Development:

Why Do So Many Drugs Fail In Clinical Trials?

How Can This Be Improved?

2012
Francis Collins and Industry Leaders

2013
“Target Validation Consortium”

2014
Accelerating Medicines Partnership

Joint NIH-Industry Target Validation Workshop
3 AMPs Alzheimer’s, T2D, RA/SLE
Focus on target tissue

Getting towards precision medicine

- Clinical/transcriptional profiling of 72 lupus patients
- Molecular and cellular stratification may improve outcomes in SLE and help identify new treatment targets

Phase 0: Data-Driven Method Development and Harmonization
- Blood cells
- Synovial, Kidney and Skin cells

Phase 1: Systems Biology - RNAseq, CyTOF, Epigenetics, Pilot Studies
- Blood
- Tissue Samples
- CyTOF
- Sorted cell subsets RNAseq, Epigenetics
- CyTOF
- Single cell RNA sequencing

Phase 2: Patient Stratification - Longitudinal Cohorts
Aims for Phase 2

Identify molecular + cellular features that define pathologically distinct subsets of nephritis

Histologic Classification

Class I

Class IV

Class V

Molecular Classification

Adapted from JC Jennette
Accelerating Medicines Partnership (AMP)

AMP RA/Lupus Network +

Acknowledgements +

Primary Network Sites

• Albert Einstein College of Medicine – Chaim Puttorman, MD
• Brigham and Women’s Hospital – Michael Brenner, MD
• Broad Institute – Soumya Raychaudhuri, MD, PhD
• Feinstein Institute for Medical Research – Betty Diamond, MD; Peter Gregersen, MD
• Hospital for Special Surgery – Vivian Bykerk, MD; Lionel Iwashkiv, MD; Alessandra Pernis, MD
• Johns Hopkins School of Medicine – Michelle Petri, MD
• New York Genome Center – Robert Darnell, MD, PhD
• New York University School of Medicine – Jill Buyon, MD
• Oklahoma Medical Research Foundation – Judith James, MD, PhD
• Rockefeller University – Thomas Tuschl, PhD
• Stanford University School of Medicine – Bill Robinson, MD, PhD; PJ Utz, MD
• University of California, San Francisco – David Wofsy, MD
• University of Colorado – V. Michael Holers, MD
• University of Pittsburgh – Larry Moreland, MD
• University of Rochester – Jennifer Anolik, MD, PhD

Funding Partners

[Logos of various funding partners]
More on clinical trials and new treatment strategies

- IFNα
- CD40
- CD40L
- CD28
- B7.1/2
- mBAFF
- sBAFF
- BR3
- TLR9
- nDC
- B
- T
- pDC
- CTLA4
- -Ig
- Abatacept
- TNF blockade
- IL-6 blockade
- Autoantibodies
- Immune complex
- Proteasome inhibitors
- Anti-B cell antibodies
- TLR inhibitors
- IFNα blockade
- B cell signaling
- small molecule inhibitors
- Proteasome inhibitors
- BAFF inhibitors
- mDC
- IFNα
- B7.1/2
- B7.1/2
- CD28
- CD40
- CD40L
- TLR9
- TNFα
- IL-1β
- IL-6
- IL-17
- N
- TNF blockade
- IL-6 blockade
- TLR inhibitors
- B cell signaling
- small molecule inhibitors
B cell targeted 2017 What’s new?

• Innovative ways to combine rituximab with benlysta

• Other B cell targeted therapies:
  • Anti-CD22: phase III completed, did not meet endpoints
  • Other anti-CD20s-approved for lymphoma
  • Anti-CD19

• Cytokine blockade
  • Benlysta: SQ recently approved, ongoing studies for nephritis, black patients, pediatric, long-term safety, treatment holiday/restart
  • Different forms of BAFF blockade in Phase 3- blisibimod (Anthera- CHABLIS study begun 7/2016), atacicept (EMD Serono) Phase 2
Interferon and Toll-like receptors

- Blocking IFN- positive results with anifrolumab (Phase 2); now in Phase 3

- Other approaches:
  - TLRs are key receptors of the innate immune system that can induce strong inflammatory responses- important in production of IFN. Interest in small molecule inhibitors of Toll-like Receptors (TLRs) 7, 8, and/or 9
  - TLR7 is one of the signals for ABCs to develop
Unexpected effects of IFN

• Type I IFN in the bone marrow influences how immune cells develop:
  • Break B cell tolerance
  • Mesenchymal stem cells: anti-inflammatory roles; differentiate into a variety of cell types - altered function in SLE because of the IFN milieu

• IFN and CNS (Bialas and Carroll; Nature 2017): inflammation and neurologic connection

Pananichamy...Anolik JI 2014; Gao...Anolik, Looney A and R 2017; Bialas et al Nature 2017
Gao article featured in Clinical Connections: http://onlinelibrary.wiley.com/store/10.1002/art.40211/asset/art40211.pdf?v=1&t=j9a75wth&s=b281217f71bd9efc5f2c1ab4b1d7a867926480ad
Is it important to eliminate autoantibodies?

- Most current therapies do not effectively target autoantibodies/plasma cells.
- Recent pilot study in 12 refractory SLE patients: proteasome inhibitor bortezomib depletes plasma cells and ameliorates clinical manifestations.
- Amgen acquires Onyx: Kyprolis=carlfizomib for myeloma.
- Kezar Life Sciences developing immuno-proteasome inhibitors- 1st in lupus trials due to start 2018.

![Illustration of Plasmablast and Plasma Cells](image)

**Anti-microbial**  
**Anti-DNA**  
**Anti-RBP (Ro, La, Sm/RNP)**

**Graph**

Ichikawa…Anolik; Arthritis and Rheum 2012
Alexander…Voll, Ann Rheum Dis 2015
Intracellular signaling pathways

- Mitogen-activated protein kinases (MAPK), tyrosine kinases (TK), Janus kinases (JAK) and nuclear factor κB (NFκB)
- Interesting therapeutic targets
- Experience in RA (tofacitinib=JAK3 inhibitor)
- Anolik lab work with SINEs
Currently (or soon) enrolling trials at UR

- Phase 3 IFN blockade
- Small molecule Btk inhibitor (through LUCIN)
- Cell based therapies
  - Mesenchymal stem cell transfer
Concluding points

• Therapy will attempt to target specific pathways in the body

• Personalized medicine

• Some drugs may provide clues about how lupus develops

• Despite barriers, novel mechanism-based therapies are in development for SLE

• Eventual treatments may involve combination therapies, i.e., “cocktails” of targeted and semi-targeted therapies
Thank You!
Learn More

- www.lupusresearch.org/research/research_update.html
- LupusTrials.org
- www.clinicaltrials.gov
- The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) and the Office on Women’s Heath have developed a strategic plan for reducing health disparities. Lupus is included as an area of research focus. Recent first-ever National Public Health Agenda for Lupus in collaboration with the National Association of Chronic Disease Directors (NACDD). Further information on disparities in lupus and educational material at:
  - http://thelupusinitiative.org
  - www.couldihavelupus.gov