Objectives

• Define the key pathogenic characteristics of:
  – Type I diabetes mellitus
  – Multiple sclerosis
  – Rheumatoid arthritis
  – Systemic lupus erythematosus

• Understand current issues involving diagnosis and treatment of these diseases
Evolving issues to consider

- How can we use biomarkers to predict autoimmunity?
- What are some caveats of therapies that are mechanistically specific?
- How does the environment affect the development of autoimmunity?
- How do biomarkers contribute to the concept of personalized medicine?
Type I Diabetes Mellitus: predictive biomarkers

Notkins AL. *Scientific American* 2007; March:72-79.
Type I diabetes develops progressively

Early pathogenesis involves T and B cells

Early autoantigen: Insulin

Notkins AL. *Scientific American* 2007; March:72-79.
Later pathology is associated with islet antibodies

Later autoantigens: Glutamic acid decarboxylase (GAD) Islet antigen-2 (IA-2)

Notkins AL. Scientific American 2007; March:72-79.
Related autoantibodies are correlated with Type I diabetes

Genetic factors are correlated with susceptibility to Type I diabetes

Biomarkers to predict susceptibility in Type I diabetes

- What are the implications of predicting the risk of Type I diabetes?
- Who gets tested?
- What to do with the information?
Can we prevent Type I diabetes in susceptible people?

- Diabetes Prevention Trial – Type I Diabetes (DPT-1)
- European Nicotinamide Diabetes Intervention Trial (ENDIT)
  - Antibody-positive relatives
  - Able to predict disease in almost 2/3 of patients
  - Interventions failed to delay or prevent the onset of diabetes

- Other prevention clinical trials are ongoing

Multiple sclerosis: Targeted therapies
Clinical features of multiple sclerosis

- Relapsing-remitting disease
- Visual changes
- Limb weakness
- Fatigue
- Numbness
- Dizziness

- Cerebrospinal fluid – increased immunoglobulins (oligoclonal bands)

Demyelination in multiple sclerosis

Can we develop targeted therapy for multiple sclerosis?
Natalizumab prevents leukocyte migration

Natalizumab is given with some risk

- Progressive multifocal leukoencephalopathy (PML)
- Herpes infections
- Pneumonia
- Urinary tract infections
- Melanoma
Design biologic therapies with caution

- Six healthy young male volunteers

• Six healthy young male volunteers
• **90 minutes:** proinflammatory cytokines, headache, muscle pain, nausea, diarrhea, erythema, vasodilatation, low blood pressure
• **12 to 16 hours:** pulmonary infiltrates, lung injury, renal failure, disseminated intravascular coagulation
• **24 hours:** severe depletion of lymphocytes and monocytes
• **8 and 16 days:** cardiovascular shock and acute respiratory distress syndrome in two patients

Persistent questions in biologic therapeutics

- How to maximize specificity and minimize adverse effects?
- How to design a drug with superior efficacy to existing drugs?
- What next after a patient fails a new biologic?
Rheumatoid arthritis:
Environment affects disease
Clinical features of rheumatoid arthritis

- Warm, swollen joints
- Morning stiffness
- Subcutaneous nodules
- Symmetric arthritis
- Serum rheumatoid factor
- X-ray changes
The antigens that initiate and perpetuate RA are unknown.
Smoking increases rheumatoid arthritis risk in genetically-predisposed individuals.

These are results for patients with anti-citrullinated protein antibodies.

Klareskog L. *Arthritis Rheum* 2006;54:38-46
Patients without anti-CCP antibodies do not have the same risk correlations

These are results for patients without anti-citrullinated protein antibodies.

Klareskog L. *Arthritis Rheum* 2006;54:38-46
What is citrullination?

Post-translational modification of proteins by **peptidylarginine deaminase (PAD)**

- Change in charge
- Protein unfolding
- Protein degradation

![Chemical structures](image)

arginine → citrulline via peptidylarginine deaminase (PAD)
Smoking may aid development of anti-citrullinated protein antibodies

Citrullinated proteins in rheumatoid arthritis

Only a few citrullinated proteins correlated with RA have been described so far (i.e. fibrin, vimentin).

- Which proteins are targeted in RA?
- What is the significance of antibodies to citrullinated proteins?
- Can anti-citrullinated protein antibodies help us predict the course of RA? Guide treatment?
Systemic lupus erythematosus: Road to personalized medicine?
Clinical features of systemic lupus erythematosus

- rash
- arthritis
- serositis
- nephritis
- myocarditis
- myositis
- cerebritis
- cytopenias

Pathophysiology of SLE

Rahman A and Isenberg D. *NEJM* 2008;358:929-939
## Biologic therapies developed to treat SLE

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# Treatment outcomes for SLE have faltered

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## Treatment outcomes for SLE have faltered

### Why are there so many clinical trial failures in SLE?

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Autoantibody profiles in SLE as biomarkers

- Can antibody specificities reflect underlying mechanisms of disease?
- Can a subset of patients respond better to specific therapy?
- Can antibody profiles reflect responsiveness to different treatments?

Personalized medicine = using antibodies to subset disease pathways
Autoantigen microarray printing and analysis

180 autoantigens

BioRad Chipwriter Pro System

Probe with sera

Evolving issues to consider

• How can we use biomarkers to predict autoimmunity?
  – Predictive autoantibodies in Type I diabetes

• What are some caveats of therapies that are mechanistically specific?
  – Natalizumab, CD28 superagonist

• How does the environment affect the development of autoimmunity?
  – Smoking and anti-CCP antibodies in RA

• How do biomarkers contribute to the concept of personalized medicine?
  – Autoantibodies in SLE to subset patients for therapies
Many persistent questions in autoimmunity

- Type I diabetes
- Multiple sclerosis
- Rheumatoid arthritis
- Systemic lupus erythematosus

Genes
Environment
Autoantibodies
Biomarkers