Innovative Programs to Advance Health Research (LSDF 07-02)

Program for Autoimmune Disease Intervention (PADI)

Immune Monitoring & Targeted Therapeutics

Interdisciplinary translational research applied to autoimmune diseases to improve health outcomes
Program for Autoimmune Disease Intervention

- Unmet medical need
- Scientific opportunities
- Economic growth opportunities
Autoimmune Diseases

Autoimmune Diabetes
Multiple sclerosis
Lupus
Alopecia areata
Ankylosing spondylitis
Addisons disease
Hemolytic anemia
Autoimmune Hepatitis
Thrombocytopenic purpura
Behcets disease
Pemphigus
Crohns disease
Dermatomyositis
Graves disease
Hashimotos Thyroiditis

Myasthenia gravis
Pernicious anemia
Polyarteritis
Polychondritis
Polymyositis
Psoriasis
Rheumatoid arthritis
Scleroderma
Sjogren’s syndroms
Stiff man syndrome
Giant cell Arteritis
Ulcerative colitis
Vasculitis
Uveitis
Vitiligo
• Unmet medical need

Autoimmune diseases affect 50 million in the US, and are one of the top 10 leading causes of death in children and women age 65 and younger.
• Unmet medical need

Morbidity and mortality are directly related to late diagnosis, lack of effective treatments, and problems in access to care;
Scientific Opportunity

Morbidity and mortality are directly related to late diagnosis, lack of effective treatments, and problems in access to care;
• Scientific Opportunity:

We now, for the first time, can identify, isolate, and study the cells (specific lymphocytes) which trigger and cause autoimmune diseases.
“Enabling Technology”: co-opt molecular mechanisms responsible for immune specificity
Precise molecular handshakes provide the cell-to-cell contacts responsible for immune specificity.
Precise molecular handshakes provide the cell-to-cell contacts responsible for immune specificity.
Mimic the body’s molecular strategy

Immune lymphocyte

Antigen presenting cell
A molecular probe for autoimmunity

Tetramer analysis of blood sample from patient

Control 0.10%

Control 0.11%

Diabetes tetramer 7.28%
Early treatment is the goal; Early identification of autoimmunity is the key.
The therapeutic window for intervention using immunomodulation

Surviving islet cells

Genetic Predisposition

Immune activation

Normal insulin release

Progressive loss of islet cells

Glucose normal

Overt diabetes

Time →
The therapeutic window for intervention using immunomodulation

- Genetic Predisposition
- Normal insulin release
- Immune activation
- Immune regulation
- Glucose normal

Surviving islet cells

Time →
The Pipeline of Immunotherapy Trials in New Onset Type 1 Diabetes

- MMF and DZB
- HSP 65 p277
- Multi-dose DZB
- Exanitide and DZB
- Multidose anti-CD3
- Anti-CD20
- CTLA4-Ig

- Rapamycin and IL-2
- Phase III Anti-CD3
- Anti-CD3 and Exanitide
- GAD 65 in Alum
- Proinsulin DNA Vaccine
- ATG
- Anti-CD3 and insulin
type 1 diabetes and multiple sclerosis and lupus?

Related by:
- genetic susceptibility,
- molecular mechanisms,
- potential therapeutics directed at fundamental immune pathways;
Health Impact “Deliverables”: A toolkit for a new approach to autoimmunity

<table>
<thead>
<tr>
<th>Genetic profile</th>
<th>Immunologic profile</th>
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<tbody>
<tr>
<td>HLA</td>
<td>Treg freq</td>
</tr>
<tr>
<td>CTLA4</td>
<td>Treg function</td>
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<tr>
<td>PTPN22</td>
<td>Teff phenotype</td>
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<tr>
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<td>B cell phenotype</td>
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<td>cytokines</td>
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<tr>
<td>CD25</td>
<td>At-risk/pre-clinical</td>
</tr>
</tbody>
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- Flares/disease progression
- Disease remission
We anticipate that a successful result from this Program will be the widespread use of such profiling tools for early diagnosis, selection of therapy, monitoring of therapy, and design of the next generation clinical trials for T1D, MS, and lupus.

...better outcomes
...reduced costs
• Autoantigen targeting – the PADI interdisciplinary approach to novel autoimmune therapy
Immediate benefits

Morbidity and mortality are directly related to late diagnosis, lack of effective treatments, and problems in access to care;
Program for Autoimmune Disease Intervention

State-wide network of collaborating providers
Access to trials,
Education of patients and families
Key LSDF elements

- Institutional Commitment
- Partnerships with other organizations
- Financial cost-sharing
- Deliverables
- Milestones
- Commercialization plan