Therapy and diagnosis utilizing peptides recognized by gluten-reactive T cells
How can CD4+ T cells that cause celiac disease be used for diagnosis and treatment?

- Diagnostic tests for gluten-specific T cells
  - overcome the need for and shortcomings of biopsy
  - overcome inaccurate or indeterminate histology

- Therapies that selectively target and tolerize gluten-reactive CD4+ T cells
  - resume unrestricted diet
  - stop disease recurrence when gluten eaten
  - less burdensome than GFD
A model of CD4+ T cell in celiac disease

- **Spleen, lymph nodes:** Activation of memory T cells
- **Intestine:** Activation of effector T cells
- **Blood T cells**
- **Thymus:** Naïve T cells

**Gluten loaded DCs**

**Gluten**

**Intestine:** Activation of effector T cells
Intestine was the only site used to study immune responses in CD.

- Spleen, lymph nodes: Activation of memory T cells
- Blood T cells
- Thymus: Naïve T cells
- Gluten loaded DCs
- Lymphatics
- Intestine: Activation of effector T cells
Blood is the only site easily sampled

Spleen, lymph nodes:
Activation of memory T cells

Gluten loaded DCs

Lymphatics

Intestine:
Activation of effector T cells

Blood T cells

Thymus:
Naïve T cells

Gluten
CD4+ T cells in the gut recognize the same peptides as T cells circulating in blood after oral challenge

Day-6

Gluten diet

Gluten challenge

Cytokine release tests for T cells

• In celiac disease - whole blood and ELISPOT assays for 2 immunodominant gliadin peptides after 3-day oral challenge:
  • Sensitivities 89-100%
  • Specificities 94-100%

• Regulatory approval for QuantiFERON®-TB Gold as diagnostic for tuberculosis:
  • 3x 1mL blood tubes – NIL, TB PEPTIDE & MITOGEN
  • 24h incubation @37°C
  • Widespread clinical use
  http://www.quantiferon.com/irm/content/pdfs/Cellestis-QFTFactSheet.pdf
Oral gluten challenge may not be necessary to detect gluten-specific T cells in blood
Elevated effector & central memory gliadin-specific T cells in CD blood

Non-CD normal diet

CD GFD

CD normal diet

Accurate and simple tests for gluten-specific CD4+ T cells for development of therapies

- Blood-based, rapid, convenient, quantitative

- **Therapeutics for celiac disease**
  - Selection of peptides for therapy

- **Biomarker tool-kit for celiac disease**
  - Standalone – identify CD patients on or off GFD
  - Companion – identify CD patients suitable for therapy
  - Monitoring – identify patients responding to therapy
Therapy using Peptides that Target Gluten-specific T cells

Patients receive intradermal injections of Nexvax2

T cells secrete chemicals to destroy gluten

Damaged intestine when gluten is eaten before Nexvax2

Healthy intestine when gluten is eaten after Nexvax2
Pharmacogenetics: Celiac disease is a composite of HLA-DQ genotypes with distinct epitope hierarchies

Gluten-reactive T cells mobilized in HLA-DQ2.5+ celiac disease: Dominant epitopes recognized after oral grain challenges

Studies have focused on adults on GFD
Nexvax2 Consists of Three Peptides

- DQ2.5-glia-α1, -α2
- DQ2.5-glia-ω1, -ω2
- DQ2.5-hor3

- Adjuvant-free
- Standard peptide synthesis
- Recognized by the majority of gluten-reactive T-cells after a combined wheat/barley/rye challenge
- Consistent pharmacokinetics (rat)
  - half life of 20-30min
- Soluble and stable in saline
- Pre-filled intra-dermal syringes
Nexvax2:
Epitope-Specific Immuno-Therapy (ESIT)

- A “model” for a new class of highly specific tolerogenic immunotherapies using peptides
- Peptide selection based on immuno-dominance in comprehensive epitope screening with cytokine release assays using fresh PBMC or whole blood
- Parallel development of diagnostics using the same peptides in cytokine release assays using fresh blood
Nexvax2: Target Product Profile

Disease Modifying T-cell epitope derived peptide immunotherapy indicated for prevention of relapse when consuming an unrestricted diet in HLA-DQ2.5+ patients with celiac disease

Allow unrestricted diet
Initial Proof of Concept: Induction of tolerance in DQ2.5 mouse

Induction

Single dose: Activation

Multiple dose regimen:
• Anergy
• Treg induction – cell markers and function
• Suppression interferon-γ, IL-2
• Induction IL-10

Maintenance

NEXVAX2® DEVELOPMENT PROGRAM:
Epitope-specific immunotherapy for CD
**Nexvax2**

- The therapy is designed to induce tolerance to gluten thereby preventing symptoms and intestinal damage associated with unrestricted diet and eliminating need for gluten free diet.

- Nexvax2 therapy can be compared to allergen immunotherapy (also known as allergy shot/ allergy vaccine) which have been shown to be effective in treating human allergic diseases.

- Chronic administration of Nexvax2 (which contains specific peptides of gluten) switches off or reprograms disease-causing T-cells and induces clinical tolerance.

- Nexax2 is paired with a companion diagnostic to identify responders and monitor response to therapy.

- Nexvax2 therapy involves an induction phase where drug is administered via **injection** to individuals identified as **potential responders identified via diagnostic test** (It is estimated DQ2.5 celiac patients would be eligible for induction therapy based on their reactivity to Nexvax2)

- At the end of induction period, responders are indentified. **Responders can resume normal unrestricted diet while following chronic maintenance therapy with self administered booster injections**

- The intradermal injections are performed using a simple easy to use device
Nexvax2 clinical studies: >100 subjects enrolled to date (DQ2.5+ CD on GFD diet)

- **Nexvax2-001**
  - 1st in human AU 2009-10
  - Dose 3x 9-90ug/wk

- **Nexvax2-1002**
  - Phase 1b AU/NZ 2012-14
  - Extended increased dosing
  - Expanded readouts, PK, OGC

- **Nexvax2-1003**
  - Phase 1b USA/AU/NZ 2012-14
  - Increased dosing
  - Expanded readouts, PK, OGC

- **Nexvax2-2001**
  - Phase 2a AU/NZ 2015
  - Companion diagnostic

- **Nexvax2-2004**
  - Phase 2a UK/EU/US/AU/NZ
  - Planned 2015
  - Proof of Concept
Evolution of Peptide-based diagnostics and therapeutics in celiac disease

- Diagnostics assessing peptide-stimulated cytokine release in blood or staining of circulating T cells assessed by flow cytometry

- Provocative diagnostics using antigen challenge and measuring blood biomarkers

- Repeated administration of immuno-dominant epitopes switches “on” T cells and then shuts down T cell response

- Nexvax2 in Phase 2 studies commencing 2015 in UK and elsewhere