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Biomarkers for Diagnosis and Management of Enteric Diseases

There is an urgent need for the development of sensitive, specific and non-invasive biomarkers for the diagnosis and management of patients with enteropathic diseases such as celiac sprue. Such biomarkers could be used in primary screening of potential patients, definitive diagnosis of suspected patients, monitoring response to therapies, drug compliance assessment, and cost-effective drug development. Two such biomarkers, summarized below, have been invented and patented at Stanford University. **For simplicity, the descriptions that follow are limited to their relevance to celiac sprue, although application to other enteric diseases (e.g. inflammatory bowel diseases) is also anticipated.**

Background:

Current diagnostic methods for celiac sprue are based on serum antibody tests, a small bowel biopsy, and a clinical response to a gluten-free diet. Although antibody tests are fairly specific, patients must be exposed to the discomfort of high doses of gluten over extended durations before they seroconvert. Whereas small bowel biopsies are the "gold standard", they are obtained via invasive and expensive endoscopic procedures; their handling and examination requires considerable expertise and is often subjective. Clinical signs and symptoms associated with celiac sprue are variable, even in the same patient, and therefore not particularly useful. For example, although patients with active celiac sprue show statistically significant differences in fat or xylose absorption or lactulose permeability compared to patients in remission, these markers are peripherally related to celiac sprue immunopathogenesis, and can undergo significant changes due to factors unrelated to the disease. There is therefore an urgent need for biomarkers that complement the strengths and weaknesses of serological and histological tests in the context of diagnosis.

Although a definitive path for celiac sprue drug development has not been established, ongoing efforts are based on clinical protocols that are adapted from existing diagnostic practices. For example, changes in histology, serology, fat or xylose absorption, lactulose permeability, and gastrointestinal symptoms are generally monitored either in the context of a gluten challenge (if the protective capacity of the drug candidate is being evaluated) or along the normal course of recovery (if the ability of the drug candidate to accelerate full recovery is being evaluated). There is an urgent need for "scaleable biomarkers" that can serve as useful, preferably primary, endpoints in early proof-of-concept clinical trials as well as late-stage registration trials.
On a longer-term horizon, as new drugs for celiac sprue are approved, one can anticipate a need for biomarkers that facilitate assessment of compliance and response to therapy. Not only would this enhance the physician's ability to manage the patient's life-long disease, but it would also add value to selected drugs in an increasingly competitive market.

The Technologies:

- **(1)** By altering key residues in naturally occurring gluten peptide, a family of synthetic peptide biomarkers has been designed to mimic immunotoxic gluten peptides in terms of their resistance to gastrointestinal proteases and susceptibility to therapeutic glutenases. However, in contrast to immunotoxic gluten peptides (e.g. the 33-mer), these biomarkers are neither substrates of human transglutaminase 2 nor are they high-affinity ligands for HLA-DQ2. Consequently, these biomarkers are non-inflammatory, and carbon-13, hydrogen-2, or alternatively labeled versions can safely be administered orally to celiac sprue patients in conjunction with a drug or placebo. If the drug is a glutenase, then the levels of the labeled amino acids in bodily fluids such as serum, breath or urine provide insight into the efficacy of a drug such as an oral glutenase. If the drug modulates the response of celiac mucosa to gluten via other mechanisms, then the level of the labeled peptide itself (or a partially proteolyzed metabolite) in a bodily fluid is useful for assessing the extent of leakiness of the epithelial barrier of the celiac small intestine. The latter analytical measurement could also be used in the context of other inflammatory bowel diseases where mucosal leakiness is elevated.
- **(2)** The second biomarker technology is designed as a non-invasive, quantitative surrogate for the small bowel biopsy in celiac sprue. Certain xenobiotic cytochrome P450 enzymes, such as CYP3A4, are highly active in

enterocytes as well as liver cells. However, in contrast to the liver, where their expression level is relatively constant, CYP3A levels can fluctuate significantly in the small bowel. For example, CYP3A4 is abundant in enterocytes near villous tips but not near the crypts, suggesting that CYP3A4 activity correlates with enterocyte maturity. Dietary gluten is known to induce abnormal enterocyte morphology and physiology in celiac patients. Consequently, celiac patients with active disease have decreased CYP3A4 protein and activity levels in their small intestine, both of which recover to normal after introduction of a gluten-free diet. Thus, the efficacy of a celiac drug can be conveniently monitored using intestinal CYP3A4 activity as a surrogate for gluten-induced enteropathy. For example, the widely used drug, simvastatin, is predominantly metabolized by CYP3A4 in the small intestine. Changes in the Cmax and AUC of oral simvastatin could therefore be correlated with the early onset of villus damage in a celiac sprue patient. Pending clinical proof-of-concept, the test could be readily adapted into a finger-stick or urine test format.

Applications

- Biomarkers for diagnosis and drug development for celiac disease, and potentially other enteric diseases such as inflammatory bowel disease

Advantages

- Large potential impact - 1 in 200 people are affected by celiac disease
- Less invasive than bowel biopsy
- Complements existing histological & serological tests

Patents

- Published Application: WO2009035510
- Published Application: 20110027891
- Issued: 8,535,946 (USA)

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