Biological Sciences Division

Second phase of PNNL diabetes research funded by NIH

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The second phase of a project that is applying advanced proteomic and metabolomic technologies to the study of type 1 diabetes recently received funding from the National Institute of Diabetes, Digestive and Kidney Disease (NIDDK). The Phase 2 award is for 3 years and totals $1.9 million.

The project, titled "Advanced Proteomics and Metabolomics Studies of Type 1 Diabetes," uses liquid chromatograph/Fourier transform ion cyclotron resonance (LC/FTICR) mass spectrometry (MS) for the proteomic and metabolomic identification of biomarkers for the development of type 1 diabetes. The overall project goal is to advance the study of the disease and human islet transplantation success rate by identifying biomarkers at the proteomic and metabolomic levels that predict both.

During Phase 1 of the project, PNNL scientists constructed accurate mass and time (AMT) tag databases for 1) peptides and metabolites from human plasma/serum comprising >16,000 and >1900 entries, respectively; and 2) peptides and metabolites from human pancreatic islets comprising >44,000 and >6000 entries, respectively. These databases will enable the high-throughput characterization of large numbers of human plasma/serum and pancreatic islet samples by LC-FTICR MS during Phase 2.

In addition, the PNNL team identified <20 potential candidate biomarkers for type 1 diabetes on both the protein and peptide level, which will be validated during Phase 2. Current efforts are focused on the comparative analysis of LC-FTICR MS datasets from healthy control and type 1 diabetes patients on the level of the metabolome to identify additional candidate biomarkers to complement those identified on the protein and peptide level. Phase 2 will involve 1) high-throughput studies of complete sample sets from the Centers for Disease Control and Prevention Diabetes Autoantibody Standardization Program (DASP), 2) validation of potential biomarkers via analysis of a blind DASP sample set, and 3) comparative studies of multiple human pancreatic islet preparations to identify potential biomarkers predictive of islet performance in vivo.

The research team members are Tom Metz, Jon Jacobs, Weijun Qian, Dick Smith, Gordon Anderson, David Camp, Ljijana Pasa-Tolic, and Yufeng Shen (PNNL) and Vincent Poitout (University of Montreal). In addition, Pat Mueller of the Centers for Disease Control and Prevention is representing the DASP.

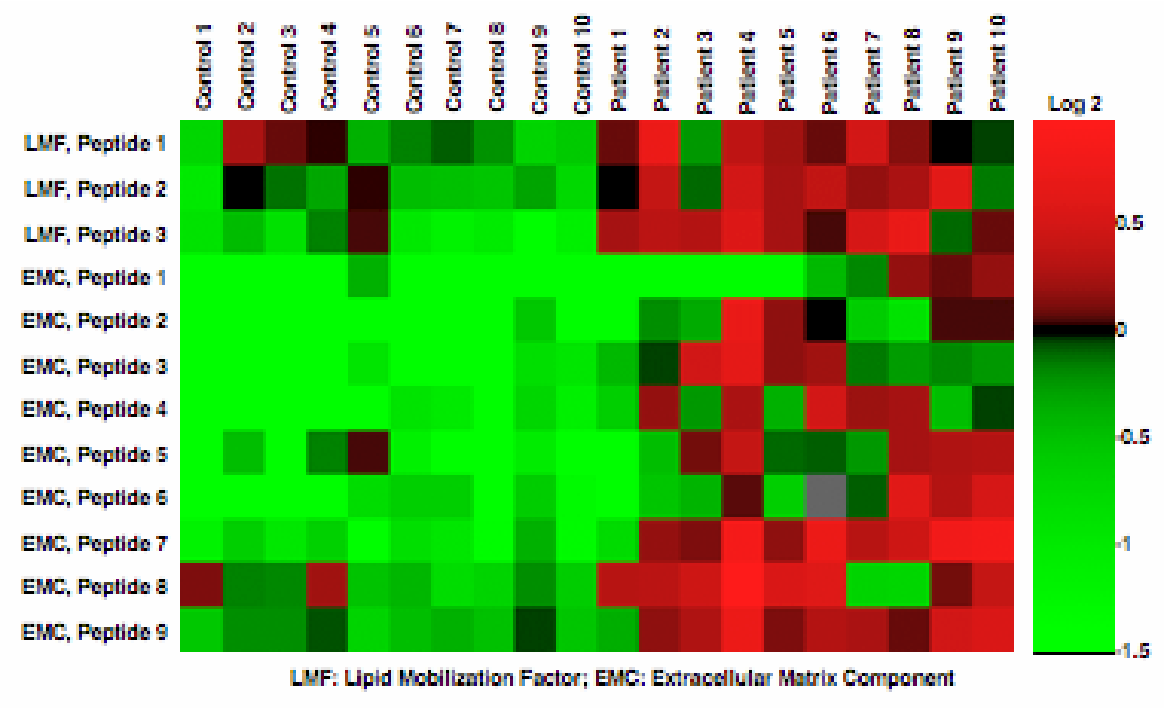

Figure caption: Shown here is a heat map of data from LC-FTICR MS matched to a human plasma peptide AMT tag database that illustrates the relative abundance of several peptides in human plasma from healthy control subjects and patients with type 1 diabetes. Lipid mobilization factor (LMF) peptides are up-regulated in patient samples versus controls, suggesting system-wide mobilization of fats for energy production. In addition, increased levels of an extracellular matrix component (EMC) were detected in patient samples. Up-regulation of both of these proteins is consistent with type 1 diabetes. A switch to fats for energy production occurs as the normal energy source, glucose, becomes unavailable because of a lack of insulin production. Increased expression of ECMs suggests thickening of the extracellular matrix, possibly in the kidney, which is known to play a role in the development of some diabetic complications. Red indicates an increase in peptide relative abundance, green indicates a decrease, and black indicates no change.