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A two-way street in metabolic disease

By Michael J. Haas, Senior Writer

A two-way flow of information between lab and clinic has enabled research collaborators at the **Sanford-Burnham Medical Research Institute** and **The Translational Research Institute for Metabolism and Diabetes** to identify markers that reflect subsets of heterogeneous metabolic diseases better than current markers.

The institutes have partnered with **Takeda Pharmaceutical Co. Ltd.** to support the pharma's obesity programs and will expand their resources as they forge additional alliances.

The Translational Research Institute (TRI) conducts clinical studies while a team at Sanford-Burnham's Lake Nona campus in Orlando, Fla., conducts preclinical research and provides metabolomics analyses.

TRI itself is a 2009 joint venture between Sanford-Burnham and **Florida Hospital** to give the institute access to patients in the clinic.

According to Stephen Gardell, leader of the metabolomics team at Lake Nona, "there is a need for cross talk and synergy between settings so that clinical data can also drive what happens in preclinical research."

He said clinical findings are underutilized as feedback to help design or refine preclinical studies. Instead, information tends to flow in only one direction—with preclinical findings determining the path of clinical research.

Gardell also is director of translational research resources and adjunct associate professor in the cardiovascular pathobiology program at Sanford-Burnham. His team also provides metabolomics support to other research groups at Sanford-Burnham.

According to Gardell, the two-way exchange of clinical and preclinical data enables the TRI teams to identify and develop markers of metabolic disease that are meaningful in both animal models and in humans.

"Our goal is to bolster confidence that the animals actually model human disease," he said.

"The ability to have an ongoing, intimate conversation with Steve Gardell and his metabolomics group is key to what our two teams are doing," said Steven Smith, TRI's scientific director and a professor at Sanford-Burnham.

"Historically, the variation in human phenotypes of metabolic disease was viewed as just noise that confounded interpretation of the data," added Smith. "But we think that phenotypic variation reflects real heterogeneity in human disease and how humans get a particular disease."

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> ***—Stephen Gardell, Sanford-Burnham Medical Research Institute***

How it works

To identify which phenotypic variations are clinically meaningful, Smith's team performs metabolic profiling on muscle and adipose tissue biopsies from the entire spectrum of human metabolic phenotypes—from marathon runners to sedentary individuals to patients with obesity, diabetes and other metabolic conditions—and looks for markers that define a particular phenotype or disease subset.

On the other side of the fence, Gardell's team studies multiple animal models to link metabolic phenotypes to metabolomic profiles, thereby providing a distinct signature for the disease state of each model.

Next, the teams match a clinical phenotype or disease subset to an appropriate animal model based on shared metabolic markers. Those markers can be used to monitor the effectiveness of therapies in both the animal models and clinical subsets and can help identify individuals at risk of developing metabolic disease, Gardell said.

As one example of the collaborative process, Gardell cited the growing interest of obesity researchers in identifying markers of fat oxidation to track the effectiveness of therapies that aim to increase energy expenditure in peripheral tissues.

He said fat oxidation in humans and animal models is commonly monitored by indirect calorimetry, which is a method of measuring oxygen consumption and carbon dioxide production. From there, researchers have to deduce the relative amounts of fat and glucose burned.

The Sanford-Burnham/TRI approach goes a step further.

"Fat oxidation generates a number of metabolites and by-products such as acylcarnitines," said Gardell. "We can monitor these compounds in a number of biological matrices, such as plasma, blood, skeletal muscle and adipose tissue" from subjects across the spectrum of metabolic phenotypes.

By linking levels of acylcarnitines and other metabolites to individual phenotypes, "we can identify markers that could provide a readout of fat oxidation" in different clinical subsets, Gardell told *SciBX*.

In turn, he said, those results "shed light on what we should be looking for in terms of potential biomarkers in animals."

Smith cited another benefit of using clinical findings to drive preclinical studies: many experiments—such as assessing the effects of an exercise program or a change of diet on a metabolic profile—are easier to conduct in humans.

For instance, "we organized one clinical study that enrolled people in exercise training programs for three weeks, and we profiled their metabolism across the study," he said. "This would be hard to do in mice—you can put a mouse on a treadmill, but it's challenging to get consistent effort from them."

Three's company

Both Smith and Gardell said it is too early to disclose details about specific markers or other findings that have emerged from the bidirectional efforts. "But our approach is working, and we are moving in directions we had not anticipated when we first began," Smith said.

The teams anticipate reporting on their findings at scientific meetings in the next 6–12 months.

Meanwhile, Gardell said TRI and Sanford-Burnham collaborators are making their approach and technology platform available to corporate clients.

In 2010, TRI and Sanford-Burnham signed a two-year deal with Takeda to support the clinical development of one of the pharma's lead compounds to treat obesity.

"Takeda is also farsighted enough to realize that TRI and Sanford-Burnham could offer insights into mechanisms in the periphery to aid the pursuit of novel therapeutic agents," Gardell said. Thus, another goal of the three-way partnership is to identify new targets and biomarkers for obesity, especially in peripheral tissues such as skeletal muscle and adipose tissue.

Terms were not disclosed, but Gardell noted that "our arrangement with Takeda is not exclusive, and we are in discussions with other undisclosed companies that have seen our services and recognize our value."

As additional partnerships are announced, Gardell added, Sanford-Burnham and TRI will expand the personnel and technical resources dedicated to their collaboration.

Haas, M.J. *SciBX* 4(16); doi:10.1038/scibx.2011.446
Published online April 21, 2011

COMPANIES AND INSTITUTIONS MENTIONED

Florida Hospital, Orlando, Fla.
Sanford-Burnham Medical Research Institute, La Jolla, Calif.
Takeda Pharmaceutical Co. Ltd. (Tokyo:4502), Osaka, Japan
The Translational Research Institute for Metabolism and Diabetes, Winter Park, Fla.