

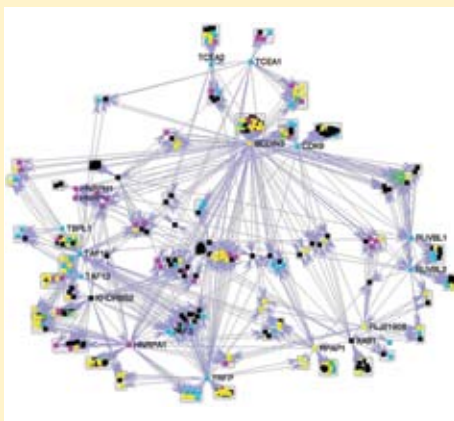
HuPI focuses on protein interactions

If someone wanted to know what you do for a living but couldn't ask you directly, he or she might start by asking your co-workers what they do. Chances are, your job is similar to those performed by the people with whom you directly interact at your workplace. By the same token, proteins that bind to each other often have similar roles. Over the years, scientists have tried to tease apart the dense interaction networks within various cell types to deduce protein functions. Most of these studies have been conducted on model organisms because expressing tagged proteins at endogenous levels in human cells is much more difficult.

In 2002, Benoit Coulombe at the Institut de recherches cliniques de Montréal (IRCM) became the director of a project funded by Genome Canada to tackle the issue of human protein-protein and protein-DNA interactions. He didn't know it at the time, but the project, which included his laboratory and several others, would eventually become the Human Proteome Initiative (HuPI). Currently, HuPI is funded by the Canadian Institutes of Health Research and by the Natural Sciences and Engineering Research Council of Canada.

Coulombe, who is also the leader of HuPI, says the initiative is different from those coordinated by HUPO. Whereas HUPO initiatives have chairs, boards, and various committees, HuPI simply consists of a few labs with little bureaucracy. Perhaps the most important difference is that HuPI "is not the type of project in which we want many different labs involved that start doing things their own way," he says. The goal is to be systematic in the use of the technology, called the "HuPI discovery engine". Members develop and

optimize parts of the method, which is tested and applied systematically at a central location. "I think it's important to go that way if we want networks and maps that are as accurate and as meaningful as possible," says Coulombe.



BENOIT COULOMBE

Networking, protein style. A HuPI map shows a protein interaction network in which proteins (nodes) are grouped according to their specific connectivity.

The first generation of the technology was described in a recent publication (*Mol. Cell* **2007**, 27, 262–274). Coulombe explains that an important aspect of the HuPI discovery engine is an inducible protein expression system that he and co-workers at IRCM, the University of Toronto, Université Laval, Université de Sherbrooke, McGill University (all in Canada), and the University of Iowa developed and tested. With the system, the researchers can tune the expression of human proteins labeled with a tandem affinity purification (TAP) tag to endogenous levels, thereby avoiding nonspecific interactions that sometimes are observed when a protein is overexpressed.

Another key part of the HuPI discovery engine is an algorithm the researchers developed to assign reliability scores to potential interactions. After

a filter subtracts out proteins that are identified in noninduced control cells, the algorithm considers the local topology of the interaction network to assess reliability. Therefore, more weight is given to an interaction if, for example, two proteins always copurify regardless of which one is tagged, explains Coulombe.

In the paper, the scientists applied the method to the study of 32 human proteins known to be involved in transcription. These proteins were TAP-tagged and purified under native conditions to preserve complexes. Bound proteins were identified by MS, and selected targets were verified with functional assays. A total of 805 high-confidence interactions that included 436 proteins were discovered, and these interactions were visualized as a large network. With the data obtained in this investigation, the researchers could suggest functions for several proteins whose roles were previously unknown.

Ultimately, Coulombe would like to expand the application of the HuPI discovery engine to the study of human diseases. In addition to investigating more protein-protein interactions, HuPI members plan to characterize the interaction networks that connect proteins to DNA, RNA, and metabolites. In the meantime, the researchers are optimizing the algorithm and developing data integration and visualization tools.

The first version of the HuPI public database, which includes data from the *Molecular Cell* study, is available at <http://hupi.ircm.qc.ca>. Coulombe says that the next version will be available by the end of 2007. Researchers who are interested in joining HuPI may email Coulombe at Benoit.Coulombe@ircm.qc.ca.

—Katie Cottingham

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