

Biologists initiate plan to map human proteome

Ambitious plans to catalogue and characterize all proteins in the human body — a Human Proteome Project — are being drawn up by a small group of researchers. But with a price tag of around US\$1 billion, some question whether the organizers can raise enough money or momentum for such an undertaking.

Researchers looked into the idea in the mid-1990s as the Human Genome Project was taking shape — the human proteome seemed a natural successor. However, a coordinated effort to index human proteins never emerged. One reason is that the scale and complexity of the problem proved daunting and nebulous. Protein-coding genes in the body can make tens of different versions of a protein, and each of these can be modified by the addition of chemical groups in countless different ways. All these proteins are being manufactured at differing levels, and at different moments in time, in the 200 or so types of human cell. “It was thought to be beyond comprehension,” says John Bergeron of McGill University in Montreal, Canada, former president of the Human Proteome Organisation (HUPO).

Now Bergeron and a group of leading proteomics researchers are putting together a proposal for a large-scale assault on the human proteome. It would reveal which proteins are present in each tissue, where in the cell each of those proteins is located and which other proteins each is interacting with. (The human genetic sequence, by contrast, shows which regions code for proteins but not which are actually making them.) Proponents say that this type of protein catalogue will be invaluable in revealing new drug targets or biomarkers to track the progression of disease. The cost “is absolute peanuts when you consider the importance of mapping the building blocks of life”, says Mathias Uhlen at the Royal Institute of Technology in Stockholm, Sweden, who is helping shape the new project.

Two preliminary workshops have been held to discuss the endeavour, most recently in Barbados in January this year. The group plans to consult with the wider proteomics community for the first time at HUPO’s Amsterdam World Congress in August.

Those involved in the draft plan say that a human proteome project is now feasible partly

because estimates of the number of protein-coding genes have shrunk. It was once thought that there might be around 50,000 or 100,000, but now, just 21,000 or so are thought to exist, making the scale of human proteomics more manageable. And the group plans to focus on only a single protein produced from each gene, rather than its many forms. “We got rid of all this complexity,” Bergeron says. “We tried to craft a project that would be doable with easy-to-track milestones.”

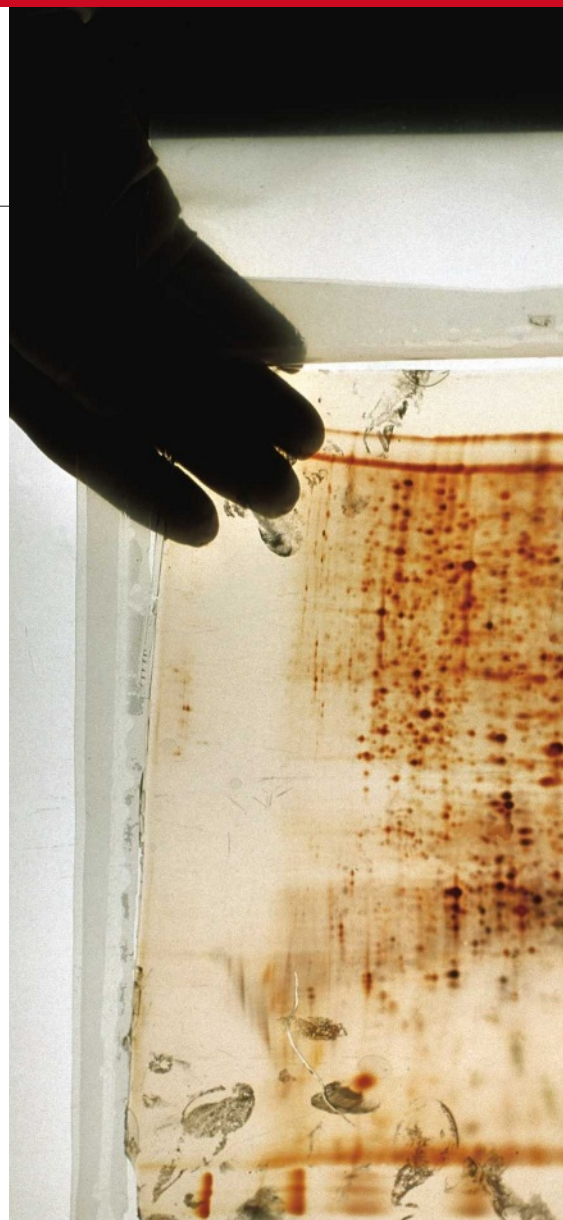
The plan is to tackle this with three different experimental approaches. One would use mass spectrometry to identify proteins and their quantities in tissue samples; another would generate antibodies to each protein and use these to show its location in tissues and cells; and the third would systematically identify, for each protein, which others it interacts with in protein complexes. The project would also involve a massive bioinformatics effort to ensure that the data could be pooled and accessed, and the production of shared reagents.

Bergeron envisages the work being divided up between labs around the world. He says that the first stage of the project — which involves amassing existing mass spectrometry proteomic data — would take around six months, and that this would be followed by a pilot project lasting one to three years to do more comprehensive analysis of all the proteins manufactured by chromosome 21, the smallest human chromosome. The whole effort could take a decade.

“It’s a huge undertaking for HUPO and they’ve never done anything like it,” says Paul Tempst, an expert in proteomics at the Memorial Sloan-Kettering Cancer Center in New York. The organization has run several large-scale proteomics efforts, such as those to catalogue the proteome in human blood plasma, the liver and the brain. But results from the Human Plasma Proteome project and other proteomics efforts showed that different laboratories — and even the same lab — often identify very different sets of proteins from exactly the same sample. “It told us that there were lots of proteins in plasma and that if you do it in different labs without any effort at technology standardization you get different results,” says Tempst.

However, Bergeron and others say that improvements in mass spectrometry tech-

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Heart proteins seen separated in gel.

niques have resolved many of the problems of reproducibility that have dogged the field, and that it is now possible to reliably identify a range of proteins if a sample is analysed many times. But an additional difficulty comes in trying to analyse samples containing proteins at wildly differing concentrations, with some present in only a few copies. The three-pronged approach is designed so that shortfalls in one technique can be made up by the others.

Steven Carr, director of proteomics at the Broad Institute in Cambridge, Massachusetts, says there is likely to be broad support for a large-scale proteomics effort, but much debate about how best to do it. Rather than analyse the proteome of one chromosome, he says it may be better to tackle the proteome of mitochondria or the cell membrane because it would reveal more about biology and diseases related to those structures. “It’s time to think about something in a systematic fashion — whether this is the project is a different question,” he says.

Coordination could also be a challenge.

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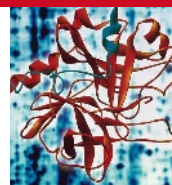


Compared with the human genome project, in which a handful of sequencing centres did the bulk of the work, a human proteome project would involve many more labs, with inevitable issues about data-sharing and competition. "It will be a battle to convince people this is worth funding," says Michael Washburn, director of proteomics at the Stowers Institute for Medical Research in Kansas City, Missouri.

Those involved in the budding project say that they must now muster support from funding organizations such as the US National Institutes of Health and the European Commission — a clear challenge in today's tight funding climate. "It will be a tough sale," says Sudhir Srivastava, head of the Cancer Biomarkers Research Group at the US National Cancer Institute in Rockville, Maryland. Srivastava says that the project may have a better chance of success with a stronger focus on diseases such as cancer. "You need to show clinical utility of the approach before launching a mega-project," he says. ■

Helen Pearson

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PROTEOMICS

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A. PASIEKA/SPL

Buckyballs give flash a boost

Flash memory, the workhorse of mobile phones and digital cameras, could be made more efficient by using buckyballs. These spherical fullerene molecules, comprised of 60 carbon atoms, would allow flash memory to operate at a lower voltage and save on power, researchers reported last week.

"We're the first ones trying to borrow molecular electronics concepts and put them into non-volatile memory," says electrical engineer Tuo-Hung Hou of Cornell University in Ithaca, New York, who led the research (T.-H. Hou *et al. Appl. Phys. Lett.* 92, 153109; 2008).

Most desktop computers use a type of random access memory (RAM) that is lost when the power is shut off. Non-volatile memory, however, keeps its content even without power, and flash has become the dominant type. Flash memory holds its zeros and ones in a circuit that contains an island transistor, insulated by a thin layer of silicon oxide.

To write or erase the memory, current is pumped across the barrier, either injecting electrons into the transistor or sucking them out. The charge stays put — most flash memory is guaranteed to last for ten years — but electrons eventually leak through the barrier. The barrier has to be thick enough to prevent leakage, but thin enough for current to pass through during a write or erase.

The necessary current is relatively

high, which translates to relatively high voltages. Cycle after cycle, the voltage can wear down the flash memory circuits. It also requires peripheral circuitry — which takes up precious space — to boost the low voltages available from batteries or USB ports. And most importantly, it wastes power that could otherwise extend battery life. "The major bottleneck of the current flash memories is the voltage," says Hou.

Enter the buckyball. By adding buckyballs to the barrier layer, the Cornell

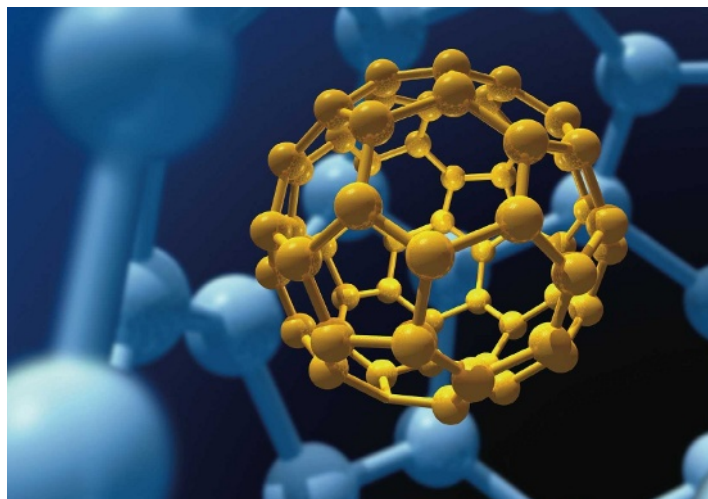
engineers create resonances that amplify the current during the high-voltage write or erase phase. So the voltage needed during writing or erasing is lowered, by an order of magnitude or more. "It's a very interesting twist," says Sanjay

Banerjee, an electrical engineer at the University of Texas at Austin, who was not involved in the research.

Chenming Hu, an electrical engineer at the University of California, Berkeley, says that the concept is attractive, and could help extend the tenure of flash as the dominant form of non-volatile memory. But he cautions that other types are already nipping at the heels of flash, such as magnetic RAM, which stores information using the polarity of ferromagnetic plates, and phase-change RAM, which relies on switching between amorphous and crystalline phases of tiny glass filaments. "The general feeling is something else will replace flash," he says. ■

Eric Hand

"The major bottleneck of the current flash memories is the voltage."



Spherical carbon molecules such as these could be used to make flash memory drives less power-hungry.

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