Samir Hanash discusses how HUPO aims to globalize proteomics research

Interview by Joanna Owens

Samir Hanash, Professor of Pediatrics
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Samir Hanash is a pioneer in cancer proteomics and was elected as the Inaugural President of the Human Proteome Organization (HUPO) in June 2001. He is Professor of Medicine at the University of Michigan (UM) where he heads a large research group that focuses on cancer proteomics, and is also on the executive committees of several research associations, including the American Society for Cell Biology (ASCB) and the American Association for Cancer Research (AACR). After obtaining a medical degree in 1972 from American University in Beirut, Lebanon, Hanash moved to UM where he studied for his PhD on haemoglobin protein and gene analysis in the Human Genetics department and was awarded the Public Health Service (PHS) Fellowship award in Biochemical Genetics in 1975. After a post-doctoral fellowship in the same department, Hanash took up a Residency position in Pediatrics at the Children's Hospital of Michigan, during which time he was awarded a Children's Leukaemia Foundation Fellowship Award. Subsequently, he has held the positions of Instructor in Pediatric Hematology (1978–1979), and Assistant Professor (1979–1984) and Associate Professor (1984–1989) of Pediatrics before taking on his present role as Professor of Pediatrics at UM. He is also Director of the Cancer Center Carcinogenesis Program and a member of the Gene Therapy Group and the Genome Center and Computer Task Force at UM. He was awarded the Rothchild Award by the Curie Cancer Institute in 1998.

How do you think the publication of the first draft of the human genome sequence has impacted drug discovery?
I would say it has impacted drug discovery in the same way it has impacted other aspects of biomedicine, in that it has provided a framework that allows us to look at gene expression, disease processes, drug targets – knowing exactly what is out there by way of an entire genome sequence. As such, it does not lead to anything in particular, but it is a framework that tremendously facilitates so many different factors in research and drug discovery.

Why was HUPO set up?
It was set up for several reasons. First, there is the need to develop much better scholarly avenues for scientific exchange, training and education relating to the proteome and to proteomics; that is the number one motivation. The second motivation is that there needs to be some initiatives – global and public – pertaining to proteome research, to see what it is that needs to be developed by way of proteome projects and HUPO, through its membership and the meetings it plans to organize, intends to examine the challenges, as well as the opportunities, that lie ahead in developing proteome initiatives.

Do you think that HUPO will benefit from the success of the Human Genome Organization (HUGO), in terms of raising awareness, recruiting members and obtaining funding?
I am not sure how the success or failure of HUPO is going to be linked to the success or failure of HUGO. We are proceeding perhaps a little differently, having basically benefited from the experience that the genome community has been through. A major implication of this for HUPO is that we would not like to be perceived as academics wanting to promote academic-related activities. We would like to be perceived as a common vehicle for academic, industrial, and government and other philanthropic organizations to pursue proteomics research. We are not in the exclusive domain of academia.

Why do you think we need such an organization now?
With or without HUPO, there are proteomics efforts under way in many countries, and there are proteome organizations that are being, or have been, set up. Those organizations have expressed the need to have communication across initiatives and organizations in different countries and so HUPO would serve as an umbrella for these local initiatives.

What are the aims of HUPO?
One aim is to encourage scientific exchange, education and training – this is our number one mission – and another is to conceptualize initiatives in proteomics and promote their funding. We do not intend to become a major funding organization, but want to identify what the real issues are in proteomics and how to facilitate research and development in those areas.

'To encourage scientific exchange, education and training – this is [HUPO's] number one mission.'

What are the difficulties you foresee in reaching these aims, and how will you circumvent these?
Well, there are lots of difficulties whenever you are dealing with any international organization. For example, how well are you going to be able to communicate and integrate among people in different countries who might have their own individual priorities? However, this might not be the most challenging aspect; rather, the greatest challenge is that the proteome is totally overwhelming and so how do we conquer it? How do we go about beginning to decipher the proteome in a logical, coherent fashion, and how do we deconvolute all of its complexities into specific initiatives that are achievable? For example, the notion, 'Let's do the whole proteome' is very ambitious, vague and diffused, and so we want to move away from notions like this.

One particular effort would pertain to information that is already out there – there is a lot of protein-related information

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stored as many different types of data and databases in a way that is not successfully being mined. It has been projected that the amount of protein-related data is going to increase exponentially. So we need to figure out how to develop the tools to effectively mine the information that is out there. There are people out there who think that this initiative would be best done by informatics companies, and at a certain level this might be true; however, if you want to develop a knowledge base, it is going to be very hard to do that for the proteome without involving the scientific community.

'The proteome is totally overwhelming and so how do we conquer it?'

Where HUPO would like to make an impact, therefore, is in actively engaging the scientific community in developing a knowledge base for the proteome. So you do not have, for example, an annotator who does not know much about a particular protein dealing with that particular protein. We would much rather have a learned individual with particular expertise in the subject matter to curate the information for a particular protein. When you think that there are so many different proteins, pathways and diseases to be studied, it would be very hard for a company itself to engage the scientific community to do this. So, HUPO, and maybe other public organizations, would be in a much better position to rally the scientific community around a knowledge-based proteome effort.

What specific problems and bottlenecks in proteomics research do you hope HUPO will help overcome?

The first would be how to effectively mine and manage protein data. Second, what sort of proteome initiatives can we actually contemplate doing that involve benchtop research. For example, it seems, based on the first meeting that we organized in Leesburg (VA, USA; 7 October 2001) and the second meeting at the NIH (29 April 2002), that there is some consensus that plasma proteins might well represent a good major proteome initiative with which to start. This is in contrast to doing the whole proteome of a tissue or organ system, or disease state, and so on.

If we start with this focus then we can begin talking about the major initiatives that we can accomplish, and set some specific goal as to what is within the realm of a plasma proteome project or other equally focused projects. For example, what do we expect to have by way of individual components and individual milestones, what technologies we can adopt at the present time, and what technologies still need to be developed? How do we go about standardizing reagents and the way in which we generate data? Focusing on a single project like this can serve in a positive way to define what issues might need to be tackled before embarking on a major proteome project.

How will the organization be run and financed?

I am hoping that the organization itself is not going to require a whole lot of financing, it all depends on the specific activities that we are engaged in. At the present time, HUPO would comprise members in individual societies in individual countries. For example, there is a Korean Proteome Organization, the members of which would automatically become members of HUPO. In that sense, therefore, we would have an international membership base, and could well have several thousand members by the end of 2002. We would also have affiliations with other societies other than proteome societies. Many organizations that have proteomics as an important component of their agenda could be very suitable and beneficial for HUPO to be associated with. Once we have this membership base, this could serve as a major asset for us in terms of developing our own agenda.

With respect to where funding might come from, we expect some contributions from industry, and in addition we expect some funding from philanthropic organizations. We also expect some funding from government organizations (such as the NIH) in support of specific activities of HUPO – annual meetings, workshops, and so on. The NIH has a mechanism for providing support for organizations such as HUPO for its scientific and educational activities, and so we intend to tap into those. With respect to industry in particular, there are several types of partnership that we could have. One could be to develop joint educational activities – a series of workshops on the theme of expression or functional proteomics, for example – with sponsorship coming from a particular pharmaceutical or biotechnology company.

Specific initiatives, such as the plasma protein project that might require a substantial amount of funding, could be funded by pharmaceutical industry together with other funding bodies such as the NIH. However, there will not be money going to HUPO to do its own big project, HUPO will act in concert with other agencies and in partnership with industry to develop a kind of consortium, with the money going directly to the individuals or laboratories that will actually do the research. So we don't expect a major amount of funding for actual executable projects to go to HUPO. We would much rather that the money be distributed directly without having to go through HUPO.

'The notion, "Let's do the whole proteome" is very ambitious, vague and diffused… we want to move away from notions like this.'

What is the first thing that you are going to do as President of HUPO?

My first task was to provide an infrastructure for HUPO to help develop the organization, assign particular activities, and organize HUPO membership into individual committees. So, we currently have committees dedicated to HUPO membership and business development, as well as a committee that will look into what informatics tools need to be developed and how HUPO could facilitate that process. We also have a committee to look into what resources and technologies still need to be developed, and a scientific committee. All of these will be actively involved in formulating and conceptualizing what proteomics means and what it could do.

Will researchers be able to access the resources provided by HUPO for free?

Obviously, there are going to be some major league databases that come out of initiatives that HUPO would have promoted, but saying that HUPO is going to possess that information or resources would not be correct. Those databases would be in the hands of actual institutions, laboratories, or government-funded informatics centres that could directly make their content available to individuals. If the funding for those types of initiatives were part of a public-funded

effort, then of course I think the information would be available in the same way as any other public databases. However, with respect to reagents that HUPO had identified a need for and would want to see developed: any time you are dealing with handling materials there is cost involved and so it might happen that we would go to technology companies and ask them to make a reagent available to the scientific community with a modest fee to cover costs. I do not see that HUPO would have the warehouse itself to be able to provide that role.

What do you think have been the key successes of the HUGO and what could you learn from the project?

It would have to be the fact that they have developed an international organization that rallies people who are interested in the genome all over the world. That is the key success – organizing the meetings to provide scientific interchange and education.

There are two things I think we could learn from HUGO: One is not to be overly ambitious and end up wanting to be engaged in more than we could possibly deliver on, and the other is to leave project funding, for example, to people who are in organizations that are committed to that activity, and play a scholarly role instead. I think that is the best that we can deliver.

'It seems like there is a Great Wall of China between those who are engaged in genomics and those who are engaged in proteomics.'

What are you focusing on in your own research at the moment?

Well, at the moment it is more or less the same as what I have focused on over the past 20 years, which is looking at global gene expression in cancer – identifying cancer-related genomic, transcriptomic and proteomic changes and integrating genomic and proteomic data. I started out basically by training as a geneticist and I am just as comfortable at the genomic end as at the proteomic end, which I think is something of a rare situation in the present time. It seems like there is a Great Wall of China between those who are engaged in genomics and those who are engaged in proteomics, and I have been very comfortable moving from one to the other, so we intend to continue our combined genomic–proteomic approach to cancer.

My specific focus is on the translational aspects of cancer – being able to identify novel markers for early diagnosis and finding novel classifications for specific types of cancer. We realize that there are tremendous needs for improvement in proteomic technology, and so in addition to my own discovery type of research we are greatly involved in technology development specifically for proteomics. Although we are applying genomics we are not developing any genomics technologies at the moment.

Having an obsession with the ability to deliver at the clinical end puts a lot of perspective on what proteomics technologies can or cannot be utilized for clinical material. For example, technologies that would take a month to profile two different tissues are just not practical to use in clinical research, because no comparison between two tissues is going to be informative, you would have to look at hundreds. We have to work on improving these technologies to provide the necessary sensitivity, as well as the throughput, to be able to meet the needs of projects with a clinical focus.

Which proteomic technologies do you think are really innovative and will accelerate drug discovery?

Well, innovative ways of doing protein microarrays would definitely be on that list. Also, a way of doing multi-dimensional liquid-based protein separation in an automated fashion would be on the list, and improvements in two-dimensional gel technologies would have something to contribute. Improvements in these technologies do not necessarily represent a great paradigm shift, but I think that in reality there is still a lot that can be gained by improving existing technologies. So this is one area that we are working on.

What technologies do you think still need to be developed?

I think technologies need to be developed that are able to do two things: (1) isolation and in-depth analysis of subcellular proteomes; and (2) analysis of post-translational modifications. Right now, the second point is a big challenge. Although there are ways that you can effectively look at phosphorylation, there are so many other post-translational modifications, and one of the interesting aspects of proteomics is that you can work on real native proteins. To mine real proteins you need to be able to determine all the post-translational modifications and all the shifts in protein location. Also, we need to develop technologies to manipulate protein expression because, right now, most manipulations at the protein end are really genomic manipulations (e.g. gene knockouts or transiently transfecting increasing amounts of a gene), but those types of manipulation do not give you much control. So, you might know that a protein is often in the nucleus, sometimes in the cytoplasm and occasionally on the membrane, and want to specifically knockout the presence of the protein only in the nucleus to study what happens. We also need to find out how to inhibit or promote certain types of protein interactions, and these studies are all going to need the development of new technologies.

'I felt that I would be somewhat of a rare bird if I kept with proteomics and carved a little territory there.'

How did you come to work in cancer proteomics?

My PhD was in the area of haemoglobin protein and gene analysis, but I do have a clinical hat, and haemoglobin, being linked to haematology, is kind of linked together with oncology and so it was that route that led me to focus on cancer in my research activities. Proteomics has been of interest to me since my PhD days, with everybody else switching almost exclusively to genomics, I felt that I would be somewhat of a rare bird if I kept with proteomics and carved a little territory there. I did not think that there was a whole lot of competition when applying for grants if you had a proteomics focus, as opposed to RNA or genomics. Having said that, it was still a challenge trying to convince reviewers of the merits of looking at proteins, but if you keep trying to convince them then eventually they get convinced! So, luckily I have been fairly successful in maintaining funding in proteomics over my entire career. The only difference today is that I do not need to convince as many people as I needed to 10–15 years ago! Now it seems the other way around – there is tremendous encouragement for going into that area. So that provides a lot of satisfaction.

The publication of the first draft of the human genome is perceived as a huge milestone in biological research. What do you think will be the next one?
Well, I am not sure that there is going to be a next one that will be such a landmark and an equivalent of the genome and, again, right now my obsession is to think about proteome activities and I can think of many different potential follow-ups to the landmark finishing of the human genome sequence. It could be along the lines of taking a whole cell or subcellular proteome and analyzing its complexity, doing a very exhaustive search for protein–protein interactions, or working on a project that allows you to exhaustively characterize the different constituents of a challenging area such as the cell membrane. I think that these as applied projects would have tremendous benefits.

Once we get to a post-proteomic era, what do you think will be the next bottleneck in drug discovery? The human metabolome or tissuome projects?
Well, a lot of people are talking about the metabolome, and again it seems to me that as we go from one major milestone to the next, embedded in the next milestone is what we gained from the previous one. For example, we could not possibly be talking about a proteome project or initiative without the genome being sequenced. So that has provided a framework for wanting to move in the next direction. So if we want to think beyond the proteome and into the metabolome, again the metabolome would have to be built on top of the proteome. In that sense there is a logical succession of major initiatives, but I think that the proteome is going to keep us busy for a long time.

When do you think we will be in the post-proteomic era?
Not for another 20 years, but that does not mean that we are not going to be working on anything else. There would be a lot of activities in parallel, but I think that major chunks of the proteome are going to keep us busy for at least a couple of decades.

What are your main concerns for drug discovery?
I can look at this from the context of proteomics, and specifically, how will proteomics deliver in relation to drug discovery efforts. A large proportion of drugs target membrane proteins, and I think for proteomics to be able to deliver drugs, then we need to develop better tools to globally analyze membrane proteins and look at the complexities of their interaction with each other and the manner in which they signal and determine all post-translational modifications.

Following the wave of HTS, genomics, proteomics and bioinformatics companies, what do you think will be the next type of platform technology companies that will form?
I do not think that biology and biomedicine can be compartmentalized in that fashion, and at some point you have to integrate activities across many different levels. So I think that the companies able to do that will be most successful. Bioinformatics is going to play a tremendous role in integrating the different types of data from the proteome and so the companies that have the necessary platforms and bioinformatics and other computational tools to integrate across many compartments should be most successful.

'I am not sure that there is going to be a next [milestone] that will be such a landmark and an equivalent of the genome.'

What do you think of the systems biology approach to drug discovery?
I think it is very interesting in terms of trying to understand various aspects of regulation. However, whether by using systems biology you are going be able to develop drugs – I would have a hard time picturing that at the present time. I think there is a long way to go before systems biology becomes so predictive that it could effectively point the finger at a specific target.

What do you think are the pitfalls of the systems biology approach and what do you think could be difficult to achieve?
For systems biology to be effective you would have to work within a particular environment and within a particular context, and could change only one variable at a time to study its contribution and its effect. To then try to predict what it could do under different circumstances, knowing how environments can change so radically and how much heterogeneity there is in cells and tissues – to be able to turn all of that into a systems biology approach is going to be very difficult. The initial steps that are being taken, which is to look at well-defined cell populations such as yeast, is a good place to start, but it is a much greater level of complexity to take a systems biology approach to tissues, organs and human diseases.

When do you think we will be able to cure cancer?
There are already several cancer cures, and what we are seeing is a gradual shift away from toxic types of therapies to more targeted therapies, which is something that makes a lot of sense. However, the more you try to target therapy, the more you realize that the targeted therapy is not going to work for all patients with a particular disease, because the genetic changes in their tumours and the targets are not the same. So how well, or how effectively, we are going to be able to develop this individualized type of therapy and move away from globally toxic therapies is going to be quite a challenge. Still, I would say that it will not be too far into the future that we have many targets to choose from when it comes to treating a particular type of cancer.

Where do you think drug discovery will be in 10 years' time?
Well, that is a tough question. I would say again that we face the challenge of finding drugs that work for the largest patient population versus finding drugs that work effectively for a subset of patients. So it would seem to me that 10 years from now that rather than talk about a single therapy for a particular disease, we are going to be looking at several therapy options for one disease and making the right choice for an individual patient – I think there is going to be a lot more of that.

When do you think proteomics will really start to have an impact on the speed of drug discovery?
As technologies for proteomics begin to be implemented that have the necessary speed and sensitivity, I would say that is when it could effectively impact on drug discovery and development. It is not going to happen overnight, although there are already some platforms out there that could be further enhanced in terms of throughput and sensitivity. The development of those platforms would

have a good impact on drug discovery as would the direct accumulation of knowledge coming out of proteomics initiatives.

What do you think have been the major advance in proteomics in the past six months?
Well I think the emergence of protein microarrays as a tool to scan the proteome is a big advance There are now effective surfaces to bind proteins and effective means to detect signals resulting from probes binding to specific protein targets. This is an area I think will undergo exponential growth in the next couple of years and could well reach the point where it could become, for protein analysis, the equivalent of the DNA microarray for genomic analysis.

What would you like to have achieved by the end of your career at HUPO?
I would like to ensure that HUPO has a broad membership base, that it has already developed its own scientific, education and training agenda, and that there are some funds in the HUPO account to enable it to sustain itself.

What would you like to have achieved by the end of your career?
I would like to think I have succeeded in what I originally set out to do, which was to be a cancer physician on the one hand, and a cancer investigator on the other. If I were able to impact in any way on an aspect of cancer medicine, be it earlier diagnosis or better therapy, I would be elated.

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Protein kinase drugs – optimism doesn't wait on facts ▼

Current reviews of research directed towards protein kinases present an optimistic view of the field. In a recent issue of *Drug Discovery Today* [1], Scapin discusses how structure-based drug design has been applied to great effect against several protein kinases. Other encouragement is drawn from the approval of Gleevec™ (Novartis; http://www.novartis.com) for the treatment of chronic myeloid leukemia [2] and the potential to assay lead compounds for selectivity against an ever-growing panel of protein kinases [3].

Although it would be churlish to detract from some great achievements in this field, one cannot escape the observation that drugs targeting protein kinases are still rare, as seen in Figure 1. This leads one to question whether the current optimism is well founded, given that protein kinase programs account for approximately a fifth of the current research programs in many large pharmaceutical companies [3,4] and that protein kinases comprise the largest gene family coded for by the human genome that has proven tractable to inhibition by small-molecule therapeutics.

One could argue that the industry has only recently begun to focus on protein kinases as drug targets; indeed Figure 1 shows that the vast majority of kinase drugs are still in the discovery research phase. However, the targets of most launched drugs have been identified following functional assays. This traditional approach revealed few protein kinases; the Rho-dependent protein kinase ROCK, one possible target of the drug fasudil (used to treat cerebral vasospasm) is a rare example of this. Perhaps the timelines of such assays are poorly suited to identifying compounds operating in the signal transduction cascade, where longer term gene expression effects are the endpoint. One could also reason that these processes might be less relevant to the diseases that the pharmaceutical industry is focused on.

The vast majority of kinase inhibitors target, at least in part, the ATP binding site, which has been proven to bind a wide selection of chemical types [5]. There is no evidence to suggest that these compounds have physicochemical properties that are at odds with those required by orally bioavailable drugs [6]. It is also hard to imagine that the necessary chemical tools, fundamentally adenosine mimics, have only recently been a focus of synthetic chemists. Inhibition of protein kinases by ATP competitive compounds is, however, made more difficult by the high cellular level of ATP, a problem that is circumvented by compounds that prevent activation of the kinases, rather than competing with endogenous cofactor [7].

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