

# Pioneers of Proteomics

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In early 2004, the National Cancer Institute established an Ad Hoc Working Group of the National Cancer Advisory Board (NCAB) to assess the technologic needs of current cancer research efforts and to identify the strategic opportunities available to accelerate the development of breakthrough diagnostic, therapeutic, and preventative technologies that will have an impact on cancer patient outcomes. The suggestions of this Working Group were among many inputs received by the NCI over a two-year period in the development of the Clinical Proteomic Technologies Initiative for Cancer.

Dr. Leland Hartwell, president and director of the Fred Hutchinson Cancer Research Center, and recipient of the 2001 Nobel Prize in Physiology or Medicine for his pioneering work in yeast genetics is one of the Working Group's co-chairs. Dr. Hartwell has over 35 years in discovery research and is also professor of genome sciences and adjunct professor of medicine at the University of Washington School of Medicine. His efforts are directed toward improving the quality and sharing of information across laboratories and stimulating team science and technology development in the area of protein diagnostics.

In a visit to NCI, Dr. Hartwell discussed clinical proteomic technologies and cancer biomarker discovery.

## **1. On the importance of early detection of cancer**

We have not been near as effective in eliminating death from cancer as we would like to have been. Over the last decade, roughly, there has been a one percent, per year decrease in mortality from cancer. Now, that's – that's great. That's wonderful, but we'd like to see a much bigger effect than that. And if this was successful, then yes, I think it would be a big leap forward, because we know for most cancers, early detection leads to 90 percent, five-year survival on the average.

The ultimate goal of this project is to discover cancer earlier. It's that simple. People whose cancer is discovered at an early stage almost always survive their disease, whereas when this cancer is discovered late, it's almost always fatal.

## **2. On current methods of detection**

Current methods for detecting cancer early are sometimes quite effective, and they depend upon looking, visually, for the cancer, like colonoscopy is very effective. The pap smear is very effective. And so we know that early detection can save lives. The problem is we can't use those methods for internal cancers, like ovarian cancer, or pancreatic cancer, or some of these other cancers. And it's those cancers that could benefit the most from early detection, because their symptoms usually only occur when the cancer is at a late stage. So we want to be able to detect the cancer from a blood test rather than by having to look visually for it.

## **3. On blood as a source of "biomarkers" of cancer**

Well, the blood is a very, very complex mixture of proteins. It's estimated that there's as many as a million species of proteins. And it's constantly bathing all of our tissues, and proteins are leaking into it if tissues are diseased and dying, and various things are happening. And so, there's very good reason to believe that proteins indicative of cancer are in the blood. But they're probably – they're at very low concentration, and so we have to have technologies that can sort through many, many species of proteins and find the important ones at very low concentration. That's the challenge.

## **4. On proteomic technologies**

The new technologies that have become available recently for discovering protein biomarkers do not perform near as well as I'm sure they will at some future date. Nevertheless, I think they perform well enough that with a very specific approach and the development of reagents to enable their use, it is reasonable to expect that we could discover biomarkers now. Mass spectrometry, which is the most powerful technology, is capable of identifying and analyzing about 100 proteins at a time in a sample. Now if there's a million proteins present in the blood, that's clearly not enough. So, we propose starting at the cancer tissue itself and identifying the 100 to 1000 proteins that are most characteristic of a particular cancer, and then developing sensitive reagents to detect those particular candidate proteins in the blood.

## **5. On reagents and standardization in proteomic research**

The reason that we need reagents is because it takes reagents like antibodies and specifically labeled peptides in order to search for very low abundance proteins in blood that you've already identified as being candidates that you want to see. And in order for those reagents to be effective, it's important that everybody who's working in a particular cancer area use the same reagents so we can compare their data, and so that someone can standardize those reagents and know how well they perform. That's one of the major reasons why this initiative is needed, because no single laboratory that's trying to do this kind of work can afford to carry out that kind of development of reagents and standardization.

## **6. On the complexity of finding biomarkers**

Yes, I think that there will be different biomarkers for different cancers. Some will probably be overlapping, but ultimately the goal would be to find many, many biomarkers that are indicative of cancer and will tell you not only what stage it's at but what type of cancer it is.

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## **7. On the new research strategy**

Well there are two ways in which this is a paradigm shift. One is that there's just recently become technologies available that would permit this kind of work and also information in the form of the human genome that is necessary to be able to do it. So, this is a moment in time when something new is possible that wasn't possible before. The second thing that's a paradigm shift is that it requires a team effort and there are not very many examples in biology where we have effectively carried out team efforts. But the Human Genome Project is one great example, so we know we can do it.

## **8. On a team approach to proteomic research**

One of the reasons that we need a consortium of laboratories working on this is because there are so many different places that one can look and we don't know where the answer is. For example, one could look for cell-surface proteins. One could look for secreted proteins. One could look for proteins involved in angiogenesis. And if you make a list you could easily come up with 20 categories of corners that people ought to be looking at. I don't think any laboratory can really do an effective job on more than one of those areas, so that's why we need ten laboratories working on a particular cancer site, each taking a part of the problem, to divide it up and conquer it.

...the project is just too big for any single laboratory to carry out. That's a lot like the Genome Project. It was not possible for any one laboratory to sequence the genome, and so what was done was to divide it up into many parts, and have different people do those parts, and establish standards for their data so that the data could be assembled together. And that's very much the same thing we want to do here. There's a lot of different ways to approach this problem. They're all good ways to approach it. We need to do all of those things and then be able to combine the data.

## **9. On the clinical impact of proteomics**

Well, I think ultimately the way that we will eliminate most death from cancer is first to be able to assess people's risk for cancer, and we still need more work in that area. But, you know, for example, we know that smokers are the high-risk group for lung cancer. So if we can establish risk, then those are the people who need to be screened for a particular type of cancer. Then, I would see probably yearly tests, blood tests, for early stage markers of disease. If a person is positive for those markers, that probably won't assure that they have cancer, but it will put them in a much higher-risk category. That will need to be followed by imaging technology, which can look for the cancer and where it is and what size it is and those kinds of things, and then for interventions.

## **10. On the role of NCI**

Certainly the NCI is the proper place for this initiative to be home because the NCI, first, has the resources, it has the leadership credibility in the community, and it has many other initiatives that will augment what we're trying to do.

## **11. On the connection to other NCI programs**

Well I believe this initiative, if successful, will connect with many other initiatives that are already going on at the NCI. Obviously the Early Detection Research Network will be able to validate the use of these markers. The Mouse Consortium Group is providing mouse models that will be very useful for testing these approaches for detecting cancer in mouse models. The nanotechnology initiative will be able to use these biomarkers as potential reagents for imaging and for targeted therapy delivery. So there are many, many – it's hard to imagine, in fact, I think an activity or initiative at the NCI that wouldn't in some way interface with this project.

## **12. On the role of patients in the discovery of new biomarkers**

There certainly is an important role for patients in this exercise. We need to obtain samples from patients in order to do this work. Patients need to give their consent for those samples to be used for the research studies. Patients can also be very effective advocates for the work that needs to be done.

## **13. On the role of industry**

There's a lot of reasons why industry is a very important partner in this activity. First, they're developing technologies that could be extremely useful, so we will need to partner with new-technology development and improvement as it goes forward. Secondly, I think the pharmaceutical company is very much in need of biomarkers that can monitor therapeutic

response to drugs, and so they could be an important partner even in helping funding this kind of work. And then finally, once we develop these effective biomarkers, their ultimate implementation in clinical tests requires commercialization, and so, industry will be involved in developing the final platforms and measurement technologies for clinical application.

#### **14. On proteomics research and personalized medicine**

I think that if we had effective biomarkers that could reveal physiological responses, disease states, in real time, then this would really empower individualized medicine, because a person could be getting a certain drug intervention or treatment, and you would be able to monitor their response and know whether they were responding to that drug, whether the concentration was right, and modulate the treatment to get the right response that you were looking for.

#### **15. On the clinical impact of proteomics research**

It's always very hard to predict how long something is going to take, but this is an endeavor that, once we have the reagents, once we have the informatics platform, once we have laboratories committed to this – I don't think it would take more than three to five years to really explore a given cancer site and discover effective biomarkers.

I think there will be a day when cancer is much less a killer and more of a disease that needs to be managed. We're making enormous progress in understanding cancer, in developing abilities to monitor it in the body, to image it and to treat it...so yes, it has taken a long time, but I think there is continual progress and you know, within our lifetimes we will see dramatic changes.

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