Interview with Kurt Wüthrich – Why Structural Biology Matters

by **V. K. Sanjeed**

Expand the known universe of three-dimensional atomic-level protein structures and you will be amazed at what else you can achieve, asserts Nobel Laureate Professor Kurt Wüthrich. His nuclear magnetic resonance (NMR) method for determining three-dimensional structures of proteins in solution earned him half of the Nobel Prize in Chemistry in 2002. While NMR has become virtually indispensable in molecular structural biology, the field itself is not being developed as much as it should be in the biologicals industry. In an exclusive interview with APBN, Prof Wüthrich reveals how basic sciences like structural biology can make a difference between sweet success and dismal failure in the highly competitive but burgeoning biopharmaceutical industry

APBN: There is a tendency for science research nowadays to be geared towards applied science. Is basic science in any danger from lack of funding?

Kurt Wüthrich: There is a genuine danger of this happening. Applied science quite naturally receives much support because industries have research groups setup for applied science, especially in the pharmaceutical industries. For politicians it is more difficult to set aside large amounts of money for basic science research, simply because at face value one cannot really know what to expect. By definition, in my line of basic science I can often not make a proposal which clearly outlines what results I would like to have at the end of my day. This is because I should advance into the unknown. While this statement clearly applies to my own research in molecular biology, there are different situations as well.

Let us take the Higg's Particle, for example. It is an elementary particle that was predicted by Peter Higgs in 1963 and now they have built the Hadron collider at the European Organization for Nuclear Research (CERN) in the hopes of experimentally confirming the existence of the Higg's particle. In this case, scientists had a theory and to confirm it they spent billions of dollars to construct the necessary apparatus. For me this is clearly an example of basic science, since it remains to be seen whether it leads to the Higg's particle or perhaps some other surprising discoveries..

In any case, although the aims of this scientific endeavor may have been highly esoteric, in the process of getting such an experimental setup put together, incredible advances in technology have been made. For example, in the past the establishment of an information management system was introduced at CERN to handle the colossal amounts of data generated. This system helped lay the groundwork for the proliferation of the Internet. It so happens that this year we celebrate the 20th anniversary of the Internet – a technology we almost cannot do without today. Could the particle-physics researchers at CERN have initially anticipated this? It is hard to tell.

APBN: Do you think the issue of basic science versus applied science is more pronounced today than it was 50 years ago?

Kurt Wüthrich: Well it was not discussed so much 50 years ago. It is only once we know what we have to do, for example – characterizing three-dimensional protein structures – that we can define what needs to be done, buy apparatus and hire people. The other question is whether this is basic or applied science – this is not so unambiguous. Certainly I would classify the results as basic science, whereas the approach is rather applied science.

APBN: So there is no real danger to basic science, because the need for such research is being recognized and funded in most countries?

Kurt Wüthrich: Basic research may be very slow in developing, because you cannot tell exactly what will happen. It is not that trivial to fund properly because it is something that you are still looking for, which is not really defined properly. What you do need is a small number of special people who can work in quietude and with long periods of time in search of something, but they do not necessarily in all fields need huge sums of money. Let me put it another way — giving freedom and appropriate support to some special individuals who pursue basic science cannot be replaced by donating large amounts of money to consortia of scientists with well-defined research plans.

APBN: Singapore has invested a lot in its push to become a biomedical hub in the Asia-Pacific region. Comment on this.

Kurt Wüthrich: I think the situation is impressive because Singapore has worked very hard to import not

only top-notch instrumentation but top-notch scientists as well. This is not so different from the situation in Switzerland, where more than 50 percent of researchers in leading universities are not Swiss-born. That being said, the quality of the research and instrumentation in my field, structural biology and structural genomics, is *not* yet up to international standards in Singapore. What they may not have realized is that they may not get into the market of biologicals without strong structural biology and structural genomics expertise.

What you have to understand is that when you create generic biologicals, you have to prove that they have the same three-dimensional structure as the original. This is in addition to proving chemical structure and biological activity. For new drugs as well as generics, what information should a regulatory agency require to characterize a biological as a good drug? During manufacture, it is quite unfeasible to run three-dimensional structure determination routines all the time. So, you have to develop criteria which run short of doing structure determination but which give us enough information on structure, conformation and activity to make a case for the drug.

APBN: In the next 10-20 years, what upcoming technologies in protein characterization and visualization do you foresee gaining ground?

Kurt Wüthrich: X-Ray Crystallography and NMR are still the main technologies. I see no other technique coming up right now, capable of churning out the thousands of measurements and data necessary to describe a three-dimensional array of hundreds or thousands of atoms. Electron microscopy will play an important role, but probably not at the atomic resolution.

APBN: The current opinion is that in the West, there is a lack of recognition of drugs developed and manufactured in Asia. What can be done to change this opinion?

***Kurt Wüthrich*:** This is exactly why it is so crucial to properly characterize biologicals and other drugs during production. You need to establish criteria that will be internationally accepted, and you of course have to live up to these criteria. The scandal with tainted milk-formula in China is just one example of failing to establish and live up to proper criteria.

APBN: Who should take the initiative in establishing these stringent criteria for Asian countries – the private sector or governing bodies?

Kurt Wüthrich: It has to be the Governments' responsibility. It cannot be the private sector, although Governments could delegate the task to certain private enterprises. Whatever the case, the regulatory agency has to be outside of the manufacturing industry. The big problem is that the manufacturers of the new compounds usually also have the best analytical tools. They may thus be the only ones who can properly analyze their product, but since the risk of biased analyses is there, we cannot rely solely on their results. You need a lot of thought, effort and investment to create a separate entity technically capable of doing this validation.

APBN: Would this established authority in every burgeoning Asia-Pacific biomedical hub resemble the U.S. Food and Drug Administration(FDA)?

Kurt Wüthrich: Absolutely. My only word of caution is that such an agency will also need time to establish confidence.

APBN: How can such agencies be set up in the fastest possible time?

Kurt Wüthrich: Delegate the task to a non-governmental enterprise — but in Singapore's context, it would almost necessarily have to be done by foreigners, since nearly all the scientists working in Singapore are from abroad.

APBN: Will there be increasing migration of prominent scientists from USA and Europe to Asia?

***Kurt Wüthrich*:** It is already happening because the treatment of scientists in USA has been rather poor in the last few years and many are attracted by better prospects in Asia, especially in Singapore. Even though President Obama has lifted restrictions on federal funding for stem-cells, it will still take some time for those changes to take effect.

APBN: Finally, what can scientists and the various agencies involved in the drug industry do to make drugs cheaper?

Kurt Wüthrich: Firstly, nobody wants cheap drugs. What we want are good drugs which are inexpensive but not cheap. We cannot afford to have cheap drugs. When we talk about inexpensive generics, we should not forget that the pharmaceutical companies made huge investments to develop the original drugs. If they cannot make money from these investments, they will hardly have a keen interest in creating new drugs in their pipeline. No new drugs – no new generics. Therefore, the manufacturers of generics may eventually start to pay part of the original drug development cost. If that happens, the price of the generics will go up, but we will still get inexpensive drugs without being cheap. ■

Bio-data of Professor Kurt Wüthrich

Professor Kurt Wüthrich was awarded the Nobel Prize in Chemistry for 2002 "for his development of nuclear magnetic resonance spectroscopy for determining the three-dimensional structure of biological macromolecules in solution". Prof Wüthrich is a professor of biophysics at the Swiss Federal Institute of Technology (ETH), Zürich, and professor of structural biology at the Scripps Research Institute (TSRI) in La Jolla, U.S.A.