CHRISTIAN KIELMANN

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On the wings of imagination

Biochemist at Technion, the Israeli Institute of Technology in Haifa. Shared the 2004 Nobel Prize in Chemistry for the discovery of the ubiquitin system, which mediates protein degradation in all plant and animal cells by destroying proteins that are denatured, misfolded or no longer needed. Family moved from Poland in the 1920s, and he was born in Haifa in 1947. The following year the state of Israel was established.

You won a share of the Nobel prize for your discovery of the cell's protein degradation process. How has the field changed since those early days?
The field has changed dramatically. The ubiquitin proteolytic system is now known to regulate many basic cellular processes, such as cell division, differentiation, transcription and quality control. Altogether, components of the system comprise 6–7% of all genes in the human genome: well above what was expected for just a 'protein scavenger system'. Consequently, it is no surprise to find that aberrations in this system are implicated in the pathogenesis of many diseases. This knowledge has led to the development of mechanism-based drugs, including one on the market to combat multiple myeloma. It is very exciting. When we started we were not looking for the ubiquitin system; we were after an answer to the question of how proteins are degraded. We had no idea that such a complex system was behind it.

How optimistic are you that diseases of protein accumulation, such as Alzheimer's disease, will be treatable?
There are diseases that involve gain of function and diseases that involve loss of function. With the former, one can be more optimistic because the solution is to develop inhibitors and antagonists, which are easier to develop than agonists or stimulants. In pharmacology, it is easier to slow down a system than to speed it up, so it depends which side of the ubiquitin system you are talking about. On the cancer side — as it involves a gain of function — progress will come faster; on the neurodegenerative side, such as Alzheimer's or Parkinson's disease, it may take longer.

What are the limitations of modern medicine and how can they be overcome?
Modern medicine is rather primitive. We can only detect diseases like cancer and neurodegenerative disorders when they are well advanced; the challenge is to diagnose them much earlier, or even to predict and prevent them. We also tend to group different diseases under a single umbrella, for example grouping prostate or breast cancers together and treating them similarly. The fact the treatment succeeds in some people yet fails in others suggests that these groupings are erroneous and each disease is comprised of distinct sub-groups. With personalized medicine, we will be able to profile individual patients more precisely. Such profiling will be based initially on the patient's genome, but later it will use the transcriptome, proteome and metabolome. The road is long; the technologies and, crucially, the interpretation of results are not there yet, but the future is bright. The power of personalized medicine will reside not only in our ability to develop new drugs to currently incurable diseases, but also to predict, and therefore to prevent diseases based on individual patients' susceptibility. Along the way it will be important to pay special attention to bioethical issues concerning exposure of patients' most intimate information.

What are the challenges of translational medicine?
There are two potential approaches: carry out curiosity- and hypothesis-driven research that flies on the imagination of brilliant scientists, or carry out disease- and drug-oriented research. Curiosity-driven research in the last century brought tremendous development in biomedicine — novel drugs and sophisticated devices — and I strongly believe this is the way to go. If we shift mostly to translational research, the springs of knowledge will dry up, and there will be nothing left to translate. Perhaps the public and our political leaders think that things are going too slowly, but that's a dangerous perspective.

Do you have any advice for graduate students trying to pick a research topic?
Choose a good mentor who asks original questions. Be patient, do not give up: work hard and persevere. Be passionate and excited about what you are doing: think of your scientific profession as if it were your hobby. Luck is important too, but remember, very often luck is not blind: it hits those who are ready. ■

It is interesting that our preparations for combating complex diseases such as Alzheimer's and cancer are described as 'primitive'. What are the hurdles for progress — is it a lack of funding or are there knowledge gaps? Also, what attitude and skill set do young researchers need to tackle such complexities of multidisciplinary research?

G. N. Viswanath, professor of management, Bharatiya Vidya Bhavan, Bangalore, India, who posed the original question on lindau.nature.com.