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巻頭言

Structural Biology at the crossroads

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These are heady times for structural biology. Recently I visited Yale University where I was able to sit in front of a computer graphics machine and be guided through the web of structures of proteins and RNA in the ribosome by two marvellous young scientists. With this structure crystallography, based on a synchrotron radiation, will change fundamentally the way we think about how proteins are made. We will see how a complex machine operates to perform the basic chemical processes of life.

Crystallography sits in the midst of other structural techniques, NMR can address smaller systems and can focus in on interactions between molecules. Conversely, cryo-electron microscopy is weaker at addressing the atomic details but it can see the big picture, in particular of transient macromolecular assemblies. Together these structural techniques are redefining the challenges of cell biology and will allow us to piece together the structures of the fundamental molecular machines of the cell. This process will cohere innumerable fragments of knowledge and (since many of the basic cellular functions are common across broad sweeps of cells and organisms) should provide the appropriate context to reveal the simplicity underlying the disorder introduced into the genome by evolution, which at present masks so much.

Alongside these conceptual goals we are also aware that structure is an appropriate level at which to address our search for understanding disease and finding new therapies. In recognition of this challenge our laboratory has recently moved into a building devoted to understanding the genetic basis of common human diseases and we have had links with pharmaceutical companies for a number of years. Structural biology can contribute to the search for new drugs in several ways. At one level the identification of

the structure of essential proteins of human pathogens can (due to the conservation of 3-D structure) reveal a biochemical function, which can immediately focus efforts in directions more likely to lead to useful inhibitory compounds. High throughput crystallography may also suggest entirely new methods of lead/target identification, for instance by the forced binding of simple chemical scaffolds at very high concentration, revealing latent sites. Finally the structure of the target can be used directly for the design of inhibitors as witnessed by the latest anti-influenza compounds. The elucidation of the structure of such compounds in complex with their target can then greatly sharpen the development of the final potent drug. For the present our understanding of protein structure and energetics is still woefully incomplete and we therefore make many errors in such compound design This is one reason why the ability to quickly check ideas against reality by structural methods is likely to be important for some years. Aided by Professor Sakabe's TABA project we have ourselves exploited a combination of structural analysis and chemical reasoning to design a relatively easy to produce, nanomolar inhibitor of HIV-1 RT that is resilient to most drug resistant mutations. Finally, any structural biologist who has been involved in the process of moving from inhibitor to drug knows that learning how the compounds interact with their target is a surprisingly small part of a path that is strewn with difficulties. In some ways however, the difficulties in producing effective drugs makes the contribution of structural biology more important, there are still terrible holes in the armoury of drugs available and even a modest gain in the process of drug discovery would produce substantial health benefits. So we are happy to carry on working away producing dozens of structures and even talking to the organic chemists.

What makes the present time particularly exciting is that we are starting to realise the double-edged possibilities of synchrotron radiation, to simultaneously push the limit of complexity so that structures of many millions of Daltons will reveal themselves whilst also facilitating the rapid evolution of the mass of detailed structures needed to translate these visions into useful therapeutics.

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