EMBO reports

opinion

Big science, little science

In the USA, where I live and work, it is well known that I have little love for structural genomics—the attempt to determine the structures of most or all of the proteins in an organism by some combination of high-throughput X-ray crystallography, nuclear magnetic resonance spectroscopy and homology modelling. My reasons are a matter of public record: structural genomics is based on an assumption about the value of structural information that is obsolete; it leaches scarce resources away from individual projects for which structure determination has real value; its heralded technological innovations have been of limited use to the practicing scientist; and its value for training young scientists is nil. The relative worthlessness of structural genomics is self-evident to me; the topic for any discussion should be how to phase it out in the least painful manner.

But structural genomics is only a symptom. The real disease is the creeping hegemony of 'big science' over 'little science' and the issue of who sets priorities in biomedical research. Western science has been one of the triumphs of human endeavour but it is easy to overlook some of the reasons for that success. Generous public support of basic research is certainly the main factor, but I would argue that almost as important is the fact that such support has come without much government control. Unfortunately, with the rise of big science, that situation is changing. Thus, it is useful to look at how structural genomics began and why it survives despite widespread agreement that it is largely a waste of money and talent.

These initiatives originated in the heady days after the completion of the human genome sequence. They were the brainchildren of a small cohort of mostly senior structural biologists who, I suspect, wanted their share of the fame and resources that were being showered on Craig Venter, Francis Collins and others. Their proposals were attractive to scientific bureaucrats at the National Institutes of Health and other funding agencies because they, too, wanted to be linked to successful large data-gathering programmes with the magic word "-omics" at the end of their name.

But the analogy between genome sequencing and structural genomics is flawed. The genome sequences were good big science projects because they were probing the unknown; the data were from uncharted territory, in much the same way that Darwin explored a part of the world that was then largely unknown, at least to Europeans. This is not the case for structural genomics: 25 years ago one might have argued that we didn't know what the universe of protein structures looked like in broad terms, but certainly that argument cannot be made today.

The same applies to other big science projects born out of the success of the human genome sequence. Among those I dislike are genome-wide association studies that attempt to link common polymorphisms with severe illnesses. Thus far, these endeavours have pretty much been complete failures—the likelihood of finding such associations is small to begin with. Not only that, but it is simply silly to waste so much effort looking at variations that we have no *a priori* reason to think are a risk for anything, especially when we have a much more interesting set of variations that no one is looking at. I refer to the heterozygotes for autosomal recessive inborn errors of metabolism. Many of these are widely enough distributed in the general population to be extremely important if they confer risk for other illnesses, and there is tantalizing evidence that they do. For example, carriers of Gaucher disease have no symptoms of the devastating lysosomal storage disorder but are more than five times as likely than non-carriers to develop sporadic, idiopathic Parkinson's disease. Similar examples of cross-disease haploinsufficiency probably abound, but I know of no systematic effort to identify them. All the effort and money is being expended on mining the common polymorphisms, even though that's similar to casting your line at random places in the Atlantic Ocean to look for one specific type of fish.

So, why do these projects—even those that have produced little in the way of important results—continue to garner outrageous levels of financial support? One reason is that bureaucrats love them because they produce reams of results that can be summarized easily to superiors and politicians. And this is precisely why such projects are dangerous: they are helping to perpetuate the trend of setting scientific priorities in a top-down manner by bean-counters and non-practicing scientists.

I believe that the right way to direct science is almost not to direct it at all. Attention must certainly be paid to what the public wants and what the political system can be persuaded to support, but the notion that bureaucrats—even those who were once scientists—know what our scientific priorities should be and can steer us in the appropriate direction strikes me as a recipe for disaster. Scientific priorities must, for the most part, be set by the free exchange of ideas in the scientific literature, at meetings and in review panels. They must be set from the bottom up, from the community of scientists, not by the people who control the purse strings.

We do need some big science. But the best kind of big science is the kind that supports and generates lots of good little science. For those bureaucrats who know in their hearts that we ought to terminate some of the current big science programmes, but who are afraid to do so because it would seem to be an admission of failure, let me give you a way out. It's the one that the late Senator George Aiken of Vermont suggested to extricate the USA from the quagmire of Vietnam. It's the one that the Obama Administration seems to be using to extricate the USA from the quagmire of Iraq. Declare victory, and pull out.

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