Correspondence

An idea whose time has come

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A response to **An idea whose time has gone** by Gregory A Petsko, *Genome Biology* 2007, **8:**107

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In the June 2007 issue of *Genome Biology* Gregory Petsko published [1] a sweeping attack on both the objectives and achievements of the Protein Structure Initiative (PSI) [2]. As members of the Forum for European Structural Proteomics [3]) and SPINE2-COMPLEXES (a European Commission (EC) Integrated Project which is a continuation of the Structural Proteomics in Europe (SPINE) consortium [4], the first structural proteomics integrated project funded by the EC), we wish to respond from a European perspective.

It is not unusual for new and challenging scientific endeavors to arouse the criticism of parts of the scientific community. As an example, few would now wish to argue against the value of the Human Genome Project, although in its early days there were many eminent contrarians. Although direct benefits to drug companies may not have been initially intended, they are a positive outcome.

Petsko claims that the PSI has not contributed to his own work, and makes a bet that this is true for his readers. We find this claim hard to swallow. Petsko is, of course, entitled to speak for himself, but we find it difficult to believe that even he has not benefited from the rapid advances in protein production, crystallization and the automation of both data collection and structure determination that are direct added value of the combined efforts worldwide. Their utility to the community can easily be assessed by citations in the literature and visits to websites. In particular, we would dispute the assertion that there are no longer problems in the process of structure determination. For interesting high-value targets, both protein production and crystallization remain significant challenges and require further development. An example of the hunger for such developments from the broader structural biology community is the remarkable interest in a publication from SPINE [4], cited recently by the Faculty of 1000 as a 'hidden' gem.

Moreover, any structural biologist who makes repeated visits to synchrotrons in the United States, Europe and Japan is each time amazed by the rapid and ongoing advances in automation of data collection and structure analysis, and in the quality of the optics. Taken together, they permit rapid data collection, with remote access at some synchrotrons, and use of crystals so small as to have been unusable just a few years ago, making it possible to attack previously intractable problems. Nuclear magnetic resonance methodology has been similarly boosted by the PSI initiative, resulting in dramatically increased efficiency in structure determination, as well as in fast, efficient and precise approaches to a variety of biological problems that would have been hard to imagine even a few years ago. All these achievements are an invaluable spin-off of the PSI, and of its cousins outside the United States, and would not have been attained without the focused funding and, perhaps more importantly, the integrated and oriented teamwork associated with these dedicated large-scale centers.

As a result of the efforts of all consortia (US, Japanese and European), 2,525 protein structures have been deposited

in the Protein Data Bank as of August 2007. Although some of these structures may be redundant (1,729 PSI structures are unique by the 30% sequence identity criterion) or even appear uninteresting at first sight, many are of the highest technical quality, of fundamental and/or medical importance and, taken overall, provide a valuable database. Moreover, in 2005, structures arising out of structural genomics and structural proteomics efforts accounted for 44% of the total number of novel structures reported [6].

Until quite recently, most would have agreed with Petsko's comments on the limited value of the large number of new structures produced by the PSI for use in homology modeling, and would have questioned how valuable such structures might really be for accurately predicting novel protein structures or for use in drug design. But there are now an increasing number of examples where predicted structures have proved of utility, including in drug design [7-9]. Obviously, the larger the database at the disposal of the scientist, the better will be the quality of the homology models generated, whether of native proteins, engineered proteins or of drug-protein complexes. Thus, although protein structures arising out of structural genomics projects have not yet led to a drug in clinical use, the situation might well change quite rapidly.

The fact that the only targeting guidelines for the first round of the PSI were to increase coverage of structure space, permitted centers to focus on sets of proteins from, for example, a single organism. This was a reasonable initial choice, as it permitted benchmarking of a variety of parameters highly relevant to the entire chain from cloning to structure determination, and highlighted the bottlenecks at the stages of expression and crystallization, resulting in such insights as the Gravy plot [10]. In its second round, the emphasis of the PSI is still on increasing coverage of structure space, but in a more specific fashion, and with tight central integration of target selection by the various centers.

In the European Commission's Vth Framework Programme for Scientific and Technological Cooperation, the SPINE integrated project already placed emphasis on identifying protein targets related to human health and disease, particularly on the solution of human and pathogen protein structures [11]. SPINE2-COMPLEXES, in the VIth Framework Programme, has moved from upgrading technologies and solving structures of single proteins to developing approaches to solving the structures of protein complexes, with the eventual challenging objective of integrating such complexes into higher-order cellular structures. The measure of the success of the project will not be the number of structures solved but rather their biological impact. The Structural Genomics Consortium [12], an international project funded by Canada, Sweden, the Wellcome Trust in the UK and industry, with laboratories in Oxford, Stockholm and Toronto, has also focused on sets of proteins related to human health. It is using structural genomics methodology to develop high-throughput approaches for attacking these difficult targets with a high degree of success [13].

In conclusion, it should be kept in mind that scientific research, and the cutting-edge technologies that both drive and are driven by it, are constantly and rapidly evolving. Some of Petsko's criticisms are constructive, and should be noted by policy-makers. But one should not throw the baby out with the bathwater, rather tune the scope and objectives of the PSI to the needs of the life-science community as a whole, much in the spirit of SPINE, the SGC and other European structural genomics/proteomics projects [14]. If such a constructive approach is adopted, we feel confident that the structural data provided by the PSI and its cousins will serve as no less valuable a resource than genome sequences.

Gregory A Petsko responds:

The arguments of members of the Forum for European Structural Proteomics in response to my column on the Protein Structure Initiative (PSI) don't persuade me to change my view of the usefulness of large-scale structural genomics. Ultimately, the disagreement is a philosophical one. Supporters of the PSI - a group that, I still say, consists largely of members of the PSI - believe that the creation of a large database of solved protein structures has great value, at least potentially. I don't think it does, and I made my reasons clear enough in my column.

But a few of their comments are worth responding to further. They "find it difficult to believe that even he (that is, me) has not benefited from the rapid advances in protein production, crystallization and the automation of both data collection and structure determination, that are direct added value of the combined efforts worldwide". Believe it, gang: it hasn't done a thing for me. The 'benefits' the correspondents set out are the automation of both data collection and structure determination - that is, things that benefit primarily high-throughput structure determination. I don't do high-throughput structure determination. It's against everything I believe about the role of structure determination in biology. The advances they are talking about are primarily advances that benefit themselves and others involved in such projects.

The other comment I would respond to is their suggestion that the larger community should work with them to recraft their mission so that it serves us better. I suppose I ought to thank them for making my point for me: after all the time and money spent on this program, they still are not sure themselves what it is really good for. I'm sorry, but I think that in this era of tight funding for research, when there is so much exciting, hypothesis-driven science that needs to be done, there simply is no room for a project that

never had a compelling reason for existence in the first place, and still doesn't.

I don't think we should engage the structural genomics groups in a dialog over how to reformulate their goals because I don't believe there is any goal they can accomplish that is worth the cost, in either money or human resources. I still am convinced that the kindest thing, and the only right thing, we can do is to figure out how to phase this program out with as little pain as possible to those involved.

Gregory A Petsko

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