Proteomics - Boom or Bust?

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Although the fanfare and not just a little hype that surrounded the release of the (almost) complete human genome was a little theatrical for my taste, it clearly marked a watershed in human scientific endeavors and was unquestionably the product of the efforts of a relatively small number of visionaries. Unlike other mammoth biological projects, such as the "War on Cancer" of the 1970s, this endeavor had a reasonably well defined goal that was approachable and only lacked superior technological support, which was duly developed. Thus it was really an engineering problem, and its success can and has been likened to the equally successful "Man on the Moon" program. This comparison diminishes neither accomplishment and may also be apt in another way. At the time of their successes, both held (and still do) the promise for providing the groundwork for great future advances in man's knowledge, one in space science and the other in the molecular basis of life. The only difference is that we have some 30 years to assess the impact of the moonshot on astral and physical sciences whereas the knowledge of the human (as well as other) genome(s) is still much too new for any serious evaluation of its effect on biological sciences. That it will be great is a given. Nonetheless, it is not too early to appreciate some of the problems that will likely be encountered in the era following the human genome milestone, some of which may be altogether too accurately presaged by the problems of the space program.

The opportunities kindled by the moon landing programs for the further development of knowledge about our universe and even beyond have indeed lead to a variety of important discoveries, and these are ongoing. They have taken many different forms, such as the Mars explorer and outer planetary flybys, that have been highly successful, but there have also been major disappointments and even tragedies. The breadth of these activities underscores the vast, even infinite, nature of space science, and the realization that was eventually visited on NASA (and other space-related efforts) was that the magnitude of the problems to be addressed was daunting and that their pursuit was and would be hampered seriously without focus. None of this was made any easier by political and social agendas of a wide variety of organizations and interested (and invested) individuals. Thus, despite some very successful ventures, few would argue that accomplishments in space since 1969 have had the impact of the first manned lunar landing.

The future opportunities afforded by the genome project are equally open-ended and are certainly no less affected by political and social factors. The positive prognosticators for this field are everywhere. For example, it is not uncommon to hear statements to the effect that various applications of genomics (functional, structural, toxicological, pharmacological, etc.) will completely change the practice of medicine in the next decade and beyond. Clearly Wall Street and the biotechnology/pharmaceutical industry strongly subscribe to this view, and various government and private funding agencies have begun to seriously ramp up their support for a variety of genomic-driven approaches. And, accepting that all of these "genomic" disciplines are a part of proteomics (by almost any definition to which you feel you can subscribe), there is the appearance of new journals (including this one) to meet the predicted needs of this rapidly expanding field. Some of this sounds a little like the colonies on the moon we were going to enjoy by the year 2000 (that idea has, as at least some will have noted, come and gone). In short, is proteomics doomed to disappoint many of the high hopes that we all have for it right now?

The answer to this last question is not now available and won't be for years. But it is possible to pose at least a few thoughts, attention to which may have some impact on what that answer will eventually be. In the first place, it is essential to realize (particularly in terms of expectations) that the study of the proteome is not the same as the study of the genome, and this is species-independent. Some would argue that "completeness," *i.e.* the full understanding of what every protein in an organism is up to, is a key part of any definition. If one really seeks this information in terms of each protein in a living, functioning cell, then it is probably a fool's errand. There may be a finite number of genes and a finite, if larger (much larger in higher organisms), number of splice variants, but there is almost certainly an essentially infinite number of protein derivatives when all co-/post-translational modifications that can occur in the lifetime of each protein are considered. Understanding the state of all these different proteins at any given moment in any given cell (notwithstanding with whom they may be interacting during this snapshot and the effects of those interactions), even recognizing that it is likely to be only a subset of the genes in the genome that are being expressed, will be not only formidable but in all likelihood impossible. Of course, completeness can be defined to various degrees. It should be possible, for example, to at least understand the structure of each protein and what its basic function is in a genome. This will hardly provide all information necessary to understand cell and organ function, but it would

be another major step forward. The real payoff for proteomics will be solving the dynamic problems, or at least some of them, and this will require a higher level of analysis, minimally involving protein-protein interactions and temporal expression, and one that will be far more challenging. Here completeness is just as likely to be an obscuring detriment as it will be an achievable incentive. Thus setting priorities in proteomics at any level should recognize not just the tremendous potential but also the realities.

Second, and this is a lesson from the space program, is the necessity for all participating parties, practitioners, regulators, supporters, etc., to understand the objectives, both long and short, and how to mobilize resources, which are always limiting, to achieve both. This can take several forms. Proteomics will require a rich and continuous investment in technology, and this has traditionally been underfunded in the life sciences in general and during the ongoing National Institutes of Health budget doubling in particular. The sequencing of the human genome would not have been possible without significant improvements in DNA sequencing. An important portion of this came from the private sector, in part, because the end product (the sequence) was deemed to have intellectual property value and therefore could be exploited for profit. A similarly situation does not generally apply to proteomics. It is too broad an enterprise, and it will not be driven solely by any single technology. In this situation, the best support comes from the government to academic researchers, who make the advances while providing the infrastructure to move the field forward. The government agencies need to look long and hard at their policies here. This also applies to grant-review panels. It is already common discussion among scientists "gathered around the coffee pot" that study sections are giving proteomic proposals short shrift. Many of these investigations are indeed exploratory, and these have traditionally been dismissed by these bodies as "fishing expeditions," so the rejection rate is not surprising. This attitude tends to exclude the small investigator, dependent on R01 grants, from this enterprise as only large groups with support that is insulated from this sort of peer review will have the capacity to do such experiments that are required to reveal the dynamic features of protein interactions, particularly with proteins whose structure and function is still a complete mystery. The field will not move forward as rapidly as it could as long as this insular attitude prevails.

Proteomics is certainly a prime example of the elephant described by the five blind men. However, as long as those five blind (but wise) men talk to each other, the elephant will be well cared for (and this journal will accordingly flourish).