Online journal ISSN - 1676-5680
GMR Genetics and Molecular Research
EVOLUTION AND TECHNOLOGY

Coordinated, network-based research as a strategic component of science in Brazil

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Genet. Mol. Res. 3 (1): 18-25 (2004)
Received October 13, 2003
Accepted January 12, 2004
Published March 31, 2004

ABSTRACT. Scientific research plays a fundamental role in the health and development of any society, since all technological advances depend ultimately on scientific discovery and the generation of wealth is intricately dependent on technological advance. Due to their importance, science and technology generally occupy important places in the hierarchical structure of developed societies, and they receive considerable public and private investment. Publicly funded science is almost entirely devoted to discovery, and it is administered and structured in a very similar way throughout the world. Particularly in the biological sciences, this structure, which is very much centered on the individual scientist and his own hypothesis-based investigations, may not be the best suited for either discovery in the context of complex biological systems, or for the efficient advancement of fundamental knowledge into practical utility. The adoption of other organizational paradigms, which permit a more coordinated and interactive research structure, may provide important opportunities to accelerate the scientific process and further enhance its relevance and contribution to society. The key alternative is a structure that incorporates larger organizational units to tackle larger and more complex problems. One example of such a unit is the research network. Brazil has utilized such networks to great effect in genome sequencing projects, demonstrating their relevance to the Brazilian research community and opening the possibility of their wider utility in the future.

Key words: Network, Sequencing, Genome, Brazil

In a country such as Brazil, with its impressive agricultural capacity, vast biodiversity, and highly complex health challenges, biological and biomedical research is a critical component of the overall scientific endeavor. As is the case elsewhere in the world, most such research is publicly funded through either federal or state agencies, which provide grants to individual researchers in response to proposals for the execution of defined, relatively short-term projects. Since it is ultimately funding that defines organizational structure, the implications of the funding model are far reaching.

The funding strategy that has been adopted around the world, including Brazil, holds the individual scientist as the basic unit of scientific organization, rather than the research institute, university, department, or collaborative network. Over the last 50 years it has been the United States that have led the development of science and it is in the US that the individualized funding system is most highly evolved. In the US system, almost all funding comes from a small number of centralized agencies, and there is fierce competition among applicants, who are judged against one another in regular rounds of project assessment. In addition to the clearly desirable criteria of assessment of scientific quality, relevance, feasibility and originality, there is also great emphasis placed on the demonstrated independence of the "Principal Investigator", or PI. Even in so-called project grants, the collaboration has to be among strong independent investigators. The grants are for relatively short periods of time, and there is great pressure to accomplish the declared objectives, and indeed generate additional data that can be used as the preliminary information necessary for the next round of funding. The stakes are high. The long-term tenure of the scientist in his or her institution is dependent on the ability to successfully raise research funds. These are required not only to pay for equipment and reagents, but also may be used to cover the investigator's salary, as well as to keep the institution itself running through an overhead that is generally around 60% of the value of the direct costs of the grant. The host institution as a rule has no alternative to project overhead to cover its basic costs and pay the salaries of its scientific staff. Since the grants are paid to individuals, who in turn sustain the host institution, the individual becomes the powerful (albeit vulnerable) central component of the research enterprise. Those who are successful in raising research funds thrive and dominate those who are not lost to the system.

The spectacular pace of discovery in the biological and biomedical sciences in the US over the last 25 years has led to the belief that the organizational principles that have been adopted are optimal for the advancement of science. The problem is that the essentially universal application of this system supports a rather narrow range of scientific activity. The research in a funding proposal has to be achievable by an individual researcher, or by a small group of individuals working directly under that researcher. Furthermore, the work must be possible to complete within a rather short time frame, usually three years. Most importantly, there is absolutely no incentive within this system to either attempt to tackle truly complex and ambitious projects or to collaborate with other scientists in an organized coordinated fashion. This is an important shortcoming, with practical consequences that are readily apparent in the field of cancer research, for example. While we have made great strides over the last half century in beginning to understand the molecular basis of cancer and the identity and function of many of the genes and proteins that play a direct role in tumor development, patients who are smitten by this terrible disease are treated today in essentially the same way as they were 50 years ago. There have been almost no new treatments, and for most of the more common forms of cancer the same dismal prognosis applies as in the 1960s. Thus, although the scientific system is well suited to discovery, at least at the level of individual molecules and genes, it is not well suited to translating that discovery into practical application. A far larger coordinated effort is required than a single laboratory can muster to advance a basic research discovery into a drug for human application. Once a potential target for cancer therapy is identified, means of inactivating or otherwise exploiting it need to be identified, the molecule (or other substance) produced in a way that it can be safely administered to humans, regulatory issues satisfied, clinical trials designed, executed and monitored, and finally, the effective transfer to a large-scale manufacturer negotiated. It is often argued that it is not the place of academic science to do this, but rather the place of industry. However, it is equally clear that reliance on this option has also not been completely successful, at least in the case of cancer research. The problem that industry faces is that it is obliged to make money, while drug development is extremely expensive. Thus, only leads that are judged highly likely to pay off can be pursued, and there is a concentration of effort on common chronic diseases, as a new drug would be taken by a large number of patients over a long period of time. Since cancer is seldom a chronic disease, and actually comprises a very diverse group of different diseases, each of which is rather rare, it does not fall into the priorities of most companies. Nevertheless, it would be a much more attractive proposition if academic research were able to not only make the basic discoveries but also take this further down the road to their translation into practical application, leaving industry a smaller and less risky challenge in taking the basic practical application to market. However, academic science dominated by hypothesis-based research is incapable of achieving this.

One emerging, partial solution to this problem is the phenomenon of small start-up biotechnology companies that generally raise venture capital to pursue individual ideas or pieces of intellectual property generated from academic research. The nature of venture investment is such that it is expected that a significant percentage of such initiatives will not succeed. Those that do are normally bought out by larger more-established companies, which thus essentially use the biotech community to undertake the initial highly speculative work in untried areas, reducing their risk in further development. It is noteworthy that in the area of cancer many of the more promising and novel therapies in the pipeline are being pursued by small start-up companies rather than by the ever-dwindling number of very large multinational pharmaceutical companies. As important as the biotechnology industry is, however, it too is incapable of solving the entire problem, as the funds that any individual company is likely to be able to raise are limited and very large projects are impossible.

For Brazil's relatively small scientific community, situated far from the mainstream of worldwide research, the situation is exacerbated by the absence of a meaningful private biotechnology sector on the one hand and pharmaceutical, high technology agriculture or biochemical industries on the other. In this scenario, basic research that is undertaken at the level of individual investigators can certainly contribute to the global pool of knowledge available to the worldwide scientific community, but it is extremely unlikely to lead to practical developments within the country where the research is being undertaken. Such research, which has as its only real product a piecemeal contribution to fundamental knowledge, would appear to be a luxury that can be ill afforded in a country where there are so many deserving options for the investment of public funds. Indeed, for a country such as Brazil to be able to close the gap on the richest and most advanced nations, it is crucial that it is capable of independent technological advance so as not to be completely reliant on the countries that do have this capacity and thus be systematically at a disadvantage. Indeed, it would seem that alternatives to the smaller scale copy of the US system, as a strategic plan for the advancement of science in Brazil, should be considered. On the other hand, the utilization of the US model until now has served the country well. The first goal of a scientific community must be its growth to a self-sustainable level. This has been achieved through the establishment of federal, state and private funding agencies, universities, research institutes and research hospitals, and the training of significant numbers of individuals in laboratories throughout the world who are now, in turn, proving more than adequate for the preparation of the next generation of young scientists. All of this has established Brazil as a participant in the world stage of academic research, and has led to the establishment of myriad productive individual relationships and interactions between Brazilian scientists and those in the rest of the world. All of this has been achieved in a relatively short period of time and is to the great credit of the community and the country as a whole. The interdependence with existing communities that was required for this to occur necessitated the reproduction of the systems that they had developed. Today, however, the Brazilian research community has reached a stage of maturity where a wider discussion of the options that might best enable it to effectively contribute to the development of the nation is warranted.

Interestingly, a practical exploration of alternative organizational paradigms has been ongoing and has met with considerable success. This alternative is a large, multicentered, centrally coordinated, goal oriented research project, involving hundreds of scientists and executed by a collection of traditional research groups dispersed over a wide geographical area. Perhaps the best example is the project that undertook the sequencing and analysis of the genome of *Chromobacterium violaceum* (Vasconcelos et al., 2003), many of the results of which are described in this series of articles. Although the *C. violaceum* project was not the first project of this kind to be undertaken in Brazil, the *Xylella fastidiosa* project undertaken in Brazil has this honor (Simpson et al., 2000): it is the first to be undertaken on a national scale, and it clearly established the feasibility of this model in the context of continental geographic dispersal. The organization and execution of this project stands in complete contrast to the normal international model. First, following the decision of the Ministry of Science and Technology and CNPq to undertake such a project, the community as a whole was asked to submit suggestions as to what genome to sequence and in addition applications were invited to participate, without at that stage knowing what the project was to be. A committee was formed, which selected the organism and the participants, who then went on to execute the project with a minimum of outside influence. The project had a single, well-defined, but complex and technically demanding goal, which required the coordinated and significant contribution of all the participants to achieve. The participants, the majority of whom were not specialists in the field effectively being studied (the biochemistry and environmental adaptation of free-living bacteria), had to solve many individual problems associated with the installation and technical mastery of the equipment utilized, learn many novel techniques and apply themselves in an intense and focused manner to the project. More than thirty groups, and over 200 individual scientists, technicians and students, were involved throughout the duration of the project, with other collaborators and consultants being called in as required. Most impressively, the group was capable of functioning as a coordinated unit, despite being separated by thousands of kilometers, and with only the very occasional meeting. A strong logistical plan had to implemented to provide the reagents, and indeed the DNA to be sequenced. More than anything the network functioned via the internet, using this route both to send the results of the work to the central bioinformatics laboratory for collation, the subsequent continuous access to the centralized data bank to permit the analysis of the genome, and in addition using e-mail as the main means of communication. Indeed, the open e-mail system (discussion group), through which all members of the group can simultaneously see and respond to messages being passed between the participants in the project, provides a very strong cohesive force for coordinated activities and also represents an extremely efficient means of disseminating information. Not all members of the project participated equally; some limited themselves to the minimum allotted tasks, while others became increasingly involved in the project, contributing not only to the generation of the basic data but also to its minute and painstaking analysis, as well as the preparation of the results for publication. Such inequality is typical of any collective activity and is to be expected. The reasons are on the whole circumstantial, and the inequalities tend with time to even themselves out. Even within the *C. violaceum* project itself, some who contributed very large amounts of sequence data did not make significant contributions to analysis and writing, while in other cases the opposite was true. In addition, as the group moved on to other projects, different individuals took on more dominant roles. Indeed, and this is most clearly seen in the genome projects in São Paulo, where many more projects have now been undertaken, it is quite possible in a large and cohesive group for the central coordination roles to also be rotated, so that experts in different areas are able to lead projects with surprisingly similar degrees of effectiveness. There is no equivalence to an endeavor of this kind in the normal world of individual research projects, which are usually undertaken within a single laboratory or together with one or two selected collaborators.

The end results of the project are impressive, with a large and previously totally unknown genome being sequenced and expertly annotated in a short time by a group with almost no previous experience, the creation of a strong and effective DNA sequencing capacity, the establishment of a powerful computational center capable of undertaking many such projects in the future, a publication in one of the world's most prestigious journals, a patent submitted for selected genes of potential biotechnological utility and, as witnessed by the manuscripts published here, an effective interactive group for the study and exploitation of this organism. What is of importance here is not so much that a large and complex bacterial genome has been sequenced and analyzed, but that the efficacy of group-based research has been demonstrated in a very challenging situation. A problem that was beyond the capacity of any of the groups involved individually was rapidly solved by a collective effort. This model could be applied to any number of problems and challenges. In São Paulo State, for example, large coordinated projects encompass not only genome sequencing but also a full scale analysis of the biodiversity of the whole state, a precise molecular documentation of the viral epidemiology of the population, and a coordinated collection and analysis of clinical specimens for the identification of novel tumor markers and therapeutic targets. Furthermore, there are several coordinated projects, where groups are working together to exploit genome data to move towards practical application and to develop commercial projects. In all cases, the ideas for the projects originated from the community, were vetted and were then adopted by the coordinating funding agency (FAPESP), and then executed by groups of laboratories and individuals. Not all proposals and ideas have matured into actual projects, but all projects that were started have been successfully completed. This is a model that really works, and it significantly broadens the scope of science to include much more ambitious and challenging projects. However, it should be noted that participation in the group projects is not the sole activity of any of the participants. In addition to their normal teaching and administrative activities in their host institutions, the participants all simultaneously maintain individual research projects, many of which are completely unrelated to their network activities. Thus, the adoption of coordinated network projects in no way diminishes the possibility of smaller scale, more creative activities. Rather, the latter appear to be enhanced by participation in the former. Not only is it possible to have access to more advanced equipment and additional funding through the network, but there is also a spread of expertise, the extension of collaborative contacts to be called upon whenever necessary, and a general increase in the level of enthusiasm that comes from participation in large, successful collective enterprises.

Lastly, large projects provide a good point of interaction with industry, which can sponsor and influence the projects undertaken, and use them to elaborate more effective forms of interaction with the research community. It is also perhaps no coincidence that following the adoption of the network paradigm in São Paulo, the first effective biotechnological start-ups have appeared, populated almost entirely by members of the collective genome projects.

It should be emphasized that one of the most innovative aspects of the collective science paradigm being developed in Brazil is that it does not involve the construction of institutions or the hiring away of scientists from their universities, where they are currently employed. This provides for flexibility, speed of execution and reduction of costs. In addition, when a particular network is no longer appropriate or has begun to run out of steam, it can be simply abandoned or reconfigured with a minimum of adverse consequences for those involved.

Overall, the collaborative research network appears to bring many advantages and few if any disadvantages to the scientific system. For Brazil it is a route to increased international competitiveness whereby more complex and challenging projects can be undertaken and areas explored that would otherwise be left to larger scientific communities. In addition, it provides a route towards the accelerated integration of science with industry and the development of an effective biotechnological industry. Its widespread and routine adoption, however, depends, more than anything, on recognition of the importance of the contribution of the individual scientists to the overall project, so that this can be taken into account in promotions and selection for leadership positions within the scientific community. On the whole in Brazil, unlike most of the rest of the world, this recognition appears to be given spontaneously, and institutions generally hold their network participants in high esteem. Obviously success also depends upon the percentage of the overall research funds made available for large coordinated projects. This should probably not be more than 5 or 10%, and such projects should not be seen as an alternative to individual-based research. Nevertheless, the continuous inclusion and further development of such projects throughout the biological sciences could make a crucial and significant difference in the evolution of these sciences in Brazil and the contribution that they are able to make to further progress and development. Moreover, since the rigidity and resistance to change in the US and other more developed scientific systems is strong enough to make their adoption of similar strategies extremely unlikely in the foreseeable future, the opportunity exists to make important steps forward in Brazil that are not likely to be achieved elsewhere. This situation is likely to change with time, as a more collective approach to science would appear to be ultimately inevitable, as it has with most forms of higher human activity. Indeed, the industriousness and willingness to confront the experimental and novel that the Brazilian biological science community has demonstrated provides a golden opportunity to lead the world into the next era of achievement, discovery and invention.

ACKNOWLEDGMENTS

The authors, who were the central coordinators of the *Chromobacterium violaceum* genome sequencing project, would like to express their sincere thanks to the entire network for their hard work, creativity, enthusiasm and solidarity during the course of this challenging and unique project. We would also like to acknowledge the vision and courage of the staff of the Ministry of Science and Technology and CNPq in taking the decision to commit to such an adventurous and unprecedented project. Lastly, we are indebted to the leaders of our own institutions who supported us in our decision to embrace and commit to the network vision despite the demands of time and energy that it made to activities outside the immediate scope of our normal institutional activities.

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