Opinion

Breaking barriers through collaboration: the example of the Cell Migration Consortium

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Abstract

Understanding complex integrated biological processes, such as cell migration, requires interdisciplinary approaches. The Cell Migration Consortium, funded by a Large-Scale Collaborative Project Award from the National Institute of General Medical Science, develops and disseminates new technologies, data, reagents, and shared information to a wide audience. The development and operation of this Consortium may provide useful insights for those who plan similarly large-scale, interdisciplinary approaches.

Cell migration is a complex cellular process that is not only critical for development and survival of higher organisms but also contributes to important pathologies [1,2]. The migration of a cell requires the careful integration of several distinct cellular phenomena, including polarized actin assembly and disassembly, formation and dissolution of adhesions, and contraction [1-4]. Thus, cell migration is the result of spatial and temporal integration of many regulatory networks that orchestrate the functions of scores of molecules that comprise the migration machinery of the cell.

The complex and interdisciplinary nature of cell migration presents particular challenges for research in this area. These challenges require new technologies and approaches along with collaborations among those investigating different components of the process. The large-scale collaborative, 'Glue Grant' initiative sponsored by the National Institute of General Medical Science (NIGMS) [5] provides an innovative funding mechanism to address complex research projects of this type. It is through this mechanism that the Cell Migration Consortium [6] evolved. To date three other large-scale collaborative grants have been awarded. The Alliance for Cell Signaling [7] addresses the mechanisms by which cellular signaling networks regulate cell behavior; the goal is to develop and utilize a set of standardized assays of signaling intermediates and endpoints in response to single and multiple stimuli and to model these responses using a variety of bioinformatic approaches. The Inflammation and the Host Response [8] project addresses the response to trauma and burns; its goal is to determine the set of observable phenotypes and then to apply high-throughput biological discovery tools, such as proteomics, gene-expression analysis, and transgenic mice, to identify the molecular responses to trauma and burns and to determine the relationships that produce the observed phenotypes. The Consortium for Functional Glycomics [9] is defining the ways in which carbohydrate-binding proteins function in cellular communication; the goal is to characterize the specificity and affinity of the carbohydrate-binding proteins for carbohydrate ligands, establish their roles in communication of various cell types, and determine the structures of carbohydrate ligands and their mechanisms of synthesis. While these are currently the only Glue Grants supported by the US National Institutes of Health (NIH), there are several other large-scale initiatives funded by NIH, including one directed at protein structure determination [10] one directed at developing mouse models of human cancers [11] and another, the Pharmacogenetics

Research Networks, aimed at providing the genetic information necessary for better tailoring of pharmaceuticals to individuals [12], for example.

Large-scale collaborative programs such as these are usually directed at high-throughput approaches to generating and analyzing data - but the challenges to researchers in the field of cell migration focus primarily on the need for greater integration of disciplines in order to generate novel reagents and technologies. It appears that these kinds of collaborative initiatives will continue to emerge, so we outline the organization and operation of our nascent Consortium as one model for others to consider in areas with analogous needs.

Several years before the opportunity arose to create the Cell Migration Consortium it was evident to two of us (ARH and JTP) that 'barriers to progress' were hindering movement in cell migration research. Many of these barriers were research needs and issues that could not be readily addressed by a single laboratory. Thus, it became apparent that multi-investigator, interdisciplinary collaborative approaches were needed because these barriers represented technical and intellectual challenges at the frontiers of our present knowledge of protein structure and proteomics, cell imaging, signal transduction, and modeling. Initial small-scale interdisciplinary collaborations in one of our own laboratories in the 1990s proved very successful [3,13], and it became evident that other areas within cell migration research would also benefit from such an approach. On the ski slopes at a Keystone meeting in Colorado, the two of us discussed our common views and a vision for an integrated approach to cell migration research; thus the seeds were sown for the Consortium. The nascent ideas were developed and greatly expanded by discussions with several colleagues who had already shown an interest in collaborative, interdisciplinary research. With the call for proposals from NIGMS for Glue Grants, the Consortium became a reality.

The Cell Migration Consortium's approach to addressing the 'barriers to progress' was to develop highly collaborative, multi-disciplinary and multi-institution working groups, or Initiatives, each consisting of multiple researchers focused specifically on addressing a defined barrier. Perhaps the most unique aspect of the Cell Migration Consortium's approach is that the overall goal of these Initiatives is to generate novel reagents, technologies, models, and to organize information relevant to the field, rather than conducting individual investigative experiments or generating large amounts of data in a high-throughput type of effort. In this way, the non-hypothesis-based nature of the goals allows Initiatives to focus on producing technologies, reagents and information for use by the migration community as a whole. Although the stated objective of the Consortium is to solve problems related to cell migration, the scientific barriers that we outlined are germane to research areas that extend well beyond cell migration, and the information and reagents that will be produced bear on research in many related areas and thus will feed a large list of other research endeavors.

The Consortium and its Initiatives were not modeled on any other large-scale initiatives or programs but rather emerged from a focus on specific needs associated with cell migration research and the formulation of a strategy to address them. For example, the full repertoire of genes and gene products that contribute to cell migration is not known since there has been no concerted effort to identify it. The composition and organization of the large, supramolecular protein complexes that mediate cell attachment and other migration-related processes are not known. The signaling networks that regulate cell migration are not completely defined and need to be characterized and understood in the context of both space and time. There is a paucity of cell culture and animal models available for the study of cell migration, particularly *in vivo*. The conceptual and mathematical tools required to describe and integrate the component processes comprising cell migration have not been developed, and pertinent quantitative measurements to test these models are not available. The Consortium Initiatives were designed to address these specific kinds of issues.

As with any enterprise there are administrative, financial and legal issues to be addressed. Prior experiences as holders of individual grants from NIH, as principal investigators on Program Projects and as Department Heads provided the necessary budgetary and organizational experience for the administrative and financial components of the proposal. The Consortium's objective at the outset was to make technologies and information available to the research community as a whole as quickly as possible while also ensuring validity. It was therefore important to develop a data-sharing and intellectual-property agreement that would reflect this eagerness to share information while continuing to protect the patent rights of the investigators and their host institutions. The agreement developed by the Consortium (available from [6]), which was readily accepted by all Consortium members, assigns all royalties and other interest to the responsible individuals and also ensures timely publication and public disclosure.

An administrative structure takes care of the day-to-day operations of the Consortium and provides a focal contact point and source of administrative assistance to the Consortium members (see Figure 1). This staff includes an associate director and administrative, fiscal and communications specialists responsible for the day-to-day scientific scheduling, financial and communication activities of the Consortium. With Consortium members distributed throughout the United States and overseas, communication is critical to its success. A state-of-the-art video-conferencing system enables pairs or groups of investigators to meet 'face-to-face' and present and share or exchange data. Most Initiatives have a formal monthly meeting, while subgroups often meet

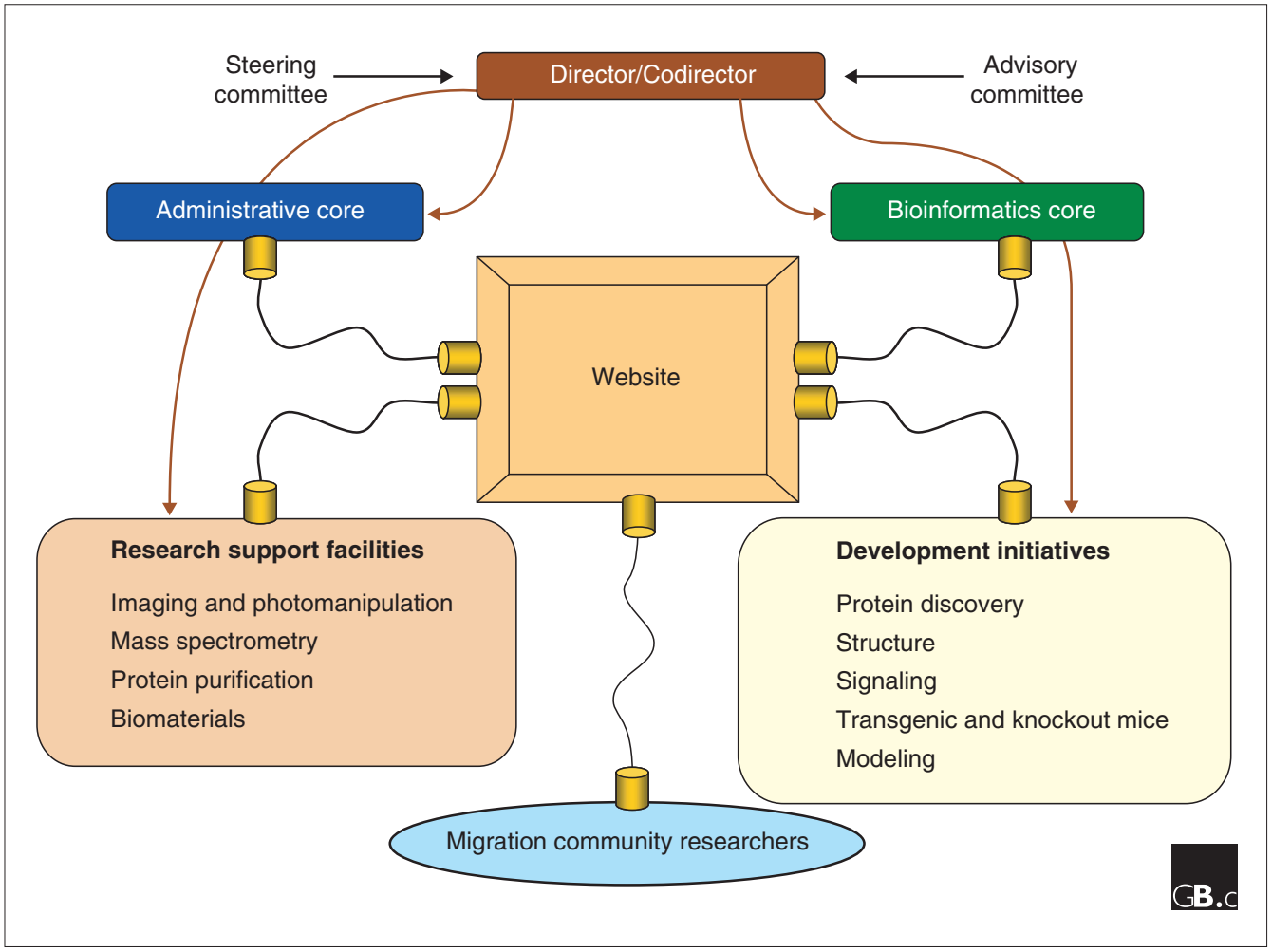

Figure 1
Organization of the Cell Migration Consortium. See text for further details.

more frequently. An internal Steering Committee and an external Advisory Committee provide advice to the principal investigators in the evaluation of progress, setting of annual milestones, allocation of resources, and changes in personnel and research direction. The establishment and evaluations of annual milestones are a key management activity.

The Bioinformatics Core is also critical to the success of the Consortium. This component serves to organize information and data for dissemination to the Consortium and to the community of all migration researchers as a whole. It has become apparent in this first full year of operation that the Consortium's bioinformatics needs will stretch the current state of the art and potentially move it forward. The Protein Discovery Initiative, for example, uses mass spectrometry to identify and characterize the migration proteome, the repertoire of proteins and their regulatory modifications that contribute to cell migration. The plethora of peptide sequences identified by mass spectroscopic analysis of a single immuno-precipitation study must be analyzed to identify particular proteins under differing experimental conditions. The challenges of analyzing and organizing this information alone has required an interdisciplinary approach combining the efforts of cell biologists, biochemists, chemists and computer scientists.

A major objective of the Consortium is to interact with the migration community, with the intention of creating a robust, synergistic discipline. Several strategies are used with this aim, including an annual meeting or workshop, a cell-migration website [6] detailing Consortium activities and progress, and the sharing of all technology, reagents and data developed by the Consortium as quickly as is feasible without jeopardizing quality, but no later than at acceptance for publication. The Consortium has considered several potential venues at which it can present its activities and progress to the public and receive input. On a day-to-day basis, the comprehensive, multi-purpose website provides a

means to interface with the migration field as a whole. Its contents include bibliographies, protocols, educational information, and important publications. In addition, all materials and data developed by the Consortium will be posted on the website and made available to the community upon or before acceptance for publication. In January 2003, the Consortium will sponsor a two-hour afternoon workshop at the Keystone meeting on Cell Migration and Invasion [14]. Finally, the Consortium is open to input from the migration community and investigators from other disciplines for new directions and opportunities for Consortium activities. We anticipate that a number of particularly innovative ideas for new technologies will emerge from the community. A major goal is to identify and facilitate the entry of new investigators, who bring new approaches, into the discipline of cell migration research.

Although it is too early to evaluate the Consortium's progress, the interdisciplinary synergies are already striking and have had great impact on a number of activities. The objectives of the bioinformatics component, for example, have been greatly expanded and incorporate new approaches to organizing migration-related information. The Protein Discovery Initiative has also benefited greatly from its interdisciplinary character and is tackling key problems intrinsic to large-scale mass spectrometry, on the one hand, and developing high-throughput methods for gene discovery using expression techniques, on the other. In this way, the original notion of attacking 'barriers to progress' via interdisciplinary working groups really does seem to be working.

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