The shifting geography and language of cell biology

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With the increase in scientific activity globally, the geographical focus of basic research is shifting away from the West. At the same time, multidisciplinary approaches are uncovering new layers in our understanding of how cells work. How will these trends affect cell biology in the near future?

The molecular biology revolution in the 1950s and 1960s is credited with the transformation of cell biology from a mainly descriptive science to a more reductionist and mechanistic one. This transformation occurred mainly in the United States before spreading to other centers of research. Arguably, the open-ended, basic research–oriented approach of funding strategies at the time, coupled to a pioneering spirit, provided the confidence to explore new vistas of biology without the fetters of finding obvious applications of this research (Bush, 1945). Ironically, it is the very success of this enterprise coupled with the ever-increasing emphasis on the "translational potential" of research that could threaten the research engine that has driven basic research in cell biology. Regardless, the current climate of research funding in the major economies of the world is to bring this investment made in research and development to fruition amid the shrinking funds available for basic and fundamental research.

In contrast there is an expansion of research and development (R&D) expenditure in Brazil, China, and India (Grueber and Studt, 2013). Here, these large, growing economies are still trying to catch up in terms of investment in direct scientific research activity. Brazil has been spending 1.3% of its GDP on R&D. In China, targeted goals have been 2.0% of GDP by 2010 and 2.5% by 2020; today, China spends ~1.6% of its GDP on R&D. In India, a goal of 2.4% of GDP was announced with much fanfare several years ago, but, given the pace of growth in the economy, it has only achieved a 0.8% GDP funding level. Although lower than the proposed pace, it is clear that both of these Asian countries plan to sustain R&D growth in the immediate future.

By 2025, this investment will rival the volume of combined bioscience activity in America and Europe. Asian science (with Japan and South Korea already spending >3.0% of GDP) will certainly emerge as a formidable locus of scientific activity. This has implications for global biosciences in the not-too-distant future. First, we will see a huge expansion in the fabric of biosciences; the people and cultures engaged in biosciences will be stretched across many more continents and ideologies. Second, the confidence in the biological research activity in Asia will continue to grow. This is already on the rise, as clearly evidenced by the huge increase in the number of papers published from Asian countries, with an increasing proportion in top-tier journals. Third, in addition to augmenting the capacity for more conventional cell, molecular, and systems biological research, the increase in the quality and quantity of research in these countries will undoubtedly spur a focus on more geographically defined questions of bioscience research, including those related to biomedical research. How will this shift influence the questions we ask at the cellular level? This is not easy to forecast, but I offer some possible predictions.

India, Brazil, and China are host to some of the world's most diverse habitats, and house some of the Earth's richest biodiversity (Wilson, 1999). We barely know anything about the ecology of the unique terrestrial and marine niches in these regions of the world, let alone how and what is endangered and in need of sustainable conservation. Understanding the cell biology, phylogeography, and population dynamics of diverse flora and fauna will provide valuable insights into our natural world. With the projected increase in basic bioscience research, it is likely that there will be a significant emphasis on understanding the rich biodiversity of these countries if appropriate steps are taken to allocate scientific resources toward these areas of research. This has implications for all of cell biology research, particularly evolutionary cell biology (Brodsky et al., 2012), and in expanding the repertoire of model systems to study specific aspects of cell and developmental biology (Warren, 2015; Fig. 1).

India and China also house some of the world's most diverse human populations. A majority of the questions about

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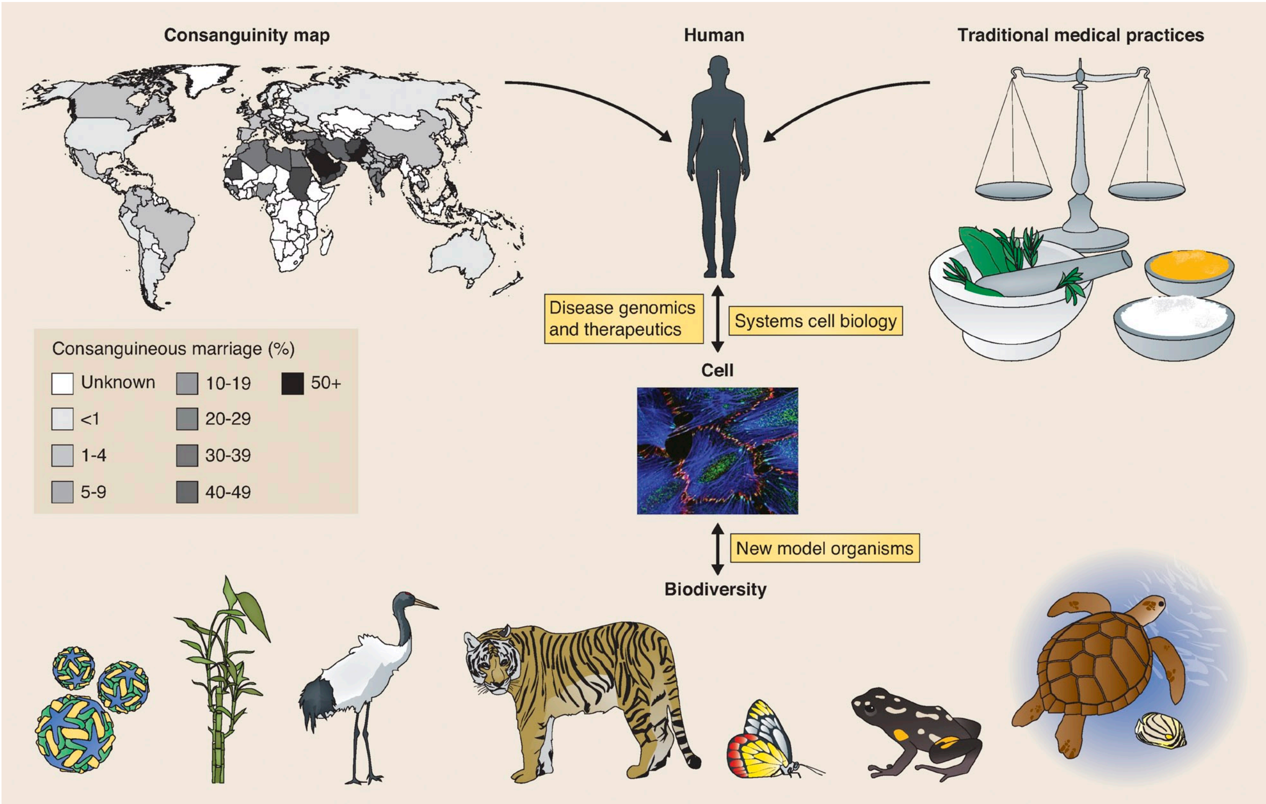

Figure 1. **Expanding the geographical distribution of research activities will broaden the scope of cell biology.** Note that the regions in which research in cell biology is likely to grow are areas where consanguinity rates in human populations are very high (notably in India and some parts of China; map adapted from Bittles and Black, 2010; © Bittles and Black) and are located in regions of high biodiversity (biodiversity hotspots; Wilson, 1999). Both in India and China, traditional medical practices are also very prevalent, and their cellular and molecular bases are now becoming amenable to modern biological analysis. Robust and locally connected research will surely be influenced by these geographical attributes, contributing to new understanding of the genetic basis for drivers of diseases, new opportunities for therapeutics, and uncovering the cell biology of novel model organisms. Micrograph courtesy of Stephan Huveneers.

disease mechanisms have emanated from studies in Western populations. With greater research activity in the East, "omics" technologies can be easily applied to local populations with the help of clinical collaborators. The shifting geography of research will undoubtedly have a great impact here. For example, the high level of consanguinity in south Indian populations (∼10–15%; Fig. 1) offers a unique opportunity to track genetic mutations leading to specific diseases (Bittles and Black, 2010). With the ability to obtain stem cells from adult tissue in order to create appropriate disease models of tissues in a dish, understanding the drivers of diseases at the molecular level becomes a tractable proposition. These systems are already providing very interesting and fundamental insights into basic cell biological process and their relationship to developmental processes in real-life contexts. These studies will undoubtedly pose new questions about disease mechanisms at the cellular scale and could accelerate the "bedside-to-bench" process globally. Indeed, at the Shanta Wadhwani Centre for Cardiac and Neural Research at inStem in Bangalore, as well as several similar centers across the world, interdisciplinary teams are assembling to address the scales of biology necessary to exploit the power of such an approach.

Another interesting consequence of the enlargement of a basic cell biological research environment in Asia is an opportunity to understand the unique traditional medicine practices of China, India, and Tibet (Fig. 1). These practices have been viewed with skepticism by Western medical practice and biomedical scientists. Yet these systems of medicine emphasize an integrative vision of the body, a viewpoint that is gaining traction even in Western medicine. With omics technologies, the cell and molecular underpinnings of these medical systems could be deciphered along with an understanding of how these traditional medical systems may function at this scale. This could in turn inform areas of systems biology and personalized medicine.

These predictions also pose certain challenges. First, sustaining this enormous growth in research capacity requires a highly skilled workforce. Luckily, in both India and China, education is highly valued, making it likely that the manpower for this research will also come from these populous economies with a younger median age, specifically in India. However, a matter of clear concern is the nature of the educational systems in these countries, where, traditionally, the focus has been on rote-based learning in preparation for highly competitive examinations rather than inquiry-based education. This approach will have to change to engage effectively in research.

A major issue faced by cell biologists across the globe now and in the near future is that the language of cell biology today is dramatically different from the 1950s and '60s. It has moved beyond molecular and mechanistic reductionism, and instead a truly interdisciplinary outlook is emerging. Cell biology today positions itself at the interface of physics (soft matter, statistical physics, and complex system), chemistry (physical, synthetic, and analytical chemistry and nano-materials), mathematics (computational methodology to aid explanations based on multiscale simulations, and dynamic systems), engineering (constructivist approaches), and of course genetics and contingent explanations from evolutionary history. The contributions of these disciplines are necessary for a sophisticated understanding of the fundamental unit of a living system. More specifically, deep insights coming from contemporary soft matter physics into the physical and chemical environment of the cell are transforming our capacity to understand cellular processes (Gardel, 2015). In particular, a formal understanding of the role of energy dissipation in creating form and function at the subcellular and cellular level will be central to this revolution. Correspondingly, powerful explanations in biology will emerge from the application of information theory to many biological problems. Although there are some technical challenges to applying these disciplines to biology, once tackled, they will greatly contribute to our ability to manipulate or engineer cells (such as stem cells) into specific tissue types for therapeutic purposes.

Another major shift is the emphasis on studying the cell in its natural microenvironment or developmental context in a multicellular organism, which has become more tractable due to the availability of new in vivo imaging modalities (Megason and Fraser, 2007). Examining the cell in its "natural" context is revealing new principles in cell biology: for example, we are starting to understand the role of the mechanical and chemical environment on cellular physiology (Fig. 2). This is likely to contribute to our understanding of how the environment may shape cell fate and function almost as profoundly as the role of the genetic code (Iskratsch et al., 2014). It is no surprise that a new interdisciplinary initiative to study the role of forces on cell physiology has emerged in Singapore in the form of a Mechanobiology Institute, generously supported by the National University of Singapore.

As a result of these shifts, new educational paradigms will be necessary for the development of the interdisciplinary cell biologist. Are there changes occurring in training programs across the globe? One could argue that in countries that are ramping up their research activities, it might be easier to implement new training programs. I can speak about a shift in the nature of higher education that is taking place in India. An ambitious program started five years ago seeks to locate undergraduate training in the biological sciences in centers where equal emphasis is given to studying chemistry, physics, mathematics, and engineering. The five Indian Institutes for Science Education and Research (IISERs) spread across India and the Indian Institute of Science (IISc) at Bangalore have taken the lead in this regard. If a similar model of exploring research in biological sciences is followed in the 15 Indian Institutes of Technology (IITs), where emphasis is currently placed mainly on undergraduate training in engineering, a clear path for creating the new generation of cell biologists sufficiently versed and confident about natural science may be envisaged. Coupled with educational opportunities, there are a growing number of job and research opportunities in India (Vale and

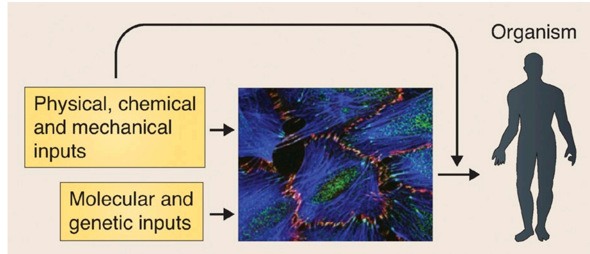

Figure 2. **The changing language of cell biology.** Key to the future of cell biology is understanding the role of the cell's physical and chemical environment in addition to the more traditional molecular and genetic influences. The new interdisciplinary language that is emerging allows adoption of physical and chemical influences into the fundamental molecular and genetic script that determines much of cellular physiology, and provides a way to carry this forward to the whole organism. Micrograph courtesy of Stephan Huveneers.

Dell, 2009) that are ramping up to keep pace with the expanding funding environment for research in India. I imagine that there are similar initiatives in China and Brazil.

The shifting geography of cell biology and the change in its language from the molecular to something more interdisciplinary in nature will define new directions and uncover new mechanisms, thereby bringing vitality to the field. There are exciting times ahead for those with an open mind and an adventurous spirit as we continue our quest to understand the operation of the basic unit of a living system, now even more expansively, in a myriad of native contexts.

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