SCIENCE AND SOCIETY

Post-genomic challenges for collaborative research in infectious diseases

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Abstract | Although high-burden pathogens have been prioritized for sequencing, genomic research has yet to yield effective vaccines, diagnostics or therapeutics for the infectious diseases that burden developing countries. International research partnerships are needed more today than ever before, and we propose that increased participation by scientists in endemic areas would overcome current roadblocks and is an essential path towards translational research outcomes.

The first bacterial genome sequence, that of *Haemophilus influenzae*, was published in 1995. Since then, the rate of microbial genomic research, together with funding for such research, has increased exponentially, and over 2,000 bacterial genome sequences are now publicly available for research purposes through the Genomes OnLine Database (see Further information). Public funding of microbial genomic research has generally been justified based on the promised impact on the prevention and control of infectious diseases worldwide. Genomic data have, however, been slow to yield diagnostics, vaccines and therapeutics for infectious diseases, thereby initiating a shift in research funding priorities towards areas of research that are overtly translational[1].

There are many challenges associated with interpreting and applying genomic data to real-world problems, not least of which is the fact that a single microbial genome does not describe the genetic variation that is necessary for the rational design of globally effective vaccines and diagnostics. New technologies are being used to resequence multiple related genomes[2], but the application of genomic knowledge is still hampered because the limited tools that are currently available for mining and comparing microbial genomes are underused.

The burden of infectious diseases is predominantly borne by the developing countries of Africa and Asia (TABLE 1). In tropical medicine, collaboration with scientists in developing countries is considered to be vital for the translation of clinical research[3], and we argue that such collaboration is also vital for the translation of genomic data into health-related outcomes. Scientists from developing countries need to be directly and equitably involved in collaborative research, and the tools to exploit publicly available genomic data must be adapted for their use. Scientists in developing countries are not only in the best position to determine which questions might translate into impact, but also represent a skilled human resource that could contribute to the at-capacity use of genomic data and could therefore accelerate the development of translational outcomes.

In this Science and Society article, we propose that the potential for developing-country participation in genomic research that is relevant to infectious diseases is underexploited. We discuss the ethical and practical reasons why this must change and highlight some promising and successful initiatives.

Assuring translational outcomes

Tremendous progress was made in elucidating the pathogenesis and subsequent control of a number of deadly diseases in the past century. Examples of early and successful collaborations include research into yellow fever and cholera. These collaborations were often driven by the paternalistic interest of imperialism rather than altruism, but are useful models because they illustrate how scientists based in different parts of the world, including endemic and under-developed countries, can use emerging technologies to effectively battle a challenging infectious disease problem (BOX 1). By contrast, when collaborations are weak or under-developed, progress is stalled (BOX 2).

If translational outcomes are to be assured, the traditional paradigm for biomedical research must be connected to the outcome. For cholera and Lassa fever (BOXES 1,2), observation and phenotypic characterization of a whole organism and its virulence factors in the laboratory occurred in tandem with field and clinical testing. Genomic research has moved away from considering only single factors towards the evaluation of genomes and systems, which makes it essential, rather than only desirable, to recruit different types of expertise to focus on a single problem. As new technologies are developed to address this new scale of research, field research must be scaled up in parallel. If we are to

Table 1 | **Pathogen sequencing projects targeting infectious diseases that affect developing countries***

Pathogen	Year first genome was published	Europe		Africa		South-East Asia	
		Cases	Deaths	Cases	Deaths	Cases	Deaths
Haemophilus influenzae	1995	4,000	Data not available from source	34,000	Data not available from source	17,000	Data not available from source
Mycobacterium tuberculosis	1999	559,000	~68,400	1,528,000	~350,000	2,777,000	~599,000
Plasmodium spp.	2002	0	0	357,180,000	~1,135,000	28,519,000	~65,000
Bordetella pertussis	2003	2,768,000	~140	13,056,000	~131,000	9,803,000	~111,000

*Mortality and morbidity data from the WHO global burden data for 2002.

address tropical infectious diseases, scientists in endemic regions must be placed at the core of the research process, which could be envisaged in a Koch's postulates like framework.

First, an association between a genetic entity (for example, a plasmid, genomic island, regulon, single gene or even a single-nucleotide polymorphism) and a clinical feature or epidemiological signature is identified by analysing genome-wide variation in collections of strains in the context of clinical data from field studies in an endemic region.

Second, the genomic entity from the pathogen is introduced into a neutral microbial background and shown to reproduce an aspect of the predicted clinical phenotype in a laboratory model.

Third, for final 'proof', the association between the genomic element and the clinical phenotype is shown again in a second population in a study that is designed to validate this specific association in an endemic region.

Finally, the findings form the basis for an experimental diagnostic, drug or vaccine target that can be tested in an endemic region.

The addition of the last, application-driven postulate is an idea that was pioneered by Daniel Salmon[4], who devised a more stringent version of Koch's postulates to infer causation. This translational postulate requires a mechanism to destroy the pathogen or block disease and underlines the need for demand-driven research.

All but the second of these postulates must be fulfilled in endemic areas, as they require systematically and appropriately collected field data. The collection and evaluation of field samples is a painstaking and often underestimated task that is inadequately rewarded, even though it defines the research that can be carried out and must therefore be considered at the inception of the research idea. Although some research material can be obtained from diagnostic laboratories, these laboratories are in short supply, are inadequately resourced and might not have a research agenda[5]. The identification of bacterial isolates in a diagnostic laboratory must be timely and clinically useful, whereas absolute identification is necessary for the development of diagnostic tests or establishment of vaccination priorities. Combining research and diagnostic facilities in centres of excellence is perhaps the best solution in limited-resource settings, but this requires a certain level of science education in schools and the provision of university departments that are linked to hospital and public health laboratories. From the perspective of UK-supported science, the Wellcome Trust Major Overseas Programmes and the Medical Research Council Unit in The Gambia (see Further information) are examples of research centres that also provide competent diagnostics for patient care and support clinical trials in hospital or community settings. These centres of excellence have an obligation to teach and to use the most relevant techniques to investigate locally prevalent infections. If these techniques include genomic capability, then it is vital that funding agencies, both from developing and developed countries, support such initiatives.

Box 1 | **Cholera: a long-standing global research initiative**

Cholera is an ancient pandemic disease[29]. In the nineteenth century, Rudolf Virchow[30] examined Indian intestinal biopsies that had been shipped to him in Germany and concluded that intestinal damage was a hallmark of cholera infection. Only when similar studies were performed at the site of an epidemic in Asia did it come to light that Virchow's specimens had deteriorated in transit and that the cholera bacillus did not damage the mucosa[30]. Analysing the composition of rice-water stools at an epidemic site in Thailand in the 1950s was the first step towards understanding the need to replace electrolytes during a bout of cholera, and paved the way for the simple but effective rehydration protocols that are used today[31]. Thus, the value of "taking science to where the diarrhoea is" (REF. 32) was clear early on in cholera research.

With this objective, a cholera research laboratory was established in Dhaka in 1960. The laboratory became the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B) in a charter that was ratified in 1978 by the Bangladeshi government and the United Nations Development Programme (UNDP)[33]. The ICDDR,B was established after the aetiological agent, the mode of transmission and the fundamentals of cholera treatment had been established. The centre has been instrumental in implementing life-saving oral rehydration therapy and in elucidating many facets of *Vibrio cholerae* biology[33], and was the essential base station for the discovery of the marine reservoir of *V. cholerae*, a finding that required years of observation of the bacillus in the Bay of Bengal[34].

The discovery and characterization of cholera toxin, the virulence factor that is sufficient to cause the disease, began in two independent Indian laboratories, which paved the way for vaccine development, and was completed in the United States[35–38]. US-based cholera researchers uncovered accessory virulence factors and mobile elements that are involved in pathogen evolution, as well as one of the most intricate and sophisticated bacterial regulatory networks, a requirement for an intestinal pathogen that must thrive in marine and brackish environments. It was obviously essential to return to the Bay of Bengal to establish the mechanisms by which pandemic cholera strains evolve in the wild. International collaborative studies were used to unravel the mystery of why cholera epidemics appear, mushroom and then subside of their own accord[39,40].

Several features characterize the successful and continuing collaborations that have been promoted over the past 100 years of *V. cholerae* bacteriology and pathogenesis research. Cholera is life-threatening, and although the disease is predominantly a problem in developing countries, the threat of a pandemic remains worldwide. Cholera is entirely preventable and treatable, and therefore there is little hesitancy in sharing research materials. An international research station in the part of the world that is most affected by the disease was justified and built at a time when early findings had begun to impact treatment and the disease had been eliminated from Europe and North America but was recalcitrant to control in developing countries[33]. The interdependency of developing- and developed-country research efforts was recognized and nurtured by dedicated, talented and productive researchers with a culture of sharing expertise, knowledge and materials with each other and from one generation to the next. Additionally, *V. cholerae* and the cholera toxin have been developed and applied as biological models and tools, as well as being studied for their basic biology. These factors have ensured that cholera research remains innovative, cost-effective and truly global.

The need for collaborations

Fifty years ago, the molecular biology revolution promised to advance medicine, and this promise has been fulfilled. To those who deliver health care in the poorest countries of the world, however, the advances that have been made seem "more theoretical than real" (REF. 6), and the disparity between biomedical knowledge and improvements in health care has even widened in developing countries since the genomic era began. A recent brainstorming exercise by experts produced a list of the *Top 10 Biotechnologies to Improve Health in Developing Countries within a Decade*[7]. Most of these biotechnologies have direct ties to genomic research and 'top of the list' was molecular diagnostics. Better diagnostics could have a considerable impact on health delivery and disease control, and the time from target discovery to product development is typically shortest for diagnostics.

Despite increased awareness of the '10/90 gap', which refers to the fact that only 10%

Box 2 | **Lassa fever: the rise and fall of endemic-area research**

Compared with cholera, the history of Lassa fever is brief. Lassa fever was first recorded in a hospital-amplified outbreak in Northern Nigeria in 1969. Infections had undoubtedly occurred before this time in West Africa but it was only from the 1969 outbreak that the causative agent was identified. Initial studies on the virus were based at the Arbovirus laboratory at Yale University in the United States. A serological survey of former UK missionaries was used to estimate the geographical distribution of the virus but the need for endemic-area research quickly became obvious. The US Centres for Disease Control and Prevention engaged in long-term research, with field outposts in Sierra Leone and collaboration with the Virus Research Laboratory at the University of Ibadan, Nigeria. Kenema hospital in Sierra Leone soon became the world centre for Lassa fever disease management and clinical research. The number of staff at the hospital dwindled as the Americans returned home, but it continued to function and was headed by Sierra Leonean Aniru Conteh, who was trained in Ibadan, Nigeria[41]. As a result of endemic-area research, the Lassa fever virus and its vector, the *Mastomys* rat, are known and risk factors for nosocomial outbreaks have been defined[42,43]. The antiviral ribavirin has been identified as an effective treatment when administered early in infection.

Cholera is far from optimally controlled worldwide, but Lassa fever research is in a worse situation. Soon after Conteh acquired Lassa fever through needle-stick injury, and lost his life to the disease in 2004, research all but ended in Sierra Leone[41]. The University of Ibadan, once a world centre for tropical virology, is one of many victims of the decline in educational and research infrastructure in Nigeria. This decline has been paralleled by a regional decline in diagnostic infrastructure and care facilities for patients with Lassa fever.

Lassa fever research was established in endemic areas with a small, local research force, which did not grow. Few research findings were translated into large-scale preventive or curative impact in endemic areas, even though a tentative estimate suggests that up to 3 million cases and 67,000 deaths can be attributed to this disease across West Africa each year and there have been over 20 exported cases of the deadly haemorrhagic disease in recent history[44]. Endemic countries have had little incentive to support the research effort, which faded away when international participation dwindled. There have been recent initiatives to revive Lassa fever research in endemic areas[45], but these will have to begin almost from scratch, rather than build on existing infrastructure. The question of how to motivate global research that impacts disease control and patient care is an important one in the current age when imperialism is out of fashion, neo-colonialism is unacceptable and true global interest has yet to be inspired.

of global biomedical research resources are used to investigate 90% of the world's health problems, this gap persists[8]. Resource-intensive genomic research programmes that are based in, and address the problems of, developed countries have easy access to technological infrastructure and might be partly responsible for maintaining the 10/90 gap. International collaboration with these programmes could narrow this gap in several ways. Collaboration would make it possible for researchers in developed countries to ensure that, irrespective of the technologies that are used, resources are directed to areas of global importance. Researchers from developing countries, who are either under-represented in the global genomics research community or have difficulties accessing it, would therefore be able to contribute productively. Well-executed multi-participant research projects typically have outcomes that surpass their initial goals because the best collaborations are synergistic. Finally, in addition to the mutual benefits for all partners, successful research that is carried out in developing countries has the potential to produce further technological growth, which could have an impact on health, education, agriculture and the industrial sector.

The term collaboration should be qualified as those associations in which there is true partnership. Just as the idea that developed-country partners are 'providers' and developing-country partners are 'takers' is a shaky foundation on which to build long-lasting and effective collaboration, so is the 'Cinderella and the Ugly Sisters' idea that scientists from developing countries are generally exploited[9] and cannot function within existing frameworks. It is important that supporters of collaborative biomedical research institutions and researchers view a collaborative partnership as a way to make mutual gains and mutually build capacity[9,10].

Using genomic data

Knowledge, and genomic information in particular, has been described as a global public good[11]. However, several indicators show that scientists from developing countries are not using genomic information or the tools that are available to analyse genomic information. There is no ideal way or tool to capture the 'use' of information, as not all productivity is, or should be, measured by the standards of academics from developed countries. Nonetheless, we have observed that scientists from developing countries in endemic regions are less likely than those from developed countries to be authors of indexed papers that cite the *Plasmodium falciparum* or *Salmonella enterica* subsp. *enterica* serovar Typhi (*S.* Typhi) genome papers[12,13] (FIG. 1). For those that cited the *P. falciparum* paper[13], only 18, 13 and 9 of the 69 African-based authors were first, corresponding or last author, respectively, and, although most papers had 5 or more authors, only 24 (2.6%) papers included more than 1 African author. Authors from Asia, which is a part of the world that is most affected by typhoid fever, were similarly under-represented among authors who cited the *S.* Typhi genome paper. We found that a typhoid fever review (FIG. 1), which was published soon after the genome paper[14], was cited most often by papers that included at least one Asian author; this is consistent with the idea that Asian researchers are using information on typhoid fever but are less likely to use genomic information that is related to *S.* Typhi.

Artemis (see Further information) is a freely available, Java-based tool that is used to browse, annotate and analyse genomic data[15]. It can be run off-line, which is important for scientists who might not have affordable, reliable or high-speed internet access, and training workshops are run both in the United Kingdom and in developing countries (see Further information for a link to Wellcome Trust Advanced Courses). Although many Artemis users might not publish their research, several do. Again, when we examined citations of the paper that first described Artemis[15], we found that 83% of authors were based in Europe or North America, whereas only 4% were based in Africa. Surprisingly, despite well-developed bioinformatics sectors in India and China, less than 10% were based in Asia. The number of downloads for Artemis in 2007, which were not confounded by acknowledged publication biases, were 124 in Africa, 3,053 in Asia, 12,686 in Europe, 9,741 in North America, 1,737 in South America and 845 in Oceania. Overall, the data suggest that the limited use of genome data in publications from developing countries is not being overcome by open access alone. It will be interesting to see whether the Artemis workshops that were held recently in developing countries will have an impact.

Although there have been earlier observations about the dearth of genome-paper authors from developing countries, it is important to acknowledge that genomic

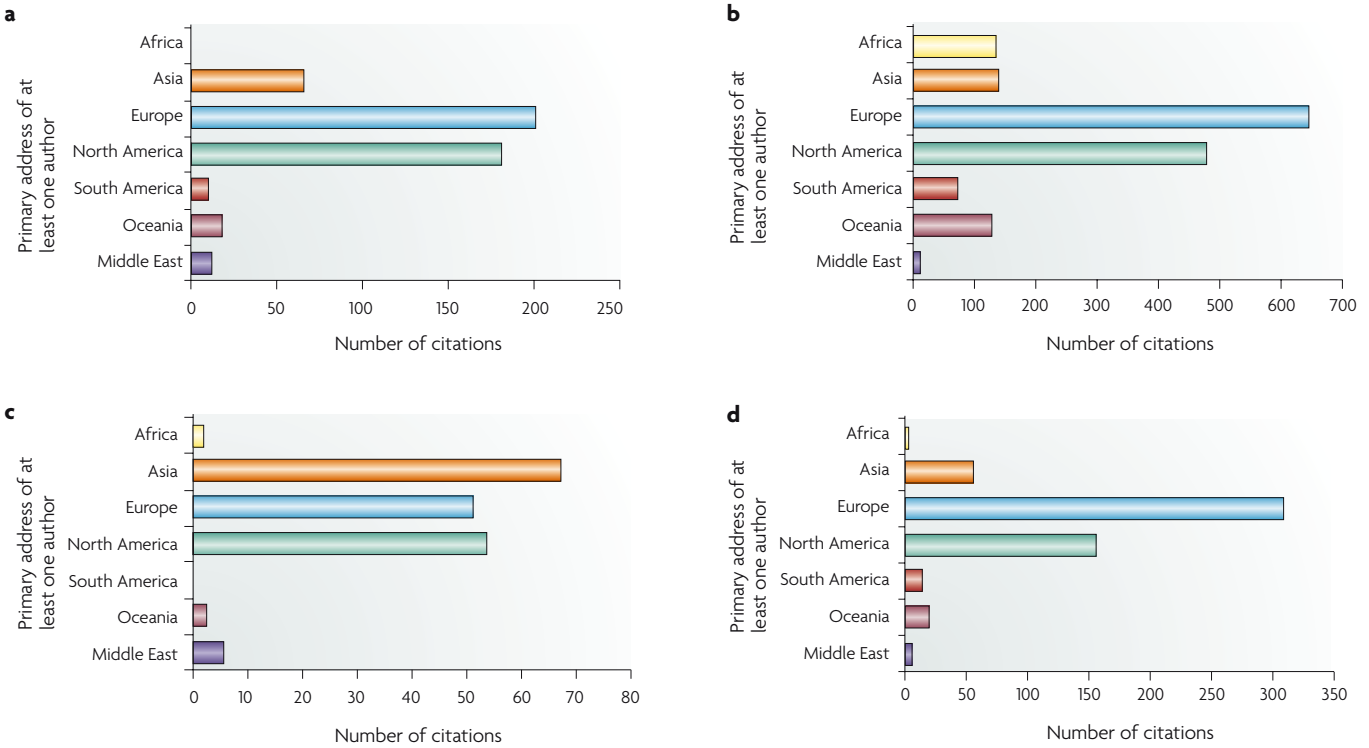

Figure 1 | **A comparison of the use of genomic and clinical information in different regions of the world.** ISI (Web of Science)-indexed papers that cite the *Salmonella enterica* subsp. *enterica* serovar Typhi genome paper[12] (**a**), the *Plasmodium falciparum* genome paper[13] (**b**), the most-cited typhoid fever review[14] (**c**) and the Artemis sequence viewer and annotation tool paper[15] (**d**).

data are generated by few centres worldwide and that these do include some institutions from developing countries[16,17]. Furthermore, the provision of data on open-access sites has made it possible for scientists from all types of institutions to apply these data to their research. Other than genomic sequence centres, which are only a 'spark for change', the flames of the genomic revolution will be fanned not by the generation of data but by the use of these data by a broader scientific community to address biological problems. It is therefore the application of, rather than the lack of participation in, genome sequencing by scientists from developing countries that gives us most cause for concern.

Drivers of research collaboration

Current research is often resource, rather than need, driven. It is too soon to rigorously assess genomic research along these lines, but important lessons could be learned from intercontinental research programmes in other biomedical disciplines. Jentsch and Pilley[9] presented a case study of a failed project in which the individuals who were to perform most of the bench and field research, and the major beneficiaries of the research, had not contributed to research prioritization or project design. Subsequent remodelling of the project design with improved cultural insights allowed the project to succeed and enabled mutual capacity building[9].

Research projects that incorporate a genomic approach are typically large, high-budget initiatives. Intellectual input into co-conceived, expensive projects is often biased towards collaborators with better access to, and more experience of attaining, funding, rather than those with closer proximity to need[18]. Thus, partners from developed countries are often in a better position to have creative input because of their material and logistic input. By being slightly less averse to risk, funding agencies could encourage well-funded research programmes and institutions to be more flexible, more adaptable and therefore more accommodating of potentially unexpected requirements from comparatively resource-poor partners. One of the keys to successful research collaboration is to be reactive to needs as they become apparent.

Because the availability of resources is one of the main driving factors for collaboration, middle- and low-income countries are unlikely to address shared health problems collaboratively[19]. The director of TWAS (the academy of sciences for the developing world; see Further information) proposed that the scientific gap between high-income countries and developing countries is narrowing[20], but observed that this is because Argentina, Brazil, China, Cuba, India, Malaysia, Mexico and South Africa are the successful part of an emerging 'south–south' gap. This provides an opportunity for collaboration between researchers with similar problems from either side of this new divide.

Equitable partnerships

Following initial contact, an authentic collaboration is built on mutual respect and benefit. Although responsibilities can vary among participants in a collaboration, each partner must see that the other brings essential and otherwise unobtainable skills and knowledge[21]. In spite of the structural inequalities that arise from uneven distribution of research resources, it should be noted that funding agencies, as well as the researchers they support, need to be aware that researchers in less-affluent countries do make contributions and even build capacity in richer countries[9].

In our experience, a typical collaboration between a large institution (such as a genome research centre) in a developed country and an institution in a developing

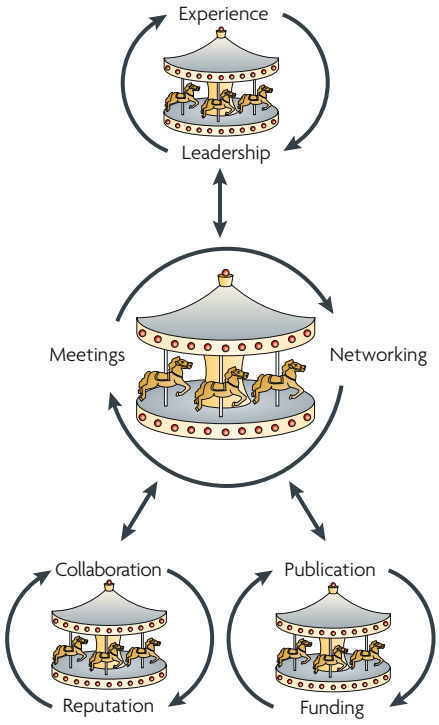

Figure 2 | **The merry-go-rounds that make it difficult for qualified outsiders to enter the research arena.** Fast-moving, inter-related merry-go-rounds prevent scientists from developing countries from participating in productive research. Unless the merry-go-round slows down or they break into a run, obtaining a ride is almost impossible. The objective for inclusive research must be to allow scientists from developing countries onto some of these merry-go-rounds, as this will allow access to others. Perhaps the easiest way to participate in collaborations is to network at meetings.

country (such as a teaching hospital) starts with personal contact between partners at a conference (FIG. 2) or after publication. Either party can initiate the contact but the progression is often made from initial discussions about what is possible and what needs to be done to what can be funded and what outputs could be expected. Most collaborations begin informally with discussions between sessions at scientific meetings, but participants in a collaborative enterprise might have different objectives. A partner from a developed country might seek to advance knowledge on a particular infectious disease in an under-studied area and ultimately make a novel contribution to the scientific literature as part of a long-term focused research programme. A partner from a developing country might be more interested in improving the understanding of an infectious disease in his or her local area to inform public health. The desired output for the partner from the developed country would be a scientific paper in a widely accessed and well-regarded scientific journal. However, such a journal would be unlikely to be read by health policy makers in the endemic area, and therefore the scientist from the developing country might wish to prioritize the preparation of a more accessible report. As both papers are not mutually exclusive, there is no reason why the desire for one should preclude the other, but the possibility of different objectives must be appreciated from the outset.

Dissemination of results and conclusions by publication is an important goal in collaborative projects that are based on the developed-country research model, as without papers, securing and maintaining funding is almost impossible, and without funding, research is imposible. However, the application of journal publication quality and quantity requirements and other developed-country measures of success can shift control from the developing-country partner to the developed-country partner. Such a shift could reduce skilled developing-country scientists to field assistants or little more than specimen collectors and thereby create inequitable partnerships[22]. This inequality can be amplified by the publication funding cycle, which is one of many fast-moving merry-go-rounds that make it difficult for qualified outsiders to enter a research arena (FIG. 2). Unless the excluded individual manages to 'break into a run', or the merry-go-round slows down, it becomes difficult to make the successful leap into high-impact research. Research-project design and leadership is often left to the 'experienced' partner, whose 'experience' can lead to outcomes that are of lower priority for other partners. This, in turn, typically leads to publications being written and submitted by the partners from developed countries, with the attitude that authorship is a 'just reward' for the involvement of scientists from developing countries[23], and thus an inequitable partnership is created. The ideal collaboration would involve equal input, or at least the potential for equal input, from each partner at each stage, permit the desired outcomes of each partner to have equivalent weighting and promise a fair share of credit to each participant.

Enhancing collaborative potential

Many of the roadblocks that scientists from developing countries face in integrating their work into developed-country-designed and developed-country-dominated structures are cultural. Integration should be smoothed for partners who are unfamiliar with developed-country research etiquette and, more importantly, the developed-country model needs to be adapted to other scientific research cultures. Discussed below are practical steps that could enhance the ability of scientists from both developing and developed countries to build fruitful collaborative links and complete genomic projects that impact global health.

Online and open-access information. Research outputs are cumulative and interdependent. Access to knowledge from previous and on-going research therefore spurs current and future research. The advent and expansion of open-access scientific literature has been a levelling advance for researchers in global research. Many genomic scientists and most funding agencies have joined the effort to assure accessibility to their data, so that most of the available sequence data, many of the computational tools that are required to analyse genomes and some 'post-genomic' wet-laboratory data are now freely available. Indexing regional journals from developing countries has also expanded access to knowledge. Researchers from developed countries now have access to abstracts and in some cases full texts of work published by researchers from developing countries who might be prospective collaborative partners. The internet has been criticized for creating a digital divide. However, the postal and telephone systems in many countries are too ineffective or unreliable to support communication and information access for a vibrant research collaboration, and in these cases, the internet, even when difficult to access, can be levelling.

International research networks. Over the past 50 years, cholera research has benefited from an informally constructed but vibrant network that allows materials and techniques to be shared and innovative and productive collaborations to be stimulated (BOX 1). Formal research networks also exist, but it is often difficult to prevent them from becoming developed-country dominated[18]. Online networking databases, some of which are specifically tailored for scientists, also offer promise. For example, Scientists Without Borders (see Further information) has the explicit objective of fostering international collaborations that include scientists from developing countries. One model, which was the basis for the African Health Research Forum (see Further information), is to create developing-country

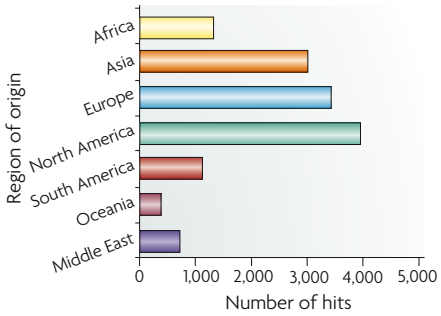

Figure 3 | **Success of a journal that is aimed at scientists from developing countries.** The number of 'hits' on the web site of the open-submission journal the *Journal of Infection in Developing Countries*.

networks, which might enable south–south collaborators to gain collective access to the broader scientific community. More recently, a semi-formal *Salmonella* network (see Further information) was built with the primary goal of recruiting predominantly, but not exclusively, in developing countries. Scientists from developing countries in the network articulated the pressing need for a truly international publication outlet that was tailored to their needs and would counterbalance the low rates of acceptance in existing highly ranked international journals. The subsequent list-serve discussions led to the conception of the *Journal of Infection in Developing Countries* (see Further information), the editorial board members of which are drawn predominantly from middle- and low-income countries and which involves a unique enhanced peer-review process that includes manuscript mentoring, as well as open access and charge-free publication[24]. Analysis of web-site hits suggests a worldwide readership that includes scientists from both developed and developing countries (FIG. 3).

Research-focused training programmes. Numerous training programmes, including genomic, bioinformatic and molecular biology initiatives, are targeted at, or implemented in, developing countries, and it is impossible to discuss them all. However, it is clear that the need for research-focused training programmes is yet to be satisfied. Purpose-designed workshops are currently the main method that is used to introduce new technologies to many developing countries. Ultimately, isolated, piecemeal training programmes cannot solve the continued need for true expertise. Academic centres in developing countries, which are driven by local need, must be invested with the ability to train the next generation of academic researchers. Undergraduate and graduate curricula must be modified to include updated and relevant courses in molecular biology and bioinformatics, and local faculty must therefore be trained to teach these courses. When training becomes integral to sponsored research, participants will have the immediate opportunity and facilities to apply newly gained skills to problems. This would provide them with greater dexterity and opportunities to tailor protocols to local needs and increase the chance that they will gain sufficient competence to train others and lead new initiatives.

Conferencing in developing countries. One of the reasons why scientists from developed countries carry out little research in developing countries is their unfamiliarity with foreign terrain and difficulty in accessing partners. These could be overcome by a model that is currently implemented by Mangosteen (see Further information), which organizes biomedical research conferences in resource-poor developing countries to enhance the participation of local scientists and permit scientists visiting from developed countries to engage in discussions with scientists from developing countries and become familiar with 'on-location' resources and challenges.

Exploiting collaboration builders. Potential contributions from scientists from developing countries who have migrated to work in developed countries are currently underexploited. The knowledge that these scientists have of their home countries and of global research etiquette can mean that they are well-suited to be participants in international collaborative efforts[25]. However, most of these scientists are not involved in collaboration building or in developing scientific infrastructure in their home countries; they express interest in doing so but lack the organizational infrastructure and motivation[26]. Developing ways to involve younger diaspora scientists with recent contacts to their host countries, without hurting their careers, could further enhance international collaborations.

Conclusions

In 2003, Varmus *et al.*[27] published a list of 14 important technological roadblocks that must be overcome to advance global health. In an initiative from the Bill and Melinda Gates foundation, these roadblocks became the Grand Challenges for Global Health (see Further information), which were announced at a time when genomic science was in its infancy but molecular biology was well established. These challenges therefore represent roadblocks that earlier technological advances of the twentieth century did not overcome. Pang[18] has suggested that the application of knowledge to health and disease is a separate research challenge and proposes that application of knowledge, rather than technological roadblocks, is the limiting factor for impact in global health. With the sequencing of the *Plasmodium*, *Anopheles* and human genomes, new drug, diagnostic and therapeutic malaria targets came to light almost immediately[28]. There is hope that in the long-term, genomic science will improve the quality of life of most people on the Earth, in part, by releasing them from the burden of infectious disease. Furthermore, genomics has increased both the portability and scale of molecular science. Given that an earlier promise from the molecular biology revolution remains largely unfulfilled, it is not enough to hope that the enduring, balanced, intercontinental collaborations that are needed to ensure translational outcomes will be built of their own accord. They must be strategically stimulated and carefully nurtured. In the long-term, successful collaborative, genomic-scale research projects will enhance the regard of all those who are involved, in the eyes of international funding agencies and endemic-country health systems. Such projects are more likely to generate diagnostics, vaccines or therapeutics than partner scientists who are working independently. Cross-continental collaborations therefore offer the prospect of a win–win situation that could accelerate health-related gains from genomic research.

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DATABASES

Entrez Genome Project: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=genomeprj
Haemophilus influenzae | *Plasmodium falciparum* | S. Typhi | *Vibrio cholerae*

FURTHER INFORMATION

African Health Research Forum: http://www.afhrf.org/
Artemis: http://www.sanger.ac.uk/Software/Artemis/
Genomes OnLine Database: http://www.genomesonline.org/gold.cgi
Grand Challenges for Global Health: http://www.gcgh.org/Pages/default.aspx
Journal of Infection in Developing Countries: http://www.jidic.org
Mangosteen: http://mangosee.com/mangosteen/index.htm
Medical Research Council Unit in The Gambia: http://www.mrc.ac.uk/AboutUs/UnitsandCentres/UnitCentreDetails/MRC002099
Scientists Without Borders: http://scientistswithoutborders.nyas.org/Splash.aspx?ReturnURL=/default.aspx
The *Salmonella* Network: http://www.oloep.org/salmnet.asp
TWAS: http://www.twas.org/
Wellcome Trust Advanced Courses: http://www.wellcome.ac.uk/Professional-resources/Courses-and-conferences/Advanced-Courses/index.htm
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Iruka N. Okeke's homepage: http://www.haverford.edu/faculty/iokeke

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OPINION

What really happens to dendritic cells during malaria?

Michelle N. Wykes and Michael F. Good

Abstract | As dendritic cells (DCs) initiate all adaptive and some innate immune responses, it is not surprising that DC function during malaria is the subject of intensive investigations. However, the results of these investigations have so far been controversial. Here, we discuss various aspects of these studies, including the influence of the species and strain of *Plasmodium* on DC function, the effects of *Plasmodium* infection on the activation of $CD8^+$ T cells by DCs, the effects of haemozoin and the effects of *Plasmodium* infections on DC Toll-like-receptor signalling.

Malaria affects 300–500 million people and causes more than 1 million deaths per year, mostly in children younger than five. The disease is caused by parasites of the genus *Plasmodium*, which are transmitted by the bite of an infected anopheline mosquito. Four species infect humans: *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale* and *Plasmodium malariae*. The parasite first develops in the gut of the mosquito and is passed on in the saliva of an infected insect each time it takes a new blood meal. This asexual stage of the parasite life cycle, which is known as the sporozoite, is then carried in the blood or lymph to the host's liver, where it invades hepatocytes and multiplies. After approximately 1 week, sporozoites develop into merozoites, leave the liver and invade red blood cells (RBCs), where they again multiply, progressively destroying infected RBCs. This results in bouts of fever and progressive anaemia in infected individuals. By adhering to the endothelia of diverse host organs, infected RBCs can be sequestered from the peripheral circulation, which is an important pathogenic mechanism. The obstruction of blood