

Look west: UK-Brazil tropical medicine and parasitology

Workshop report

December 2011

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São Paulo Research Foundation – FAPESP – is an independent public foundation with the mission to foster research and the scientific and technological development of the State of São Paulo.

SIN Network

The Science and Innovation Network (SIN) is a network of UK national and locally engaged staff, who are based in UK Embassies and Consulates abroad. It comprises almost 100 staff who work in British Embassies and consulates around the world, in some twenty five countries of scientific interest. The Network's purpose is wide ranging, and involves science diplomacy and fostering collaboration in science and innovation.

This summary sets out the discussion at the associated workshop and does not represent the corporate position of the Academy of Medical Sciences, FAPESP or SIN.

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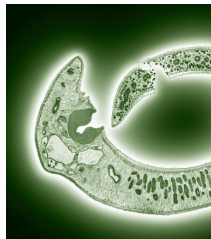
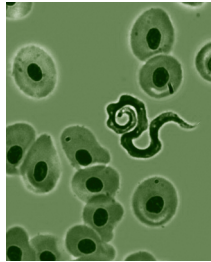
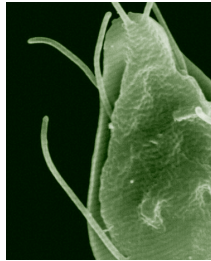
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Summary

The rapid recent expansion of science in Brazil and the UK's long standing scientific strength offer significant opportunities for research collaborations. One area of mutual strength for both the UK and Brazil that offers fruitful opportunities for partnership is tropical medicine and parasitology. To help harness the opportunities for scientific alliances between tropical medicine and parasitology researchers in the UK and Brazil the UK Science and Innovation Network (SIN), Fundacao de Amparo a Pesquisa do Estado de São Paulo (FAPESP) and the UK Academy of Medical Sciences held a two day workshop on this topic in São Paulo, Brazil. This document provides an outline of that meeting.

The workshop participants identified a number of scientific opportunities for collaborative research:

- Fundamental studies on *Plasmodium vivax* (*P.vivax*).
- Anti-malarial drug candidates that have potential to kill the parasite at multiple lifecycle stages.
- Inflammatory and immune responses to malaria.
- Cytoadherence of malaria infected blood cells to the lining of small blood vessels.
- Helminth biology, in particular *Schistosoma*.
- Genomic and post-genomic biology of *Leishmania*.
- Mechanism of transmission of leishmaniasis, particularly in animal hosts.
- Immunology of leishmaniasis, including vaccine development.
- Development of agents to treat leishmaniasis and Chagas' disease.
- Use of genetically modified yeast to aid design and development of drugs against parasitic diseases.



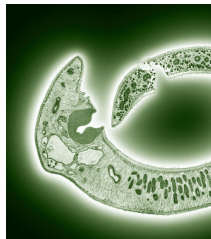
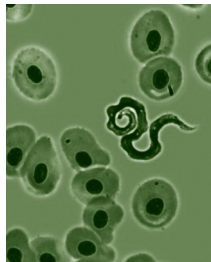
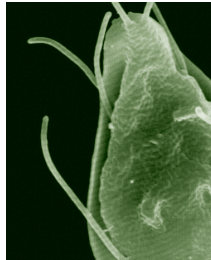
The workshop participants also identified a number of measures that might strengthen tropical medicine research collaboration between the UK and Brazil including:

- Highlighting existing international research agreements and opportunities for collaboration.
- A summer school for young scientists.
- Databases to help identify potential research partners.
- Building technical expertise.
- Facilitating the mobility of researchers.

Background

Dynamic scientific growth in Brazil and a strong research base in the UK have, in recent years, contributed to a considerable increase in scientific collaborations between the two countries.^{1,2} The UK has recently overtaken France as Brazil's second largest overall research partner, after the USA, with the number of co-authored papers more than doubling since 1999.³ Data published by the UK Department of Business, Innovation and Skills (BIS) show that these collaborations increase the impact of scientific publications. For example, when working with Brazilian scientists, the impact of publications by UK scientists is multiplied by 1.3, more than with many other 'BRIC' (Brazil, Russia, India, China) countries. The recent agreement between the UK and Brazil to facilitate scientific collaboration, signed by Research Councils UK (RCUK) and FAPESP, is a step forward that needs to be better known among medical scientists in the UK, especially given other successful Brazilian agreements with nations such as France, Germany and Canada.⁴

Substantial increases in funding and a raft of policy measures introduced to encourage science and innovation from the late 1990s are helping to transform Brazil into a major scientific power.⁵ Between 1997 and 2007 Brazil's scientific output and funding more than doubled, although very recently federal funding for science has been cut.^{6,7,8} Every year Brazil produces over 500,000 new graduates and about 10,000 new PhD researchers – similar numbers to France and South Korea.⁹ The strong Brazilian commitment to science is illustrated by the State of São Paulo that generates over half of Brazilian science much of which is funded by FAPESP - the state research foundation that receives 1 per cent of state tax revenues.¹⁰ The rapid expansion of science in Brazil offers opportunities for partnerships with the UK - that is second in the world in terms of scientific quality and impact, is distinguished by over 30 Nobel Prize winners and created nearly a quarter of the world's top 100 medicines.^{11,12,13} As international science becomes more multipolar the UK must look for opportunities beyond its traditional partners.



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One area of mutual scientific strength for both the UK and Brazil that offers opportunities for scientific collaboration is tropical medicine and parasitology. Complementary strengths in these areas present a focus for partnerships between the UK and Brazil that would increase the scientific impact of such work and provide significant health and economic benefits. Brazil is responsible for 18.4% of the world's scientific output in tropical medicine and 12.3% of the world's scientific output in parasitology; while the UK has a long history of excellence in research in these areas.¹⁴ In light of these important developments, the UK Government Science and Innovation Network (SIN) office for Brazil, FAPESP and the Academy of Medical Sciences decided it would be timely to hold a joint workshop in tropical medicine and parasitology to explore research collaboration between the UK and Brazil. The workshop consisted of two days of discussions between senior investigators from Brazil and the UK, and discussions with research leaders at FAPESP and institutions in São Paulo. The scientific opportunities presented in this paper are specific for tropical medicine and parasitology, but the suggestions for mechanisms that might increase collaboration are applicable to other areas of biomedical science.

Scientific horizons for UK and Brazilian tropical medicine

The workshop participants identified a number of scientific opportunities for collaborative research in tropical medicine and parasitology that are set out below. These are intended to illustrate potential areas for future research collaboration rather than provide a comprehensive review list of all such opportunities:

Malaria

Plasmodium vivax

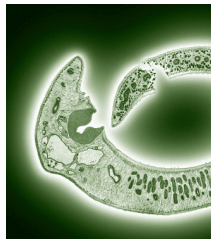
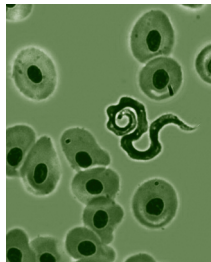
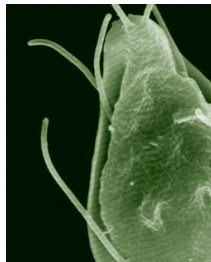
Most of the UK research effort in *P. vivax* is at present in collaboration with Indonesia and Malaysia. Given the UK's strengths in malaria research there are substantial opportunities for collaborative research with Brazil. An example of a possible area for investigation is the role of the Duffy antigen that has differing degrees of prevalence within the ethnically diverse Brazilian population and provides some protection against malaria caused by *P. vivax*.

Sexual stage of the parasite

Drug discovery programmes for anti-malarials now recognise the need for candidate agents that have the potential to kill the parasite at multiple lifecycle stages, particularly the sexual stage (gametocytes) as this will influence transmission dynamics. Of particular interest is research on the processes by which the asexual stages commit to differentiation into gametocytes. This would be underpinned by UK expertise in gametocyte biology and drug development, and a strong research community in signalling pathways in Brazil.

Inflammatory processes and immune response

A major question in malaria biology is how people become protected from severe disease. These studies are further complicated by the need



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to consider co-infection with other pathogens and the way that this influences subsequent host protection (and pathology). The extensive immunopathology community in the UK would benefit greatly from access to the clinical cohorts available in Brazil, through a shared research agenda with Brazilian laboratories.

Cytoadherence

Our knowledge of how the malaria parasite causes disease is incomplete but it is thought to include the property of the malaria infected red blood cell to adhere to the host cells lining small blood vessels. This phenotype was previously thought to be unique to *Plasmodium falciparum*, but recent work led by a group in Brazil has identified cytoadherence in *P.vivax*. Further work to understand the clinical consequence of this will need direct access to patients with *P.vivax* infections, such as those found in Brazil, and would benefit from the research base in this area available in the UK.

Leishmaniasis

A productive and continuing area of collaboration between scientists in the UK and Brazil is research into leishmaniasis, a disease that is endemic in Brazil and other tropical and sub-tropical regions of the world:

Genomic and post-genomic biology, including expertise in bioinformatics

Access to new sequencing technologies is accelerating comparative analysis of different *Leishmania* species and strains that cause a spectrum of disease in man and other mammals. Building on existing links between Brazil and the UK, developed through the Leishmania Genome Network, will provide excellent opportunities, using both computational and laboratory-based methods, to advance collaborative projects that address parasite evolution and adaptation in South America.

Mechanisms of transmission, particularly in animal hosts

Despite pioneering work in Brazil, and a history of related research in the UK, the vectors and reservoir hosts of some *Leishmania* species causing disease in man are still poorly understood. Collaborative research using new molecular tools for biological and epidemiological studies could resolve these issues and impact on public health programmes.

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Potential for immunology research including vaccine development

Understanding the complexities of the human immune response to infection with different *Leishmania* species is a common research theme for Brazilian and UK scientists. Vaccine development for leishmaniasis has not yet yielded an effective product in man but research programmes that link immunological expertise with translational technologies may alleviate this problem, providing new opportunities for innovative and collaborative research in South America.

Chagas' disease

Brazilian scientists have had success in developing inhibitors for targets in *Trypanosoma cruzi*, the causative agent for Chagas' disease, and would like to collaborate with UK scientists to harness their strengths in synthetic and medicinal chemistry, structural biology, drug development and translational science to turn these into treatments that benefit patients. These skills could also be applied to drug development programs for malaria, leishmaniasis and schistosomiasis.

Use of genetically modified yeast in the design and development of drugs against parasitic diseases

The exacting nutritional requirements and complicated life cycles of many parasites mean that they are not easily amenable to high-throughput drug screening using automated procedures. Indeed, many parasites, such as *P. vivax*, cannot be cultured outside of a living host.

'Research collaborations must be established by the researchers themselves...'

Scientists at Cambridge have engineered the yeast *Saccharomyces cerevisiae* to act as a surrogate for expressing drug targets from a range of biomedically important pathogens, to facilitate the rapid identification of new therapeutic agents. These strains are being exploited, in collaboration with colleagues at the University of Aberystwyth, to screen for novel anti-parasitic agents in an 'intelligent' automated manner using a Robot Scientist. Future collaborations with scientists in São Paulo are anticipated to test promising candidates *in vivo*. In addition, in a collaboration between Cambridge and Campinas, engineered yeast has been used to identify the site of action of a novel anti-malarial agent isolated from a bacterium found in the Amazon river.

Strengthening tropical medicine research collaboration

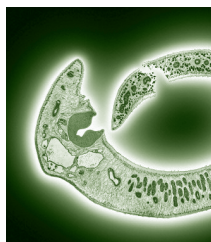
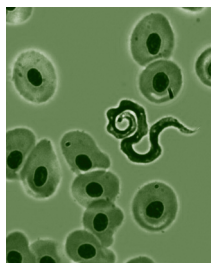
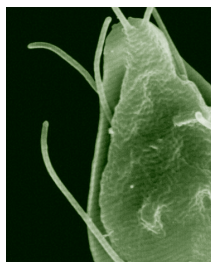
Research collaborations must be established by the researchers themselves, but much can be done to ensure that the research environment facilitates collaboration and that researchers have the opportunity to meet, particularly at the beginning of their careers. Outlined below are some measures identified by those at the workshop and at the meetings with research leaders in São Paulo that participants felt would benefit from modest dedicated resources:

Highlighting existing international agreements and opportunities for collaboration

In 2009 Research Councils UK (RCUK) and FAPESP signed a Memorandum of Understanding (MoU) to strengthen the existing research links between the UK and Brazil, to help encourage and support proposals that involve international collaborative teams.¹⁵ The MoU provides for a lead agency agreement whereby UK and Brazilian researchers may apply for funds from both countries primarily through the UK Research Councils response mode schemes. Proposals can be made through this mechanism at any time, although no earmarked funding supports this agreement. The agreement strengthens the existing valuable research links between the UK and Brazil and avoids 'double jeopardy' in funding applications whereby applicants need to obtain approval for funding from two organisations.

Although this mechanism seems to be working well for the Biotechnology and Biological Science Research Council (BBSRC) and the Natural Environment Research Council (NERC), many in the tropical medicine and parasitology communities in both the UK and Brazil, who might benefit from this mechanism, are not aware of this agreement. Greater efforts should be made to raise its profile.

In the future there may be opportunity for similar arrangements between the UK and other Brazilian states such as Rio de Janeiro and Minas Gerais



'Much can be done to ensure that the research environment facilitates collaboration and that researchers have the opportunity to meet.'

that are taking an increasing interest in science and whose state science foundations already have agreements with FAPESP. There are also benefits to be had from agreements at the institutional level that can be more flexible than regional or national arrangements. This approach is being pioneered by institutions such as the State University of São Paulo, the Federal University of São Paulo, Kings College London and the University of Southampton.

International summer school for young scientists

A major opportunity to encourage collaboration between UK and Brazilian scientists in tropical medicine and parasitology would be to establish an annual residential summer school for early career researchers. A summer school involving lectures and laboratory visits is likely to forge stronger bonds than a one-off meeting. It might be linked to an existing parasitology or tropical medicine conference. The opportunity for young scientists to spend an extended period of time together would help build strong international bridges. It would also allow young researchers the opportunity to access training and expertise from researchers with whom they might not otherwise have had contact.

A summer school would not require substantial resource and might even be piloted by the SIN network with support from others such as societies for tropical medicine and parasitology. The São Paulo School for Advanced Science that is supported by FAPESP provides a model for this sort of activity.¹⁶ Young Brazilian scientists tend to spend time in the UK but fewer young UK scientists spend time working in Brazil so the first such summer school might take place in Brazil, then alternate annually between the two countries.

Database to help identify potential research partners

The Ministerio da Ciencia Tecnologia, the Brazilian Ministry of Technology, hosts the Lattes Platform – a database of curricula, institutions and research groups involved in science and technology in Brazil – that offers an excellent tool for researchers seeking to establish collaborations.¹⁷ The participants at the workshop were not aware of a similar easy to find

and well publicised one-stop-shop mechanism that provided details of UK researchers as this would be most valuable to Brazilian researchers in identifying potential collaborators.

Building technical expertise

While there has been some recent progress, research groups in both Brazil and the UK often do not have sufficient numbers of highly skilled technical staff required to operate complex specialised equipment and analyse data. Too often research funding cannot be used to sustainably employ these staff. To train more technical staff, clear career structures need to be provided that offer opportunities for progression. Technical staff also need to be more closely integrated with researchers and involved in research projects as partners. A model that is reported to work well is the Technology Facility at the University of York in which a well-resourced pool of technical staff is integrated into the various research groups across the Department of Biology and beyond.¹⁸

Both the UK and Brazil are losing their cadres of experts in the phenotypic biology of parasitic diseases, particularly schistosomiasis and leishmaniasis. For parasitology and UK-Brazil collaboration to flourish both countries need to ensure they maintain expertise in both pre- and post-genomic biology. The challenge here may be more the lack of young scientists who want to develop careers in phenotypic biology of parasitic disease rather than lack of funding.

Facilitating international mobility of researchers

Secondments for medical scientists between the UK and Brazil offer a further opportunity to foster partnerships between researchers in the two countries; for example 'sandwich' PhD programmes with secondment part way through. Although some resources for secondments are available, a few modifications to existing schemes would further encourage collaboration. One challenge for UK-Brazil collaboration is that, unlike many of their Brazilian counterparts, UK universities sometimes charge 'bench fees' that are not generally covered by Brazilian funders such as FAPESP. This can discourage Brazilian

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'the UK Government should ensure its immigration policies facilitate and encourage international collaboration.'

researchers from working in the UK as extra resources need to be found to cover these fees.

Another challenge is that Brazilian grants and Fellowships for Brazilian scientists visiting the UK often only provide support for one year when two years support is needed to give enough time to tackle serious scientific questions. This means UK researchers are less willing to take on Brazilian scientists as they will have to find new resource to support a second year.

One mechanism to facilitate secondments and collaborations is the provision of small amounts of supplemental funding to existing collaborations by research funders in the UK and Brazil to allow them to send and receive post-docs. This approach has been successfully used since 2005 by FAPESP and the French funding agencies INSERM and CNRS. Details of these agreements can be found at: <http://www.fapesp.br/en/5399>.

While the UK Government has gone some way to reduce the impact of the recent immigration cap on medical research, by giving extra weight to scientific qualifications when making decisions about visas, concerns still remain. To maximise the mutual benefit from collaborations between scientists in the UK and Brazil the UK Government should ensure its immigration policies facilitate and encourage international collaboration. One challenge is that PhD exchange students with Brazilian degrees often cannot extend their stay in the UK beyond six months without formal registration on a course, which significantly increases costs as they then have to pay fees. This might be tackled by building fees into the secondment grant or counting secondees as staff members at their host institution in the UK, although this may impact on visa arrangements.

Workshop participants

- Professor Sergio Verjovski de Almeida, University of São Paulo, Brazil
- Professor Paul Bates, University of Lancaster, UK
- Dr Elizabeth Bilsband, University of Cambridge, UK
- Professor Katia Denise Saraiva Bresciani, State University of São Paulo, Brazil
- Professor Carlos Eduardo Pereira Corbett, University of São Paulo, Brazil
- Professor Alister Craig, Liverpool School of Tropical Medicine, UK
- Professor Angela Kaysel Cruz, University of São Paulo, Brazil
- Dr Marcos Leoni Gazarini Dutra, Federal University of São Paulo, Brazil
- Professor Luiz Tadeu Moraes Figueiredo, University of São Paulo, Brazil
- Professor Eduardo Finger, Santa Casa School of Medicine, Brazil
- Professor Celia Regina da Silva Garcia, University of São Paulo, Brazil
- Professor Richard Charles Garratt, University of São Paulo, Brazil
- Professor Hiro Goto, University of São Paulo, Brazil
- Cristina Hori, British Consulate São Paulo, Brazil
- Professor Ross King, University of Aberystwyth, UK
- Rafael Lane, British Consulate São Paulo, Brazil
- Dr Ricardo de Marco, University of São Paulo, Brazil
- Professor Jeremy Mottram, University of Glasgow, UK
- Professor Steve Oliver FMedSci, University of Cambridge, UK
- Damian Popolo, British Consulate São Paulo, Brazil
- Professor Laura Rodrigues, London School of Hygiene and Tropical Medicine, UK
- Professor Nilce Maria Martinez Rossi, University of São Paulo, Brazil
- Professor Sergio Schenkman, Federal University of São Paulo, Brazil
- Professor Marie-Anne Van Sluys, University of São Paulo, Brazil
- Professor Deborah Smith OBE, University of York, UK
- Laurie Smith, Academy of Medical Sciences, UK
- Professor Robert Souhami CBE FMedSci, Academy of Medical Sciences, UK
- Professor Anita Hilda Straus, Federal University of São Paulo, Brazil
- Professor Hélio Kiyoshi Takahashi, Federal University of São Paulo, Brazil
- Professor Silvia Reni Bortolin Uliana, University of São Paulo, Brazil
- Professor Alexander Henning Ulrich, University of São Paulo, Brazil
- Dr Eric Kors Vidsiunas, FAPESP, Brazil
- Dr Lucile Maria Floeter Winter, University of São Paulo, Brazil
- Dr Carsten Wrenger, University of São Paulo, Brazil

In addition the Academy's Foreign Secretary, Professor Robert Souhami CBE FMedSci, met with the following scientific leaders to discuss UK-Brazil collaborations:

- Professor Carlos H de Brito Cruz, Scientific Director, FAPESP
- Professor Arnaldo Colombo, Research Pro-Rector, Federal University of São Paulo
- Professor Marco Antonio Zago, State University of São Paulo
- Health Secretariat of the State of São Paulo

Further information

- Academy of Medical Sciences: <http://www.acmedsci.ac.uk>
- FAPESP: <http://www.fapesp.br/>
- FAPESP agreements with INSERM and CNRS <http://www.fapesp.br/en/5399>
- FAPESP agreement with Kings College London <http://www.fapesp.br/en/5341>
- FAPESP agreement with the University of Southampton <http://www.fapesp.br/en/6303>
- Federal University of São Paulo <http://www.unifesp.br/>
- Lattes Platform – a database of curricula, institutions and research groups in science and technology <http://lattes.cnpq.br/>
- RCUK/FAPESP Memorandum of Understanding: <http://www.rcuk.ac.uk/international/funding/collaboration/Pages/RCUKFAPESPMou.aspx>
- UK Science and Innovation Network: <http://www.fco.gov.uk/en/about-us/what-we-do/working-in-partnership/working-with-stakeholder-groups/science-innovation/science-innovation-network/>
- University of São Paulo: <http://www.usp.br/internacional/home.php?idioma=en>

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- 2 Academy of Medical Sciences (2010). *Reaping the rewards: a vision for UK medical science*. <http://www.acmedsci.ac.uk/p48prid78.html>
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- 12 Further details about Nobel Prizes are available from: http://nobelprize.org/nobel_prizes/
- 13 Association of the British Pharmaceutical Industry (2004). *Innovating for a healthy tomorrow*. http://www.abpi.org.uk/publications/pdfs/annual_report_05.pdf
- 14 Adams J & King C (2009). *Global research report for Brazil. Research and collaboration in the new geography of science*. <http://researchanalytics.thomsonreuters.com/m/pdfs/GRRBrazil-Jun09.pdf>
- 15 Further details are available from: http://www.rcuk.ac.uk/international/funding_collaboration/Pages/RCUKFAPESPmou.aspx
- 16 Further details are available from: <http://www.espc.a.ifsc.usp.br/>
- 17 Further details are available from: <http://lattes.cnpq.br/>
- 18 Further details are available from: <http://www.york.ac.uk/biology/technology-facility/>

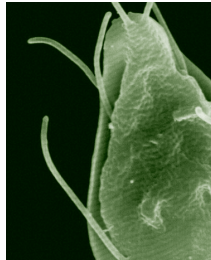
A pair of *Schistosoma haematobium* blood worms.

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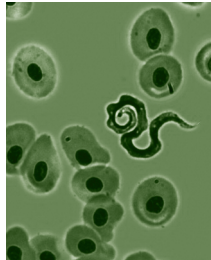
Colour-enhanced, scanning electron microscope view of the underside of *Giardia lamblia*, a flagellate intestinal parasite.

David Gregory & Debbie Marshall,
Wellcome Images



Trypanosoma granulosum
infected blood

Pablo Rojas, Wellcome Images



False colour SEM image of
a *Toxocara canis* worm.

EM Unit, UCL Medical School, Royal
Free Campus', Wellcome Images



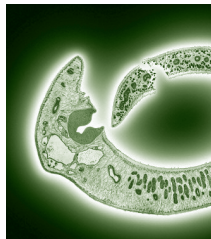
Anopheles stephensi full of blood

Hugh Sturrock, Wellcome Images



Photomicrograph of a longitudinal section
of the *fasciola hepatica* parasite.

Pablo Rojas, Wellcome Images



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