Profile

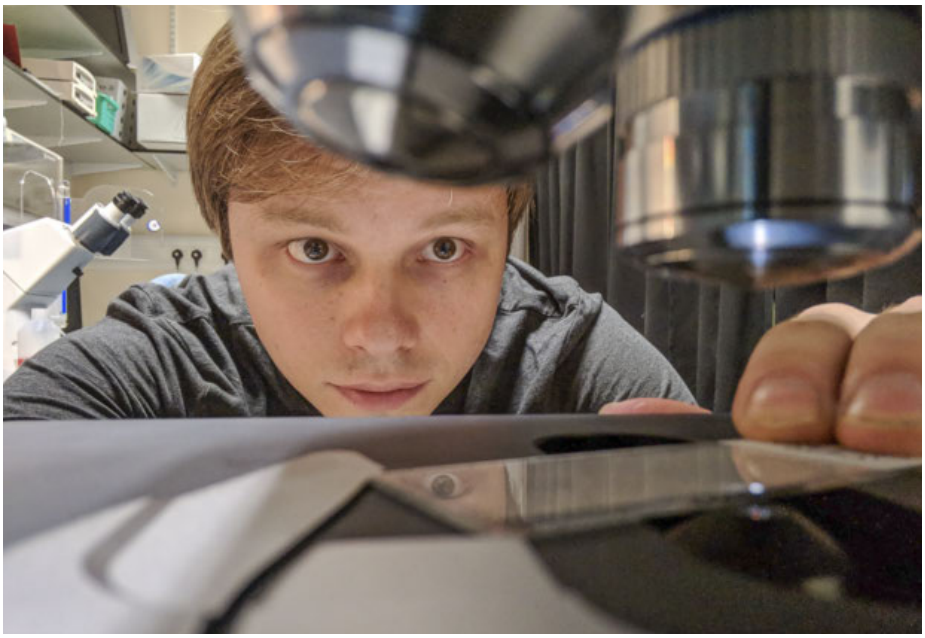
SECTION EDITOR

Simon Page
simon.page@cantab.net

An interview with Richard Wheeler

Principal investigator in parasite cell biology at Oxford University and expert in the tropical parasites *Leishmania* and *Trypanosoma*

You step out of the plane and into a blast of baking heat and the taste of dust. The relative cool of the airport provides a brief moment of calm, before you clamber into a sweltering taxi, which is quickly surrounded by a crush of cars and lorries, their horns adding to the clamour of street merchants shouting from corrugated iron shacks. Your car inches through the crawling traffic, the road flanked by an ever changing mix of tumbledown buildings and modern tower blocks, before eventually escaping to an arcadian green university campus. This is the University of Ghana, in Accra, and you've come here to meet Dr Richard Wheeler, research fellow at Oxford University and published expert in tropical diseases.



MEW: Hi Dr Wheeler, thanks for agreeing to be interviewed by us. Firstly, I'd love to know a little about your research career to date: when it started, how it developed, and where it's taken you.

RW: My parents were always worried I would become a scientist. The signs were there from a young age when, one morning, they walked into the back garden to discover a six-year-old Richard measuring the size of a fungus fairy ring on the lawn. I have always had a fascination for how things work, and at school I loved the subjects that allowed you to explore this. Science was my strongest suit and so, supported by some fantastic teachers, I continued my education at the University of Cambridge, reading Natural Sciences. This modular science course (relatively unusual at the time, but becoming more common) allowed me to explore the interfaces between biochemistry and physics.

My first experience of parasite cell biology was pure coincidence. I was looking for lab work experience during my undergraduate degree and was lucky enough to get a place at Oxford University in the laboratory of Keith Gull, a world expert in *Trypanosoma* parasites.

That work experience has turned into a full-blown academic research position! My research focuses on two poorly known unicellular parasites: *Leishmania* and *Trypanosoma*, which both cause deadly tropical diseases. They are a little like malaria parasites, in that they're unicellular nucleated cells with a devastating effect on human life – taken together, they are responsible for around one hundred thousand deaths per year – but they are from a totally different branch of the tree of life to malaria parasites, and are as different from malaria as a human is from a tree.

MEW: OK, so Cambridge, Oxford, and now … Ghana? What led you here to the west coast of Africa?

RW: *Trypanosoma* and *Leishmania* parasites affect the tropical and subtropical parts of the world, particularly Sub-Saharan Africa, India, and Brazil/Central America. I wanted to make the most of this link. The connection with Ghana comes specifically from *Trypanosoma brucei* which causes sleeping sickness in people and nagana in animals across huge areas of Sub-Saharan Africa.

About 8 years ago I was given the opportunity to help run a roving science course, teaching parasite biochemistry to some of the brightest young students in Africa. It absolutely grabbed my attention – to see the people and places directly impacted by these diseases, and then teach local scientists how to combat them – so I jumped at the chance.

It is impossible to describe quite how much I learnt from my first long drive through Africa

Dr Wheeler teaching graduate students in the West African Centre for Cell Biology of Infectious Pathogens at the University of Ghana

(5 hours through the middle of Tanzania from Dar es Salaam to Morogoro), and since then I've been out to Africa to run many similar courses, most recently at the University of Ghana. I have always found teaching a vital way to look to the future, and helping people carry out research into these diseases situated in the places it impacts is truly inspirational.

MEW: And – speaking of teaching – what can you teach us about these diseases?

RW: *Trypanosoma* and *Leishmania* cause several neglected tropical diseases, including sleeping sickness, Chagas disease, leishmaniasis, and nagana. However, there are many surprising gaps in knowledge about how they act as a parasite. For example, it was only discovered in the last couple of years that *Trypanosoma* parasites don't just swim in the blood but also often hide in the skin.

My research focuses on understanding the fundamental biology of how these parasite cells work, and what that might mean for the disease. The parasites are single cells which are highly organised, and the textbook view of a eukaryotic cell (a bag of cytoplasm full of organelles with a nucleus in the middle) is an extreme over-simplification. My work is aimed at understanding how the organisation of the cell is controlled and adapted for different stages of the cell's life cycle.

As well as combating tropical diseases, understanding parasites can also help us to understand human biology. For example, a defining part of the parasite cell is the flagellum (or "cilium"). This is the 'tail' part that the cells use to swim, or to move material around them (see bottom right opposite). However, flagella are extremely important in people too – they're what keep our airways clear of debris and what keep our sperm swimming! – so an improved understanding of parasite biology may help to improve human health in a number of ways.

MEW: Is there any tool or technique that has been particularly important to your research career?

RW: The key inspiration for my research career has been microscopy. The first time I used a research-grade fluorescence microscope was exhilarating. The realisation that I could look into a cell that is 100 times narrower than a human hair, at individual molecules even, was incredible. And not only that it's possible, but that it's beautiful too.

Much of my current work revolves around microscopes as a measurement tool, and I use advanced image analysis to extract the data. This plays to my strength as a visual thinker, and my hobbies (design and photography) often merge into my work.

Images can be seriously big data: One of the projects I am co-running involves images of 5 million cells and tens of terabytes of image data! This "big data" project is called TrypTag (http://tryptag.org/). We are using high-throughput genetic modification tools to go through all 8,000 genes of the *Trypanosoma* genome, modifying each one in turn so that the protein is fused to a green fluorescent protein–like fluorescent marker. We then look where each individual protein is located within the cell. This type of sub-cellular map of proteins has only previously been done in yeast and (to some extent) human cells, so this will be the first time that it has been achieved in a pathogen, and the first time in such a highly structured cell where protein localisation is so strongly indicative of likely function.

MEW: You obviously chose to work in academia over industry. Why was this, and what would you advise as being the main pros and cons of each career path?

RW: My choice of an academic career was driven by the appeal of intellectual freedom: To drive my own research and address the questions I want to answer. However, having never worked in industry it is hard to know how true this is! Moreover, it is somewhat naïve to view academic research as true intellectual freedom; while you can choose what research to do, it must still generate results that people view as important, in order to secure funding from agencies who view your output as worthwhile. I can imagine that working in the biotechnology industry, particularly smaller companies, could be very similar – perhaps substituting "shareholders" for the academic field and "venture capital" for funding agencies.

I do think that the perceived separation of academia and industry is somewhat artificial, especially as funding agencies are increasingly focused on research that is "translational" or has good "pathways to impact" or other such jargon. Personally, I find this attitude frustrating, as it results in the government being the sole arbiter of which research has the clearest useful applications, leading to a risk that basic science (so called "blue skies research") will suffer. A common joke goes that, in this funding climate, Einstein wouldn't get funding to work on relativity, as he would have had to invent GPS first.

Interestingly, some academic research is now pushing to be more "industry-like". I spent over a year working in the Dresden Max Planck Institute for Molecular Cell Biology and Genetics, which runs an unusual research institute management structure with extremely large and well-funded core facilities (alongside traditional "research groups"). This was a very different way for me to do science, and is a structure that is clearly inspired by industrial research management and organisation.

MEW: Many of our readers work with their clients to publish scientific research in high-impact medical journals. What are your

perspectives from an academic viewpoint on the publishing industry as a whole?

RW: A major problem in academia is that the assessment of research quality by funding agencies and interview panels is often based – fairly or otherwise – on metrics directly derived from publications (e.g., journal impact factor). Sadly, it is quite normal to receive feedback on grant applications which focuses strongly on the quality of your journals rather than the quality of your work.

However, journal impact factor is not a good measure of either the quality or the impact of research. There are many examples of papers in high-impact journals which are simply not good quality science, and many excellent science papers in low-impact journals. Indeed, my most cited paper is published in the lowest impact factor journal of any of my publications.

Fundamentally, the entire concept of impact factors stems from an artificial scarcity (i.e., the limited number of papers per issue) which is a historical hangover from physical, printed journals. Online journals have essentially unlimited space in them, and yet the impact factor of a journal is entirely defined by editorial selection of the work, a feedback loop which can easily lead to fields having artificially inflated perceived value.

Many academics feel that the direction of the publishing industry is driven by profit, not by research quality, and that a major review is needed to combat issues such as artificially inflated publishing costs, exploitation of reviewers' time, and arbitrary biases arising from editorial decisions.

MEW: In the last edition of this magazine, Chris Winchester of Oxford PharmaGenesis presented some research showing that the pharmaceutical industry is actually better at disclosing the results of its clinical trials than academics. Do you feel this is likely to be true and, if so, why do you think that academics aren't publishing as much of their research as pharma?

RW: The research Chris presented is very interesting, and highlights a wider problem about publishing negative results. In an academic environment dominated by a pressure for high-impact journal papers, how can we expect researchers to spend time writing a paper with a negative result which will end up in a low-impact journal?

Chris's comments about deploying resources to meet legal and ethical obligations are accurate, but I think policies from funding agencies are exacerbating the situation. There is a massive pressure on academics to do research that can be translated into practical applications. If you get a negative result from trying to apply it (e.g., through a clinical trial) then you are disincentivised from publishing it.

There are all kinds of ideas for how to incentivise publishing negative or contradictory results linked to previous studies – things like journal policies which guarantee the publication of a refuting or contradictory perspective on an article – but in practice nothing seems to have been done about it, and no number of Nature Editorials has changed that!

MEW: The literature is becoming increasingly vast and complex, with new journals being introduced every year. However, medical writers often work at the cutting edge of drug research, and are expected to be fully conversant in the diseases that they are working on. How would you advise people to stay abreast of the topics that are of relevance to them?

RW: You might think that, with my background of computational analysis and general data geekery, I'd have some clever algorithm to search and curate the literature for me. I don't. I talk to people! Almost every really useful or inspirational article I have read has come from a recommendation. Of course, trying to gain a deeper understanding of a field will always take some serious searching and reading. However, to some extent, I think that academia's approach to reading the literature has reversed a bit. Nowadays, if you come up with an idea inspired by some key paper, it's almost easier to do the experiment, see if the result is interesting, and then work out how it fits into the existing knowledge, rather than the other way around.

MEW: I'm sure that travelling to Africa and back takes up a lot of your time, but what do you get up to away from the lab bench?

RW: I love illustration, design, photography, and playing the trumpet. I also like computer games, but frequently get distracted by reprogramming and redesigning them!

MEW: And finally, some quick-fire questions:

Oxford or Cambridge? (or Ghana?)
Oxford

Microscope or telescope?
Microscope

Craft beer or vintage bubbles?
Craft beer

Rock bar or baroque?
Rock bar

Chess or Monopoly?
I love playing *Race for the Galaxy*

Cat or dog?
I plead the fifth!

Sun-drenched summer or white Christmas?
White Christmas, it's all about the cold!

Contact information

Richard Wheeler can be contacted by email (richard.wheeler@path.ox.ac.uk) or via LinkedIn (https://www.linkedin.com/in/richard-wheeler-a20b213b/).

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Different cell cycle stages of the Leishmania parasite, viewed by scanning electron microscopy. The cells are around 10–15 µm long and swim with the flagellum forwards (i.e., tail-first).