

A conversation with Professor David Russell, February 3, 2015

Participants

- Professor David Russell – William Kaplan Professor of Infection Biology, Cornell University College of Veterinary Science
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Note: These notes were compiled by the Open Philanthropy Project and give an overview of the major points made by Professor David Russell.

Summary

The Open Philanthropy Project spoke with Professor Russell of Cornell University as part of its investigation into tuberculosis scientific research and development (R&D). Conversation topics included the current state of tuberculosis R&D and Professor Russell's research on immune correlates of protection.

Basic scientific research and drug development

Basic scientific research on tuberculosis (TB) is very connected to drug development. The field of TB drug development currently looks more promising than vaccine development. There are no drugs that are currently in the product pipeline or ready to go to the market, but new and creative drug development approaches are attracting funding and starting to generate data.

Research on host-target interactions

Research on host-target interactions is an example of basic science research that could have direct implications for drug development. There are creative people working on this topic and several labs have been well funded. One potential application is the development of host-targeted therapeutics. However, host-targeted therapeutic approaches could have unintended side effects:

- There will be some off-target effects and uninfected cells will be affected. Getting sufficient specificity to only target cells infected with TB is a challenge.
- Making macrophages more hostile to bacteria will result in a drop in total bacterial numbers, but the bacteria that survive are likely to show increased drug tolerance. In the long term, this may be a surmountable obstacle, but in the short term it is possible that this therapy may interfere with effective drug action. The extent to which this might occur is an ongoing scientific question.

Progressing lead compounds through drug development

The first stage of drug development where families of analogs of lead hit compounds (pharmaceutically promising chemical compounds) are synthesized is expensive and underfunded. Even after promising compounds are identified, the chemical synthesis required for drug development involves a considerable financial investment. Academic groups cannot afford to fund this type of research, so potential compounds must be promising enough that industrial funders will invest in them.

Ideally, the government should be supporting this work. When the standard commercial model is non-viable, such as with TB drug development, the National Institutes of Health (NIH) would be an obvious candidate to fill the void.

Vaccine development

Currently, there is a lot of funding available for TB vaccine development, but funding has mainly gone toward incrementally improving existing approaches. There is a strong need to explore new directions in vaccine research for TB. Because TB is a disease unique to humans that has no animal reservoir, a vaccine that significantly reduced transmission would be truly transformational.

However, all available TB vaccines appear to arrive at the same endpoint. They control the infection and turn TB into a chronic condition by reducing replication and then “stabilizing” the enduring bacterial burden. No current vaccines can actually prevent infection or reduce the bacterial numbers in a chronic infection.

The nature of the bacterium that causes TB, *Mycobacterium tuberculosis*, complicates vaccine development. The bacterium produces an incredibly strong immune response. Usually, a large immune response makes controlling the disease and developing a vaccine easier, but in TB, the bacterium evades the consequences of the immune response by surviving within a granuloma, a collection of immune cells that surrounds and unintentionally provides a privileged niche for the bacterium. Later, in active TB, the bacterium takes advantage of its immunogenic properties to drive immune-mediated lung damage and that culminates in transmission.

Better approaches

Research on the correlates of immune protection

Understanding immune correlates of protection may be a prerequisite for designing better vaccine candidates. Progression of TB disease occurs at the level of the individual granuloma, and it is still unclear what the most desirable protective immune response to TB actually looks like. Identifying these processes and defining them in experimental systems (both in mice and in humans or non-human primates) is likely a better long-term strategy to produce more viable and promising

vaccine candidates, because it would allow earlier, cheaper, more efficient testing of potential vaccines.

Currently, vaccine development appears to rely heavily on trial and error. Vaccine candidates are tested in animals before it is clear what a successful immune response will look like.

Professor Russell believes work on immune correlates has more immediate application than research on biomarkers. Current data indicate that biomarkers identified to date are more diagnostic of disease state than predictive of disease progression.

Even though it is cheaper than clinical trials, research on immune correlates has not been a major focus of funding organizations in the past and it is unlikely it will become a major focus in the future.

Supporting research in humans and non-human primate models

While we have learned much from the mouse, current vaccine development may be too dependent on the mouse model. Other animal models are probably more appropriate vehicles for vaccine development, but it is much easier and less expensive to work with mice. Research with non-human primates is especially expensive and can be emotionally taxing.

Human studies are also expensive and can be difficult to get published, because they are often evaluated by scientists who work in mice, and who expect control groups that are not possible or ethical. However, more clinical research into disease progression or control would be of tremendous value.

Fostering collaboration

Vaccine development groups frequently work in isolation. Each group uses different models to evaluate its possible vaccine candidates, and every model has its own unique strengths and weaknesses. To promote direct comparison of different vaccine candidates, it might be advantageous to agree on appropriate models for testing and a single product pipeline.

Ideally, a central body would help foster collaboration. All vaccine development groups could submit their potential candidates to the central body for analysis. This is similar to what happens in drug development. The Global Alliance for TB Drug Development synchronizes much of the drug development and evaluation process. There are criticisms of this model, but generally there is a tremendous benefit to having a central organizing body.

Aeras, a nonprofit biotechnology company, receives funding from various not-for-profit organizations to organize vaccine development. However, the challenges that

Aeras faces in coordinating the evaluation of vaccine candidates with vastly differing levels of scientific provenance might be compared best to herding cats.

Longitudinal Human TB studies

The value of a large, international longitudinal study of human TB is often discussed but would only be useful in areas where there is high endemic TB and low endemic HIV, because it would be better to try to understand TB on its own without the added perturbation of HIV.

Sub-Saharan Africa has high rates of co-morbidity, so it would not be a good candidate location for one of these large longitudinal studies of TB. Professor Russell collaborated on a research project on human TB in Malawi in 2000. Broncho-alveolar lavage was conducted on 128 TB patients and, on clinical work-up over 97% of the patients were found to be HIV positive. There is now free HIV testing and HIV drugs in Malawi so rates of TB in HIV infected individuals have decreased, but currently around 80% of all TB patients in Malawi are HIV positive. It is impossible to ignore HIV when looking at TB in sub-Saharan Africa, but it is difficult to look at the two infections together because so little is understood about their synergy in the lung.

There is less co-morbidity in Asia, so Asia may be a better candidate region for a large study. In order to learn more about human TB, a reasonable percentage of the population study needs to progress to active TB disease, without also being infected with HIV. This is more likely to occur in Asia than in Sub-Saharan Africa.

Professor Russell's research

Drug screening

Professor Russell has received a grant from the Bill & Melinda Gates Foundation to expand his drug-screening platform. He is working with an academic institute, Calibr, in San Diego, to run a 1 million compound screen for small molecules that impact bacterial survival in its host macrophage. He recently published a paper in PLoS Pathogens (PLoS Pathogens. 11(2): e1004679. PMID: PMC4335503) that detailed a similar screen conducted in collaboration with Vertex Pharmaceuticals.

Correlates of immune protection

Professor Russell is working on developing tools that will allow researchers to identify correlates of immune protection. He has developed two bacterial reporter strains:

1. One set of strains responds to host derived stresses by up-regulating expression of fluorescent proteins

2. Another strain expresses the green fluorescent protein fused to the chromosomal replication machinery and gets a green dot every time it divides.

It is a long-term approach. He is currently working with mice to validate these reporter strains in in vivo infections. While the mouse is not the perfect model to study TB, but it is necessary to test these tools before thinking about using them in non-human primates or other more valued models.

His research team is also examining how these reporter strains behave in cells isolated from human lungs. By studying the fitness of these strains, it may be possible to identify what cell types are best at controlling bacteria growth and what types are most permissive.

2010 Science paper

Professor Russell co-authored a 2010 Science paper titled, *Tuberculosis: What We Don't Know Can, and Does, Hurt Us*. Most of the points made in that paper are still relevant today.

Professor Russell's funding

Currently, Professor Russell's work is well funded by the NIH, but he is always concerned about securing funding for future studies. It is understandably challenging to go to the NIH or philanthropic organizations with a grand ambition and ask for funding for the entire project. For example, before receiving funding for a large non-human primate study, researchers would be expected to present data on the work they've done in mouse models or in isolated human cells. Professor Russell takes this iterative approach.

Professor Russell is hoping that after his team collects data on the reporter strains in human lung cells infected ex vivo, he can apply for the more extensive support required to fund challenge experiments with monkeys in order to identify the cell type that controls tuberculosis. This would entail infecting the animal, isolating the lungs, harvesting the cells, and using the reporter strains to determine the fitness of the bacteria in different cell types.

Clinical Work in Malawi

If Professor Russell were able to secure funding, he would also like to conduct clinical work in Malawi to examine the immune competence of accessible cells in the lungs. This would involve:

- Using bronchoalveolar lavage to harvest macrophages, lymphocytes, and other cells from the lungs
- Conducting analyses of immune competency on the harvested cells

This approach represents a reasonable surrogate for the kinds of experiments that researchers in the lab do on mice and other animal models. HIV is very relevant to

this work, but because the interaction between TB and HIV is so complex, Professor Russell is trying to take a step back and examine the infections individually.

NIH TB funding

At the NIH, it can be challenging to get human TB work funded because grants for TB research are generally reviewed alongside all other bacteriology research – so human research on actual disease and mouse research on model organisms frequently end up competing for the same grants. There is minimal to no sequestered money for research on human TB. Often the research in mice wins out over the human TB research in competition for grant funding because research on TB in humans will never be able to use the kinds of controls or experimental measures that are possible in laboratory mice. Many bacteriologists that review grant applications work with mice and expect research to generate data very quickly, which is simply not the case in human clinical studies.

The NIH does fund a lot of clinical work, but its main focus is on diseases relevant to the United States. In order to get clinical studies of tuberculosis funded (such as Professor Russell's proposed study in Malawi), researchers have to market them as scientific programs so they can compete effectively with applications on tractable model infections. This can be a serious challenge.

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