A conversation with Dr. Christine Sizemore, January 29, 2015

Participants

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Note: These notes were compiled by the Open Philanthropy Project and give an overview of the major points made by Dr. Christine Sizemore.

Summary

The Open Philanthropy Project spoke with Dr. Sizemore of the National Institutes of Health as part of its investigation into tuberculosis scientific research and development. Conversation topics included the need for further investment in high-risk projects and the possibility of funding an international, longitudinal cohort study.

Tuberculosis scientific research and development

The National Institutes of Health (NIH) and the Bill & Melinda Gates Foundation are the biggest funders of tuberculosis (TB) scientific research and development (R&D). The NIH funds both scientific research and product development and supports efforts in diagnostics, vaccines, and therapeutics. TB R&D has only been well supported since the early 1990s.

Early stage TB biomedical research is well funded. Finding funding for product development is more challenging. Because TB primarily affects low-income countries, pharmaceutical companies have little interest in investing in product development.

The ultimate goal of all R&D is product development. A fundamental understanding of disease processes is a prerequisite to product development. It is not possible to rank the relative importance of vaccines, diagnostics, or drug development. These areas are all interconnected and could all use further funding. All three areas contribute to the goals of identification, avoidance, and treatment of TB.

Moderate funding need: investment in high-risk projects

It is difficult to find funding for high-risk projects that challenge the currently accepted scientific knowledge of TB. These high-risk projects could have tremendous impact and revolutionize scientific dogma. A moderate amount of funding ($250,000 - $700,000) would make a big difference in this area.

The grant process at NIH and many other funding organizations relies on external peer review. Projects that lack preliminary data generally don't receive funding. For

example, studies that are exploring an entirely new way that a bacterium might cause disease or entirely new models or technologies to study TB are unlikely to get funding.

Grants intended for high-risk projects could operate on the same scale as NIH funding programs:

- R01 grants are NIH's flagship funding mechanism. The majority of hypothesis driven and hypothesis generating research is funded under this program. Each grant has an upper limit of $500,000 of annual, direct costs. Including overhead and administrative costs, R01 grants usually cost around $700,000 per year. The NIH has found that well-developed studies with solid hypothesis can be covered by these amounts.
- The NIH also offers smaller grants, covered under both the R03 and R21 programs, which are directed at more high-risk, exploratory, hypothesis generating work. R21 and R03 grants provide up $250,000 of funding over two years.

The Gates Foundation gave many small grants (around $50,000) to stimulate innovation. It discovered that it was difficult to distinguish which high-risk projects had the greatest potential to transform the field.

Dr. Sizemore believes it would be relatively easy to create a framework for high-risk grants that could identify projects that have potential direct implications for applied science, such as drug or tool development. The projects themselves could focus on assays, technology, or platforms, but it would be important for them to have measurable, tangible outcomes.

Large funding need: an international, longitudinal TB cohort study

The TB research community has requested funding for an international, longitudinal cohort study for a long time. This study could:

- Span microbiology, immunology, and other aspects of tuberculosis
- Trace the natural history of the disease
- Utilize new technologies and tools to document specific disease conditions and the variability of the host-pathogen relationship

A study like this would be especially useful if it was conducted over five to seven years, which is longer than funding organizations can usually accommodate.

The complexity of human TB

Tuberculosis models in the laboratory do not accurately represent the diversity and complexity of human tuberculosis as it occurs in patients. Mouse and other animal models are designed to produce consistent results in a clean system, which is why a large longitudinal cohort study of human clinical TB would be valuable.

In humans, TB is a reasonably chronic disease with uncertain outcomes:

- Not everyone who is exposed to the bacterium gets infected
- Not everyone who is infected gets the disease
- Disease progression differs in individuals and across countries

In general, clinical research and trials are underfunded compared to basic laboratory research. The field has evolved since the early 1990s and it is now possible to do a lot of research in humans. Researchers are no longer confined to working in the mouse model.

Cost

Clinical research and advanced collaborative work is very expensive. An international, longitudinal study would require multiple millions of dollars, up to the low tens of millions of dollars.

High quality clinical trials and clinical cohort studies typically cost around two million dollars per year. Completing this work across multiple countries would require even more funding.

A lower-cost alternative

An alternative, lower-cost approach is to fund a mechanism that would bring existing cohort studies under one umbrella. Cohort studies are run in response to individual research questions and there is little collaboration. If there was more collaboration between groups and researchers collected data in a more standardized way, it would be possible to generate a large data set on human TB that would be very valuable.

Potential benefits

An international longitudinal study would produce more information about TB across many different human conditions and bacterial strains. This could help support existing tuberculosis programs and answer fundamental scientific questions about the diversity and complexity of human TB.

A large collaborative study would create additional opportunities for more advanced research that can't currently be completed through any existing mechanisms. It would not duplicate previous research. Scientists who are already funded by NIH or another group could use the data this study would generate to answer further questions and leverage the funding they are already receiving.

Currently, there are many cohort studies, but there is not a single entity that can organize and motivate research in different countries. A well-organized, collaborative cohort study could provide the necessary infrastructure.

Organizational challenges

Multiple organizations are managing smaller cohort studies. It is possible that an academic center could manage a project like this, but given its size and scope, creating an independent overarching body might be the best strategy.

Creating standardized procedures across all sites will be a challenge. If a new organization were to manage a study like this, it would be helpful to collaborate with groups that have experience running smaller cohorts.

The Gates Foundation has tried to organize a large cohort study in the past. The Gates Foundation currently funds some smaller cohort studies, but they are limited in size due to financial constraints.

International data sharing

In general, countries are often hesitant to share scientific data or samples. Countries prefer to retain complete control of their research. The NIH has started to do some international data sharing in its human genome initiative and its program on pathogen sequencing.

Hesitancy regarding international data sharing is understandable. Sometimes, a clinical finding is made in one country using its patients and volunteers. The product development that follows from this discovery occurs in another country. The final product is then not made available to the original country. Any international collaboration needs to address these issues.

A new, independent entity might be able to recognize and address these sensitivities better than pre-existing organizations. It is possible to design international, collaborative research that won't violate the needs or expectations of partner countries. Ideally, a well-organized clinical research consortium could direct scientifically advanced research and provide benefits to the countries that host this research. However, given limited funds and the need to prioritize among many (especially short-term) needs, current funders are struggling with how to pay for the efforts of a consortium like this devoted to expensive but important human clinical work.

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