A conversation with the TB Alliance, March 4, 2015

Participants

- Anna Upton, PhD – Director, Biology, TB Alliance
- Kari Frame – Senior Manager, Resource Mobilization, TB Alliance
- Willo Brock – Senior Vice President, External Affairs, TB Alliance
- Nader Fotouhi, PhD – Chief Scientific Officer, TB Alliance
- Lily Kim, PhD – Science Advisor, Open Philanthropy Project

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

Summary

The Open Philanthropy Project spoke with the TB Alliance as part of its investigation into tuberculosis research and development (R&D). Conversation topics included TB Alliance’s drug development goals, the chief scientific barriers to reducing TB cure time, and available funding for TB R&D.

Tuberculosis R&D parallels cancer R&D and interesting fields for philanthropists are:

- **Drug discovery** – Drug developers are just beginning to design targeted treatments that can target specific cells including the tuberculosis bacteria.
- **Biomarkers** – TB research is just beginning to think about biomarker development and use it to identify specific pathways and predict success in new TB cures.
- **Immune based therapies** – There are only a few labs currently studying how to modulate the immune system to boost TB cures, but it is a promising area of study.

Important recommendations for philanthropists with an appetite for scientific discovery could have a large impact. A new funder could support:

- **New drug discovery programs** – It is possible to more rationally design efficient drug discovery programs and to translate their advances to the clinic as quickly as possible.
- **Hypothesis driven, collaborative research** – It is important to fund work that spans basic science and clinical applications and to encourage collaboration across these stages.
- **Product development** – Pharmaceutical companies and other private sector players have been leaving the TB drug development space and this has left the product development stage especially uncertain.
**Burden and complexity of tuberculosis**

There are over 9 million cases of TB worldwide. 480,000 of these cases are drug resistant (and 45,000 of which are extensively resistant). TB will rob $1-3 trillion from the world’s poorest communities over the next decade. Over the next 35 years, if nothing is done to address the emergence of drug-resistant tuberculosis could kill 75 million people and cost the global economy a cumulative $16.7 trillion - the equivalent of the EU’s annual output.

**Tuberculosis drug discovery and development**

The TB Alliance’s long-term goal is to develop a treatment that could cure all tuberculosis (TB) in less than two weeks. Current first line treatment takes six months. Current regimens in development are aiming to reduce cure time to three-four months. Currently, the most efficacious drugs and drug candidates, when combined as regimens, can cure TB in animal models in approximately six weeks.

These new drugs will treat drug-sensitive and drug-resistant TB. Current therapy for drug-resistant TB lasts 18-24 months. Treatment is not very effective and the drugs are highly toxic, expensive, and difficult to administer. In the case of drug resistant TB, an effective all oral six-month therapy would be a significant step forward. Any new drug with a novel target or novel binding mode to a validated target will likely be applicable to all cases of TB, making it possible to produce a universal regimen that can be given to all patients irrespective of how they would be “classified” today (as drug resistant or drug sensitive). Given the current cost and complexity of treating drug resistant TB, a breakthrough regimen that gets the world closer to a “universal treatment” will make at least as much impact and will be as important as treatment shortening.

There have been several recent advances in TB drug development. Most modern day TB drug discovery efforts only began 10-15 years ago, so new candidate drugs are just beginning to emerge. Two new drugs were recently approved for multidrug-resistant and extensively drug-resistant TB. These are the first new TB drugs in several decades. Finding funding for clinical trials remains a big challenge. There are an increasing number of clinical trials occurring now, especially later stage phase III trials. Because TB drugs are always given in combinations, these late-stage clinical trials evaluate the efficacy and safety of new drugs combined with other TB drugs. In some cases, clinical trials are evaluating regimens containing more than one novel drug at once; this is an innovative development paradigm for TB, and seeks to bring the most improved regimens to market as quickly as possible.

The TB Alliance drives a significant portion of this drug discovery and development work, especially from the lead optimization stage of discovery through development of novel drug combinations. In general, there are few actors in the clinical drug development space and insufficient funding to generate data and assess results quickly.
Scientific barriers

There are three main scientific obstacles slowing drug development:

1. **Understanding bacterial subpopulations within the lung**

For example, a TB patient may have 100 billion bacteria. Even if all the bacteria are from the same genetic strain, they will behave differently because they exist in different environmental conditions – inside macrophages, granulomas, etc. There is growing evidence that these differing environmental conditions drive sub-populations of bacteria into different physiological states, for example:

- Bacteria adapt their metabolism to carbon sources available, such that one sub-population of bacteria may metabolize sugars and another may metabolize fats.
- Bacteria in low oxygen environments adjust their metabolic rate such that they grow and divide at lower rates than other bacteria.
- The different sub-populations will rely on different proteins and enzymes to survive.

Because of this, a drug that targets an enzyme that is required for bacteria in a low oxygen environment may not kill bacteria that live inside a more oxygen-rich environment or inside macrophages.

Knowledge of what pathways, processes, proteins, and enzymes are critical for survival in different environmental conditions is necessary to design drugs that will effectively kill all, or at least, multiple, sub-populations of bacteria. Breakthroughs in genetic tools have allowed researchers to get a better understanding of the different proteins that are critical for the survival of the hardest to kill bacterial populations. Researchers also use genetic screens and construct genetic knockouts in order to deprive bacteria of particular enzymes and test if they survive in the test tube or in an animal model. Despite this progress, there are still a lot of gaps in understanding. All research in this field is indirect because it can’t be done directly in patients.

Researchers are using information generated from these kinds of experiments to identify new drug targets. After targets are identified, drug developers will work to design compounds that inhibit them. These compounds can then be tested in the clinic with patients. Ideally, new compounds that target hard-to-reach subpopulations can be added to drug regimens to shorten treatment courses.

2. **Improving drug delivery**

Some areas of the lungs are more accessible to drugs than others. In order to shorten the TB treatment course researchers need to develop drugs that can access bacteria in different compartments within the lungs.

Researchers are beginning to use in vitro systems and animal models to understand how physical properties of compounds (e.g., their solubility) affects their ability to reach areas within the lung. Understanding how to alter molecules in order to increase their penetration will take a lot more work.
Thanks to improved imaging technology, it is now possible to use mass spectrometry to track the location of drug compounds within the lungs, even if they have been metabolized. It is possible to use color staining to get semi-quantitative information on drug concentration in different areas of the lungs. This has been done in animal models and human patients.

In general, there isn't a lot of funding available for this work and few top scientists are exploring this field. Researchers also need access to sophisticated mass spectrometry tools. Current research is aiming to understand and boost drug penetration. Research is not advanced enough to begin to think about targeting drugs to specific areas within the lung.

3. Understanding immune system modulation

The immune system has been harnessed to help drugs clear bacteria and cure the patient in other infectious diseases. No one has figured out how to do this with TB. Even if drug penetration is improved and all subpopulations of bacteria with the lung are targeted, a short treatment duration may also depend on an increased immune response.

An understanding of how to target and modulate the patient’s immune system is just starting to emerge. Some compounds are ready to be tested in animal models or potentially in the clinic. The research, however, remains in its early days and isn’t receiving adequate funding. Basic science research that examines how the immune response can be modulated to respond to bacteria is undervalued.

The National Institute of Health (NIH), the Bill and Melinda Gates Foundation and others are very interested in this area. Compounds have been researched that modulate the immune system that are already on the market (e.g., anti-inflammatories). It’s easier to design a clinical trial with these compounds because they have already been approved. For now these compounds aren’t targeting anything specific to TB. One example is Allen Sher’s research on immune modulation that has received funding from the NIH.

Funding situation

TB R&D has been woefully underfunded for a long time. The funding that is available often follows very traditional models and is distributed between various research stages: basic science, early drug discovery, late drug discovery, clinical research, etc. It is easier to get funding for a single stage of the research than to get funding for a single hypothesis and see it through several stages of research. It’s possible that investing in this hypothesis-driven research over a long time period would yield more impactful results. The TB Alliance believes strongly in this process driven approach.

Many of the hypotheses that require more funding are very new. The funding has not caught up with the new pace of research. Because modern-day TB R&D has progressed and changed as a field, funders may be favoring traditional approaches in order to go after “low-hanging fruit.” Also, because the total amount of funding is
limited, funders may not want to gamble that away on a single hypothesis. Traditional funding strategies have validity and yield incremental advances, but they are largely used as a response to scarcity and not as a way to pursue the most promising new ideas.

A new funder with more of an appetite for risk could have a large impact. A new funder could support:

- **New drug discovery programs** – Most TB drug discovery still follows the empirical or classical approach: researchers examine large libraries of compounds and test whether they kill TB in the test tube. With recent advances, it is possible to more rationally design efficient drug discovery programs and to translate their advances to the clinic as quickly as possible.

- **Hypothesis driven, collaborative research** – It is unlikely that a single piece of information related to a single hypothesis will lead to a breakthrough in TB, due to the complexity and heterogeneity of the disease. Rather, it is important to fund work that spans basic science and clinical applications and to encourage collaboration across these stages. Clinical work is deeply connected to basic science research, and vice versa. Every idea that is tested in the clinic confirms (or negates) a hypothesis that was generated in basic science.

- **Product development** – Pharmaceutical companies and other private sector players have been leaving the TB drug development space over the last five years. This has left the product development stage especially uncertain. Even as there is increasing scientific potential, there are fewer actors and resources and less expertise. A new funder could help support these commercialization efforts. Scientists are beginning to worry that even if their research is successful, it may not ever proceed through the product development stage.

**Biomarker research**

TB drug development is very resource intensive in part because there are no biomarkers of cure. In order to test if a new regimen of drugs has successfully cured patients, researchers have to follow up with patients for a long time to check if they relapse. Developing successful biomarkers would have a huge impact on the clinical development pathway.

In early stage clinical trials, researchers are trying to use the rate at which the level of bacteria in the sputum (mucus from the lungs) is reduced to predict how many weeks or months will be necessary to cure the patient. For existing TB drug regimens, it takes significantly longer to cure a patient than it does to eradicate the bacteria that are detectable in the sputum.

Many patient samples are necessary to begin to identify biomarkers. Ongoing clinical trials are beginning to collect samples for this work. Because there haven’t been a lot of clinical trials in the past several years, there hasn’t been a lot of opportunity for this work. Once many patient samples are collected, basic science
researchers can begin to use them to identify biomarkers. With recent advancement in genomics and proteomics, biomarker research is increasingly affordable. A large database of clinical data, including information on drugs with different mechanisms of action, would also help to identify the most effective treatments and guide drug discovery.

**Funding**

It is difficult to get funding for biomarker research. This research effectively needs long-term funding that spans basic science and clinical work. Current funders are more interested in getting patients through ongoing clinical trials, rather than expanding into new fields. Biomarker research is not seen as essential.

When applying for funding for a later stage trial, it is difficult to include and incorporate funding for biomarker research in that application. The TB Alliance is getting funding to collect samples for biomarker research during some of its clinical trials. However, maintaining the samples in a bio-bank over several years and ensuring they are available to researchers takes additional funding. This is a significant cost. The Bill & Melinda Gates Foundation has been willing to fund sample collection in its clinical trials and have also funded some of the bio-banking. The Food and Drug Administration (FDA) and the NIH have also funded some of this work, but in general, biomarkers remain a new idea that doesn’t fit into traditional TB funding categories.

A new funder could make a difference in this space. Any donor interested in biomarker research would have to understand that this is likely a 10-year initiative and any successes will occur over a long time frame.

**Cancer R&D analogy**

Tuberculosis R&D parallels cancer R&D. However, because TB R&D hasn’t seen the same investments, it probably lags behind cancer R&D by about 25 years.

- **Drug discovery** – 25 years ago, cancer drug discovery was slow, incremental work that aimed to identify cytotoxic compounds that killed healthy cells as well as cancer cells. Since then, research has moved beyond toxic compounds and scientists are designing more targeted treatments. Drug developers are just beginning to design treatments that can target specific cells. There is potential to take these same lessons and apply them to TB. A targeted TB cure is still far off.

- **Biomarkers** – Biomarkers are now critical to cancer drug discovery. Years of collecting patient samples led to these discoveries. Now that more of the pathways, genetic backgrounds and critical enzymes of various cancers are understood, researchers and clinicians can begin to use biomarkers to translate this into information about clinical outcomes. TB research is just beginning to think about biomarker development. Many more patient samples need to be collected before researchers can work on identifying specific pathways in TB.
• Immune based therapies – 15 years ago, no one took cancer immunology seriously, but it is now at the forefront of cancer research. There are only a few labs currently studying how to modulate the immune system to boost TB cures, but it is a promising area of study. Identifying the top cancer immunologists and funding them to apply what they’ve done with cancer to TB could yield interesting results.

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