“LOST IN TRANSLATION”: VACCINES AND THERAPIES FOR TUBERCULOSIS

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The supersonic speed with which the COVID-19 vaccines (mRNA and others) were developed, clinically tested, and delivered to the world was spectacular! So the question is, why have we not done this for TB and other rare, neglected, and infectious diseases that kill millions worldwide? Indeed, a recent publication has asked the question, "Where are the RNA vaccines for TB?" (1).

Let's put this in context. In 1921, exactly 100 years ago, the first dose of Bacillus Calmette-Guérin (BCG) vaccine for TB was given to an infant in a Paris hospital (2). It's stunning that BCG is still the only approved vaccine[1] for TB today, which infects over 10 million and kills over 1.4 million people worldwide which is estimated to prevent approximately 5-10% of preventable illnesses caused by TB (WHO, 2019, 3). Moreover, we still have only a few drugs and poor diagnostics, although Mycobacterium tuberculosis (Mtb) originated in Africa 70,000 years ago, and the complete genome was deciphered in 1998. The early 1900s were simple times with fewer regulatory, financial, marketing, and commercial hurdles.

The answer to the question of why we do not have more effective vaccines (and therapies) for TB to date is more complex. The sad truth is that the difficulties lie in translating new discoveries in the biology of the pathogen and the host's immunological response into the clinic. An elegant review in 2020 (4) addressed the issues related to TB and the development of new vaccines. However, a quick search in the literature revealed that mRNA and DNA technologies for TB vaccines were reported in 2004 (5) and again in 2010 (6) but were not pursued for development even in 2021[2], demonstrating the difficulty in the translational process.

Translational science and research[3] is a long hard jog that is mainly hidden from public view but has long been systematically practised in the pharmaceutical industry (7). It was an art and science with years of experience that was almost handed down from "Guru to Pupil" in the laboratory and the clinic. Only in the last 20 years since the sequencing ofhuman genome, the discipline of translational science and research has gained attention in the public domain. Let us go through briefly the process of translating the basic sciencecited above from the lab to the patients.

It's the "Biology Stupid"

We use this term with some levity, but it is crucial.

With the sequencing of the human genome in the early 2000s, it became apparent that we are no longer closer to treating human illnesses. The sequence was a series of letters (A, T, G, C) that was like a computer code consisting of 0s and 1s, with no information on the genes and effector proteins that carried out the functions of the cells. What was worse, even after identifying all 20-25,000 genes in our genome and expressed proteins, we still had to decipher epigenetics, post- translational modifications in proteins, related changes in function, their expression patterns and distributions in diseased and normal tissues and organs.Not to mention the differences in the same genes and proteins in animal modelsand humans.

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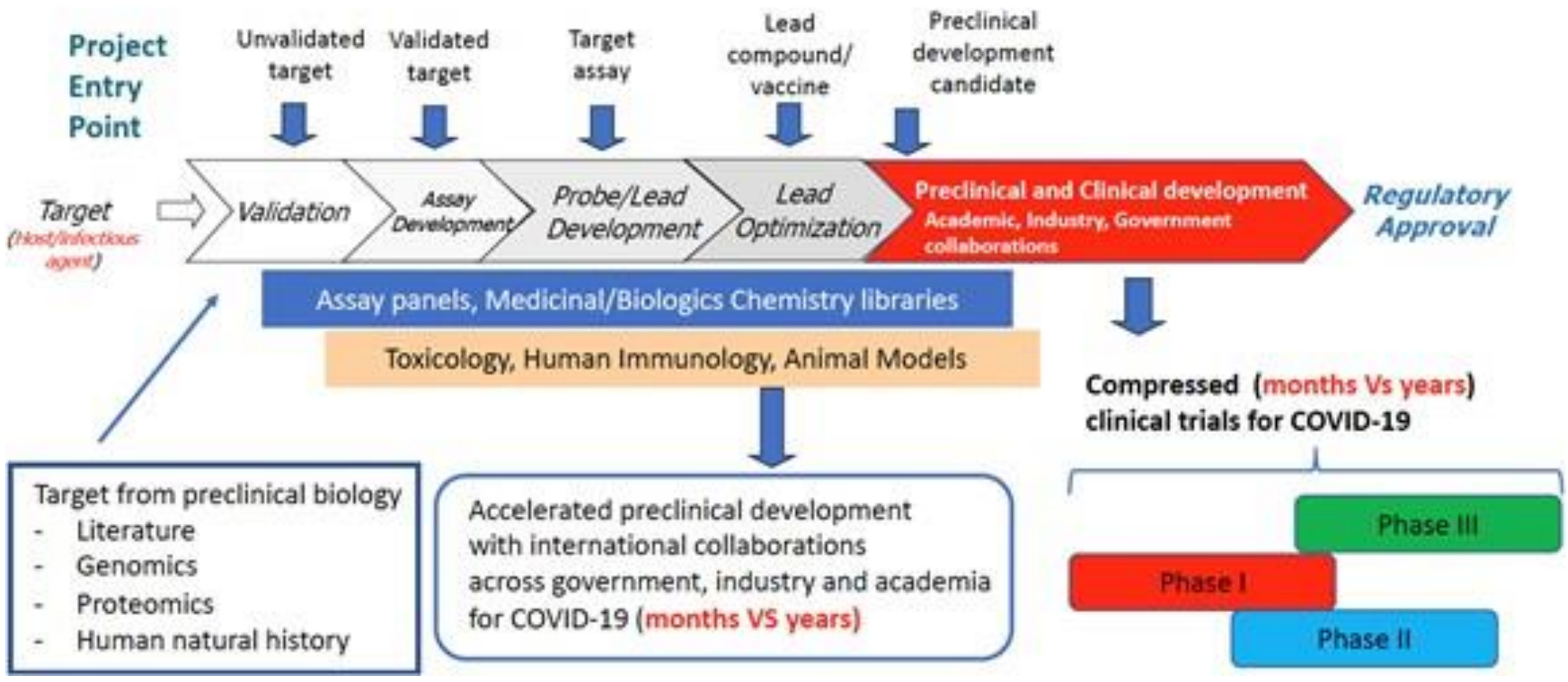
[1] Three vaccines are in phase IIa (MTBVAC) and Phase III (VPM1002) and M72 are in development.

[2] Indeed several recent reports have also described the development of DNA and other vaccines with potential new targets in the alveolar macrophages, airway epithelial cells and neutrophils (4) in addition to the Mtb. The concepts intranslation described above for mRNA will apply here as well. Note that addressing host cells takes us to host vs pathogen choices in Mtb infections which adds additional complexity in developing vaccines and therapies.

[3] Translational science and research are distinctly different. The terms are extensively discussed in reference 7.

In the case of infections such as COVID-19 and TB, we must further elucidate the positive immune responses and the lack of it in the host. What are the adaptive, innate, and trained immune responses in the host? How does the pathogen circumvent these defenses? In a pandemic with an unknown pathogen, these complexities are urgent. In known pathogens like Mtb, these responses still can be complex based onresponses in populations with various regional and genetic backgrounds related to age, sex and ethnic diversity. These hurdles can never be assessed when the first publications onthe biology of the disease or pathogen become available. Much of this is known for TB (4). However, we still must navigate the biological complexity and variability in developing vaccines and therapies for diverse human populations with relevant geographic and economic realities.

In general, preclinical efforts to deconvolute basic and disease biology take approximately 3-5 years and costs about $20-30 million dollars or more in the pharmaceutical industry. A costly affair that is generally beyond academic and non-profit organizations. Simultaneously with preclinical studies, toxicological and clinical trial approaches related to patient populations and regulatory considerations must be evaluated ina somewhat parallel fashion. A typical development paradigm and the accelerated program for COVID-19 illustrates the complexity of translational science and research in the graphic below.



Note that the accelerated development paradigm developed for COVID-19 is remarkable and an exception during this pandemic than ever before- a perfect storm. The fundamental question is why we cannot repeat these achievements globally for the epidemic of neglected tropical diseases.The answer probably lies with the regional and global bureaucracies that do not play well together.

As biology is being addressed there are other critical steps in translational research.

Now we need molecules that can become drugs

This is a special aspect of translational science and research that is somewhat hidden in the graphic above. Molecules, whether targets, assay reagents, drugs or vaccines are the real currency in the development of therapies and vaccines. Much work on making these molecules and owning them are the domain of the pharmaceutical industry and highly coveted. Many hundreds and even thousands of potential drug molecules (or vaccine candidates that involve DNA and RNA) must be tested before potential candidates are selected for clinical trials.

When we see a pill, a capsule, or an injectable medicine, we take it for granted. It has an active pharmaceutical ingredient formulated appropriately to maintain efficacy, safety and stability. In the early days of drug discovery (1950s -1970s) many molecules of therapeutic value originated from plant extracts or were synthesized painstakingly by biochemists, chemists, and pharmacologists. They are rigorously tested in animals and modified chemically or biochemically one to few molecules at a time to improve efficacy and reduce toxicity. In the last 25 years orso, High Throughput Screening (HTS), sophisticated bioanalytical instrumentation, libraries of medicinal chemistry compounds, and automation and information technologies have revolutionized the early discovery landscape, with theconcomitant effect of increasing the cost of drug discovery, albeit increasing the efficiency of early discovery. Billions of virtual molecules and millions of small molecule libraries are currently available for computer-assisted drug discovery and biological testing in HTS and lead optimization laboratories. Valid disease targets must be identified (a difficult, albeit necessary step) and physiologically and pharmacologically relevant robust assays must be developed to test large librariesof molecules (8). Once active molecules have been identified in the initial screening, multiple batteries of assays are needed to validate their activities in disease pathways, bioavailability, pharmacokinetics, pharmacodynamics, and toxicity in animals and possibly in human tissues (preclinical development box inthe figure). These studies are needed to move lead molecules to be tested in Phase I clinical trials that cannot be initiated without regulatory approval.

Failure rates in the preclinical discovery and development stage can be large, with 1 in 100 to 1000 molecules advancing to regulatory applications. Note that if valid targets and pathways were not used in the initial stages of screening and lead optimization, the chances of success in very expensive clinical trials become limited increasing economic risk. In infectious diseases, there is double jeopardy since targets and pathways can come from either the infectious agent or the host tissues and immune system, or both, that need to be considered for finding therapies. This is indeed the case with TB, malaria and almost all infectious diseases.

One last hurdle is the intellectual property and funding considerations on novel molecules and development technologies (drug formulations, manufacturing know-how/infrastructure). These issues are equally important and critical and should not be ignored since resolving these issues allow molecules available for clinical testing and eventually as medicines or vaccines for patients.

The big elephant in the room- Clinical Trials and Funding

Clinical trials are costly affairs mainly as it involves testing new therapeutic candidates in large populations of patients. Many researchers focused on the basic biology of the diseases generally are unaware of the requirements in clinical trials to tailor their studies appropriately. The phase I clinical trials explore safety in healthy volunteers at pre-determined dose levels along with pharmacokinetic and dose-limiting toxicities. There may be exceptions in some trials that combine efficacy and safety in phases IIa and IIb trials with cancer patients. The number of patients is limited in Phases I and II (in the hundreds), but Phase III efficacy trials involve thousands of patients in multiple clinical centers, including diverse patient populations with age, sex and ethnic considerations. Ethical design and execution, patient selection and exclusion criteria, adverse event reporting are carefully monitored by both regulatory agencies and the sponsor of the clinical trials. Generally, the resources for clinical trials are in the industrial domain and requires close collaborations managed by well-financed private Clinical Research Organizations, academic medical centers, government research laboratories, regulatory agencies, and pharmaceutical companies. Traditionally these phases of clinical trials can last 5-10 years, depending on the disease and trial objectives and patient outcomes, costing several hundred million dollars.

There are, of course, clinical trials that can be carried out exploiting the potential of repurposing of medicines and vaccines with rich human exposure data that have already been approved for human use. Therefore, repurposing or repositioning these candidates for new indications, with potentially less preclinical and clinical development costs, have been pursued aggressively.

However, one should be careful, since many obstacles must be overcome to carefully justify the biological mechanisms that ensure efficacy and toxicity for the new indications in the targeted patient population, drug development and manufacturing costs, funding for clinical trials and intellectual property considerations. Nevertheless, there are very active efforts all over the world by many non-profitsand in some cases by Pharma organizations themselves, summarized in a recent review (9).

A timely example is the use of the anti-diabetic drug Metformin repurposed for TB in a combination trial that has been funded by multiple organizations in India (10). It is known that Metformin, an AMPK modulator (adenosine monophosphate- activated protein) inhibits the growth of Mtb in host cells by controlling the autophagy pathway by augmenting the activity of anti-TB drugs. In this clinical trial Metformin (1000 mg) is administered in combination with a standard regimen of rifampicin, isoniazid, pyrazinamide, and ethambutol. This is a classic example of enhancing both host response to the pathogen and exploiting the activities of existing approved drugs against the pathogen. More such efforts should be undertaken to tackle the epidemic of Neglected Tropical Diseases (NTD).

Going forward

The hidden problem is a lack of understanding of translational science and research efforts that are required in the “valley of death” for many drugs and vaccine development (11). In many cases, failures occur during the lead optimization and preclinical development that involves efficacy and toxicity testing, not to mention failures in clinical trials that involve human genetic diversity. In the current environment and available infrastructure, this effort can take 10-15 years. None of our graduate curricula is geared to include translational science and research for obvious reasons. The costs associated with pre-clinical and clinical studies and the lack of translational science and research expertise in the academic and non-profit research community is a serious problem worldwide. This gap requires urgent attention by the governmental and non-governmental funding organizations.

Note that the organizational structure and processes required (the science of translation) (7) and the research effort to convert discoveries in biology as medicines are enormous. The trick is to make the valley of death into a “valley oflife” where we increase the probability of success, as we witnessed in the development of the COVID-19 vaccines. In addition, the clinical trial costs and timelines should be coordinated on a large scale to ensure safety and efficacy to demonstrate and clearly define patient outcomes that are economically viable. The timeline for vaccines for COVID-19 was just 1 year, with many hurdles in the translational pipeline that were overcome during this pandemic. The same can be achieved for TB and NTD epidemics in the next few years, and that’s an achievable challenge. Today, biomedical advances in biology, chemistry and pharmaceuticalsciences have the muscle to make this happen. However, there must be cultural, social, and political will to allocate the necessary resources and organizational structure to accomplish such an undertaking.

Simply put, there needs to be focused effort from not only the citizens, but also the from the healthcare industries, affluent philanthropies, international NGOs with a sense of urgency for the epidemic of NTDs. Interestingly, the US government alone has spent over 1 billion dollars on seven targeted NTDs from 2006-2020 (12). With over 3 billion people affected by these NTDs globally, this is a pittance comparedto what has been spent on the COVID 19 pandemic in 2020-2021.

Since we live in a global village, addressing NTDs is an imperative that should be undertaken not just by one nation but on a global scale for TB, and other infectious diseases that would probably get worse with changing economic and climate catastrophes that face us.

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Declaration

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