Extended Abstract

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EARLY PROOF OF CONCEPT WITH HUMAN VIRAL CHALLENGE MODELS IN VACCINE DEVELOPMENT

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The pharmaceutical industry is constantly searching for efficiencies for the development of new medicinal products. Viral vaccine development is no exception. The Human Viral Challenge (HVC) model has, for several decades, helped within the understanding of respiratory viruses and their role in disease pathogenesis. In a controlled setting using small numbers of volunteers faraway from community exposure to other infections, this experimental model enables proof of concept work to be undertaken on novel therapeutics, including vaccines, immunomodulators, and antivirals, also as new diagnostics.

Crucially, unlike conventional phase 1 studies, challenge studies include evaluable efficacy endpoints that then guide decisions on how to optimize subsequent field studies, as recommended by the FDA, and thus licensing studies that follow. Such a strategy optimizes the benefit of the studies and identifies possible threats early on, minimizing the risk to subsequent volunteers but also maximizing the benefit of scarce resources available to the research group investing in the research. Inspired by the theory of the 3Rs (Replacement, Reduction, and Refinement) now commonly applied within the preclinical trial, HVC studies allow refinement and reduction of the next development phase, accelerating progress towards further statistically powered phase 2b studies. The breadth of data generated from challenge studies allows for exploration of a wide range of variables and endpoints that can then be taken through to pivotal phase 3 studies.

Acute respiratory infections (ARIs) declare as Upper (URI) or Lower (LRI) tract infections and should move between the 2 compartments; ARIs represent the foremost common infectious diseases and are predominantly of viral etiology. The global burden of ARI is substantial with significant morbidity and mortality occurring in children, the elderly, and immunocompromised.

Influenza, RSV and HRV infection have similar symptomatology, but this differs in severity and predominance of upper, lower or systemic symptoms as has been described by the middle for Disease Control. However, it is not easy to diagnose between the different aetiologies of ARIs, and better diagnostics are needed. Symptoms are common to every infection and manifest on a gradient. Generally, but faraway from always, influenza infection is more likely to end in a patient feeling so unwell on fancy their bed and have a fever, than RSV, an HRV, CoV, or other cold viral infection, during which lifestyle is typically less impacted. The shared symptomatology of respiratory viruses requires one standard research platform which will be wont to evaluate respiratory illness pathogenesis and therefore the efficacy of candidate therapeutics. The HVC model allows the chance to review an epidemic in isolation. HVC studies and field studies are complementary research stratagems necessary for the event of effective ARI therapeutics. More work is required to identify and define more effective/predictive correlates of protection.

The lack of understanding behind some vaccine models must serve to reduce the impact of the many studies, both early and late phase if such poorly understood or inconsistent correlates alone are used as the primary outcome.

Vaccine development and usage over the years have significantly reduced the number of infections and diseases. Improved knowledge of immune protection and an enormous leap in gene-splicing has allowed the induction of a spread of the latest sorts of vaccines through the manipulation of DNA, RNA, proteins, and sugars. The creation of attenuated mutants, expression of potential antigens in live vectors, and purification and direct synthesis of antigens in new systems have immensely improved vaccine technology. Both infectious and non-infectious diseases are now within the realm of vaccinology. The profusion of the latest vaccines has enabled the targeting of the latest populations for vaccination also because of the cure and removal of infectious agents from their natural reservoirs. Still, like ancient infections like malaria and new infections like HIV, a potent vaccine is elusive, which poses an enormous challenge to the scientific world.

It is becoming widely accepted that HCMs can tangibly accelerate certain pipelines and add on to the body of data concerning a product and its interactions, both with the challenge agent and the host. As the HCM becomes popularized as part of the route to licensing, accessibility to the model, and relevant challenge agents may become more of an issue than acceptability. Efforts to form cGMP challenge agents more widely available are being supported by the NIH; however, historically, private investors have funded and thus driven the model, bridging the transition of HCM from academia to industry. Given the considerable investment required, it's unlikely that a lot of new players will enter the sector within the short-term which the challenge will remain a premium service with limited access.

With a global need for new antibiotics and antivirals and a low take-up rate by the industry for less-rewarding avenues and indications, it may fall to state institutions, including regulators alike to promote novel means of bringing investigational products rapidly to plug, where safety isn't compromised, and early efficacy data can enable the rapid prioritization of promising candidates.

In conclusion, although further evolution of the model may be required before it can address all the regulatory strictures, the HCM has already provided efficacy data for a large number clinical trials, principally for upper-respiratory-tract infections, and has been instrumental in providing

timely non-inferiority data for a range of new anti-influenza drugs. Requests for HCS still increase year over year, and it's to be expected that as early phase trials are potentiated, the amount and size of late-phase studies may be reduced in accordance with the value of the EP data.

The Human Viral Challenge Model (HVCM) may be a widely accepted alternative to field studies. The standardized exposure of intentional viral inoculation of volunteers in a controlled clinical environment enriches the prevalence of infection. This also permits the study of the entire disease lifecycle from health to disease and recovery back to health. These methods reduce study population size requirements and therefore the overall trial duration. The cumulative effect of these advantages is a risk and cost containing the accelerated route to market for antiviral drugs, diagnostics, and vaccines.