Moderna jockeys into Harvard

Moderna Therapeutics is powering up its immuno-oncology ambitions by tapping into the expertise of Harvard Medical School (HMS) researchers. The preclinical research collaboration, announced in September, includes setting up the Alliance for RNA Therapies for the Modulation of the Immune System (ARTiMIS), with $1.2 million in funding from the company. As part of the initiative, HMS-affiliated researchers will gain access to Moderna's synthetic mRNA (modRNA) and nanotechnology platform, in exchange for sharing insights into basic immunological processes with the ultimate aim of developing new agents to treat or prevent disease. A broader research collaboration set up with $2.45 million funding from Moderna will be led by Ulrich von Andrian. Von Andrian, a professor and director of HMS's Center for Immune Imaging, serves on Moderna's Scientific Advisory Board. His previous work has included studying the migration of immune cells in animals, and the new project will use Moderna's technology to manipulate immune cell migration between blood and tissues. He will also serve as program director for ARTiMIS.

Moderna was founded on the idea that messenger RNA can be reengineered to direct cells in the body to produce proteins with therapeutic effects. Such mRNA medicines and vaccines to treat infectious diseases and cancer have advanced into human trials, including phase 1 testing of a chikungunya antibody and personalized cancer vaccines, but these are still at the early stages of development. Moderna has 11 vaccines in human trials, and competitor BioNTech, based in Mainz, Germany, has 6 mRNA cancer vaccines of its own in clinical development. BioNTech had raised $150 million in an IPO by October 10. Moderna closed its own massive IPO a year ago.

mRNA vaccines hold particular promise when designed for local administration, and as agents for treating hepatic diseases because mRNA is taken up in the liver. Systemic delivery, however, remains a significant challenge. The company gave some details of its next-generation immune nanoparticle program at a Science Day event in May. In a presentation to investors, the company announced unpublished preclinical data showing it could deliver mRNA to 10–20% of T cells, natural killer cells, B cells and myeloid cells in vivo in animals and ex vivo in human blood.

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advocacy group Parent Project Muscular Dystrophy (PPMD). Feedback from regulators had to that point been overwhelmingly positive, according to Ingram But the FDA cited two main issues: safety concerns surrounding the risk of infection for intravenous infusion ports, and mouse study data suggesting the potential for renal toxicity.

"Neither of these issues were raised during the review," said Ingram. The company saw no signals of renal toxicity in the clinical trials, and the animal data corresponded to doses an order of magnitude higher than the doses proposed for use in humans. Ingram added: "There is nothing about the medicine itself that is increasing infection-related issues associated with ports."

The ports had been requested by the patient advocate community, noted PPMD founding president and CEO Pat Furlong on the same call. And children with DMD are often on chronic steroid treatment that could compromise their immune systems, predisposing them to infections.

Both concerns should be easy for Sarepta to address. But Stanley Nelson, a codirector of the Center for Duchenne Muscular Dystrophy and professor of human genetics at the University of California, Los Angeles, says a general risk of infection and renal toxicity at high doses in animal data and with other antisense oligonucleotides "don't seem like reasonable ways to be essentially denying approval, for the time being."

If the safety concerns aren't new and Sarepta wasn't given a chance to respond before the letter was issued, this could be the FDA's way to slap the company on the wrist for taking too long over the post-marketing study for Exondys 51, or to reset expectations following criticism it approved the drug despite safety concerns. Nelson says the decision is confusing, given data published in the Journal of Neuromuscular Diseases that in his opinion demonstrate that exon-skipping drugs like Exondys 51 and Vyondys 53 work as advertised.

The FDA would not comment on specifics surrounding the Vyondys 53 CRL or a link to the Exondys 51 approval. An agency spokesperson acknowledged there are many reasons why a company may need to modify post-approval timelines, but said the FDA is committed to working with companies on resolving issues causing delays.

In DMD, a mutation in the dystrophin gene blocks production of the protein needed for muscle contraction. The crux is whether any of these therapies can restore dystrophin to clinically meaningful levels. For Exondys 51, for instance, this is not clear, and Johns Hopkins's Alexander said Sarepta's problematic method of quantifying dystrophin increases were "one of the many elephants in the room." Much of the scientific debate at the FDA before the Exondys 51 approval revolved around whether relatively small increases in dystrophin expression seen in boys with DMD after treatment were likely to predict clinical benefit, and the fear that demonstrating efficacy once the drug was on the market would be difficult without a post-marketing study. Vyondys 53 leads to similarly small increases in dystrophin expression in boys by skipping exon 53.

Nelson says that evidence has accumulated showing small, naturally occurring dystrophin increases seen in some boys with similar DMD-causing mutations can lead to slower progression of pulmonary impairment. And in June a paper published in *Medicine* showed boys on long-term Exondys 51 are deviating from the disease natural history.

Speaking to the parent advocacy group, Ingram vowed to schedule a formal meeting with the FDA to begin addressing its concerns, but a date has not been confirmed. Despite the surprise decision, he remained optimistic Sarepta could get Vyondys 53 back on track by developing a risk mitigation plan, with the potential for a resubmission and rapid review within two months. ❐

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"What if the next Mila is treated when she is 4 or 5 [instead of 7]?" The development of milasen "is opening up an entirely new treatment path." Julia Vitarello comments on the treatment given to her daughter Mila, who suffers from Batten's disease; the so-called *N*-of-1 trial tested an oligonucleotide designed to correct her specific mutation. (*The New York Times*, 9 October 2019)

"This depends on having the support of regular people. If you can't convince the public that it's safe, it's going to go away." Diahan Southard, who led a course in forensic genealogy in October, on the new federal rules that restrict law enforcement's use of consumer genetic databases to those that explicitly inform their users that law enforcement might be using their site. (*The New York Times*, 5 October 2019)