Podcast Interview: Rino Rappuoli

I'm your host Prashant Nair, and welcome again to Science Sessions. The rise of antibiotic-resistant microbes is now a well-documented threat to global public health. Among the superbugs that have received widespread attention is methicillin-resistant *Staphylococcus aureus*, commonly called MRSA, a bacterium that can cause life-threatening skin, lung, and blood infections against which last-resort antibiotics are of little use. According to the Centers for Disease Control and Prevention, the rates of hospital-acquired MRSA have been declining over the years, but the bacterium remains formidable, with more than 75,000 people infected in the United States alone, by some estimates. Pharmaceutical companies have tried unsuccessfully to fashion a vaccine to protect against *Staph aureus*. Notably, a vaccine made by Nabi Biopharmaceuticals, now called Biota, and another made by Merck both failed in Phase 3 clinical trials. But given the range of health conditions the bacterium can cause and the ease of its spread, interest in a MRSA vaccine has not flagged, and some drug giants and biotech firms are still on the trail. Last fall, for example, Pfizer reported preliminary findings from a Phase 1/2 clinical trial of its combinatorial vaccine candidate, showing that the formulation was safe, well-tolerated, and functional in healthy adults. Also in the pipeline is a candidate from GlaxoSmithKline called 4C-Staph. That effort is led by Rino Rappuoli, formerly Global Head of Vaccine Research at Novartis in Siena, Italy, a division now acquired by GSK. Rappuoli, who is a foreign associate of the National Academy of Sciences, recently reported preclinical trials of 4C-Staph in PNAS. I spoke to Rappuoli about the promise of this vaccine candidate and the challenges facing its eventual approval. The biggest challenge, says Rappuoli, might be the bacterium’s complex biology. *Staph aureus* has a range of weapons in its armory to attack and evade the human immune system. These virulence and immune evasion factors – some secreted and others on the bacterium’s surface – render the pathogen a slippery target.

Rappuoli: So we need to find something which is universal that allows the bacterium, basically, not to escape, and that will basically provide immunity against any form or virulence of the bacterium.

PNAS: To do that, Rappuoli’s team used a reverse engineering approach, sequencing several strains of the bacterium to identify common virulence factors that could together compose a potent vaccine. The team homed in on five antigens crucial to the pathogen’s disease-causing ability, modified the antigens to make them safe, and combined them with an adjuvant that stimulated the immune system and enhanced efficacy. The team then tested the formulation, named 4C Staph, in four different mouse models that mimicked various manifestations of human *Staph aureus* infection, including peritonitis and pneumonia. The mouse models revealed that the combined vaccine was better at protecting against clinical strains of *Staph aureus* than single antigens. Adding the immune-stimulating adjuvant further increased the protection.

Rappuoli: Therefore, now we believe we have a pretty strong vaccine, which is a combination of very well-screened virulence factors, and one very powerful adjuvant that basically not only increases the immune response, but also provides the right type of immune response.

PNAS: But the mouse studies are merely the first step in what will no doubt prove to be a long road to clinical trials. It can take up to a year just to manufacture a trial-ready version of the vaccine candidate, and a few more to test its safety, dose, and
immunogenicity in humans before a full-on trial of efficacy can be launched. I asked Rappuoli to provide a rough estimate of a timeline.

**Rappuoli:** I would say three, four years before we will know whether the vaccine that we have actually has a chance to work, and then, if as we expect, we are going to get some proof of concept that the vaccine works in men, we’ll take another six years before it’s going to be licensed. So if we are lucky we will be 10 years away.

**PNAS:** Despite the poor showings of previous vaccine candidates in clinical trials, Rappuoli says he is optimistic about 4C-Staph, given the promise shown in the preclinical studies. I asked Rappuoli how a major pharmaceutical firm decides whether or not to take on a particularly challenging vaccine target, such as *Staph aureus*.

**Rappuoli:** For a vaccine company there are a few factors which are important. The first one is medical need; in this case, it’s clearly evident. The second one is feasibility: Do we have the science right to expect the vaccine will be possible, say, in 10 years from now? Finally, if the vaccine is feasible, then the next question is what will be the return of investment, because obviously companies need to make sure that if you invest a billion to develop a vaccine, at the end that investment is going to be recovered.

**PNAS:** Those questions, says Rappuoli, factored into the decision to pursue a protective vaccine against *Staph aureus*. You can find more podcasts at pnas.org