

## Laudatory speech for Rino Rappuoli

[Check against delivery.]

Rino Rappuoli hails from one of the most beautiful spots on earth, the hills of Tuscany, Italy. He was born near Siena and went to school there, including his Ph.D. degree at the University of Siena. A homegrown son!

Despite the beauty of Tuscany and especially of Siena, there is also a dark aspect of this region. In 1348, almost 700 years ago, Siena was one of the largest cities in Europe but it was decimated by the bubonic plague. About 70% of the population died, and the ruins of the never-finished cathedral still stand so many years after the plague afflicted this beautiful city. The cathedral would have been the biggest church in the world were it not for the plague caused by the bacterium, *Yersinia pestis*. Early on, Rino was attracted to science and what pathogens can do; he was reminded of this each day as he walked past the unfinished walls of the Siena cathedral on the way to University. In 1978, he joined Sclavo which was a local company developing preventive and therapeutic vaccines.

Despite his deep ties to Siena (where he still lives), Rino visited the U.S. several times working at the Washington University in St. Louis, at The Rockefeller University with Emil Gotschlich, and at Harvard University working with John Murphy and Alwin Pappenheimer.

During 1978-1984, Rino developed *Corynebacterium diphtheriae* strains hyper-producing CRM197 (cross-reactive material 197) which did not result in a vaccine against diphtheria, per se, but CRM197 became the carrier protein for conjugate vaccines against *Haemophilus influenzae*, meningococcus, and pneumococcus. Most infants worldwide receive vaccines containing CRM197.

During the period of 1984-1995, Rino cloned and sequenced genes coding for the pertussis pathogen. This work led to the first acellular whooping cough vaccine approved in Italy in 1993 and in the U.S. in 1995. Within two years, the disease whooping cough – Keuchhusten in German – was essentially eliminated in Italy. Pretty impressive for someone barely 40 years old!

Meningococcus comes in five flavors: A, B, C, Y, and W135. In 1989, Sclavo started making meningococcus vaccines for subtypes A and C, taking advantage of CRM197 (the elimination of meningococcus C from the U.K. by the year 2000 was the reward).

In 1992, Sclavo was sold to Chiron, and Rino in time became vice president for this California-based high-tech company. While searching for a way to make a vaccine against meningococcus type B, Rino saw a solution. Although conjugate vaccines consisting of CRM197 and the polysaccharide capsule were successful the other flavors of meningococcus, the type B meningococcus has sialic acid as the terminal sugar on its polysaccharide. No protective antibodies can be made against this sugar in humans as sialic acid is a terminal sugar on many components of the human host, and thus we humans can't make good antibodies against sialic acid. Rino's solution was Craig Venter, who had just sequenced the entire genome of a bacterium, *Haemophilus influenzae*.

Rino persuaded Craig Venter to get the sequence of meningococcus type B, and Rino and his colleagues were then able to identify surface proteins of the bacterium which could be used as vaccine components (rather than the capsule of polysaccharide). This process is now called reverse vaccinology as it first involves sequencing (the bacterial genome) and then the building/construction of the vaccine, rather than the other way around. Meningitis B vaccines based on this approach are sold worldwide and this technology (reverse vaccinology) is now one of the most accepted ways to make vaccines against old and newly emerging pathogens. The concept of reverse vaccinology was first published by Rino in *Current Opinion of Microbiology* in 2000. It has been cited more than 513 times per Google Scholar, which is a very high number in this field of science. In fact, Rino's h-index is an extraordinarily high 110, meaning that he has 110 papers which have been cited more than 110 times.

In Italy in 1997, an influenza virus vaccine was licensed containing the adjuvant MF59. No adjuvanted vaccine had been approved since the introduction of alum in the 1920s. The licensure of the MF59 adjuvanted influenza virus vaccine was a major breakthrough and was only possible through the extraordinary talents of Rino who married basic science with the industrial know-how to get to a licensure. Today, we have many vaccines which have novel and highly protective adjuvants. SHINGRIX, a vaccine against herpes zoster – Gürtelrose in German – is a major improvement over older vaccines because of the use of the adjuvant AS01. Even 80 year old patients show wonderful, protective responses to this novel adjuvanted vaccine. This is just one example of a novel generation of adjuvanted vaccines which would not have been possible without Rino's exceptional work in the 1990s.

In 2006, Chiron was acquired by the Swiss company Novartis. Rino continued his trailblazing, rational approach to introduce novel vaccine candidates. He reported the first vaccine built from synthetic biology in an effort to prepare for a possible emerging H7N9 pandemic influenza virus strain.

Another new way to design vaccines was formulated by Rino and it is referred to as structural vaccinology. There, Rino takes advantage of novel, structural technology such as cryo-electron microscopy or x-ray crystallography which opens the way to design vaccine constructs which do not exist in nature or are improvements over what was possible to manufacture in the past.

Rino does not stand still. Novartis sold most of the vaccine business to GlaxoSmithKline and he is now trying to merge the culture and expertise of big pharma into new, safe, and effective vaccine products. In 2008, he developed a non-profit vaccine institute with the help of Novartis aimed at producing vaccines against selected diseases which are outside of the profit-making domain of big pharma. This institute in Siena is named the GSK Vaccine Institute for Global Health (GVGH).

In summary, Rino Rappuoli has succeeded to transfer basic science knowledge towards commercial vaccine products and has thus succeeded where many scientists fail. He deserves the credit for having persevered over many years to make this dream become reality. And we are thankful to him for that. Congratulations!