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Vaccine-Development Collaborations Strengthen Ability to Respond to Pandemics

Disease-preventing vaccines are medical stalwarts of our age, defending us against infectious maladies as diverse as influenza, measles and smallpox. Much less-known are their cohorts in immunization, adjuvant compounds that are often added to vaccines to increase their effectiveness, versatility and reach.

“In the past, vaccines have largely been ground-up bits of the pathogens they target to create immune responses that protect the body,” notes Darrick Carter, Ph.D., vice president for adjuvant technology at the Seattle-based Infectious Disease Research Institute (IDRI). “As the science has advanced, they’ve become cleaner and cleaner. Modern vaccines are so pure that they may not activate a sufficient immune response. “That’s where adjuvants come in. They trigger and enhance the immune response. In fact, they do much more.”

Opening the Door to Innovation

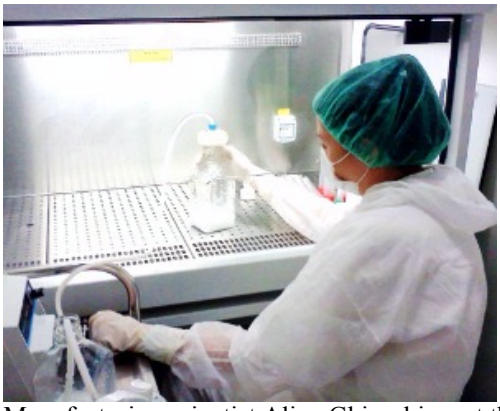
For IDRI, vaccine adjuvants’ catalytic nature might stand as a science metaphor for the real-world process that makes the agents possible—an alliance of partners working together to immensely expand the effectiveness of all members. IDRI’s core mission is to advance new products for fighting disease in poverty-stricken countries, with an emphasis on collaboration with other organizations. Prime examples are partnerships the institute has undertaken with scientists in Romania and India to share adjuvant technology and expand vaccine capabilities in each case—but in decidedly different ways.

“For Romania, our collaboration with IDRI has been essential to our effort to develop a capability for manufacturing influenza vaccine in the event of a ‘bird-flu’ pandemic,” says Adrian Onu, Ph.D., project director at the Cantacuzino Institute in Bucharest. “We have the technology to produce the vaccine, in limited quantities. IDRI’s adjuvant technology gives us the ability to significantly expand the doses available and produce adequate supplies for our people, if the need occurs.”
The stable emulsion adjuvant technology transferred to Gennova Biopharmaceuticals Ltd. (referred to as Gennova or GBL) in Pune, India, is essentially the same as for the Cantacuzino partnership, but with different objectives, Carter notes. “Our partnership with them opens the door to new breakthroughs,” he says.

Adds GBL’s CEO Sanjay Singh, MD, Ph.D.: "Bringing effective vaccines to India will not only end death and disease, it will help many of our poorer citizens to lead more productive lives, and move out of poverty. The malaria vaccine candidates under development at GBL with MVI and IDRI as partners will get the priority, but we will also be able to work with other diseases of significant concern in the Indian subcontinent, such as leishmaniasis, tuberculosis, and cervical cancer caused by human papilloma virus.”

Adjuvants: Helpful Partners

Vaccines work by exposing the body to weakened, killed or fragmented particles of a specific targeted pathogen, such as an influenza virus. These agents—called antigens—stimulate the immune system’s antibody-producing cells to become sensitized and in place to fight the potential full pathogen in the event of actual exposure.



Manufacturing scientist Alina Ghiorghisor at the Cantacuzino Institute performs sterile filtration of one of the three adjuvant batches manufactured by the Cantacuzino Institute in July 2011. Photograph by Adrian Onu.

Adjuvants don’t have any kind of immunizing capability themselves but by mimicking the pathogen’s traits they do have a tremendous ability to stimulate the immune system much more vigorously. There are many types of adjuvants, including salts (ionized compounds) of aluminum and other minerals, oil-based emulsions (suspensions of oil in water or water in oil), and virus-derived proteins called virosomes. Adjuvant compounds can be developed from sources as diverse as bacteria, the bark of the South American soapbark tree, mineral oil and squalene, a derivative of shark liver oil. Aluminum salts—based on substances like aluminum hydroxide and aluminum phosphate—have been known for more than 70 years and have long been the adjuvant type most commonly used in human vaccines in the United States.

Adjuvants do their work in varied ways, depending on their type and formulation, the antigens they are paired with, the target and even the delivery process. Thus, research continually focuses on finding the most effective combinations of compounds to optimize effectiveness. For example, adjuvants may contain agonists that directly activate specific cell receptors to stimulate the immune system or hold onto the vaccine, releasing it slowly to extend its period of exposure and enhance the immune response. That said, it's a given that nobody completely understands the process. What is understood are the effects.

"Adjuvants don't just boost vaccines' effectiveness by stimulating the immune system," says formulation engineer Christopher Fox, Ph.D., a member of IDRI's adjuvant team. "They can improve a vaccine's reach through 'dose-sparing'—reducing the amount of vaccine needed for a dose and increasing the available doses of a vaccine supply many times over. They can make 'dosage-sparing' possible—reducing the need for a three-shot dosage to two. They can broaden the protection a recipient receives from a vaccine—stimulating immunization to a wider range of viruses.

"The conservative estimate," Fox says, "is that the SE compound transferred to Romania will yield a three-to-four-fold dose sparing advantage. The emulsion adjuvant literature has documented influenza antigen dose-sparing as high as eight-fold. We're anxious to see what further research says."

Placing Medicines in the Hands of Those Who Need Them

Inspired by a college advisor who worked with infectious diseases in Central America, IDRI Founder and President Steven Reed, Ph.D., established the nonprofit Infectious Disease Research Institute in 1993 as an organization committed to diagnosing, preventing and treating neglected diseases endemic in poverty-stricken nations.

"We're different from most research groups," he says. "Our goal isn't simply research for its own sake but placing medicines in the hands of those who need them. I thought there would be a clear benefit to an institution that could combine quality research with the production capabilities of a biotechnology company."

IDRI accomplishments include development of the first defined vaccines for tuberculosis and leishmaniasis (both in Phase II clinical trials in 2012), a second defined TB vaccine (in Phase I trials) and novel adjuvants for multiple infectious and chronic diseases. IDRI is supported with funding from a range of sources, including the Biomedical Advanced Research and Development Authority (BARDA), the Bill and Melinda Gates Foundation, the Defense Advanced Research Projects Agency (DARPA), Eli Lilly Laboratories, the National Institutes of Health, the international nonprofit organization PATH, the World Health Organization (WHO), the Murdock Charitable Trust and the American Leprosy Missions.

"We've worked on diagnostic, preventive and therapeutic agents for disorders as varied as tuberculosis, leprosy and Chagas disease," Reed says. "We've been able to make a difference in millions of lives around the world and we look forward to helping millions more."

Refined and Improved

IDRI's current adjuvant technology originated at a different Seattle-based organization, a for-profit biotechnology company called Corixa. There, Carter, Thomas Vedvick, Ph.D., and other colleagues developed highly regarded formulations, including an oil-in-water emulsion of monophosphoryl lipid A (MPL). MPL is a component of the recently approved human papilloma virus vaccine Cervarix. In 2005, after Corixa was acquired by GlaxoSmithKline Biologicals, the team and their research moved to IDRI.

"Since we've been here we've been able to refine and improve the adjuvant formulations so that it's not the same project it was," notes Vedvick, who serves as IDRI's director of process sciences. Refinements include replacing the MPL molecule with synthetic analogues like glucopyranosyl lipid adjuvant and making the compound more stable and scalable to mass production.

The scientists note that one of their reasons for coming to IDRI was the thought that they could make an important contribution to IDRI's overseas health mission. The institute's first adjuvant technology transfer effort was to a biomedical research Institute in Brazil for work on human vaccine development. But, while cooperation was good, the project didn't progress well.

"We picked up the ball and moved on," Vedvick says. "We looked at a list of 10 or 12 sites preapproved by WHO, and it included the Cantacuzino Institute in Romania. They were quite a bit further along with their antigen work and were really motivated to create mechanisms to expand their capacity."

Enhancing Romania's Capabilities

The Cantacuzino Institute is officially the National Institute of Research and Development for Microbiology. Originally founded as a private laboratory in 1901 by Ioan Cantacuzino, M.D., it's universally known by his name. As the principal technical and scientific medical unit affiliated with the Romanian Ministry of Health, it was the country's first line of flu vaccine development in 2009, when the possibilities of swine flu (H1N1 virus) and bird flu (H151 virus) pandemics were a worldwide concern.

"We made something like three million doses of the H1N1 vaccine," Cantacuzino's Onu says. "We could have made up to six million, but as it turned out the vaccine wasn't needed. For H5N1, two shots would be needed, so the most we would have would be three million doses."

It was clear that against Romania's population of some 23 million, the potential supply would have been inadequate. More ominously, when government officials sought to purchase additional H1N1 vaccine from other European nations to support a vaccination campaign, none was available. "Every country has its own priority," Onu says. "It's quite important for us to have our

own manufacturing capacity."

As for avian flu vaccine, Cantacuzino had made progress on producing H5N1 vaccine, but the work was limited. The Romanian scientists didn't have a vaccine but they could demonstrate that they were close to having one. On that basis, they received a WHO grant to support additional work. And, they were placed on the WHO list that led to discussion with IDRI.

Training and Equipment

"The Cantacuzino project was pretty straightforward—providing the emulsion technology to increase the availability of dosages for influenza," Fox notes. "The idea was to come up with a potential product as quickly as possible so we went with the SE formulation since its regulatory pathway would be the most straightforward based on the extensive safety and efficacy history of a similar formulation produced by Novartis called MF59."

Once the project was underway, two-way site visits and training followed. Onu and three technicians came to IDRI's Seattle facility for a week of training in adjuvant production. The IDRI team produced a batch while the Cantacuzino team observed. Then the Romanian scientists made two batches while monitored by their IDRI counterparts.

Cantacuzino had to acquire some advanced—and rare—equipment available only in the United States. Needed was a high speed mixer to prepare the materials and a microfluidizer to make the tiny particles involved even smaller. About six weeks after the Romanians' visit to IDRI, Vedvick and Fox visited Cantacuzino to make sure the proposed equipment installation plans were in order.

Participants from the Cantacuzino Institute are discussing topics of interest with Dr. Vedvick during the one-day adjuvant course presented by IDRI in Bucharest at the Cantacuzino Institute on June 10, 2011. Photograph by Patricia Hon.

Three months later, a six-member team from IDRI returned to oversee the Cantacuzino staff's production of two more adjuvant batches. They also conducted a day-long workshop on adjuvants for everyone at the institute. Face-to-face visits were important but consistent biweekly teleconferences throughout greatly facilitated progress in the project.

"We are quite a long way toward getting the vaccine accomplished," Onu says. "We're working toward achieving the ultimate vaccine, the lowest dose that can be used. From there we will go to animal testing and clinical trials. Only then can we talk about having a vaccine."

Once a vaccine is achieved, the question of what to do with it will depend on circumstances. Since the adjuvant is quite stable, it makes sense to prepare it in advance. Mass production of antigen can wait until the strain of influenza to be dealt with is clear, Onu says. He notes that the devices acquired in 2010 are sized to the pilot project. Once the vaccine/adjuvant formulation is perfected, more extensive equipment will be needed to support mass production.

Onu appreciates the process that has gotten Cantacuzino as far as it has. "IDRI's assistance has been essential for us," he says. "Nobody can do it alone. You cannot do this work without collaborations. It would be like reinventing the wheel each time." The approximately $1.4 million funding for the project, including both technology transfer and preclinical evaluation of the adjuvanted vaccine, is being underwritten by the Biomedical Advanced Research and Development Authority, a U.S. Department of Health and Human Services agency.

IDRI/Gennova: "A Fantastic, Innovative Partnership"

While the basic emulsion technology transferred to Gennova Biopharmaceuticals Ltd. in India is the same, the work envisioned is very different—an effort to advance vaccine capabilities for a range of diseases.

"With Gennova," Fox says, "the adjuvant won't be used as it was in the Cantacuzino project. We expect to use it against different disease targets with tailored recombinant anitgen proteins paired with synthetic TLR agonist emulsions and other formulations."

The IDRI/GBL partnership had its beginnings in a visit IDRI staff made to India. Singh had served as head of malaria-vaccine antigen research at the National Institutes of Health in the United States. In 2006, he decided to leave his position at the NIH and start a biotech company in Pune, India.

"GBL is now one of the leading biotech companies in the area of biotherapeutics, focusing on applying innovative technologies for large-scale manufacture of recombinant biotherapeutics that results in lowered product costs without any compromise in quality," Singh says. Using this model of affordable health care through innovations, GBL has worked since 2007 on developing several malaria vaccine candidates from process scale-up to clinical trials. "When IDRI visited," he says, "I suggested the organizations collaborate on the same model to improve antigen/adjuvant formulations for malaria as well as focus areas of IDRI."

Events moved quickly. Reed and Carter visited Pune in early 2010 and in August GBL researchers went to Seattle for two weeks of training in adjuvant manufacture and quality control. The process culminated not only in a partnership but in construction of a new building named as Gennova Vaccine Formulation Center (GVFC)—dedicated to the work. The new facility opened in early 2012.

Complex Processes, Multiple Targets

"Within about a year's time," Carter notes, "the technology had been transferred and a new facility for infectious disease vaccines was underway in Pune with the goal of manufacturing both antigen and adjuvants for infectious diseases."

The new GVFC encompasses some 44,000 square feet, including multiple analytical laboratories, antigen and adjuvant formulation development labs, manufacturing and filling suites, materials management facilities, and extra room to accommodate future expansion. The overall project represents an investment of $8.4 million. The project was supported with funding and consultation from the Malaria Vaccine Initiative, a global program of the international nonprofit organization PATH.

The initial target for the facility is an improved vaccine/adjuvant formulation for malaria but the scientists on both sides look forward to the work on tuberculosis, leishmaniasis, leprosy and human papilloma virus. The leishmaniasis technology has already been transferred to Gennova.

"We anticipate an innovative, creative and productive association with Gennova," Carter says. "This is a fantastic partnership."

A Model Approach

"In and of themselves," Reed says, "the Cantacuzino and Gennova projects represent important contributions to overseas health issues. More than that, the process has given us a model for antigen and adjuvant technology transfer that can be followed with other partners in other countries. We're currently looking at possibilities for this approach in China, where we're seeking to identify partners to work with."

In-country manufacturing offers significant advantages, he notes, since local partners can work more effectively with their country's regulatory agencies, are almost certain to understand the human and logistical challenges there and are likely to develop a beneficial sense of ownership for the product. Furthermore, the product can most likely be developed at lower cost in-country.

"This collaborative approach ensures that our partners have the resources and expertise for future vaccine development," Reed says. "This is a process in which we can fulfill our commitment and they can gain essential capabilities. It's a win-win."

By Ralph Fuller