Ludwig and CRI have for many years been at the leading edge of cancer immunology and immunotherapy.
A MARRIAGE OF LIKE MINDS

At some point in the early 1990s, Ludwig’s former CEO and scientific director Lloyd Old concluded that the field of tumor immunology had matured sufficiently to have its implications put to the test in clinical trials. A legendary cancer immunologist, Old had helped launch the Ludwig Institute for Cancer Research in 1971, right around the time he was appointed medical director of the Cancer Research Institute (CRI). Over the next quarter century, he worked with researchers in both organizations to help build the scientific foundations of cancer immunotherapy.

Under Old’s direction, Ludwig and CRI had by the mid-1990s both begun funding small immunotherapy trials. “After a few years of doing this, we looked back and realized we really hadn’t moved the dime,” recalls Jill O’Donnell-Tormey, who is today CEO and scientific director of CRI. The problem, Old concluded, was that there was too little coordination between the funded researchers and their various studies. A more cohesive effort was in order. That recognition culminated in the establishment of a research network that Old named the Cancer Vaccine Collaborative. The network’s scientists, based mainly in New York at the outset, were tasked with developing an effective cancer vaccine.

Fifteen years on, that venture has expanded to include leading clinical and research immunologists in a dozen countries on four continents and is now known as the CVC Clinical Trials Network, or CVC for short. It has forged partnerships with 15 pharma and biotechnology companies and become a vital force in the design and testing of novel immunotherapeutic concepts and combination strategies. In 2015, Ludwig and CRI launched two new immunotherapy trials through the CVC, bringing the total running under its banner to five. One is testing the effects of durvalumab, a checkpoint blockade antibody against PD-L1 made by MedImmune, as a treatment for the aggressive brain cancer glioblastoma multiforme (GBM). The other, led by George Coukos, director
of Ludwig Lausanne, seeks to treat advanced, drug-resistant ovarian cancer by combining durvalumab with another investigational immunotherapy named Motolimod—a Toll-like receptor 8 (TLR-8) agonist—made by VentiRx Pharmaceuticals.

“Ludwig and CRI have for many years been at the leading edge of cancer immunology and immunotherapy,” says Jonathan Skipper, Ludwig’s executive vice president for technology development. “We’ve supported many studies critical to the advancement of this promising therapeutic strategy and we plan to maintain our leadership in the field.”

The New York Protein
By 2001, Ludwig had already built a formidable infrastructure for translational research. It was also assembling a capable clinical trials management team that could support global, multicenter studies and had rights to NY-ESO-1, a protein Old had co-discovered that is found almost exclusively on cancer cells. Preclinical studies suggested it showed promise as a target antigen for a cancer vaccine.

The fledgling CVC began studying how best to design, formulate and deliver an NY-ESO-1 vaccine. “It took about 10 years and over 50 small trials getting there,” says O’Donnell-Tormey. “Our candidate vaccine elicited potent anti-vaccine immune responses, but we couldn’t consistently see clinical responses in patients.”

The effort wasn’t wasted, however. Ludwig’s Chief Medical Officer Ralph Venhaus points out that a decade of honing and testing the NY-ESO-1 vaccine turned the members of Ludwig’s clinical management team into experts in immunotherapy trials. The studies had been equally instructive for the growing network of CVC immunologists. As a bonus, they now had a viable cancer vaccine candidate, one that elicited the right kinds of immune responses. Old, who died in 2011 of prostate cancer, suspected it just needed some kind of extra immunotherapeutic boost to cut past the tumors’ defenses.

Catching a wave
Such candidate therapies, as it turned out, were coming up fast in the industrial pipeline, and the CVC’s clinical immunologists wanted to get their hands on them. Some in earlier stages of development (like GITR agonists, which Ludwig and CRI are developing) were designed to directly amp up anti-tumor immune responses. Others—particularly the checkpoint blockade antibodies against cell surface proteins PD-1 and CTLA-4—released the brakes the immune system imposes on its cellular foot-soldiers. These, pushed by Ludwig MSK’s former director James Allison and others, were closer to market, or already there by 2011. But the network’s researchers couldn’t get their hands on any of them.

The trouble was drug companies were not enthusiastic about academic researchers interfering with the development of their products and even less so about supporting the expense and administrative bandwidth required to run the trials that the scientists requested. There were strategic barriers as well, especially when it came to combination therapies—a particular goal of Ludwig and CRI—since agents of interest were frequently owned by different companies. “Back then,” says Skipper, “different companies very rarely tested their products together in clinical trials, let alone their investigational agents.” Yet the network’s true potential could only be unleashed if its immunologists had access to proprietary, investigational agents.

Aware of this, Adam Kolom—a former private equity investor who had devised and brought to CRI a philanthropic venture capital
mechanism to hasten drug development—began working with Skipper to identify ways to overcome industry’s resistance. Their model powers the network today. “It removes the obstacles to getting proprietary agents into the hands of the CVC’s academic researchers, allowing them to do their most ambitious clinical research,” says Kolom, who is managing director of the CRI Venture Fund. “We’re like a Make-A-Wish Foundation for our principal investigators.”

The wishing machine
The model is structured to be guided above all by the needs of Ludwig and CRI’s primary constituencies: cancer patients and clinical researchers. Patients who enroll in the trials get early access to cutting edge combination therapies or to agents that might not otherwise have been used for their particular type of cancer. The CVC trial examining checkpoint blockade for GBM—a swiftly lethal cancer for which there are essentially no effective treatments—falls into the latter category.

The researchers, meanwhile, get to ask important clinical and scientific questions using rigorously characterized and clinically pedigreed samples obtained from trial participants. They also set the research agenda and get hassle-free access to the proprietary drugs they need to test their clinical hypotheses. “We come to the researchers with a virtually turnkey operation,” says O’Donnell-Tormey. CRI calls the combination of all these elements—the venture fund, access to experimental drugs, the partnership with Ludwig—the Clinical Accelerator.

The CVC’s management team includes, among others, Skipper, Kolom, O’Donnell-Tormey, Venhaus, Vanessa Lucey, associate director of the Clinical Accelerator at CRI, and Ludwig MSK’s Jedd Wolchok, who serves as director of the CVC Clinical Trials Network. The team canvasses the opinions of network members about the key questions that the field would like answered. “In no way is this a monarchy,” says Wolchok, “nor is it an anarchy. This is crowdsourcing at the highest level.”

Once the leadership team has picked winning hypotheses, Skipper, Kolom and their colleagues scan the industry for agents essential to their evaluation. If, as is often the case, drugs from different companies are to be tested together, they have developed a formula for managing data access, safety reporting, publication rights and intellectual property that makes the partnership as painless as possible for all parties.

Such collaborations are of obvious benefit to small, possibly cash-strapped biotech startups. But they’re also of value to larger pharma players. “We’re effectively doing a business development function for them,” notes Skipper. “If the combination therapy tested in a trial proves successful, they will not only have clinical data supporting the new immunotherapeutic
strategy for their drug, but will have also found a partner for product development without having had to invest very much in the usual due diligence."

The drug companies also benefit from access to the CVC’s brain-trust of leading cancer immunologists. “We hear from MedImmune and our other pharma partners that this opportunity to interact with people who have a depth of experience in immune oncology is very valuable to them,” says Wolchok. “The occupational half-life of someone in academia is quite a bit longer than that of an equally qualified person in industry, so it’s good for them to have a stable source of cognitive and clinical power.”

A gazillion little wheels
To alleviate the financial concerns of companies, CRI covers a share of the cost of running clinical trials through its non-profit CRI Venture Fund, which is structured to be replenished by success-based milestone payments from partner firms. Another obstacle, industry’s reluctance to take on the sponsorship and management of externally proposed trials is solved by Ludwig’s Clinical Trial Management (CTM) team, which is well versed in the requirements of regulatory agencies.

“The Clinical Trials Management operation has a gazillion little wheels,” says Venhaus. “It is a giant project.”

Ludwig’s CTM oversees everything from creating trial protocols that meet industry standards to obtaining approvals from ethics boards and regulatory agencies. It also vets and prepares clinical trial sites and oversees the conduct of the trials. The CTM, further, manages the proper collection, processing and storage of the clinical samples—a resource that has yielded critical insights into the molecular and cellular biology of immunotherapeutic responses.

The CTM’s institutional experience with immunotherapy has proved invaluable. “Because of that knowhow, we can take an idea on the back of an envelope and turn it into a workable, fully developed clinical trial protocol,” says Venhaus. “If researchers wanted to get that done with a contract research organization, they’d have to spend weeks and weeks to get them to execute it correctly.”

Online and active
In 2012, Ludwig and CRI launched an ongoing partnership with MedImmune, the global biologics research and development arm of AstraZeneca. The agreement gave CVC researchers access to the company’s checkpoint antibody portfolio for evaluation alone or in combination with other immunotherapies.

Such combinations are a particular focus of the field, thanks in substantial measure to work done by Wolchok and other researchers.
demonstrating their complementary effects in advanced melanoma. Wolchok is co-chair of a CVC trial running now in which durvalumab and MedImmune’s anti-CTLA-4 antibody, tremelimumumab, are being used together to treat a variety of other solid tumors. Many patients in the trial might not otherwise have had access to these promising agents as treatments for their particular malignancies.

At the same time, Ludwig and CRI are increasingly turning their attention to targeting less exploited immunologic pathways to target tumors. They recently signed, for example, an agreement with the biotech Targovax to test its candidate oncolytic virotherapy—in which an engineered virus is used to target tumors—with other immunotherapies. This trial too is based on a preclinical study in which Wolchok and Ludwig MSK’s Dmitriy Zamarin showed that a separate oncolytic virus they’re developing induced dramatic regressions of tumors in a mouse model of melanoma when it was delivered with CTLA-4 blockade.

The ovarian cancer trial being led by Ludwig Lausanne’s Coukos is another such example. It combines durvalumab with VentiRx’s drug Motolimod to treat drug-resistant ovarian cancers in patients receiving standard of care chemotherapy. Durvalumab strips away a defense used by cancer cells, exposing them to attack by killer T cells. Motolimod, meanwhile, activates a protein called Toll-like receptor 8 (TLR8), which is found in a variety of immune cells and serves as an alarm for the frontline forces of the immune response.

The expectation is that Motolimod’s activation of TLR8 will create conditions within tumors that are optimal to enhancing the effects of durvalumab. Further, given with chemotherapy, Motolimod might additionally boost anti-tumor responses by helping the immune system better “see” the molecular signs of cancer. Together, it is hoped, the therapies might decimate the most resistant of ovarian tumors.

Old’s endlessly characterized NY-ESO-1 has not been forgotten either. Ludwig and CRI have tested their cancer vaccines in combination with a checkpoint blockade and are preparing to expand this combination to a pair of checkpoint blockade therapies. That’s in addition to efforts by many researchers and institutions to devise their own NY-ESO-1-related therapies based on the work done by Ludwig and CRI researchers.

In any case, there’s no shortage of immunotherapeutic pathways for Ludwig and CRI to explore and exploit. “The question in the field now is how to expand that proof of concept we’ve obtained for immunotherapy in such cancers as melanoma and kidney and lung cancer to a broader variety of cancer types and patients,” says Kolom. “To get to where we want to be for the next generation, where we have the right drug picked for the right patient, we have to have a much more sophisticated understanding of what to look for in the tumor’s interaction with the immune system. Data from the Ludwig-CRI trials will provide the road map for that endeavor.”

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