The Pulse on Global Trials

By Matthew Howes

Since being named "Breakthrough of the Year" by *Science* magazine less than two years ago, cancer immunology has been taken from the fringe to the forefront. In a 2014 Global Innovation Survey by inVentiv Health, immunotherapy was ranked number one—the most important area of cancer research, ahead of gene therapy and targeted chemotherapy. Susan Swain, past president of ASCO, calls it "truly remarkable."

Over a hundred years ago, the Father of Cancer Immunotherapy, William Coley, noticed a pattern of spontaneous tumor regressions in patients who experienced a serious skin infection called erysipelas. He theorized that a bacterial "toxin" from the infection was somehow the key.

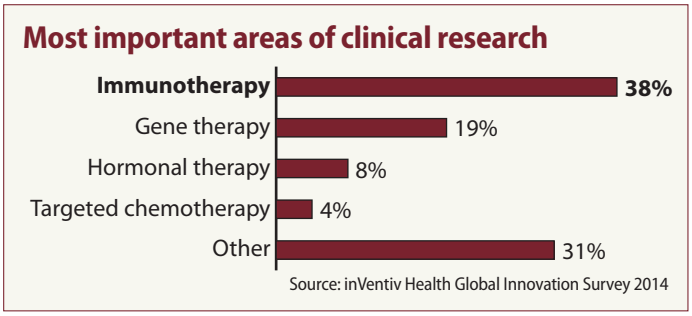
"Nature often gives us hints to her profoundest secrets, and it is possible that she has given us a hint which, if we will but follow, may lead us on to the solution of this difficult problem," Coley wrote in 1891. He began performing inoculations and seeing success with patients who had only weeks to live instead lived for years.

For 40 years, Coley treated hundreds of patients, many of whom went into remission. But because his work was not understood by the medical community, his method fell out of use. His approach was regarded by many professionals as junk science, and the American Cancer Society put Coley's toxins on the list of unproven quack methods.

After Coley's death, his daughter, Helen Coley Nauts, founded the most important organization in cancer immunology you've probably never heard of: Cancer Research Institute. CRIs mission was to build the scientific body of evidence that the body's own immune system can fight cancer.

The story of CRI essentially is the story of cancer immunology itself. Without CRI, cancer immunology would not exist today. For over 60 years, CRI has supported the scientists who identified first the T cell receptor—the part of a T cell that binds to antigen and functions as the T cell's ignition switch—and later the molecule called CD28 that functions as the T cell's gas pedal.

Then, in 1995, CRI identified the T cell's brakes, opening up a whole new view into cancer treatment. James Allison, Ph.D., pioneer in the field and director of CRI's scientific council, said, "Once you've generated T cells that can recognize cancer, you've got them basically for the rest of your life."



Known as checkpoint blockade, the treatment approach has seen some dramatic clinical responses in recent years, including ipilimumab (anti-CTLA-4), approved by the FDA for metastatic melanoma in 2011, and nivolumab (anti-PD-1), approved in 2014.

"I really believe that immunotherapy is what holds the promise for durable control, not just of melanoma, but of many cancers," said Jedd Wolchok, associate director of the CRI scientific council, who is conducting clinical trials of checkpoint antibodies and leading CRI's clinical program.

CRI is important not only for pioneering the vision of what cancer immunology could bring to oncology, but also for structuring a better model in which clinical trials take place in a collaborative community.

Core to that model is the Clinical Accelerator, designed to speed the development of new cancer immunotherapies. The most promising therapies involve combinations of different drugs that work in tandem to stimulate the immune system. But the existing model of drug development, which relies heavily on private pharmaceutical companies to conduct clinical trials, is not well suited to testing these combinations in a smart and coordinated way.

The Clinical Accelerator is the only nonprofit drug development incubator of its kind. It fosters collaboration among roughly 50 top academic researchers and 15 leading biopharmaceutical companies. By breaking down the natural competitive silos that tend to slow progress, the Clinical Accelerator helps bring better immunotherapies to patients more quickly.

"For reasons that have nothing to do with science, but everything to do with business, it's very difficult to get the proper pieces to come together in a way that makes the most sense," said Allison.

The Clinical Accelerator has made available to CRI scientists more than 25 new drugs that can be combined and tested in the clinic.

Trial funding comes largely from CRI's nonprofit venture fund, but by securing returns on investment from partner companies if drugs become successful, the model is designed to become self-sustaining over time. "It's a win-win-win situation," said Adam Kolom, managing director of the venture fund, "providing significant and immediate benefits to patients, researchers and industry."

But research doesn't end there. "We need to get at the science of why a drug does or doesn't work," said Ellen Pure, a member of CRI's scientific council. Insights generated from clinical trials need to feed back into basic laboratory research which, in turn, will lead to new discoveries that enhance treatment.

To facilitate this exchange, CRI established its Clinic and Laboratory Integration Program (CLIP), which supports researchers working at the intersection of basic and clinical research. CRI's interest in supporting the next generation of talent in the field is strategic.

"When I began my career in cancer research in 1989, CRI was the only organization that believed in supporting junior researchers as the future of cancer immunotherapy," said Drew Pardoll of Johns Hopkins University, "Without CRI, I would not be doing this today."

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