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Innovations

Corixa

Powering Immunotherapeutics

There is arguably no cellular system in the human body more complex or more diverse than the immune system. The body's ability to mount a successful attack upon a foreign pathogen or wayward cancer cell requires the collaborative efforts of a myriad of different cell types, often with amusingly anthropomorphic titles such as "professional" antigen presenting cells (APCs) and "helper" or "killer" T cells. Our incomplete understanding of the elegant complexity of the immune system has complicated our efforts to exploit it in the battle against cancer and infectious and autoimmune disease. Until recently, our therapeutic weapons have been limited predominantly to preventative or prophylactic vaccines and global immunomodulators like interferon or cyclosporin. The emergence of the human immunodeficiency virus (HIV) in the last quarter of the last century added extra urgency to the need to decipher the cellular and molecular communications that lead to an effective immune response.

Corixa, a Seattle-based company that develops immunotherapeutics, hopes to add significantly to our immunological armamentarium over the next few years. Corixa was created eight years ago this month, the result of a fittingly complex set of collaborations between both academic and industrial scientists, each bringing to the table his or her own scientific or commercial expertise. The company takes a collaborative approach to immunotherapeutics that integrates a wide range of technology platforms, each of which alone possesses significant partnering potential with other developers of immunotherapeutics and vaccine technology.

After twelve years at Seattle-based Immunex, Corixa cofounder Kenneth Grabstein was looking for a new challenge. Together with Steve Reed of the Seattle Biotechnology Research Institute (SBRI), he was interested in founding a company that would focus on the development of new tools to fight infectious disease, such as therapeutic vaccines. Little attention was being paid in the early 90's to the idea of therapeutic vaccines—vaccines that could be used in individuals in whom infectious agents had already taken hold, such as the growing legions of people living with HIV. The vaccines of the day were primarily effective in generating a humoral response, mediated by antibody-producing B cells, that was only effective in preventing infection by a microbe. However, once microbes have invaded the cells of the body, a cellular response, mediated by T cells, is key, particularly for viruses or pathogens that live intracellularly, such as HIV or *Leishmania*. Clearance of such agents requires cytotoxic T lymphocytes (CTLs) that actually seek out and destroy cells of the body that are infected. "We had learned that an effective immune response required activation of the cellular arm of the immune system," adds Grabstein, "but to accomplish this with a vaccine, we needed to develop technologies that could trigger and boost the CTL response."

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Immunex was one of the first biotech companies devoted to the development of immunotherapeutics. Steve Gillis, now Corixa's CEO, was founder of Immunex and was a key player in Corixa's genesis. According to Grabstein, Gillis' backing was instrumental. "Steve was well-known in the VC and industrial communities, and his experience was key to establishing and realizing Corixa's philosophy of partnering with big pharma." Gillis elaborates, "Our philosophy has been to rely not only on organic, internal discovery but also opportunistic product in-licensing and company acquisition. This approach serves us well, particularly in times when institutional investor interest is low." The advantages of this approach are compelling, as Gillis explains, "Working with larger companies to develop certain products can provide valuable financial resources as well as development skills or marketing muscle. Partnerships also diversify risk associated with biotechnology product development across the backs of multiple stakeholders."

An enthusiastic proponent of Grabstein and Reed's project from its inception, Gillis offered the duo $3 million in funding from Immunex if they could find matching funds from outside investors. 1993 was a tough year for biotech ventures looking for financing, however, and they came back empty handed. As it turns out, Gillis was being courted around the same time by Joe Lacob of the influential venture capital firm Kleiner-Perkins, based in Menlo Park, California, to head up a company Lacob was incubating to develop therapeutic vaccines—not against infectious agents but against cancer, a potentially huge market. Lacob echoes Grabstein's views on Gillis' star power in the biotech arena. "Getting a great CEO—one with vision and strong management experience—is key to any successful venture, " he says, "and Steve (Gillis) was very attractive to us for this reason." Gillis realized that many of the challenges the two groups were facing in devel-

oping therapeutic vaccines were similar, and he managed to get the two groups working together. "At first I thought the idea of merging the groups was unwise as it created a broader focus for the company, but the reality is that many of the necessary technologies, from antigen identification and delivery to adjuvants, were similar," says Lacob, "and when Gillis agreed to come on board to lead the new organization, I was convinced."

While Lacob's venture had the concept and the cash, he had yet to secure the "scientific capital" in the form of people and technology. The technologies covered three important components of the antigenic response: antigens, adjuvants, and efficient ways of delivering the latter to APCs. Working together, the group recruited top-notch scientific partners with the required expertise and licensed their technology. These academic founders included Martin "Mack" Cheever of the University of Washington and Olivera Finn from the University of Pittsburgh, both engaged in the discovery of cancer antigens. They were joined by Kenneth Rock of Harvard University, an expert in the study of antigen presentation leading to a CTL response. Rock, too, had been thinking of setting up a similar venture in the Boston area, but was sufficiently impressed with the Corixa blueprint to throw his hat in the ring. "I was impressed by their integrated and comprehensive approach," he says, "they saw the larger picture and understood that multiple components had to be in place for an effective T cell vaccine." With a scientific team in place, a venture capital round in 1994 raised $15 million based on the premise that the company would focus on transactions and partnerships with other biotech companies and with big pharma.

An early priority of the new company was antigen discovery. The development of any vaccine, whether prophylactic or therapeutic, first requires the identification of the antigenic "Achilles' heels" that trigger the body to mount a response. These were the days of the so-called "genomic revolution," as companies raced to identify disease-related genes with the hopes of patenting them, and Corixa was no exception. Their efforts have led to 800 "antigen" patent applications worldwide, with about 120 already issued. To be effective, these pathogen- or cancer-associated antigens had also to be shown to induce an immune response in the greatest fraction of affected individuals. According to Reed, Corixa's current CSO, Corixa does this by focusing on antigens that are recognized by the immune cells of those infected individuals who show no signs of disease, suggesting that the antigens may offer protection. A technique known as "direct expression cloning" can then be used to clone the genes that encode such antigens.

These antigens can be exploited for the development of other potential therapeutics, such cancer-fighting monoclonal antibodies exemplified by Corixa's BEXXAR, an investigational radioimmunotherapy for non-Hodgkin's lymphoma. BEXXAR incorporates a cytotoxic radioisotope into a monoclonal antibody that targets a B-cell antigen on tumor cells. Acquired when the company took over Coulter Pharmaceuticals in December 2000, BEXXAR has had a rough ride through the FDA review process, however, and additional studies have been requested. Lacob freely admits that the acquisition of Coulter and its BEXXAR product was a costly one for Corixa, and recent layoffs have been linked to its troubles. "We knew we were taking a risk, but I remain very confident that the product will be approved before not too long, " says Lacob. The setback has given a similar, competing product from IDEC Pharmaceuticals (San Diego) called Zevalin a head start in the market. According to Grabstein, the eventual outcome of the BEXXAR review is key to Corixa's future, as it represents one of two products on which the company is relying for survival in the near term.

The other product is Corixa's powerful and popular MPL adjuvant, which came on board with another of Corixa's acquisitions, Ribi ImmunoChem in 1999. Adjuvants represent a second important component of successful vaccines. Most but not all antigens are composed of short polypeptides that are poorly immunogenic on their own. Adjuvants boost antigen potency by effectively flagging their presence to the immune system. To date, most adjuvants have worked by enhancing the antibody response. However, the last decade has seen an explosion of knowledge in the molecular and cellular bases of T cell responses to both viruses and cancer. Activation of the cellular arm of the immune system is dependent upon a diverse set of costimulatory signals that act upon APCs. It is precisely these signals that adjuvants must trigger, and the family of Toll-like receptor (TLRs) represents a particularly important nexus of such signals. Corixa scientists have shown that TLR4 is a key target of MPL. MPL stands for monophosphoryl lipid A and is a derivative of a bacterial endotoxin. The formulation has either completed or is being tested in late-stage clinical studies of vaccine formulations for both infectious diseases and cancer, and licenses have been granted to both Glaxo-Smith-Kline and Wyeth-Lederle, two leading developers of vaccines.

Knowledge that TLR4 is a target for MPL has allowed Corixa to develop small molecule agonists for the receptor, such as their RC-529 compound. This synthetic adjuvant has shown good results in a phase III clinical trial when used in conjunction with a yeast-based recombinant hepatitis B antigen from Rhein-Biotech, who inked a license and supply agreement for RC-529 in April of this year. "Our partnership with Rhein-Biotech affirms the potential value of our proprietary adjuvant portfolio," says Gillis. The synthetic adjuvant is also in preclinical studies for use in treating cancer and autoimmune disease.

RC-529 is not the only product Corixa is developing to fight autoimmune disease. Rheumatoid arthritis and multiple sclerosis are two conditions in which the body erroneously mounts a T cell response against a self-antigen and attacks its own cells. The better understanding we now have of the T cell response is also providing strategies to fight these diseases by manipulating the balance between antigen presentation and the costimulatory signals described earlier. Both inputs are necessary, and if either is too great or too small, the T cell response can

be interrupted. In the case of RC-529, the idea is to overload the costimulatory response. In the case of Corixa's AnergiX treatments, the idea is to overload the antigen-delivery pathway. These products were once again the fruits of a strategic acquisition, that of Anergen. Once APCs have taken up antigens, the latter are bound to peptide binding receptors (major histocompatibility complexes [MHC] class I or class II) that sit on the outer membrane of the cells. The MHC-antigen complexes on APCs then bind and stimulate CTLs and helper T cells. However, if the T cells do not receive the costimulatory signals from the APCs at the same time, they do not respond. AnergiX products are soluble MHC complexes previously loaded with antigenic peptide that bind the T cell receptors but bypass the costimulatory signals, effectively flooding out the APC cell-bound autoantigen and shutting down the autoimmune T cell reaction. Corixa has partnered with Organon in the development of such a formulation to treat rheumatoid arthritis and with Beaufour-Ipsen to treat myasthenia gravis.

With the exceptions of the MELACINE vaccine for melanoma (marketed only in Canada at this point), BEXXAR, and the MPL adjuvant platform, the remainder of Corixa's vaccine products are either in early clinical or preclinical stages of development and are not predicted to give rise to revenue for some time. Indeed, Corixa continues to rely on revenue from investors and partnership deals, and they have their sights set on technologies and patents held by the vast number of small public biotech companies, many of which are left with less than a year of funding. Amazingly, given the current market conditions in the biotech community, the company did manage to pull off a private placement in August 2002 worth about $45 million—testimony to the influence of Corixa's management in the investor community. This influence could be key to Corixa's survival and could yet lead to profitability within the next five years. Either way, what is certain is that Corixa has put together the right components to succeed in the complex field of immunotherapeutics. Whether they do, however, depends on a myriad of factors in the world of biotech over which they have little control.

***Chemistry & Biology* invites your comments on this topic. Please write to the editors at chembiol@cell.com.**

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