First-in-class cancer therapeutic to stimulate natural killer cells

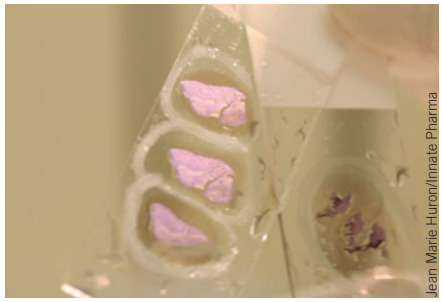
The first ever clinical trial of a therapeutic that binds to natural killer (NK) cell receptors is slated to take place before the year end. Its goal is to harness directly the therapeutic potential of NK cells in the treatment of a wide range of immune-related conditions, including cancers, autoimmune disease and infection. Despite its promise, however, progress of the treatment, a human antibody, through clinical development could be slow. That's because of the more intense regulatory scrutiny that novel immunomodulatory antibodies will undergo in the wake of the recent clinical trial disaster involving a 'superagonistic' monoclonal antibody developed by German biotech TeGenero of Würzburg.

Privately held French biotech firm Innate Pharma, of Marseilles, is the prime mover in this field. And it has already secured big pharma validation for its strategy. The company unveiled a broadly based partnership with Novo Nordisk, of Bagsværd, Denmark, on April 5. Under the terms of the deal, each company will contribute around 20 full-time employees to the discovery and development of novel antibodies and other biologics that modulate NK cell receptors.

Innate did not have many competitors for the deal. Only one company, Natspears of Tel Aviv, has adopted a similar strategy. Its programs are also in preclinical development. Natspears, whose scientific founders are Ofer Mandelboim, of the Lautenberg Center for Tumor Immunology at the Hebrew University in Jerusalem, and Angel Porgador, of Ben-Gurion University of the Negev, is developing biologics that mimic the actions of activating NK cell receptors.

NK cells have long been recognized as key components of the 'innate' immune system—the body's first line of defense against foreign invaders—alongside dendritic cells and macrophages. They are already targeted, albeit nonspecifically, in existing immunomodulatory treatment regimens involving, for example, cytokines or their receptors.

NK cells express, among others, inhibitory receptors that recognize major histocompatibility complex (MHC) class I molecules, which play a central role in enabling the body to distinguish between self and non-self. Ultimately, these will influence the ability of NK cells to kill disease cells. "What's complex about the repertoire is you don't have one receptor per cell, as you do for a T-cell receptor," says David Raulet, Choh Hao Li professor of immunology at the University of California, in Berkeley, who is also a member of Innate's scientific advisory board. "Some receptors are expressed in all NK cells. Some are expressed in a variegated pattern.



Jean Marie Huron/Innate Pharma

Innate Pharma is exploiting the immune system's first line of defense, NK cells, in cancer treatments (biopsy sections pictured).

One of Innate's founders, Alessandro Moretta, professor of experimental medicine at the University of Genoa, Italy, has been a leader in the identification of NK cell receptors since the late 1980s, and the company has licensed the university's intellectual property in this area. Innate is also collaborating with another Italian scientist, Andrea Velardi at the University of Perugia, who has shown that donor-derived NK cells that are not perfectly matched for the recipient can actually protect against graft-versus-host disease during bone marrow transplants and eliminate graft rejection and leukemia relapse (*Science* **295**, 2097–2100, 2002).

"It's one of the most spectacular breakthroughs in cancer immunotherapy in the last three or four years," says Innate CEO Hervé Brailly. The rationale is that a mismatch between a donor NK cell inhibitory receptor and a recipient tumor MHC class I molecule will result in the donor NK cells becoming activated on transplantation. In turn this will lead to tumor cell killing, engraftment and protection against opportunistic infections.

In their lead program, Innate and Novo Nordisk are attempting to unify these two strands by developing a monoclonal antibody for treatment of hematopoietic cancers that do not require bone marrow transplants. They are targeting the killer immunoglobulin-like (KIR) receptor family.

Interactions between KIR and MHC class I molecules are complex. This is because there is a high degree of genetic variation within each system, says Mary Carrington, principal investigator at the Laboratory of Genomic Diversity at the National Cancer Institute, in Frederick, Maryland, who is investigating links between susceptibility or resistance to disease and variation in both KIR receptor and a subset of MHC genes, human leukocyte antigen genes . "I think it could be difficult if you're trying to [develop drugs that] target the polymorphic loci. It's going to be difficult to have one drug that fits all," she says.

To bypass this issue of variability, Innate is in its lead program targeting a highly conserved sequence within a particular subfamily of KIR inhibitory receptors. "It can work in every patient, irrespective of the immunogenetic context," Brailly says.

Natspears is taking a different approach. Instead of targeting NK cell receptors, the company is developing biologics to mimic NK cell receptors, consisting of the extracellular portions of activating NK cell receptors, such as NKp44, NKp30 or Nkp46, fused to an IgG1 antibody molecule. It has demonstrated proof of concept in a mouse model of prostate cancer, says Mandelboim, and the company is also commencing a program in melanoma.

Targeting NK cell receptors is "a logical next step," says William Murphy, a professor in the department of microbiology & immunology, at the University of Nevada Medical School, in Reno. He has shown that an antibody blocking an inhibitory NK cell receptor in a mouse model elicited a sustained anti-tumor effect. However, because of the complexity of the signaling involved, a single antibody may not have the desired effect in humans. "In the long term you may be combining it with other blocks or other stimulants so your net effect is even greater activation," he says.

A group led by Jeffrey Miller, professor of medicine at the University of Minnesota, in Minneapolis, has already demonstrated the feasibility of such a combined approach. In a trial of 19 people with advanced acute myeloid leukemia, five achieved complete remission after an infusion of partially mismatched NK cells combined with the administration of the cytokine interleukin-2 (IL-2; Proleukin). "My concept is, to better exploit NK cell activity, you have to stimulate NK cells in the recipient with IL-2," he says.

Post-TeGenero, the specter of autoimmunity will inevitably cast a shadow over drug development work in this field, particularly as so much of the biology is not fully understood (*Nat. Biotechnol.* **24**, 475–476, 2006). "All these strategies are predicated on giving some stimulation but not too much," says Raulet. Finding just the right amount will be the big challenge for Innate and Novo Nordisk as they seek to open up this new therapeutic field.

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