

VAN DEN EYNDE

BENOÎT



BRUSSELS

LUDWIG

THE TUMOR DEFENSE DISMANTLER

He began his career helping to lay the scientific groundwork for modern immunotherapy. Now he's unraveling the myriad ways tumors thwart immune attack—and showing how to undo those defenses.

In science, as in many other things, it's the surprises that tend to stick with you—and sometimes in more ways than one.

Benoît Van den Eynde got a big one nearly three decades ago, while working with Thierry Boon, the founding director of the Brussels Branch of the Ludwig Institute for Cancer Research. Boon had previously shown in a series of milestone studies in the late 70s and early 80s that the mammalian immune system can detect and clear cancer, a possibility most scientists doubted at the time. By the mid-80s, his team was racing to find in mice and humans the first example of a naturally occurring cancer antigen, a molecular flag that marks diseased cells for targeting by T cells of the immune system. Van den Eynde was working on the mice.

Based on their previous studies on tumors with chemically induced mutations, the

researchers expected the antigen would be a randomly mutated version of a normal gene—a neoantigen—which would appear foreign to T cells, provoking attack. “To our surprise, the antigen turned out to be identical to the normal gene,” recalls Ludwig Member Van den Eynde. “We called it P1A and realized quite quickly that the gene is expressed in the tumor but mostly silent in normal tissues.” Reported in 1991, it was the first of what would come to be called the “MAGE-type” or “cancer testis” antigens, which are expressed in human cancers as well and would become central to several immunotherapy strategies.

P1A, for its part, stuck around as a useful tool. Roughly a decade and a half later, Van den Eynde used it to construct a mouse model for an inducible cancer that provides a venue for a more realistic assessment of immunotherapies. In 2017,

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he and his colleagues reported in *Nature Communications* how they used that model to elucidate a novel mechanism of immune resistance in tumors. In another study published in *Cancer Immunology Research* in 2017, Van den Eynde and his team probed a separate mechanism of malignant immunosuppression and showed that it might be overcome with the use of an anti-inflammatory drug already on the market.

Becoming a scientist

When Benoît Van den Eynde was in high school near Brussels, his grandparents bought him a subscription to a science magazine. The gift opened his mind to scientific discovery. “I thought, ‘This is a cool job to do,’” he recalls.

The thought stuck with him and, at 18, in his second year of medical school at Université catholique de Louvain in Brussels, he asked a biochemist if he could join his laboratory as a student researcher. After graduating with honors with his medical degree, Van den Eynde qualified for a five-year program in internal medicine. But, still feeling the tug of science, he exercised an option to claim

a year of credit in his clinical training for two spent on research and joined Boon’s newly opened Ludwig Branch in 1985.

Based on its studies of mice, Boon’s team was by the mid-’80s creating what amounted to personalized cancer vaccines for a small group of melanoma patients. The vaccines worked quite well, even curing a German patient’s widely metastasized cancer—a landmark, if rarely repeated, event in the history of cancer immunotherapy. Van den Eynde, for his part, joined an effort to identify the melanoma antigens and asked his medical school administrators for another two years to continue his research. Once again, his request was granted.

In 1989, Van den Eynde published a paper in the *International Journal of Cancer* showing that the German patient’s T cells appeared to target at least six naturally occurring antigens on her melanoma cells. Thrilled, Van den Eynde dropped his medical studies and, leading a small group by 1994, set about discovering antigens in melanoma and other human cancers. He received his PhD in 1995.

Over the next few years, Boon’s team raced to translate its discoveries—particularly the MAGE cancer antigens—into cancer vaccines for more general use. Van den Eynde’s research, however, would take him down a scientific path more fundamental in nature yet just as relevant to cancer immunotherapy.

Incisive science

Sick cells alert the immune system to their condition by chopping up abnormal proteins associated with their pathology and presenting the fragments, or peptides, to T cells. The chopping is done by an enzymatic machine known as the proteasome, the presenting by a family of proteins called MHC (HLA in humans and H-2 in mice). In 2000, Van den Eynde’s group published a paper in *Immunity* describing a cancer antigen derived from a protein that was expressed in all cell types; the antigen seemed normal in every

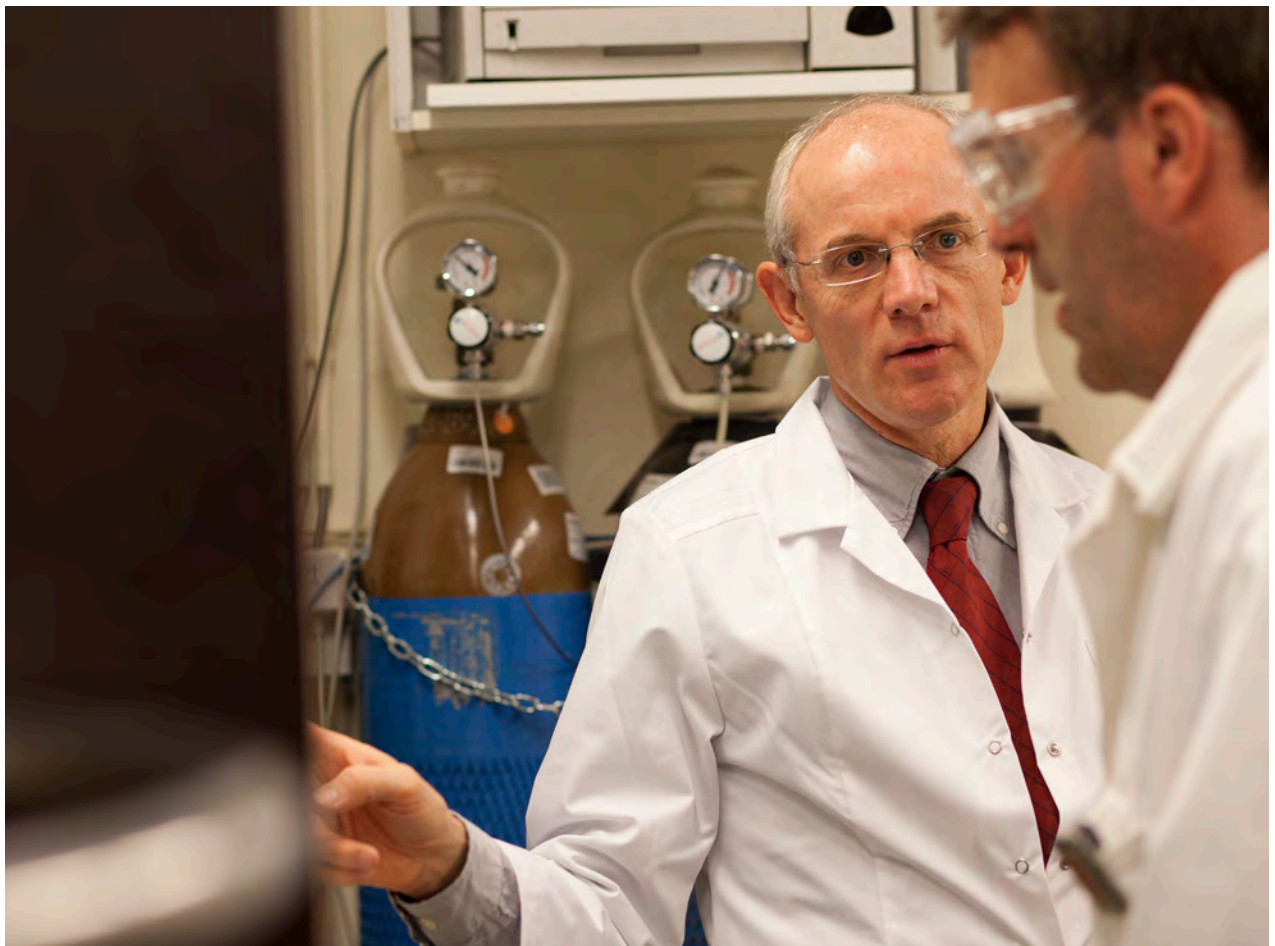


Photo by Flynn Larsen

way, yet it elicited a T cell attack only on cancer cells, not healthy ones.

“There was a paradox there,” says Van den Eynde, “and it was in trying to understand that paradox that I became interested in antigen processing.”

Van den Eynde’s subsequent exploration of the anomaly—which continues today—was rich with discovery. He and his colleagues reported in 2004 in *Science* an entirely novel type of antigen processing, in which peptides are spliced and then shuffled so that their amino acid sequence no longer resembles any part of the original protein. A recent independent study suggested as many as a third of the peptides presented to T cells could be of that variety. “People are trying to confirm those findings but, if correct, spliced peptides will have to be taken into account in

vaccine design and across immunology,” says Van den Eynde.

His team also discovered that cancer cells tend to deploy a standard proteasome, while normal antigen-presenting cells express what is known today as the immunoproteasome—which is built from a different mix of enzymatic subunits that generate distinctly different peptides for presentation. “If you want to trigger an immune response that is meaningful in cancer patients,” explains Van den Eynde, “it would be better to trigger T cells activated by peptides produced by the standard proteasome.”

La resistance

While exploring cancer antigens, Van den Eynde also became increasingly interested in the mechanisms by which tumors evade immune attack. In 1998, he came across a

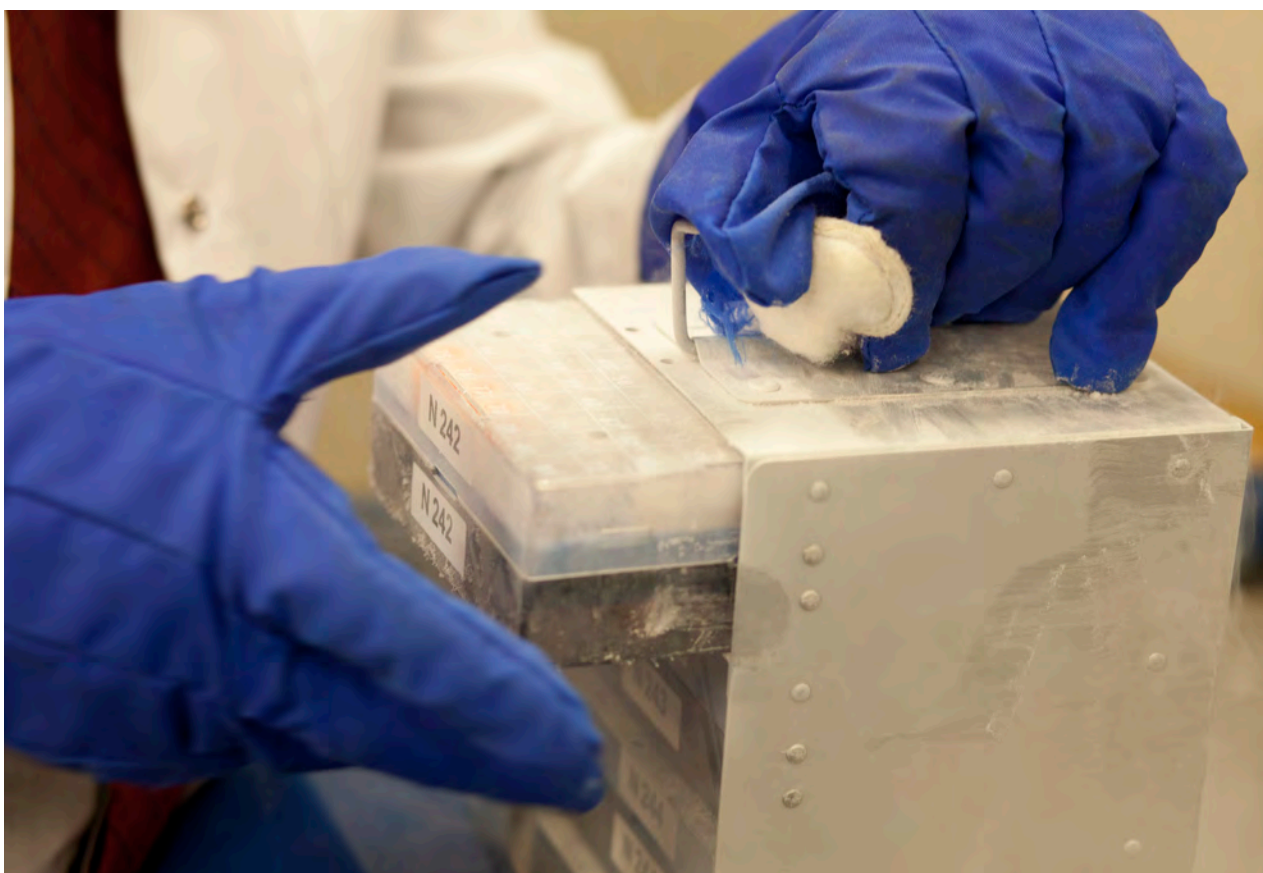


Photo by Flynn Larsen

paper showing that cells in the mammalian placenta help prevent T cell attack of the embryo by harnessing an enzyme known as indoleamine 2,3-deoxygenase-1 (IDO-1), which deprives killer T cells of a vital nutrient—the amino acid tryptophan. Van den Eynde and his colleagues reported in *Nature Medicine* in 2003 that tumors do the same. This sparked an industrywide race to develop IDO inhibitors as cancer therapies. Van den Eynde himself launched, with Ludwig's support, a spinoff named iTeos—a story covered in the 2014 Ludwig Research Highlights report.

Unfortunately, the 2018 failure in Phase III trials of an IDO-1 inhibitor prompted developers to pull back from the therapeutic class. But Van den Eynde remains optimistic that IDO inhibition still holds promise. A better selection of tumors for IDO inhibition, he believes, could improve efficacy in trials. It might, for example, work better in tumors that continuously express IDO and lack killer

T cells almost entirely, rather than those in which IDO expression is induced by stimuli such as immunotherapy.

Tumors of the former category were, in fact, a focus of the study Van den Eynde and his colleagues published in *Cancer Immunology Research* in 2017. Van den Eynde and his colleagues suspected steady IDO expression might account for the immunologic chill of such “cold tumors” and set about probing why it occurs. Their study revealed that the steady expression of IDO depends on COX-2—an enzyme involved in inflammation—and its primary product, a long fat molecule named prostaglandin E2 (PGE2).

PGE2, they showed, is produced by those tumors and activates a signaling cascade within cells that triggers IDO1 expression. Van den Eynde and his team showed in an immunologically reconstituted mouse model of human ovarian cancer that blocking COX2

with a drug named celecoxib effectively shut down the constitutive expression of IDO-1 and led to tumor rejection.

“Celecoxib is already on the market, so you don’t need to do a drug development program before you test it in patients,” says Van den Eynde. Indeed, he is already in discussions with oncologists at the University Hospital Saint-Luc in Brussels about running a small clinical trial combining celecoxib and checkpoint blockade as a cancer therapy.

Countering countersurveillance

Around the time Van den Eynde began mulling IDO in the late 90s, he was also thinking about how to develop a tumor model that might more faithfully recapitulate immune suppression in tumors. Mouse models available in the 90s were made by injecting cancer cells into mice to seed fast-growing tumors. But as Boon’s team had formally shown, tumors in patients evolve gradually against a patrolling immune system. The transplanted models don’t quite recapitulate that process.

In 1998, Van den Eynde began working with colleagues in Marseille, France, to construct a model that would. By the middle of the last decade, he and his colleagues had engineered a mouse in which melanoma could be induced with the administration of a breast cancer drug and whose tumors expressed P1A. Next, the researchers engineered a nearly identical mouse to make T cells targeting P1A. “This was a cool tool because we could now isolate large numbers of T cells that recognize the P1A antigen and inject them into a mouse with an induced tumor that expresses that antigen,” says Van den Eynde.

As they reported in *Nature Communications* in 2017, the induced tumors were resistant to a battery of immunotherapies, including anti-P1A vaccines and even adoptive T cell therapy (ACT) that involved injecting 10 million P1A-targeting T cells into the mice. “Honestly,



Photo by Flynn Larsen

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I was expecting that in this case the T cells would be able to reject the tumor,” says Van den Eynde. “But they had no effect at all.”

When the same P1A-expressing cancer cells were transplanted into mice, however, they were cleared by ACT. Comparing the noncancerous cells present in both types of tumors revealed that one type of cell, the polymorphonuclear myeloid-derived suppressor cell (PMN-MDSC), was present exclusively in the induced tumors. These cells, it seemed, were engaging a previously unknown system of immune suppression to thwart the T cell attack.

Van den Eynde and his team showed that the PMN-MDSCs express high levels of a surface protein known as Fas-ligand, which induces T cell suicide when it binds its receptor on the T cells. Blocking this interaction restored the ability of the T cells to kill the induced tumors.

“We didn’t have a full rejection of the tumor, but we did get a reduction in T cell suicide and better control of the tumor,” Van den Eynde explains. This is, in his view, a good sign, as it suggests the tumors are engaging other methods of immune suppression as well, all waiting to be discovered and undone. “I think this mouse model will give us many more important findings on tumor immunosuppression,” he says.

In Van den Eynde’s hands, it probably will. ■