Releasing the brakes to fight cancer

The recent discovery of checkpoints has boosted the field of cancer immunotherapy

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US President Richard Nixon declared “War on Cancer” in 1971, but it was not until 45 years later that his successor called the country to arms for the final battle. “For the loved ones we’ve all lost, for the family we can still save, let’s make America the country that cures cancer once and for all”, said US President Barack Obama in his last State of the Union address in January 2016. And, yes, he used the word “cure”, which is not easily said when it comes to cancer.

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Indeed, scientists are talking about a cure. This hope for new treatments that could really cure cancer, rather than extend lifespan by a limited time, is fuelled by new discoveries in cancer immunology. “For many years, tumor immunology was not really interesting for the medical world. But now it has become clear that tumor immunology theory translates into clinical success”, said Pierre van der Bruggen from the Ludwig Institute for Cancer Research at the de Duve Institute in Brussels, Belgium. The breakthrough came in 2011 when the first drug of a new class, a so-called checkpoint inhibitor, was approved for the treatment of late-stage melanoma. Before, there were few treatment options for this devastating disease and life expectancy was measured in just months. But approximately 20% of the patients from the first trials that

used the checkpoint inhibitor ipilimumab are still alive today. “That’s what lets people talk about a cure for cancer. A patient is still here after 10 years and hasn’t been treated for the last 9 years”, said Gordon Freeman, immunologist at Dana-Farber Cancer Institute in Boston, Massachusetts. Since 2011, more checkpoint drugs have been approved and more are in the pipeline.

The idea behind a checkpoint blockade, as scientists describe it, is releasing the brakes of the immune system. The natural function of checkpoint molecules is to halt the immune response, or step on the brakes, so it will not turn against the own body after launching an attack against invaders. But these checkpoints also restrain the immune system’s ability to attack tumor cells. “Once you block these checkpoints, it lets the immune system do what it wants to do: Attack the cancer”, Freeman described.

In addition, checkpoint drugs can also improve the efficacy of a whole array of other treatments when used in combination. “Checkpoints represent a very central mechanism that we need to manage to have clinical effects in patients”, said Axel Hoos, senior vice president of Oncology Research and Development at GlaxoSmithKline. There is another aspect though that may be equally important. “Checkpoints helped the field gain recognition. We will see other immunotherapies that are effective. But the first ones that work broadly are checkpoint blockers. This helped the entire field to launch”, Hoos said.

An old idea

The road to success in immunotherapy has been long and fraught with obstacles. It began more than 100 years ago, when William Coley (1862–1936), a surgeon from New York City, stumbled across the records

of a cancer patient who had a very large inoperable tumor on his neck. The patient went through surgery more than once, but the cancer kept growing. After the last surgery, which only partially removed the tumor, the patient developed a severe infection. Thereafter, the cancer disappeared. Coley suspected that his patient’s remission had something to do with the infection and started testing his idea by injecting bacteria—and later a vaccine containing inactivated bacteria—into patients’ tumors. This did not always lead to success, but it helped a number of patients. According to a retrospective study, “patients treated with surgery and Coley toxins between 1890 and 1960 experienced survival rates comparable to those of patients diagnosed in 1983 and treated with nonradiotherapeutic conventional approaches” [1]. However, Coley’s experiments fell into oblivion, partly because James Ewing, the Medical Director of Memorial Hospital at that time and Coley’s boss, was a strong supporter of the then-emerging radiation therapy.

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Cancer immunotherapy resurfaced half a century later, when Frank McFarlane Burnet and Lewis Thomas explored the idea that the immune system protected the body against cancer. This led to the immunosurveillance hypothesis, which states that lymphocytes are continually patrolling tissues and eliminating transformed cells. However, this idea came under attack when

Osias Stutman put it to the test in 1974. He reasoned that if the immune system would suppress tumors, nude mice—the only model for immunodeficiency at that time—should be more susceptible. They were not. Decades later it was recognized that nude mice are not completely immunodeficient.

Thus, when van der Bruggen entered cancer immunology in the late 1980s, it was not the most popular field of research. “Many people were skeptical about the fact that specific anti-tumor antigens exist”, he recalled. But, together with his colleagues in the laboratory of Thierry Boon at the Ludwig Institute in Brussels, he cloned the first such antigen and his study was published in *Science* [2]. “After the *Science* paper, people could not deny the fact that antigens recognized on tumors by T cells distinguish tumor cells from normal cells”, van der Bruggen recalled. Once there was proof of anti-tumor antigens, more scientists began to look out for them.

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Several other discoveries strengthened the re-emerging field of cancer research. Garth Anderson's laboratory showed that tumor cells were profoundly genetically instable. Robert D. Schreiber and his colleagues clarified the confusion around nude mice and immunosurveillance and showed that immunodeficient mice do have a higher incidence of spontaneous or chemically induced tumors by using more elaborate mouse models. Their work also led to the immunoediting hypothesis, which states that there is a constant battle between tumors and the immune system, with tumor cells evolving mechanisms to evade immune attacks [3].

Overriding checkpoints

T cells are activated by antigen-presenting cells, which display fragments of engulfed pathogens or tumor cells on their surface. T-cell activation occurs when the T-cell receptor binds to these fragments. In addition, the CD28 receptor on the T cell needs

to bind its own ligand on the antigen-presenting cell as a co-stimulatory signal.

In the mid-1990s, researchers realized that immune activation using this process is limited owing to checkpoint mechanisms. Once T cells are activated, they start expressing CTLA4, which competes with CD28 and halts T-cell activation. CTLA4 was the first checkpoint molecule to be discovered and gave scientists the first hint at the immune system's negative feedback loops. “Most of our immune system is dedicated to fighting infectious diseases. Once you eliminate the disease you want to turn the immune response off so it doesn't harm the body”, Freeman explained.

Many laboratories were involved in unraveling CTLA4 function, but it was James Allison, then at the University of California, Berkeley, who made the connection to cancer. He proposed that checkpoints impede the immune system's ability to fight cancer and that blocking this negative regulation might give the immune system enough vigor to attack tumors efficiently. In a seminal paper in 1996, he showed that antibodies against CTLA4 could help reject pre-established tumors in mice [4]. “I did what I think any basic scientist should do: occasionally stop and think about the implications of your fundamental findings for application to human disease”, he wrote [5]. With these results, Allison, who later received the Lasker award for his work, started looking for a clinical partner. “There is a gap between lab discovery and the clinic and in the early 1990s, it was even larger than today. Jim was really a champion for the idea that CTLA4 blockade should be developed and tested in patients with cancer”, said Suzanne Topalian, a researcher at Johns Hopkins University School of Medicine in Baltimore, Maryland. Allison teamed up with Alan Korman at a small company called Medarex, where they developed a human anti-CTLA4 antibody and started the first clinical trials. Medarex then soon teamed up with Bristol Meyer Squibb, which acquired Medarex in 2009. The drug that came out of this research, ipilimumab, was approved by the FDA in 2011.

Clinical success

The approval of ipilimumab marked a sea change in immunotherapy and the whole field picked up momentum. Finding the right target—a checkpoint molecule—was a key

to the success of the drug. However, there is an equally important aspect to the ipilimumab success story: a change in clinical trial design. “The Cancer Immunotherapy Consortium (CIC) evolved a new paradigm, realizing that we need to measure things differently for immunotherapy”, explained Hoos, who is also Co-chair of the CIC, an international association that involves pharmaceutical companies, academic investigators, and regulators. Immunotherapies differ from more conventional therapies, such as chemotherapy, in that it does not target the tumor directly, but rather engages the immune system's anti-tumor activity. As a result, patients may show a different response pattern and clinical endpoints have to be redefined to capture these effects.

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At the time ipilimumab was developed, Hoos was medical lead in immunology-oncology at Bristol-Myers Squibb (BMS). “When I started working at BMS it became clear that ipilimumab is an active drug that worked, but we did not have a measure to capture all of its activity and then this paradigm became quite useful”, Hoos recalled. One of the main criteria for evaluating the success of chemotherapy is a reduction of tumor size after starting the treatment. But this criterion caused confusion when applied to patients on ipilimumab. “In some cases, patients said they were feeling better, but CAT scans showed the tumor was growing. We investigated this further and realized that the tumor is actually inflamed and invading immune cells were making it look bigger. A month or two later, it shrank and sometimes disappeared completely”, Hoos explained. Patients showing this “delayed effect” would have been judged as having a progressive disease under the chemotherapy paradigm, but applying immune-related response criteria shows patients are profiting from the treatment. “The ultimate measure for any response is if it improves or extends life”, Hoos said.

Eliciting a T-cell immune response is a multistep process. T cells are activated by

antigen-presenting cells, they proliferate, differentiate into effector T cells, migrate to infection sites or tumors, and finally recruit further immune cells to mount an attack. Each step is regulated by checkpoints. CTLA4 is a global checkpoint that is active early in the immune response when T cells are educated to recognize the tumor. PD1, another checkpoint molecule, is an inhibitory receptor expressed on T cells, just like CTLA4 but it works on a different level: its ligand, PDL1, is induced by inflammatory signals in the tumor. “The tumor cells specifically express PDL1 and use PDL1 to turn off the anti-cancer immune response”, Freeman explained.

“One promising approach is combining checkpoint therapies with conventional therapies [...] because these may induce an immune response that is further enhanced by checkpoint blockade.”

Two anti-PD1 antibodies, pembrolizumab and nivolumab, were approved by the FDA for the treatment of advanced melanoma in 2014, and they are used for a number of different cancers today. Recent data from Topalian and her colleagues show a high rate of responsiveness and a durable impact of anti-PD1, even in patients who had not responded to other forms of therapy. “One out of three patients from a phase I study with advanced melanoma are still alive today—five years later. This is a landmark for oncology”, she said.

New targets and combinations

The fact that antibodies against CTLA4 and PD1 target different pathways also makes them ideal to use in combination. In one recent melanoma phase II trial, for example, the objective response rate was 61% for patients who received the combination therapy of ipilimumab and nivolumab, vs. 11% in the group that received ipilimumab and placebo [6]. There are a number of further checkpoints, termed LAG-3, KIRs, B7-H3, TIM-3, VISTA, and TIGIT, and co-stimulatory molecules that include ICOS, OX40, and

4-1BB. All of them offer targets for novel drugs and opportunities for a large number of combinations.

Before checkpoints set foot on the stage of cancer therapy, the field of immunoncology was rather quiet. “Immunology has tried to cure cancer for many years by vaccination, adoptive T-cells, or adjuvants. We have cured a lot of mice with these strategies, but not very many people. But once you open the door with checkpoint blockade, these other strategies become enabled”, said Freeman.

The discovery of tumor antigens by van der Bruggen and Boon also opened the doors for cancer vaccines. “We thought that now that we know the target, we can develop therapies that elicit an immune response to destroy the tumor. But it became rapidly clear that this was not the case”, van der Bruggen said. Vaccination had been extremely successful in the field of infectious diseases, but in cancer, only one therapeutic vaccine, Sipuleucel-T, ever made it to the market in the USA, in addition to two types of vaccines against cancer-causing viruses. Therapeutic cancer vaccines are designed to work by introducing tumor-specific antigens into the patient’s body, thus activating T cells to recognize cancer cells. “There were many trials of a variety of different cancer vaccines. What we learned over several years is that vaccines by themselves are usually not powerful enough to make advanced cancers regress. But we also learned that the immune cells that were stimulated by vaccines highly express checkpoints”, Topalian said. And this may, in fact, be one of the reasons why cancer vaccination did not live up to its expectations. Vaccination may initiate an immune response, but before it has dealt with the cancer, it is downregulated by checkpoints.

Vaccinating against a tumor should ideally lead to an activation of T cells that will attack the tumor. But each time T cells are activated they will switch on CTLA4 and pull the brake. In addition, an immune response may trigger PDL1 expression in the tumor, thus impeding anti-tumor activity on-site. At some point, the vaccine might even trigger the off-signal rather than the on-signal. “This led to the notion that maybe it would be a good idea to combine vaccines with checkpoint blockers”, Topalian said. “This was tested in animal models of cancer and studies showed that the combination of a vaccine with a

checkpoint was more powerful than either the vaccine alone or the checkpoint blocker alone”.

Improving conventional therapies

Checkpoint blockade may also be sensibly combined with a number of other therapies that induce an immune response. “I could give you a list of 100 different things that work better with PD1 and if you read the journals next month you will find 5 new ones. There is a tremendous amount of work going on to take a response rate of, for example, 20%, and bring it up to 50% or more”, Freeman noted.

“Naturally, not every therapy would fit every patient and a large area of research concerns defining biomarkers to predict individual drug sensitivity.”

One promising approach is combining checkpoint therapies with conventional therapies, such as chemotherapy or radiation, because these may induce an immune response that is further enhanced by checkpoint blockade. “Five years ago I would have said radiation just kills tumor cells. It turns out it does that, but when you kill tumor cells they get taken up by antigen presenting cells and presented to T cells, thus giving T cells a good look at the tumor. And if at the same time you block PD1, you let those T cells be much more active”, Freeman explained. Another immune therapy that has received a lot of enthusiasm lately is CAR-T cells: immune cells that have been genetically engineered to produce chimeric antigen receptors that combine both antibody-like recognition with T-cell-activating function, thus making them more efficient at targeting tumors. “When you treat patients with CAR-T cells, you usually have to give them more than once. But blocking PD1 may let those CAR-T cells work longer and better”, Freeman said.

Aside from hijacking checkpoints, tumors have adopted other strategies to escape recognition by the immune system. For example, they secrete galectin proteins to create an immunosuppressive microenvironment and fend off T cells—a mechanism that is currently studied by van der Bruggen.

“Galectin is a glue that links sugars on the cell surface, thereby impairing mobility of surface molecules. This blocks the function of T cells”, he explained. His research has also revealed some details about the impact of galectins on T cells. “They still produce cytokines, but the secretion is impeded”. Thus, blocking galectins could restore T-cell function. Again, this approach may be combined with other strategies, for example, checkpoint therapies. “Checkpoint inhibitors will release the brake of T cells so that they will proliferate much better. But releasing the brake of galectin could help the T cells to lyse tumor cells much more efficiently”, van der Bruggen said.

There are many potential targets for developing cancer therapeutics. But often, one target may just not be enough, because the tumor has developed multiple strategies to avoid immune attack. “I do think that more individual therapies emerge in immunooncology and they will have their effect. But we will ultimately make the big transformational effect for patients with combination therapy”, Hoos said.

Naturally, not every therapy would fit every patient and a large area of research

concerns defining biomarkers to predict individual drug sensitivity. Although the field is still in its infancy, there is some success. One example is the expression of PDL1 in the tumor as an indicator for the therapeutic potential of anti-PD1 antibodies. “There are now several commercial tests, but the prediction is not perfect”, Topalian commented. Another potential biomarker is microsatellite instability—a condition of hypermutability that results from a failure of DNA mismatch repair. “Cancers that have microsatellite instability accumulate mutations and thus they have more for the immune system to see because they are more different from normal cells. Therefore, colon cancers with high microsatellite instability are very responsive to anti-PD1”, Topalian explained.

“Immunotherapy will come as a puzzle”, Hoos said. More drugs are being developed, more combination therapies are being tested, more biomarkers discovered that will allow doctors to optimize therapies for the patients. “I think we will be able to cure larger populations of patients, but it will take some time to test all these different approaches”, Hoos said.

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