OLLI 492: Human Immune System

Session 9: May 4th Summary and Observations

Chapter 8: Future Medicines

The focus of this chapter is using the body's own immune system to fight disease. This is immunotherapy, the "future medicines" of the title. And the disease the author selected to illustrate this approach is cancer.

Davis begins by introducing us to Jim Allison of the MD Anderson Cancer Center in Houston, a true pioneer in the development of immunotherapy. And once again, the work done to establish the efficacy of immunotherapy to fight cancer was performed in recent decades. Part of the delay in researching this possibility was the beliefs held by many researchers that cancer could not be attacked by the immune system. "Cancer was once thought to be invisible to our body's defences. As cancer is rarely caused by a germ and is rather an abnormal expansion of our body's own cells, there tends not to be anything as obvious as a molecule from a virus, bacteria or fungus to mark out a cell as cancerous, and for a long time a view was widely held that cancer displayed nothing to the immune system that it could recognise as alien." No telltale molecule for the immune cells' receptors to latch onto.

However: "Work by Belgian scientist Thierry Boon, among others, established definitively that the genetic and epigenetic changes that turn a cell cancerous are sufficient for it to be detected by the immune system. Boon identified fragments of proteins that had been altered in cancer cells which can be **detected by T cells** as not having been in the body before. The implication of this discovery is that, as well as seeking invading germs, the immune system helps maintain the integrity of our own body's cells, screening against detrimental genetic mutations that can arise whenever cells divide."

In addition, "Natural Killer cells are also able to fight cancer…. Like T cells, they do so by sending a packet of toxic proteins into a cancerous cell, but they have different strategies for detecting when a cell has turned cancerous, one of which involves recognising protein molecules not normally found on healthy cells but which cancer cells sometimes display at their surface – the so-called '**stress-inducible proteins**' we met in Chapter Five."

These discoveries led to the realization that the immune system can destroy cancer cells, and do so more effectively. "…this type of therapy, often called **immunotherapy**…" has a long history. Davis recounts the work of William Coley "a surgeon at the Memorial Hospital, New York", carried out in the 1890s. He noticed that cancer patients who got a subsequent bacterial infection, improved - an early example of an immune reaction that attacks the bacteria, and then moves on to attack cancer cells. To fight cancer, Coley produced "… a mixture of heat-killed bacteria – known as 'Coley's toxins." He had some successes with these "toxins" but the results were inconsistent and hard to duplicate.

Davis points to the "scatter gun" approach of Coley's toxins as part of the problem. "if there's one word that encapsulates everyone's idea as to what is most important when harnessing the immune system to fight cancer, it's **precision** – in terms of selecting only those patients for treatment who are actually predisposed to respond to it (something we'll come back to), and, most importantly for understanding Allison's success, in terms of boosting only the precise set of immune cells that will target a patient's cancer."

He reminds us of the use of antibodies to treat rheumatoid arthritis by blocking the action of a cytokine - the anti-TNF antibody. Allison's approach also used antibodies, but in a wholly new way. "… in the course of a normal immune response, T cells, and other immune cells, must

switch off so that the immune response winds down and the system returns to its normal resting state, usually after the threat has been cleared. Maybe, Allison thought, by stopping this 'switch off' signal, immune cells could be set free to attack cancer cells more effectively, for longer. Building upon the idea that antibodies can be used to block the activity of proteins, his idea was to find a way to block the receptor protein that normally **puts the brakes on** an immune cell's activity."

"Allison's idea was… 'To unleash, not harness … the anti-tumour response,' as he puts it. The great advantage of this approach is its **precision**: only those cells that have been switched on to attack the tumour would in turn have their brakes put on, so only these cells, not every immune cell in the body, would be unleashed by the intervention. This approach has become known as **immune checkpoint therapy**."

Davis recounts how the T cell is switched on when the antigen presented by a dendritic cell, in the presence of the co-stimulatory proteins, matches its receptor - the T cell receptor (TCR). But Allison focused on a second receptor on the surface of T cells, "…. a second receptor protein on the surface of T cells that was uncannily similar – about 30% identical – to the one 'unlocked' by co-stimulatory proteins, but whose role in our immune system remained a mystery."

The receptor was named the "… cytotoxic T-lymphocyte-associated molecule 4, or CTLA-4… it was present at the surface of T cells switched on to participate in an immune response – whereas it was not present on T cells that were resting, simply waiting for signs of trouble. This indicated that the molecule was somehow important only once an immune response had got going. Not much to go on, but intriguing."

"The results of experiments aimed at revealing what CTLA-4 does in the body were, at first, interpreted in line with expectation: that the protein receptor helped stimulate T cells….. But in 1994, Jeff Bluestone and his research team at the University of Chicago …stumbled across the fact that what CTLA-4 seemed to do was the complete opposite to what was expected."

"… Bluestone's team had produced an antibody to block the CTLA-4 receptor… which allowed them to test what would happen to T cells if CTLA-4 was incapacitated…. Bluestone presumed that CTLA-4 was likely to be a stimulatory receptor – an on-signal – and that by blocking it, the immune system would be rendered less effective."

The results of the experiment proved quite the opposite: "… blocking CTLA-4 with an antibody caused T cells to **react more, not less**. If blocking CTLA-4 led to a stronger reaction, then CTLA-4 must normally deliver an **off-signal**, not a stimulatory signal. Because the result went so directly against the prevailing view, finding it didn't feel like a eureka moment." Bluestone dreaded the effort to convince others that he was correct.

Davis recounts the effort of Allison's team, beginning in 1989 when he was at the U.C. Berkeley Cancer Research Laboratory, to find out what CTLA-4 did. It took 4 years to develop the needed antibody, but when they performed the experiment they got the same results as Bluestone's lab.

"Even though both Bluestone's and Allison's labs came to this same conclusion, their discovery was still controversial. In part, this was because an antibody stuck to CTLA-4 may block a receptor from working, but it may also, in principle, do the opposite and trigger it, and blocking a switch-off signal would provide the same result as triggering a stimulatory signal. The controversy was resolved when mice genetically altered to lack CTLA-4 were found to die at a young age because of a massive expansion of immune cells, overrunning the animal's body,

producing toxic levels of inflammation. This plainly showed that CTLA-4 was vitally important for **switching off** an immune response – and also established that switching off an immune response is just as vital to health as switching it on."

Allison's lab produced more of the antibody and continued testing the effect of blocking CTLA-4 on other immune responses. But, "Allison asked a new arrival in his lab, Dana Leach, to test how blocking CTLA-4 affected the **immune response to tumours**."

"Leach injected the antibody into mice with bowel cancer. Allison hoped that by blocking the T cell switch-off signal, tumours in the colon might be attacked more effectively by the immune system and their growth might slow down. The results were even better than he had hoped. 'When Dana Leach … showed me the initial data, I was shocked and surprised,' Allison later recalled. In all the animals treated, the tumours had regressed completely. Over the Christmas holiday of 1994, they repeated the experiment blind, so that the person analysing the mice wouldn't know which animals had been given the treatment…. Allison himself measured the tumours. At first, the tumours stayed the same size. Then, after two weeks – 'as if by magic' – the tumours began to regress in just one group of mice. A little later, they had completely disappeared. That group of mice was, of course, the one that had received the treatment. 'The fact that blockade of a single molecule could lead to complete tumour regression was astonishing,' Allison said."

"Over the next fifteen years, Allison's team, and others, found that blocking CTLA-4 could help treat many different types of cancer in mice. Once again, **good news for mice** but the next step was to test this in humans." Here, Allison ran into a major roadblock. Because of previous failures, skepticism about the efficacy of the immune system to fight cancer abounded among funding agencies and pharmaceutical companies. Davis describes how, eventually, a few small biotech firms came on board, and produced an antibody at scale. "All this led to an antibody – named MDX-010 – which Allison and others could use in clinical trials."

Davis goes on to describe all the deals that occurred among pharmaceutical companies as the antibody worked its way through clinical trials. More importantly, he notes that the larger clinical trials gave mixed results; but what saved the drug from being dropped was the realization that the criteria for success needed to be changed: "… astute clinicians realised that in some cases, according to the existing rules, this new medicine would be regarded as a failure even when patients actually benefited."

"The reason was that success for cancer drugs had been defined with chemotherapy in mind. These agents often kill cancer cells directly and if the treatment is successful, a person's tumour can become smaller within weeks. For trials using the antibody to block CTLA-4 – unleashing the power of the immune system – little might happen at first. Measurements of the tumour would sometimes show that its **size increased**, formally indicating that the treatment had failed. But these numbers lied. Later, presumably after the immune system had been given enough time to get going, the tumour might then shrink. We now know that a tumour might initially get bigger after treatment – seemingly bad news for the patient – because immune cells move into the tumour causing it to swell – which is actually good news for the patient."

The realization that using the immune system to fight cancer is different from other treatment methods, led the World Health Organization (WHO), to change its criteria of success, and to issue new rules. "These rules – now known as the Immune-Related Response Criteria – included an increase in the time allowed for the treatment to work…. These changes transformed the fate of what would become a life-saving cancer drug…."

Davis describes more deal-making by pharmaceutical companies involved with this drug. But Medarex persisted. "Shortly after Medarex was acquired by Bristol-Myers Squibb, blocking CTLA-4 was proven to work, thanks to the new Immune-Related Response Criteria. In a decisive trial of melanoma patients, overall survival was used as the principal criteria for evaluation rather than other measures of a response such as a change in tumour size. For all the patients in this trial, their cancer had spread from the skin to other places in the body and life expectancy was short. The results, announced on 5 June **2010** to over 30,000 delegates at an annual cancer meeting in Chicago and simultaneously published in the prestigious *New England Journal of Medicine*, showed that the average survival of patients went up from about six to ten months when they were treated with the antibody that blocked CTLA-4. This was an unprecedented result: no previous clinical trial had revealed anything to be capable of increasing the average lifespan of such late-stage melanoma patients. Even more amazing was that some patients enjoyed a long-term benefit. Over 20% lived another two years or more. Some of those who received the drug early on have since survived more than ten years."

"In March **2011**, the US Food and Drug Administration approved the new medicine, by which time it had been given a generic drug name ipilimumab (not necessarily a huge improvement on MDX-010) and the brand name Yervoy." Davis recounts the success of the drug in the marketplace, and observes that "… the development of medicines to harness the immune system has become the fastest-growing area of the entire pharmaceutical industry."

But much improvement is needed: "Perhaps the most challenging problem of all is that only a fraction of patients respond. Allison is all too aware of this: 'I wish it worked more'."

Davis notes: "There are many brakes in the system, other **checkpoints** that can be tampered with, other ways to unleash immune cells to fight cancer more effectively."

"In 1992, a different protein receptor on T cells was discovered by Japanese scientist Tasuku Honjo." He was searching for genes that encode proteins involved in programmed cell death, apoptosis. The protein receptor was called "programmed cell death 1 or PD-1." But this protein was misnamed. "it eventually turned out that this receptor has nothing to do with T cells dying – and for many years, the role of the PD-1 receptor remained mysterious. A big clue came when mice were genetically altered to lack the gene which encodes for the PD-1 receptor. Without PD-1, the mouse immune system reacted more vigorously; immune cells multiplied more when stimulated, and some of the mice, especially those that were elderly, spontaneously developed an autoimmune disease. This fitted with the idea that PD-1 also sends a **switch-off signal** to immune cells – **another brake** on the system – and that without it, the immune system is more reactive, overly so when autoimmune disease develops."

"… after being switched on to participate in an immune response, all kinds of immune cells, including T cells, present the PD-1 receptor protein at their surface. This receptor locks onto proteins on the surface of other cells that have been exposed to cytokines released as part of the immune response. Once its PD-1 receptor protein is engaged in this way, a switch-off signal is triggered and the immune cell ceases its response. In this way, PD-1 is instrumental in stopping a reaction from being overly aggressive or going on for too long."

A complementary role for each receptor: "…the roles of PD-1 and CTLA-4 overlap – both serve as brakes on the immune response – but they act in different circumstances. The proteins which PD-1 lock onto are induced in cells exposed to inflammation while CTLA-4 locks onto proteins on other immune cells, such as dendritic cells. An implication of this is that PD-1 may be particularly important in dialing down an ongoing local immune response, while CTLA-4 is perhaps more important in dampening the system as a whole in order to prevent a

body-wide type of autoimmune disease. Understanding the complementary roles of different immune system brakes is at the frontier of research but from what we already know, blocking PD-1 might be especially potent in boosting a local anti-tumour response, unleashing immune cells that have managed to infiltrate a tumour but which are being held in check there by the PD-1 brake."

The hunt for antibodies for PD-1 accelerated, leading to clinical trials: "Clinical trials soon established that blocking PD-1 was even more effective than blocking CTLA-4 in melanoma patients, and led to fewer adverse side effects. Other difficult-to-treat cancers were shown to succumb to attack by the immune system when the PD-1 brake was taken off. Scientifically, this meant that the successes derived from blocking CTLA-4 were no mere fluke. The idea behind it – that we can fight disease by making sure the immune system doesn't turn itself off – was right. For showing this and thereby establishing an entirely new approach to medicine, Allison and Honjo were awarded a Nobel Prize in 2018."

Davis notes that we are still just at the beginning of understanding all the brakes in the immune system (over 20), and the impact removing them has on diseases. "Unfortunately, we can't predict which types of cancer or other diseases will be most affected by taking the brakes off a particular type of immune cell; the system is too complex and our understanding too slight. But we have identified many brakes in the system and have the technology to shut them off one by one."

"At the level of patients, however, as new checkpoint inhibitors are discovered, it becomes ever more important to find ways of determining in advance who has the best chance of responding to them. Simply trying each one in turn is too crude…. we need ways to find out precisely what is happening inside the patient beforehand. The various measures used for this purpose are referred to in the jargon as '**biomarkers**'."

"One potential biomarker would be to test which brakes have been switched on in a patient by testing which brake receptors are present at the surface of a person's immune cells. This would allow us to select a checkpoint inhibitor that targets those particular receptors. A person's tumour can also be analysed to determine whether or not it contains the protein molecules that trigger particular brake receptors on immune cells. This could, in principle, predict whether or not blocking the PD-1 brake system, for example, is likely to benefit a patient." Davis notes the complexities in trying to achieve this goal. "The quest for predictive biomarkers is important but as a research field it is still young."

Davis notes the problems associated with the identification of biomarkers - how this information could be misused, how it could lead to "social engineering". But he thinks these problems won't come to pass. "A closer look at how the immune system's brakes actually work shows just how complex the system is." He gives several examples of the complexity of the activity of just CTLA-4 in support of this argument.

A further complication arises from the use of antibodies: "… while the front end of Allison's therapeutic antibody might block the CTLA-4 receptor from working, the back end of the antibody could, at least in principle, attract immune cells to simply destroy the T cells that the antibody has stuck to. Killing off the body's immune cells doesn't, on the face of it, seem like a useful thing to do in order to boost an anti-tumour response. But there's an important twist here."

Namely: "Regulatory T cells… have high levels of CTLA-4 at their surface. So Allison's antibody could, in theory, lock onto regulatory T cells and tag them for destruction. Whether or not this is what happens in patients is controversial. But if this is correct then Allison's antibody

might lift the brakes off the immune system in a way that is entirely different to how he thought it would: it may work in part by triggering the destruction of regulatory T cells."

Resulting in a not helpful conclusion: "… the precise way in which an antibody against CTLA-4 helps cancer patients is **not entirely clear**; it may well have many effects." Davis views this uncertainty as a challenge to further, in-depth research.

"One way to realise Allison's wish – to boost the success of checkpoint inhibitors – is to use them not just on their own, but alongside other medicines. A combination of four – a tumour-targeting antibody, a cytokine, a vaccine and a checkpoint inhibitor – has been shown, in mice, to eradicate large established tumours which were otherwise untreatable. Each medicine has a modest effect alone but together they became a cure."

Davis now takes an extended diversion into the formation and functioning of the Parker Institute. The initiative and funding for this institute comes from Sean Parker, the billionaire founder of the music sharing (pirating?) internet service, Napster. I won't try to summarize the workings of this institute here, but it has attracted the cooperation and participation of many of the leading researchers in the field. Bluestone is its first president. He says the resources available through the institute constitute a "biomedical revolution."

"This revolution he talks of involves more than just checkpoint inhibitors; there are now hundreds of branches of immunotherapy. One of the areas where the Parker Institute aims to make a difference is in testing whether or not different ideas can be combined." Davis notes that checkpoint inhibitors don't work for everyone. "One way of tackling this problem is to combine checkpoint inhibitors with another treatment that makes absolutely certain that a patient has immune cells capable of detecting their cancer."

"So how might this be done? Recall from Chapter Three how Steven Rosenberg attempted to treat cancer in the 1980s. He isolated immune cells from patients, boosted their activity in a lab dish (with cytokines) and then infused them back into patients. This was occasionally successful but there were serious problems with side effects. One reason the method did not work especially well is likely to be that the batch of immune cells grown in a lab dish contained immune cells of many different types, only a small number of which would have been able to attack the tumour. In **2011**, Carl June at the University of Pennsylvania used a more sophisticated approach – and cured a patient of their leukaemia."

"Like Rosenberg before him, he [Carl June] extracted T cells from the patient, but before being infused back into the patient the T cells were genetically manipulated in such a way that a new receptor was added to them, one which targets the patient's cancer. This is called **CAR T cell therapy,** named for the added receptor – CAR stands for **chimeric antigen receptor** – which is made up of the front end of an antibody that locks onto cancer cells and a back end that triggers a T cell to kill. In this way, a patient's T cells are reprogrammed to specifically target and kill their own cancer cells." June used a disabled HIV virus to insert the gene to produce the CAR proteins into the T cells.

"June and his colleagues had hoped that CAR T cell therapy might bring benefit to cancer patients but did not dare dream of a complete remission. Two of the first three patients achieved such remission…. On 30 August **2017**, the FDA approved the use of CAR T cells for one type of cancer and a few weeks later for another, making this living drug unquestionably revolutionary."

Davis points the way to further research: "The optimal version of this type of therapy is what is needed now. "

After citing all the unknowns regarding this approach, Davis notes the potential: "At least in principle, this type of therapy could be used more widely than in cancer patients. For example, CAR T cells can also be engineered to kill off the fraction of a person's immune cells that are causing an autoimmune disease. One of the greatest problems is the toxicity of genetically enhanced immune cells." Davis does not elaborate on this toxicity.

Davis sums up: "June, Bluestone and others at the Parker Institute are seeking to combine the idea of CAR T cell therapy with the idea of checkpoint inhibitors. New technology for genetically manipulating cells makes it easy for the same immune cells to be tweaked in more than one way. The new plan is to engineer the same T cells not only to have a receptor that can recognise a person's cancer but also to lack a brake system. That way, it is hoped, the enhanced T cells will fight for longer in the body. And because these T cells will be engineered to recognise the person's cancer cells directly, it is hoped that taking the brakes off these cells will cause fewer side effects compared with treatments that unleash the immune system more broadly."

But he concludes on a somber note: "**We are at the dawn of a health revolution**. But the elephant in the room is **global poverty**. Nearly half the world lives on less than $2 a day, and the economics of making and providing new medicines is another kind of tragedy. Our lackluster effort to develop a vaccine for the Ebola virus since its discovery in 1976 is a case in point; the virus was hardly studied until richer countries felt threatened. Though it deals in matters of life and death, the pharmaceutical industry is a business, not a charity, and when deciding research priorities, the potential for financial gain is a critical factor, if not the decisive factor. Although this is a book about ideas, science, history and our trajectory as a species, it would be deceptive – dishonest – to write about new medicines without mentioning the financial problems that stand in our way: we sorely need new international institutes and different ways of funding medical research and medicines, where the well-being of humanity, and other life on earth, is paramount and financial profit irrelevant. I hope this is the brave new world that awaits us."

"As with all scientific revolutions, new knowledge isn't all that counts. We will be judged by our children and grandchildren, not by what we know, but by what we do with what we know."