Totally Nuts! How your immune system can beat cancer!

— Associate Professor Andrew Weickhardt

Pleasure to be here, I must admit I always assumed the speaking slot is reserved for people at the their apex of their career—feel that at this stage after only a few brief years working as a consultant that I am at the start, with much to learn, and the journey has just begun.

I am delighted to be invited here at all, given this hall and its surrounds were the scene for me and my college friends in the late 90s of excessive port consumption, and the inevitable consequences. Though, I'm here to tell a different story, a story that will hope to somehow blend some varied and disconnected items into an update on immunotherapy and cancer that involves Arsenic, Roughy, cashew nuts, Obi Wan, exercise, Christopher Columbus, Ragnar Lothbrok and Vikings, and poo. I know, it's totally nuts.

The background to my involvement in cancer treatment and research is not a straight and inevitable line of pursuit. I suspect many of you, either in training or in your careers have found your life influenced by people and circumstances that couldn't have been predicted. I didn't always want to be an oncologist. After finishing my med degree, I felt that I had an opportunity based on academic results to apply for the 'rewarding' career of ophthalmology. I even applied for the training program, based falsely on a love for a predicted easy life of lasers, phycoing cataracts out for astronomical sums, and a beach house in Bermuda. There were two events that made me realise however this wasn't the career for me. As much as I loved the idea of great money operating, I realised soon that technically I wasn't going to be any good. It came to me while trying to put together an Ikea set while having my wife and mother-in-law look at me with intense scrutiny, sweat pouring from me as I struggled. What would I be like at the end of a long list with an anaesthetist, fresh from completing a sodoku marathon, but now eager to drive down to her Red Hill property for the weekend, tut tutting at me while I struggled/hacked away at someone's eye? I don't think it was going to work out.

It was approximately this time that I did a haem/oncology rotation, and looked after a young patient, Adam, who was admitted on the ward with acute leukaemia. I met him late at night, when he was quite unwell—his room was festooned with family photographs of the young kids. We talked for a bit. The notes told me that he was receiving arsenic and Vitamin A (retinoic acid) as treatment for this life threatening Acute Promyelocytic Leukaemia. This form of leukaemia results from a switch from one arm of chromosome 15 to 17. The result is a proliferation of white cells—blocked from maturing. Imagine lemmings, breeding rapidly, contained by a fence, but near a cliff; Vitamin A when given, opens the gate, and allows the white cells to mature—off they go, becoming normal cells, with arsenic inducing cell death, sheparding the lemmings off the cliff. This combination of strange compounds was based on basic scientific discovery, tailored to this man's cancer. This combination would put his cancer in remission, and give those two small children a father. I realised then how amazing a career I could have—how difficult it might be, but also how rewarding.

So I completed my training at Peter Mac and the Austin, doing two years of lab research, and two years of work overseas, living in Colorado with my wife. These were fantastic years, at the dawn of targeted therapy in oncology, and of exciting changes in immunotherapy treatment.

I'd love to tell you a story about how I predicted/was somehow the founder of immunotherapy for cancer treatment. It was probably the opposite however. I remember distinctly having a coffee with a colleague and discussing the failure of a large randomised trial of a cancer vaccine to make any difference, and talking sympathetically about how a colleague's research was in the balance—he was a pivotal designer of the trial. Imagine spending your entire career on a pointless immunotherapy treatment my co-worker and I wondered!

But here we are now, with drugs that are routinely used to treat a range of cancers—footballers, diagnosed with incurable metastatic melanoma, treated with immunotherapy are kicking match winning goals a year later. How did we get here, who made the leap? And what are the consequences?

Immunotherapy treatment of cancer has been tantalising researchers for years … For over 2000 years dating back to Ancient Egypt there have been case reports of tumours disappearing when cancers have been exposed to bacteria. William Coley, a New York surgeon, published a series on outcomes when a toxic bacterial mix "Coley's toxin, a mix of Strep pyrogenes, Serratia marcens", was slopped into open wounds near growing sarcomas. Numerous doctors have been motivated to try these approaches—most recently at UC Davis, two prominent neurosurgeons were disbarred after infecting the brains of patients hoping for a miraculous bystander effect, where the immune system, stirred up and angry by the bacteria, might also attack the cancer. So doctors have for years tried to capture anecdotal responses of tumours, seemingly stimulated by the immune system, without much luck. These approaches have been crude, and many times cavalier. Perhaps. Their efforts, as well as those trying to inoculate cancer patients with vaccines—vaccines with specific antigens that replicate what the immune system sees on the surface of the cancer, have often failed.

In many ways, the important people in this story are the slightly mad but also methodical scientists who have plodded away in this field with research ideas that many shunned. Obtaining research funding, many of you know, through grants, is an art, akin to being an early seafarer/explorer such as Christopher Columbus—approaching first the King of Portugal, France and England, with his idea to find a new passage to Asia. It was his third "grant" submission, that he persuaded the Spanish Crown to finance his endeavour. Critically, in research, proposing an obvious idea that can be carried out easily by someone with more resources is useless—Colombus would have been as unsuccessful proposing to the European monarchs he follow the coastal long route to Asia—someone had already done it. Research has to be novel, sailing out into the open water, with risks—where someone hasn't previously been. The proposal has to be sound, with a well-resourced institution. But without risks there wouldn't have been Colombus sailing out into the ocean with a grant financed project. So it's amazing to reflect on the skill and success of the immunotherapy teams that did sail out into the ocean.

One of these was Jim Allison, a larger than life harmonica playing researcher that identified some pivotal machinery in how the body's immune system works. By the mid 1990s, there were established theories regarding immune surveillance and cancer. Paul Elrich in the early 20th Century had ventured that the immune system reduced the numbers of cancers that developed. This concept was refined by amongst others our Macfarlane Burnett, with the identification of

T cells as playing an essential role in cell mediated immunity, and immunosurveillance. But here was the quandary—why wasn't there more overactivity of the immune system—an explosion of T cells attacking a single cell? For instance a virus, which infects a cell, causing abnormal proteins to be expressed on the surface, can be recognised by a neighbouring surveillance dendritic cell. That dendritic cell will circulate to a lymph node and tell resting T cells to wake up, recognise this antigen and attack any cells that have this protein on the surface. Similarly, cancer cells have abnormal proteins on their surface, which are recognised by dendritic cells, similarly have T cells educated about the antigen. But they often sit there in the immune system doing nothing! Jim Alleson, a father of modern immunotherapy, identified a particular protein that is produced by the T cells, in the lymph node, as it sits being educated by the dendritic cell. Called CTLA4, it interacts with the dendritic cell, to decrease T cell activation, and act as an internal brake on 'over-activity'.

Who here watches Vikings the TV show? Imagine a scout on the horse sees Ragnar Lothbrok and Vikings pull up on the beaches of northern England, and rides to York to raise the alarm. On arriving he yells out "The Vikings are here—attack them on the beaches". However at the same time, the local publican comes out and tells everyone "relax"—those guys might just be some bearded Scottish fisherman. The army does nothing ...

So, a drug, ipilimumab, a CTLA4 blocking antibody, was designed to block this brake on the immune system. Now imagine the Viking scenario—the alarm is raised, the army rides off to fight the Vikings. T cells ride off to attack the cancer. In the case of melanoma, this alone is enough to sometimes result in amazing shrinkage of the cancer. But not in many patients, and at the expense of horrendous toxicity for some patients as the immune system, whipped into a frenzy can attack the liver, lungs, skin, bowels. That army, whipped into a frenzy, may well rape and pillage on the way to fight the Vikings ...

So how to activate the immune system in a more targeted way, with less side effects? It turns out that the immune system in many untreated cancers has already sent T cells to investigate—biopsy and resection of these cancers often show immune T cells infiltrating cancers, surrounding cancers, but doing bugger all to actually kill the cancer. These are the T cells that have actually worked out where the Vikings are on the beaches and nearby villages but can't find them even though they are right next to them ... Why? The cancer has ingeniously disguised itself from the immune system. Those Vikings have put on a dress, a blond wig, and wander freely among the villages and the army wearing a ridiculous disguise. This again is like a brake—cancers have a protein PD-L1 on their surface to turn off the T cells looking for them. Its like the Obi Wan trick from Star Wars: "These are not the droids you are looking for." "These are not the droids we are looking for. Move on." The clueless T cells, turned off, do nothing. Now, newer drugs, pembrolizumab and other PD-L1, PD-1 antibodies, prevent the cancer from performing the Jedi mind trick. Boom —the disguise the cancers had has gone. The Vikings are exposed—the army is right there—attack! Side effects are less ... the cancer and the army of T cells are in close proximity ...

These drugs, these concepts sound perhaps foreign. But their effects are miraculous for some patients. I met Steven when he was weakened by metastatic bladder cancer, depressed that he was going to die of his metastatic bladder cancer in the coming few months. He wanted to avoid chemotherapy, smoke his medical marijuana, and end his depressed life early, leaving his wife and teenage children tragically early, but sparing them the ordeal of watching him die. I wanted him to try pembrolizumab—and he agreed to self fund a few doses, as he frustratingly failed to qualify for a trial we had open at that time. I noticed the difference only 3 weeks later after 1 dose—his skin was no longer sallow, he was vibrant and his pain had disappeared. Reluctantly he admitted to me

he probably didn't need to smoke medical marijuana anymore! After only a further one dose, his pain had totally disappeared, and he went to Italy for 2 weeks—who does that? What was going on? I organised a PET scan before his third dose. I checked it late on a Tuesday afternoon, before our planned review the next day—I was excited to see what had happened—his cancer had simply disappeared. Gone. I called him, he was apprehensive, he was at a restaurant—who wants their doctor to call with results—it spells doom. I told him the opposite news. He yelled—JESUS FUCK! Then apologised to others in the restaurant. We hugged and we shared tears. He wrote me an email … "Andrew, I've been telling total strangers in the street, service station attendants have become my best friends, I've hugged petulant next door neighbours and small dogs. The whole gamut of humanity looks so beautiful and real today. The only thing I haven't done is punch the air—best left to tennis players and white rap artists … I'm over the moon and beyond somewhere between Pluto's icy mountains and Saturn's rainbow rings."

Is this a typical day in my rooms now? Tears of happiness? Hardly—how about the young woman with lung cancer, who I met the other day with young children, who was dying despite a trial of immunotherapy. What was she going to tell her children? Why didn't these miracle drugs work for her? We now know that these drugs work remarkably well for some cancers—melanoma, lung, kidney, bladder, head and neck cancer and lymphoma—are all cancers where spectacular results happen—but still in only 10-20% of patients. Perhaps 30% more have some stabilisation of their cancer for a few months, but 50% no response at all. But many other cancers these drugs don't work at all. And the cost of these drugs is staggering—so treating patients with a few doses when they don't work leads to terrible wastage—$100,000s of dollars per patient. We'll bankrupt the health system if we don't work out the right drug for the right patient at the right time.

Why is this? Well, some cancers aren't foreign enough—those Vikings on the beach may actually look like English soldiers—cancers that look very similar to normal cells. Cancers have abnormal genes—genes with mutations that encode abnormal proteins, proteins that appear on the surface of the cell. Antigens that are recognised by the immune system. So cancers with more mutations have more chance perhaps that the T cells will recognise the cancer and attack. Melanoma—UV light, Bladder cancer—smoking. But despite some cancers having this type of profile, they may still fail to respond, and we are just beginning to understand more about these reasons.

For instance, Tom Gaweksi in Chicago noticed that mice in his laboratory with a particular strain of melanoma responded to a CTLA4 ipilimumab type antibody. The same strain of mice from a lab in New York did not—their melanomas grew. There were no genetic differences between the mice—the only difference was the diet fed to the mice. So his laboratory did a faecal transplant—with poo taken from the responding mice and given to the mice that the cancer was resistant. Amazingly, the melanomas now began to shrink. Possibly this effect is due to very specific gut bacteria, bifido bacterial species, that when isolated and given to resistant mice, reverses resistance. Even more intriguing are the following observations—after bone marrow transplants, patients with diverse microflora have better outcomes, as do patients with melanoma. Patients treated with antibiotics have worse outcomes if receiving the antibiotics in 3 months prior to treatment with the immunotherapy. Remarkably, eating nuts may also transform the faecal microbiome. A recent study correlated outcomes with tree nut intake—and in fact this is consistent with longitudinal dietary studies that show tree nuts can reduce lifetime cancer risk by 20%. Exercise as well may exert some influence on the immune system. Very sick bed ridden patients do not often respond to these treatments—perhaps the immune system is overwhelmed. Exercise clearly reduces cancer recurrence after surgery—but how? Perhaps through immune mechanisms.

This is all premature speculation of course—and much work and good research needs to be done. But here I am—working at the Olivia Newton-John Cancer Centre with inspiration from my patients and promising tales of changing peoples lives with probiotics, nuts and maybe faecal transplants. The latter topics are so interesting that I am writing grants on the topics— embarking on my own voyage of discovery looking for funding for some wacky ideas. So wish me luck as I write these grants up—hopefully I'll be making amazing discoveries, and not stuck up shit creek without a paddle.

And may I end by wishing you all good luck in your careers—may you stumble upon a career that challenges you, with the courage to pursue slightly mad ideas … Hopefully you too will have the honour of touching patients' lives with your work.