From scientist to patient and back again – the ultimate in clinical translation?

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Steve's research career has been in transplantation and he was part of the team that developed CAMPATH, the first humanised therapeutic antibody. He recently received a live, paired donation kidney transplant together with CAMPATH treatment to reduce the chances of rejection.

In a distant age, when health and safety was just a twinkle in some administrator's eye, I was a new PhD student in the Cambridge University Department of Pathology, learning to make monoclonal antibodies (mAbs) with my supervisor, Herman Waldmann. In the run up to Christmas 1979 we each performed the cell fusions that led to the mAbs that would eventually demonstrate transplantation tolerance in rodents and to the eventual approval of the lymphocyte depleting drug **CAMPATH** (or alemtuzumab) which is now used all over the world to reduce the chance of rejection after organ transplants. During my PhD, we had a young surgeon, Peter Friend, working with us towards his MD, and Peppy Rebello, who later became his research assistant.

The first signs of kidney problems

The first signs that anything was wrong was blood in my urine after a bout of food poisoning (Campylobacter from a dodgy Chicken Madras). After various investigations by Urology (including an IVP – a special X-ray exam of the kidneys and cystoscopy where they have a look in your bladder) they could find nothing wrong and declared I had a harmless "foot stomp haematuria" caused by playing too much squash. Unconvinced, I spoke to some rheumatologist friends and they suggested it might be IgA nephropathy, but this was then still thought to be "mostly harmless" and as there was no treatment, to ignore it. I was then 28.

Twenty years later…..in Oxford

It was after a routine health check some 20 years later that my blood pressure was found to be 210/140 and I was told to see my GP the NEXT DAY. Over the next few weeks they kept increasing my tablets, but despite telling them about my ancient history they didn't check for protein or blood in the urine until my blood pressure was normalised. Finally, after a 3+ for protein in the urine, I was referred to the renal unit, and eventually a kidney biopsy proved IgA nephropathy (a sort of autoimmune disease) and an eGFR (% kidney function) around 30% and falling. A couple of years later it was down to 14% and I was assessed to go on the transplant waiting list. During this time we had Christian prayer for healing and, to the surprise (but delight) of my renal consultant, my kidney function miraculously improved

to around 30% again, and with the help of more than 20 different medications at different times, I remained stable for the next 12 years.

Peppy and Steve on one of their ski trips

Heading towards dialysis?

My kidney function suddenly deteriorated in November 2014 (probably as a result of a rather intractable chest infection the year before) and in January 2015 I was put on the transplant waiting list. Peppy (now my wife) offered to donate me a kidney but we are not a blood group match, which would likely cause me to reject her kidney within minutes. However, after Peppy had all the necessary tests to see if she was healthy enough to donate, we were able to enter a UK wide pooled donation scheme and in June we found a reciprocal matched pair at the very first attempt. By this stage it was touch and go whether I could have the transplant before I needed to prepare for dialysis, but everything went smoothly and the operation took place on 17th August.

Peter Friend and CAMPATH

Peter Friend (now the Professor of Transplantation and Director of the Oxford Transplant Centre) surprised us by coming in when he was on holiday just to do both Peppy and my surgeries. He popped in while I was waiting nervously on the transplant ward to give me the news that Peppy's kidney donation had gone well. He also recommended that I didn't stick to the national protocol of basiliximab and steroids as the kidney was a slight (2,1,1) mismatch and he was sure I would prefer **CAMPATH**! After that the assisting surgeon came in with my consent form and said "so I presume you want **CAMPATH**", followed later by the anaesthetist who then asked the same thing with a big grin on his face. So I received 1 x 30mg of the **CAMPATH** through my central line while in recovery (with no side effects) and I will be on MMF and low dose tacrolimus with no steroids (assuming no rejection episodes – the chances of which should be reduced to about 7% after **CAMPATH**).

The transplant: 5 days in hospital

The first thing I remember as I awoke in the recovery room after the operation was a nurse saying my name, and as soon as I mumbled some sort of recognition she said "the **CAMPATH** is going in now"! After the transplant both Peppy and myself were recovering well, with no pain – neither of us needed to use the magic button provided to self-administer morphine, and Peppy even refused paracetamol. They got me up and about the day after the operation but I was feeling very tired – although the transplant ward is all private rooms they insist on leaving the doors open and run a regime similar to Chinese water torture and sleep deprivation. They constantly wheel noisy trolleys up and down the corridors and surround you with a whole series of machines designed only to provide a continuous beeping sound. Then, just in case you fall asleep they put timed alarms on your intravenous drips and catheter bag. I think it is all because they are too short staffed to

come and take your blood pressure and temperature more frequently. Peppy went home on day 3, but came back with my parents to see me on day 4, and I was allowed out to walk down the street to the coffee shop (together with my "yellow handbag"). I was supposed to be pushed in a wheelchair, but I ended up pushing my mum in it instead.

I now have a 20cm half-moon wound that was sealed with a superglue (note to lab members: presumably NOT "VetBond"!) as the only external sign that I had surgery. The transplanted kidney started producing urine immediately (5L in the first 24 hours) but the creatinine and potassium took a little longer to come down, but were improving each day. They were injecting iv Hartmans solution for the first 3 days at output plus 50 which meant by the third day I had put on 10kg of weight in excess fluid and every part of my body seemed swollen, but once they stopped it I lost 4kg a day. I presumably lost some blood during and after the operation (not least to the phlebotomists) so my haemoglobin initially dropped to 8.0 (normal 14.0) but rapidly improved to 10.5, so I hope to be back on a squash court in another 6-8 weeks. I now have to go to the Churchill clinic for monitoring 3 times a week for the next 2 weeks and twice a week for the next month and take all precautions to avoid infections.

2 weeks post-transplant

Peppy is recovering well, although she has a total of five external wounds to heal (due to the keyhole surgery) which makes it difficult to avoid them rubbing against clothing and making them sore or itchy. She has not needed to take any pain medication at all since the surgery. Neither of us can drive yet, so Peppy's sister has come to look after us, but as she lives in Canada she finds driving, especially all the roundabouts and roadworks on the way to my clinics, a bit of a challenge. We are both trying to go for walks every day and are gradually getting faster - yesterday we walked 3 miles up and down hills around our village.

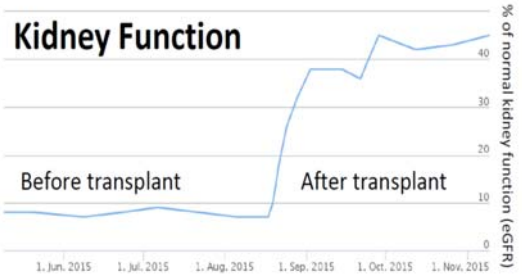
I went to the first clinic last week Monday and the doctor decided I was doing so well they have halved the normal number of clinic visits, which is really good as the trip to the Churchill Hospital is an early morning journey through the severe traffic of the northern bypass roadworks.

3 weeks post-transplant

I am now 3 weeks out and all is going very well and I am feeling really good – neither Peppy nor myself realised quite how ill I had become (my creatinine was over 700 at transplant but is now down to 170) – the doctor has reduced my clinic visits and even allowed me to start driving again (this normally takes 4-6 weeks)! Everyone keeps saying how pink I look – before the transplant my skin was covered in grey-brown blotches as well as the scars of all the itching, but all that has completely cleared up. I hope to start doing some work at home, but won't return fully to work until the beginning of October (assuming all continues well). I am hoping to start playing squash again then (the anaesthetist rang to check on my health status the week before the operation, but when Peppy told him I was out playing squash he decided that pretty much answered his questions) and we have a target of getting back to skiing next March or April.

4 weeks post-transplant

My new kidney is working well – the creatinine is now steady at about 170, which equates to an eGFR (or % of normal kidney function) of about 40. I would have liked it to get to 50%, but although I know nothing about the donor, everything suggests the kidney was from a female donor over the age of 50. This would also fit with my initially high blood pressure (as the female kidney goes into vasoconstriction until it gets used to the lack of oestrogen). I haven't noticeably developed any female traits as yet though (insert your own politically incorrect examples here)! Statistically speaking the half-life of a living donor female to male kidney transplant with an eGFR of 40 in the absence of any other complications is apparently 27 years, so it will hopefully keep me going for the foreseeable future.



Last Friday I had the stent removed (that was put in to hold the new ureter where it is joined to the bladder open). We had to check in to day surgery at 12.30 for the operation due at 1.30pm. Unfortunately they had failed to get my notes from the transplant clinic and although it would have taken 10 minutes for someone to pick them up, (union?) rules are that it is the job of a hospital porter – however none was apparently available, so we ended up waiting 5 hours for the 10 minute operation. The surgeon explained the stent removal from the bladder would be a minor operation using a camera inserted through "natural channels" under local anaesthetic and may cause some discomfort. However, in the theatre a different surgeon (a nice black lady who had assisted in my transplant) said "this will sting a bit" as she injected anaesthetic gel (delete the "a bit"). Moments later as she inserted the cystoscope she said "I'm afraid this is going to be painful for about 10 seconds" – it was in fact excruciating. Anyway, at least the stent is now gone (which now reduces the chances of bladder infection). Monday I had to go for my routine clinic visit and blood tests, but, of course, my notes hadn't made it back from Day Surgery, but thankfully I could give the doctor all the information he needed without having to wait again.

5 weeks post-transplant

Both Peppy and myself are still recovering well – we went for a vigorous 7 mile walk up and down hills on Sunday – I could even do the hills without getting out of breath (my haemoglobin is now around 12 (from 8 at the time of transplant, with 14 being normal, unless you are a pro cyclist where the limit is 18.5). The doctor says I can start some gentle running in a week or so to start getting properly fit again. Peppy is still not yet driving as she has 5 wounds in her abdomen that need to be fully healed.

I have been keeping more than busy reading a thesis and some papers as well as reminding myself how to play guitar (having bought myself a genuine Fender Stratocaster with effects boxes, mixer and multitrack recorder – something I have always intended to do but never found the time for in the last 30 years). I was hoping to do some painting too (art not decorating) but have still not found he time! We also go for walks most days (unless it is

pouring with rain) as we are encouraged to do as it helps with healing and particularly reduces the risk of urinary tract infections (UTIs). Peppy and myself both have our first major review clinics during the week of 28th October, so I am planning to be back full time at work in the Dunn School starting the week of the 5th October.

6 weeks post-transplant

Peppy had her 6 week clinic assessment the week before last and was signed off (written off?) as healthy and has started running again with her personal trainer – she just seems to get a little more tired than before. I am now back at work full time, but am trying to do a vigorous walk (round the 1.5 miles of the University Parks in under 20 minutes) each lunchtime – I also went for a 3 mile run last week. As long as I can avoid infections - my blood lymphocyte count post **CAMPATH** is still 0.0, which hopefully keeps the risk of a rejection episode low but also means I have to keep my distance from all the infectious undergraduates.

Life post-transplant has definitely improved. Peppy notices the biggest changes – my breath and clothes apparently smelled like a gent's urinal before the transplant but now all she can smell is my after shave! I can also sleep the whole night without trips to the bathroom every hour on the hour. Peppy, however, is disappointed that the new kidney failed to cure my snoring!

8 weeks post-transplant

Clinic at 8am this morning went fine, but had to wait an hour because there were NO phlebotomists (they were stuck in traffic). Had to wait another 20 minutes in the hospital pharmacy as I was nearly out of the antibiotic Septrin. I can now drop two more of my tablets (so I now take only 8 different medications), although I will have to be on immunosuppression indefinitely. Lunchtime today I walked the 1.5 mile circuit round the University Parks in 17 minutes 37 seconds (a little over 5mph)! I also booked my first "gentle game" of squash for tomorrow evening (with the over 70's Scottish Masters champion)!

Well, my first squash game post-transplant was OK – after a gentle warm up and checking that I could play all the shots without discomfort (I was a bit worried the overhead backhand might be tricky) - I played 4 games, getting around 5 points in each (9 wins), without pushing too hard. I am a bit stiff the next morning, but nothing untoward.

I've also noticed other improvements since the transplant. I can now use my fancy expresso machine (bought over 10 years ago but rarely used after my GP rang up in a panic about my dangerously high potassium levels just 1 week later). I can grow my fingernails without them cracking or splitting (useful on my right hand for playing the guitar). I can actually do something useful in the evenings after work rather than falling asleep in front of the TV.

3 months post-transplant

Well, no infections or side effects so far, and my new kidney's function continues to improve. I'm down to just 5 different medications now. A few lymphocytes are beginning to

come back, so it's now probably time to go get my flu jab. I'm playing squash 2 or 3 times per week and have won my first competitive game 9-0, 9-0, 9-2. My first trip on public transport was "interesting" (a real Friday 13th trip with 1st train cancelled due to a fire, 2nd train cancelled - fatality on the line, then a 3rd standing room only slow train through every south London station amongst crowds of coughing and sneezing passengers), to examine a PhD student's thesis on potential new ways of treating and monitoring for graft rejection.

Looking ahead

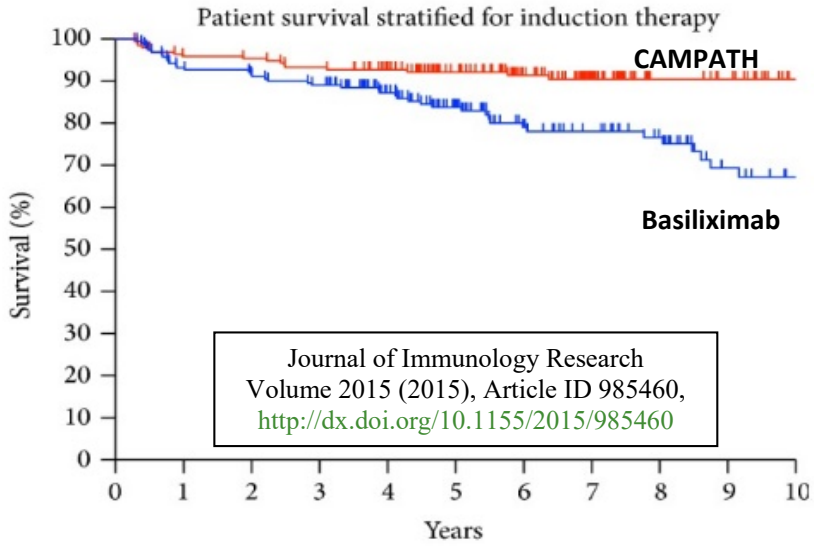
So far, so good, but there are still a number of potential pitfalls ahead – the risk of serious infections, heart disease, diabetes and cancer are all much higher in transplant patients than the normal population and there is still a small risk of graft rejection or failure. Many of these risks are due to the need to continually take immunosuppressive drugs for the life of the transplant. This is why we still need to continue basic research into how we might one day induce transplantation tolerance in the clinic (where the graft is no longer seen by the immune system as "foreign"), so these drugs can be safely reduced or even stopped.

Final thoughts

So I guess I have done the ultimate in clinical translation of my research – participating in the development of a new drug that I eventually received to get my life back. I seem to remember some guy with an ulcer who did something similar once got a Nobel Prize……..

I would like to think that **CAMPATH** treatment is at least part of the reason the transplant has gone so well, but as Geoff Hale (who coordinated many of the early academic clinical studies) once remarked about the **CAMPATH** trials, there were also so many people around the world praying that we can never be quite sure. However, see Figure 1……

Figure 1



Disclosure: Stephen Cobbold is the Professor of Cellular Immunology at the University of Oxford and receives royalties from Genzyme/Sanofi for the sales of alemtuzumab, which is now marketed under the tradename Lemtrada, for the treatment of relapsing, remitting multiple sclerosis.