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# A cycle of life of T cell activation

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Prof. C.U. Blank MD

# ‘A cycle of life of T cell activation’

Universiteit Leiden
The Netherlands

Discover the world at Leiden University

# ‘A cycle of life of T cell activation’

Oratie uitgesproken door

Prof. C.U. Blank MD

bij de aanvaarding van het ambt van Bijzonder hoogleraar

Interne Geneeskunde

aan de Universiteit Leiden

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Universiteit
Leiden
The Netherlands

I can't recall each time I've been sick,
but my T-cells surely have the trick

cause they've got them etched from first to last,
dating back my fifty years in past.

And if my thymus weren't a master
I fear my life would end in disaster.
My body would self-cannibalize.

And if I had to think about it all the times,
that my NK-cells killed a potential tumor,
I couldn't have maintained my humor.

With this small poem from Bernie Gourley, that summarizes nicely how important our immune system is for our well-being, I want to welcome you all.

Mevrouw de Rector Magnificus, Leden van de Raad van Bestuur van het Nederlands Kanker Instituut, Leden van het Curatorium van deze bijzonder Leerstoel, geachte collega's van het LUMC en AvL, geachte aanwezigen, dear colleagues from abroad, my friends, and family.

I want to start with the take home message of my talk:

The inhibition of our immune system by tumors can be best overcome by neoadjuvant PD-1 and CTLA-4 blockade, and for IFN-signature low tumors we likely need some additional unspecific T cell activation.

So, if you still remember tonight after a long party, the words PD-1, CTLA-4, neoadjuvant, IFN-signature, and unspecific T cell activation, then I have achieved my goal.

But let's start first in some more detail.

**The Immune System**

Our immune system is a wonder of a network consisting of 3 trillion cells; that is a 3 with 12 zero's (3.000.000.000.000), that all speak to each other via small molecules, we call them chemokines and cytokines.

With the weight of 2.5kg our immune system is our largest internal organ, followed by the liver with 1.6kg and the brain with 1.3kg.

On and in our body are living about 30-100 trillion inhabitants, namely bacteria, viruses and fungi, we call them together our microbiome.

The main function of our immune system is to defend our body against evil intruders, but also not to over-react against all our bugs in our bowel or on our skin. Our co-habitation with bugs is for example important to keep our skin pH constant or having a functioning digestion.

Our immune system likes diversity, a topic that seems to me at the moment to be the most important topic in the NKI. A diverse microbiome has namely been associated with a better outcome upon immunotherapy if you have cancer.[1] Several meta-analyses - which are huge combinations of several studies - have also shown that the microbiome of the mother has an impact on the onset of eczema and allergies of her baby[2].

So please embrace diversity and stop with all these disinfectant sprays, gels, tissues and start eating your food that has fallen one millisecond on the ground. Your immune system wants to have some training.

Our immune system comprises of of functionally specialized cells with many subsets within each of these cell types. I want to name you only five:

First there the macrophages, they belong to the innate immune system, are fat cells eating everything, chopping it into pieces, and presenting it to the other immune cells.

A more elegant cell are the dendritic cells. They also present peptides, but preferentially only upon activation and have thin elegant long arms.

Then we have the natural killer cells, a warrior cell that kills every cell that tries to hide.

My favorite cells, however, are the lymphocytes, very small agile cells, reacting only specific to individual structures, we call them the antigens, and belonging to the acquired immune system – I explain innate and acquired immunity at once – T cells are the most important effector cells of our immune system because they also form the memory of our immune system.

And finally, there are the neutrophiles, they kill what the lymphocytes have marked for them and are sometime blue and sometimes red in our H/E staining.

As just mentioned, our immunity can be broadly divided into innate and acquired immunity. The innate immune system is found in almost all species and gets activated by so-called pattern recognition receptors. These receptors recognize characteristic foreign structures of sugars, lipids, proteins, but also foreign RNA and DNA. Via this mechanism our fat macrophages can be activated, for example by LPS, a bacterial lipopolysaccharide, and then other cells are alerted about the presence of that harmful microbe.

Superantigens, for example SEB, which are also microbe derived molecules, can also activate unspecifically the immune system, but in this case about 20% of all our T cells.

This is very special, because .... does everybody have paid attention? ... because T cells normally belong to the acquired immune system, thus are normally only specifically activated by their antigen.

During my PhD period in Munich with Klaus Heeg, being my promotor, and Herman Wagner our institute head, we tested the synergy, thus the bridging between these two immune systems by combining LPS and SEB. We found strong synergistic upregulation of the most important network molecules of our immune system (IL-2, IL6, TNF, and IFN).[3]

The potency of SEB I tested also accidentally on myself by spilling some SEB during a mouse experiment into my eye. Within minutes my eye was swollen and pus was flowing constantly out of my eye. Steroid eye drops finally could cool down my strongly activated T cells. I can tell you, from that Saturday afternoon on, I have been convinced that T cells are the most potent cells in our body.

While some way of innate immunity is found in all species, acquired immunity is found only in higher species, mammals, birds, reptiles, fish, and us human beings, although the term 'higher species' I sometimes doubt being attributable to us human beings, seeing all the wars, our absence of honest actions against climate change, nature destruction, and sea pollution.

Innate immunity can only react on the presence of foreign, while acquired immunity can learn, remembers previous infections. This allows us to faster react upon re-infection, and this is also how vaccinations works.

Every of our 2 trillion lymphocytes, has an individual T cell receptor, that potentially could recognize a different structure, their antigen. In addition, T cells can alter their receptor further during an infection. Thus, our T cell receptor repertoire is theoretically endless.[4]

But how can lymphocytes recognize all various foreign structures with their individual receptors, while not attacking our own body. During their maturation, lymphocytes go to school, the thymus school. Only T cells, that can interact with presentation molecules, the MHC complex, but do not react too strong our own body's structures pass and are allowed to patrol through our body.[5]

When T cells met their specific foreign antigen, they are activated and can divide at top speed. You might question me, when comparing a T cell division speed of 8 hours with the 20 minutes of an E. coli bacterium. However, the diameter of a T cell is 10-fold larger than a bacterium (10 versus 1um), thus its volume is 1000-fold larger. If T cells would divide at the speed of a bacterium, it would take them 330 hours instead of the 8 hours.[6]

Our T cells are also not simple minded, with being turned on when the T cell receptor meets the antigen and staying turned off when not seeing it.

On the T cell surface are about thirty, so called, checkpoint receptors. They are up and down regulated during activation and are additional switches, that mediate plus and min signals. A T cell receives, thus, aside the T cell receptor signal a full orchestra of different signals from the checkpoint receptors, fine tuning the T cell activation.

In one of my projects during my post-Doc time in Tom Gajewski's lab in Chicago we found, that one of these inhibitory checkpoint receptors, the programmed death receptor-1, PD-1,[7] plays an important role for T cell maturation in the thymus. It is up until today a great honor for me that Tasuku Honjo, the researcher who first described PD-1 and later became Nobel Prize winner, was co-author on our paper.[8]

**Tumor Immunology, CTLA-4 and PD-1**

But my main interest was the tumor immunology, the idea to learn the immune system to fight cancer. This idea was established already 50 years ago by Frank MacFarlane Burnet and Lewis Thomas,[9,10] but was at my time in Chicago totally exhausted after many failed tumor vaccination trials.

People didn't believe in tumor immunotherapy anymore, and

considered to shut down whole tumor immunology research departments, even at the NKI.
But every disadvantage has an advantage. The research field was small and clear with 18 papers on PD-1 when I started in 2001 and 58 papers when I finished my post-Doc time in 2003 (in comparison to that, in 2021 we had over 5000 papers on PD-1 in only one year).
This allowed me easy to become an expert in my field of checkpoint molecules. Everybody knew each other and research material was exchanged on trust and not after long material transfer agreement procedures. Tom, I do not remember, that I ever signed an MTA, when you allowed me to take all these interesting reagents with me back to Germany at the end of my post-Doc time.
But switching gears back to my main work in Chicago.
We wanted to design a melanoma cell line with a certain model antigen that could be recognized by T cells from a TCRtg mouse, a mouse that has only this one specific T cell recognizing the model antigen. But all my efforts failed. My T cells didn't want to kill the melanoma cells, despite of being well activated, the antigen being on the tumor cell, and even the MHC was strongly upregulated by us by adding interferon. This led us to the idea that the melanoma cells actively suppress our T cells. Some of the already discussed checkpoint receptors were known at that time, and also the corresponding hands, we call them ligands, that press on these switches. Therefore, I stained my melanoma cells for all ligands before and after interferon exposure. We observed, what is meanwhile common knowledge, that PD-L1,[11] which is one of the two ligands for PD-1, was strongly upregulated upon interferon. In the following nightshift I stained all tumor cell lines, that we had in our lab in culture, for PD-L1 before and after interferon exposure. All tumors expressed or upregulated PD-L1, indicating to me that this mechanism must be an important mechanism for tumor cells to escape from the immune cells. We were scooped by Gordon Freeman describing PD-L2, the second ligand for PD-1, some weeks later, showing in a side figure that interferon indeed upregulated PD-L1 and PD-L2.[12] Nevertheless, our work[13] has been cited nearly 1000 times and has been the Eureka moment in my research career, believing in targeting checkpoint receptors.
I want to disclose, that tumor immunotherapy is much broader, and consists also of cellular therapies, local viral therapies, and vaccinations, but for the sake of time I will not discuss them all and want to refer to the former oration of John Haanen and the future oration of Miriam Heemskerk, both experts on cellular therapies, and both professors here at Leiden University. They are in the audience. So, if you have questions, please contact them tonight.
Being back to Germany in 2003, I started establishing my own research group, working close together with Andreas Mackensen in the department of hematology and oncology in Regensburg headed by Reinhard Andreesen. Together with Jürgen Kuball from Mainz, nowadays head of the hematology department in Utrecht, and whom I knew from my US time, we showed that our PD-1/PD-L1 observations in mice holds also true for human tumors and human T cells.[14]
While us being very enthusiastic about our data, this manuscript was rejected one by one by the journals. It was finally published in a low impact factor journal after several revision rounds, that changed our manuscript dramatically. I have to admit that these rounds improved the quality so strong, that we even considered to resubmit it elsewhere, but we were to exhausted. This manuscript has become also a highly cited paper, and is a nice example for us all, that we always should first focus on the research question and our scientific answers, and just later on the impact factor.
In 1996, Jim Allison has designed a small and simple experiment, showing that blocking another inhibitory checkpoint receptor on T cells, namely CTLA-4, resulted in improved tumor control.[15] The brilliance of this landmark experiment was, that it showed for the first time, that modulating a T cell response without touching the tumor itself at all can control tumor growth. Jim Allison won together with Tasuku Honjo the Nobel Prize in Physiology or Medicine in 2018 for his work on CTLA-4.
With the first phase 3 study data in 2010 on ipilimumab, an antibody that blocks CTLA-4, the hype around tumor immunotherapy broke off. A therapy, that was only given for 12-weeks, showed for the first time, and after 30 years of failed clinical research in late-stage melanoma, that about 20% of the patients can be cured.[16]
You will understand our enthusiasm, if you imagine that at that time, we lost all our patients within one year treating them

with chemotherapy. We had even a sarcastic joke about this chemotherapy with my dearest clinical colleague, Hans van Thienen. He always planned the staging CT scan after 3 courses of chemotherapy, while me after two courses, me blaming him, that he only wanted to delay the bad news conversations.
From that ipilimumab time, every clinical tumor immunologist has her/his signature patient - the first impressive responder upon immunotherapy, as Jedd Wolchok lays out in the worth-seeing documentary 'Breakthrough' (https://www.breakthroughdoc.com). This documentary describes the life of Jim Allison, and his life-long effort in the development of ipilimumab.
My own signature patient is Astrid, a young mother of three coming to me with brain, lymph node, and bowel metastases from her melanoma. A metastases-combination that was normally fatal within months at that time. The combined therapy of brain stereotactic irradiation, surgery of the bowel metastasis, and ipilimumab cured her miraculously and I am very honored that she is my guest today.
An early access program allowed us at the NKI, to provide ipilimumab to our patients before registration, resulting in a flood of patients from all over the Netherlands to our institute, giving John Haanen and me, the only two melanoma specialists at the NKI at that time, outpatient clinics till late in the nights to see all these patients.
Meanwhile, we have 14 melanoma centers in the Netherlands, that give immunotherapy for melanoma. This construct is regularly challenged by other centers, that also want to treat melanoma. But I would like to warn here strongly against giving up this construct. A rare disease like melanoma needs to be treated in high-volume specialized centers. Only so we can offer our patients the highest quality and the most innovative therapy and ensure further innovation by comprehensive patient data collection, investigator-initiated studies, and early phase trials coming to the Netherlands.
I cannot understand, why we do not apply this success model to other rare cancers in the Netherlands, for example to renal cell carcinoma.
Anti-PD-1 antibodies, namely nivolumab and pembrolizumab, soon followed in the clinic after ipilimumab,[17,18] and it was a very emotional moment for me to give the first anti-PD-1 infusion of the Netherlands to a patient at the NKI. I have to admit that this was not without the help from one of our fantastic outpatient oncology nurses, because doctors generally do not know how to operate the saline drip machines.
Anti-CTLA-4 and anti-PD-1 antibodies kept their promises, and we saw more and more patients having ongoing anti-tumor immune responses, so that our outpatient clinic was growing exponentially, a fact that our managers in line of communication long-time ignored leaving the whole melanoma team continuously overworked.
The combination of ipilimumab and nivolumab gave even higher responses, but at cost of much higher side effects, requiring even more intense managing of our patients.[19]
I want to mention here our nurse practitioners, who respond daily to the flood of questions and manage our patients with their side effects. Without you, our melanoma team would have broken down already. I do not understand why your work is still so undervalued and you are not recognized as own group in our institute nor in the Netherlands.
Internationally, the melanoma doctor community became a close and strong group, implementing extremely fast trials, resulting in the fact, that within only one decade we nowadays cure more than 50% of late-stage melanoma patients, a fact that is hardly seen in any other solid cancer.
By analyzing patient characteristics associated with long-term benefit from these immunotherapies, Ton Schumacher and me developed the 'Cancer Immunogram', a theoretical tool to stimulate new immunotherapies.[20] While we saw our immunogram figure passing by regularly as introduction slide at conferences, the implementation of this idea remained pending.

**Neoadjuvant cancer immunotherapy**

On a Friday afternoon, short before the 2014 ASCO conference, Ton and me were drinking coffee together, for the foreigners here in the room – drinking coffee together is very important here in the Netherlands. But if you are young and a beginner, you need to be careful, because if somebody is asking you 'shall we drink a coffee together', this means regularly, that you get an additional task.
Not with Ton, drinking coffee together with you is always fun and a great brain-storm session. This special Friday's topic was about how immunotherapy could be most effective for our patients.
We knew already from our work before that low tumor burden, for example as measured by LDH, was associated with a better

outcome.[21] Thus, cancer immunotherapy should work better in earlier stages of disease with lower tumor burden. These stages we call stage III melanoma, when the tumor cells have been detectable spread from the primary site in the skin to the draining lymph nodes, but not yet further.

If such early-stage disease patients came with enlarged lymph node metastasis to us, the standard therapy was the extensive surgical removal of the whole lymph node bed, curing about half of the patients, but leaving them often with long term side effects, as seroma, lymph edema, pain, and restricted motility.

An upcoming idea at that time was to treat these patients with additional anti-PD-1 after the surgery to improve the survival of our patients by preventing the return of their disease; we call such a therapy adjuvant immunotherapy. This adjuvant anti-PD-1 immunotherapy is given for one year and costs 60-90 thousand Euro per patient.

While we meanwhile know that the relapse free survival can be improved by adjuvant immunotherapy, even years later, we still have not seen an overall survival benefit for our patients.[22,23]

Coming back to the Friday: the landmark idea from this Friday was to move the immunotherapy to upfront surgery. We call this neoadjuvant immunotherapy. This would allow the immune system to recognize the whole variety of cancer cells and give so a better immune response. It also allows us to judge our therapy better and possibly adjust the subsequent surgery and adjuvant therapy, and so improving the quality of life of our patients.[24]

In the OpACIN trial, that we designed the next days, we could indeed show that exact the same therapy just given before surgery, induces a stronger and broader expansion of the tumor resident immune cells found patrolling through the body, and that after only six weeks of therapy.[25]

In two-years rhythms, which is top class speed for clinical trials implementation, we were able to identify in the OpACIN-neo trial the best neoadjuvant combination therapy,[26] omit the extensive surgery in the PRADO trial,[27] personalize the adjuvant therapy according to response in the PRADO trial,[27] use a baseline biomarker, the interferon signature, in the DONIMI trial, and currently hope to define our combination scheme as standard therapy in the ongoing NADINA trial.

Each of these trials is result of tremendous work and has the signature of one of my MD PhD students. Therefore, I want to mention them here. Lisette, Irene, Judith, Minke, and Lotte ... you are doing an unbelievable great job that these trials are implemented so fast.

However, these trials would also not have been possible without the great collaboration with Georgina Long, who believed also very early in the clinical impact of neoadjuvant immunotherapy. Together with all colleagues from the International Neoadjuvant Melanoma Consortium (INMC, www.melanoma-inc.org) that we have set-up in 2018, we have been able to show up until today

a) that neoadjuvant checkpoint inhibition can improve the long-term outcome of our patients,[28]

b) pathologic response is an excellent baseline surrogate marker for long-term outcome of our patients,[28]

c) we likely can omit the large, often mutilating surgeries in about half of the patients,[27] and

d) only 40% of the patients need adjuvant therapy.[27]

This personalization of neoadjuvant combination immunotherapy, will reduce cost (world-wide about 1 billion Euro), will improve the overall survival (about 10,000 lives per year can be rescued in addition, also due to broader access for poorer people of this less expensive therapy), and finally will also improve the quality of life of our patients due to shorter therapies and the reduced extent of surgery.

In a first step, our US colleagues have last month shown in their large randomized SWOG S1801 trial, that moving only three courses of anti-PD-1 monotherapy from adjuvant to neoadjuvant reduced already the relapse rate by absolute 20% (LBA6, ESMO 2022). In our NADINA trial we expect to show that the neoadjuvant combination therapy does this in even 30%.

So, for the future, we can expect, that we have for melanoma soon two options, namely neoadjuvant mono- and combination immunotherapy.

When curing more and more patients, long-term toxicity from our therapies, and not only the physical, but also psychological, becomes more and more important.

I regularly see the impairment in the quality of live from surgical morbidities, such as pain or impaired mobility, impairing the role you had before.

I regularly see the impairment from long-term immunotherapy side effects, for example adrenal gland insufficiencies, not being able to live a spontaneous life anymore.

I regularly see the fear in our patients waiting way too long for

their CT scan results, for days or even weeks in fear.
I regularly see the increasing fatigue from coming and coming to the hospital for their infusions, getting one year adjuvant therapy, which length is based on no scientific rationale.
I regularly see, how our follow up programs restrict our patients from getting back into normal lives, for which frequency we also do not have scientific data.
In that way we have to start to scientifically collect on large scale patient reported outcome data and quality of life data aside our clinical data. Based on this we not only have to personalize the extent of surgery, personalize the neoadjuvant immunotherapy, but also should innovate our communication and follow-up with our patients.
Judith Lijnsvelt developed together with a Finns app developer an immunotherapy module to just-in-time check for side effects, collect their quality of life, and directly communicate in a WhatsApp style with our patients.
I envision that such approaches will not only increase the safety during therapy, but also can be used to replace the structured follow-up by artificial intelligence-driven early identification of symptom deviations, indicative of a possible return of the disease.
A major hurdle, I however foresee, in connecting such innovative tools to our Dutch MS DOS based EPD that is provided and maintained by a monopolistic company.
This is an example, amongst many, showing that neoliberalism in health care does not work, hampering at the end real innovation, and produces higher cost than it would have been in good old social market economy.
I promise to fight all these obstacles, and if we succeed, treatment of stage III disease and so preventing late-stage cancer will become in many patients a six weeks life event, allowing them to proceed faster to their normal lives, for example also being able to work again.
In their milestone work in empiric social science from 1933, Maria Jahoda and colleagues showed the impact of not being able to go to work on the daily structure and the psychological well-being. They followed the families of a working neighborhood near Vienna, Marienthal, that was strongly impacted by the shut-down of the only factory at place in 1929.[29]
Inspired by her findings we analyzed the return to work as surrogate marker for well-being of our patients. Our small preliminary results showed that neoadjuvant treated patients start to re-integrate into their previous work way earlier than adjuvant treated patients. And, only 60% of adjuvant treated patients finally worked full-time, while this was the case for more than 80% of the neoadjuvant treated patient group.
Thus, aside the individual psychologic aspects of being longer patient when treated adjuvant, our shorter neoadjuvant therapy seems to have, also favorable socioeconomic aspects for the society.

**Future aspects of neoadjuvant cancer immunotherapy**

For the future, I envision that neoadjuvant mono- and combination therapies, and not only of checkpoint inhibitors, but also with chemotherapies, vaccines, cytokine therapies, and even with cellular therapies, will become focus of intense research in all solid cancer.
For stage III melanoma we will have three subgroup of patients that we can characterize already by baseline and on treatment interferon signatures.
1) Interferon signature high patients will be treated with anti-PD-1 monotherapy for only 6 weeks without extensive surgery and no adjuvant therapy.
2) Patients with a baseline low IFN signature, who develop a high IFN signature after the first combination of ipilimumab + nivolumab can go on with that combo and will have the same excellent outcome as the first group
3) The remaining 25% of patients, however, have highly unfavorable tumors, as identified by low baseline and low on-treatment interferon signatures. They will need intensified double or triple combination therapies.
I want to discuss here in my last minutes three possible options for our group 3 patients.
Option 1: Patients from group 3 have also a low BATF3 signature. BATF3 dendritic cells are very interesting cells.
They can pick-up antigens in the tumor, transport them to the draining lymph node, present them here to the effector T cells, and can travel back to the tumor to produce chemokines that attract the activated T cells into the tumor.
In a high throughput drug screen, our group tested in a project of Esmee Hoefsmit, and with great help of Disha Rao, 5632 drugs for their capability to improve cross-presentation in a tumor-DC-T cell co-culture assay. The immunologist here in the room can confirm, that this co-culture for so many drugs is a hell of a job.

While we got help from a robot, the whole team was working in shifts day and night for several days for this experiment, and the preparation and subsequent analyses took almost three years. Luckily, we identified several promising drugs that we hope to see once in the clinic.
Option 2: Our bioinformatician, Petros Dimitriadis, found that patients that do not respond to neoadjuvant immunotherapy have a low IL-2 signature in their tumor. So why not just adding interleukin-2 to ipilimumab + nivolumab. Indeed, in tumor fragments from non-responding patients and in a neoadjuvant mouse model, a great collaboration with Daniella Thommen from the NKI and Michel Teng working at that time in Brisbane, and this during COVID lock-down, we saw indeed promising signals that this triple therapy could work in our most unfavorable patients.[30]
Option 3: Coming now back to the beginning of my talk.
I told you about the impressive immune activation, that I experienced myself after spilling SEB into my eye. I want to share with you in the last minutes an idea, that nicely closes the circle with where I began my research career.
We have observed that injecting SEB into mouse tumors that resemble our IFN-signature low patient tumors led to increased T cell activation and tumor control in combination with PD-1 and CTLA-4 blockade, while the immunotherapy alone failed completely.
In that way I believe that unspecific immune activation, will face a renaissance in combination with modern checkpoint targeting immunotherapies.
If we succeed in setting-up an SEB trial for our patients, my 'cycle of life of T cell activation' will be closed.
You might ask yourself already some time, why this old pharmacist pot of talcum is standing beside me.
This pot, belonged to my mum, who was pharmacist and unfortunately can't be with us today, because she passed away from pancreatic cancer some months ago.
Talcum induces an unspecific inflammation that is used in the clinic to glue together membranes between the lung and the chest wall. This is a therapy for cancer patients who suffer from shortness of breath due to a malignant effusion compressing their lungs.
So, you might already guess, where this unspecific inflammation induction is going to.
Femke, my second signature patient, who is also in the audience here today, suffered from enormous shortness of breath due to such an effusion and a massive growth of her melanoma in her chest wall after failure of our neoadjuvant combination immunotherapy. Her tumor had one of the coldest interferon signatures that we ever have measured.
She had so many plans with her family of two kids and it broke my heart to tell her short before Christmas 2021 that many of her dreams will not come true anymore.
To buy her some last time, we instilled talcum and I restarted the same combination immunotherapy, that she had already before, just in another dosing, but in parallel with the talcum instillation.
I admit that this was an act of desperation. But after only one infusion, she developed extremely high fever and chills, persisting almost over two weeks, a symptom, that you normally do not see in that extreme from any of both, the talcum alone, or the combination immunotherapy.
I was intrigued by this strong immune activation and asked Femke in our daily telephone calls to stand it, and not to start steroids, stopping this strong immune activation.
At the end, she received only one course of immunotherapy, because of additional side-effects.
Her cancer disappeared and is still absent until today.
Femke, I want to give this pot as a souvenir from my mum to you.

From a physician perspective, this means to me, that we need to follow in our daily work not only textbooks and standard protocols, but also need to follow our hearts. And sometimes, there is a wonder happening.

From a scientific perspective I believe, that strong unspecific immune activation, as used already by the Romans and given a renaissance by William B Coley,[31] combined with modern checkpoint inhibitors might become the key to efficient neoadjuvant therapies in low interferon signature tumors.

And I, myself believe, and this I want to give to to you, the young, on your way: respect the knowledge and the achievements of our ancestors, combine it with a curious view on the unexpected, and create new good for the future.

As our body is too complex to be fully understood, medicine will be always art and science.

**Acknowledgment**
Looking back on my career, it is evident that many people have impacted my way. The once that influenced my career most, I have mentioned already during my speech, the once that I will forget to mention, please forgive me.

I would like to thank

The Executive Board of the University and the Boards of Directors of the LUMC and the Netherlands Cancer Institute for the trust placed in me. By establishing this chair, you clearly demonstrate that the believe in cancer immunotherapy research is back.

I want to thank all our patients, participating in our trials. Without you taking your personal risk, innovation would have been never possible. I also want to thank all sponsors of my trials and all donators, supporting our research.

I want to thank my mentors Klaus Heeg, Herman Wagner, Reinhard Andreesen, Tom Gajewski, and Andreas Mackensen – you not only teached me internal medicine, oncology, and cancer immunotherapy, but always showed me, that there is also fun of live outside work.

I want to thank my close colleagues on our cancer immunotherapy journey, Juergen Kuball, Ton Schumacher, John Haanen, Wolfgang Herr, Jennifer Wargo, Roda Amaria, Paolo Ascierto, Alex Menzies, Alexander van Akkooi, Winan van Houdt, Hussein Tawbi, Liz Burton, Monica Gonzales, Ellen Kapiteijn, and Karijn Suijkerbuik, and all the others of the melanoma community all over the world – without the continuous exchange, our scientific dispute, our friendship, and all your efforts, we never would have been able to come this far for our melanoma patients.

Dear Georgina, what we have built together is unique - a practice changing collaboration of two large teams of clinicians and researchers, thousands of miles apart, COVID isolated, and despite all these hurdles functioning amazingly. You are a tough, smart, and sometimes challenging person, but at the end always with a big heart. It is a great honor and fun for me to work with you together.

Bauke – without your belief in neoadjuvant therapies and your support from within pharma, many of our trials would have not been possible
Lindsay, Lidwina, Suzan, Sanne 1, Sanne 2, Marloes, Shureila, Karolina, Harm, Marije, Koen, and Hylke – you are the backbone of all our trials giving my ideas the right structure.

All my colleagues and research colleagues from Regensburg, Munich, the NKI, B3 and B6, the AvL, MIA, the INMC – without you we have never come so far in our mission.

My fantastic research team – Kerstin, Lisa, Lukas, Jules, Aurelie, Anna, Ruben, Mesele, Lisette, Huma, Petros, Irene, Judith, Lotte, Minke, Esmee, Disha, and Anne – I am so proud of all your work, you are the team that every PI dreams of to have.

The melanoma group – and represented for all of them Sandra, Henk, Wilma, Judith, Saskia, John, Hans, Sofie, Aafke, Kishan, Winan, Bart and Bernies – it is an honor to work with so many dedicated and so smart people together.

Karin, Bea and Kim – you are the ones knowing where I have to be, what to do, when to do, covering my back, enabling us to live this 150% job.

U3 south – you are the best think tank in the world.

My dear friends Markus, Andy & Alex, Julia, Susanne & Niels, Jim, Reinhard & Christiane, Matthias & Wolfgang, Lindsay, Astrid & Daan, Lonneke, Marc, the Molenzwemmers and Bikers – you all have helped me in one way or the other through my often very chaotic private life.

Barbara and Tanja – you were long time part of my life, and the ones that stood behind me. Science asks a lot, sometimes too much for two.

Dear Mum and Dad – you both died way to early, but you live further in Alex and me. Thank you so much for this easygoing inspiring education and life you gave us – you let us fly in good times, but were always there for us, when we were falling.

Alex, Johanna, Ebba, Gustav – you are my inner circle family – we are a small family, but so strong – Alex my dearest brother – you are also the best friend of the world to me.

Ik heb gezegd

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'A cycle of life of T cell activation'

## Prof. Christian U. Blank MD

Christian Blank obtained his MD from the Medical School of the Technical University Munich, Germany, where he also completed his Doctoral thesis summa cum laude at the Department for Medical Microbiology in 1997. He worked as Junior House Officer (1997-1998) at the University Clinic Munich, at the Royal Infirmary of Edinburgh, and the University of Birmingham. He went on to attain the position of Physician at the Department of Hematology and Oncology, University of Regensburg, Germany (1998-2001). During 2001-2003, Christian Blank held a Postdoctoral Research Fellowship at the lab of Professor Thomas Gajewski, University of Chicago, IL, USA. Subsequently he was appointed as Physician and Research Group Leader at the Department of Hematology and Oncology, University of Regensburg, Germany (2003-2007). He has obtained two Specialist Degrees in Internal Medicine (2007) and in Hematology/Oncology (2009). Since 2007, he has been appointed Staff Member at the Department of Medical Oncology, and a Group Leader at the Division of Molecular Oncology and Immunology, The Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital (NKI-AVL), Amsterdam. In 2010, Christian Blank became University Lecturer (Privatdozent) at the University of Regensburg. In addition to his academic background, he obtained his Master of Business Administration (MBA), from the University of Warwick, England, UK (2006). Christian Blank is committed to teaching, lecturing on medical courses at the NKI-AVL, the VUMC, and the Medical School of the University of Regensburg, where he was appointed Professor in 2015. In 2020 he was additionally appointed Professor at the Leiden University Medical Center (LUMC) in The Netherlands. He is a member of several societies, including ESMO and ASCO. Christian Blank has been invited speaker at more than 250 national and international congresses, and is the author of more than 200 publications. His research interests broadly include neoadjuvant immunotherapies, targeted and biological response modifiers, and prognostic markers for cancer immunotherapies. Christian Blank has been the principal investigator of several investigator initiate trials testing neoadjuvant immunotherapy in melanoma that are currently changing the treatment landscape.

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