



Universiteit
Leiden

The Netherlands

The selfish cell: cancer, competition, and the company we keep

Miranda, N.F. de

Citation

Miranda, N. F. de. (2026). *The selfish cell: cancer, competition, and the company we keep*. Leiden.
Retrieved from <https://hdl.handle.net/1887/4309335>

Version: Publisher's Version

License: [Leiden University Non-exclusive license](#)

Downloaded from: <https://hdl.handle.net/1887/4309335>

Note: To cite this publication please use the final published version (if applicable).

The Selfish Cell: cancer, competition, and the company we keep

Inaugural lecture by
Prof. dr. Noel de Miranda



Universiteit
Leiden

The Selfish Cell: cancer, competition, and the company we keep

Inaugural lecture by

Prof. dr. Noel de Miranda

on the acceptance of his position as Professor of
Translational Oncology, in particular immunogenomics of cancer
at Leiden University
on Friday, 11 September 2026



Universiteit
Leiden

Mevrouw de Rector Magnificus, geachte leden van het College van Bestuur van de Universiteit Leiden, geachte leden van de Raad van Bestuur van het Leids Universitair Medisch Centrum, beste collega's en studenten, lieve vrienden en familie.

Dear colleagues, students, friends, and family

Origins

I will start my inaugural lecture by sharing a recipe with you: if a dirty shirt is placed over a container of cereal, like wheat, substances from the shirt will mix with vapors from the cereal and, after about twenty-one days, transform the cereal into mice. This recipe was an attempt by Jan Baptist van Helmont to explain the origin of life.^{1,2} Van Helmont was an accomplished 17th-century Flemish scientist, who, amongst other important scientific contributions, discovered that gases other than atmospheric air exist and coined the word *gas*,² but who was considerably less successful when it came to explaining where mice come from. I was taught this recipe of spontaneous generation in high school, and, at the time, it was easier to understand this theory, despite its absurdity, than the concept of Darwinian evolution, in which complex organisms evolved from simpler organisms as a consequence of alterations or mutations in their DNA followed by natural selection.

Take as example the anglerfish that dangles a bioluminescent lure from its forehead to attract

prey. It is, basically, a fishing rod that evolved on its face. But that is not even the strangest part about this animal. In some deep-sea species, the male, considerably smaller than the female, has one biological purpose: to find a female, bite into her, and fuse permanently with her body. His organs dissolve, he loses his independent existence, and he becomes little more than a sperm-producing appendage for reproductive purposes.³

It was fascinating to realize that such animals (ourselves included) are the product of chance: random mutations, accumulated and filtered by natural selection, over billions of years. For a biologist, this is perhaps our equivalent of the fascination that most of us have with the universe and infinity.

The Selfish Cell

Looking back, I think cancer research has been the perfect vehicle for this fascination. Cancer develops from alterations in the DNA of our own cells and triggers an arms race within our body, where cancer cells compete with healthy cells for survival. Cancer cells reject the organized, multicellular structure that is our organism and revert to something closer to the selfish, independent behavior of a single-celled organism (the *Selfish Cell*), which is how life existed for about 3 billion years before multicellular organisms appeared.

Multicellular organisms succeed because they can perform complex tasks, in parallel, that no single cell could carry out alone. As I speak, your body is simultaneously regulating body temperature, pumping blood, potentially digesting, mounting immune responses against viruses we are generously exchanging with each other in this room. All while, hopefully, paying attention to my lecture. Maintaining such complexity requires order, rules, and sacrifice. Cells that are old or no longer function properly can receive instructions, or instruct themselves, to die. Cancer cells reject this order, multiplying without control and forming what is, in fact, an organism within our organism, one that can evolve and compete with the healthy cells. Because they are no longer bound by the rules that govern healthy cells, they have the advantage in this arms race. Left untreated, or once the disease is too advanced, cancer usually prevails.

Not quite in the same league as the anglerfish in terms of improbability, but despite being so common, cancer is, from a statistical point of view, actually rather unlikely to occur, at least if we speak of a single cell that divides and accumulates mutations in its DNA. A cell's DNA can be thought of as a book, and not just any book. With 3.2 billion base pairs, each corresponding to a letter, it would be hundreds of times longer than the longest novel ever written. Every time a cell divides, that book has to be copied, letter by letter, by molecular

copyists called polymerases. Think of them as monks transcribing the entire text by hand. And mistakes are inevitable. But because these monks have a built-in self-checking mechanism that catches most errors as they write, and because a separate team of molecular editors (the DNA repair system) scans the finished text and corrects whatever mistakes were made, the end result is only about 1 mutation per cell division. And what is one misplaced letter in a 3.2 billion letter book? In most cases, nothing. Replace a single letter in any book, and you will not change its meaning. The problem arises when mutations occur in the parts of the book that carry the instructions for proteins that are important for the function of our cells. Those vulnerable parts of the book represent less than 0.1% of the entire book. But when mutations do occur in the wrong place, our book can transform from a harmless gardening manual into a manual for building a nuclear bomb.

If we take the average life expectancy of a person living in the Netherlands, the cells responsible for renewing the inner layer of our intestine, so-called stem cells, will have divided tens of thousands of times, thereby increasing the probability that a mutation eventually lands in the wrong place. Beyond chance, we are also not all born equal when it comes to cancer. The genetics we inherit from our parents define different starting points for each of us, making some of us more vulnerable than others to

developing cancer. Having had the opportunity to work on explaining the genetic causes of increased predisposition for cancer has been one of the most rewarding research periods, together with Professor Tom van Wezel, Dr. Maartje Nielsen, and our former PhD student, Dr. Stephanie Schubert, among other colleagues.

But genetics is only one piece of the puzzle. There is also behavior. The way we live has a tremendous impact on the likelihood of developing most cancer types, and that raises uncomfortable questions about the choices we make. About how we want to live and how we want to age. There are no easy answers, as individuality and freedom are important values, provided people are well informed. In line with this, I want to praise initiatives like those driven by Dr. Danielle Cohen, who is working in the educational and political arenas to reduce smoking and in particular vaping, which has become increasingly popular among younger generations. Initiatives like hers, focused on prevention, can have far greater impact than most therapies we develop to treat the disease once it's already there.

The Immune System and Cancer: have they met?

You may be surprised that I have not spoken about cancer immunology so far. Let me fix that: the immune system is one of the agents imposing selective pressure on cancers, potentially limiting their development and eventually shaping

cancers to acquire characteristics that allow them to escape immune recognition.⁴ When I started doing research as a trainee student, cancer immunologists were regarded as exotic birds. Many people claimed the immune system would never be used to treat cancer patients. Over the past decade, however, checkpoint blockade immunotherapies, which are treatments that boost and revive the capacity of a patient's immune cells, have transformed the treatment of several cancer types.

Evolutionarily speaking, however, those early cancer immunology skeptics may not have been entirely wrong. To capture students' attention, I often start by asking the audience how many people think the immune system is effective at fighting cancer. Most students believe it is. I then argue the opposite, presenting a deliberately provocative, black-and-white picture: "the immune system did not evolve to deal with cancer cells. Most of the systems in our organism evolved to bring us to reproductive age, and because cancer incidence peaks well after reproductive age, evolution simply does not care about cancer".

This is, of course, not entirely true. Evolution did develop mechanisms to prevent the malignant transformation of healthy cells, but it has done so primarily by developing protection mechanisms within the cell itself: the molecular monks with proofreading capacity (polymerases),

the molecular editors (DNA repair), and the processes that instruct a cell to sacrifice itself when it has gone beyond repair. The immune system, instead, is geared towards dealing with external threats like viruses, bacteria, and other pathogens that were, and without vaccines would remain, the greatest threats to our survival.

This brings us to one of the immune system's most fundamental properties: its ability to distinguish our own cells from external threats. Macfarlane Burnet called this the distinction between *self* and *non-self*.⁵ T cells are one of the most important cells of our immune system and, in our book analogy, are highly trained readers capable of recognizing an unfamiliar book on sight, doing so by sampling the proteins that each book produces. A virus or a bacterium produces proteins that read like an entirely different book, and the immune system identifies and responds to them vigorously. A cancer cell is still largely the same book as a healthy cell: a few letters have changed, but the proteins it produces remain largely familiar. The reader (the T cells) glances at it and, more often than not, does not see a difference. One could say a cancer, in most cases, qualifies as *self*: a *selfish self*. To bring the point home and to provide evidence that the immune system does have limitations regarding the recognition of cancer: the incidence of most common cancer types is not significantly elevated in immunosuppressed individuals, apart from a few exceptions, such as cancers of viral origin.

That being said, and paradoxically, the immune system does have a profound impact on the biological behavior of cancer and, consequently, on the prognosis of patients. This brings us to the last part of the title of this lecture: *the company we keep*. Cancer cells are not alone when a tumor is formed. Instead, a tumor is a complex ecosystem of many different cell types collectively referred to as the tumor microenvironment, and the nature of that company matters.⁶ In general, for most cancer types, tumors rich in CD8⁺ cytotoxic T cells tend to be associated with better clinical outcomes for patients. These are the readers from our book analogy that have the capacity of eliminating cells with abnormal proteins. This observation provides circumstantial evidence that the immune system, through the killing capacity of cytotoxic T cells, does have the ability to keep cancer in check. On the other hand, the presence of immune cells with regulatory or suppressive functions, such as certain myeloid cells typically involved in wound healing, tends to be associated with worse outcomes. The company cancer cells keep can, thus, be as important as cancer cells themselves, and this constituted an important paradigm shift in the field, not that long ago, to which many people in this room contributed.

So, how does the immune system *see* cancer cells? It turns out that some of the mechanisms the immune system uses to deal with bacteria or viruses can also be used for the recognition

of cancer cells. And not surprisingly, the more a cancer differs from the *self*, the more likely it is to be recognized. For instance, cancers developing as a result of defective molecular editors (the DNA repair systems), as well as lung cancers induced by smoking or melanomas resulting from sun exposure, all accumulate large numbers of mutations and are particularly likely to be recognized by a patient's immune system.⁷ Based on the work of teams led by Robert Schreiber, Steven Rosenberg, and Professor Ton Schumacher, among others, we now know that those mutations can be directly recognized by the T cells of our immune system when presented in the context of molecules called Human Leukocyte Antigen (abbreviated as HLA)⁸: what I like to think of as the cellular informants of our immune system, constantly showing the contents of our cells to T cells that are patrolling our bodies.

When I progressed from a trainee to a PhD student in the department of pathology at the LUMC, I was given an exciting project by Professor Hans Morreau, Professor Cees Cornelisse, and Dr. Jan Willem Dierssen on studying aspects of tumor immunology in colorectal cancer in relation to the genetics of the cancers. We described that the loss of HLA class I (the cellular informant allowing T cell recognition of cancer cells) was more frequently observed in cancers carrying a high number of mutations due to a defect in the DNA mismatch repair system, one of the molecular editors I

mentioned earlier.⁹ This loss of HLA class I represented an evolutionary trait, selected by the pressure exerted by T cells. In our book analogy, this was a cancer that was particularly easy to read for our immune system, and one that therefore had to adapt in order to survive. For someone with a passion for evolution, who could ask for a better project?

By the end of my PhD, several questions remained unanswered. Loss of HLA class I is, in fact, a distinct category within the *self/non-self* classification, known as the *missing-self*.¹⁰ Importantly, the immune system has cells that specifically evolved to detect the *missing-self*: most notably, the so-called Natural Killer cells (or NK cells), which are extremely efficient killers adapted to eliminate cells displaying this *missing-self* phenotype. So why were these tumors not being eliminated? And more puzzling still, in some contexts, cancers that had acquired this apparently effective immune evasion mechanism seemed to be associated with a better prognosis for patients than those that had not.

This puzzle became more complex after the introduction of checkpoint blockade immunotherapy for the treatment of these cancers. Surprisingly, the majority of DNA mismatch repair deficient colorectal cancers, including those with loss of HLA class I, turned out to be highly responsive to it. But how could this be? This therapy is thought to depend on

CD8⁺ cytotoxic T cell activity, and CD8⁺ T cells, in turn, depend on HLA class I expression on cancer cells to recognize and eliminate them. As always, and I'll admit Occam's razor is a principle I often favor, biology tends to be more complicated than the textbook suggests.

NK cells did not seem to explain what we were observing, and at the time, we had no idea which immune cells might be mediating these responses instead. It has been quite a journey from those initial observations to the proposal that more obscure immune cell subsets with innate properties, like $\gamma\delta$ T cells, are not merely evolutionary relics or living fossils, but active participants in anti-tumor immune responses, potentially involved in recognizing tumors that have lost HLA class I expression. That journey began with the work of Dr. Natasja de Vries, carried out together with Professor Frits Koning.¹¹ It would not have been complete without the demonstration, in a clinical context, that $\gamma\delta$ T cells may indeed mediate responses to immunotherapy.¹² For that, collaboration with our colleagues at the Netherlands Cancer Institute was essential, including Dr. Myriam Chalabi, Professor Emile Voest, Dr. Joris van der Haar, and other colleagues.

This ever-present possibility of being surprised by biology is, I think, part of what draws so many of us to research. It is also humbling and somewhat puzzling how much remains to

discover about things we know to exist. I find it striking that in 2026 we still know so little about cells of our own immune system. While there is a good side to this, meaning we can keep our jobs for years to come, I also fear there are biases that explain some unknowns. Science suffers from a significant herd effect, driven in large part by the way we fund research through competitive calls.¹³ Whatever we tell ourselves about rewarding quality and innovation in whatever fields, the system is highly permeable to trends and to what is fashionable in the field at any given moment, and that, I am afraid, often pulls researchers toward similar questions, at the expense of the diversity of the scientific landscape. Some things remain unknown not because they are uninteresting, but because they are not fundable.

Why are tumors not stopped at the start?

Conversely, through a combination of teaching and research, I also realized that there are a number of things we think we know about but for which there is little evidence. Take cells with innate properties like $\gamma\delta$ T cells or NK cells. They act by recognizing molecular patterns at the surface of target cells that signal something is wrong, for instance when a healthy cell transforms to a cancer cell. Through this mechanism, our cells do not rely solely on presenting altered proteins through HLA molecules to the T cells of our immune system; they are equipped with systems capable of transmitting to the immune system that

something is not right, like DNA damage, or faulty signaling instructing a cell to divide when it should not. These are the so-called danger signals, manifested in the expression of stress ligands recognizable by immune cells with innate properties.¹⁴ If these signals arise early during cancer development, why does the immune system not block carcinogenesis early on? These danger signals would operate independently of how different the book reads to a T cell. Yet while we teach that these protection mechanisms exist, there is surprisingly little evidence, in humans, that they are actually engaged during the earliest stages of malignant transformation.

Together with Dr. Jessica Roelands and the lab of Dr. Luuk Hawinkels, we applied spatial technologies to investigate which biological processes occur at the earliest moments of malignant transformation.¹⁵ Since we cannot go back in time, we made use of early colorectal cancer lesions that, within the space of a few centimeters, encompass normal intestinal mucosa, early stages of malignant transformation, and invasive cancer. By analyzing these lesions, we could link biological processes to different stages of transformation, and one thing became clear: immunity is not the dominant reaction of our body to an early malignant lesion, which is consistent with what I previously told you. During early transformation the body often reacts as it would during wound healing, suppressing immune responses,

promoting cell proliferation, and stimulating cell migration to resolve the damage. This supports the long-standing idea that *cancer is a wound that does not heal*, a concept proposed by Harold Dvorak.¹⁶ At some point, as the immune system detects that something abnormal is present in our bodies, there could be a shift in the body's response. But I am convinced that for the large majority of cancers, the initial response of the body is to treat it as a wound.

Tough nuts to crack

While immunotherapy has been tremendously successful for colorectal cancers with defects in the DNA mismatch repair system, the large majority of colorectal cancers (about 85%) lack such defects and are less recognizable to the immune system. This group remains the most important clinical challenge: treatment options for advanced disease have not significantly improved in decades. Demonstrating that these cancers could also be amenable to immunotherapeutic intervention has been a major research pillar of our group. Dr. Jitske van den Bulk demonstrated during her PhD that although these cancers carry few mutations, the majority were infiltrated by T cells capable of recognizing cancer cells.¹⁷ This means that personalized approaches such as neoantigen vaccination or TCR-based therapies may one day be viable immunotherapeutic options for these patients. The path to get there is not short: these therapies must fit within realistic clinical

timelines and remain affordable, and their efficacy still needs substantial improvement. But the foundation is there. This work would not have been possible without the support of Professor Sjoerd van der Burg and Dr. Els Verdegaal.

And while immunotherapy still does not benefit the majority of cancer patients, based on current evidence and the pace of technological and scientific progress, I believe that within the coming years we will be able to offer most cancer patients an effective immunotherapeutic option selected from a broad toolbox based on a cancer's characteristics.

Nevertheless, some cancers will remain formidable challenges in the coming years. Pancreatic cancer is a clear example. It presents a clinical problem from the outset: it develops without symptoms until it is too late, and we have yet to devise reliable strategies for early detection. It is also particularly elusive to the immune system. In collaboration with Professor Alex Vahrmeijer, Dr. Bert Bonsing, and Dr. Thomas Brouwer, Ricki Krog demonstrated during his PhD that neoadjuvant chemotherapy can trigger immune responses in a substantial proportion of pancreatic cancer patients. In a separate project led by Dr. Jessica Roelands, we identified a rare subgroup of pancreatic cancer patients with exceptionally good prognosis, characterized by the presence of effector immune

cells within their tumors. Understanding how such responses are mounted in this subgroup may teach us how to trigger them in the remaining patients, and in doing so, improve the overall prognosis of this disease.

Another particularly challenging group of cancers are bone and soft tissue sarcomas, a highly heterogeneous group of tumors that offers a fascinating model for cancer immunologists, potentially linking chromosomal instability to immune recognition. Effective spontaneous or therapy-induced anti-tumor immune responses are rare, and when they do happen, they tend to occur in cancers with a high degree of chromosomal instability. Returning to the book analogy, it is not so much that letters in the book have been replaced by others, but more as if pages have been ripped out, duplicated or shuffled around. Experimental evidence suggests that DNA removed from the book and scattered elsewhere in the cell can function as a signal, activating DNA sensing pathways and engaging immune cell activity.¹⁸ But, again, evidence that this actually translates into effective immune-mediated elimination of these cancers in humans remains insufficient. Bone and soft tissue sarcomas could offer an important model to help fill this gap. Given the complexity of this group of diseases, and the fact that I knew nothing about sarcomas when I entered this field, having Professor Judith Bovée (a world-leading expert in sarcoma pathology) as a colleague has been

invaluable. The PhD theses of Debora Meijer and Siddh van Oost are a testament to how productive this collaboration has been, and the work continues through the ongoing projects of Sara Cardoso, Zeynep Erdem, and Eleonora Assarioti.

A biologist, not a technologist

Technology has been central to much of the work our group has developed throughout the years: next-generation sequencing for the identification of T cell targets in cancer cells, and single-cell and spatial technologies for the analysis of the tumor microenvironment. This has included the development of new wet-lab and analytical approaches, such as the multimodal integration of imaging mass cytometry and MALDI-MSI by Dr. Joana Brás Gomes Nunes (in collaboration with the Center for Proteomics and Metabolomics),¹⁹ and methodologies for the analysis of spatial omics data by Dr. Ana Marta Sequeira.²⁰ All of these are powerful tools. But that is what they are: tools to address biological questions. At some point I became aware that our group had acquired a reputation as a spatial biology group, which I have mixed feelings about. On one hand, I take it as recognition of our collaborative mindset and of our expertise, and for that I must acknowledge Dr. Marieke IJsselsteijn, the spatial expert of the lab, who has supported dozens of collaborations and without whom we would not have had the opportunity to be involved in so many interesting research projects. On the other hand, I think we live

in a time of insufficiently critical technology adoption, and that raises some concerns. We have all read papers in which something already known was rediscovered using methodology that cost orders of magnitude more than the original work, and which is rewarded not because of the new knowledge it delivers but because that knowledge is packaged in much fancier wrapping paper than before. And this raises important questions about the responsible use of research funding: are we spending appropriately to generate knowledge, or spending more than necessary for the sake of a fancier method? That said, replication of knowledge is fundamental to the scientific process and not often sufficiently recognized. I also think there is a real bonus to technologies that generate large amounts of data: because they capture so much more than what a single question requires, new and unanticipated questions tend to arise simply from having that much information available, if one is paying enough attention. Nevertheless, at the start of an endeavor, it is important to ask the question “what does this approach actually add?” To make it clear: I am not a technologist. I am a biologist who thinks anglerfish are fascinating, who happens to use technology, and who tries hard to use it in a way that is actually meaningful.

Competition and the company we keep in academia

Alongside my research, and arguably at the expense of it, and to the frustration of the people

in my lab who occasionally cannot find me, I got involved in too many things which are now, I think, recognized as academic citizenship. On a more serious note, it has been a true privilege to meet so many smart and dedicated people that genuinely care about institutions, academia, and their colleagues, through my involvement with the LUMC's Young Faculty Network, the Young Academy Leiden, De Jonge Akademie, or the Young Academies Science Advice Structure. It is also fascinating how different fields shape people, or how different personalities are attracted to certain fields. I still remember the moment, early in my involvement with Young Academy Leiden, and again, later, at De Jonge Akademie, when I felt in awe, and also intimidated, by the fact that people thought and spoke in very different ways than I was used to. We have so much energy, so many ideas, and such a diversity of fields already within our institutions, and yet faculties often operate largely independently of one another. I think that is a missed opportunity, and one we are collectively responsible for. It was also revealing to realize how different careers look across academia. For instance, when a colleague from another faculty told me they had to buy their way out of teaching using external grants in order to do research, while I had assumed that a predominantly research-focused position alongside teaching was the norm. It was not, and I was quickly reminded of my own privilege. It still strikes me as strange, though, that research,

often described as a core pillar of academic mission, is something one has to buy into rather than something structurally included as part of the academic role.

That process of stepping outside my own context made me realize that while working in academia and science is a privilege to some extent, quite a few things about how it functions do not make a lot of sense, which is paradoxical for an institution that concentrates so much intellectual capacity. Perhaps the most striking is how little scientific evidence we use to shape the system itself. Take competitive granting schemes. There is now a substantial body of evidence that peer review is a rather unreliable mechanism for evaluating the scientific quality of grant proposals or predicting scientific success.²¹ The system pushes researchers toward safe, fundable science at the expense of higher-risk, potentially more ground-breaking work.²² And because peer review cannot reliably determine quality on scientific merit alone, other factors fill the void: institutional prestige, whether a topic is fashionable, the applicant's name, their mentor's reputation, and the well-documented Matthew effect where money attracts money.²³ Add to this the considerable resources consumed by the system itself: the researcher time spent on applications, and the resources granting agencies spend on evaluation and administration, and it becomes very difficult to defend this system. The counterargument is that without competition,

complacency will thrive. Perhaps. But it is worth asking whether complacency at scale would consume more resources than a system in which a substantial proportion of effort goes into sustaining the system itself rather than producing science. I remain of the view that competitive granting, whatever its original purpose, now functions in part to make an underfunded system feel meritocratic rather than scarce.

Grant agencies may argue that universities and research institutes do not have a strong track record in managing people or finances. In many cases, they are right. If we want greater autonomy over financial resources and less dependence on external agencies, we need to demonstrate that we can manage ourselves better. This brings me to leadership. Traditionally, leadership positions in academic institutions have been awarded on the basis of scientific merit. And while scientifically distinguished individuals may have delivered in terms of vision and ambition, they may have fallen short in management, and in particular in people management. A head of department, a dean, or a board member requires a specific set of skills that should be treated as a distinct professional role, filled by people with the relevant expertise. It should not function as a career promotion for scientific achievement.

I am very pleased that Leiden University, and the LUMC in particular, has not only embraced

the Recognition and Rewards initiative but has gone further, asking what it actually means in practice for these institutions. As part of the Academia in Motion team at the LUMC, and within the Leadership workstream, we drafted a leadership profile for research group leaders. Not as a punitive instrument, not a checklist against which people will be judged, but as a framework for awareness: a description of what we consider important traits and goals, and how we can best support current and future group leaders in developing them. I am looking forward to what the broader initiatives on leadership being implemented at the LUMC will deliver. I want to be clear that we are not even close to fixing a highly dysfunctional system. But what we have seen in recent years is a shift in the conversation: an acknowledgment that leadership in academia requires a different set of skills than scientific excellence, and that it is an institutional responsibility to promote the development of such skills.

I have a confession to make: I am not organized, poor with timelines, and not always effective at keeping people on track. And that brings me to another point: I doubt that many people genuinely combine all the traits that define good leadership in a single person. Which makes me question whether the Principal Investigator (PI) model is actually the best model for science. The PI system exists largely because incentives are structured around the individual: grants, first and

last authorship, bibliometric profiles. But I am not aware there is any evidence that this is the model that produces better science. On the other hand, flat collaborative structures are difficult to manage and would require a fundamental restructuring of how science is funded and evaluated. But a middle ground, such as research teams led by more than one senior investigator with complementary expertise, seems to me a more honest response to the reality that no single person is good at everything. Otherwise, how, for instance, does one deal with excellent scientists who lack social or management skills?

No translation without foundation

The PI model may also stand in the way of strategic directions adopted by institutes, such as increasing collaborative research between fundamental researchers and the clinic to advance translational research. Also, if clinicians want to develop research projects based on clinical observations, they currently lack the means to do so unless they either hold a research group leadership position themselves or can find a research group willing to take on the project. To address this and other challenges in bringing fundamental, translational, and clinical research together, the management team of Theme Cancer at the LUMC has proposed the concept of TORCH (which stands for Translational Oncology Research Collaborative Hub). TORCH would be a service facility with a strong scientific component, including a scientific coordinator and

committee, where co-creation of projects and generation of preliminary data can bring together clinicians (especially those at the start of their careers) with translational and fundamental researchers.

While it is a logical endeavor for a medical hospital to perform translational research and to walk the path from bench to bedside and back, it is important to realize that the very existence of translational research, and the applications derived from it, are highly dependent on fundamental research. Knowledge and technology alike depend on it. I am concerned about political and institutional discourses highlighting the importance of valorization, in particular when presented in timelines that do not align with the reality of scientific research. Further, it is important to keep in mind that the main purpose of universities is to generate knowledge, and I would take this even further: in particular, knowledge that is not likely to be pursued elsewhere. I would also argue that applied research with immediate economic turnover is likely better pursued elsewhere, with greater efficiency than universities can offer. It is therefore important that universities feel the responsibility of pursuing activities independent of their economic valorization, and that government and society recognize this role. Finally, if we look around the world today, we see one increasingly shaped by technocracy, where economic valorization has become a guiding

principle in how knowledge itself is judged. I fear a path where we further defund the social sciences and humanities to accentuate this focus. Technology can help us build almost anything. But it cannot tell us what is worth building, for whom, or how to fairly share its benefits. Nor can it tell us how to resolve our differences and navigate conflicts between people and nations. And in the current age, it feels as if these are the most urgent questions we face.

Acknowledgements

The only reason I am here today is because I received invaluable help and support from many people, and it would not be realistic to name them all, so please forgive my selectivity.

First of all, I want to thank the Executive Board (CvB) of Leiden University and the Board of Directors of the LUMC, as well as the management of the previous Division 4 and the current management team of Cluster 4. Thank you for the trust you have placed in me.

I want to thank Professor Hans Morreau. Hans, I could not have asked for a better PhD mentor. The freedom and encouragement you provided have been extremely generous. Also, I have met few people who know so much about so many things at a specialist level. I cherish most the lunch discussions we had, not only about science but also about politics and life in general.

To the rest of my PhD supervision team, Professor Gert Jan Fleuren and Professor Tom van Wezel, my sincere thanks for your support. Tom, I must thank you further for offering me a postdoc position after my postdoc in Sweden, while knowing that I would be applying for grants to work on another topic, without ever showing a concern that this would affect our projects.

Professor Koning, dear Frits, I am of the opinion that no matter how old or experienced one is, one always needs a mentor, and it has been a privilege to have you as a mentor and a friend.

Professor Smit, dear Vincent, I have always felt backed up by you, to the point where sometimes I would be hesitant to share some problems with you because I knew you would try to solve them for me. Thank you for that. In general, I would also like to thank everyone at the Department of Pathology. I could not ask for a better place to work.

Professor Hogendoorn, dear Pancras, the path to my Professorship started under your term as Dean, and at some point I think you believed in it more than I did myself. Thank you for your support and friendship.

Professor Bovée, dear Judith, it has been a pleasure to work side by side in recent years,

and now to be office mates. We prove that the shared PI model works, and I am very thankful that I can count on you to compensate for my shortcomings.

Dear students, teaching remains one of my most fulfilling tasks where reward in the form of your interest and engagement comes much faster than anything I can get from research. Thank you for this. My advice would be: don't take life (or exams) too seriously, and learn for the sake of learning.

To the Cancer Immunogenomics group, I am here because of your work, and this Professorship is a reflection of it. To the ones not mentioned during the lecture: Dr. Dina Ruano and Ruud van der Breggen, you have been essential to the group, in particular in laying its foundations at the start. Manon van der Ploeg, you joined a bit later, but you have been a sort of glue that keeps everything together somehow. Zheng, Scott, Fleur, Miguel, Marie, and Rui, it's a privilege to co-supervise you.

To my parents and sister: you have shaped a great deal of what I am today. I always felt I could count on you, and that you would be there whenever I needed you. That support has provided comfort more often than I have told you.

Filipa, you are the strongest person I have ever met. I would not have survived all the obstacles that came our way without your strength and unconditional love. You are the better half.

José Afonso, you are not listening to this, and even if you were, you would not understand it, but it will nevertheless stay for posterity. Since you were born, everything else outside the family matters a little bit less. I will forever be grateful for that.

Ik heb gezegd.

References:

1. Pasteur, L. (1864). *On Spontaneous Generation* [Address delivered at the Sorbonne, April 7, 1864]. Trans. A. Levine (1993).
2. Van Helmont, J. B. (1648). *Ortus Medicinae*. Amsterdam.
3. Pietsch, T. W. (1976). Dimorphism, parasitism, and sex: reproductive strategies among deep-sea ceratioid anglerfishes. *Copeia*, 1976(4), 781–793.
4. Schreiber, R. D., Old, L. J., & Smyth, M. J. (2011). Cancer immunoediting: Integrating immunity's roles in cancer suppression and promotion. *Science*, 331(6024), 1565–1570.
5. Burnet, F. M., & Fenner, F. (1949). *The Production of Antibodies* (2nd ed.). Macmillan, Melbourne.
6. Gentles, A. J., Newman, A. M., & Liu, C. L., et al. (2015). The prognostic landscape of genes and infiltrating immune cells across human cancers. *Nature Medicine*, 21(8), 938–945.
7. Rooney, M. S., Shukla, S. A., & Wu, C. J., et al. (2015). Molecular and genetic properties of tumors associated with local immune cytolytic activity. *Cell*, 160(1–2), 48–61.
8. Schumacher, T. N., & Schreiber, R. D. (2015). Neoantigens in cancer immunotherapy. *Science*, 348(6230), 69–74.
9. Dierssen, J. W., de Miranda, N. F., & Ferrone, S., et al. (2007). HNPCC versus sporadic microsatellite-unstable colon cancers follow different routes toward loss of HLA class I expression. *BMC Cancer*, 7, 33.
10. Ljunggren, H. G., & Kärre, K. (1990). In search of the 'missing self': MHC molecules and NK cell recognition. *Immunology Today*, 11, 237–241.
11. de Vries, N. L., van Unen, V., & IJsselsteijn, M. E., et al. (2020). High-dimensional cytometric analysis of colorectal cancer reveals novel mediators of antitumour immunity. *Gut*, 69(4), 691–703.
12. de Vries, N. L., van de Haar, J., & Veninga, V., et al. (2023). $\gamma\delta$ T cells are effectors of immunotherapy in cancers with HLA class I defects. *Nature*, 613(7945), 743–750.
13. Azoulay, P., & Greenblatt, W. H. (2025). *Does peer review penalize scientific risk taking? Evidence from NIH grant renewals* (NBER Working Paper No. 33495).
14. Raulet, D. H. (2003). Roles of the NKG2D immunoreceptor and its ligands. *Nature Reviews Immunology*, 3, 781–790.
15. Roelands, J., van der Ploeg, M., & IJsselsteijn, M. E., et al. (2023). Transcriptomic and immunophenotypic profiling reveals molecular and immunological hallmarks of colorectal cancer tumourigenesis. *Gut*, 72(7), 1326–1339.
16. Dvorak, H. F. (1986). Tumors: Wounds that do not heal. Similarities between tumor stroma generation and wound healing. *The New England Journal of Medicine*, 315(26), 1650–1659.
17. van den Bulk, J., Verdegaal, E. M. E., & Ruano, D., et al. (2019). Neoantigen-specific

immunity in low mutation burden colorectal cancers of the consensus molecular subtype 4. *Genome Medicine*, 11(1), 87.

18. Mackenzie, K. J., Carroll, P., & Martin, C. A., et al. (2017). cGAS surveillance of micronuclei links genome instability to innate immunity. *Nature*, 548, 461–465.
19. Nunes, J. B., IJsselsteijn, M. E., & Abdelaal, T., et al. (2024). Integration of mass cytometry and mass spectrometry imaging for spatially resolved single-cell metabolic profiling. *Nature Methods*, 21(10), 1796–1800.
20. Sequeira, A. M., IJsselsteijn, M. E., & Rocha, M., et al. (in press). GRIDGENE: Guided Region Identification based on Density of GENEs — a transcript density-based approach to characterize tissues by spatial transcriptomics. *Bioinformatics Advances*.
21. Pier, E. L., Brauer, M., & Filut, A., et al. (2018). Low agreement among reviewers evaluating the same NIH grant applications. *Proceedings of the National Academy of Sciences*, 115(12), 2952–2957.
22. Nicholson, J. M., & Ioannidis, J. P. A. (2012). Research grants: Conform and be funded. *Nature*, 492, 34–36.
23. Merton, R. K. (1968). The Matthew Effect in Science. *Science*, 159(3810), 56–63.



PROF. DR. NOEL DE MIRANDA

Noel de Miranda (20-06-1982) obtained his degree in Applied Biology from the University of Minho, Portugal, in 2004. From 2005 to 2010, he pursued his PhD at the department of Pathology at Leiden University Medical Center (LUMC), where he worked at the interface of cancer biology and immunology. His PhD thesis was entitled *Mismatch Repair and MUTYH Deficient Colorectal Cancers: At the Crossroad of Genomic Stability and Immune Escape*. Between 2010 and 2013, he was a postdoctoral fellow at the Karolinska Institutet in Stockholm, Sweden, where he applied next-generation sequencing technologies to study the genetics of B cell lymphomas. After a brief return to the LUMC as a postdoctoral researcher, he established his own research group, the *Cancer Immunogenomics* group, at the department of Pathology in 2016.

The *Cancer Immunogenomics* group studies how cancer genetic alterations and phenotypic features impact the interaction between cancer cells and the immune system. Using advanced genomic, spatial, and single-cell technologies, the group investigates this interplay across cancer types (from colorectal cancer to sarcomas and pancreatic cancer) and across the disease course, from early malignant transformation to resistance and response to immunotherapy.