Inaugural Lecture for Obtaining Professor Title in Translational Pediatric Nephrology in the University of Amsterdam

FOUND IN TRANSLATION

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Dear Rector Magnificus of the University of Amsterdam,

Dear Dean of the Faculty of Medicine,

Dear members of the Board of Directors,

Dear patients and families,

Dear colleagues, family and friends,

Prologue

My parents were born in Ukraine, my father in Kiev and my mother in Kharkov, but both studied in Moscow where I became a side product of their study.

Ukrainian in my Soviet passport, Russian – for Belgians, and in The Netherlands 'that doctor with a funny Belgian accent'… This uncertain identity was not an issue until February 2022, when the Russian - Ukrainian war became my everyday reality and forced me to make choices, while I have family and friends on both sides of the border and where my little cousin Olga is asking every evening whether or not she is going to die during the night…

I would like you to remember victims of war (among them more than 2000 children), all those who are 'Lost in Translation' when the dialogue is replaced by aggression and terror …

I feel an incredible privilege to have the opportunity to plan for the future, also realizing that all my plans can be wiped away if the war comes closer to our door.

With this context in mind, let's unpack my topic of today what can be 'Found in Translation' in a dialogue between patients, clinicians, researchers and industry in Paediatric Nephrology.

What is Paediatric Nephrology?

Paediatric Nephrology is a medical specialty for the treatment of children with kidney diseases. My predecessor Jaap Groothof compared Paediatric Nephrology with his Jack Russel terrier – a small dog with big demands. We are indeed a big academic discipline for a relatively small number of very sick patients.

To become paediatric nephrologist, a person has to complete 6 years of medical school followed by 5 years of residence in paediatrics and then - 3 years fellowship in paediatric nephrology. Mostly 4 years of PhD training are added to these 'Donkey's years', to become after 15 to 18 years, what we call, 'jonge klare' or a junior staff member – good enough to take the calls, but still 'very unexperienced ' according to more senior colleagues. This is a long way to go, but fortunately, some courageous young doctors still choose our specialty as we have an amazing job!

The spectrum of patients we see at our clinics spans from foetuses to adolescents! Children are not 'small' adults and their kidney physiology is very different. For example, a newborn has a kidney function of 40% compared to a child of 2, and it is even lower in preterm babies. This function would be considered as an advanced stage of chronic kidney failure in adults!

The kidney

For nephrologists, kidneys are the most beautiful and the most intelligent organs in the body, each containing between 200,000 and 2 million structural units called nephrons that filter blood, excrete waste and reabsorb water and solutes regulating our homeostasis and blood pressure. Healthy kidneys keep our body in balance even if when we drink too much, eat unhealthy food or are climbing the mountain and need more oxygen for our tissues! While representing only 0.5 % of the total body weight, kidneys consume 20% of the cardiac output.

Almost 500 hundred years ago a Flemish anatomist Andre Vesalius wrote a 760-pages long manuscript containing among other organs a detailed description of kidney anatomy. In his book Vesalius heavily criticized the Cladius Galenus description of the kidney as an organ containing two cavities separated by a sieve – a view that was accepted for 1400 years. Based on numerous dissection studies Vesalius made a revolutionary conclusion, that the whole kidney mass filters blood to produce urine! Vesalius and I used to work at the same University in Leuven, but unfortunately, not during the same time period! Vesalius was 28 years old when he finished this book – nowadays he would be a 3rd year resident who would not have any time to do research! During recent years, we are witnessing a new revolution when 500-years history of classical anatomy is being replaced by a new body anatomy based on single cell special transcriptomics studies revealing even more complex organization of our body!

The recent paper published in the journal Nature presented a new single cell kidney atlas describing 51 different cell types and 28 different cell states that can be altered during injury (Lake at al. Nature 2023). This means that we have to start thinking about the kidneys not in terms of kidney filters (glomeruli) and tubules, but in a much more sophisticated manner realizing that kidney contains many more cell types that we have learnt in the medical school. A new generation nephrologists will need a new generation brain to apply this level of knowledge in their clinical practice! And this is hopefully where the artificial intelligence can help us.

Due to their complex organization and highly specialized nature, kidneys have a limited capacity to regenerate and are extremely vulnerable to injury. Therefore, paradoxically, the progress in nephrology has been pushed by wars! Ans even now our Ukrainian colleagues are struggling to develop new technologies during the force-major situation!

It was in 1943 during the 2nd world war, when Willem Kolff invented the first artificial kidney in a small town of Kampen, built from wooden drums, cellophane tubing, and laundry tub. This first dialyzer, in best cases, could prolong lives of the patients for a few hours or days and could only be applied in adults.

Nowadays, dialysis techniques have become available for children of all ages, and even kids of 2 kg or less can be put on the machine that saves their lives.

History of Paediatric Nephrology

Our discipline was founded by a Scott Gavin Arneil and by our Dutch compatriot Harmen Tiddens, who wrote the first constitution of the European Society of Paediatric Nephrology (ESPN), while visiting whisky distilleries in Scotland. They organized the first scientific meeting of ESPN in Glasgow in 1967 – which is considered the official year of birth of Paediatric Nephrology in Europe.

Interestingly, Tiddens not only founded Paediatric Nephrology in Europe, but he also saved Paediatric Nephrology in Amsterdam. In 1992 there was a crisis in our division, two doctors suddenly left, and one – was seriously sick. Tiddens, who was chair of Paediatrics, had an option to close the division, but instead, he hired a young high potential fellow, to be trained by Ray Krediet, an adult nephrologist, and this was Jaap Groothoff, with his high demands! The division flourished again and I'm proud to be a part of it!

Among 37 founding members of ESPN there were only 4 women – a clear gender issue, as we would call it now! Since then the number of paediatric nephrologists in Europe has grown, but we are still a rather cozy group of around 1000 doctors, highly specialized, treating very sick kidney patients and also providing service to many other pediatric disciplines who require extra-corporal techniques such as dialysis, hemofiltration or pheresis because of neurological, hematological, metabolic or cardiac condition. Therefore, paediatric nephrology is a cornerstone of any University Children Hospital.

The dark side of our profession is that for over 150 paediatric kidney diseases 80% have no curative treatments. Many of our patients, once they become a kidney patient, they will stay a patient for the rest of their life. I'm working on changing it in the future!

What is Translational Paediatric Nephrology?

The title of my professor chair is Translational Paediatric Nephrology. What I'm going to translate and for whom?

Fifty years ago a professor in physiology Julius Comroe and a professor in anaesthetics Robert Dripps published a controversial paper in the journal 'Science'. They identified 10 major clinical achievements in cardiopulmonary diseases and analysed 4000 papers to delineate facts and ideas essential for these 10 discoveries. Among key articles underlying the discoveries, 62% described mechanistic studies on a bench, leading to a conclusion that basic research is a foundation of the medical progress (Comroe, Dripps. Science 1976). This statement had opened an era of what we now call 'translational medicine' that arises from fundamental research, with subsequent translation of the findings into clinical trials and potential clinical applications. But what do you think is the percentage of promising bench discoveries that finally reach the patient? Unfortunately, it is less than 5% (Joannidis; Plos Clinical Trials 2006), and this I would like to change during the coming years!

Personal translational journey in Cystinosis

My personal translational journey started 25 years ago when I became a fellow in paediatric nephrology in Nijmegen and asked my mentor Leo Monnens to give me some scientific work. Leo had piles of so called 'unsolved' patients' records that covered tables and chairs in his office. Rather randomly, he took one of those records and told me 'dit moet jij kunnen oplossen' 'you should solve this 'unsolved' patient!'. The patient that Leo gave me was a sibling of a known patient with cystinosis. Cystinosis was a disease that I had never heard about before.

It appeared to be a lysosomal storage disorder caused by a defect in the lysosomal cystine transporter. The key disease feature is an accumulation of one amino acid cystine in the lysosomes resulting in crystal formation. At the time we are talking about the only way to diagnosis cystinosis was to measure cystine in white blood cells – and this was normal in that patient, while he had diseases features - this was really unusual! The gene of cystinosis still had to be discovered and couldn't be tested.

The mecca of cystinosis research was Paris, and Leo thought that my French was good enough to present this interesting case at the Hopital Enfants Malades – and literary to translate his question to the French colleagues.

My experience in this nice historic building in Paris was terrible. After hours of rehearsal, I did my best to present the case, but the public verdict of renown French experts was devastating:

'votre labo a Nijmegen save pas comment mesurer cystine!'

'your lab in Nijmegen just can't properly measure cystine!'…

First sad and then angry, I came back to Nijmegen, being determined to 'solve the case' and we started digging into cystine measurements together with my co-promotor Henk Blom and a very dedicated lab technician Addy de Graaf. This was a start of my career in cystinosis!

We could demonstrate that among all blood cells in cystinosis cystine accumulates in neutrophils and not in lymphocytes. In young children, lymphocytes predominate, and therefore measuring cystine in mixed leukocytes can generate false negative results, what happened in our patient. The case was solved, the paper was published and the new technique of cystine measurement was introduced into the routine clinical practice – a nice example of successful translational story (Levtchenko et al. Clin Chem 2004). This paper was reviewed by a godfather of cystinosis research Jerry Schneider from San Diego, who wrote me a personal letter and with whom we became friends and who mentored by career during many years.

But why is it important to make the diagnosis of cystinosis as early as possible?

Because we have a treatment that improves patients' prognosis. The drug called cysteamine discovered by Jerry Schneider depletes cystinosis lysosomes from cystine by breaking cystine into two compounds that can leave the lysosome bypassing the defective cystine transporter. A great biochemical achievement, but how does it translate into patients' lives?

Cystinosis is a multi-organ disorders initially affecting kidneys. Cysteamine postpones kidney failure and delays disease manifestations in many other organs. A recent study by Koenraad Veys comparing siblings within one family has shown that in the oldest siblings diagnosed when disease symptoms are present, almost 30% of kidney function is definitively lost. In contrast, in the youngest siblings, when diagnosis is made directly after birth, kidney function can be preserved until adult age by early administration of cysteamine– an important message to defend including cystinosis in the neonatal screening program.

While cysteamine dramatically improved patients' prognosis, it doesn't cure the disease! The number of pills that cystinosis patients need to take every day during their whole life is something beyond believe even for prescribing physicians. Therefore developing better therapies for cystinosis is a high priority on my 'translational research agenda'.

Finding disease model

Developing these new therapies requires disease models that can be used for testing drugs, and this was a problem in cystinosis as the animal models of cystinosis do not fully recapitulate the human phenotype.

In search for a suitable disease model I turned my attention to patients' urine as a potential source of kidney cells, together with my co-promotor Bert van den Heuvel and Martijn Wilmer, who had just graduated from the lab school and applied for his first job!

We were able to establish cystinosis proximal tubular cell lines from urine of the patients. This was extremely exciting as cystinosis cells showed disease features, but we needed a healthy comparison, and that was a challenge. While all of us, even sitting in this aula, are constantly losing some kidney cells into urine, in healthy people the amount of these cells is extremely low and they are difficult to catch! A hunt for healthy kidney cells in urine started among children of the lab personnel in Nijmegen and at the school of my son Philippe. Little friends of Philippe were eager to participate in

my research project as for each pee they got a candy, so during my study days there was a line of volunteers next to the school to deliver the precious study material. Finally, from 38 control urines, 4 samples appeared to contain cells that we were looking for, and we could grow these cells in the culture flasks.

Together with Roos Masereeuw and Frans Russel from the pharmacology department in Nijmegen, we had put a lot of effort in characterizing these cells and were very proud when the manuscript describing our findings was ready to be published. We thought that it deserved a high impact factor journal. Nothing was less true than this naïve assumption. The paper was submitted in at least 10 medical journals, with each rejection taking a bite from our enthusiasm. As the sad fate of this paper seriously disturbed my night sleep, I had finalized the last submission in Cell Tissue Research around 4 o'clock in the morning. To my great surprise, at 8 am when I looked in my emails, I've found a message from the journal editor that our paper was accepted! Probably, the Editor also had an insomnia!

This paper became one of my most cited papers (Wilmer *et al.* Cell Tissue Research 2010). We could patent the cell line, despite the protest of Leo Monnens, who thought that we lacked the idealism and had to focus on science and not on money! Personally, I haven't earnt one single penny from this patent, but cells started their own translational journey and has been used by many kidney researchers in the world, by several pharma companies and click are now commercialized by Cell4Pharma!

Our pipeline for establishing patients'-derived cells from urine represents a unique tool for the personalized medicine as these cells carry specific characteristics of each individual patient. Being part of Emma Centrum of Personalized Medicine offers my group an opportunity to develop new therapies using these individual patients' cell lines. Cells can be generated from urine of any kidney patient, not only cystinosis, making our tools interesting for many different diseases.

What are the barriers of successful translational research?

The 2009 a letter from a former chair of the Ethical Committee in Nijmegen Frans Huysmans concluded that our study on urine cells didn't require ethical permit. This decision sounded logical as we were using material that otherwise would be flushed away in the toilet. The situation is very different under the current ethical rules and privacy protection. To give you an example, in 2012 the ethical permission for studying urine cells was already required, but one page of patient's information letter written by my former PhD student Martine Besouw was sufficient, in 2016 – for a similar study we wrote 6 pages and in 2023, of about 12 pages.

For my last research project the only family who refused to participate in the study was the one who read and tried to understand patients' information letter! All others signed the consent form without reading it as they trusted their doctor!

Under current ethical rules, many brilliant ideas will be lost in translation and will never reach the patient! The solution would be to drastically simplify the process, and to give more voice to patients who are in best position to decide what type of ethical protection is required for one or another project.

Dreaming about cure

Patients and doctors have the same dream – to find a cure for a sick child! But sometimes the dream becomes a nightmare… The patient whom I wanted to cure was an adolescent boy with cystinosis who couldn't tolerate cysteamine and whose kidney function was deteriorating. Moreover, he hated the drug because of its smell. At that time the group of Stephanie Cherqui in San Diego, based on promising results obtained in the mouse studies, was planning a clinical trial using allogenic hematopoietic stem cell transplantation to cure cystinosis.

You might wonder how bone marrow cells can correct genetic defects in various tissues affected by cystinosis. The answer to this question is fascinating! While cells cannot talk, they have several ways to communicate, by secreting microvesicles or by building nanotunnels between cells that can transfer the messenger, proteins and even whole organelles. Healthy hematopoietic stem cells of the donor migrate to cystinosis tissues where they correct the genetic defect in somatic cells. And this is an illustrative example on how studying rare diseases can provide general mechanistic insights (Naphade et al. Stem Cells 2015).

My patient didn't meet the criteria for participating in US trial as he had no suitable stem cell donor in the family and we decided to transplant him with a perfectly matched hematopoietic stem cells from a non-family donor. The initial results of the transplantation were promising – we found an expression of healthy cystinosis gene in different organs, white blood cystine normalized while cysteamine was discontinued. The drama occurred when the patient developed a therapy-resistant graft-versus-host disease (GvHD) – a condition when donor stem cells attack the recipient. After three years, we had lost the battle and the boy passed away. The terrible death of my patient, however, prevented the continuation of the US trial, that could cost the lives of more patients.

This first stem cell transplantation in cystinosis pushed forward another clinical trial that uses patients' own (autologous) hematopoietic stem cells that are corrected outside of the body using a lentiviral vector containing normal cystinosis gene and injected back to the patients. Six cystinosis patients got this treatment so far, with no mortality and no unexpected side effects. The long-term results on efficacy are pending and will determine whether this potentially curative treatment will move forward to the clinics.

Using viral vectors for gene therapy poses safety issues as they can integrate in the genome and disrupt the expression of other genes. My laboratory is working on alternative strategy of gene replacement using the gene translation code, a messenger RNA.

Together with a Dutch biotech company Mercurna, a PhD student Tjessa Bondue tested cystinosis messenger RNA in patients' derived proximal tubular cells and in a zebrafish model of cystinosis, that was also established in our lab by Mohamed Elmonem and Sante Berlingerio. The RNA is packed in the lipid nanoparticles similar to those used for the COVID vaccines.

The results in cells and in fish are promising, and the next step will be to move our translational research to a rat model of cystinosis to find a right vehicle to deliver the messenger to the kidney, and to other organs. When results are positive, this new type of therapy can be easily translated from cystinosis to a large number of other genetic kidney disorders as the messenger inside of the nanoparticle can be easily adapted just as we have seen during COVID pandemics !

Studying rare diseases is challenging as granting agencies are frequently skeptical to support projects on rare disease due to a low number of patients who would potentially benefit from new findings, and consider investing in more common diseases as more cost-effective. As most pediatric kidney diseases are rare conditions, pediatric nephrologists are frequently disadvantaged when financial resources are distributed.

From Rare to Common

My own translational study of an ultra-rare disease cystinosis brought me to the broad field of kidney transplantation. When kidneys stop working and body is intoxicated by uremic wastes, kidney transplantation is the best type of renal replacement therapy we can offer our patients. While regular dialysis replaces only 10-20% of the normal kidney function, successful kidney graft gives patients

chance to live normal life. Tony Bouts leads our kidney transplantation program in Emma Children Hospital, as one of the three pediatric centers in The Netherlands performing pediatric kidney transplantation, and we see many of our patients celebrating the date of their kidney transplant as their second birthdate! The downside of this success is a growing number of patients on the waiting list for the kidney transplantation, especially in adults, and some patients have to wait for years leading to high morbidity and mortality. On the other hand, ~30 % of donor kidneys are discarded due to poor quality.

During my study of stem cell therapy in cystinosis, I was searching for alternative sources of kidney stem cells. At that time Fanny Arcolino came as a Marie Cure PhD student to my lab. We had a crazy idea to study urine of preterm babies, as they are born when their kidneys are still in development and we thought that they might pee some kidney stem cells. Indeed, to our great excitement, Fanny has found kidney stem cells in the urine of these preterm babies!

We called these cells neonatal kidney stem progenitor cells or nKSPC. From one pee we could grow millions of cells during a short time period. The cells could differentiate in the test tube into mature kidney cells and could even protect our 'former baby', proximal tubular cells, from drug-induced cell death (Arcolino et al. JASN 2016).

Thinking about how to use our neonatal cells for the needs of the patients, we decided to test their capacity to improve kidneys that were discarded for transplantation due to their poor quality. We used a kidney perfusion model developed by our collaborators from Cambridge, Sarah Hosgood and Michael Nicholson. They have shown that perfusing donor kidneys with red blood cells at body temperature prior to transplantation, rather than keeping them on ice, substantially reduced kidney damage and improved graft function (Hosgood et al. Nature Medicine 2023). We wanted to know whether injecting our neonatal cells in the renal artery prior to putting the kidney on perfusion machine could further improve the quality of donor kidneys.

Thrillingly, we have found that when the severely damaged kidneys were perfused with our cells, less damage and less inflammation occurred compared with kidneys perfused without cells. But what was even more interesting, we found that our cells induced expression of developmental kidney genes in donor kidney cells suggesting that our cells have a regenerative potential! (Arcolino et al. AJT 2022).

Many questions still need to be answered prior to using nKSPC or their derivatives in the clinical setting. What is the mechanism of action of nKSPC? Can they modulate immune response? Can cells be cultured in a xenofree medium so that they can be used in humans? How long can cells survive in the donor kidneys? Do they really induce the regeneration? For answering these questions, I've applied for the European Research Council grant, and was very fortunate to get it. The work is now being conducted by PhD students Sara Akalay and Junyu Chen, Hildo Lantermans, a postdoc, our research technicians Willem Kraan, Sandra van Aarschot and Inge Bongaers, and many other collaborators, and will keep our lab busy during the coming years.

If all goes well, our estimation is that one urine sample of one preterm baby will generate enough cells for treating 100 kidneys!

Moving translational wheel forward

Moving our translational wheel forward to the needs of individual patients, what could be other applications for our neonatal stem cells?

So far we have generated nKSPC from urine of babies having healthy kidneys. But can nKSPC derived from urine of patients with kidney anomalies be used for studying disease mechanisms, predicting prognosis or searching for new therapies? This question will be addressed by my colleagues Rik Westland and his research team.

Alessandra Tammaro together with Sandrine Florquin and Joris Roelofs in our pathology laboratory are investigating the effect of air pollution on kidney development and premature kidney aging. I wonder whether nKSPC derived from babies born in areas with high air pollution are less potent than those derived from newborns living in the ecologically better regions.

Another interesting question to be addressed is whether nKSPC derived from preterm babies can be used for the autologous transplantation in patients who will develop kidney disease or acute kidney injury in the future?

In Belgium we call urine 'Pipi'. 'Wil jij pipi doen?' is what Belgian moms are asking their children.

This slide shows you a 'Pipi bank', that we are establishing together with our neonatology colleagues, not for keeping money, but for biobanking our baby 'the neonatal kidney stem progenitors' for the future research project.

How innovative research will impact patients' lives?

While we are doing fancy research that cost a lot of money, most kids dying from kidney diseases live in under-resourced area's and don't have access to expensive treatments. In the University Hospital of Kinshasa in Democratic Republic of Congo before 2018, every week at least 3 kids died from acute kidney failure due to malaria, sepsis or hemolytic uremic syndrome.

With financial support of the Flemish government, Pepe Ekulu, Agathe Nkoy and their team from DRC, together with our team in Leuven, managed to start an acute peritoneal dialysis program in Kinshasa! During last 5 years 230 kids were dialyzed and 75% of them survived! Otherwise all those kids would be dead!

Will my research help these children? The answer should be 'yes', if we find a treatment of acute kidney injury, at this for a fair prize making it available for the low-income countries!

While in Africa there are not enough doctors for treating a large number of patients, in the Western world – we have an opposite situation! Each academic hospital has a relatively low number of patients.

Therefore concentrating complex patients' care seems logical for decision makers. The patients should go to the expert who will provide the best care!

But, is concentrated 'expert centered care' under the roof of one hospital the best solution for all types of pathology? I don't think so! Pediatric kidney diseases are, for example, very different from pediatric cancers. The latter require intensive treatment periods, but during a rather limited time frame. The disease journey of our kidney patients frequently starts in infancy and further continues to childhood, adolescence and adulthood.

Imagine yourself having a child with a severe kidney disease being obliged to travel to the expertise centrum in the other part of the country several times per week or per month, and this during many years? How much time will you spend in the train or in the car, how much money will it cost, how many hours your child will miss school and you – your work?

COVID pandemics costed lives of millions of people, but it learnt the world that health care can be organized without extensive travel. A so called 'shared care' based on a close contact between local physicians and the expert center will, in my opinion, meet the expectations of pediatric kidney patients who will get the best treatment close to their door without traveling long distances. I would defend a health care model, centered around patients' needs rather than around experts in one hospital.

Here the opinions of patients and their families should direct decision makers.

What will be the future of Pediatric Nephrology in 10-20 years?

Looking into my crystal ball, I **predict** that the number of pediatric patients requiring dialysis and transplantation will decrease due to better conservative treatments, and we will hopefully reach a time when pediatric renal replacement therapy will become redundant.

I **expect** that breakthrough in technology will make gene and cell therapy a routine treatment of congenital kidney diseases, and this, hopefully, not only in developed, but also in resource-limited countries.

I **foresee** that artificial intelligence and machine learning will become our daily assistants, but will not replace us.

I **hope** that disease prevention and early disease detection will further reduce the number of patients, allowing my young colleagues to spend more time on research, but also with their friends and families.

And I **wish** that violence and wars will not preclude us from realizing these plans!

Words of gratitude

My translational journey would not be possible without many of those who believed in me and inspired me, who gave me chances and who supported me during my many more downs than ups, my patients who trusted me and taught me that life is such an precious gift!

Our Cystinosis Patients Group, Marjolein Bos, Fons Sondag, Irene Kinds, all my beloved cystinosis patients and families, you are the most important source of motivation and support of my work. I always feel you being behind me, and I've got thousands ideas and suggestions from you. I'm glad that a new generation doctors and researchers is taking over the torch of cystinosis research to guarantee the future of the patients!

I'm grateful to the Board of Directors of Amsterdam UMC for giving me an opportunity to work in our wonderful hospital! I will never forget my conversations with Hans van Goudoever, first in his role as a department chair and then as a dean of the medical faculty, who convinced me with his 'dry humor' that Emma Children's is the best place in the world to realize my research plans.

I'm grateful to the evaluation committee for approving my application for full professor position.

I thank Willem de Vries for leading our pediatric department to new horizons and for including pediatric nephrology and transplantation on the priority list for future development.

I thank Ans van Wijk who after our informal chat during the congress diner approached me for probing my interest to join the division, followed by enthusiastic discussions with the team and with 'the boss' Jaap Groothoff.

Jaap, without you I would never come to Amsterdam! We share a lot in common, our passion for patients and for research, our love for Dostojevski and Mahler, our hatred for overregulation and unnecessary rules, and our constant drive to color 'outside the lines'! Thank you for guiding me through the challenging process of adaptation to AUMC complex organization and work culture!

My great team, Ans, Arend, Tony, Michiel and Rik, I'm extremely grateful that you have accepted me in your 'family'. You are not only excellent doctors and researchers, but are extremely high-level intellectuals with broad interests and knowledge of literature, musique, politiques, food and wines! I enjoy enormously our coffee and lunch conversations that vary from deep going discussions to funny story telling. You are much more a team that you realize yourself! I hope that bringing a bench expertise in our team will give the whole group a new boost of ideas and research opportunities.

I would also like to thank Eva Zoet-Wissink for coaching my team to become 'a family', and for wisely supporting my first steps to join it.

I'm extremely grateful to our competent and dedicated paramedics, our nurses, dieticians, psychologist, social worker and doctor-assistants. I truly believe that the quality of care is to the largest extent dependent on the quality of paramedics, and not so much on doctors. I'm looking forward to work together with you for the best care of our patients.

Our secretary, dear Astra, you have survived a storm of extra tasks related to my appointment and more recently, the organization of symposium and 'oratie'. You stay calm and friendly, and keep your 'ToDo' lists in order. Without you, this organization would never be possible.

I'm grateful to the speakers and chairs of the symposium prior to my lecture, Paul Grimm, Fanny Arcolino, Roos Masereeuw, Sarah Hosgood, Maarten Naesens, Antonia Bouts, Frederike Bemelman and Rik Westland, to make it a great event.

My promotor, Leo Monnens, 'professor', you gave me wings and you have taught me flying, you are a role model not to give up and to keep kicking against all odds, to be creative without money, and to

'fight' for each patient. I've learned from you not only how to treat patients or to do science, but not to stay indifferent for people in need, for social inequalities and injustice, about politics and football, and more recently - about 'boerencrisis' and nitrogen production by cows. Thank you for being in my life and in my mind!

Ons "Oud-Nefro Uitje", Jacqueline, Magriet, Anneke, ik vind het ontzettend bijzonder om onze jaarlijkse uitstapjes met 'professor' te organiseren – ik geniet enorm van onze vriendschap!

My co-promotor Henk and Bert, together with Leo and Martijn, we've started our translational journey in cystinosis together – a passion that keeps me busy during the last 25 years! We have 'solved' several patients and research questions, and there are more to come. You have taught me that working in a team is much better that playing a 'solo' and we keep friendship over all these years.

Dear Bert, we've stayed a research 'couple' after my leaving to Leuven, where together we have established a lab with 10-15 people, bought infrastructure, opened a biobank now containing more than 10,000 vials, wrote numerous grants and papers. We were 'mama' and 'papa' for more than 20 PhD students and not to count master and bachelor candidates. We really can be proud about what we have accomplished together. We share pain in our hearts that after our departure from Leuven, the lab will be closed. We discussed it a lot, and I'm happy that the technology and know-how we've developed will receive a new life in our new laboratory in Amsterdam, with our pupil Fanny Arcolino being a junior faculty pushing it forward.

Dear Nine (Knoers), starting from my training in Nijmegen, you have been a role model for me! Your way of combining clinics and science, being correct and honest, always being 100% prepared makes you a recognized top scientist in the world. I'm grateful that I could learn from you!

Dear Roos, starting from our project-writing in Nijmegen during the 'mothers' day' we became research partners and friends for many years. I always admire your creativity and your ability to bring different expertise together making you a great leader at the university and of different research consortia! And as a friend, you are always available for an advise!

My first PhD student, Martijn Wilmer, I was so lucky to have you as a research technician and then as a PhD student on our cystinosis project. Without you no ciPTEC cell line would be 'born' – the technology you have brought from Bristol and applied for proximal tubular cells; your 100% reliability, your 'trust but check' attitude was the ground of our research. You brought the techniques from the lab in Nijmegen to Leuven and taught Sandra Van Aarschot how to culture cells while you stayed in my 'under construction' house without heating and warm water, as at that time I had no money to pay your hotel. Thank you for being part of Cell4Pharma and taking care of the future applications of our ciPTEC cell line.

Our lab in Leuven, Sandra Van Aarschot, Inge Bongaers, our research technicians, you are the main pillars of the lab!! We had an incredibly productive time together! You have 'pampered' an army of students, teaching them doing cell culture, PCR, western blot, being secure and accurate in the lab, and most importantly being a team player! Sorry, that I have to leave you behind, but I'm sure that your future at KU Leuven is well secured!

My second PhD student, Martine Besouw, you came together with me from Nijmegen to Leuven to combine a clinical training in pediatrics with PhD – a difficult task that required not only a full mental effort, but also a bid adaptation for a 'no-nonsense' girl from Dutch Limburg in a rather elite and sophisticated KUL environment! You have managed perfectly and have got both qualifications, but most importantly, you have 'solved' several problems for cystinosis patients. I'm extremely happy that we have becomes colleagues and can continue research together, so that the future of cystinosis patients in The Netherlands is secured.

All my PhD students, my bachelor and my master students – the space of this lecture doesn't allow me to write about each of you individually – this will be quite a book, if I put on paper all stories we share about your applications, solicitations, start and finish, winning and failing, laughing and crying, parting and going to congresses!! Something to do after my retirement! I did my best to transfer the attitude and the value scale that I've learnt from my mentors to you, and I'm proud to see all of you thriving and making good new steps in life. Thank you for finding your way in life and research despite my sometimes chaotic supervision!

Koenraad Veys, after finishing your PhD, we stayed research partners in cystinosis and you became a recognized research expert in our field, which makes me very proud. Your talent as a clinician and a researcher will give you opportunities to be creative an to perform research in different settings, and I'm glad that we can continue working together on many exciting projects!

Our NEOGRAFT team, Sara Akalay, Junyu Chen, Hildo Lantermans, Willem de Kraan, Timothy Devos, Mieke Gouwy, Paul Proost, Patrick Matthys, Sarah Hoosgood and Michael Nicholson – thank you for such a productive collaboration, I'm looking forward for the next steps of the project and to all unexpected findings we are going to make!

Our home base, the pathology lab in Amsterdam, dear Sandrine Florquin, Joris Roelofs, Jasper Kers, Alessandra Tammaro, Nike Claessen - thank you for hosting our new laboratory and for being so supportive. Together we form a solid basis for pushing forward translational nephrology research in AUMC.

My colleagues adult nephrologists, Frans van Ittersum, Frederike Bemelman, Liffert Vogt, and others, thank you for such a wonderful collaboration with your pediatric colleagues, giving us an access to your enormous expertise and guaranteeing a smooth transition of pediatric patients to the large world of adult medicine! Our joint weekly research meetings are a fantastic forum for scientific exchange between different research groups stimulating cross-fertilization and joint research projects.

Emma Centrum of Personalized Medicine, dear Clara van Karnebeek and Mieke van Halst, thank you for giving my group an opportunity to become a part of the centrum, with Fanny Arcolino being one of the assistant professors, and cystinosis – one of the diseases that is being explored. I greatly value your support and I trust that 'cystinosis' will be solved in a joint effort with the Centre. Clara, thank you for your enthusiast welcome to me in Amsterdam! You are one of the people who justify my decision!

Dear Fanny Arcolino, without your courage to move with me to Amsterdam, I would never have come here. We are 'partners in crime' and understand each other in one second. I'm proud to having seen you growing from a brilliant PhD student to an independent researcher who leads the team and builds your own way in science!

Dear Rik Westland, as the youngest in the group, you have high potential to be a research leader for pushing forward pediatric nephrology progress for the better future of our patients. You have excellent mentors, Ans, Jaap and Simon, and I'm proud to 'join the team' for supporting you in your further plans.

Our cystinosis group in Nijmegen, Mirian Janssen, Marlies Cornelissen, Annemarie de Vreugd, Marti Eickhoff – van der Akker, Leo Kluijtmans and Siamak Nobach, thank you for bringing together cystinosis expertise which is unique in the world.

My clinical pediatric nephrology team in Leuven, during the last 15 years, we built together an excellent division and share joy and tears, and so many memories to cherish… I miss you a lot and hope that we will continue working together with my new team in Amsterdam for the best care of our patients.

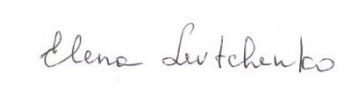
My international colleagues and friends, it is impossible to mention you all in a short acknowledgement text, and I can't select some and leave out the others. Being part of ESPN, ERKNet and IPNA allowed me to make research connections and friendships that give my life an incredible richness and I'm grateful forever to be part of our global pediatric nephrology community.

My family and my friends… it is difficult to describe emotions that fill your heart with joy and sadness, love and gratitude, fear of uncertain future.. we are spread around the world… some being very privileged to live in Western countries, some – still where I come from… now in danger and terror.

My parents would be very proud to see me giving this lecture… Ivan, too frail to attend… I was privileged to be born in the family that gave me all chances to study and to follow my dreams.

Aime, Anja, Duncan, Noah and Philippe – you are a joy of my life, and all the rest – is just something to keep me busy!

Ik heb gezegd.



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The lecture included two musical fragments:

Opening: “Shining Moon” (Місяцю ясний) from Opera ‘’The Zaporozhian Cossack” (Cossack Beyond the Danube) by Semen Hulak-Artemovsky (1813 - 1873)

End: “Beau Soir” by Claude Debussy (1862 - 1918)