Prof.dr. Martine J. Jager

Travels in the world of the eye

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Travels in the world of the eye

Inaugural lecture by

Prof.dr. Martine J. Jager

on the acceptance of her position as professor of

Ophthalmology, especially Eye Melanoma

at Leiden University

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Rector Magnificus, members of the Board of the Leiden University Medical Center, dear attendees,

Last year, you had the opportunity to participate in the National Science Agenda, which is going to be used for planning scientific research in the Netherlands: you could propose items for research. Many proposals were related to health: "How is knowledge about genetics going to help us understand the screening and treatment of (rare) diseases? How can we develop new drugs to help us stay healthy into old age?" And another one: "Every tumor is different: how can we get enough knowledge to treat each type of malignancy?" A lot of research takes place in Academic centers, which responded quickly with a joint National Plan Academic Health. This plan proposes plans for prevention, early detection, individual care (known as personalized medicine) and costs. I quote: "Scientific collaboration and innovation are the key words to use the available resources as efficiently as possible. Only with such an approach will we be able to keep Europe above average in science and to excel in the international scientific league." In size, The Netherlands is a small country, but especially our Academic centers such as the LUMC deliver an internationally high scientific output.

In the next 45 minutes, I will discuss some of the items mentioned in the National Science Agenda, as they are relevant for the eye and the subject of my professorship: the eye melanoma. The Dutch Federation of Universities has recognized the Department of Ophthalmology of the LUMC as the Center of Excellence for eye melanoma and excellent medical care needs to be combined with research. We ask ourselves: what are we doing right, what can we do better? I will first discuss the importance of education and of collaborations, including international ones. After this, I will discuss the peculiarities of the eye and the influence of the intraocular environment on intraocular tumors as well as systemic tumor growth. I hope that after my presentation, you will understand that the eye has unusual features with regard to the immune system, and that those are relevant to tumors, tissue transplants, and ocular infections. I hope to open your eyes to all of this.

The uveal melanoma

Eye melanoma are rare tumors, they can develop on the ocular surface, where they are known as conjunctival melanoma and inside the eye, which is the uvea melanoma. My story is about this latter tumor. It is called uvea melanoma, because it develops in the uvea (named after a grape). The uvea is made up of the iris, the ciliary body, which produces our ocular fluid and the choroid. These three locations contain melanocytes, just like the skin, which can develop into malignancies. People with a light skin and blue eyes do not only carry an increased risk to develop cutaneous melanoma, but also of uvea melanoma. In The Netherlands, we have about 200 new cases a year and people are usually between 50 and 70 years old. This malignancy may however also occur in younger people. I would like to introduce Mrs. A to you: when she was 39-years old, her vision decreased in one eye and she consulted an ophthalmologist. A uvea melanoma was found and she was directed to the LUMC. Our ophthalmologists and radiologists are very experienced in treating the intraocular tumor; this tumor was treated with a radio-active plaque. The tumor regressed and her vision returned to 90%. However, four years later, Mrs. A developed a single metastasis in the liver, found thanks to regular screening. This metastasis was treated with radiofrequency ablation. What can we do when she develops new metastases, elsewhere in the body? Regrettably, up to 50% of patients may develop metastases. Currently, no systemic treatments are available. In some cases, radiofrequency treatment, liver resection, or liver perfusion with chemotherapy are successful, but often, the metastases are not sensitive to any existing drugs.
Furthermore, what is striking, is the young age of Mrs. A. In addition, her father developed cancer of the gut, her mother a cutaneous melanoma, and she has blue eyes and many nevi on

her back. Why did she develop an eye melanoma?
Please recall the questions of the National Science Agenda: "How is knowledge about genetics going to play a role in understanding cancer, and how can we understand cancer well enough to treat every type of malignancy?"

Travel in the world

This one patient indicates that we are able to do a lot, but we have to learn more about the genetics and the biological behavior of the tumor, in order to develop new treatments. We do not yet know the gene(s) that play(s) a role in this patient's melanoma at this early age. Research is difficult when you work with small numbers, and only by collaborating with similarly-interested researchers in many countries can one obtain enough knowledge. In The Netherlands, we collaborate with Rotterdam and internationally with many centers. Much of the research work in our department is performed by PhD students and medical and biomedical students.

To learn about the newest developments, our students visit the yearly congress of the association of Research in Vision and Ophthalmology (ARVO), the largest congress in scientific ophthalmology. It is important for students to spend time abroad for research and their own education. I want to illustrate this with a story, from another time and in another place.

"The hero of my story is Tiuri. This Tiuri had performed all the necessities to become a knight, he would be knighted the next day. He spent the night prior to his great day in a chapel, amongst his peers, when he heard a voice, asking for help. Tiuri was the only one who heard the voice and decided to go outside and help. This subsequently led him on a long voyage, wherein he met many interesting people, made friends, and visited a strange country. Upon returning home from his travels, he saw his friends, who had been knighted, riding beautiful horses. He wondered: "I could have been one of them, if I had not listened to that voice" but he knew that he did not want things to be different, as he would not have missed his experiences.

For those who do not know my story: Tiuri is the hero of the book "The letter for the King" by Tonke Dragt. This book was chosen as the most important children's book of the prior century. Tiuri describes an experience that is shared by many students that have worked abroad. Andrea, a Brazilian student who worked in our lab, wrote this, after she had returned to Brazil: "I got so lost: I changed so much, and nobody else did. Things are getting better now, but at the beginning it was really hard to get used again."
A Dutch student, Anne, who did her rotation in Ophthalmology in Nepal, wrote: "My trip was crazy and life-changing. Out of my comfort zone, which was an exceptional experience. Although I refer to my experience with Nepal in general, my stay at the Himalaya Eye Hospital certainly contributed to this."
Many students that went abroad, left as children and came back as adults. The LUMC considers it important that its students spend some time abroad, as is currently the case in 70% of students.
Since 1996, we have continuously had students at the Schepens Eye research Institute, Harvard Medical School, Boston. As a student, I first experienced lab work in Edinburgh, and subsequently worked as an ophthalmologist and researcher in Miami and Boston. As adjunct scientist at Harvard, and professor in Bejing, I had the pleasure to experience other cultures, and this experience has influenced much of my work.

Function of the eye

Prior to discussing my scientific research, I would like to share with you the functions of the eye. Let's go back to Tiuri. After following the voice, he had to travel through a forest, where he saw movement: when he looked carefully, he saw figures in the distances and the glittering of weapons. He needed several important functions of the eye: seeing movement, color, visual acuity and depth. He saw the figures because of a well-functioning peripheral vision and excellent contrast vision. This is only possible when all parts of the eye function well: signals have to travel from the front of the eye, through the

lens, to the retina in the back of the eye, and subsequently to the brain.
Many of us need a simple object to see well, either in the distances or nearby. Would those who use glasses or contact lenses please put up their hand?

The eye takes care of the first step of seeing, for which it is important to have clear media. The media are the tissues that we look through and the fluids of the eye. The most important causes of blindness in the world are clouding of the lens (nr 1) and diseases of the cornea (nr 2), the outer layer in the front of the eye. One can elegantly remove the lens (cataract surgery), and for instance the Lions Working Group for the Blind tries to help to reduce cataract blindness worldwide.
When the cornea is cloudy, it can be transplanted. According to old books, it cannot be rejected, but that is only the case when the cornea is not inflamed and has no blood vessels. The healthy cornea contains many molecules that can indeed inhibit immune responses. This phenomenon is known as immune privilege.

Ocular immune privilege
A foreign body is not easily recognized when it is placed inside the eye. I ran into a thesis from 1873: "About the consequences of placing living tissues and dead objects in the eye" by J.C. van Dooremaal, a pupil of Donders. Van Dooremaal looked at what happened when one introduces different materials such as cork, wood, or tissues into the anterior chamber of the eye. He placed a piece of skin from a new-born mouse in the eye of a large dog. The piece of skin was encapsulated, the media (cornea and lens) remained clear. When this tissue had been placed in the skin, this would have led to a severe inflammation.
That immune reactions are suppressed in the eye was demonstrated again in 1946 by Medawar, who named this immune privilege. It is also known as ACAID, anterior chamber associated immune deviation, and further investigated by my teacher in Miami and Boston, professor Wayne Streilein. The eye shares this active immune suppression with the brain, the testis and the uterus. The local immune tolerance allows the fetus to grow in its mother's uterus, although half the tissue characteristics in the child come from the father. Recently, the immune privilege of the eye and the testis became world news. Men that have survived an ebola infection still had the virus in their semen months after the infection seemed to have disappeared. The eye reached the news as well: Dr Crozier described that he developed an inflamed eye three months after recovery from ebola. His inflamed eye was shown to harbor incredible amounts of virus, as the only known location in his body.

The anterior part of the eye
The advantage of immune privilege is the easy acceptance of corneal transplants, as I already mentioned. The local immune privilege, however, makes the eye more sensitive to infections. We see this in the easy development of corneal bacterial ulcers in people wearing contact Lenses, and the development of infections after cataract surgery. The fluids and tissues in the eye actively suppress immune responses, up to a certain level. After that, the inflammation is no longer inhibited, and we will find inflammatory cells (lymphocytes and macrophages) in the cornea, as well as vessel ingrowth. At that stage, donor cornea can be rejected. When a donor cornea is placed on an inflamed recipient cornea, transplant rejection can occur. Such a response is directed against the proteins of the HLA system, the tissue histocompatibility antigens, in 1958 discovered here in Leiden by Van Rood. The chance of rejection can be decreased by matching donor and recipient for these HLA antigens, as has been demonstrated by the Leiden ophthalmologist professor Völker-Dieben. However, the chance of rejection may be such, that performing a transplant is not a good idea. By transplanting either only the front or the back of the cornea, Melles from Rotterdam has been able to reduce the chance of rejection already. This lamellar technique that he has developed is now being used worldwide.

Where a clouded lens can be replaced by an artificial lens, we still rely on human material for replacing damaged corneas. There is a chronic shortage. Developing an artificial cornea made of a fish scale is one of our areas of interest, together with the Leiden company Aeon Astron and the members of the Horizon2020 group Arrest Blindness.

Tumors in the back of the eye

I just discussed the ocular immune privilege, which allows the acceptance of a cornea transplant in a quiet eye. A disadvantage is that the eye is less resistant to infections. Another aspect is that, tumor cells that would be rejected elsewhere in the body, can grow inside the eye. Leiden has been the main eye cancer center since the 70ties, especially for eye melanoma. I already told you about Mrs. A. Her primary tumor can be treated properly with a radioactive plaque. In the near future, we may do this even more precisely with the new proton facility that is being built in Delft. However, our options for treatment of metastases are still limited.

MABJES

Are you ever home on time to watch "De wereld draait door"? On March 9, Haanen explained the data of a recent paper published in Science. New research suggested that we should be able to treat all types of cancer with immunological techniques. Let us hope so. One of the new approaches in personalized medicine is the use of monoclonal antibodies, with so-called Mabjes. These are being applied successfully in cutaneous melanoma and kidney cancer. The newspapers reported the discussion between minister Schippers and pharmaceutical companies. For one drug, Nivolumab, the cost was originally estimated at 134.000 €per survival year. What do these Mabjes do? A comparison: their activity is similar to placing little corks on the spines of a sea urchin: the enemy can now attack. It works the same with the attacking cell of the immune system, the lymphocyte can now attack the tumor cell: the Mabje has disabled the defense of the tumor cell. The treatment is expensive, but works very effectively in some patients with cutaneous melanoma or lung cancer. We need the same for eye melanoma!

Immunology of eye melanoma

Why would a cornea doctor study eye melanoma? Expression of HLA antigens is considered important in immune attacks. I wanted to study that in cornea transplantations. Others were looking into the role of HLA antigens in cancer. Professor Ruiter in Leiden studied cutaneous melanoma, and suggested I would not only look at corneas but also at ocular malignancies, especially uvea melanoma. We observed that some uvea melanoma had a low and others a high HLA expression. Those with a high expression also had a lot of macrophages and lymphocytes. One would expect these tumors to be the ones that would get rejected, as was the case in cornea transplantations. And one would expect that inflamed tumors would not develop metastases. Surprisingly, it was the other way around.
Maat and Bronkhorst studied which inflammatory cells occurred in uveal melanoma, and the cells were found to carry many immunosuppressive characteristics. Does the eye itself play a role, just as what happened when Dooremaal introduced mouse skin in the eye of a dog?

Together with Toes and Kast, Schurmans and Boonman, we set up the first mouse ocular tumor model in mice, and studied the effect of placing tumor cells in the eye. We noticed a striking phenomenon: after placing tumor cells in the eye, they were also no longer recognized when injected in the skin. Placing tumor cells inside the eye had inhibited the anti-tumor immune response in the whole body. This is where the Mabjes should come in, to block the immunosuppressive effect of tumor cells. However, the first clinical results have been disappointing, and we intend to research this area extensively in the coming years. Why do the Mabjes often work well in treating metastases of cutaneous melanoma but not those of eye melanoma?

Macrophages

Why do tumors with many macrophages more often give rise to metastases than tumors with a few macrophages? We already know a lot about the characteristics of uveal melanoma that will lead to metastases. One often sees loss of one chromosome 3 and that has been identified as the most important prognostic factor. Maat and Bronkhorst reported that the inflammatory phenotype, that contains high numbers of T cells, macrophages and an increased HLA expression, occurs especially in tumors with loss of one chromosome 3. This has recently been acknowledged by The Cancer Genome Atlas, an international study on 80 cases of uvea melanoma.

Several different types of macrophages have been described: M1 macrophages, which can stimulate the immune system, for instance against infectious diseases and M2 macrophages, which may repair tissue damage and can help to build blood vessels. A tumor needs blood vessels to grow, and a uvea melanoma has many more vessels than a benign naevus. When we studied a series of uvea melanoma, we noticed that tumors with a lot of macrophages also had many blood vessels, as has previously been described by Kivelä. And as Bronkhorst showed here in Leiden, those macrophages belong mainly to the pro-angiogenic M2 type. The blood vessels form a highway for metastases to migrate to the liver. Just think of Mrs. A.

We had a nice hypothesis: if the tumor macrophages belong to the M2 type, which is pro-angiogenic, one has to deplete macrophages in order to stop tumors from growing. We tried this in a mouse model. To our surprise, it did not work in young mice. However, many eye diseases only develop in elderly patients and we already know from research on macular degeneration, that age plays a role in macrophage function. We did the same experiments in old mice: after macrophage depletion, hardly any tumor growth occurred! Our theory was right, macrophages play a role in intraocular tumor growth, but only in elderly mice.

Studies involving the eyes of normal old mice revealed that their eyes already contained many more macrophages than the eyes of young mice. This phenomenon has become known as age-related para-inflammation, and this is also seen in humans. Our PhD student Khanh Vu has shown in the laboratory of Professor Dong Feng Chen in Boston that macrophages are also important in glaucoma, another age-related disease.

Importance for patients

How does this help the patient? The LUMC is an important player in the field of T-cell mediated therapies in cancer, especially in cutaneous melanoma. Why do we then not treat metastases of uvea melanoma patients with T cells? This has been tried, but this was not a success. It seems that the immunosuppressive forces of the eye have been transferred to the tumor's metastases. We are going to investigate how we can modify this immunosuppression and will study why it is so hard to kill the uvea melanoma cells. What makes them resistant? Can we find any drugs that can attack the tumor cells in culture or in a zebrafish or mouse model? And combine this with immunotherapy? Furthermore, we will study the early beginning of melanoma. How do macrophages stimulate the change from nevus to melanoma? What is the role of having a blue eye?

Together with Van der Burg, Jochemsen, Van Hall, Snaar, and Van der Velden we will try to develop a new treatment.

We are very happy with the already started plans of the Board of the Leiden University Medical Center to bring the oncology researchers together, especially of the Departments of Ophthalmology, Oncology and Dermatology. We hope that the current collaboration will be further strengthened by the development of one oncology laboratory, so that we will not only work together in mind. As I already mentioned, we collaborate within the Medical Delta with Annelies de Klein and Rob Verdijk van Erasmus MC to understand more about the role of chromosome aberrations and the behavior of ocular tumors. Internationally, we collaborate in the Horizon2020 CURE UM project with the universities of Liverpool, Birmingham, Krakow, Trento and with the Champalimaud

Institute in Portugal. By collaborating with professors Michelle Madigan in Sydney, Bruce Ksander and Dong Feng Chen in Boston, we learn more about the role of macrophages in ocular tumor development and aging.

Conclusion

I have discussed with you the special characteristics of the immune system of the eye and explained that all kind of immunological processes work different in the eye than elsewhere in the body. This immune tolerance may lead to the acceptance of tissue transplants, but on the other hand may allow viruses and tumor cells to proliferate. We want to try to modify the immune system in such a way, that the body may learn to attack tumor metastases so that eye melanoma patients will also benefit from the new developments that benefit so many other cancer patients.

Thanks to the support of the Royal Netherlands Academy of Arts and Sciences I had the chance to study in Miami, and thanks to the support of the Macropa Foundation and the Haags Oogheelkundig Fonds, I was able to set up a lab here in Leiden to study the immunology of corneal transplantation and eye melanoma. The meetings of the Department of Immunohematology, especially those held on the Eendracht and the Dageraad, opened my eyes for the international world of research and showed me the importance of international collaboration. With our participation in The Cancer Genome Atlas Project, the American Joint Committee on Cancer, already 18 PhDs and 11 current PhD students, over 200 publications, and my recent election as president-elect of the International Society of Ocular Oncology, and now this chair, it is clear that the translational research in ocular oncology has come of age.

In The Netherlands, eye researchers collaborate. We started as ARVO-Chapter ARVO-Ned, and under the leadership of Imhof we have developed into a group called "Strijders against Blindness". We now have the organization "Niet Blind" which is involved in raising money for eye research. Together, we are building a National Plan for Eye Research.

It is important that future ophthalmologists can perform research. As professor De Graeff told me before I started my PhD: "It is important to learn to understand the importance as well as the relativity of research." We do not only need to train excellent researchers, but also train good clinicians who understand the literature, know the newest treatments and can apply them properly. By using our international connections, we can offer students in Medicine and Biosciences a chance to work in another country. Our lab is an example of "Internationalisation@home", where Dutch and international students can learn about the attitude of international research. It is important to provide a heterogeneity in backgrounds. This spring, Athena's Angels have drawn a lot of attention to the still present underrepresentation of women in the higher academic positions. Only by giving men and women and people from different cultural backgrounds the chance to participate in financial, organizational and leadership courses, will the academic staff and one day the professors have the diversity that has for a long time been present in students and PhD students. I am glad that our department under the leadership of Professor Luyten and Schalij has already developed such a heterogeneic character.

Back to the beginning of my presentation. I myself have felt a great affinity to Tiuri. After his return from his travels, he indicated that he would not have wished to have missed his experiences, although he had not become a knight like his colleagues. A friend said to him: "you do not have to wear a sword and shield to be a knight." This is how I felt during recent years and how I tried to behave. It is unusual to become a professor in your own university after already having been made a member of the Academia Ophthalmologica Internationalis and the European Academy of Ophthalmology. I can put your mind to rest with regard to Tiuri: he was soon knighted as he had shown he had the right attributes to be a knight.

Similar to him, I would not have liked to have missed my travels and my experiences.However, I hope, that with my new dignity, I will be able to do my work even better.

Word of thanks

I like to use this opportunity to thank several individuals. First, het College van Bestuur van de Leidse Universiteit and de Raad van Bestuur van het Leids Universitair Medisch Centrum, who made this appointment possible.
I also thank the Advisory Board for its persistance: during a period when the whole board of directors of the hospital changed, the committee under the guidance of Koning, stayed intact. I wish to thank Marjan Knijp for all her advice and support. You are terrific!

Professor Luyten, dear Gre: you now have a department with a lot of research and many grants. And about 25 PhD students? Thanks your creativity and capacity to build, our department has developed a lot. I am glad that you already early on saw the importance of my international connections.
Professor Schalij, dear Nicoline: your great capacity to organize things leads to good academic care, in which we are amongst the best, and always ahead of the pack. Thank you very much!

Many thanks to the workers and colleagues in the ophthalmology clinic and the lab, who support me in taking care of our patients and our research. You rock! PhD students, medical students, residents: it is a daily pleasure to work with you.

Many thanks to the many researchers in other departments of the hospital, especially the people at the Department of Immunohaematology and Clinical Oncology.
Professor van der Burg, dear Sjoerd, dear Thorbald van Hall, dear AG Jochemsen, dear Ewa
Snaar, thank you for the collaboration.

I furthermore thank the organizations that support our research, such as the Stichting Blinden-Penning, the LSBS, ANVVB, the SNOO, the Rotterdamse Stichting Blindenbelangen, het Nelly Reef Fonds, and the KWF.

For new initiatives, we received the support of private people, and I especially wish to mention Mrs. Tine van Notten-van Royen, Mr Otto Röell, de heer en mevrouw Dirk and Nel Parlevliet, Ms. Alice Swalm and Mr. Piet Vrolijk.

I thank my parents for giving me a good education: from both, I learned what is expected of a good doctor, and what science is, in which both excelled. My father was an ophthalmologist, my mother a genaecologist at the University of Amsterdam. I learned early on the importance of science, when on holiday in Drenthe, I did not have to come to dinner on time when I was counting migrating birds. My mother was my example that women can do anything, from my father I learned to look closely at things.

Dear friends, thank you all for coming. Many thanks to Marianne, Rinus, Erna, Marieke and Ton. Always warm, friendly, always there, even when we have not seen each other for a long time. That you are all here 40 years after we first met is terrific. Thanks to the many friends who know that I think of them, but who also know that my work (often) takes precedence.

Dear Lady Lions and partners, you are my extended family, and you are here en masse. You have been cut from the best cloth!

What I do comes forth from the example of some special teachers that I met during my study. My enthusiasm for tumor research comes from the fantastic lectures in biochemistry by professor van der Eb. I was later able to start my laboratory using your old equipment. For me they were like new. Dear Titia and Lex, thank you for all your support. Titia, I wear the gown of your father with much pride.

Professors Sterk and De Keizer: you saw how important translational research was going to be and helped me to build a laboratory. Thank you very much.

Professor van Rood: you have influenced almost all steps of my career. My interest in immunology and HLA come forth from a lecture that you gave in the fourth year of my study. Great teachers can raise enthusiasm in their students. I wanted to do a PhD in your laboratory and managed to do that. When I had almost finished my PhD, you advised me, as Professor Querido had advised you, to visit the United States, a trip that influenced the rest of my life in many ways. When after spending several years in Miami, I wanted to return to Leiden, you and Lex van der Eb helped me through Macropa. When I wanted to apply for a KNAW grant, the Department of Ophthalmology did not have a professor, and you were ready to help out again. Great people help others.
You always know how to ask the right questions to help me find my way.
Dear Jon and Sacha, many thanks for your inspiration, the fantastic sailing, your support. I am very grateful to have run into such fantastic friends as you two.

Dear James Davis, dear Jim. Staying at your house in Miami is always a holiday. The love and support that you have given me for over 20 years are immeasurable. I learned from you the strength of kindness and of giving and I thank you with all my heart. Without you, I would not be who I am today.

Dear Wouter,
Attending a concert of Dead Mouse with you in a snow-covered London was a special experience. Visiting the new proton center in Krakow showed me how much you have learned in Delft. It is great that you had just started at the Nikhef when the announcement of the gravity waves from outer space were being announced. I am glad I have such a fun nephew and I hope that with your study of physics you will be able to combine electronics and thinking.

My alter ego, my other half, dear Joke. We were together in my mother's womb, we have been fighting, playing and working together since we were born. I learned very early on that together you achieve much more than alone. Sometimes we travel together, but often it is me who is on the road. We have contact every day, wherever I am. Your advice is very sensible, as fits an engineer. You look after me, often before I know I need help, as when I was leaving for Boston. You brought me a warm jacket and gloves. I had not noticed that even the Charles River was frozen over, but you had.
I have the best sister in the world and being a twin with you is fantastic. I am extremely happy that we celebrate this day together.

Ik heb gezegd.

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Prof.dr. Martine J. Jager

Dr. Martine J. Jager is Professor of Ophthalmology, especially Ocular Melanoma, at Leiden University, The Netherlands. She received her MD degree and PhD in Immunology from Leiden University, did her residency in Ophthalmology at the University of Amsterdam, and a research and clinical ocular surface fellowship at the Bascom Palmer Eye Institute in Miami. She is a frequent visitor at the Schepens Eye Research institute, Harvard Medical School, Boston, where she holds a position as adjunct scientist. Her research interests are immunology and development of uveal melanoma, and ocular surface diseases, on which subjects she has published over 200 peer-reviewed papers as well as three books and over 40 book chapters. She is International Advisor and Guest Professor at Peking University, Bejing, China.

She mentors medical students and PhD student in the Netherlands as well as abroad. She has lectured worldwide, and has been principal investigator on numerous grants dealing with the development and immunology of uveal melanoma. Many projects involve international collaborations.
Dr. Jager has served as President of the Association for Research in Vision and Ophthalmology (ARVO), is a member of the Advisory Board of the International Council of Ophthalmology, and of the Academia Ophthalmologica Internationalis. She was recently elected to become the President of the International Society of Ocular Oncology.

Ocular melanoma is a rare type of cancer, with a high chance of metastases. Metastases of conjunctival and uveal melanoma are often resistant to therapy, including to immunological treatments. For uvea melanoma, this may be due to the environment in which this tumor arises, which is inside the eye. The eye has many immunological peculiarities: it is a location with immune privilege, which means that immune responses are down regulated. This has the advantage that corneal transplants will be accepted in a non-inflamed recipient cornea and thus usually not rejected. On the other hand, this immune privilege allows viruses such as ebola to proliferate inside the eye. Similarly, in mouse experiments, tumor cells may not be rejected when placed inside the eye, while they would be rejected when injected in the skin. Professor Jager's research is focused on obtaining a better understanding of the influence of this immune privilege on the behavior of human ocular tumors, and on the possibilities of still using the immune system to develop an effective therapy to treat metastases of ocular melanoma.

In order to develop good research, (inter)national collaborations are essential. Within the LUMC, the department of Ophthalmology collaborates with the laboratories of Clinical Oncology, Immunohematology and Blood Transfusion, Human Genetics and Dermatology, among others. Collaborations also exist with the department of Ophthalmology and Clinical Genetics of the Erasmus MC, Rotterdam. Internationally, the research group of Professor Jager participates in the European Ocular Oncology group (which has led to the Horizon2020 Cure UM collaborative group), the International Society of Ocular Oncology, the American Joint Committee on Cancer and The Cancer Genome Atlas Project.

As a cornea specialist, Professor Jager treats patients with severe corneal and ocular surface diseases, searching for better treatments. A second international consortium, Horizon Arrest Blindness group, focusses on the immunological aspects of the cornea and stem cells, with the goal of developing an artificial cornea.

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