

Festschrift in honor of professor Ellen Catharina Zwarthoff



INTRODUCTION

It is a great pleasure to write a short introduction on the festschrift of Prof. Ellen Zwarthoff, celebrating her work and immense contribution to the field of molecular diagnosis in bladder cancer. In particular her contribution to characterization of non-muscle invasive bladder tumors and development of urine markers for the diagnosis and follow-up of bladder cancer as well as her support for many PhD students and her staff. She is a true pioneer in the field of urine-based biomarkers and her work has changed our views on surveillance of bladder cancer patients.

Prof. Zwarthoff was born in Zwolle and studied biochemistry at the Free University of Amsterdam in 1976. As one of the very few females at her faculty she was a pioneer and received her PhD Cum Laude: “Strategic nucleotide sequences in the RNAs of alfalfa mosaic virus”. She was a guest scientist at Massachusetts Institute of Technology, USA and University of Wisconsin, USA and started working as a postdoc at the University of Amsterdam in 1990. Finally, she decided her home base should be at Erasmus MC where she focused on pathogenesis of bladder tumors, detection and validation of prognostic and diagnostic markers. Through her work, the Erasmus MC Bladder Cancer network has expanded significantly and her contributions have led to a new way of looking at urine-based surveillance.

In this festschrift we have a contribution from many people whose lives have been influenced by Prof. Zwarthoff and who would like to show their appreciation.

Dear Prof. Zwarthoff, dear Ellen,
Thanks for everything you have done for our patients and for us.

Tahlita Zuiverloon

FESTSCHRIFT PRESENTATIONS

Professor Chris Bangma, MD PhD, Chairman of Department of Urology Erasmus MC, The Netherlands

Professor Ellen Zwarthoff has always been in my memory a remarkable figure in Erasmus MC. Tough lady at the outside (first impression), warm hearted deep down (digging takes time). Well, there are more people like that around me, but no one that has an office that is somewhere hidden at the end of the corridor, after finding your way through the first lab of somebody else, the second lab from herself, a door, and then entering an enormous

room just for Ellen. And she plays golf. When you have arrived in such a room, you feel really modest. Rightly so, as Ellen was one of the first female professors at Erasmus (and she supported the female issue well!). Not unusual in the rest of the world, but for Erasmus this really was an accomplishment having even less female professors than the other Dutch universities that are bottom of the list in Europe . . . Ellen was sensible enough not to spend too much time on that issue. Her first official honorary public lesson, her oration in front of hundreds of people on a celebration day, was just like her last lesson for her students: this was bladder cancer, these were the markers, such and so you can find them, and this is what we are going to do with it . . . And yes, 100 % outcome of that prediction. Her work changed the world of bladder cancer diagnosis and follow-up.

Though it took some time. We conducted together the bladder cancer screening study (with another tough female professor Monique Roobol) that was more or less negative. No room for genetic diagnostic markers for early detection of relevant bladder cancers or reduction of cystoscopies at that time in that format. Sorry, even Ed Messing could not help us . . . Sitting in a car from Brussels to Rotterdam having visited a company that was going to support, she explained the game of golf (extremely simple no brain sporting activity where you have to find balls the same way as you find Ellen's office) and the setup of marker based bladder cancer screening. Ellen had it organized, and very well. There was hardly anybody to find that was able to motivate or push her students in such a way that not only everyone at the operation rooms knew that you had to send the bladder cancer sample always to Ellen first, but also in all the operating rooms in the neighboring hospitals in the region. With that, she (and her team of angels) accomplished the first design of the regional networks that all other persons after her are boosting upon.

Her work paid off internationally. She was a well-known guest at the European urologic stages, was honored, and remained intensely loyal to her team, her institute, her subject. And now she is still generous to share her knowledge and experience and funds to her research and her youngsters. All marvelous people in itself, thorough scientists, and admirable clinicians spreading over the world. Ellen's contribution to the bladder cancer research, the education of people, and the current departments of Pathology and Urology at Erasmus MC is highly respected. If there is a hard core in Ellen, then it is hard core science. And golf, I presume.



Joost Boormans, MD PhD, urologist, Director of Erasmus MC Bladder Cancer Institute. Department of Urology Erasmus MC, the Netherlands

It's a great honour for me to contribute to this Festschrift on Ellen Zwarthoff's career. As an independent woman in science, Ellen has to be commended for her achievements in the field of bladder cancer research. She really has moved the field forward and she is a true role model for many young (female) researchers nowadays.

My first encounter with Ellen was during my PhD training (on genomics in prostate cancer) when I had to present my research at the Josephine Nefkens Institute of Erasmus MC. Being a young MD who was making his first steps in the field of molecular oncology I prepared my 45 min talk well ahead. I was pretty confident I would be able to counter all critical remarks until a lady in the back starting tackling me on certain technical issues. I tried to talk my way out of it and kept smiling friendly but there was no mutual interest in smiling back I noticed. Later I realized that the points she was raising were very important and that my experiments would improve by changing the approach. One of my fellow PhD's later told me 'That was Professor Zwarthoff. She is really tough for PhD's.'

My second encounter with Ellen was years later being a fellow in oncological urology and I was invited to join her at the annual meeting of the International Bladder Cancer Network in the Baltics. In the hotel bar 80 meters above sea level Ellen advised me on how to realize my swap from genomics in prostate cancer to bladder cancer. She introduced me to many famous and important scientists in the bladder cancer field, which helped me enormously to build my network. From that meeting on I was very lucky to become her clinical counterpart at the Department of Urology at Erasmus MC. The backbench lady that gave me such a hard time a couple of years ago was further away than ever . . .

The collaboration in recent years with Ellen have been extremely exciting and fruitful. The field of bladder cancer research took off and with the rapid improvements of molecular techniques and new available therapeutic strategies for urothelial cancers, many interesting research projects were initiated at Ellen's lab. Collaborations with MDxHealth on urinary diagnostics in hematuria patients, gene expression profiling of MIBC together with GenomeDx, and important contributions to The Cancer Genome Atlas were established. Together, we supervised (and still do) several PhD students and one of the absolute highlights was Kim van Kessel's PhD thesis in October 2018 that was rewarded 'Cum Laude' by the committee of Erasmus University. This is an example on Ellen's ability to deliver important scientific output of very high quality within short time frames.

In 2014, together with my head of department Professor Chris Bangma and colleague Professor Guido Jenster, we nominated Ellen for the Dominique Chopin Award by the EAU Section of Urological Research (ESUR). In recognition of her work, the board of ESUR decided to honour her with this award. A true honour and very well-deserved.

Dear Professor Zwarthoff, dear Ellen, my deepest gratitude for everything you have done for our department, our PhD's, and the bladder cancer community!

The "Jong" boys: Christiaan de Jong, MD PhD candidate; Joep de Jong, PhD Candidate, Department of Urology Erasmus MC, the Netherlands

Ellen was the program director of a 10-week 'diagnostics in oncology' course during my second year of medical school. In the first week Ellen gave an introductory lecture on bladder cancer and it was immediately clear that Ellen was passionate about her profession and that she cared about her students, while making them understand the concepts of molecular diagnostics. Two years later I was looking for a lab to do a research internship, while at the same time my mother was referred to the urologist for hematuria. Luckily, Tahlita (dr. Zuiverloon) was the consulting urologist and when I expressed my wish to do a research internship, she directly referred me to Joost (dr. Boormans), who, on his turn, re-connected me with Ellen. From this moment, I started to work on the prospective validation study of the diagnostic urine assay to triage patients with hematuria for cystoscopy, together with Kim (dr. van Kessel), who has been a great mentor and 'partner-in-crime'. I am still convinced that I could not have been more fortunate with this coincidence, because from day one, Ellen and Joost have been two top-notch supervisors, creating all kinds of projects and opportunities. Ellen, I hereby want to thank you for your life lessons (I will never forget the second law of Zwarthoff ϑ) and your caring personality. Working on bladder cancer at the Zwarthoff laboratory is simply great and meeting you has already proven to be valuable for both my personal, and my working life.

I am very happy that you and Joost made it possible for me to continue our projects during the coming years and I think that I do also speak on behalf of my PhD-roommate (and name-shareholder) Chris de Jong, when I say that we look forward to the coming years together.

Cheers, Joep

Several years ago, I was nearing the end of medical school. At the time, Tahlita was my clinical mentor during my final clerkships at the urology department. After a lengthy day with outpatients I presented a case to her and discussed the upcoming role of immunotherapy in (bladder) cancer. At the time I was eager to find an interesting topic to start my master's thesis. When Tahlita came up with not only an interesting proposal, but also the perspective of a PhD trajectory, I immediately signed up. She explained me though, the "boss" still had to agree with our proposition. And luckily, she did (yeah!). Soon after I was prepping for my first meeting – a presentation – at the professors' lab. I can vividly remember the nerves, because I already overheard some stories

about her: a quick thinker and a very sharp tongue! The professor wants you to be concise! After the meeting – I must have called her professor a dozen times – she came to me, told me I had done well (phew!), but I really had to stop calling her professor! In the weeks following the meeting, the professor “transformed” into Ellen and since then, I have come to know Ellen as a warm, dedicated and goal-oriented mentor with whom I also share many off work passions: Mediterranean journeys full of bistros & bodegas! And these stories about her . . . also true! Yet it makes the Ellen all the more interesting as a person.

Thank you, Ellen, for what I’ve learned, undoubtedly will learn and your continuing mentorship. I hope that you and Jan-Willem can play golf all around Europe for many years to come. Although you are retiring, together with my buddy Joep and the others in the Erasmus MC Bladder Cancer team we hope to keep you JONG and involved in our projects when you are a professor emerita.

Best, Chris



The “Older” girls: Kim van Kessel, MD PhD; Tahlita Zuiverloon MD PhD, Department of Urology Erasmus MC, the Netherlands

Dear Ellen,

I remember my trip to Bruges in 2006 like it was yesterday. Not only because Bruges is just a wonderful city, but more because I was in Bruges on a boat with my mom when you called me to congratulate me on a job in your lab. Through all these years, you have been a great mentor and supportive when I needed you, like we would say in Denglish “through thick and thin”. When I needed support or in case of a panicking situation in the lab or concerning a grant, a whatsapp message to Ellen and she is always there to calm us down. You have thought me many aspects of research and always pushed me in the right direction in your own special way. Also, I have enjoyed our many talks about win, luxury vacations and 3 Michelin star chefs. I loved it.

Ellen you are a true inspiring mentor to me in all parts of life and I thank you for all you have done for Erasmus MC, the international bladder cancer community and women in general.

Tahlita



Dear Ellen,

What a great opportunity to share my personal thoughts and memories of working with Professor Ellen Zwarthoff. She is an impressive character and inspiring mentor. My first encounter with Ellen was ‘the weekly Bladder Cancer Laboratory meeting’, during my final year finishing my Masters in Clinical Epidemiology. Ellen and Tahlita (dr. Zuiverloon) were working on bladder cancer biomarkers and I was (supervised by Prof. E.W. Steyerberg) working on decision modeling in cancer surveillance. We decided to collaborate and create a decision model for urine surveillance in bladder cancer. Since that time, I hoped to join the bladder cancer research team. This group of powerful women had set an inspiring example, with dedication and hard work, they produced high quality translational scientific work. Luckily, after a couple of years, dr. Joost Boormans and Ellen were able to facilitate a PhD position for me.

During my time in the lab Ellen has been a wonderful mentor, and inspiring leader. At times, laboratory meetings could become heated and intense, at those moments a sparkle appeared in Ellen’s eyes. She loves a passionate discussion and enjoys the input from dedicated people around her. To outsiders Ellen might appear strict at times, however people closer to her know her kind heart and genuine interest and appreciation for people surrounding her. The level of her knowledge is truly impressive and will be hard to match in the future. Above all, she is deeply concerned with the well-being of bladder cancer patients around the world.

Ellen is a woman with many interests. She has thought me numerous lessons in life on many different themes outside work; feminism, golf, wines and good food, art and classical music. On our numerous trips around the world we have spent many hours in art galleries, fine restaurants and wine-bars. Scientific discussions combine well with a good glass of wine!

Dear Ellen, you have left a lasting impression on so many; scientists all over the world, women in academics, and the bladder cancer community as a whole. You are the embodiment of girl-power and a true inspiration to us all. Thank you for everything you have done!

Kim



Professor Dan Theodorescu, MD PhD, Director of Samuel Oschin Comprehensive Cancer Institute, Los Angeles, CA, USA

I don’t recall exactly when I met Ellen the first time, but it seems like I’ve known are forever. That’s because her work has impacted my thinking about the field of bladder cancer and where we are going and what we should do for our patients. Actually, it’s approximately 15 years ago that I met Ellen while I was at a poster authored by one of her post-doctoral fellows that was being presented at an AACR Annual Meeting. I remember being quite impressed by the translational potential of the work and especially by how well prepared her trainee was in answering questions. In addition, it was very clear based on that abstract and subsequent work that Ellen was on a single-minded mission to use current scientific knowledge specifically that of the genetic characterization of bladder cancer to improve clinical care. Over the ensuing 15 years I have been privileged to interact with Ellen in a variety of scientific forums as well as be involved in training some of her students. During this time I have been impressed by her ability to synthesize and then apply genetic information to not only develop the foundation for what I believe to be the standard of care in the future for bladder cancer surveillance but also her ability to marshal a variety of collaborations both national and international to accomplish this goal. In biological science especially when one wants to translate basic science findings to the clinic and evaluate those

findings for their clinical utility it is critical that large patient cohorts be examined. Therefore, bringing together international coalitions to accomplish these goals is necessary. Ellen has demonstrated the ability to do this and established very clearly that genetic detection of bladder cancer based on noninvasive urinary analysis is not only possible but is clinically feasible and has significant utility. In fact, one could argue that probably no other single individual has contributed in to the establishing the next generation of bladder cancer surveillance approaches as much as Ellen. I have no doubt that her contributions will change clinical practice worldwide with consequent significant improvements in patient quality of life, burden of follow-up, and significant cost savings to the health care system. Because of those contributions and for her contributions to the training of several generations of physician-scientists and scientists in the field of bladder cancer, she is in my opinion one of the giants in bladder cancer research and indeed in the field of cancer diagnostics overall. Ellen, you are admired by many and we owe you a great debt of gratitude for what you have done for the field of bladder cancer and for our patients today and in the future. Thank you.

Professor Margaret Knowles, PhD, Leeds Institute of Medical Research at St James's, Leeds, United Kingdom

I am most grateful to be asked to share my personal thoughts about Ellen. We met in 2000 at the Annual Meeting of the AACR in San Francisco. I believe that this was the first time there was a session dedicated to bladder cancer (corroborative evidence is that Peter Jones was Program Chair that year). I didn't keep a record of the session or my slides but I'm sure that at least two of the talks related to mapping of deletions of chromosome 9. Ellen had started to work on bladder cancer at around that time and was also working on chromosome 9, so she and her student Angela von Tilborg introduced themselves after the session. This was the beginning of a long friendship and from that time we organised a series of memorable "Bladder Dinners" at AACR meetings. During the 1990s and early 2000s there were no dedicated meetings on bladder cancer where we could present our data, so meeting once a year at AACR presented an opportunity for the few groups working in the field to interact. During those early years of deletion mapping, an important finding by Ellen's group was that the most recent recurrent lesion in the bladder was not always the most genomically "advanced", demonstrating that although non-invasive bladder cancer is usually monoclonal in origin, sub-clonal evolution is temporally diverse and genomically "early" lesions may not become clinically apparent until late in the disease course. In accord with the suggestion that undetected tumor or precursor cells lurk within the "normal" urothelium, Ellen's group later described positive urine biomarker detection in the absence of overt tumours, "anticipating" disease recurrence. A fascinating organ in which to study disease pathogenesis!

More recently, in addition to AACR meetings, IBCN and ESUR meetings have provided great opportunities for bladder cancer researchers and Ellen and I have sampled many good wines whilst discussing our work and generally putting the world and the field to rights on these occasions. We have had much fun – recently and memorably in Athens with a group of bladder cancer researchers ascending and descending Lycabettus Hill in the funicular railway for a meal at the highest point in the city (a slow ride experienced at high decibels nevertheless!).

Ellen was by training a biochemist and I was a microbiologist turned cell biologist. My approach has always been more descriptive and less quantitative than Ellen's, and this has allowed us easily to avoid overlap in our work despite shared interests. Ellen's quantitative approach has been clearly exemplified in her work on urine biomarker identification. She is to be applauded for her dedication over many years to the identification and validation of urine biomarkers. I recall that when she first started this work, some urologists voiced concerns about replacing any cystoscopies with a urine test. Nevertheless, she persisted and following identification of potential DNA-based biomarkers, development and optimisation of relevant assays and screening of huge numbers of voided urines, clinical application in some settings now seems close. In recognition of her work in this area, Ellen received the Dominique Chopin Award by the EAU Section of Urological Research (ESUR) in 2014. Within the community of bladder cancer researchers with translational intent, Ellen may well be the first to actually translate an assay into the clinic. A great achievement from a highly-respected colleague.



Professor Arndt Hartmann, MD PhD, University of Erlangen, Erlangen, Germany

It is a great pleasure to share my memories of working together with Ellen Zwarthoff. and thank her for many great years of cooperation working on the most interesting tumors of all - bladder cancer. When starting a residency in pathology in the late nineties of last century and going into bladder cancer research it became very fast obvious that there was this great group in Rotterdam asking the right questions and doing things often faster! Ellens group very early was trying to translate the molecular findings into the clinic. At this time bladder cancer was a “neglected cancer type” which changed considerably in the last years. Ellen Zwarthoffs group published many important findings which are now the base for new therapeutics and diagnostic-tests in bladder cancer. I first met her (as many of other friends and collaborators) at the AACR, first at the poster and then at the wine-bar and during the famous AACR bladder cancer dinners. Discussions there led very quickly to a great cooperation with joint studies investigating for instance the FGFR3 mutation frequency in several cohorts of bladder cancers. Working in the pathology department in Rotterdam she always understood that molecular changes translate into phenotypically diversity under the microscope. Her work on clonality in bladder cancer showed that bladder cancer is a dynamic disease and subclonal evolution of genetically different tumor clones can lead to tumor heterogeneity during the disease course. The discussion with Ellen on clonality of bladder cancer was greatly influencing of our own research in Regensburg and later in Erlangen. Most importantly it was a pleasure to collaborate with Ellen and the many students and fellows who grew up in her lab in Rotterdam. In the last year Ellen was fundamental in translating the molecular findings into clinical diagnostics of bladder cancer. After identifying several urinary biomarkers and developing relevant assays she screened large series of patients and conducted clinical studies leading to a urine bladder cancer test which has the potential to replace some of the cystoscopies in the future and change the way we treat patients with bladder cancer.

Ellen - it was a pleasure to work with you for twenty years, we will greatly miss you in the bladder cancer research community!

