The passion behind big cancer projects

Peter McIntyre

Kris Vantongelen, now managing director of the Breast International Group, has played a pivotal role in two arenas that have been essential to the progress of oncology in recent decades: the development of systems for data collection and analysis, and the organisation of international interdisciplinary collaboration. She describes herself as 'a believer'.

Looking back, Kris Vantongelen takes a tough line about her own merits and credibility. "What was my knowledge?" she asks about setting up the first quality assurance programme in European cancer research trials. "Who were we to come and judge them?" she recalls some researchers asking on one of her visits to European hospitals. "I had no idea where to start," she says about the first conference she organised.

She is almost forensic in scrutinising her own qualities, mentioning more than once her lack of formal medical training. Yet she also describes herself as "addicted to a challenge". Her first instinct is to question whether she is the right person for the job – her second is to learn to do it.

Her rule of life is, "Passion should be the driver for everything you do, even though it's not necessarily a guarantee that you can do everything well."

She has left her mark on the development of cancer research in Europe in three ways. She worked alongside Emmanuel van der Schueren, one of the driving forces in building international collaboration and research in Europe, to develop quality control of data collection in clinical trials.

As conference and programme manager of the Federation of European Cancer Societies (FECS), she put together a succession of ECCO conferences and developed the FECS conference unit that brought a string of specialist meetings into being.

Today, she is managing director of the Brussels-based Breast International Group (BIG), managing the process of collaborative research into breast cancer work across continents.

She has done her share of writing papers and speaking at conferences, but for the most part Vantongelen has worked as a catalyst, facilitator and manager, bringing ideas to life and making things happen.

Martine Piccart, President of the European Organisation for Research and Treatment of Cancer (EORTC), recruited her to run BIG from her base at the Jules Bordet Institute in Brussels in 2006, because of her "truly remarkable skills".

"Kris immediately understands where the key cancer projects are and which deserve to be supported," says Piccart. "She brings talented people together and helps them to build a great educational conference or innovative research protocol.

She has a good feeling about what is achievable and makes it happen, and she can develop a project step by step, helping to overcome all human and bureaucratic obstacles."

Vantongelen graduated in 1968 from the Leuven Catholic University, during a tumultuous year in which student radicalism and the increasingly fractious divisions in Belgian society collided. She met her husband to be, Jos Van Grunderbeeck, as a student and they married soon afterwards. In 1969, a young married graduate in management studies, she needed a job with security and a future.

The director of Leuven University Hospital, Gerard van der Schueren (Emmanuel's father), was looking for someone with knowledge of statistics to organise the data in his oncology department. Van der Schueren was unworried that Vantongelen professed a complete lack of knowledge of medicine. He told her to join any medical course that interested her.

She jumped at the chance. "I did part of the training that radiotherapy oncologists followed and I followed the training that the nurses in oncology had from the head of the department.

"What made it so fantastic was I was 100% supported by the medical staff – multidisciplinary mentors who helped me understand how to benchmark research and the clinical implications.

A PASSION TO KNOW

"For me it became a passion to know. It was a puzzle that at first looked like 1,000 pieces. The more I learned, the more I realised that it was perhaps a 10,000 piece puzzle. It was an unbelievable opportunity and a great learning experience."

PETER MCINTYRE

Thinking BIG. Vantongelen with (left) Martine Piccart, chair of the Breast International Group, and (centre) Eleanor McFadden of Frontier Science, which does the randomisation and statistical work for BIG

Vantongelen developed a system from scratch, later taken over by the hospital registration system, to allow doctors to analyse retrospectively what had happened to the patients they treated for cancer. "We had no computer in the early '70s and developed a manually searchable database including patient and tumour characteristics, pathology, treatment and follow-up data. It is amazing thinking of that now."

In the late 1970s, Emmanuel van der Schueren became head of radiation oncology at Leuven in succession to his father, and prospective clinical trials were introduced. He asked Vantongelen to manage the protocol for the H5 trial in early-stage Hodgkin's disease – their first multi-centre prospective study.

"They said, 'You learn the protocol by heart and tell us what we need to do.' Now what does that mean? What is a protocol? What are the issues involved in conducting cancer clinical trials at a local level?" These were all things that she had to work out and learn.

Later Vantongelen acquired a computer, "like a monument, huge and very heavy", and began to devise systems to make data collection and analysis easier.

The introduction of clinical protocols required careful attention to the documentation of treatment, response and toxicity in the patient file, but consistency was difficult to achieve because doctors often had their own way of classifying symptoms and side-effects. During the 1980s, as computerisation made comparisons easier, Vantongelen became increasingly aware of discrepancies.

"I was really intrigued by the difference in interpretation of protocol guidelines and instructions between medical staff. For instance, variations in defining the dominant site of the disease, a key

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stratification in metastatic breast cancer trials, was one of these issues that gave rise to serious concern. I mentioned this to the medical staff and asked what I could do to guarantee that what I was transferring was correct." Vantongelen organised a test amongst investigators attending the EORTC Breast Group, and this confirmed the lack of consistency in determining the dominant site of disease.

By the mid-1980s, EORTC was coordinating 200 multi-centre clinical trials across Europe, supported by a core grant from the American National Cancer Institute (NCI). The NCI warned EORTC that it would not continue financial support without quality assurance procedures. Vantongelen was asked to set up a data quality control system for EORTC and produce a report within six months that would satisfy the NCI.

With little guidance on how to devise a system that would work for researchers at different sites using many different protocols, Vantongelen used "common sense and my own experience" to set up a two-stage data quality control procedure, using a questionnaire followed by on-site visits.

With Nicole Rotmensz from EORTC, she visited hospitals, comparing their records with data on trial case report forms. The original concern was whether data were being accurately recorded. They found few errors. However, up to 14% of entries could not be checked as they were not in the patient notes.

"If the data are not in the patient's file, the origin can still be a trustworthy source, like the doctor himself, but if you cannot check it in the file you have to take it on trust. If the doctor filled the form in front of the patient that is one story. But if he did it retrospectively at the end of the week, or perhaps even later, that was a concern."

Alarming variations

Vantongelen and Rotmensz found a lack of systematic recording and alarming variations in the way that chemotherapy regimens were being implemented, especially the sequencing and intervals of drugs. Since many trials were concerned with the toxicity of treatments, with subtle but important differences between regimens, the quality of toxicity data in particular was critical.

In one year, Vantongelen and Rotmensz visited 56 hospitals in Europe and their work led directly to an improvement in data collected for clinical research. They did not always feel welcome. "In the very first visits, it looked to most investigators like we were the police coming to judge them. But trust was gradually built, supported by encouraging results."

The first findings, published in the *European Journal of Cancer Clinical Oncology* in 1989, recommended "good local organisation with tight internal control".

With a group of medical oncologists, Vantongelen devised a system to ensure the integrity of research results, with a check list for every patient entering EORTC clinical trials. However, "tight internal control" was not always easy to achieve. "The introduction of clinical trials induced a lot of extra work. Most hospitals did not have proper support systems for data and clinical research management. If the investigator was the only one to deal with all that, the administrative burden became a problem."

However, she says, "Over the years, quality assurance programmes developed for radiotherapy, chemotherapy and even for surgical procedures, together with more precise documentation of these processes. Undoubtedly this had a beneficial impact on quality of treatment, not only restricted to patients in clinical trials."

Vantongelen was increasingly in demand as a speaker about quality control at ECCO and the European radiology and oncology society, ESTRO, and at meetings of the American Society for Clinical Trials. In 1989, Rotmensz, Vantongelen and Josette Renard, from the EORTC data centre, published a book on data management and clinical trials. Further international work included a visit to MD Anderson in Houston to evaluate data management in clinical trials at the radiation oncology department.

Now chairing the EORTC data management group, Vantongelen set up training courses to bring nurses, doctors and administrators into clinical trial management – and to introduce new researchers to EORTC procedures. She produced, with Jean-Claude Horiot, from Dijon, the first written practical guide to EORTC studies, and followed this with the first edition of the EORTC manual on clinical research in breast cancer.

In 1988, it was decided to hold the 1991 EORTC European Breast Cancer Working Conference in Leuven, and Vantongelen 'volunteered' to organise it with a small team of people in the oncology department. "I had no idea where to start, but I was addicted to challenges, and this was something new. I know now that I am stress resistant. We did it and it was one of the best EORTC Breast Cancer Conferences. But I remember my words on the last day when everybody left. I said, 'Never, ever again in my life will I organise a conference.'"

By 1994 Leuven University Hospital had outgrown its city centre site, and the oncology department moved to the Gasthuisberg campus. As Vantongelen started to pack into boxes 25 years of history, she decided it was time to move on. "I thought: What would I like to do now? I only know about oncology, but I am not a specialist in anything particular."

Organising ECCO

Emmanuel van der Schueren had been a leading light in the formation of the Federation of European Cancer Societies (FECS), originally run from the same Leuven University corridor. FECS was looking for somebody to put together scientific programmes for its ECCO conference.

For the next 12 years, Vantongelen planned and organised scientific programmes for ECCO, the largest cancer conference in Europe, covering not only medical oncology, surgery and radiation oncology, but also pathology, basic science, nursing and every aspect of multidisciplinary working. The scientific committee assigned someone to be responsible for the programme, assisted by experts from other disciplines. Synergy with the committee and the chair was crucial for achieving an interesting and balanced programme. "It was a fascinating time. I knew a lot of people and we were very complementary."

Vantongelen worked on six ECCO conferences, and before she left FECS, set up the core programme for the seventh in Barcelona in September 2007. Although sometimes overshadowed by the prestigious American ASCO conference, ECCO flourished and attendances doubled.

"ECCO is still the cathedral of oncological conferences in Europe. It is the unique platform for multidisciplinary collaboration in oncology in Europe. It is prestigious if you are invited to speak, and should be seen as an acknowledgement and stimulus for the increasing efforts in research in Europe. The only factor working against conferences of that size is the growing tendency for people to focus on conferences in their specific area of research, very much the result of science and research becoming fragmented.

"One of the most important issues is that European research needs to be distributed in the first place amongst communities in Europe. Americans promote their own research. We should do that more."

The FECS conference unit also grew: at one time,

"Still the cathedral of oncological conferences in Europe". Vantongelen put together the core scientific programme for ECCO 14 before leaving FECS for new challenges

"ECCO is the unique platform for multi-disciplinary collaboration in oncology in Europe"

"The new generation of oncologists, who are not stuck in old politics, are the driving force of this future"

12 staff were organising meetings, symposiums and conferences across Europe. Vantongelen coordinated the first European Breast Cancer Conference (EBCC) in Florence in 1998, which put clinicians, scientists and advocates on the same platform and astonished the organisers by attracting 3,000 people.

The other event of which she is most proud is the annual Flims (Switzerland) Workshop on Methods in Clinical Cancer Research for young researchers, sponsored by FECS with the American Association for Cancer Research (AACR) and ASCO.

Oncologist Jean-Pierre Armand took Vantongelen to visit the Vail Clinical Trial Workshop in the US. He was determined to start something similar for Europe, and commissioned Vantongelen to make it happen.

"This was a fantastic idea. A young researcher comes with a study proposal and, during the workshop, is guided towards a feasible design addressing a sound scientific question. With the help of top experts in the field and individual counselling, they go home in five days with the finished protocol written. They work day and night, but when they go home on the Friday morning you can see great relief and victory in their eyes."

Over the eight Flims workshops with which she was associated, 95% of the researchers went home with a completed protocol, and half were approved by local ethical committees.

The Flims Alumni Club contains many future leaders in oncology, and an increasing number of previous Flims fellows now present research at ASCO and at ECCO.

Vantongelen left FECS in 2006. She will not discuss her departure, but it was clearly an unhappy time in her professional life.

Return to research

She arrived at BIG last November, delighted to be back with clinical research, but characteristically, with some self-doubt. "I was a bit frightened that I missed too many important translational research developments and the legal- and regulatory-related issues that I absolutely need here. I caught up reasonably rapidly, but still there are so many things to learn, specifically about the new complex trials we run and plan for the future."

BIG's aim is to facilitate the conduct of large and difficult breast cancer clinical trials and to reduce wasteful duplication. Vantongelen arrived as BIG was about to launch the ALTTO and Neo-ALTTO trials, evaluating lapatinib, a small tyrosine kinase molecule, given either adjuvant or neo-adjuvant, alone, sequentially or in combination to trastuzumab (Herceptin) for patients with HER2-positive, early-stage breast cancer. The ALTTO trial is jointly conducted with the US North Central Cancer Treatment Group and BIG is coordinating the activities between research groups in Europe, Japan, Taiwan, Australia, New Zealand, South Africa, and in North and South America, altogether representing over 1,200 institutions. ALTTO is indeed the first truly global adjuvant trial for breast cancer.

Vantongelen has seen clinical research in oncology develop from the early prospective clinical trials to the complex modern global trials with the fascinating translational research opportunities of today.

"I'm a believer. I believe in the future of oncology in Europe; there are many challenges, but there are also many good and enthusiastic people around. Times are changing and research is moving faster than ever before – so are people and opportunities, and the new generation of oncologists, who are not stuck in old politics, are the driving force of this future."

As her 60th birthday approaches, Vantongelen looks forward to spending more time with her grandchildren and husband. She recalls the time when her three children were under the age of seven as a period of complete exhaustion that went by in a blur.

"I was studying. I was working. I was raising children, Suddenly, you realise that they are teenagers. Now with the grandchildren you get a second chance, but you never get a third one! I enjoy every minute of it and, while I don't have too many spare minutes right now, I want to make firm plans for that."