Laura van 't Veer: the person behind personalised treatments

Marc Beishon

Our new-found ability to profile the gene expression of a tumour is transforming the way we characterise cancers and decide on treatment. Laura van 't Veer was there from the start, and she's now splitting her time between the academic and biotech sector, driving the translation of the new technique into diagnostic tools not just for research but for everyday clinical use.

When Laura van 't Veer was asked to apply for a job in the pathology department at the Netherlands Cancer Institute (NKI) in Amsterdam back in 1993, research colleagues warned her off, saying that diagnostics was rather a boring area to work in. What they did not appreciate – unlike the more far-sighted institute management – was that the post involved setting up a brand new subdivision in the NKI's hospital, namely molecular pathology, which is now among the hottest areas of cancer research, with excellent prospects for a wave of new diagnostic – and prognostic – tools that should hit clinics worldwide in the next few years.

Van 't Veer's own work as head of molecular pathology at the NKI has led to the rapid development of a microarray gene expression profiling technique for breast cancer that has propelled her onto the world cancer stage. She is now also chief operating officer of Agendia, a biotech company jointly set up by the NKI and venture capital funds, which has been the first firm to launch a commercial implementation of the technique, called MammaPrint. Since she and colleagues authored a letter to *Nature* in 2002, explaining how the gene expression profile could largely eliminate unnecessary and possibly harmful treatment for women at low risk of disease spread, she's barely stood still as commercial interests have weighed in with offers – and the 'competition' with critiques of the results.

"When people realised that it could change their way of clinical practice they tried to find holes in it – some got very worried and overreacted," says van 't Veer. "That is fine for me – it means we are on to something very promising as they wouldn't pay so much attention to it otherwise." In fact, she adds, there could be as many as 200 papers already published that use her group's data – "And we've always been honest and fully described the possible pitfalls."

In any case, she points out, reproducing results with independent cohorts was always going to take time, and indeed more papers that build on the findings are due out this year. Further, the microarray technique is a

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highly complex amalgam of technology, bioinformatics, biostatistics and oncology – at present it simply is not feasible for any laboratory to achieve reproducible results using home-grown equipment. "That is why Agendia was set up – to create a 'black box' system that can be widely used for breast and other cancers," says van 't Veer.

"My driving force for bringing it forward is that it is really of benefit to implement this type of diagnostic – it will give a better insight into the disease someone has, and insight into best therapy – so it's important that everyone starts using it. But sometimes I feel I'm pushing too hard."

Although her eye is now firmly on this clinical setting, van 't Veer's background is in basic research, and it was the scope of the job offer at the NKI that has been a key enabler. "I was the first molecular biologist to be appointed to work in both the hospital and the research part of the NKI," she says. "Few people have appointments in both." The dual role has been especially beneficial as not only has she been able to proceed with both diagnostic and research-based molecular pathology, but she also moved quickly to

The gene pool. On holiday with her family in Schiermonnikoog, an island off the north coast of the Netherlands

establish a family cancer clinic to help and gather data on those with hereditary disease.

So there could hardly be a better place to work for someone whose primary interest at school was biology – and in particular DNA and genes. At high school in the 1970s, her biology teacher was a ready source of such information, and when van 't Veer went to university to study biology she thought at first that embryology would be her speciality, until by chance she met the wife of a colleague who worked at the NKI, who asked if she would like to do a placement there.

This proved to be a fruitful route during her undergraduate and masters years, as she first carried out work on DNA repair and then worked with Roeland Nusse (now at Stanford) on a human homologue of a mouse gene – "This went very quickly – in a couple of weeks I had identified the gene, which was really spectacular." She ended up working for a year with Nusse and majoring in molecular oncology, and was present at the founding stages of the science. "When I cloned this human homologue involved in mouse breast cancer, I also started to see whether we could find alterations in genes in human tumours, which was quite new then. I can remember reading Robert Weinberg's paper on the activated *Ras* oncogene in a human bladder cancer cell line, which was really very new. It's amazing progress that in 20 years I've moved from working in laboratory research on human oncogenes, as we called them then, to working with patients."

Van 't Veer moved on to take a PhD at the University of Leiden, completing an education that took some 13 years, which she followed up with two years in Boston.

Although recognising that it is not necessary to go to the US to gain post-doc research experience, van 't Veer reckons that it is just as important to experience a change in cultural attitudes to research and life in general that America can bring to young scientists and practitioners. "I enjoyed it greatly and of course there are just so many people in Boston working in molecular and cell biology and oncology research that there is critical mass that just speeds things up."

She was fortunate to join a group of five young principal investigators at a new cancer

centre at Harvard Medical School, including René Bernards, a Dutch countryman who is now a close colleague at the NKI and Agendia, and Stephen Friend, who went on to co-found Rosetta Inpharmatics (now part of Merck and co. Inc), set up in 1996 to develop the microarray gene expression technology that van 't Veer was later to use in her own work.

"This group generated a lot of excitement – they'd all come from big labs and were working on experimental cancer biology, and I did the most basic research I've done, on cell cycle control. But in Friend's group they found germline mutations in the *P53* gene that could help explain part of Li-Fraumeni syndrome [a rare autosomal dominant syndrome in which patients are predisposed to cancer]. The result was that several of us who returned to Europe and elsewhere from this group started family cancer clinics in the hospitals where we ended up working – because for the first time we could see that genes could explain hereditary cancer syndromes." So focused was this group, she adds, that their computer database was dubbed the 'candidate gene approach', thanks to the work on *P53*.

René Bernards was then appointed a professor at the NKI, and asked van 't Veer to join him as a fellow in the department of molecular carcinogenesis. 'The post-doc time is when you have the most freedom but you have to decide at some point what you want to do," she says. "I was very lucky – I didn't have to return home and worry about writing proposals and applying for grants, which is a struggle for many when they look for work."

Then a year later, the then NKI director, Piet Borst, led a brainstorm on where advances would be, and came up with the new molecular pathology post to further interest in translational research. "As I'd worked on gene characteristics of human tumours in my PhD, it was of interest to me, and as a new job, it would be up to me to create the work programme. And as it also involved research I thought I'd be an idiot not to take it." Despite the rather negative image of diagnostics, she first had to beat off 50 other applicants for the post.

She started with just two technicians, working alongside 'conventional' pathologists, and began to develop relationships with surgeons, medical oncologists and radiotherapists. "I gave presentations and we started to understand each other's language," she says. "I explained what a mutated BRCA 1 gene could mean to cancer risk to our head of surgery – afterwards he told me I was the first person he dared to ask what point mutations are – there was no one else so close he could directly ask."

She did a similar knowledge exchange with Emiel Rutgers, head of the breast clinic (and a current close colleague in the microarray research) – the NKI is a first-line centre for breast treatment. "I discovered what adjuvant treatment was, and found that many women were asking them for advice. But they didn't deal with the genetic side – it was not yet part of their clinical practice. In any case, 12 years ago it was only haemato-pathologists treating leukaemia and lymphoma who used the chromosomal break points as molecular diagnostics."

Van 't Veer established a family cancer clinic to provide advice and support on hereditary disease, and notes that now everyone treating cancer patients needs to know about genes in daily practice. She's stayed mainly with breast cancer for her work, thanks to the NKI's specialism and because so many things happen first with this disease. Another branch of her work is molecular epidemiology – a current large study, for example, is on gene–environment interactions in hereditary breast cancer.

After five years, van 't Veer split her team into diagnostic and research groups, and worked

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to gain ISO quality certification for DNA diagnostic work. "While it's not obligatory we felt that in doing genetic tests for heredity cancers major decisions were going to be made on a single result, so we made sure it was quality controlled." On the research side, she focused on single-gene, single effects – until the NKI, like many other institutes, decided to start work with microarrays in the late 1990s. "We had to decide whether to wait until it was developed and buy something, or start our own microarray facility and build up experience, and we chose the latter. I became involved together with other pathologists because we had tumour series that would be very interesting to study using microarrays. But it was a big hurdle in the first years to produce microarrays to high standards. There can be a lot of variation in hybridisation between one array and another."

There are several types of microarrays and applications apart from cancer (for a good primer on the subject, see www.ncbi.nlm.nih.gov/about/primer/microarrays.html). However, the gene expression segment has become one of the biggest application areas, and already represents a market approaching a billion dollars. Van 't Veer and colleagues – including Marc van de Vijver, co-author on many papers – realised that one of the main planks in making progress is the production of reliable microarrays, where the private sector had a role, and it was Bernards who used his contacts with Rosetta Inpharmatics to start a collaboration that led to the breast cancer gene expression profile.

"Rosetta had the microarrays and analysis expertise, but we came up with the clinical question and the patient information," explains van 't Veer. The NKI is one of the few centres with a large bank of frozen breast cancer tissue, thanks to a far-sighted pathologist who started a standardised biobank back in 1983, and the particular microarrays used by the NKI are able to profile gene expression in frozen tissue. As breast cancer patients have long been followed up at the institute, clinical outcomes were also known.

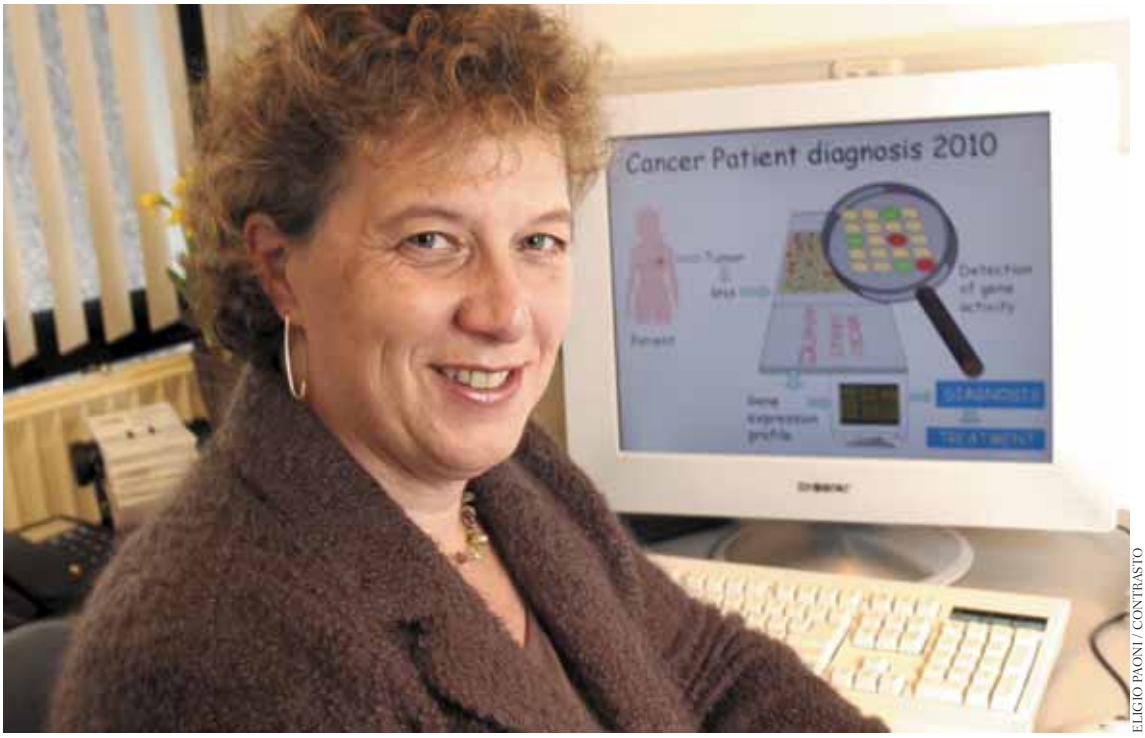
Van 't Veer found herself in the centre of a multidisciplinary team that took the initial question – predicting the risk of metastatic disease – and after much mathematical analysis and discussion emerged with a translation into the clinical setting – reducing unnecessary treatment of women at low risk using a 70-gene 'signature'. It has involved working with physicists at Rosetta on the bioinformatics methodology, checking and refining the data analysis with a biostatistician at the NKI, and talking with many research colleagues, and has been a hugely enjoyable experience for van 't Veer.*

"Reducing unnecessary treatment was one of two main discussion points we came up with – the other was that the profile actually shows you very early on in the development of a tumour that the programme for metastatic risk is laid down, or hard-wired." In a news item van 't Veer co-authored for *Nature* in 2003, she references a paper published in the *Lancet* in 1889 that hypothesised this hard-wiring – a startling connection with medical history.

"The impact of both findings has surprised me, as has the ongoing work on the integration of all the specialities. I never expected this small group to go so far and that everyone would know the paper in *Nature* and I would have people coming up to me in meetings saying, 'Ah now we can see you for real.'"

Van 't Veer has presented the gene profiling story many times now, and continues to do so – "It's because people thought microarray technol-

*For more on gene expression profiling and breast cancer, see *Nature* 415:530-536 and *Journal of Clinical Oncology* 23:1631-1635



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ogy would bring advances never seen before and it shows that all the billions of dollars invested in universities and institutes can make fast progress."

The NKI, she says, soon realised it could not attract funding to take the 70-gene test (MammaPrint) and other research to market, and decided to set up a spin-off company, namely Agendia, with van 't Veer and Bernards as two of the directors. The company has grown rapidly and now numbers over 30 employees (and much credit must go to a commercial director poached from British biotech giant, Amersham). The major investors are Europe-based, while some funding arrives via the European Union Framework programme. Although a bit hesitant at taking the plunge into commercial life, van 't Veer feels that such start-ups are critical for rapid realisation of the results of translational research, commenting that larger companies are not as fleet of foot when it comes to innovation. "This type of academic spin-off is common in the US but not so much in Europe," she notes.

Further, she says that having been at the centre of the profiling research, she felt a responsibility to continue to play a key role, not least to drive the quality and robustness of the use of microarrays and DNA diagnostics, and to benefit NKI by collaborating in trials. There has, however, been a steep learning curve in dealing with the venture capital community and also with regulatory processes, while there have been quite a few criticisms levelled at the work. She and colleagues have had to fend off accusations of conflict of interest between the NKI and Agendia, for example.

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Private profile. Van 't Veer with Agendia co-directors Bernhard Sixt (left), and René Bernards

"But as we look at more complicated diagnostics and targeted therapies, such as the EGF receptor drugs, it's hard to do the development quickly," she says. "Small companies have a role to play in being close to academic centres and moving things out into the commercial setting."

Agendia now buys in custom microarrays from Agilent (to which Rosetta had sold its technology) and is both a fully commercial supplier of MammaPrint and other products, and a clinical trials collaborator with the NKI and other research organisations. Trials involving the 70-gene signature include a 500-patient cohort started in 2004 in the Netherlands, where the test result is given in addition to other information on risk of recurrence. "What we are evaluating here is what patients and doctors do with the information," says van 't Veer. Another trial is the major European Union-sponsored MINDACT (Microarray for Node Negative Disease may Avoid Chemotherapy) prospective project, run by the EORTC (European Organisation for Research and Treatment of Cancer) and TRANSBIG, the translational research network of the Breast International Group (see also *Cancer World* 7).

Other critics have felt that gene expression signatures such as the Amsterdam one are being rushed out too quickly, are over-optimistic, and do not pass methodological 'litmus tests'. One recent paper asks, for example, whether a doctor would be "prepared to withhold adjuvant chemotherapy in a young patient with a node-negative, HER2-positive breast cancer and a good-prognosis signature". Van 't Veer and colleagues, such as Martine Piccart, founder of TRANSBIG, report that independent validation of the Amsterdam signature is more than good enough to proceed with prospective clinical trials, while recognising that refinements and new signatures are bound to arrive sooner rather than later.

Van 't Veer adds that a group in Rotterdam has come up with near identical results using a different microarray platform, and that different mathematical techniques used have all been found to point at the same tumour subgroups, i.e. low- and high-risk groups. "As we have more tumours analysed we will be able to have more subgroups. I do realise the 70-gene signature can be improved – but to do that we need to do trials such as MINDACT."

Outside of trials, van 't Veer says that "technically the profile can be used now in clinical practice – with Agendia we have shown you can carry out robust and reliable testing using microarrays. But it's not that simple. The same person who set up the ISO certified lab at the DNA diagnostics department at NKI has moved to Agendia to set up a similar approved lab – but there are still only a handful of such laboratories in the world that can do microarray work to this standard." That of course is where the 'black box' system comes in. Colorectal cancer will be the next tumour type to benefit from this type of profiling, she says, noting that leukaemia already has a number of tests available, albeit for a much smaller patient population.

The rapid availability of the Agendia test has

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taken some by surprise, it seems. While the company has approval to run MammaPrint in Europe, they are waiting to see whether additional approval by the Food and Drug Administration (FDA) will be required before it – and other such tests – can be used in the US. Agendia, which has a US partner (the Molecular Profiling Institute) for MammaPrint, received a letter from the FDA last year expressing concern that the test may require clearance as a diagnostic device. Presenting a united front, van 't Veer and a representative from Agendia's main competitor – US firm Genomic Health, which is actively marketing its Oncotype DX breast cancer test – shared a platform at the recent American Association of Cancer Research conference, and she says that discussions with the FDA are planned.

Some pharmaceutical companies, meanwhile, initially gave the test a lukewarm reception, according to van 't Veer, as the technique could potentially cut the market for their 'blockbuster' drugs. "But they are realising that healthcare systems just cannot pay for expensive treatments such as Herceptin for everyone," she says. "We need to come up with more molecular tests that show who will benefit from these drugs – and the FDA is thinking along these lines for its approval process." Oncologists in private practice, who, in some countries, are paid per course of chemotherapy, will also be affected by new genomic approaches.

Outside of her immediate work, van 't Veer is involved with wider healthcare issues in the Netherlands – she's a member of the advisory committee to the Dutch Cancer Society, for which she's currently writing a paper on biomarkers. She is also a member of the scientific research council of the Dutch Ministry of Health, where she is helping to set the agenda for biotech research over the next 10 years.

As a woman, van 't Veer has been more conscious of her gender during her time in the basic science community, which she says is far more male dominated than clinical research. But as a role model, she reckons that some women are put off by the sheer amount of work she does. Recognition outside of oncology came last year, in Oprah Winfrey's magazine, of all places, which included her and Martine Piccart in a feature on 'the five biggest health breakthroughs by women scientists'.

Beyond her personal achievement, this level of public interest says a lot about how the status of molecular pathology has grown since van 't Veer decided to go for that job at the NKI. Once very much a poor relation among oncology disciplines, it is now leading the way into the new era of personalised therapies. And with a Europe-wide shortage of molecular pathologists, and pathologists in general, it is surely a tempting career option for any young oncologist with the determination to navigate themselves into a specialty that is too young, as yet, to have established pathways.

Van 't Veer reckons she's a fairly forceful character, but not aggressively so, and the realities of running a commercial enterprise have certainly been an eye opener. A good clue, though, to her drive for success lies in one of her main hobbies – she's been a competitive rower since her teenage years. Another big interest is contemporary classical music.

Presently, the working arrangement she has with the NKI is to do four days a week for the institute and just one at Agendia. A decision point is bound to come soon as to whether she will do more on the commercial side – she won't be drawn though, "I like doing both." But with Agendia put forward by the EU as one of the most successful biotech firms involved in the Sixth Framework programme – and her desire to see the gene signature tests widely used – in practice, that nominal 'one day' is no doubt already a lot more time in her overall working week.