



Eminent Talent

2006 – The twelfth year

Prof. J.M. (Jozien) Bensing (1950), clinical psychologist at the Netherlands Institute for Health Services Research (NIVEL) and Utrecht University. Bensing demonstrated that the relationships between doctors and their patients can be investigated on a sound empirical basis. She also developed a research method for non-verbal communication that is now used throughout the world.

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I want to turn the art of medicine into science

Nobody should feel ashamed about fear for the doctor. Even the most assertive patient can turn into a lump of jelly in the consultation room, if there is a reason to fear a serious condition. The style of communication between the doctor and the patient plays a key role in this, is the conclusion of Jozien Bensing, professor of Clinical Psychology and Health Psychology. "It is a matter of overrated skills and underestimated problems."

Since the start of the 1980s, Jozien Bensing (1950) has built up the world's largest video archive of consultations between doctors and patients (she was a pioneer in this field). The fifteen thousand odd filmed consultations are the basis for her research. "I must be something of a voyeur, as I find these consultations extremely fascinating", she says in her office at the Netherlands Institute for Health Services Research (NIVEL), where she has been the director since 1985. "You see life in all its aspects. People who tell a doctor about their fear of having a serious disease or an STD or who talk about their fear that things are going wrong with one of their children, it is all there on my videos."

Bensing makes use of American observation methods to completely unravel the consultations. She encodes not just verbal but also non-verbal expressions. A computer-guided system can completely unravel the consultations on the video films. "Down to the level of molecules", says Bensing. "This makes it possible to perform a scientific analysis of such consultations. By doing this I can make the 'soft side' of medicine more evidence based. Bensing views her receipt of the NWO-Spinoza Award as recognition of this. **"Moreover I see it as a recognition of the societal relevance of my research. And that is the most important aspect for me."**

That the communication between a doctor and a patient during a 'bad news consultation' is different from that during a consultation about a twisted ankle is obvious. However that the nature of these consultations can also influence the outcome of the healing process is far less known. Bensing: "The American researcher George Engel once stated that patients have two important needs: 'the need to know and understand' and 'the need to feel known and understood'. You can link two types of doctor behaviour to these two needs. I have discovered that both are required. If a doctor fails to build up a relationship of trust with a patient then the patient will no longer listen to the technical information that the doctor provides."

Is there a lot wrong in the communication between doctor and patient? Certainly, believes Bensing. Yet that is not always down to the 'bluntness' of doctors, she emphasises. "Dutch TV presenter Mies Bouwman once talked in an interview about how she had visited a hospital due to heavy headaches. Two friendly young doctors helped her. They scanned her with a device that made a noise at a certain point on her head. 'Yep, that's one of them' said one of the doctors. Mies could not remember what happened during the rest of the investigation or what the doctors said after that as she was frozen with fear. The only thing that she could remember was that the doctors were dumbfounded when she said at the end of the investigation: 'So I have cancer?' Since then she takes her husband with her every time she sees a doctor. After the consultation he then tells her what the doctor had said. Conclusion: even an experienced TV personality can be unnerved in such a situation!"

From her analysis of the video consultations Bensing has learnt that Mies Bouwman's story is exemplary. Hospital specialists in particular often have difficulty in putting patients at their ease or fail to apply even the most basic principles of communication. However the problem is not solely the responsibility of the doctor; the patient is also responsible for ensuring that important matters are discussed, emphasises Bensing. She observes that doctors need to use the full range of communication skills – both verbal and non-verbal techniques – to get the patient talking, as patients only say what is wrong when they are invited to do so. Bensing: "Patients have their own responsibility. It takes two to tango; a doctor does not have a crystal ball." A doctor can express empathy verbally, but the most effective means is eye contact or allowing a moment of silence. Verbal and non-verbal approaches can sometimes undermine each other. **For example, with the inviting final question 'Is there anything else?' some doctors inadvertently shake 'no' with their head.** "Fatal of course for the communication" says Bensing.

Can communication that puts patients at their ease be learnt? To a certain extent yes, says Bensing, who travels around the world to give continuing professional development courses to doctors. Yet some are more open to this than others.

She observes a striking difference between male and female doctors. "In general men are task-oriented and efficient, whereas women are far more empathic and interested in the patient's story. An example: I have two video recordings each of which concerns a consultation with a patient with a shoulder problem. One shows a male doctor with a male patient, the other a female doctor with a female patient. The outcome is identical – the patient receives an injection in the shoulder – yet the first consultation takes two minutes and the second one fifteen minutes. The male GP is therefore very efficient but with the women a whole world of underlying problems came to the surface."

Bensing wants to know to what extent that extra element plays a role in the healing process. "In the traditional medical world the 'placebo effect' is always somewhat glossed over. Some people feel better when they are given a small ball of bread instead of a drug. Similarly some people brighten up after a doctor's consultation. I want to unravel the mechanism of 'The doctor as the drug'. And the NWO–Spinoza Award will certainly help to realise this. Of course it would be fantastic if doctors could make active use of that mechanism in the future."

Prof. C.G. (Carl) Figdor (1953), immunologist at the Nijmegen Centre for Molecular Life Sciences and the University of Twente. Figdor was one of the first in the world to apply dendritic cell therapy – training the individual's immune system to attack tumour cells – to cancer patients. Furthermore, he played an important role in the development of the Nijmegen Centre for Molecular Life Sciences.

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I want to push back the boundaries of what is possible

Cell biology is a branch of science that has close links with physics and chemistry. Yet Carl Figdor's experience is that if you allow physicists, chemists and biologists to converse at a fundamental level then they soon fail to understand each other. "It took us ten years before we could chat together."

Yet it is clear that such cross-disciplinary work can produce striking results. For example thanks to such work, Figdor (1953) was one of the first in the world to apply dendritic cell therapy to patients. In this technique dendritic cells are modified in the laboratory so that they can teach a patient's immune system to recognise tumour cells. "We isolate these cells from the white blood cells of patients and then teach them to adequately respond to cancer", says Figdor. "At present the technique is still very expensive – the preparation of the vaccine takes place in clean rooms. Now the challenge is to find a way of producing the vaccine so that it is interesting for the pharmaceutical industry. Ideally you should be able to put it in a pot in the cupboard. I want to push back the boundaries of what is possible". For example, I can only realise my ambitions for the vaccine by closely working with chemists: a chemical substance with the same properties as the living cells needs to be developed. Figdor wants to use part of his NWO–Spinoza Award for this. "Chemists need to synthesise the moveable polymers I need. They would probably never think to produce these because they are not biologists. And that is why it is so important that we have learned to understand each other." Figdor's own interest for technology and the technological development of new discoveries undoubtedly plays a role. For example, he currently owns eleven patents for biotechnical findings.

Carl Figdor believes it is pure chance that he ended up becoming a molecular biologist. "I never really knew what I wanted to do, but my father convinced me that biology could well be my thing." After completing his degree in biology he even obtained his teaching diploma. "During a teaching practice at a grammar school I amused the pupils with a mouse maze." Yet in the end research attracted him more and he ended up doing a Ph.D. at the Netherlands Cancer Institute, became professor of Cell Biophysics at the University of Twente and eventually also accepted a professorship in Experimental Immunology at the Radboud University in Nijmegen – the city where he is also scientific director of the Nijmegen Centre for Molecular Life Sciences (NCMLS). "I defy classification as a scientist because I work in a highly multidisciplinary environment and operate over the boundaries of my subject area."

Six years ago Figdor shot to fame with his discovery of the DC-SIGN receptor protein. During HIV infections the protein enables viruses to penetrate dendritic cells. Figdor: "Fascinating cells! At the NCMLS we spend the entire day looking at these cells." They are tree-like, highly-branched cells that act like army scouts within the body. As soon as bacteria or viruses try to enter the body the dendritic cell scrambles and intercepts the intruder. However the receptor protein DC-SIGN can enable a HIV virus to penetrate the dendritic cell. And then it can use the scout to help spread the virus. Pathogenic organisms can then hitch a ride with the dendritic cells to the nearest lymph gland. The T cells that normally take over the combating role there on a large scale instead become infected and the immune system collapses. And with that the spread of the disease through the body becomes a piece of cake. Figdor: "The dendritic cells are therefore used as a sort of Trojan Horse."

Figdor's study into the mechanism underlying the infection of dendritic cells also enabled him to devise new treatment methods for cancer. The successful treatment of cancer patients with trained dendritic cells is one of his most striking achievements. During this immunotherapy dendritic cells are supplied with tumour antigens – pieces of protein from a tumour cell. After coming into contact with these antigens, T cells go and search for all cells with a similar antigen and destroy these.

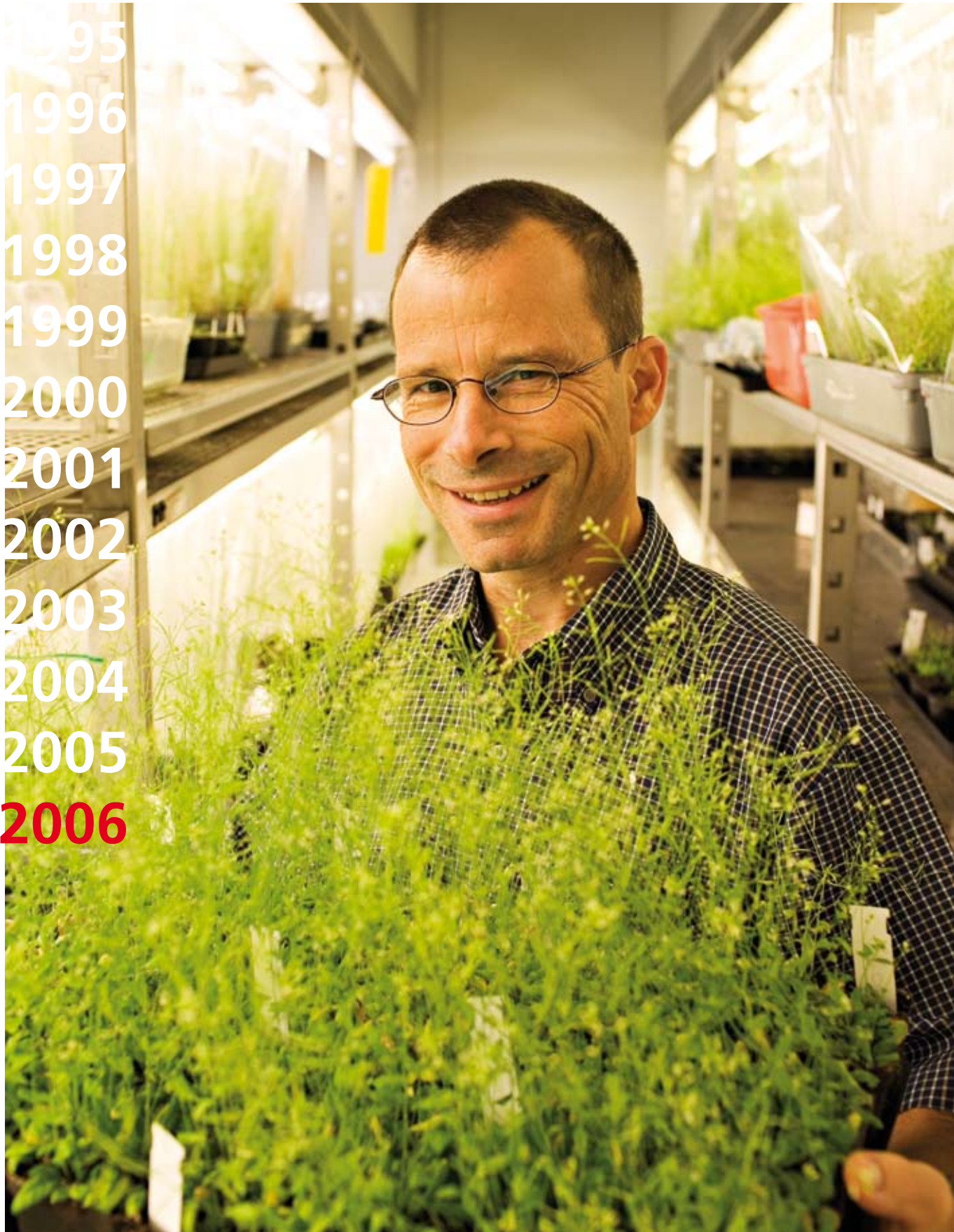
That sounds as if an effective anti-cancer drug is within reach. Figdor: "Not quite! 'Cancer' is an umbrella term for more than two hundred different diseases with a common characteristic: cell proliferation. There will never be one single anticancer drug, rather a drug against certain forms of cancer. Within about fifteen years vaccination against inherited forms of colon and breast cancer must be possible."

Fascination for 'the molecular life behind the cell' is the driving force behind Figdor's work: "A cell is an autonomous unit with its own little factories for energy supply, cell division and waste processing. We also know that in each cell about 5000 genes are active. Yet we know virtually nothing about how the molecules which form this entity cooperate."

Finding this out will require close cooperation between different disciplines. That is why Figdor cooperates in interdisciplinary projects for postdocs. Figdor: "These are necessary! I can get really angry about the fact that it is now possible to complete a high school education without having studied biology and that no scientific education is provided at primary schools!" Within NCMLS intensive master study programmes are also being set up in which highly-promising graduates under intensive supervision are prepared for interdisciplinary research. Intensive communication training programmes are also provided. Being able to effectively communicate with others in the same discipline, but also with other disciplines is, in Figdor's opinion, the key to progress in scientific research. This conviction is what motivated him to be intensively involved in the architectural design of the NCMLS building. Even when the construction was in progress, a large vertical shaft was bored through the building on Figdor's insistence so as to facilitate the communication between the 350 staff on the different floors. "The investment that requires is easily paid back! Let there be no misunderstanding: I want this organisation to become an international top institute. And that is impossible if you shut yourself off from others."

Prof. B.J.G. (Ben) Scheres (1960), molecular geneticist at Utrecht University. Scheres discovered which role stem cells play in pattern formation and growth of plant roots. He successfully demonstrated that many mechanisms in plants are closely related to processes in animals.

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When it comes to stem cells most researchers never think of a plant

Every organism starts off as a single cell. This further develops according to a specific blueprint into a completely functional living organism, which can consist of several billion cells. This is just as true for a humble grass as for an elephant. What makes this possible is the fascinating question that motivates molecular biologist Ben Scheres to carry out stem cell research in plants. And he has made groundbreaking new discoveries.

A schoolboy trip to the Evoluon in Eindhoven set Scheres (1960) on the path towards molecular biology. In the science museum that has since closed he saw an image of a DNA helix on a lighted screen. Scheres: "I just had to find out more about that. I thought it would be fascinating to understand how living organisms could be explained on the basis of a code. And this ongoing curiosity is what drives me."

This passion has carried Scheres via a study in phytopathology (Wageningen University) and a post as a laboratory researcher in genetics (University of Ghent) to a professorship in molecular genetics at Utrecht University. There he narrowed down his study to the root of a small plant: *Arabidopsis thaliana*. He unravelled the regulatory mechanisms responsible for the development of stem cells in the root tip (publications in the journals *Nature*, *Science* and *Cell*) and translated this information into a computer program. "Look at this picture", says Scheres, while he enthusiastically conjures up an image of a rapidly growing root tip with a few mouse clicks. "You are watching a virtually growing system in which genes became active or inactive and in which the production and transport of substances is visible. It is a self-organising system that via simple interactions leads to a stable outcome. And thanks to the computer model we can understand this process as well."

About twenty years ago a lot was already known about molecular development in animal systems. And because relatively little was known about the developmental biology of plants, Scheres decided to specialise in this. "Throughout the world most researchers never think about plants when it comes to stem cells." Scheres discovered the role played by stem cells in the pattern formation and growth of the *Arabidopsis thaliana* root. He also demonstrated that there are strong similarities between the mechanisms active in both plants and animals. "You see the same principles, molecules and genes at work whether you study a sponge or a mammal. So was the development of these mechanisms a one-off event or did they arise on more than one occasion by chance?", he explains during a tour of his laboratory, where countless *Arabidopsis thaliana* plants at various stages of development and ready for dissection can be found between microscopes and an arsenal of molecular biology equipment. "The most important similarity is that all multicellular organisms program in a similar fashion via certain proteins, 'transcription factors' which activate or inactivate a DNA region. The only difference is the type of proteins that plants and animals use for this. **Conclusion: plants and animals have found a similar solution during the course of evolution but – very important – they have realised this independently of each other.** Therefore perhaps this is a necessary principle for life.

To prove this beyond doubt we would have to be able to look inside the cells of aliens.” Further Scheres discovered that stem cells in plants are ‘kept’ according to the same principles as in animal stem cells. And that this continuous stem cell state seems to be driven by a common mechanism. Fascinating facts, even if they are difficult for a lay person to understand. But what is the use of such information? Scheres: “We want to know what makes a stem cell a stem cell but also what makes different stem cells different.”

Everyone knows that stem cells are a hot issue. Stem cells are undifferentiated cells from which, in principle, all types of cell can grow. They are therefore viewed by the scientific community as a possible solution to many complex diseases. For example, stem cells could help diabetes patients to resurrect their insulin production and could ensure dopamine production in Alzheimer patients. Yet if we remain in the plant kingdom: Scheres could use these insights to design completely new plants for the agro industry. However this is not his primary interest. He would rather leave the work of developing practical applications to others. “Not that I want nothing to do with it. We already own several patents and have applied for a few more. You never know, we might still make our fortune one day.”

Research on stem cells could also reveal why some organisms live much longer than others. Scheres: “If an alien were to be discovered with stem cells that enabled it to become a thousand years old then everyone would be fascinated by it. Yet we already have organisms that can live for two thousand years here on earth. Sequoias that grow in the US carry the same stem cell population in their crowns more than one hundred metres above the ground, as which they started to grow with at the time of Christ’s birth.”

Comparative research between plants and animals could also reveal which genes deserve extra attention. Scheres: “We have about 30,000 genes. If we could find out which genes are most relevant for developmental biology then we could focus our research on these. That is the most interesting puzzle at present.” With this in mind Scheres developed a method to kill individual cells in a growing root with the aid of a laser. By combining this approach with the targeted knocking out of specific genes, he discovered which cells were responsible for which biological processes. “Of course that is donkey work. **For ninety percent of the time you only get pleasure from being technically thorough.** But the ten percent which gives the greatest pleasure is the inspiration: when several aspects fall into place and you can see how something works. Just like the moment of pleasure when after hours of fiddling, you solve the Rubik’s cube.”

How far has Scheres got with his quest, thirty years after his experience in the Evoluon? “I know more, but in terms of what I understand perhaps a bit more. If you understood everything then you would be able to simulate the entire process, from the first cell to the development of an entire organism. Yet even if we were to get so far, we would still not be finished: there are always more puzzles to solve in science!”

Prof. J.J. (Jan) Zaanen (1957), physicist at Leiden University. Zaanen made an important contribution to the understanding of the concept of high-temperature superconductivity. This is the phenomenon where the electrical resistance of some materials suddenly disappears at temperatures far above absolute zero.

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Disney World for adults

For the average man on the street, quantum mechanics is an inaccessible, almost mystical temple of incomprehensible wisdom. But not for Jan Zaanen. The Leiden professor of Theoretical Physics knows no greater pleasure than wracking his brain about problems that go way beyond our intuitive and comprehensible reality. “Quantum mechanics is the Disney World for adults!”

“We humans are 97 percent apes. We like to sit next to each other, groom each other, and eagerly seek the best food as well as the best partner to produce our offspring. Of course I also enjoy driving a car or looking at pretty women, but what I enjoy so much about quantum mechanics is that it is completely independent of that ape-like life. It concerns the world underlying all of that”, says Zaanen in his office at the Lorentz Institute. “Plato and Aristotle were already talking about such a world that lay beyond our senses. And 2500 years later we have discovered that such a world can only be penetrated using mathematical concepts. These help you to find the way, just like walking through a wood or driving in a car through a busy town.”

Jan Zaanen (1957) has been snooping around in the ‘world behind everyday reality’ for some twenty years now. A radical new perspective which brought him a lot of fame was his theory about the existence of stripes: wave-shaped patterns of electrical charge, which he is firmly convinced play a role in high-temperature superconductivity. A distant predecessor of Zaanen at Leiden University, physicist Kamerlingh Onnes, established back in 1911 that certain materials lost all of their electrical resistance at a temperature just above absolute zero. Three-quarters of a century later, just when Zaanen was about to gain his doctorate in physics, it was discovered that superconductivity could also arise in certain copper oxide compounds at much higher temperatures. Superconductivity at room temperature would lead to innovations in numerous areas. Finding an explanation for this new, highly-promising phenomenon of high-temperature superconductivity was right up Zaanen’s street. For example, he established that in thin layers of copper atoms, electrons can move rapidly if they are located in long stripes alongside the copper atoms. Individual electrons were found to form so-called Cooper pairs which in turn were assimilated into a collective moving entity of rapidly-twisting stripes. A sort of quantum fluid that made the unimpeded flow of electrons possible. Initially Zaanen’s ideas were heavily criticised but in recent years an increasing number of experiments have upheld his views.

Meanwhile Zaanen reluctantly admits that after twenty years in the field there is still no general theoretical explanation for the phenomenon of high-temperature superconductivity. A bitter disappointment? “No not really! Einstein also wrestled for more than twelfth years with concepts such as the uniformity of slow and heavy matter, before all of the elements fell into place in his amazingly beautiful General Theory of Relativity. For twelfth years he did not really know what he was doing, yet he still followed the path of beauty which he saw. And from this emerged the theory which can still send chills down your spine, with predictions that were later demonstrated to be correct. The Yang-Mills theory arose in a similar fashion: in 1957 it appeared to be completely wrong, yet due to its fascinating beauty physicists continued to work on it.” Zaanen does not miss such a beauty in the theories concerning high-temperature superconductivity.

Although experimental physicists are still hard at work producing evidence for the stripes theory, Zaanen is now preoccupied with completely different issues. On his desk is a copy of the recently published Ph.D. thesis 'Quantum Liquid Crystals' from the Serbian Ph.D. student Vladimir Cvetkovic. Extremely complex and the result of years of cooperative work. In brief this research concerns the possibility that quantum versions of liquid crystals can be formed in highly-organised quantum fluids of copper oxide – classical liquid crystals are the secret behind flat screens. "Everyone is just talking about stripes, but I now find the predictions made in this thesis far more interesting. However, it costs an experimental physicist five years and an awful lot of money to measure our predictions and then to formulate answers to them." In this study as well, however, the effect of collectivity at the quantum mechanical level also takes centre stage. The collective entities exhibit an entirely different behaviour from individual particles. Zaanen: "That is still one of the basic questions in need of an answer in this field."

Whether the Ph.D. student will attract the same attention as Zaanen remains to be seen. In about 1990 Zaanen had more or less given up on his idea of stripes ('then absolute heresy'), due to a lack of interest in the scientific world. Yet in the US, where he went to work as a researcher at AT&T Bell Laboratories, he was encouraged to pursue his idea. "In my experience, you need to have a beautiful picture for your idea. The image of stripes captures people's imaginations", says Zaanen. **"I went against the flow and that gained me recognition. That also has its disadvantages, as from that moment onwards there are an increasing number of less important issues that continually interrupt you."** As a professor he is happy in his role of helping young people and warning them for the pitfalls. Yet he sometimes regrets not having the opportunity to get down to 'core business' without being interrupted; "Just like the Russian recluse Grigori Perelman who refuses to talk to anyone, but on his mother's settee in St Petersburg solves the Poincaré theorem!"

Zaanen wants to use the NWO–Spinoza Award for research into the as yet poorly understood phenomenon of quantum critical fluids, which might play a role in superconductors. Is Zaanen really motivated by all his detective work yielding something of general use? Zaanen: "That is such an ape-like question: can we soon drive even faster in a car or purchase an even better laptop? No, I am not in the slightest bit interested whether you can do something with the research or not. If I can produce something that ends up in physics textbooks then I will be more than satisfied. But first and foremost I just want to find out how things work."



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