

## Van Loghem Laureaat 2010 - Prof. dr. Jacques J.M. van Dongen:

"All research must aim at improving diagnosis and therapy"

*"Our research must always contribute to the health of our patients, in the most direct manner possible", says Van Loghem Laureate 2010 prof. dr. Jacques J.M. van Dongen (1955). He is adamant when it comes to the purpose of research conducted at the department of Immunology at the Erasmus University Medical Center Rotterdam. This is remarkable, given the fundamental nature of his group's research. The impressive palmarès of the scientist shows how he turns his convictions into reality. "It is extremely rewarding to see research results applied in patient care."*

Jacques van Dongen keeps his eyes on the ball. As a high school student, he already pushed himself to obtain the grades that would allow him to study at his medical faculty of choice, being the Erasmus University Rotterdam. "It was the place to be. The faculty was young, ambitious and one of the few places where students could actually conduct research themselves", he says. Medicine was the only option for him. "All my life I have been intrigued by nature. As a child, I spent many hours dissecting animals, trying to figure out why they are built the way they are. But I always knew that in my professional life I wanted to contribute to human health."

### Breakthrough study on MRD

While studying Medicine, he worked as a research assistant at the departments of Pathology, Microbiology and Cell Biology & Genetics. A few months before receiving his M.D. degree, in 1981, Prof. Benner offered him a job at what is now the department of Immunology. From then on, he has worked in the field of immunology research, with special focus on human T- and B-cell differentiation as well as lymphoid malignancies and immunodeficiencies. Together with Herbert Hooijkaas he initiated the Immunodiagnostic Laboratory of the Erasmus University Medical Center in 1985. Today it is one of the leading centers for immunodiagnostics and translational research of lymphoproliferative diseases and immunodeficiencies in Europe. "We are always working towards better or quicker diagnoses, better classification of patients and more adequate monitoring of therapy effectiveness", he says.

Illustrative for this assertion, as well as one of the highlights of his career, is a large study on the prognostic value of minimal residual disease (MRD) in acute lymphoblastic leukaemia (ALL) in childhood. The study, executed in four European countries, was coordinated from Rotterdam. "We monitored 150 patients with childhood ALL who were treated according to national protocols. We collected bone-marrow samples at up to eight time points during and after treatment. With sensitive PCR-techniques for the detection of MRD, we gained insight in the effectiveness of cytotoxic treatment. Already in the first three months of treatment we could distinguish patients with good prognoses from those with poor prognoses. In fact, there are three different risk groups: 43% were in a low risk group with a relapse rate of only 2% in three years, 15% were in a high risk group with a relapse rate of 75% and 43% were in an intermediate risk group with a relapse rate of 23%."

### Made-to-measure therapy

The results were published in the Lancet in 1998. They caused quite a stir. "MRD outclassed all other prognostic markers", Van Dongen says. "Also, the PCR-techniques were revolutionary." The results were challenged, but there was no fault to be found. "Our results were both extremely sensitive ( $10^{-4}$  or  $10^{-5}$ ) and reliable. Laboratories that adopt our technical directive arrive at the same results, independent of country or analyst", says Van Dongen. He stresses the importance of well-founded diagnostic methods with a high level of reproducibility, an area in which, according to Van Dongen, much remains to be improved. "Thanks to the quality of our research, we were able to bring about a real change in leukemia therapy. In our ambition to save lives we treat all children with maximum intensity. But such treatment has many serious side effects. It frequently leads to permanent organ damage. Since we are now able to single out the children with a very low relapse rate, we can reduce the therapy for this group. This however is an extremely difficult decision. Doctors are, understandably, afraid a child relapses because it did not receive the most intensive treatment. Only after eight years of

promoting our research results, the Stichting Kinder Oncologie Nederland (Dutch Childhood Oncology Group) decided to comply with a lighter therapy for children with an excellent early treatment response. This brave decision will be beneficial to many children."

## IKAROS

One study led to another. Van Dongen: "Why do some children respond so well to treatment, whereas others don't? What is the difference between them? Could it be explained by a variation in the DNA? Researchers at the Radboud University in Nijmegen compared the genes of children with childhood ALL. They focused on the MRD-based intermediate group of 43% of children with a relapse rate of 23%. Since three quarters of this group do not relapse, there is a lot to be gained if treatment can be made more to measure for them."

The team profiled the genomes of 40 childhood ALLs at high resolution and detected multiple genetic lesions affecting genes involved in cell cycle regulation and B-cell differentiation. Defects in the 'IKAROS-gene' appeared to be crucial, says Van Dongen: "Deletion of this gene, together with MRD-diagnosis, proves to be very accurate in predicting relapse in childhood ALL. In the next Dutch ALL treatment protocol, this combined diagnostic information will become important for guiding therapy intensity. Such individualized medicine will increase quality of life."

## Lymphoma diagnosis and immunodeficiencies

Where the introduction of the PCR-technology was necessary for the MRD-findings, the introduction of micro array technology made the profiling of the genomes possible.

"Technology enables us to take giant steps", concludes 'early adopter' Van Dongen. "We get closer and closer to a thorough comprehension of the immune system, especially of the development and functioning of the T- and B-lymphocytes, one of the key research topics at my group."

Van Dongen relates to another European study he coordinated. "If a lymph node is swollen, this may indicate an infection or a cancer. But how do we know whether we are dealing with a cancer or an infection? We can find out by determining if the cells are all alike, in which case it's a cancer. This is, however far from easy. We discovered that all T- and B-lymphocytes have a different receptor. PCR-analysis of the receptor-genes can tell us quickly whether we are dealing with clonal cells or not. This allows to start therapy at short notice."

The knowledge of B- and T-lymphocytes can also explain why someone suffers from immunodeficiency. Van Dongen: "Patients with a serious infection that do not respond well to antibiotics may have a genetic disorder, preventing them to develop the B-cells or T-cells necessary to battle the infection. They need to receive antibodies permanently or even need bone marrow transplantation. In Rotterdam, we discovered four new types of immunodeficiencies in the last four years, a rather impressive result."

## Sources of inspiration

Van Dongen contributed to more than 500 manuscripts, coordinated seven European networks in the field of diagnostics in hemato-oncology and immunology and his citation index exceeds 12,000. He is closely connected to researchers all over the world and could have pursued his career *n'importe où*. But he always stayed faithful to Rotterdam. "The facilities are excellent and the team is brilliant", he says. "The members inspire, correct and challenge me everyday. Also, in Rotterdam we are blessed with the close cooperation of, among others, internists, pediatricians, hematologists and pathologists; an immunologist never works alone, for translational research we always depend on others." A special source of inspiration is Mrs. Van Dongen-Melman, a renowned pediatric clinical psychologist. "She explained to me how damaging cytotoxic treatment can be to children, thus urging me to really become an advocate for made-to-measure therapy."

For the next five to ten years, Van Dongen already has his plans worked out. "I have plenty of ideas for projects that can be successfully executed in this period." Although the subjects remain undisclosed, one may safely assume that they are aimed at improving diagnostics and therapy.

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