

Dick W van Bekkum - 1925-2015

On July 17 2015, Dirk W. van Bekkum (Dick), one of the pioneers of bone marrow transplantation, one of the giants who helped to shape the discipline of stem cell transplantation, has passed away after a short illness. He had begun making plans to celebrate his upcoming 90-ieth anniversary 2 weeks later.

### **His life**

Dick van Bekkum was born in the Netherlands Indies, today Indonesia, where his father worked. He graduated as an MD at Leiden University (1950) and completed his thesis on on d-animo acid oxydase in 1952 cum laude (with honors) after having spent a year at the Department of Biochemistry at Oxford with Professor Rudolf Peters.

Dick worked initially as head of Radiobiology at the Medical Biological Laboratory (MBL) of the National Defense Organization TNO in Rijswijk. But Dick with his flow of scientific ideas and plans considered the conditions at MBL too restricted for him so that he decided to establish his own institute next doors. In 1960 at age 35 Dick founded the Radiobiological Institute of the Dutch Health Organization TNO in Rijswijk and became its director. Before the building was completed he already moved into the basement of the building and started doing experiments, he was just too impatient to wait any longer. This institute would become one of the leading scientific institutions with prominent scientific programs on radiobiology, bone marrow transplantation, stem cell research and experimental leukemia research. Radiobiology had become a hot topic after the atom bombing on Hiroshima and Nagasaki at the end of World War II and radioprotection of the bone marrow syndrome following excess radiation exposure would become a central scientific subject of his research.

The atmosphere in the Institute typically carried the Van Bekkum stamp. There was an ambitious spirit of team work and scientific entrepreneurship. The seminar evenings preceded by the Indonesian Rijsttafel were famous and attracted attendees from far away as scientists elsewhere did not want to miss the stimulating presentations and discussions. There was also a lot of fun and humor in the air of the institute. Cabarets would be produced at party evenings in which Van Bekkum himself would play a major part. Table tennis during lunch hours would offered a popular break. Dick himself was actively participating in these activities.

The international workshops that he organized in the Institute to assemble scientists with opposing viewpoints or conflicting research data were unique and are memorable. For instance the Workshop on In Vitro Colony Forming Cells held in 1971 at the exciting time of the emerging field of progenitor cell research prompted researchers like Ray Bradley, Don Metcalf, Malcolm Moore, Dov Pluznik, Ernest McCullough, John Till, Fred Stohlman and others to bring their culture sytems to the lab, actively perform their experiments at the bench and demonstrate their assays for data comparisons. These were unique events.

In 1966 Dick van Bekkum became Professor of Radiobiology at the newly founded Medical Faculty of Erasmus University Rotterdam and in 1967 he also became Professor of Experimental Transplantation Biology in Leiden.

In 1973 Van Bekkum was elected to the Royal Academy of Arts and Sciences of The Netherlands. In 1987 he received a royal honor: Knight of the Order of the Lion of the Netherlands. In 1990 he received the highest award of the City of Rotterdam (Wolfert van Borsele Medal).

Dick has been involved in the early phase of the foundation of European Bone Marrow Transplantation Group, CIBMTR (International Bone Marrow Transplantation Registry), the International Society of Experimental Hematology, and he is also one of the founders of the Dutch Society of Immunology. Van Bekkum was one of the founders of EORTC (European Organization for Research on Treatment of Cancer) and served as its President from 1969-75.

In 1975 he was awarded a Fogarthy Scholarship which he spent at the National Cancer Institute in Bethesda. He took that opportunity to study the US National Cancer Program "Conquest of Cancer" that had been initiated 5 years before, in particular the functioning of the Comprehensive Cancer Centers. Upon his return he initiated the organization of a network of similar Centers in the Netherlands and founded in 1977 at Rotterdam the first "Comprehensive Cancer Center" of which he was Executive Director for 20 years.

After retiring from TNO Van Bekkum was cofounder with Dinko Valerio and Bob Löwenberg of the biotech company IntroGene to develop gene therapy for treating stem cell diseases and cancer. In 2000 IntroGene merged with U-BiSys BV (Utrecht) to become Crucell BV which currently develops vaccines and monoclonal antibodies. In 2010 at age 85, he founded Cinderella Therapeutics the first not-for-profit organization in the Netherlands that would promote the availability of orphan drugs for an acceptable price. Cinderella pursued an innovative approach to tackle the commercial business model of Pharma industry and eliminate obstacles to access to orphan drugs for patients .

Dick van Bekkum has written several books but the book Radiation Chimaeras published 40 years ago in 1967 by Dirk van Bekkum and M. J. de Vries can be seen as the "Bible" of the Experimental Bases of Bone Marrow Transplantation. The book discusses the discovery of hematopoietic chimerism resulting from intravenous injection of bone marrow cells into lethally irradiated recipients, the comparative pathology and immunologic complications after stem cell transplantation, the basis of pretransplant conditioning with radiation, antigenic differences between host and donor, stability of chimeric state and various transplantation methods. It describes acute graft versus host disease and secondary disease, and their clinical laboratory and pathologic presentations.

The Van Bekkum Lecture at the annual scientific meeting of the EBMT Congress has been established in honor of his formidable contributions to stem cell transplantation science.

Dick is survived by his 4 daughters, Marion, Pleuntje, Joos, Nienke, and 11 grandchildren and several great grandchildren, and his lifetime companion, his wife Ada.

## **Scientific highlights of Dick van Bekkum – a history of transplantation and stem cell research**

### **The foundation of hematopoietic stem cell transplantation**

Van Bekkum simultaneously with workers in Oxford and San Francisco, published in 1956 the first convincing evidence for the cellular mechanism –that is the occurrence of chimerism– to explain the protective effect of bone marrow transplantation (BMT) in lethally irradiated animals.

Van Bekkum was the first to report that engraftment and the degree of chimerism is not only dependent on the degree of myelo-lympho-ablation induced by the conditioning of the recipient, but also increases with the number of bone marrow cells transplanted, and that for the engraftment of allogeneic marrow many more cells are needed than in the case of syngeneic marrow.

During the period 1956-1966 his laboratory, in collaboration with O. Vos, L.M. van Putten, H. Balner, M.J. de Vries and G. Mathé (Paris) produced the by now classical description of the pathology and the pathogenesis of Graft versus Host Disease (GvHD) in mice, rats, monkeys and man and established the similarity of GvHD with transplant rejection and cellular autoimmune reactions. Using parent to F1 and the reverse donor-host combinations in mice he provided proof of the mechanism of “secondary disease” being due to an immune attack of the grafted lymphocytes on the host tissues and demonstrated quantitatively the direct relation between the number of grafted allogeneic lymphoid cells and the severity and incidence of GvHD. He also showed that the bone marrow of monkeys like that of man contains a much higher proportion of GHD initiating lymphocytes than that of rodents, which explained the difference in patterns of GvHD between these species.

Accordingly, van Bekkum showed, first in mice and later in rhesus monkeys and dogs that selective elimination of (PHA reactive) lymphocytes from the allogeneic graft could effectively prevent GvHD. For this purpose he had developed with Karel A. Dicke a method for the purification of stem cells on discontinuous albumen density gradients. The fractions enriched in stem cells were depleted of lymphocytes. They demonstrated in several animal models that successful engraftment of T cell depleted allogeneic marrow requires a somewhat stronger immunosuppressive conditioning regimen. These fundamental relationships were subsequently confirmed in pediatric patients in collaboration with Leo Jan Dooren and JaakM. Vossen (Leiden) and in adult patients in collaboration with Bob Löwenberg (Rotterdam).

### **Clinical translation of stem cell transplantation concepts**

During the years 1966-1976 Dick van Bekkum and his team demonstrated that anti-lymphocyte serum (ALS) effectively prevents GvHD and mitigates existing GvHD in mice as well as in monkeys. This led to the application of ALS in various conditioning,

and post-transplant regimens and its use for treating patients with GvHD. In the course of his studies on the temporary immune deficiency that develops following allogeneic BMT, especially during GvHD, van Bekkum became interested in the role of the thymus in these processes and in similarities with some of the congenital immune deficiency diseases of children, in particular severe combined immune deficiency disease (SCID). At that time SCID was thought to be caused by a developmental defect of the thymus. Based on their observations in hematopoietic chimeras, neonatally thymectomized animals and autopsy material of SCID patients, van Bekkum et al postulated that SCID was instead due to a defect of the hematopoietic stem cell, resulting in failure of thymocyte precursor cells to mature in the thymus into competent lymphocytes, and consequently that cure of these children should be possible by transplanting stem cells from a normal donor.

In 1967 the team of Vann Bekkum, Jon van Rood, and the pediatricians Leo Jan Dooren and Jaak Vossen performed the first successful allogeneic BMT (with purified stem cells which prevented GvHD) in man in a baby with severe combined immunodeficiency (SCID) in Leiden. Baby Marijt would grow up with healthy marrow cells from a sibling donor. A US team led by Robert Good also succeeded at the same time to transplant an infant with SCID in Minneapolis. Subsequently, BMT became a standard treatment for patients with SCID.

In a separate line of experimental studies the role of micro-organisms in the development of GvHD was investigated by van Bekkum, initially with Dick van der Waay. With the use of germfree animals the histological lesions of GvHD were delineated from those due to infection. Subsequently, it was shown that certain constituents of the Gram negative flora of the intestinal tract exert an initiating or triggering influence on the donor derived immune competent cells, which aggravates or even initiates the GvH reaction. The team showed in mice, dogs and monkeys that bacterial decontamination prior to BMT with nursing of the recipients in isolators, reduces the incidence and severity of GvHD.

### **Stem cell and radiation research**

Having developed the means to concentrate stem cells, van Bekkum and collaborators were the first in 1971 to define the morphological and submicroscopical features of the stem cells in highly purified fractions. They showed that these features were similar for the stem cells of mice, rats, monkeys and man and distinct from those of the so called small lymphocytes, which were at that time thought to be the hematopoietic stem cells. With the arrival of the method of fluorescent light activated cell sorting van Bekkum took the opportunity to further develop the identification of stem cells and early precursor cells. Due to the achievements of coworkers Ger van den Engh and Jan Visser, his laboratory became a leader in this field during the late 70's.

The most recent contribution of van Bekkum relates to the application of BMT for the treatment of autoimmune diseases. Using animal models of arthritis he showed that these diseases can be cured by myelo-ablative treatment and BMT. He also discovered that autologous bone marrow grafts, provided these are T cell depleted, are as effective as allogeneic bone marrow. This finding paved the way for

explorative clinical trials of BMT for treating a variety of severe autoimmune diseases.

From this knowledge of radiation biology van Bekkum contributed important preclinical data in support of BMT. Examples are the determination of the dose correction factor required for comparing doses of fractionated total body irradiation with single dose exposures, and establishing the maximal radiation doses that are tolerated by infant monkeys without causing inhibition of skeletal growth and cataract.

Finally, in response to the uncertainties that arose after the Chernobyl nuclear reactor accident about the safety and the efficacy of the administration of stable Iodine for protecting human fetuses and infants against radioactive contamination, van Bekkum and colleagues carried out a series of studies in chimpansees. The results published in 1997 provide a solid experimental base for protection guidelines in case of radiation accidents.

Bob Löwenberg  
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