THE TOBIAS FOUNDATION: TWENTY FIVE YEARS OF BUILDING HOPE

Tobias Foundation was founded by Marcus and Gunilla Storch in 1992
Their work contributed strongly to Sweden receiving a national stem cell register

TOBIAS
STIFTELSEN

The Tobias Foundation

Stockholm 2018

Dedicated to Tobias

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Foreword

Bo Angelin

The Tobias Foundation was established in 1992 with the purpose "to support the establishment of a Swedish bone marrow/stem cell registry and to support research concerning diseases that can be treated with bone marrow or stem cell transplantation". The Tobias Registry established the same year has today over 100,000 registered donors, estimated to cover a majority of all Swedes in need of a donor. To date, over 900 transplants have been performed involving a donor from the Tobias Registry. More than half of the recipients have resided outside of Sweden, making registry an important partner in the world. In addition, the Tobias Foundation has provided 102 smaller grants to 51 researchers from its establishment through 2007. In 2001, the Tobias Foundation granted a 15-year professorship in stem cell research to Professor Jonas Frisén at Karolinska Institutet.

Since 2008 the focus has been to support longer term research initiatives requiring more substantial funding. The Tobias Prize, a 10 MSEK grant for research during a 5-year period and 0.1 MSEK in prize money was created. The recipients, selected by The Royal Swedish Academy of Sciences have been professor Katarina LeBlanc, Karolinska Institutet (2008), professor Stefan Karlsson, Lund University (2009), professor Hans-Gustaf Ljunggren, Karolinska Institutet (2011), professor Sten Eirik Jacobsen, Karolinska Institutet (2014), and associate professor David Bryder, Lund University (2016).

After 25 years, the Tobias Foundation continues to be a unique player in the support of research within the field of stem cell transplantation. It is also a highly inspirational story of how a family can meet deep sorrow and frustration after the loss of a young son in the most constructive way. This initiative has markedly expanded and improved life-saving medical treatments and promoted the exploration of future therapies based on brave scientific projects. In order to celebrate the 25 years of the Foundation, we have asked active scientists and clinicians led by professor Eva Hellström Lindberg to prepare this booklet, describing the fantastic development as well as some of the most exciting trends for the future. I would like to thank all who have participated in this work, and also to thank Gunilla and Marcus Storch and their family for their marvelous contribution over the years.

Evaluation of clinical allogenic stem cell transplantation and other cellular therapies for patients with hematological diseases

Per Ljungman, Mats Bengtsson, Gunnar Juliusson, Stephan Mielke

Background and European statistics

Allogeneic hematopoietic stem cell transplantation (HSCT) has been used for more than 40 years to treat patients with mainly hematologic malignancies. During this time, the number of patients undergoing allogeneic stem cell transplantation has continuously increased. In 2016, 263 patients underwent HSCT in Sweden and since the first transplant performed in Sweden 1975, approximately 5500 patients have been transplanted. The activity is increasing worldwide. In 2015 more than 17000 transplants were reported to the European Society for Blood and Marrow Transplantation (EBMT) registry, and more than 8000 US transplants to the Center for International Blood and Marrow Transplant Research (CIBMTR). An increasing number of transplants are performed in China, India, Brazil, and many other countries all over the world.

The main indications and the respective annual numbers of European transplants for these diagnoses are acute myeloid leukemia (6000), acute lymphoblastic leukemia (2500), myelodysplastic syndromes/myeloproliferative diseases (2500), and lymphoma (1500). In addition, an increasing number of transplants are performed for non-malignant diseases such as aplastic anemia, sickle-cell disease, and immunodeficiencies (together 2000).

During the first two decades of transplant activity almost all transplants were performed from matched sibling donors. Today more than 8500 patients are annually transplanted from volunteer unrelated donors, as compared to 5800 patients transplanted from matched sibling donors. A recent development is the increasing use of mis-matched usually haploidentical family donors, lately around 2000 patients per year receive this type of transplants.

Another important development is the availability of different stem cell sources for transplantation. The original stem cell source used during the first decades of transplant activity was bone marrow. Today more than 13000 transplants are annually performed with peripheral blood stem cells compared to 3700 with bone marrow. A small proportion of transplants mainly in children are performed with cord blood cells.

Donor registries

The first register of unrelated donors was created in the UK in 1975 with the help of Shirley Nolan who had a son-Anthony - diagnosed with Wiskott-Aldrich Syndrome with transplantation as the only cure. The Anthony Nolan Trust was the first donor registry to give access for international recipients to its donors. The success of the Anthony Nolan Trust paved the way for similar registries. Jon v Rood in Leiden was the pioneer that created the Bone Marrow Donors Worldwide, a global catalogue of HLA phenotypes, now operated by WMDA, giving transplant centres worldwide the possibility to perform preliminary searches. There has been a tremendous increase in the number of volunteer unrelated donors in registries all over the world. Currently more than 32 million donors and cord blood units are registered in 132 different registries in World Marrow Donor Association. The annual rate of donors now exceeds 2 million. The majority of the donors are registered in Europe and the Americas providing more than 86% of available donors. More than 16 000 HPC products are shipped each year and 50% of those cross an international border.

The Tobias Registry started in May 19 1992 and is owned by Stockholm Care AB. The start was possible by equal financial support the by Stockholm County Council and the Tobias Foundation. The support from the Tobias Foundation was in the form of a loan that was paid off until 2006. The Stockholm County Council then became solely responsible for the operations of the Registry. Since 2009 all regions participate in the funding after decisions in the Swedish Association of Local Authorities and Regions (SKL).

Between 1992 and 1996, 40 000 donors were recruited to the registry and for several years no new donors were added. In order to maintain a donor pool of 40 000, a limited number of donors were added in 2000 to replace donors who had been deleted for health issues or for reaching the upper age limit of 60 years. At the end of 2010 more than 90% of the donors were over the age of 36. In 2012 a new strategy was developed to focus recruitment on younger donors (18-30 years), and to increase the level of HLA typing. The presence on social media was pivotal to reach out to a younger population and since 2013 60 000 new young donors have been recruited, resulting in more than 105 000 available donors. The level of HLA typing has also improved. From the beginning only HLA A and B were typed by serology. In 2000 HLA DR typing was starting to be performed, and in 2005 HLA C typing was added in selected donors. The resolution was intermediate but allele matching could be predicted with bioinformatics. New studies then showed that allele matching for HLA ABC and DRB1 DQB1 was superior with regard to transplant outcome, and since 2013 all new donors are typed at all 5 loci at high resolution, from 2015 also including HLA DPB1.

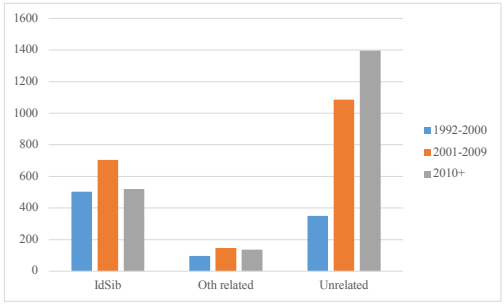
The first matching donor was identified in the Tobias Registry already in the first year, 1992. During 1993 and 1994 only a few donors were identified but in 1995 thirty transplants were performed with grafts from Tobias Registry donors. Until now more than 900 patients have been given a second chance trough a transplant with donated cells from the Tobias Registry. Of the transplanted patients 48% reside in Sweden while 52% are international patients.

Patient outcome Swedish allo HSCT

The outcome of allogeneic HSCT over the last decades in Swedish patients are shown in the following graphs (produced with the help of Carmen Ruiz de Elvira, EBMT registry). It should be recognized that the patient populations in the different time periods are not comparable. Most important is the increase in the median age, as shown below.

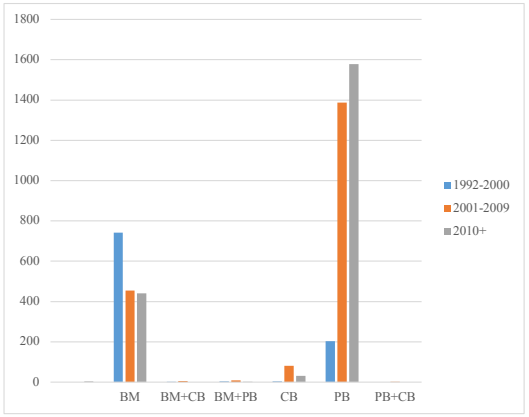
	1992-2000	2001-20009	2010-2016
All patients	32.8	40.1	49.9
AML CR1	38.2	47.6	54.5
ALL CR1	26.7	25.5	36.7

Furthermore, the donor type has changed, the underlying disease risks have changed to more high-risk patients, the conditioning has changed from more to less intensive, and the stem cell sources have changed. Some of these changes are shown in figures 1 and 2.



IdSib = HLA-identical sibling; Oth related = Other related donor

Figure 1. Donor types used for allogeneic HSCT in Sweden 1992-2016



BM = Bone Marrow; CB = Cord Blood; PB = Peripheral Blood Stem Cells

Figure 2. Stem cell sources used for allogeneic HSCT in Sweden 1992-2016

These differences can explain the lack of change in overall survival in the entire patient cohort transplanted during the three periods between 1992-2016, despite major advances e.g in infectious disease management and better matched unrelated donors (figure 3). The non-relapse mortality in the entire cohort has decreased (figure 4) but the risk for disease progression has not decreased and therefore the OS has not improved. One of the main challenges for the future is to develop concepts to prevent relapse of disease

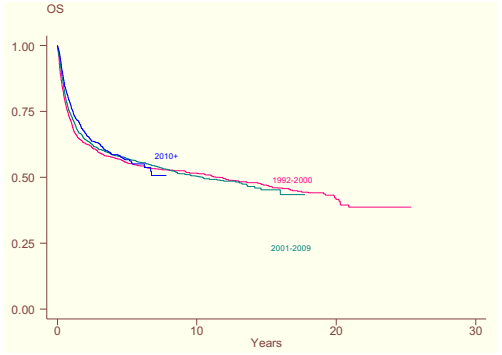


Figure 3. Overall survival in patients undergoing allogeneic HSCT in Sweden 1992-2016

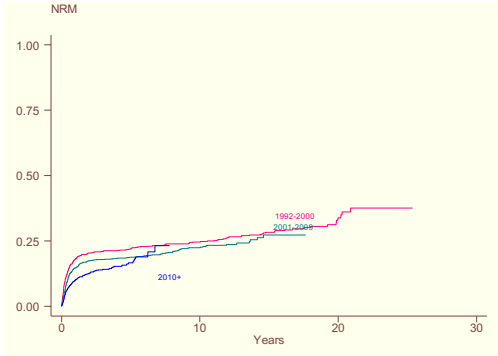
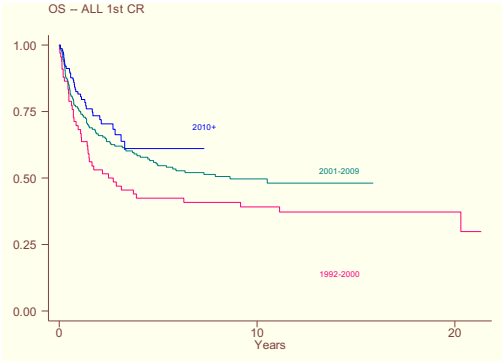


Figure 4. Non-relapse mortality in patients undergoing allogeneic HSCT in Sweden 1992-2016

There are, however, exceptions such as for acute lymphoblastic leukemia for which OS has improved successively during the period (figure 5).



Regional reports

Göteborg: *Sahlgrenska University Hospital: Jan-Erik Johansson (adults)*

Clinical development

Under the leadership of Jack Kutti in collaboration with Jan Carneskog and Berit Lönnqvist from Huddinge, the adult allogeneic stem cell program was started in 1993. Until his death in 1998 Jan Carneskog was the head of the program and he was then succeeded by Mats Brune. Since 2015 Jan-Erik Johansson is program director.

During the first two years only transplants from matched related donors after myeloablative conditioning were performed but in 1995 unrelated donors were introduced. In 1999 the first transplant using reduced intensity conditioning was performed. Cord blood transplants were introduced 2009 and transplants from haploidentical family donors using post-transplant cyclophosphamide as GVHD-prophylaxis was started in 2014. In total 612 allogeneic transplants in adult patients have been performed between 1993 and 2017 (Figure 1).

The collection facility was started in 1991 for autologous apheresis procedures and in 1993 for donors. Annually, during the last five years about 20 allogeneic apheresis procedures has been performed in donors for patients in both Europe and United States. The number of donor work-ups and collection procedures has increased hugely the last year owing to the successful recruitment of new donors to the Tobias registry.

In addition, since 2015 around 400 extracorporeal photophoresis procedures have been performed annually in patients with acute and/or chronic GVHD.

All parts of the transplant program (clinical, apheresis facility, bone-marrow collection and processing facility) are accredited according to JACIE since 2011-2015.

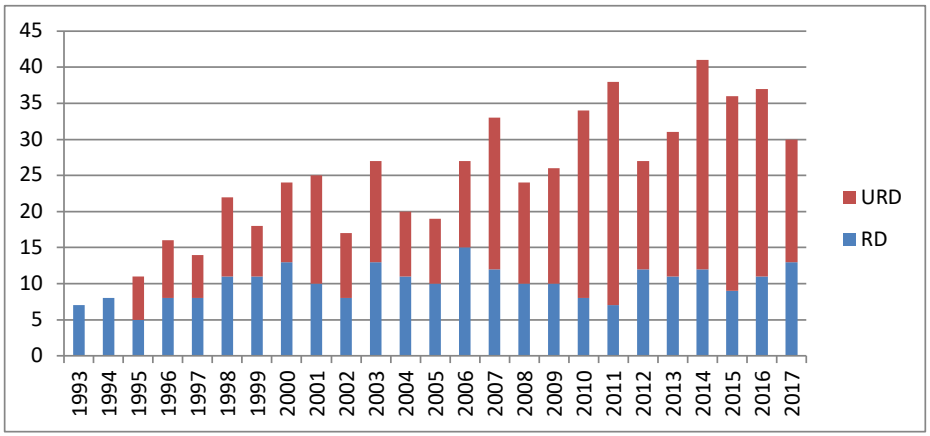


Figure 1. Adult allogeneic transplant activity from 1993 to 2017. URD; Unrelated donor, RD; Related donor

Scientific activities – brief overview

The main research areas have included studies of the role of eosinophils in GVHD (C Wennerås & Jan-Erik Johansson) and with Mats Brune as PI, a randomized study evaluating the role of allogeneic transplant for elderly AML patients. In addition, our unit has studied genital cGVHD in females (E Smith Knutson).

GÖTEBORG: *The Queen Silvia's Hospital for Children: Karin Mellgren (children)*

Clinical development since the opening 1984

The first transplantation took place in October 1984. A 14-year-old boy with Wiskott-Aldrichs syndrome, received stem cell transplantation from his sister. This patient is now completely healthy 33 years later. The Queen Silvias Hospital for Children has the largest purely pediatric transplant program in Sweden. Between 1984 and 2017 we performed a total number of 454 stem cell transplantations in pediatric patients; 186 patients with leukemia or lymphoma, 91 with immune deficiency, 85 with solid tumor including brain tumor, 66 with a benign hematological disease, and 26 patients with other diseases. The donor was a matched unrelated donor in 164 transplants, matched family donor in 120, a haploidentical or mismatched family donor in 50 transplants, and autologous cells in the remaining 120 transplants. The preferred stem cell source is bone marrow, used in a majority of patients, but 25 transplantations with cord blood were performed.

During the first years SCT was mainly used to treat congenital immunodeficiencies but transplantations for hemoglobinopathies have increased since 2000, with 19 and 11 transplantations performed for thalassemia and sickle cell anemia, respectively. Major advances in leukemia treatment have meant that fewer children with acute leukemia require transplants, and those who do receive transplantations have often a more difficult-to-treat form of the disease.

The Swedish national cord blood bank was started in 2006 and is located at Sahlgrenska University Hospital in Göteborg. The bank operates completely non-profit and funded by the government, Tissue Directive, Sweden's municipalities and county councils and Childhood Cancer.

Narrative report of scientific activities

Immunology

Göteborg has a long history of immunological research. The transplant program was initially lead by Prof Anders Fasth, who early performed many international collaborative studies on patients with immundeficiencies. Today, we have ongoing studies on immune reconstitution after HSCT, and B-cell development and immune profiling in patients with post transplantation lymphoma.

Leukemias

We have strong ongoing leukemia and Non-Hodgkin Lymphoma (NHL) research, with researchers from Göteborg, including Jonas Abrahamsson and Karin Mellgren, in the lead for international ALL, AML and NHL protocols. We focus in particular on translational research looking for genetic markers as predictors for high risk leukemia and indications for transplantation in these patients.

Late effects

We also have a history of studies on late effects after transplantation and other treatment for cancer. With a late effect clinic for young adults we are able to perform long time follow ups in our transplanted patients. We have also ongoing studies on fertility, cardiac function, hemorrhagic cystitis and nutrition and the influence of microbiota after HSCT.

Virus specific T-cells

In collaboration with Ass prof Mats Bemark, we have recently developed production of tri-virus specific T-cells, and intend to have them available for clinical use later this year

LINKÖPING: *Bone marrow transplantation unit at Linköping University Hospital: Jörg Cammenga*

Dr. Gunnar Juliusson working at the Department of Hematology in close collaboration with Prof. Dr. Gösta Berlin from the blood bank established allogeneic bone marrow transplantation at Linköping University hospital in 1996.

Dr. Juliusson had been recruited from the Karolinska Institute to become the Head of Hematology in Linköping in 1994. At that time, the Department of Hematology performed already autologous bone marrow transplantations and had a well-functioning blood bank that was well versed in the collection of peripheral stem cells.

In 1996 the first three matched related donor allogeneic bone marrow transplantations were performed in Linköping. The Department of Hematology at Linköping University Hospital was using peripheral hematopoietic stem cells quite early when the majority of centers in Sweden (and Europe) was still using bone marrow as a source of hematopoietic stem cells.

Since 1996 the number of allogeneic transplantations performed in Linköping has steadily increased and in the last ten years 20-25 allogeneic HSCTs have been performed each year. The hematopoietic stem cell transplantation unit at Linköping's University Hospital has 8 beds and serves the region of Östagötaland with regard to autologous and allogeneic bone marrow transplantation with many patients being referred from Kalmar, Jönköping and Norrköping.

Overall, 403 allogeneic hematopoietic stem cell transplantations have been performed since 1996 of which 174 were matched-related donor (MRD) and 229 unrelated donor (URD) transplantations. In 2015 the first haploidentical transplantation was performed, and so far 3 haploidentical transplantations have been done. At the moment, the transplantation unit in Linköping is in the process of getting JACIE accredited thanks to the dedicated work of Dr. Anna Sandstedt-Bergendahl and Ulla Frödin.

From 2004 when Prof. Dr. G. Juliusson was recruited to Lund, and until the recent recruitment of Prof. Dr. J. Cammenga the department of Hematology did not have a professor of hematology. While this has not negatively affected the clinical routines and outcomes it had a negative impact on the scientific output of the transplantation unit and the Department of Hematology.

LUND: *Stig Lenhoff, Stefan Scheding and Jacek Toporski (adults and children)*

Allogeneic SCT started in Lund in 1986 when an adult with CML was transplanted with bone marrow from her sister. The first child, suffering from ALL, was transplanted in 1987. In the beginning the volumes were small, until 1995 less than 10 patients were transplanted annually. Due to the development of donor registries the numbers the gradually started to increase. Our first transplantation with a registry donor was performed in 1990, but the use of registry donors was rather scarce until the end of the 90´s. Another reason for the expansion of the number of transplantation was the use of peripheral blood stem cells as cell source, which at our centre started in 1996.

Since the 2000´s there has been a continuous increase in the numbers of transplants. Contributing factors are, as in other centres, the ongoing development of the registries, the introduction of haploidentical transplantation, broader indications, better supportive care and development of alternate conditioning regimens enabling also elderly to undergo transplantation. The number of transplantations have increased from about 20 per tear annually around year 2000 until now around 60. Approximately 20% of the transplants are performed in children. During the last 10 years transplantation with cells from registry donors has been the most common process, accounting for approximately 60% of all transplants. Transplantations with cells from HLA-identical siblings have been quite steady around 25%, while we see an increase of haploidentical donors, now accounting from approximately 15% of all transplants. Cord blood has only occasionally been used at our centre. Apart from allogeneic transplants also autologous transplants are performed, nowadays about 90 per year.

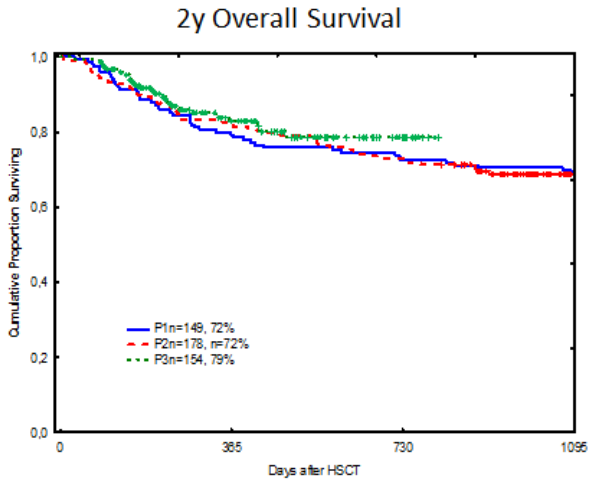
Our center is accredited by JACIE including the adult and pediatric transplantation program and the clinical cell processing facilities at the Institute for Laboratory Medicine.

Our program has ongoing and strong research programs related to transplantation, which is also reflected by the fact that several of the Tobias

awardees are or have been active in Lund. A number of strong research groups work on preclinical and translational projects such as stem cell expansion and development of gene therapy. These groups are part of the Lund Stem Cell Center which is located in close proximity to the clinical facilities, thus allowing for an optimal cooperation of research groups with the clinical program. Other translational research programs aim at the development of novel methods to process stem cell products (cooperation with the Technical University, Lund). Development of novel cell therapies and the so called ATMPs is performed within a recently established common initiative of Region Skåne, the University of Lund, Medicon Village as well as local SMEs. We are furthermore represented in the national cell therapy group and part of the recently-funded national ATMP project "CAMP". Own ongoing research aims at the identification of GvHD biomarkers, and we participate in several clinical multicentre studies within the Swedish Transplantation network and the EBMT. A recent dissertation from our centre focused on the experiences of being transplanted with cells from a sibling donor.

STOCKHOLM: *Per Ljungman (adults)*

The first allogeneic stem cell transplantation was performed at Huddinge Hospital, today Karolinska University Hospital Huddinge, in 1975 under the leadership of Prof Carl-Gustav Groth, Prof Gösta Gahrton and Prof Erna Möller. Since then a total of 2144 transplantations have been performed; 1542 in adults and 602 in children. The first unrelated donor transplant was performed in 1988. Altogether 1041 transplants have been performed using family donors and 1103 using unrelated donors. Of these, 58 have been cord blood transplants and 37 haploidentical transplants. The transplant program is JACIE accredited since 2011. Today the program is located at a newly constructed ward with 20 isolation rooms also to be used for cellular therapy. The overall survival has increased over time as seen is figure 1 showing the development during the last 6 years (P1 = 2011-08 – 2013-08; P2 = 2013-08-2015-08; P3 2015-08-2017-08).



Key developmental areas result from close collaboration between several different departments within and outside the hospital. During the entire period of allogeneic stem cell transplantation at Huddinge/Karolinska, laboratory and clinical research have been important parts of the transplant activity. A large number of papers have been published and

many doctoral dissertations presented. In addition, several members of the group have been very active in international transplantation societies and collaborating registries such as the EBMT and the CIBMTR.

Important areas of research encompass graft-versus-host disease prevention and treatment, allogeneic transplantation in multiple myeloma, diagnosis and management of infectious complications including CMV, fungal infections, and vaccination of stem cell transplantation recipients, stem cell transplantation in children including diagnosis and management of complications, transplantation of children with metabolic disorders, home care after allogeneic stem cell transplantation, busulphan farmacokinetics and associated complications, and T-cell and NK-cell adoptive therapies.

STOCKHOLM: *Mikael Sundin, Jacek Winiarski (children)*

Clinical

A regular pediatric allogeneic bone marrow transplant (BMT or HCT) program was initiated in the early 1980s. During this decade only children with HLA-identical sibling donors could be transplanted, leaving out 70% of patients who might have been rescued by a transplant, but who had no matched donor available. A more precise genomic HLA-typing and the rapid expansion of unrelated donor registries worldwide allowed for using the first matched unrelated donors (URD) in 1990 in our center. Alternative graft sources, i.e., unrelated banked umbilical cord blood and haploidentical grafts have become increasingly used in the last decade. Consequently, grafts can now be provided for most patients.

While leukemias initially were the dominating HCT indications in children and still are among adults, overall, children with leukemia today less often require HCT than 10 years ago. The proportion of patients with non-malignant blood disorders or immunodeficiencies has instead increased, making up a half of all the yearly transplants in our center. While allele-level high resolution HLA-typing and a more than hundredfold increase of searchable URDs over the last 30 years undoubtedly have improved survival and reduced the risk of GVHD, other important developments in diagnostics and preemptive treatment of opportunistic infections such as CMV, EBV and fungi have also been crucial. Moreover, conditioning regimes have been significantly modified to reduce toxicity. Total body irradiation, which in the early years was standard, is now seldom used and mainly limited to patients with ALL. Comparing outcomes in 2 decades, 1992-2002 and 2003-2013, transplant related mortality in children at one year post-transplant had decreased from 18 to 12%, while chronic GVHD more than halved from 32 to 15%. In children with a matched sibling donor the 5-year TRM had decreased from around 10 to 3%.

In total, 602 transplantations in pediatric patients (<16 years) have been performed at our hospital and in 298 the graft came from matched URDs

(NB: >50% matched URDs since the late 1990's). Umbilical cord blood is used seldom nowadays, but occurs. Haploidentical donors are used more frequently, especially in patients with ethnicities where the existing donor registries have poor coverage.

Scientific

Monitoring outcomes after HCT in children, with focus on new methods, complications and side effects were initially the subjects of research and still are the core of scientific activities. In the 1990's we were early to report successful outcomes of unrelated transplants in children and the impact of chronic GVHD in reducing relapse rates in children with leukemia. Our hospital's HCT program developed a cell-line specific PCR-based chimerism assay for B-, T- and myeloid cells, an important aid to interpreting engraftment and rejection dynamics. Another translational project, with the department of MTC, Karolinska Institutet, was the culturing of donor EBV-specific cytotoxic T-cells that were infused after HCT to patients with increasing intracellular EBV-DNA, preventing post-transplant lymphoproliferative disease.

The above mentioned and other projects covering endocrine side-effects, prognostic factors in leukemias, visual and ocular outcomes after HCT, pioneering long-term follow up of health-related quality of life and psychosocial sequelae long into adulthood and on neurological complications after HCT, all led to succesful dissertations. In a multicenter study, we found no benefit of standard intrathecal chemoprophylaxis in ALL after HCT. These results widely led to discontinuation of this tedious routine. The pediatric program has also recently been the clinical hub of a 3-year regional trial of neonatal TREC/KREC based screening for SCID, that may become a nation-wide program, enabling earlier treatment with HSCT.

Our ongoing research activities aim to further improve pediatric HCT for both malignant and non-malignant indications, mainly by reducing late complications and "boosting" function; e.g., endocrine long-term effects and post-transplant immune system regeneration with regards to micronutrients, innate effectors and long-lasting immune responses.

UMEÅ: *Anders Wallin, Cecilia Isaksson*

first allogeneic transplantation was performed in 1998. We had been performing autologous transplantations since 1993, and had for several years been given post-transplant care to allo-transplant patients from North Sweden who had been transplanted at other centers. This meant that we had experience of some of the fundamental processes when we started. We also had a well-functioning stem cell laboratory and apheresis unit.

In 1998-2016 we performed 426 allogeneic transplantations; 146 patients had family donors, 280 unrelated donors. PBSC were used in 378 instances, marrow in 48 cases. Cord blood was used in one case only. All patients were adults.

Fewer than one million people live in our scarcely populated referral area covering more than fifty percent of Sweden. Most patients and donors have a long distance to our hospital, so logistics is a fundamental process at our unit. Improved transplantation protocols and methods for prediction of complications have now made it possible to select and transplant patients who are older. In the last years, the possibility to use haplo-identical siblings has also contributed to reduce the risk not to find a donor for the patient. The mean age of our patients has increased from 42 years in 1998-2002 to 50 years during the last years, and some are 72 years old. We practice no age limit, but we use established scores for estimation of risk and chance to success. The annual number of allogeneic transplantations is now around 25 at our centre, but the number is increasing, in spite of the fact that one of the previously largest patient groups, chronic myeloid leukemia, has almost disappeared, thanks to new effective drugs for treatment of this disorder.

Family donors were used for 59 % of our patients in1998-2002, but the fraction of unrelated donors increased to over 75 % after 2010, reflecting continuously improving chances to find a suitable donor for the

patient. The recent efforts to increase the number of unrelated donors in the Swedish Tobias registry has been successful and resulted in a larger number of Swedish donors in the past few years, so we have now better HLA-matches and shorter transport travels in many cases. We have also harvested an increasing number of Tobias Registry donors at our unit recently.

Most of our contributions to research in this field have been performed in cooperation with national Swedish groups and EBMT. In cooperation with CAST at Karolinska Hospital, Huddinge, we have found and reported that serum ferritin acts immunosuppressive, resulting in lower GVHD rate, but also high risk of reduced graft-versus-leukemia effect and impaired survival in patients with high ferritin levels. We have also reported that estimation of fecal calprotectin can be used for detection of gastro-intestinal GVHD.

UPPSALA: *Kristina Carlson (adults) and Johan Arvidsson (children)*

The Statistics regarding allogenic hematopoietic SCT (adults and children)

The first allogenic bone marrow transplantation at Uppsala University Hospital was performed in 1983. During the 25-year period from 1992 to 2017, 432 RD (related donor) and 471 URD (unrelated donor) transplantations were performed. In 157 of these transplantations, the recipient were younger than 18 years (68 RD, 89 URD). Since 1999, there have been more URD transplantations than RD transplantations. In 1992, the first haplo-identical transplantation was performed, donor was mother and recipient was son. Haplo-transplantation with conditioning according to the Genua model was started in 2015, and since then 6 adults (aged 38-71 years) and one child (age 6) have been transplanted according to this protocol. During 1998-2017, umbilical cord blood (UC) has been used as a source for stem cells to 13 patients (12 children and 1 adult, RD1, URD 12, the adult got double UC). Under perioden 1998 till 2017 har navelsträngsblod (UC) använts som stamcellskälla till 13 patients (11 children and 2 adults; RD1, URD 12). Between 1998 and 2017 cord blood has been used as stem cell source for 13 patients (11 children and 2 adults; RD1, URD 12).

Clinical scientific activity (adults)

The majority of the clinical research is performed in collaboration with other stem cell transplantation centers and can be divided into therapeutic studies, corporate studies, or academic studies, registry reports and retrospective registry studies. Work performed locally encompasses mobilization of blood stem cells in healthy volunteers and follow-up after EBV reactivation.

Clinical scientific activity (children)

Since 1995 both allo and autologous HSCT have been performed in children. The initial project was in close collaboration with adult hematology, and their department has since then performed the transplantations until take

of the bone marrow transplant. Papers on the combined pediatric and adult patient material have been published from the start of the program. Head of the pediatric program was Professor Gudmar Lönnerholm. He supervised the initial research on transplanted patients, and long-time follow up of organ function, neuropsychological and psychological functioning resulted in two dissertations, written by Johan Arvidson, associate professor, and Per Frisk, associate professor. Anders Öberg, paediatrician, continuous with this type of research under the supervision of Per Frisk.

The HSCT program in Uppsala is JACIE accredited, and reports patients to EBMT including details of patients to the various sub-studies that emanates from EBMT and the working groups. There is both a Swedish and Nordic pediatric HSCT working group, and we have contributed with patients to joint studies.

We have used cell therapies like mesenchymal stem cells and decidual stem cells in single patients, and reported these in peer-reviewed journals. In February 2018, the first child was treated with CAR-T cells in Uppsala, not a transplant per se, but maybe a bridge to HSCT. Some of our young PhD students work with HSCT-related issues. Tanja Christoforaki is Uppsala's representative in a national joint study on gastrostomy/PEG in HSCT. Gustaf Leijonhufvud 's research plan for future registration deals with HSCT patients to a certain extent. Both these are supervised by Professor Britt Gustafsson, an experienced researcher in the HSCT field who recently joined our Uppsala forces.

Future perspectives

Stephan Mielke, Stockholm and Gunnar Juliusson, Lund

With more and more allogeneic hematopoietic stem cell transplantations performed worldwide over the last decades this sophisticated approach has become a standard of care therapy for several malignant and non-malignant diseases. Actual developments focus on the optimization of the control of the malignant disease before and after transplant, increasing the limits of feasibility to the elderly and frail, substituting classical endpoints such as survival with more appropriate composite endpoints such as GvHD-free, relapse-free survival as well as optimizing donor availability. Whilst it has become evident that matched unrelated is not inferior to matched related allogeneic stem cell transplantation, today's ability to identify an appropriate donor in one of the worldwide registries is more and more challenged by society's increasing ethnical mix resulting in a reduced likelihood to identify donors in a timely fashion. Whilst cord blood transplantations are declining worldwide haploidentical stem cell transplantation has undergone a remarkable development leaving today's haplotransplanter with a variety of options. Several randomized trials are on their way comparing innovative T-deplete strategies with the applied T-replete standard of post-transplant cyclophosphamide. Finally, feasibility and applicability in relation to cost and outcome will further streamline this fascinating development opening the applicability to benign hematology and inborn diseases such as sickle-cell anemia and thalassemia where the only other curative option is gene therapy. Haploidentical stem cell transplantation could also challenge matched unrelated transplants as today's standard of care if composite outcomes are comparable or even better due to less relapse and/or less GvHD. Advances in genetic profiling of malignant diseases allow earlier individual risk assessment and thereby a faster track to transplant where needed but open also room for optimized post-transplant tracking of the malignant clones favoring faster intervention where required. Several novel immune therapies such as multi-specific antibodies, CAR-T-cells, NK-cells and CAR-NK-cells can reduce disease burden upfront transplantation and could serve as a bridge to transplant if they should not be able to provide cure in the first place. Therefore, today's transplant units will serve more and more as platforms for advanced cellular and complex immuno-therapy in the future thereby widening the indication to solid tumors and paving most likely the way towards gene therapy for both inborn and acquired errors in malignancies.

Research performed within the program supported by the Tobias Foundation

Donation professorship Jonas Frisén 2001-2016

The Tobias Foundation decided to finance a professor position in stem cell research for 15 years and invited the Swedish universities to apply for the position being placed at their university. It was decided that the position should be placed at the Karolinska Institute and Jonas Frisén was appointed the Tobias Foundation professor of stem cell research in 2001. The Tobias Foundation in this way provided the possibility to build up a research program with long term generous economic support.

Jonas Frisén's research has focused on stem cells and cell renewal in the adult body. The brain and spinal cord has often been a focus of the studies, but also the heart, gastro-intestinal tract, adipose tissue, the immune system and cancer been of keen interest. The research is often basic in its nature, but there has always been a strong interest in studying the human situation and not only experimental animals, as well as to contribute to knowledge that can be valuable for the development of new therapies.

A modern myth states that all cells in our bodies are exchanged every seventh year, but our knowledge of the extent of cell generation in the human body has actually been surprisingly limited. It was for example, until recently, not known if we are born and die with the same brain cells and heart cells, or if these cells are exchanged during the lifespan of an individual, The reason for this limited knowledge is that these types of questions have been very difficult to address in humans. Jonas Frisén's research group developed a strategy to determine the age of cells in humans, which built on taking advantage of the release of a substance from nuclear bomb tests during the Cold War that was taken up by cells. By using this method, the research group could demonstrate which types of nerve cells that are exchanged thoughout life and that there is a continuous, albeit at a low pace, generation of heart muscle cells in humans. These studies have demonstrated that cell generation in humans is not predictable from experimental animals, but that there are important differences.

To study the regulation of stem cells and cell generation, model systems have often been employed by the group. This has for example revealed how cell generation in the nervous system in response to injury is controlled. The research group has identified cells that gives rise to scar tissue after spinal cord injury, and have demonstrated how modulation of these processes can promote functional recovery in experimental animals. Other studies have unveiled the regulation of nerve cell generation in the adult brain and has demonstrated that generation of new neurons in the adult brain can be induced in parts of the brain where it does not normally take place.

The perhaps most important long term effect of the generous support from the Tobias Foundation has been the fostering of a new generation of scientists. A large number of independent new research groups have been started, both in Sweden and internationally, by previous PhD students and postdoctoral fellows from Jonas Frisén's research group.

Key publications

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TOBIAS PRIZE WINNERS

Tobias Prize winner 2008: *Katarina Le Blanc, Karolinska Institutet*
Stromal cell treatment of inflammatory disorders

Certain types of leukemia can only be cured by hematopoietic stem cell transplantation (HSCT). As a sequelae of the treatment, the blood cells can attack the patient's healthy tissue, causing an inflammatory reaction that has been termed Graft-versus-Host disease (GvHD). HSCT has greatly improved over the last 20 years but overall survival remains quite similar, mainly limited by severe GvHD reactions and leukemic relapse. Our research aims to, using combined cell therapies, improve the environment for the hematopoietic cells to reduce and dampen GvHD while at the same time, allowing the new immune system to mature to be able to prevent relapse through a maximal Graft versus Leukemic effect. The bone marrow contains both blood and mesenchymal stromal progenitor cells (MSCs). MSCs can mature to various tissues and they can nourish blood cells. MSCs are scarce in the human body but can be cultured to many millions of cells in the laboratory. We have previously shown, in the laboratory and in clinical studies, that MSCs reduce inflammation. Unlike blood cells, MSCs hide from the immune system, avoiding immune reactions, and can therefore be transplanted between HLA mis-matched individuals. We have generated MSCs from more than 150 donors and given several hundred infusions to patients, as treatment of GvHD reactions, and to promote healing of organs and tissues that have been damaged by the chemotherapy. The mode of actions of MSCs, both in reducing inflammation and in their immune evasiveness, is incompletely understood. We have investigated, both in vitro and in experimental animals, the differences between MSCs given to patients that have responded to the treatment and to patients that have not responded. We have also studies differences in the biology between patients with GvHD disease, to better understand what patients will respond to therapy. We realize more and more that the anti-inflammatory properties of MSCs' are properties of healthy tissue, maintaining tissue homeostasis. To understand this, we have studied the interplay between tissue and the inflammatory system in more detail, how the cells communicate through the complement and the coagulation systems. Our hypothesis is that, the natural balance is skewed in chronic GvHD, an entity characterized by fibrosis of skin and mucous membranes, with very little inflammation. We have studied how stromal progenitor cells from the oral cavity participate in GvHD pathogenesis; the cells cytokine profile and interaction with immune cells. In parallel, we study how MSC adoptive transfer changes both the behavior of tissue resident progenitors as well as the cytokine profile in the blood of treated patients. In order to make MSC treatment safe in the future, we have collaborated internationally to create standards for how MSCs as a therapeutic should be cultured and characterized. MSCs treatment continues to be evaluated in clinical trials – a concept applicable to many diseases beyond HSCT.

Key publications

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Tobias Prize winner 2009: *Stefan Karlsson, Lund University*

The research program has focused on the regulation of hematopoietic stem cells (HSC) by discovering new regulators of HSC. A second aspect of the program has been to develop mouse models for genetic diseases and use these to develop lentiviral gene therapies. We discovered Cripto and Dppa5 as novel regulators of HSC and discovered a novel mechanism by which Cripto regulates HSC in the bone marrow niche. Dppa5 acts on HSC through reduction of endoplasmic reticulum stress reduction and improves HSC survival. We have similarly explored various aspects of the TGF-beta family of growth factors/receptors/transduction molecules. We have discovered in the past that Smad4 is a critical regulator of HSC in vivo but Smad1, Smad2, Smad2 and Smad5 are redundant for HSC function. Similarly, we discovered that the SKI proto-oncogene enhances repopulation of HSC but causes myeloproliferative disease. Angiopoietin-like 4 maintains repopulation capacity of HSC in vivo but cannot effectively expand HSC.

Mouse models have been developed for the lysosomal storage disorder, Gaucher disease. Similarly, we have developed a mouse model for Ribosomal Protein S19 deficient Diamond Blackfan anemia with the characteristic anemia and bone marrow failure found in Diamond Blackfan anemia patients. We have used our mouse model for type 1 Gaucher disease to develop lentiviral gene therapy for the disease. The glucocerebrosidase gene has been inserted into lentiviral vectors using cellular promoters to drive the transgene and these vectors have been used to transduce HSC from the Gaucher mice. Full correction of the metabolic deficiency was achieved with disappearance of glucocerebroside accumulation, correction of spenomegaly and the anemia. These findings have supported the development of a clinical gene therapy protocol for type 1 Gaucher disease which is currently being pursued in collaboration with a commercial partner. Similarly, we have used our mouse model for RPS19 deficient Diamond Blackfan anemia to determine the mechanism of the anemia and to develop lentiviral gene therapy for the disease. In two recent publications, we demonstrate that lentiviral vectors using the RPS19 transgene can fully correct the anemia and bone marrow failure in the RPS19 deficient mice. The findings indicate that successful human gene therapy for this disorder will be possible to develop in the future.

Key publications

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Tobias Prize winner 2011: *Hans-Gustaf Ljunggren, Karolinska Institutet*
Novel NK cell-based immunotherapy to patients with hematological cancer

Natural killer (NK) cells, a type of innate lymphocyte, were originally discovered at Karolinska Institutet in the mid-1970s. In mice, NK cells were able to reject tumor grafts in vivo, and in humans high endogenous NK cell-activity was associated with reduced incidence of cancer. Furthermore, risk for relapse following clinical hematopoietic stem cell transplantation had in a series of studies been shown to correlate with NK cell maturation, differentiation and function in newly transplanted patients. These and other findings suggested that NK cells could efficiently target malignant cells, and opened up for the design human NK cell-based immunotherapeutic strategies to treat human malignant diseases. In 2011, after extensive regulatory work and validation studies based on our prior studies of human NK cells, we finalized an allogeneic NK cell-based immunotherapy protocol to be applied to patients with incurable hematologic malignancies of myeloid origin. A clinical trial became possible through the generous support provided by the Tobias Prize 2011. In the case of allogeneic NK cells, conditioning (immunosuppression) regimens are necessary to support engraftment and in vivo expansion of NK cells. To further support in vivo expansion of allogeneic NK cells, inclusion of systemic IL-2 has been a matter of discussion in the field. However, both the conditioning and systemic administration of cytokines may have severe adverse effects. To minimize unwanted effects of commonly used myeloablative conditioning, we therefore opted for the development of a milder non-myeloablative conditioning regimen. Furthermore, we omitted subcutaneous IL-2 administration to avoid unnecessary stimulation of Treg cells. Within the frame of an academic phase I/II clinical study, an adoptive immunotherapy trial with short-term ex vivo IL-2 activated NK cells was initiated in 2012. In total, sixteen patients with refractory disease were included in the trial; five with high-risk MDS, eight with MDS-AML and three with primary AML. The NK cell infusions were well tolerated, with only transient adverse events observed. Excitingly, six patients achieved objective responses with complete remission (CR), marrow CR, or partial remission (PR). Five of these patients proceeded to allo SCT. Three patients have been free from disease >3 years after treatment and one of them for >5 years. Detailed follow up studies showed that objective clinical responses and reduction of high-risk clones were associated with detectable donor-derived NK cells, immune-editing of residual blast cells, and less pronounced host immune activation. The study was published in 2018. Overall, the study suggests that high-risk MDS, secondary MDS-AML and AML is responsive to NK cell-therapy and supports the use of allogeneic NK cell-infusions as a bridge to hematopoietic stem cell transplantation in treatment-refractory patients. These encouraging results open up for new clinical trials with novel NK cell-based protocols, currently undertaken in our group.

Key publications

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Tobias Prize winner 2014: *Sten Eirik Jacobsen, Karolinska Institutet*

Sten Eirik W. Jacobsen was awarded the Tobias Prize in 2014 for "groundbreaking scientific contributions to the field of haematopoiesis, particularly with respect to identifying factors that regulate the maturation process of haematopoietic stem cells, factors of great importance for successfully transplanting stem cells". Establishing the normal lineage commitment pathways from hematopoietic stem cells (HSCs) to lineage-restricted progenitors remains an important goal towards unravelling the regulation of blood lineage development, and how this is perturbed in hematological malignancies. Supported by the Tobias Foundation the Jacobsen Laboratory has since 2014 continued to unravel and refine lineage commitment pathways in normal fetal and adult hematopoiesis (Drissen et al, Nature Immunology 2016; Luis et al Nature Immunology 2016), also resulting in the identification of novel classes of lineage-biased HSCs, including multipotent HSCs dedicated to a megakaryocyte-platelet fate (Carrelha et al, Nature 2018). In other studies, supported by the Tobias Foundation, the Jacobsen Laboratory has made further progress towards the identification and characterization of distinct and rare candidate leukemic stem cells (LSCs) and their therapeutic responsiveness in chronic hematological malignancies, including myelodysplastic syndromes (MDS; Woll et al, Cancer Cell 2014) and chronic myeloid leukemia (CML; Giustacchini et al, Nature Medicine 2017). Relapses after therapy-induced complete clinical remissions remain a significant challenge in leukemia therapy. This suggests that a small proportion of leukemic cells escape therapeutic targeting and persist during remission. Distinct LSCs might therefore underlie relapses after otherwise complete remissions. In ongoing studies in MDS patients after allogeneic stem cell transplantation (allo-SCT) the Jacobsen Laboratory and collaborators have established at the time of reported complete clinical and cytogenetic remissions, a selective persistence of resistant MDS clones in distinct MDS stem and progenitor cell compartments. Experiments are under way to understand whether the resistant and rare MDS stem cells selectively escape the immune-surveillance and targeting, known to be critical for the curative potential of allo-SCT. Furthermore, the Jacobsen Laboratory has in mouse MDS models explored and established the potential of thrombopoietin, an essential growth factor for HSCs, to promote MDS stem cell activation and subsequent cytotoxic elimination in vivo. Importantly, this treatment seems to selectively target the MDS stem cells leaving the normal HSC compartment relatively protected. Based on these findings, a phase I trial is being planned at the Karolinska University Hospital, in which Romiplostim, a clinical grade thrombopoietin analog will be combined with chemotherapy in order to enhance killing of MDS stem cells prior to allo SCT.

Key publications

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Tobias Prize winner 2016: *David Bryder, University of Gothenburg*

Blood cells are formed via a hierarchically organized developmental process. Rare hematopoietic stem cells (HSCs) in the bone marrow are found at the top of this hierarchy. The high inherent potential of HSCs can be utilized in the form of bone marrow transplantation (BMT); a clinical replacement therapy used for a number of life-threatening diseases where the blood system of an individual needs to be replaced and / or renewed. A central feature of HSCs is their ability to regenerate all types of blood cells during a lifetime. An increased knowledge on how this is achieved is important for understanding how blood diseases develop, and for the development of new clinical therapies that involve the use of HSCs. Historically, the functional properties of HSCs have been defined based on experimental transplantation models; which as mentioned also has clinical relevance. As HSCs are defined based on their functional properties, model systems are absolutely necessary, and mouse models have a dominant position. Typically, purified HSCs are isolated and transplanted into hosts in which the blood systems have been removed by cytostatics or irradiation. However, in order to understand the normal biology of HSCs, BMT has limitations. This is because only those HSCs that successfully establish themselves in connection with BMT can be evaluated; the ability to home to the bone marrow might not be a normal behavior of HSCs. In addition, BMT is associated with an unphysiologic stress on HSCs that is caused by the transplantation process. It is therefore unknown if the properties associated with HSC in connection with BMT are the same in a more physiological, non-transplanted situation. These considerations are also relevant for a wider use of HSCs. For example, in allogeneic BMT, in which a donor provides HSCs, there is generally a need for strong cytostatic and immunosuppressive conditioning to prevent immunological rejection. Since such conditioning can associate with life-threatening side effects, BMT is not an option for many diseases. We and others have recently shown that there are fundamental differences between how HSCs form blood cells in a normal situation and after BMT.

Earlier (Säwén et al, 2016) we could show that HSC usually undergoes cell division very rarely, while BMT induced HSCs to divide. The ability to divide is necessary in conjunction with BMT, but our studies showed that HSCs continues to divide faster than normal also a longer time after BMT. In recent work, we have very recently shown that HSCs in a normal situation gives rise to different types of mature blood cells with dramatically different kinetics. HSC's ability to give rise to platelets is robust and very fast, whereas HSC's ability to produce lymphocytes is a very slow process (Säwén et al., 2017). This is fundamentally different from what HSC does in a BMT situation, where all types of blood cells are initially formed more synchronously. Such studies have been made possible by the development of new transgenic model systems where individually defined blood cells and their relationship to each other can be studied. A more detailed insight will require further development of model systems and their application to relevant scientific issues. In our Tobias Foundation supported project, we develop and implement model systems that allow determinations of the relationships between HSC and their offspring in a non-transplant scenario, which simultaneously provide data on the function of individual HSCs. This is important as individual HSCs can vary greatly in function. We will utilize new developments in Crispr / Cas9 mediated gene editing, which enables us to change a defined piece of DNA in a unique way in different HSC. Since DNA is inherited into the daughter cells of HSCs, we will be able to use the altered region of DNA as a unique identifier to trace the origin and relationship between different blood cells.

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Selected publications from transplant centers

Göteborg: Jan-Erik Johansson (adults)

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Göteborg: Karin Mellgren (children)

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