

# CENTER FOR HEMATOLOGY AND REGENERATIVE MEDICINE (HERM)

Karolinska Institutet

## SCIENTIFIC ADVISORY BOARD REPORT November 2019

### Introduction

The Scientific Advisory Board (SAB), composed of Professors Ana Cumano, Anthony Green, Klas Kärre and Urban Lendahl (chair), met on October 22<sup>nd</sup> to 24<sup>th</sup>, 2019, at the Center for Hematology and Regenerative Medicine (HERM) in the Neo building in Huddinge, Karolinska Institutet (KI), to evaluate the current research at HERM as well as the center's interactions with relevant clinical and basic research departments at KI. The remit was also to specifically review the research of 13 group leaders at HERM and to provide comments on the future directions for HERM. This SAB carries out the third review of HERM and with a broader scope than the two previous SABs, which have focused on a review of the structure and initial accomplishments of the center (2015) and an evaluation of three junior HERM group leaders (2017).

Prior to the meeting, the members of the SAB received comprehensive written documentation on the activities of HERM as a whole as well as detailed information on the 13 group leaders to be evaluated. During the visit, HERM's Director Professor Eva Hellström-Lindberg presented an overview of the structure of HERM, its scientific achievements as well as potential future challenges. The SAB also met separately with the PhD student/postdoc group and with the junior group leaders at HERM. The site visit included a walk-around in the laboratories and the research facilities and a poster session with posters from the HERM research groups, which allowed the SAB to engage in more informal discussions with HERM scientists. The site visit ended with the SAB meeting with the staff of HERM, which provided an opportunity for the SAB to provide some immediate, preliminary reflections on the site visit as well as to respond to questions from members of HERM.

The review of the 13 group leaders was carried out in a closed session format, each interview attended by the group leader, the SAB and Professors Eva Hellström-Lindberg and Sten Eirik Jacobsen. This format was felt to be well-functioning and allowing for in depth discussions with each group leader. For the group leader discussions, the conflict of interest rules from the Swedish Research Council were applied, and a SAB member with a conflict of interest did not participate in the discussion or in the following deliberations and report writing for the group leader.

The SAB report is divided into two parts. The **general part A** can be made public to all members of HERM as well as to other relevant bodies. It also contains a short summary of the individual evaluations of the 13 group leaders. The **second part, part B**, contains the more detailed evaluations of the individual scientists, and part B is intended for the Director of HERM and the individual group leader, but not for public disclosure.

## **Part A: General comments on HERM**

### **Current Research Status**

HERM was inaugurated in 2012, with the mission of becoming a translational research center in the areas of hematology, immunology and regenerative medicine, to improve patient care and treatment outcome. The SAB was generally impressed by HERM's scientific journey over the first seven years, and the view is that the overall mission is in many aspects fulfilled or well on its way to be fulfilled. HERM is currently composed of 16 research groups, with approximately 75 scientists, working on important problems related to the mission topics, spanning from basic to the clinical research, and importantly, forging productive synergies between basic and more clinically oriented scientists in the center.

A number of important publications have emerged as result of the high level of research at HERM. The SAB was also pleased to see an excellent pipeline of additional potential breakthrough discoveries, although the scientific productivity differs somewhat between the HERM research groups. The SAB was impressed by the collaborative spirit among the research groups, with an increasing number of collaborations between basic and more clinical scientists, which is viewed as an important asset to continue to fuel new discoveries, particular in the translational space. The breadth of technologies on the molecular side and the increasing use of state-of-the-art methodologies in analyzing unique patient and animal model material was appreciated by the SAB. The systematic collection, biobanking and exploration of unique patient cohorts and material across many hematological disorders, as well as an increasing number of clinical trials (including a growing number of investigator-initiated early phase trials) is another important accomplishment of HERM. The launch of a Guest Professorship program, with Professor Seishi Ogawa, University of Kyoto, as the first appointee, is viewed as a very good initiative. Professor Ogawa regularly visits HERM, and this has in a short time period spurred interesting scientific collaborations and an opportunity for HERM scientists to learn new techniques in Professor Ogawa's laboratory. The HERM research groups share equipment and lab space, which appears to be cost-effective and enhance interaction. It was however noted that there are currently FACS services provided and run by two laboratories in addition to the FACS platform in HERM in the Neo building. While there may have been historical reasons for the origin of this organization, it would seem rational to explore possibilities of merging the services and resources. HERM runs two seminar series, a weekly series with invited speakers and a weekly series with presentations from PhD students and postdocs. Both series appear to function well, but as in all such programs, it has been challenging to identify mechanisms that safeguard good attendance, not least from group leaders. In 2018, HERM moved to new premises in the Neo building in Huddinge. This move appears to be largely positive, with access to brand new laboratory and office space, but possibly at the expense of some of the cohesiveness and cosiness of the old premises, as HERM now is spread out on two floors in Neo. Here, efforts to create more spontaneous meeting places to further encourage cross-research group interactions, may be considered.

In conclusion, HERM has in a relatively short time span established itself as a leading research unit with a unique research profile and a vibrant cross-disciplinary research environment.

## General Issues and Suggestions

### The funding situation

When HERM started in 2012, funding from a larger grant from Knut och Alice Wallenbergs Stiftelse (KAW) supported the initial phases of development. The KAW grant allowed for the recruitment of three junior group leaders (Drs. Hong Qian, Robert Månsson and Julian Walfridsson), establishment of a state-of-the-art FACS unit as well as recruitment of Professor Sten Eirik Jacobsen as Guest Professor (25%). In addition, the Karolinska University Hospital (KUH) provided support for refurbishing lab and office space for the center in the Novum building in Huddinge. The expiration of the KAW grant a couple of years ago puts HERM in a different, and more challenging, financial situation. Scientists at HERM have responded to this challenge by being successful in attracting funding, both at the individual group leader level and importantly in the form of larger block grants (for example from Vinnova and KAW), where several HERM scientists have joined forces, playing to the strengths of the center. Similarly, the increasing number of clinical trials has a positive financial effect for HERM. Furthermore, the FACS facility has been partially financed from core facility funding directly from KI, and the Guest Professorship program could be launched thanks to donations from patients.

While all these activities are applauded, and a measure of the strong science at HERM, the current funding situation is admittedly more *ad hoc*, with little room for the HERM leadership to launch long-term strategic initiatives and to make targeted recruitments. The SAB sees this as a challenge for the center and believes that centers of this scientific caliber should in some way be eligible for direct funding from KI and/or KUH. In the interim, various approaches were discussed during the site visit, and the possibility to continue to apply for block grants with several HERM group leaders as applicants and to explore various fundraising initiatives, are interesting options. HERM should be well positioned for both activities. The question of long-term funding also relates to the question of the size of HERM, and HERM may be a little small to have critical mass in its current research areas. It is noted that HERM in 2019 has approximately the same size as in 2015, with some turn-over of research groups in the center. Some of the recently recruited research groups provide important new technology, for example in the area of imaging and biophysics, which are important assets if integrated well with other research lines in the center. Important recruitments have also been made in the area of immunology, in line with the recommendations from the SAB in 2013.

### The organizational situation *vis-à-vis* KI and KUH

HERM operates in a complex organizational environment, both at the KI and the KUH side. In the revised hospital organization, hematology is split between the Solna and Huddinge hospital sites, such that most of the myeloma research and treatment is carried out at the Huddinge site, while lymphoma research and treatment is conducted at the Solna site. While this is largely a positive development for HERM, there are still some lingering problems with the current organization, for example with regard to collaborations and access to research material in pediatric hematology. At the KI side, although most scientists at HERM belong to Department of Medicine in Huddinge, there are some scientists with other departmental affiliations, adding to the organizational complexity. A number of research groups at HERM are also geographically split, with only part of their activities at HERM proper in the Neo building, and with other parts of their activities at the Solna Campus or in Uppsala. While this generally

appears to function, such arrangements pose a potential risk for example by lowering the attendance in meetings and seminars and participation in the everyday life at HERM in the Neo building.

During the site visit, the SAB met with Professors Maria Matl (Head of Department of Transfusion Medicine and Immunology) and Åsa Rangert Derolf (Head of Department of Hematology). The head of Center for Allogeneic Stem Cell Transplantation (CAST) (Professor Stephan Mielke) could not be present due to a parallel international evaluation of the KUH Cancer Theme to become a Comprehensive Cancer Center, but information was obtained from the HERM Leadership and PIs during the interviews. This meeting was very enlightening for the SAB and provided an opportunity to discuss the complexity of the interactions with the clinical side as well as potential ways of strengthening collaboration. The SAB was impressed with the program whereby many clinical haematologists undergo PhD training, which seemed well synchronized with HERM and hopefully can be further expanded in the future. It may however be advisable to not opt for a 50/50 division between clinical training and the PhD project throughout the training program, but instead have sequential periods of essentially full-time clinical or research activities. This would allow a period of proper immersion in research and would also make scheduling in the clinic easier. Staffing at the clinical side should also be planned such that time off from clinical duties for PhD training is feasible. The ambition from the Department of Transfusion Medicine and Immunology to further accelerate research in transfusion biology was viewed very positively by the SAB, and should provide opportunities for further interactions with HERM, where this research direction is also prioritized.

In sum, the SAB appreciates the challenges for HERM to navigate in a complex organizational environment at both the KI and KUH sides but considers the increasing interactions and collaboration with Department of Transfusion Medicine and Immunology and Department of Hematology as very positive for HERM in the long-term.

### **The governance structure at HERM**

The SAB learned that there will be a deep-drilling discussion at HERM later in 2019 on a reorganization of the leadership structure at HERM. The SAB felt that such a review and revision would be very timely, and that a few aspects emerging from the SAB's discussions with the different research categories could be considered. The SAB felt that it would be appropriate for Sten Eirik Jacobsen to be part of the Management Group and that terms of office for the Management Group could be better defined. There was also a sense that some group leaders felt they would like more involvement in strategic decisions. It is important to ensure that the minutes from decisions in the HERM Management Group are disseminated to the center in its entirety, as this will better anchor the decisions in the organization and further enhance the spirit of togetherness in HERM.

### **Training and mentoring**

During the discussions with the junior HERM group leaders, it was felt that there is a desire and need for additional mentoring, for example with regard to how to best prioritize among different research projects and how and when to approach different funding agencies. In addition to the in-center mentoring, it was discussed that when a new group leader starts, an external mentor, who should not be a member of HERM but be a senior and experienced KI or KUH scientist, could be assigned along with an intra-HERM mentor. The problem for junior group leaders in recruiting good postdocs was also brought up, and strategies for this could be further discussed in the center. The group leaders also felt an increasing workload in complying with a more demanding regulatory landscape, for example with

regard to biobanking, MTAs, storage of genetic data in various repositories and writing applications to ethics committees. It may be suggested that some of these activities could be centralized, possibly at the departmental or more central KI/KUH levels. This seems like a worthwhile route to explore, in order to ease the burden on group leaders and also to minimize the risk for mistakes in complying with the regulatory framework. Finally, concerns were expressed over how the management situation at the animal facility (Preclinical Laboratory, PKL) and that the cage costs for holding mice were different between the Solna and Flemingsbergs Campus (higher on the Flemingsbergs Campus). The SAB feels that it would be in the interest of KI generally to strive for the same cage costs irrespective of location, to provide equal opportunities to conduct mouse work at both campuses. The SAB realizes that this is not a question that HERM alone can tackle, but during the meeting with the KI leadership it was encouraging to learn that a working group has been initiated at the KI central side that will look into the future organization of animal facilities at the two campuses.

In the discussions with the PhD students/postdocs, it was suggested that the yearly follow-ups on the PhD student research plans could be stricter, in order to catch potential problems in a project at an early stage. This was felt to be a good suggestion (also to be implemented generally across KI). Another idea that resonated with the SAB was the suggestion that PhD students or postdocs should be introduced to scientists at other parts of KI and KUH in an effort to broaden their scientific networks. Overall, it should be emphasized that there generally is a very positive spirit and enthusiasm for the center from the PhD students, postdocs and junior group leaders.

## **Concluding Recommendations for the Future**

- Overall, the SAB was very impressed with the scientific achievements and general research direction of HERM, and how HERM has established itself as an important entity at the international arena for a number of hematological disorders. Going forward, the translational space appears to be a continuous fruitful avenue of research for HERM, as the combination of unique and well-curated patient cohorts and material with frontline expertise in advanced molecular analysis methods creates a strong research niche for HERM. To further accelerate the translational research, it may be considered to bring some of the basic research groups in closer contact with a larger and well-focused clinical context, which may have a positive effect on their scientific output.
- The planned reorganization of the leadership structure of HERM is appreciated by the SAB, and there were several interesting ideas presented during the SAB visit to further enhance transparency and information flux in the center.
- The links with the clinical departments (Department of Hematology, Center of Allogeneic Stem Cell Transplantation (CAST), and Department of Transfusion Medicine and Immunology) appear to be growing stronger. The SAB appreciates that HERM has a strong presence in the PhD training program at the Department of Hematology, the research program and in particular novel protocols for cellular therapies at CAST, and that transfusion medicine is a prioritized area in the Department of Transfusion Medicine and Immunology. Both these activities are well aligned with the research portfolio at HERM.
- To explore whether there could be more centralized functions assisting HERM group leaders when navigating the increasingly complex regulatory landscape is judged as a good initiative.

- HERM should be acknowledged for conducting regular overviews of the science in the center. The SAB encourages HERM to continue along these lines, possibly with a new SAB convening three-to-four years from now with a remit similar to this year's review.

## **Evaluation of 13 Group Leaders at HERM**

In total, 13 group leaders were evaluated during the site visit. The evaluation was conducted in a closed session format, with a 15-minute presentation from the group leader, followed by a 10-minute discussion with the SAB. Here, a brief summary of all evaluated group leaders (in alphabetical order) is presented:

### **Evren Alici**

Dr. Evren Alici is Assistant Professor since 2008 and leads the cell and gene therapy group. Alici runs a vibrant research program focusing on cellular therapies, with a particular focus on NK cell therapies for multiple myeloma. He is responsible for multiple clinical trials and has developed a large network of links with industry. Alici's research provides an excellent fit with the research directions of HERM, with a clear vision for how novel NK cell-based therapies can be developed and implemented.

### **Yenan Bryceson**

Dr. Yenan Bryceson was recruited to HERM in 2017 after international training and a group leader position at Center for Infectious Medicine at KI. He also serves as co-chair for HERM. Bryceson is an internationally well-established scientist in the area of NK cell biology and rare immune disorders. In the research proposal, Bryceson addresses important questions regarding maturational stages of NK cells and immunodeficiencies affecting NK and other immune cells. The recruitment of Bryceson to HERM is seen as a very valuable addition, providing additional strength in the immunology arena.

### **Mattias Carlsten**

Dr. Mattias Carlsten was recruited to HERM in 2016 after a postdoc in Professor Richard Childs' laboratory, NIH. Carlsten is an MD/PhD with expertise in immunology and translational hematology, and with particular focus on NK cells. The proposed work focuses on engineering NK and T-cells to improve their homing to sites where malignant cells be attacked. The project represents a very good balance between basic and clinical work, and also brings in new interesting technologies to HERM. The recruitment of Carlsten to HERM is seen as a very valuable addition to the center.

### **Petter Höglund**

Dr. Petter Höglund is Professor of Immunology and appointed as the new Chairperson of the MedH Department, starting in December 2019. He has a long productive history in NK cell biology and has during the last few years developed a new research trajectory in the area of transfusion medicine. The proposed work in transfusion medicine plays to his clinical strengths and also benefits from Höglund's expertise in NK biology. Höglund's transition to transfusion medicine resonates well with the suggestion that transfusion medicine is a prioritized area for the future from the hospital side.

### **Sören Lehmann**

Dr. Sören Lehmann is a physician scientist and Professor in Hematology at Uppsala University. He conducts research both at HERM and Uppsala University, focusing on various aspects of AML, including epigenetic regulation via DNMT3A. He has made important contributions in several areas, including

early drug development. Lehmann has a good international network, both at the academic and industrial and is considered a valuable addition to the HERM research environment. His double affiliation between Stockholm and Uppsala appears to currently work well.

#### **Sidinh Luc**

Dr. Sidinh Luc was recruited to HERM in 2017 after a postdoc in Professor Stuart Orkin's laboratory, Harvard Medical School, where she addressed questions on epigenetic regulation of hematopoietic stem cell lineage bias, with a particular focus on the transcription factor Bcl11a. Luc provides a clear and interesting research plan to further explore these questions and her research interests and expertise provide a good fit with the overall HERM research and technology portfolio.

#### **Vanessa Lundin**

Dr. Vanessa Lundin was recruited to HERM in 2018 after a postdoc in Professor Georg Daley's laboratory, Harvard Medical School. Lundin is trained in bioengineering and the postdoctoral work focused on decoding biophysical cues that can regulate hematopoietic differentiation in vitro. Her future plans involve the analysis of leukemic iPS cells, with an aim of understanding mechanical forces in the bone marrow niche. Lundin's biophysical expertise and approach are valuable additions to HERM.

#### **Robert Månsson**

Dr. Robert Månsson was recruited to HERM in 2012 after postdoctoral work in Professor Cornelis Murre's laboratory at UCSD. Månsson focuses on elucidating the molecular basis for the B-cell lineage and gene regulation in multiple myeloma, an area which is internationally highly competitive. He uses a battery of advanced molecular technologies in these ambitious projects. Månsson's deep technical molecular expertise is an asset for HERM, and many projects in the center can benefit from his expertise.

#### **Hareth Nahi**

Dr. Nahi has been a member of HERM since its inauguration in 2012. He has built up an impressive myeloma practice over the last decade together with an extensive network of collaborations. Nahi's research focus is on multiple myeloma, and he has been PI for more than 70 clinical trials, some of which are investigator-led. His myeloma work has the potential of becoming highly internationally recognized, and an even closer integration with cell therapy as well as genetic and molecular studies would further accelerate the progress.

#### **Hong Qian**

Dr. Qian was recruited to HERM in 2012 after postdoctoral work in Professor Mikael Sigvardsson's laboratory, Linköping University. Qian has a background in hematopoietic research and with a current focus on the stromal cell compartment in the bone marrow and its role in hematopoiesis. Qian presents a robust research program with the aim of isolating several stromal cell types, and to study them in CML and AML. An important future aspect will be to devise strategies by which the properties of the bone marrow stroma can be functionally validated.

#### **Johanna Ungerstedt**

Dr. Johanna Ungerstedt is a physician scientist, who after completing her MD and PhD conducted postdoctoral research in Professor Paul Marks' laboratory, Memorial Sloan-Kettering. Her research focus is diagnosis and therapy in myelomonocytic leukemia (CMML) and systemic mastocytosis (SM). She has built up an impressive SM biobank and been a leader in developing national guidelines. The

research rests on a good combination of well-curated patient material and advanced molecular profiling and is an important asset for HERM.

#### **Julian Walfridsson**

Dr. Julian Walfridsson was recruited to HERM in 2012 after postdoctoral work in Professor Kristian Helin's laboratory at the BRIC Institute in Copenhagen. Walfridsson has considerable expertise in epigenetics and uses this to address questions in hematopoiesis and AML. Walfridsson presents a broad and diverse portfolio of research projects, with creative ways to develop and implement assay and screening systems, and productive links with industry. Walfridsson's deep technical molecular expertise is an asset for HERM, and many projects in the center can benefit from his expertise.

#### **Petter Woll**

Dr. Petter Woll was recruited to HERM in 2015 after international PhD and postdoc training at Univ Minnesota and Univ Oxford, respectively. He has a background in normal and malignant hematopoietic stem cell biology and has produced important work in the area of MDS cancer stem cells. He continues this research line and also proposes to develop immune targeting of MDS stem cells. This research topic resonates well with the overall research direction for HERM and Woll thus represents a good recruitment for HERM. Many of his projects are quite ambitious and collaborative in nature, and hence it will be important for Woll to carve out a truly unique independent research trajectory going forward.

Group leaders not evaluated during this SAB:

Sten Eirik Jacobsen

Eva Hellström Lindberg



Urban Lendahl (on behalf of the SAB)

Stockholm, November 15, 2019

#### **Members of the SAB:**

##### **Ana Cumano**

MD, Research Director INSERM,  
Head of the Lymphopoiesis Unit  
Department of Immunology,  
Institut Pasteur, Paris, France

##### **Klas Kärre**

MD, PhD, Professor of Molecular  
Immunology  
Department of Microbiology, Tumor and  
Cell Biology  
Karolinska Institutet, Stockholm, Sweden

##### **Anthony R. Green**

Professor, PhD, FRCP, FRCPath, FMedSci  
Director, Wellcome-MRC Cambridge Stem  
Cell Institute  
Head, University of Cambridge  
Department of Haematology  
Jeffrey Cheah Biomedical Centre,  
Cambridge, UK

##### **Urban Lendahl (chair)**

PhD, Professor of Genetics  
Department of Cell and Molecular Biology  
Karolinska Institutet, Stockholm, Sweden