CIR final report

2007–2017

Vision statement

This centre identifies and investigates novel mechanisms of immune dysregulation to advance the development of therapeutics.

contents

Director's comments

There is a proverb saying that all good things come to an end. So also for CIR. When I write these words, we are in the final leg of operations at the Centre for Immune Regulation. Nearly 10 years have passed since we enthusiastically started our centre. It has been 10 amazing years! We have published nearly 450 papers, 45 doctoral candidates have defended their PhD, and we have had 16 Visiting Professors in our faculty. Looking in the rear mirror and questioning myself what made the biggest change with the creation and the operation of CIR, I am tempted to say the Visiting Professor programme. Having the very best immunologists in the world spending time in Oslo with our PhD student and postdocs discussing the nuts and bolts of their projects has been a truly great experience. I am sure it has changed the ambitions and scientific perspectives of our young researchers. By sharing their vast knowledge, the Visiting Professors have helped us to fulfil the goal of CIR; to undertake world leading research in a centre of excellence. I am envious that I did not have this kind of "service" back when I was a PhD student. Scientists at CIR have been very fortunate. The Visiting Professor programme is also what I am going to miss most when CIR is no more. Getting to know all these world-leading researchers has been great. The Visiting Professors have changed my perspectives of science.

CIR has been a very important part of my life for more than a decade. In the beginning, I spent more time and effort on leading the centre than I had anticipated. New infrastructure and programmes were to be established. I had great help though. In every step of my leadership, I have been assisted by a person who served as administrative co-ordinator. Elin Lunde, Stine Bergholtz, Anders Sandvik and Lise Kveberg have all held this position, and they have been my right hand over these years. Thank you so much for all your help and also for standing out with me and all my idiosyncrasies. Further, without the close interaction with Inger Sandlie, the Deputy Director of the centre, I would have been in trouble. Thank you, Inger for your skills, enthusiasm and warm empathy. I do surely cherish the moments we have spent together.

Ludvig M. Sollid
Centre director

I have also been greatly helped by the Board and the Scientific Advisory Board of CIR. Various people have served at the Board over the years. I thank you all. I particularly thank Hilde Nebb who has been the Head of the Board in the final years. As part of the Scientific Advisory Board, Sirpa Jalkanen, Rikard Holmdahl and Søren Buus have poured from their deep insight and advised us how to run a knowledge centre. One of their strong advice was that a centre like ours should not have the same group leaders at the start and at the end. There should be renewal and adaptation. We have followed their advice. We were five group leaders at the start, and now we are seven. Speaking about you group leaders, I of course thank you – old and new – for your team-spirit, enthusiasm and never-ending effort. Without you, CIR would not have been a success!

Finally, I need to thank the Research Council of Norway for funding the CIR-operation. I hope we have lived up to the expectations and that no one is disappointed. On my side, I utter that I am a little disappointed that CIR cannot continue. It has become an internationally recognised centre, and it is very well functioning. Having said that, I agree that a national centre of excellence programme at any given time should support the science that has the biggest potential. Hence there has to be renewal over the years. Given these facts, I and the other group leaders of CIR, together with our hosting institutions, the University of Oslo and Oslo University Hospital, will in the continuation strive to cultivate the best elements of CIR and to support the tremendous human resources of the centre. In this way, the spirit and legacy of CIR have a chance to live on.

CIR, Congratulation for the success of ten years as Centre of Excellence!

Through all these years, CIR has been at the scientific forefront that has led to outstanding research and new understanding in its field. Important features of the success of CIR, as I see it, is the scientific vision with clear strategic focus combined with strong and dynamic leadership in terms of both scientific directions and management which have involved the very best scientists at all levels and from all parts of the world. Furthermore, the understanding of original and innovative research together with the highly multidisciplinary environment and thinking in CIR, have provided the researchers an optimal setting for frontline research that further foster excellence in science, new innovations and development of young research talents. The Centre's scientists have received awards and honors for excellent science and innovation. I will especially mention the UiO and Inven2 innovation honorary awards to Professor Inger Sandlie, the deputy leader of CIR, for her many innovations that are getting close to entering the clinic and Prof. Ludvig Sollid, the Center leader that was honored with among others Anders Jahre's Medical Nordic Prize, The Rank Prize and The 2012 United European Gastroenterology Prize for excellent research.

The Faculty of Medicine, UiO has been a proud host of CIR throughout all these years in close cooperation with Oslo University Hospital. I have been the chairman of CIR the last six and half years and it has been inspiring to witness the progress and success of CIR during its lifetime. I wish to commemorate Prof. Ludvig Sollid for his enthusiasm and vision that has been so important for the center and for his excellent leadership during these ten years. Although the Centre period is now coming to an end, it is time for celebration since what has been built in these years cradles promising aspects for the future in this field.

Wishing you all good luck for the future and new rewarding scientific achievements.

Professor Hilde Nebb
Deputy Dean of Research and Innovation,
Faculty of Medicine, UiO

10 years of CIR – a personal view from inside and outside the center

I have had a relationship with CIR from its conception until this day. As a researcher under the auspices of the late Per Brandtzaeg I remember well the first meeting in Centre for Vaccinology and Immunotherapy (CEVI) and our bid to become a center of excellence in the first call from the Research Council of Norway. The application brought some strong research groups together, but lacking a strong coherent joint vision, CEVI did not make it all the way. However, the financial support received by the University for being a finalist was encouraging (and very useful) and five years later Ludvig was the clear choice to head the new application, this time as Centre for Immune Regulation. I was a fresh faculty member at the time, but was given room at the table with Ludvig, Bjarne, Inger and Oddmund and backstage I continually conferred with Frode. I learned a lot from the application process and discovered that I also had something to contribute: sometimes as mediator and one finding compromises, sometimes with my own ideas.

When the funding of CIR came through it was a great sense of satisfaction, relief and security (at least for 10 years). Frode and I had more or less merged our groups at this time and now we felt we were able to plan for the long term. However, life sometimes takes unexpected turns and a couple of years later I was on my way out although I stayed a group leader for the first 5-year period. In my new position as department head at IMBV (now IBV) I followed CIR from the outside. A great success was how Inger's "technology group" integrated with the "disease groups" at Rikshospitalet. The word synergy is often misused, but in this case, I think it is fair to say CIR created synergy. Unfortunately, Oddmund's other commitments and the fact that the imaging facility could not be moved hampered an equally successful integration of his group in CIR, but of course they have continued to do excellent science.

Now that the 10-year period as an RCN-supported center is ending, I have once again changed positions. As Dean of Research at The Faculty of Mathematics and Natural Sciences, I will do my best to ensure that the legacy of CIR lives on, not just at the Medical Faculty, but also at MatNat. In a few years we will see the erection of the new Life Science building and hopefully interdisciplinary top level research, as that done at CIR will find a new home in that building.

CIR will go down on record as a very wise investment by the RCN. I would like to congratulate original group leaders as well as those who became group leaders during the great 10-year run. I would also like to thank everybody that has been involved in CIR, whether it be masters' students, technicians administrators or researchers. The success of CIR would not have come without you.

Finn-Eirik Johansen
Dean of Research at The Faculty of Mathematics and Natural Sciences

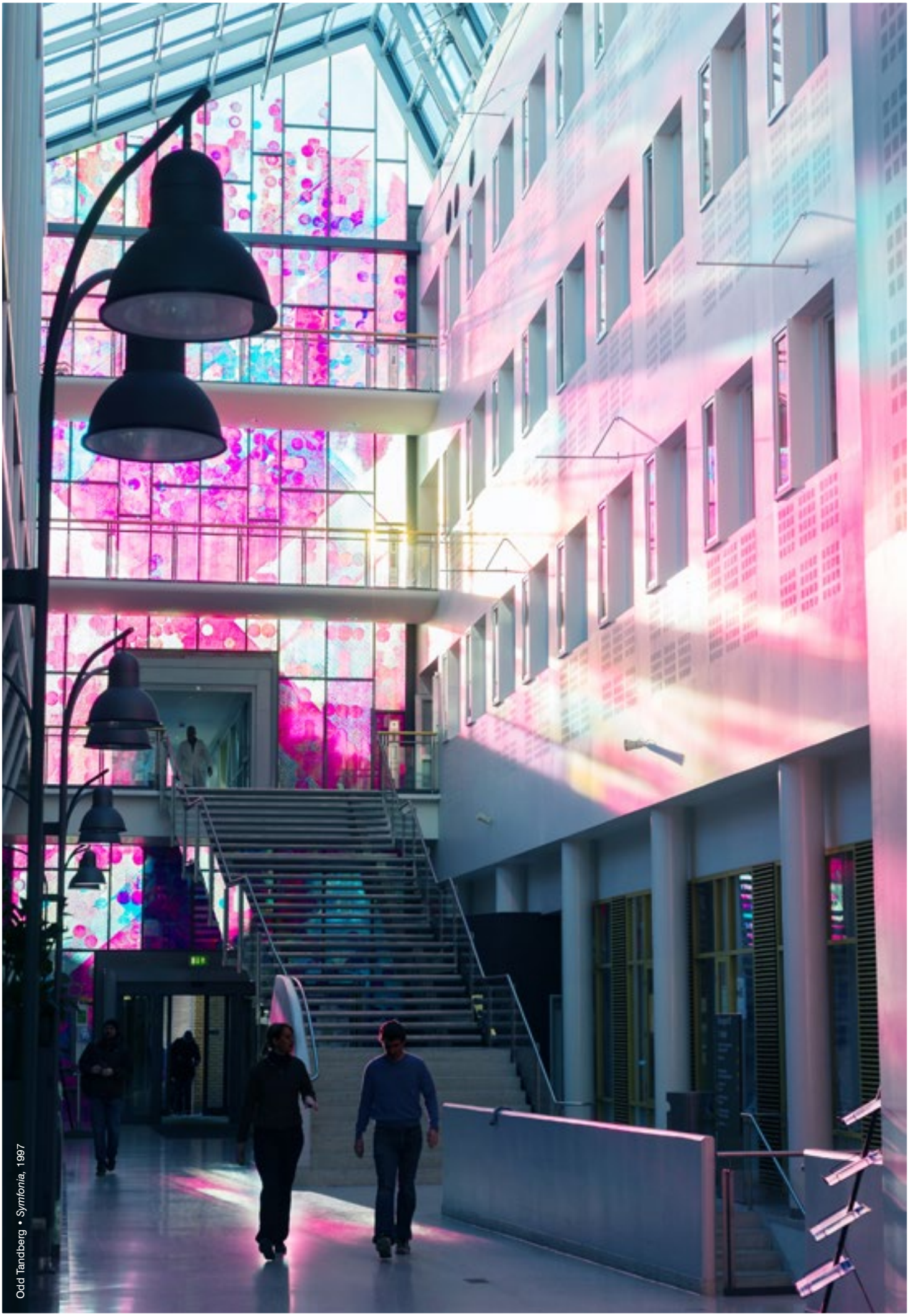
The CIR groups will continue to be very important for future translational research at OUH

University of Oslo has been the host institution for Centre for Immune Regulation (CIR), while Oslo University Hospital was an equal consortium partner. CIR has been a very successful Centre of Excellence and has been very important for our institution. The conclusion of the mid-term evaluation was "exceptionally good" and we are extremely proud of the achievements obtained throughout the 10-year existence of the Centre. The Centre has performed international top-level translational research, studying mechanisms of immune dysregulation that contribute to autoimmune disease and allergy. During the existence of the Centre, many articles have been published in international top journals and some of the Centres researchers, including the Director of the Centre, have received prestigious prizes for excellent research. Furthermore, two K.G.Jebsen Centres have emerged from the research groups involved in the Centre, and part of the Centre has been recognised as a World-leading research milieu at University of Oslo. Of note, the Centre has also had a very strong innovation profile, and promising start-up companies have been established based on innovations from members of the Centre.

19 nationalities have been represented at the Centre, and the international collaboration has been enforced by an impressive arrangement with high-profiled guest lecturers and visiting professors.

Excellent research is an important basis for updated patient care of high quality. CIR has contributed significantly to strengthening of the translational research, which is an important goal for the hospital. Its multidisciplinary nature has contributed to bridging the gap between basic sciences and clinical medicine. With the high quality of the research personnel, it is our strong belief that the groups will continue to play important roles for the development of molecular medicine and for the research at OUH.

Erland B. Smeland
CIR Board member and Director of Research,
Education and Innovation, Oslo University Hospital



Odd Tandberg • *Symfonia*, 1997

Facts and figures

Centre for Immune Regulation (CIR) was established in December 2007 as one of the Research Council of Norway's Centres of Excellence. Following a successful midterm evaluation in 2011, the funding was extended to November 2017. CIR will continue to operate as a Centre of Excellence until the end of November 2017.

The host institution has been the University of Oslo, with Oslo University Hospital as an equal consortium partner. The centre has had a governing with members from these institutions. The Centre Director has reported to the Board which again has reported to Dean of the Faculty of Medicine. The research groups of the centre have either belonged to the Faculty of Medicine or to the Faculty of Mathematics and Natural Sciences. Centre staff has been employed at the University of Oslo or Oslo University Hospital, and they have, in addition to their affiliation with CIR, also had affiliations with Department of Biosciences, the Department of Immunology or the Department of Pathology.

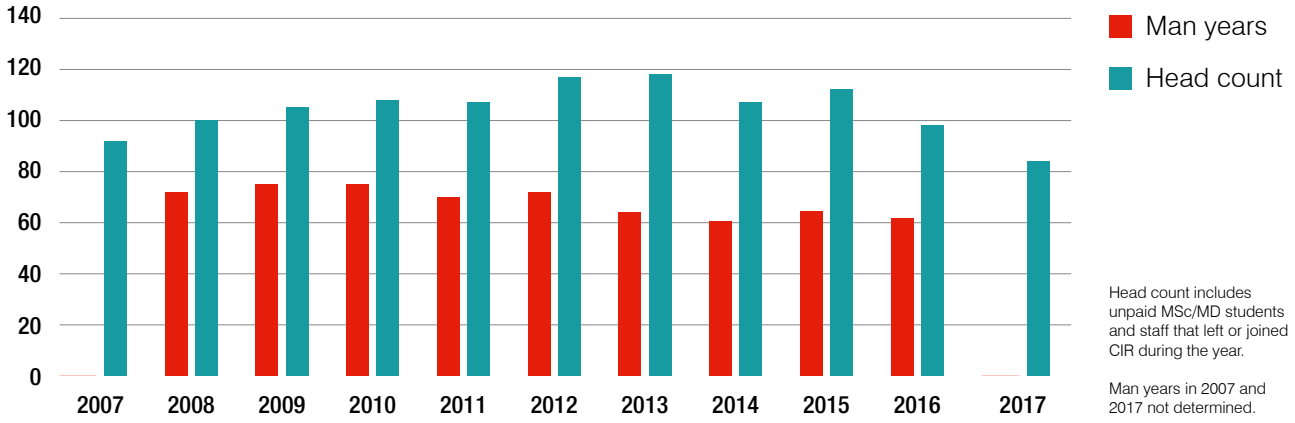
Since 2010, CIR has been a FOCIS (Federation of Clinical Immunology Societies) Center of Excellence. The status as a FOCIS Center of Excellence (FCE) has provided an opportunity to build an interdisciplinary translational immunology community, giving access to an effective training environment for translational researchers and clinicians and an international network promoting new links for researchers and clinicians.

The number of CIR staff members increased from the start of the centre until 2013, reaching 118 members. In 2014 some members were transferred to the K.G. Jebsen Centre for Influenza Vaccine Research, and later in 2016 to the K.G. Jebsen Coeliac Disease Research Centre. As per September 2017, 84 persons from 18 nationalities are involved in research at CIR (fig. 1).

The percentage of Phd and MSc students peaked at 49 % of the total staff in the middle of the ten-year period, indicating the centre facilitated increased recruitment and scientific growth. In total, 45 Phd students and close to 50 MSc students and students in the medical student research program, have graduated from the centre per September 2017. The number of group leaders increased from 5 to 7 after recruitment of two younger group leaders during the last 5-year period.

The overall gender balance at CIR in 2017 is 50 females/34 males (fig. 3) with an overweight of female members among PhD students, MSc students and technicians, and an overweight of male members among group leaders and senior researchers (fig. 4).

FIGURE 1. CIR staff development 2007–2017 (Sept)



Head count includes unpaid MSc/MD students and staff that left or joined CIR during the year.

Man years in 2007 and 2017 not determined.

FIGURE 2. Centre personnel 2007–2017 (Sept)

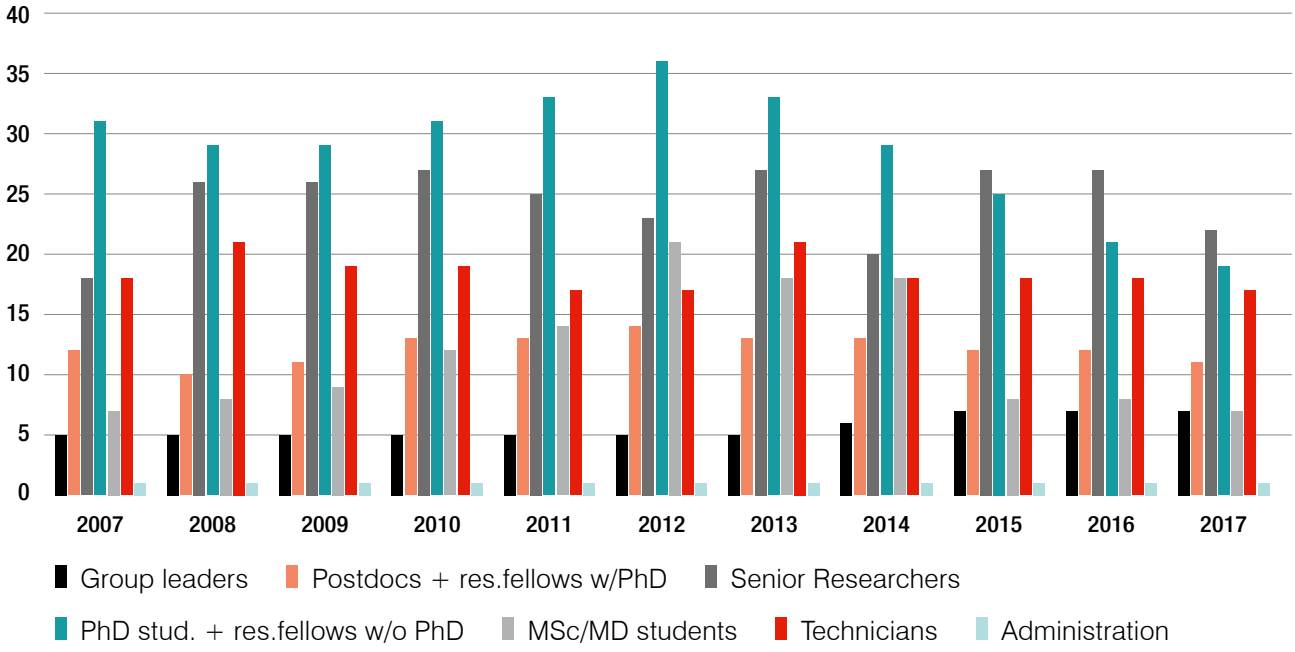


FIGURE 3. Gender distribution, all members

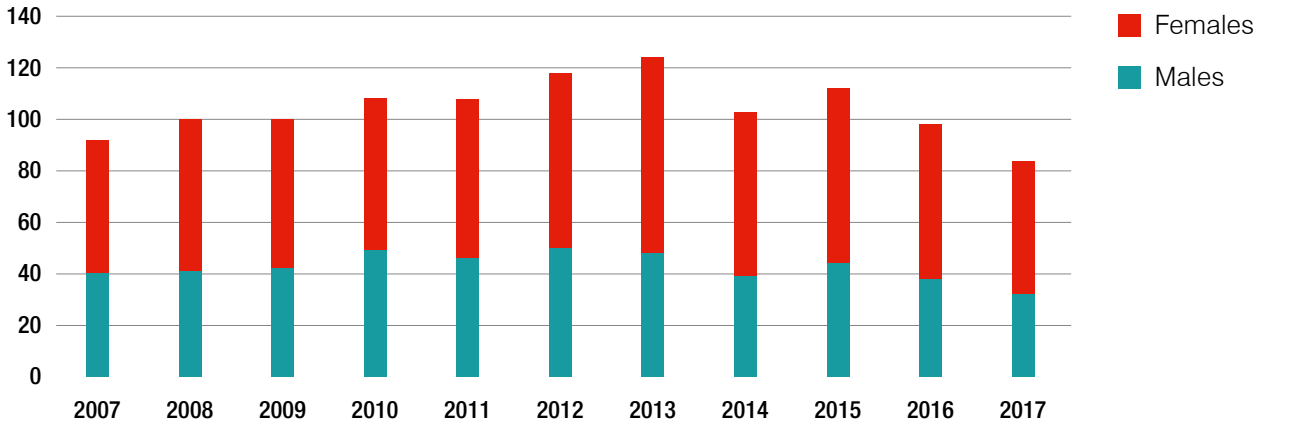
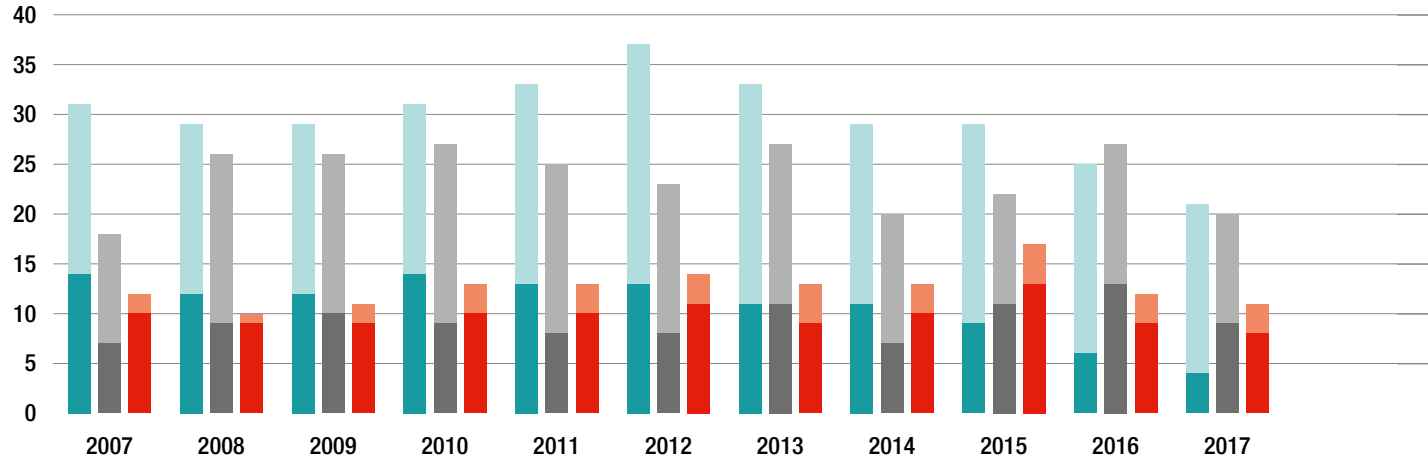


FIGURE 4. Gender balance



THE RESEARCH GROUPS

CIR consists in 2017 of research groups headed by the following principal investigators:

- Professor Ludvig M. Sollid (from start)
- Professor Inger Sandlie (from start)
- Professor Oddmund Bakke (from start)
- Professor Bjarne Bogen (from start)
- Professor Frode L. Jahnsen (from 2013, group headed by Finn-Eirik Johansen from start)
- Professor Ludvig A. Munthe (from 2014)
- Associate Professor Shuo-Wang Qiao (from 2015).

In 2014, the Medical Faculty also announced through the "phasing in scheme" an associate professorship for a junior faculty member within CIR. Among strong applicants from all over the world, Shuo-Wang Qiao was recruited to the position and offered a group leader position at CIR from August 2015.

MANAGEMENT

The centre has for the whole 10-year period been headed by Director Ludvig M. Sollid with support from the Deputy Director Inger Sandlie. The Director has the responsibility for project management, administration and delivery. The centre management has been supported by an administrative coordinator. This position has been hold by:

- Lise Kveberg (2014-2017)
- Anders Sandvik (2009, 2010-2014)
- Stine Bergoltz (2010)
- Elin Lunde (2008-2009).

THE CIR BOARD

The governing board of CIR included four members; two from the University of Oslo (UiO) and two from the Oslo University Hospital (OUS). The board was appointed by UiO. The authority of the board has been to ensure that the intentions and terms of contract described in the Centre of Excellence agreement are fulfilled. Furthermore, the board has approved the annual budgets and ensured that centre activities are completed as outlined in the project description and funding plan, within the adopted time frame.

CIR board 2017

- Hilde I. Nebb (chair 2011–2017), Dean of Research, Faculty of Medicine, UiO.
- Svein Stølen (2013-2017), Dean of Research, Faculty of Mathematics and Natural Sciences, UiO.
- Erlend B. Smeland (2013-2017), Director of Research, Innovation and Education, OUS.
- Lars Eide (2015-2017), Head of Research, Division of Laboratory Medicine, University of Oslo/Oslo University Hospital

Previous board members

- Sigbjørn Fossum (chair 2007-2010), Dean of Research, Faculty of Medicine, UiO
- John Torgils Vaage (2007-2015), Head of Department of Immunology, OUS
- Anders Elverhøi (2007-2012), Dean of Research, Faculty of Mathematics and Natural Sciences, UiO
- Inger Nina Farstad (2009-2012), Head of Department of Pathology, OUS
- Jahn Nesland (2007-2008), Head of the Clinic of Pathology, OUS

SCIENTIFIC ADVISORY BOARD

From 2007-2015, CIR had an active scientific advisory board (SAB) consisting of European world-class scientists. The SAB's mandate was to critically evaluate and advice on the centre's scientific performance and progress. Their effort and good advises has been valuable and highly appreciated.

- Professor Søren Buus, University of Copenhagen, Denmark.
- Professor Rikard Holmdahl, Karolinska Institutet, Stockholm, Sweden.
- Professor Sirpa T. Jalkanen, University of Turku, Finland.

F M PhD stud. + research fellows without PhD

F M Postdocs + res.fellows with PhD

F M Senior Researchers

The Federation of Clinical Immunology Societies (FOCIS) Centers of Excellence (FCE) network creates a community of researchers and clinicians that provides an effective translational training environment by promoting interdisciplinary innovation. www.focisnet.org

FOCIS-COE

CIR is a Federation of Clinical Immunology Societies (FOCIS) Centre of Excellence (FCE) (www.focisnet.org). The FCEs represents an exclusive community of institutions of outstanding clinical and scientific quality. There are 74 FCE's worldwide, with approximately 45 centres in North-America and 29 in Europe. The FCE status represents an international recognition of the quality and impact of CIR and provides an opportunity for CIR to strengthen our translational immunology activities.

CIR FUNDING

The CoE/SFF core funding from RCN makes up about 15% of the total funding of the Centre. The distribution of the different sources of income to the Centre for the period 2007 to 2016 was as follows: -Host institution (UiO): 27 %. -Partner (OUS): 13%. -Other external projects: 45 %. The total CIR budget of external funding and host/partner institution support has from 2008 (first full year)-2016 amounted to 61-85 MNOK per year.

About 4% of the RCN funding has been allocated to the gender equality programme. About 25-50% (annual variation) of the remaining RCN funding has been allocated to salary for the centre management and administrative coordinator as well as common strategic investments prioritised and agreed upon by the group leaders and centre Board. Such investments have been advanced equipment and centre infrastructural activities like meetings and seminars, the visiting professor programme, guest lecturers, student mobility support, and means for career development.

POST CIR STRATEGY

After this 10 year period, the Centre for Immune Regulation will cease to exist as a unit, but it is important that the scientific legacy of CIR will be maintained. The host institution has committed to have a "phasing in strategy" to ensure the CIR exit will leave a strengthened institution with capability to continue to attract excellent international researchers and students, and publish in high impact journals. It is also expected that the scientific environment will have increased capacity to attract external funding from EU and other larger funding schemes. The "phasing in strategy" has been termed "Scientific Excellence Research Thematic Area" (SERTA) and includes two permanent academic positions to the scientific environment and some continued financial support. One position is held by CIR scientist Shuo-Wang Qiao who in 2015 was recruited as Associate Professor and new group leader of CIR, in competition with many strong international and national candidates. The second position is included as part of the larger funding from University of Oslo to further strengthen and develop a world-leading research community on human immunology, in particular autoimmunity and coeliac disease, that has emerged at the Department of Immunology/CIR. The position was announced in the new research field of Systems Immunology and includes a startup package of two postdoc positions and running expenses for three years. The recruitment was recently successfully completed, and Dr. Victor Greiff from ETH Zürich, Basel, Switzerland, will start in this position in January 2018 as an Associate Professor.

Funding	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	Total
CoE		5688	16717	5515	16545	10175	11050	11050	11050	11050	10500	109340
UiO	1992	20473	19392	16214	17515	22412	21086	21686	15869	16483	*	173122
OUS	919	12018	11482	8624	9183	10155	7864	9086	3733	8730	*	81794
Other funding	1041	32700	30870	31177	42004	30674	24411	30740	30514	38672	*	292803
Total	3952	70879	78461	61530	85247	73416	64411	72562	61166	74935	10500	657059

*Data for 2017 not available at publication date

Scientific currency

Timeline
CIR key events

2007

Vaccibody AS was founded

2008

Agnete B. Fredriksen His Majesty the King's Gold Medal for the best PhD thesis at the Medical Faculty at the University of Oslo

Melinda Ráki The Norwegian Society for Immunology Research Award for first author of an outstanding original scientific paper in the field of immunology

Visiting professor: Maria Rescigno

CIR retreat • Hafjell

2009

Michael M. Zangani The Norwegian Society for Immunology (NSI) research award for first author of an outstanding original scientific paper in the field of immunology

Spin-out company, Nextera AS, was founded

Gender equality programme is operative

Visiting professors: Richard Blumberg, Jacques Neefjes, Mark Shlomchik, Kai Wucherpfennig

2010

Ludvig M. Sollid The Rank Prize for Nutrition in recognition of his work on the mechanism of coeliac disease

Ingebjørg Skrindo Klosterstiftelsens research award for her work on the mechanisms of airway allergy

Inger Sandlie and Jan Terje Andersen The Dep. of Mol. Biosciences Innovation Prize for their work with albumin/FcRn.

Ludvig M. Sollid received a prestigious ERC Advanced Grant for the project "Coeliac disease: Understanding how a foreign protein drives autoantibody formation"

Sandlie's group moves to Rikshospitalet

CIR becomes a FOCIS Centre of Excellence

Visiting professors: Jacques Neefjes, Mark Shlomchik, Richard Blumberg

CIR retreat • Geilo

2011

Inger Sandlie The University of Oslo's Innovation Prize. The prize is established to acknowledge and stimulate research driven innovation and entrepreneurship

CIR scientists organise the 14th International Coeliac Disease Symposium and 40th meeting in the Scandinavian Society for Immunology

Passed the midterm evaluation

Visiting professors: John Trowsdale, E. Sally Ward, Fiona Powrie, Maria Rescigno, Kai Wucherpfennig

CIR retreat • Sundvolden

2012

Ludvig M. Sollid Fridtjof Nansen's Prize for excellent research in science and medicine («Fridtjof Nansens belønning for fremragende forskning innen realfag og medisin») for his ground-breaking work on coeliac disease

Ludvig M. Sollid The United European Gastroenterology's (UEG) Research Prize. The prize was awarded for his major contributions to advancing the understanding of coeliac disease on the molecular level

Melinda Ráki Professor Kreyberg's Prize in experimental pathology. The prize is awarded for the best doctoral degree dissertation in experimental pathology the last four years

Roberto Di Niro Oslo University Hospital prize for an excellent research paper

Visiting professors: John Trowsdale, Fiona Powrie, Susan Pierce

2013

- Inven2 “idea prize” to Aram Andersen, Inger Øynebråten, and Bjarne Bogen
- K.G. Jebsen Centre for Influenza Vaccine Research established
- Frode Jahnsen replaces Finn-Eirik Johansen in the management group
- NorMIC-UiO imaging platform opened as national facility
- Cinzia Progida and Shuo-Wang Qiao entered the CIR Career Development programme for female scientists
- **Visiting professors:** Mark Shlomchik, Bana Jabri, Peter Cresswell
- CIR retreat • Geilo

2014

- **Inger Sandlie** The Inven2 honorary award for the registration of a total of 100 innovational ideas to Inven2
- **Ludvig M. Sollid** The Oslo University Hospital’s Excellent Researcher Award for his outstanding research on the pathogenesis of coeliac disease
- **Per Brandtzæg** The Nordic Fernström prize for his major contribution throughout his career to the understanding of the role and function of the immune system in the intestinal mucosa
- **Cinzia Progida** recieved a “Unge forskertalenter” grant from FRIMEDBIO, and the reseach prize from Lab Norge for her work on molecular mechanisms for intracellular transport
- **Visiting professors:** Mark M. Davis, Susan K. Pierce
- CIR retreat • Soria Moria

2015

- **Ludvig M. Sollid** Anders Jahre’s Awards for Medical Research. This prize honor research of outstanding quality in basic and clinical medicine. The prizes are awarded by the University of Oslo and are among the largest within Nordic biomedical research. The prize was shared with Rikard Holmdahl, Karolinska Institutet
- **Ludvig M. Sollid** «Innovator of the month» by South-Eastern Norway Regional Health Authority, for his two ideas for new diagnostic tools for coeliac disease
- **Ludvig M. Sollid:** Honorary membership in the Norwegian Society of Immunology for his contributions to the immunological community
- **Jan Terje Andersen** The Fridtjof Nansen Prize for Early Career Achievements
- **Jan Terje Andersen** The Oslo University Hospital Early Career Award
- **Malin Bern** and **Kine Marita Knudsen Sand** Innovation award from the Department of Biosciences
- **Ludvig M. Sollid** Awarded funding from UiO to develop a world leading research community within the field of human immunology (one of five research communities)
- Nextera AS enters research agreement with Janssen Biotech. Inc
- Vaccibody AS initiates first clinical trial
- Britt Nakken and Jorunn Stamnæs entered the CIR Career Development programme for female scientists
- **Visiting professors:** Bana Jabri, Mark M. Davis, Bernard Malissen

2016

- **Inger Sandlie** Honorary member of the Norwegian Society of Immunology for her many scientific contributions to immunological research.
- K.G. Jebsen Coeliac Disease Research Centre established
- CIR scientists organise the international "Cells on the move" conference.
- **Visiting professors:** Gwendalyn Randolph, Adrian Hayday
- CIR retreat • Geilo

2017

- **Jan Terje Andersen** “Innovator of the month» by the South-Eastern Norway Regional Health Authority
- **Shuo-Wang Qiao** receives funding through UiO: Life Science convergence environments “COMPARE” in collaboration with scientists from CEES and CIR scientists Bakke/Progida
- New K.G. Jebsen Centre finalist (Ludvig A. Munthe). Topic: B cell cancer
- **Visiting professor:** David Nemazee
- CIR final retreat • Holmen Fjordhotell

FIGURE 5. Number of publications from CIR

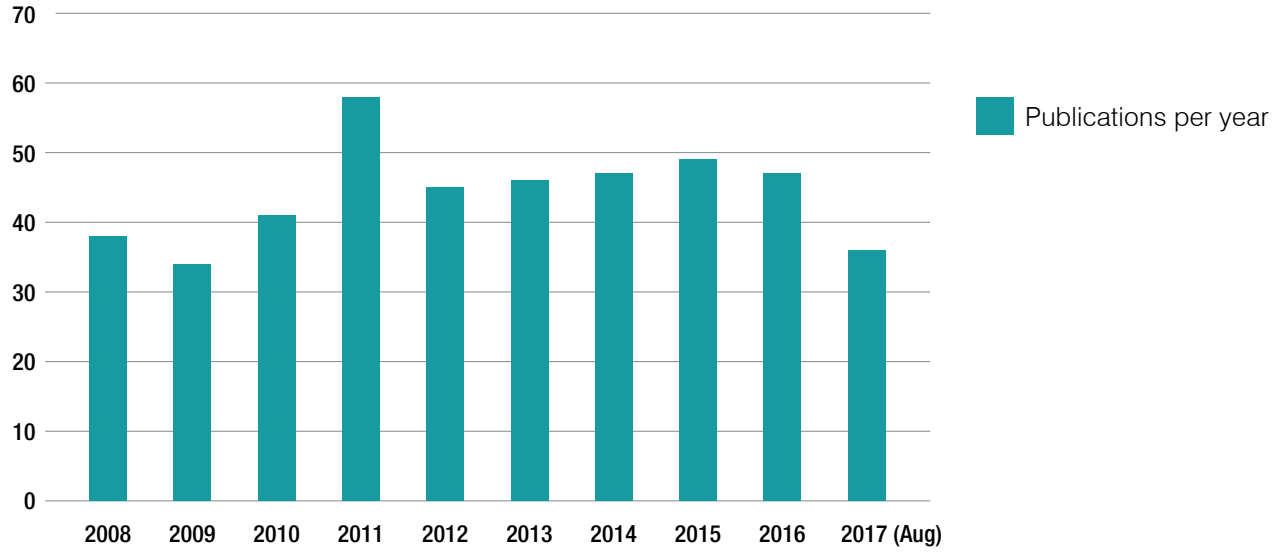
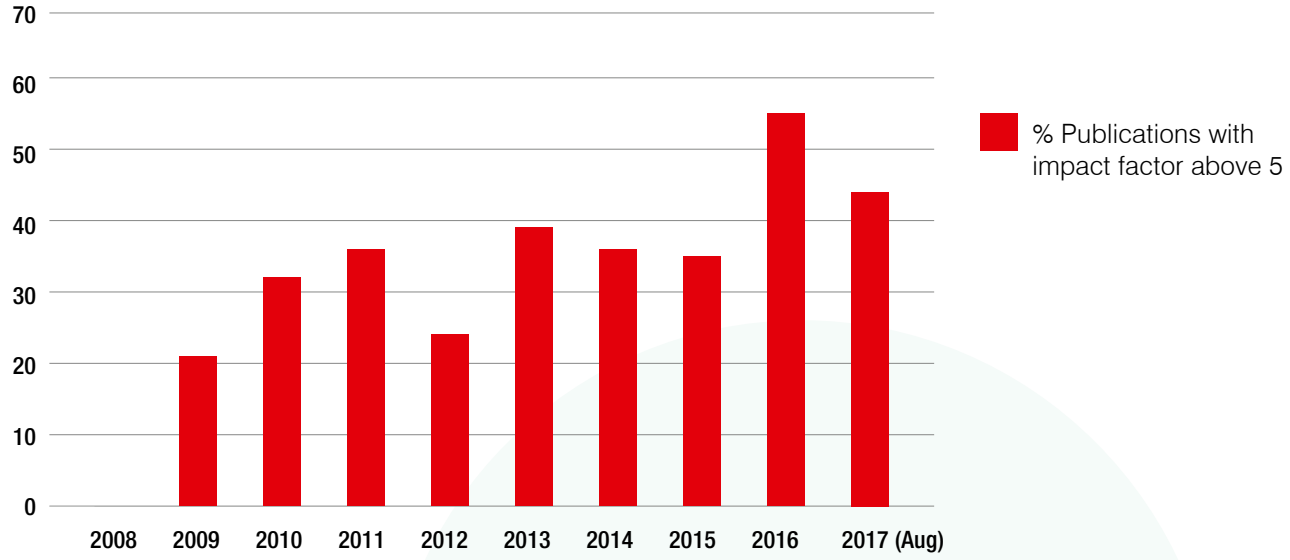


FIGURE 6. % publications with impact factor above 5



PUBLICATIONS

CIR scientists authored or co-authored close to 450 papers in international peer-reviewed journals and more than 35 monographs in the centre period. The total number of publications per year remained stable, with a large increase in the percentage of publications with impact factor above 5 the last two years (fig. 6). CIR scientists have extensive collaboration with national and international research groups, and on average 51% of the publications result from collaboration with international institutions. 11% of the publications are results of direct collaboration between CIR research groups.

PATENTS

Researchers at CIR have a strong interest in, and record of, innovation and securing of intellectual property rights from research. The accumulated number of patents granted or patent applications filed by CIR scientists since CIR commenced operations until 2017 is 28.

DISSEMINATION OF RESEARCH RESULTS

CIR members have given more than 750 presentations at conferences as invited speakers or by oral/poster presentations, approximately 110 new media events/publications, and more than 60 popular science publications.

Photo: Bård Gudim

In Memoriam, Per Brandtzæg 1936–2016

It was as the founder of LIIPAT and its leader for more than 40 years that Per became internationally recognised and a true leader in the field of immunology. Per used physiochemical and immunochemical methods to study immunoglobulins in external secretions and defended his PhD degree in 1971 with a thesis entitled 'Human Secretory Immunoglobulins'. The mucosal immune system was a new area of research. Staining tissue sections with antibodies was a new discipline, and Per developed this method to study immune cells in situ. Through his pioneering work of the secretory IgA system, which included both structural characterization of IgA and studies on the transport mechanism for IgA, Per's scientific breakthrough came in 1974 when he described the model by which secretory antibodies are selectively translocated through the glandular epithelia. This finding stimulated a broad international interest in this field, and over the next few years, the 'Norwegian' model was supported by many international laboratories. Indeed, the model now found in most immunology textbooks such as Janeway's Immunobiology describes how transmembrane secretory component (SC, known as poly immunoglobulin receptor, pIgR) acts as a receptor/carrier protein for polymeric IgA across epithelia. About the same time, Per also showed that the small polypeptide associated with polymeric IgA and pentameric IgM, joining chain (J chain), was a product of plasma cells synthesised independently of the class of immunoglobulins present in the same cell. Important to Per's model was the fact that only J chain-containing IgA and IgM could bind SC/pIgR. Human pIgR was cloned in Per's laboratory in 1991, and later, Per and his co-workers performed several important studies on the regulation of this transport protein. The final proof that the transport model was correct came in 1998 when Per and co-workers demonstrated the absence of epithelial IgA transport in mice deficient for pIgR.

LIIPAT expanded rapidly, and over the next 40 years, Per supervised more than 40 PhD students and numerous postdocs. Together, he published more than 600 articles, 8 monographs and 132 book chapters, and had a strong impact on the development of both pathology and immunology in Norway. He recognised early the importance of establishing binding collaborations between research groups to move the field of immunology forward, and in 2002, he formed the thematic research group 'Centre for Vaccinology and Immunotherapy' consisting of five research groups at the University of Oslo. This thematic research group was the forerunner for CIR. After his retirement in 2006, Per continued as an active researcher as part of CIR.

Modified from Jahnsen, F. L., Johansen, F.-E. and Haraldsen, G. (2016) ***Obituary – In Memoriam Per Brandtzaeg*** Scand J Immunol, 84: 370–372. doi:10.1111/sji.12505"

Core competency at CIR

The centre consists of research groups with complementary scientific expertise. Two groups, headed by Inger Sandlie and Oddmund Bakke, are affiliated with the Department of Biosciences at the Faculty of Mathematics and Natural Sciences. Four research groups, headed by Bjarne Bogen, Ludvig A. Munthe, Shuo-Wang Qiao and Ludvig M. Sollid are affiliated with the Department of Immunology at the Faculty of Medicine. One group, headed by Frode L. Jahnsen, is a member of the Laboratory for Immunohistochemistry and Immunopathology, Department of Pathology, at the Faculty of Medicine.

- **A wide variety of cellular and humoral immune assays**
- **Advanced methods in molecular biology, proteomics and cellular imaging**
- **Disease models in humans and animals. The models are used to understand the molecular mechanisms of immune regulation and autoimmunity**
- **Transgenic mouse models**
- **Functional characterisation of immune cells in human tissue**
- **Study of immune molecules and their intracellular functions in antigen presenting cells**
- **Molecular engineering for the development of new therapeutic agents and research reagents**
- **High-throughput sequencing**

SOLLID GROUP

- Human cellular immunology
- Antigen specific T cells and B cells
- Recombinant soluble HLA molecules
- Mass spectrometry and proteomics
- Characterisation of lymphocyte antigen receptors

BOGEN GROUP

- Cellular and molecular immunology
- Tumor immunology
- Idiotype (Id)-driven T-B cell collaboration
- Autoimmunity
- Lymphogenesis

BAKKE GROUP

- Live cell Imaging
- Confocal microscopy
- Characterisation of intracellular trafficking pathways
- Transfection of cells and the study of binding kinetics of cytosolic molecules

SANDLIE GROUP

- Structure and ligand binding properties of antibodies and T-cell receptors
- Phage display
- Recombinant molecule expression and purification
- Interaction studies

JAHNSEN GROUP

- Human model of airway allergy in vitro and in vivo
- Human mucosal immunology
- Functional studies on dendritic cells and macrophages
- Advanced microscopic techniques
- Flow cytometry and cell sorting

MUNTHE GROUP

- Cellular assays, B and T cell culture
- Mouse experiments including human->mouse xenograft of primary cells
- Cell culture, functional biology, drug sensitivity assays
- Flow cytometry, phosphoflow, mass cytometry
- RNA Sequencing, ChIP-Seq

QIAO GROUP

- Molecular biology
- Single cell receptor sequencing
- Molecular and transcriptional profiling of antigen-specific T cells
- Droplet technology for single-cell transcriptomics


BIOTERM ART.

research groups

Bakke group

A major aim of the Bakke group is to understand the endocytic pathway and how peptide loading of the major histocompatibility antigens (MHC) are regulated. An antigen presenting cell expresses specialised immune molecules such as invariant chain that contributes to the biogenesis of a specialised endocytic pathway in antigen presenting cells. Our focus on the intracellular trafficking includes the study of the small GTPases. We have in the CIR project period extended our studies to intracellular membrane traffic from model cells to human dendritic cells (DCs). This basic work has led us to immunotherapy using the patients own dendritic cells introducing invariant chain as an RNA based immunotherapy vector. Finally the Bakke group is also the co-host for a light microscopy imaging node, NorMIC Oslo now a national and European node within the EuroBioImaging imaging network serving the research community in general.

OVERVIEW OF RESEARCH IN THE GROUP

Invariant chain and generation of an antigen loading compartment in immune cells

MHC II molecules are expressed on the cell surface of professional antigen presenting cells. MHC II molecules present to CD4+ T cells a fragment (peptide) from proteins degraded in the endosomal pathway. Invariant chain (Ii) plays a vital role in MHC II assembly and intracellular transport, and this molecule has been attributed an increasing number of additional functions. An evolutionary conserved property of Ii is to induce the convergence, or fusion of early endocytic vesicles, and this property may serve vital functions in antigen presentation. The endocytic pathway common to all cells is uniquely adapted by specific immune cells to achieve efficient antigen loading. We have contributed to the current understanding of cell biological processes in the endocytic pathway in general and our current goal is to use this foundation to elucidate the unique adaptations to this system in antigen-presenting cells. This will provide the basis to better understand vaccination regimes and protocols for immune therapy of cancers, autoimmune-, and infectious diseases.

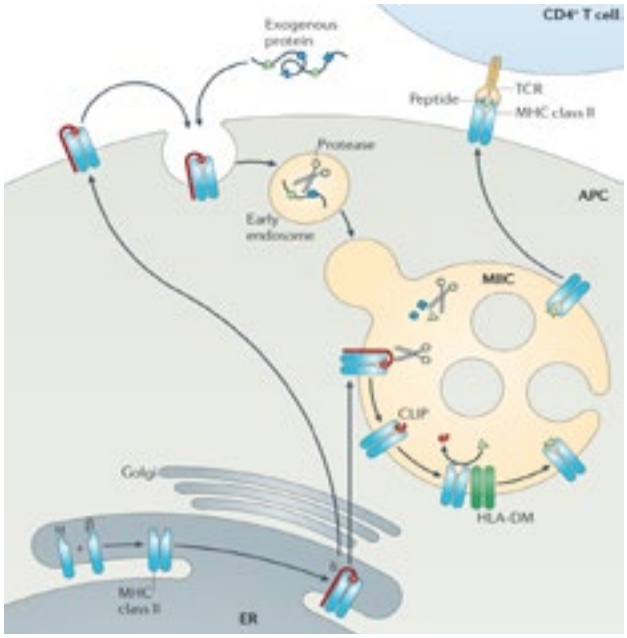
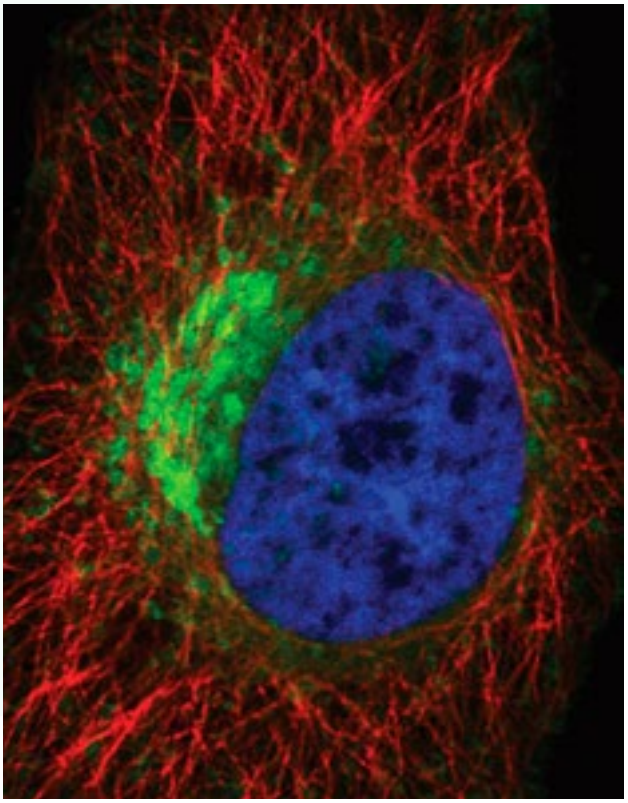


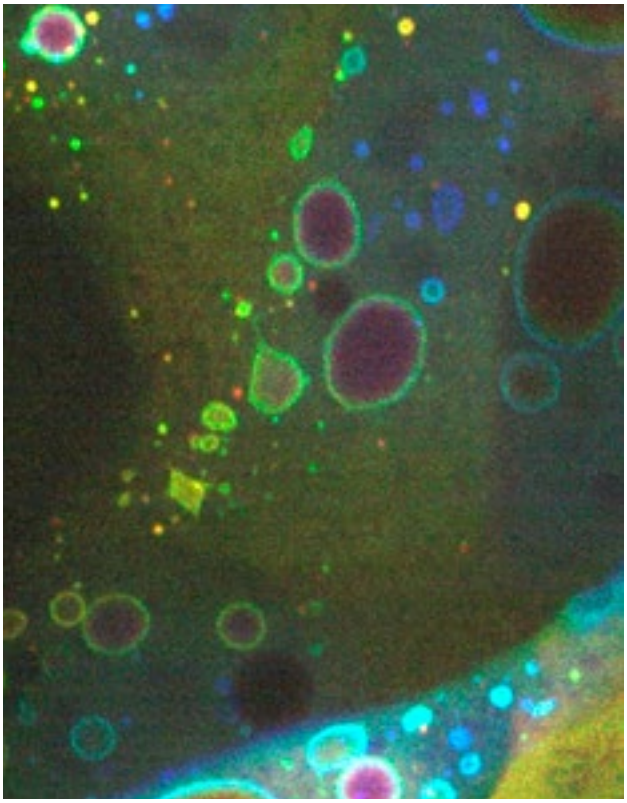
Figure. The MHC class class II antigen presenting pathway. (From Neefjes et al., 2011)

Rab proteins in intracellular traffic and in dendritic cells

Rab proteins are the master regulators of intracellular trafficking, controlling steps from the formation of vesicles from a donor membrane, through their detachment, transport, tethering and fusion with the acceptor compartment. Rabs are small GTPases, members of the Ras superfamily. More than 60 different Rabs have been identified in humans and each Rab is believed to regulate a different step of the intracellular trafficking, such as budding, uncoating, transport along the



From Borg, Bakke and Progida, *J Cell Sci*, 2014.



From Skjeldal et al. *J Cell Sci*. 2012.

cytoskeleton, tethering, docking and fusion of vesicles. However, so far, the functions of only a fraction of known Rab proteins have been characterised in detail.

Rab7b is a very interesting protein that we found to be directing traffic from the endosomal pathway to the Golgi apparatus (Progida et al. *J Cell Sci* 2010, Progida et al. *Traffic* 2012), and highly expressed in cells of the immune system. We have in the CIR period been the only group elucidating this essential Rab. In one study we found that Rab7b as strongly upregulated 4 hours after LPS induction (Berg Larsen et al. *PLoS One* 2013). We have also found that this Rab interact with the actin motor myosin and is involved in cell migration (Borg et al. *J Cell Sci* 2014). We have also worked on other Rabs in particular Rab5,-7a and 9 all implicated in transport within the endosomal pathway (Kucera et al. *Traffic* 2016) and at the end of the CIR period we have performed a Rab screen to detect all Rabs that are involved in migration, an essential feature of the function of dendritic cells.

Regulation of the endosomal pathway, fusion and fission

A major effort has been towards the understanding of the endosomal pathway in cells and how fusion and fission is correlated (Skjeldal et al. *J Cell Sci* 2012) and what regulates maturation within the endosomal pathway. We have studied how EGF/PDGF can stimulate the tyrosine kinase receptors and downstream influence mediators such as cbl and grb2 and on endosome regulate HRS and EPS15 on endosomes thereby connecting signalling to regulation of endosomal coat proteins (Haugen et al., in press).

In antigen presenting cells this pathway is altered creating a slower degrading antigen loading pathway where antigens are proteolytically processed and able to load both MHCI and MHCII. This is regulated by invariant chain itself thereby defining the antigen presenting cell (Landsverk et al. *J Leukoc Biol* 2011).

Invariant chain as an immunotherapy vector

Invariant chain is the molecule that sorts molecules to and generates the antigen loading compartment. Ii is then an ideal candidate for bringing tumor antigens to this compartment for better antigen loading of both MHC I and II (Wälchli et al. *Eur J Immunol* 2014). We have so far much in vitro data supporting such immunotherapy, but the clinical trials have not yet started.

Building NorMIC Oslo, a light microscopy platform

To study intracellular transport of molecules it is essential with top imaging equipment and since the mid 1990-ies the Bakke group has acquired confocal microscopes and built an imaging platform for the Department of Biosciences. During the CIR period this has been extended to a National Platform and an European imaging platform together with another CoE at our University, the Center for Cancer Biomedicine located at the Radium Hospital. This platform is functionally operational for national and international researchers and instrumental for much of our own research.

3 selected publications

Bakke group

2012

The fusion of early endosomes induces molecular-motor-driven tubule formation and fission

Skjeldal FM, Strunze S, Bergeland T,

Walseng E, Gregers TF, Bakke O.

J Cell Sci. 2012,125:1910-9. doi: 10.1242/jcs.092569

In this report we studied fast homotypic fusions and found that immediately after the fusion a highly active and specific tubule formation and fission was observed. The tubule formations were dependent on microtubule interactions, and specifically controlled by specific molecular motors. This shows that the machinery for endosomal fission is set up and only awaits for incoming membrane by fusion so that tubes can eminate from the vesicles without force, in other words evidence for that “fusion stimulates fission”.

2014

Invariant chain as a vehicle to load antigenic peptides on human MHC class I for cytotoxic T-cell activation

Wälchli S, Kumari S, Fallang LE, Sand KM, Yang W, Landsverk OJ, Bakke O, Olweus J, Gregers TF.

Eur J Immunol. 2014, 44:774-84. doi: 10.1002/eji.201343671

The general view is that MHC I gets its peptide antigen in the endoplasmatic reticulum whereas we here find that MHCI may also be loaded in the endosomal pathway, This was shown both in model cells and human dendritic cells. These results show that Ii carrying antigenic peptides can promote efficient presentation of the epitopes cytotoxic T cells independently of the classical MHCI peptide loading machinery, facilitating novel vaccination strategies against cancer.

2014

A novel interaction between Rab7b and actomyosin reveals a dual role in intracellular transport and cell migration

Borg M, Bakke O, Progida C.

J Cell Sci. 2014,127:4927-39. doi: 10.1242/jcs.155861

In his article we show that Rab7b, a Rab that controls the transport between late endosomes and the trans Golgi network, interacts directly with an actin motor, myosin II. We further find that myosin II mediates the transport of Rab7b endosomes, regulates actin remodeling and, consequently, influences cell adhesion, polarisation and migration. Our findings thus reveal a new role for Rab proteins outside of their usual role in intracellular trafficking, identifying this new Rab7b as a coordinator of cytoskeletal organisation.

Bogen group

The Bogen group runs projects with three areas: 1) Idiotype(Id)-driven T-B collaboration and its role in health and disease 2) The mechanism by which CD4+ T cells can reject cancer cells 3) Novel vaccine molecules for cancer and infectious diseases (organised in K.G. Jebsen Centre for Research on Influenza Vaccines).

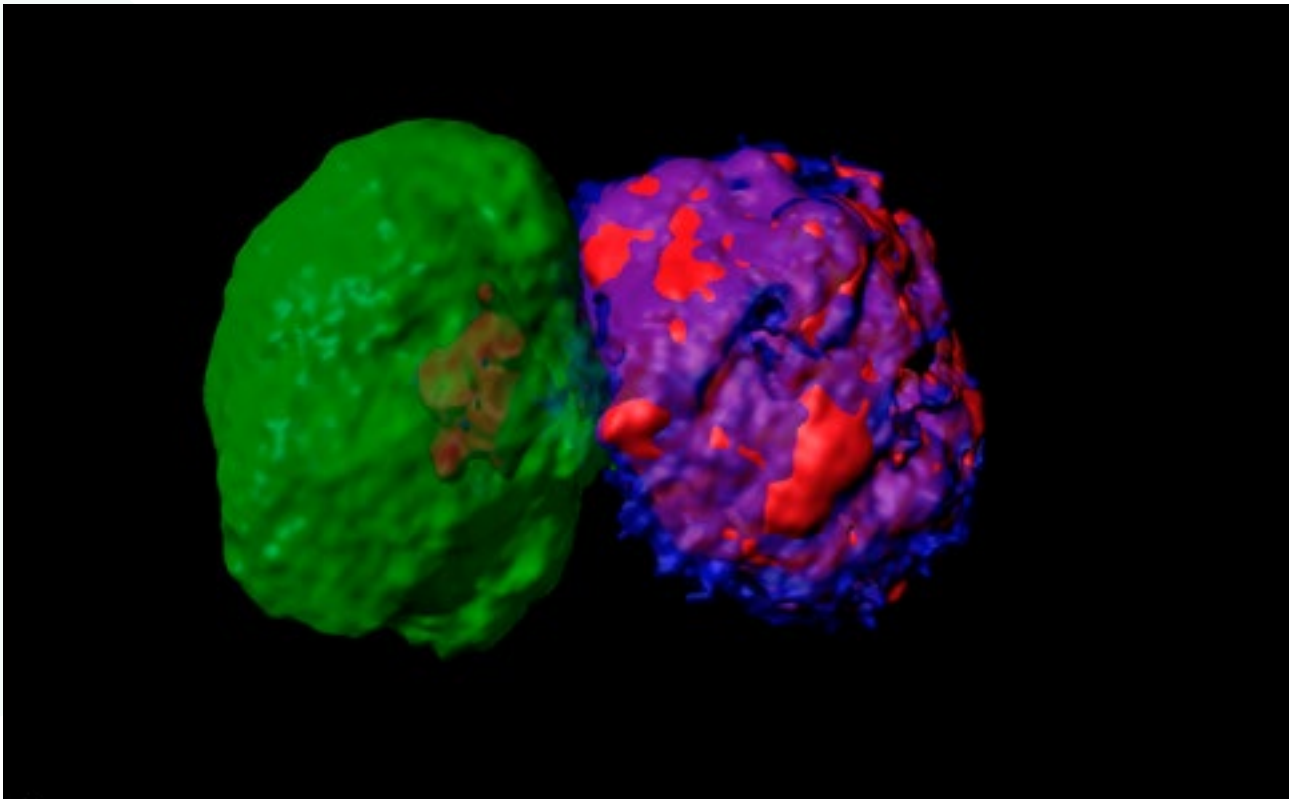
OVERVIEW OF RESEARCH IN THE GROUP

Immunoglobins (Ig, antibodies) are extremely diverse. The heterogeneity is localised to their variable (V) regions. Bogen and co-workers showed more than 25 years ago that Ig is partially broken down inside B cells and that proteolytic fragments of the V-regions [Idiotypic (Id)-fragments] are presented on Major Histocompatibility Complex (MHC) class II molecules to Id-specific CD4+ T cells. This phenomenon forms the foundation for the CIR-related projects of the research group, outlined below.

Key project summaries

Id-driven T-B collaboration: The basis for Id-driven T-B collaboration is that B cells spontaneously degrade their B cell receptor (BCR) for antigen, and display Id-peptides bound to MHC class II molecules on their cell surfaces. Such Id/MHCII complexes can be recognised by Id-specific CD4+ T cells. We have hypothesised that if a B cell recognises a self-antigen with its BCR, and at the same time receives help from an Id-specific CD4+ T cell, the B cell receiving these two distinct signals will be activated, proliferate and differentiate. This can result in immune dysregulation, auto-immunity and B lymphoma development. A focus of the BB group's CIR-related activities has been to substantiate this hypothesis.

In previous studies we have used Ig-transgenic mice that have certain un-physiological aspects. Moreover, it was difficult to study the influence of BCR-ligation on Id-driven T-B collaboration in the old model. To solve these problems, we have now (with CIR-funding) generated two novel BCR knock-in mice. In the first of these two strains, a defined Id-sequence is expressed in a few B cells and at a physiological level. In the other strain, a rearranged VDJH is expressed by most B cells. In offspring of these two strains, a few B cells (1%) will express a BCR with the defined Id-sequence in its L chain and a BCR that can be ligated by a defined antigen. To generate the first mouse, three codons (94-96) in a germ-line V gene segment have been exchanged with three codons that encode part of a mutated Id-sequence. Upon rearrangement to a J gene segment in a B cell, the VJ encodes a CDR 3 Id-peptide that after antigen processing is presented on the MHC class II molecule I-Ed on the B cells surface. To generate the second mouse, a rearranged VDJH was inserted into the JH locus. Offspring from these two mice express a defined Id+ BCR on 1% of their B cells, and the Id+ BCR can be ligated by defined antigens. The pId:MHCII complexes on the surfaces of Id+ B cells are recognised by Id-specific CD4+ T cells from TCR transgenic mice. Such an interaction is called Id-driven T-B collaboration. The new model has enabled us to show that BCR ligation is a requirement for efficient Id-driven T-B collaboration, resulting in a GC reaction, generation of plasma cells and antibody formation. An implication of this finding is that a B cell, when its BCR is ligated by antigen, not only process and MHCII-present antigen to antigen-specific CD4+ T cells but also process its BCR and MHCII-present Id-peptides to Id-specific CD4+ T cells. Presumably, processing of antigen and BCR occur in the same endosomal compartment. These results indicate that a B cell is not only regulated by antigen-specific T cells but also Id-specific T cells. This might have a profound influence not only on basic processes such as immune regulation and memory, but also on induction of disease. Indeed, in offspring of a cross between the V gene codon-modified mouse and the Id-specific TCR-transgenic mouse,



Imaging of interaction between two B cells with complementary B cell receptors (that bind each other). Photo: Frode M. Skjeldal

offspring appear to first develop autoimmunity and then B cell lymphomas. The B lymphomas have an autoreactive BCR and hyper-express pId:MHCII complexes. This finding is consistent with the hypothesis described above. The hypothesis is also strongly supported by recent observations in humans: First, in a collaborative study with Ludvig Munthe, it was shown that growth of Chronic Lymphatic Leukemia (CLL) cells is enhanced by Id-specific CD4+ T cells (Os et al. *Cell Reports* 2013). Second, B lymphoma cells strongly present Id-peptides on their MHC class II molecules (Khodadoust et al. *Nature* 2017). A reasonable explanation of the latter findings is that it represents an end-result of Id-driven T-B collaboration, consistent with our hypothesis and previous findings in mice. In humans, it is challenging to study Id-driven t-B collaboration in vivo, while this can be done in the mouse model we have established. Together, the two approaches make a compelling case for the importance of Id-driven T-B collaboration in B lymphoma development.

Tumor immunology: The basis for the tumor immunological experiments of the group is that Ig secreted by multiple myeloma cells (malignant plasma cells) is processed and presented on MHC class II molecules of tumor-infiltrating macrophages. An interplay between Id-specific CD4+ T cells and macrophages results in activation of macrophages that in turn kill the tumor cells. Ongoing experiments focus on the molecular mechanisms by which M1-like macrophages, activated by Id-specific Th1 cells, kill tumor cells. A bone-marrow model for multiple myeloma (the MOPC315.BM model), published by our group in 2012, has now been distributed to a large number (>30) collaborators world-wide. Using this model, we have ourselves recently demonstrated that CD4+ T cells can kill multiple myeloma cells growing in the bone marrow. We have also knocked out MHC class II molecule (I-Ed) expression in the MOPC315.BM cell line, nevertheless Id-specific CD4+ T cells reject these MHCII-deficient MM cells. This study conclusively demonstrates that CD4+ T cells in a collaboration with macrophages can kill tumor cells that lack expression of MHC class II molecules.

CIR-contribution to studies

Id-driven T-B collaboration and its ability to induce disease has been a central part of the CIR project portefolio. The experiments have been quite time- and resource-consuming, but we have apparently succeeded. The model we have established will clearly give important results in the coming years. The importance of Id-driven T-B collaboration is supported by recent studies in humans, and the interest in this area of research is likely to increase. In addition to CIR, funding has been obtained from The Research Council of Norway, HSØ, EUROSTAR and EU-INDIGO. Collaboration within CIR has clearly contributed to the success of the projects.

3 selected publications

Bogen group

2014

Naive idiotope-specific B and T cells collaborate efficiently in the absence of dendritic cells

Jacobsen J, Haabeth OA, Tveita AA, Schjetne KW, Munthe LA, Bogen B.

J Immunol 2014 May 1; 192(9):4174-83. doi: 10.4049/jimmunol.1302359

This paper demonstrates the usefulness of BCR knock-in mice in studies on T-B collaboration. The studies were done in a model of conventional T-B collaboration rather than Id-driven T-B collaboration. The results show that naive B and CD4+ T cells can efficiently collaborate.

2015

Tumor escape from CD4+ T cell-mediated immunosurveillance

Tveita AA, Schesvold F, Haabeth OA, Fauskanger F, Bogen B.

Cancer Research, 2015 Aug 1;75(16):3268-78. doi: 10.1158/0008-5472.CAN-14-3640

This paper demonstrates that cancer cells can escape rejection by CD4+ T cells by changing the quaternary structure of the tumor-specific antigen they produce. The change in quaternary structure abrogates processing of tumor-specific antigen by tumor infiltrating macrophages, thereby abolishing activation of tumor-infiltrating Th1 cells.

2015

Idiotype-specific CD4+ T cells eradicate disseminated myeloma

Haabeth OA, Tveita A, Fauskanger M, Hennig K, Hofgaard PO, Bogen B.

Leukemia 2016 May 30(5): 1216-20 Oct 9 PMID: 26449664. doi: 10.1038/leu.2015.278

The paper demonstrates that CD4+ T cells can reject multiple myeloma cells that have had their MHC class II molecules ablated by CRISPR/Cas9. The results conclusively demonstrate that CD4+ T cells can reject tumor cells that lack MHC class II molecules. This result is important since most tumor cells do lack MHC class II molecules.

Jahnsen group

The Jahnsen group has projects within two areas:

- Understanding the immunopathology of allergic airways disease
- Dissecting the functions of immune cells in the human gut related to health and disease (e.g. celiac disease and transplantation pathology)

CIR has been extremely important for our research. We have established several very fruitful collaborations; especially with the Sollid group. CIR has provided a very creative atmosphere for discussions and for the transfer of knowledge including new methods and techniques. The visiting professor and the invited speaker programs have been most inspiring and have initiated several international collaborations. CIR has also been a driving factor in improving the quality of core facilities at the hospital.

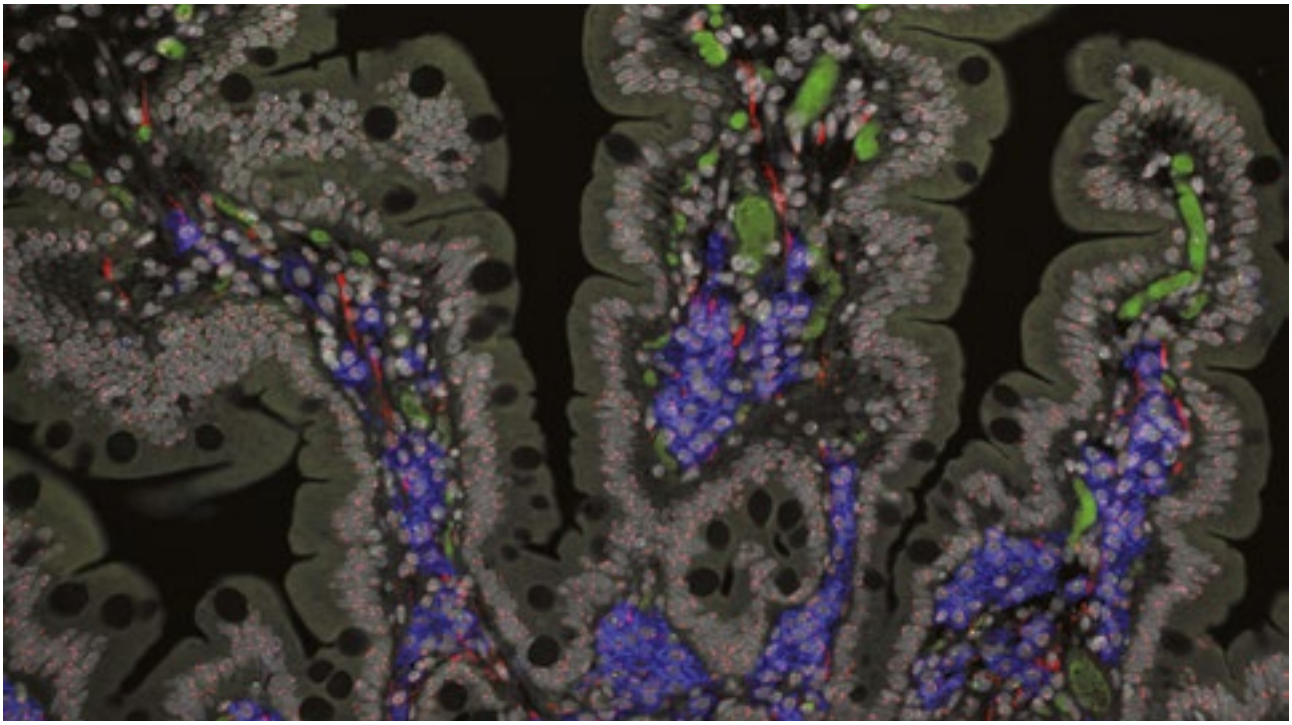
OVERVIEW OF RESEARCH IN THE GROUP

Immunopathology of airway allergy

In some predisposed individuals, harmless foreign substances, such as pollen may trigger adverse immune reactions and cause airway allergy. Our aim has been to study immunopathology as an underlying cause of allergic airway inflammation. For this purpose we established a unique human model of allergic rhinitis in which we sprayed grass or birch extracts locally in the nose of hay fever patients (and controls) once daily for up to a week. Immune cells in tissue and blood were isolated and analysed by different techniques including phenotyping by flow cytometry, global transcriptomics and various functional assays. Based on a series of experiments our salient findings are as follows: The nasal mucosa of hay fever patients habors long-lived allergen-specific T cells that rapidly become activated. This is followed by a massive influx of blood monocytes (within hours) to the nasal mucosa. These cells produce proinflammatory cytokines and chemokines that attract Th2 cells and eosinophils that further aggravate the inflammation. Later DC2 accumulate in the mucosa. These cells are activated by TSLP, an inflammatory Th2-promoting cytokine, which increased the DC2's ability to activate allergen-specific Th2 cells locally. Moreover, TSLP increased DC2's ability to migrate to regional lymph node to further activate allergen-specific T cells. In a parallel study we found a similar massive influx of monocytes in the central airways of children with asthma attack. Together, our studies have identified several early triggers of the allergic reaction that are testable targets for anti-inflammatory treatment.

Studies on macrophages and dendritic cells in the gut

We have shown that DCs isolated from the coeliac lesion were superior to macrophages in their ability to activate gluten-specific T cells. However, DCs share many properties with macrophages and novel information suggested that we had to redefine the distinction between these cell types. Applying a new phenotyping strategy we found that monocyte-derived cells were selectively increased in the coeliac lesion. Monocytes can give rise to both DCs and macrophages. We decided to take a step back and performed detailed characterisation of all CD45+HLA-DR+ cells in the human gut by phenotyping, and functional and transcriptomic analysis. The salient results are as follows: The macrophage population are extremely homogeneous consisting of newly derived monocytes that gradually differentiate into two types of mature macrophages. The macrophage subsets were unresponsive to microbial stimulation but were highly efficient as phagocytic cells. The subsets were differently distributed; one subset was mainly found in the mucosa whereas the other was mainly residing in the submucosa and muscularis propria. The latter expressed many genes involved in nerve-cell interactions. The DC populations were distinct from macrophages, being



Low and high magnification: Section of small intestine from female transplanted into a male patient one year after transplantation. Nuclei are grey. Intranuclear X and Y chromosomes are coloured red and green, respectively. Plasma cells (blue), blood vessels (green) and nerves (red) are shown.
Photo: Ole Landsverk.

superior at antigen presentation but less efficient at endocytosis. These studies show a clear distinction between macrophages and DC in the gut and suggest that monocytes recruited to the intestine become macrophages and do not acquire DC properties. In contrast to the gut we found that macrophages in the lungs live for years, indicating that macrophages in different human tissues are very different.

Longevity of plasma cells and T cells in the gut

How long immune cells can survive in the tissue has received a lot of attention over the last few years. However, most data are derived from studies in mice and little information exists regarding longevity of cells in human tissue. To study this phenomenon we followed the replacement kinetics of plasma cells and T cells in segments of transplanted duodenum. To our surprise we found that a large fraction of plasma cells survived at least for one year. To determine their lifespan more exactly we measured radio-active carbon 14 in their DNA which is a method to retrospectively determine their age. We found that a large fraction of plasma cells lives for several decades. This finding represents an important shift in the concept of gut humoral immunity and shows that antibody responses in the gut can be extremely persistent.

We also studied the replacement kinetics of T cells and found that a large fraction of T cells also survives for at least one year. This finding was substantiated showing that a large fraction of T cells obtained from the same gut one year apart contained the same clones determined by single cell T-cell receptor sequencing. We have demonstrated that gut T cells live for a very long time in different disease settings; both organ transplantation and allogeneic stem cell transplantation. We are currently studying whether these cells play a role in the immunopathogenesis of organ rejection and graft versus host disease.

3 selected publications

Jahnsen group

2016

Rapid recruitment of CD14(+) monocytes in experimentally induced allergic rhinitis in human subjects

Eguiluz-Gracia, I., Bosco, A., Dollner, R., Melum, G.R., Lexberg, M.H., Jones, A.C., Dheyauldeen, S.A., Holt, P.G., Baekkevold, E.S., and Jahnsen, F.L. (2016)

J Allergy Clinical Immunol 137, 1872-1881 e1812. doi: 10.1016/j.jaci.2015.11.025

This paper shows that the mononuclear phagocyte population is directly involved in the production of proinflammatory chemokines that attract other immune cells in allergic airway inflammation. Rapid recruitment of monocytes to the challenged site indicates that these cells have a central role in orchestrating local allergic inflammation. This paper had received international attention and led to invitations to speak at international meetings.

2017

Antibody-secreting plasma cells persist for decades in human intestine

Landsverk, O.J., Snir, O., Casado, R.B., Richter, L., Mold, J.E., Reu, P., Horneland, R., Paulsen, V., Yaqub, S., Aandahl, E.M., Øyen O.M., Thorarensen H.S.,Salehpour M., Possnert G, Frisén J, Sollid L.M., Baekkevold E.S, Jahnsen F.L. (2017)

J Exp Med. 214, 309-317. doi: 10.1084/jem.20161590

This is the first paper to demonstrate that plasma cells in the gut are extremely long-lived, which has implications both for vaccine development and how we may treat dysbiosis-associated disorders. It has received extensive attention and the research output has an Altmetric Attention Score of 48, which is in the top 5% of all research outputs ever tracked by Altmetric. It has been commented in the social media (Facebook, Twitter), in news outlets (Aftenposten, Forskning.no, etc.), research highlights and recommendations (F1000 Prime), and has already generated several citations in several high impact journals.

2017

Transcriptional and functional profiling defines human small intestinal macrophage subsets

Bujko, A., Atlasy, N., Landsverk, O.J., Richter, L., Yaqub, S., Horrneland, R., Øyen, O., Aandahl, E.M., Aabakken, L., Stunnenberg, H.G., Baekkevold, E.S. and Jahnsen F. L.(2017)

J Exp Med. (in press)

This paper shows that macrophages in the gut are extremely heterogenous ranging from recently recruited proinflammatory monocyte-like cells to hyporesponsive mature macrophages with high phagocytic activity. Transcriptomic analysis furthermore shows a clear distinction between macrophage and dendritic cell subsets.

Munthe group

In our RCN CoE period, we have established how interactions between T helper cells and B cells can cause autoimmune disease as well as allow development and maintenance of B cell cancer. We have established that Th cells are important drives for B cell cancer and have been able to utilise this information to initiate personalised medicine trials and high throughput drug sensitivity screens for patients with relapsed B cell cancer after failure of conventional treatment. We have become attractive partners and have been able to recruit top-level scientists from abroad.

OVERVIEW OF RESEARCH IN THE GROUP

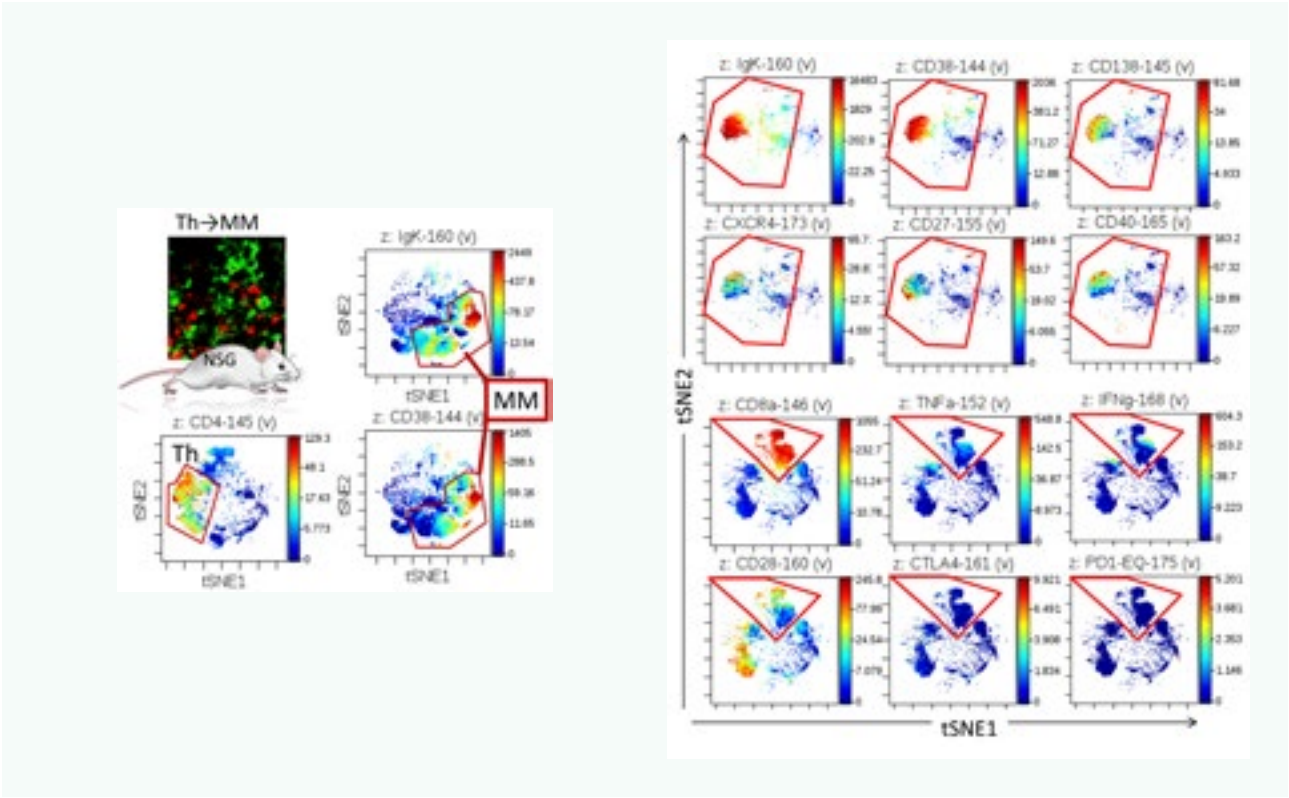
Ludvig Munthe (LM) was affiliated to CIR via Bjarne Bogen's group before 2013, but after attaining a professorship and starting a new group (Autoimmunity and Lymphoproliferative disease), we have been CIR-members. In a 2007 J Exp Med paper, LM et al found that Id-specific (autoreactive) T helper (Th) cells could chronically stimulate B cells and generate B cell cancer in mice. Since then, we have been translating results to human patients. In 2013, we published the first of these results. PhD candidate Audun Os, postdoc Simone Bürgler, PhD candidate Anna Parente Ribes et al showed in a *Cell Reports* paper that human B cell cancer patients also had Th cells in the blood and lymph nodes that stimulated malignant B cells (the patients had chronic lymphocytic leukaemia, CLL, the most common leukaemia. CLL is also classified as a Non-Hodgkin lymphoma).

We continued these studies by characterising the Th cells and their interaction and mutual attraction with CLL cells (Bürgler et al. *J Immunol* 2015). The findings suggest that this malignancy is driven by autoreactive Th cells that support the proliferation of CLL cells in patients.

In parallel, we followed up earlier results in systemic lupus erythematosus (SLE) where we had characterised that Id-specific (autoreactive) Th cells could induce lupus. In a breakthrough, PhD candidate Kristin Aas-Hanssen, postdoc Ane Funderud, et al showed that lupus was generated by Id-specific Th cells that supported the oligoclonal expansion of classical pathogenic B cells. These B cells had an anti-dsDNA binding signature (Aas-Hanssen et al. *J Immunol* 2015). In a bioinformatics follow up, we found that Th cells in lupus could have multiple cross-reactive specificities (Aas-Hanssen et al. *Front Immunol* 2015). Th cells could both respond to anti-dsDNA antibodies as well as to peptides derived from DNA-associated proteins motifs. Results converged previous divergent results and theories on what Th cell specificity drives lupus disease.

Following up the work on malignant B cells in patients (CLL, see above), postdoc Dong Wang extended our analysis to the cancer of end differentiated B cells: multiple myeloma. This is a cancer that resides in the bone marrow of patients. Here we found that patients had Th cells that were both sufficient and necessary to drive the proliferation of malignant B cells in vitro as well as in vivo in xenografted human mice. We thereby can conclude that Th cells play a role in the support of mature B cells as well as end differentiated plasma cell B cells (Dong et al. *Leukemia* 2017). Current work by Simone Bürgler in Zurich (previously a postdoc in the group) is now extending this principle to immature B cells (acute lymphoblastic leukemia).

In the cross roads between autoimmunity and malignancy we find the anergic B cell. This cell has been triggered by a ligand for the B cell receptor (BCR). Anergic B cells are important effector cells in patients with autoimmune disease, patients with B cell cancer



Mass cytometry analysis of myeloma and Th cells in mice (left) and gated MM cells (right).

often have malignant B cells that mimic the anergic state. Following up findings from a Journal of Experimental Medicine paper of 2009, Researchers Peter Szodoray and Britt Nakken found that anergic human B cells are rescued by Th cell signals and that these helper signals revived the BCR pathway in the B cells. Th cell help was delivered in a CD40L-IL-4 dependent process that increases the functional activity of the CD45 phosphatase (Szodoray et al. JACI 2016. The CD45 phosphatase activated the Src family member Lyn and Syk and rescued B cells from non-responsiveness, allowing normal differentiation. In malignant B cells, this same CD40L-dependent pathway is relevant as BCR pathway blockers completely inhibited CLL cell responses but not those of normal B cells (Parente-Ribes et al. *Haematologica* 2016). The work of Nakken and Szodoray promises to open new research avenues in autoimmune diseases and B cell malignancy and to describe how B cell function and malignant state is regulated through receipt of Th cell help and the CD45 phosphatase.

In 2016, we recruited Hilde Schjerven, assistant professor (UCSF) and researcher OUS in Oslo to the team. Current work focuses on the transcriptomics of leukemias and myelomas – a research profile that matches that of our own. The RCN CoE period has allowed us to be an attractive partner as well as relocation cite for scientists from abroad. Following up the innovation track of the CIR spin-out *Nextera*, we have recruited Postdoc Ine Jørgensen from USA to the team. She will be part of the development of novel biologicals for the treatment of CLL in an RCN-BIA supported collaboration.

The description of drugs that target malignant B cells and completely spare normal B cells (see above) spurred our interest in defining drugs that work in B cell malignancy where other therapy have failed. We therefore established collaboration with NCMM and Kjetil Taskén's group where we are now conducting high throughput drug sensitivity analyses for CLL and multiple myeloma patients (Postdocs Deepak Thimiri, Andrea Cremaschi, researcher Sigrid Skånland). We have established a precision medicine protocol and have secured support from both industry and clinical partners. We thereby aspire to bring therapeutic options to patients with minimal delay.

The RCN CoE period has allowed us to establish very strong partnerships with our clinical collaborators, who continue to partner with us to bring the field forward. A number of new trials and collaborations have emerged, for example the newly formed Oslo Myeloma Centre led by Fredrik Schjesvold that both organises clinical trials, provide samples for analyses and take part in discussions on drug sensitivity profiles. The Department of Haematology is headed by Geir Tjønnfjord that has been an essential supporter and contributor to the team. Together we have initiated large research applications, including qualifying for KG Jebsen Centre finalist status (to be decided end of the year).

3 selected publications

Munthe group

2013

Chronic lymphocytic leukemia cells are activated and proliferate in response to specific T helper cells

Os,A., Burgler,S., Ribes,A.P., Funderud,A., Wang,D., Thompson,K.M., Tjonnfjord,G.E., Bogen,B., Munthe,L.A.

Cell Reports. 4, 566-577. 2013.
doi: 10.1016/j.celrep.2013.07.011

This paper demonstrates that T helper cells play an integral role in supporting CLL in patients and is the first demonstration that suggests that autoreactive Th cells drive the expansion of B cell cancer. This paper has allowed us to start detailed mechanistic dissection of the microenvironmental support of this B cell cancer as well as develop a platform for drug sensitivity screens and precision medicine trial. The study also allowed us to participate in a successful RCN-BIA grant as partners of Nextera, and to now make important steps towards developing novel biologics.

2016

T-helper Signals Restore B-cell Receptor Signaling in Autoreactive Anergic B-cells by upregulating CD45 phosphatase activity

P Szodoray, SM Stanford, Ø Molberg, Ludvig A. Munthe, N Bottini, B Nakken. JACI, 2016.

J Allergy Clin Immunol. 2016 Sep;138(3):839-851.e8.
doi: 10.1016/j.jaci.2016.01.035.

This study starts a new era of our understanding on how B cells are regulated by Th cells and how they receive and integrate help signals. It has been followed up by very extensive ongoing studies in autoimmunity and B cell cancer.

2017

Autologous bone marrow Th cells can support multiple myeloma cell proliferation in vitro and in xenografted mice

Wang, D., Floisand, Y., Myklebust, C. V., Burgler, S., Parente-Ribes, A., Hofgaard, P. O., Bogen, B., Tasken, K., Tjonnfjord, G. E., Schjesvold, F., Dalgaard, J., Tveita, A. and Munthe, L. A.

Leukemia, Oct;31(10):2114-2121.
doi:10.1038/leu.2017.69 (2017)

This paper demonstrates that Th cells are sufficient and necessary for the expansion of Myeloma cells from patient bone marrow when cells are transferred into xenografted mice. Results also show that autoreactive Th cells play a role in the in vitro expansion of MM cells in cell culture. This paper has allowed us to unravel the cellular and molecular basis of this B cell cancer in ongoing studies as well as allowing us to develop a drug sensitivity platform and precision medicine trial.

Qiao group

The research group studies the immune response at the single-cell level by receptor sequencing as well as single-cell transcriptomics. Using coeliac disease as a model disease but also extending into other human inflammatory and autoimmune diseases, we focus on the antigen-specific immune response. In particular, we study the disease-specific T-cell response to gluten in coeliac disease, and in collaboration with Jahnsen group the disease-specific CD4+ T cells in idiopathic pulmonary fibrosis (IPF). In addition, we have also initiated collaboration with the Munthe group to study the T- and B-cell interaction at the molecular level in myeloma.

OVERVIEW OF RESEARCH IN THE GROUP

The Qiao group is the most recently established research group in CIR, starting its operation in August 2015. The main achievements of the group during its relatively short time of operation are refinement of single-cell T-cell receptor (TCR) repertoire analysis and successful establishment of three different single-cell transcriptomics protocol.

In close collaboration with the Sollid group where three PhD candidates were co-supervised by the two group leaders, we have refined and streamlined the TCR sequencing and bioinformatics on the single-cell level. We have optimised the protocols for tetramer staining, sorting followed by single-cell paired TCRαβ sequencing. During the last few years, we have increased the number of paired TCRαβ sequences of gluten-specific CD4+ T cells from a few hundred to several thousands. These sequences are derived from blood and intestinal biopsy samples taken from over 30 coeliac disease patients, many of whom were followed either longitudinally after commencement of treatment by gluten-free diet, over a course of gluten challenge, or taken decades apart from individuals who were first recruited to coeliac disease studies in the 1980- or 90's. By using bioinformatics tools that were tailor-made for handling the large single-cell TCR data, we found that the gluten-specific T-cell repertoire in coeliac disease patients is remarkably stable. We found T cells belonging to the same clonotypes in samples taken decades apart from the same individual. These findings have implication for disease treatment for coeliac disease and other chronic inflammatory diseases where more focus should be put on immune modulation of memory T cells rather than interfering with activation of naïve cells.

Our expertise in single-cell TCR sequencing was used by the Jahnsen group in two different projects; tracking T-cell clonotypes in duodenum in the transplantation model and investigation of the repertoire composition of disease-specific INF-γ and IL-13 double-producing CD4+ T cells in IPF. Similarly, we have shared TCR sequence data with the Sandlie group where our sequence data compliments with the structure insights generated by Sandlie group's detailed molecular characterisation of a few selected prototype gluten-specific TCRs.

The other major achievement of the Qiao group and its main research focus is to use single-cell transcriptomics to characterise the adaptive immune response. We have successfully established three different protocols for creating single-cell transcriptomics libraries; namely STRT, Smart-Seq2 and Drop-Seq. The technology has been applied in the characterisation of gluten-specific T cells from coeliac disease patients. We have established bioinformatics pipeline in the analysis of the large body of data generated from these experiments. This is done in close collaboration with the group led by Geir-Kjetil Sandve at the Department of Informatics. In collaboration with Espen Bækkevold in

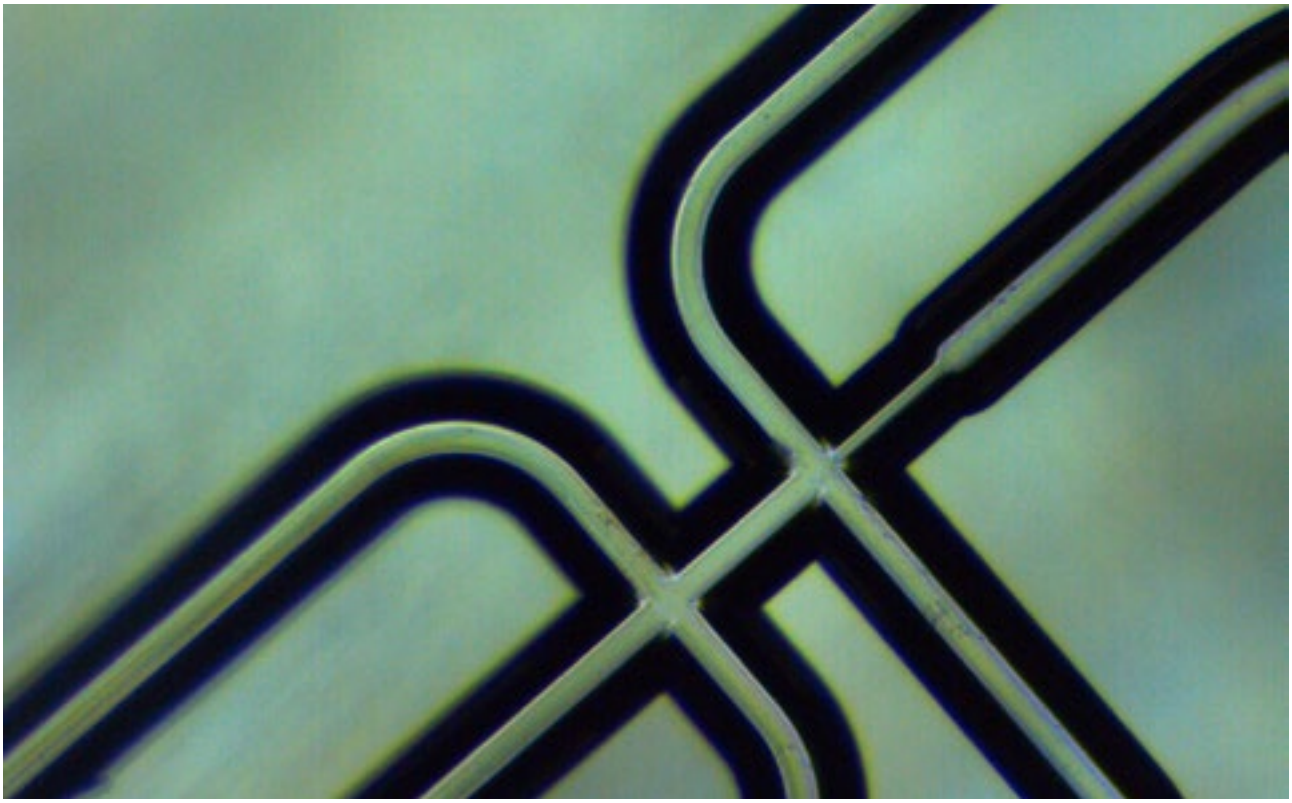


Image of microfluidics that is used in generating droplets. The inner diameter of the micro-channels are 100 μm. Photo: Asima Zia

the Jahnsen group we have used the Drop-Seq protocol to investigate the transcriptomics profile of CD4+ T cells from bronchoalveolar lavage of IPF patients. This particular protocol can profile the transcriptomics of thousands of cells at a time and therefore is particularly useful in the investigation of immune cells in diseases where the antigen specificity is not known.

Being a part of CIR has been absolutely essential for the Qiao group. Indeed, the group is created thanks to funds raised by CIR. CIR is the most important funding source for the Qiao group. We have enjoyed fruitful collaborations with most of the groups in CIR; from continuing collaboration with the Sollid and Sandlie groups and from more recent collaborative efforts with the Jahnsen and Munthe groups.

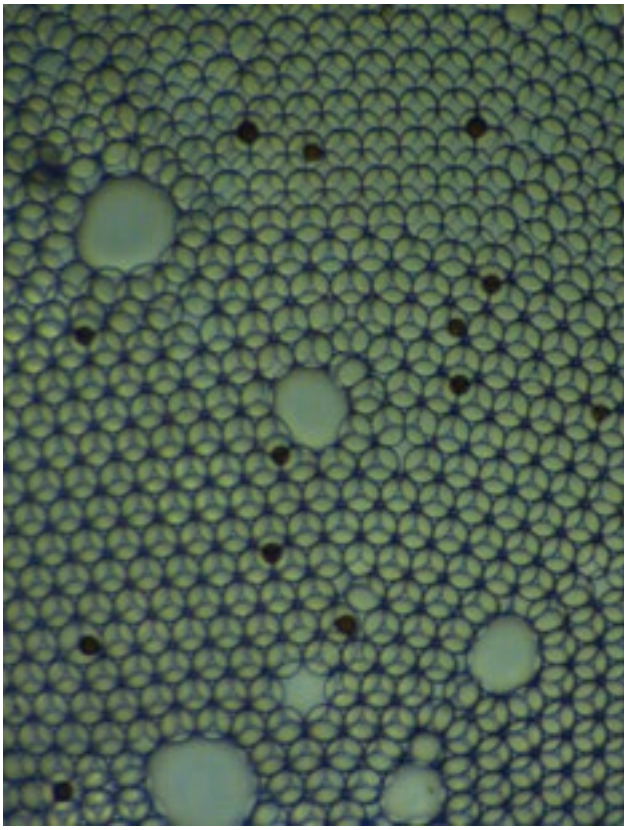


Image of ~80 μm droplets that are generated for single-cell transcriptomics with two layers of droplets on top of each other. Photo: Asima Zia

3 selected publications

Qiao group

2014

Tetramer-visualized gluten-specific CD4+ T cells in blood as a potential diagnostic marker for coeliac disease without oral gluten challenge

Christophersen A, Ráki M, Bergseng E, Lundin KE, Jahnsen J, Sollid LM, Qiao SW

United European Gastroenterol J 2014; 2(4):268-78. doi: 10.1177/2050640614540154

We showed for the first time that detection of gluten-specific T cells by staining with HLA-DQ2.5-gluten tetramers could be used to diagnose coeliac disease, both in subjects that consume gluten and those who are on gluten-free diet.

2016

TCR sequencing of single cells reactive to DQ2.5-glia-α2 and DQ2.5-glia-ω2 reveals clonal expansion and epitope-specific V-gene usage

Dahal-Koirala S, Risnes LF, Christophersen A, Sarna VK, Lundin KE, Sollid LM, Qiao SW

Mucosal Immunol. 2016;9(3):587-96. doi: 10.1038/mi.2015.147

This is our first paper with TCR data obtained by single-cell high-throughput sequencing. We showed that despite sequence similarity between the DQ2.5-glia-α2 and DQ2.5-glia-ω2 epitopes, the TCR repertoires responding to these two epitopes are largely different.

2017

Disease-driving CD4+ T cell clonotypes persist for decades in coeliac disease

Risnes LF, Christophersen A, Dahal-Koirala S, Neumann RS, Lundin KE, Qiao SW, Sollid LM

Manuscript in preparation

This manuscript contains accumulated TCR sequencing data of gluten-specific T cells from coeliac disease patients collected over a period of 3-4 years. It contains over 1 800 paired TCRαβ clonotypes from 17 patients. Samples from blood and gut biopsies were collected from coeliac disease patients in different disease stages, during gluten challenge and from historic cryopreserved samples taken in the 1980 and 90´s. This is by far the most comprehensive TCR sequencing project performed in coeliac disease, and one of the largest of antigen-specific CD4+ T cells in human disease. We found that gluten-specific cells visualised as effector memory gut-homing CD4+ T cells binding to HLA-DQ2.5-gluten tetramers in blood have the same clonal origin as pathogenic gluten-specific T cells residing in the intestinal tissue. We showed that the gluten-specific memory T cells dominate the response during antigen re-exposure by gluten challenge. Most remarkably, the same clonotypes could be found in samples taken 27 years apart showing that the gluten-specific T-cell repertoire is strikingly stable for decades.

Sandlie group

The Sandlie group has studied the structure and function of antibodies and T-cell receptors, the specific detection molecules of the adaptive immune system. The purpose of the work has been to engineer antibodies and other molecules for use in therapy and research.

OVERVIEW OF RESEARCH IN THE GROUP

Studies of coeliac disease

Coeliac disease (CD) develops in individuals with certain MHC class II types, and in particular, DQ2.5, which is characterised by its ability to bind and present modified gluten peptides on the surface of antigen presenting cells. To answer questions regarding the nature of these antigen presenting cells in the gut of CD patients, we designed antibodies that bind gluten-DQ2.5 complexes with very high specificity. In collaboration with the Sollid and Jahnsen groups, we then found the antibodies to bind B cells and plasma cells in patient biopsies. We hypothesise that the interaction between these cells and disease-associated T cells is a key driver of disease. A focus for CIR is the concept of faulty B:T collaboration that drives autoantibody production. CD patients produce autoantibodies against transglutaminase 2, the enzyme that modifies the gluten peptides. Interestingly, at least some of the gluten-DQ2.5 presenting plasma cells are transglutaminase 2 specific.

The T cell response against gluten-DQ2.5 complexes is socalled biased in CD patients, in that their T cell receptors are often composed of signature variable segment pairs that must be selected on the ground of being particularly well suited for complex binding. Collaborating with the Sollid and Qiao groups, we have unraveled the molecular basis for a common signature, and identified an MHC recognition motif centered on a certain amino acid residue in the T cell receptor. This one residue not only contacts MHC, but also directs a pivotal part of the T cell receptor to contact the gluten peptide (Gunnarsen et al. *JCI Insight* 2017).

Immunoreceptor engineering

We call our novel phage display platform Signal Sequence Independent phage display – SSIp display. The finding is that two viral capsid proteins, pVII and pIX, display fusion proteins extremely well, and they do so without the need for translational signal sequences (Nilssen et al. *Nucleic Acids Res* 2012)(Løset et al. *PLoS One* 2011). Importantly, we have found that the SSIp display phage particles can display not only antibodies and T cell receptors (Høydahl et al. *Sci Reports* 2016) (Gunnarsen et al. *Sci Reports* 2013), but also MHC class II peptide complexes, and we call the MHC class II displaying phages "Phagemers". Phagemers bind to specific T cell receptors, and thus detect T cells based on this specificity. We have explored the use of Phagemers as diagnostic tools. SSIp display is the core technology of the spin-out company Nextera AS (www.nextera.no). Nextera AS commercialises and develops the Phagemer technology and selects binders from large phagemer libraries, the aim being target discovery for drug development.

Half life of IgG antibodies and albumin fused drugs

Most proteins in blood degrade within a few hours or days, but IgG and albumin, which are the two most abundant, are rescued from degradation and have half-lives of three weeks. This is due to the fact that they bind the neonatal Fc receptor (FcRn), and we study how FcRn binding regulates the serum half life and biodistribution of both ligands.

The long half life is important for the therapeutic success of IgG antibodies, and thus, there is an intense interest in increasing the strength of the FcRn interaction to prolong the half-life even further. The FcRn interaction is pH dependent, with histidine dependent strong binding at acidic pH and little or no binding at neutral pH. We have studied how FcRn binds IgG molecules of different subclasses, and found that IgG3 degrades faster than the others because of a slight alteration in FcRn binding kinetics (Stapleton et al. *Nat Commun* 2011). This is due to a single amino acid being arginine in IgG3 and histidine in the other subclasses. We have also engineered an IgG variant with increased binding at acidic pH (PCT/IB2017/000327). The variant is described in a patent application that was recently licensed by a large international drug development company. We have found that engineering of IgG for increased binding to FcRn may well negatively influence binding of both classical FcγRs and complement factor C1q, which ultimately results in a reduced ability to induce effector functions (Grevys et al. *J Immunol* 2015). The variant engineered by us induces effector functions on a level on par with or better than native antibody molecules.

We have also unraveled the interaction between FcRn and albumin (Andersen et al. *Nat Commun* 2012). Again, it is pH and histidine dependent as well as largely hydrophobic in nature (Sand et al. J Biol Chem 2014). Studies of the interaction with albumin fused to other protein sequences have then given information on how long half-life can be conferred upon albumin-fused therapeutics (Andersen et al. *J Biol Chem* 2013). We have designed albumin variants with increased binding to FcRn at acidic pH that have increased half life in rodents and monkeys (Andersen et al. *J Biol Chem* 2014).

The Veltis ®technology (albumin attachment to drugs) is commercialised by Albumedix A/S, a collaborating drug development company, and involves both normal albumin and our engineered albumin variants.

Biodistribution of IgG antibodies and albumin fused drugs

FcRn is expressed intracellularly, and binds IgG taken up by fluid-phase endocytosis. It can then direct monomeric IgG to the surface of the opposite side of the cell (transcytosis) or to the side of entry (recycling). We study both processes using the natural ligands as well as engineered variants (Foss et al. *J Control Release* 2016). A new *in vitro* recycling assay designed by us predicts the behavior of designed FcRn-binding molecules *in vivo* in animal models (Grevys et al. *Nat Commun* 2017). Furthermore, we recently found that albumin is transcytosed efficiently from the apical to the basolateral side. We think this observation holds great promise for mucosal delivery of albumin based vaccines and therapeutics (Bern et al. *J Control Release* 2015).

All drug candidates must be tested in preclinical animal models, and in the case of albumin fused drugs this is complicated by the fact that rodent FcRn does not bind human albumin. Furthermore, human FcRn encoded by a transgene in mice binds the murine albumin very strongly, making it impossible for injected human albumin variants to compete for binding (Andersen et al. *J Biol Chem* 2013). Therefore, new transgenic mice are generated with human FcRn as well as human albumin by collaborator Derry Roopenian at the Jackson laboratory that hold great promise.

FcRn is the only Fc receptor required for transport of IgG across cellular barriers and placenta (Mathiesen, Blood 2013), and in collaboration with CIR guest professor Richard Blumbergs laboratory, we have found that it enhances antigen presentation and cross presentation in specialised dendritic cells (Baker et al. *Proc Natl Acad Sci* 2011). Furthermore, it directs albumin produced in the liver to the bloodstream, and away from the bile (Pyzik et al. *Proc Natl Acad Sci* 2017).

CIR-contribution to studies

Collaboration within CIR has clearly contributed greatly to the success of our projects. The design of research tools and therapeutics was initially motivated by the needs of our collaborators, and their research interests then triggered us to ask new questions using the tools.

Furthermore, collaboration within a translational research environment, has motivated research with clinical relevance. The guest professor program has been of particular importance for us, and we have benefited from the networking opportunities, the research collaboration and the guidance given by top international research leaders. Last, but not least, the long term funding has allowed us to undertake some very ambitious research projects.

3 selected publications

Sandlie group

2012

Structure-based mutagenesis reveals the albumin-binding site of the neonatal Fc receptor

Andersen JT, Dalhus B, Cameron J, Daba MB, Plumridge A, Evans L, Brennan SO, Gunnarsen KS, Bjørås M, Sleep D, Sandlie I

Nat Commun. 2012 Jan 3;3:610. doi: 10.1038/ncomms1607

In this paper we present structure-based modelling of the FcRn-albumin complex, supported by binding analysis of specific mutants. We provide evidence for the presence of a pH-sensitive ionic network at the interaction interface. The network involves conserved histidines in both FcRn and albumin. Histidines also contribute to intramolecular interactions that stabilise otherwise flexible loops at both the interacting surfaces. This is an important paper that helped us design albumin variants with altered serum half-life as carriers of drugs.

2015

Fc Engineering of Human IgG1 for Altered Binding to the Neonatal Fc Receptor Affects Fc Effector Functions

Grevys A, Bern M, Foss S, Bratlie DB, Moen A, Gunnarsen KS, Aase A, Michaelsen TE, Sandlie I, Andersen JT

J Immunol. 2015 Jun 1;194(11):5497-508. doi: 10.4049/jimmunol.1401218.

The constant Fc part of therapeutic IgG may be engineered for improved effector functions and clinical efficacy. A main focus in such development is tailoring of in vivo half-life and transport properties. This is done by engineering the interaction between IgG and the neonatal Fc receptor, as it is the main regulator of IgG half-life and biodistribution. Here we show that such engineering may well affect binding to other Fc-binding molecules, such as the classical Fc□Rs and complement factor C1q, and this ultimately results in alterations of antibody-dependent cytotoxicity, phagocytosis and complement-mediated cell lysis. This has been important for us and has guided the design of new IgG variants with increased half life and effector functions on par with or better than normal IgG antibodies.

2016

Multivalent pIX phage display selects for distinct and improved antibody properties

Høydahl LS, Nilssen NR, Gunnarsen KS, Pré MF, Iversen R, Roos N, Chen X, Michaelsen TE, Sollid LM, Sandlie I, Løset GÅ

Sci Rep. 2016 Dec 14;6:39066. doi: 10.1038/srep39066

In phage display technology, libraries, or collections of antibodies, are displayed on the surface of filamentous phages, and searched for the presence of useful binding specificities. Here, we created an antibody library fused to phage protein IX, and compared the quality of this library with one consisting of the same antibody collection, but fused to protein III. We particularly wanted to learn how easy it was to retrieve good binders from each of the libraries. We found the pIX system to allow for increased retrieval of desired specificities, and also for retrieval of binders with favorable biophysical properties such as high stability. This pIX display platform has been, and will continue to be very important for us in our molecular design efforts, and it has also allowed display of MHC class II.

Sollid group

The Sollid group aims to dissect the interplay of environmental and genetic factors that leads to development of autoimmune disorders. Most of the work is done with human biological material studying disease relevant T cells and B cells. The group has flourished being part of CIR. The research has benefitted from collaborations with other CIR-research groups as well as from interactions with the Visiting Professors.

OVERVIEW OF RESEARCH IN THE GROUP

The Sollid group is using coeliac disease (CD) as a model to understand autoimmunity. CD is a disorder caused by an inappropriate immune response to cereal gluten proteins. While clearly being a food intolerance disorder, the disease also has many autoimmune features including highly disease specific autoantibodies. The condition only develops in subjects with certain MCH class II allotypes. In coeliac patients, ingestion of gluten induces CD4+ T-cell responses to posttranslationally (deamidated) gluten peptides as well as antibody responses to the autoantigen transglutaminase 2 (TG2) and to deamidated gluten peptides.

MCH class II and T cells

We have established the molecular basis for the difference in disease risk for HLA-DQ2.5 and HLA-DQ2.2 (Fallang et al. *Nat Imm* 2009). This work demonstrated the importance of peptide-MCH stability for *in vivo* activation and clonal expansion of T-cells. Gluten T-cell epitopes of DQ2.5 patients bind stably to DQ2.5, but not DQ2.2. Our prediction from this work was that if DQ2.2 CD patients have gluten-specific T cells, they should recognise different epitopes that bind stably to DQ2.2. We later found that DQ2.2 patients indeed have gluten specific T cells, and all epitopes had serine at position P3. This residue serves as an anchor for binding to DQ2.2, but not to DQ2.5. (Bodd et al. *Gastroenterology* 2012). Elution and mass spectrometric identification of thousands of endogenous HLA bound peptides from various cell lines expressing different HLA-DQ molecules confirmed the key role of serine in P3 for binding of peptides to DQ2.2 (Bergseng et al. *Immunogenetics* 2015).

Antigen presenting cells

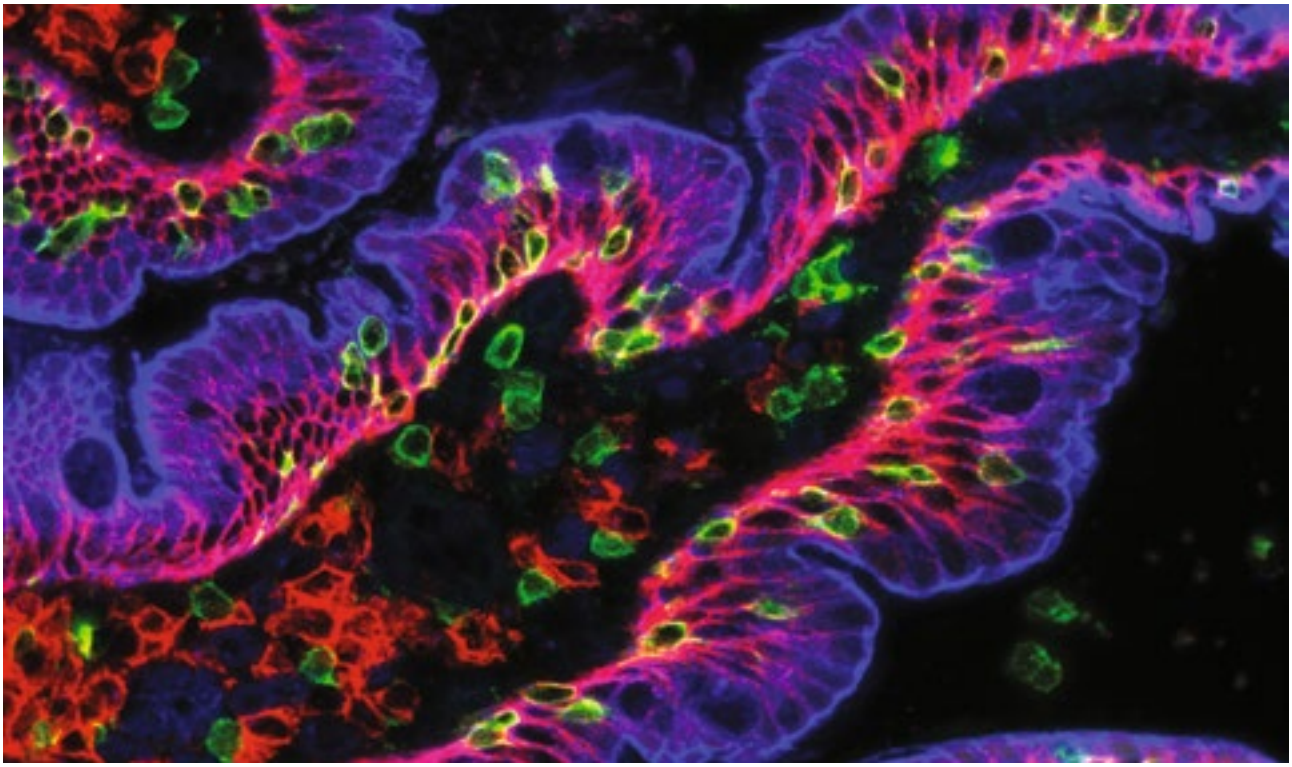
We identified a unique subset of CD11c+ CD163+ antigen presenting cells that are increased in the small intestine of untreated CD patients compared to treated patients and controls (Beitnes et al., *Scand. J Immunol* 2011). This subset was found to infiltrate rapidly the gut mucosa of treated CD patients in response to gluten challenge (Beitnes et al. *PLoS One* 2012). Plasmacytoid dendritic cells were found to be scarce in the coeliac lesion (Ráki et al. *Muc Immunol* 2013). These studies were done in close collaboration with the Jahnsen group.

Peptide:MHC tetramers and T-cell receptors

We now routinely use recombinant peptide:MHC tetramers to detect by flow cytometry gluten specific CD4+ T cells in blood and intestinal biopsies of CD patients. We have identified several new gluten T-cell epitopes and expanded our panel of peptide:MHC tetramers. Gluten T-cell epitopes are similar and preferentially deamidated both for children and adults with CD (Ráki et al. *Gastroenterology* 2017). We have established robust protocols for high-throughput sequencing of T-cell receptors that minimise ex vivo handling and the potential introduction of bias by tissue culturing. We have shown that gluten-specific T cells have a biased gene in the response to dominant T-cell epitopes which is the same that is seen across patients (Qiao et al. *J Immunol* 2011, Dahal-Koirala et al. *Muc Immunol* 2016). This knowledge has allowed us to monitor T-cell clonotype longevity and the sharing of clonotypes between different compartments (Risnes, Christophersen, Dahal-Koirala et al. unpublished).

B cells and B-cell receptors

Anti-TG2 autoantibody production occurs only in subjects with CD associated HLA-DQ allotypes when they consume dietary gluten. The TG2 enzyme catalyses gluten deamidation, but it also generates covalent TG2-gluten complexes. The knowledge of this complex formation led to the hypothesis that gluten-specific T cells can provide help to TG2-specific B cells via a hapten-carrier mechanism. Gluten-specific T cells can thereby fuel the autoantibody response to TG2. At the start of CIR, very little was known about the B-cell response in CD. Our group has made significant contributions to this field over the past eight years. We found that intestinal IgA+ plasma cells express surface immunoglobulin (Ig) receptors (Di Niro et al. *J. Immunol* 2010). This allowed for isolation of viable plasma cells by use of labelled antigen and flow cytometry. In a landmark study, we sorted and cloned the immunoglobulin genes from 58 TG2 specific IgA+ plasma cells isolated from intestinal biopsies of four patients (Di Niro et al. *Nat Med* 2012). We found stereotyped and biased usage of variable region genes with limited or no somatic hypermutation – findings that later were corroborated by high throughput sequencing of bulk cell populations and single cells (Snir et al. *J Immunol* 2015; Roy et al. *J Immunol* 2017). This work was also supported



Staining of plasma cells (red, CD138) and, T cells (green, CD3) and epithelium (blue, cytokeratin) in the small intestinal mucosa. Photo: Ann-Chistin Røberg Beitnes

by an advanced grant from European Research Council to Ludvig Sollid (ERC-2010-Ad-268541). Using the same cell isolation strategy, we later characterised the B-cell response to deamidated gluten peptides and found similar stereotyped variable gene usage and little somatic hypermutation (Steinsbø et al. *Nat Comm* 2015).

B-cell antigens: TG2 and gluten

TG2 is essential for the adaptive immune response in CD, and several aspects of TG2 biology have been studied throughout the time-course of CIR. We found that TG2 substrate specificity likely determines the gluten T-cell epitope repertoire in CD (Dorum et al. *J Proteome Res* 2009). Further, we found that the B-cell epitopes of coeliac anti-TG2 antibodies are clustered in the N-terminal part of the TG2 molecule (Iversen et al. *J Immunol* 2013). Several interesting structure-function relationships have been uncovered (Iversen et al. *J Immunol* 2015, Iversen et al. *PNAS 2014*, Hnida et al. *J Biol Chem* 2016). Similarly, the deamidated epitopes of gluten being recognised by patient derived antibodies have also been characterised (Dorum et al. *Sci Rep* 2016). In a complex enzymatic digest of gluten, the antibodies preferentially recognise long peptide fragments with many repeats of the antibody epitopes. Studies of TG2 biology have also been performed. Perhaps the most interesting finding is that the TG2 protein binds differently to the extracellular matrix of the gut wall than previously believed, exposing all coeliac B-cell epitopes (Cardoso et al. *FEBS J* 2015; Stamnaes et al. *PLoS One* 2015; Stamnaes et al *FEBS J* 2016).

A mouse model to study T-B cell collaboration in CD

The original project description of CIR described establishment of a B-cell receptor knockin mouse strain to study T-B cell collaboration in CD. Ten years later, we have established such a mouse model based on an anti-TG2 antibody cloned from a patient derived single plasma cell (Di Niro et al. *Nat Med* 2012). This antibody binds with high affinity (nM) to an epitope conserved between human and mouse TG2. With the help of the company Ozgene from Australia we have generated a knockin mouse strain based on the rearranged VDJ (heavy chain) and VJ (light chain) genes of this antibody. We are in the process of studying B-cell tolerance to TG2 by comparing B-cell development in immunoglobulin knockin mice that are on a TG2 proficient or TG2 deficient background. We observe that the anti-TG2 BCR is expressed in a high number of B cells in the periphery both in presence and absence of TG2, suggesting that there is little or no B-cell tolerance induction towards TG2 in the mice. Thus, the main control of antibody production to TG2 appears to operate at the level of provision of T-cell help. Preliminary data indicate that gluten-specific T cells indeed can provide such T-cell help (du Pré, Blaszevski et al. unpublished) – results which are then in support of the hapten-carrier model outlined above.

3 selected publications

Sollid group

2009

Differences in the risk of coeliac disease associated with HLA-DQ2.5 or HLA-DQ2.2 are related to sustained gluten antigen presentation

Fallang LE, Bergseng E, Hotta K, Berg-Larsen A, Kim CY, Sollid LM.

Nat Immunol. 2009 Oct;10(10):1096-101. doi: 10.1038/ni.1780

This work demonstrates the importance of peptide:MHC stability for the in vivo establishment of CD4+ T-cell responses. We found that a single polymorphism in HLA-DQ2.5 results in differential binding of gluten peptides compared to DQ2.2. More gluten peptides bind stably to DQ2.5 than to DQ2.2 and this result in broader and stronger CD4+ T cell responses in DQ2.5 patients. This finding explains the higher genetic risk of CD by DQ2.5 compared to DQ2.2.

2012

High abundance of plasma cells secreting transglutaminase 2-specific IgA autoantibodies with limited somatic hypermutation in coeliac disease intestinal lesions

Di Niro R, Mesin L, Zheng NY, Stamnaes J, Morrissey M, Lee JH, Huang M, Iversen R, du Pré MF, Qiao SW, Lundin KE, Wilson PC, Sollid LM.

Nat Med. 2012 Feb 26;18(3):441-5. doi: 10.1038/nm.2656

This work represents the first in-depth study of the TG2-specific B-cell response in CD and was the first study to clone TG2-specific monoclonal antibodies from IgA plasma cells of coeliac patients. Several unexpected observations were made that now have been confirmed in larger datasets. TG2-specific IgA autoantibodies were found to have restricted Ig heavy and light chain gene repertoire usage and very limited degree of somatic hypermutation compared to other intestinal IgA+ plasma cells, suggesting that they have a different mechanisms of generation. The panel of antibodies generated in this study has served as research tool for many subsequent studies.

2014

Restricted VH/VL usage and limited mutations in gluten-specific IgA of coeliac disease lesion plasma cells

Steinsbø Ø, Henry Dunand CJ, Huang M, Mesin L, Salgado-Ferrer M, Lundin KE, Jahnsen J, Wilson PC, Sollid LM.

Nat Commun. 2014 Jun 9;5:4041. doi: 10.1038/ncomms5041

CD patients also generate disease specific antibodies towards deamidated gluten peptides. This study describes the isolation and cloning of deamidated gluten-specific antibodies from intestinal plasma cells of CD patients. Despite the different nature of this antigen compared to TG2 (exogenous and dietary), we observed several similarities with the anti-TG2 response such as restricted usage of Ig heavy and light chain genes and limited somatic hypermutation. This speaks to a common mechanism of generation for these disease specific B-cell responses.

CIR Retreat 2017

activities

Visiting professors

One of the core activities at CIR is the Visiting Professor program. The scientific quality of the CIR environment has made it possible to attract some of the world's most important scientists in medical sciences to visit Oslo. The invited professors have stayed for one week at CIR. During this week they engaged in scientific discussions with researchers, supervision of CIR students and gave public lectures for the whole scientific environment at the University of Oslo and the Oslo University Hospital. Their visits have resulted in fruitful collaborations resulting in joint publications, researcher mobility and new ideas. A total of sixteen professors have been included in the Visiting Professor program, and most of them have visited us twice. In total 26 weeks. We are deeply honored by their visits and grateful for their superb scientific contributions to CIR and the immunological research environment in Oslo.

Richard S. Blumberg
Harvard Medical School, US

One of the great highlights of my scientific career has been the relationships that I have had over many years with numerous scientists in the Center for Immune Regulation and University of Oslo. Starting with my dear friend Per Brandtzæg, who directed the LIIPAT and for whom I have many fond memories, these interactions have involved numerous students, who have incidentally evolved into highly successful CIR and related faculty (such as Shuo-Wang Qiao, Espen Melum and Eric de Muinck), and many other faculty with whom I have collaborated and with great pleasure (such as Oddmund Bakke, Ludvig M. Sollid, Finn-Eirik Johansen, Jan Terje Andersen and Inger Sandlie). My scientific collaborations with Inger and Jan in particular have in recent years have been the most deep and enduring due to our common interests in the neonatal Fc receptor; they studied albumin and we IgG in this relationship. It was FcRn (and CIR) who were the scientific match makers through this interest and my role as visiting Professor to CIR (in a February in Oslo!), and of course great camaraderie and respect, that have now lead to highly exciting new discoveries together. Congratulations to CIR and to all of my friends in Oslo.

Bana Jabri
University of Chicago, US

Being a scientist is a rare privilege and among the biggest privileges is the chance to encounter colleagues with whom one can, in total trust, exchange endlessly ideas and share the excitement of discovery. I was impressed by the vision of Ludvig Sollid to bring in scientists as visiting professors from around the world and give them and the trainees of the Center for Immune Regulation at the University of Oslo the chance to have in depth and free interactions. The vibrant scientific community of the CIR, and the quality and rigor of the science that I witnessed impressed me. I was also touched by the kindness and humanity of the young scientist and faculty I met. It was also a joy to observe growing young talented scientists such as Rasmus Iversen and Jorunn Stamnæs, and see others such as Shuo-Wang Qiao becoming successful independent investigators. I want to thank Inger Sandlie, Frode Jahnsen, Bjarne Bogen, Oddmund Bakke and Ludvig Munthe for welcoming me, and Ludvig Sollid for his friendship. I have enjoyed every visit to the CIR and come to love Norway. Congratulations to all the members of the CIR. I know that many new adventures and exciting discoveries are awaiting you.

Peter Cresswell
Yale University School of Medicine, US

Mark M. Davis
Stanford University, US

Adrian Hayday
King's College London, UK

Bernard Malissen
Centre d'Immunologie de Marseille-Luminy (CIML), France

Jacques Neefjes
The Netherlands Cancer Institute, The Netherlands

David Nemazee
The Scripps Research Institute, US

Susan Pierce
National Institute of Allergy and Infectious Diseases, NIH, US

Fiona Powrie
University of Oxford, UK

Gwendalyn J. Randolph
Washington University School of Medicine, US

Maria Rescigno
European Institute of Oncology, Italy

Mark Shlomchik
University of Pittsburgh, US

John Trowsdale
University of Cambridge, UK

E. Sally Ward
Texas A&M Health Science Center, US

Kai Wucherpfennig
Harvard Medical School, US

Guest lecturer program

The guest lecturer program has been organised by a post-doc committee with representatives from all the research groups at CIR. The committee has invited high ranked international researchers to come to Oslo to stay with our centre one or two days to interact with researchers at the centre and give a public guest lecture. The result is a long visitor list of thirty researchers from excellent research institutions all over the world. Their knowledge and expertise has contributed strongly to shape the research at CIR, and several collaborative projects and researcher exchange have been initiated as a result of these visits.

Committee members 2007–2017

Jan Terje Andersen • Espen Bækkevold • Sudhir Kuman Chauhan • Elena Danilova • Roberto DiNiro • Even Fossum • Dominik Michael Frei • Ramakrishna Gopalakrishnan • Tone F. Gregers • Lisa M. Gruber • Kristin S. Gunnarsen • Peter Huszthy • Johanne T. Jacobsen • Ole J.B. Landsverk • Maria H. Lexberg • Nadia Mensali • Cinzia Progida • Shuo-Wang Qiao • Charlotta Sandin • Omri Snir • Peter Szodoray • Inger Øynebråten

Guest lectures

Arne Akbar, University College London, UK
Defective T Cell Immuno-surveillance During Ageing

Mats Bemark, University of Gothenburg, Sweden
Beyond the bone marrow – defining peripheral B cell differentiation

Andrea Cerutti, Mount Sinai School of Medicine, US
Class switching at the mucosal interface

Matthew Collin, Newcastle University, UK
Human dendritic cells in health and disease

Simon J. Draper, University of Oxford, UK
Development of broadly-neutralising vaccines against the blood-stage infection of human malaria

Deborah Dunn-Walters, King's College London, UK
Spectratype and High Throughput Sequencing analysis of B cell repertoire

Michael Dustin, Oxford University, Kennedy Institute of Rheumatology, UK
T cell signal integration and decision making based on synapses and kinapses

Zoltan Fehervari, Nature Publishing Group, US
How to get published: the agony and the ecstasy

Frederic Geissmann, King's College London, UK
Differentiation and functions of monocyte/macrophages

Rajesh Grover, The Scripps Research Institute, California, US

A Battle for Survival: Chronic Bacterial Infections – Unexpected Consequences and B Cell Lymphoma and Myeloma – Bacterial Origins?

Marc K. Jenkins, University of Minnesota, US

The CD4+ T cell response to bacterial infection

Steffen Jung, Weizmann Institute of Science, Israel

Macrophages – development & tissue specialisation

Ludger Klein, Ludwig Maximilians Universität München, Germany

Shaping of the CD4 T cell repertoire by a self-antigen of the central nervous system

Thomas Seth Kupper, Harvard Medical School, US

T cell memory: new insights

Ralf Küppers, University of Duisburg-Essen, Germany

Generation and function of human memory B cells and aspects of CLL pathogenesis

Ana-Maria Lennon-Duménil, Institut Curie, France

Coordinating cell migration with function: the example of dendritic cells

Vivianne Malmström, Karolinska University hospital, Sweden

Dissecting autoimmunity - T and B cell responses in Rheumatoid Arthritis

Eric Meffre, Yale University, US

The establishment of B cell tolerance: of humanized mice and men and Self-reactive VH4-34 IgG systemic responses and gut homeostasis defects

Lill Mårtensson-Bopp, University of Gothenburg, Sweden

Autoreactive B cells; a road to autoimmune disease?

Oliver Pabst, Hannover Medical School, Germany

Dynamics of the IgA response

Roberta Pelanda, National Jewish Health and University of Colorado Denver School of Medicine, US

Click your heels: you are in the land of B cells

Shimon Sakaguchi, Osaka University, Japan

Molecular basis of regulatory T cell development and their functional stability

Bernd Schröder, Christian-Albrechts-University of Kiel, Germany

SPPL intramembrane proteases – How they control immune cell development and function

Michael Sieweke, Centre d'Immunologie de Marseille-Luminy, France

Beyond stem cells : Marophage self renewal and identity

Caetano Reis e Sousa, The Francis Crick Institute, UK

A DaNGeRous talk about dendritic cells

Sarah Teichmann, EMBL European Bioinformatics Institute & WT Sanger Institute, UK

Understanding cellular heterogeneity

Gabriel D. Victora, Whitehead Institute for Biomedical Research, US

Darwin in miniature: antibody evolution in germinal centers

Hedda Wardemann, Deutsches Krebsforschungszentrum, Germany

The B cell antibody repertoire in health and disease

Patrick C. Wilson, University of Chicago, US

Human antibody responses

Gur Yaari, Bar-Ilan University, Israel

Mining B cell repertoire dynamics from next-generation sequencing studies

SEMINAR

"Transition from academia to industry"

The postdoc committee has also arranged a seminar with national speakers who have either performed a successful transfer from academia to industry or are involved in the transition process.

Øystein Rekdal, CSO, Lytix Biopharma, Oslo

From bench to bedside with a first in class oncolytic peptide

Geir Åge Løset, CSO, Nextera, Oslo

Basic research and industrial translation – the ultimate blend

Agnete Fredriksen, CSO, Vaccibody, Oslo

From PhD to CSO in Clinical stage Biotech Company – my experience from Vaccibody

André Borka, Head hunter, Borka Consulting, Oslo

(Work)Life after PhD within the pharmaceutical industry, medical technical equipment and life science. Advice on LinkedIn, CVs and job applications

Ana Kucera, Regional Sales Manager Carl Zeiss AS, Oslo

From PhD to industry: the pros and cons and the process behind

Guest lectures

by visiting professors and other guests

CIR has arranged an extensive number of seminars, symposiums and lectures with external international and national speakers, open for the whole scientific environment in Oslo. Some of the events have been arranged in collaboration with other research centres in Oslo and the Norwegian Society of Immunology. External speakers have also been invited to our seven CIR retreats. In total, including the guests invited by the postdoc committee, more than 100 different speakers have contributed to activities initiated by the centre. Centre members have also contributed with a multitude of lectures at the seminars and symposiums.

External speakers and lectures 2007–2017

William Agace, University of Lund, Sweden

Intestinal Dendritic cells, retinoic acid, and their role in the regulation of intestinal T cell responses

Maria Therese Ahlen, The Arctic University of Norway

Fighting FNAIT – murine models and antibody prophylaxis

Paul Antony, University of Maryland, School of Medicine, US

Restoring immune function of tumor associated antigen specific CD4 T cells during recurrence of melanoma

David Artis, University of Pennsylvania, US

Mechanisms of immunoregulation at barrier surfaces

Richard Blumberg, Harvard Medical School, US

Endoplasmic Reticulum Stress and Intestinal Inflammation

Regulation of Lymphocyte Function by Carcinoembryonic Antigen Adhesion Molecule 1: Implications for Inflammation and Cancer

The immunobiology of the (not so) neonatal Fc receptor (FcRn) for IgG in antigen presentation

IBD pathogenesis

Juan Bonifacino, NIH, US

Mechanisms of CD4 Downregulation by the Nef protein of HIV-1

Maria Bottermann, MRC Laboratory of Molecular Biology, UK

Adenoviral gene delivery is inhibited by sequential complement-mediated virion inactivation and TRIM21 neutralization

Søren Buus, University of Copenhagen, Denmark

Development of pan-specific HLA class I predictors and large scale HLA tetramer capabilities

Analysis of the specificity of human T cell responses

Drug hypersensitivity caused by alteration of the MHC-presented self-peptide repertoire

Harald Carlsen, University of Oslo

Optical imaging of gene regulation in living mice

Hyun-Dong Chang, Deutsches Rheuma-Forschungszentrum Berlin, a Leibniz Institute, Germany

Adaptation of proinflammatory Th lymphocytes to chronic inflammation

Yueh-hsiu Chien, Stanford University, US

Gamma Delta T cells: First line of Defense and Beyond

Peter Cresswell, Yale School of Medicine, US

Viperin: an interferon-inducible metabolic regulator co-opted by human cytomegalovirus

Mark M. Davis, Stanford University, CA, US

Systems immunology and its application to human beings

Molecular Aspects of T cell recognition and applications to human responses

Immunology Taught by Humans

Sigbjørn Fossum, University of Oslo

The role of APLEC receptors in adjuvant induced arthritis

Johan Garssen, University of Utrecht and Danone Research Centre for Specialised Nutrition, The Netherlands

Immunomodulation by dietary intervention: the cutting edge between food and pharma

Marcos González-Gaitán, University of Geneva, Switzerland

Sara endosomes during asymmetric cell division

Gareth Griffiths, University of Oslo

Development of biodegradable nanoparticles enclosing antibiotics against Mycobacterium tuberculosis in macrophages and in a zebrafish model system

Thorbald van Hall, Leiden University Medical Center, the Netherlands

Tumors with processing defects display novel tumor antigens via the non-classical HLA-E

Kristian Hannestad, Oslo University Hospital

Anti-nucleosomal antibodies in a mouse model for SLE

Adrian Hayday, King's College London, UK

The dominant role of body surface epithelia in shaping local T cell immunity

Dag O. Hessen, University of Oslo

The Red Queen principle in nature and culture

Mark Hogarth, Burnet Institute, Australia

Antibody and Fc-receptor interactions in humans and other primates. Implications for the development of vaccines, therapeutic antibodies and the induction of inflammation

Trygve Holmøy, Oslo University Hospital

The immunology of multiple sclerosis

Patrick Holt, Telethon Institute for Child Health Research in Perth, Australia

Interactions between innate and adaptive immunity in asthma pathogenesis: new perspectives from studies on acute exacerbations

Treg-mediated control of IgE-mediated acute phase responses??

Bana Jabri, University of Chicago, US

Host, environment and microbes, a love-hate triangle

Intraepithelial lymphocytes at the frontier of adaptive and innate immunity

Tissue control of effector responses

From human to mouse: Reverse engineering of a mouse model for CD

Kjetill S. Jacobsen, University of Oslo

Genome sequence of Atlantic cod reveals a unique immune system through the loss of MHC II function

Jørgen Jahnsen, Aker University Hospital

Treatment goals for IBD

Sirpa Jalkanen, University of Turku, Finland

Homing associated molecules as targets to prevent cancer growth and spread

Leo James, MRC Laboratory of Molecular Biology, UK

Intracellular Antibody Immunity and the Cytosolic Fc Receptor TRIM21

Intracellular Immunity: targeting and neutralizing viruses inside infected cells

Marc Jenkins, University of Minnesota, US

The CD4+ T cell response to bacterial infection

Imre Kacskovics, Eötvös Loránd University, Hungary

Accelerating antibody discovery using transgenic animals overexpressing the neonatal Fc receptor as a result of augmented humoral immunity

Frits Koning, Leiden University Medical Centre, The Netherlands

Gluten-specific T cells cross-react between HLA-DQ8 and the Type-1 diabetes-associated HLA-DQ2 /DQ8 transdimer

Christian Kurts, University of Bonn, Switzerland

Signal o chemokines enhance cross priming of cytotoxic T cells

Olivier Lantz, Institut Curie, France

MAIT cells, an evolutionarily conserved T cell subset with anti-bacterial reactivity

Antonio Lanzavecchia, Institute for Research in Biomedicine, Switzerland

Dissecting the human antibody response to pathogens and self antigens

Jeanette Leusen, University Medical Center Utrecht, Netherland,

Inside-out regulation of Fc receptors; consequences for antibody therapy of cancer

Sten Linnarsson, Karolinska Institutet, Stockholm, Sweden

Unbiased cell-type discovery using large-scale single-cell RNA-seq

Eric O. Long, National Institute of Allergy and Infectious Diseases, National Institutes of Health, US

Regulation of NK cell activation

Annalisa Macagno, Institute for Research in Biomedicine, Switzerland

Analytic vaccinology and human cytomegalovirus infection: from humoral immunity to vaccine design

Inger Helene Madshus, University of Oslo

Endocytic downregulation of ErbB proteins

Bernard Malissen, Centre d'Immunologie de Marseille-Luminy (CIML), France

Integrative biology of T cell activation and Harnessing skin dendritic cells

Luisa Mearin, Leiden University Medical Center, The Netherlands

Prevention of coeliac disease: Report from an ongoing pediatric trial

Jenny Mjösberg, Karolinska Institutet, Sweden

Heterogeneity and plasticity of innate lymphoid cells in tissue homeostasis and inflammation

Allan Mowat, University of Glasgow, UK

Local control of dendritic cell and macrophage heterogeneity in intestinal homeostasis and inflammation

Jacques Neefjes, Netherlands Cancer Institute, The Netherlands

How Salmonella causes cancer and the epidemics of gallbladder carcinoma in India

A Genome-wide multidimensional siRNA screen to reveal pathways controlling MHC class II antigen presentation

High throughput analysis of MHC class II antigen presentation and how to make sense of it

A science career? Smart moves?

Biophysical techniques used to define how cholesterol controls the positioning of late endosomes and how motor proteins do the job

David Nemazee, The Scripps Research Institute, US

Novel phospholipase family proteins in innate immunity

B cell tolerance : Genetics and vaccinology

Johanna Olweus, Oslo University Hospital

Manipulating dendritic cells to tease out cancer-targeted T cells

Petra Paul, the Netherlands Cancer Institute, The Netherlands

The MHC class II pathway of antigen presentation: A genome-wide screen and what comes after

Gøri Perminov, Ahus University Hospital

Mucosal macrophages and regulatory T cells in pediatric IBD

Susan K. Pierce, National Institute of Allergy and Infectious Diseases, National Institutes of Health, US

The acquisition of immunity in malaria

Regulating the initiation of antigen-driven B cell responses

A Tale of a Tail Wagging the Dog. On the generation, maintenance and activation of memory B cells

Borrowing from Peter to Pay Paul: Why Immunity to Malaria is so Slow to be Acquired

Philippe Pierre, Centre d'Immunologie de Marseille-Luminy (CIML), France

A role for the ER stress pathways in dsRNA innate responses

Hidde Ploegh, Whitehead Institute for Biomedical Research, US

Interplay between immunity and infectious agents

Fiona Powrie, University of Oxford, UK

Host microbial interactions in the intestine and their breakdown in inflammatory bowel disease

Gut reactions: Immune pathways in the intestine in health and disease

The IL-23 axis and intestinal inflammation

Regulatory mechanisms that control intestinal homeostasis

Gwendalyn Randolph, Washington University School of Medicine, US

Lymphatic transport and chronic inflammatory disease

Exploring mononuclear phagocytes in mouse and man

Jeffrey V. Ravetch, The Rockefeller University, New York, US

Novel roles for IgG glycans

Maria Rescigno, European Institute of Oncology in Milan, Italy

Bacteria as anticancer agents and Probiotics: friends or foes?

Dendritic cells in the gut: directors or players of the immune response?

Dendritic cell-epithelial cell cross-talk in bacterial handling in the gut

2-photon imaging to visualize dendritic cells in the gut

Mark Shlomchik, University of Pittsburgh, US

NETworks in Lupus: T-B or not T-B, DC is the question

Germinal Center Selection and the Development of Memory B and Plasma Cells

How does autoimmunity get started? Mechanistic and therapeutic implications

Development and Function of Memory B Cells

Activation and regulation of autoreactive B cells: the myeloid connection

Activating Autoreactive B Cells: Roles of Tolls, T Cells, and Time

Ziv Shulman, The Weizmann Institute of Science, Israel

Dynamic signaling by T follicular helper cells during germinal center B cell selection

Erlend Smeland, University of Oslo and Oslo University Hospital

Evidence for involvement of the BCR in diffuse large B-cell lymphoma development

Devin Sok, The Scripps Research Institute, California, US

Rational vaccine design for HIV

and HIV broadly neutralizing antibodies and their conserved epitopes

Jo Spencer, King's College, London, UK,

From bone marrow to gut-associated lymphoid tissue; a novel route in human B cell development

Jon Sponheim, Oslo University Hospital

Interleukin-33 in IBD

Anne Spurkland, University of Oslo

HLA association in multiple sclerosis

Harald A. Stenmark, University of Oslo and Oslo University Hospital

Ubiquitin-mediated endosomal sorting - role in growth factor signalling and cell migration

Nils Christian Stenseth, University of Oslo

Plagues: Past, Present and Future

Andreas Strasser, The Walter and Eliza Hall Institute of Medical Research, Australia

The role of apoptosis in tumor development and cancer therapy

Per Thor Straten, Copenhagen University Hospital, Denmark

T cells; magic bullets in cancer therapy?

Kunchithapadam Swaminathan, National University of Singapore, Singapore

Happy marriages among biophysical techniques

Pavel Tolar (MRC National Institute for Medical Research, UK)

Mechanical extraction of antigens from the B cell immune synapse: a unique way to measure receptor-ligand affinity

John Trowsdale, University of Cambridge, UK

Regulation of MHC genes and proteins

Genetics and functions of genes in the leukocyte receptor complex

Genetic and functional interactions between MHC and NK receptors

Variation in the Major Histocompatibility Complex (MHC)

Hendrik Veelken, University of Leiden, the Netherlands

The B-Cell Receptor and Pathogenesis of B-Cell Lymphomas: A Functional Immunopathology Perspective of Lymphoid Neoplasia

Gestur Vidarsson, University of Amsterdam, The Netherlands

Regulated IgG Fc-glycosylation in humans and it's significance

Ioana Visan, Senior Editor Nature Immunology

From bench to publishing – an editorial perspective

Sally Ward, University of Texas – Southwestern Medical Center, US

FcRn as a global regulator of IgG levels: from single molecule imaging to the development of therapeutics

The role of FcRn in IgG homeostasis: from protein engineering to imaging single molecules in 3D

Subcellular trafficking analyses of FcRn and IgG using high resolution microscopy: implications for antibody engineering

Kai Wucherpfennig, Harvard Medical School, Boston, US

Mechanism of HLA-DM induced peptide exchange in the MHC class II antigen presentation pathway

The Earliest Events in T cell Activation

Isolation of rare memory B cells for the generation of therapeutic antibodies

Work package strategy

In the last five-year period, the research plan were structured into four work packages (WP) that cut across established disease models and research group boundaries. The aim was to advance synergy and promote discovery through enhanced scientific interaction between research groups across disease models and technologies. Young senior researchers were appointed as WP-coordinators and were provided financial resources and administrative support to initiate activities.

WP1: Function of APCs in autoimmunity and allergy

ESPEN S. BÆKKEVOLD

WP2: T-cell repertoire in autoimmunity and allergy

SHUO-WANG QIAO

WP3: Pathogenic T-B collaboration

LUDVIG A. MUNTHE

WP4: Pathogenic and regulatory antibodies

JAN TERJE ANDERSEN

WP seminars

“Function of APCs in autoimmunity and allergy”
Coordinator: Espen S. Bækkevold

“Pathogenic and regulatory antibodies”
Coordinator: Jan Terje Andersen

“Pathogenic and regulatory antibodies: placenta and the impact of glycosylation”
Coordinator: Jan Terje Andersen

“Generation of recombinant antibodies and derived fragments”
Coordinator: Jan Terje Andersen

“B cell day”
Coordinator: Ludvig A. Munthe

“Core Facility services and technological expertise at OUS/UiO”
Coordinators: Shuo-Wang Qiao, Espen S. Bækkevold, Ludvig A. Munthe, Jan Terje Andersen

Internal activities

Project meetings

The core internal activity at CIR has been the monthly project meetings. These meetings have been very important for scientific progress and building centre identity, and to initiate collaboration between the research groups. In these meetings, postdocs and PhD students present their current projects, technical challenges, and new data, and get advice and feedback from the other researchers in the centre. Ample time is reserved for discussion following the presentations and discussion is encouraged. At the end of the meeting snacks and soft drinks is served to promote interaction and to continue the discussion in a less formal atmosphere.

CIR retreat

During the period of 2007-2016 it has been arranged 6 retreats for the centre members, CIR Board, and the Scientific Advisory board, and the last retreat will take place in the end of October 2017. Many international and national highly ranked scientists have participated at the retreats, sharing their knowledge and giving excellent keynote lectures.

Journal club

In collaboration with the department of Immunology, CIR has arranged a journal club for students and younger researchers. Professors have been excluded from these journal clubs to facilitate the active participation and performance of junior scientists.

Innovation and industrialisation

A Culture for Innovation

"CIR identifies and investigates novel mechanisms of immune dysregulation to advance the development of therapeutics for immune-mediated diseases."

AGNETE FREDRIKSEN

GEIR ÅGE LØSET

Commercialisation of the research at CIR has been a healthy mixture of sharing new technology and new knowledge with existing industry and inventing new technology that have been "taken all the way" by startups.

We have fostered two founders who burn for their inventions, who work inexhaustibly and have succeeded: Agnete Fredriksen with Vaccibody A/S and Geir Åge Løset with Nextera A/S. Both have secured public and private funding and created new jobs. Vaccibody has already a product which is tested in clinical trials, and is also expanding into new areas. Nextera develops new technology, the use of which will surely give very important information on disease mechanisms.

Enthusiasm and creativity are two crucial factors for innovation. More important however, are the actual data that lead to the innovation and the results that show whether an invention actually works. Many clever and hardworking young scientists at CIR have participated, and made our commercialisation efforts successful.

While companies were established based on ideas from CIR research group, the groups continued their research and generated more ideas and patents. Many were licensed by the startups to strengthen their patent portfolio. This has been extremely positive, a win win situation. The scientific groups have continued their research, and recruiting post-doctoral fellows and other scientific staff that have pursued their own new innovative ideas.

Research conducted by CIR scientists has strengthened the patent portfolio of Novozymes A/S. The company had already established technology where

drug molecules are attached to albumin to give long half-life in blood. CIR scientist Jan Terje Andersen found albumin variants with super long half-life that give the drugs an even longer half-life, which is a great improvement. Novozymes has established a new company, Albumedix A/S, which aims to develop new drugs based on CIR research.

MORE ON EXTENDING IN VIVO HALF-LIFE OF DRUGS

The efficacy of chemical drugs, peptides, small proteins and engineered antibody fragments are hampered by short serum half-life, ranging from minutes to a few hours. Therefore, strategies to tailor their serum persistence and biodistribution are needed. Inger Sandlie and Jan Terje Andersen have developed a unique technology that may extend the in vivo half-life of potentially all chemical and protein drugs. This will ultimately result in drugs with stabilised serum levels, less side effects and the need for less frequent dosing. Together with Inven2, they have signed agreements with Novozymes Biopharma, and together with Novozymes, established a very successful research program. So far, six patent families have been filed by Novozymes based on the results of the collaborative research. As a result of this collaboration, Novozymes has launched new products initially named Albufuse Flex and Recombumin Flex, and recently the Veltis® technology. In short, the new products are based on a list of new albumin variants. All differ from normal albumin at one or a few amino acid positions. They bind the neonatal Fc receptor with a range of different affinities, and when tested in rats and rhesus monkeys show greatly altered half-life. The best binders have increased and the poorest binder decreased half-life. Now, either genetic fusion (peptide or protein) or chemical conjugation of small drugs to either of these albumin variants will greatly alter the serum half-life of the drug. During 2015 new albumin variants were designed with increased half-life beyond that of earlier versions. The first drug to use the Veltis® half-life extension technology was launched by GlaxoSmith-Kline in 2014 as Tanzeum® (US) and Eperzan® (EU). Tanzeum® is a GLP-1 fusion to recombinant albumin for once weekly treatment of type 2 diabetic patients. During 2016, Novozymes established a new company, Albumedix A/S, which aims to develop new drugs based on the Veltis® technology.

MORE ABOUT VACCIBODY AS

Two of the CIR groups (Bogen and Sandlie) have developed novel vaccine molecules, known as Vaccibodies, which induce superior immune responses. A spin-out company, Vaccibody AS, was founded in 2007 based on the patented technology. Coinventor Agnete Fredriksen serves as Chief Scientific Officer. Vaccibodies target antigen presenting cells for efficient delivery of antigen and induction of immune responses. The vaccines are delivered as DNA plasmids administered intramuscularly. The muscle cells produce and secrete Vaccibody proteins that target antigen presenting cells and load them with antigen for presentation to lymphocytes.

The patent portfolio is continuously strengthened with clinical use and novel targeting units for a variety of applications. In 2014 the European Patent Office granted European patent No. 1599504 and the U.S. Patent Office issued patent No. US 8,932,603 B2, covering the Vaccibody format. The patent protects Vaccibody's platform technology on which the company has based its lead human drug candidate VB10.16, as well as a license agreement with the Phibro Animal Health Corporation, covering vaccines for poultry. The company has made significant progress with VB10.16, a therapeutic vaccine against cervical pre-cancerous lesions, and initiated its first clinical trial in 2015. Results from the interim analysis in the first phase showed excellent safety and tolerability, induction of strong T cell responses and promising early signs of lesion regression. In addition, Vaccibody is dedicated to develop individualised cancer vaccines based on mutation-derived neoantigens (VB10.NEO). A clinical trial application is submitted in 2017 for evaluating VB10.NEO in patients with melanoma, non-small cell lung cancer, kidney, bladder and head and neck cancer at three centers in Germany.

MORE ABOUT NEXTERA AS

Phage display is the dominating technology for discovery and refinement of novel protein-based diagnostics and therapeutics. A significantly improved version of phage display, termed SSIp display, has been developed by the Sandlie group, and commercialised by the spin-out company Nextera AS. Nextera was established by the key inventor, CIR scientist Geir Åge Løset, and Biomedical Innovation AS in 2009. Geir Åge Løset is the Chief Scientific Officer. Additional jointly developed IPR was acquired from Affitech AS in 2012, and Nextera furthermore holds the rights to innovations related to MHC class II expression that were jointly developed by the Sandlie and Bogen groups, and commercialised as Phagemers. The technology platform has a broad patent protection separated into five patent families granted in all major markets.

The core activity of the company is focused on discovery of disease relevant antigens presented on MHC class II and development of therapeutic leads towards these targets. Nextera has performed joint research with the Sollid and Sandlie groups at CIR with the aim of validating and expanding the use of the Phagemer, and will continue to do so. In 2015, Nextera entered into a research agreement with Janssen Biotech, Inc., one of the Janssen Pharmaceutical Companies of Johnson & Johnson, to determine the applicability of its Phagemer technology within rheumatoid arthritis (RA). Janssen funds the research program, and has an option for an exclusive worldwide license to the technology platform within RA. In addition, the company has a drug development program within hematological cancer in collaboration with Ludvig A. Munthe.

Dear all scientists at CIR

We at Inven2 would like to express great appreciation to you for the excellent collaboration over many years. Your openness and curiosity for innovation and the value and arenas it can open up, has been very inspiring to us.

In many ways, you have been a leading star for this area at the University. You have had, and still have, made a significant contribution by putting the University of Oslo and Inven2 on the map when it comes to bringing knowledge and technology to benefit for society.

Your innovations have led to a number of new technologies that are being developed by national and international companies, with the aim to offer patients a better diagnostic and a better treatment. This is foremost due to your knowledge and willingness to share with a several parties. You are a great example of the considerable synergy there is between excellent science and great innovation.

We hope each one of you will continue to find inspiration from each other within this field, and that you take this insight with you in whatever career you choose. We will continue to work closely with most of you, which is something we look very much forward to.

Congratulations with 10 excellent years in research and innovation!

Best regards,

Ole Kristian Hjelstuen
CEO Inven2

inven2

The Nextera-team is sincerely grateful

The Centre for Immune Regulation (CIR) has through its decade of existence contributed with deep knowledge, moved the boundaries of scientific insight, as well as shown a strong ability to translate its basic findings to commercially viable projects for the benefit of society.

Nextera is one of these translational offsprings born in a tradition of profound dedication to science, and represents an excellent example of how scientific excellence and novelty combined with devoted and competent investors can form new enterprises valuable to the local community and society.

Indeed, the Nextera-team is sincerely grateful for past and present collaboration with CIR, which have provided imperative and valuable input, advice and support from world leading researchers in the autoimmune field. Thus, the Nextera-team would take this opportunity to thank both the management and collaborating scientists in CIR – it has been a privilege and honor sharing the journey with you.

Thomas Andersen
CEO Nextera

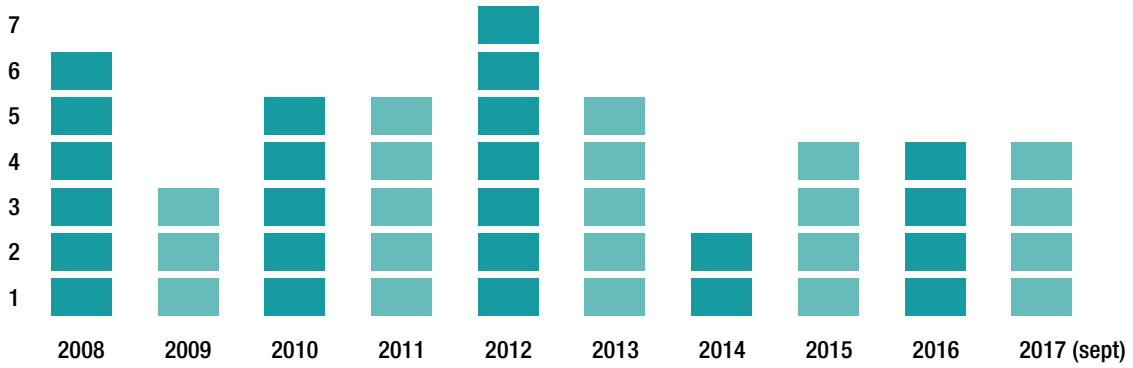
nextera

Education and career development

Doctoral degrees

In the CoE agreement with the Research Council of Norway, CIR committed to graduate 35 PhD students. A total of 45 PhD students, 23 females and 22 males, have defended their thesis since the start of the centre until September 2017, and several students will graduate within the spring of 2018.

COMPLETED PHD DEGREES PER YEAR



2008

Melinda Raki

Antigen presentation and T cell response in coeliac disease

Silja Amundsen

Mapping of non-HLA genes predisposing to coeliac disease

Even Walseng

Regulation of MHC-II Endocytosis in Antigen Presenting Cells

Jan Terje Andersen

Expression and ligand binding properties of recombinant soluble neonatal Fc receptor

Elin Bergseng

Peptide binding to HLA-DQ2 and development of blocking agents for the treatment of coeliac disease

Trygve Bergeland

Cell-cycle-dependent trafficking in the endocytic pathway

2009

Lars-Egil Fallang

Investigating coeliac disease using recombinant soluble MHC class II molecules

Michael M. Zangani

Idiotope Driven T-B Collaboration – Autoimmunity and Lymphomagenesis

Anders Sandvik

A study on immunomodulating beta-glucan: Effects of oral application on inflammation, tissue injury, and the mucosal immune system in experimental animals

2010

Jorunn Stamnæs

Transglutaminases in gluten sensitive diseases

Siri Dørum

Substrate specificity of transglutaminases for gluten peptides

Eirik H. Halvorsen

Investigation of immune processes in rheumatoid arthritis

Ulrike Jüse

Exploring peptide binding to the disease associated HLA-DQ2.5 molecule by the use of peptide libraries

Ingvild Heier

Studies on antigen presenting cells and T cells in airways and skin

2011

Maria Stensland

Peptidylarginine deiminase 4 and citrullination in Rheumatoid arthritis

Ingebjørg Skrindo

T lymphocytes in upper airway allergy: Effector T cells and regulatory T cells in pollen induced allergic rhinitis

Audun Os

T cells specific for endogenous B cell antigen: Consequences for autoimmunity and mature B cell malignancies

Ole J.B. Landsverk

MHC II and the Endocytic Pathway; Regulation by Invariant Chain

Dag Henrik Reikvam

Mucosal homeostasis and inflammatory bowel disease

2012

Kristin Støen Gunnarsen

T cell receptor expression and engineering

Luka Mesin

Plasma cells of the human small intestine

Muluneh Bekele Daba

The neonatal Fc receptor: Characterization of its ligand binding properties and its function in human hepatocyte and endothelial cells

Margit Brottveit

Gluten challenge in coeliac disease and non-coeliac gluten sensitivity

Johanne T. Jacobsen

Anti-Idiotypic B cells and Idiotype-specific Th cells in the context of Id+ Ig: interaction and mechanisms of regulation

Michael Bodd

Gluten-reactive CD4+ T cells in coeliac disease

Ann-Christin Beitnes Røberg

Antigen-presenting cells in coeliac disease

2013

Ole Audun Werner Haabeth

Inflammation driven by tumor-specific Th1 cells protects against cancer

Pier Adelchi Ruffini

Translational Development of targeted DNA vaccines for idiotypes of B cell malignancies

Rasmus Iversen

Transglutaminase 2-specific autoantibodies in coeliac disease

Gunnveig Grødeland

APC-targeted DNA vaccines against influenza

Kristina Berg Lorvik

Inflammation mediated by tumor-specific Th1 or Th2 cells protects against B-cell cancer

2014

Astrid Elisabeth Voorham Tutturen

Enrichment and identification of citrullinated proteins in biological samples

Synne Jenum

Mycobacterium tuberculosis infection and disease – a contribution to the understanding of immunological diagnostics in children

2015

Axel Berg-Larsen

Potential roles of Rab GTPases during dendritic cell maturation

Guro Reinholt Melum

Mucosal dendritic cells in immune homeostasis and upper airway allergy

Asbjørn O. Christophersen

Studies of gluten-reactive CD4+ T cells in healthy subjects and coeliac disease patients

Øyvind Steinsbø

On the IgA response to gluten in coeliac disease

2016

Ibon Eguíluz-Gracia

Studies of monocytes and macrophages in the respiratory tract with focus on airway allergy

Stian Foss

Intracellular Fc receptors: Role in transcytosis and protection against human adenovirus 5 infection

Fredrik Hellem Schjesvold

CD4+ T cell-induced macrophage cytotoxicity against tumor cells

Kristin Aas-Hanssen

Idiotype driven T cell-B cell collaboration in a mouse model of systemic autoimmune disease

2017

Inês Cardoso

Extracellular transglutaminase 2: Binding partners and relevance to coeliac disease

Kathrin Hnida

Anti-transglutaminase 2 autoantibodies in coeliac disease: Structural basis for antigen recognition and functional properties

Kine Marita Knudsen Sand

The FcRn-albumin interaction

Malin C. Bern

Engineering of the albumin-FcRn interaction

Equality measures

Professor Inger Sandlie

Equality measures are often associated with processes aiming to make women more capable, to give them knowledge or courage. It is suggested that women lack something. More and more people now ask whether this is the way to go. I am one of those who think we're pretty OK as we are. Should something change, then it is the way the organisation treats women. Astrophysicist Jocelyn Bell Burnell says in *Science 2004* "I do not believe that making women more courageous, more assertive, 'more like me' is the right way to move forward. Women should not have to do all of the adapting. It is time for society to move toward women, not women toward society."

Our goal was to increase the number of female post-docs that would choose to continue their research career.

Let me tell you about our experiences at the Centre for Immune Regulation (CIR), at the University of Oslo and Oslo University Hospital. We started a gender equality project in 2008. At the PhD student and postdoctoral level, the female ratio was 58% and 65%, while only 1 in 10 researchers and 1 in 5 professors at the centre were women. We therefore wanted to introduce measures at the postdoc level. 17 out of 26 postdocs were women. Our goal was to increase the number of female post-docs that would choose to continue their research career. We saw that talent and important skills were lost at CIR when the female postdocs left. Furthermore, the women left CIR during their most productive years. They left while they still had funding for continued research.

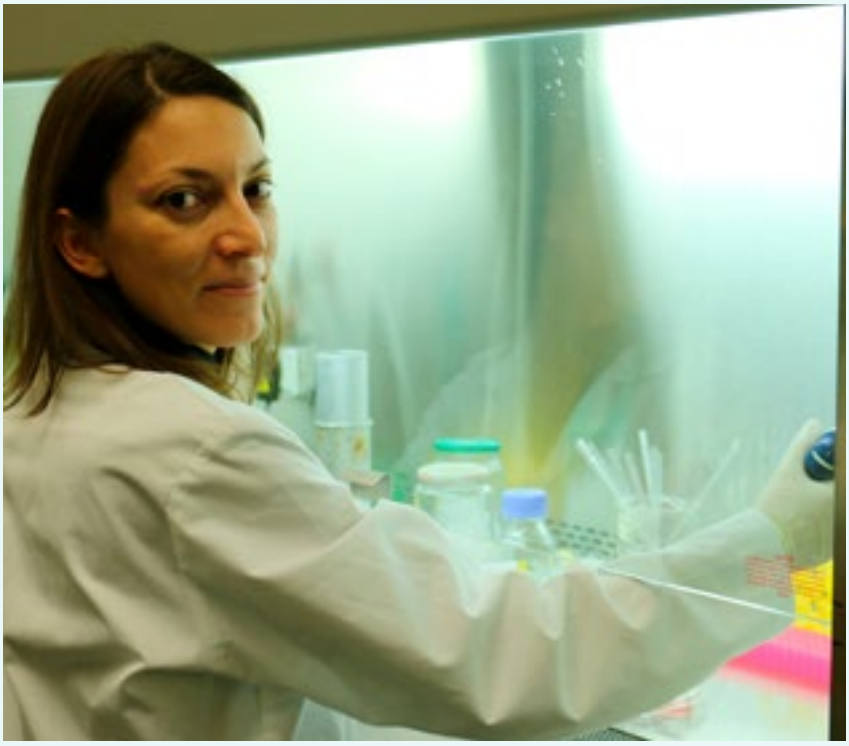
CIR's research activities are based on time-consuming laboratory work. We employed three laboratory technicians who were to assist the female post-docs. This gave the postdocs more time for planning of experiments, writing articles, applications and more. We also set aside funds that each participant in the program could use as they thought best. Some candidates used funds to pay for teaching assistance, others asked for help with application writing. The offers were only given to a few, selected by the centre group leaders and the SAB, and felt to be particularly talented. Furthermore, in the first few years of CIR, everyone in the postdoc group received an offer to participate in a mentoring program. We employed a mentoring group of 5, and the women chose who they wanted to work with. We also put emphasis on role models, and inviting top-qualified female guest professors and talented female guest lecturers.

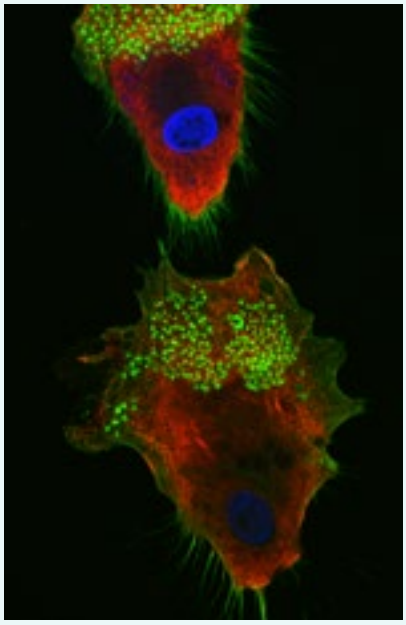
Having research funds at their own disposal is undeniably a good thing for all who wish to establish themselves as independent researchers. In applications for research scholarships and career grants, the candidate is the project manager and responsible for the design of the application. One generally applies for funds to cover wages for several people, so award of such applications is really an opportunity for the candidate to establish her own group. Therefore, we offered guidance for application writing. We also felt it was important to collaborate with the candidates to improve the application before the next submission date, in case of rejection. It was I, as the deputy head of CIR, who offered such guidance.

Now after 8 years, we can see the results of the project. Surprisingly, the mentoring scheme was only used to a limited extent. The young women said they felt it was yet another thing they had to find time for, in their busy life juggling research and family. On the other hand, assistance with laboratory work and teaching duties gave respite and focus on research. Most women made use of the help and guidance with application writing. Several received funding, others received very good evaluation, but no support, and were then encouraged to apply again with an improved application. Importantly for us in CIR: The women in the focus group did not quit, and two have been appointed in permanent scientific positions. What we achieved was to show these young employees that we would really help with reducing the unpredictability of their job situation. And job unpredictability is what the young women most often state as the reason why they choose to leave the university and academia.

Results from research conducted by the Swedish Research Council show that young women and men who apply for their own research funds largely experience the same: their applications are not funded. The men apply again, whereas the women hardly ever do so. For us at CIR this is an interesting observation. Why don't these men give up? At the centre we have learned how much it means for the young women to gain recognition, being one of the few really invested in. The attention and the interest given to their research has been an important instrument and one effective single-action. Is this what young men experience in informal men's networks?

We believe that all research environments have their specific challenges in terms of gender equality. Recruitment and dropout, motivation and choice. Every organisation should analyze how the situation is with them and what actions they need to put in. The good examples must be known and shared. We will also recommend the Research Council to develop a comprehensive policy for gender equality and employee involvement in its recruitment policy. The women choose, and for the moment they too often choose other employers and other careers, and leave the university. It is our job to make arrangements so that they want to stay.





Migrating monocyte-derived dendritic cells. Punctate spots that are rich in actin (labelled in green) are podosomes, adhesive structures localised to the front in migrating cells. Myosin is labelled in red and nuclei in blue. Photo: Marita Borg Distefano

Message from Cinzia Progida

Career Development programme for female scientists, 2013–2014

When I applied to the Career Development programme for female scientists at CIR, I did not image how important that support would have been for me. This was definitely an excellent measure to support women who want a career in research and indeed I feel it has been of help for my career. I received the Career Development support from CIR in 2013, during the last year of my personal post-doctoral fellowship. Therefore, it was very important for me to receive this support at exactly that point of my career. CIR Career Development programme allowed me to have both technical assistance in the laboratory (meaning practical help for running projects when I was writing grant applications), and also mentor's advice in connection with the preparation of grant applications. I received special mentor guidance and gained valuable insight into the grant writing process, which I strongly believe was crucial for writing competitive and successful applications and to attract my own research funding.

The project that I was able to start thanks to the support from the CIR Career Development programme was actually recently published on the prestigious journal EMBO Reports (Kjos et al., 2017). In this work we identified novel regulators and molecular mechanisms modulating autophagy, the process used by cells to destroy waste materials and recycle them to maintain cellular homeostasis. Understanding the molecular mechanisms controlling autophagy is incredibly important as alterations in this process occur in several diseases, including cancer and inflammatory diseases.

From 2017, I am now an associate professor at the Department of Biosciences, UiO. My group is focusing to understand how intracellular membrane traffic is regulated, and how it functions in concert with the cytoskeleton to coordinate cell migration. We are particularly interested in understanding how this is regulated in dendritic cells, specialised antigen-presenting cells, whose function is dependent on their migratory ability, an aspect we are investigating with the collaboration of internationally renowned researchers in the field. A collaboration also initiated thanks to the activities promoted within CIR. My direction to work on the extremely important intra-cellular mechanisms in immune cells is thus a result of the CIR focus and I hope in the future to continue collaborations also with my present colleagues in CIR.

Cinzia Progida

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