The advent of immunological research in Norway and NSI as a catalyst

Per Brandtzæg
per.brandtzaeg@medisin.uio.no

Laboratory for Immunohistochemistry and Immunopathology (LIIPAT), CIR, University of Oslo; and Department of Pathology, Oslo University Hospital, Rikshospitalet, Norway

During 1962-64 I was supported by a Fulbright Fellowship to obtain postgraduate training in pathology, microbiology and immunology at the Dept. of Microbiology, Medical Center, University of Alabama at Birmingham, Ala., USA.

My supervisor was Frederick W. Kraus


Drawing («Black Vultures» or «Gribbenes») by Ragnhild Danielsen, Secretary to Prof. Olav Torgersen

I returned to Oslo with a UiO fellowship to “The House of Horror” (the Old Pathology Building from 1876) in 1964

Prof. Olav Torgersen

Drawing of the Old Pathology Building, Rikshospitalet (1876-1970)

The beginning of the first Norwegian laboratory fully devoted to immunology and immunopathology, LIIPAT, which Torgersen wanted me to develop

Opening of LIIPAT, spring 1965

Professor Olav Torgersen (1907-1978): Searchlight on pathology

In contrast to earlier days’ misunderstanding of pathology as a «dead» science concerned mainly with descriptive morphology, modern pathology even more than before aims at correlating function with structure of cells and tissues - -

Tidsskr. Nor. Lægeforen. 82: 224, 1962
World-famous mucosal immunologist, Prof. John J. Cebra, became a good friend and supported LIIPAT (Univ. of Pennsylvania–Univ. of Oslo connection)

John’s connections with LIIPAT
- 1994: John is a guest lecturer at Rikshospitalet, Oslo
- 1995: John obtains a fellowship from the Research Council of Norway to spend 3 months as a Visiting Scientist at LIIPAT
- 1998: John is elected member of the Norwegian Academy of Sciences

Celebrating LIIPAT’s 30th Anniversary at Bae farm, September 1995

John is ready to teach at a LIIPAT seminar, December 1995

The beginning of John’s impact on LIIPAT’s development
- 1965: John’s seminal paper on fluorescent antibody conjugates
- Per met Gerald in 1965, and invited him to Oslo
- Gerald visited LIIPAT in April 1966, on his way from Stockholm
- Gerald taught Per how to purify and characterize fluorescein (FITC) and rhodamine (TRITC) fluorochrome conjugates by chromatography

A lot of time was spent to purify fluorescent antibody conjugates
We produced many rabbit antisera and waisted too much time!
Per’s freezer from 1965

Fluorescent IgG prepared from rabbit antiserum detected human antibody-producing cells, but the old glass filters provided indistinct colour signals (LIIPAT, 1966)

IgA (fluorescein)  IgG (rhodamine)

But praise the Dutch, LIIPAT was provided with the first prototypes of the "Ploemopak 1" (1969, 1971) and "Ploemopak 2" (1972) employing incident excitation light and narrow band (30-nm) interference filters

But colours disclose cancer!

A great moment in my life: featuring James Bond and Wenche Myhre, together with Per’s double immunofluorescence

Aftenposten
26 June, 1985

Brandtzaeg P. Mucosal and glandular distribution of immunoglobulin components. Immunohistochemistry with a cold ethanol-fixation technique. Immunology 1974; 26: 1101-14

The first publication based on colour separation with a Ploem-type fluorescence epi-illuminator

The paper was initially rejected because the referee wanted "... the addition of ultraviolet excitation with a colourless barrier filter to ... have enhanced histological discrimination", and concluded that "The fluorescence microscopy employed is a limiting technical feature of the study".


Gut mucosa (IELs)
Metastasis of mammary carcinoma to regional lymph node

B cells (CD20)

T cells (CD3)

Cytokeratin

Estrogen receptor

Helge Scott was important in developing diagnostic immunohistochemistry at LIIPAT for Rikshospitalet (solid line) and for outpatients (stippled line).

Pathologist’s dream

Diagnostic reports based on ELISA measurements of food antibodies developed for his doctoral dissertation (1985) on coeliac disease by Helge Scott at LIIPAT. Arrow indicates transfer of the tests to Allergenlab, Nycomed AS, and later on to Fürst Med.Lab. Since then LIIPAT has only been responsible for the evaluation of the results on a consultant basis.

The New Pathology Building, 1971-2000

The new facilities made the scientific activities much more efficient.

European MRC network at LIIPAT (1991-1996)

Medisin og helse

Ny periode for det norske nettverket
LIIPAT’s integrated approach to understand mucosal immunity in health and disease

Clinical material

- In situ mapping of functional markers (hypothesis driving)
- Mechanistic ex vivo and in vitro studies (tissue and cell cultures)

**Experimental in vivo studies**

But mice are not men

Several PhD students from LIIPAT have obtained important leading immuno-clinical positions in Norwegian medicine (3 examples)


Calprotectin is a heterodimer of S100A8 and S100A9 subunits (also known as L1 heavy and light chain, Mep8/14, calgranulin A/B, and cystic fibrosis antigen)

CALPRO AS (Arnstein Arnebergs vei 30, 1366 Lysaker)
E-mail: mail@calpro.no


LIIPAT had grown big in 1990 at its 25th Anniversary

LIIPAT’s Jubilee Book 1965-1990 was well received

The LIIPAT mucosal immunology group 2005

There is a need for a simple non-invasive readout as a proxy for intestinal induction of secretory immunity in field trials of oral vaccine

Brandtzaeg P. Do salivary antibodies reliably reflect both mucosal and systemic immunity? Ann NY Acad Sci. 2007;1098: 288-311

RESEARCH ARTICLE

Experimental infection of healthy volunteers with enterotoxigenic Escherichia coli wild-type strain TW10598 in a hospital ward

Aase A ... Brandtzaeg P: Salivary IgA as a non-invasive readout for intestinal immune response against experimental enterotoxigenic Escherichia coli (ETEC) infection. Submitted, 2014.
and ITI, and got his PhD on research fellow at LIIPAT Ludvig M. Sollid was a joint Halvor Sommerfelt (PI)

Co-directors:●  Halvor Sommerfelt (PI)
   Center for International Health,
   Univ. of Bergen, Bergen; and Norwegian Institute
   of Public Health, Oslo
●  James (Jim) P. Nataro
   Center for Vaccine Development, Univ. of
   Maryland School of Medicine, Baltimore, MD

The first new aera of Norwegian Immunology began when
Jacob B. Natvig came to Oslo in 1966

- Jacob was cand.med. from UIO (1959) and PhD from Gade's Inst. and Broeengolm Research Lab. for Microbiology, Univ. of Bergen (1966)
- His mentor was Prof. Olav Tønder who in 1980 was succeeded by Prof. Roald Matre as Head of Broeengolm Res. Lab. and then in 1991 by Prof. Roland Jonsson
- After his doctoral degree about autoantibodies, Jacob went for a research stay as postdoc with the famous physician and immunologist Henry G. Kunkel at the Rockefeller University in New York
- Jacob was then, in 1966, offered to be the Chief Physician and Head of the Institute of General and Rheumatological Immunology (IGRI) - newly established as part of Rikshospitalet by generous donations to rheumatological research from the Norwegian people and initiated by the Head of the Rheumatological Hosp., Prof. Erik Kass
- It was important for the development of LIIPAT that I for several years was invited to participate in the research seminars at IGRI, with the requirement that I contributed on the same terms as Jacob's scientists

The second new aera of Norwegian Immunology began when
we in 2000 moved into the hospital at Gaustad

- Erik Thorby was first trained in surgery at Ullevål Hospital where he obtained his PhD on HLA molecules, supervised by Prof. Morten Harboe at the Inst. for Experimental Med. Res.
- When the transplantation surgeon Prof. Audun Flatmark was able to establish a Tissue Typing Lab. at Rikshospitalet in 1970, he also succeeded in employing Erik as its first Head; the lab was in 1984 attached to UIO with the name Inst. for Transplant. Immunol. (ITI)
- Erik transplanted a piece of skin from one colleague to another and the specimen before (left) and after (right) the rejection reaction is depicted. This generated antibodies in the recipient against an as yet unknown tissue type (HLA-B5) expressed by the donor cells
- Since 1999, ITI has been named Inst. of Immunol. (IMMI) after merging with IGRI, and Erik became Head of the institute
- An important «bridge» to the clinics is Knut Lundin who got his PhD at ITI/IMMI and then became a Senior Consultant and Lecturer at the Dept. of Med., Rikshospitalet

This book from 2014 covers the development of the Medical Faculty, UIO, during the last 200 years

- It also gives a description of the history of the Excellence Initiative (SFF) announced by the Norwegian Research Council in 2001, and the development of CIR (established in 2007), headed by Prof. Ludvig M. Sollid at IMM.
- Citation from Ø. Larsen: Seniør for immunregulering (CIR) springer ut fra sterke immunologimiljøer ved UIO og Rikshospitalet. Fra 2010 er CIR også et «Federation of Clinical Immunology Societies (FOCIS) centre of excellence. CIR består av fem forskningsgrupper og blir ledet av Prof. Ludvig M. Sollid (www.med.uio.no)
- Citation from Ø. Larsen: Netwerkert Centre for VaccinoLOGY and Immunotherapy (CEVI), et tematiske forskningsområde ved Det medisinske fakultet, etablert i 2001 og var fastset ved utbyggingen av første generasjons SFF-er (2002), ledet av professor Per Brandtzæg, er en forløper til CIR.

New leader and professor at IGRI from 1983

- When Jacob B. Natvig became the Director of Rikshospitalet (1978), Prof. Morten Harboe moved with his immunological research group at Ullevål Hosp., UIO, where he had been for 20 years, to become the Head of IGRI in 1983
- Morten had received the first immunological doctoral degree in Norway (1961) on the genetics of immunoglobulins at the Inst. of Forensic Med., Rikshospitalet, and continued his work with Kunkel at Rockefeller Institute (1961-62)
- After Jacob resigned as a Director of Rikshospitalet (1986), he returned to IGRI as prof. of immunology and continued with an active research group, while Morten was the Head of the Institute until he retired (1999)
- An important bridge between IGRI (and later IMMI) and the clinics is Morten’s previous res. fellow on complement, Prof. Tom Eirik Mollnes, who collaborates closely with clinical researchers such as Prof. Pal Aukrust, Head of the Section of Clin. Immunol. and Infect. Dis., Dept. of Med., Rikshospitalet

The history of immunology at Rikshospitalet (RH) is well covered in this chapter (pp. 250-260) from 2001

- One of the doctoral fellows from IGRI, Stig S. Frøland (PhD in 1973) subsequently (from 1975) trained in clinical infection medicine at Ullevål Hosp., and was then employed at the Dept. of Internal Med., Rikshosp. (1979), for later to become prof. associated with the Section for Haematol. Disorders
- Stig is a prominent clinical immunologist with a profound interest in HIV/AIDS and immunodeficiencies
- He has a special sense of humor!

Dr. Knut Lundin

Dr. Knut Lundin
The Norwegian Society for Immunology (NSI) became an important catalyst for modern Norwegian immunology

- Jacob B. Natvig was a strong promoter of clinical immunology, both internationally as Secretary General (1977) and later President (1992) of IUIS, as well as in Norway. In 1972 he founded «Norsk Forening for Immunologi» to promote general immunology, to get a specialty in clinical immunology, and to obtain fees for diagnostic tests. Because the society was founded under the Norw. Med. Assoc., it excluded non-medical members from the board, which frustrated those who had an interest in immunology without being physicians.
- In 1979 I was invited to give a lecture by an informal group called «Molecular Immunology» under the Norw. Biochemical Soc. This group was headed by Terje Mælandset (NIPH) and Tor Lea (IGRI), both with their PhD from IGRI.
- We established an Organizing Committee lead by P.B. to explore the possibility to create an NSI open for all with an interest in immunology. At that time the Norw. Soc. for Immunol. and Immunohaematology was led by Dr. Ove Mellbye at IGRI, and in 1977 they decided to merge with Natvig’s society and collaborate for the creation of NSI. The negotiations were successful in that all scientific issues related to immunology should be the responsibility of NSI.
- NSI was formally established in 1982 with P.B. as the first President (1982-86). We attempted to have the large Norw. Soc. for Immunol. and Immunopathol. make an association with NSI as well, but the Head of their board, Prof. Kjell Aas, simply replied: «Who is going to associate with whom?»

Thanks for your attention!