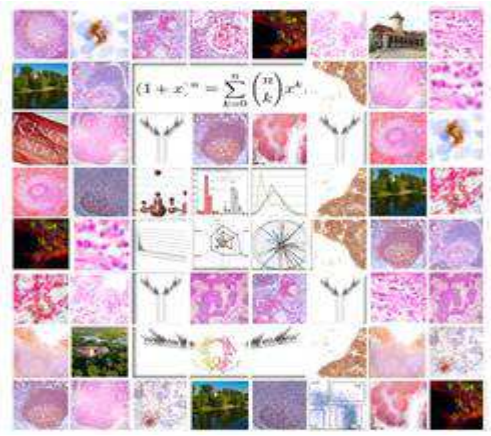
RESEARCH CONFERENCES



ESF-EMBO symposium with support from EFIS

B Cells from Bedside to Bench and Back Again

2-7 September 2013
Polonia Castle in Pultusk, Poland

Chaired by: Dr. Deborah Dunn-Walters, King's College London, UK

Co-chaired by: Prof. Idit Shachar, Weizmann Institute of Science, IL

http://www.esf.org/conferences/13408

Highlights & Scientific Report

Conference Highlights

Please provide a brief summary of the conference and its highlights in non-specialist terms (especially for highly technical subjects) for communication and publicity purposes. (ca. 400-500 words)

B cells are white blood cells that are crucial for a good response to infection. Different types of B cells have different functions. B cells differentiate into plasma cells that produce antibodies, which in turn have a variety of functions in helping the immune system to protect the body. Until recently T cells were considered to be the prime orchestrators of the fine balance and control required for an effective immune system. However, the advent of therapies designed to deplete B cells, for example to treat B cell cancers or autoimmune conditions, have highlighted the fact that B cells also play an important role in regulation of immunity.

The meeting "B cells from Bedside to Bench and back again" was held in Polonia Castle in Pultusk, Poland in order to explore what we can learn about B cell biology from observations in the clinic, and how we can use this new knowledge to add to our understanding of basic B cell biology in order to identify possible targets for new therapies to be used against immune-associated diseases. The meeting concentrated in particular on evidence showing how B cells activate/regulate other cells of the immune system, and how the environment in which the B cells are situated affects their survival and activity. Data from new technologies, in particular high throughput sequencing of B cell repertoires, was also presented.

Altogether there were 23x45 minute lectures, 7x20 minute lectures from young researchers and 32 poster presentations. The closed nature of the conference was conducive to much discussion between delegates both in the sessions and in the refreshment breaks. The poster sessions in particular were a forum for lively and constructive discussion.

The new data that has emerged and been discussed at this conference has highlighted the fact that environment of the B cell is particularly important. Not only for survival and activation, but also possibly for educating lymphocytes during their development. Tissue sites such as bone marrow, spleen and gut require much more research in order to determine their role in the health of the immune system and the next B cell conference is planned to concentrate on these aspects of B cell biology.

x	I hereby authorise ESF – and the conference partners to use the information contained in the above section on 'Conference Highlights' in their communication on the scheme.

Scientific Report

Executive Summary

(2 pages max)

B cells are lymphocytes that play a key role in the immune response. A principal function of B cells is to differentiate into plasma cells that secrete antibodies against exogenous antigens, and into memory B cells that retain the memory of the encounter against future challenges. However, the advent of B cell depletion therapies, originally developed against B cell malignancies, has revolutionised the way we see the role of the B cell. Observations from the clinical use of agents such as Rituximab have resulted in the recognition that B cells have extremely important effector and regulatory roles other than antibody provision. Diseases such as rheumatoid arthritis that were previously thought to be T cell mediated are now responding to B cell depletion treatment, and such treatment is also being investigated as a prophylactic measure to prevent transplant rejection. This has highlighted the fact that there is much that is not understood about B cell biology, and that if we increased our understanding we may well be able to take innovative solutions back into the clinic to complete the translational cycle. The control of B cell, Plasma cell and memory B cell homeostasis is the result of a very fine balance between their production, survival, and proliferation. Survival factors have been shown to play a critical role in maintaining lymphocyte homeostasis and B cells are found in specialized niches, which provide factors to ensure their long-term survival or to facilitate their differentiation into effector cells. As our appreciation of the multifunctional nature of the B cell grows, so does the requirement for knowledge of factors affecting the proper control and development of the B cell. The tools at our disposal for investigating biomedical issues are becoming ever more sophisticated, with high throughput sequencing enabling many repertoire studies that were otherwise impossible, high resolution imaging of cellular and subcellular compartments facilitating the visualisation of spatial organisation in unprecedented detail, and a genomics revolution that opens our eyes to new concepts such as cell-cell transfer of miRNA, or protein variation due to transcriptional mutation.

Scientists of different disciplines, working on different problems, have ideas and results applicable to areas of research other than their own. This conference brought together clinicians, cell biologists, molecular biologists bioinformaticians and mathematicians in order to discuss the latest advances in B cell biology. The sessions were not subdivided by discipline, rather they were divided by topic and included people from different disciplines where it was appropriate. Since it is in the clinic where convergence of information is most often seen the conference started with the session ***Revelations from the bedside*** on observations in the clinic that have lead to new ways of thinking about biology**.** After the keynote presentation from Frances Lund, the session ***Regulation and communication*** included many talks highlighting the roles of B cells in interaction with other cells of the immune system. The evening poster session was the first of two (with 14 posters in each in order to give at least half of the poster presenters chance to move around to see the other half) and the whole afternoon of the second day was devoted to short talks from junior researchers. These presentations were well received and the more senior faculty spent considerable time in discussion with the young scientists. After the evening talk on the second day there was a special session for young scientists to

discuss their career plans. The session ***New insights into antibody function*** included the very latest data from the Spencer, Cerutti and Carsetti labs which particularly highlighted the role of the gut and spleen microenvironments in B cell development, which was a good introduction to the final session ***B cell microenvironment- regulation of differentiation, survival and function***, including discussion of some of the critical environmental and survival factors responsible for effective functioning of the B cell compartments.

The atmosphere of the conference was highly conducive to scientific discussion between all delegates and the younger researchers in particular appreciated the chance to mingle with more senior faculty. A substantial amount of additional sponsorship was raised and used to distribute bursaries to young scientists.

There were 24 main session speakers, including the chairs, 4 of whom were chosen from the submitted abstracts. The gender balance of session speakers/chairs was F/M 42%/58%. The gender balance of the participants as a whole was F/M 55%/45%. Conference attendees were of a wide variety of nationalities, resident mainly in Europe and affiliated countries, but also from Canada and USA. In total 15 countries were represented. Additional sponsorship was obtained from Miltenyi, Mabtech, Biolegend and EFIS and some of the speakers funded their own travel. With these extra funds 24 grants were disbursed to enable younger researchers to attend.

Scientific Content of the Conference

(1 page min.)

- *Summary of the conference sessions focusing on the scientific highlights*
- *Assessment of the results and their potential impact on future research or applications*

The conference was opened by Professor Ludvig Sollid from Norway, who presented his data showing the interplay of HLA, T cell recognition, antibody specificity and antigen modification by tissue transglutaminase combine in the aetiology of coeliac disease. He was the first to present high throughput sequencing (HTS) data, in this instance illustrating the skewing of the B cell repertoire towards cells carrying the VH5-25 gene. Continuing the use of HTS data was Pan Hammarstrom from Sweden, who showed her extensive analysis of B cell lymphomas and how it could identify new candidate DNA modification enzymes that are used in B cell development. Sai Reddy from Switzerland was chosen from the applicants to present a full talk on technical and bioinformatic considerations in HTS immune repertoire sequencing, and introduced his new software algorithms that can speed up the gene identification process to the levels required from big data. Also in this session Andrew Chan from Genetech USA talked about the use of B cell depletion therapy in diseases such as multiple sclerosis, pemphigus, type 1 diabetes and ANCA associated vasculitis/GPA. Andrew's contribution to the conference was greatly appreciated, not only in his presentation and participation in discussion, but in his willingness to talk about life in industry with the younger researchers. His talk was the first that would point to emerging data that suggests that different biological niches have a dramatic effect on the survival and function of B cells.

The first talk of the afternoon was from the keynote speaker Frances Lund (USA). Frances provided a huge amount of exciting data on how cytokines and antibodies produced by B cells can modulate different cells in the rest of the immune system. Some of the effects are direct from B cells to T cells, and some were indirect via the effect of B cell education of dendritic cells.

Ramit Mehr (Israel) develops computational tools for B cell research and presented her systems for measuring diversity and relationships in the repertoire, and Yves Renaudineau (France) was another speaker selected from the applicants and discussed STIM1 and calcium signalling in B cells in SLE. The first day ended with Claudia Mauri presenting her new data on the effect of microbiota on the immune system. A serendipitous finding after moving labs to a new animal facility, this sophisticated unpublished work showed that the development of regulatory B cells is dependent on the type of gut flora in the animal.

After the dinner the first of two poster sessions was held, with 14 poster presentations. The session was characterised by lively and long lasting discussion.

The second day started with a continuation of the theme regulation and communication. Richard Lo-Man (France) produced data to show that early life immunity is strongly regulated by B regulatory cells, and therefore the dogma that infant immunity is low because the immune system has not fully developed needs to be modified to account for infant levels of regulatory cells. Padraic Fallon (Ireland) presented data from his studies on Helminth infected mice which illustrated that the immune response in these animals is skewed. In particular there is an increase in germinal centre-like B cells that secrete inflammatory factors. Christophe Jamin (France) was another speaker chosen from the applicants and continued the theme of B cell regulation showing his data on regulation of T follicular helper cells and B-T interaction by Bregs.

The whole afternoon of the second day was devoted to short talks from the younger researchers, who all gave excellent presentations on topics such as endocannabinoid receptors in lymphoma, Ig responses in periodontal disease, function of CXCR7 in GC B cells and effects of plasmablasts on differentiation of T follicular helper cells. Two prizes were awarded (at the conference dinner). After Dinner Lucia Mincheva Nilsson (Sweden) gave an overview of exosomes in immunology and Ramit Mehr chaired a session for the younger researchers to discuss career opportunities and how to plan for career progression.
The first two talks on the third day were by Rita Carsetti (Italy) and Jo Spencer (UK) who both presented very new data which highlighted the growing importance of the gut associated tissue in B cell development. Rita's talk showed that IgM memory cells are the precursors of IgA cells in the gut and that the colonisation of the gut by bacteria is important for this process, while Jo's work showed evidence in support of the gut as an educational environment for transitional B cells and showed that patients with SLE have transitional B cells with impaired gut homing abilities. Andrea Cerutti (Spain) then talked about his work illustrating that innate lymphoid cells in the spleen can help T-independent marginal zone B cell responses. The last taqlk of the day, before the excursion to Warsaw, was from a young research fellow in the UK, Edwin Hawkins. Edwin introduced the Cyton software that he developed during his PhD in Melbourne and went on to illustrate how he is now using it to measure the effect of histone deacetylase inhibitors to affect the proliferation and differentiation of B cells in vitro.

After dinner the second poster session took place and was equally as lively as the first. Prizes for both poster sessions were awarded at the conference dinner.

On the final day of the conference the focus was on B cell microenvironment and signals regulating survival. Stephane Mancini (France) presented data on signals provided to pre B cells by stromal cells in the bone marrow. Deborah Dunn-Walters (UK, Conference Chair) presented data on the BCR repertoire in different populations of B cells and how they are altered with challenge and with age and Idit Shacher (Israel, conference co-chair) presented her work on the roles of CD74 and 84 in B cell survival and how these molecules are important in the survival of B-CLL in the stromal niches. Bernd Schroeder (Germany) was the last of the speakers chosen from submitted abstracts and talked about the role of signal peptide peptidase Sppl2a in cleavage of CD74 and its possible role in transitional B cell development. After lunch Claudia Berek (Germany) presented her data on the role of eosinophils on B cell survival both in the bone marrow and in the gut lamina propria. Ken Duffy (Ireland) then presented his mathematical modelling/in vitro work which elucidates the competing cell fates of division, differentiation or death that affect survival and function and highlights some of the potential pitfalls in interpretation of biological data in vivo. The last talk of the conference was given by Mikael Karlsson (Sweden) who gave a comprehensive overview of the effect of innate cells iNKT and neutrophils on B cell function and presented data on the effects of these on IgE production. Idit Shachar closed the conference, airing the views of many canvassed for opinion during the meeting that this meeting was an invaluable forum for B cell immunology in Europe and we hoped to be able to repeat the meeting in 2015.

Most of the speakers included unpublished data in their presentations and were received very well - with numerous questions. Discussion during coffee breaks and over lunchtimes was lively. A number of delegates opined that they liked the format of having fewer longer presentations as it gave people chance to think about the work in the context of their own knowledge/research and ask more pertinent questions. A number of collaborations were initiated at the meeting, and some existing collaborations re-kindled.

Forward Look

(1 page min.)

- *Assessment of the results*
- *Contribution to the future direction of the field – identification of issues in the 5-10 years timeframe*
- *Identification of emerging topics*

At the time of writing this report we haven't had the official feedback results, but we have had many messages of support from speakers and attendees. The overall feeling was that the conference was a unique networking opportunity and everybody came away having learned something. The fact that many other immunology conferences are broad ranging so the B cell immunologists don't get such close networking opportunities was commented on by many.

Moving forward from here it was agreed that B cell conferences in Europe were of high importance, and we should aim eventually to have them at least once per year if possible. It is clear that B cells play many more important roles in immunology than merely producing antibodies. To fully understand the reason behind immune failure in disease conditions the contribution of B cells to the overall control of the system should not be overlooked. Particular attention needs to be paid to the

fact that the location of B cells in the body can determine how well they survive various challenges, and how they respond to challenge. The role of external influences such as gut microflora has been identified as important, with recent data from three different labs at this meeting showing differences in immune control effected by the gut.

Business Meeting Outcomes

- *Election of the Organising Committee of the next conference*
- *Identified Topics*
- *Next Steps*

The next conference will be Chaired by the Co-chair of this one, Idit Shachar. Assisting her in the role of Co-chair with be Professor Claudia Mauri, a world-renowned expert on regulatory B cells and the role of B cells in autoimmune disease. Since emerging data at this conference has indicated that different tissues play varied and crucial roles in the immune response then the central theme of the next conference will be the effect of tissue-specific niches on the survival and function of B cells. Professors Shachar and Mauri are currently writing the application for funding for the future conference.

Atmosphere and Infrastructure

- *The reaction of the participants to the location and the organisation, including networking, and any other relevant comments*

All the feedback received to date (13th September 2013) by the Chair and Co-chair regarding the scientific program and the ESF organisation has been excellent. The networking opportunities between all participants, and the general atmosphere of the conference were particularly appreciated by the delegates.

x	I hereby authorise ESF to publish the information contained in the above Scientific Report on the ESF Research Conferences webpages. No sensitive or confidential information has been included in this report