Cancer immunotherapy

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Welcome to the March 2016 edition of Immunology News, with its new design and content. Our aim in this redesign is to provide an interesting and thought-provoking read that accurately covers the interests, views and concerns of our members. As well as a new look, we have a wonderful new editorial advisory board working with us to advise on content.

In this edition, we take a look at the recent advances made in the field of cancer immunotherapy. We also revisit the age-old debate about the representation of science in the press and what the BSI can do to help. Additionally, we hear the BSI clinical secretary Sofia Grigoriadou on what life as a clinical immunologist is like while BSI member Matthias Eberl starts the debate on the benefits of immigration to UK science.

This magazine is for BSI members and as such, we want to hear from you on what issues you want us to discuss, both in the field of immunology and the wider research environment. In the meantime, we hope you enjoy this edition. Please do send us your thoughts on the new design and what topics you want us to cover.

Best wishes,

Jennie Evans
j.evans@immunology.org

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Welcome to a new-look Immunology News, and we hope that you'll enjoy the more informative content and cleaner design. We've designed it to try and reflect the different immunological interests and careers, and to have those broader discussions, such as the topic of EU immigration which Matthias Eberl writes about in this issue, and which many of you have told us that you are interested in. Contributions from you are much needed, so please do write in with your views and thoughts.

It's our 60th anniversary in 2016, and to mark the occasion the Society will publish a report on the future of immunology, and hold a public debate at the Royal Society. The actual date of the BSI's inception, rather lost in the mists of time, was in October 1956, when a group of immunologists who led the remarkable renaissance in immunology during the post-war years decided they needed an organisation to enable a greater sharing of ideas. We owe a huge debt of gratitude to this founding group for their foresight and diligence in founding the Society.

Today, as we develop a five-year strategy for the organisation, that passion for immunology – and the need to share it through meetings and publications – remains as strong as ever. So too does the desire to enable current and future generations to thrive. Our recent membership survey told us that support for proper career development is enormously important to you. As we consider how we can help further immunology careers, we are also refreshing our website so that it can communicate better, showcase the work that is being done, celebrate the achievements and enable members to access information which will be of use in different fields.

At the same time, the BSI is moving offices to avoid a substantial rent rise and to gain some more space, so our home from 4 April will be in Holborn, central London. It will be sad to leave our room overlooking the Thames on the Albert Embankment but, for the BSI, it's a good move as we will be more central, save money and have a space that is more convenient for those who come in for meetings and discussions. We will host an office warming party in April; the date will be in an eNews so please do join us if you are in London on that date.

Jo Revill
Chief Executive,
British Society for Immunology

2016 is an important year for the British Society for Immunology. Not only do we see the launch of our new five year strategic plan and our joint congress with the Dutch Society of Immunology, but we also celebrate our 60th anniversary!

The BSI was founded in October 1956 by a small group of hard working, visionary immunologists, who wanted to come together to share ideas. The concept of a society had been mooted some two years earlier at a meeting at Trinity College, Cambridge and the founding group included such names as John Humphrey, Bob White, Robin Coombs and Av Mitchison.

Sixty years on and the BSI, its membership and the discipline continue to go from strength to strength. Immunology is at the forefront of scientific and medical research. Our comprehension of how the immune system works is critical to our ability to understand human and animal health and to treat some of the major diseases affecting humans, including infectious diseases (such as influenza and Ebola), autoimmune conditions (such as type 1 diabetes) and a variety of cancers.

To commemorate our 60th year, we want to both celebrate the achievements of the past while looking forward to the exciting future of immunology. We have commissioned a special logo, which you can see here, to use to highlight our anniversary. We have a series of events and projects planned for later this year, which we hope will bring the membership together to celebrate the wonder of immunology as well as communicating these ideas to outside audiences. We will bring you more information on these projects in the next issue of Immunology News.

If you want to get involved, or have any ideas for events or activities that would be suitable to commemorate this event, do get in touch at media@immunology.org.

We look forward to celebrating with you!

Jennie Evans
Communications Manager,
British Society for Immunology

Save the Date

We’ve set a focal date of Tuesday 11 October, around which several of the major projects and events to celebrate our 60th anniversary, including our debate at the Royal Society, will take place. Mark the date in your diaries and we’ll bring you more news shortly!

You can read more about our 60th anniversary celebrations on our blog at http://bit.ly/1PyXJ1K.
New BSI education videos released

At the BSI, we’re always looking out for additional ways to communicate the science and wonder of immunology beyond our membership to students and the public. For our latest project, we’re pleased to announce the launch of a new collection of short videos that explain different aspects of the immune system. Featuring interviews of BSI members by students from their institutes, the videos are designed to support sixth form studies or just for members of the public who want to find out more about how their immune systems work.


BSI acknowledged in House of Commons report on Ebola

In January, the House of Commons Science and Technology Committee published a report on its inquiry into the Ebola epidemic, quoting evidence submitted by the BSI. The report highlights what it calls ‘structural weaknesses’ in the UK’s capacity to withstand infectious disease threats, including a failure to invest in interventions against rare emerging or re-emerging infectious disease.

In our written evidence, the BSI noted that ‘the UK lacks a truly effective and co-ordinated platform for the research, development and manufacturing of new vaccines and treatments against novel or emerging disease threats’. The Committee acknowledged this and urged the Government to rectify the situation through the development of a new infectious disease strategy to co-ordinate action in this area. You can read more at http://bit.ly/1ZYyiVX.

We’re moving…

The headquarters of the BSI will be moving offices. From 4 April 2016, our new contact details will be:
34 Red Lion Square, London WC1R 4SG
Telephone: 0203 031 9800
All email addresses will remain the same. Please update your address books accordingly.

Immunology Undergraduate Prizes

The next round of applications for our Immunology Undergraduate Prizes is now open. These awards aim to promote excellence in the study of immunology at undergraduate level, and to encourage gifted students to pursue further postgraduate study and a career in immunology. The first application deadline is 29 April 2016 and further details can be found at http://bit.ly/1JXvwU1.
BSI WINTERSCHOOL A GREAT SUCCESS

On 1–2 December, the BSI held our second Winterschool for MSc Immunology students. Organised in conjunction with the MSc Immunology course organisers of King’s College London, the Winterschool runs in the years when there is no annual congress to provide Masters students with an opportunity to hear from some of the leading lights in immunology and experience the atmosphere and benefits of a scientific conference.

Over 120 students from six universities attended and you can see some of their feedback on the event here. Further reports from students who attended can be found on our website. Our thanks go to BSI Programme Secretary Leonie Taams and Education Secretary Helen Collins (both from King’s College London) for their work in putting this event on.

“It was amazing. Really enjoyed it.”

CEI & IMMUNOLOGY IN YOUR POCKET

Recent visitors to the BSI offices may have been bamboozled to see us hunched over mobile phones or huddled around the company tablet. No, we haven’t all turned into Flappy Angry Whatssit addicts, nor have we been whiling away our days watching cat videos (honest). The reason we have cricks in our necks and callouses on our thumbs is that we have been enjoying the terrific new Android apps for our journals, Immunology and Clinical & Experimental Immunology.

The apps are a genuine delight to use – our colleagues at Wiley have done a brilliant job at replicating the experience of leafing through a journal in a digital handheld format. They are intuitive, smart and an engaging new way of accessing our journals’ content. Features include in-line pop-up references, hyperlinked authors, beautifully optimised images and the ability to download articles for offline access (great for the morning commute).

Alongside our popular iOS apps, these latest launches mean that our journals boast 90% coverage of all smartphone users in the UK via a native app. If you have an Android device, we would heartily encourage you to download these free apps for yourselves – they’re available through the Google Play store, and if you log in using your BSI membership details, you will have full access to the previous 12 months of issues as well as the latest early view articles.

Will Strange
Journals Marketing Assistant,
British Society for Immunology
Join us at BSI NVVI Congress 2016

Here at the BSI we’re already looking forward to the end of the year and the much anticipated Joint BSI NVVI Congress 2016 taking place at the Arena Conference Centre in Liverpool on 6–9 December. This conference promises to be especially memorable as not only does this year mark the BSI’s 60th anniversary but additionally we see the return of the successful collaboration with our colleagues from the Dutch Society for Immunology.

This flagship event will comprise three days of plenary lectures, parallel sessions, poster sessions and our ever popular Bright Sparks event. The BSI and NVVI Programme Committees have worked hard to ensure that all areas of immunology are catered for, with something to suit all immunological tastes. This year sees a slight change to our timetable meaning that we will have more slots available for oral presentations from submitted abstracts, so the time has never been better to submit your research for presentation at the Congress.

To whet your appetite, we’re excited to announce that the keynote speaker will be Akiko Iwasaki, Professor of Immunobiology and Molecular, Cellular and Developmental Biology at Yale University. Professor Iwasaki’s research is at the cutting edge of understanding how immunity is initiated and maintained against viruses at mucosal surfaces, with a focus on how innate recognition of viral infections can lead to the generation of adaptive immunity, and how adaptive immunity mediates protection against subsequent viral challenge. This is sure to be a fascinating session and a must see for all immunologists.

Additionally, we have plenary sessions lined up on ‘Vaccinations’, ‘Orchestrating the immune response in vivo’, ‘Barriers and bugs: microbial-host interactions’ and a closing session. Confirmed plenary speakers so far include Yasmin Belkaid (NIH), Doug Fearon (Cambridge), Gabriel Nunez (Michigan, USA), Andrew Pollard (Oxford), Bali Pulendran (Emory, USA), Gerd Sutter (Munich, Germany) and David Wraith (Bristol).

So, mark the dates in your diary and visit www.bsicongress.com for more information on the many topical and cutting-edge parallel sessions that the BSI and NVVI have planned.

Leonie Taams
Programme Secretary,
British Society for Immunology
BSI committees: we need you

As you’re probably aware, the BSI is governed by its Board of Trustees, but did you know that we have a variety of other committees overseeing specific areas of our work, including Programme Committee, Forum, Clinical Immunology and Allergy Section (CIAS) Executive Committee and the Patient Advisory Panel? The last two are made up of representatives from constituent groups, but the Board, Forum and Programme Committee are all open to BSI members to put themselves forward for consideration when a vacancy arises. We also have a range of ‘Secretary’ roles that take responsibility for particular areas of BSI work, such as Congress, Public Engagement, and Education, working closely with BSI staff and the Board of Trustees. More locally, the numerous BSI Regional and Affinity Groups have their own committees who help to run regular meetings programmes and events.

Applications for Board and committee vacancies are available to all UK-based members, irrespective of age, gender, career stage or any other factor. Sometimes of course, vacancies are for positions which may require specific experience or regional representation, but we will always make that clear in the call for nominations. Do keep an eye on the BSI homepage and e-news alerts for information about vacancies.

In 2016, we will advertise a wide range of positions, including Trustee, PhD Representatives, Early Career Representatives, Programme Secretary and Groups Secretary. We are particularly keen to engage young professionals in the Society, especially to join the Board. Being part of a BSI committee gives you a front-row seat to all the action, giving you the chance to inform how we support our members and promote and champion immunology and science to all.

Emilie Thomas
Committee and Governance Manager, British Society for Immunology

BOARD OF TRUSTEES:
This is the BSI’s governing body and is responsible for ensuring the organisation operates properly and effectively. The Board’s main areas of responsibility are finance, governance, strategy and the appointment and supervision of the CEO.

FORUM:
This is the BSI’s ‘think tank’ and the place where the issues, ideas and policy initiatives of importance to the Society and its members are raised, discussed and developed.

PROGRAMME COMMITTEE:
Their primary focus is the planning and delivery of our flagship event, BSI Congress. They also review the BSI contribution to the European and International Congresses of Immunology.

What is it like to be on a BSI committee?
We hear from three of our committee members about their experience.

ANNE ASTIER
Anne is an academic fellow at the MRC Centre for Inflammation Research at the University of Edinburgh. She has served two terms of office on the BSI’s Forum as an Early Career Representative.

Why did you apply to join the BSI Forum?
I had recently moved from the USA and thought it was a good opportunity to get involved in the BSI and meet other colleagues.

What does being a Forum member involve?
Meeting in London a few times a year with the Forum members and discussing the items on the agenda. These vary from the BSI’s involvement in public engagement and the teaching of immunology to broader aspects such as preparing position statements on the benefit of vaccination or the impact of EU membership for immunologists in the UK. There is some work between meetings, for example, giving feedback on statement drafts.

What’s your experience of being a committee member been like?
I really enjoy the meetings. Most discussions centre on shaping the future of immunology or science in the UK, and to be able to be part of the ‘public voice’ of the BSI is an amazing opportunity.

Has being on the BSI Forum brought any benefits to you?
For me, networking and getting to know the other members has been the most important.

What’s your advice to someone thinking of putting themselves forward to join a BSI committee?
Go for it!

What’s your advice to someone thinking of putting themselves forward to join a BSI committee?
Go for it!
**EMMA CHAMBERS**

Emma is a research associate in the Division of Infection and Immunity at University College London. She was elected to the BSI’s Forum in 2014 as an Early Career Representative.

**Why did you apply to join the BSI Forum?**

I applied for a number of reasons including wanting to provide a voice for ‘younger’ immunologists in the policy making and views of the BSI. I wanted to learn more about how the BSI is run, becoming more involved in the BSI as I have been a member since the first year of my PhD, and have always found the events and support very useful.

**What does being a Forum member involve?**

There are quarterly meetings. The idea of the Forum is to be the BSI’s ‘think tank’ – to come up with ideas and to give opinions on various issues. As an Early Career Rep, it’s important to try and give a voice to early career immunologists and to bring this perspective to the committee. There are also opportunities to get involved in various activities, such as commenting on position papers, helping out with social media and getting involved in sub-committees.

**What’s your experience of being a committee member been like?**

I have actually really enjoyed being a Forum member. I’ve always had an interest in politics, and the recent BSI policy statements on issues such as immigration have really clarified to me the impact of government policy on immunology in the UK. Being on the BSI Forum has highlighted to me the importance of the BSI in educating the general public as well as MPs on the importance of immunology to the UK as a whole and specifically to the economy.

**Has being on the BSI Forum brought any benefits to you?**

It has improved my networking skills as I have met immunologists from across the whole of the UK, many of whom have different specialty areas to me. Through being on Forum I have gained experience of being on a committee and confidence in contributing my opinion on important issues affecting immunologists, both of which will help me in my career going forward. On a purely personal level, I hope that being a BSI Forum member and achieving these new skills and networks may enhance my immunological impact and chances of being awarded a fellowship in the future to continue my career in immunology.

**What’s your advice to someone thinking of putting themselves forward to join a BSI committee?**

Just do it, what is there to lose?

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**BETH HOLDER**

Beth is a postdoctoral research associate at Imperial College London. She was elected to the BSI’s Forum in 2012 as an Early Career Representative.

**Why did you apply to join the BSI Forum?**

Honestly, I think my primary reason was to have something extra on my CV! Obviously, I was also attracted by what their main priorities are and better understand the importance of being a member. Additionally I’ve been lucky enough to receive a BSI travel grant as well as attending the excellent BSI Congress, so I felt it was my turn to give something back.

**What does being a Forum member involve?**

I attend meetings four times a year in London. The minutes of the previous meetings and any necessary documents are emailed out before the meeting to read. The meeting lasts 2–3 hours with discussions on a wide range of topics including BSI policy statements on subjects such as immigration and animal research. Recently there has been much discussion on the Government’s comprehensive spending review and Sir Paul Nurse’s review of research councils. We hear and have input into the BSI’s contribution and stance on these issues. There are always updates from the BSI on the numerous public engagement events that the BSI attend and additional updates on BSI finances.

**What’s your experience of being a committee member been like?**

I have thoroughly enjoyed the experience. The committee members are extremely welcoming. At my first meeting, as a young scientist, I was a bit intimidated to find myself in a room with some senior people, but I found that everyone was interested to hear my opinion and was very encouraging. It’s been fantastic to be involved in the decision process of various initiatives and hear opinions from other people at different institutes.

**Has being on the BSI Forum brought any benefits to you?**

It’s made me more aware of the BSI’s wide range of activities. It’s fantastic to meet all the lovely BSI staff and realise they are not some faceless organisation with rigid rules. They always try to help you with any issues you have regarding bursary applications or with any careers questions, so it’s always worth getting in touch.

**What’s your advice to someone thinking of putting themselves forward to join a BSI committee?**

Only that to be a good committee member, you need to be proactive, willing to voice your opinion and to get stuck into various opportunities as they arise.
The immune system as a therapeutic tool

The immune system has evolved to recognise and eliminate cells that are infected with viral or bacterial pathogens or abnormal such as cancer cells. Accumulating evidence suggests that the immune response, in particular T cells, plays an important role in the clearance of cancers. However, these responses do not always result in resolution of disease, as cancerous cells are often able to 'hide' from the immune response, resulting in tumour growth and progression.

The induction of an effective anti-tumour T cell response requires engagement between peptide-MHC (pMHC) presented on the surface of tumour cells and the T cell receptor (TCR) on circulating T cells. The ability of peripheral T cells to respond to the presented antigen is determined during their development by the strength of interaction of their TCR with self-MHC. If the interaction is too strong, the T cell is deleted from the repertoire (negative selection), preventing recognition of self in the periphery leading to autoimmunity.

As tumours are derived from normal cells, the vast majority of pMHC presented on tumour cells consists of self-peptides preventing their detection. Thus, a much greater amount of a self-peptide or a new peptide distinct to the tumour must be presented in order for the T cells to detect them. Ultimately, the success of harnessing T cells to target tumour cells is dependent upon their ability to distinguish tumour from normal cells.

As cancers develop, they acquire a number of somatic mutations in DNA which, if they occur in exons of expressed genes, may alter the sequence and result in formation of neo (new) antigens. The recognition of these neo-antigens by T cells indicates a possible 'Achilles heel' of tumour cells, ideal for therapeutic exploitation. Our understanding of anti-tumour T cell responses has paved the way for immunotherapies which utilise patient T cells, such as adoptive transfer of autologous tumour infiltrating lymphocytes (TIL) and re-activation of TIL by blocking inhibiting molecules, termed checkpoint inhibition. In both these therapies, T cells specific for somatic mutations in tumours have been shown to play a key role in their efficacy.

Mutanome based personalised immunotherapy

The ability to identify somatic mutations within an individual's tumour represents a highly attractive target for potential immunotherapy. However, until recently, the ability to scan a tumour genome to identify these potential targets was limited. The emergence of next generation sequencing (NGS), a collective
‘The success of harnessing T cells to target tumour cells is dependent upon their ability to distinguish tumour from normal cells.’

term for a number of different high throughput sequencing technologies, has revolutionised the study of cancer genomics. This technology allows sequencing of each patient’s tumour genome, identifying tumour-specific mutations, termed the mutanome. The reduction in both cost and time of NGS, alongside ever increasing bioinformatics and protein prediction tools, has led to advances in tumour genome analysis and neo-antigen prediction. Currently, many collaborative efforts are underway, such as the 100,000 genomes project and The Cancer Genome Atlas (TCGA), to catalogue cancer mutanomes across an array of tumour types. Employing this technology has led to the discovery of a greater number of tumour-specific mutations than initially thought, with up to 100s of mutations identified in different tumours. These analyses also revealed that the mutational load of a tumour correlates with the efficacy of immunotherapy, with a greater number of mutations giving better responses. It is currently thought that >95% mutations identified are unique to the individual patient’s tumour and are not shared between tumour type or healthy cells, a feature that has hampered the ability to exploit differences therapeutically. As a result, personalised vaccines may be required to target neo-epitopes regardless of the mutational load of the tumour to maximise therapeutic efficacy. Therefore a key challenge is how immunogenic cancer mutations of relevance can be identified and therapeutically exploited for an individual.

**Identifying tumour antigens and future directions**

While a vast number of mutations have been identified from mutanome analysis of tumours, only a small proportion of these result in the formation of a neo-antigen presented on MHC class I (MHC I) or II molecules. Therefore, to enable prediction of neo-antigens many aspects have to be considered such as i) whether the mutated gene is transcribed and translated into protein that is expressed within the cell; ii) the many processing steps that generate the peptide epitopes; and iii) how well these will bind to MHC I to allow stable presentation at the cell surface. The use of biochemical assays, prediction algorithms and molecular modelling techniques have allowed the accurate prediction and identification of a number of cancer neo-antigens. However, the final and possibly most complex aspect that is yet to be well defined is whether these presented neo-antigens are immunogenic. Proof of concept studies, using current methodologies, have identified neo-antigens from both mouse and human tumours, although, the only way to determine immunogenicity was to examine responses *in vivo*, with varying success of predicting responses providing little correlation. This suggests that the propensity of neo-antigens to elicit an immune response may only occur in a small fraction and is difficult to predict.

In order to better predict immunogenic neo-antigens, each aspect needs to be carefully considered. One parameter that excludes many potential neo-antigens is selection of high affinity MHC binding peptides, since they would be expected to have a longer half-life at the cell surface and maximise T cell recognition. Emerging evidence, however, shows that low affinity antigens are as efficacious in activating tumour-specific T cell responses as their high affinity cousins. It is therefore important to identify ways to predict immunogenicity that do not rely on binding affinity alone. Developments in our understanding of pMHC and TCR interactions through crystallography and molecular modelling provide us with valuable insights for predicting immunogenicity of neo-antigens. Nevertheless, at present the time taken for these analyses does not make it amenable to identify good neo-antigen candidates for clinical adoption. A greater understanding of how antigens are generated and the biochemical properties that underpin immunogenicity is needed to better predict neo-antigens. These advances will allow development of personalised cancer vaccines and advance the success of immunotherapy in combatting cancer.

**Edd James,**
Associate Professor in Cancer Immunology
Emma Reeves,
Postdoctoral Research Fellow
University of Southampton
Hedgehog signalling in vertebrates – it all happens at the cilium

A major scientific breakthrough in our understanding of the Hh pathway was the observation that, in vertebrates, Hh signalling is tied to the primary cilium, an ancient sensory organelle that projects from the surface of cells. In canonical Hh signalling, Hh ligands are secreted by Hh-producing cells, which generates an extracellular ligand gradient. Hh-responsive cells respond to this signalling cue; Hh ligands bind to the transmembrane receptor, Patched (Ptch), at the base of the primary cilium of the responding cell. Upon ligand binding, Ptch exits the cilium and releases its inhibition of the key signal transducer, Smoothened (Smo). Smo moves into the cilium and activates Gli transcription factors. These leave the cilium and enter the nucleus to initiate a Hh-specific target gene programme (Figure 1a).

The immunological synapse as a ‘modified cilium’

While primary cilia are found on nearly all cells in our body, the haematopoietic lineage, including lymphocytes, was thought to be unable to form a primary cilium. Gillian Griffiths and Jane Stinchcombe were the first to discover that the immunological synapse formed between a cytotoxic T cell (CTL) and a target cell is structurally very similar to sites of primary cilia formation. In both structures, the centrosome is ‘docked’ at the plasma membrane via distal appendage proteins, and the Golgi apparatus and endocytic recycling compartment are polarised towards this point making the area a focus for endo- and exocytosis. This has led to the notion that the immunological synapse may represent a ‘modified cilium’.

Investigating the Hedgehog pathway in mature CD8 T cells

When I joined Gillian Griffiths’ lab as a postdoc, I wanted to know whether the structural similarities between the immunological synapse and the cilium would extend to functional properties. Pioneering work by Tessa Crompton and co-workers over the last 15 years had already identified the importance of Hh signalling for multiple steps of T-cell development in the thymus and more recently in CD4 Th1-Th2 differentiation. The role of Hh signalling in mature CD8 T cells, however, was unknown. In my research, I asked whether ciliary signalling is active in CD8 T cells and started with looking at the Hh pathway that had been shown to rely on a functional primary cilium. CD8 T cells are crucial for the body’s defence against infection and tumours through their ability to differentiate into CTLs and kill infected and tumour cells. Upon target cell recognition, CTLs form an immunological synapse: cortical actin clears away from the centre of this synapse and allows the centrosome to dock at the plasma membrane – precisely at the point where target cell recognition has occurred. The cytotoxic granules move along the microtubules towards the centrosome and are secreted at the site where the centrosome is docked making killing very efficient and specific to the target cell.

Hedgehog signalling targets Rac1 required for CTL killing

During my stay in the Griffiths lab, I showed that Hh signalling plays a major role in CTL killing and discovered a novel signalling mode of the pathway. Naive CD8 T cells and CTLs readily upregulate Hh signalling after T-cell receptor (TCR) triggering. Importantly, when Hh signalling was inhibited genetically or via small molecule Hh inhibitors, CTL killing was diminished. Analysing conjugates between CTL and target cells using
immunohistochemistry I found that Hh-inhibited CTLs were unable to clear actin from the centre of the synapse and to dock the centrosome at the plasma membrane. This combined defect in actin and microtubule reorganisation prompted me to investigate the small Rho GTPase Rac1, which had been shown to regulate actin remodelling and microtubule dynamics at the leading edge of non-immune cells. I identified Rac1 as a novel Hh target gene in T cells that provides the CTL with the cytoskeletal machinery needed for centrosome polarisation and cytotoxic granule secretion. I next asked whether Hh ligands were involved and found that CD8 T cells do not produce Shh or Dhh, but express Ihh. Upon TCR stimulation, CD8 T cells upregulate their production of Ihh but this ligand is not processed for secretion. Subcellular localisation of Hh components revealed that Ihh colocalizes with the receptor Ptch on intracellular vesicles ready for signalling. The finding that CD8 T cells produce their own Hh ligand makes biological sense, since CTL have to eliminate infected and tumour cells throughout the body in many different environments and therefore cannot rely on an exogenous Hh gradient for function (Figure 1d).

Taken together, my work has uncovered a novel role for Hh signalling in immune cell function and identified a new cell autonomous intracellular signalling mode. This has opened a new field of research and might pave the way for future therapeutic interventions to modulate Hh signalling in T cells. Right now we have only scratched the surface of Hh signalling in T cells. The role of the pathway during an immune response in vivo as well as its molecular make-up is likely to keep us busy for many more years to come. Furthermore, we know that other immune cells also polarise their centrosome to form synapses and so may form a modified cilium. It will be interesting to investigate whether Hh plays a role in these cells as well.

**Hedgehog inhibition in the clinic – a double-edged sword?**

Hh inhibitors have attracted attention in the clinic due to the role of amplified Hh signalling in the development of many cancers. Different Hh inhibitors are currently in trials as therapeutics for various cancers. However, in the majority of cancers, Hh inhibitors have been unsuccessful and alarmingly a trial in pancreatic cancer had to be prematurely stopped since the placebo group of patients was doing better than those treated with the Hh inhibitor. Our in vitro work suggests that Hh inhibitors also inhibit CD8 T cell killing and thereby diminish our body’s very own anti-tumour response. It is thus very timely and urgent to find out how Hh signalling works in T cells in vivo and whether we can modulate the pathway to improve T cell function – not only in patients with tumours, but also during infection and vaccination.

**Maike de la Roche**

Sir Henry Dale Fellow and Junior Group Leader
Cancer Research UK Cambridge Institute & University of Cambridge

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Figure 1. a. Canonical Hedgehog (Hh) signalling in ciliated cells; b. Hh signalling in thymocytes and mature T cells in the periphery. Hh signalling initiated by an extracellular Hh ligand (produced by the thymic stroma, thymocytes or peripheral tissues) is indicated in dark green, and intracellular Hh signalling in light green; c. Migrating CTL (left) and synapsing with a target cell (right); d. Intracellular Hh signalling in cytotoxic T lymphocytes (CTL).
The public’s appetite for all matters immunology-related (even if they don’t always realise it) is insatiable. Immunology is one of the most written about and discussed topics in all of health science, and for that, we should be incredibly grateful. It means our subject is of relevance and importance to people’s everyday lives, it brings stronger public support for funding research in this area and, let’s face it, it goes to show that immunology and its findings are just plain cool (although hopefully I am preaching to the converted here!).

Misrepresentation in the press

Believe it or not, the UK is somewhat ahead of the field in that most national news outlets have specialist health and science reporters who cover these types of stories, and overall the quality of reporting is fairly good. However, we can all name a time when we’ve opened the morning paper and groaned to see a poorly reported story misinterpreting the science or hugely exaggerating the implications of research. This is disappointing from the point of the researchers and immunology community who have a vested interest in seeing the results properly communicated. What’s far more concerning however is the effect that this may have on patients at a time when they and their families are vulnerable — claims of a miracle cure can induce false hope followed by additional heartache.

With immunology in particular, these misconceptions can have a huge effect on public health — just think of the impact even now of the MMR stories from the ’90s. Every day, members of the public need to make decisions about their own health and treatment using factors that immunology research contributes to. Vaccines, allergies, autoimmune conditions — these are all common medical subjects upon which it’s important that the public have access to reliable, evidence-based information, and news stories represent a significant method by which this information is accessed. With the advent of personalised medicine, cancer immunotherapy and potential antibody treatments for Alzheimer’s on the horizon lito name but a few, the omnipresent nature of immunology in the medical field is only set to increase, making the way that immunology news stories are reported even more important.

Who’s to blame?

A recent study in the BMJ set out to identify where in the supply stream changes or exaggerations to a study’s main conclusion started, be it with the journalist, press release or original paper. They found that exaggeration in news stories was strongly associated with exaggeration in the press releases on which those stories were based, i.e. on the whole (although not in every case), the journalists were only repeating the claims made in the press release, not building on them. Overall, 40% of press releases contained exaggerated advice, 33% exaggerated causal claims and 36% exaggerated inference to humans from animal research. These figures are pretty startling and suggest that we certainly can’t lay all the blame for misrepresentation of findings at the door of journalists.

Press release pressures

And so, to the press release... Writing a successful press release is a tricky skill to master. Traditional wisdom states that you have seven seconds to be appropriately witty and relevant to catch the attention of your journalist. Combine that with the fact that you need to bring together public friendly language with an exact grasp of facts involved and you see that writing a press release is an art in itself. The press release should be a joint project between the press office and the researchers involved, and both parties need to take some responsibility for getting it right.
‘Immunology is one of the most written about and discussed topics in all of health science, and for that, we should be grateful.’

Now, you may ask why do journalists take press releases at face value and not check the facts behind them? Well, one answer is time. It’s worth remembering the extreme pressure that health and science journalists at national newspapers are now under. They are routinely expected to file three to five stories per day, each of 800 words. Could any of us claim to be able to write with 100% accuracy on topics we weren’t familiar with in that time scale?

One thing that can help is easy access to independent and reliable comment on stories, and this is where the BSI media office comes in. Through our network, we can put journalists in touch with experts who can provide external comment on immunology stories. This is crucial as it allows the journalist to put the findings into context and assess the view of the scientific community on the work, thus hopefully allowing the journalist to put the findings into context and assess the view of the scientific community on the work, thus hopefully leading to more accurate reporting.

So, what can you do?

As well as the BSI working as an organisation with the media, there are lots of things you yourself can do to address misreporting in the news.

1. Work with your press office.
   If you are approached by a press officer to do some media work on your research, be it from your university, funding body or a journal, be active in the process and work with them to produce a press release. If you think the draft release has misinterpreted or over-exaggerated your results, say so. Press officers are generally friendly folk and will thank you for pointing this out and be pleased you are actively engaged in the process. Press releases are a collaboration between the researcher and the press officer and it is the responsibility of both parties to ensure the information contained in it is accurate.

2. If you see something wrong, tell us.
   The BSI press office monitors the news daily for immunology stories but we are always keen to hear from members if you spot an article where you think reporting has been sub-optimal. Depending on the situation, there are a number of actions the BSI can take, for example, writing to the editors page of the newspaper or producing our own blog on the research to set the record straight.

   If we are aware that there is a recurrent problem with a particular topic, we can also work on a longer-term basis. For example, last year we partnered with Sense About Science to produce the ‘Making Sense of Allergies’ booklet. This was in response to many news reports, online discussions, and so on, which were promoting fake allergy tests and misrepresenting the science around the causes and treatments of allergy. To develop this resource, some of the leading scientists and clinicians working on allergy were brought together to produce a booklet providing the public with accurate, evidence-based information on what we do and don’t know about allergies. As well as making considerable headlines with its launch (including BBC Radio 4 Today programme and front pages of The Times and Daily Telegraph), the booklet now acts as a long-term resource for us to use to improve the reporting around allergy.

3. Get media training.
   Media training is available through various routes and is a great way for you to acquire the skills needed to contribute to public debates on immunology and feel confident in doing so.

   The BSI is currently recruiting for members to become media spokespeople on various topics, with free media training provided as part of this. Additionally, media training is available free of charge through some research funders, e.g. BBSRC. For early-career researchers, Sense About Science run regular free media workshops to encourage participation in public debates. Media training is a great way to boost your CV. It can help you to develop transferable skills, and can lead to new ways to promote your research to a wider audience.

Representation of immunology in the press is a topic that we should all care about. By working together with its members, the BSI hopes to engage with the press to improve the scope, depth and accuracy of reporting on immunology.

Jennie Evans
Communications Manager, British Society for Immunology
Email: j.evans@immunology.org

If you are interested in becoming a BSI media spokesperson or have any queries on working with the media, please do get in touch.

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3. BBSRC media training – http://bit.ly/1Zn0TU

Further resources
The Science Media Centre produces a series of guides that list effective ways of talking to journalists within the context of a short interview about various issues that cut across the sciences. You can download free from www.sciencemediacentre.org/publications/publications-for-scientists.

NHS Behind the Headlines service provides unbiased and evidence-based analysis of health stories that make the news. It’s a useful place to start to see how to put arguments on scientific method etc. across to a more general audience. www.nhs.uk/news
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Congratulations

This is the section of the magazine where we celebrate the achievements of our members. Our congratulations to all who are mentioned here.

Communicating Immunology Grants

The BSI is delighted to fund two events through our Communicating Immunology Grants.

Adam Hart (University of Gloucester) will run an Edinburgh Science Festival event entitled ‘Our friendly bacteria’ featuring BSI members Fiona Powrie and Lindsay Hall.

Megan Dunn and Fiona Menzies (University of Strathclyde) will run a project entitled ‘Next generation woman in immunology’ to encourage the recruitment of women to study immunology at the university.

Next grant deadline is 1 April. For more details visit: http://bit.ly/1rpXUX

Travel grant success

The following members were recently awarded BSI travel grants:

Carly Bliss, Davide Bommarito, Joana Campos, Bianca De Leo, Alice Denton, Yifang Gao, Christine Graham, Robert Haas, Joanne Hay, Oliver Kay, Elizabeth Mann, Claudio Mauro, Jennifer Mueller, Matthew O’Shea, Theres Oakes, Anna Schurich and Carolyn Thomson.


Medical Elective and Summer Placement Award Scheme

This BSI scheme supports young scientists to conduct extended placements in labs other than their own. For more details, visit http://bit.ly/1kmuLy0. Recent awards are:

Jonathan Jung (University of Glasgow) to study macrophage development with Tiffany Horng (Harvard University) and Alexander Godlee (University of Oxford) to study the rheumatological microbiome with Dan Littman (New York University).

Wellcome Trust awards

The following BSI members have been awarded a Wellcome Trust Investigator Award in the recent grant round:

Dan Davis
[University of Manchester]

Denise Fitzgerald
[Queen’s University Belfast]

James Kaufman
[University of Cambridge]

Paul Klenerman
[University of Oxford]

PhD success!

Congratulations to the following BSI members who have passed their PhD viva:

Michael Bramhall, Ryan Costello, Kathryn Lagrue, Emma Murphy (all University of Manchester).

We would love to hear from you about your achievements. Have you or a colleague recently received grant funding, passed your PhD viva or accepted a new appointment? If so, let us know by emailing media@immunology.org.
Scientific research has always been about an exchange of ideas bringing together people from different backgrounds. However the recent anti-immigration rhetoric of the UK Government and the UK popular press threaten to significantly change the landscape of international collaboration within UK research institutions. We talk to Cardiff University’s Matthias Eberl, a German who has made Wales his home, about his experience of working in and running a lab in the UK given the current immigration backdrop and the implications that policy decisions might have on UK science.

What was your experience of coming to the UK to work? Despite having spent a quarter of my life in the UK, initially in York during my first postdoc and then in Cardiff where I eventually set up my own lab, I confess that I still don’t drink tea and I still don’t understand cricket. Other than that, the process of coming to the UK to work couldn’t have been easier – as an EU national, I simply moved to the new place, signed my contract, arranged my accommodation and started to work.

Working and living in a foreign country is of course challenging but I have always felt welcome and appreciated by my colleagues and the wider community (that is, if I block out the current hysteria about the alleged problems of ‘immigration’). As an aside, I always find it amusing that at no point have I ever had to produce an English language certificate to be able to work in the UK while all my students to work in the UK while all my students from abroad need to pass their TOEFL test before they can enrol at university and study under my supervision.

What do you think are the benefits and/or harms of scientists from outside the UK being able to come here for work? There are no harms at all. On the contrary, the UK benefits enormously from its rich tradition in education and science and, for centuries, has successfully attracted some of the most talented individuals of their time to work here.

The prestige of UK universities and research institutions combined with the undeniable advantage of being an English-speaking country makes it many people’s first choice for study and work in Europe. Weather and food might be more appealing in other countries, but I might struggle to give lectures in Greek or write grant applications in Portuguese! Even more, with many countries, especially in southern Europe, being severely hit by the economic crisis and their science budgets reaching all time lows, the UK is still in a relatively comfortable position with respect to funding and as such has a significant advantage over most EU countries.

How do you think current Government policy concerning immigration affects the UK’s ability to attract foreign scientists here for work or study? The current policy makes it very difficult for certain groups of people to come to the UK for work and study, and I believe we are losing out significantly by not being able to mobilise the full potential of available skills. Many studentships are only advertised for UK residents, instead of making them available to all EU nationals. The exorbitant overseas tuition fees are equally counter-productive. Recruiting talented young researchers from outside the EU is virtually impossible when studentship schemes do not cover overseas fees – unless a person is desperate enough to pay them from their own pocket (I have witnessed such extreme examples). Attracting postdocs from overseas is similarly difficult, and extending contracts for non-EU nationals and moving them to a new project in the same lab is a major bureaucratic challenge. People working as technicians or research assistants at relatively low salaries are especially vulnerable and need better protection, and, in general, regulations and costs for visa applications should be revisited. Any attempt to make the current policy even more stringent will have detrimental consequences for science in the UK. Most worryingly, the proposed £35K salary threshold for non-EU citizens settling in the UK would effectively represent a recruitment ban for non-EU postdocs.

The UK is due to have a referendum on membership of the European Union soon. What do you think the implications of this vote are for UK science? UK science will undoubtedly suffer, not only from the looming threat to eventually leave the EU, but already during the referendum build-up. The political discussion is beginning to heat up, with more and more populist and polemic opinions being voiced that are likely to put off excellent candidates from applying for a UK studentship, postdoc fellowship or faculty position. Even if the end result of the vote is in favour of staying in the EU, it will take the scientific community and society as a whole a long time to recover from the negative connotations throughout the campaign.

As an immigrant myself, I am absolutely gobsmacked by certain views on the general impact of immigration, with the word ‘immigration’ always associated with something that is indiscriminately negative and potentially threatens the UK economy and society, even in well-
respected media – and I’m not referring to Nigel Farage’s ridiculous insinuation that immigrants are even to blame for heavy traffic on the M4! With a toothless UK not being able to participate in, and influence, important EU-wide decisions, and without direct access to the considerable funding available from EU sources, the UK will lose out in the long run, with Germany happily taking over and becoming the new powerhouse in basic, translational and applied science in Europe.

What changes to the immigration policy or visa system would you like the Government to implement to improve the current environment for UK science?

There should be a clear acknowledgment that highly skilled specialists from abroad are absolutely essential for the UK to stay competitive in a globalised world. From my own experience, over the past nine years in Cardiff our laboratory has hosted students and postdocs from France, Germany, Greece, Italy, Netherlands, Slovenia, Spain, Sweden, Switzerland, Canada, China, Taiwan, India, Pakistan and Mauritius – with roughly a third of our lab members coming from the UK, a third from the rest of the EU and a third from non-EU countries. This fascinating mixture of nationalities has been an absolute pleasure, both scientifically and personally, and has contributed significantly to creating a productive and enjoyable working environment.

What strikes me is the largely underappreciated effort and cost non-EU nationals have to invest to apply for UK visas and get them renewed. More than once have I seen highly skilled people being forced to leave the UK despite being of invaluable help to their research teams and to UK science as a whole, simply because the tight visa regulations did not allow them to stay longer.

EU nationals should be granted free movement within the whole EU including the UK, and this includes of course unrestricted access to studentships and to in-work benefits. Being able to recruit motivated and skilled students and scientists from abroad is a direct investment in the immediate and longer term future of this country, and will help consolidate the leading position of UK science.

Matthias Eberl
Systems Immunity Research Institute, Cardiff University

Matthias is a migrant from a family with refugee background. Belonging to the ethnic Sudeten German minority, his parents and grandparents were expelled from Czechoslovakia in 1946. He was born in 1971 and grew up in West Germany during the Cold War, with the fall of the Iron Curtain in 1989 leaving a deep impression on him. He has worked in Germany, Switzerland and the UK, with colleagues and collaborators of many different nationalities, and has been to a further 14 European countries. Living with a Spanish scientist and their Welsh-born daughter, he is a firm believer in European integration and freedom of movement.
What is a clinical immunologist?

I am a clinical immunologist and I am frequently asked the question, ‘what does a clinical immunologist do?’, so here is my answer... Clinical immunologists are physicians involved in the care of patients with disorders resulting from the failure of the immune system (immunodeficiency) or immune dysregulation (allergy and autoimmunity). With respect to the former, we often deal with the human knock-outs of several immune pathways and are able to discover their significance in the ‘real world’. We are lucky to have already seen the rewarding results of the first gene therapy trials in humans; for example the recent announcement from Great Ormond Street that a young girl with leukaemia had been successfully treated with genetically engineered donor T cells and is now in remission. In the fields of autoimmunity, the use of monoclonal antibody therapies has revolutionised our ability to modulate the immune system and improve the quality of life of patients with conditions such as rheumatoid arthritis and ankylosing spondylitis. In allergy, we have seen great progress in desensitisation therapies, such as the work carried out at Addenbrooke’s Hospital in Cambridge on peanut allergy, and food desensitisation is now a reality.

A varied day

Clinical immunology has been and still is a laboratory specialty, so a significant amount of our routine daily work includes laboratory work in relation to the diagnostics and monitoring of immunological diseases. We are involved in results validation and interpretation, quality assurance and assay development. In this aspect of our work, we seek to ensure the quality and reproducibility of diagnostic laboratory tests. This, in some ways, contrasts to the hypothesis driven tests performed at the research bench with unpredictable results. I would argue however that it is exactly the beginning of the patient’s care pathway where research findings apply to improve disease diagnostics. We liaise with other clinicians and specialties such as paediatricians, rheumatologists, respiratory physicians, nephrologists, GPs and infectious disease physicians to name just a few, and are very often asked to solve diagnostic enigmas and therapeutic dilemmas.

Like other clinicians, we work in multidisciplinary teams with nurses in the clinic, but also biomedical scientists and clinical scientists in the laboratory. We are involved in research as well as undergraduate and postgraduate teaching. Much of our time is spent dealing with rare and perplexing diseases, meaning clinical...
trials are often scarce and solid evidence is often lacking. This means that we have to keep up-to-date with any literature available and often rely on networking with our colleagues. This paucity in data and rarity of conditions can also make the funding of new therapies challenging.

In my view, clinical immunology is unique as it combines clinical and laboratory skills, providing the opportunity to improve our insight into the mechanisms underlying the evolution and complications of many immunologically-mediated disorders. The recent advances in genomics have contributed immensely to an ever expanding variety of diseases making the field a really exciting part of medicine. So for any of you who thought that we are simply sitting in offices behind a microscope reading slides all the time, this is simply not true!

**Current hot topics under discussion**

Many clinical immunologists attend the biannual conference organised by the UK Primary Immunodeficiency Network, which focuses on primary immunodeficiency disorders (PID), the most recent of which took place in November 2015 in Belfast. Among other conditions, there was focus on the auto-inflammatory syndromes, from the historic discovery of familial Mediterranean fever [an inherited disorder that causes recurrent fevers and painful inflammation of the joints and serous tissues lining the lungs, heart and abdomen] to the recently described gene defects in NLRC4, adenosine deaminase 2 (ADA2) and STING. Another new condition caused by gene overexpression, the activated PI3K-δ syndrome (APDS), which causes lymphopenia, recurrent respiratory infections and progressive lung damage, was also discussed in length including the promising therapeutic approach with mTOR inhibitors.

Recent advances in whole genome sequencing (WGS) genomics were in the spotlight for much of this conference; NHS England Genomics 100,000 genomes project is underway and the immunology community is excited to participate in one of the clinical interpretation partnerships (GeCiP) for immunological and non-malignant haematological disorders. This project brings together 128 immunology clinicians and scientists from around the country who are currently busy networking to make it happen. We are seeking to gain clinically relevant genomic data for our patients and their families and extend our knowledge and understanding of the genetic basis of PID and the function of the immune system. Inevitably the ‘great debate’ of the conference was on genomics and whether WGS will make diagnostic immunology redundant. We concluded that whilst we have learned a great deal about PID because of next generation sequencing, the immunology laboratory and functional tests will continue to play a fundamental role for the evaluation of these patients.

If you missed this meeting, don’t worry – the next UK Primary Immunodeficiency Network meeting in 2017 will run sequentially with the BSI Annual Congress in Brighton, making it easier for research and clinical immunologists to come together to share ideas.

I hope I have provided a flavour of what clinical immunologists do and some of the hot topics in our clinical practice. For those of you who are interested to learn more, have ideas you wish to share or news and updates which can bring clinicians and researchers together, please do not hesitate to contact me.

**Sofia Grigoriadou**
BSI Clinical Secretary
Consultant Immunologist,
Barts Health NHS Trust

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**Great success at BSI Winterschool**

Here’s a picture of all the speakers and delegates who recently attended the BSI’s Winterschool, aimed at MSc Immunology students to provide them with an opportunity to hear from some of the leading lights in immunology and experience the atmosphere and benefits of a scientific conference. As you can see, attendance at the conference was extremely healthy and we received very good feedback on the meeting [see page 6]. As one delegate commented, “It was a very worthwhile experience that I feel I benefited from greatly and is something I would encourage other immunology students to attend.”
Planning to succeed in your career

You’re proud of the way you conduct your research. Experience has taught you to maintain a strategic overview and review plans regularly to keep research goals in sight. You remain open to new ideas and possibilities by collaborating and engaging in discussion within and beyond your field. Do you apply the same approach to developing your own career? If not, it might be worth a few minutes of your time to stop and think about why this is.

Career development planning

48% of respondents to the 2015 UK ‘Careers in Research Online Survey’ said they did not have a clear career development plan. A similar number kept no formal record of professional development activities. If you’re with the 48%, reflect on why. Are you too busy with your project to think beyond it? Or are you just putting it off? Do you prefer to ‘go with the flow’? Perhaps you feel your dream career should be a natural extension of excellent research. Understanding yourself is a good place to start, but what then?

Vitae, an organisation that champions researchers’ professional development, offers online resources for individuals to aid career planning: one such resource is the Vitae Researcher Development Framework (RDF). Depending who you are, that might sound highly appealing or deeply uninteresting but hear me out while I explain how you might find it useful!

Researcher Development Framework

The RDF is grounded in research and describes the knowledge, behaviours and attributes of a successful researcher. It breaks all this down into four domains, 12 sub-domains and 63 descriptors then expands on each for up to five phases of development. So far so methodical, but what can you actually use it for? It’s great as a thinking tool. Simply looking systematically through each area can help you identify and prioritise development needs as well as recognise areas of existing strength. You might even see attributes that you hadn’t previously associated with research. Still undecided on career direction? Focus thinking by asking yourself what RDF areas you excel in and which you’re most excited about developing. The RDF is appropriate to researchers at any career stage, whether you already have a career master plan or no plan at all. If you don’t want to continue in academia or even in research, it can help you identify skills you developed as a researcher, consider how these might be transferable to other contexts and articulate that.

The importance of planning

Most good things need a plan to make them happen, whether it’s a simple or an elaborate one. To start, you could list areas from the RDF (for example the 12 sub-domains) and brainstorm possible actions to develop knowledge or skills in your own priority areas. You might also note down evidence to demonstrate existing strengths by area: think about evidence that would be useful for your CV.

‘We don’t have much time to think about career development. When it’s already written down, you can keep coming back to it and see if you are complying with your own recommendations.’

First year doctoral candidate asked to try out the RDF
‘Most good things need a plan to make them happen, whether it’s a simple or elaborate one.’

If you have an existing career development plan, check it against the RDF to identify any gaps. Ask peers, a line manager or mentor for feedback on the strengths and development needs you’ve identified and ask for ideas on opportunities to gain new knowledge and skills. Can you use your plan in a formal appraisal?

OK, so this is all very well in theory but actually, there are 63 descriptors and each has up to five phases of development – ‘help, I’m overwhelmed!’ This is something we’ve heard before at Vitae so we’ve produced some complementary tools. Our ‘Lenses on the RDF’ picks out a sub-set of knowledge, behaviours and attributes with relevance to a specific context. For example, we have lenses for getting started in research, teaching and knowledge exchange. If you want something to make planning and storing information easier, you might try our online app, the RDF Planner, which is available by subscription (before you subscribe as an individual, find out whether your institution holds an organisational subscription you could use).

Good luck, and remember, in the words of Louis Pasteur, “Chance favours the prepared mind.”

Jane Sugars
Project Manager, Vitae

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Unfortunately there is a large body of evidence, including from the NC3Rs (the National Centre for Replacement, Refinement & Reduction of Animals in Research) to show that many animal studies are poorly designed, analysed and reported and that this has significant implications in terms of reproducibility and the translation of findings into potential clinical benefits. For example, failure to translate pre-clinical findings to the clinic in multiple sclerosis has been attributed to shortcomings in the design of animal experiments. Here at the NC3Rs, we have developed a new exciting online tool which is designed to tackle this problem – the Experimental Design Assistant (EDA; www.nc3rs.org.uk/experimental-design-assistant-eda).

Scientists using animals in research have a responsibility to ensure that their studies are appropriately designed, conducted, analysed and reported so that they impartially and robustly answer the question they are intended to and truly add to the knowledge base. Failure to fully embrace this responsibility wastes animals and other resources and ultimately undermines the ‘contract’ with the public that permits the use of animals in research.

We are really excited to have launched the EDA and look forward to hearing what you think about it. We have done extensive testing with scientists from a whole range of disciplines, institutions and career stages and the feedback so far has been fantastic. As with any new software, the first release of a system may have some teething issues. If you do encounter any problem, please do let us know at eda@nc3rs.org.uk. Your feedback will help us ensure that the system improves and evolves according to your needs.

Nathalie Percie du Sert
NC3Rs Programme Manager

NC3Rs is a UK-based scientific organisation dedicated to replacing, refining and reducing the use of animals in research and testing (www.nc3rs.org.uk). This article is adapted from a post that originally appeared on the NC3Rs’ blog [http://bit.ly/1ni7Song].

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Delphine Parrott passed away peacefully at home in London on 17 January 2016. Over the course of her career, she made many outstanding contributions to immunology.

Delphine was a native of Dulwich in south London, and graduated in 1949 with an honours degree in Physiology from Bedford College, University of London. She undertook her PhD at King’s College Hospital Medical School, graduating in 1952. At that time she was an endocrinologist (immunology was not yet an independent discipline), so she spent two years at the MRC Clinical Endocrinology Unit in Edinburgh, before returning to become a staff member at the National Institute for Medical Research in Mill Hill, London. With Sir Alan Parkes, who hired her because of her skill in working with small animals, Delphine worked on restoring fertility in irradiated mice using orthotopic ovarian grafts.

During her PhD, Delphine discovered the thymus. In 1960, she joined the group of Hilda Brace, a pupil of Peter Medawar, and wrote a thesis entitled ‘The role of the thymus in neonatal life and its influence on lymph node development’. She worked on lymphocytes using the olfactory bulb as a model system to study their migration. Delphine’s collaboration with Maria de Sousa, a Gulbenkian scholar from Portugal, led her to the thymus. Maria was interested in the role of the thymus in neonatal life, and Delphine performed a surgical procedure on neonatal mice to study the impact of the thymus on their immune system. This led to the discovery of thymocyte-dependent areas in the lymph nodes of adult mice thymectomised at birth, which were later named ‘thymus-dependent areas’.

Delphine and Maria christened those areas ‘thymus-dependent areas’, and published their findings in Nature and Journal of Experimental Medicine in 1966. In 1967 Delphine moved to Glasgow University to become a Senior Lecturer in the Department of Bacteriology and Immunology. In 1973, she was given a personal chair at Glasgow, the first woman professor in the university’s 432-year history, and in 1974 was made a fellow of the Royal Society of Edinburgh. She had also begun work on lymphocyte recirculation, at first with Maria de Sousa, then Antonio de Freitas and Marlene Rose, and later Cliff Ottaway. She continued to publish, reporting in Nature that small lymphocyte migration was random. She also did seminal work on mouse intraepithelial lymphocytes, drawn from work she conducted with Spedding and Micklem in Edinburgh, who was at the forefront of the new technology of flow cytometry. They identified IEL that were Lyt2-, Lyt3-, yet when she presented the results in New York at the Mucosal Immunology Conference, she was not believed. She had, of course, identified thymus-independent CD8αα T cells, but such was the resistance to the idea that the work was rejected by Nature, and only published in the conference proceedings!

1980 also saw other major changes also in Delphine’s life when, with two days’ notice, the incumbent professor suddenly retired, and she was made both Head of Department and Gardiner Professor – a position she occupied with distinction until 1990 when she retired and passed the responsibility to Eddie Lieu. During this period, she helped many trainees with their work whilst putting her own research on the back-burner. After retirement, she returned to Mill Hill, where she enjoyed her garden, her allotment and her extensive network of friends. Although teaching was not always at the forefront of her duties, it is here, paradoxically, that her contribution equals that of her excellent science. In the late 1970s, Delphine and others had negotiated with the science faculty in Glasgow to set up a BSc. devoted to immunology; the first of its kind in the UK – they eventually succeeded. This course has produced many excellent immunologists, who now occupy senior positions in industry and academy – and largely account for the Scottish Immunology ‘Mafia’!

Delphine uttered many memorable things that I remember, but one that particularly sticks in my mind is her insistence that scientists need time for reflection and thinking. In the frantic rush to get grants and papers, it is worth remembering that there is no substitute for a good idea, and Delphine had lots of them. She was very much admired and loved by everyone and she will be sorely missed.

Tom MacDonald
During delivery of the 1899 Croonian lecture, Professor Paul Ehrlich introduced his ‘side-chain’ theory by first inviting his audience to contemplate the constitution of the cell ‘from the purely chemical standpoint’. Ehrlich then proposed that a series of chemical reactions could describe an organism’s reaction to bacterial toxins. Adopting the nomenclature of organic chemistry, Ehrlich described chemical ‘side-chains’, produced by cells, which can bind and neutralise a toxin, then be regenerated once the host has survived the toxin, resulting in effective immunisation. Today we understand the chemical ‘side-chains’ proposed by Ehrlich as antibodies, engaging antigenic partners in a molecularly precise manner.

We will bring together leading international experts to highlight work at the interface of immunology and the chemical sciences. The focus of the conference will be on framing immunological questions as molecular problems uniquely tractable to collaboration across the two disciplines. Themes will include the influence of post-translational modification in immune processes, emerging examples of cross-talk between immune pathways, chemical control of immune processes, autoimmunity and rational approaches towards vaccine design.

We believe that ‘cross-talk’ between chemists and immunologists has the potential to revolutionise the molecular understanding of the immune system.

As Ehrlich advised, we propose that scientists again consider aspects of immunity from a ‘purely chemical standpoint’. To promote and advance work undertaken at the molecular and chemical levels of immunology, we have founded the BSI Molecular Immunology Affinity Group (Mol.i.G). Our first meeting will be held on 4–5 April 2016 and is titled ‘The Oxford Chemical Immunology Conference’.

“Cross-talk” between chemists and immunologists has the potential to revolutionise the molecular understanding of the immune system.”

The Oxford Chemical Immunology Conference is taking place on 4 – 5 April 2016 in Oxford. Online registration is available at oxchemimm.chem.ox.ac.uk.
Although the brain is considered an immune-privileged organ, there is a clear interaction between the immune system and the function of the nervous system in many disorders of the peripheral and central nervous systems. In this context, neuroimmunology can be considered to encompass studies of diseases of the nervous system as well as the interaction between the neuro- and immune systems. While the origins of neuroimmunology pre-date the establishment of the British Society for Immunology by nearly a century, the subject has its roots firmly in the interdisciplinary collaborations in the early 1950s. The first International Congress of Neuroimmunology was held in Stresa, Italy in 1982 and strongly promoted the idea that immunity in the central nervous system played an important role in many disorders. Although the International Society of Neuroimmunology was only founded after the second congress in 1987, the Journal of Neuroimmunology had already been launched in March 1981, shortly followed by the Journal of Clinical & Experimental Neuroimmunology in 1988.

In line with the rapidly developing field, the Neuroimmunology (NI) Affinity Group of the BSI was founded soon after the 2nd BSI Annual Congress in 1994. I remember submitting two of the seven abstracts for the British Neuroimmunology Group Workshop. At the time (from what I remember), the members included John Greenwood, Chris Bolton, Neil Scolding, David Baker, John Fazakerley, Azy Khalili-Shirazi, Angela Vincent, Nicola Woodroofe and myself. While we have indeed changed, as has the number of members, the idea behind the Neuroimmunology Affinity Group has not. Promoting neuroimmunology in a world where neurodegenerative diseases are rapidly becoming a major concern has not been difficult. Similarly, the growing number of immune-directed therapies is providing real opportunities to target neuroimmunological mechanisms for the benefit of patients. The rapidly growing number of journals and papers in this field also reflects the international research interests.

While I have now taken over from Nicola as Chair of the NI group, Nicola and I (as her second in command) organised several NI meetings within and outside the BSI annual meeting over the past few years. As Chair, I have continued this effort with a new band of NI board members to contribute ideas and enthusiasm for the group. For BSI members with an interest in NI, please check out the upcoming joint BSI-NVVI annual meeting in Liverpool in December 2016 where we are running a session on neuroimmunology and rheumatology and also the Federation of Clinical Immunology Societies (FOCIS) in Boston, USA where, on 22 June, the NI affinity group has a session on ‘Immune tolerance in multiple sclerosis’.

The board members are:

- **Chair – Sandra Amor**, VUMC, Amsterdam and Blizard Institute, Barts and the London Hospital
- **Secretary – John Curnow**, Institute of Inflammation & Ageing, University of Birmingham
- **Treasurer – Bruno Gran**, Division of Clinical Neuroscience, University of Nottingham School of Medicine
- **Denise Fitzgerald**, Wellcome-Wolfson Institute, Queen’s University Belfast
- **Anne Astier**, MRC Centre for Inflammation Research, University of Edinburgh

If you have any queries or ideas for the group, do get in touch with us via our contact details on the website.

**Sandra Amor**
BSI Neuroimmunology Affinity Group
Ectopic lymphoid follicles: cellular and molecular mechanisms

Lymphoid neogenesis is traditionally viewed as a pre-programmed process that promotes the formation of lymphoid organs during development. Here, the spatial organisation of T and B cells in lymph nodes and spleen into discrete structures regulates antigen-specific responses and adaptive immunity following immune challenge. However, lymphoid neogenesis is also triggered by chronic or persistent inflammation. Ectopic (or tertiary) lymphoid organs frequently develop in inflamed tissues in response to infection, autoimmunity, transplantation, cancer or environmental irritants. Jones & Jones review the mechanisms responsible for ectopic lymphoid neogenesis and consider their relevance in human disease.

Jones & Jones 2015 Immunology http://bit.ly/1K8weU1

Microbiota and host immune responses: a love–hate relationship

A complex relationship between the microbiota and the host emerges early at birth and continues throughout life. The microbiota (including prokaryotes, viruses and eukaryotes) interact to different extents with various organs and tissues in the body, including the immune system. Although the microbiota is most dense in the lower intestine, its influence on host immunity extends beyond this. These interactions with the immune system operate through the actions of various microbial structures and metabolites. Outcomes, ranging from beneficial to deleterious for the host, are dictated by host factors, environment and the type of microbes or products present in the ecosystem. It’s also becoming clear that the microbes are in turn affected and respond to the host immune system. Disruption of this complex dialogue can lead to immune pathologies such as inflammatory bowel diseases, diabetes and obesity. This review discusses recent advances regarding how the host immune system and microbiota interact and communicate with one another.

Tomkovich & Jobin 2016 Immunology 147 1–10 http://bit.ly/1OYKgV5

The ageing human B cell repertoire: a failure of selection?

B cells undergo a number of different developmental stages, from initial formation of their B cell receptor (BCR) genes to differentiation into antibody-secreting plasma cells. Because the BCR is vital in these differentiation steps, autoreactive and exogenous antigen binding to the BCR exert critical selection pressures to shape the B cell repertoire. Older people are more prone to infectious disease, less able to respond well to vaccination and more likely to have autoreactive antibodies. Dunn-Walters reviews evidence of changes in B cell repertoires in older people, which may be a reflection of age-related changes in B cell selection processes.

Dunn-Walters 2015 Clinical & Experimental Immunology http://bit.ly/1nOVzrZ

Membranous nephropathy (MN), the leading cause of nephrotic syndrome in adults, is characterised by the accumulation of subepithelial immune deposits consisting mainly of immunoglobulin (Ig)G and complement. Most cases are primary or idiopathic (iMN), while 25% are secondary to a known disease such as systemic lupus erythematosus or hepatitis B. Our knowledge on iMN pathogenesis has mostly relied upon old experimental models (i.e. Heymann nephritis) that showed that immune deposits are formed in situ by the reaction of autoantibodies against the respective podocyte antigen. Recent findings indicate podocyte proteins also act as an autoantigen in human iMN. The M-type phospholipase A2 receptor (PLA2R) has been identified as the main target antigen, as it’s found in approximately 70% of iMN patients but only rarely in other glomerulonephritides. Genome-wide association studies have demonstrated a genetic background for iMN that showed highly significant associations of the PLA2R1 and the human leucocyte antigen (HLA)-DQA1 loci with iMN.

Sinico et al. 2015 Clinical & Experimental Immunology http://bit.ly/1SJPzNP
**The origins of self-renewing resident arterial macrophages**

The origin of tissue macrophages is coming under increasing scrutiny with studies using fate-mapping techniques and gene profiling to reveal that such cells are highly heterogeneous, exhibit different homeostatic properties and appear to be derived from different sources. In this paper, Ensan and colleagues identify that arterial macrophages in mice are derived from both the embryonic yolk sac and after birth via bone marrow-derived monocytes. The former originating from a CX3CR1+ precursor, with the CX3CR1–CX3CL1 interaction playing a crucial role in macrophage maintenance and survival. Interestingly, the authors observed that the recovery of arterial macrophages after exposure to LPS primarily occurred locally and not from blood monocytes. These studies highlight the diverse nature of tissue macrophages.

Ensan et al. 2015 *Nature Immunology* **17** 159–168

**Deactivating IL-17 results in increased gut permeability**

The IL-17/IL-23 axis contributes to inflammatory bowel disease (IBD) pathogenesis; however, protective functions of IL-17A in the gut have also been reported. Lee and colleagues utilised a DSS-induced colitis mouse model and demonstrate increased permeability and damage to the intestinal epithelial barrier in IL17-/- mice compared to WT mice. IL-17A protects the epithelial barrier by signalling through the Act-1 adaptor protein of the IL-17R pathway, and regulates cellular localisation of tight junction protein occludin. Furthermore, γδ T cells were identified as the main early source of tissue-protective IL-17A, produced in an IL-23-independent manner. This study confirms the protective function of IL-17A, and suggests the clinical relevance of neutralising IL-23 in IBD, leaving IL-17A production by γδ T cells intact to maintain the intestinal barrier.

Lee et al. 2015 *Immunity* **43** 727–738

**Tolerance to commensal microbes in neonatal skin**

Our cutaneous immune system recognises vast numbers of commensal organisms without causing inflammatory responses. Using a murine model system, Scharschmidt and colleagues demonstrate that a critical window of opportunity exists in which tolerance to commensal bacteria is established. Tolerance was dependent on the migration of large numbers of activated Treg cells to the skin between postnatal days 6–13. Concomitant colonisation of skin with Staphylococcus epidermidis induced a local and systemic expansion of antigen-specific Treg cells and subsequent protection from *S. epidermidis* rechallenge with concurrent skin abrasion, which in adult mice induced a marked inflammatory response. These findings highlight the critical importance of neonatal barrier immunity in supporting immune homeostasis, giving credence to the notion that early life provides unique opportunities for inducing tolerance to exogenous antigens.

Scharschmidt et al. 2015 *Immunity* **43** 1011–1021

**The role of tumour necrosis factor 2 in colitis in mice**

Tumour necrosis factor 2 (TNFR2) regulates aspects of the pathogenesis of inflammatory bowel disease. In this paper, Punit and colleagues crossed TNFR2-/- mice with interleukin (IL) 10-/- mice, generating IL10-/- TNFR2-/- mice which spontaneously developed colitis. Compared to IL10-/- mice, IL10-/- TNFR2-/- mice developed more severe colitis and had an expansion of colonic CD8+ T cells. Using chimeric mice, TNFR2-/- bone marrow transplanted into wild type mice resulted in increased incidence and severity of colitis. Additionally transfer of TNFR2-/- increased the severity of colonic inflammation when transferred into Rag 2-/- mice. This study highlights the importance of TNFR2 in controlling colitis by inhibiting the expansion of CD8+ T cells.

Punit et al. 2015 *Gastroenterology* **149** 993–1005

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**New method drives primary CD4+ T cell response to influenza**

The current understanding in antigen presentation is that MHC class I (MHC I) and II (MHC II) molecules present endogenous and exogenous antigen respectively with MHC I also presenting exogenous antigen to T cells. Through the use of a murine influenza model, Miller et al. demonstrate that MHC II molecules can also present endogenous antigens, at least in infected dendritic cells (DCs). In addition, the MHC II processing components, H-2M and endosomal reductase GILT (thought to be essential for endosomal processing) were not required for presentation of most of the peptides, whereas the MHC I processing components, TAP and the proteasome were. This work therefore has important implications for our understanding of antiviral responses and vaccine development.

Miller et al. 2015 *Nature Medicine* **21** 1216–1222
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