Progress in the fight against Inflammatory Diseases and Cancer

The 2nd Joint Symposium of the Trinity Biomedical Sciences Institute and The Weizmann Institute of Science

June 9-10, 2015
Wolfson Hall, Wolfson Building for Biological Research

June 11, 2015
The David Lopatie Conference Centre

at the Weizmann Institute of Science, Rehovot, Israel

Abstract Book

Welcome to the second TBSI-Weizmann joint meeting

Recent years have seen dramatic advances in our understanding of the molecular basis for immune defense. Studies of the molecular interactions that contribute to innate and adaptive immunity keep providing new insights of the mechanisms by which our body responds to infection and injury. Detailed analysis of the structural basis for these interactions provides basis for design of new drugs that are successfully applied to fight infections, autoimmune diseases and cancer.

These subjects of research are intensely explored both at the Trinity Biomedical Sciences Institute (TBSI) and at the Weizmann Institute. A year ago, in July 27-29 2014, the two institutes held a joined conference in Dublin with the aim of promoting cooperation between the two institutes. An agreement signed on this occasion between the two institutes provides the basis for exchange of students and of visiting scientists between them.

The second joint meeting of the two institutes will be held at the Weizmann Institute on June 9-11 this year (www.weizmann.ac.il/conferences/TBSI2015/). Scientists of both Institutes will present recent advances in their studies. On this occasion, the Department of Immunology at the Weizmann Institute will also host several visiting students from the TBSI, and these students as well as Israeli students and scientists from both TBSI and Weizmann will present their work at the meeting.

The first two days of the meeting will be dedicated to recent advances in the study of the cellular and molecular basis for immune response and inflammation. Keynotes will be delivered by Richard Flavell, the Chairman of Immunobiology at the Yale school of Medicine and the President of the International Cytokine and Interferon Society, and by Ze'lig Eshhar, the 2015 winner of the Israel prize.

The last session on the second day will be held jointly with the International Conference on Structural Genomics that will also be held at the Weizmann at that week (www.weizmann.ac.il/conferences/ICSG2015/). A keynote in this session will be given by Roger Kornberg, the 2006 Nobel Prize winner in Chemistry.

The session of the third day will be devoted to the structural basis for the function of biological molecules. It will also be held jointly with the International Conference on Structural Genomics.

We wish you all an informative and friendly conference and a pleasant stay in Israel.

Shalom agus Slán

Luke O'Neill        Idit Shachar         David Wallach
Tuesday, June 9, 2015
The Wolfson Hall

09:00 OPENING OF MEETING  Chairs: David Wallach & Idit Shachar
David Wallach & Idit Schachar (Weizmann Institute of Science)
Opening of Symposium

09:10 Daniel Zajfman, President, Weizmann Institute of Science
Welcome to Weizmann Institute of Science

09:20 Patrick Prendergast, (Provost, Trinity College Dublin)
Welcome Address

Session 1: Adaptive Immunity  Chair: Kingston Mills

09:30 Kingston Mills (TBSI)
Regulatory and Pathogenic Role of Innate and Adaptive Immune Cells in Autoimmune Diseases

09:55 Idit Shachar (Weizmann Institute of Science)
CD84 is a Novel Mediator of the Interaction of CLL Cells with their Microenvironment Inducing Cell Survival

10:20 Padraic Fallon (TBSI)
Regulatory Functions of B Cells in the Suppression of Autoimmunity

10:45 Eszter Bakos (Weizmann Institute of Science)
The CCR2 Chemokine Receptor as a Direct Regulator of CD4+ Effector T Cell Responses

11:00 Sarah Edwards (TBSI)
γδ Cells, A Novel T Cell Subset with a Pathogenic Role in IL-17-Mediated CNS Autoimmunity

11:05 Coffee Break

11:30 Michal Polonsky (Weizmann Institute of Science)
Characterizing the Dynamics of T-Helper Cell Differentiation Using Live Cell Imaging and Single-Cell Analysis

11:45 Jacob Abramson (Weizmann Institute of Science)
Sirt is SIRTantly Important for Induction of Immunological Self-Tolerance and Prevention of Autoimmunity

Session 2: Metabolomics and Bioenergetics  Chair: Richard Porter

12:10 Richard Porter (TBSI)
The Role of Mitochondrial Uncoupling Proteins (UCPS) in Thymocyte/T-Cell Development and Function

12:35 Yochai Wolf (Weizmann Institute of Science)
Brown Adipose Tissue Macrophages Control Homeostatic Energy Expenditure

12:50 Christoph Alexander Thaiss (Weizmann Institute of Science)
Coordinated Harmonics of Immunity and Metabolism in the Meta-Organism

13:05 Lunch

13:50 Group Picture

14:00 Richard Flavell (Yale School of Medicine)
Keynote Address (Introduced by Idit Shachar)
Humanized Mice for the Study of the Human Condition

Session 3: Vaccines and Immunotherapy  Chair: Gavin Davey

14:45 Ed Lavelle (TBSI)
Particulate Adjuvants for Injectable and Mucosal Vaccines

15:10 Elizabeth Carroll (TBSI)
The Vaccine Adjuvant Chitosan Promotes Type I Interferons and Dendritic Cell Maturation via A cGAS-STING Dependent Mechanism

15:25 Natalia Zabolinsky (Weizmann Institute of Science)
Elucidating the Effects of the PD-1 Pathway on the Dynamic Interactions between Cytotoxic T Cells and their Targets

15:40 Mieszko Wilk (TBSI)
Lung Resident Memory cd4+t Cells (Trm) Play a Critical Role in Protective Immunity to Bordetella Pertussis

15:55 Coffee Break

16:10 Gavin Davey (TBSI)

16:35 Emma O’Connor (TBSI)
Identification of Gb3-Positive Drug-Resistant Cancer Cells and their Sensitivity to Verotoxin
**Wednesday, June 10, 2015**  
The Wolfson Hall

<table>
<thead>
<tr>
<th>Time</th>
<th>Speaker</th>
<th>Institution</th>
<th>Title</th>
</tr>
</thead>
</table>
| 9:00 | Zelig Eshhar | Weizmann Institute of Science | Keynote Address (Introduced by David Wallach)  
Redirection of Gene-Engineered T Cells against Cancer |
| 9:45 | Andrew Bowie (TBSI) | TBSI | The Role of PYHIN Proteins in Innate Immunity: DNA Sensing and beyond |
| 10:10 | Cliona O’Farrelly (TBSI) | TBSI | Innate Immune Mechanisms and Resistance to HCV Infection: Towards an Effective Vaccine. |
| 10:35 | Bar Nathason (Weizmann Institute of Science) | Weizmann Institute of Science | Perforin-Positive Dendritic Cells Exhibit a Novel Immuno-Regulatory Role in Metabolic Syndrome and Autoimmunity |
| 10:50 | Conor Finlay (TBSI) | TBSI | Helminth-Induced IL-33 and IL-5 Protect Against Autoimmunity |
| 11:05 | Coffee Break | |
| 11:30 | Mark Robinson (TBSI) | TBSI | Immune Profiling of Uninfected Irish Women with Iatrogenic Exposure to Hepatitis C Virus |
| 11:45 | Seamas Donnelly (Trinity College Dublin) | Trinity College Dublin | Macrophage Migration Inhibitory Factor (MIF), a Unique Cytokine & Human Disease |
| 12:10 | Steffen Jung (Weizmann Institute of Science) | Weizmann Institute of Science | The Role of Dicer And MicroRNAs in Microglia of the Developing and Adult Brain |
| 12:35 | Coffee Break | |
| 13:00 | Eran Elinav (Weizmann Institute of Science) | Weizmann Institute of Science | Microbiome Time |
| 13:15 | Danny Johnston (TBSI) | TBSI | The Role of MicroRNA-21 in gut Homeostasis and Disease |
| 13:30 | Lunch | |
| 14:10 | Ido Amit (Weizmann Institute of Science) | Weizmann Institute of Science | Shaping the Blood: Lessons from Single RNA-Seq Dynamics |
| 14:35 | Ann Byrne (TBSI) | TBSI | Epigenetic Markers of Reprogramming of Induced Pluripotent Stem Cells from HCV Innate Resistant Individual |
| 14:50 | Karin Golan (Weizmann Institute of Science) | Weizmann Institute of Science | Different Daily Light and Darkness Signals Regulate Bone Marrow Stem Cell Development and Leukocyte Production |
| 15:05 | Assaf Weiner (Weizmann Institute of Science) | Weizmann Institute of Science | Chromatin Dynamics during Blood Formation |
| 15:20 | Tsvee Lapidot (Weizmann Institute of Science) | Weizmann Institute of Science | Hematopoietic Stem Cells and Their BM Stromal Microenvironment share a Dynamic Inverse Metabolic State via Mitochondria Transfer |
| 15:45 | Coffee Break | |
| 15:50 | Roie Korsberg (Stanford University School of Medicine) | Stanford University School of Medicine | Keynote Address  
Chromatin and Transcription |
### Thursday, June 11, 2015
The David Lopatie Conference Centre

Combining low and high resolution data and modeling for structural biology
Joint session with the 2nd Trinity Biomedical Sciences Institute-Weizmann Conference
Chairpersons: Israel Silman - Rehovot & Jose-Maria Carazo - Madrid

<table>
<thead>
<tr>
<th>Time</th>
<th>Speaker</th>
<th>Topic</th>
</tr>
</thead>
<tbody>
<tr>
<td>09:00</td>
<td>Martin Caffrey (Trinity College Dublin)</td>
<td>Membrane Protein Structure-Function Studies with Lipid Mesophases</td>
</tr>
<tr>
<td>09:30</td>
<td>Yvonne Jones (University of Oxford)</td>
<td>New Insights into the Regulation of Wnt Signalling</td>
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<tr>
<td>10:00</td>
<td>Priyanka Joshi (U Cambridge)</td>
<td>Targeting IDPs: A Drug Discovery Strategy for Intrinsically Disordered Proteins</td>
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<td>10:30</td>
<td>Liron David, (Harvard Medical School)</td>
<td>Molecular Elucidation of the CBM Complex in NF-kappaB Activation by using Single Molecule Imaging and Structural Studies</td>
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<tr>
<td>11:00</td>
<td>Coffee Break</td>
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</tr>
<tr>
<td>11:30</td>
<td>Abraham Minsky (Weizmann Institute of Science)</td>
<td>Replication Cycles and Analyses of Viral Factories of Giant Viruses</td>
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<tr>
<td>12:00</td>
<td>Michael Levitt, (Stanford University)</td>
<td>Birth &amp; Future of Multiscale Modeling of Macromolecules</td>
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<tr>
<td>12:30</td>
<td>Joel Sussman (Weizmann Institute of Science)</td>
<td>Concluding Remarks</td>
</tr>
<tr>
<td>12:40</td>
<td>Lunch &amp; departure to airport</td>
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Humanized Mice for the Study of the Human Condition

Richard A. Flavell

Department of Immunobiology, Yale University School of Medicine, New Haven, CT 06520

Howard Hughes Medical Institute, Yale University School of Medicine, New Haven, CT 06520

Immunodeficient mice transplanted with human hematopoietic stem and progenitor cells represent a promising approach for studying human immune function and diseases in vivo. Within the last decade significant progress has been made in improving humanized mice by genetically inserting human genes that are essential for the proper development and function of human immune cells in the mouse. For example, the combination of the human signal regulatory protein alpha (SIRPA) and the human cytokines IL-3/GM-CSF, M-CSF and THPO in the MISTRG mouse led to improved development and function of human myeloid and NK cells. However, some limitations still restrict the utility of humanized mice in translational research. In particular, the development and survival of human T lymphocytes is suboptimal. We have therefore generated a new human knock-in mouse on the Rag2-/- Il2rg-/- background. Transplantation of human hematopoietic stem and progenitor cells into these mice led to an improved development of human NK cells and T cell subsets. This humanized mouse model thus paves the way towards a better environment for human adaptive immune cells in the mouse host and will facilitate the study of human antigen-specific immune responses in vivo.

Short Bio:
Dr. Flavell is founding chair of the Department of Immunobiology at Yale and an Investigator of the Howard Hughes Medical Institute. After obtaining a Ph.D. degree in biochemistry from the University of Hull in 1970, he carried out postdoctoral training at the University of Amsterdam and the University of Zurich. Working with Charles Weissmann in Zurich in 1974, he modified genes in a virus and studied the resulting phenotype - the first example of what scientists now call “reverse genetics.” Subsequently, as a faculty member at the University of Amsterdam, he demonstrated the presence of introns in mammalian genes. In 1982, Dr. Flavell left academics to serve as the chief scientific officer of Biogen, but returned to academia in 1988 to join the faculty at the Yale School of Medicine. Dr. Flavell’s research uses mouse genetics to study innate and adaptive immunity, T cell tolerance, apoptosis and autoimmunity, and the regulation of T cell differentiation. Among his recent discoveries is the finding that genes interact across chromosomes in T cells, where a master control gene on chromosome 11 may physically touch a gene on chromosome 10, inducing it to produce a protein that primes the cell to fight infection in a specific way. This finding has wide-ranging implications for diseases including autoimmune disorders and cancer. Most recently, he has established the connection between inflammasomes, microbial homeostasis and chronic diseases. He showed that dysbiosis of the microbiota leads to IBD and Metabolic Syndrome, including Obesity, Fatty Liver disease and Type 2 diabetes. Dr. Flavell has received the FEBS Anniversary Prize (1980), Colworth Medal (1980), Darwin Trust Prize (1995), Rabbi Shai Sachnai Memorial Prize in Immunology and Cancer Research (2008), AAII Invitrogen Meritorious Career Award (2008), Andrew Lazarovitz Award (2011), the William B. Coley Award for Distinguished Research in Basic and Tumor Immunology (2012) and most recently, the 2013 Vilcek Award, shared with Dr. Ruslan Medzhitov. He was elected to EMBO in 1978, the Royal Society in 1984, the National Academy of Sciences in 2002, the Institute of Medicine in 2006 and the first President of the newly formed International Cytokine and Interferon Society (ICIS) from 2014.
The CAR T-Cell Approach: From the Mouse Cage to the Patients Health

We have pioneered the chimeric antigen receptor (CAR) approach, nick named “T-Body”, and demonstrated its antitumor activities in different mouse experimental models bearing syngeneic tumors as well as human cancer xenografts. In these systems, using different configurations of the modular CAR we have tested and established the optimal requirements to obtain persistence of the CAR T-cells and durable anti-cancer responses. Moreover, we have worked out the conditions that allow to generate a time window in which allogeneic CAR T-cells can reject systemic metastases without graft versus host response. In parallel, we have used CARs specific to antigens related to autoimmunity or graft rejection and introduced them to regulatory T-cells (Treg). Such genetically modified Treg cells were capable of effectively suppressing both these syndromes. Altogether, our murine studies taught us how to modify and manipulate effector and regulatory T cell, redirect them to their target antigen and thus significantly improve the fate of patients. The current success recorded with CD19 CAR T – cells in the therapy of end-stage patients with CD19 malignancies is one extremely promising example.

Short Bio:
Prof Zelig Eshhar, PhD, a professor emeritus of the Weizmann Institute of Science and Chair Center of Immunology Research at Tel Aviv Sourasky Medical Center, Israel. His research has focused on molecular recognition in the immune system. He pioneered and has been instrumental in developing a unique immune cell approach that involves genetic modifications of T lymphocytes to produce a specific cell – called a “T body” (or CAR T-Cell)– that can be used to fight cancer. These genetically-engineered T cells have been shown to effectively kill human tumor cells both in vitro, and in experimental model systems in animals. In pre-clinical animal models systems, Prof. Eshhar established the conditions for a protocol to treat local as well as metastatic disease. Eshhar’s original, adoptive cell transfer approach is being practiced in pilot trials of end-stage patients with B cell lymphomas and leukemias. A large proportion of patients who have been treated with CD19 CAR T-cells/T bodies – genetically engineered versions of their own T cells have come with complete and objective responses.
Chromatin and Transcription

Short Bio:
Professor Roger D. Kornberg received the Nobel Prize in Chemistry for his studies of the molecular basis of eukaryotic transcription. He is Professor in the School of Medicine at Stanford University and a fellow in the Department of Biological Chemistry at the Hebrew University of Jerusalem.

His pioneering research in the area of the structural biology of macromolecules has contributed to the understanding of how we view the structure and role of genetic expression and has furthered our understanding of the basic process of life. He has conducted highly important research in the field of genetic expression of eukaryotic organisms, research whose essential contribution has been the revelation of nucleosomes, the elementary parts of chromosomes that participate in the control of genetic expression. Prof. Kornberg has also done pioneering research on the subject of the structure and role of large enzymes that carry out the process of transcription of RNA, the first step in genetic expression.
The Role of PYHIN Proteins in Innate Immunity: DNA Sensing and Beyond

Our major research interest is understanding how the innate immune system senses viruses and subsequently signals altered gene expression. The innate immune system responds to viruses using several classes of germline-encoded pattern recognition receptors (PRRs) to recognise pathogen-associated molecular patterns (PAMPs), and trigger anti-viral signalling pathways. This leads to the induction of interferons (IFNs) and cytokines, which control infection locally as well as coordinating the adaptive immune response. PRRs, such as the Toll-like receptors (TLRs), RIG-like receptors (RLRs) and cytosolic DNA sensors are important not only for responses to pathogens but also in sepsis, sterile inflammation, and autoimmune diseases. It has been known for some time that microbial DNA in the cytosol is immune-stimulatory, leading to IFN-beta induction, and we identified a novel human cytosolic DNA sensor called IFI16, which is a PYRIN and HIN domain-containing (PYHIN) protein that mediates IFN-beta induction by cytosolic DNA. The mouse functional ortholog of IFI16 is p204. Another PYHIN protein, AIM2, had been shown to mediate DNA-induced activation of the inflammasome in both mouse and human cells. Thus, we have proposed that the PYHIN proteins IFI16, p204 and AIM2 form a new family of innate DNA sensors termed 'AIM2-like receptors' (ALRs). Humans have five PYHIN proteins (IFI16, AIM2, POP3, PYHIN1, MNDA), and mice have many more. Apart from roles in DNA sensing, PYHIN proteins also regulate transcription of specific cytokines and IFNs induced by PRRs. Recently we have shown that the PYHIN protein MNDA controls the type I IFN induction cascade in human monocytes by regulating IRF7 expression.

Short Bio
Andrew Bowie is currently Head of Immunology in the School of Biochemistry and Immunology, TCD. He obtained his PhD in Biochemistry from TCD in 1997, and was appointed to his current post in 2001. He was elected a Fellow of TCD in 2008, and a member of the Royal Irish Academy in 2014. He is internationally recognized for his work on pathogen detection leading to innate immune signalling, and how such detection processes are subverted by viruses. In particular, he is currently interested in immune mechanisms of intracellular DNA sensing.
In February 1994, batches of anti-D immune globulin used in Ireland during 1977 and 1978 to prevent Rh isoimmunisation were found to be contaminated with hepatitis C virus (HCV) from a single infected donor (Kenny-Walsh, 1999). 1342 women who received at least one injection from a contaminated batch were tested for HCV infection and of these approximately 776 showed evidence of infection (defined as HCV-specific antibody responses or the presence of viral genomic RNA indicating chronic infection). The remaining 566 showed no evidence of an adaptive immune response, despite the fact that at least 71% of these women received a 'high viral titre' batch (Lawlor et al., 1999). To date research on this cohort has revealed that HCV targets interferon-α JAK/STAT pathway by promoting proteasomal degradation in immune cells and hepatocytes (Stevenson et al., 2013), HCV-specific Th17 cells are suppressed by virus-induced TGF-beta (Rowan et al., 2008) and the presence of altered natural killer (NK) cell subset distribution in resolved and persistent infection (Golden-Mason et al., 2008). We hypothesise that these women are uniquely resistant to HCV and where able to clear the virus due to strong innate immune responses. These HCV-resistant individuals, because of their gender, age and racial homogeneity, form the key cohort of our analysis; they provide an important and unique resource for defining the molecular mechanisms of viral resistance.

Through the use of personalised iPSC-derived in vitro models we plan to explore the unique aspects of JAK/STAT signalling pathways as well as NK and DC function, that results in this resistant phenotype. The development of experimental procedures capable of reverting healthy adult cells into stem cell-like pluripotent cells (termed induced pluripotent stem cells (iPSC)), has the potential to revolutionise in vitro models of important biological processes such as the immune response to infection. With the maturation of technologies we are now at a point where it is possible to produce iPSCs from an individual and use these iPSC to derive multiple cell types, which can be used in in vitro models. We can study immunological processes involving multiple cell types in personalised in vitro systems and we can develop these models from a range of individuals to capture the spectrum of responses present within the human population.

The overall aim of this project is to develop iPSC from this cohort of women in order to create in vitro models of innate hepatitis C virus (HCV) resistance, with the goal of dissecting the innate immune pathways that led to resistance.

References
Chemical Synthesis of Ubiquitin Chains and Polyubiquitinated Proteins for Biochemical Studies

In this talk, I will present our non-enzymatic approaches for protein ubiquitination to shed light on the various unknown aspects of the ubiquitin signal in cellular pathways. The enzymatic attachment of ubiquitin to a specific protein target is a widely utilized posttranslational modification in eukaryotes, which is involved in various aspects of cellular functions and has been implicated in several diseases. The overwhelming majority of biochemical, biophysical and structural studies in the field rely on the in vitro enzymatic reconstitution of this complex modification for the protein of interest. However, the enzymatic approaches are often challenged by the isolation of the specific ligase, the heterogeneity of the modified protein and obtaining workable quantities of the ubiquitinated conjugates. Our group is developing novel non-enzymatic methods for the efficient and site-specific protein ubiquitination to overcome the limitations of the enzymatic machinery. These approaches allowed for the preparation of free ubiquitin chains for various studies as well as of homogeneous ubiquitinated protein such as alpha-synuclein and histone H2B to support the ongoing efforts aiming at studying the effect of ubiquitination in these systems.

References

Short Bio
Ashraf Brik is a Professor of Chemistry at the Schulich Faculty of Chemistry in the Technion-Israel Institute of Technology. Brik received his B.Sc. in Chemistry from the Ben-Gurion University of the Negev (1993-1996) and his M.Sc. degree in Organic Chemistry in 1998 from the Technion-Israel Institute of Technology. His Ph.D. was obtained in 2001 from the Faculty of Chemistry in the Technion in Bioorganic Chemistry. From 2002 to 2006, Brik was a Research Associate in the Scripps Research Institute. In 2007, Brik joined the Department of Chemistry in the Ben-Gurion University of the Negev as an Assistant Professor and was promoted to an Associate Professor in 2011 and to a Full Professor in 2012. In 2014, Brik received an offer to join the Schulich Faculty of Chemistry in the Technion and since 2015 became a Neubauer Professor. Professor Brik serves in the Editorial Board of Organic Biomolecular Chemistry and in the International Advisory Board of Asian Journal of Organic Chemistry. Brik is the recipient of the Bessel Award of the Humboldt Foundation for 2015, the 11th Hirata Award, Teva Award for Excellence in memory of Eli Hurvitz for 2013, the Tetrahedron Young Investigator Award in Bioorganic and Medicinal Chemistry for 2013 and the 2011 Israel Chemical Society prize for Outstanding Young Chemist.
Chromatin Dynamics during Cellular Reprogramming and Differentiation

Covalent histone modifications are highly conserved and play multiple roles in eukaryotic transcription regulation, from short-term transcriptional response to long-term cell differentiation. Studies of histone modification localization and function under steady-state conditions provide surprisingly little insight into the functions of histone marks in transcriptional control, whereas following chromatin changes in a dynamic process can reveal more widespread functions for these modifications.

In this talk I will discuss chromatin dynamics in two different systems. First I will show how we elucidate the temporal order of histone modifications changes during the induction and repression of genes in response to stress in S. cerevisiae. Next I will describe chromatin state dynamics during hematopoiesis. Using a new revolutionary method to perform ChIP-seq in only hundreds to few thousands of cells we characterized chromatin modifications across 16 stages of hematopoietic differentiation. We find that lineage commitment involves de novo establishment of 30% to 40% of the lineage-specific enhancers. These enhancer repertoire expansions foreshadow transcriptional programs in differentiated cells. Combining our enhancer catalog with gene expression profiles, we elucidate the transcription factor network controlling chromatin dynamics and lineage specification in hematopoiesis.

Short Bio:
Starting from 2015, I am a postdoctoral fellow in Ido Amit’s lab at the Department of Immunology in the Weizmann Institute. I did my PhD at the Hebrew University under the supervision of Prof. Nir Friedman in computational biology. My PhD research combined high throughput genomic experiments with machine learning and algorithms to study the genome regulation during cellular differentiation and during the response to external signals such as stress, focusing mainly on the role of chromatin in this complex regulation process. During my PhD I was a Clore doctoral scholar and won several awards. In my postdoc I am studying the molecular circuits controlling hematopoiesis by quantitative single-cell dynamics.
Perforin-Positive Dendritic Cells Exhibit A Novel Immuno-Regulatory Role In Metabolic Syndrome and Autoimmunity

Immature dendritic cells (imDCs) can have a tolerizing effect in the steady state or following transplantation. However, due to the significant heterogeneity of this cell population it is difficult to study mechanisms mediating their tolerizing activity. Previous study in our lab described the generation of a highly defined population of imDCs expressing perforin and granzyme A (Perf-DCs) from hematopoietic progenitors. Perf-DCs induce specific tolerance by deleting CD4+ and CD8+ T cells. While the former are deleted via an MHC-independent mechanism through the nitric oxide system, CD8+ T cell deletion occurs through MHC-dependent perforin-based killing. Importantly, this novel subpopulation of Perf-DCs was also detected in various lymphoid tissues in normal animals, and its frequency is markedly enhanced upon GM-CSF administration.

Here, we investigated the potential regulatory role of Perf-DCs in steady state in-vivo, by selectively knocking out the expression of perforin in these cells. To this end, we generated BM chimeras using a 1:1 mixture of BM from perforin KO mice and from BM of mice ablated of CD11chigh DCs using diphtheria toxin expression under the CD11c promoter (DTA-PKO chimera). At 6 months post transplant, DTA-PKO chimeric mice spontaneously gained more weight than chimeras created using a mixture of normal BM with BM from perforin KO mice (WT-PKO). The increased weight gain observed in DTA-PKO mice was accompanied by other metabolic alterations including all the symptoms of the metabolic syndrome. Furthermore, DTA-PKO chimeras maintained on HFD displayed more pronounced weight gain compared to their HFD-maintained WT counterparts when tested 6 weeks after HFD initiation.

Notably, this phenotype was associated with a modified T cell repertoire in the adipose tissue and could be completely prevented by T-cell depletion in-vivo.

Considering that the antigens involved in the observed adipose tissue inflammation are not known, we further attempted to investigate the regulatory role of Perf-DC in a more defined model of autoimmunity, namely MOG mediated EAE. Indeed, Perf-DC KO mice were found to be substantially more prone to induction of EAE, exhibiting significantly elevated levels of MOG specific autoimmune clones compared to their WT counterparts.

Taken together, our results suggest that Perf-DCs have a unique immune regulatory role under steady state, controlling unwanted inflammatory processes in adipose tissue and autoimmunity in EAE.
Coordinated Harmonics of Immunity And Metabolism in the Meta-Organism

The mammalian organism is comprised of only a minority of eukaryotic cells. The large majority of all cells that compose the “meta-organism” are actually the bacteria, fungi, viruses, and parasites. This community of microorganisms, collectively termed the microbiota, colonizes all mucosal surfaces of the body. This means that the immune and metabolic system of the host has co-evolved with trillions of microorganisms which collectively encode a genome that is 100-fold larger than the genome of the host. In our work, we are studying the principles of trans-kingdom regulation in the immune and metabolic system. We identified circadian rhythms as an important principle in shaping the activity of the meta-organism on the level of the metagenome, metatranscriptome, and metabolome. Since different compositions and functions of the microbiome have been associated with a large number of modern, multi-factorial diseases, we are studying the impact of circadian host-microbiota interactions on physiological and pathophysiological processes.

Short Bio:
Christoph grew up in Germany and performed his Bachelor’s studies at the University of Bonn, Germany, and Yale University, USA. He then continued his studies at ETH Zurich, Switzerland, and the Broad Institute, USA. After obtaining his Master’s degree, he joined the lab of Eran Elinav at the Weizmann Institute, where he is currently performing his PhD studies, working on host-microbiota interactions in the immune and metabolic system. He is supported by a Boehringer Ingelheim Fonds PhD fellowship.
Innate Immune Mechanisms and Resistance to HCV Infection: Towards an Effective Vaccine

C.O'Farrelly, N.Stevenson on behalf of ICORN (Irish Hepatitis C Outcomes and Research Network)
Trinity BioSciences Institute, Trinity College Dublin 2, Ireland

A focus on adaptive immunity dominates current perceptions of anti-viral immunity and vaccine development. However, the reliance (until relatively recently) on type 1 interferon as the sole therapy for HCV infection has alerted the research community to the ability of the hepatitis C (HC) virus to evade clearance by targeting innate immune mechanisms, thereby stalling classic vaccination strategies. Indeed several novel immune evasion strategies involving innate immune molecules have been ascribed to the HC virus. HCV has been shown to block RIG-I, TLR3, STAT3, and OAS activity by different mechanisms, as well as suppressing DC and NK function. Resistance to these inhibitory activities must therefore explain the ability of some individuals to resist HCV infection. We are exploring this hypothesis in a cohort of Irish women who were exposed to hepatitis C virus (HCV) via contaminated anti-D, of whom up to 40% resisted infection. Studies on this cohort have shown that distinct HLA class 1 alleles protect against HCV, probably through their interaction with NK cells; we also found that NK cell genes interact with type 3 interferon genes to influence susceptibility to HCV infection and that the C allele of TLR9 rs187084 (OR=2.36 [95% CI: 1.37-4.05] p=0.002) is associated with HCV clearance. We propose that the constellation of innate immune mechanisms responsible for HCV resistance should be exploited in the design of an adjuvant that will drive a successful HCV vaccine.

Short Bio
Cliona O'Farrelly, is Professor of Comparative Immunology and Fellow of Trinity College Dublin. A recipient of the Irish Research Scientists’ Association Gold Medal, the Graves Medal, the Conway Medal, the Isla Haliday Award, Cliona was recently awarded the 2014 Nature Mentoring Award. Having been President of the Irish Society of Immunology from 2000-2007 and on the Board of the Irish Cancer Society from 2006-2012, Cliona currently serves on the Boards of the Royal Dublin Society, Trinity College Dublin and TCD’s Science Gallery. Cliona completed her undergraduate degree in Microbiology and PhD in Immunology at TCD during the ‘70s/early ‘80s, before undertaking postdoctoral research at St.James’s Hospital Dublin and Sussex University in the UK, and becoming Lecturer on Biology at Harvard University. While Director of the Research Laboratories at St. Vincent’s University Hospital, Dublin from 1993-2007, she was instrumental in developing one of the world’s first research programmes into human liver immunology. This continues to be one of Cliona’s main research interests as she and her group try to understand how the liver’s immune system influences susceptibility or resistance to liver infections and malignancy. She and her group have published over 200 papers, reviews and book chapters and have raised more than 10 million Euro in grant funding. She is passionate about science communication and education and promoting young researchers. She has graduated more than 30 PhD students, 8 MD and 4 MCh students from her laboratory and has mentored almost 20 post-doctoral fellows; she has started a new MSc in Immunology at Trinity College Dublin and spearheaded several initiatives for communicating science to school children and the public.
Helminths Protect Against Autoimmunity Through IL-5 and IL-33-Induced Eosinophils

Conor M Finlay1, Anna M Stefanska4, Kevin P Walsh1, Benjamin Doyle1, Louis Boon2, Ed C. Lavelle3, Patrick T Walsh4 and Kingston H G Mills1

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Epidemiology studies in humans have demonstrated that infection with helminth parasites is associated with a reduced risk of developing autoimmune diseases. Mechanistic studies in mice have linked this to the suppressive effects of helminth-induced regulatory T (Tregs) or Th2 cells. Although treatment with live helminth is under clinical evaluation for autoimmune disease in humans, helminth products may be a more acceptable therapeutic approach. Here, we demonstrate that treatment of mice with Fasciola hepatica excretory/secretory products (FHES) attenuated the clinical signs of experimental autoimmune encephalomyelitis (EAE), a mouse model of multiple sclerosis. Protection was associated with a significant reduction in the infiltration of pathogenic Th1 and Th17 cells into the brain. Although FHES enhanced anti-inflammatory cytokine and Th2 responses, protection against EAE was independent of IL-4, IL-10 and Tregs. However, administration of FHES induced production of the type-2 cytokines IL-33 and IL-5, which promoted expansion of eosinophils. FHES-induced expansion of eosinophils and protection against EAE was lost in IL-33−/− and in IL-5−/− mice. Furthermore, transfer of FHES-induced eosinophils conferred protection against EAE. This study is the first to report that helminth-induced IL-5 and IL-33 and eosinophils in protection against autoimmunity.

Short Bio:
Conor Finlay graduated first in his class from Trinity College in 2007 with BA (Mod) in Biochemistry with Immunology. In 2008, Conor started PhD under the mentorship of Kingston Mills where he studied immune modulation by the helminth parasite Fasciola hepatica. He graduated in 2013 and has since continued his research in the Mills laboratory as a post-doctoral fellow studying helminth immunoregulation and the regulatory capacity of type-2 responses induced by IL-33.
The Role of MicroRNA-21 in gut Homeostasis and Disease

MicroRNA(miR)-21 is a widely expressed post-translational regulator of mRNA expression involved in regulation of several immune signaling pathways. It has been shown to be directly involved in the negative regulation of TLR4 signaling in macrophages as well as being implicated in a variety of disease states. Inflammatory bowel disease (IBD) and colorectal cancer are two such diseases that are both marked by miR-21 overexpression. Our study aims to elucidate the role of miR-21 in gastrointestinal homeostasis and disease using various disease models and in vitro approaches. We have confirmed that miR-21 knock-out mice are protected from DSS induced colitis compared to wild-type controls in various conditions. In addition, using co-housing and cross fostering models, we have generated preliminary data suggesting that miR-21 knock-out mice may have an altered microbiota which contributes to their protection in this disease model. We hope to further explore this idea in the Weizmann. We have observed that bone marrow derived macrophages and dendritic cells generated from miR-21 knock-out mice progenitors secrete significantly higher levels of interleukin-12p70 (IL-12p70) in response to various TLR agonists than wild type controls. As it is well known that IL-12p70 is an inducer of Th1 cells, and that Th1 cells are implicated in IBD, there is an interesting conflict in these results which we are currently exploring.

Short Bio:
Daniel graduated from Trinity College Dublin in 2012 with a BA (Mod) in Biochemistry with Immunology having completed a research project focused on IL-10 translation in the laboratory of Prof Luke O’ Neill. In 2013 he began his PhD in the same lab, now based in the TBSI, under the supervision of Dr Sinéad Corr studying the effects of microRNA-21 expression in gut homeostasis and disease. The current focus of the project is on the possible altered microbiota of miR-21 deficient mice as well as the apparent altered inflammatory cytokine expression profiles in response to various TLR agonists.
Particulate Adjuvants for Injectable and Mucosal Vaccines

The effectiveness of vaccines and their capacity to promote and direct adaptive immunity depends on their activation of innate immunity. In particular, dendritic cells are central to the initiation of antigen specific cellular immunity and the sensing of vaccines by dendritic cells is a key factor underlying their efficacy. There is a move away from live attenuated and killed vaccines towards subunit vaccines due to their highly characterized nature, established expression techniques and safety. While the effectiveness of ‘traditional’ vaccines based on attenuated viruses and killed bacteria is understood in terms of the ‘stranger theory’ proposed by Charles Janeway, the effectiveness of subunit vaccines adjuvanted by alum and other particulates is less well understood. In the past the adjuvanticity of these systems was attributed to a ‘depot effect’ or controlled antigen release but we now have evidence that these adjuvants act by specific activation and modulation of innate immunity. In addition, adjuvants may promote localized cell death, resulting in the release of endogenous danger signals and the consequent triggering of innate cell activation. Many particulate vaccine adjuvants can strongly activate the NLRP3 inflammasome and our recent data suggest that while NLRP3 is not essential for adjuvant driven humoral immunity, with certain particulate adjuvants it can play a key role in the promotion of antigen specific cellular immunity and particularly Th17 responses. Therefore the development of inflammasome promoting adjuvants may have potential for the generation of antigen specific cellular immunity. In this talk the ability of specific adjuvants to direct adaptive immune responses will be addressed with examples from both injectable and mucosal vaccination approaches.

Short Bio
Dr Ed Lavelle graduated with a BSc in Microbiology from University College Galway and a PhD in Immunology from the University of Plymouth. He carried out postdoctoral research at the University of Nottingham on nano and microparticles as vaccine adjuvants. This was followed by further postdoctoral positions at the Rowett Research Institute and Trinity College Dublin on vaccine adjuvants and immunomodulators. He was appointed as a lecturer in Immunology in 2004 and associate Professor in 2012. His main research area is the mechanism by which particulate adjuvants modulate innate and adaptive immune responses with a strong focus on translating this work in order to develop novel adjuvants for injectable and mucosal vaccines. His work has been published in journals including PNAS, J. Exp Med, PLoS Pathogens, Nature Immunology and Immunity. The group works closely with a number of Biotech companies and also with international Pharma engaged in vaccine research. Dr Lavelle has published more than 80 peer-reviewed papers, is an inventor on 5 patents and collaborates with leading academic groups throughout Europe and the U.S.
The Vaccine Adjuvant Chitosan Promotes Type 1 Interferons and Dendritic Cell Maturation Via A Cgas and Sting Dependent Mechanism.

Liz Carroll1, Lei Jin2, Andres Mori1, Andrew Bowie1, Paul Hertzog3, Colm Cunningham4, Katherine A. Fitzgerald2,6, Ed. C. Lavelle1.

1School of Biochemistry and Immunology, Trinity College Dublin, Dublin, Ireland, 2Centre for Immunology and Microbial Disease, Albany Medical College, Albany, New York, USA, 3Monash Institute of Medical Research (MIMR), Clayton, Victoria, Australia, 4School of Biochemistry and Immunology and Trinity College Institute of Neuroscience, Trinity College Dublin, Dublin, Ireland, 5Program in Innate Immunity, Division of Infectious Diseases and Immunology, Department of Medicine, University of Massachusetts Medical School, Worcester, Massachusetts, 01605, USA, 6Centre of Molecular Inflammation Research, Department of Cancer Research and Molecular Medicine, Norwegian University of Science and Technology, 7491 Trondheim, Norway.

Chitosan has emerged as a promising candidate adjuvant for the induction of potent cellular immune responses and may have application in the development of vaccines against malaria, TB and HIV/AIDS. Aluminate phosphate, and calcium phosphate adjuvants inhibit the secretion of the Th1 polarizing cytokine, IL-12 by dendritic cells (DCs). The ability to activate antigen presenting cells (APCs), in particular dendritic cells (DCs) is a key attribute of effective adjuvants. The activation of DCs is characterised by upregulation of surface costimulatory molecules as well as an enhanced capacity to secrete cytokine. The objective of this research was to study the ability of chitosan to promote DC activation and address the underlying mechanism. An in vitro model of DC activation was employed in which the ability of chitosan to upregulate costimulatory molecules on DCs was assessed by flow cytometry. Furthermore, cytokine secretion in response to chitosan was evaluated by quantitative PCR (qPCR) and ELISA. Chitosan enhanced the expression of CD40, CD80 and CD86 on DCs and promoted induction of type I interferons (IFNs) and interferon dependent genes. Type I IFNs were essential for chitosan mediated DC activation. In contrast to chitosan and the published literature, the ability of TLR ligands including LPS to promote DC maturation was IFNAR independent. Induction of type I IFNs in response to chitosan required the enzyme cyclic GAMP synthase (cGAS) and the adaptor protein stimulatory of IFN genes (STING). We further show that type I IFNs are essential for chitosan induced cellular immunity. This is the first demonstration that a particulate vaccine adjuvant can activate the cGAS-STING pathway. This research was funded by IRCSET.

Short Bio:
Liz Carroll graduated with BSc in Microbiology from University College Dublin. In 2013, she was awarded an IRCSET scholarship to carry out her research in the adjuvant research group at the Trinity Biomedical Sciences Institute (TBSI) under the supervision of Dr. Ed Lavelle. The focus of her PhD research is on the candidate vaccine adjuvant chitosan.
The platinum-based, anticancer agent, cisplatin, is one of the most commonly used and
effective chemotherapeutic drugs for the treatment of a variety of solid tumours, but often
yields temporary clinical results due to the development of acquired chemoresistance,
leading to disease relapse and therapeutic failure. Resistance can develop not only to
cisplatin and structurally similar, platinum-based analogues, but also to a range of structurally
diverse antineoplastic agents. This is known as multi-drug resistance (MDR) and is a major
impediment for the successful treatment of a number of cancers. Increased expression
levels of the glycosphingolipid, globotriaosylceramide (Gb3), also known as the B cell
differentiation antigen, CD77, have been documented in a range of cancers, including colon
cancer, breast and ovarian tumours, malignant meningioma, astrocytoma and in several drug
resistant cancer cell lines but particularly in those with acquired cisplatin resistance. Thus,
Gb3 represents a potential cancer cell biomarker and therapeutic target for the treatment of
a number of these cisplatin-resistant cancers. Gb3 is reported to have a number of functions,
one of which is to serve as the receptor for verotoxin-1 (VT-1; also known as shiga-like
toxin-1), the primary virulence factor of pathogenic enterohaemorrhagic Escherichia coli. The
upregulated expression of Gb3 in cisplatin-resistance may render these cells more vulnerable
and sensitive to VT-1-induced apoptosis. Therefore, the targeting of Gb3 with VT-1, in concert
with chemotherapeutics, may improve the response to chemotherapy by having a synergistic
effect on the induced cytotoxicity in cisplatin-resistant cancer cells, representing a potential
therapeutic strategy to overcome cisplatin-induced drug resistance.

Short Bio:
Emma O'Connor graduated with a B.A. in Physiology from Trinity College Dublin in 2013. She
went on to do an M.Sc. in Molecular Medicine in Trinity College, carrying out her research
project in the lab of Dr. Richard K. Porter. In 2014, she was awarded the John Scott scholarship
to carry out research in Dr. Porter’s group at the Trinity Biomedical Sciences Institute (TBSI).
Currently, Emma is working there as a Ph.D. student in the School of Biochemistry and
Immunology, focusing on the role of mitochondrial uncoupling proteins in T-cell metabolism
and function.
Microbiome Time

The mammalian intestine contains trillions of microbes, a community that is dominated by members of the domain Bacteria but also includes members of Archaea, Eukarya, and viruses. The vast repertoire of this microbiome functions in ways that benefit the host. The mucosal immune system co-evolves with the microbiota beginning at birth, acquiring the capacity to tolerate components of the community while maintaining the capacity to respond to invading pathogens. The gut microbiota is shaped and regulated by multiple factors including our genomic composition, the local intestinal niche and multiple environmental factors including our nutritional repertoire and bio-geographical location. Moreover, it has been recently highlighted that dysregulation of these genetic or environmental factors leads to aberrant host-microbiome interactions, ultimately predisposing to pathologies ranging from chronic inflammation, obesity, the metabolic syndrome and even cancer. We have identified various possible mechanisms participating in the reciprocal regulation between the host and the intestinal microbial ecosystem, and demonstrate that disruption of these factors, in mice and humans, lead to dysbiosis and susceptibility to common multi-factorial disease. Understanding the molecular basis of host-microbiome interactions may lead to development of new microbiome-targeting treatments.

Short bio:
Dr. Eran Elinav joined the Weizmann Institute of Science in 2012 as a senior scientist leading a research group in the Department of Immunology. His lab focuses on the interactions between the innate immune system, the intestinal microbiota and their efforts on health and disease, with the goal of personalizing medicine and nutrition.
Dr. Elinav completed his medical doctor’s (MD) degree at the Hebrew University of Jerusalem Hadassah Medical Center in 1999 summa cum laude, followed by a clinical internship, residency in internal medicine at Hadassah (2000-2004), and a clinical and research position at the Tel Aviv Sourasky Gastroenterology institute (2005-2009). He received a PhD in immunology from the Weizmann Institute of Science in 2009, followed by a postdoctoral fellowship at Yale University School of Medicine (2009-2012). Dr. Elinav has published more than 70 publications. His honors include multiple awards for academic excellence during his medical, PhD studies, postdoc and independent research, including the Fulbright (2009) and cancer research foundation (2010-2012) scholarships, the 2011 Claire and Emmanuel G. Rosenblatt award from the American Physicians for Medicine in Israel Foundation, the Alon Foundation award (2012), and the Rappaport prize for biomedical research (2015).
Chemokines and chemokine receptors build up a complex network regulating the migration and positioning of leukocytes during homeostasis and inflammation. Additionally, numerous studies indicated that besides regulating cell motility the chemokine system directly induce the differentiation and effector functions of APCs and T cells. In our study we investigated the role of the CCR2 chemokine signaling on directly shaping the effector T cell responses in vivo. To date, numerous studies demonstrated that the CCR2 chemokine receptor influences the fate of CD4+ T cells under various inflammatory conditions. However, these studied were limited in completely delineate the effects of CCR2 on T cell functions due to the affects of the CCR2 deficient immune cell microenvironment. To this end we chose the highly T cell specific inflammatory model of colitis, in which we transferred normal and CCR2/- CD4+/CD45RBlowCD25− T effector/memory (Teff) cells into RAG1/- immuno-compromised hosts and analyzed the development of the wasting disease. Our study revealed that the hosts transferred with CCR2 deficient Teff cells had ameliorated colitis as analyzed by the weight management and macroscopic changes in the colonic wall by live endoscopy. Analyzing the transferred Teff cells in vitro revealed a significant downregulation in the inflammatory cytokines IL-17A, IL-17F, INF-γ, and IL-10 in CCR2-/- Teff cells. Importantly, this defect was apparent in the colons of RAG1/- mice transferred with CCR2-/- Teff cells in vivo. Moreover, analyzing the colonic lamina propria of host mice injected with CCR2-/- Teff cells uncovered a significant raise in the CD4+Foxp3+CD25+Helios+ iTreg pool compared to the relevant control. These data indicated that CCR2 on T cells is not only essential to mount normal inflammatory responses but the loss of this receptor creates a program that favors Treg development.

Short Bio:
Im from Hungary and attended University of Debrecen, where I received an MsC Degree in molecular biology. During this period I researched the molecular mechanisms leading to drug resistance of the HIV-1 Protease. Quickly after my MsC degree I joined the Department of Immunology at the Weizmann Institute of Science as a PhD student, where ever since I analyze chemokine signaling in the T cell response.
New Tools for Deciphering N- and O-Linked Glycosylation Networks
– Implications for Bio- and Immunotherapeutics

Andrew M McDonald, Jerrard M Hayes and Gavin P Davey
School of Biochemistry & Immunology

The development of next generation biotherapeutics has been hampered by the inability to synthesize homogenous glycoforms and control the levels of heterogeneity during bioprocess. The lack of knowledge on N-linked and O-linked glycosylation networks has contributed to this bottleneck. We have generated computational models of both types of glycosylation, allowing in silico knock-out experiments to generate insight into how mammalian cells synthesize glycoforms. These models have been advanced to consider kinetic fluxes through the glycosylation systems and their relationship to metabolic flux control. Following the identification of control points in the networks, mammalian cells were in vitro glycoengineered to validate the predictions. β-1,4-galactosyltransferase was found to be a major control point for glycan complexity in the cell. Glycoengineering cells at this control point enabled the production of different glycoforms of the same biotherapeutic, with consequences for in vivo biological activity. Glycoengineered antibodies in the Fc region also affected interaction with Fcγ Receptors. This work demonstrates that by controlling kinetic flux through the glycosylation system it is possible to bioengineer mammalian cells to produce protein with specifically tailored glycan profiles. New advances in these computational models have generated insight into how mucin glycosylation may be affected in cancerous tissue.

Short Bio:
Gavin Davey is Head of the School of Biochemistry and Immunology in Trinity College Dublin. He has 25 years’ experience in the area of enzymology and metabolic flux, particularly in relation to mitochondrial bioenergetics and cellular metabolism. His laboratory uses a mixture of systems biology approaches to (1) investigate mitochondrial energetics and fusion/fission dynamics specific to cancer cells and neurons (2) identify metabolic control points as new targets for anti-cancer therapeutics (3) understand control of N-linked and O-linked glycosylation pathways in cancer and immune cells (4) glycoengineer IgG biotherapeutics for enhanced ADCC, CDC and enhanced immunomodulatory properties (5) identify glycosylation-based biomarkers for cancers.
CD84 is a Novel Mediator of the Interaction of CLL Cells with their Microenvironment Inducing Cell Survival

Ayelet Marom1, Avital F. Barak7, Matthias P. Kramer1, Sivan Cohen1, Hadas Lewinsky5, Afroditi Tsitsou-Kampeli1, Inbal Binsky-Ehrenreich1, Shirly Becker-Herman1, Pamela L. Schwartzberg1, Vyacheslav Kalchenko3, Michal Haran5, Yair Herishanu5, Idit Shachar1*

Department of Immunology1 and Department of Veterinary Resources3 Weizmann Institute of Science, Rehovot 76100, Israel; 2National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland, USA; 3Hematology Institute, Kaplan Medical Center, P.O.B. 1, Rehovot 76100, Israel; 5Department of Hematology, Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel.

Chronic lymphocytic leukemia (CLL) is characterized by the accumulation of CD5+ B lymphocytes in peripheral blood, lymphoid organs and BM. The main feature of the disease is accumulation of the malignant cells due to decreased apoptosis. It has been recognized for several years that signals from the CLL microenvironment make pivotal contributions to the progression the malignancy. The complex cellular and molecular contexts created in the tissues, collectively referred to as the CLL microenvironment, provide signals for the expansion of the CLL clone and inducing primary drug resistance. This phenomenon is largely dependent on direct contact between the malignant B cells and stromal cells. CD84 belongs to the Signaling Lymphocyte Activating Molecule (SLAM) family of immunoreceptors, and has an unknown function in CLL cells. Since CD84 is involved in cell-cell interaction, we hypothesized that CD84 on CLL cells interacts with CD84 expressed on cells in their microenvironment. The interaction mediated through CD84 induces secretion of CCL3 from CLL cells. CCL3 binds to CCR1/5 on stromal cells, inducing Bcl-2 expression and cell survival and expression of IL-6 that supports survival of CLL cells. Blocking CD84 abolished the CLL-microenvironment interaction resulting in induced cell death. Thus, our findings suggest novel therapeutic strategies based on the blockade of this CD84-dependent survival pathway.

Short Bio:

Born in Israel, Prof. Idit Shachar earned her BSc (1987) and MSc (1989) degrees with honors in biochemistry from Tel-Aviv University, and a PhD in Biochemistry in 1993 from the same institution. Her postdoctoral research was undertaken at Yale University School of Medicine from 1993-1997. In 1998, she returned to Israel and joined the Weizmann Institute. She is the incumbent of the Dr. Morton and Anne Kleiman Professorial Chair. In 2014 she became the head of the department of Immunology.

Prof. Shachar investigates the immune system, focusing on white blood cells called B cells. Adaptive immunity depends on the production and maintenance of a pool of mature peripheral lymphocytes throughout life. Most of these cells circulate in the periphery in a quiescent state, without actively contributing to a given acute immune response. Thus, homing and survival are two essential mechanisms that regulate the maintenance of peripheral lymphocytes. Prof. Shachar’s research is focused on the molecular mechanisms regulating these mechanisms in health and disease.

Prof. Shachar has about 50 peer-reviewed papers, reviewers and book chapters, has given numerous invited seminars world-wide, and is inventor on five patents. She has also worked as a consultant to the CytoD, Meytav technology incubator.

Prof. Shachar and her husband Ron, a professor of marketing and the dean of the business school at the Interdisciplinary Center in Herzliya, have two children: a daughter, Yuval, and a son, Daniel.
Hematopoiesis, where a single hematopoietic stem cell gives rise to the entire blood system, is an important model for differentiation with great medical importance. While the hematopoietic system is perhaps the most characterized model system of cellular commitment and differentiation, we currently lack understanding as to the prevalence of heterogeneity in progenitor populations. In recent work, we took an important first step towards unbiased characterization of hematopoiesis decisions, by measuring and modeling chromatin state dynamics during hematopoietic development. These detailed chromatin maps pointed to large discrepancy between the common hematopoietic tree and the enhancer profiles we uncovered. I will discuss how using massively parallel single cell RNA-seq we find unexpected developmental states and heterogeneity among hematopoietic progenitor populations and the regulatory circuits driving hematopoietic decisions. Together, these result show that lineage commitment in hematopoiesis likely occur earlier than appreciated before and highlight the importance of further exploration of developmental decisions using single cell genome-wide approaches.

Short Bio:
Born in kibbutz Yizrael, Ido Amit did his PhD research with Dr. Yosef Yarden at the Department of Biological Regulation in Weizmann Institute, Israel. He was a postdoctoral fellow, at the Broad Institute of Harvard and MIT, Cambridge, USA. He is currently an assistant professor at the Department of Immunology in Weizmann. Research in his lab aims at understanding how mammals encode complex regulatory functions in their genomes with focus on haematopoiesis and immune responses. For this Ido's group combine development of novel methods and models for gene regulation and epigenetic research coupled to computational techniques, modern high throughput sequencing technologies and targeted experiments. His goal is to uncover fundamental principles of genome function and regulation and how they impact blood development and immune homeostasis in both health and disease. His lab was among the first to discover several fundamental mechanisms of transcriptional and chromatin regulation in hematopoiesis and immune response.
Sirt1 is SIRTanly important for induction of immunological Self-Tolerance and Prevention of Autoimmunity

Anna Chuprin1, Ayelet Avin1, Yonatan Herzig1, Ben Levi1, Asaf Sela1, Adi Jacob1, Moran Rathaus1, Clotilde Guyon3, Matthieu Giraud3, Michael McBurney4, Eystein S. Husebye5 & Jakub Abramson1

1Department of Immunology, Weizmann Institute of Science, Rehovot, Israel; 2Institute of Nanotechnology and Advanced Materials, Bar-Ilan University, Ramat-Gan, Israel; 3Department of Immunology, Institut Cochin, INSERM U1016, Université Paris Descartes, Paris, France; 4Ottawa Hospital Research Institute, Ottawa, Canada; 5Department of Clinical Science, University of Bergen, Bergen, Norway

Autoimmune regulator (Aire) is a unique transcriptional regulator that induces promiscuous expression of thousands of tissue-restricted antigens (TRAs) in medullary thymic epithelial cells (mTECs), a step critical for induction of immunological self-tolerance. Although several recent studies provided very important molecular insights into how Aire operates, a more comprehensive understanding of this process still remains elusive. Here we demonstrate that a lysine deacetylase Sirtuin-1 (Sirt1) is predominantly expressed in mature Aire+ mTECs, where it is required for expression of Aire-dependent TRA genes and a subsequent induction of immunological self-tolerance. Specifically our data demonstrate that Sirt1 and Aire are both highly and specifically expressed in mature mTECs, where they physically interact with each other and co-localize into nuclear speckles. We further demonstrate that both constitutive, as well as mTEC-specific inactivation of Sirt1 (or its catalytic capacity) almost completely impairs the expression of Aire-dependent, but not independent, TRA genes and results in organ-specific autoimmunity. Moreover we show that Sirt1 abolishes acetylation of Aire on multiple lysine residues, a step required for induction/maintenance of Aire’s transcription transactivation capacity. Our study elucidates a previously unknown molecular mechanism for Aire-mediated transcriptional regulation and uncovers a unique functional role for Sirt1 in preventing organ-specific autoimmunity.

Short Bio:
Dr. Jakub Abramson joined the Weizmann Institute of Science in 2011 as a senior scientist leading a research group in the Department of Immunology. Dr. Abramson completed his MSc degree at the Institute of Chemical Technology in Prague in 2000, followed by PhD studies at the department of Immunology of the Weizmann Institute of Science under the supervision of Prof. Israel Pecht (2000-2005). He then performed postdoctoral training at Harvard Medical School (2005-2010) in the lab of Profs Diane Mathis and Christophe Benoist. His research work has been published in leading immunology and biology journals including Cell, Immunity, Nature Immunology and Journal of Experimental Medicine.
Daily Light and Darkness Signals Regulate Bone Marrow Stem Cell Development and Leukocyte Production

Karin Golan1, Anju Kumari1, Aya Ludin1, Tomer Itkin1, Shiri Cohen-Gur1, Orit Kollet1, Eman Khatib1, Alexander Kalinkovich1 and Tsvee Lapidot1

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Blood forming stem cells are mostly retained in a quiescent, non-motile mode in the bone marrow (BM), shifting to a cycling, differentiating and migratory state to give rise to all mature leukocytes and blood cells as part of host defense and repair. How murine BM stem cells replenish the blood with mature cells while maintaining their BM reservoir of undifferentiated cells, remains poorly understood. We report that BM stem cell levels and leukocyte production are regulated via light and darkness signals. We identified two different daily BM stem cell peaks: one following light initiation, which is accompanied by increased stem cell egress and differentiation and the other after darkness, which is associated with increased stem cell proliferation, retention and reduced differentiation. Both peaks are preceded by increased reactive oxygen species (ROS) in stem cells which induce their cycling. The morning peak is initiated via norepinephrine (NE), leading to BM stem cell proliferation, differentiation and enhanced motility. Upon light termination TNFα and S1P levels are increased, leading to ROS augmentation, but also induce PGE2 signaling in BM stem cell niche regulating COX2high αSMA/Mac-1 macrophages, which restore low ROS levels, preventing stem cell egress and differentiation. Since murine leukocytes differentiate predominantly during day time they are more responsive to inflammatory challenges. Mimicking bacterial infections, endotoxin-induced mortality depends on the time of its administration, with high mortality in mice treated in the afternoon and low mortality following their midnight challenge. We found that LPS administration in the afternoon resulted in increased BM neutrophils and monocytes recruitment to the blood, in contrast to LPS injection at midnight, which induced only low levels of myeloid cells in the blood. In summary, we identified two daily peaks in BM stem cell levels which are regulated via light and darkness cues and concomitantly maintain dynamic host immunity and blood cell replenishment.
HAMLET and Related Alternatively-Folded Proteins with Tumoricidal Functions

Soyoung Min¹, Yongjing Xie¹, Nial P. Harte¹, Louise M. Sullivan¹,², André Brodkorb² and K. H. Mok¹,³

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HAMLET/BAMLET (Human/Bovine α-lactalbumin Made Lethal to Tumour cells) and its related partially unfolded protein–fatty acid complexes are novel biomolecular nanoparticles that possess relatively selective cytotoxic activities towards tumour cells [1,2]. Pioneered by C. Svanborg (Lund Univ, Sweden), significant progress has been made to deduce the underlying mechanism(s) of cell death brought about by HAMLET and other related complexes such as BAMLET [3]. From a protein biophysical chemists’ / structural biologists’ point of view, we have chosen to ask what would be the ‘minimal cytotoxic unit’ to give rise to this remarkable property. It is now well known that one of the key characteristics is the that the protein is partially unfolded - also resulting in endowing native proteins with additional functions in the alternatively folded states – but how important is this property in terms of the cytotoxic activity?

In relation to this, significant results have confirmed previous suggestions that the fatty acid moiety may be the ultimate cytotoxic agent, and that the protein moiety simply serves as carrier (or ‘mule’) by increasing its effective critical micelle concentration [4]. Through the examples of other cases, we show that the partially unfolded property of the protein as well as the nature of fatty acid binding is as much as important in determining the cytotoxicity – in other words, there is a delicate balance of structural malleability and related changes in binding affinities that determine the tumoricidal properties. Any efforts to design small-molecule mimics appear to require a better understanding of these structural aspects.

References:

Short Bio:
K. H. Mok joined Trinity College Dublin in 2006 and is currently a PI in the Trinity Biomedical Sciences Institute (TBSI) and the School of Biochemistry and Immunology. He finished a freshman year of Pharmacy at Seoul National University, then received a Bachelor’s degree (AB) in Biochemistry from the University of California, Berkeley, and a Ph.D. in Chemistry from Purdue University, Indiana, USA. He subsequently entered the biopharmaceutical industry as a Senior Research Scientist in protein therapeutics development and holds eight patent families. Prior to coming to TCD, Dr Mok worked as a KOSEF Fellow at the Korea Institute of Bioscience and Biotechnology (KRIIBB), then a postdoctoral research fellow (first on a UK Foreign and Commonwealth Office Chevening Scholarship) at the University of Oxford, Oxford Centre for Molecular Sciences (OCMS) and the Physical and Theoretical Chemistry Laboratory (PTCL) of the Department of Chemistry working jointly with Profs Christopher M. Dobson and Peter J. Hore. He is currently Director of Undergraduate Teaching and Learning of the School of Biochemistry & Immunology, and Director of the NMR Facility of the TBSI which serves as a core facility for Irish universities and industry. His research interests deal with the theories and applications addressing the “protein and peptide folding-misfolding-aggregation problem”, with an instrumentation specialty in biomolecular NMR spectroscopy, and with an applications / human disease relevance in cancer and separately, neurodegenerative diseases.
Regulatory and Pathogenic Role of Innate and Adaptive Immune Cells in Autoimmune Diseases

Kingston HG Mills, Shauna Quinn, Conor Finlay, Sarah Edwards, Niamh McGuinness, Patrick Kelly, Anna Malara and Caroline Sutton

Immune Regulation Research Group, School of Biochemistry and Immunology, Trinity Biomedical Sciences Institute, Trinity College Dublin, Dublin 2, Ireland

Cells of the adaptive immune system, especially IL-17-secreting CD4+ T cells (Th17 cells), are considered to be the key pathogenic lymphocytes in mediating inflammatory pathology in autoimmune diseases, such as multiple sclerosis (MS), psoriasis and rheumatoid arthritis. However, in the last few years there has been increasing evidence that innate-like lymphocytes, including γδ T cells, NK cells, NKT cells and innate lymphoid cells also have a key role in the pathogenesis of many autoimmune diseases. We have demonstrated that γδ T cells and a novel subset of Vγ4+ cells, which respond to IL-1 and IL-23 without TCR engagement, play a critical role in promoting the activation of Th17 cells through early IL-17 production in experimental autoimmune encephalomyelitis (EAE), a mouse model for MS. Furthermore, early IFN-γ from NK cells plays a role in the induction of EAE by promoting M1 macrophage activation and VLA-4 expression on CD4+ T cells, thus conferring encephalitogenic activity on T cells. The control of Th1 and Th17 cells is mediated by regulatory T (Treg) cells, but there is growing evidence that regulatory cells of the innate immune systems, that secrete IL-10, TGF-β and other anti-inflammatory mediators, also function to suppress pathogenic T cells in autoimmunity. We have shown that helminth parasites can attenuate EAE, not through Th2 or Treg-mediated suppression, but through activation of immunosuppressive macrophages and eosinophils. Furthermore, prophylactic treatment of mice with parasite products 1 and 3 weeks before induction of EAE attenuated clinical symptoms of disease. These findings add a new dimension to the hygiene hypothesis, and suggest that innate immune cells can be trained to become regulators of inflammatory responses.

Short Bio:
Kingston Mills is Professor of Experimental Immunology, School of Biochemistry and Immunology, Trinity College Dublin (TCD). He is Head of the Immunology, Inflammation and Infection research theme at TCD. He trained at as a Postdoctoral Fellow at University College London and the NIMR, Mill Hill, London, before joining the Scientific Staff of NIBSC, Herts, UK. He was appointed to a Personal Chair at Trinity College Dublin in 2001 and was Head of the School of Biochemistry and Immunology from 2008-2011. He is a co-founder of University spin-out companies Opsona Therapeutics and TriMod Therapeutics. He heads an active research team focusing on T cells in infection and autoimmunity.
Structural and Functional Studies of Membrane Proteins Using the Lipidic Cubic Phase

The lipidic cubic phase or in meso crystallization method, which is used to grow well-diffracting crystals of membrane proteins for X-ray crystallographic structure determination, has recently seen a rapid increase in worldwide adaptation and success. The in meso method allows membrane proteins to be embedded in lipid bilayers mimicking their natural environment during the entire crystallization process. Therefore the method facilitates crystallization by stabilizing membrane proteins as well as making their entire surface available for the formation of crystal contacts, often resulting in increased crystallization success rates and higher quality crystals. Here the usefulness of the method will be demonstrated using structural and functional studies of the integral membrane protein DgkA (diacylglycerol kinase).

Short Bio:
Dr Lutz Vogeley graduated with a German diploma degree in Molecular Biology and Biochemistry from the Friedrich Schiller University Jena in 2001. In 2005 he obtained his PhD in Biological Sciences, specifically X-ray crystallography, from the University of California, Irvine, where he continued to work as a postdoctoral researcher until the Fall of 2006. He then received EMBO and Marie-Curie fellowships to work as a postdoctoral researcher at the ETH Zurich on crystallographic studies of ribosome complexes. Since 2012 he has been working as a postdoctoral researcher in the Martin Caffrey group at the Trinity Biomedical Sciences Institute (TBSI) on X-ray crystallographic studies of membrane proteins.
Immune Profiling of Uninfected Irish Women with Iatrogenic Exposure to Hepatitis C Virus

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Individuals exposed to hepatitis C virus (HCV) via iatrogenic transmission provide a unique opportunity to study mechanisms of viral resistance in well-defined human cohorts. In Ireland two single-source HCV outbreaks associated with contaminated anti-D immunoglobulin occurred, the first in 1977-9 and the second in 1991-3. To explore innate immune responses that confer viral resistance, we studied immune function in uninfected recipients of contaminated anti-D immunoglobulin who tested negative for anti-HCV antibodies (exposed uninfected, n = 16). We hypothesised that this cohort would show enhanced antiviral interferon (IFN)α responses. Analysis of STAT phosphorylation following IFNα stimulation identified enhanced STAT3 signalling in natural killer (NK) cells of the exposed uninfected individuals compared to matched unexposed controls (n = 9; mean MFI fold change 2.81 vs 1.96, P-value = 0.0034). This enhanced responsiveness in NK cells was specific to STAT3 and no difference in STAT1 phosphorylation was evident. Furthermore, NK cells from exposed uninfected individuals had increased production of IFNγ in NK cell functional assays, supporting a general enhancement of NK cell activity in these individuals. Our results describe a unique innate cell phenotype in exposed uninfected individuals that may represent a human model of enhanced innate cell function.

Short Bio:
I am a postdoc working on hepatitis C virus immunology within the Comparative Immunology Group in the School of Biochemistry and Immunology. My main research interests are: 1) The effect of chronic infection on immune responses; and 2) Innate signalling in highly resistant individuals. Previously I was based at the MRC - University of Glasgow Centre for Virus Research (working with Dr. McLauchlan and Dr. Patel) where my focus was investigating the genotype-specific host response to HCV and biological aging in chronically infected patients. Prior to this I completed my Ph.D. at the University of Otago, NZ, studying host responses to mycobacterial infections in large ruminants.
Membrane Protein Structure-Function Studies with Lipid Mesophases

One of the primary impasses on the route that eventually leads to membrane protein structure through to activity and function is found at the crystal production stage. Diffraction quality crystals, with which structure is determined, are particularly difficult to prepare currently when a membrane source is used. The reason for this is our limited ability to manipulate proteins with hydrophobic/amphipathic surfaces that are usually enveloped with membrane lipid. More often than not, the protein gets trapped as an intractable aggregate in its watery course from membrane to crystal. As a result, access to the structure and thus function of tens of thousands of membrane proteins is limited. In contrast, a veritable cornucopia of soluble proteins have offered up their structure and valuable insight into function, reflecting the relative ease with which they are crystallized. There exists therefore an enormous need for new ways of producing crystals of membrane proteins. One such approach makes use of lipid liquid crystalline phases (mesophases). I will describe the method, our progress in understanding how it works and recent community-wide advances in applying the method for membrane protein structure determination. The use of bicontinuous mesophases for the functional characterization of membrane proteins and for serial femtosecond crystallography using an X-ray free electron laser will also be described.

Short Bio:
Martin Caffrey grew up in Dublin and was awarded a first-class honours degree in Agricultural Science at University College Dublin in 1972. With an MS in Food Science and a PhD in Biochemistry from Cornell University, Ithaca, New York, he embarked on a professorial career in the Chemistry Department at The Ohio State University, Columbus, Ohio. In 2003, he returned to Ireland to establish a multi-disciplinary programme in Membrane Structural and Functional Biology at the University of Limerick with funding from Science Foundation Ireland and the USA National Institutes of Health. Its mission is to establish the molecular bases for biomembrane assembly and stability and to understand how membranes transform and transmit in health and disease. In 2009, his research group moved to Dublin when Prof Caffrey received a Personal Chair at Trinity College Dublin with joint appointments in the School of Medicine and the School of Biochemistry and Immunology.
Characterizing the Dynamics of T-Helper Cell Differentiation Using Live Cell Imaging and Single-Cell Analysis

In order to study the decision making process of differentiating CD4+ T cells, we developed a methodology that facilitates live cell imaging of primary T cells cultured individually or in small numbers (up to ~10 cells) over long time periods. Our experimental system combines standard cell culture plates with PDMS based arrays in which primary T cells are trapped, activated and continuously monitored for up to 96 hours. We used this system to study CD4+ expansion and gene expression, and analyze the influence of T-T interactions on these processes.

We show that the activating cells exhibit four expansion patterns: Fast, Intermediate and Slow expansion and Non-Responders. We show that the ‘Slow’ group has the highest IL2-GFP expression and is CD44hiCD62Llow after 96 h, while the ‘Fast’ and ‘Int.’ show lower IL2-GFP expression and are CD44hiCD62Lhi after 96 h. We also show that cell proliferation and CD44 expression are cell-autonomous processes, while CD62L expression is non autonomous and encouraged by T-T interactions.

Short Bio:
In my undergraduate studies I studied biology in the Ben-Gurion University. I conducted my MSc research in Nir Freidman’s Lab in the Immunology department at the Weismann institute where I’m currently conducting my PhD research studying CD4 T cell activation and differentiation.
Lung Resident Memory CD4+ T Cells (TRM) Play A Critical Role in Protective Immunity to Bordetella Pertussis

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2 Department of Physiology, Trinity College Institute of Neuroscience, Trinity College Dublin, Dublin, Ireland

CD4+ T cell responses play a key role in natural and vaccine-induced immunity to Bordetella pertussis. However, the role of local pulmonary versus systemic T cells in protective immunity is unclear. In this study we used FTY720 (Fingolimod) to block T-cell egress from draining lymph nodes. We showed that treatment of mice with FTY720 greatly impaired clearance of a primary infection with B. pertussis and this was associated with a significant reduction in the numbers of lung infiltrating B and T cells, especially naive (TN) and central memory (TCM). However, T cell subpopulations in the lungs recovered during the course of infection, but these were exhibited exclusively CD62L-CD44hi effector memory (TEM) phenotype.

We also examined the role of lung T cells in protective immunity induced in mice immunized with pertussis whole cell or acellular vaccines (wP and aP). We found a significant increase in infiltrating T cells in the lungs after immunization with wP, but not aP, and these were mainly resident memory CD4+ (TRM) cells. Treatment with FTY720 significantly reduced the number of B cells, naive T and TCM cells infiltrating the lungs but did not substantially compromise bacterial clearance post challenge in immunized mice, suggesting that resident memory T cells population that may proliferate locally mediated adaptive immunity to B. pertussis infection in the lungs.

This study shows that the protective immunity to B. pertussis is mediated by specific CD4+ TRM cells and that wP is a more potent inducer of specific CD4+ effector memory cells in comparison to aP which preferentially reside in the lungs.

Short Bio:
Dr Mieszko Wilk graduated with MSc in Biochemistry from the Jagiellonian University in Krakow, Poland. In 2007, he was awarded the Irish Research Council for Science, Engineering and Technology (IRCSET) scholarship to carry out his research at the Regenerative Medicine Institute (REMEDi) where he obtained his PhD in Biomedical Sciences from the National University of Ireland, Galway for research in novel gene therapeutic approaches to prolong corneal allograft survival. In 2011, he moved to Dublin to work as a research assistant in Dr Rachel McLoughlin group at the Trinity Biomedical Sciences Institute (TBSI) on manipulation of autophagy in phagocytes by Staphylococcus aureus. Currently, Mieszko is working as a postdoctoral researcher under the mentorship of Prof. Kingston Mills in the Immune Regulation Research Group at the TBSI. His research is focused on the mechanisms involved in clearance of Bordetella pertussis infection and establishment of long-term memory after infection and vaccination.
Elucidating the Effects of the PD-1 Pathway on the Dynamic Interactions Between Cytotoxic T Cells and Their Targets

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Melanoma tumor cells can evade immune destruction by engaging the inhibitory PD-1 receptor of T cells. Blockade of PD-1 or its ligand PDL1 releases this inhibition and improves tumor rejection dramatically. The recent approval of anti-PD-1 by the FDA is transforming the treatment of advanced melanoma, but strategies to further improve response rate are sought. PD-1 engagement is known to suppress T cell proliferation and inhibit cytokine release but it is unclear whether and how it directly compromises the lytic activity of CTLs inside tumors. We propose to address these questions by imaging the dynamic interaction of OVA-specific OT-I CTLs with OVA-expressing B16 melanoma cells in vitro (using spinning-disk confocal microscopy, and intravitaly (using two-photon microscopy) while manipulating PD1 engagement.

Our preliminary findings indicate that antiPD1 treatment enhanced tumor rejection by mature CTLs and increased the frequency of killing events in vitro, indicating that PD-1 signaling directly affects CTL-mediated cytolysis. Imaging CTL-tumor interactions we unexpectedly found that PD-1 blockade accelerated overall CTL speed, suggesting that CTLs disengage from target cells faster, or are chemotactically recruited to attack select targets. We also observed CTL clustering around dying tumor cells.

We propose to quantify the influence of PD-1 engagement on CTL infiltration, the dynamics of CTL polarization, synapse formation, degranulation and the kinetics of target cell killing and disengagement. We will also study the molecular signals employed in clustering of CTLs around select targets.

Better understanding of PD-1 inhibition at the site of its action could advance immunotherapy by suggesting new target molecules, processes and strategies for combination therapies.

Short Bio:
In my undergraduate studies I studied biochemistry and food sciences in the Faculty of Agricultural, Food and Environmental Quality Science, The Hebrew University of Jerusalem. I conducted my MSc research in Prof. Orna Halevy’s lab in the Animal and Veterinary Sciences department at the Faculty of Agricultural, Food and Environmental Quality Science, The Hebrew University of Jerusalem. I’m currently conducting my PhD research in Guy Shakhar’s lab in the department of immunology of the Weizmann Institute studying the effects of PD-1 blockade on anti-tumoral CTL activity.
Regulatory Functions of B Cells In The Suppression of Autoimmunit.

Classically, B cells are considered to be potent antibody producers. However, specific B-cell subsets can also negatively regulate T cell immune responses, and have been termed regulatory B cells. We have previously demonstrated that helminths can expand a B regulatory cell population that can suppress allergic inflammatory conditions in mice in an IL-10-dependent manner. We undertook RNA microarray analysis of Breg cells from helminth-infected mice and identified genes previous not associated with Bregulatory cells. Such genes were involved in activation (Tlr7), migration (Cxcr7) and functions (Pdl1) of Breg cells. These Breg cell genes were functional in the capacity of the cells to suppress allergic lung inflammation or experimental autoimmune encephalomyelitis in mouse models. B regulatory cells suppressed inflammation via Tregulatory cells and T follicular helper cells in IL-10 dependent and independent mechanisms.

Short Bio:
Padraic G. Fallon is Stokes Professor of Translational Immunology in the School of Medicine, Trinity College Dublin. His research uses both mouse models and patient studies to elucidate new mechanisms of modulation of immunity that can regulate inflammation and have therapeutic potential. He completed his PhD in 1995 (University of Wales) in immunoparasitology, and was awarded a Wellcome Trust Fellowship in University of Cambridge, UK - researching immune-modulating helminth molecules - before returning to Trinity College Dublin in 2001. Fallon leads research programmes in allergic lung and skin inflammation, and inflammatory bowel disease. Fallon has published over 130 research publications in leading international journals in the field of immunology, including Nature, Science, Science Translational Medicine, Nature Immunology, Nature Genetics, Nature Communications, Journal of Experimental Medicine and Immunity.
The 2nd Joint Symposium of the Trinity Biomedical Sciences Institute and The Weizmann Institute of Science

Richard K. Porter
TBSI

The Role of Mitochondrial Uncoupling Proteins (UCP's) in Thymocyte/T-Cell Development and Function

The thymus is the site of thymocyte maturation and development. After a rigorous self and non-self antigenic selection process, naïve T-cells are released from the thymus to the circulation and peripheral lymph sites. We have demonstrated that specific members of the mitochondrial inner membrane transporter family, namely the uncoupling proteins (UCP's), are present in thymocytes/T-cells, and that the absence of these transporters effect T-cell development and function. The research has direct relevance to understanding immune cell function and modulation and has clinical implications for cancer and autoimmune diseases.

Reference:

Short Bio:
Education and Qualifications: B.A. (Moderatorship) in Biochemistry, Trinity College Dublin (1986); Ph.D. Biochemistry, Trinity College Dublin (1991); Employment: Elected Head of Biochemistry (2011 to present); Associate Professor in School of Biochemistry and Immunology (2011); Senior Lecturer in School of Biochemistry and Immunology (2006); Permanent Lecturer in Biochemistry, Trinity College Dublin (2000-present); Lecturer in Biochemistry, Trinity College Dublin (1997-2000); Health Research Board of Ireland Post-doctoral Fellow (1994-1997) based in The Department of Biochemistry, University of Dublin, Trinity College Dublin; Postdoctoral Researcher, Department of Biochemistry, University of Cambridge, UK. (1991-1994); Honours and Awards: Provost's Teaching Award Commendation (2014); Fellow of Trinity College Dublin (2007); Professional Achievements and Responsibilities: Current Editor with Biochimica Biophysica Acta Bioenergetics, Elsevier Publications. Guest editor for: (1) Biochemical Society Transactions, Portland Press; (2) Biochimica Biophysica Acta Bioenergetics (Special issue), Elsevier Publications. (3) EBEC Short Reports; Elsevier Publications. Scientific advisor to Iperboreal Pharma Pescara Italy. Member of the Nominating Committee for the International Union of Biochemists and Molecular Biologists (IUBMB); Member of the European Bioenergetics Committee. Treasurer of the Irish Area Section of the Biochemical Society (2010- 2013).
Ubiquitylation in Differentiation

Ron Benyair and Yifat Merbl
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Protein post-translational modifications in the cell can take on many forms, including the addition of protein and chemical-based modifications. The most prevalent form of chemical-based modifications in the secretory pathway is N-linked glycosylation. N-glycosylated proteins are commonly known as glycoproteins and these undergo a stringent process of quality control in the endoplasmic reticulum. Examination of these quality control processes offers a unique view of cellular stress states in various immunological conditions.

Short Bio:
I have finished my PhD studies at Tel Aviv University in the field of cell biology, where I conducted research into glycoprotein quality control in the endoplasmic reticulum and post-ER compartments. I am currently conducting a post-doc in the laboratory of Dr. Yifat Merbl where I am studying post translational modifications in various cellular scenarios.
γβ T Cells, a Novel T Cell Subset With A Pathogenic Role in IL-17-Mediated CNS Autoimmunity

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Vγ4+ T cells have been identified as the main IL-17-producing γδ T cell in the CNS of mice with experimental autoimmune encephalomyelitis (EAE), an animal model of multiple sclerosis. This study demonstrates that Vγ4+ T cells are present in T cell receptor (TCR)δ−/− mice, and these Vγ4+ T cells co-express TCRβ. The data reveals that Vγ4β T cells respond to IL-1β and IL-23 stimulation in the absence of TCR engagement to produce IL-17 and express the master transcription factor, RORγt. Furthermore, Vγ4β+ T cells were found in the brains of TCRδ−/− mice, and together with Vγ4δ+ T cells in the brains of wild type (WT) mice with EAE. Although, the course of EAE is somewhat reduced in TCRδ−/− compared with WT mice, depletion of Vγ4+ T cells from TCRδ−/− and WT mice significantly attenuated clinical disease and weight loss in mice with EAE. Anti-Vγ4 treated mice with EAE had a significantly reduced frequency of infiltrating IL-17+, IFN-γ+ and IFN-γ+IL-17+ CD4+ T cells into CNS. Furthermore, in the adoptive transfer model of EAE, depletion of Vγ4+ cells from lymph node and spleen cells from TCRδ−/− mice significantly impair their ability to induce EAE, with a reduction in inflammatory T cells infiltrating the CNS. Our study has identified a novel γβ T cell subset, Vγ4β T cells, which together with conventional Vγ4δ T cells, play a critical role in the pathogenesis of EAE through innate IL-17 production, enhancing Th17 and Th1 activation and migration into the CNS to mediate inflammation and autoimmunity.

Short Bio:
Sarah Edwards graduated with a B.A. (Mod) in Biochemistry and Immunology from Trinity College Dublin in 2011. In 2011, she was awarded a PRTLI scholarship to carry out her research in the Immune Regulation research group, Trinity College Dublin. Under the supervision of Prof. Kingston Mills, she is completing her PhD on the regulation and function of T cells in experimental autoimmune encephalomyelitis.
Macrophage Migration Inhibitory Factor (MIF), a Unique Cytokine & Human Disease

The Donnelly Laboratory works encompasses three defined areas:
Defining key regulatory pathways which drive chronic inflammation
Personalised Medicine and how genetic expression profiles predict prognosis and response to therapy in disease.
Enhancing our understanding of how pathogens evade the host's immune defenses.
This talk will illustrate these research interests via our work over the years in defining the key regulatory roles for the pro-inflammatory cytokine, Macrophage Migration Inhibitory Factor (MIF). This body of work defines the important role for this protein in a variety of key cellular processes translating to a variety of diseases and presents persuasive data supporting academia and industries current interest in targeting this cytokine as an anti-inflammatory and anti-cancer therapeutic agent.

Short Bio:
Seamas Donnelly is Professor of Medicine at TCD. He is an international leader in Translational Medicine whose research encompasses defining key regulatory processes driving disease to how pathogens evade the host immune response. He is a medical graduate of University College Galway and was funded via the Wellcome Trust to undertake postgraduate studies at the University of Edinburgh and the Picower Institute, New York. Returning to Ireland in 2001, he has generated > €35 million grant funding either as PI or CoPI. He was recently awarded an honorary Professorship by the University of Edinburgh for international leadership in Translational Medicine. He is currently Editor-in-Chief of the Quarterly Journal of Medicine (QJM).
The Role of Dicer and Micrornas in Microglia of the Developing and Adult Brain

We recently developed experimental systems that allow to investigate microglia functions during development and adulthood (Goldmann et al., 2013; Yona et al., 2013). Specifically, we took advantage of the uniquely high and robust expression of the chemokine receptor CX3CR1 in microglia cells (Jung et al., 2000, to target expression of constitutive (Cre) or tamoxifen (TAM)-inducible (Cre-ER) Cre recombinase expression to these cells (Yona et al., 2013). When compared to other tissue macrophages, microglia are defined by unique gene expression signature and enhancer usage (Lavin et al., 2014), but also microRNA expression profiles. The latter short non-coding RNAs are believed to be critical for the establishment and maintenance of cell identities and fine-tune activation states. To investigate the role of microRNAs in microglial quiescence we generated mice that harbour a microglia-restricted deficiency of dicer, the enzyme that is required for the production of functional microRNAs. Interestingly and defying anticipation, TAM-induced dicer ablation in CX3CR1CreER:dicer-/- mice did not result in an overt phenotype unless the animals are challenged. Microglia quiescence can thus be maintained in absence of the regulation by microRNAs and we are currently studying the rewiring of their gene expression profile to cope with the absence of this important regulatory network. In stark contrast, microglial dicer ablation during development leads to profound microglia hyper-activation in the adult, associated with astrocytosis and eventually culminating in an ALS-like motor neuron defect (Varol et al. in preparation). Collectively, the differential sensitivity of embryonic and adult microglia to dicer absence highlights the fundamental changes this cellular compartment undergoes with time.

References:
Hematopoietic Stem Cells and Their BM Stromal Microenvironment Share a Dynamic Inverse Metabolic State via Mitochondria Transfer

Hematopoietic stem and progenitor cells (HSPC) are mostly retained in the bone marrow (BM) in a ROSlow quiescent mode via adhesion interactions with their stromal microenvironment. In order to generate new mature blood cells, HSPC detach from their microenvironment and start to proliferate and differentiate in a ROShigh state. However, the metabolic cross talk between the BM stromal cells and quiescent or cycling HSPC is poorly understood. The bioactive lipid S1P is an important inducer of ROS in HSPC, increasing their motility. Augmentation of S1P levels in the murine BM, resulted in increased HSPC levels via elevated ROS production and cell cycling. Unexpectedly, we discovered an opposite effect of S1P on BM stromal cells, which contained less mesenchymal stem and progenitor cells (MSPCs) and also lower ROS levels. These results suggest an inverse metabolic state between BM HSPC and their stromal microenvironment. As expected, mice with reduced S1P levels exhibit lower levels of BM HSPCs accompanied by reduced ROS levels. Concomitantly, S1P low mice have BM MSPCs with increased ROS levels and higher colony-forming unit fibroblasts (CFU-F) potential in vitro. This data suggests that the dynamic, inverse metabolic state between HSPC and the stromal microenvironment is induced by energy transfer between the two populations. Since the main organelle responsible for massive energy production is the mitochondria, we established chimeric mice with GFP marked mitochondria of either hematopoietic or BM stromal compartment. We report that mitochondria are preferentially transferred from BM hematopoietic cells to their stromal microenvironment and almost not vice versa. Co-culture of primary BM stromal murine cells with mitochondria GFP marked hematopoietic cells show that this transfer is dependent on connexin gap-junctions and on calcium signaling. Altogether, we have discovered a dynamic, opposite metabolic state between BM HSPCs and their supporting stromal microenvironment during quiescence, proliferation and differentiation of the two populations, which are both ROS regulated on a one population at a time basis. Thus, either blood cell production or bone development takes place at the expense of the other.

Short Bio:
Incumbent of the Edith Arnoff Stein Professorial Chair in Stem Cell Research
Prof. Tsvee Lapidots laboratory investigates how blood forming stem cells (both normal and leukemic) migration and development are regulated. These studies include the dynamic interactions between the nervous and immune systems, blood and bone forming stem cells and the bone marrow microenvironment.

Born in Jerusalem Israel, Prof. Lapidot received his B.Sc. degree from the Hebrew University, and his M.Sc. and Ph.D. from the Weizmann Institute. In 1990, he moved to Toronto, Canada, where he spent four years as a postdoctoral fellow at the Hospital for Sick Children in the laboratory of Prof. John Dick. In Toronto he established functional preclinical models for normal (Science 92) and leukemic (Nature 94) human stem cells, in transplanted immune deficient mice. He returned to the Weizmann Institute's Department of Immunology as a Senior Scientist in 94; he was appointed Associate Professor in 2001 and Professor in 2006.
Post Translational Modification (PTM) Profiling: From Global Patterns to Mechanistic Insight of PTM Regulation

Ubiquitin and ubiquitin-like (Ubl) modifications are implicated in every aspect of cellular regulation but we still lack comprehensive understanding of their broad functions and the range of their cellular targets. We recently developed a quantitative, rapid and tractable high-throughput system which enables monitoring of multiple PTMs of thousands of proteins in parallel, under conditions that are relatively close to those of the complex cellular environment. The system makes use of biochemically-active cellular extracts applied to protein microarrays. Using the PTM profiling approach we generated a map of Ubl interactions and profiled the protein targets of ubiquitin and six additional Ubl modifiers (SUMO, NEDD8, FAT10, UFM1 and ISG15) in mitosis1. The Ubl interaction network exhibited a nonrandom structure with most substrates mapping to a single Ubl. We identified distinct molecular functions for each Ubl, suggesting divergent biological roles. The analysis also predicted an unparalleled number of putative substrates involved in mitotic regulation, which await further investigation.

Interestingly, we found a class of kinases in our network which was especially enriched in the set of Ubl targets. Among them was the cyclin b1-Cdk1 complex. Indeed, we were able to show that cyclin B1 is modified by SUMO in a phosphorylation-dependent manner, prior to mitosis entry. Further, we show that the SUMOylation of cyclin B1 controls spatial and temporal events required for mitotic progression. Our analysis highlights the ability of the 'PTM profiling' approach to reveal not only global patterns of regulation but also novel mechanistic insight of fundamental cellular processes.

Short Bio:
Dr. Yifat Merbl completed her BS summa cum laude in Computational Biology at Bar Ilan University in 2003. She earned an MSc in Immunology at the Weizmann Institute in 2005 with Prof. Irun Cohen.
She joined the first PhD program in Systems Biology at Harvard Medical School, completing her PhD there in 2010. She stayed on at Harvard as a postdoctoral fellow until joining the Department of Immunology at the Weizmann Institute in 2014.
She is the incumbent of the Leonard and Carol Berali Career Development Chair.
Dr. Merbl has developed a high-throughput system to identify the targets of protein modifications on a proteome-wide scale and under various cellular and physiological conditions. With this system, her lab now explores molecular mechanisms underlying the biology of protein modifications in health and disease, focusing primarily on cancer and immune regulation.
Macrophages are specialized in ingesting pathogens and orchestrate inflammatory responses. In recent years it was shown that these cells also contribute to development, tissue homeostasis and regeneration. In order to study functions of tissue macrophages in their physiological tissue context, we generated mice harboring transgenes encoding either constitutive or inducible Cre recombinase in their CX3CR1 loci. Here we utilized these mice to delete the X chromosome-linked nuclear transcription factor methyl-CpG binding protein 2 (MeCP2) in macrophages. MeCP2 is strongly linked to a neuro-developmental disorder, the Rett syndrome (RTT), which predominately occurs in females during early childhood. Mice harboring a MeCP2 deletion in most mononuclear phagocytes do not develop symptoms of RTT, and MeCP2-null microglia do not show overt inflammatory phenotype. However, unexpectedly we found that the animals displayed obesity. Importantly, the phenotype is also seen in mice displaying a more restricted, tamoxifen-induced MeCP2 deletion that targets only long-lived CX3CR1-expressing macrophages. We found that the spontaneous obesity, which is associated with accumulative insulin resistance, results from reduced energy expenditure. It is hence likely due to the impact of the MeCP2 deletion in macrophages of brown adipose tissue (BAT), the primary thermogenic tissue in the organism. Indeed, the latter is malfunctioning in CX3CR1CreER:MeCP2fl/Y mice, as evident by enlargement and increased fat load of brown adipocytes and decreased levels of the thermogenic gene UCP1. Conversely, MeCP2-deficient macrophages residing in the BAT, display reduced expression of the predicted MeCP2 target, the enzyme tyrosine hydroxylase (TH), that is required for catecholamine (neuroepinephrine) production and the communication with adipocytes. In summary, we describe a novel mechanism for macrophage-dependent steady-state maintenance of thermogenesis and metabolic balance.

Short Bio:
Yochai Wolf was born in Hadera, Israel in 1983. In 2005, he started his undergraduate degree in psychology and biology in the Hebrew University in Jerusalem, graduating in 2008. He then continued to an M.Sc in neuroscience in the Hebrew University, and since 2010 he is part of Prof. Steffen Jung’s lab in the Weizmann Institute as PhD student. Yochai studies the origin and function of various tissue macrophages, including the role of adipose tissue macrophages in the regulation of metabolism and obesity, contributions of microglia and monocyte-derived macrophages within the central nervous system, and the origin of newly described cardiac macrophages. He currently lives in Kadima-Tzoran, married, and has one boy.