Medical Research at the Cutting Edge

Progress in the fight against Inflammatory Diseases and Cancer

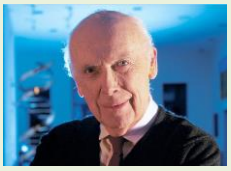
July 27-29th 2014

Trinity Biomedical Sciences Institute

Venue - Chartered Accountants House, 47-49 Pearse Street

The first joint yearly conference of the Trinity Biomedical Sciences Institute and The Weizmann Institute of Science will present cutting edge progress in the study of mechanisms of inflammation and cancer in the two institutes. The conference will involve keynote presentations by five Nobel Laureates. There will also be a discussion on research commercialisation, an area where the Weizmann truly excels.

Keynotes will be delivered by



James Watson

Aaron Ciechanover

Bruce Beutler

Ada Yonath

Jules Hoffmann

Marc Feldmann

James Watson, the 1962 Nobel Prize winner in Physiology and Medicine, (the double helix structure)
Aaron Ciechanover, the 2004 Nobel Prize winner in Chemistry, (ubiquitin-mediated protein degradation)
Bruce Beutler, the 2011 Nobel Prize winner in Physiology and Medicine, (the activation of innate immunity)
Ada Yonath, the 2009 Nobel Laureate in Chemistry, (studies on the structure and function of the ribosome)
Jules Hoffmann, the 2011 Nobel Prize winner in Physiology and Medicine, (the activation of innate immunity)
Marc Feldmann, the 2003 winner of the Albert Lasker Award (Clinical Medical Research)
and 2014 winner of the Gairdner Prize, (the discovery of anti-TNF therapy for rheumatoid arthritis).

TBSI-Weizmann 2014
Medical research at the cutting edge –
Progress in the fight against inflammatory diseases and cancer

Sunday 27th July 2014

- 5.30 pm **OPENING OF SYMPOSIUM – Luke O'Neill and David Wallach**
- Welcome to TCD: **Professor Vinny Cahill, Dean of Research**
- Welcome address: **Professor Mary Daly**, President of the Royal Irish Academy
- Signing of Memorandum of Agreement for student exchanges:

  For the Weizmann Institute: Professor Mordechai Sheves (Vice President for Technology Transfer) and Professor Irit Sagi, (Dean of the Weizmann's Graduate School)
  For Trinity College Dublin: Professor Juliette Hussey (Vice President for Global Relations) and Professor Luke O'Neill (Director, TBSI).

- 5.50pm Keynote Nobel Presentation 1: **James Watson** (CSH, USA)
  Why Metformin Prevents Much of Incurable Cancer

- 6.20pm Special Guest Speaker - **Doug Golenbock** (UMass, USA)
  The innate immune response in malaria is driven by DNA and enhanced by the crystal hemozoin.

- 6.50pm Keynote Nobel Presentation 2: **Aaron Ciechanover** (Technicon, Israel)
  The ubiquitin proteolytic System: From basic mechanisms through human diseases and on to drug development.

Monday 28th July 2014

- 9am — Keynote Nobel Presentation 3: **Jules Hoffmann**
  (introduced by Douglas Golenbock)
  Innate Immunity : From Flies to Humans

Session 1: Immunology/Inflammation I - Chair: Idit Shachar

- 9.30am — **Luke O'Neill** (TBSI)
  Metabolic reprogramming in innate immunity
- 9:55am — **Ido Amit** (Weizmann Inst)
  Unbiased characterization of the immune system using massively parallel single cell RNA-Seq.
- 10:20am — **Andrew Bowie** (TBSI)
  Recognition of pathogen DNA and innate immune gene regulation by PYHIN proteins
- 10.45am — **David Wallach** (Weizmann Inst)
  Regulation of immune response by signaling proteins activated by the TNF family
- 11.10am — BREAK

Session 2: Immunology/Inflammation/Drug Development II - Chair: Steffen Jung

- 11.40am — **Orla Hardiman** (TBSI)
  Why Clinical Trials in ALS Have Failed: The Hidden Inflammatory Signal that Drives ALS
- 12.05am — **Idit Shachar** (Weizmann Inst)
  Molecular Mechanisms Regulating B cell survival in Health and Disease.
- 12.30pm — **Cliona O'Farrelly** (TBSI)
  Innate Immune Resistance to Hepatitis C Virus: a Role for the JAK/STAT Pathway?
- 12.55 — Special Guest Speaker: **Marc Feldmann** (Oxford)
  (Introduced by David Wallach)
  The discovery of anti-TNF therapy for rheumatoid arthritis
- 13.30 — BREAK

Session 3: Immunology/Inflammation III - Chair: Andrew Bowie

- 14.30 **Eran Elinav** (Weizmann Inst)
  The role of host-microbiome interactions in the metabolic syndrome
- 14.55 **Kingston Mills** (TBSI)
  Function and regulation of IL-17 cytokine family in inflammation and autoimmunity
- 15.20 **Yehuda Kamari** (Sheba Med Center)
  The Role of Interleukin-1α in Metabolic Inflammation
- 15.45 **Padraic Fallon** (TBSI)
  Innate cell priming of adaptive inflammatory diseases.
- 16.10 BREAK

Session 4: Immunology/Inflammation IV - Chair: David Wallach

- 16.35 **Aisling Dunne** (TBSI)
  Inflammasome activation, from infection to inflammatory disease
- 17.00 **Steffen Jung** (Weizmann Inst)
  Macrophage Contributions to Gut and Brain inflammation
- 17.25 **Alan Irvine** (TCD)
  Early mechanisms in atopic disease: genetic and functional insights
- 17:50 Keynote Nobel Presentation 4: **Bruce Beutler** (Texas)
  (Introduced by Eran Elinav)
  Finding genes that affect immunity by "real time" positional cloning.
- 18.45 Musical Performance by **Yehuda Kamari**

Tuesday 29 July 2014

- 9.00am Keynote Nobel Presentation 5: **Ada Yonath** (Weizmann Ins., Israel) (Introduced by Martin Caffrey)
  Combating species-specific antibiotics resistance?

Session 5: Cancer and anti-cancer therapy I- Chair: Eran Elinav

- 9.30am **Yossi Yarden** (Weizmann Inst)
  HER2 and EGFR: at last, cancer therapy meets systems biology
- 9.55am **Martin Caffrey** (TBSI)
  A marvelous mesophase
- 10.20 **Ashraf Brik** (Weizmann Inst and BRU)
  Chemical Biology with Deubiquitinases
- 10.45 **Seamus Martin** (TCD)
  Inflammatory Outcomes from Cell Death Signals
- 11.10 BREAK

Session 6: Cancer and anti-cancer therapy II - Chair: Yossi Yarden

- 11:30 **Paul Browne** (TCD)
  Immunophenotyping and haematological neoplasms
- 11.50 **John O'Leary** (TCD)
  New insights into the metastatic cascade: where cancer and immunology meet
- 12.10 **Yinon Ben-Neriah** (Weizmann Inst)
  Parainflammation effects in cancer
- 12.30 **Thorfinnur Gunnlaugsson** (TBSI)
  Targeting cancer cells with supramolecular nanotechnology: The use of luminescent ruthenium polypyridyl complexes and gold nanoparticles
- 12.50 **Gavin Davey** (TBSI)
  Targeting mitochondrial fusion/fission dynamics in tumor cells

- 13.10 **Irit Sagi** (Weizmann Inst)
  Controlling extracellular remodeling as a strategy to fight inflammatory diseases and cancer

- 13.30 BREAK

Session 7: Technology Transfer – reaping the benefits of outstanding research -
Chair: Kingston Mills

- 14.20 **Mark Ferguson** (Director General, Science Foundation Ireland)
  Impact from excellent research: programmes, metrics and international benchmarking of small advanced nations

- 14.50 **Mudi Sheves**
  (The Weizmann Institute's vice president for technology transfer)
  The Weizmann Institute of Science for the Benefit of Society: Technology Transfer Mechanism

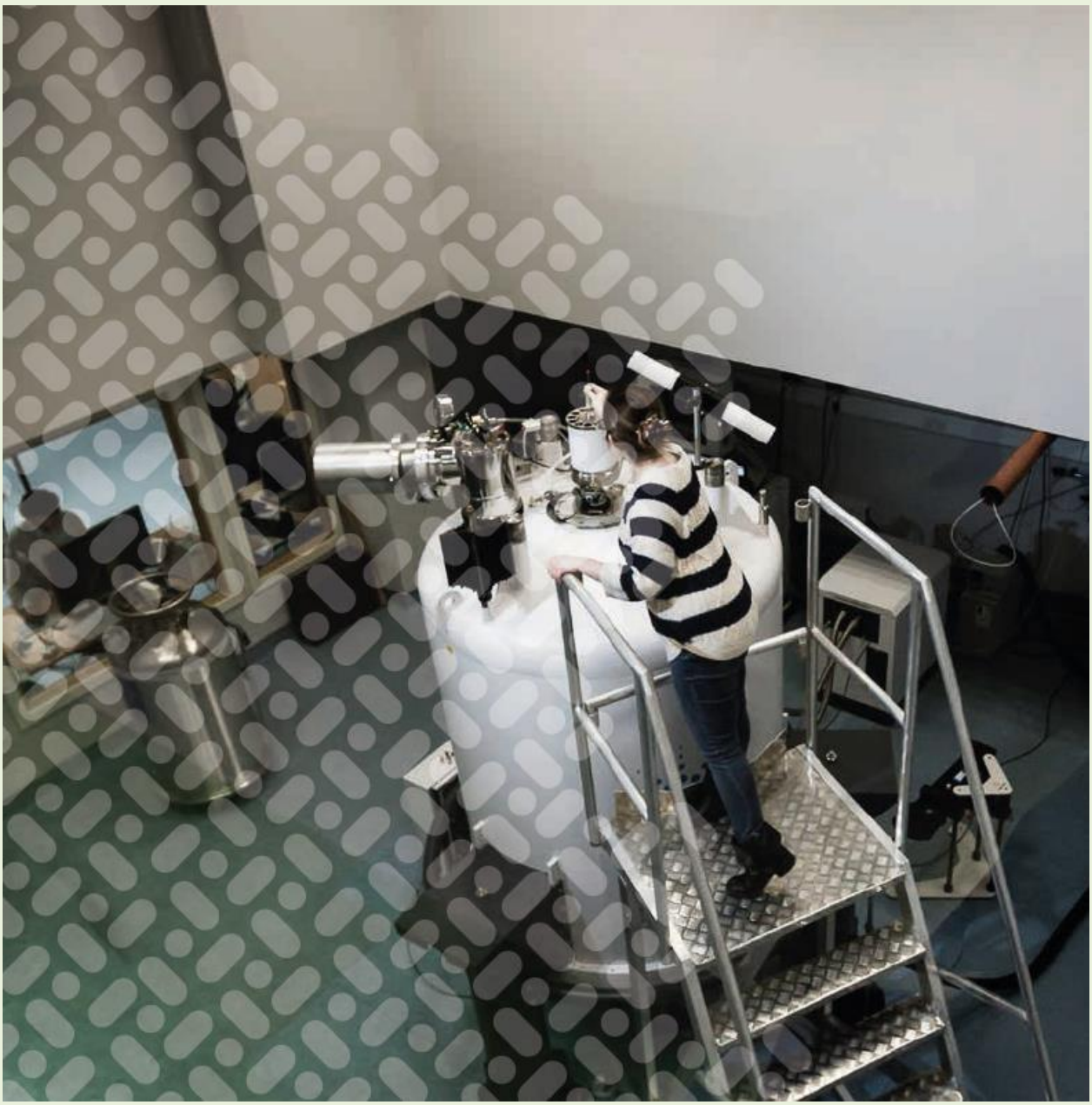
- 15.20 BREAK

- 15.50 **Diarmuid O'Brien** (Director of Trinity Research and Innovation)
  Research to Impact from an Ireland, Trinity and TBSI perspective.

- 16.20 **Ruth Arnon** (President of the Israeli Academy of Science and Humanities)
  The contribution of the academia in Israel to society and the economy

- 16.50 **Tom Lynch**, Chair of Board, TBSI

- 17.10 CLOSING REMARKS



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'Investing in your future'

Abstracts and Biographies

James D. Watson, Ph.D.
Why Metformin Prevents Much of Incurable Cancer

Cold Spring Harbor Laboratory

Most highly effective chemotherapeutic agents indirectly kill cancer cells through their induction of reactive oxygen species (O_2^-, H_2O_2, OH^-) whose subsequent oxidative modifications of key mitochondrial components lead to apoptosis (programmed cell death). Unfortunately, resistance to oxidant-mediated cancer cell killing almost inevitably follows through the mutation driven unleashing of the Nrf2 transcription factor. Its binding to DNA specifically leads to the synthesis of many important cellular antioxidants. Cancers driven by the RAS and RAF oncogenes produce such very high levels of ROS that they turn up antioxidant synthesis to levels that make their respective cancers (e.g. pancreatic) inherently resistant to all currently effective cancer cell killers. If means could be found to diminish antioxidant levels, much of today's incurable cancer would vanish.

Type 2 Diabetics treated with the long used drug metformin were reported in 2006 to have significantly less cancer (e.g. 50% less pancreatic cancer) than diabetics who use alternative medicines for controlling blood sugar levels. It does not, however, do so by producing reactive oxidants. Instead it preferentially kills cancer cells by a totally different mechanism. Now we know it lowers ATP levels through binding to Complex I of the mitochondrial oxygen requiring respiratory pathways that generate most of cellular ATP. The resulting low ATP levels turn on the key metabolic stress control enzyme AMP dependent kinase whose downstream phosphorylations inhibit key cell growth promoting anabolic metabolic pathways.

Only in 2013 did Kevin Struhl's lab at Harvard Medical School make the much unanticipated observation that metformin through the activation of AMP dependent kinase also turn off inflammation by stopping the synthesis of the transcription factor NfKß. Its absence blocks the synthesis of the cytokine IL6 – the primary driver of inflammatory responses. Until then the Struhl lab had no explanation for their earlier observation that metformin preferentially kills cancerous mesenchymal stem cells whose high antioxidant contents make them resistant to the most widely used chemotherapeutic drugs. Metformin's anti-cancer attributes thus arise through its turning off IL6 synthesis thereby blocking late stage mesenchymal stem cells from multiplying. If so, IL6 likely takes over the driver role for much of EMT generated mesenchymal cancers that cell surface growth factors like EGF play in the driving of epithelial cancers.

BIOGRAPHY: Born in Chicago, Illinois in 1928, James D. Watson was educated at the University of Chicago, from which he received a B.S. in 1947, and Indiana University where he earned a Ph.D. in Zoology in 1950. In 1953, while at Cambridge University, he and Francis Crick successfully proposed the double helical structure for DNA. They and Maurice Wilkins were awarded the Nobel Prize in Physiology or Medicine in 1962. While a professor at Harvard, Watson commenced a writing career that generated *The Molecular Biology of the Gene* and *The Double Helix*. He was a driving force behind the Human Genome Project that led to his receipt of the Royal Society's Copley Medal in 1993. Among many honorary degrees and awards are election to the National Academy of Sciences [1962], Medal of Freedom [1977], National Medal of Science [1997], City of Philadelphia Liberty Medal [2000], Benjamin Franklin Medal [2001] and Honorary Knight of the British Empire [2002]. Watson has served the Cold Spring Harbor Laboratory since 1968 as its Director, President, Chancellor, and now is Chancellor Emeritus.

Douglas Golenbock
The innate immune response in malaria is driven by DNA and enhanced by the crystal hemozoin.

Douglas Golenbock, Kate Fitzgerald and Ricardo Gazzinelli. UMass Medical School, Worcester, MA. USA E: douglas.golenbock@umassmed.edu

Despite great progress in therapy and prevention, malaria remains one of the greatest causes of premature mortality and morbidity in the world. The symptoms and effects of malaria suggest that the disease is caused by a cytokine storm, and , in fact, extremely high levels of IL-1□, TNF□ and other inflammatory mediators have been documented during severe disease. Surprisingly, little is known at the molecular level about why infection with plasmodium results in life threatening disease. Indeed, plasmodial endogenous ligands that activate the innate immune response have been poorly defined, and the receptors involved in the response are still controversial. Our original hypothesis was that malaria activates the innate immune response via its glycosylphosphatidyl anchors. However, although these molecules are present on the surface of the parasite, the quantity of GPI on blood stage forms of the parasite are too low to be responsible for symptoms of the disease. We next focused on hemozoin, a crystalline hemoglobin waste product that is produced in abundance by the parasite. Hemozoin itself was not capable of activating cytokines, however, it had the capability to enhance TLR9 activation by carrying plasmodial DNA into the phagolysosome. In addition, hemozoin causes phagolysosomal instability, allowing DNA (and other phagolysosomal products) access to

the cytosol of immune cells. This results in activation of the type I interferon pathway via cytosolic DNA receptors. In addition, cytosolic DNA appears to result in activation of the NLRP3, AIM2 and NLRP12 inflammasomes. Finally, patients with malaria have high levels of circulating immune complexes. We have evidence that these complexes contain plasmodial DNA. We believe that ICs traffic DNA into subcellular compartments that also activate the innate immune system.

Aaron Ciechanover
The Ubiquitin Proteolytic System - From Basic Mechanisms thru Human Diseases and on to Drug Development

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Between the 50s and 80s, most studies in biomedicine focused on the central dogma - the translation of the information coded by DNA to RNA and proteins. Protein degradation was a neglected area, considered to be a non-specific, dead-end process. While it was known that proteins do turn over, the high specificity of the process - where distinct proteins are degraded only at certain time points, or when they are not needed any more, or following denaturation/misfolding when their normal and active counterparts are spared - was not appreciated. The discovery of the lysosome by Christian de Duve did not significantly change this view, as it was clear that this organelle is involved mostly in the degradation of extracellular proteins, and their proteases cannot be substrate-specific. The discovery of the complex cascade of the ubiquitin solved the enigma. It is clear now that degradation of cellular proteins is a highly complex, temporally controlled, and tightly regulated process that plays major roles in a variety of basic cellular processes such as cell cycle and differentiation, communication of the cell with the extracellular environment and maintenance of the cellular quality control. With the multitude of substrates targeted and the myriad processes involved, it is not surprising that aberrations in the pathway have been implicated in the pathogenesis of many diseases, certain malignancies and neurodegeneration among them, and that the system has become a major platform for drug targeting.

BIOGRAPHY: Aaron Ciechanover was born in Haifa, Israel in 1947. He is currently a Distinguished University Professor in the Faculty of Medicine of the Technion-Israel Institute of Technology. He received his M.Sc. (1971) and M.D. (1973) from the Hebrew University in Jerusalem. Following national service as a military physician (1973-1976), he completed his graduate studies in biological sciences (D.Sc., Technion, 1982). There, as a graduate student with Dr. Avram Hershko and in collaboration with Dr. Irwin Rose, they discovered the ubiquitin proteolytic system. As a post-doctoral fellow with Dr. Harvey Lodish at the M.I.T., he continued his studies on the ubiquitin system and made additional important discoveries. Along the years it has become clear that system plays major roles in numerous basic cellular processes, and aberrations in the system underlie the pathogenesis of many diseases, among them certain malignancies and neurodegenerative disorders. Consequently, the system has become an important platform for drug development. Among the prizes Ciechanover received are the 2000 Albert Lasker Award, the 2003 Israel Prize, and the 2004 Nobel Prize (Chemistry; shared with Drs. Hershko and Rose). Among many academies, Ciechanover is member of the Israeli National Academy of Sciences and Humanities, the American Philosophical Society, the National Academy of Sciences of the USA and the Institute of Medicine of the National Academies of the USA (NAS, IOM; Foreign Associate) and the Pontifical Academy of Sciences at the Vatican

Bruce Beutler (Texas)
Finding genes that affect immunity by "real time" positional cloning

Regental Professor and Director of the Center for Genetics of Host Defense at the University of Texas Southwestern Medical Center at Dallas.
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Bruce Beutler discovered an important family of receptors that allow mammals to sense infections when they occur, triggering a powerful inflammatory response. For this work he received the 2011 Nobel Prize in Physiology or Medicine.

Beutler received his undergraduate degree from the University of California at San Diego in 1976, and his MD degree from the University Of Chicago in 1981. After two years of residency at the University of Texas Southwestern Medical Center, he became a postdoctoral fellow and then an Assistant Professor at the Rockefeller University (1983-1986), where he isolated mouse tumor necrosis factor (TNF), and was the first to recognize TNF as a key executor of the inflammatory response. Returning to Dallas in 1986 as an HHMI investigator, he designed recombinant inhibitors

of TNF that are widely used in the treatment of rheumatoid arthritis and other inflammatory diseases. He also used TNF as a biological endpoint in order to identify the receptor for bacterial lipopolysaccharide (L*ps*). This he achieved by positionally cloning the LPS mutation of mice, known to prevent all biological responses to LPS, including TNF production. He concluded that Toll-like receptor 4 (TLR4) acts as the signaling core of the LPS receptor and proposed that Other TLRs might also recognize conserved molecular signatures of infection.

Moving in 2000 to the Scripps Research Institute, Beutler developed the largest mouse mutagenesis program in the world, and applied a forward genetic approach to decipher the signaling pathways activated by TLRs. He also identified many other molecules with non-redundant function in the immune response.
Beutler is currently a Regental Professor and Director of the Center for Genetics of Host Defense at the University of Texas Southwestern Medical Center at Dallas, He also holds the Raymond and Ellen Willie Distinguished Chair in Cancer Research in honor of Laverne and Raymond Willie, Sr. Before he received the Nobel Prize, his work was recognized by the Shaw Prize (201 1), the Albany Medical Center Prize in Medicine and Biomedical Research (2009), election to the National Academy of Sciences and Institute of Medicine (2008), the Frederik B. Bang Award (2008), the Balzan Prize (2007), the Gran prix Charles- Leopold-Mayer (2006), the William B. Coley Award (2005), the Robert-Koch-Prize (2004), and other honors.

Ada Yonath (Weizmann Inst)
Combating species-specific antibiotics resistance?

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The incredible global increase in resistance to antibiotics that we are currently witnessing is a serious threat. Thus, it seems that the world is headed for a post-antibiotic era, in which common infections and minor injuries, which have been treatable for decades, could become fatal again. Ribosomes, the universal cellular machines that translate the genetic code into proteins, are paralyzed by almost half of the clinically useful antibiotics that bind to their functional sites. By investigating ribosomes from non-pathogenic bacteria as models for genuine pathogens, antibiotics binding modes, inhibitory actions and synergism pathways have been determined for almost all ribosomal antibiotics. These indicated the principles of differentiation between patients and pathogens and suggested common principles of mechanisms leading to bacterial resistance. However, as species specific diversity was detected in susceptibility to infectious diseases and in developing specific resistance mechanisms, our structural studies have been extended to ribosomes from genuine pathogens. By determining the high resolution structures of the first ribosomal particle from a genuine multi-resistant pathogen with several antibiotics, we identified subtle, albeit highly significant structural elements in the antibiotics binding pockets that can account partially or fully for species specificity in resistance. Consequently, shedding light on species specificity should pave ways for improvement of existing antibiotics as well as for the design of advanced therapeutics capable of minimizing antibiotics resistance

BIOGRAPHY: Ada Yonath, graduated the Hebrew University, earned Ph.D. from Weizmann Institute (WIS) and postdoced at Mellon Institute and MIT, USA. In the seventies she established the first laboratory for structural biology in Israel, the only laboratory of this kind in the country for almost a decade. She is WIS Kimmel Professor and the Director of Kimmelman Center for Biomolecular Structure. In parallel, during 1986-2004 she headed Max-Planck-Research-Unit for Ribosome Structure in Hamburg. She is a member of the US National Academy of Sciences (NAS); the American Academy of Arts and Sciences; the Israel Academy of Sciences and Humanities; the European Academy of Sciences and Art; the Korean Academy for Science and Technology; the European Molecular Biology Organization (EMBO); the Microbiology Academy; the International Academy of Astronautics and the UK Royal Society for Chemistry. She holds honorary doctorates from Oslo, NYU, Mount Sinai, Oxford, Cambridge, Hamburg, Berlin-Technical, Patras, Greece and most Israeli Universities. Her awards include the Israel Prize; Paul-Karrer Medal; Louisa-Gross-Horwitz Prize; Ehrlich-Ludwig Medal; Linus Pauling Gold Medal; Anfinsen Prize; Wolf Prize; UNESCO/L'Oreal Award; Albert-Einstein World Award for Excellence; DESY pin; KEK distinction; Erice Peace Prize; Florence Cite Medal; Maria Sklodowska-Curie Medal; Nobel Prize for Chemistry

Jules Hoffmann
Innate Immunity : From Flies to Humans

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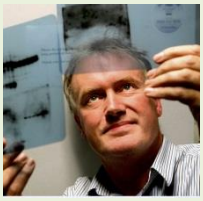
Flies challenged with bacteria or fungi rapidly transcribe a battery of genes encoding potent antimicrobial peptides which oppose the invading microorganisms. Genetic analysis has identified two signaling cascades which control their expression: (1) the Toll pathway, activated in response to fungi and Gram-positive bacteria, has significant similarities with the Toll-like receptor (TLR) pathway in mammals, and (2) the IMD pathway which controls infection

by Gram-negative bacteria, and exhibits stringent similarities with the mammalian TNF-Receptor pathway. The roles of these pathways in innate immunity of insects will be discussed, as well as the origin of this first line antimicrobial defense which is now understood to have originated with the first multicellular organisms.
J. Hoffmann is a Professor at the University of Strasbourg and has spent most of his career working with the French National Research Agency CNRS. The studies of the Hoffmann laboratory have been devoted over the last 30 years to unravelling the mechanisms of antimicrobial defenses in insects, namely in *Drosophila*. They have identified inducible antimicrobial peptides as primary immune response genes and have deciphered significant steps in the signaling cascade leading to gene reprogramming. They have further characterized the receptor proteins interacting with bacterial peptidoglycans and fungal β-glucans. Of major interest was the discovery of the involvement of the Toll receptor (initially identified by Ch. Nüsslein-Volhard for its role in embryonic development) in the response to fungal and Gram-positive bacterial infection. Altogether the studies of the Strasbourg laboratory have established *Drosophila* as an important model system for innate immunity and have contributed to a reevalution of this defense arm in the physiology of antimicrobial defense..
J. Hoffmann is the past President of the French National Academy of Sciences and a Member or Associate Member of the German, the Russian Academies, the National Academy of Sciences of the Unites States and the American Academy of Arts and Sciences. He is the recipient of many international awards, including the 2011 Nobel Prize in Medicine and Physiology.

Marc Feldmann (Oxford)
The discovery of anti-TNF therapy for rheumatoid arthritis.

Professor at the University of Oxford where he is a head of the Kennedy Institute of Rheumatology. E: marc.feldmann@kennedy.ox.ac.uk

While there has been considerable progress in the understanding of the molecular pathogenesis of rheumatoid arthritis, permitting the development of effective therapy, notably with TNF inhibiting antibodies or fusionproteins, it is important to note that these treatments ameliorate disease. They are not a cure. 15 years after these treatments were approved for regular use it is more than time to consider how to get closer to a cure. The Pharmaceutical industry has not faced up to this challenge. There are problems, but a rational approach is possible and will be discussed.
BIOGRAPHY: My initial studies in medicine at University of Melbourne were followed by a PhD with Sir Gus Nossal at Walter and Eliza Hall Institute, on *in vitro* immune responses and immune regulation. Subsequent work in London led to the generation of a new hypothesis for mechanisms of autoimmunity linking upregulated antigen presentation and cytokine expression. Testing this hypothesis led to the discovery with colleague Ravinder Maini of the pivotal role of TNFa in the pathogenesis of rheumatoid arthritis, which we established by studying synovial cultures, animal models and clinical trials. This discovery has revolutionized therapy not only of RA but other chronic inflammatory diseases, and helped change the perception of monoclonal antibodies from niche products to main stream therapeutics. Current interests are to work with colleagues to define new treatments for unmet needs, eg fibrosis, fractures, atherosclerosis, and post-operative cognitive decline using a cytokine approach. The other major interest is towards more cost-effective therapy of RA, and trying to get closer to a cure.



Luke O'Neill (TBSI)
Metabolic reprogramming in innate immunity

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Metabolic changes triggered by innate immune receptors have become a recent focus for researchers interested in immunity and inflammation. LPS-activated macrophages undergo metabolic reprogramming with a major increase in glycolysis, which is required for ATP production and also the generation of biosynthetic intermediates. Changes in the TCA cycle also occur such that intermediates such as citrate are withdrawn for lipid biosynthesis. We have found a role for the Kreb's cycle intermediate succinate in activated macrophages. Succinate has 4 potential roles here – 1. induction of HIF-1alpha and it's target genes, which include that encoding IL-1beta; 2. Histone and DNA modification via effects on demethylases; 3. Activation of the succinate receptor SUCRN1 on cells (which can synergise with TLRs) and 4. Covalent modification of target proteins by succinylation. Succinate might therefore act as important signal for inflammation. We have also found that the dimeric form of PKM2 is critical for the altered metabolism occurring in macrophages activated with LPS. The activation of PKM2 with small molecules inhibits macrophage activation and also limits the effect of LPS in vivo. These insights are providing new possibilities for immunomodulation in infection and inflammation.
BIOGRAPHY: Professor Luke O'Neill was appointed to the Chair of Biochemistry at Trinity College Dublin in 2008, where he leads the Inflammation Research Group. He is also Academic Director of the Trinity Biomedical

Sciences Institute. He has a PhD in Pharmacology from the University of London and carried out Post-Doctoral research at Cambridge U.K. on the pro-inflammatory cytokine IL-1 and innate immune signaling. He has won numerous awards for his research, notably the Royal Irish Academy Medal for Biochemistry, The Irish Society for Immunology medal, the Royal Dublin Society/ Irish Times Boyle medal for Scientific Excellence and the Science Foundation Ireland Researcher of the Year Award 2009. He was elected a member of EMBO in 2005. He is a co-founder and director of Opsona Therapeutics, a drug development company working in the area of Toll-like receptors. In 2008 he was appointed Chair of the Immunity and Infection panel of the European Research Council. His research is in the area of the molecular basis to inflammatory diseases.

Ido Amit (Weizmann Inst)
Unbiased characterization of the immune system using massively parallel single cell RNA-Seq

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The Amit group (http://wws.weizmann.ac.il/immunology/AmitLab/) studies the function of the Immune system in health and disease. Our main focus is to understand how gene and chromatin regulatory networks control hematopoiesis and immune response. We develop and apply state of the art high throughput genomic tools for single cell and chromatin applications to address these critical biological and therapeutic questions

Thirty years of dedicated research have enabled the categorization of functionally similar hematopoietic cells into a lineage tree by means of a combination of a small number of cell surface markers. Nevertheless, our understanding of the hematopoietic cell lineage remains coarse and biased, limited by preselecting of specific markers. A wealth of new studies highlight the crux of using cell populations for genome-wide measurements as even state-of-the-art classification approaches are limited and retain a heterogeneous population masking gene expression heterogeneity, uncharacterized cells and functions.

In order to understand in a comprehensive and unbiased approach the immune cell lineage and activity *in vivo*, we have developed an automated massively parallel RNA single cell sequencing approach (MARS-Seq) for measuring the genome wide expression of tens of thousands of single cells in their native context. Importantly, MARS-Seq enables transcriptome measurement of thousands of cells per experiment.

I will demonstrate how using this combined experimental and computational approach; we characterize the cell fate and activity of thousands of immune cells from mouse spleen in various physiological contexts, focusing of the dendritic cell (DC) lineage. We show that using our single cell approach we can build a high resolution *ab initio* immune identity map without the use of any predefined cell markers. Focusing on subpopulations of DCs, I will demonstrate that these DC populations include highly heterogeneous mixtures of transcriptional states that are only coarsely approximated using surface marker sorting and how these cells respond differently to stimulation. I will discuss how, our approach is greatly expanding the knowledge of transcription regulation heterogeneity and immune functional diversity beyond the limited numbers of cells/marker currently used to describe populations of immune cells. Finally, I will combine these results with unpublished work on chromatin regulatory maps of DC to connect between chromatin dynamics and gene expression heterogeneity.

Andrew Bowie (TBSI)
Recognition of pathogen DNA and innate immune gene regulation by PYHIN proteins

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The type I interferon (IFN) response to viruses is initiated by the recognition of pathogen-associated molecular patterns (PAMPs) by pattern recognition receptors (PRRs). Anti-viral PRRs detect viral nucleic acid in particular and are stationed at endosomes (Toll-like receptors) and within the cytosol (RIG-I-like receptors and DNA sensors). Delineating how PRRs signal to altered gene induction after sensing viral PAMPs is important not only to defining innate anti-viral responses but also to understanding sterile- and pathogen-induced inflammation. Furthermore, PRR-induced IFNs have been implicated in autoimmunity. The PYHIN family are IFN-inducible proteins characterized by the presence of a Pyrin and a HIN200 DNA binding domain. AIM2 was the first PYHIN protein shown to sense dsDNA, leading to caspase 1 activation and IL-1□□production, and as such defines a sub-family of PYHIN proteins termed AIM2-like receptors (ALRs). Human IFI16 and mouse p204 are also ALRs and mediate type I IFN induction in response to dsDNA, via the STING-TBK1-IRF3 signaling axis. Apart from roles as ALRs, PYHIN proteins also contribute to innate immunity as transcriptional regulators of distinct cytokines and IFNs. For example, mouse p207 is required for optimal PRR-stimulate TNF production.

BIOGRAPHY: 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.

David Wallach (Weizmann Inst)
Regulation of immune response by signaling proteins activated by the TNF family

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David Wallach[1], Tae-Bong Kang[1,2], Seung-Hoon Yang[1], Akhil Rajput[1], Jin-Chul Kim[1], and Andrew Kovalenko[1]

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There is practically no cell of the immune system, or any immune function, that is not subject to regulation by members of the TNF family. This wide multiplicity of effects is initiated via a limited set of proximal signaling proteins. One can generally distinguish between two modes of induction of functional changes by these signaling proteins: gene regulation, and regulation of cell death that occurs in gene-activation independent way. Studies in my laboratory aim at clarifying how the few proximal signaling proteins that the TNF family employs contribute to the regulation of so many different cellular functions and how are molecular 'decisions' taken as to which of a various potential effects of a given receptor and signaling protein is taken at a given situation. Part of our studies concerns the function of caspase-8, a signaling protein that we have initially discovered in exploring the mechanisms of death induction by cytokines of the TNF family. This protein serves as the proximal enzyme in the signaling for apoptotic death by the TNF family (the extrinsic cell death pathway) and as a principal negative regulator of signaling to programmed necrotic cell death (necroptosis). Studies in transgenic mice models indicated that caspase-8 serves several different functional roles including inhibition of inflammation. Control of inflammation by cytokines can be mediated both via protein-synthesis dependent effects and through induction of necrotic cell death that occurs in a protein-synthesis independent manner (yielding release of Damage Associated Molecular Patterns). The finding that caspase-8 – a signaling protein controlling cell death induction – also has pronounced effects on inflammation, poses a challenge to our ability to define the relative contribution of these protein synthesis-dependent and –independent mechanisms to inflammation in distinct in vivo situations. The approaches that we are taking to explore this distinction will be briefly overviewed.

BIOGRAPHY: Born in Israel, David Wallach did his M.Sc. research with Dr. Izak Ohad and his doctoral research with Dr. Michael Schramm at the Department of Biological Chemistry, The Hebrew University of Jerusalem, Israel, and his postdoctoral training under Ira Pastan at the National Cancer Institute, Bethesda, Maryland, USA. He is currently a professor at the Weizmann Institute of Science, Rehovot, Israel. His initial studies at the Weizmann Institute provided for the first time conclusive evidence that the 'type I' and 'type II' interferons act through distinct mechanisms and have distinct patterns of effects. Over the past 30 years, Prof. Wallach and his colleagues have been engaged in elucidating the mode of action of proteins of the TNF family, multi-functional cytokines that play a major role in immune regulation and in the regulation of cell death. They did pioneering work in isolating TNF, isolating and cloning the soluble and cells surface forms of the TNF receptors and exploring their shedding mechanisms, in cloning the major components of the extrinsic cell-death pathway (FADD/MORT1, caspase-8/MACH, and cFLIP/CASH) and several of the signaling proteins that mediate effects of the TNF family on the NF-kB transcription factors, and in exploring the mechanisms of action of these signaling proteins.

Orla Hardiman (TBSI)
Why Clinical Trials in ALS Have Failed: The Hidden Inflammatory Signal that Drives ALS

Professor of Neurology and Head of the newly established Academic Unit of Neurology at TBSI. E: hardimao@tcd.ie

Amyotrophic lateral sclerosis (ALS) is motor system degeneration characterized by progressive loss of motor neurons and culminating in respiratory failure and death, usually within 3 years of first symptoms.

The only approved therapy is riluzole which prolongs survival by 2-3 months , and which has been available for over 20 years.

During the intervening time, over 40 large Phase II and Phase III clinical trials have been conducted in ALS, with uniformly negative results.

Recent studies have demonstrated that ALS is a heterogeneous condition, and up to 11% of cases of ALS are associated with an intronic hexanucleotide expansion in C9orf72. This form of ALS is associated with a recognizable clinical, imaging and pathologic phenotype.
Existing animal models of ALS are limited. However, recent pre-clinical studies have implicated inflammatory mechanisms and inappropriate immune activation in the pathogenesis of some forms of ALS. There is increasing recognition of the involvement of inappropriate NF-κB activation in motor neuron degeneration, at least in animal models, and there is an evolving consensus that disease progression in some forms of human ALS may be associated with systemic inflammation, coupled with abnormal inflammatory macrophage activation in affected spinal cord and brain regions.
Future clinical trials in ALS will require stratification of subcohorts of ALS characterized by biomarkers both of disease pathogenesis and progression, including markers of inappropriate systemic inflammation. .

BIOGRAPHY: Professor Hardiman is Professor of Neurology and Head of the newly established Academic Unit of Neurology at TBSI. She is Deputy Chair of the European Network for the Cure of ALS (ENCALS), and is a recipient of the AAN Palatucci Award in Advocacy, the ALSA/AAN Sheila Essey Award, and the International ALS Alliance Forbes Norris Award. She is the Editor in Chief of the flagship journal ***Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration.*** She has authored over 200 peer review publications, and a textbook **Neurodegenerative Disorders** (second edition in preparation) . Her primary research interests include the epidemiology and pathogenesis of amyotrophic lateral sclerosis (ALS) and related neurodegenerative diseases. She has established a multidisciplinary group comprising over 30 researchers, based at TBSI and the Clinical Research Unit at Beaumont Hospital. Her group engages in applied research in deep phenotyping using modern neuropsychology, neuroimaging, bioengineering, epidemiology and genetic tools. Her previous work includes the discovery of ANG as an important susceptibility gene in ALS. Her work in epidemiology and population genetics has generated hitherto unrecognized evidence of population based differences in genetic susceptibility to ALS. More recently her group has shown a previously unrecognized overlap between ALS and neuropsychiatric disease. Current work focuses on the clinical and genetic overlap between ALS, frontotemporal dementia and related conditions, and on the development of novel biomarkers that underpin disease heterogeneity. She has generated over €11 million in research funding

Idit Shachar (Weizmann Inst)
Molecular Mechanisms Regulating B cell survival in Health and Disease

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In B cells, as in every other tissue, the balance between cell survival and apoptosis is essential for homoeostasis. Long-term B cell persistence in the periphery is dependent on survival signals that are transduced by cell surface receptors. Chronic lymphocytic leukemia (CLL) is characterized by the accumulation of CD5+ B lymphocytes in peripheral blood, lymphoid organs and bone marrow (BM). The main feature of the disease is accumulation of the malignant cells due to decreased apoptosis. CD84 belongs to the Signaling Lymphocyte Activating Molecule (SLAM) family of immunoreceptors, and has an unknown function in CLL cells. We show that the expression of CD84 is significantly elevated from the early stages of the disease, and is regulated by macrophage migration inhibitory factor (MIF) and its receptor, CD74. Activation of cell surface CD84 initiates a signaling cascade that enhances CLL cell survival. Both downmodulation of CD84 expression and its immune-mediated blockade induce cell death *in vitro* and *in vivo*. In addition, analysis of samples derived from an on-going clinical trial, in which human subjects were treated with humanized anti-CD74 (milatuzumab), shows a decrease in CD84 mRNA and protein levels in milatuzumab-treated cells. This downregulation was correlated with reduction of Bcl-2 and Mcl-1 expression. Thus, our data show that overexpression of CD84 in CLL is an important survival mechanism that appears to be an early event in the pathogenesis of the disease. These findings suggest novel therapeutic strategies based on the blockade of this CD84-dependent survival pathway.
BIOGRAPHY: Prof. Shachar investigates the immune system, focusing on white blood cells called T and B cells. She studies the "homing" process by which these cells reach the sites of inflammation in body tissues. For instance, B cells are created in the bone marrow and then migrate to the spleen, where they receive the specialized instruction they need to do their jobs. Only afterwards do they take up their positions in the bloodstream. How do the young B cells know the way from the bone marrow to the spleen? Why don't they end up anywhere else in the body? In other words, what mechanism directs B cell migration? She has identified two biochemical pathways regulating such homing and demonstrated that the movement of immune cells can be restricted by blocking these pathways. She has shown that a membrane protein called CD74 plays a crucial role in B cell survival and is currently investigating the molecular mechanisms related to this protein's activity. In the future, Prof. Shachar is planning to examine whether interrupting the activity of CD74 and its target proteins can interfere with the survival of solid tumors.

Her awards and honors include the Wolf Foundation Award (1993), Israel Science Foundation's Investigator Prize for the Advancement of Education and Science (2001) and the Teva Prize for Excellence in Research (2003). She holds four U.S. patents in the treatment of inflammation and a provisional patent for treating cancer.

Prof. Shachar and her husband Ron, a professor of marketing and the dean of the buisness school at the Interdisciplinary Center in Herzliya, have two children: a daughter, Yuval, and a son, Daniel.

Cliona O'Farrelly (TBSI)
Innate Immune Resistance to Hepatitis C Virus: a Role for the JAK/STAT Pathway?

Mark Robinson, Nigel Stevenson, Cliona O'Farrelly and ICORN (Irish hCv Outcome & Response Network).
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Individuals within outbred populations respond differently to pathogenic viruses: a proportion of exposed individuals will become infected, while others are able to resist infection with no signs of illness. Infected individuals may succumb to the infection, clear the virus through the development of adaptive immune responses, or develop a state of persistent infection. Importantly, some exposed individuals show no sign of infection and are able to completely resist infection via innate immune mechanisms. Defining the molecular mechanisms of innate resistance to viral infection will lead to novel therapeutic and vaccination strategies

We are studying innate resistance in a cohort of Irish Rhesus factor negative women who were exposed to Hepatitis C contaminated anti-D in 1977. While many women were identified as have been infected through antibody screening, several hundreds of women were exposed to contaminated anti-D immunoglobulin but showed no clinical or immunological signs of infection. We propose that this subpopulation of exposed, HCV-resistant women, who have never before been studied, have particularly effective innate anti-viral immunity. Our previous work has found that HCV can function as an E3 ligase in chronically infected patients, targeting STAT3 for proteasome degradation and compromising the innate Jak/STAT signalling pathway required for interferon anti-viral activity. This mechanism of viral immune evasion is shared by a number of viruses and we hypothesise that the innately resistant women have specific polymorphisms within their STAT genes that prevent viral degradation, enabling efficient innate immune responses to block infecting virus.

Eran Elinav (Weizmann Inst)
The role of host-microbiome interactions in the metabolic syndrome

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Mammalian mucosal surfaces host tens of trillions of microbes, forming a community that is dominated by members of the domain Bacteria but also includes members of Archaea, Eukarya, and viruses. In the gastrointestinal tract, this microbial ecosystem, named the gut microbiota, encompasses one of the densest microbial populations on earth, and intimately interacts with its host to orchestrate a multitude of physiological functions. The mucosal immune system co-evolves with the microbiota beginning at birth, acquiring the capacity to tolerate components of the community while maintaining the ability to respond to invading pathogens. We, and others, have recently highlighted that dysregulation of the delicate balance between the microbiota community and the mucosal immune system have been linked to pathologies ranging from chronic inflammation, obesity, the metabolic syndrome and cancer. We have identified various possible mechanisms for this reciprocal regulation between the mucosal innate immune system and the intestinal microbial ecosystem, including the newly recognized nod-like receptor (NLRs) family member NLRP6, which has been implicated in the pathogenesis of intestinal auto-inflammation, the metabolic syndrome and inflammation-associated colorectal cancer. Deciphering the mechanisms by which both host and its microbiota regulate host-microbiota interactions, and how these interactions drive homeostasis and the propensity for pathological processes has profound implications on our understanding of multi-factorial disease.

BIOGRAPHY: 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 60 publications. His honors include multiple awards for academic excellence during his medical and PhD studies, 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, a Keystone Foundation award (2012), and the Alon Award (2013). He has been granted four biomedical patents in the field of inflammation and pathological weight loss (cachexia).

Kingston Mills (TBSI)
Function and regulation of IL-17 cytokine family in inflammation and autoimmunity

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CD4+ T cells that secrete IL-17 (Th17 cells) play a pathogenic role in many autoimmune diseases, but also function with Th1 cells to mediate protective immunity to infection by promoting recruitment and activation of neutrophils and macrophages respectively. Stimulation of dendritic cells by pathogen-derived molecules promotes maturation and the production of T-cell differentiating cytokines. We have shown that TLR and NLR agonists induce innate IL-1 and IL-18 which synergize with IL-23 to activate memory Th17 cells, but also IL-17 production by γδ T cells without TCR engagement.

In the field of autoimmunity, much of the focus in drug discovery has been on IL-17A production by $CD4^+$ Th17 cells and its induction by IL-23. However $CD8^+$ T cells, γδ T cells, NKT cells and other innate lymphoid cells are all capable of secreting IL-17A. There is also evidence that other cytokines, including IL-17F, GM-CSF, IL-21 and IL-22, are produced by Th17 and IL-17A-secreting innate immune cells. Furthermore, the role of IFN-γ, secreted by Th1, NK and type 1 innate lymphoid cells (ILC1) cells, is still unclear, with some evidence that IFN-γ is protective in autoimmunity by inhibiting Th17 cells. However, we have demonstrated in experimental autoimmune encephalomyelitis, a mouse model for multiple sclerosis, that early NK cell-derived IFN-γ plays a pathogenic role through activation of M1 macrophages and VLA4 expression on T cells, required for their migration into the CNS.

The induction and function of Th1 and Th17 cells is regulated by cytokines secreted by the other major subtypes of T cells, especially IL-10 and TGF-β production by Treg cells but also by regulatory cells of the innate immune system. The induction of adaptive Treg cells is stimulated by retinoic acid, TGF-β and IL-10 in response to certain virulence factors from pathogens, such as helminth parasites that have evolved sophisticated mechanisms to subvert host protective immunity. Pathogens and pathogen-derived molecules can also promote activation of alternatively activated M2 macrophages, ILC2 and tolerogenic dendritic cells that can suppress Th1 or Th17 cells, either directly or through the induction of Treg cells. We have identified approaches for activation of anti-inflammatory cytokines, regulatory innate immune cells and Treg cells, without Th1 or Th17 cells. These approaches have been effective in attenuating inflammatory disease in pre-clinical models of autoimmunity.

BIOGRAPHY: Kingston Mills is Professor of Experimental Immunology, School of Biochemistry and Immunology, Trinity College Dublin (TCD). He is Head of The Centre for the Study of Immunology at Trinity Biomedical Sciences Institute and Theme Champion for Immunology, Inflammation and Infection at TCD. He is a graduate of TCD and trained at as a Postdoctoral Fellow at University College London and the National Institute for Medical Research, Mill Hill, London, before joining the Scientific Staff of NIBSC, Herts, UK. He returned to Ireland in 1993 to take up an academic position at National University of Ireland, Maynooth. 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 heads an active research team focusing on T cells in infection, autoimmunity and cancer. He is co-founder of Opsona Therapeutics and TriMod Therapeutics, biotech companies focusing on the development of immunotherapeutics for inflammatory diseases and cancer.

Yehuda Kamari (Sheba Med Center)
The Role of Interleukin-1α in Metabolic Inflammation

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Cytokines play an important role in the chronic inflammatory vascular response that is typical of atherosclerosis, as well as in non-alcoholic fatty liver disease (NAFLD) and obesity-induced insulin resistance. IL-1α and IL-1 are produced both by resident vascular cells and macrophages in response to various stimuli associated with inflammation. The role of IL-1α in metabolic inflammation was less studied compared to IL-1 . IL-1RI is expressed on arterial wall resident cells and on bone marrow-derived inflammatory cells. It was not known which IL-1 producing cell is most critical for atherogenesis and which cell type is the main target for the effects of IL-1. In my talk, I will present the data showing the importance of tissue specific IL-1 in the development of atherosclerosis and steatohepatitis. Our results suggest that IL-1α and IL-1 from bone marrow-derived cells promote the development of atherosclerosis and that vascular wall resident cells are the main target for the pro-atherogenic effects of IL-1 through IL-1RI. Deficiency of IL-1α or IL-1 also inhibited the progression of simple fatty liver to inflammatory fatty liver (steatohepatitis) and liver fibrosis in mice. Our results indicate that in contrast to atherosclerosis, IL-1 deficiency in liver cells is critical for steatohepatitis development.

Padraic Fallon (TBSI)
Innate cell priming of adaptive inflammatory diseases

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Atopic dermatitis (AD) is an inflammatory skin condition that can predisposes children to subsequently develop asthma, a phenomenon known as the atopy march. While genetic and environmental factors are known to contribute to AD and asthma, the mechanisms underlying the atopic march remain poorly understood. In man loss-of-function mutations in filaggrin are a major genetic predisposer for initial development of AD and the progression to AD-associated asthma. We have generated a mutant mouse model of filaggrin-deficiency and the atopic march; mutant mice spontaneously develop AD that progresses to compromised pulmonary function in older mice. The skin inflammation develops independently of adaptive immunity, with an adaptive response required for the secondary progression to lung inflammation. Innate development of cutaneous inflammation involves type 2 innate lymphoid cells (ILC2s) and is dependent on interleukin-25. These mouse studies translate to man, with basal and allergen-induced infiltration of IL-25 receptor expressing ILC2 into the skin of AD patients. This presentation will explore underlying mechanism of innate immunity evoking dermatitis and priming adaptive immunity to evoke the secondary development of pulmonary inflammation.

BIOGRAPHY: Padraic G. Fallon is Science Foundation Ireland Stokes Professor of Translational Immunology. 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 immuno-parasitology, 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. Since 2007 he has generated over €12 million of funding as Principal Investigator for his research, supporting programme on paediatric immunology and fundamental mechanistic research using animals models of innate and adaptive immunity. 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*, *Journal of Experimental Medicine* and *Immunity*. His research group are based in the Trinity Biomedical Sciences Institute, Trinity College Dublin, Institute of Molecular Medicine, St James's Hospital and National Children's Research Centre, Our Lady's Children's Hospital, Crumlin.

Aisling Dunne (TBSI)
Inflammasome activation, from infection to inflammatory disease

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The recognition of pathogen-derived molecules by the innate immune system is mediated by a number of receptors, including members of the TLR (Toll-like receptor), RLH ([RIG (retinoic acid-inducible gene)-like helicase] and the NLR (NOD-like receptor) families. NLRs in particular are also involved in the recognition of host-derived damage-associated molecules which are produced under conditions of cellular stress or injury. Activation of these receptors leads to the assembly of high-molecular-mass complexes called inflammasomes which in turn leads to the generation of active caspase-1 and the production of mature IL-1β (interleukin 1β). The discovery that NLRP3 (NLR-related protein 3) can recognize host-derived particulate matter such as uric acid and cholesterol crystals has lead to the inflammasome being implicated in a number of diseases including gout, atherosclerosis and Type 2 diabetes. In addition, aberrant NLRP3 activation has been observed in a class of heritable disorders now referred to as cryopyrinopathies. On the other hand, several studies have reported that recognition of microbial products by NLRs is

required for effective pathogen clearance. This talk will provide an overview of both aspects of inflammasome activation and how the generation of active IL-1β governs the outcome of not only inflammatory disease but also bacterial, viral and fungal infection.

BIOGRAPHY: Dr Dunne completed a PhD in Enzymology in Trinity College Dublin in 2002. She went on to carryout postdoctoral Research in Monash Medical Centre, Melbourne before returning to a postdoctoral position with Professor Luke O'Neill, Trinity College Dublin. She then went to become Head of Molecular Biology and Protein Biochemistry at Opsona Therapeutics between 2006-2009 before taking up a Senior Research Fellow position with the Immunology Research Centre (IRC) which is an SFI funded research cluster comprising principal investigators from Trinity College Dublin, NUI Maynooth and St. James Hospital. She was awarded a Lectureship with the School of Biochemistry and Immunology and the School of Medicine, Trinity College Dublin in 2011. Her research to date has focused on specific events involved in Toll-like receptor (TLR) and Nod-like receptor (NLR) signalling as well as the identification of novel TLR and NLR agonists from pathogens such as *Bordetella pertussis.* Her most recent work has addressed the role of endogenous damage associated molecules in driving inflammation in conditions such as atherosclerosis, osteoarthritis and brain inflammation. Her group is currently funded by Science Foundation Ireland, the Health Research Board and PRTLI.

Steffen Jung (Weizmann Inst)
Macrophage Contributions to Gut and Brain inflammation

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Macrophages are strategically located myeloid immune cells that are found throughout the body tissues, where they ingest and degrade foreign materials, dead cells and debris and orchestrate inflammation. Our understanding of tissue macrophages recently underwent two main two major recent paradigm shifts. The first was the realization that most tissue-resident macrophages are established prenatally and maintain themselves throughout adult live by virtue of their longevity and limited self-renewal, independent from input through ongoing hematopoiesis [1]. The second notion is that besides their appreciated role as immune sentinels, tissue macrophages form integral components of the host tissue they co-evolved with. This entails the specialization of tissue macrophages in response to local environmental cues to contribute to the development of their respective tissue of residence, as well as its homeostatic function in the adult. Tissue specialization is reflected in discrete gene expression profiles, as well as epigenetic signatures reflecting enhancer usage. Moreover, factors that govern the specification of macrophages in their respective host tissues are beginning to emerge.

Here we will present our efforts to study a prototype of embryo-derived macrophages, the microglia, in brain context. Moreover, we will discuss fates of monocytes in the healthy and inflamed intestine. Of note, these intestinal monocyte-derived cells are archetypes of the third cellular system [2,3], that complements tissue resident macrophages and dendritic cells upon demand to cope with inflammatory challenges.

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BIOGRAPHY: Steffen Jung was born in Homburg/ Saar, Germany. He completed his PhD training at the Institute of Genetics in Cologne in the Department of Immunology. Using a gene targeting approach he defined cis-acting control elements driving non-coding "sterile" transcripts in class switch recombination. In 1997, he went to New York to join the Skirball Institute for Molecular Pathogenesis, NYU Medical Center. His studies there focused on the newly discovered chemokine receptor CX_3CR1 and its unique membrane-tethered ligand CX_3CL1 / fractalkine. Furthermore, he developed a novel transgenic model that allowed the study of dendritic cells in their in vivo context by conditional cell ablation (CD11c-DTR mice).

In 2002 Steffen Jung joined the faculty of the Immunology Department at the Weizmann Institute, tenured since 2009. Work of the Jung lab revolves around in vivo aspects of mononuclear phagocyte biology, including the definition of developmental pathways and the investigation of functional aspects of monocytes, dendritic cells and macrophages in specific organs. They use a combination of intra-vital imaging, conditional cell ablation and precursor graft-mediated reconstitution to investigate the biology of these cells in physiological context in health and disease. A recent focus of the Jung laboratory is given to monocyte-derived intestinal macrophages and embryonic-derived brain microglia and the mechanisms that establish cell identities.

Alan Irvine (TCD)
Early mechanisms in atopic disease: genetic and functional insights

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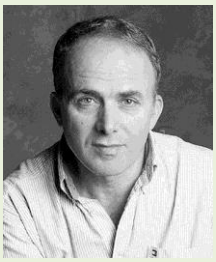
The incidence and prevalence of allergic diseases, including atopic dermatitis (AD; also known as atopic eczema), food allergy, hay fever and asthma have increased dramatically in the developed and urbanised world over the past several decades. Atopic dermatitis is the most common chronic inflammatory disease of children in the developed world. In many cases, infant AD is associated with food allergies, and is followed by development of asthma and hay fever in later childhood in a clustering and sequencing of co-morbid conditions that is sometimes the so–called 'atopic march'. The basis for the emergence and increase in the prevalence of these diseases is not well understood. Immune dysregulation and environmental change have long been assumed to be the primary drivers. For most of the latter half of the 20th Century the pathogenesis of atopic disease was assumed to be primarily immune in origin. In 2006 a paradigm shift was realised when we reported the role of mutations in the epithelial barrier protein filaggrin as the key genetic risk for atopic dermatitis and associated atopic diseases. This talk with review the role of the sin barrier in the pathogenesis of these diseases, and the potential for therapeutic intervention.

BIOGRAPHY: Alan Irvine qualified in Medicine from Queen's University Belfast in 1991. In 1998 he was awarded a research doctorate (MD) in Human Genetics, also from Queen's University. He completed Dermatology Training in Belfast in July 1999 and was then a fellow in both Great Ormond Street Children's Hospital and Children's Memorial Hospital Chicago, where he was a Fulbright Scholar.

He is Professor in Dermatology, Trinity College Dublin. His research interests are in epithelial genetics, initially in relation to single gene disorders and more recently in complex disease, in particular atopic dermatitis. His work on the genetics of atopic dermatitis with long term collaborative partner Irwin McLean has helped refocus attention on the role of the skin barrier in the pathogenesis of this disease and of allergic disease in general. The National Children's Research Centre and the Wellcome Trust fund his research program.

Irvine is an Associate Editor of the *Journal of Investigative Dermatology* and of *Allergy* and is the Lead Editor of the 3rd Edition of *Harper's Textbook of Pediatric Dermatology* (2011). His international awards include the 2006/2007 Paul Gerson Unna Prize from the German Dermatology Society and the 2013 Jerry Dolovich Memorial Lecture of the AAAAI



Yossi Yarden (Weizmann Inst)
HER2 and EGFR: at last, cancer therapy meets systems biology

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Tumor-specific combinations of oncogenic mutations often free cancer cells from their reliance on growth factors. One important example comprises the epidermal growth factor receptor (EGFR) and its kin, HER2. In tumors, both EGFR and HER2 frequently display overexpression, internal deletions and point mutations. Accordingly, several monoclonal antibodies and kinase inhibitors specific to these receptors have been approved for clinical application. However, similar to the application of chemotherapeutic drugs, the efficacy of therapies specifically targeting EGFR or HER2 is limited by primary (intrinsic) and secondary (evolving) resistance. In addition, intra-tumor heterogeneity severely reduces therapeutic efficacy.

My lecture will introduce a systems biology approach to understanding drug action and evolvement of secondary resistance. I will stress the evolutionary origin of signaling networks, the structural and functional features that confer robustness to therapeutic interventions, as well as the roles played by feedback regulation.

Martin Caffrey (TBSI)
A marvelous mesophase

Martin Caffrey, Membrane Structural and Functional Biology Group, School of Medicine and School of Biochemistry & Immunology, Trinity College Dublin, Ireland. E: martin.caffrey@tcd.ie

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.

Funded by the National Institutes of Health (P50GM073210, U54GM094599), FP7 COST Action CM0902 and Science Foundation Ireland (12/IA/1255)

BIOGRAPHY: 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.

Ashraf Brik (Weizmann Inst and BRU)
Chemical Biology with Deubiquitinases

Professor in the Chemistry Department at BGU E: abrik@bgu.ac.il

Ubiquitination—the attachment of a ubiquitin (Ub) monomer, composed of 76 amino acids, or of a polyubiquitin (polyUb) chain to a protein target, is involved in a wide range of cellular processes, including protein degradation, trafficking, transcription and the DNA damage response. Ubiquitination is a reversible posttranslational modification and the reverse reaction i.e. deubiquitination is controlled by a family of enzymes known as deubiquitinases (DUBs), which hydrolyze isopeptide bonds within Ub bioconjugates. DUBs are involved in a variety of regulatory processes, such as cell-cycle progression and differentiation, and several DUBs have been implicated in various neurological infectious and neoplastic diseases, leading to the emergence of DUBs as potential therapeutic targets. In this talk, I will present our novel chemical approaches to study and target DUBs. Specifically, I will present our efforts to develop high-throughput assay that enabling us to screen libraries of small molecules against several DUBs.

BIOGRAPHY: Professor Ashraf Brik was born in 1973 in Israel. In 1996, he completed his undergraduate studies in Chemistry at the Ben-Gurion University of the Negev. Professor Brik attended the Technion-Israel Institute of Technology for his M.Sc. degree, which he completed in 1998. He moved to The Scripps Research Institute (TSRI) where he worked with Professor Ehud Keinan and Professor Philip Dawson on a joint program between the Technion and TSRI. In 2002, he started a postdoctoral position with Professor Chi-Huey Wong at TSRI and in 2004 he was promoted to a Sr. Research Associate. In 2007, Professor Brik returned to his Alma Mater as an Assistant Professor in the Chemistry Department at BGU and was promoted to an Associate Professor 2011 and to a Full Professor in 2012. His current research involves the development of novel chemistries for selective modification of proteins and to prepare posttranslationally modified proteins e.g. ubiquitination for biological studies. Professor Brik is the recipient of the 11th Hirata Award, the 2013 Teva award for Excellence in memory of Eli Hurvitz, the 2013 Tetrahedron Young Investigator Award in Bioorganic and Medicinal Chemistry and the 2011 Israel Chemical Society prize for Outstanding Young Chemist

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Seamus Martin (TCD)
Inflammatory Outcomes from Cell Death Signals

Molecular Cell Biology Laboratory, Dept. of Genetics, The Smurfit Institute, Trinity College, Dublin 2, Ireland. E: MARTINSJ@tcd.ie

Inflammation is the set of reactions seen in response to infection or tissue damage and is critical for the recruitment of cells of the innate immune system to the correct location, as well as for the initiation of adaptive immune responses. The inflammatory response also initiates the process of tissue repair and the restoration of normal tissue integrity. Apoptosis is typically considered to be a non-inflammatory mode of cell death whereas Necrosis, as well as a recently described mode of programmed necrosis called Necroptosis, are considered to be pro-inflammatory. However, things are not quite as simple as they might seem. Many physiological triggers of apoptosis, such as TNF, Fas and TRAIL, can elicit the production of pro-inflammatory cytokines and the effects of Necroptosis on the production of such cytokines has yet to be reported. I will discuss the role of cell death stimuli as modulators of inflammation and the effects of apoptosis and necroptosis on these inflammatory signals. In contrast to the prevailing view, I will present data to argue that Necroptosis is an anti-inflammatory mode of cell death and that Apoptosis is not necessarily non-inflammatory.

Paul Browne (TCD)
Immunophenotyping and haematological neoplasms

Professor/Consultant Haematologist, Head of the School of Medicine at Trinity College Dublin E: brownpv@tcd.ie

Paul Browne is Professor of Haematology at Trinity College Dublin, and Consultant Haematologist and Director of the National Adult Stem Cell Transplant Programme at St. James's Hospital Dublin. He is currently also Head of the School of Medicine at Trinity College Dublin, where he graduated in 1986. He trained first in Dublin, and then as a Fellow at the University of Minnesota, USA. Since returning to Ireland in 1997, he has led the development of therapeutic programmes for leukaemia and myeloma, with a special interest in stem cell transplant and novel therapeutics. He is a member of several international working groups, including the European EBMT Working Party for Leukaemia / Myeloma, and the International PNH Consortium. He has collaborated on laboratory studies of myeloma biology, including a focus on genetic susceptibility in DNA repair pathways, in work funded by the HRB and the Irish Cancer Society. He was Chair of the Irish Cooperative Oncology Research Group (ICORG) from 2008 to 2012, leading the successful ICORG international peer-reviewed HRB multi-million euro grant renewal to support clinical translational research in cancer. Recently, he has led a TCD group in conjunction with colleagues in Cork and Galway which will now commence a major programme on cellular therapy funded by the National Blood Centre.

John O'Leary (TCD)
New insights into the metastatic cascade: where cancer and immunology meet

Chair of Pathology, TCD and Consultant Pathologist at St. James Hospital, Dublin E: olearyjj@tcd.ie

The cancer cell metastatic cascade is complicated and involves interactions between circulating tumour cells (CTCs), components of the peripheral blood, and the immune system.

The TBSI-Weismann talk will critically assess the influence of vascular shear, platelet cloaking of cancer cells (CTCs) and how platelet cloaking interferes with NK and iNK cell function as part of natural cancer cell immune surveillance.

Platelet cloaking of cancer cells in the peripheral circulation protects cancer cells from the effects of arterial and venous shear, and induces a cancer cell ecosystem where apoptosis and autophagy is inhibited and where angiogenesis, EMT, pro-metabolic and pro-cell cycling genes are up-regulated.

The critical biological process of cancer cell EMT appears to be driven by the platelet cloaking process through the elaboration of a cancer cell activated releasate from platelets. This releasate drives EMT, cancer stem cell plasticity and facilitates cancer invasion, which can be pharmacologically inhibited by anti-platelet agents.

The platelet cloaked cancer cells also are able to avoid immune recognition by NK and iNK cells through the formation of the platelet releasate, inhibiting the NKG2D receptor on NK cells which results in down-regulation on y-IFN production by NK cells.

This work is funded by Science Foundation Ireland as part of its CSET - The Biomedical Diagnostics Institute (BDI) and a Health Research Board (HRB) Clinician Scientist Award.

Scientists who are working on this project:
Clair Gardiner, Orla Sheils, Cathy Spillane, Michael Gallagher, Brendan Ffrench, Antonino Glaviano, Chris Cluxton, Sharon O'Toole, Gordon Blackshields, Cara Martin, Niamh Cooke, Dermot Kenny, Richard O'Kennedy, Jens Ducree.

Biography: John O'Leary is Chair of Pathology at Trinity College Dublin Ireland and is a Consultant Pathologist at St. James's Hospital and The Coombe Women and Infants University Hospital, Dublin, Ireland. He is a Principal Investigator in the Science Foundation Ireland CSET, Biomedical Diagnostics Institute (BDI).

His research group works in several areas of Pathology including: cervical, ovarian, thyroid, head and neck and prostate cancer, cancer stem cell biology, the cancer inflammasome, the metastatic cascade, biochip development, pregnancy transcriptomics, genomics and proteomics.

His group has published over 200 publications in journals such as Nature, Nature Medicine, Nature Immunology, The Lancet, Cancer Research, PLoS etc. He is a seated editor on 3 books, has published 28 book chapters and has in excess of 300 meeting abstracts published.

His current research group consists of 19 PhD students and 23 post- doctoral scientists. In the past 4 years, the group has raised in excess of 68 million euros in grant income.

Yinon Ben-Neriah (Weizmann Inst)
Parainflammation effects in cancer

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Audrey Lasry[1], Dvir Aran[2], Adar Zinger[1], Haya Hamza[1], Eliran Kadosh[1], Ela Elyada[1], Ariel Pribluda[1], Asaf Hellman[2], Moshe Oren[3], Eli Pikarsky[1] and Yinon Ben-Neriah[1]

[1]The Lautenberg Center for Immunology, Hebrew University-Hadassah Medical School; Department of Developmental Biology and Cancer Research; [2]Department of Molecular Cell Biology, The Weizmann Institute of Science, Rehovot, Israel

Inflammation has many faces, most commonly observed as an acute reaction in response to pathogen or another insult, or a chronic phase, accompanying chronic infection and chronic remittent inflammatory disease, such as inflammatory bowel disease[1]. Yet, there is another type of smoldering inflammation, harder to notice or monitor, which appears to underlie some of the major human diseases, cancer, diabetes type 2 and certain neurodegenerative diseases[2]. We have developed mouse models of cancer based on inducible CKIα knockout[3], which exhibit smoldering inflammation, and demonstrate how a low grade, infiltrate-free inflammatory reaction to persistent DNA damage response translates to an aberrant growth. We determined this unusual inflammatory repertoire denoted **parainflammation**[4] in the knockout mice and gut explants, demonstrated its association with cellular senescence and showed how in the absence of p53, parainflammation is converted from a growth inhibitory to growth promoting mechanism, both in vitro and in vivo. Anti-inflammatory reagents capable of blocking parainflammation reverse a tumor-related crypt proliferative phenotype of mutant intestinal organoids in vitro and prevent carcinogenesis in mutant mice. We investigated the prevalence of parainflammation in human cancer and found that it characterizes fifty percent of the major cancer types, showing a tight association to p53 mutations and p53 pathway deficiencies. We will discuss the significance and implications of parainflammation in human cancer.

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Thorfinnur Gunnlaugsson (TBSI)
Targeting cancer cells with supramolecular nanotechnology: The use of luminescent ruthenium polypyridyl complexes and gold nanoparticles

School of Chemistry and Trinity Biomedical Sciences Institute, Trinity College Dublin, University of Dublin, Dublin 2, Ireland. E: gunnlaut@tcd.ie

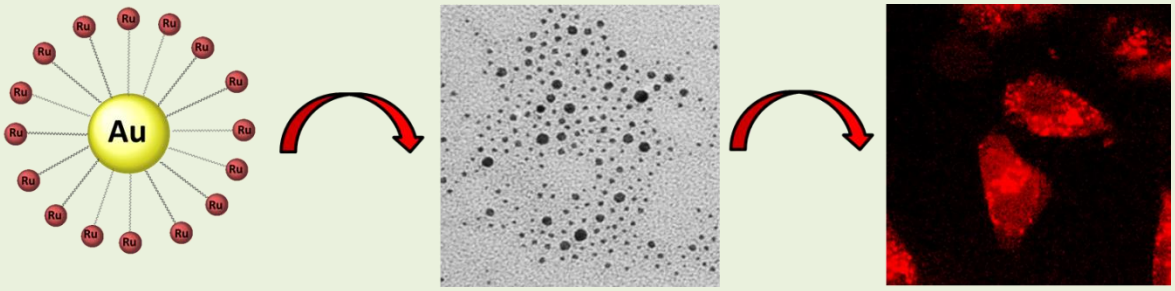
Kim N. Orange,[b] Robert B. P. Elmes,[a] Sandra Bright,[b] Miguel Martínez-Calvo, Fergus Poynton[a,] Bjørn la Cour Poulsen[a], Salvador Blasco[a] ,Marialuisa Erby[b,] Suzanne M. Cloonan,[b] D. Clive Williams[b]* and Thorri Gunnlaugsson[a]*

a) School of Chemistry and Trinity Biomedical Sciences Institute, Trinity College Dublin, University of Dublin, Dublin 2, Ireland.

b) School of Biochemistry and Immunology and Trinity Biomedical Sciences Institute, Trinity College Dublin 2, University of Dublin, Dublin 2, Ireland.

There currently exists a great interest within the chemistry community in the formation and studying of functional coordination self-assembly structures and materials for use in bimolecular and medicinal applications. In this lecture we describe our developments within this field; focusing on the design and synthesis of several novel luminescent supramolecular conjugates based on the use of novel Ru(II) polypyridyl complexes, and their application in solution or

in cells, prior and after they have been tethered to the surface of gold nanoparticles. We show that these Ru-polypyridyl complexes are attractive therapeutic candidates within cancer cells where apoptosis can be switched on by light stimulation. We further demonstrate that while the luminescence properties of such complexes are somewhat affected by the incorporation of such structures onto the gold, grate improvements in sensitivity and selectivity can be achieved, at much lower concentrations than would be achieved using single molecules and that the role between imaging and therapeutic nature can be tuned.[1-3] We also show that the size of the gold nanoparticles can greatly affect both the luminescent properties, as well as cellular uptake of such modified nano-structures.



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BIOGRAPHY: Prof. Thorfinnur (Thorri) Gunnlaugsson, FTCD, MRIA was born in Iceland. He undertook his PhD studies with Prof. A.P. de Silva at Queen's University Belfast and then worked with Prof. David Parker FRS at University of Durham (England) as a postdoctoral fellow. He was appointed as the Kinerton Lecturer in Medicinal Organic Chemistry at the School of Chemistry, University of Dublin, Trinity College, in October 1998 and a Lecturer in Organic Chemistry in 2000. He was made a Fellow of Trinity College Dublin in 2003, and appointed as an Associate Professor of Organic Chemistry in 2004. He was promoted to a Personal Chair in Chemistry 2008 as the Professor of Chemistry. In 2011 he was made a Member of the Royal Irish Academy. His research interests are in the areas of supramolecular organic and inorganic chemistry, bio and medicinal chemistry and nanotchenology. Having published over 170 papers in these areas of research he has an H-index of 59 with ca. 14,000 citations. In April 2014 he was awarded 3.1 million Euro from Science Foundation Ireland (SFI) through the SFI Investigators Programme, towards the development of novel self-assembly materials for biological applications.

Gavin Davey (TBSI)
Targeting mitochondrial fusion/fission dynamics in tumor cells

Ryan McGarrigle, Stephen Quinn, James Murray and Gavin Davey, School of Biochemistry & Immunology, Trinity Biomedical Sciences Institute, Trinity College Dublin, Ireland, E: gdavey@tcd.ie

The dynamic structure of the mitochondrial reticulum in mammalian cells is defined by the opposing forces of fission and fusion, mediated by a group of large GTPases collectively known as mitodynamins. The regulation of fission and fusion is poorly understood but it is thought that bioenergetics and fusion/fission dynamics engage in a bi-directional crosstalk, such that disturbing one will have deleterious effects on the other. Here we show that glucose metabolism prevents perturbation of mitochondrial fusion dynamics in the presence of mitochondrial oxphos inhibitors in HeLa cells. Resistance of HeLa cells to mitochondrial inhibition can be overcome by culturing them in glucose-free, galactose-containing medium, which forces the cells to derive energy predominantly through oxidative phosphorylation. Under these conditions, fusion is compromised by inhibition of mitochondrial oxphos, and is accompanied by increased migration of hexokinase II the mitochondrial outer membrane. Thus, we demonstrate that mitochondrial fusion/fission dynamics in cancer cells may be targetted by the dual approach of regulating carbohydrate supply in the presence of mitochondrial inhibitors, thus compromising bioenergetic stability and increasing cell death.

BIOGRAPHY: Dr Davey is currently Head of the School of Biochemistry and Immunology in Trinity College Dublin. He has 24 years' experience in the area of enzymology and metabolic flux, particularly in relation to mitochondrial bioenergetics and cellular metabolism. His laboratory focuses on (1) mitochondrial energetics and

fusion/fission dynamics specific to cancer cells and neurons (2) identification of metabolic control points as new targets for anti-cancer therapeutics (3) understanding control of N-linked and O-linked glycosylation pathways in cancer immune cells (4) glycoengineering IgG biotherapeutics for enhanced ADCC, CDC and enhanced immunomodulatory properties (5) identification of glycosylation-based biomarkers for cancers.

Irit Sagi (Weizmann Inst)

Controlling extracellular remodeling as a strategy to fight inflammatory diseases and cancer

Irit Sagi. Dept. of Biological Regulation. The Weizmann Institute of Science.
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The extracellular matrix (ECM) is an essential mediator of tissue function that provides both chemical and mechanical stimuli to influence cellular behavior in both health and disease. Remodelling of cellular microenvironments, including its biomineralization, and ECM by enzymes such as matrix metalloproteases (MMPs/ADAMs) and lysyl oxidases (LOX/LOXL) is a fundamental process, which is why its importance is becoming increasingly acknowledged. However, formidable challenges remain towards identifying the diverse and novel roles of such enzymatic ECM reactions, especially with regard to their distinct biophysical, biochemical, and cellular impact. Considering the heterogeneous, dynamic and hierarchical nature of both the ECM and cellular microenvironments, we set to decipher remodelling molecular mechanisms dictating cell behavior in various physiological and pathological scenarios. Accordingly, we utilize a multidisciplinary integrated research scheme which provides a three-dimensional functional molecular view of ECM remodelling, driven by proteolysis and covalent collagen cross linking. Subsequently, we employ systems biology tools to reveal changes in ECM molecular compositions, focusing on native and reconstituted ECM environments. By implementing our discoveries of these highly selective functions, into the design of novel molecular agents targeting pathological ECM remodelling, we can now impact invasive diseases causing inflammation and cancer.

BIOGRAPHY: Department of Biological Regulation , Dean of the Feinberg Graduate School . Born in Israel, Prof. Irit Sagi attended university in Washington, DC, receiving a BSc degree from American University (1988), and PhD degrees in biophysics/bioinorganics from Georgetown University (1993). That same year, she returned to Israel to perform postdoctoral research in the group of Prof. Ada Yonath, laureate of the 2009 Nobel Prize in Chemistry at the Weizmann Institute of Science. Sagi continued her postdoctoral studies at the Max-Planck Institute in Berlin, returning to join the faculty of Chemistry, Department of Structural Biology of the Weizmann Institute in 1998. Between 2005-2006 she spent a sabbatical as a visiting professor at Harvard University and at Novartis research institute. Prof. Sagi is the incumbent of the Maurizio Pontecorvo Professorial Chair. She has more than 75 publications in peer reviewed scientific journals and books. Prof. Sagi received the Weizmann Institute Scientific Council Prize for Chemistry in 2003. In 2006 she won the "Inventor of the year award" from YEDA Ltd. Since 2009, Prof. Sagi has been the president of the Israel Biophysical Society. Since 2012 she has been serving as the scientific coordinator of the Institute Pasteur-Weizmann council. Prof. Sagi is the recipient of the 2013 Juludan Prize award for outstanding research projects in the exact sciences and advanced medicinal technologies. Prof. Sagi is chairing the new "Wizo-Weizmann Institute Education Center" for the promotion of women and young scientists. In 2014 Porf. Sagi was appointed as the Dean of the Feinberg Graduate School in the Weizmann Institute of Science.

Mark Ferguson

Director General, Science Foundation Ireland

Impact from excellent research: programmes, metrics and international benchmarking of small advanced nations

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Mark Ferguson was appointed Director General of Science Foundation Ireland in January 2012. Previously he was Professor in Life Sciences at the University of Manchester (since 1984) and co-founder and CEO of Renovo Group plc (since 1998).

At the University of Manchester Mark was Head of Department and Dean, played a key role in the internationally acclaimed restructuring of Life Sciences and ran a large research group investigating scarring, wound healing, cleft palate development, alligator and crocodile biology. He is the recipient of numerous international research awards including the 2002 European Science Prize, and is the author of 325 research papers and book chapters, 8 books and 60 patent families.

Mark has a deep interest in translating scientific research findings into successful commercial entities. He founded and funded (including a £13.5M state of the art building) the Manchester Biosciences Incubator, which has successfully mentored and housed a number of start up companies. Based on inventions and patents from his University research,

Mark co –founded (with Dr Sharon O'Kane) Renovo, a biotechnology company developing novel pharmaceutical therapies to prevent scarring and accelerate wound healing. As CEO, since foundation, Mark built and led Renovo from 2 people to a peak staff of approx 200, and from being a small private start up to a listed public company.
Mark has been President of a number of Learned Societies e.g. European Tissue Repair Society, chaired the first UK Government's Health and Life Sciences Foresight Panel, and served on many committees e.g. the UKTI Life Sciences Marketing Board, the Committee of Safety of Medicines Biological Subcommittee and the European Space Agency. He has served on the Board or Scientific Advisory Board of a number of International Biotechnology and Pharmaceutical Companies.
Mark graduated from the Queens University of Belfast with degrees in Dentistry (BDS 1st class honours), Anatomy and Embryology (BSc 1st class honours, PhD) and Medical Sciences (DMedSc), holds Fellowships from the Royal Colleges of Surgeons in Ireland (FFD), and Edinburgh (FDS) and is a Founding Fellow of the UK Academy of Medical Sciences (FMedSci). He is a member or Fellow of a number of learned Societies, and was made a "Commander of the British Empire" (CBE) by the Queen in 1999 for services to Health and Life Sciences.

Mudi Sheves

The Weizmann Institute of Science for The Benefit of Society: Technology Transfer Mechanism

M.Sheves- Vice President for technology transfer. E: mudi.sheves@weizmann.ac.il

An important goal of the Weizmann Institute is the conversion of research findings and academic knowledge accumulated by its scientists into practical applications for the improvement of health and the standard of living. Thus, the Institute encourages cooperation with commercial entities to promote high-tech and bio-tech industry, especially in Israel. Marketing and commercialization of all Intellectual Property is accomplished by Yeda Research and Development Co. Ltd, the Institute's commercial arm. The Institute's wishes and priorities in the commercialization process are implemented through the Vice President for Technology Transfer.
Yeda initiates and promotes the transfer to the global marketplace of research findings and innovative technologies developed by WIS scientists. Yeda holds an exclusive agreement with the Weizmann Institute to market and commercialize its intellectual property and generate income to support further research and education.
Yeda performs the following activities:

- Identifies and assesses research projects with commercial potential.
- Protects the intellectual property of the Institute and its scientists.
- Licenses the Institute's inventions and technologies to industry.
- Channels funding from industry to research projects.

BIOGRAPHY: Mudi Sheves is Vice President for technology transfer in The Weizmann Institute. He obtained his Ph.D in Chemistry in the Weizmann and in 1978, under the supervision of Professor Y Mazur he carried out postdoctoral work in "investigations of Vitamin D" .He has held numerous appointments at the Weizmann Institute including Professor of the Department of Organic Chemistry. He has received numerous awards for his research including the Landau Research Prize, Bergman Prize for Chemistry and Miler fellowship, University of Illinois, Urbana.

Diarmuid O'Brien

Research to Impact from an Ireland, Trinity and TBSI perspective

Director of Trinity Research and Innovation Services, diarmuid.obrien@tcd.ie

Diarmuid O'Brien is the Director of Trinity Research and Innovation Services. Prior to this role he was the Executive Director of CRANN – an internationally recognised centre of excellence for nanotechnology research based at Trinity College Dublin. During his time as executive director CRANN was awarded >€250M of competitive research funding and produced research output which resulted in Ireland's global ranking of 6th and 8th for nanotechnology and material science respectively. He also developed significant linkages with industry and a strong commercialisation culture within CRANN and supported the development of the AMBER centre. Prior to CRANN he worked in senior management roles in a number of start-up companies. NTera, an electrochromic display company; Xoliox a high power battery company based in Lausanne, Switzerland and Deerac Fluidics a company developing tools to support the drug discovery process. He has a degree in Materials Science from Trinity College Dublin and PhD in Physics from the University of Sheffield, UK. He has worked as a research fellow at Kyushu University, Japan and Princeton University, USA. His research on displays has resulted in a novel licensed technology which is utilised in millions of OLED displays today, including many mobile phone devices.
In relation to the talk itself I had a view that I would be presenting out on the commercialisation landscape in Ireland – including licensing, campus company formation and industry engagement. Highlighting the maturing view in the higher education sector of the role of innovation and industry partnership. Specifically I would be talking about the

successes from Trinity over the last number of years and our ambition in this area. Finally I would focus on TBSI and the realisation of the ambition to show the direct connection from world leading academic research and measureable impact.

Ruth Arnon

The Contribution of the Academia in Israel to Society and the Economy

Ruth Arnon, Department of Immunology, Weizmann Institute of Science, and President of the Israel Academy of Sciences and Humanities. E: ruth.arnon@weizmann.ac.il

Research performed in universities and academic institutions is mostly basic, namely curiosity-driven. However, in some cases it results in innovations and reaches a stage when these are applicable. In such cases, technology transfer may lead to conversion of the applicable to Applied Research, since development into a product can be achieved only by industry. It should be emphasized that only a fraction of basic research leads to applicable innovations and only a small fraction of those become applied. Several examples from Israeli research in many disciplines of science will be presented. These include innovations based on theoretical as well as computer science; theoretical and applied physics, including contributions to Israel security; chemistry and specially nanomaterials and nanotechnology; agriculture; biotechnology and drug development, as well as development of medical devices. It may be concluded that in Israel basic research in universities and other academic institutions promotes scientific knowledge, but is often also "translated" into applied science. All universities in Israel have Technology Transfer units that secure their Intellectual Property. Technology transfer enables the inter-relations between the academia and industry (Technological Incubators, as well as Start-up Companies) in both High-Tech and Bio-Tech. This interaction promotes the economy of the country as well as its scientific reputation.

BIOGRAPHY: President of the Israel Academy of Sciences and Humanities. Formerly Vice-President of the Weizmann Institute of Science Prof. Arnon is a noted immunologist. Prior to her appointment as Vice-President, she served as Head of the Department of Chemical Immunology, and as Dean of the Faculty of Biology. Prof. Arnon has made significant contributions to the fields of vaccine development, cancer research and to the study of parasitic diseases. She is the co-developer of Copaxone® a drug for the treatment of multiple sclerosis, which is marketed worldwide. Prof. Arnon is a member of the Israel Academy of Sciences, and was the Chairperson of its Sciences division from 1995-2001. On the world scene, she is an elected member of the European Molecular Biology Organization (EMBO), and the American Philosophical Society (APS). She has served as President of the European Federation of Immunological Societies (EFIS), and as Secretary-General of the International Union of Immunological Societies (IUIS), as well as the President of the Association of Academies of Sciences in Asia (AASA). Her awards include the Robert Koch Prize in Medical Sciences, Spain's Diaz Memorial Prize, France's Legion of Honor, the Hadassah World Organization's Women of Distinction Award, the Wolf Prize for Medicine, the Rothschild Prize for Biology, The AESKU Prize for Life Contribution to Autoimmunity and the Israel Prize. She received Honorary Doctorates from Tel-Hai College; Ben-Gurion University of the Negev, Tel-Aviv University, and The Open University of Israel.

Tom Lynch
Chair of Board, TBSI
Chairman of Icon plc,

Thomas Lynch is Chairman of Trinity Biomedical Research Institute. He has extensive experience of the life sciences industry having worked in biotechnology and speciality pharma. He currently serves as Chairman of Icon plc, one of the World's largest clinical research organisations. Tom is also Chairman of the Ireland East Hospital Group, the largest grouping of acute hospitals in Ireland and a designated academic health science centre. Tom also serves on a number of boards of public and privately held biotechnology companies.