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Panorama

DC2010: Forum on Vaccine Science 26–30 September 2010, Lugano, Switzerland

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DC2010: Forum on Vaccine Science sounds like a nice name for a conference. It was indeed the name of an outstanding meeting held in the beautiful city of Lugano (Fig. 1), Switzerland, at the end of September last year. It was a great group of world leading scientists, a great environment, nice weather and a delicious catering to keep us moving. The time table was a little bit compressed and the poster/discussion session was held at the end of very long days. Sometimes it was hard to follow up. However, the free wine at the bar cheered up all poster sessions (Fig. 2). The dendritic cell (DC) scientist invaded the city of Lugano carrying the distinctive orange bags from the conference (Figs. 2 and 3).

The meeting started with the warming welcome by **Antonio Lanzavecchia** (Institute for Research in Biomedicine, Switzerland), followed by a show by two musicians Bruno Bieri and Sandro Schneegeli (Di Vento Suoni) who interpreted several pieces of folk music from this part of Switzerland with very characteristic instruments. After this nice piece of entertainment, **Rino Rappuoli** (Novartis Vaccine, Italy) gave us an overview of the 21st century vaccines. It was a perfect introduction for the keynote lecture by **Rafi Ahmed** (Emory Vaccine Center, Atlanta, USA) who extensively discussed therapeutic vaccination with PD-1 blockade within chronic or acute viral infections.

Monday morning plenary session 1 was headlined "*Signaling and adjuvants*". During a very interesting talk, **Caetano Reis e Sousa** (Immunobiology Laboratory, Cancer Research, UK) explained to us that some sensing of pathogen components (TLR9, 7 or 3 and RIG-I) are involved not only in identification but also in the recognition of self alterations that might accompany infection, such as induction of cell death. These pathways regulate DC activation and have applications in immunotherapy of cancer and infectious diseases. **Xuetao Cao**'s talk (National Key Laboratory of Medical Immunology & Institute of Immunology, Shanghai, China) was on cross-regulation of TLR-triggered innate inflammatory response. After, **Jurg Tschopp** (Department of Biochemistry, University of Lausanne, Switzerland) showed the efficacy of type I IFN in the treatment of inflammatory diseases (i.e. type 2 diabetes and multiple sclerosis) by diminishing IL-1 production and also the observed "weakening" of the immune system following viral infection. Sadly, on March 22, 2011, Prof. Jürg Tschopp, passed away due to a cardiac attack when he was skiing together with his family. The scientific community will miss him.

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Figure 1 – Landscape of Lugano Lake. Surrounded by mountains and a splendid lake, Lugano brings together all the characteristics of a metropolis of great style, despite maintaining the traits of a small city.

To finish plenary session 1, **Meredith O'Keeffe** (Department of Research in Immunology, Bavarian Nordic GmbH, Martinsried, Germany) concentrated on proteomic analyses that reveal differential sensing of cytoplasmic viruses by DC subsets of mouse spleen. Whereas the $CD8^+$ DC subsets lack expression of the rig-like helicase RIG-I, the $CD8^-$ subsets express it constitutively at high levels.

Following Monday morning, **Miriam Merad** (Department of Gene and Cell Medicine, Mount Sinai School of Medicine, NY, USA) started with plenary session 2 ("*Antigen presenting cells*"). She introduced the idea that two developmentally distinct DC subsets populate mice interface tissues including the dermis, lung and intestine. These DC subsets are best distinguished based on the expression of the integrin CD103 and the fractalkine receptor CX3CR1 and include $CD103^+CD11b^-CX3CR1^-$ DCs and $CD103^-CX3CR1^+$ DCs. She presented evidence that these DC populations arise from two distinct differentiation pathways, and they are differentially

Figure 2 – Participants at the bar after the opening ceremony. Posters were allocated at the end of the hall. Scientific discussions took place in a pleasant atmosphere.

Figure 3 – DC2010 venue at the Convention Center in Lugano.

equipped to process antigens and induce distinct immune responses to vaccine antigens. **Michel Gilliet** (The University of Texas M.D. Anderson Cancer Center, TX, USA) addressed the role of plasmacytoid DCs (pDCs) in sensing self-nucleic acids in complex with antimicrobial peptides (LL37) in the context of skin wounds and autoimmunity (psoriasis). Finally, **Steffen Jung** (Department Immunology, The Weizmann Institute of Science, Israel) identified a new subset of $CD8alpha^+$ DCs in lymphoid organs of naïve mice characterized by expression of the CX3CR1 chemokine receptor. His group found that $CX3CR1^+$ $CD8alpha^+$ DCs lack hallmarks of classical $CD8alpha^+$ DCs, including IL-12 secretion, the capacity to cross-present antigen and their developmental independence of the transcriptional factor BatF3. The microarray analysis revealed that $CX3CR1^+$ $CD8alpha^+$ DCs represent a unique DC subset, related to but distinct from pDCs.

Steven G. Reed (Infectious Disease Research Institute, Seattle, USA) led the "*Adjuvants for human vaccines*" session (Forum I). He stressed the importance of optimizing the adjuvants for safe and effective vaccines. Furthermore, he commented that the most promising approaches consist of using TLR ligands (TLRL, i.e. GLA), singly or in combination, to provide synergism between the formulation and the TLRL(s), with an emphasis on targeting DC responses. In this sense, he highlighted the idea of enhancing the quality of immune response: leading to T cell responses is essential as well as the improvement in the quality of antibody responses.

There were two different workshops consisting in eight short talks. The first workshop was focused on "*Dendritic cell ontogeny, turn-over and subsets*" and the second one was devoted to "*Dendritic cells in immunity and autoimmunity*". They both had excellent speakers but the 10 min talks only gave us a glimpse of their studies, which we could further discuss later in the evening. The same happened with the poster sessions, in which a brief selection of the best posters was allowed to be presented in a very short talk.

The attention in plenary session 3 was focused on the interaction between DCs and viral responses, ranging from neurotropic and respiratory viruses to vector-borne disease viruses ("*Viral responses and dendritic cells*"). Firstly,

William Heath (University of Melbourne, Australia) described the contribution of DC subsets in the generation of immunity in skin and lymph nodes after herpes simplex virus (HSV) type I infection in mice. In summary, after acute infection resolves, tissue-resident memory $CD8^+$ T cells can be found in the skin epidermis and lymph nodes, as a population disconnected from the recirculating memory pool, persisting in the site of original infection. In contrast, memory $CD4^+$ T cells appear to form a recirculating pool of memory, with those in the skin largely restricted to the dermis. Another presentation on neurotropic virus was carried out by **Matteo Iannacone** (Harvard Medical School, Boston, USA), but in this case the subcapsular sinus (SCS) macrophages have the lead role, identified as crucial gatekeepers to the central nervous system when using vesicular stomatitis virus (VSV), a relative of rabies virus in mice. His studies have shown that SCS macrophages prevent lymph-borne neurotropic virus from infecting the central nervous system and removal of SCS macrophages does not compromise adaptive immunity against VSV, but decrease type I IFN production, essential for antiviral protection.

The session covered neurotropic viruses to a respiratory virus, influenza virus. **Adolfo García-Sastre** (Mount Sinai School of Medicine, NY, USA) described new data on the *in vivo* dynamics of influenza virus infection in mice. His laboratory generated a new recombinant influenza virus carrying a GFP reporter gene in the NS segment that replicates efficiently in lungs and shows pathogenicity in mice. They showed high levels of immune cells harbouring influenza virus antigen during viral infection and cell type-specific effects upon treatment with antivirals, opening new avenues of research in the influenza virus field. The last talk of the afternoon was a review on the implication of "system vaccinology" by **Bali Pulendran** (Emory Vaccine Center, Atlanta, GA, USA). He discussed about the developments in innate immunity and systems biology that yield insights into the mechanisms of action of some of the most successful vaccines ever developed. He has recently used a systems biology approach to identify early gene signatures that correlate with and predict the later immune responses in humans vaccinated with the live attenuated yellow fever vaccine YF-17D, or with influenza vaccines.

As days were passing, it was apparent that most of the talks showed us microarray plots with a range of green and red in the little squares. Are we discussing science or is this a nice piece of art? Sometimes, it looked like we were looking at some piece of art at MOMA, USA (Fig. 4). Technical advances had made science progressing but we have to bear in mind that explanations to advances are sometimes hard to find.

Plenary session 4 focused on antigen targeting, processing and presentation and **Sebastian Amigorena** (Institut Curie, Paris, France) opened it showing the high efficiency of DCs to cross-present, compared with other phagocyte cells. This property resides in their ability to neutralize phagosomes through the NADPH oxidase NOX2, providing a low degradative environment and the ability to export phagocytosed antigens to cytosol and their capability to recruit ER resident proteins. **Nilabh Shastri** (University of California, Berkeley, CA, USA) followed talking about vaccines made by manipulating the antigen-processing pathway. A better understanding of antigen cross-presentation pathway was a very important issue in order to alter it and improve vaccine efficacy, as seen with the ERAAP aminopeptidase, whose inhibition leads to changes in the composition and structure of pMHC-I repertoire in normal and infected cells. **Isabelle Bouvier** (University of Minnesota Medical School, Minneapolis, USA) talked about local delivery of cell-associated antigen that results in more robust cross-priming and impacts the timing for optimal adjuvant delivery. Using a quantitative detection method, the group studied the best route of vaccination, emphasizing that local intradermal injection of cell-associated antigen resulted in the differentiation of a more robust effector T cell response and, remarkably, the timing of choice to adjuvant injection is one day after immunization.

Figure 4 – Art exhibition at MOMA (NY, USA).

Plenary session 5 was indeed a "*Late-breaking session*". Firstly, **Kenneth M. Murphy** (Washington University School of Medicine, St Louis, MO, USA) described how BATF family AP-1 transcription factors regulate immune lineage decisions. $Batf3^{(-/-)}$ mice displayed reduced priming of CD8 T cells after pulmonary Sendai virus infection, with increased pulmonary inflammation. In the MLNs and intestine, Batf3 deficiency resulted in the specific lack of $CD103^+CD11b^-$ DCs, with the population of $CD103^+CD11b^+$ DCs remaining intact. The relationship between $CD8alpha^+$ cDCs and nonlymphoid $CD103^+$ DCs implied by their shared dependence on Batf3. In a short talk, **Nicolas Manel** (Institute Curie, Paris, France) spoke about the engagement of innate immune system signals in HIV-specific adaptive immunity. Dendritic cells do not mature after HIV contact due to their resistance to infection. However, when this resistance is overcome, the association of newly synthesized HIV capsid with cyclophilin A takes place, promoting DCs activation through a pathway that involves not only cellular cyclophilin A but also IRF3. This constitutes the first description of a cell-intrinsic recognition mechanism of retroviruses. **Jolanda M. de Vries** (Radboud University Nijmegen Medical Centre and Nijmegen for Molecular Life Sciences, Nijmegen, The Netherlands) showed us the recent results on the potency of human pDCs to induce immune responses in melanoma patients. A clinical trial in stage IV melanoma patients was able to elicit both B and T cell responses against tumor in a safe and feasible manner. It

consisted of pDCs injection at low numbers (3×10^6 cells) in lymph nodes, pulsed with melanoma peptides and activated for 6 h with FSME vaccine in order to induce IFN I secretion and pDCs activation. Finally, **Matthew Collin** (Newcastle University, Newcastle, UK) spoke about a new class of immuno-deficiency with implications for DC ontogeny and induction of immunity in humans. The identification of a new syndrome, which comprises monocytes and DC deficiency together with myeloproliferation, discovers alterations in IRF8, providing new evidence about the implication of this transcription factor in monocyte and DC development in humans.

Ira Mellman (Genentech, Inc., USA) discussed about cancer immunology and tumor vaccines in Forum III. He gave an overview of the approved agents in immunotherapy and the different vaccine trials under way, from the early peptide trials to the trials using vaccinia virus, to the actual trials using agents to specifically block CTLA 4 molecule.

The role of the CCR2 expressed by inflammatory "patrolling" monocytes ($Ly6C^{hi}$) to exit the bone marrow was addressed by **Eric Pamer** (Memorial Sloan-Kettering Center, NY, USA) in plenary session 6 ("*Immune responses to microbes*"). These monocytes were recruited to sites of *Lysteria monocytogenes* infection where they differentiate in TNF-α and iNOS producing DCs. This migration was also induced by low doses of LPS injected into the mice, mimicking the infection. MCP-1 produced in the bloodstream (probably produced by endothelial cells) in response to systemic TLR-agonist was responsible for the migration. $CCR2^{-/-}$ mice had increased susceptibility to intracellular pathogens. The finding that Salmonella infection of fibroblast induces the upregulation of Cx34 (connexin) was reviewed by **Maria Rescigno** (European Institute of Oncology, Milan, Italy). Cx34 protein is involved in the formation of function gap junction between fibroblasts. Salmonella infection of tumor cells facilitates cross-presentation of tumor-associated antigens by transfer peptides through the gap junctions. DCs loaded with Salmonella-treated tumor cell line (SK-mel) induced DCs maturation and specific immune responses. This strategy to activate DCs with tumor antigens and bacteria-derived products has a great interest for *in vivo* application in patients. However, important regulatory issues must be solved before standard *in vivo* application. **Christina Zielinski** (Institute for Research in Biomedicine, Switzerland) stated that a subset of T lymphocytes known as Th17 also produce IL-10 under special circumstances. Th17 are important lymphocytes for the elimination of fungi and extracellular bacteria. Around 36% of Th17 were double positive IL-17/IL-10. IL-10 was not produced in the resting situation, but requires CD3–CD28 activation. IL-1β acted on naïve T cell differentiation toward "IL-10 producing Th17 cells"

Plenary session 7 on Wednesday was entitled "*Immune response in tissues*". **Christian Kurts** (Institute of Experimental Immunology, Bonn, Germany) focused on DCs from kidney. He concluded that kidney DCs are sentinels against bacterial pyelonephritis (PN) and they recruit and activate PMNs. So, kidney DCs initiated the innate cellular immune defense against PN. Later, **Irina Gurevich** (The Immunology Department, Weizmann Institute of Science, Rehovot, Israel) kept us all awake showing live cell imaging *in vivo* and *in vitro* about antigen transfer within DC networks for T cell activation. Keeping in tune with the theme of the session, **Bart N. Lambrecht** (Laboratory of Immunoregulation and Mucosal Immunology, University Ghent, Belgium) explained to us that antigen-presenting DCs are crucial not only in the initiation of T cell responses, but also for their maintenance in the context of allergic asthma. To finish this session, **Cornelis Melief** (Department of Immunohematology and Blood Transfusion, Leiden University Medical Center, The Netherlands) presented us the results of phase I/II studies with an HPV16 SLP® vaccine. His conclusion was that the next generation of vaccines must be consisted in TLR ligand and long peptide combination.

Following with session 8 ("*Enhancing immune response*"), **Kevin N. Heller** (Bristol-Myers Squibb, NY, USA) carried out an update on the phase II and III programs from Ipilimumab (anti CTLA-4). **Jacques F. Banchereau** (Baylor Institute for Immunology Research, Dallas, TX, USA) overviewed loading DC with antigens through DC receptors to design novel human vaccines. **Vincenzo Cerundolo** (MRC Human Immunology Unit, Department of Medicine, University of Oxford, UK) demonstrated the expansion of IL-10 secreting neutrophils in melanoma patients and the capacity of iNKT cells to abolish their suppressive activity. Lastly, **Michael Erdmann** (Department of Dermatology, University Hospital Erlangen, Germany) talked about the results of vaccination with class I and II tumor peptide-loaded, cocktail-matured monocyte-derived DCs in melanoma patients. The data demonstrated solid immunogenicity and prolonged survival in a subset of patients exhibiting a particular gene expression profile.

Ruslan Medzhitov (HHMI, Yale University School of Medicine, New Haven, CT, USA) driven "*Host defense strategies*" session (Forum V). He exposed the idea that the host defense from infections can be achieved by two distinct strategies: resistance and tolerance. Whereas the resistance mechanisms aim to eliminate pathogen burden, the tolerance mechanisms allow the host to tolerate the presence of pathogens by minimizing their harmful effects on the host.

On the last day, **K. Woollard** (INSERM, Paris, France) opened plenary session 9 entitled "*Myeloid cells in inflammation*" with the characterization of human monocytes CD14dimCD16+, the counterpart of murine patrolling Gr1(dim) monocytes. Those cells were weak phagocytes and did not produce ROS or CK in response to cell-surface TLRs, but they selectively produced TNFa, IL-1b and CCL3 via a proinflammatory TLR7-TLR8-MyD88-MEK pathway. **I. Matos** (Rockefeller University, New York, USA) continued describing a mice DC population $DC\text{-}SIGN^{+}CD14^{+}$ that migrated to LNs after LPS administration in a $CD62L^{-}$ and CCR7-dependent manner. On a different note, **V. Bronte** (University of Padua, Padua, Italy) showed that GM-CSF, G-CSF and IL-6 produced by experimental tumors allowed a rapid generation of myeloid-derived suppressor cells (MDSCs) from precursors of mouse and human BM, which possessed a very high tolerogenic activity that was entirely dependent on the C/EBPbeta transcription factor. The short talk of the session was in charge of **C.S. Boddupalli** (IRB, Bellinzona, Switzerland), who described the different roles of Flt3L on DC homeostasis during steady-state and inflammatory conditions.

The "correlates of protection" plenary session 10 began with **R.A. Seder**'s talk (Vaccine Research Center, NIH, Bethesda, USA). The speaker showed how synchronous delivery of an aggregated protein conjugated to a TLR7 agonist conjugate vaccine optimized Th1 and CD8 T cell immunity. **S.H. van der Burg**'s group (Leiden University Medical Center, Leiden, The Netherlands) developed an immunotherapeutic vaccine strategy based on the use of synthetic long overlapping peptides from E6 and E7 proteins of HPV16 and examined the virus-specific immunity in relation to lesion size. Next, **W.H. Fridman** (INSERM, Paris, France) demonstrated in colorectal cancer patients that infiltration of tumors by Th1 and CD8 T cells is the strongest prognostic factor for disease non-progression and overall survival. **D.N. Hart** (ANZAC, Sydney, Australia) ended the session presenting the Cooperative Research Centre for Biomarker Translation, headquartered at La Trobe University in Australia, where a DC Biology and Therapeutics Program took place that involved clinical colleagues in evaluating mAbs to DC surface molecules as potential diagnostic and therapeutic agents. The forum "Treg vaccination" by **H. von Boehmer** (Dana-Farber Cancer Institute, Boston, USA) ended the morning session. He explained that the combined use of Everolimus and IL-2/IL-2ab complexes *in vivo* achieved highly effective antigen-driven conversion of naive T cells into Treg and their expansion, which constituted an important tool to achieve immunological tolerance by Treg vaccination.

The last session of the congress polarized on the different mechanisms of suppression of innate and adaptive immunity (plenary session 11). **Ethan Shevach** (NIAID, USA), described *in vivo* models to analyse the mechanisms used by both polyclonal and antigen-specific regulatory T cells (Tregs) to inhibit the priming of effector $CD4^+$ T cells in immunocompetent mice. In summary, two different mechanisms to suppress immune response *in vivo* were used: the polyclonal Tregs induced multiple alterations in effector cells that potentially impeded egress from draining lymph nodes and inhibited their access to target organs, while antigen-specific Tregs inhibited effector cell expansion, activation and differentiation, impairing the DC capacity to activate naïve T cells. Also, the pathogenesis of systemic lupus erythematosus (SLE) was discussed by **Virginia Pascual** (Baylor Institute for Immunology Research, Dallas, USA). They have found that mature SLE neutrophils are primed *in vivo* by type I IFN and die by netosis, releasing extracellular traps (NETs) upon exposure to SLE-derived antibodies. SLE NETs contain DNA as well as large amounts of other two proteins that facilitate the uptake and recognition of mammalian DNA by pDC. Indeed, SLE NET-DNA activate pDC to produce, in a TLR9-dependent manner, high levels of IFNα, whose increased production and bioavailability have been already linked to SLE pathogenesis. In the last talk of the session **Anne O' Garra** (National Institute for Medical Research, London, UK) illustrated the role of IL-10 in tuberculosis (TBC). IL-10 is produced in the lung and data in knock out mice have shown that there is a better control of the disease in absence of this cytokine. IL-10 contributes to the disease by delaying and diminishing protective T helper 1 response in the lung, suggesting that *Mycobacterium tuberculosis* may induce IL-10 production to evade immune clearance.

The closing session was more relaxed as prizes and awards were given. Also, the next DC2012 in Korea was presented with a breathtaking video shown by the organizers. Lastly, Ralph Steinman closed the meeting introducing to the audience the generation of the International Society for Dendritic cell and Vaccine Science (www.DC-Vaccine.org) to the audience and wishing everybody the best in their future experiments with a warm farewell.

To end up the meeting, the organizers prepared a boat tour in the lake and a farewell dinner in the Casino. There were nice surprises in the dinner, like a flashmob by scientists and two nice bands to cheer up the evening. After all the days discussing on dendritic cells, DC scientists were not too bad at enjoying themselves and dancing on the floor!. We all had a very enjoyable time and we are looking forward to the next DC meeting.