



Conference Scenes: Immunotherapies in transplantation and cancer

Sylvain Simon, Maud Charpentier, Ignacio Anegón, Nathalie Labarrière

► To cite this version:

Sylvain Simon, Maud Charpentier, Ignacio Anegón, Nathalie Labarrière. Conference Scenes: Immunotherapies in transplantation and cancer. Immunotherapy, 2017, Epub ahead of print. inserm-01639012

HAL Id: inserm-01639012

<https://inserm.hal.science/inserm-01639012>

Submitted on 20 Nov 2017

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Conference Scenes: Immunotherapies in transplantation and cancer

Sylvain Simon^{1,2}, Maud Charpentier^{1,2}, Ignacio Anegón^{2,3,4}, Nathalie Labarriere^{*1,2, *}

¹ CRCINA, INSERM, Université d'Angers, Université de Nantes, Nantes, France

² LabEx IGO "Immunotherapy, Graft, Oncology", Nantes, France

³ Centre de Recherche en Transplantation et Immunologie UMR1064, INSERM, Université de Nantes, Nantes, France

⁴ Institut de Transplantation Urologie Néphrologie (ITUN), CHU Nantes, Nantes, France

22th NAT meeting/2nd NAT LabEx IGO joint meeting; 1-2 June 2017, Nantes, France.

22th NAT meeting/2nd NAT LabEx IGO joint meeting

1-2 June 2017, Nantes, France.

Keywords: Immunotherapy, transplantation, cancer, tolerance, costimulation blockade, T cell therapy, dendritic cells, NAT, LabEx IGO, France

* Address correspondence to: nathalie.labarriere@inserm.fr

Phone: +33 228 080 241

Fax: +33 228 080 204

Postal address: CRCINA, Inserm UMR1232, 8 Quai Moncousu, 44007 Nantes Cedex 1

Abstract

This 22th edition of the NAT (« Nantes Actualités Transplantation ») annual meeting was co-

Mis en forme : Interligne : 1,5 ligne

Mis en forme : Espace Après : 12 pt, Interligne : 1,5 ligne

Mis en forme : Interligne : 1,5 ligne

Mis en forme : Interligne : 1,5 ligne

organized for the second time with the LabEx IGO network (« Immuno-Graft Oncology »). This international meeting was held on 1 and 2 June 2017 in Nantes (Western of France).

The topic of this 2-days meeting was “Immunotherapies in transplantation and cancer”. This meeting brought together 17 international invited speakers, young researchers and 220 attendees mainly from Europe and North America. It was a unique opportunity to bring together the pioneers and leading immunologists in the fields of transplantation and cancer, focusing on shared mechanisms that control immune responses in organ or bone marrow transplantation and in cancer.

| ~~Word count: 112~~

This 22nd edition of the NAT (www.nat.nantes.inserm.fr/index.php/en) meeting, co-organized with the LabEx IGO (<http://www.labex-igo.com>) : Immunotherapies in transplantation and cancer” took place in Nantes, France (June 1-2, 2017). This meeting, divided in four sessions, focused on key molecules, molecular mechanisms or cell subsets (sessions I, II and III) involved in the control of graft tolerance and in cancer. Indeed, a given molecule/cell subset/pathway that inhibits immune responses needs to be stimulated in transplantation to favor immune tolerance and better graft outcome whereas it needs to be inhibited or neutralized in the cancer setting to favor cancer elimination. As an example, tolerance mechanisms need to be strengthened in organ and bone marrow transplantation whereas this tolerance needs to be broken in cancer. The last session was devoted to original approaches in T cell therapy.

The chairmen of the meeting were Ignacio ANEGON and Nathalie LABARRIERE, belonging to the organizing and scientific committee with Béatrice CHARREAU, Sophie CONCHON, Jean-François FONTENEAU, Joëlle GASCHET and Cédric LOUVET.

Session I: Tumour and graft microenvironment

The first session focused on the microenvironment that shapes the immune response towards tumours and grafts.

Romain Roncagalli (CIML, Marseille, France) reported about protein-protein interaction identification methods and their usefulness in deciphering T-cell signalling networks. RLTPR was described as a new protein of CD28 signalling pathway, whose mutation results in functional phenocopy of CD28^{-/-} and abrogates CD28-dependant proliferation of CD4 T-cells in a genetic lymphoproliferative disease [1]. In a second study, new partners of CBL and CBLB negative regulators of T-cell activation were identified such as the transmembrane protein CD5 [2]. The identification of interactomes improves understanding of T-cell activation pathways and may provide new targets for T-cell engineering in immunotherapeutic strategies.

The impact of microbiota on immune responses and graft outcome was highlighted by *Maria-Luisa Alegre* (University of Chicago, USA) who showed that graft survival was prolonged when using germ free mice or treatment with large spectrum antibiotics prior to transplantation [3]. Prolonged graft survival in treated mice was associated with poor proliferation of donor-specific T-cells, and a decreased activation of DCs. Additionally, the identification of some individual microbial communities that favours graft survival when transferred in animals with a less beneficial microbiota could be a great asset to avoid rejection particularly in the context of mismatched allografts.

Ivan Maillard (University of Michigan, USA) focused on the implication of the Notch system in allogeneic hSCT and GVHD induction. Inhibition of the interaction between Notch 1/2 and DLL1/DLL4 dramatically reduced the GVHD occurrence without interfering with the anti-tumour potential [4]. The use of DLL1/DLL4 blocking antibodies maintained the proliferative capacities of infused T-cells, producing less inflammatory cytokines and with a higher proportion of Tregs. Targeting individual Notch pathway components appears safe to modulate T-cell activation in bone marrow transplanted mice and prevent GVHD without toxic side effects.

Salvatore Valitutti (University of Toulouse, France) documented that melanoma cells were able to counteract CTL cytotoxic activity by mobilization of their lysosome/late endosome compartment to the immunological synapse [5]. Enriched in cathepsin B (perforin-degrading enzyme), melanoma lysosomes are secreted at the synapse to inhibit CTL cytotoxic activity. Dampening the tumour cells resistance to lytic activity of CTLs could be beneficial in immunotherapy protocols, which for the moment focus on improving the activity, proliferation and survival of the latter.

Session II: Immune check points in transplantation and cancerology

Immune checkpoints, major modulators of the immune response, represent promising targets either to induce immune tolerance or tumour rejection and the therapeutic use of immune checkpoint inhibitors (ICI) can be further combined with other therapies.

Carole Guillon (CRTI, Nantes, France) described a new immune checkpoint, CD45RC, expressed by B, NK, myeloid, and a fraction of T-cells but not by Tregs. The administration of a monoclonal antibody targeting CD45RC in a rat model of cardiac allotransplantation induced solid organ transplant tolerance and inhibited GVHD through direct cell death of CD45RC^{high} cells and preservation of CD45RC^{low/-} Tregs, inhibiting allograft rejection [6]. CD45RC targeting could represent a promising therapeutic strategy in transplantation to eliminate effector cells and promote allograft tolerance.

Comparing transcriptional programs of PD-1⁺Tim-3⁺, PD-1⁺Tim-3⁻ and PD-1⁻Tim-3⁻ TILs from tumour-bearing mice, *Ana Anderson* (Harvard Medical School, Boston, USA) identified the metallothionein MT1 as the most differentially expressed gene in the PD-1⁺Tim-3⁺ dysfunctional T-cell subset [7]. MT1 deletion in mice resulted in improved CD8⁺ T-cell functions and delayed tumour growth. Single-cell transcriptional analysis of CD8⁺ TILs from WT or MT^{-/-} mice revealed different genes modules strictly associated with T-cell dysfunction, T-cell activation or activation/dysfunction together. Gata-3 was the most enriched transcriptional factor in the T-cell dysfunction module and Gata-3 deletion in anti-tumour CD8⁺ T-cells resulted in reduced tumour growth in a melanoma mouse model. This study demonstrates the possibility to uncouple

activation and exhaustion gene programs and provides new insights in the understanding of molecular mechanisms of CD8⁺ T-cell dysfunction.

Claire Vanpouille-Box (Weill Cornell Medicine, NY, USA) addressed the superior interest of multi-fractionated low-dose radiotherapy to induce T-cell responses and synergise with anti-CTLA-4 therapy [8]. In a poorly immunogenic mouse model, multi-fractionated low-dose radiotherapy was able to induce long-term tumour regression with abscopal effect and synergized with anti-CTLA-4 antibody in contrast to radiotherapy delivered at high energy in a single dose. Fractionated radiotherapy led to the accumulation of fewer double-stranded DNA (dsDNA) unsufficient for Trex1 activation. Therefore, dsDNA accumulated and activated Type-I interferon pathway that mediated recruitment of DCs into the tumour bed leading to efficient anti-tumour immunity. This study paved the way for effective therapeutic combination with radiotherapy.

Finally, *Eric Vivier* (CIML, Marseille, France) gave a keynote addressing the roles of Innate Lymphoid Cells and their potential manipulation in cancer and viral immunity [9].

Session III: Macrophages and dendritic cells

Myeloid cells such as macrophages and dendritic cells (DC) orchestrate adaptive immune responses in transplantation and cancer settings. Their unique properties of antigen presentation and stimulation/regulation of effector T-cells make them attractive targets for immunotherapy in these two pathological contexts.

Elodie Segura (Institut Curie, Paris, France) reported about human monocyte-derived inflammatory DC, a DC subset strongly expressing CD206 (Mannose-R) and a potent inducer of Th17 T-lymphocytes [10]. Transcriptomic and single cell analyses revealed that IRF4 was the key transcription factor involved in inflammatory DC differentiation, and that these DCs were induced within tumour microenvironment, through aryl hydrocarbon receptor (AhR) signalling which synergizes with cytokine signalling for IRF4 induction.

Jolanda de Vries (Nijmegen, The Netherlands) made an overview of DC-based immunotherapy in cancer patients with a focus on two clinical trials based on BDCA1⁺-DC and plasmacytoid-DC,

loaded with melanoma-derived peptides. Immunogenicity of the vaccines and clinical outcome of the patients need to be further improved. In this respect, depletion of the CD14⁺ fraction from BDCA1⁺-DC could further improve the immunogenicity of the vaccine [11].

Yong-Guang Yang (Columbia University, NY, USA), reported about SIRP- α /CD47, a signalling pathway that could be targeted for the inhibition of xenograft rejection, mainly mediated by macrophages. In a physiological context the interaction of SIRP- α with CD47, expressed by macrophages, prevents phagocytosis of hematopoietic cells. However, pig CD47 fails to interact with mouse or human SIRP α and thus to inhibit phagocytosis [12]. Using hCD47 transgenic pigs, xenograft rejection was inhibited by macrophages through the induction of donor hematopoietic chimerism.

Aur lie Moreau (CRTI, Nantes, France) reported about an ongoing phase I clinical trial (part of the ONE Study European Consortium-NTC0225055) using autologous tolerogenic DC (ATDC) in kidney transplanted patients. Their ability to prevent a xenogenic GVHD has been documented in mice [13]. ATDC are produced from patient blood through a robust and GMP-compliant procedure, in the Unit of Cell Therapy of Nantes University Hospital. No serious adverse reaction has been observed for the first 7 treated patients. The efficacy of these cells will be further evaluated in transplantation or in autoimmune diseases.

Session IV: T cell therapy

This session was dedicated to recent advanced in T-cell based therapy, for cancer and transplantation purposes.

Giovanna Lombardi (King's college, London, UK) (part of the ONE Study consortium) presented safety results of the transfer of autologous polyclonal CD4⁺ Tregs to kidney and liver transplant patients. She further demonstrated in a humanized NSG mouse model, that alloantigen-specific Tregs were superior to polyclonal Tregs in preventing graft damage. Thus, *G. Lombardi and coll* refined the specificity of transferred Tregs with an anti-HLA-A2 specific CAR [14], protective against human skin graft damage in an NSG mouse humanized model.

José Cohen (IMRB, Créteil, France) presented results about the manipulation of the TNF/TNFR2 pathway in Tregs, to prevent GVHD or to increase GVL. Indeed, TNFR2 mainly expressed by Tregs, is crucial for the protective effect of CD4⁺ Tregs on GVHD [15]. This pathway could thus be targeted to finely tune Treg activity in allo-hSCT.

Laurent Poirot (Cellestis, France) presented a potentially universal “off the shelf” CAR-T cells therapy, gene-edited with the TALEN technology to confer to T cells specificity, optimal functions, and safety guarantees [16]. He gave the example of UCART123 (specific for a subunit of the IL-3 receptor, overexpressed by leukemic cells) for AML treatment. These UCART123 T cells do not induce GVHD in a mouse model and efficiently decreased the growth of CD123+ engrafted tumour cells.

Francois Lang (CRCINA, Nantes, France) presented the first results of the adoptive transfer to melanoma patients of natural antigen-specific T-cells, sorted and expanded from patient blood (MELSORT, NCT02424916). Specific T-cells are produced in the Unit of cell therapy of Nantes hospital, through a GMP-compliant sorting procedure with HLA-peptide coated beads (Clinimers) [17]. No treatment-related serious adverse events were observed for the two first treated patients and the patient who received the most reactive T-cells exhibited a stabilization of the disease.

In conclusion of this session, *Stanley Riddell* made an overview on functional optimizations of CAR-T cells to favour their persistence and activity within tumour microenvironment. This persistence can be improved either with the use of fully human CD19-specific scFv antigen binding domain that reduced immune rejection [18], or with a prior lymphodepletion of leukemic patients with a Cy/Flu combination [19]. Finally, *S. Riddell* documented in non-human primates that the tyrosine kinase receptor ROR1 could be a safe and relevant target for CAR-T cells in solid tumours [20].

Acknowledgements

This work was realized in the context of the Labex IGO project (n°ANR-11-LABX-0016-01) which is part of the « Investissements d’Avenir » French Government program managed by the ANR (ANR-11-LABX-0016-01) and of the IHU-Cesti project funded also by the « Investissements d’Avenir » French Government program, managed by the French ANR (ANR-10-IBHU-005). The IHU-Cesti project is also supported by Nantes Métropole and Région Pays de la Loire.

References

1. Liang Y, Cucchetti M, Roncagalli R, Yokosuka T, Malzac A, Bertosio E, Imbert J, Nijman IJ, Suchanek M, Saito T, Wülfing C, Malissen B, Malissen M. The lymphoid lineage-specific actin-uncapping protein Rltpr is essential for costimulation via CD28 and the development of regulatory T cells. *Nat. Immunol* 14(8), 858–866 (2013).
2. Voisinne G, García-Blesa A, Chaoui K, Fiore F, Bergot E, Girard L, Malissen M, Burlet-Schiltz O, Gonzalez de Peredo A, Malissen B, Roncagalli R. (2016). Co-recruitment analysis of the CBL and CBLB signalosomes in primary T cells identifies CD5 as a key regulator of TCR-induced ubiquitylation. *Mol Syst Biol* 12(7), 876 (2016).
3. Lei YM, Chen L, Wang Y, Stefka AT, Molinero LL, Theriault B, Aquino-Michaels K, Sivan AS, Nagler CR, Gajewski TF, Chong AS, Bartman C, Alegre ML. The composition of the microbiota modulates allograft rejection. *J Clin Invest* 126(7), 2736-2744 (2016).
4. Tran IT, Sandy AR, Carulli AJ, Ebens C, Chung J, Shan GT, Radojcic V, Friedman A, Gridley T, Shelton A, Reddy P, Samuelson LC, Yan M, Siebel CW, Maillard I. Blockade of individual Notch ligands and receptors controls graft-versus-host disease. *J Clin Invest* 123(4), 1590-1604 (2013).
5. Khazen B, Müller S, Gaudenzio N, Espinosa E, Puissegur MP, Valitutti S. Melanoma cell lysosome secretory burst neutralizes the CTL-mediated cytotoxicity at the lytic synapse. *Nat Commun* 4(7), 10823 (2016).
6. Picarda E, Bézie S, Boucault L, Autrusseau E, Kilens S, Meistermann D, Martinet B, Daguin V, Donnart A, Charpentier E, David L, Anegón I, Guillonnet C. Transient antibody targeting of CD45RC induces transplant tolerance and potent antigen-specific regulatory T cells. *J Clin Invest Insight* 2(3), e90088 (2017).
7. Singer M, Wang C, Cong L, Marjanovic ND, Kowalczyk MS, Zhang H, Nyman J, Sakuishi K, Kurtulus S, Gennert D, Xia J, Kwon JY, Nevin J, Herbst RH, Yanai I, Rozenblatt-Rosen O, Kuchroo VK, Regev A, Anderson AC. A Distinct Gene Module for Dysfunction Uncoupled from Activation in Tumor-Infiltrating T Cells. *Cell* 166(6), 1500-1511 (2016).
8. Vanpouille-Box C, Alard A, Aryankalayil MJ, Sarfraz Y, Diamond JM, Schneider RJ, Inghirami G, Coleman CN, Formenti SC, Demaria S. DNA exonuclease Trex1 regulates radiotherapy-

induced tumour immunogenicity. *Nat Commun* 8, 15618 (2017).

9. Vivier E, van de Pavert SA, Cooper MD, Belz GT. The evolution of innate lymphoid cells. *Nat Immunol* 17(7), 790-794 (2016).
10. Segura E, Soumelis V. Of Human DC Migrants and Residents. *Immunity* 46(3), 342-344 (2017).
11. Bakdash G, Buschow SI, Gorris MA, Halilovic A, Hato SV, Sköld AE, Schreibelt G, Sittig SP, Torensma R, Duiveman-de Boer T, Schröder C, Smits EL, Figdor CG, de Vries IJ. Expansion of a BDCA1+CD14+ Myeloid Cell Population in Melanoma Patients May Attenuate the Efficacy of Dendritic Cell Vaccines. *Cancer Res* 76(15), 4332-4346 (2016).
12. Tena AA, Sachs DH, Mallard C, Yang YG, Tasaki M, Farkash E, Rosales IA, Colvin RB, Leonard DA, Hawley RJ. Prolonged Survival of Pig Skin on Baboons After Administration of Pig Cells Expressing Human CD47. *Transplantation* 101(2), 316-321 (2017).
13. Carretero-Iglesia L, Bouchet-Delbos L, Louvet C, Drujont L, Segovia M, Merieau E, Chiffolleau E, Josien R, Hill M, Cuturi MC, Moreau A. Comparative Study of the Immunoregulatory Capacity of In Vitro Generated Tolerogenic Dendritic Cells, Suppressor Macrophages, and Myeloid-Derived Suppressor Cells. *Transplantation*. 100(10), 2079-2089 (2016).
14. Boardman D, Maher J, Lechler R, Smyth L, Lombardi G. Antigen-specificity using chimeric antigen receptors: the future of regulatory T-cell therapy? *Biochem Soc Trans* 44(2), 342-348 (2016).
15. Leclerc M, Naserian S, Pilon C, Thiolat A, Martin GH, Pouchy C, Dominique C, Belkacemi Y, Charlotte F, Maury S, Salomon BL, Cohen JL. Control of GVHD by regulatory T cells depends on TNF produced by T cells and TNFR2 expressed by regulatory T cells. *Blood* 128(12), 1651-1659 (2016).
16. Poirot L, Philip B, Schiffer-Mannioui C, Le Clerre D, Chion-Sotinel I, Derniame S, Potrel P, Bas C, Lemaire L, Galetto R, Lebuhotel C, Eyquem J, Cheung GW, Duclert A, Gouble A, Arnould S, Peggs K, Pule M, Scharenberg AM, Smith J. Multiplex Genome-Edited T-cell Manufacturing Platform for "Off-the-Shelf" Adoptive T-cell Immunotherapies. *Cancer Res* 75(18), 3853-3864 (2015).
17. Labarriere N, Fortun A, Bellec A, Khammari A, Dreno B, Saiagh S, Lang F. A full GMP process

to select and amplify epitope-specific T lymphocytes for adoptive immunotherapy of metastatic melanoma. *Clin Dev Immuno* 2013, 932318 (2013).

18. Sommermeyer D, Hill T, Shamah SM, Salter AI, Chen Y, Mohler KM, Riddell SR. Fully human CD19-specific chimeric antigen receptors for T-cell therapy. *Leukemia* PMID 28202953, in press (2017).
19. Turtle CJ, Hanafi LA, Berger C, Hudecek M, Pender B, Robinson E, Hawkins R, Chaney C, Cherian S, Chen X, Soma L, Wood B, Li D, Heimfeld S, Riddell SR, Maloney DG. Immunotherapy of non-Hodgkin's lymphoma with a defined ratio of CD8+ and CD4+ CD19-specific chimeric antigen receptor-modified T cells. *Sci Transl Med* 8(355), 355ra116 (2016).
20. Balakrishnan A, Goodpaster T, Randolph-Habecker J, Hoffstrom BG, Jalikis FG, Koch LK, Berger C, Kosasih PL, Rajan A, Sommermeyer D, Porter PL, Riddell SR. Analysis of ROR1 Protein Expression in Human Cancer and Normal Tissues. *Clin Cancer Res* 23(12), 3061-3071 (2017).