Live Talks

L1 TGF-BETA BLOCKS TYPE I IFN RELEASE AND TUMOR REJECTION IN SPONTANEOUS MAMMARY TUMORS

[1]N Bercovici*, [1]MV Guérin, [1]F Regnier, [1]JM Weiss, [1]V Feuillet, [1]L Vimeux, [2]G Altan-Bonnet, [1]E Donnadieu, [1]A Trautmann. [1]*Cochin Institute, 75014, France*; [2]*National Cancer Institute, Bethesda, MD, USA*

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Background Activation of the STimulator of INterferon Genes (STING) by DMXAA (5,6-dimethylxanthenone-4-acetic acid) can induce a strong production of IFNα/β and the rejection of transplanted primary tumors. However, the efficacy of such therapeutic approach for the treatment of spontaneous tumors had still to be evaluated.

Material and Methods We have tested whether the injection of DMXAA or other STING agonists and TLR4 agonist, could lead to the regression of spontaneous MMTV-PyMT mammary tumors. We also characterized, in time and space, the early signaling events triggered downstream STING and the distribution of infiltrating immune cells in the tumor microenvironment by fluorescence imaging.

Results We show that spontaneous MMTV-PyMT mammary tumors are resistant to immunotherapeutic intervention. We demonstrate that TGFβ, abundant in spontaneous tumors, is a key molecule limiting this IFN-induced-tumor regression by DMXAA. Mechanistically, we found that TGFβ blocks the phosphorylation of IRF3 and the ensuing IFNα/β production by tumor infiltrating macrophages. Finally, blocking TGFβ restores the production of IFNα by activated $MHCII^+$ tumor-associated macrophages, and enables tumor regression induced by STING activation.

Conclusions Based on these findings, we propose that the efficacy of many cancer therapies, which are type I IFN-dependent, should be greatly improved by combination with TGFβ blockade.

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L2 IN VIVO LIVE IMAGING OF HUMAN T/B CELL LYMPHOMA CROSS-LINKING MEDIATED BY BISPECIFIC CD20-TCB ANTIBODY

F Cremasco*, E Menietti, D Speziale, J Sam, S Sammicheli, S Chen, M Richard, C Klein, P Umana, M Bacac, S Colombetti, M Perro. *Roche Glycart AG, Schlieren, Switzerland*

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Introduction Cancer Immune Therapies have shown unprecedented results in improving tumor control.[1–3] However, many patients are still refractory to treatment. A deeper understanding of the mode of action of the different CITs sub-classes may help improving therapeutic approaches to reach better anti-tumor response. For this reason, we developed a multi-photon intra-vital microscopy (MP-IVM) approach to study *in vivo*, at single cell level, the tumor microenvironment upon treatment with CD20-targeting T-cell bispecific antibodies (TCB) [4] in a preclinical model of diffuse large B cell lymphomas (DLBCL).

Methods To selectively monitor clinical lead molecules in the context of human T cell responses, we developed a skinfold chamber model [5] in last generation humanized mice [6] that allows visualization, by MP-IVM, of labelled human T cells co-injected intra-dermally with WSU-DLCL2, a human DLBCL. We have used this model to investigate T cells recruitment to tumors upon CD20-TCB therapy: by intravenously injecting labeled T cells in mice treated with selected blocking antibodies, we were able to identify dedicated pathways induced by CD20-TCB and regulating T cell influx into the tumor bed. Furthermore, we developed a user-independent quantification platform to assess changes in the dynamics of T cell motility and time of interaction with tumor cells.

Results/Discussion We have developed an experimental preclinical model that aims to reduce xenoreaction (human T cell reaction against mouse tissue) by utilizing T cells derived from humanized mice, educated within murine thymus. We demonstrate that such model is optimal to quantify human T cell dynamics *in vivo*. We show that CD20-TCB localizes in the tumor and acts on tumor-resident T cell motility within 1 hour post i.v. injection (defined as functional PK), causing a sharp reduction in their speed (from 4 to 2 μm/min) and an increase in tumor/T cell interaction time; those changes last up to 72h post-treatment. In addition, we prove how the initial tumor/T cell interaction mediated by CD20-TCB lead to peripheral T cells recruitment into the tumor. This mechanism is dependent on the presence of tumor-resident T cells and on IFNg-CXCL10 pathway. Inhibiting any of these two parameters resulted in reduced T cells infiltration from the periphery and reduced anti-tumor efficacy.

Conclusion We developed a reliable imaging and analysis pipeline to investigate *in vivo* T cell dynamics and recruitment and applied it to the study of CD20-TCB treatment of DLBCL model. Our approach has shed new lights into the MoA of this new class of immune-therapeutics, demonstrating that the IFN□-CXCL10 pathway is involved in T cell recruitment upon CD20-TCB treatment.

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