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RNA SPLICING IN TUMORS GENERATES NEW PROTEIN ISOFORMS AND TUMOR-SPECIFIC ANTIGENS

Abstract: RNA splicing edits pre-RNA molecules right after transcription. The machinery of RNA splicing includes hundreds of effectors and regulators of the process and is critical in most fundamental cellular functions. Human cancers bear multiple defects in splicing, due to diverse mutations, including in the splicing machinery. Due to these defects, tumors express aberrantly spliced RNA (asRNA) species, recurrent among patients, but absent from normal tissues. These asRNAs code for new isoforms of known proteins and lncRNAs. In these transcripts new intronic sequences, that can include transposable elements become new exons, associated with new functions. We have characterized proteins encoded by these asRNAs, including transmembrane receptors and oncogenes/tumor suppressors. We have also shown that the asRNA species in tumors code for peptides that can be presented on HLA molecules for recognition by T cells. Certain asRNA encoded peptides are highly tumor specific and can be used for cancer immunotherapies, including adoptive T cells therapies, monoclonal bispecific antibodies and cancer vaccination.

About the speaker: Sebastian Amigorena is “Directeur de Recherche Classe Exceptionnelle” at CNRS, Director of the “Center of Immunotherapy for cancers” and the “Immune responses and cancer” Team at Institut Curie (Paris, France), in the Immunology Department "Immunity and Cancer" that he created in 2003 and directed until 2021. He obtained a PhD in Biochemistry in 1990, and joined CNRS before doing a post-doctoral training at Yale School of Medecine (1992-1994), and returned to France in 1995 to start his team at Institut Curie (Paris, France).

Dr. Amigorena made significant contributions to immunology and cell biology. He discovered ITIMs, a family of short amino acid motifs present in the cytosolic tails of numerous inhibitory immunoreceptors that play critical roles in the control of autoimmunity. He also identified specialized intracellular compartments, related to endosomes, where peptides are loaded on MHC molecules. As a group leader, he pioneered the field of antigen cross presentation, establishing the fundamental functional properties of phagosomes in mouse and human dendritic cells and showing how these specializations contribute to the initiation of adaptive immune responses by dendritic cells. Amigorena’s group also showed that regulatory T cells inhibit low avidity CD8+ T cells selectively, thus preventing autoimmune reactivity and optimizing the efficacy of effector and memory immune responses against non-self-antigens. His findings modified our understanding of antigen presentation and T cell priming by dendritic cells, with applications in the fields of cancer immunotherapy and

vaccination. In the last 10 years, his team analyzed the epigenetic programing of T cell differentiation and applied the findings to optimizing CA-T cell therapies. He also identified a new family of HLA-presented peptides derived from non-canonical splicing events, including transposable elements and lncRNAs. These studies served as a bases to initiate an ambitious cell therapy program at Institut Curie, including CAR-T clinical trials in solid tumors, and found a Mnemo Therapeutics, a spin-off of Institut Curie that develops technological innovation in immunoncology.

Dr. Amigorena published over 250 original articles, including, as a co-first or co-last author, over 30 papers in Nature, Science, Cell, Immunity, Nature Immunology, Nature Cell Biology, Science Immunology and Journal of Experimental Medicine. He is a member of the French “Académie des Sciences” and an elected EMBO member since 2005. He received numerous national and international prices and awards, including the Silver Medal from CNRS (2004), the Research award from Fondation Bettencourt (2005), the Griffuel Prize from ARC (2007), the Alt Award from CRI, and twice the prestigious senior European Research Council (ERC) award (2008 and 2014), the award Claude Bernard from Paris City (2017). He became Knight of the French "Légion d'honneur" in 2018. He co-directs the Labex (Investissements d’Avenir) DC-BIOL, awarded in 2012. He serves on numerous Editorial Boards and is a regular referee for major international journals (including as a reviewing editor in Science, since 2012) and is part of SABs in several biotechs. He mentored over 30 post docs and students. His international leadership is reflected by invitations to write reviews in the most influential journals and to speak, including as a Keynote Speaker, in over 100 international conferences.