PI	*Enrico Lugli, PhD* Lab of Translational Immunology, Humanitas Research Hospital
PROJECT TITLE	Cellular networks governing stem-like T cell responses and Treg immunosuppression during cancer progression and response to immunotherapy
ABSTRACT	Stem-like T cell responses are key to successful cancer immunotherapy, but can be hindered by immunosuppression mediated by hyperactive CD4+ regulatory T cells (Tregs) in the tumor microenvironment. We have recently defined the complex network of cellular and molecular interactions between these cells and the surrounding microenvironment in tumors and in secondary lymphoid organs from patients. The successful candidate will combine novel genomic technologies optimized in the lab, including at the level of single cells, with cellular assays and genome-wide genetic perturbation to assess the molecular characteristics that are key for: - potent immunity mediated by stem-like T cells in the long term - Treg hyperactivation and enhanced immunosuppression The final aim is to alter stem-like T cell differentiation so to render these cells resistant to immunosuppression, or target Treg hyperactivation, so to induce a hypofunctional/dysfunctional state that is permissive to successful cancer immunotherapy.
MAIN TECHNICAL APPROACHES TO CARRY OUT THE PRESENT PROJECT	High-dimensional single-cell profiling by sequencing (transcriptomics, epigenomics), flow cytometry and tissue mass cytometry CRISPR/Cas9 screening Cellular immunology of primary patients' specimens Antigen-specific assays Advanced bioinformatics
SCIENTIFIC REFERENCES RELATED TO THE PRESENT PROJECT	1. De Biasi S, Gibellini L, Lo Tartaro D, Puccio S, Rabacchi C, Mazza EMC, Brummelman J, Williams B, Kaihara K, Forcato M, Bicciato S, Pinti M, Depenni R, Sabbatini R, Longo C, Dominici M, Pellacani G, Lugli E*, Cossarizza A*. Circulating mucosal associated invariant T cells identify patients responding to anti-PD1 therapy. *Nat Commun*, *in press*. 2. Galletti G, De Simone G, Mazza EMC, Puccio S, Mezzanotte C, Bi TM, Davydov AN, Metsger M, Scamardella E, Alvisi G, De Paoli F, Zanon V, Scarpa A, Camisa B, Colombo FS, Anselmo A, Peano C, Polletti S, Mavilio D, Gattinoni L, Boi SK, Youngblood BA, Jones RE, Baird DM, Gostick E, Llewellyn-Lacey S, Ladell K, Price DA, Chudakov DM, Newell EW, Casucci M, and Lugli E#. Two subsets of stem-like CD8(+) memory T cell progenitors with distinct fate commitments in humans. *Nat Immunol.* 2020 Dec;21(12):1552-1562 3. Alvisi G, Brummelman J, Puccio S, Mazza EM, Tomada EP, Losurdo A, Zanon V, Peano C, Colombo FS, Scarpa A, Alloisio M, Vasanthakumar A, Roychoudhuri R, Kallikourdis M, Pagani M, Lopci E, Novellis P, Blume J, Kallies A, Veronesi G, and Lugli E. IRF4 instructs effector Treg differentiation and immune suppression in human cancer. *J Clin Invest.* 2020;130(6):3137-50. 4. Brummelman J, Mazza EMC, Alvisi G, Colombo FS, Grilli A, Mikulak J, Mavilio

	D, Alloisio M, Ferrari F, Lopci E, Novellis P, Veronesi G, and Lugli E. High-dimensional single cell analysis identifies stem-like cytotoxic CD8(+) T cells infiltrating human tumors. *J Exp Med.* 2018;215(10):2520-35.