

- combined nivolumab and ipilimumab in advanced melanoma. *N Engl J Med* 2017;**377**(14):1345-1356.
3. Motzer RJ, Tannir NM, McDermott DF, Arén Frontera O, Melichar B, Choueiri TK, Plimack ER, Barthélémy P, Porta C, George S, Powles T, Donskov F, Neiman V, Kollmannsberger CK, Salman P, Gurney H, Hawkins R, Ravaud A, Grimm MO, Bracarda S, Barrios CH, Tomita Y, Castellano D, Rini BI, Chen AC, Mekan S, McHenry MB, Wind-Rotolo M, Doan J, Sharma P, Hammers HJ, Escudier B; CheckMate 214 Investigators. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. *N Engl J Med* 2018 Apr 5;**378**(14):1277-1290.
 4. Teng MW, Ngiow SF, von Scheidt B, McLaughlin N, Sparwasser T, Smyth MJ. Conditional regulatory T-cell depletion releases adaptive immunity preventing carcinogenesis and suppressing established tumor growth [published correction appears in *Cancer Res*. 2010; **70**(23):10014]. *Cancer Res* 2010;**70**(20):7800-7809.
 5. Simpson TR, Li F, Montalvo-Ortiz W, Sepulveda MA, Bergerhoff K, Arce F, Roddie C, Henry JY, Yagita H, Wolchok JD, Peggs KS, Ravetch JV, Allison JP, Quezada SA. Fc-dependent depletion of tumor-infiltrating regulatory T cells co-defines the efficacy of anti-CTLA-4 therapy against melanoma. *J Exp Med* 2013;**210**(9):1695-710.
 6. Plitas G, Konopacki C, Wu K, Bos PD, Morrow M, Putintseva EV, Chudakov DM, Rudensky AY. Regulatory T cells exhibit distinct features in human breast cancer. *Immunity* 2016;**45**(5):1122-1134.
 7. De Simone M, Arrighi A, Rossetti G, Gruarin P, Ranzani V, Politano C, Bonnal RJP, Provasi E, Sarnicola ML, Panzeri I, Moro M, Crosti M, Mazzara S, Vaira V, Bosari S, Pallechi A, Santambrogio L, Bovo G, Zucchini N, Totis M, Gianotti L, Cesana G, Perego RA, Maroni N, Pisani Ceretti A, Opocher E, De Francesco R, Geginat J, Stunnenberg HG, Abrignani S, Pagani M. Transcriptional landscape of human tissue lymphocytes unveils uniqueness of tumor-infiltrating T regulatory cells. *Immunity* 2016;**45**(5):1135-1147.

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862

TARGETING PSGL-1, A NOVEL MACROPHAGE CHECKPOINT, REPOLARIZES SUPPRESSIVE MACROPHAGES, INDUCES AN INFLAMMATORY TUMOR MICROENVIRONMENT, AND SUPPRESSES TUMOR GROWTH

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Background Macrophages play an important role in cancer by modulating both the innate and adaptive parts of the immune system. In non-pathological conditions, multiple subsets of macrophages balance the immune response. In cancer, M2-like immune-suppressive tumor-associated macrophages (TAMs) dominate the tumor microenvironment (TME). TAMs promote tumor growth, support neo-angiogenesis and enable metastasis formation. Macrophage modulators driving macrophage repolarization from the M2-like to a pro-inflammatory M1-like phenotype are an attractive novel class of cancer immunotherapy. Here we present identification, validation, and pre-clinical data of a novel macrophage checkpoint, PSGL-1, which supports targeting this molecule for immune-oncology.

Methods To assess the therapeutic potential of using anti-PSGL-1 antibodies to convert macrophage phenotype and the tumor microenvironment toward a more inflammatory state, we employed in vitro primary macrophage and multi-cellular assays, ex vivo patient-derived tumor cultures, and a humanized mouse PDX model.

Results Within the multiple subsets of macrophages, PSGL-1 is expressed at high levels on immune-suppressive TAMs and in vitro differentiated M2 macrophages. We show that targeting PSGL-1 via an antagonistic antibody repolarized M2 macrophages to a more M1-like state, both phenotypically and functionally as assessed in primary in vitro macrophage assays. Further, these repolarized M1-like macrophages enhanced the

inflammatory response in complex multi-cellular assays, including SEB stimulated PBMC assays and mixed-lymphocyte reactions (MLRs).

To establish a pre-clinical proof-of-concept for targeting PSGL-1, we turned to ex vivo cultures of fresh patient-derived primary tumors, where the complexity of the TME can be most preserved. RNA-seq data show that ex vivo cultures treated with anti-PD-1 antibody recapitulate TME changes in anti-PD-1 treated patients, including a strong T-cell IFN-gamma signature and a reduction in oncogenic pathway activation. Blocking PSGL-1 resulted in a robust pro-inflammatory signature driven by TNF-alpha/NF-kappa-B and chemokine-mediated signaling. The increase in TNF-alpha signaling was accompanied by reduction in oxidative phosphorylation and fatty acid metabolism. The increase in pro-inflammatory cytokine and chemokine production was confirmed by measuring secreted protein levels, further confirming the re-polarization of macrophages within a tumor setting.

Lastly, we employed a humanized mouse PDX model of melanoma and show that anti-PSGL-1 treatment resulted in suppression of tumor growth favorably compared to anti-PD-1. At the cellular and molecular levels, anti-PSGL-1 treatment lead to a more enhanced inflammatory microenvironment, including a reduced M2:M1 macrophage ratio, increased antigen presentation, pro-inflammatory mediators, and effector T cell infiltration and activation.

Conclusions Our data support anti-PSGL-1 as a macrophage repolarizing agent and an effective macrophage-targeted therapy for Immuno-Oncology.

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Other

863

IDENTIFICATION AND CHARACTERIZATION OF AN IMMUNODOMINANT SARS-COV-2-SPECIFIC CD8 T CELL RESPONSE

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Background Global efforts are ongoing to develop vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing coronavirus disease (COVID-19). While there is accumulating information on antibody responses against SARS-CoV-2, less is known about CD8 T-cell recognized SARS-CoV-2 epitopes and the functional state of SARS-CoV-2-specific CD8 T cells.

Methods We analysed samples from 18 patients with ongoing severe and critical COVID-19 disease for CD8 T-cell recognition of 500 peptide human leukocyte antigen (HLA) class I complexes, restricted by 10 common HLA alleles. In addition we carried out an in-depth characterisation of the functional state of identified SARS-CoV-2-specific CD8 T cell responses based on peptide stimulation assays, ex vivo flow cytometry and transcriptome analysis.

Results Several epitopes derived from the open reading frame 1ab polyprotein (ORF1ab) were identified, including an immunodominant epitope restricted by HLA-A*01:01. The immunodominance was further supported by high T cell receptor (TCR) diversity within the CD8 T cells specific for this epitope. In-depth characterisation the