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Propositions belonging to this thesis

1) For successful T cell-mediated tumor control, tumor-reactive T cells must both be present in a patient and be able to exert effector functions at the tumor site. Analyses that tell which one of these two parameters is (most) defective in cancer patients should form crucial input to decide which immunotherapeutic approach is more likely to lead to clinical benefit.

2) As TCRs are MHC-restricted, redirection of T cells via TCR gene transfer inherently has a personalized aspect. As a next step, the clinical use of patient-specific TCRs is technically feasible and should be pursued (Kim et al., PLoS One, 2012; Pasetto A et al., Cancer Immunol Res., 2016).

3) The use of transposons, rather than viral vectors, for genetic manipulation of T cell has potential regulatory benefits but is hampered by limited efficiency and high cellular toxicity (this thesis).


5) CMTM6 is required for efficient surface expression of PD-L1 in every cell type that has been evaluated thus far. Beyond this documented role, it is plausible that CMTM6 has further roles in PD-L1 regulation that should be explored in further research (Burr et al., Nature, 2017 and this thesis).

6) Current screening strategies for genetic factors that modulate sensitivity towards T cell attack or immunotherapeutic approaches yield a cancer cell-centric view on immunotherapy resistance that can explain only part of the mechanisms involved (Manguso RT et al., Nature, 2017; Patel SJ et al., Nature, 2017; Pan D et al., Science, 2018; Kearney CJ et al., Science Immunology, 2018 and this thesis).

7) A dysfunctional IFN-γ receptor pathway in cancer cells is correlated with acquired or intrinsic resistance towards T cell centered immunotherapeutic approaches. IFN-γ exerts multiple effects on cancerous cells that may contribute to the success of immunotherapies, and dissecting which ones of these may explain the observed correlation would improve our mechanistic understanding of T cell-centered cancer immunotherapies (Zaretsky JM et al., N Engl J Med. 2016; Gao J et al., Cell, 2016; Shin DS et al., Cancer Discov. 2017).

8) The magnitude of the cytopathic effect of IFN-γ is highly variable and is affected by SLFN11 in a context-dependent manner (this thesis).

9) The important thing is not to stop questioning; curiosity has its own reason for existing. One cannot help but be in awe when contemplating the mysteries of eternity, of life, of the marvelous structure of reality. It is enough if one tries merely to comprehend a little of the mystery every day. The important thing is not to stop questioning; never lose a holy curiosity (Albert Einstein).

10) Nothing in life is to be feared, it is only to be understood. Now is the time to understand more, so that we may fear less (Marie Sklodowska-Curie).