Target and Biomarker identification
Nivolumab (anti PD-1) response in Ipilimumab (anti-CTLA4) resistant patients
Available data: gene expression (RNA-seq) of tissue biopsies
Responders are aggregates of stable disease and partial/complete responders
Conventional analysis of gene expression

anti PD-1 treatment activates a T cell immune response in responders

~700 genes significantly upregulated by the treatment
T cells are negatively correlated to melanocytes before and after treatment with anti PD-1

CD8 T cells vs Melanocytes in responders to anti PD-1

\[ p < 0.0001 \]
\[ R^2 = 0.75 \]

Melanocytes estimated proportion per samples in post vs pre treated patients

\[ p\text{-value} = 0.015 \]
Adjusting the data to melanocyte proportions recovered PD-L1 as a significantly modulated gene

Macrophage/Myeloid genes

PDL-1
IDO1
CD300F
TLR8

T cells genes
Adipocytes related genes are driving the response to anti PD-1 in the anti CTLA4 resistant patients
CD36 is an important immune and metabolism regulator that was linked to cancer*

NR1H3 is a regulator of macrophage function, involved in lipid homeostasis and inflammation

GAS6 is the ligand for TYRO3, AXL, and MERTK which are a family of important immuno-regulators

*Oncogene 2018 37(17):2285-2301