

Targeting metabolism in immune cells: a better way to immunodulation

Niels Olsen Saraiva Câmara

niels@icb.usp.br



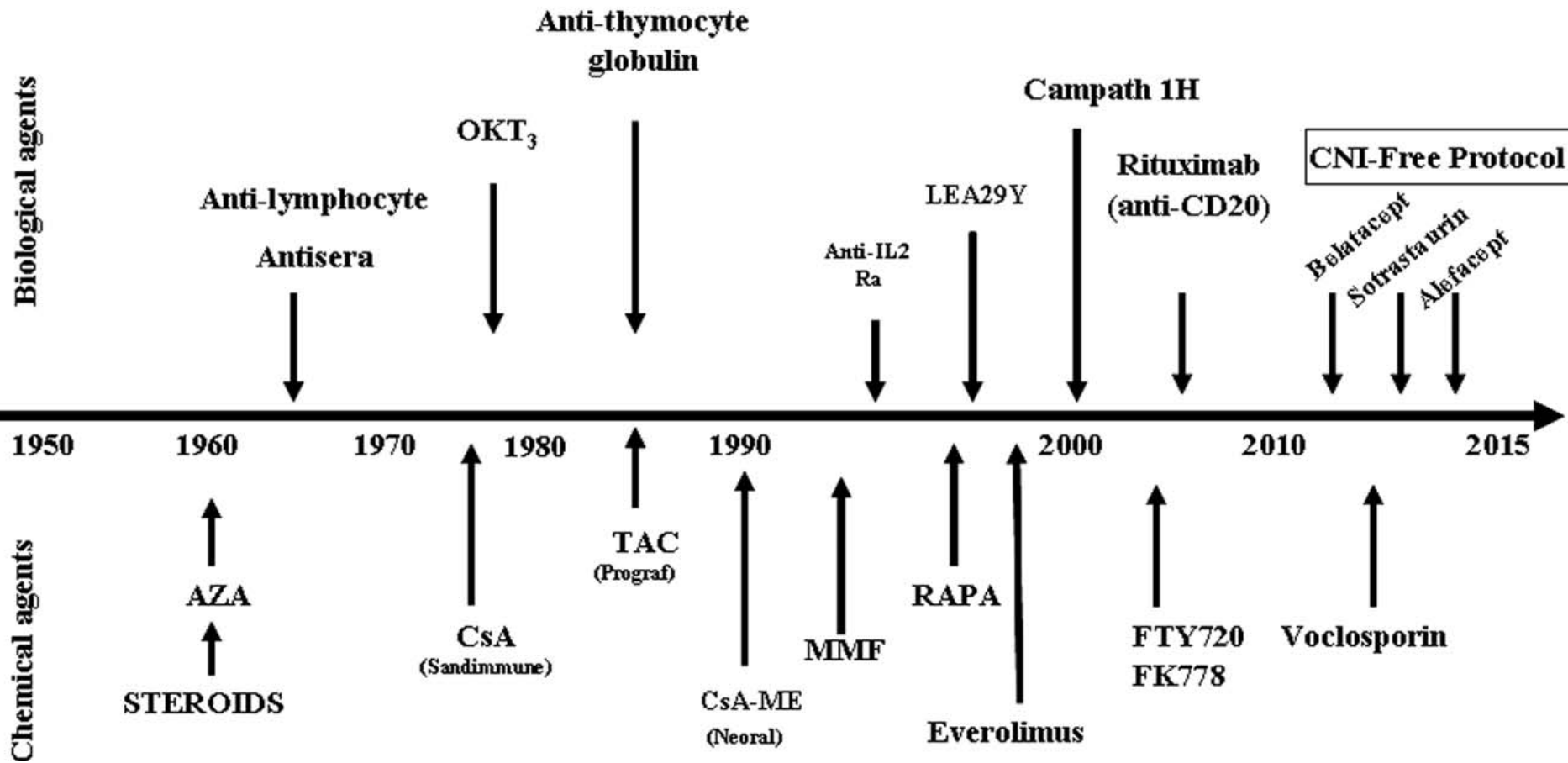
São Paulo
2016



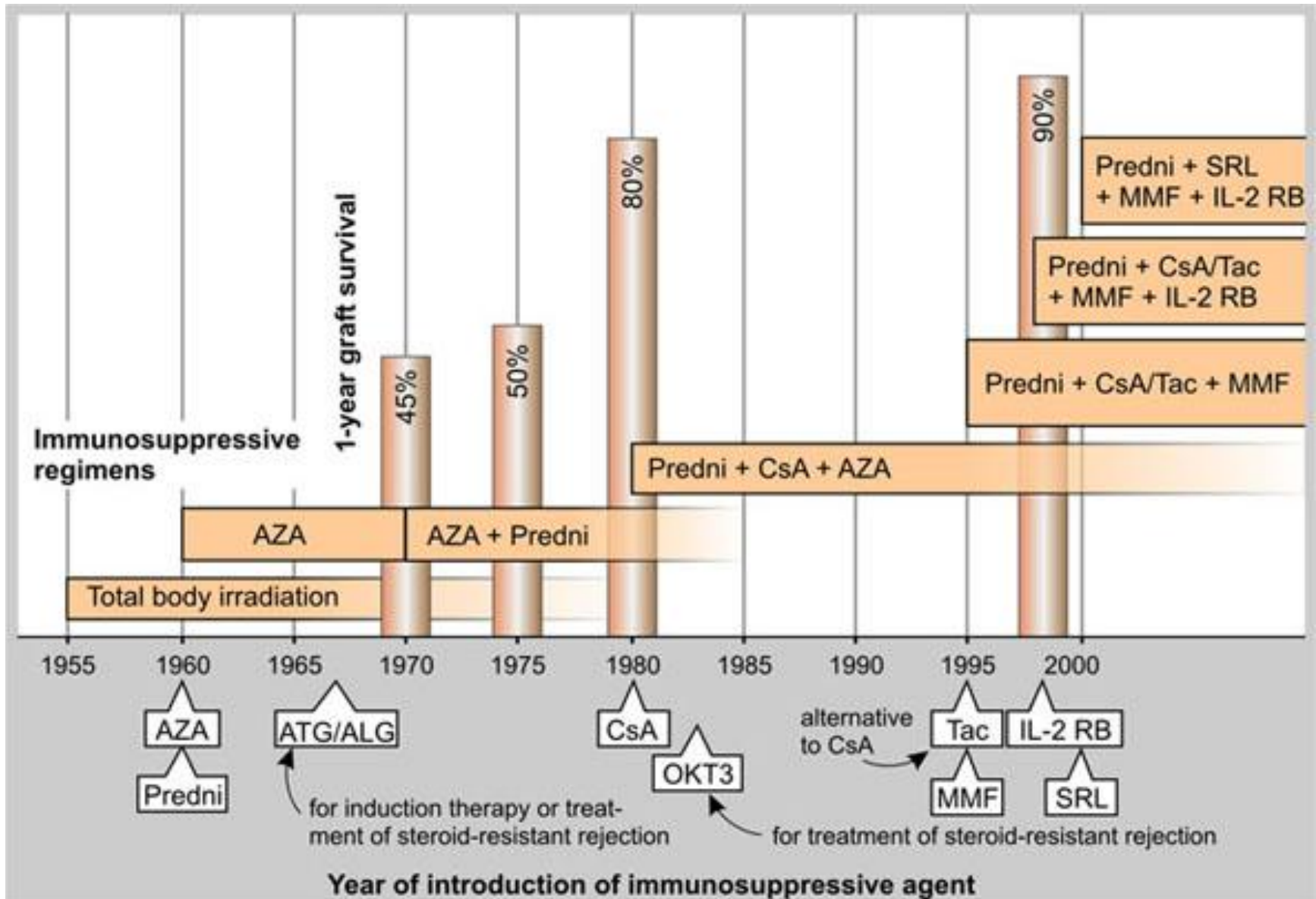
`Conventional` immunosuppression

Biological agents

Chemical agents

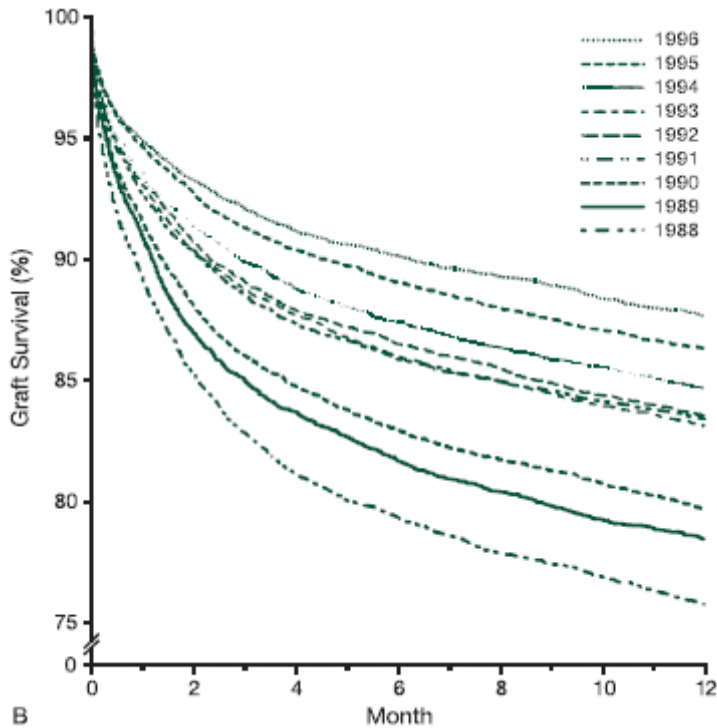


Immunosuppression in Transplantation

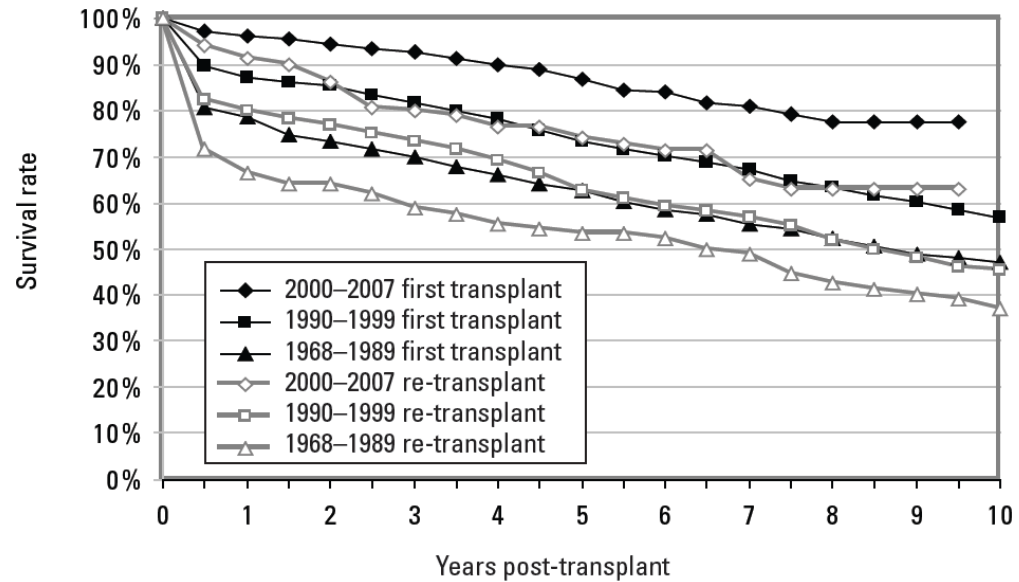


Outcomes in Transplantation

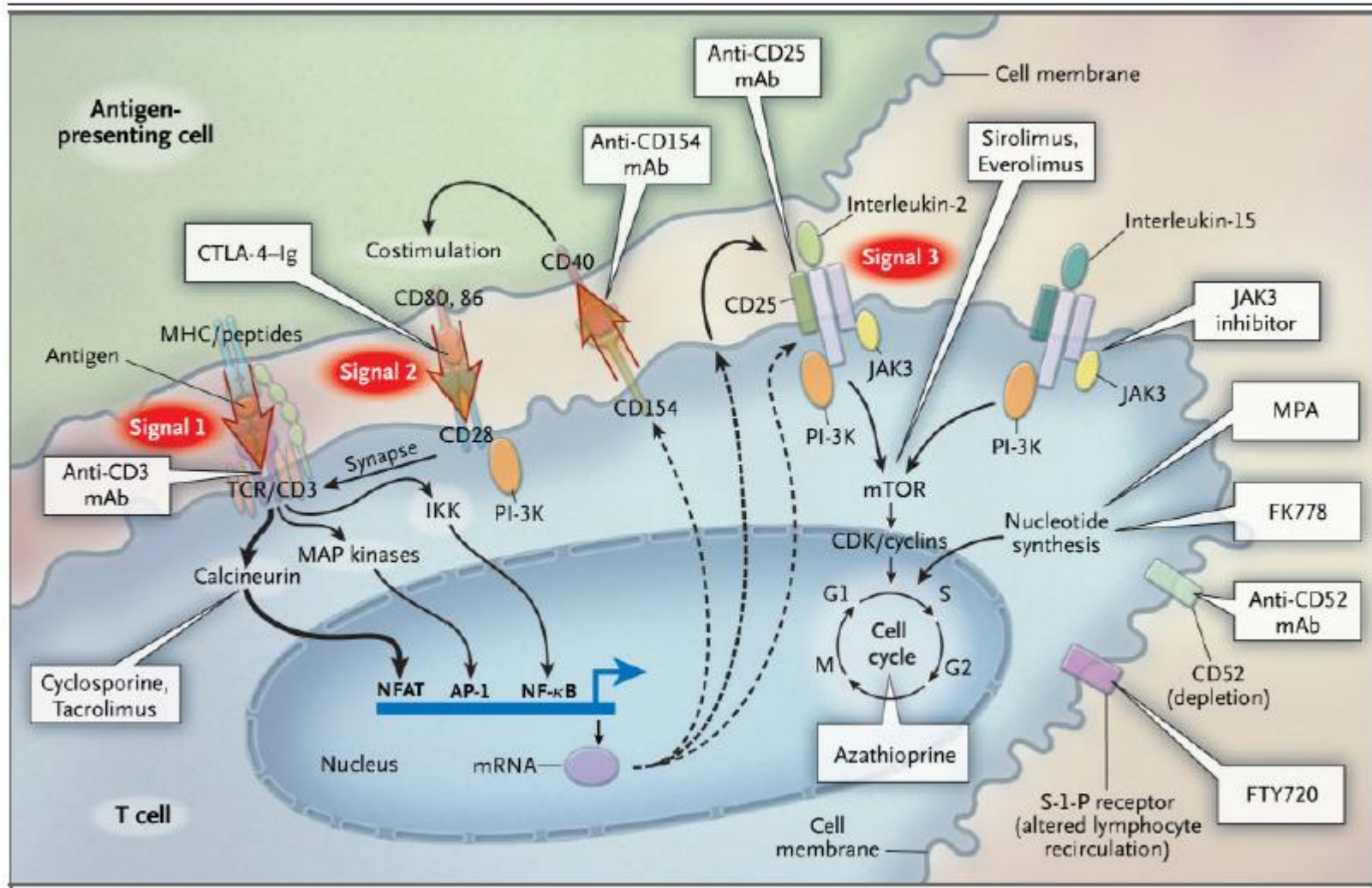
1st-yr



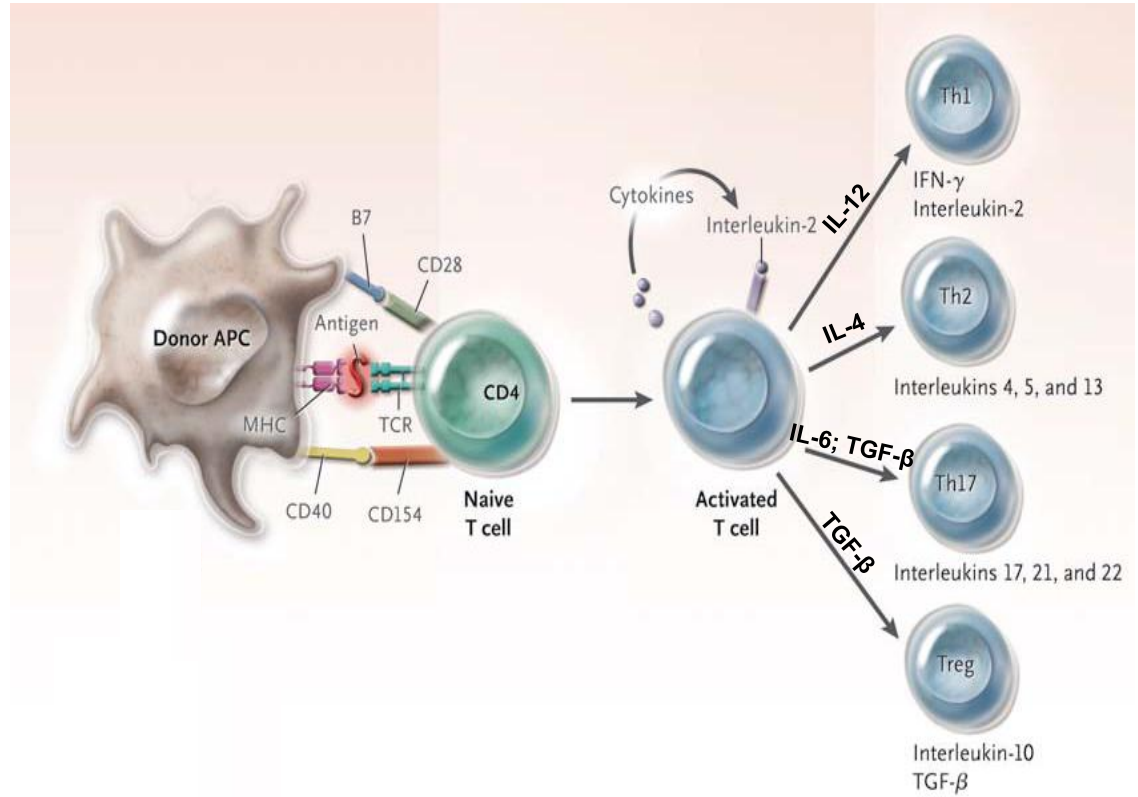
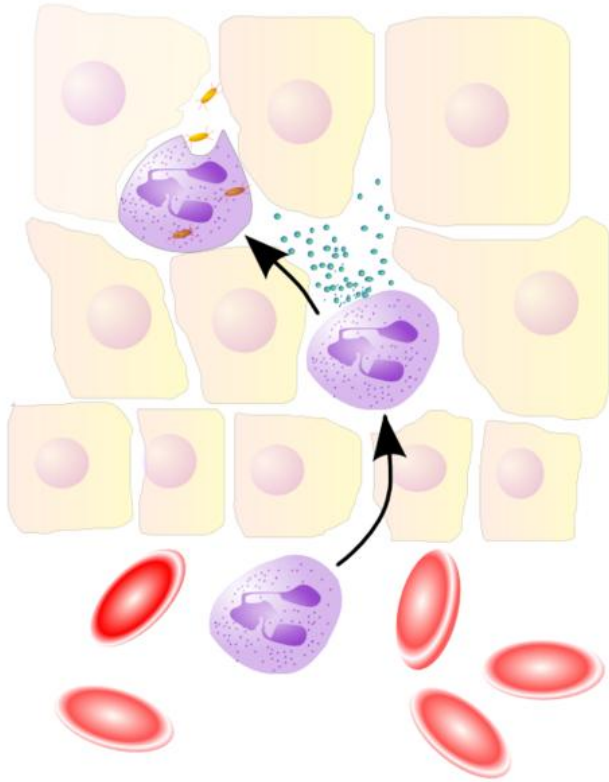
10th-yr



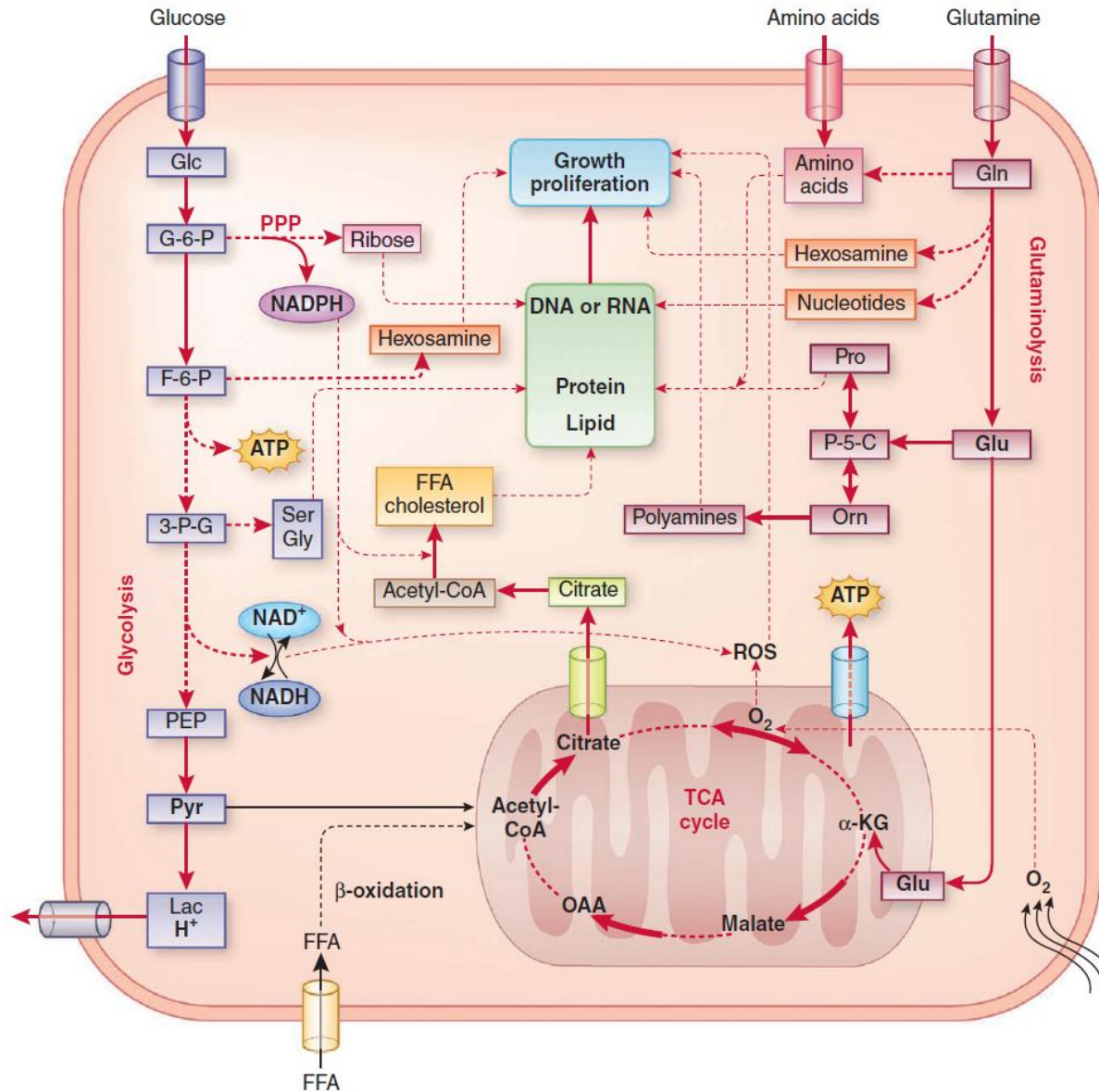
Usual targets in classical immunosuppression



Common targets

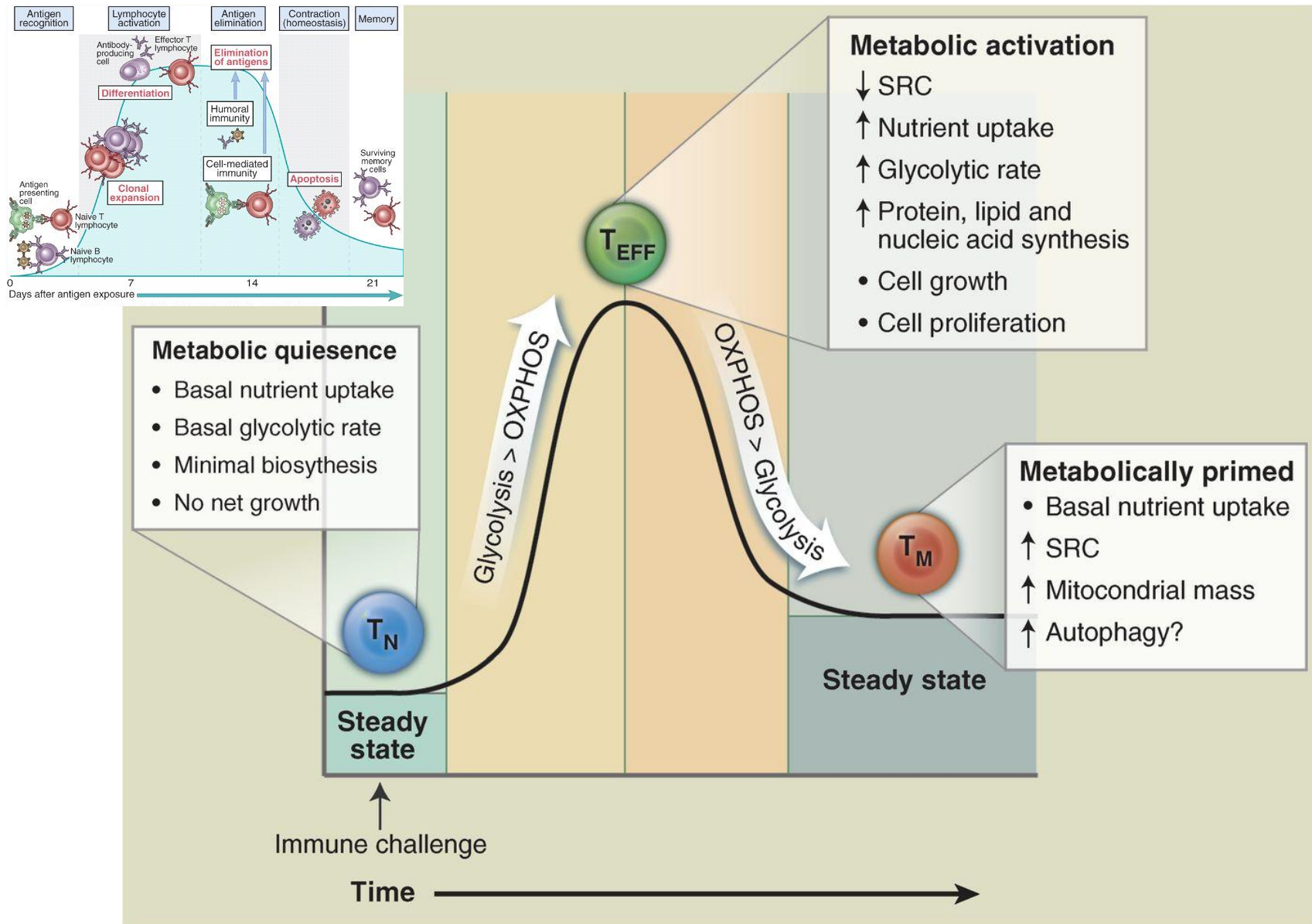


Sources of energy for expansion and differentiation of T cells

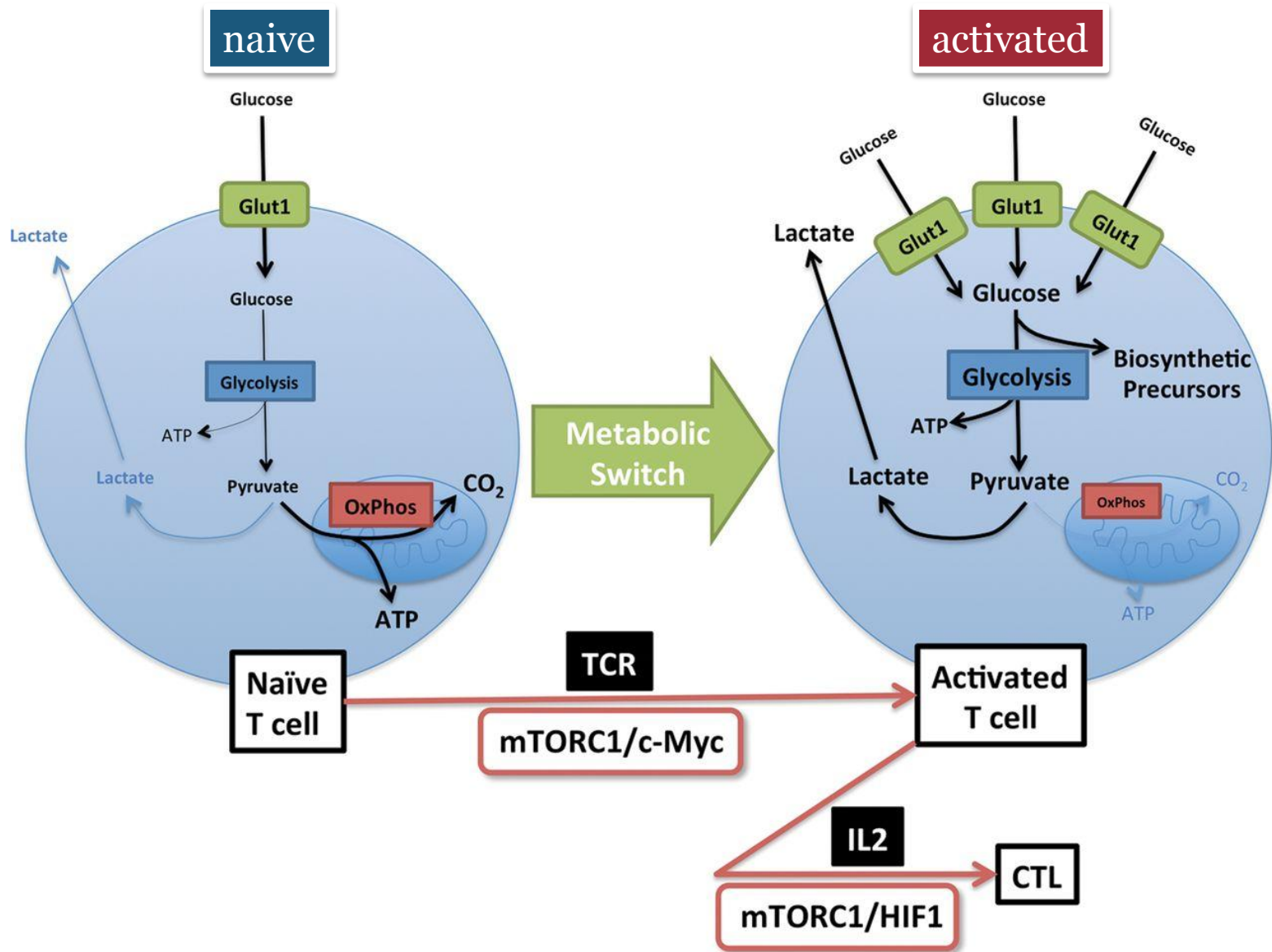


Debbie Matzels

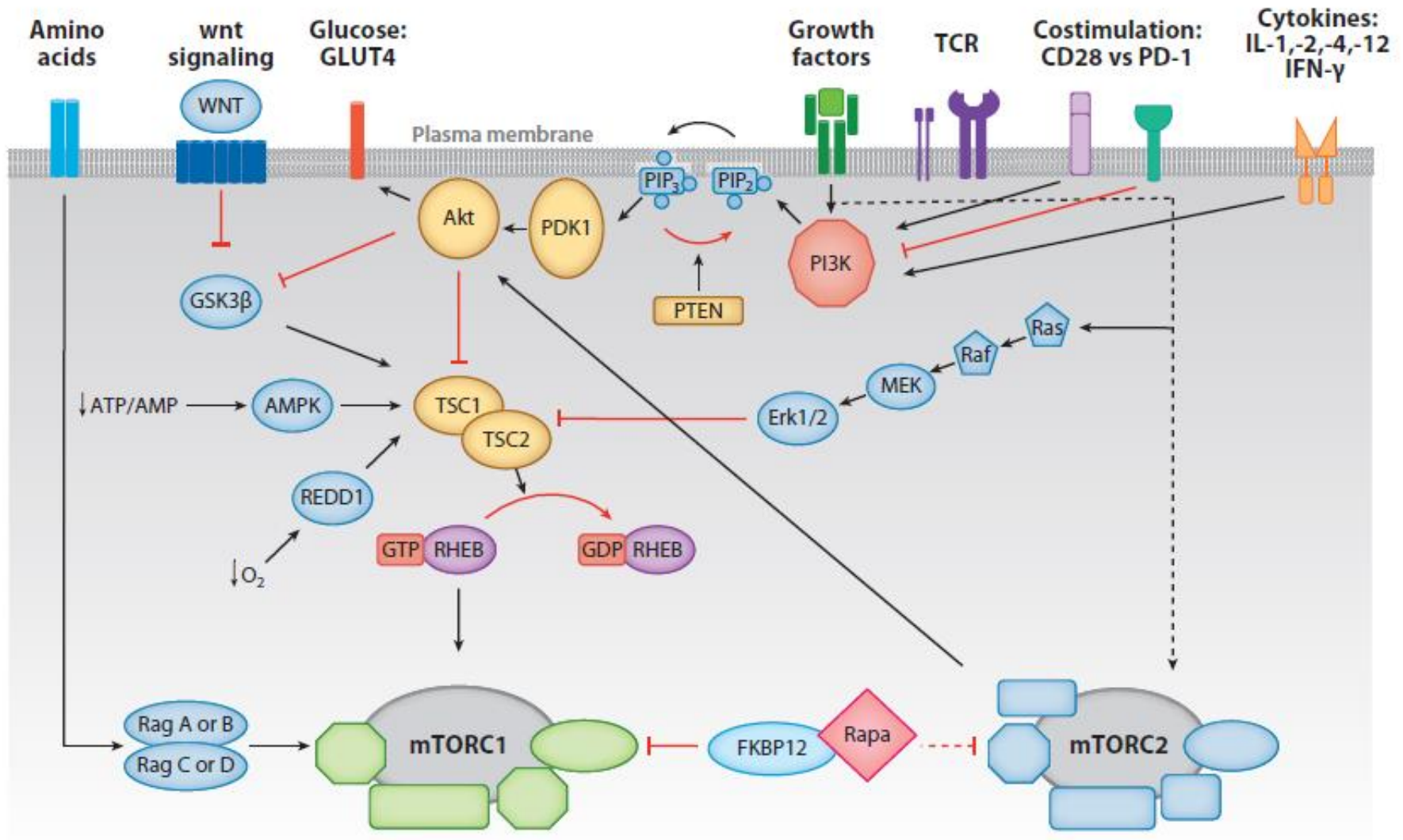
Metabolic alterations during T cell activation



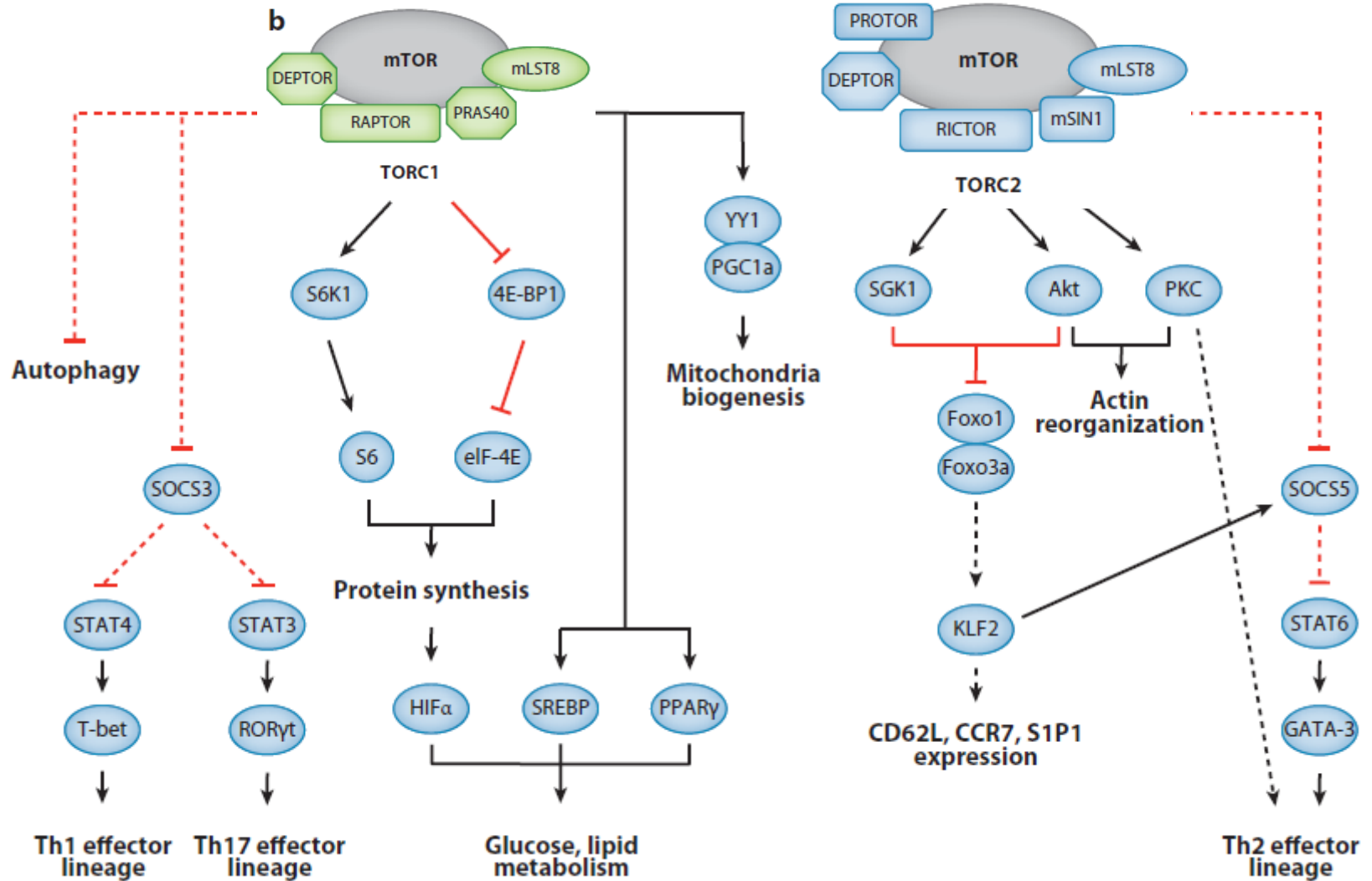
Metabolic alterations during T cell activation



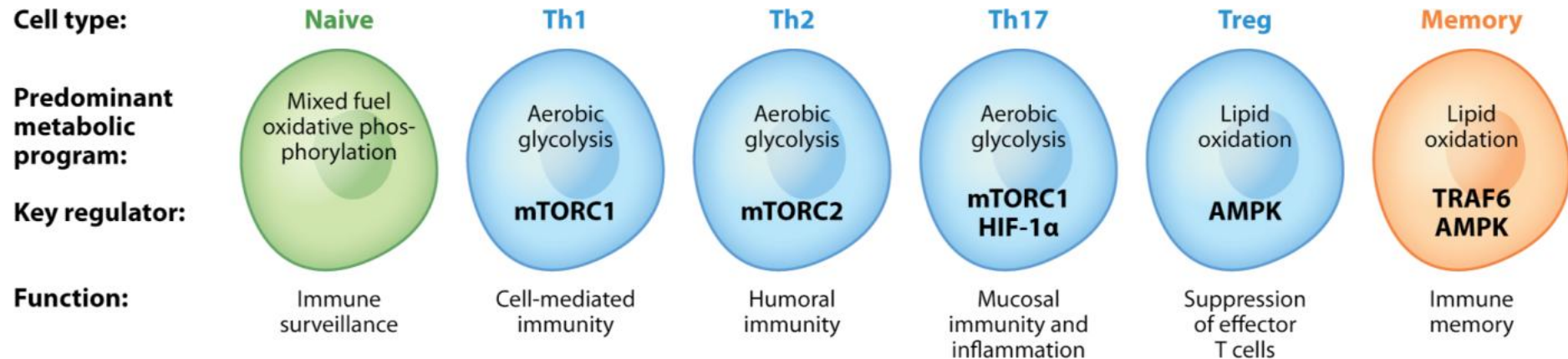
Sensors of metabolic alterations



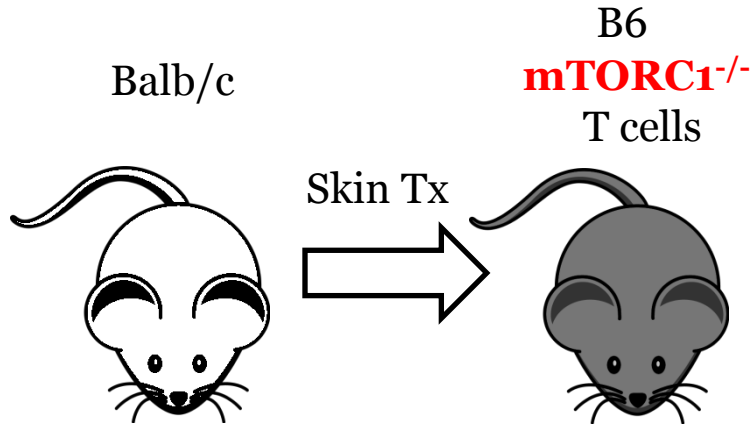
mTOR complexes



Metabolism of T helper cells



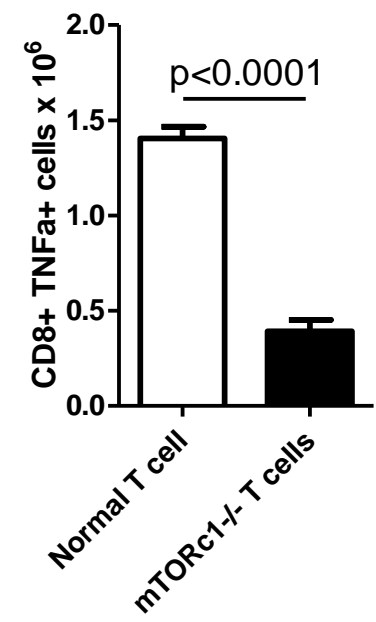
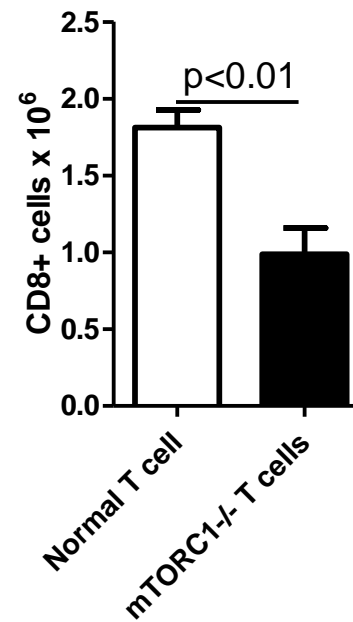
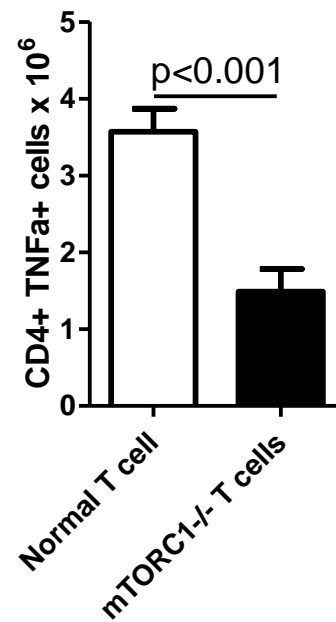
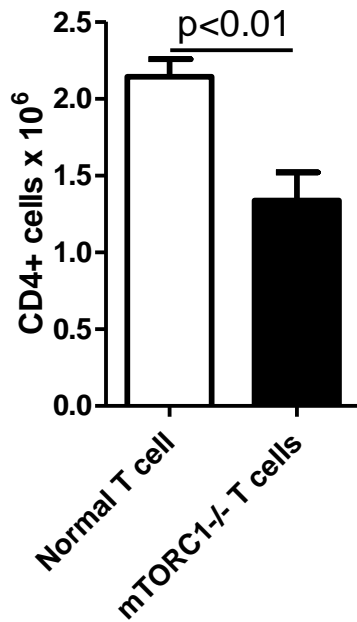
Absence of mTORC1 in T cells protects against fully mismatched graft



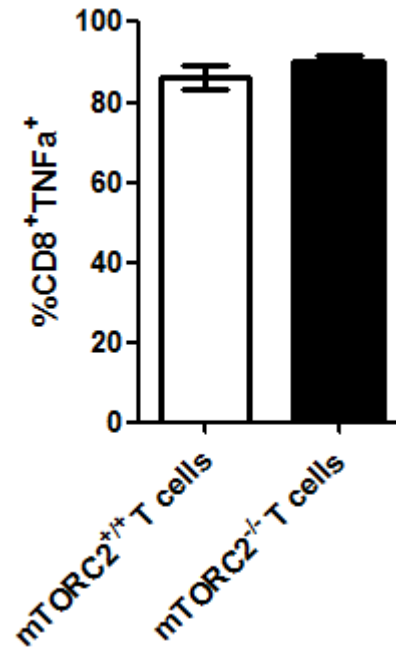
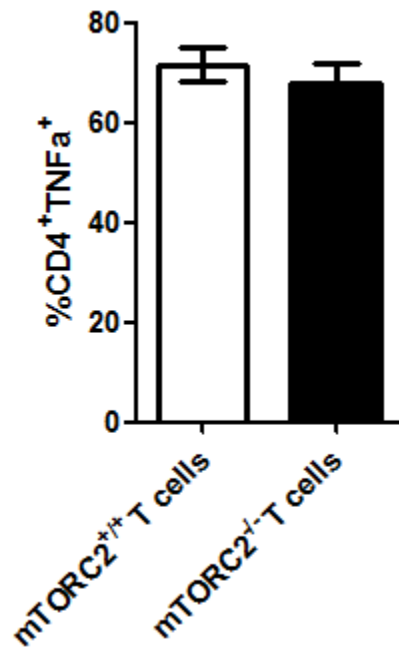
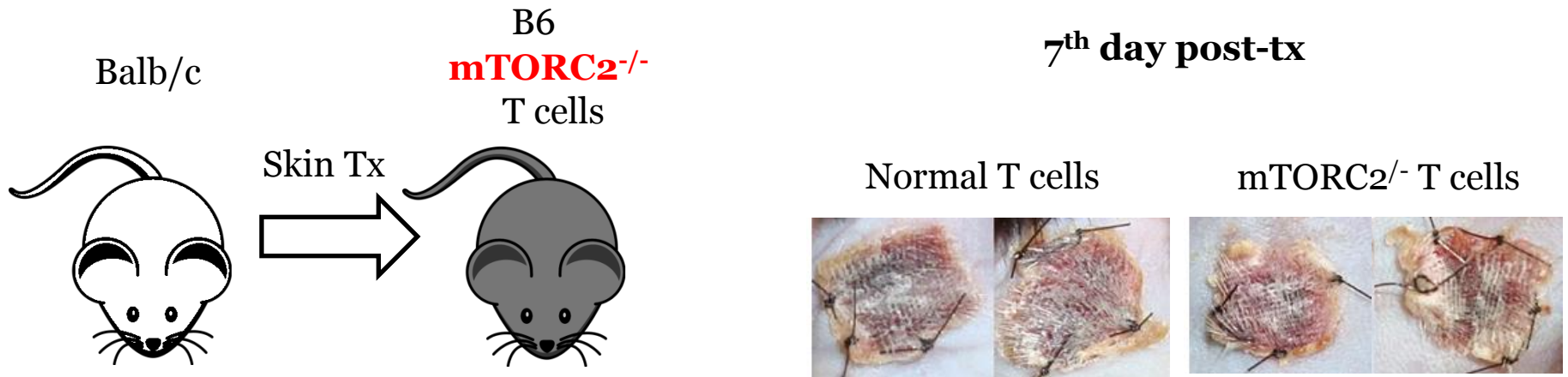
7th day post-tx

Normal T cells

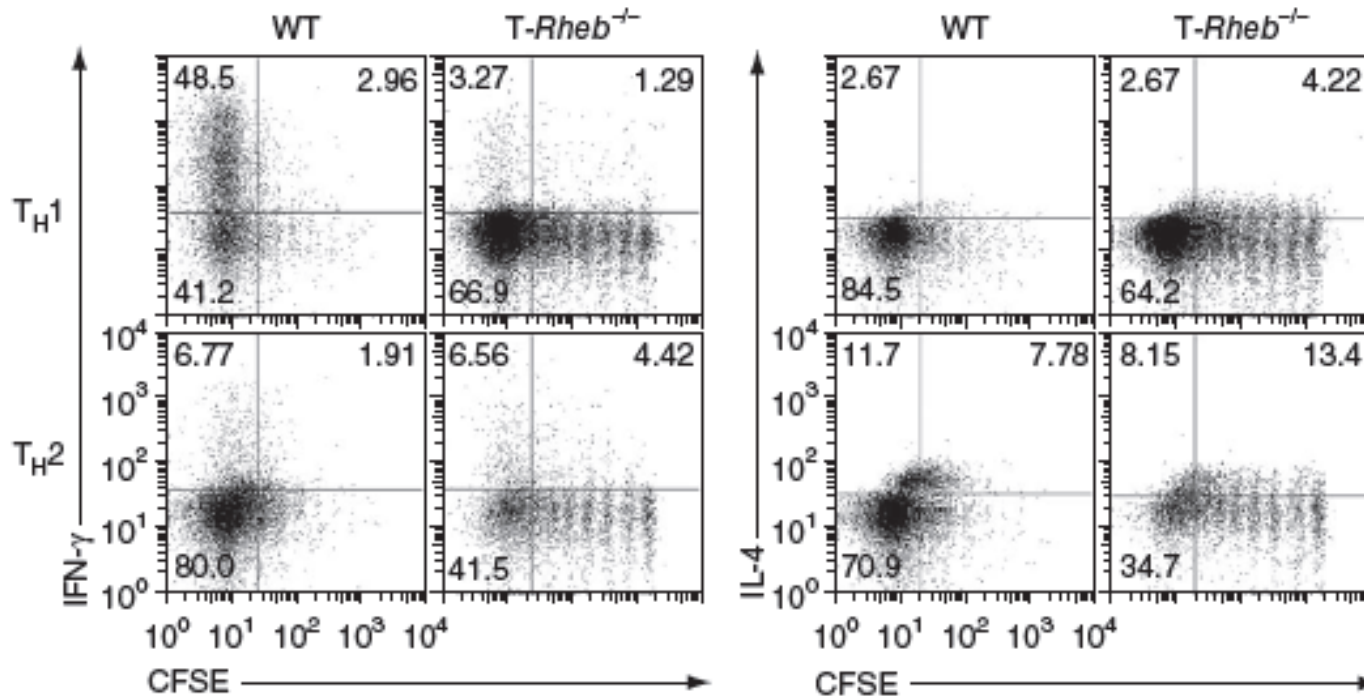
mTORC1^{-/-} T cells



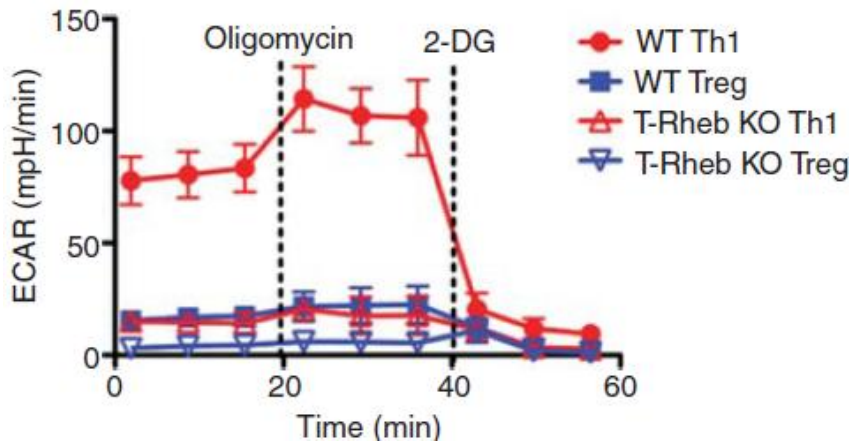
Absence of mTORC2 in T cells has not effect on fully mismatched graft



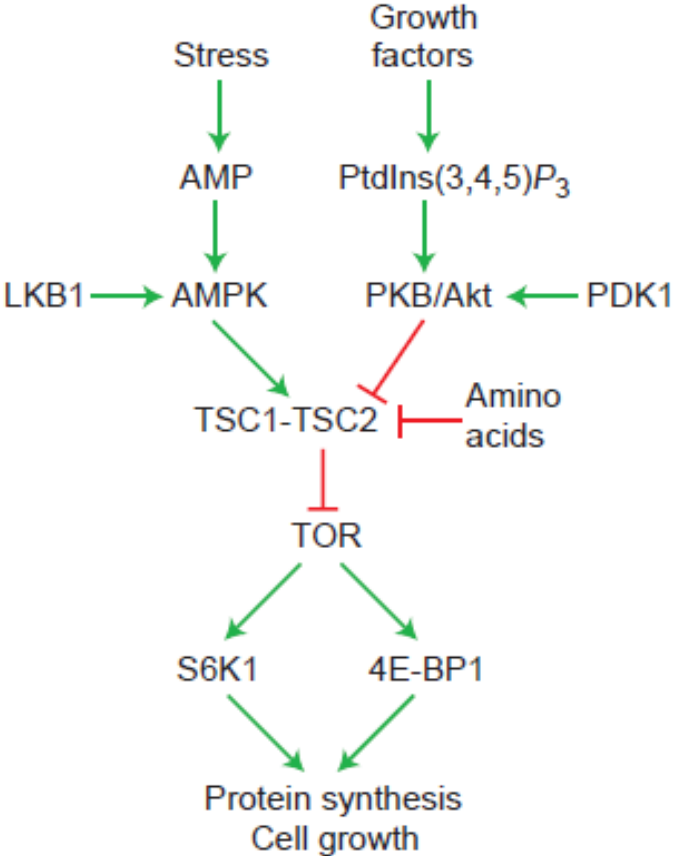
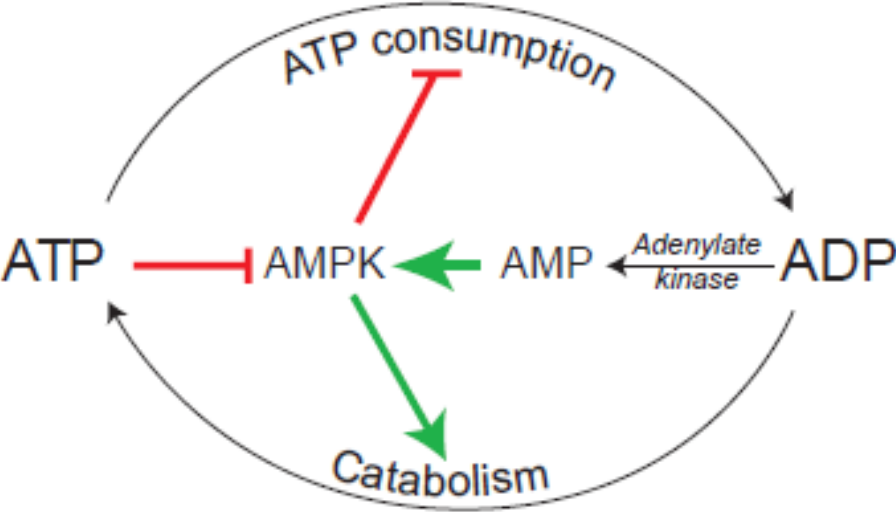
The role of Rheb (mTORC1 deficient) in Th1 and Th2 cells



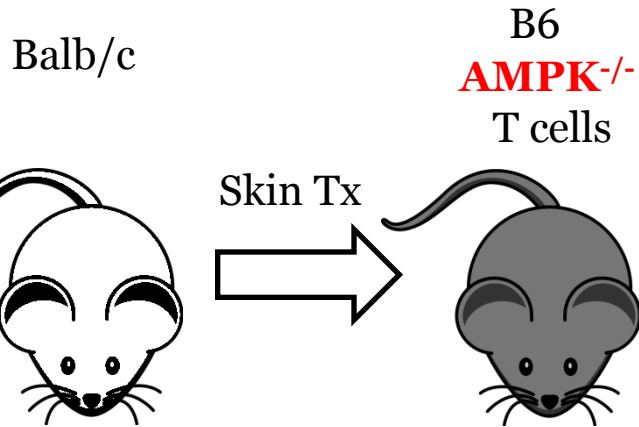
Extracellular acidification rate
Skewed CD4 + T cells



AMPK



Absence of AMPK in T cells protects against fully mismatched graft

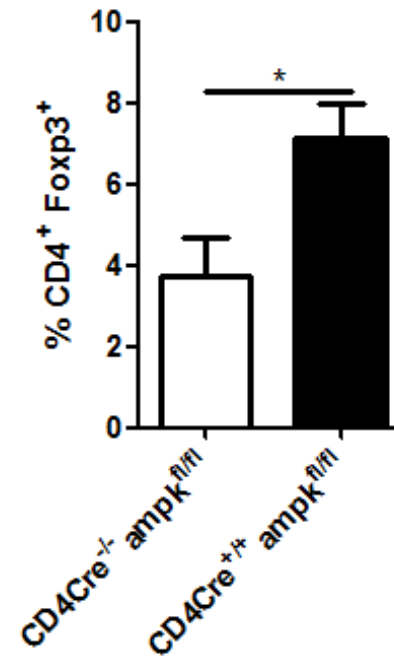
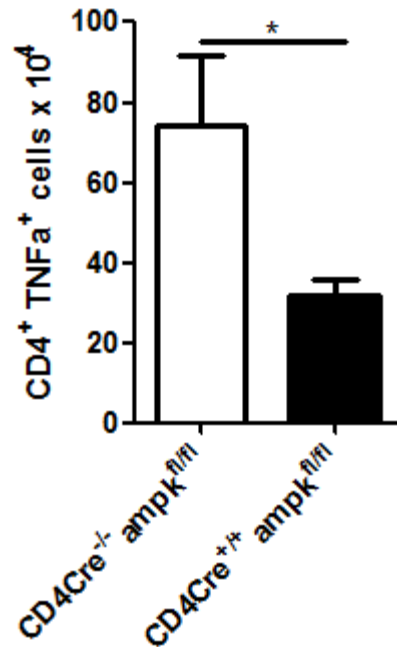
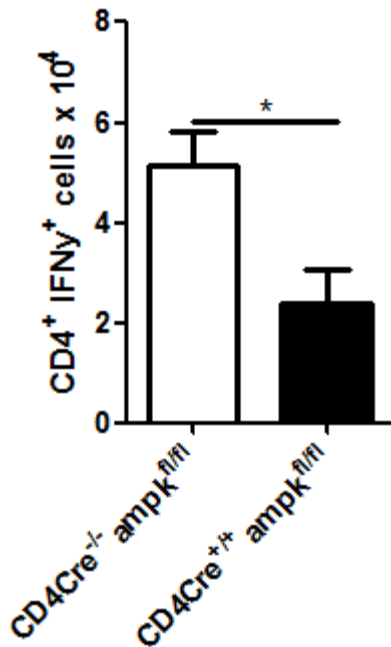


7th day post-tx

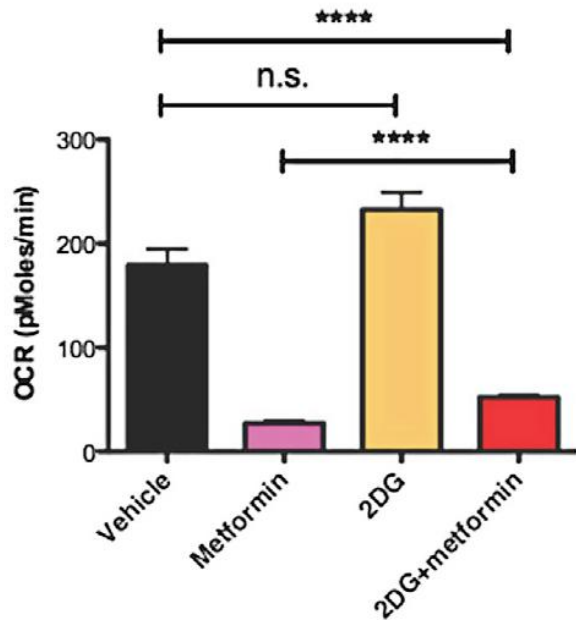
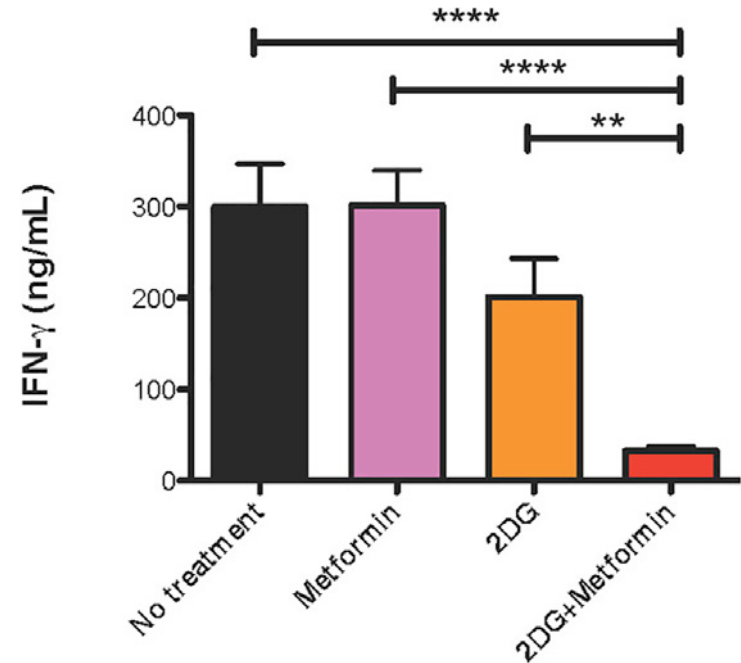
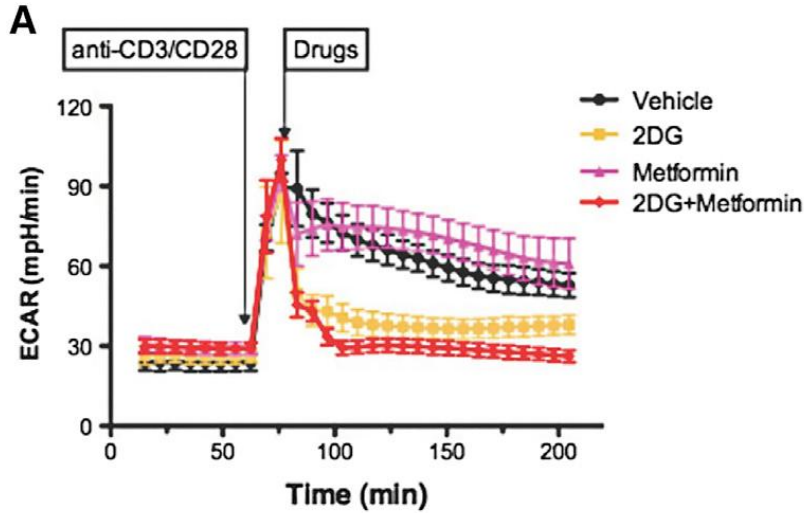
Normal T cells



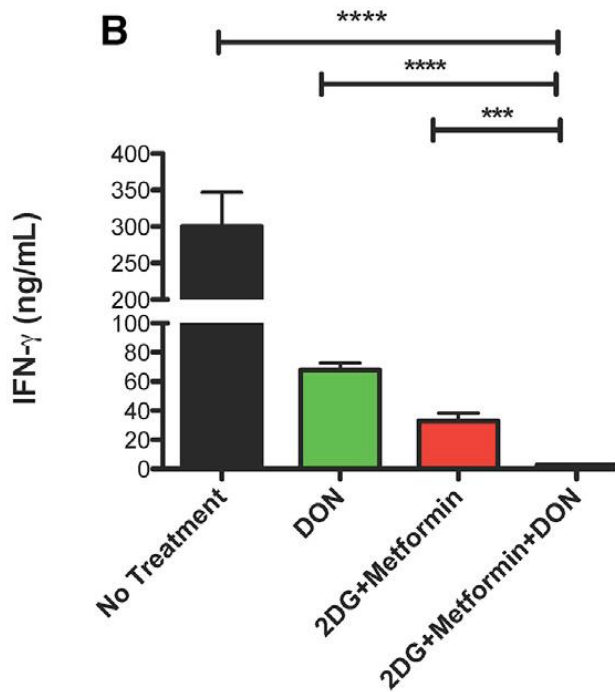
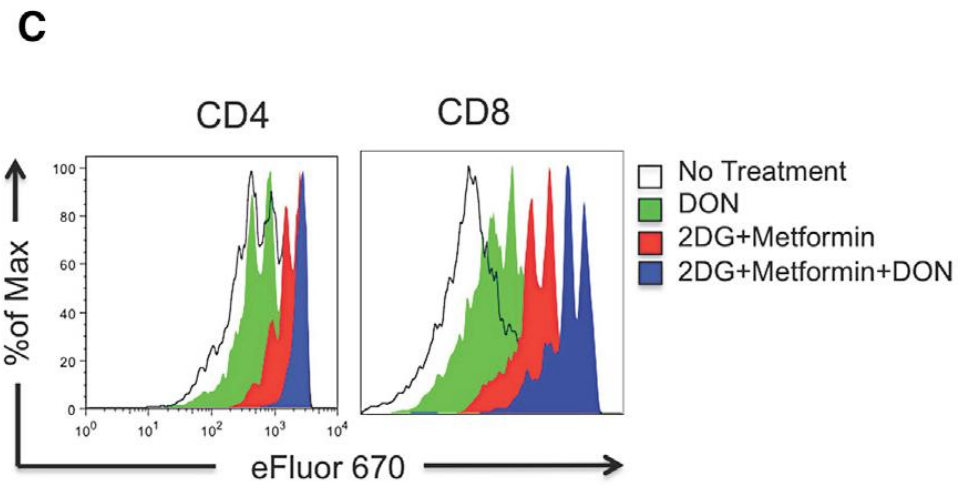
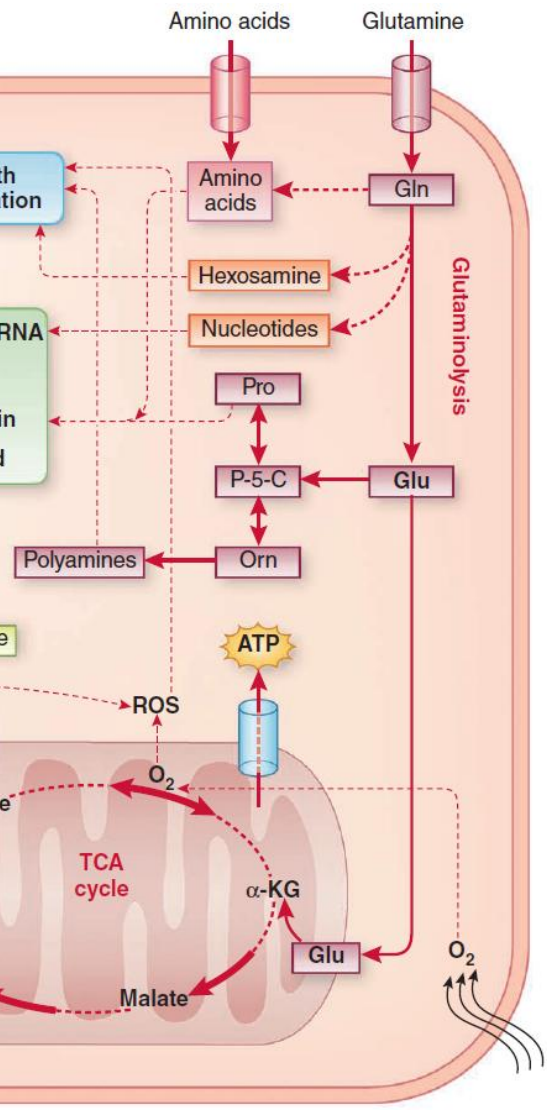
AMPK^{-/-} T cells



2-DG Combined with Metformin Inhibits T Cell Responses through Suppression of Glycolysis

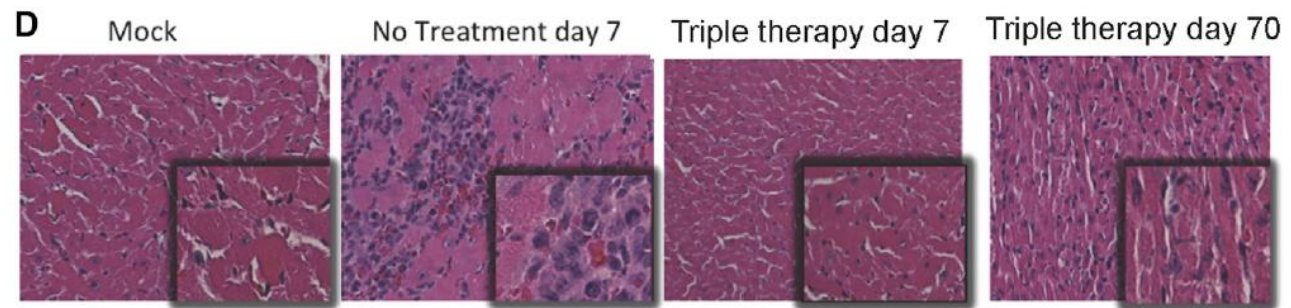
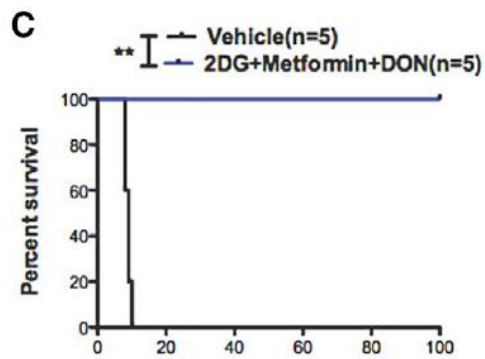
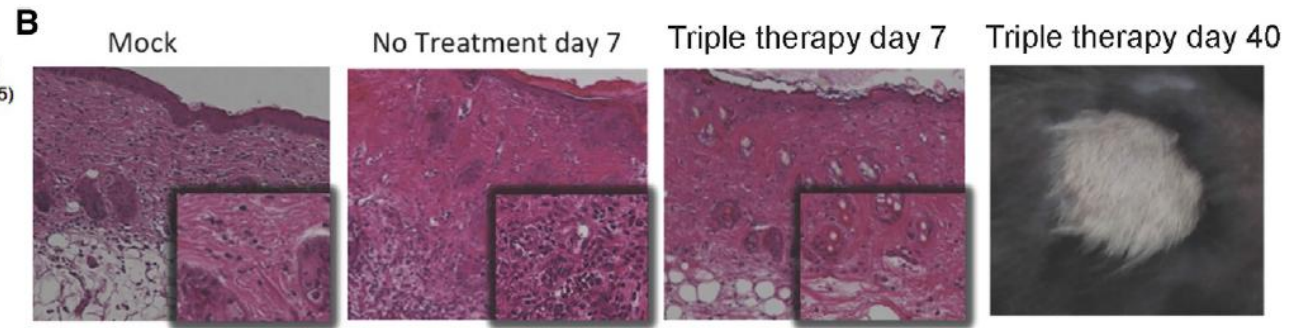
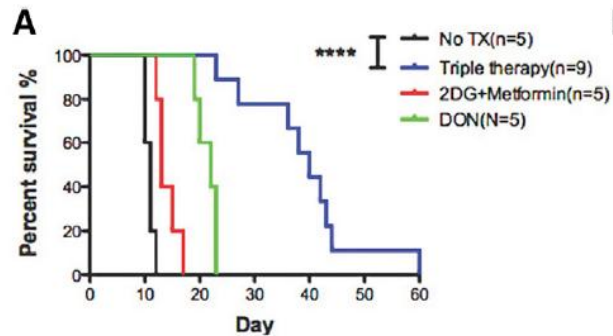


Combined Inhibition of Glycolysis and Glutaminolysis Profoundly Suppresses T Cell Responses

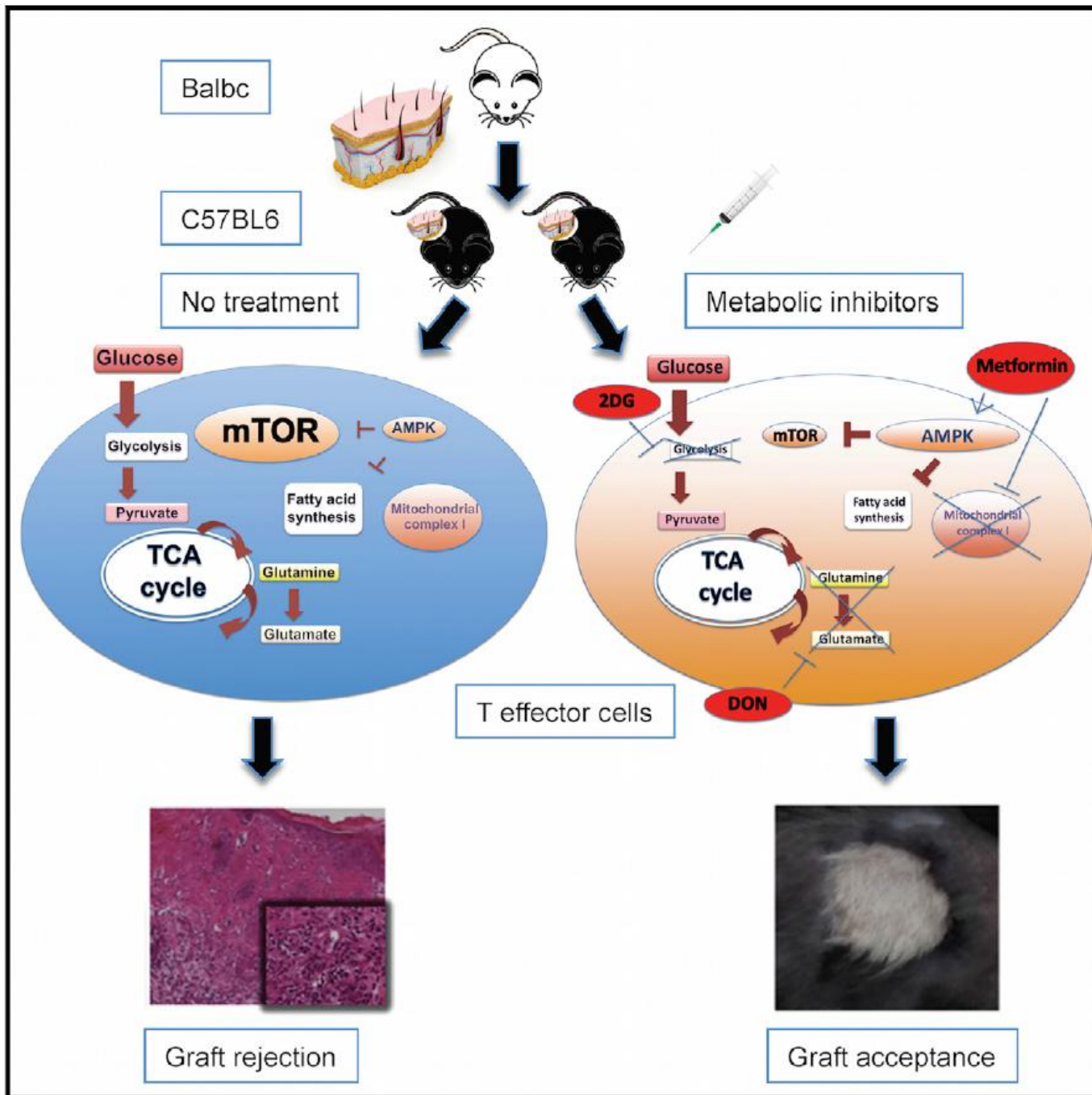


Inhibition of metabolic pathways prolongs graft survival

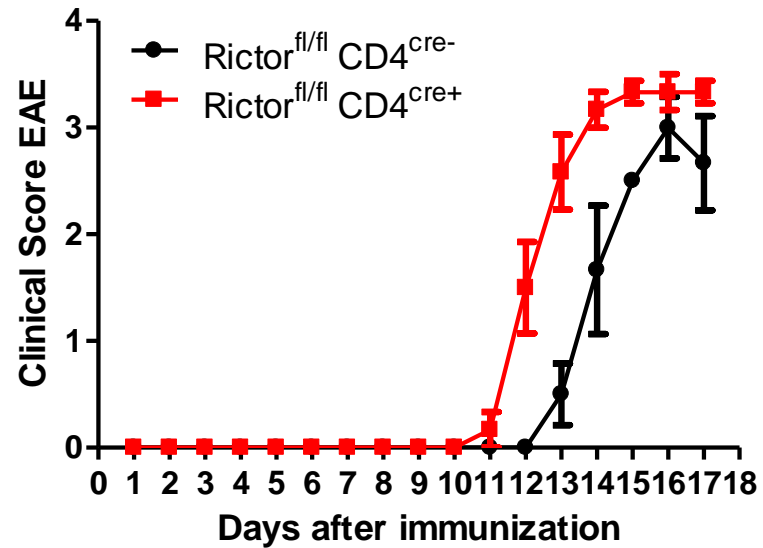
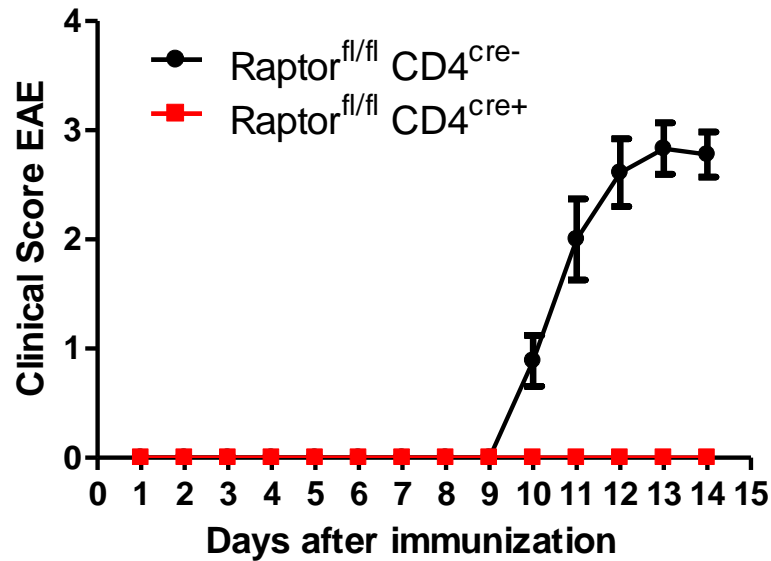
Skin



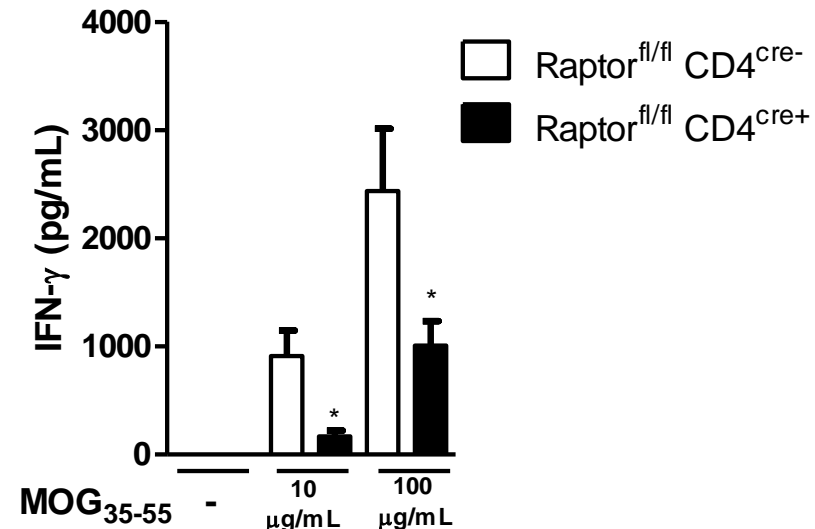
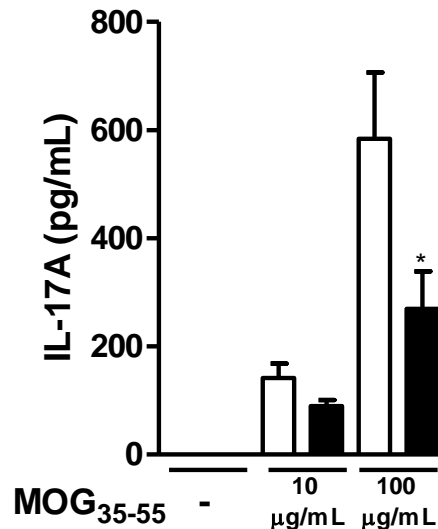
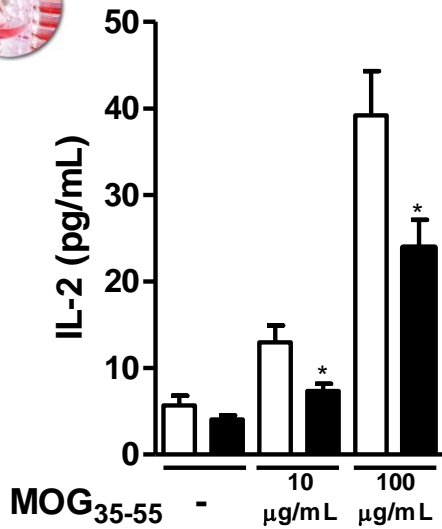
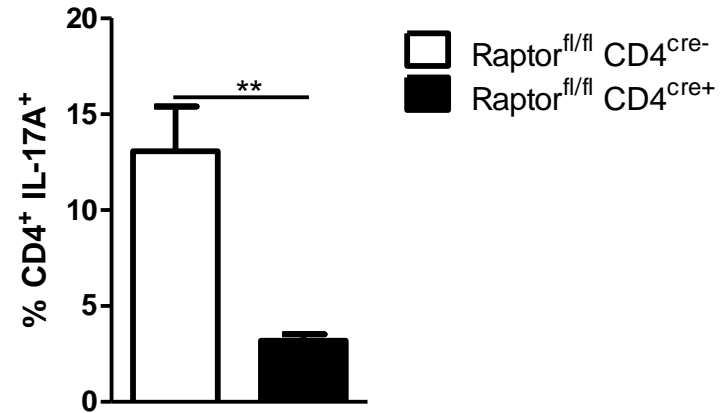
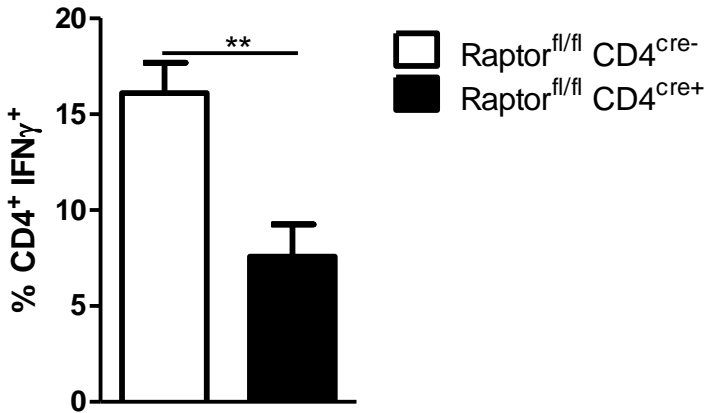
Heart



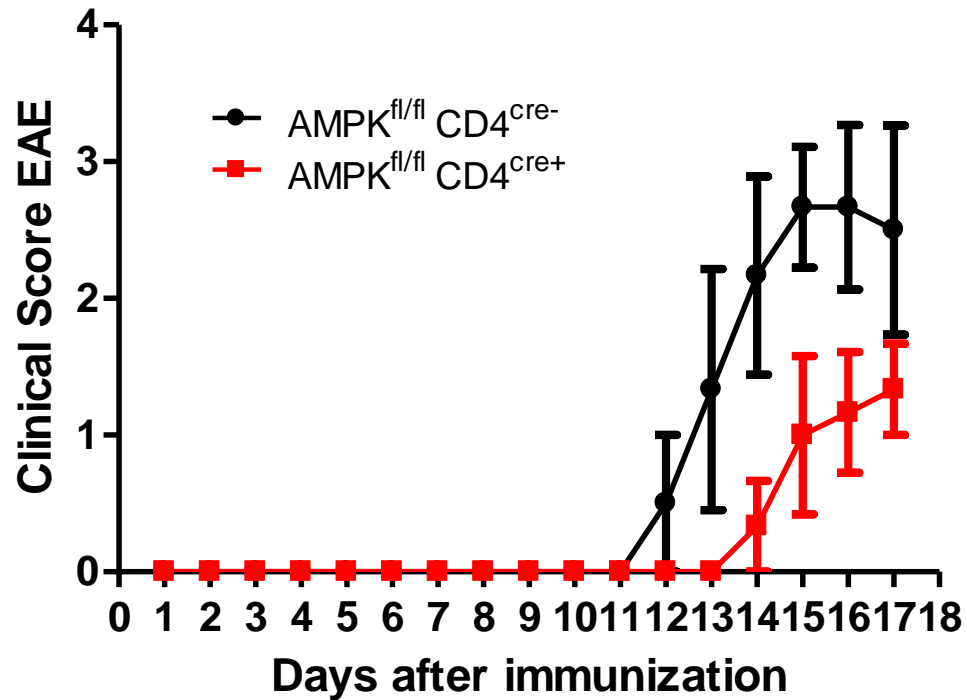
Absence of mTORC1 but not mTORC2 in T cells protects from EAE



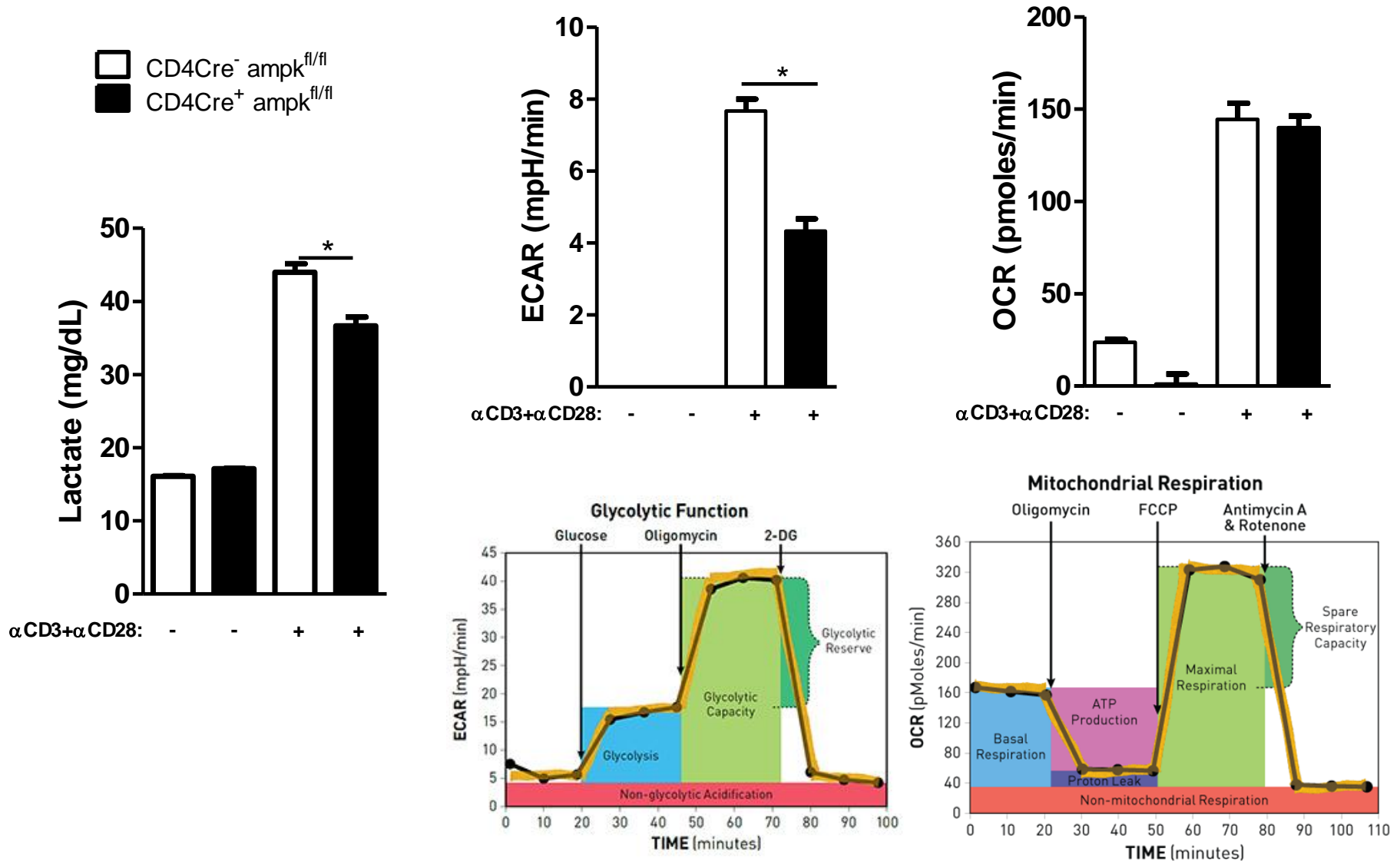
Deficiency in mTORC1 in T cells impairs T cell response



Absence of AMPK in T cells protects from EAE



AMPK is important to induce aerobic glycolysis upon TCR activation

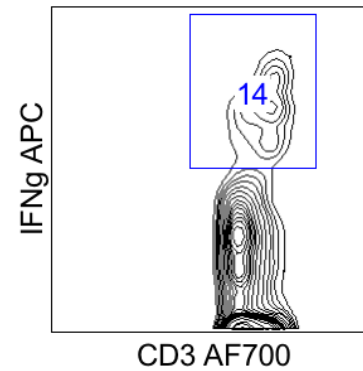
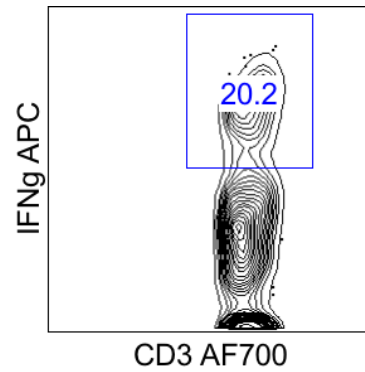


AMPK modulates Th1 differentiation

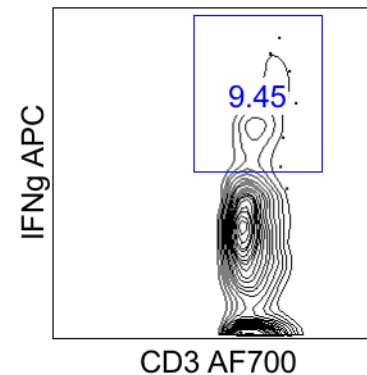
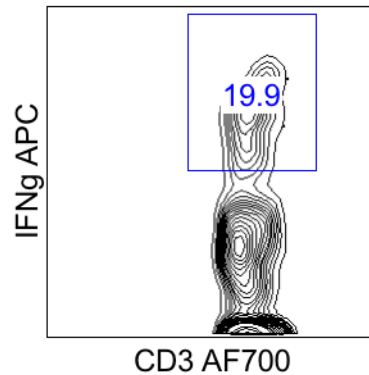
Th1

AMPK Neg

AMPK Cre



Metformin



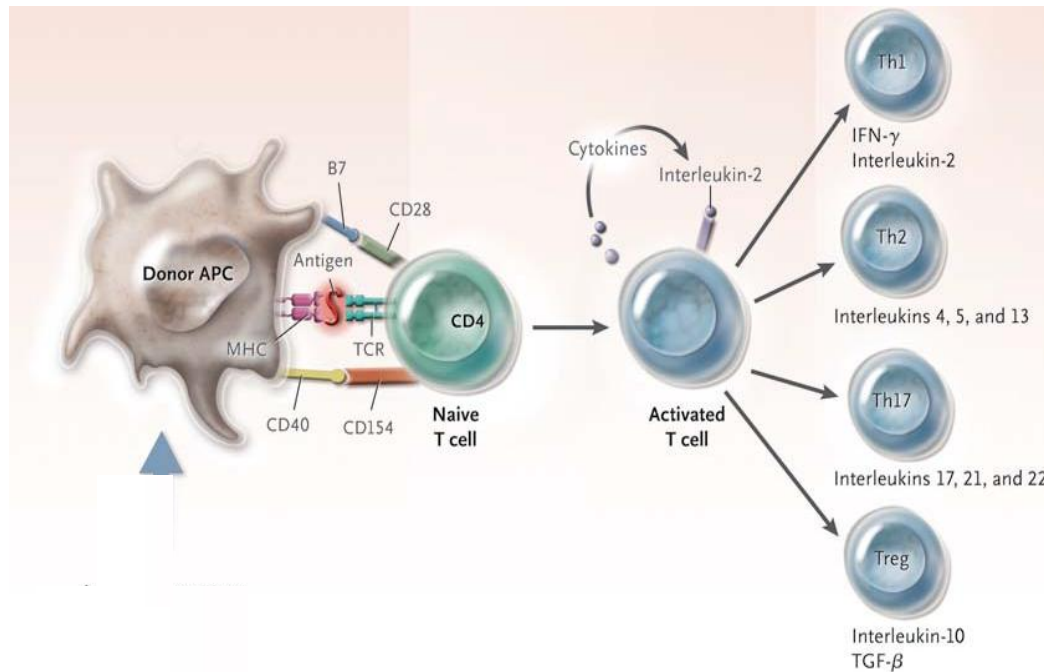
Working hypothesis

Bortezomib®

Belatacept®

Calcineurin Inhibitors

Antigen Processing Antigen Presentation T cell expansion T cell differentiation



Energy requirements Metabolic sensors T cell differentiation

To be addressed...



Prof. Jonathan Powell, Johns Hopkins

**Fernanda Terra
Amanda Campelo
Angela Castoldi
Felipe Valença
Marina Burghos
Profa. Alicia Kowaltowski
Leandro Araujo
Prof. Alexandre Basso**