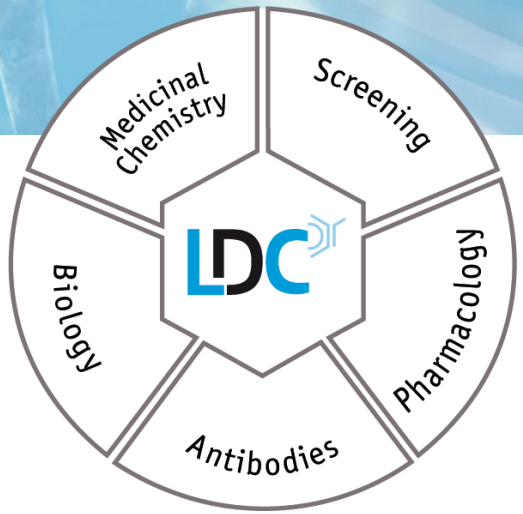
Lead Discovery Center LDC

PAVING THE WAY
FOR INNOVATIVE MEDICINES

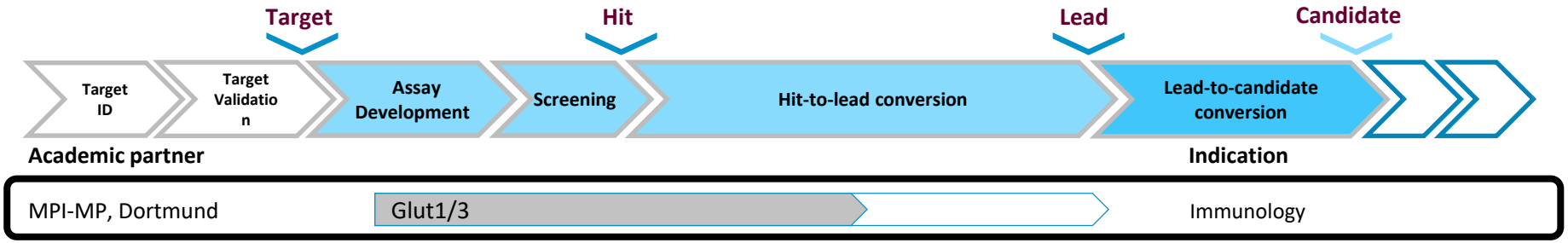
Glut1/3 Inhibitors



Glut1/3 Inhibitors: Effect on T cells

Project Partner:
Prof. Dr. Herbert Waldmann, Max Planck Institute for Molecular Physiology, Dortmund

Executive Summary



Target rationale:

- Immunometabolism of $T_{effector}$ cells allows to reduce proliferation by blocking glucose transporters, while $T_{regulatory}$ cells are not impacted
- Selective Glut1 inhibition is not sufficient due to GlutX response regulation → need for dual Glut1/3

Key achievements:

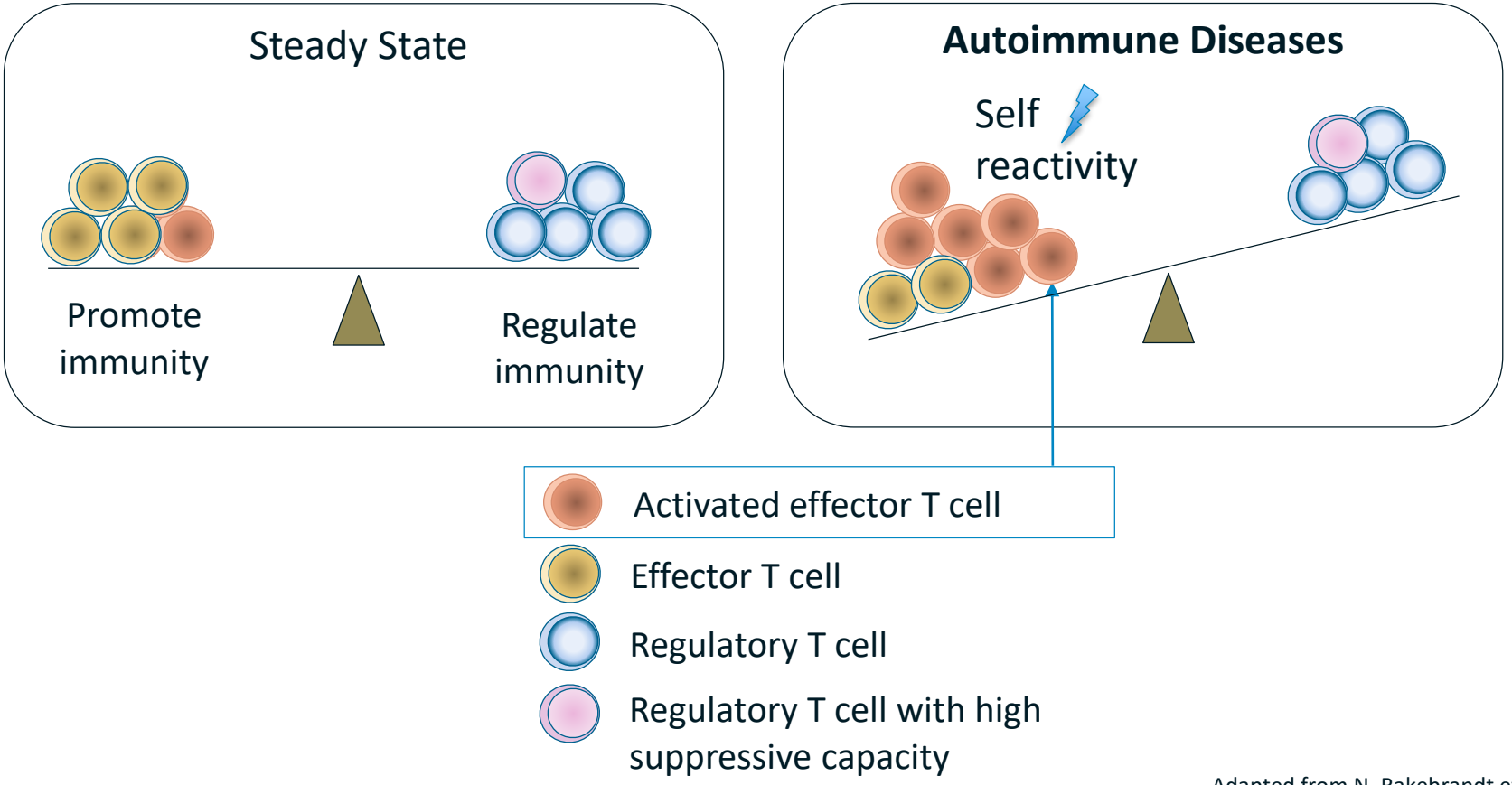
- Identification of selective small molecule inhibitors of glucose uptake (2 prioritized hit series)
- Effect on T cell proliferation shown *in vitro*
- PK of early frontrunner compound looks promising

Future plans:

- Further PK Profiling
- PoC in a GvHD model, etc.
  - ➢ Test hypothesis that LDC's Glut1/3 inhibitors show a similar effect in GvHD as seen in Glut-1 deficiency (Macintyre et al., 2014)

Autoimmune Diseases

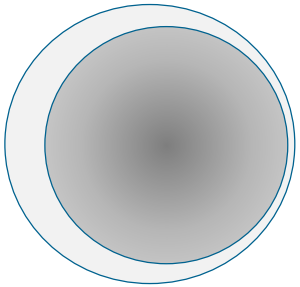
Imbalance between $T_{effector}$ and $T_{regulatory}$ cells



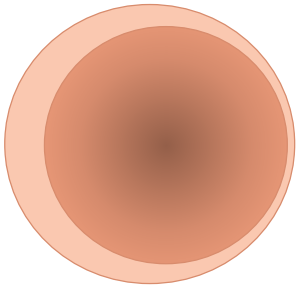
Adapted from N. Rakebrandt et al., 2016

Immunometabolism

Metabolism allows to selectively inhibit $T_{effector}$ cell proliferation

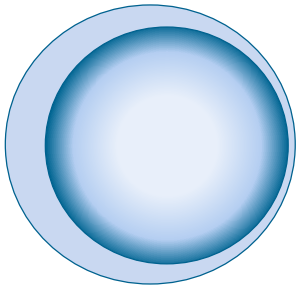


T_{naive} cells



$T_{effector}$ cells

- Promote immunity
- Enriched in autoimmune diseases



$T_{regulatory}$ cells

- Regulate immunity

→ **Preventing autoimmunity**

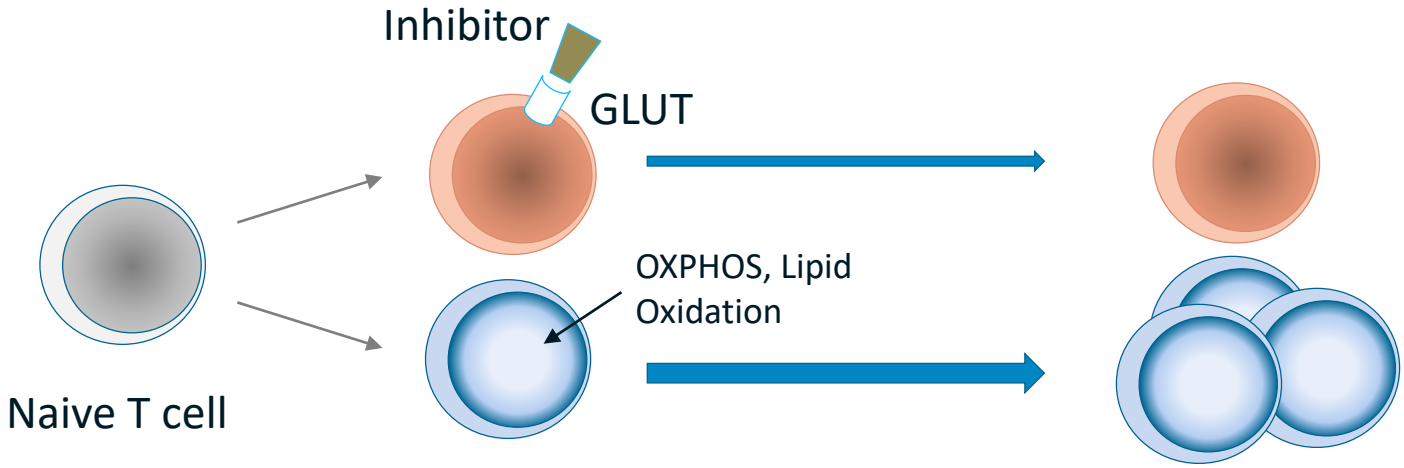
Metabolism

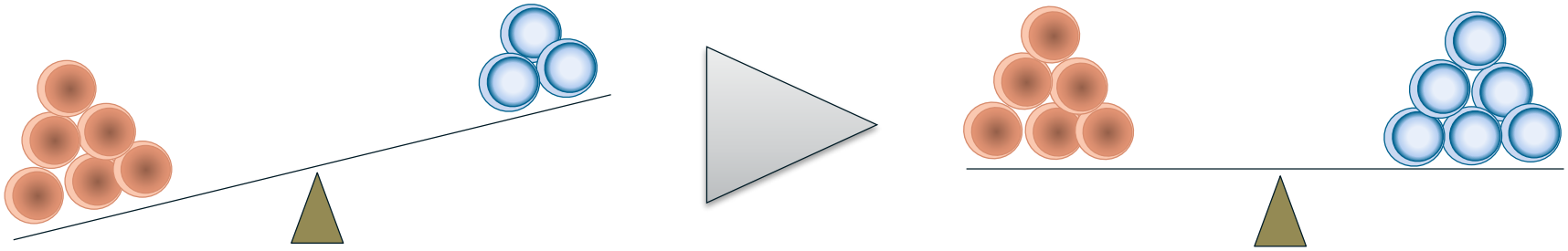
OXPHOS; Lipid Oxidation	**Aerobic Glycolysis**	OXPHOS; Lipid Oxidation

→ Target Glucose Transport

Target Rationale

GLUT Inhibition restores $T_{effector}/T_{regulatory}$ cell balance





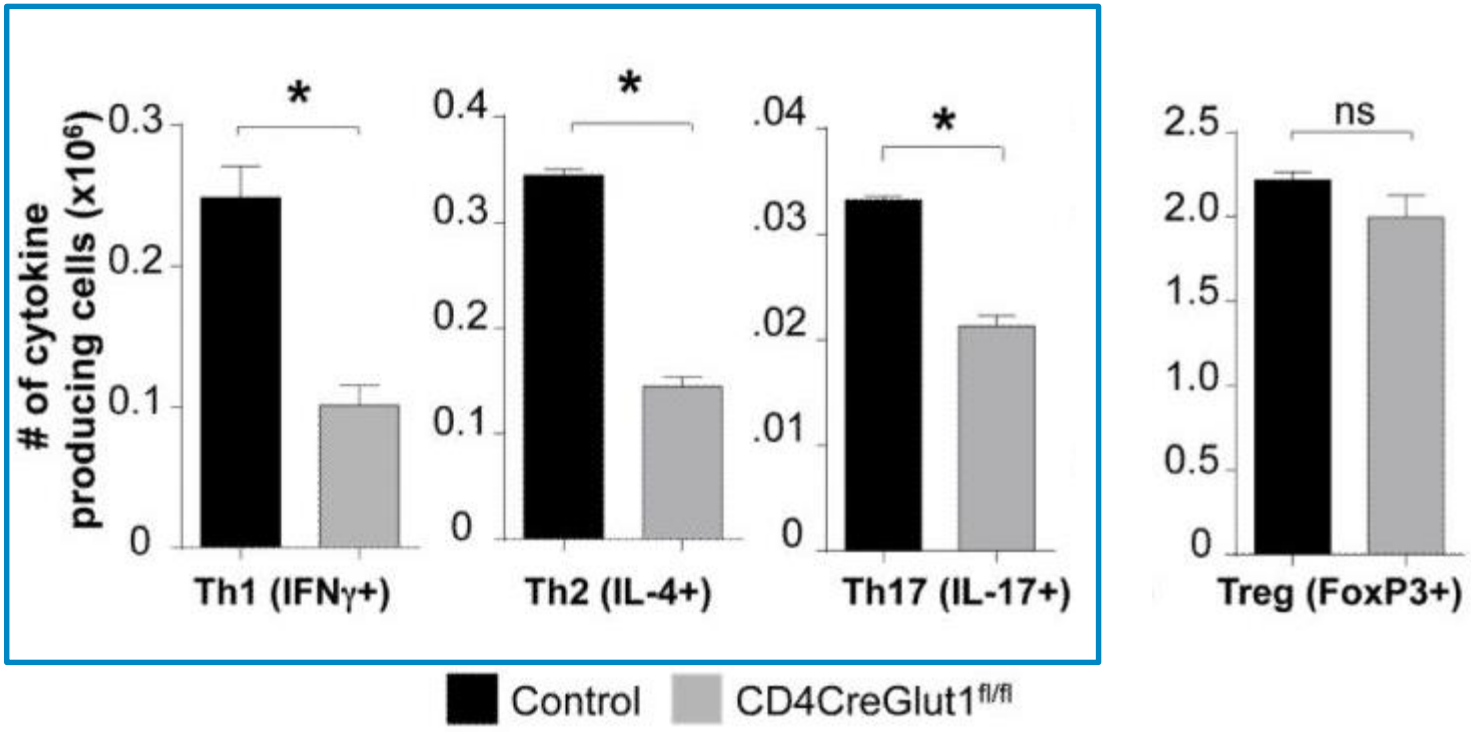
Scientific Background

Data focussing on GLUT1

- *In vitro* stimulated murine and human T cells express high levels of Glut1
- T_{eff} cells have higher Glut1 levels than T_{reg} cells
- Overexpression of transgenic Glut1 selectively increased T_{eff} frequency and leads to the manifestation of inflammatory diseases (Jacbos et al., 2008; Michalek et al., 2011)
- Glut1-deficient T_{eff} cells were unable to effectively induce Graft-vs-Host-Disease or colitis; T_{reg} cells have a suppressive role, independent of Glut1 (Macintyre et al., 2014)

Literature Data

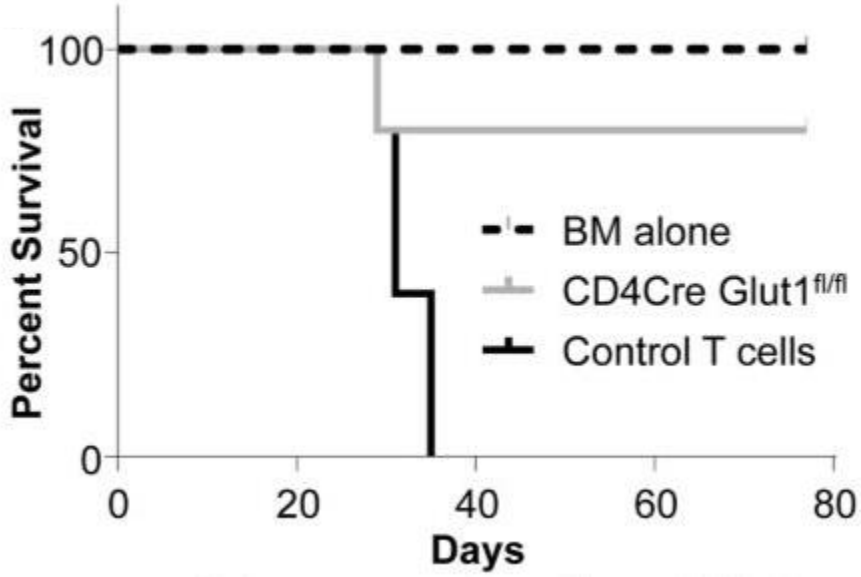
Glut1 is required for T_{eff}, but not T_{reg} or CTL generation and function



Macintyre et al., 2014

Literature Data

Glut1 is selectively required for T_{eff}, but not T_{reg} cell expansion and function in inflammatory disease



Macintyre et al., 2014

➢ Knocking out GLUT1 is effective in GvHD *in vivo*

GLUTs & T Cell Proliferation

LDC frontrunner compound & reference inhibitors

Company (compound name)	LDC	Bayer (BAY-876)	IOmet Pharma	Kadmon	(Cytochalasin B)
LDC code	1408	5017	5291	2853	2541
IC_{50} GLUT1 (DLD-1^{WT}) [nM]	80	29 (2)*	116	121 (140**)	616 (100)*
IC_{50} GLUT2 (CHO-GLUT2) [nM]	10100	17900 (10800)*	7970	n.d.	- (2800)*
IC_{50} GLUT3 (DLD-$1^{glut1-/-}$) [nM]	27	3630 (1670)*	12	104 (31**)	120 (144)*
IC_{50} GLUT4 (CHO-GLUT4) [nM]	1070	366 (290)*	163	*96 (-**)*	522 (294)*
Inhibitor type	GLUT1/3	GLUT1	panGLUT	panGLUT	panGLUT
T cell prolif. IC_{50} [µM]	**2.9**	**20**	**1.4**	**1.7****	**6**

* numbers in brackets published by Bayer
** numbers published by Kadmon

➢ Glut1/3 required for reduction in T cell proliferation

Target Product Profile of Frontrunner

Current Frontrunner		
Activity		Best Compounds: <100nM
hPBMC toxicity		>10µM, no correlation with target
SAR		Clear, Broad
in vitro SPR	Solubility	Good
	Permeability	Good
	MLM stability	Compound-dependent
	Plasma stability (mouse)	Compound-dependent
Metabolite analysis		Not Yet Performed
in vivo PK	$T_{1/2}$	Medium
	V_d	Good
	CL	Good
	$AUC_{0\text{-}inf}$	Good
	F%	Moderate
IP Position		1st Patent Application filed

Competition

Kadmon	Bayer	IOMet (MSD)	Ohio University
Glut 1/3 Patent filed for Autoimmune Diseases (WO2018201006A1) Development Status unknown: 06/2017 in mouse models → Deemed to be toxic due to Glut4 inhibition	Compound selective for Glut1 – Clinical trials were stopped in oncology → Selective Glut1 not sufficient for impact on T cell proliferation	Pan-Glut inhibitors → Deemed to be toxic due to Glut4 inhibition	Glut1 inhibitors for cancer; Preclinical stage since 2016 and no further development reported

John Hopkins University	Yeda Ltd (Weizmann)	Caladrius Biosciences	H Lee Moffitt Cancer Center
Inhibition of glucose transporters for usage in cancer, GvHD and autoimmune diseases (WO2017136731A1) → No small molecules	Peptide for inhibiting T cell proliferation in the context of autoimmune diseases (WO2018037416A1)	Technology to enhance autologous T_{reg} number → Technology rather than therapeutic	Glut1 antibodies for potential treatment of cancer

Summary

- Innovative immunometabolism program with **first-in-class** potential
- Selective inhibtion of $T_{effector}$ cell proliferation to restore homeostasis
- First PK studies concluded, further profiling ongoing
- Partnering or spin-off (supplementary project in T cell space available)