GBR 830: An antagonistic anti-human OX40 mAb with potent suppressive effect on pathological immune responses.

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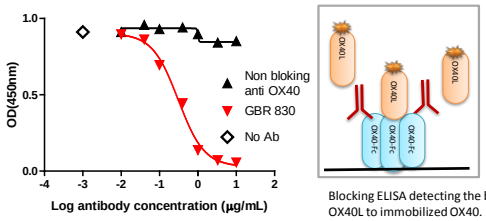
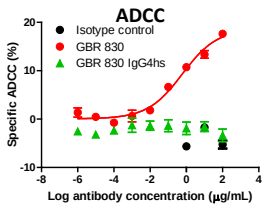
Background: OX40 is a costimulatory TNFR-superfamily receptor expressed almost exclusively on activated T lymphocytes and not on naïve or resting memory cells. OX40 signaling can enhance proliferation, survival and effector functions of T cells with a more pronounced effect on late, chronic and memory responses. Many studies have indicated that OX40 may play a central role in various T-cell mediated pathological immune responses, thus implying a therapeutic potential for antagonistic antibodies targeting OX40. However to date no antagonistic antibodies targeting OX40 have been published.

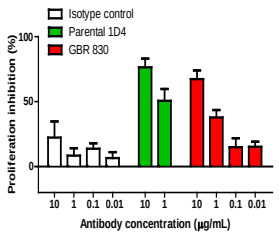
GBR 830 blocks OX40L binding and displays Fc-mediated cytotoxic functions

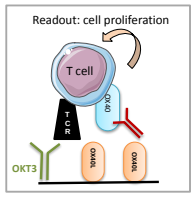


Blocking ELISA detecting the binding of OX40L to immobilized OX40.

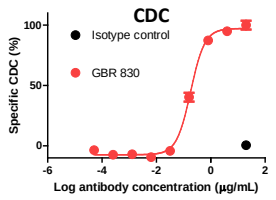


Target Cells: HPB-ALL. Effector cells: Human NK cells. E:T 10:1. Duration 4 h. IgG4hs = Hinge-stabilised IgG4.



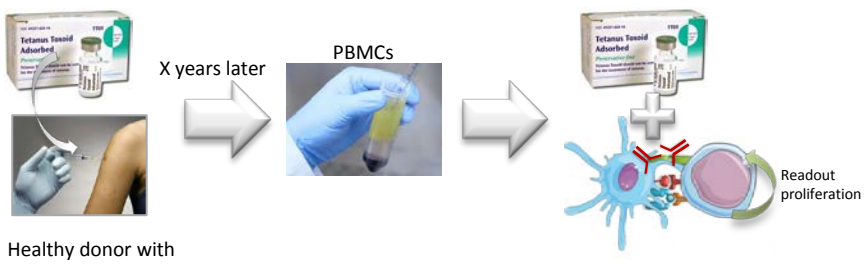


Cells: Purified human T cells. Duration 96 h. Readout proliferation.

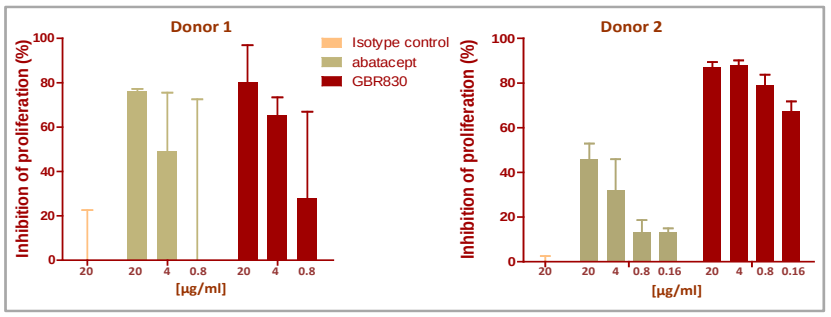


Target Cells: CHO-OX40. Baby rabbit complement. Duration 4 h.

GBR 830 blocks memory T cell reactivation



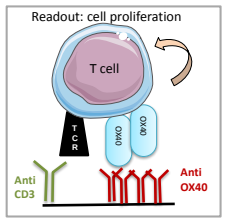
Healthy donor with historical TT vaccination



Legend: A total of 6 donors responded to TT restimulation (shown are 2 representative donors). On half of these donors, GBR 830 was superior to abatacept. The % of inhibition of proliferation was determined relative to a condition without treatment (only PBMC and TT).

GBR 830 is devoid of agonistic potential

Anti OX40 antibodies were: A10 from Genentech. 112V8 from Kirin Beer and La Jolla Institute for Allergy and Immunology. Ab 131 and 315 were described in Imura et al. J.Exp.Med 1996. These antibodies are described as antagonistic . 7H11 from Glenmark (agonistic control). OX40L is used as a positive reference.



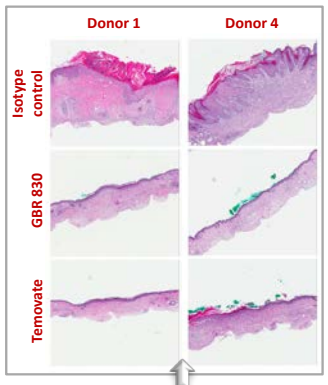
	Proliferation index							
	OX40L	Hu IgG1 ctrl	7H11	GBR 830	A10	Ab131	Ab 315	112V8
Donor 1	2.05	1.07	1.85	1.18	1.57			
Donor 3	3.44	1.17	6.22	0.82	2.51			
Donor 4	2.47	ND	9.05	1.08	2.22	6.41	3.19	0.70
Donor 5	3.03	ND	14.37	0.72	1.25	5.70	0.81	0.77
Donor 6	2.46	ND	4.00	1.79	2.78	4.31	2.81	3.07

Proliferation index (PI) : mean counts (sample) / mean counts (OKT3 only). Donor 2 was excluded because it gave a proliferation index inferior to 2 with OX40L. Red = agonism = PI>2. Green = no agonism.

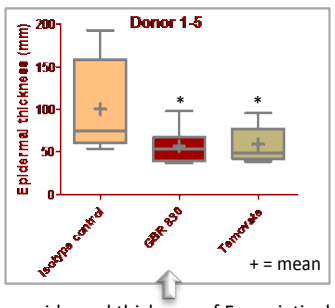
Potent therapeutic anti-psoriatic activity of GBR 830

Lesional skin biopsies from **psoriasis patient** were grafted on SCID mice. Treatments - Isotype control, GBR 830 , or temovate (topical) were initiated 3 to 5 days post-transplantation Each condition was done in duplicate for each donor..

Example of macroscopic healing of the psoriasis grafts for one donor

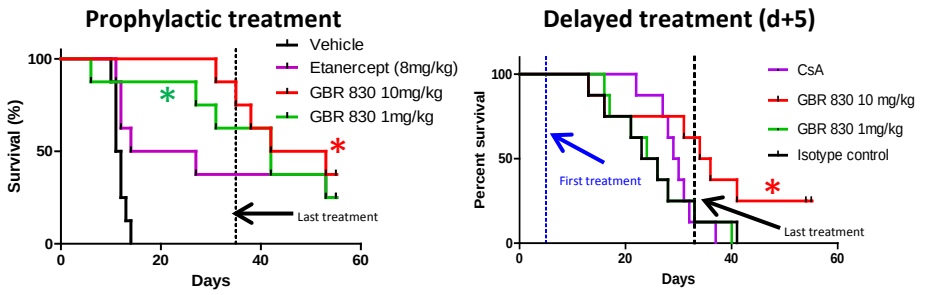


Example for two donors of the histological appearance of the graft, 16 days post graft. GBR 830 induced a complete reversion of the psoriasis phenotype



Mean epidermal thickness of 5 psoriatic donors. *p<.05 by two tailed Student t test. GBR 830 induced the same healing effect on all donors

GBR 830 suppresses xenogeneic GvHD



GBR 830 suppressed xeno GvHD. Irradiated scid mice were injected i.p with $30x10^6$ PBMCs. Antibodies or etanercept were given i.v. once a week. Cyclosporin A (CsA – Sandimmune) was given daily i.p at 15mg/kg. Not shown: GBR 830 displayed better GvHD suppression than Efalizumab in a repeat experiment. * p<0.05 compared to vehicle or isotype control. Log-Rank(Kaplan-Meier test).

Conclusion: Generation of OX40 targeting mAbs devoid of agonism is difficult but possible. GBR 830 suppressed acute xenogeneic reactions in a GvHD model. Targeting OX40 suppressed memory-T cell reactivation, more efficiently than targeting CD28. Finally GBR 830 displayed a potent therapeutic anti-psoriatic activity. These results highlight the therapeutic potential of targeting OX40 in T cell-mediated inflammatory and autoimmune diseases and warrant further clinical studies with GBR 830.