Paris NASH Meeting

International Think Tank

Gut-based immunotherapy - implications for NASH

Targeting the gut immune system for alleviation of the systemic inflammatory response without immune suppression

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Disclosure

I have financial relationships with the companies below and the content of my presentation does include a discussion of the investigative use of products being developed by the companies below. The studies described were supported in part by several of these companies.

Consultant:

Teva; Abbott; ENZO; Protalix; Therapix; Betalin Therapeutics; Immunepharma; JTI; Immuron; Chiasma Pharma; Nasvax; Alcobra; One Day Pharma; Cure Tech; Lutea; Kamedis; MedWell; Accelmed; Medial; SciM; Tiziana Pharma;

Medical Director:

Exalenz Bioscience; Natural Shield; Oberon Sciences; Plantylight;

Forward-looking statement

Please be advised that the information and projections provided in this presentation may include forward-looking statements with respect to plans, projections or future performance of the compounds and companies presented, the occurrence of which involves certain risks and uncertainties and is not under the control of these companies, including, but not limited to, changes in regulatory environment and success in implementing its research, development, sales, marketing and manufacturing plans, protection and validity of patents and other intellectual property rights, the impact of currency exchange rates and the effect of competition by other companies.

Therapy for NASH: The next decade

a. Target multiple mechanisms
b. Long term safety
c. Target the whole spectrum of the disease: from prevention to cirrhosis
d. A combination therapy
e. Alleviates concomitant disorders (e.g. diabetes, hyperlipidemia)

Oral immune therapy | **Examples** | **Advantages**

Ilan, Y Dig Dis Sci. 2018 Apr 20.
Ilan, y Ann Gastroenterol. 2018 May-Jun;31(3):296-304.

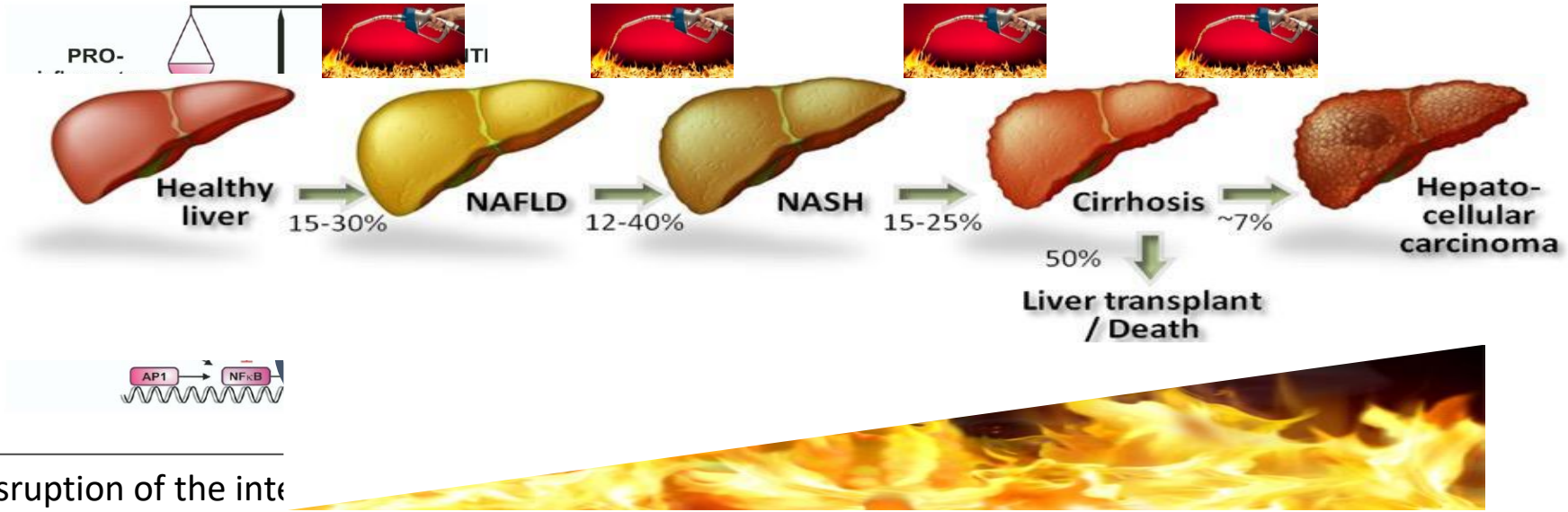
How does our environment blends into us

Oral immune therapy

Picasso Stadel Museum, Frankfurt

Metabolic syndrome – low Grade chronic inflammation
Inflammation: fueling the growing fire

Diverse immune pathways at different disease stages



Disruption of the inte
and metabolic pathways is central
pathogenesis of the metabolic syndrome

https://imarketsmart.com/why-you-should-add-fuel-to-the-fire/
https://seekingalpha.com/article/3546436-revisiting-nash-therapeutic-targets-competitive-landscape
http://oncologypro.esmo.org/Education-Library/Essentials-for-Clinicians/Lymphomas/Chapter-1-The-Immune-System
Based on: Hotamisligil GS. Nature 2006;444:860–7
Tilg H, et al. Gastroenterology 2006;131:934–45

Oral immunotherapy: modulation of the systemic immune response via alteration of the gut immune system without immune suppression

Antigen / Antibody / adjuvant

Presented to the gut-associated lymphoid tissue /dendritic cells

Target organs

- Liver
- Pancreas
- Adipose tissue
- Bowel
- Muscle

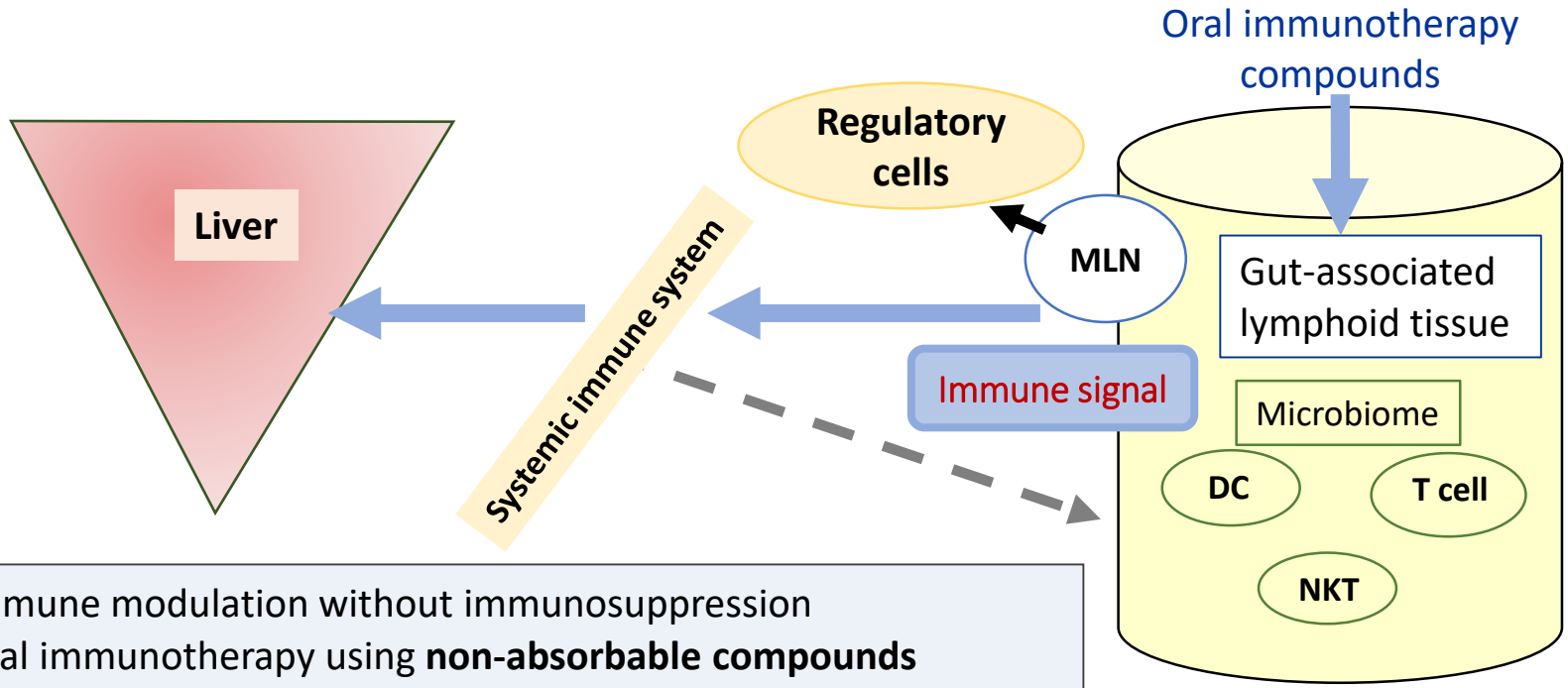
Promotion of Tregs in mesenteric lymph nodes

Tregs: Regulatory T cells

Ilan Y, et al. Immunol Cell Biol 2009;87:514–24
Ilan Y, Hum Immunol. 10:768-76, 2009

Image from Fagarasan S & Honjo T. Nat Rev Immunol 2003;3:63–72

Oral immunotherapy: Re-educating the immune system

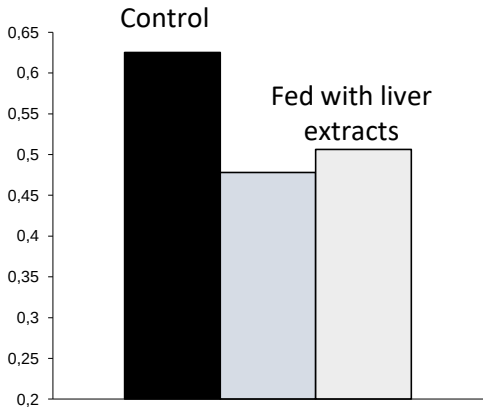


- Immune modulation without immunosuppression
- Oral immunotherapy using **non-absorbable compounds** are being evaluated in pre-clinical & phase I/II NASH trials

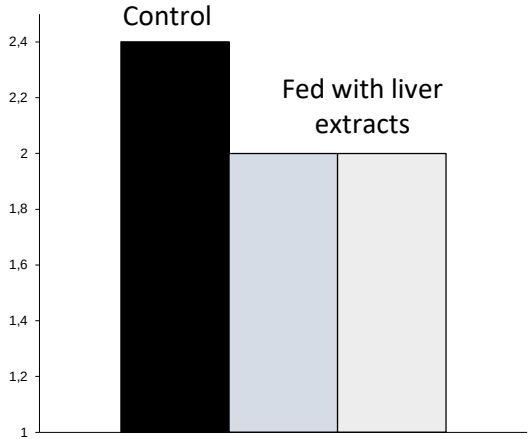
DC: Dendritic cells
MLN: Mesenteric lymph nodes
NKT: Natural killer lymphocytes

Adapted from: Ilan, Y 2016 . Alimentary Pharmacology & Therapeutics
Ilan Y, Clinical & Translational Immunology; 2016

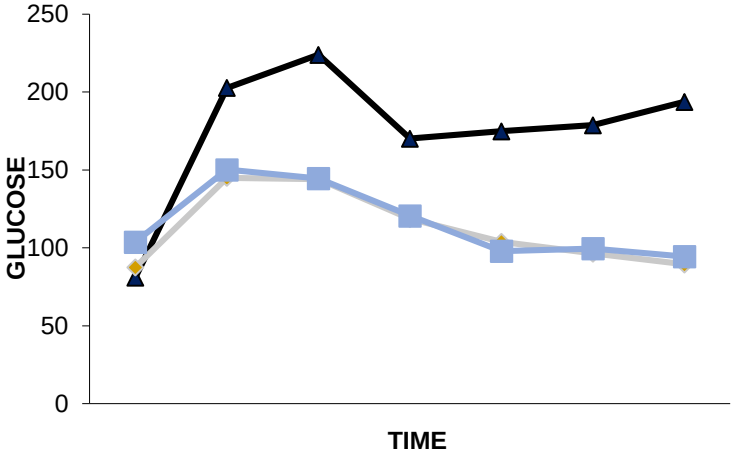
Induction of oral tolerance towards fatty liver-extracted proteins



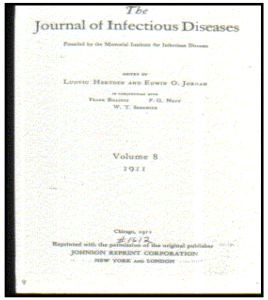
Reduction of hepatic fat content by MRI



Reduction of hepatic triglycerides content



Improved glucose intolerance



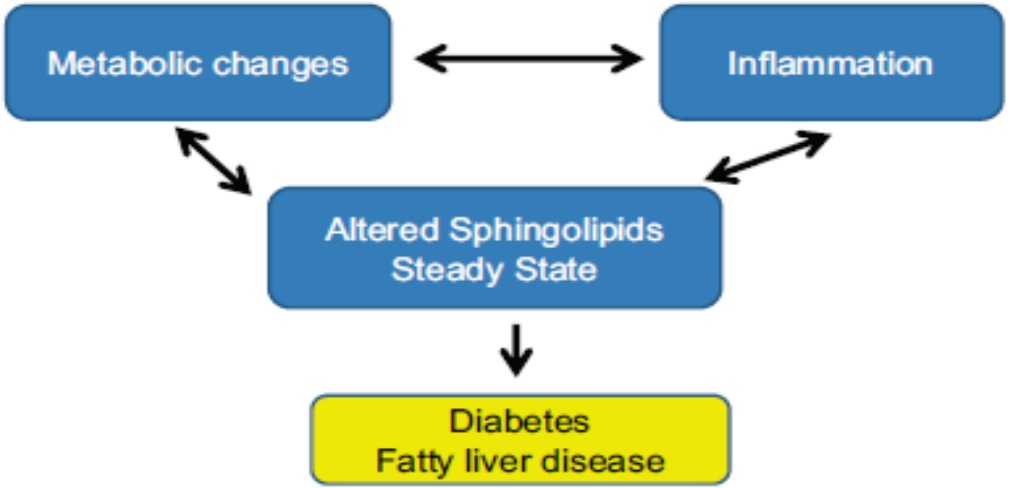
1911 Wells

Jewish sages wrote:

"*If one is bitten by a mad dog, he may eat his liver and be cured.*"

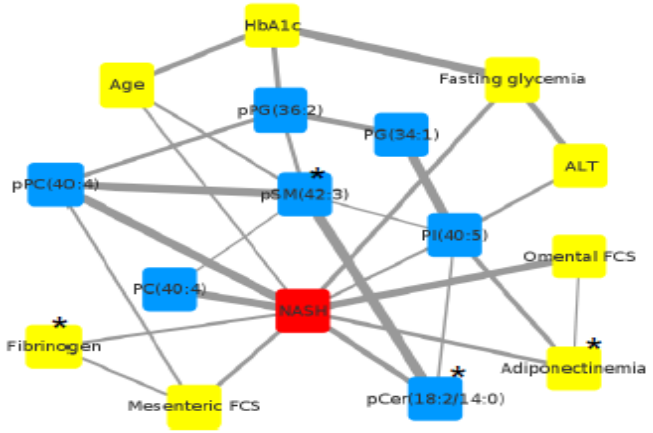
Elinav E J Pathol 2006; 208: 74–81

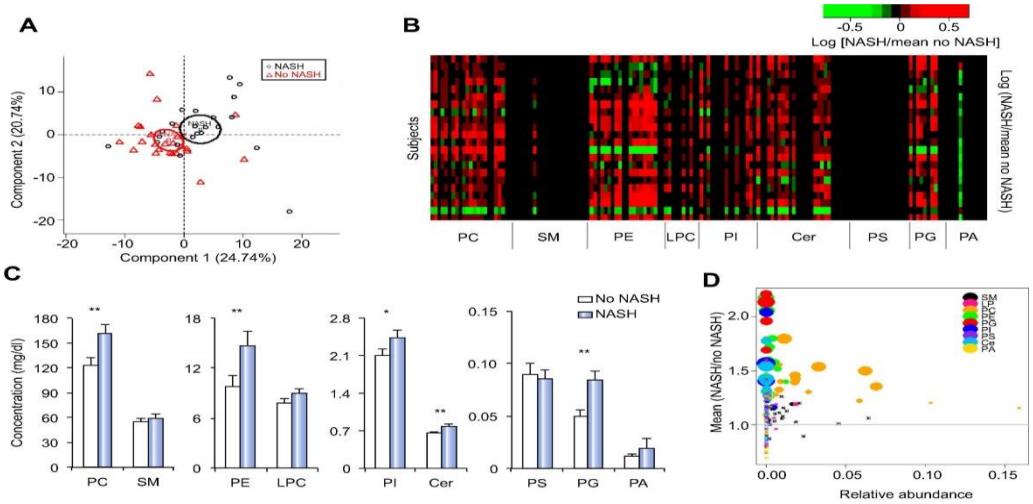
Compounds of the sphingomyelin-ceramide-glycosphingolipid pathways as secondary messenger molecules: new targets for novel therapies for fatty liver disease and insulin resistance



Ilan, Y. Am J of Physiology, 2016

Circulating phospholipid profiling identifies portal contribution to NASH signature in obesity



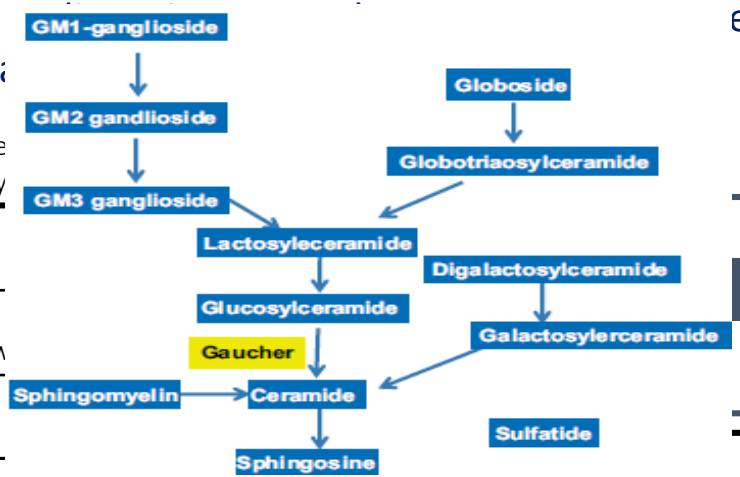


Journal of Hepatology .2014.11.002

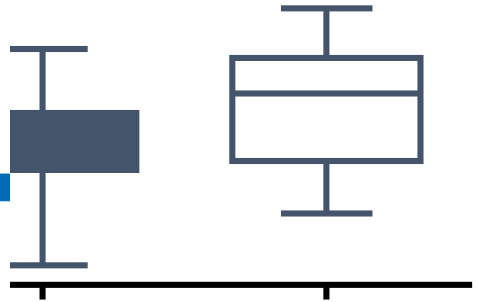
Evolutionary advantage of patients with Gaucher's disease: An immune protective effect of β-glucosylceramide (GC)

Prevalence of overweight, i
type II diabetes before and a

	Before enzyme therapy
Prevalence of being overweight (%)	16
Prevalence of insulin resistance (%)	Not know
Prevalence of type II diabetes (%)	0



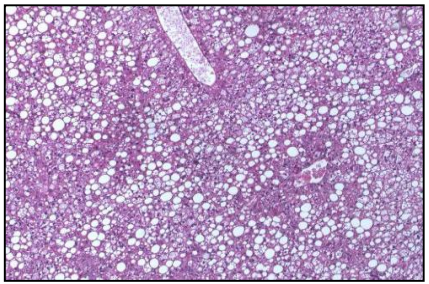
ease in BMI during treatment with ERT (n=32)



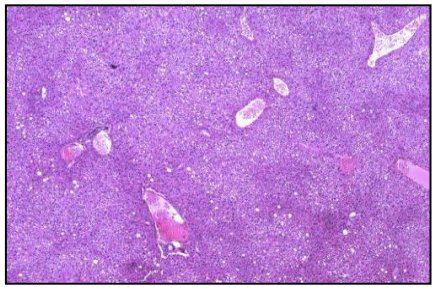
Glucocerebroside: an evolutionary advantage for patients with Gaucher disease and a new immunomodulatory agent

Langeveld M, et al. Blood Cells Mol Dis 2008;40:428–32
Ilan Y. Immunolgy Cell Biology 2008

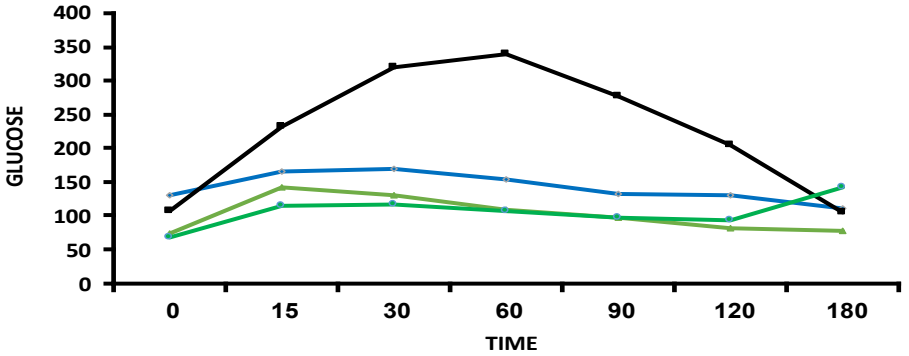
GC improves glucose intolerance and decreases hepatic fat accumulation in the ob/ob model

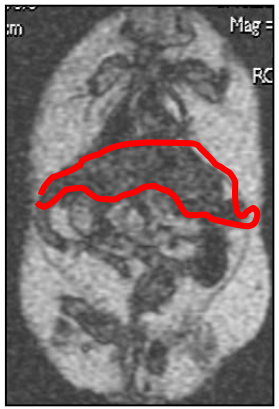


Control

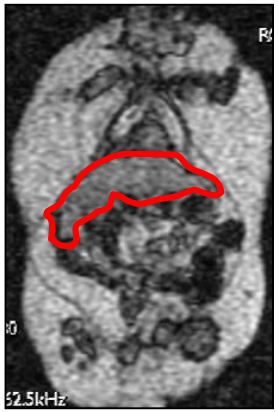


GC-treated

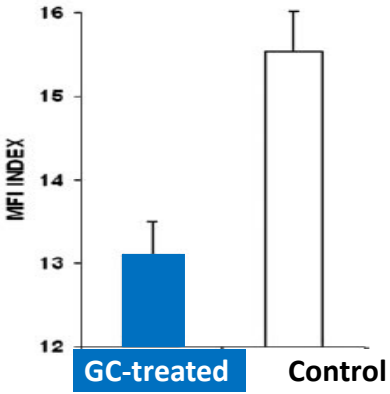




Control

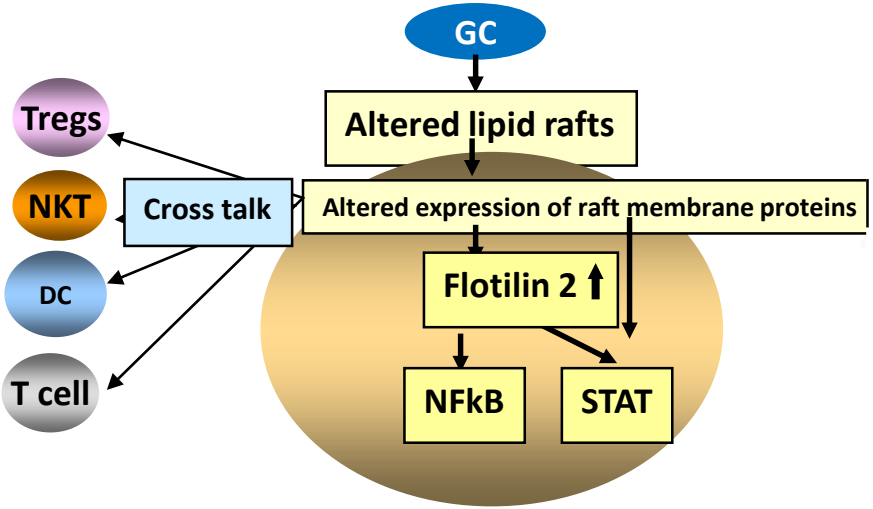


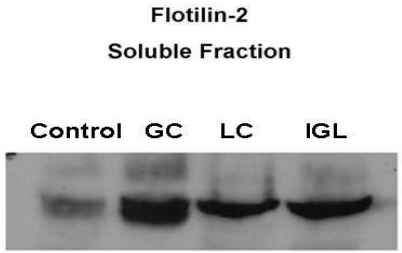
GC-treated

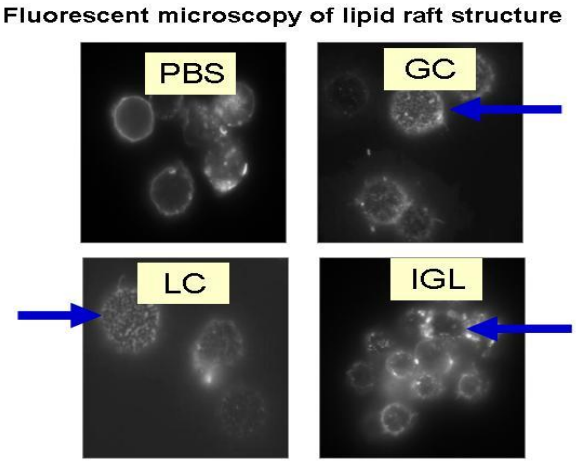


Margalit M, et al. J Pharmacol Exp Ther 2006

Oral administration of glycosphingolipids alters lipid rafts on cells membranes





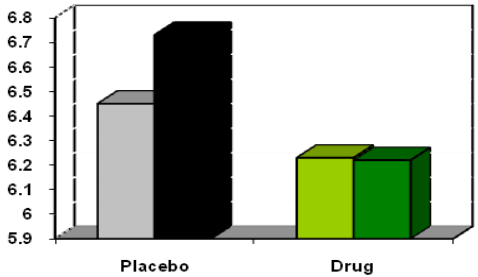


GC: β-glycosylceramide
LC: β-lactosylceramide
IGL: β-glycosylceramide+β-lactosylceramide

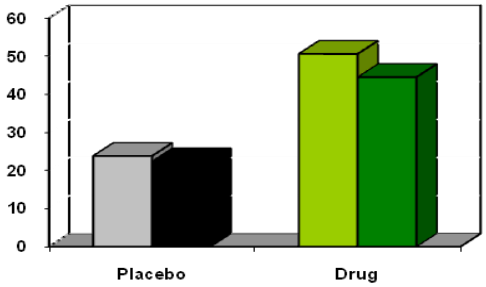
Lalazar Mole immunology 2008
Ilan Y, et al. Immunol Cell Biol 2009;87:514–24
http://acseenotes.wordpress.com/2011/03/07/cytology

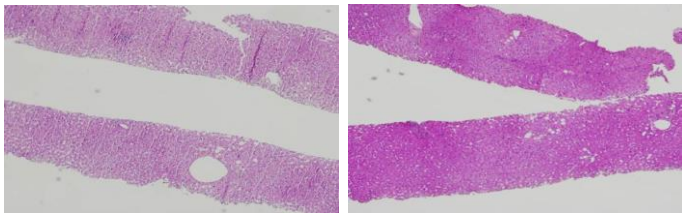
Safety and Effect of Oral Administration of GC (EGS21) in Subjects with Diabetes and NASH: Results of a double blind placebo controlled trial

Primary endpoint - HbA1c

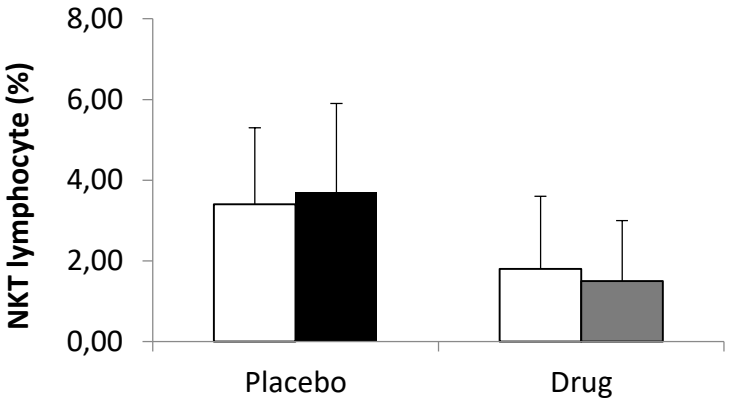


Secondary endpoint - % Fat by MRI





Week 0 Week 40



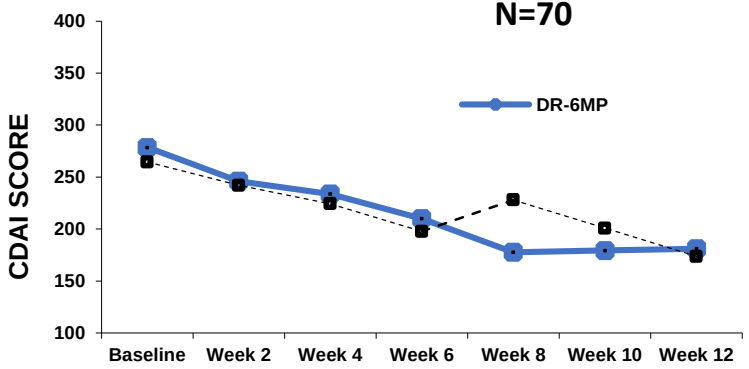
N=23
40 weeks

Lalazar, J Med Food 2017.458-464:(5)20

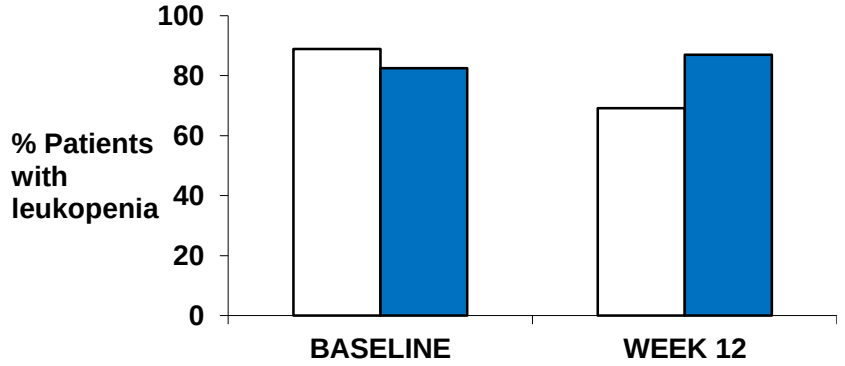
Oral administration of DR6MP:
A minimally absorbed delayed-release 6-mercaptopurine

Phase II double blind placebo controlled trial

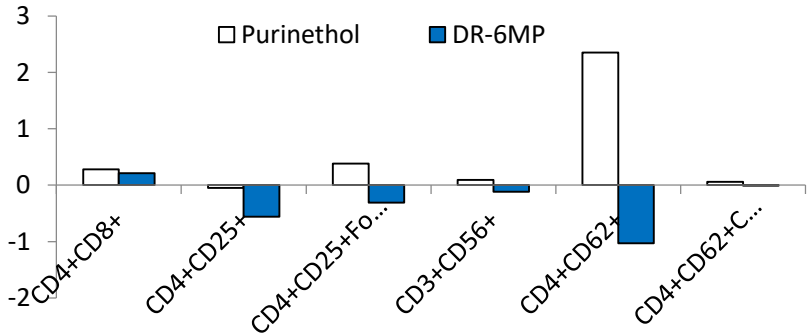
N=70



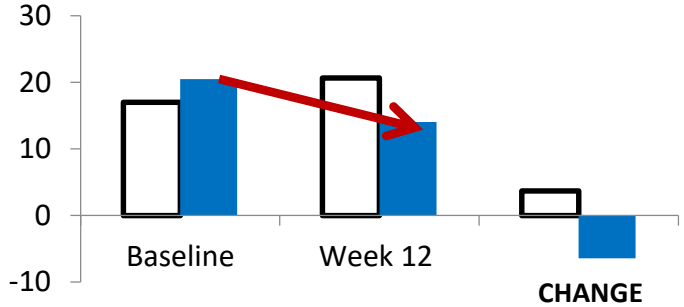
Reduction in CDAI in DR6MP-treated CD



No Leukopenia in DR6MP-treated CD



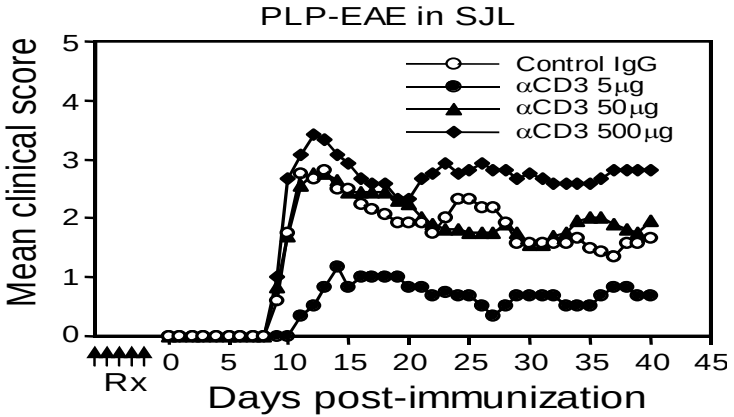
Alteration of systemic Immune system in DR6MP-treated

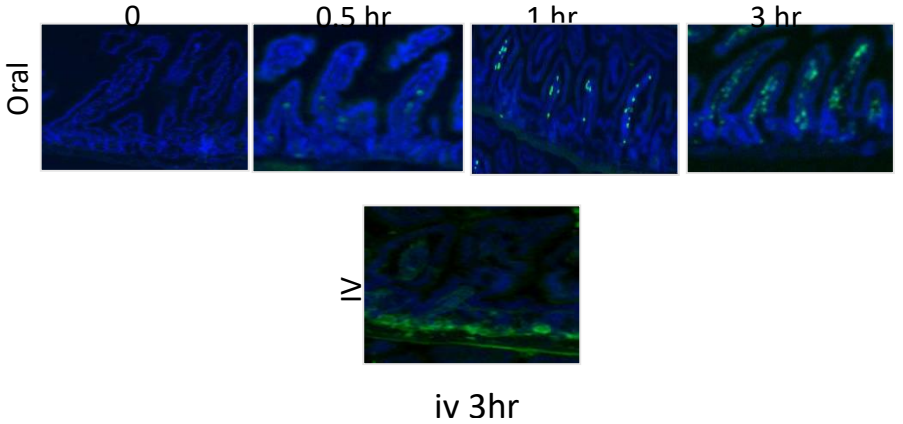


Reduction in IFN-gamma ELISPOT assay

Ilan, E. Clin Exp Immunol. 2015 181(2):362-72

Induction of oral immunotherapy using oral anti-CD3



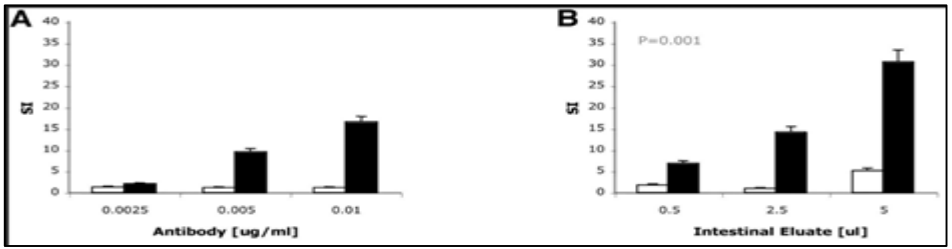


iv 3hr

GASTROENTEROLOGY 2012;143:1298–1307

An Oral CD3-Specific Antibody Suppresses T-Cell–Induced Colitis and Alters Cytokine Responses to T-Cell Activation in Mice

KATHARINA FORSTER,* ASHLEIGH GOETHEL,* CATHERINE WING–TAK CHAN,* GALLIANO ZANELLO,* CATHERINE STREUTKER,‡ and KENNETH CROITORU*,§



Molecular Cardiology

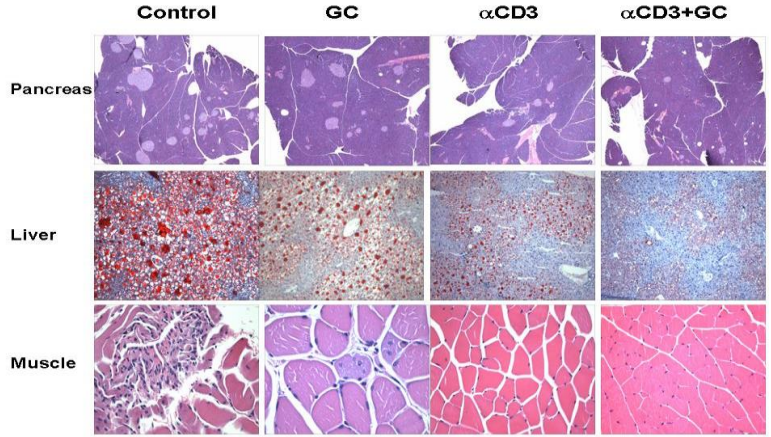
Oral Anti-CD3 Antibody Treatment Induces Regulatory T Cells and Inhibits the Development of Atherosclerosis in Mice

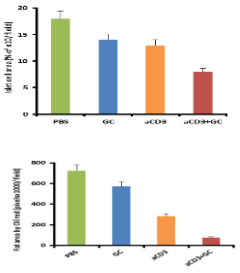
Naoto Sasaki, MD, PhD; Tomoya Yamashita, MD, PhD; Masafumi Takeda, MD, PhD; Masakazu Shinohara, MD, PhD; Kenji Nakajima, MD; Hideto Tawa, MD; Takashi Usui, MD, PhD; Ken-ichi Hirata, MD, PhD

Biologically active anti-CD3 recovered from the gut

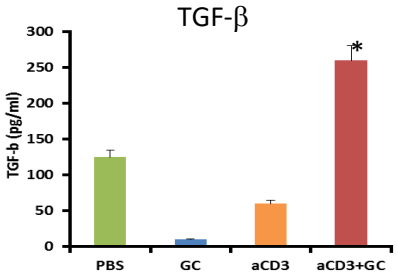
Weiner et al. Immunol Rev; Brain. 2016; Immunotherapy. 2016.

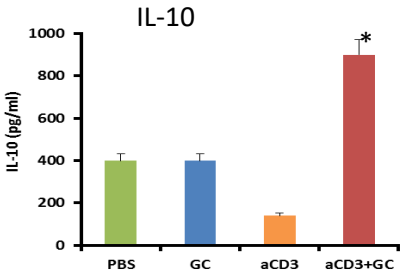
Induction of oral immunotherapy using oral anti-CD3 for NASH

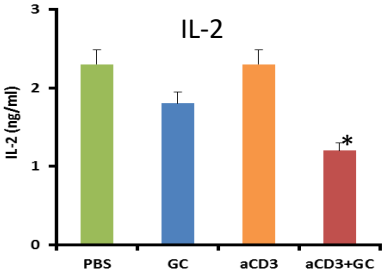


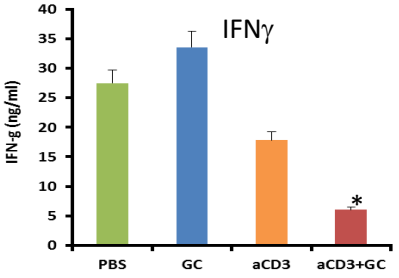


An adjuvant effect on the innate immune system in the gut

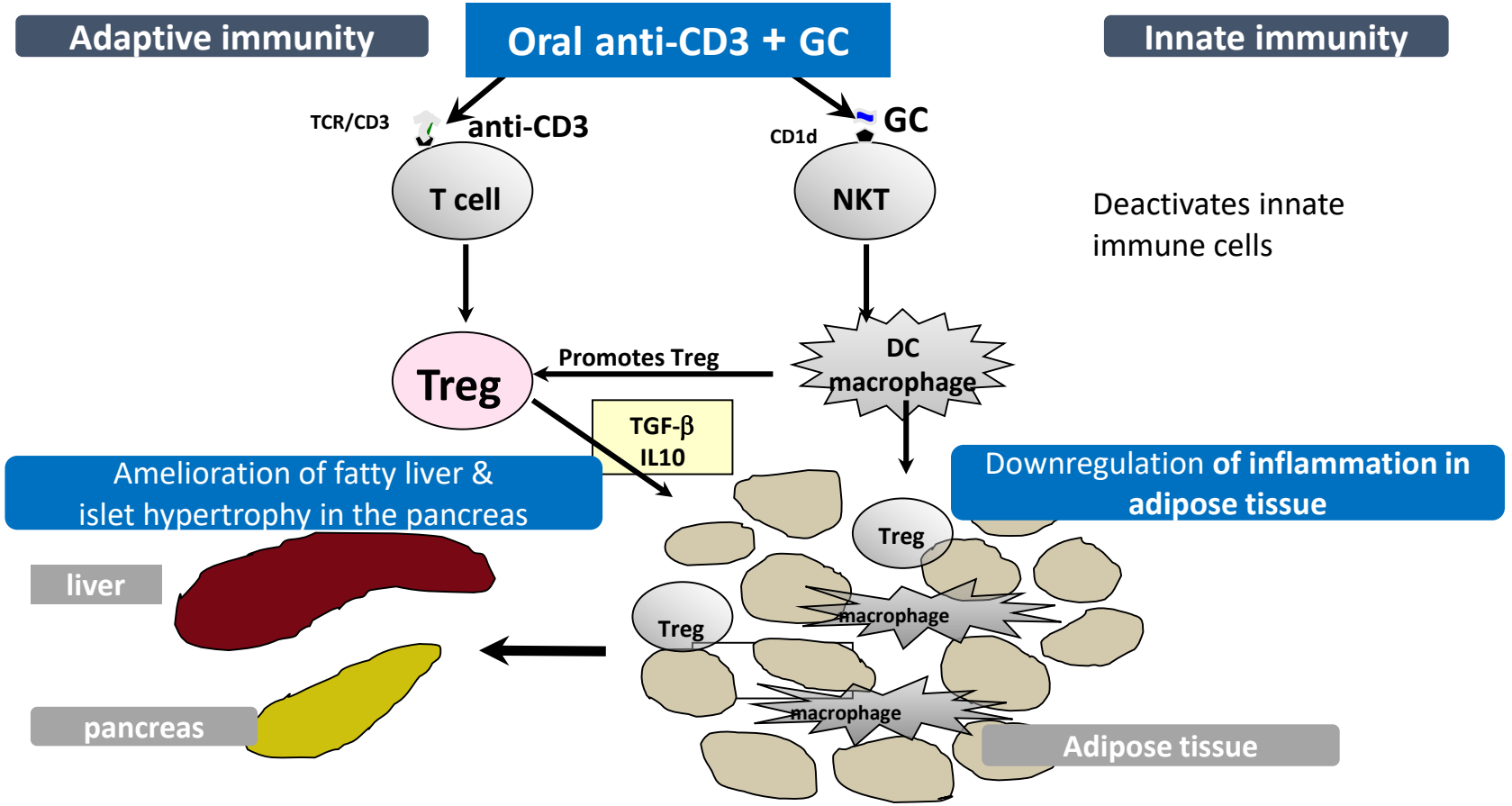








Ilan Y, et al. Proc Natl Acad Sci U S A; 2010



DC=Dendritic cells
Tregs=regulatory T cells
NKT=natural killer lymphocytes

Ilan Y, et al. Proc Natl Acad Sci U S A; 2010 107:9765–70

Oral anti-CD3 in NASH: promotes regulatory T cells, decreases liver enzymes, and alleviates insulin resistance

- Phase II, randomized single blinded clinical trial
- 36 subjects with biopsy-proven NASH with type II diabetes
- 0.2, 1.0, 5 mg or placebo daily for 30 days

Safety:

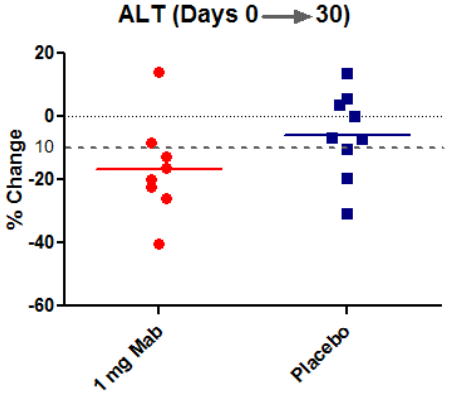
I. No treatment-related adverse events

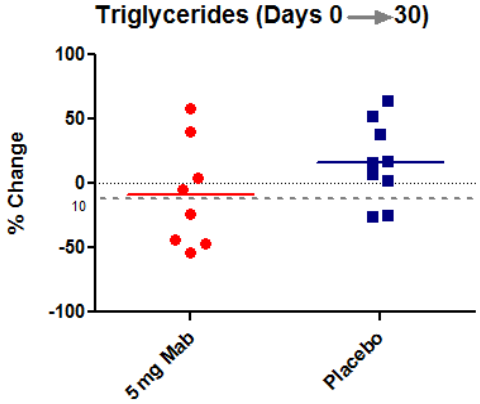
II. Normal blood cell counts: No change in $CD3^+$ counts

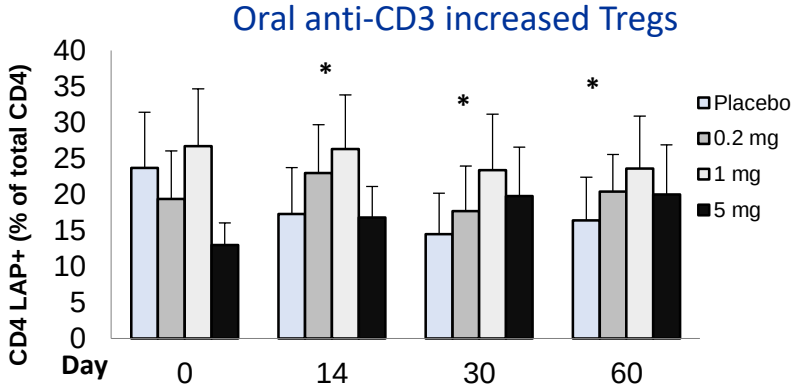
Efficacy biomarkers:

I. Liver enzymes ↓

II. TG ↓



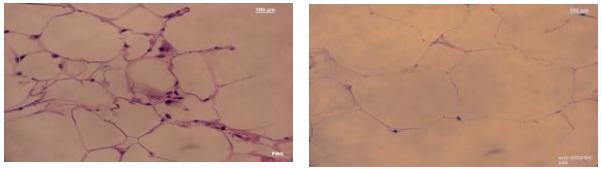




Ilan Y J Clin Immunology 2015

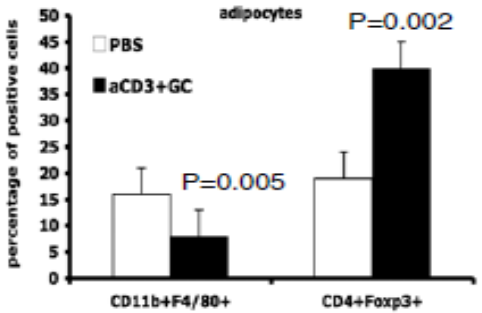
Effect of oral administration of anti-CD3 with glycosphingolipids on adipose tissue in a NASH model

A decrease in cell infiltration into adipose tissue

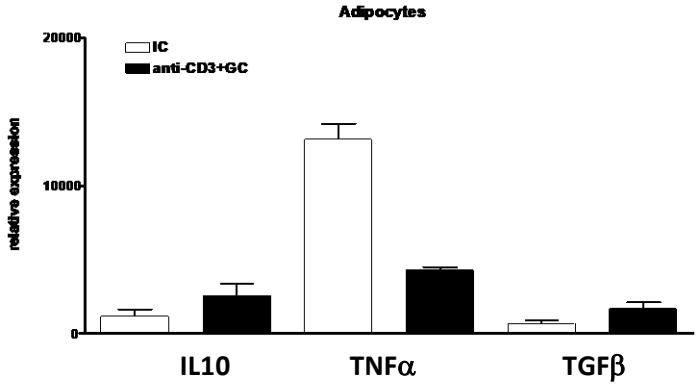


PBS anti-CD3+GC

Decrease CD11b+F4/80 macrophages
increase in foxp3 expression in CD4+ T cells

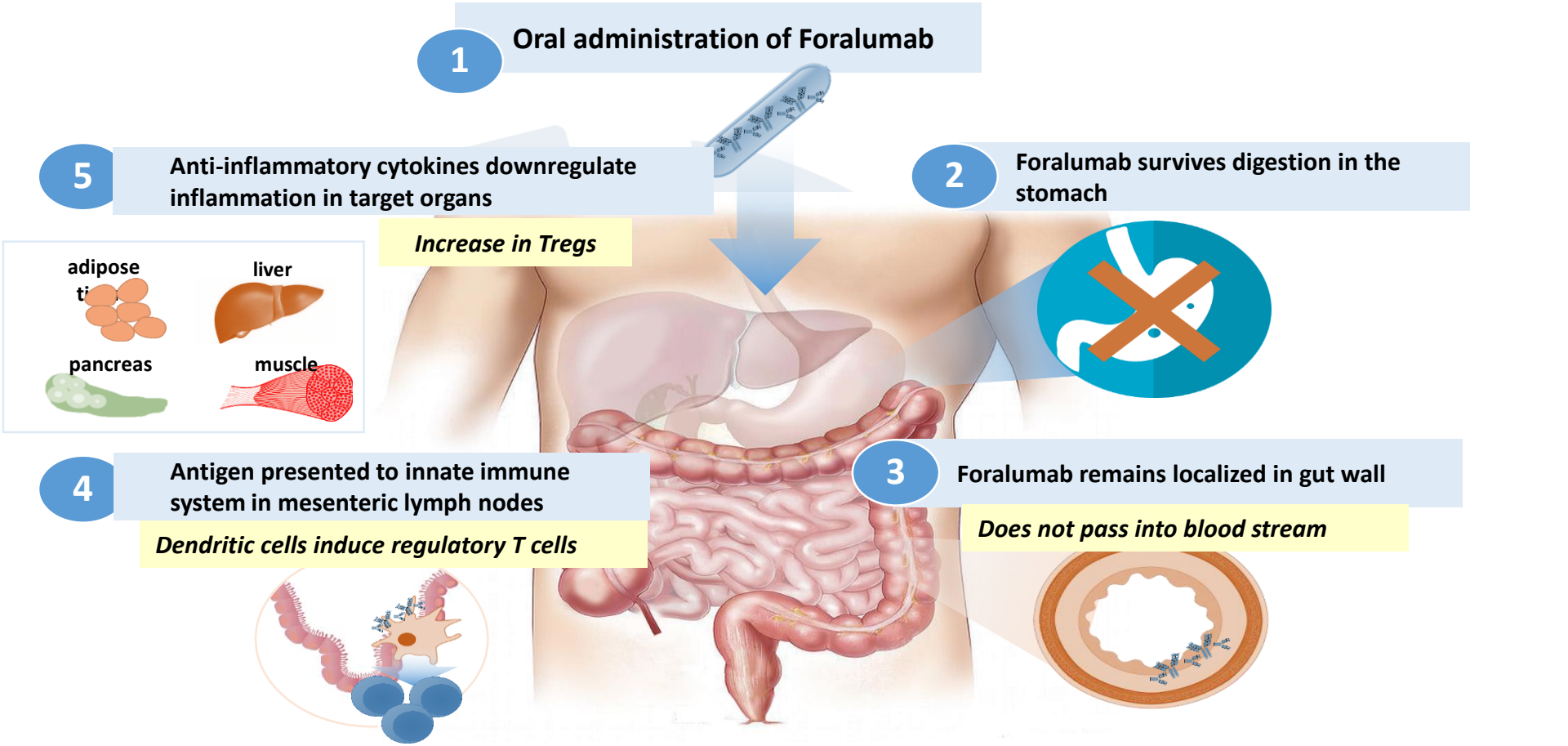


Decrease TNFα
Increase in IL10 & TGFβ



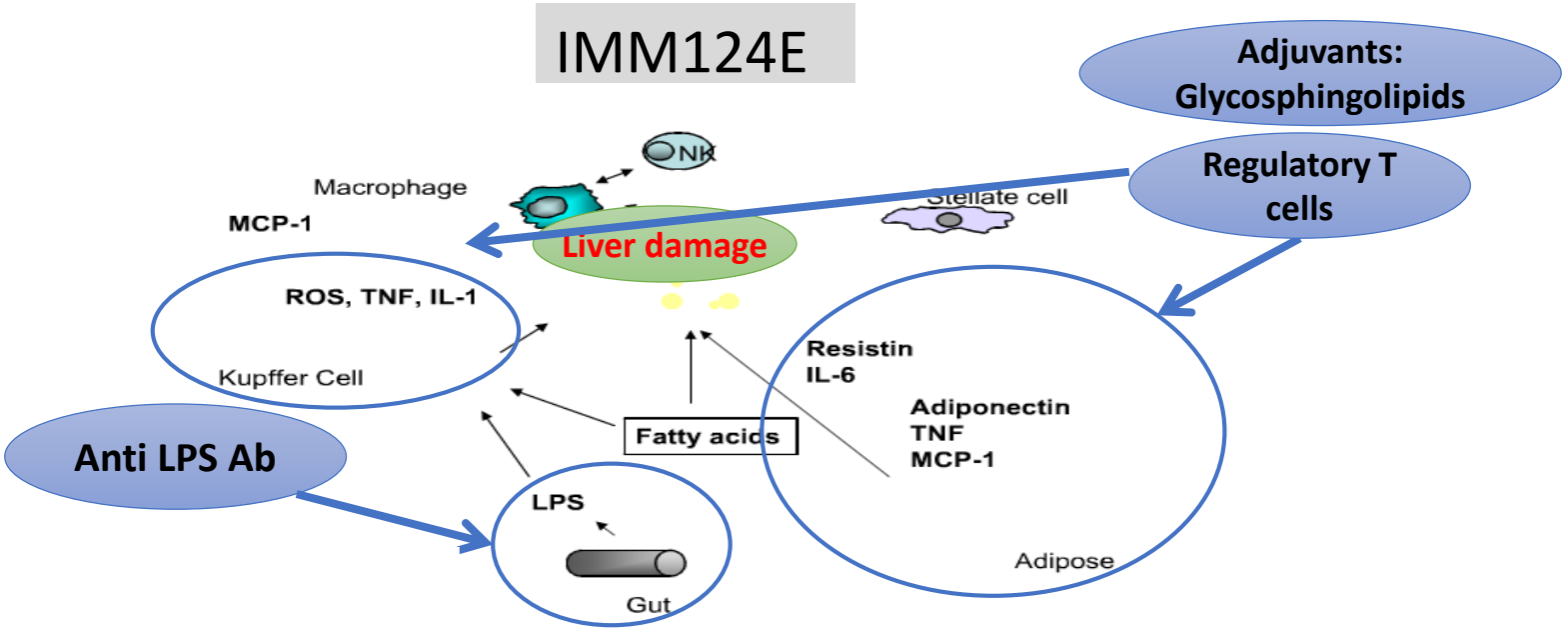
Ilan Y, PNAS, 2010

Foralumab: Humanized Oral anti-CD3 in NASH



Ilan, Shailubhai, Sanyal, Clin Exp Immun 2018 (In Press)

LPS contributes to activation of inflammatory pathways associated with inducing NASH in a background of fatty liver

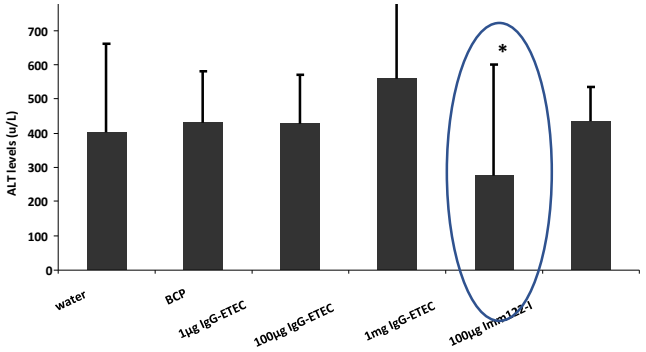


Adopted from AASLD 2010; J Hepatol 2007

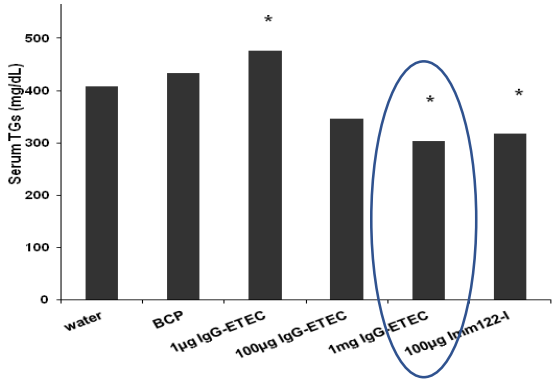
Oral administration of anti-LPS antibodies with glycosphingolipids: An adjuvant effect on the innate immune system in the gut

Pre clinical: Leptin-deficient model of NASH

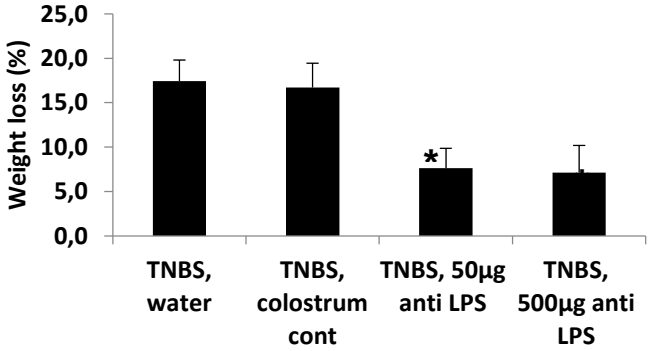
Decreased liver enzymes



Decreased serum triglycerides



* P<0.05; ** P<0.009

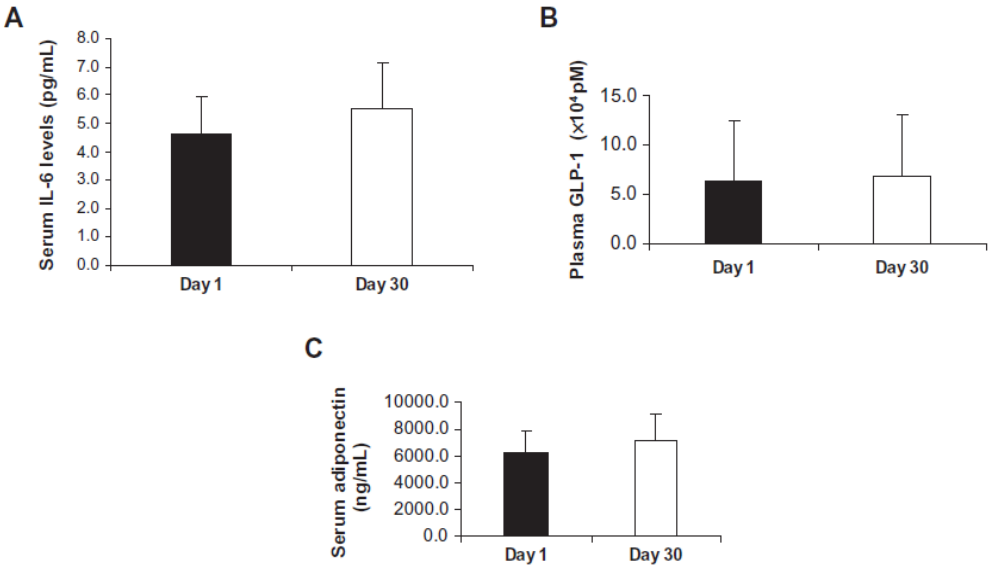


An adjuvant effect on the innate immune system in the gut in NASH &colitis

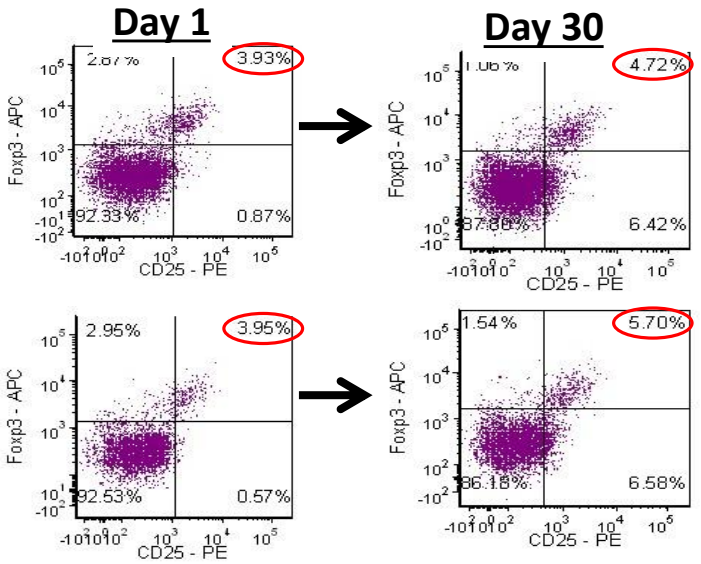
Adar T. Clin Exp Immunol., 2012
Ya'acov AB. BMC Gastroenterol. 2015

Oral administration of IMM124E in NASH: Results of a phase I/IIA

Increased GLP1 and adiponectin



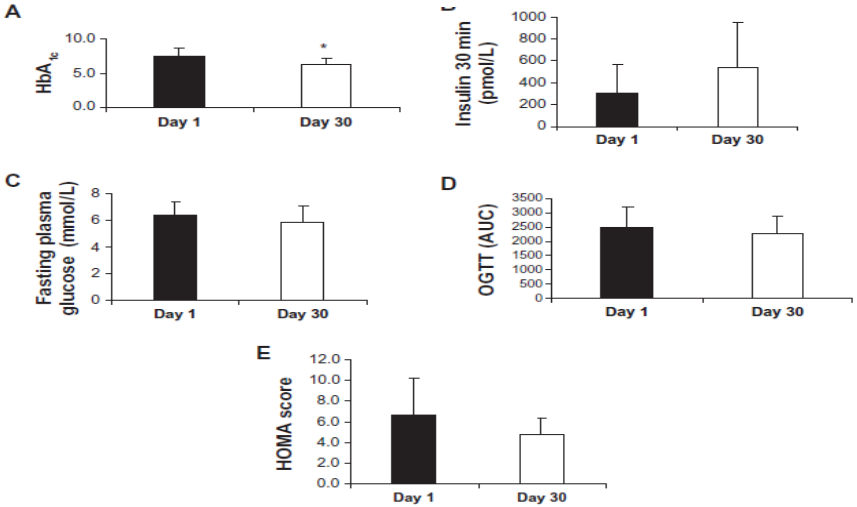
Increased CD4+CD25+Foxp3+ Tregs



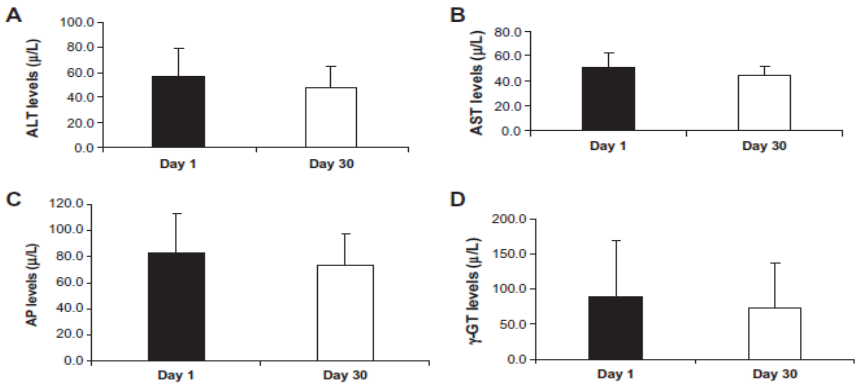
Mizrahi M. J Inflamm Res. 2012

IMM124E :Results of Phase IIA clinical trial

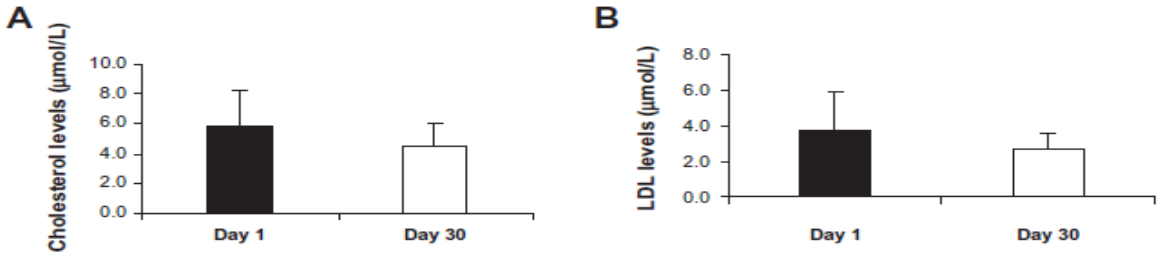
Improved insulin resistance



Decrease in liver enzymes

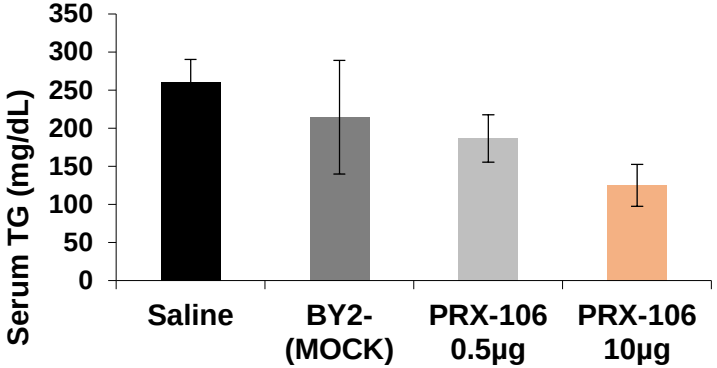


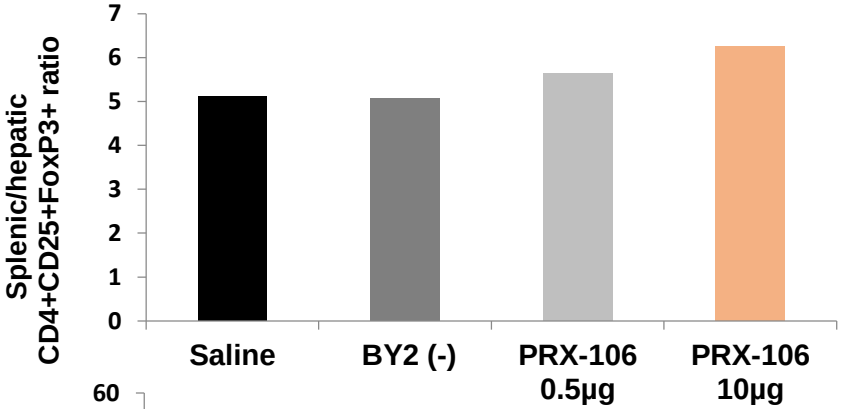
Alleviation of hyperlipidemia

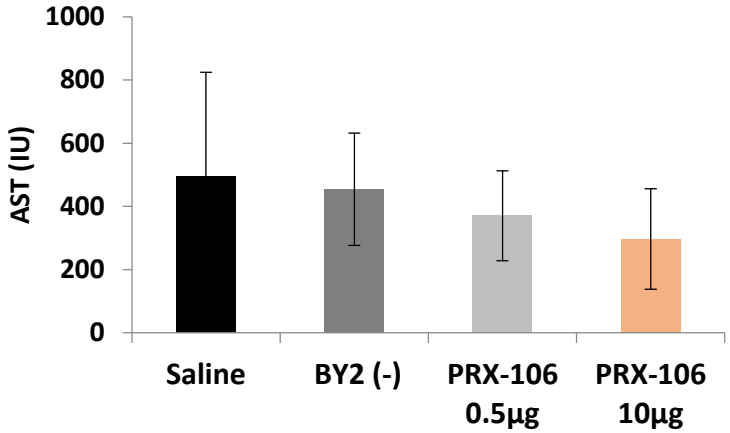


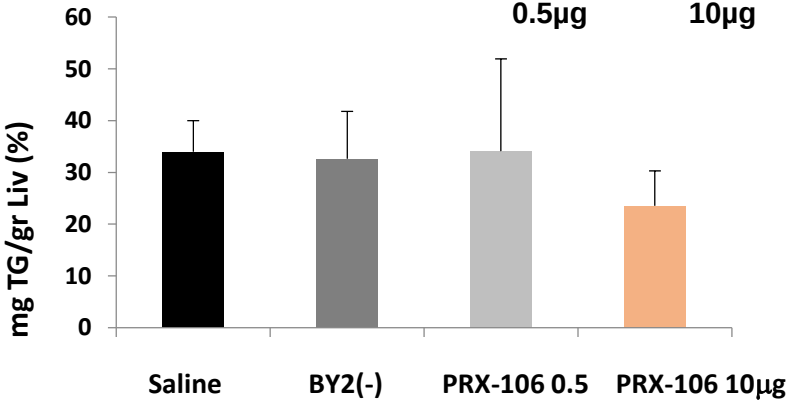
Mizrahi M. J Inflamm Res. 2012

Oral administration of a BY-2 plant cell-expressing recombinant anti-TNF fusion protein (PRX-106), which consists of soluble form of human TNF receptor fused to the Fc component of a human antibody IgG1 domain





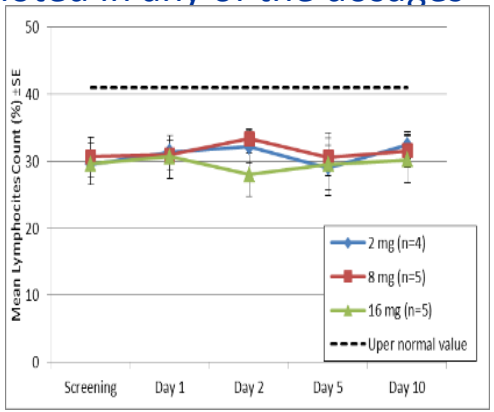




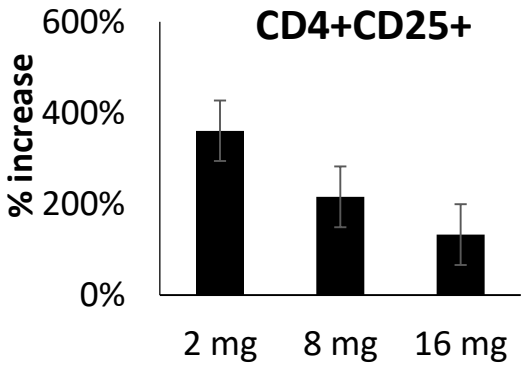
Ilan Y Immunobiology 222:544-551, 2017
Khury T, World J Gastroenterol. 2016

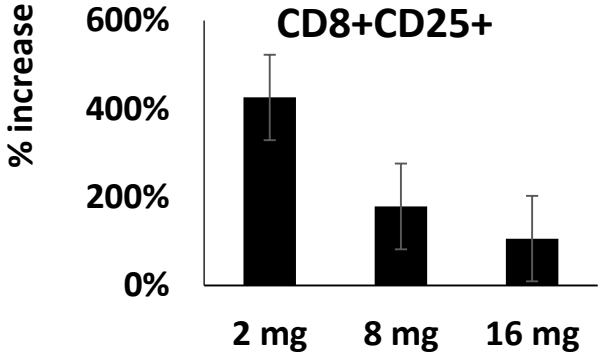
Oral administration of a recombinant anti-TNF fusion protein is biologically active in the gut promoting regulatory T cells: Results of a phase I clinical trial

No effect on white blood cells and lymphocytes counts were noted in any of the dosages



Oral administration of all three dosages was associated with an increase in CD4+CD25+ and CD8+CD25+ subset of suppressor lymphocytes

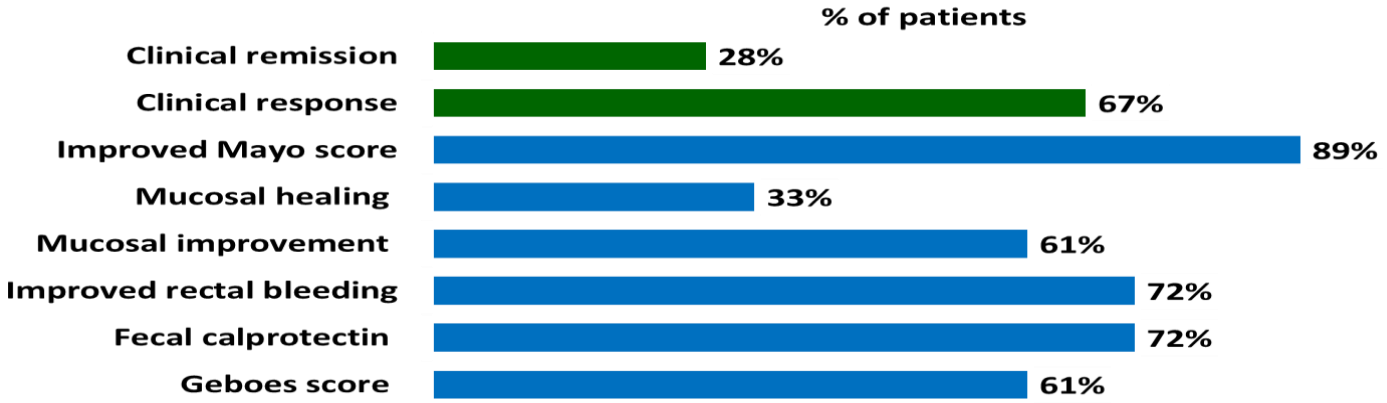




Almon E, J Immunol . Methods. 446:21-29, 2017

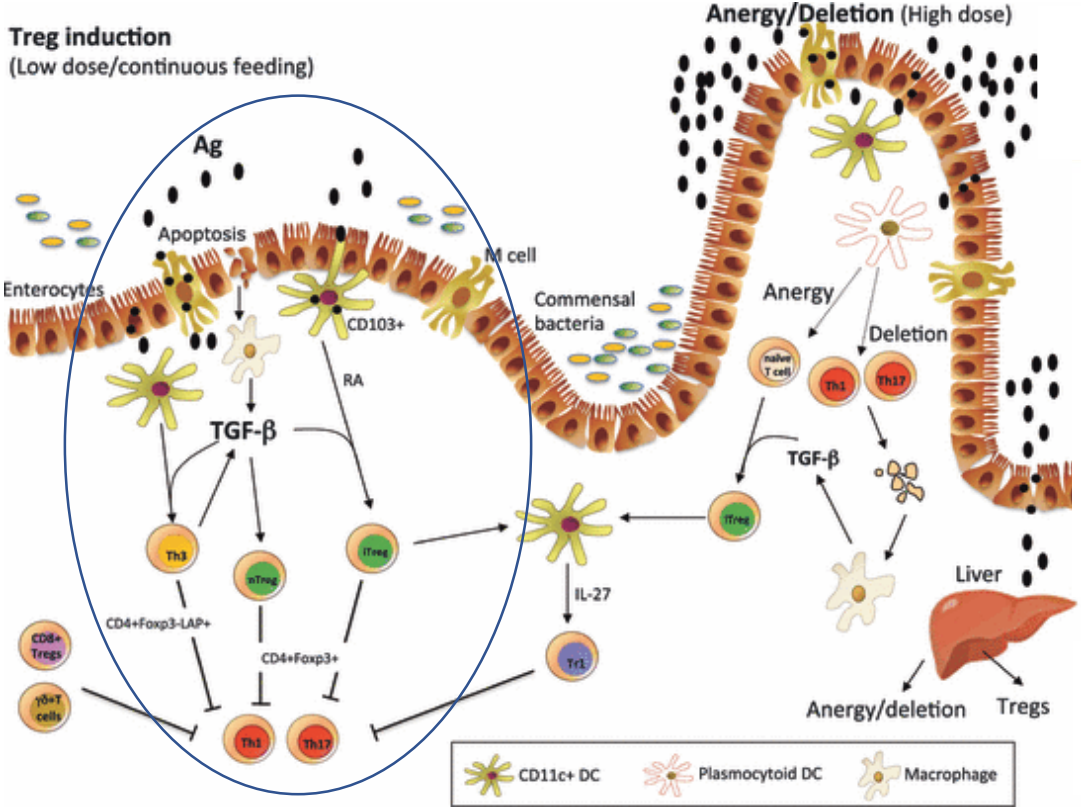
Orally administered recombinant anti-TNF alpha fusion protein for the treatment of ulcerative colitis: Phase 2a clinical trial

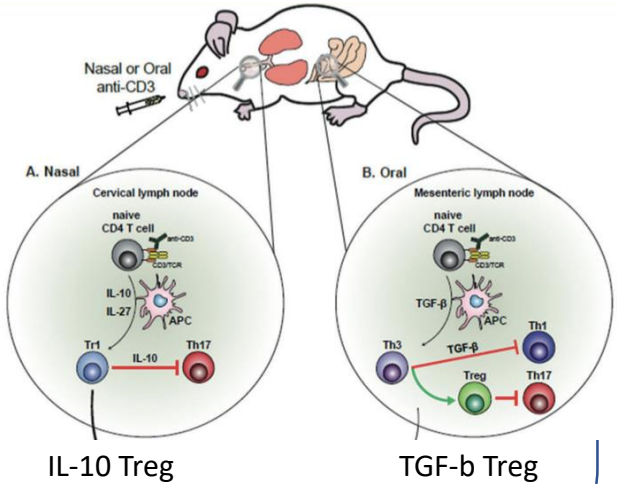
- OPRX-106 was not absorbed systemically.
- Oral administration using OPRX-106 was safe and well tolerated
- OPRX-16 was not associated with immune suppression.
- OPRX-106 was effective as demonstrated by clinical response and improvement in various disease parameters.



Ilan, y Gastroenterology 2018;154:S-153; Abst 739

Mechanism of oral immunotherapy: Promotion of regulatory T cells





IL-10 Treg

TGF-b Treg

Ilan Y, Clinical & Translational Immunology; 2016

Adopted from: Weiner et al. 2011. Immunol Rev; Brain. 2016; Immunotherapy. 2016

Oral Immunotherapy for NASH: Advantages

Mechanism	○ An ability of the gut immune system to deliver signals to control the systemic immune response
Target	○ Not dependent on a specific molecular pathway ○ Promotes regulatory T cells
Safety	○ Non-absorbable ○ No immune suppression ○ Low dose is sufficient to achieve a clinically meaningful effect
Spectrum of disease	○ Treatment for early and late stages of disease ○ Induction of remission and maintenance
Associated disorders	○ Treats type 2 diabetes and hyperlipidemia
Adjuvant	○ An adjuvant for other metabolic and anti-fibrotic drugs

Ilan, Y 2016. Alimentary Pharmacology & Therapeutics

Summary

Oral immunotherapy-based compounds: A new class of drugs for NAFLD

a. Oral immunotherapy using non-absorbable immune modulators redirect the immune system towards an anti-inflammatory pathway.

b. It provides a platform for a long-term safe therapy which targets chronic inflammation in NASH in patients of all disease stages.

Ingram Pinn

International Think Tank
Paris NASH Meeting

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Thank You