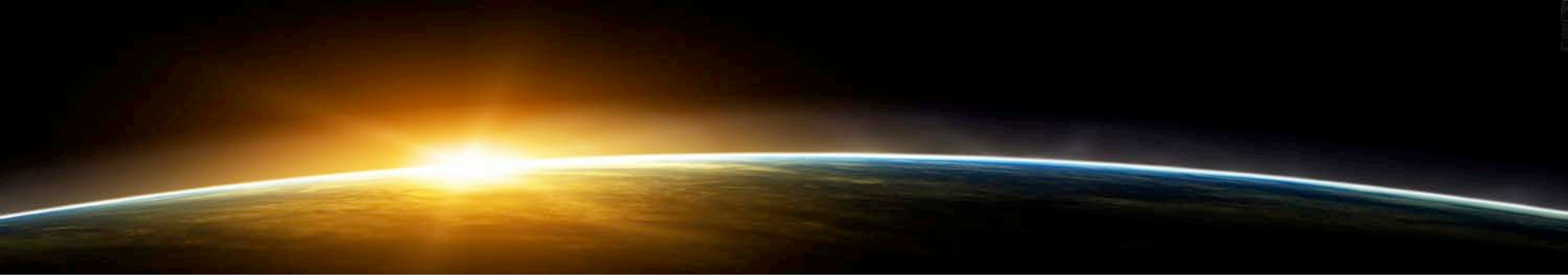
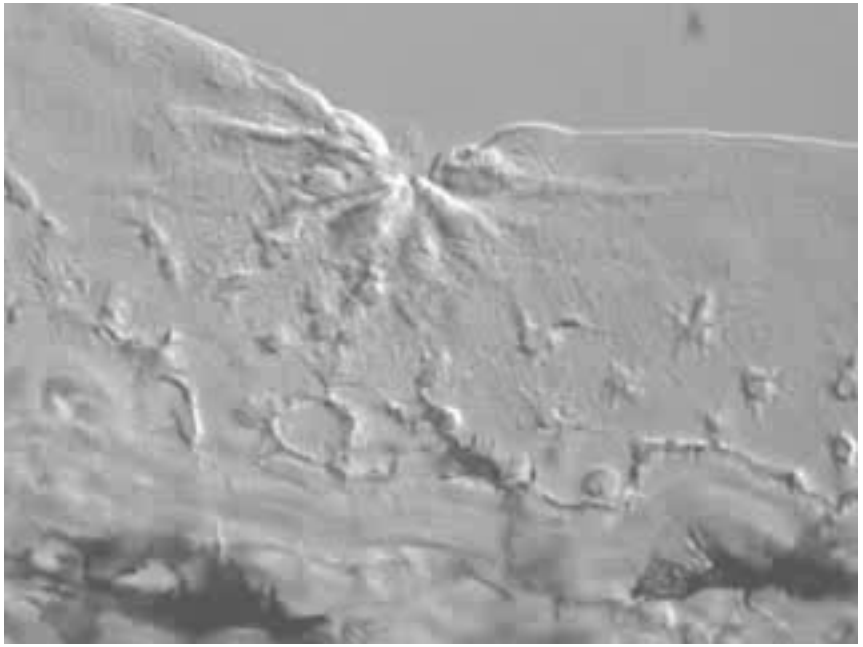
Medical Therapies on the Horizon

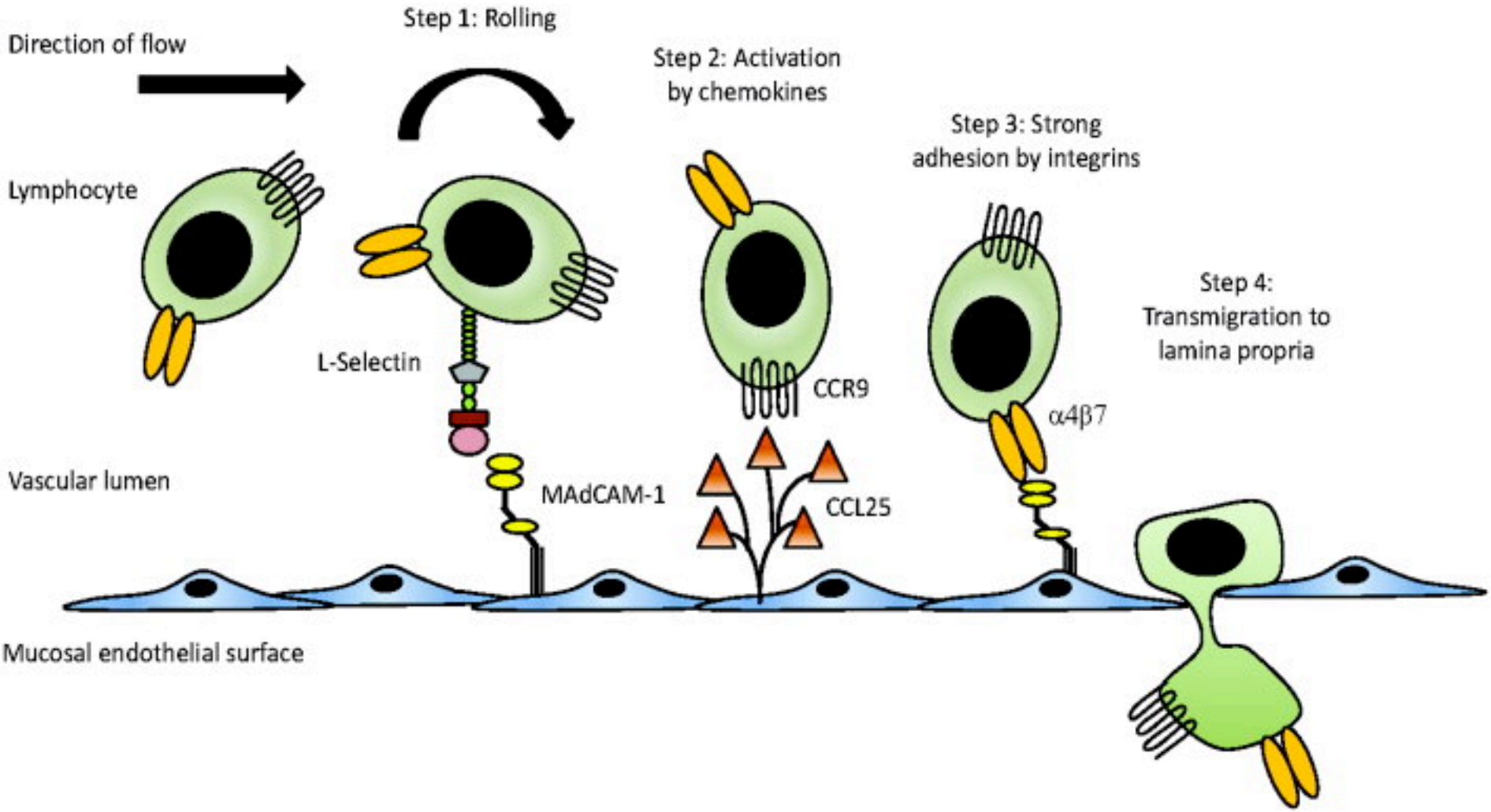
Drs. Bowlus, Selmi, Hirschfield, Melum and Zern

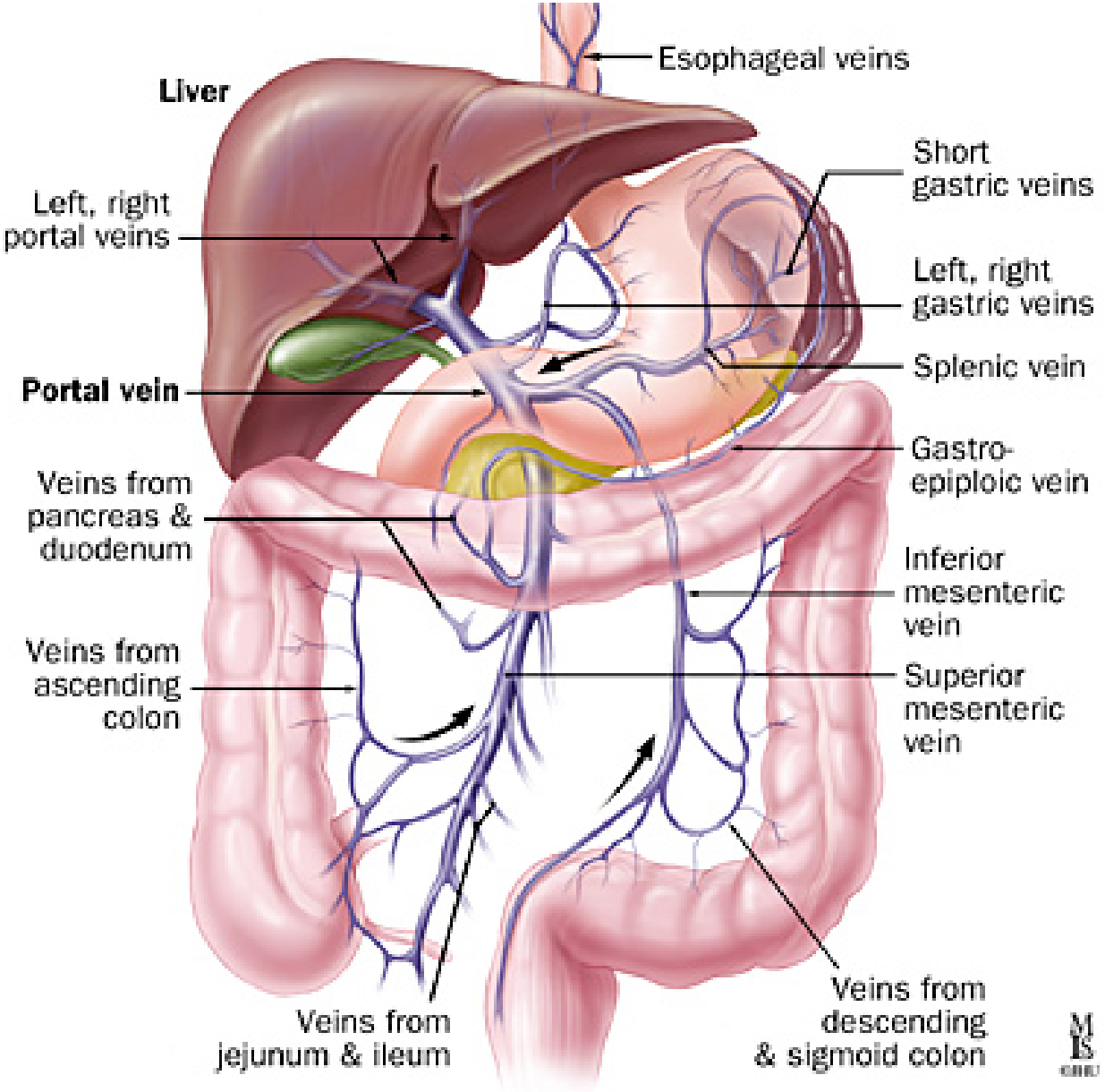


- Targeting inflammatory cells
- Antibiotics/Probiotics
- INT-747
- Novel targets based on genetic studies
- Stem cells

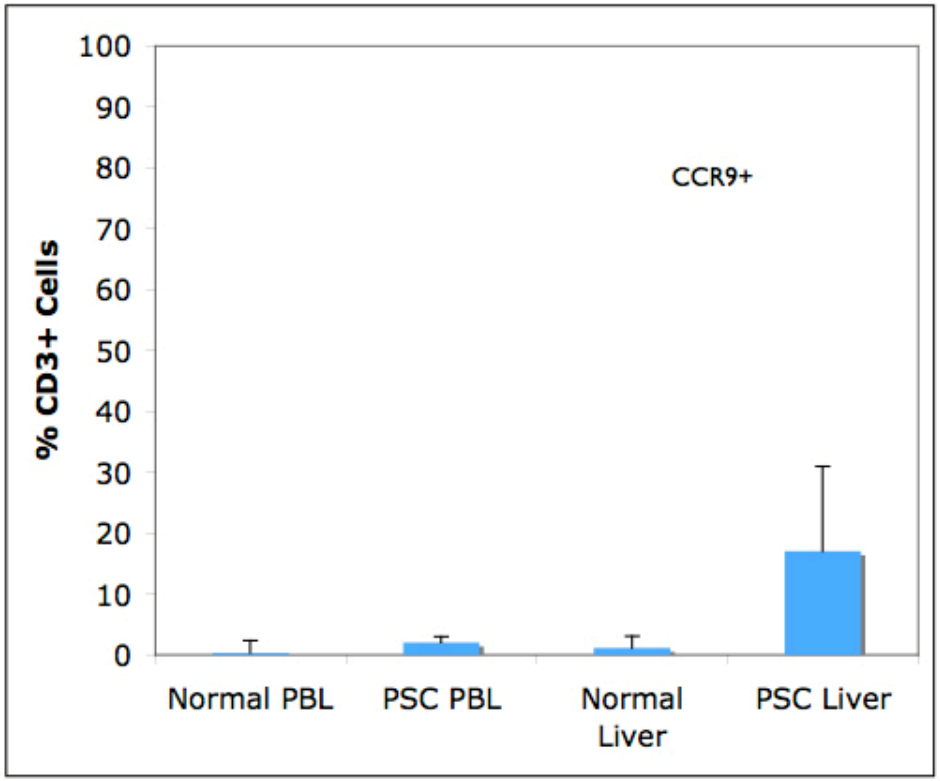
Lymphocyte Homing

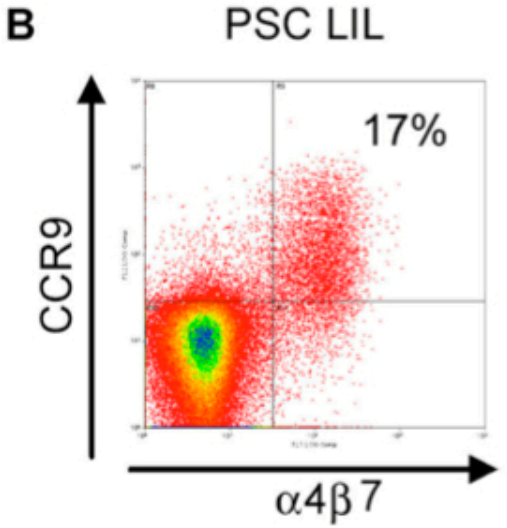



Direction of flow
Step 1: Rolling
Step 2: Activation by chemokines
Step 3: Strong adhesion by integrins
Step 4: Transmigration to lamina propria
Lymphocyte
L-Selectin
CCR9
α4β7
Vascular lumen
MAdCAM-1
CCL25
Mucosal endothelial surface


Esophageal veins
Liver
Short gastric veins
Left, right portal veins
Left, right gastric veins
Splenic vein
Portal vein
Gastro-epiploic vein
Veins from pancreas & duodenum
Inferior mesenteric vein
Veins from ascending colon
Superior mesenteric vein
Veins from jejunum & ileum
Veins from descending & sigmoid colon

α4β7+CCR9+ Liver Lymphocytes in PSC



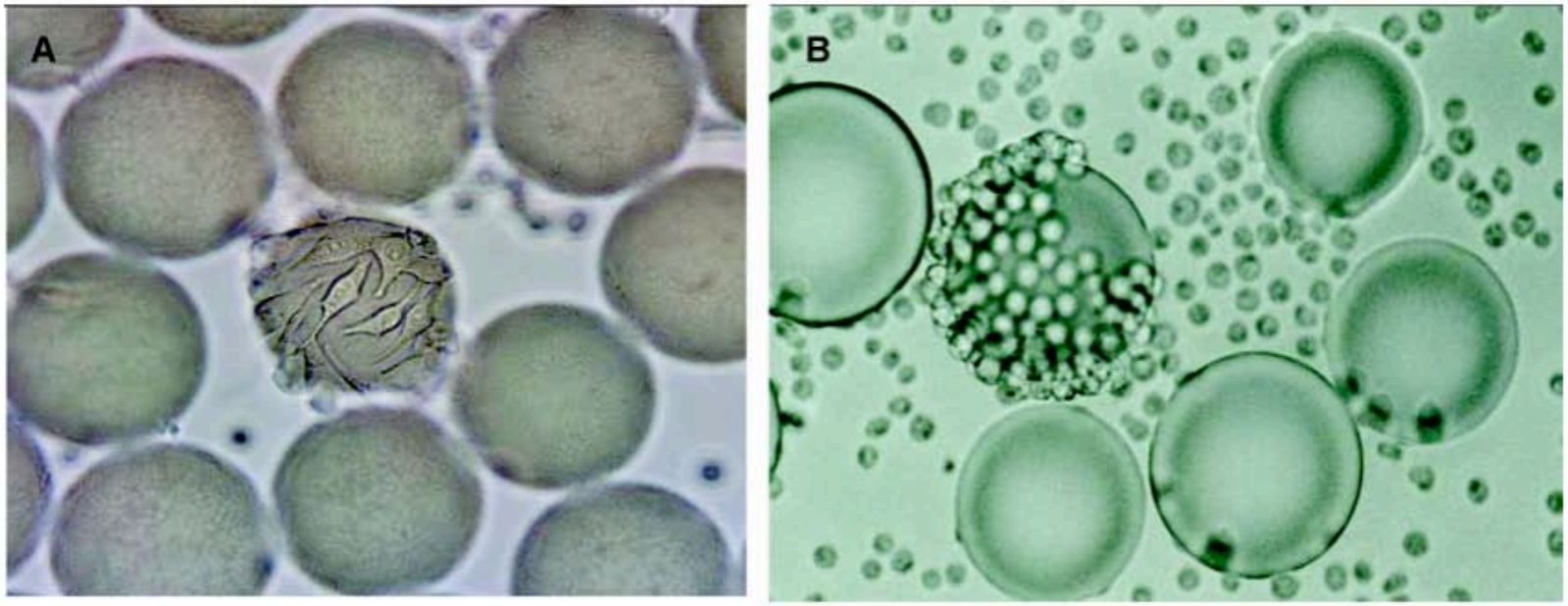


Eksteen, B, *et al.* J. Exp. Med. 2004;200(11):1511-1517.

Current and Future Prospects

- α4 Blocker (natalizumab)
  - Minimally effective in Crohn's disease
  - Currently use for Multiple Sclerosis
  - Risk of brain disease (PML) but rare
- α4β7 Blocker (vedolizumab)
  - In phase III trials for Crohn's disease and UC
- CCR9 Blocker (CCX-282; Traficet-EN)
  - Now in phase III study for Crohn's disease

Developing an α4β7-integrin antagonist



Aina OH M *et al.* Mol Pharm 2007. 4(5): 631-51.

PROBIOTICS AND ANTIBIOTICS

Carlo Selmi

Department of Internal Medicine
IRCCS Istituto Clinico Humanitas
University of Milan

Division of Clinical Immunology
Department of Internal Medicine
University of California, Davis

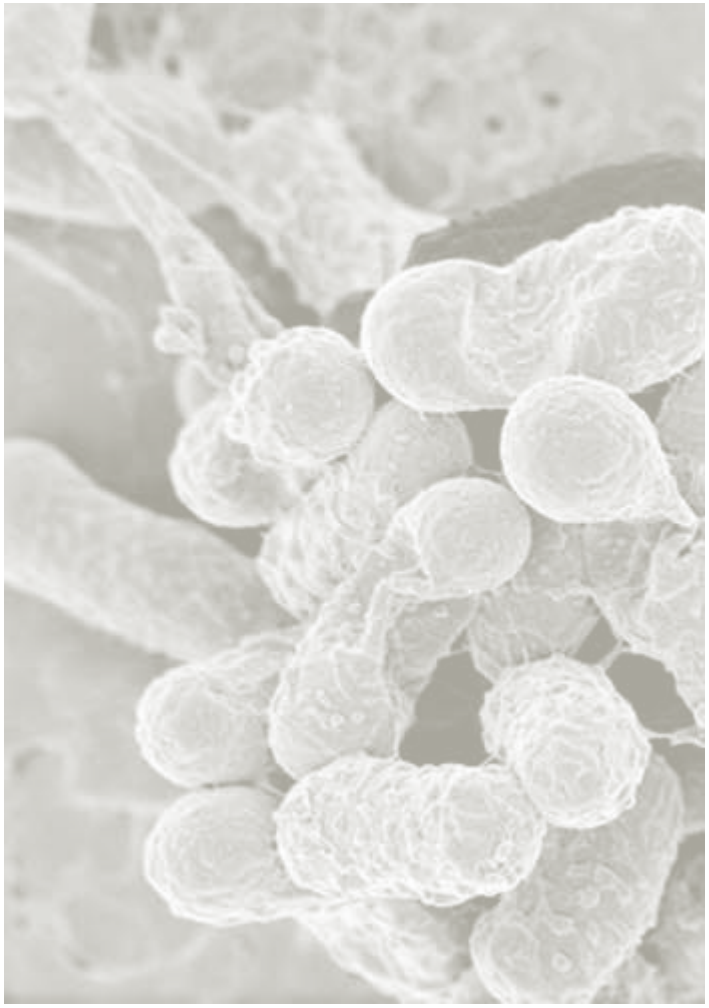
INTESTINAL FLORA

Thousands of commensal bacterial and fungal species generate a complex micro-environment called:

"INTESTINAL FLORA".

It grows and co-evolves with the host, participating to:

- *DIGESTION OF NUTRIENTS*
- *PROTECTION OF MUCOSA*
- *DEVELOPMENT OF A HEALTHY GUT*
- *THE EVOLUTION OF A BALANCED MUCOSAL IMMUNE SYSTEM.*



PROBIOTICS

Intestinal flora status can be influenced by administration of exogenous PROBIOTICS.

WHO DEFINITION: "*PROBIOTICS ARE LIVE MICROORGANISMS WHICH, WHEN CONSUMED IN ADEQUATE AMOUNTS AS PART OF FOOD, CONFER A HEALTH BENEFIT ON THE HOST*".

MECHANISMS OF ACTION

Several studies demonstrate the great properties of immunomodulation on intestinal epithelial cells (IEC) and immune system cells (ISC).

Probiotics explain their actions through:

- *PRODUCTION OF ANTIBACTERIAL SUBSTANCES*
- *SECRETION OF MUCOSAL CYTOPROTECTIVE AGENTS*
- *COMPETITIVE INHIBITION OF PATHOGENS ADHERENCE*
- *ENHANCING BARRIER FUNCTION AND IMMUNE ROLES OF IEC*
- *REGULATION OF MUCOSAL IMMUNE RESPONSES*

IMMUNOMODULATORY ACTIVITY

Probiotics regulate immunologic responses balancing the interactions between exogenous microorganisms and local ISC in both hyper or hypo activation status.

- *ENHANCING HOST INNATE IMMUNITY*
- *INCREASING ANTI-INFLAMMATORY CYTOKINES*
- *SUPPRESSING PRO-INFLAMMATORY CYTOKINES*
- *UP-REGULATING HOST DEFENCES AGAINST INFECTION*

Probiotics and Inflammatory Bowel Diseases (IBD)

The intake of probiotics could improve patients conditions reducing disease activity.

Rationale:

Counteracts the abnormal immune response against commensal flora.

Evidence:

Double blind clinical trials conducted with probiotic mixture (VSL#3): reduced chronic relapsing pouchitis.

PROBIOTICS AND PSC

RATIONALE:

- 90% of PSC patients are affected by IBD.
- The main hypothesis refers PSC as a translocation of a pathologic process from the bowel to the liver.

AIM:

- Liver damage could be *REDUCED* extinguishing IBD activity.
- Monitoring bowel disease it will be able to *PROTECT* and *PREVENT* biliary tree damage.

RESULTS:

Nowadays there is not any clinical trials that sustains the use of probiotics in PSC patients. Further studies are required.

VANCOMYCIN (I)

Bactericidal antibiotic poorly adsorbed by intestinal tract.

ACTION:

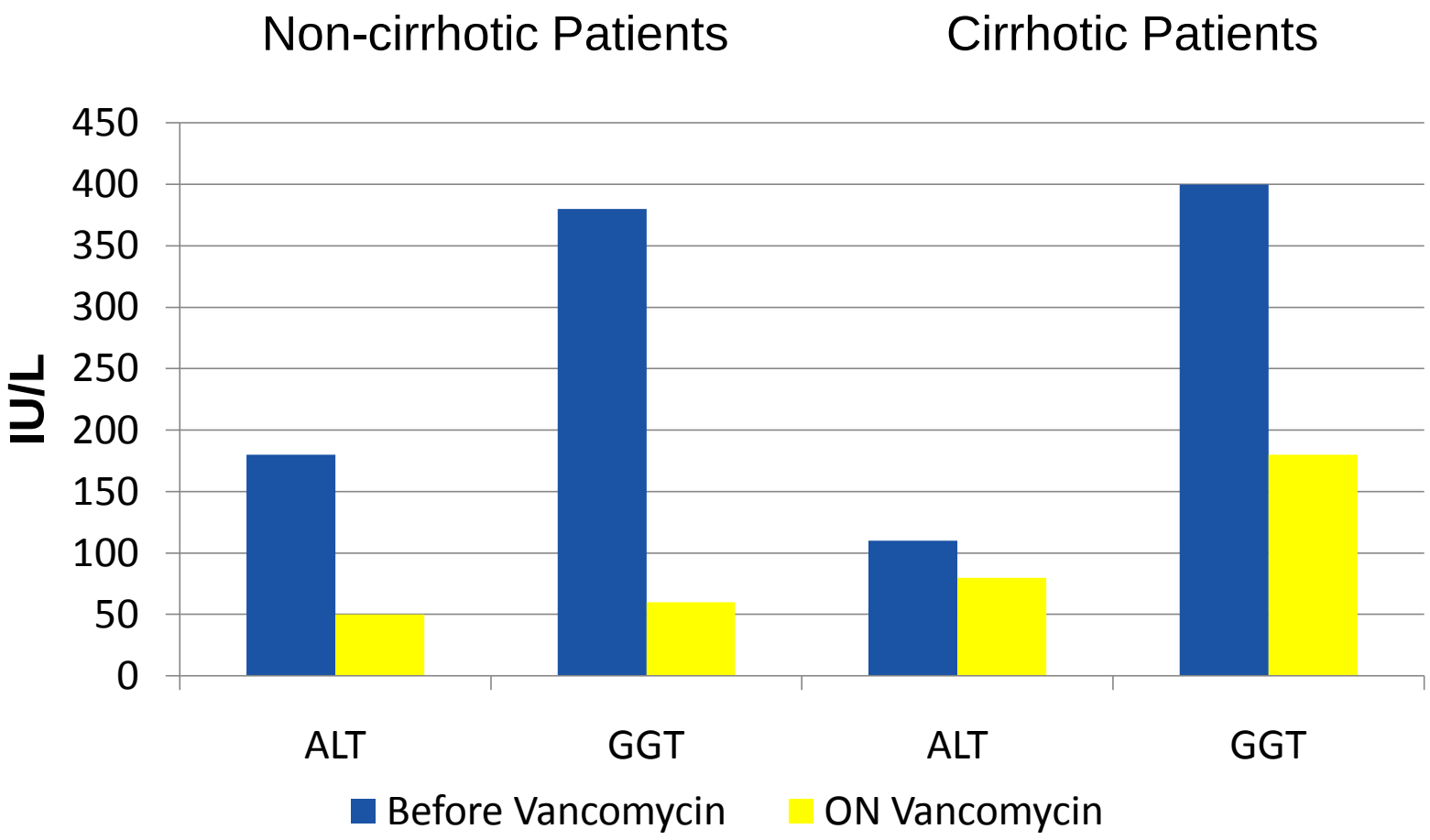
Given orally it acts on gut Gram positive bacteria, modifying the composition of intestinal flora.

CLINICAL EVIDENCE:

A study on 14 PSC + IBD pediatric patients treated only with sulfasalazine and vancomycin (50mg/kg die) reported promising data.

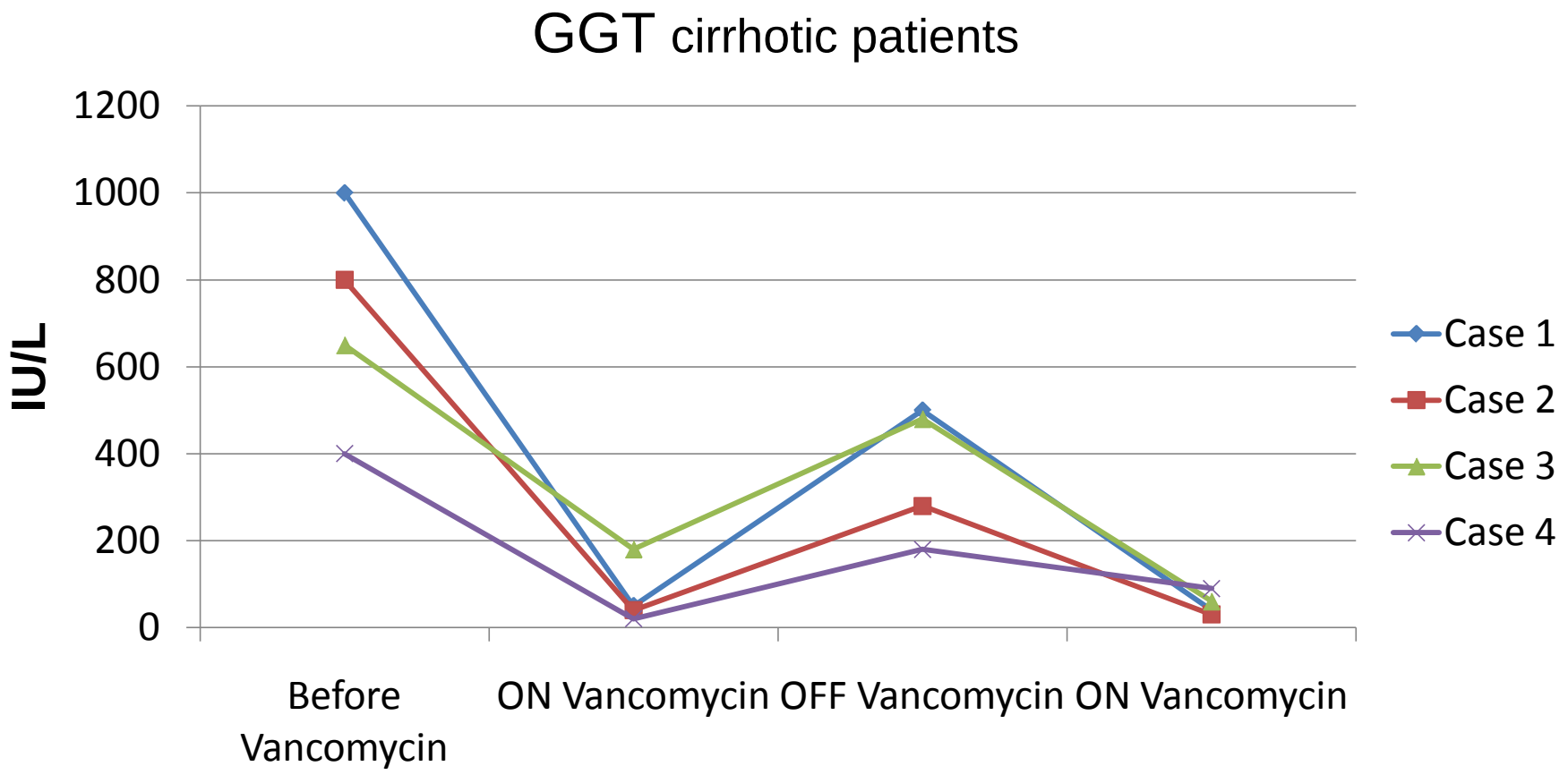
Davies et al, J Pediatr Gastroenterol Nutr, 2008.

VANCOMYCIN (II)



Davies et al, J Pediatr Gastroenterol Nutr, 2008.

VANCOMYCIN (III)



Davies et al, J Pediatr Gastroenterol Nutr, 2008.

Novel drug targets based on genomic studies

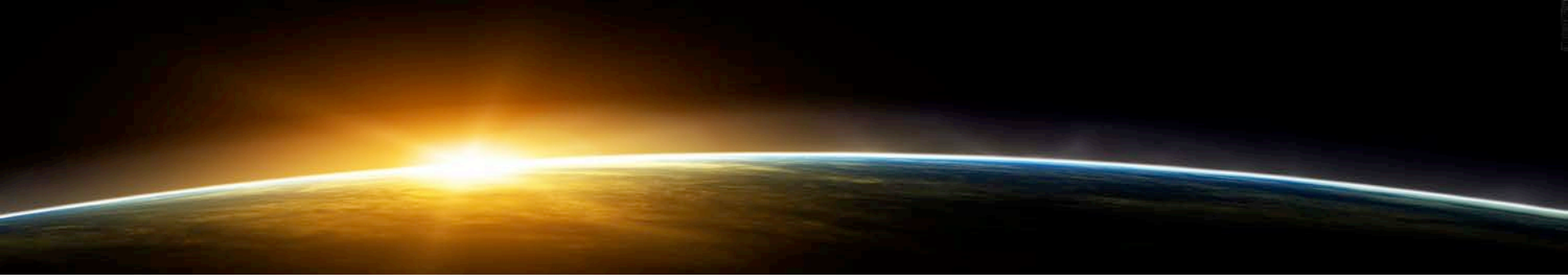
PSC partners meeting, Sacramento, April 30th, 2011

Espen Melum, MD, PhD

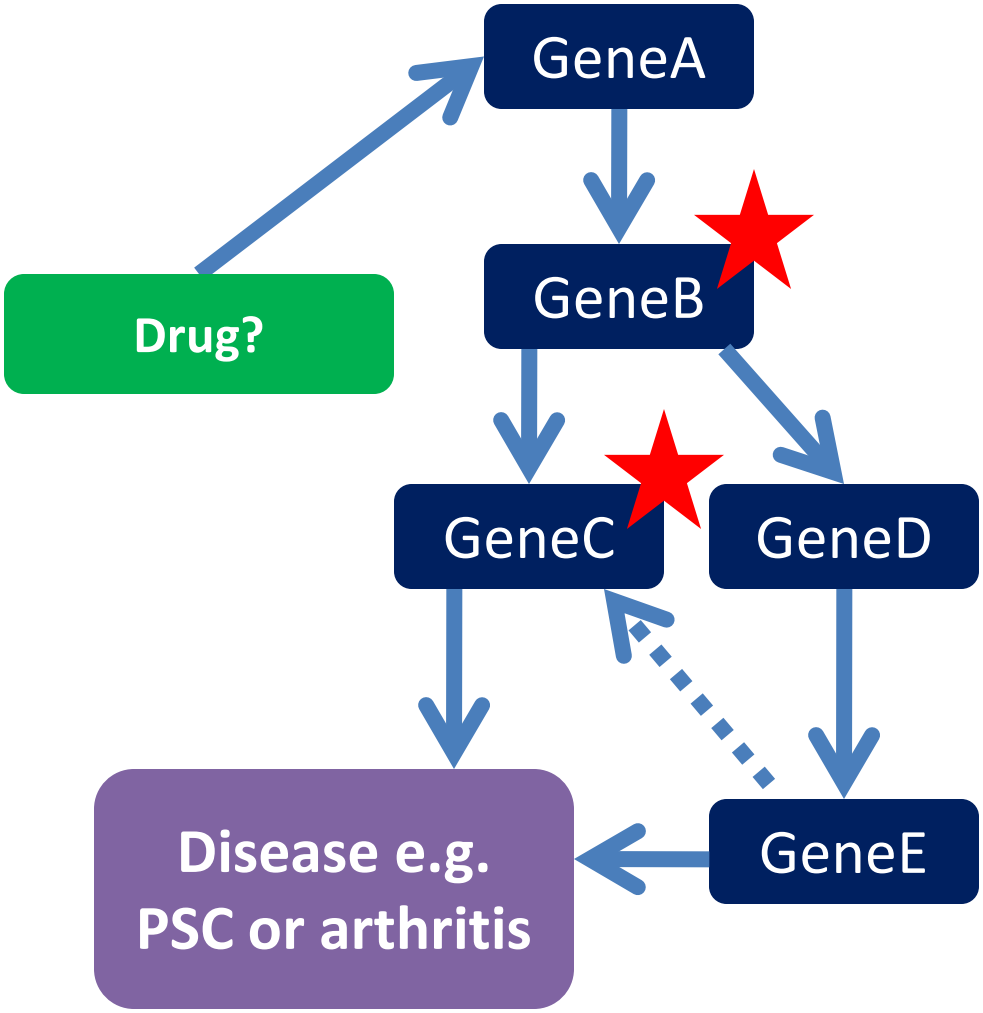
Norwegian PSC Research Center
Oslo University Hospital, Rikshospitalet
Oslo, Norway

and

Division of Gastroenterology, Hepatology and Endoscopy
Harvard Medical School / Brigham and Women's Hospital
Boston, MA

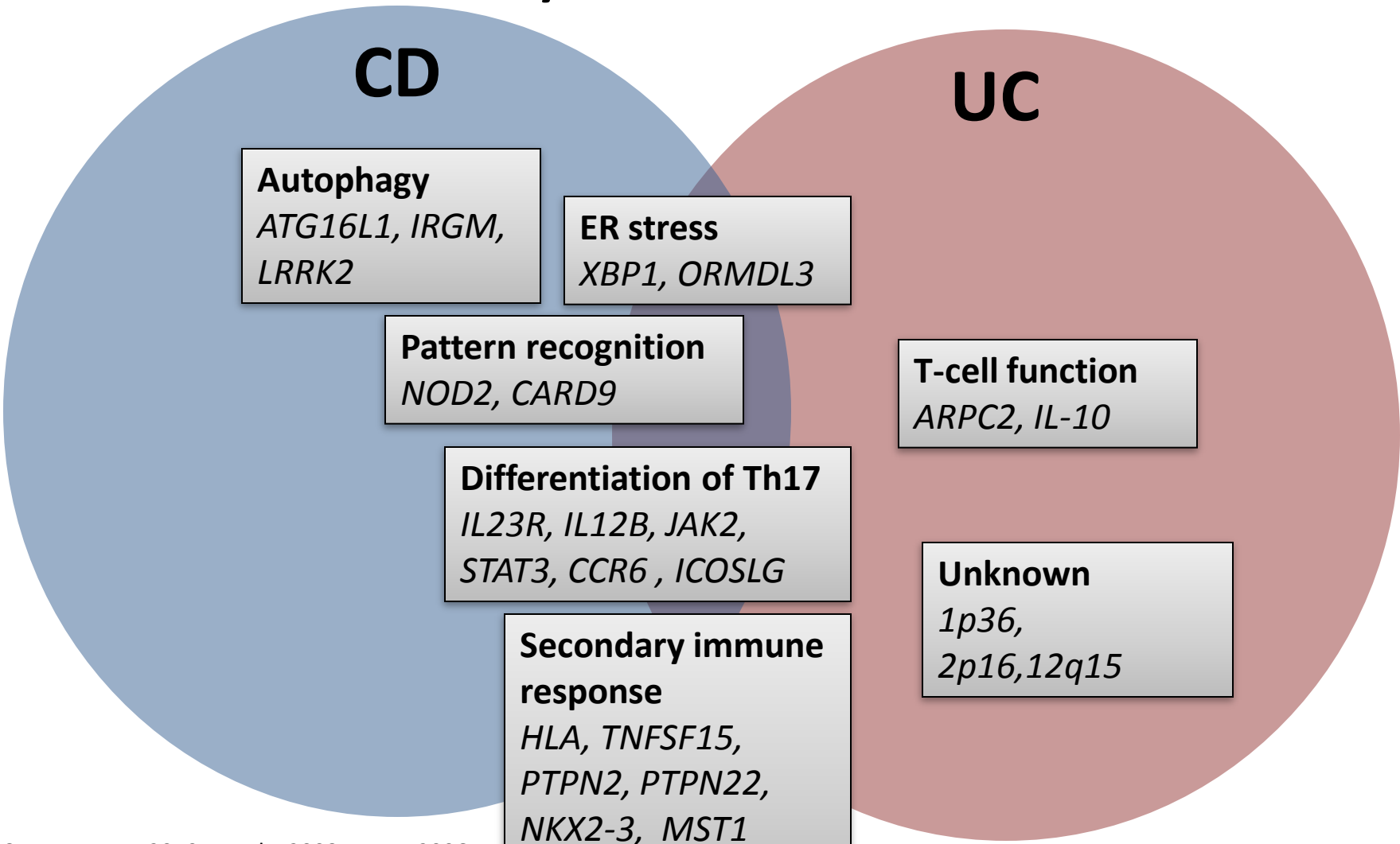


Beyond the horizon


GeneA
GeneB
Drug?
GeneC
GeneD
GeneE
Disease e.g.
PSC or arthritis

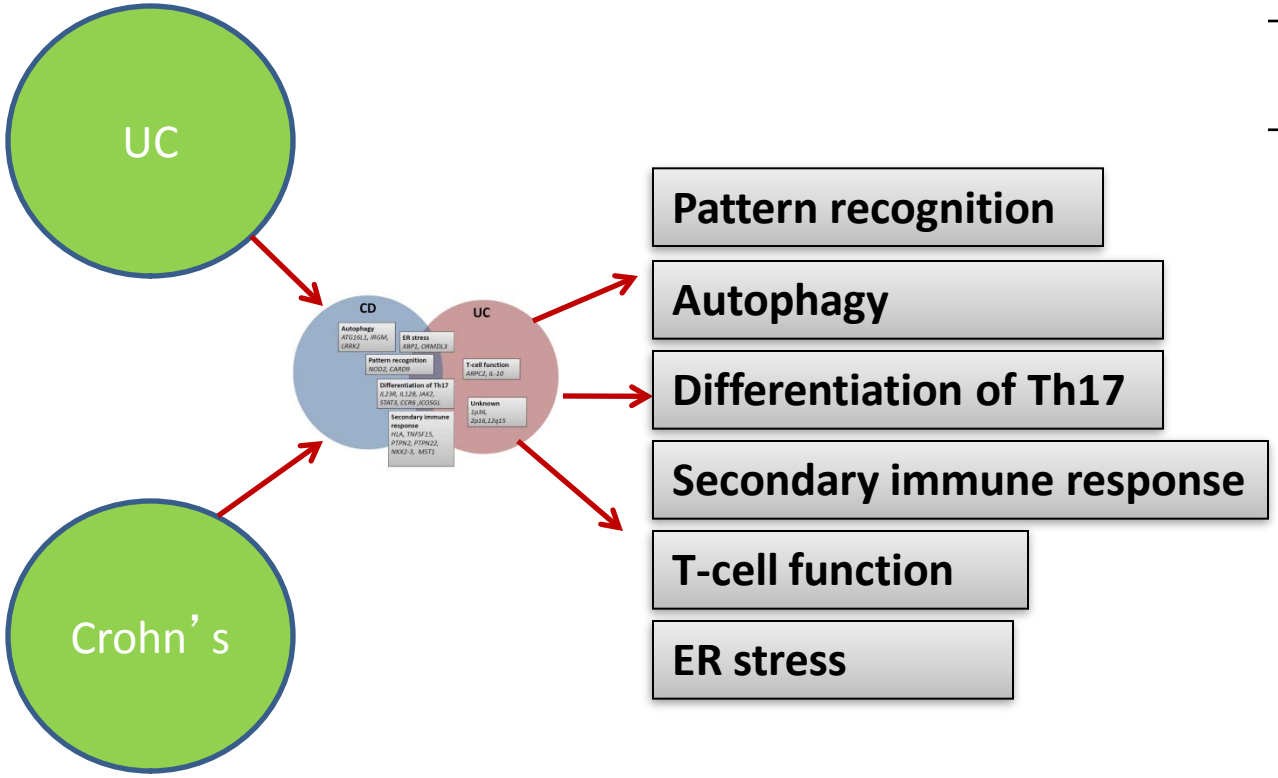
POSSIBLE SCENARIO IN THE FUTURE – EXAMPLE FROM IBD

Genetic findings in IBD segregate in systems



Barrett 2008; McDermot 2010; Franke 2008; Duerr 2006; Van Limbergen 2009

Potential for patient tailored treatment



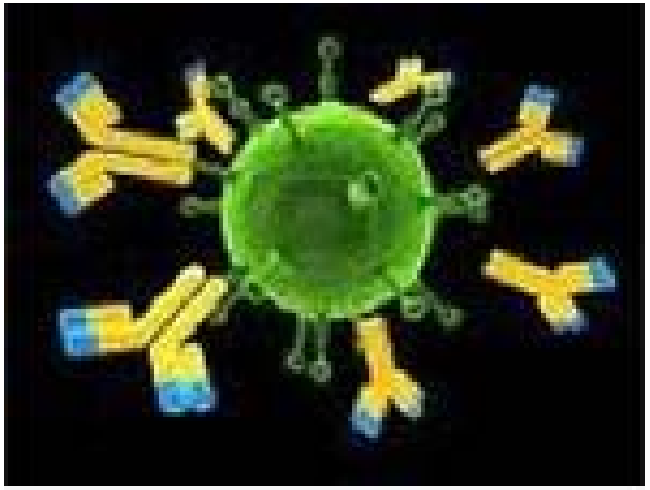
Breaking clinical phenotypes into molecular phenotypes

“HITCHHIKING” WITH OTHER CONDITIONS

Dedicated genotyping arrays

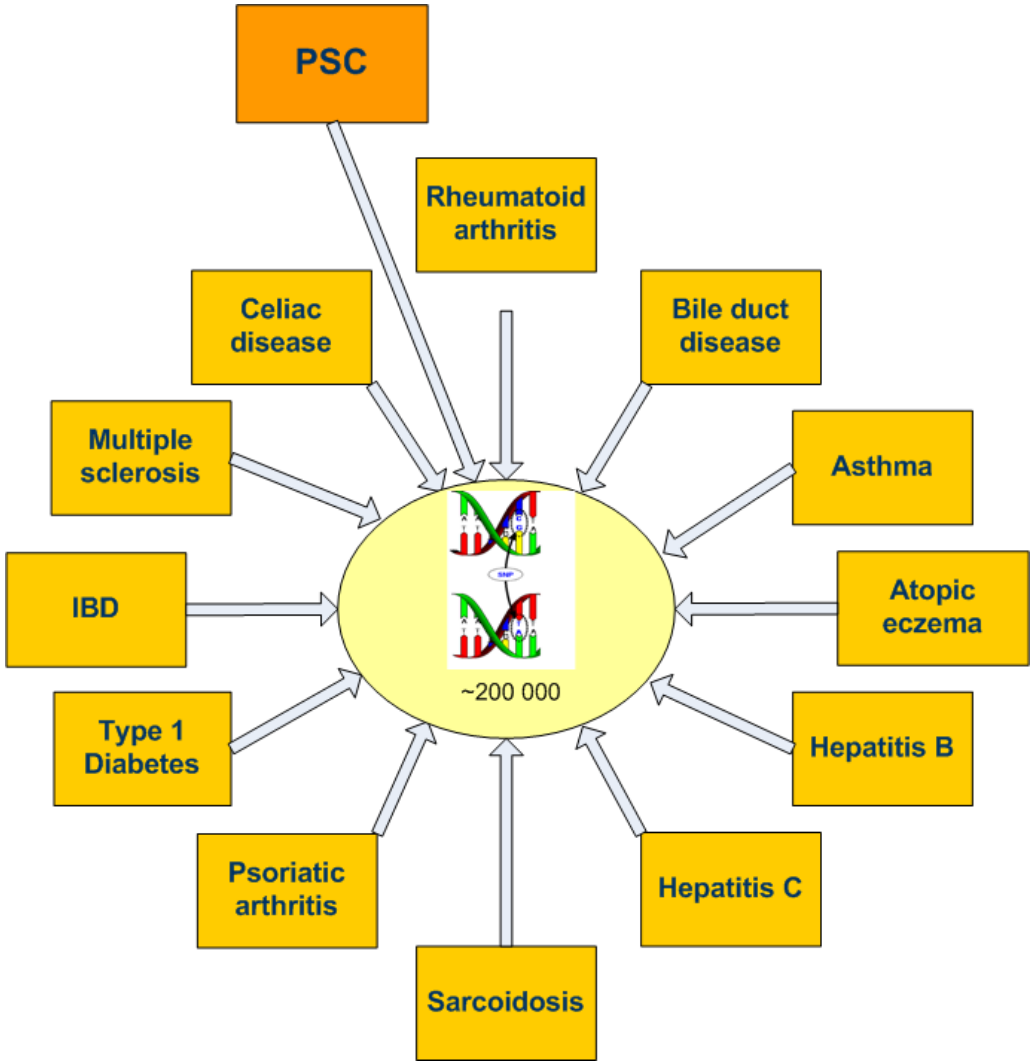
- Metabo Chip
- Cardio-Metabo Chip

→ **Immunochip**

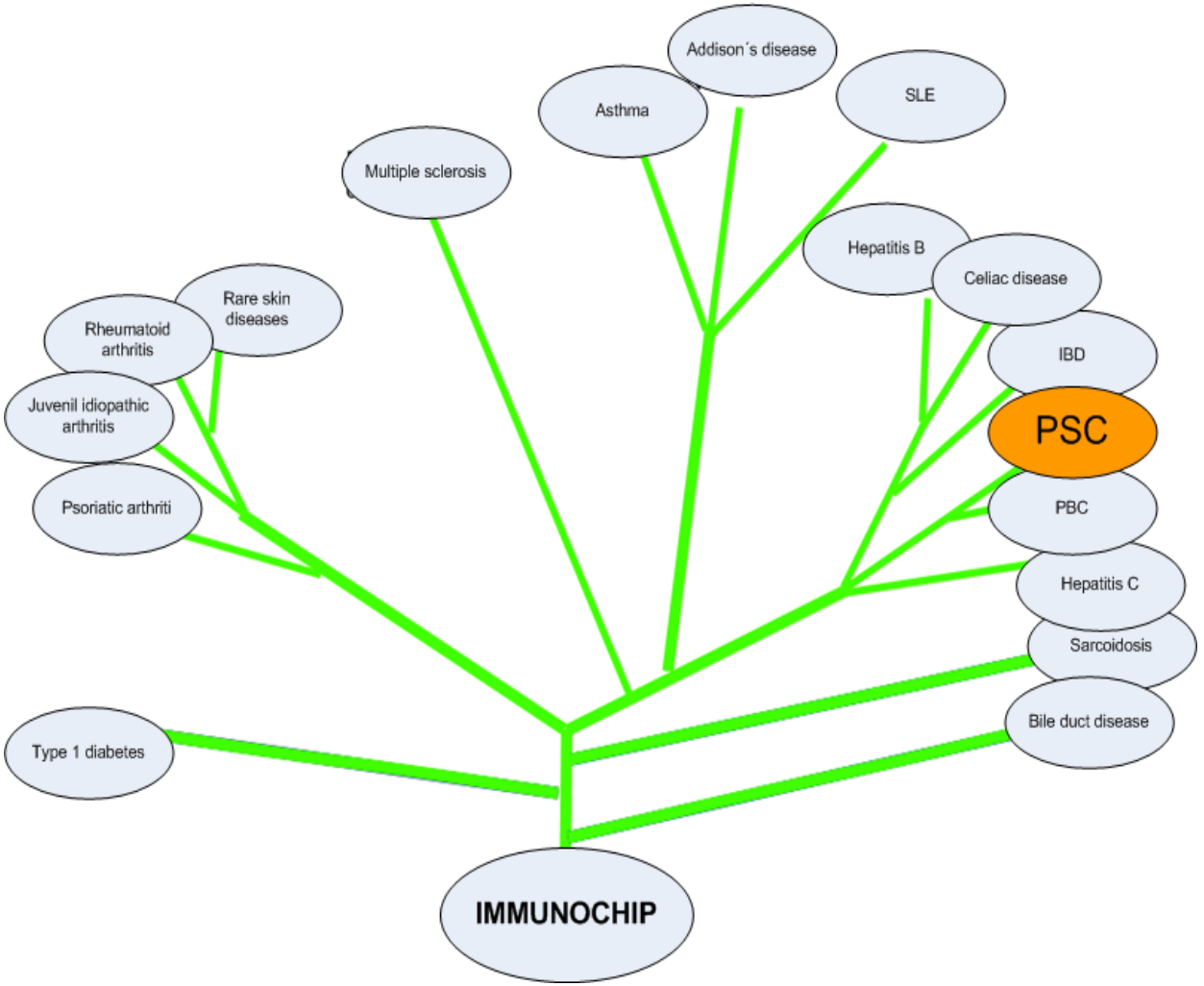


The Immunochip Project

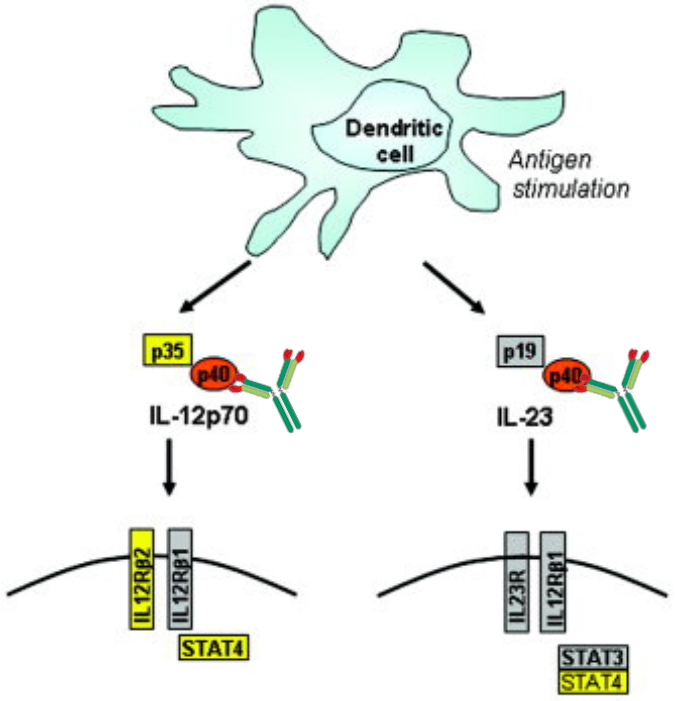
- **PSC:**
- **n≥ 4000**



The immunochip project



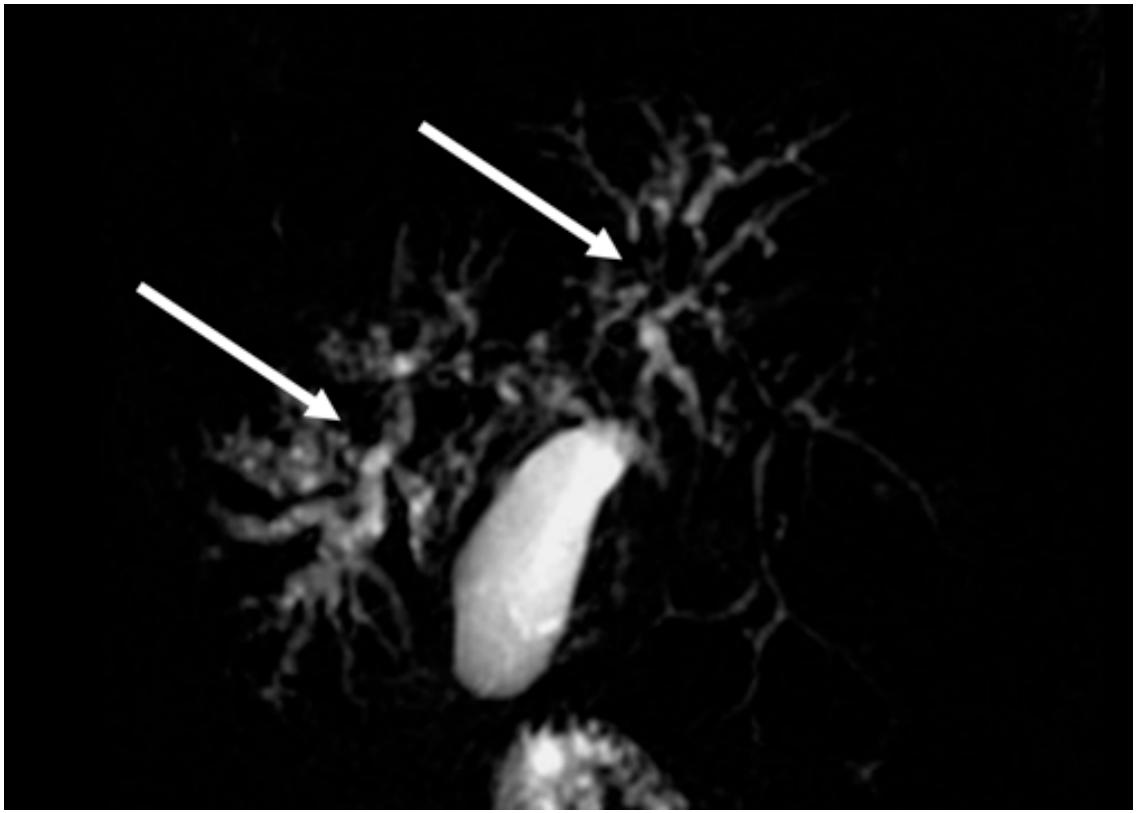
Example: Overlapping risk factors for PBC



Ustekinumab (anti-p40):

- **Psoriasis: Effective**
- **Crohn's: Suggestive**
- **MS: Not effective**
- **Sarcoidosis: Ongoing**
- **PBC ???**

New Therapies- UDCA and beyond



Conflict of interest statement

Company Name	Relationship
Intercept Pharma	Consultant, Investigator
Axcan Pharma	Speaker, Consultant
Centocor	Advisory board, Consultant
BMS	Investigator
Boehringer Ingelheim	Investigator
Tibotec	Investigator
Sanofi-Aventis	Advisory board
Merck	Speaker, Research support
Roche	Speaker

Over past 24 months

Bile Acids: Detergents and Homeostatic Regulators

- Detergents in gut - Solubilize fats in intestine → absorption
- **Farnesoid-X Receptor** – Liver, bile ducts, fat
  - Nuclear receptor for bile acid signaling
  - Natural ligand: Chenodeoxycholic acid
  - Bile acid synthesis regulation
  - Hepatic regeneration, intestinal bacterial overgrowth/translocation protection
  - Modulation of insulin sensitivity & adiposity

Obeticholic Acid

FXR Agonist

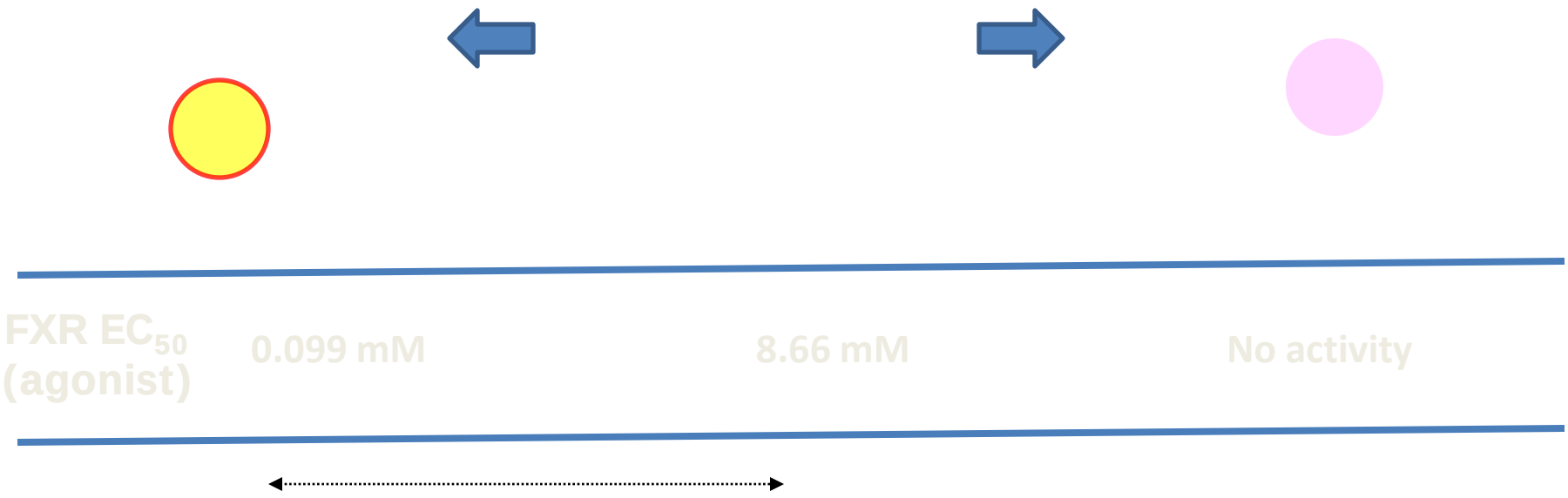
6α-Ethyl Chenodeoxycholic Acid - INT-747

Obeticholic Acid [OCA]

OCA
6a-ethyl chenodeoxycholic acid

CDCA
chenodeoxycholic acid

UDCA
ursodeoxycholic acid



FXR EC_{50} (agonist)

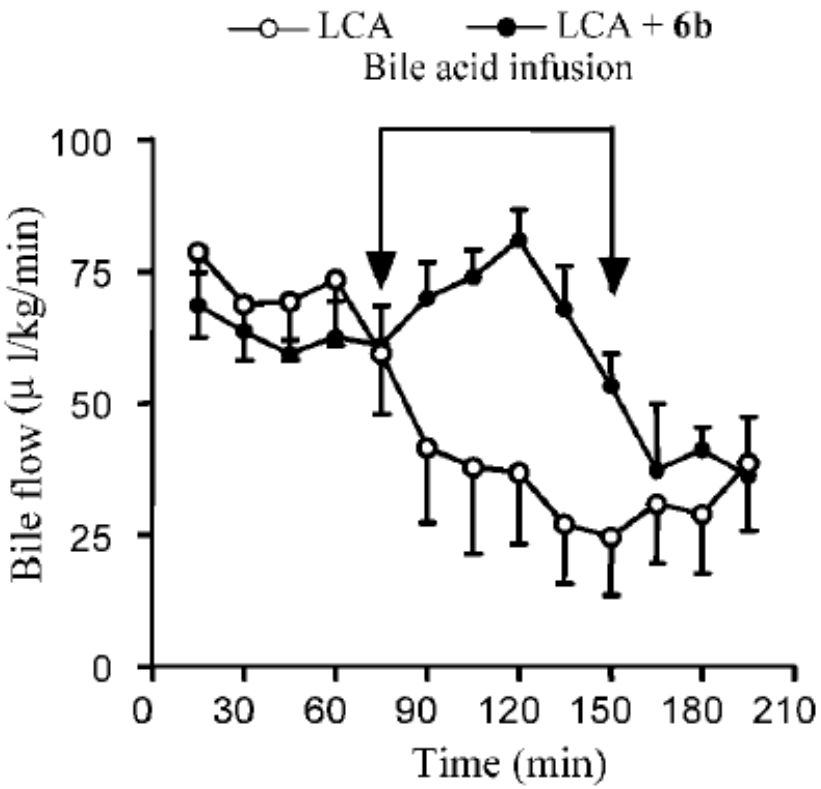
0.099 mM | **8.66 mM** | **No activity**

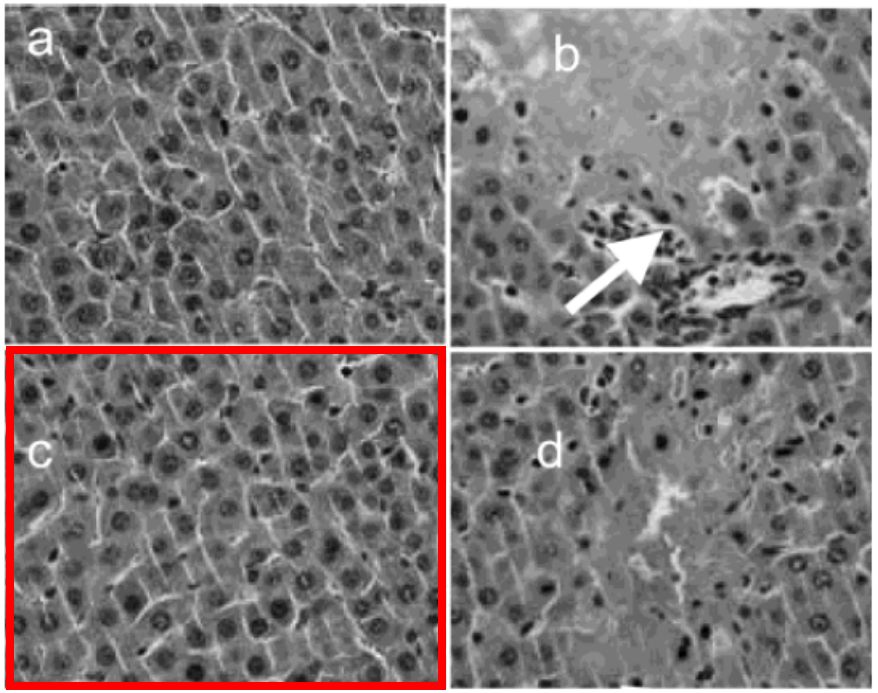
~ 2 log ↑ FXR agonism

Pelliciari R. J.Med.Chem 2002

Anti-Cholestatic Effects of OCA

Lithocholic acid (LCA) model





Bile Flow

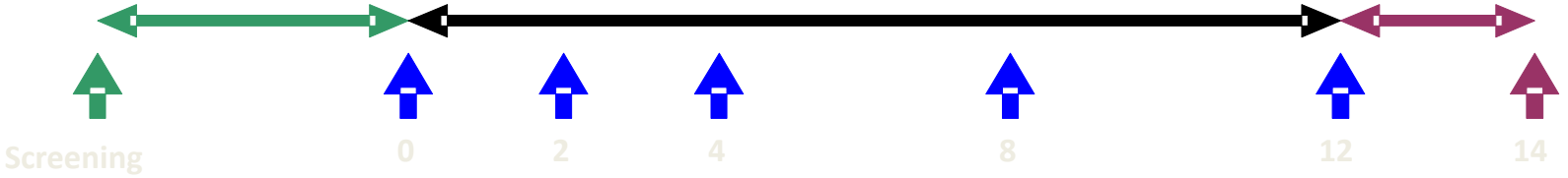
Infusion of :

- **LCA alone -o- [b] or**
- **LCA + INT-747 -●- [c]**

Data from C. Clerici ;Pellicciari et al., J. Med. Chem., 2002;45:3569–3572

Study 747-201 – PBC MONOTHERAPY

No UDCA use for ≥ 3 mo

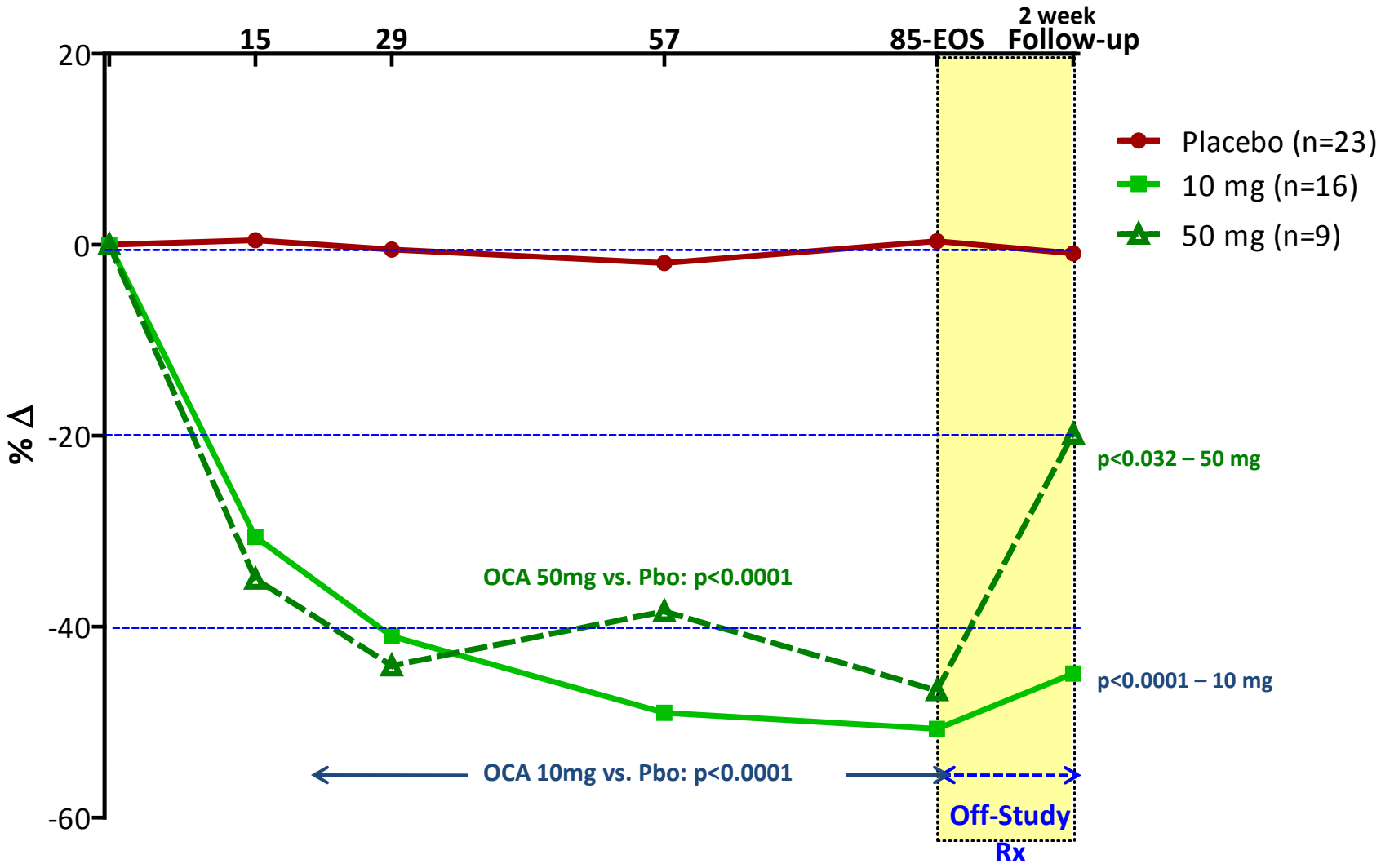


Baseline
1 -4 weeks
predose

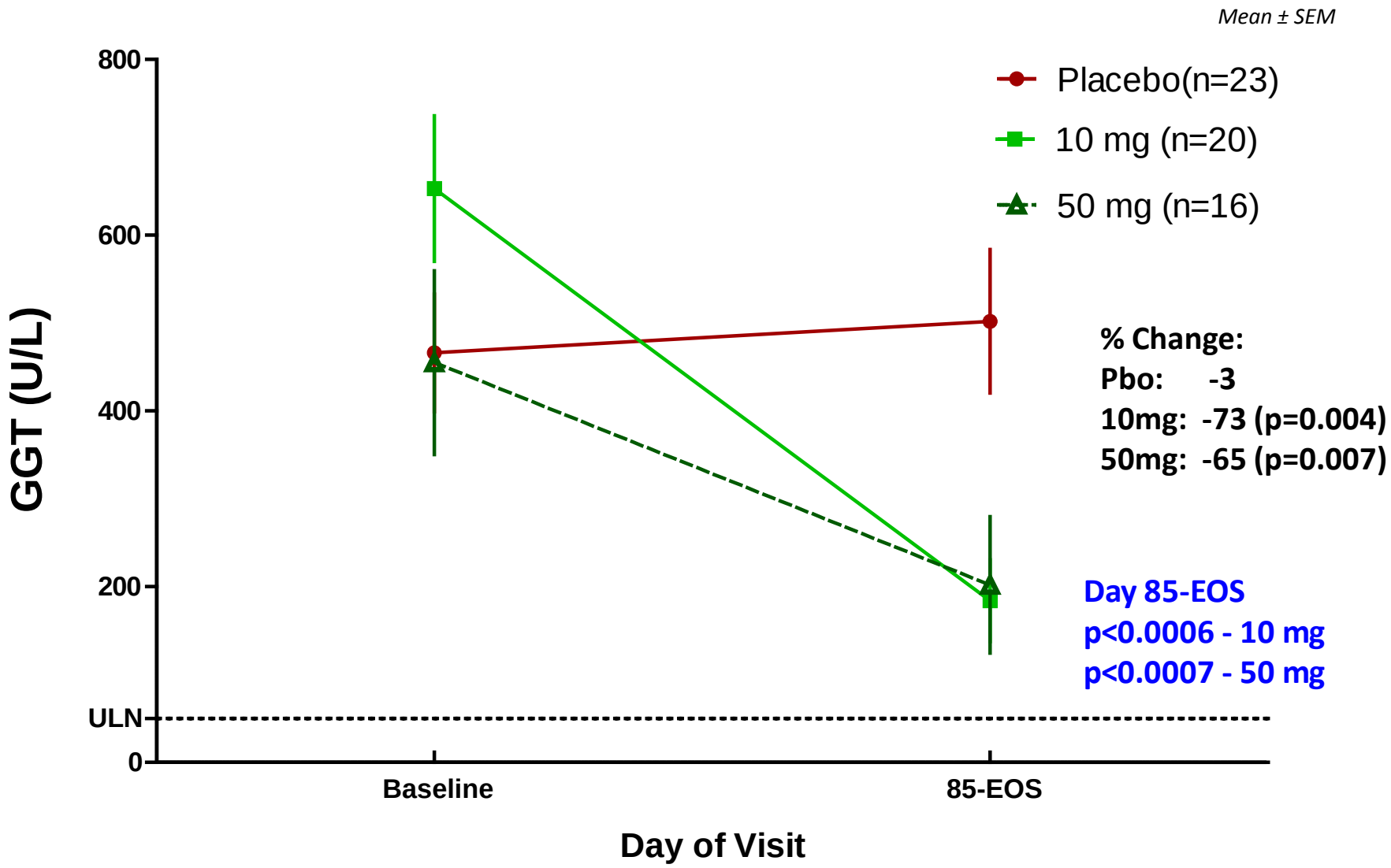
Double Blind Phase
12 weeks

Follow-Up
2 weeks

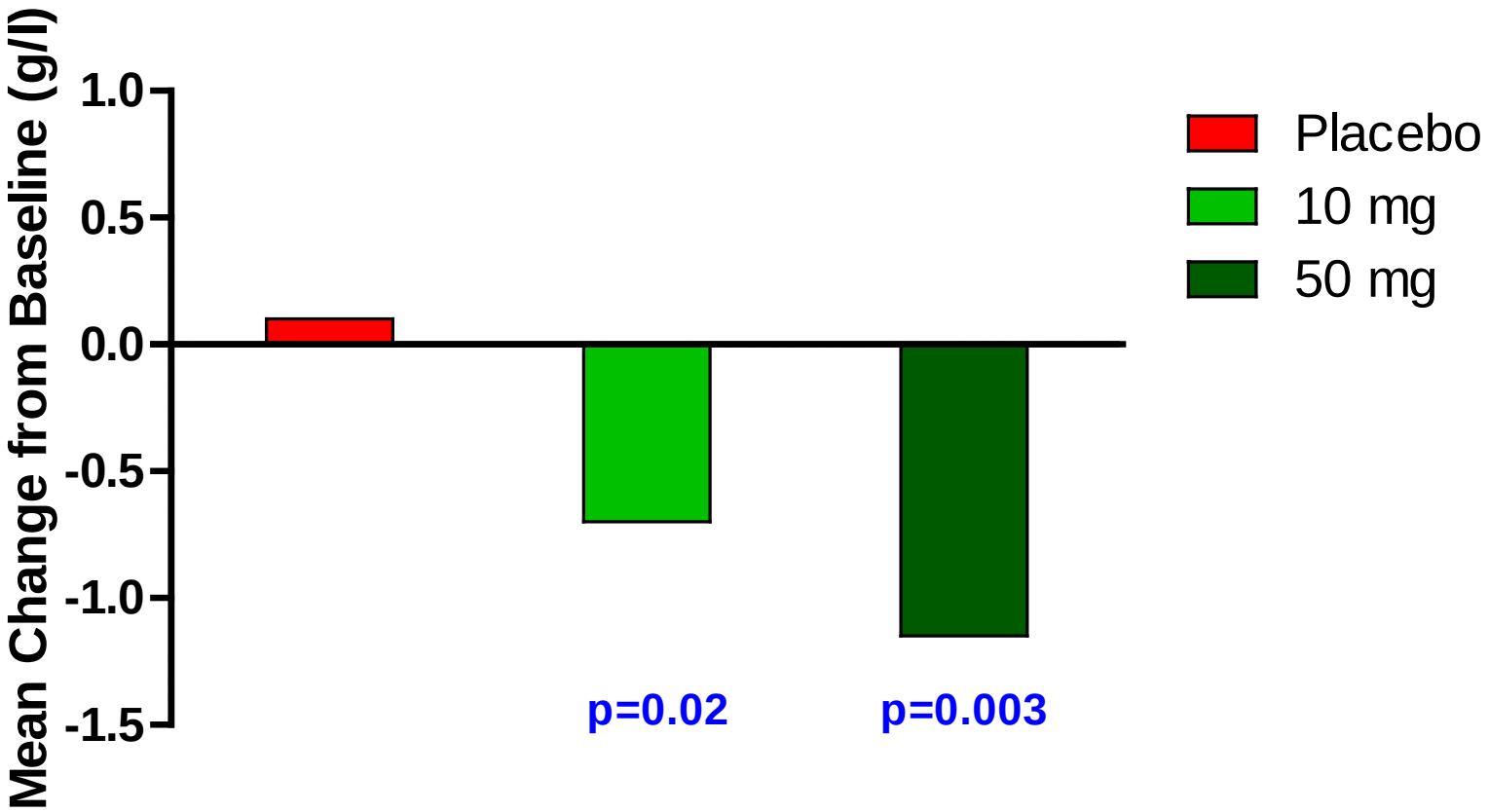
% Δ AP By Visit – Patients Completing Study



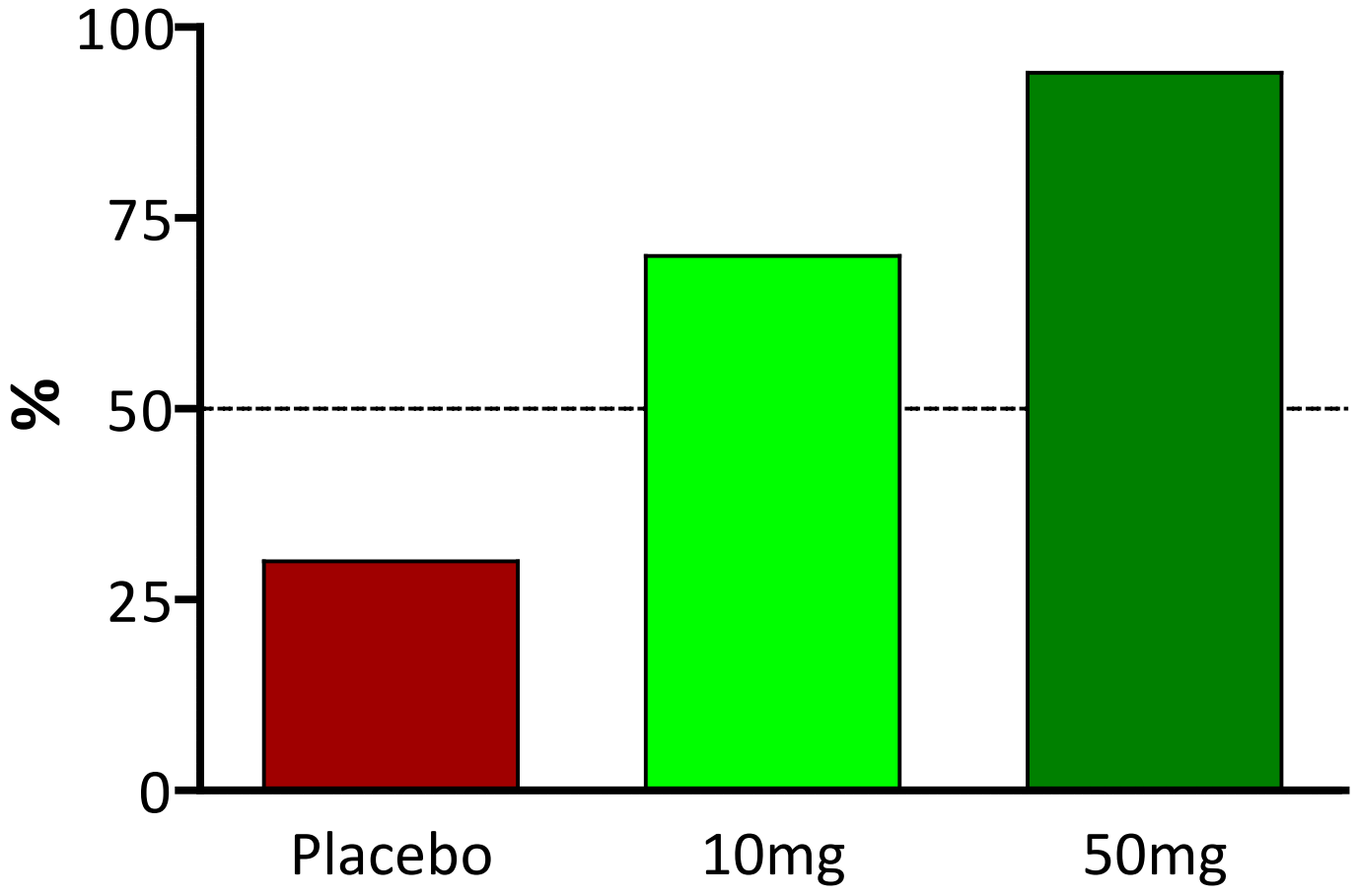
γ-Glutamyl Transpeptidase - γGT



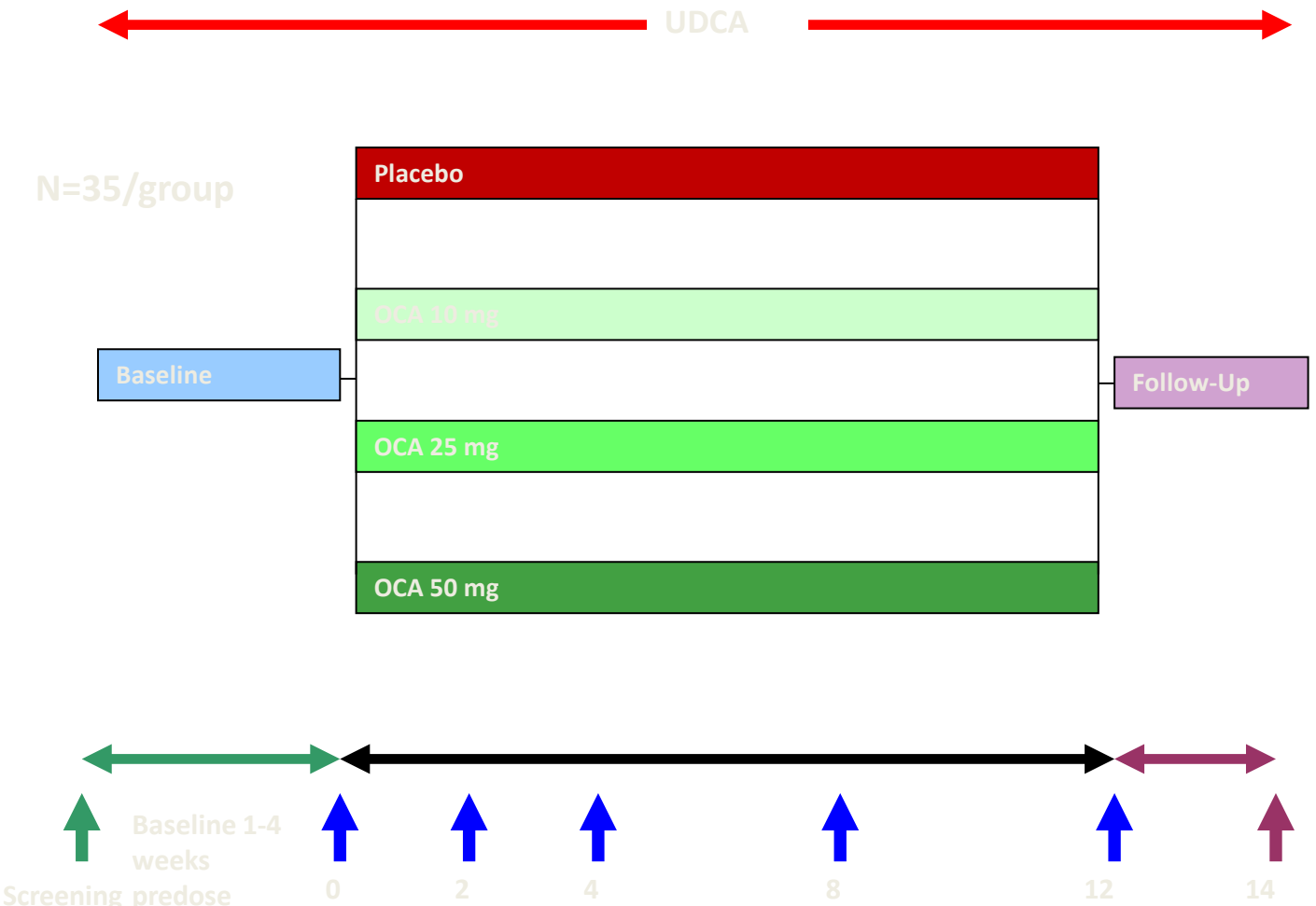
IgM


Mean Change from Baseline (g/l)
1.0
0.5
0.0
-0.5
-1.0
-1.5
p=0.02
p=0.003
Placebo
10 mg
50 mg

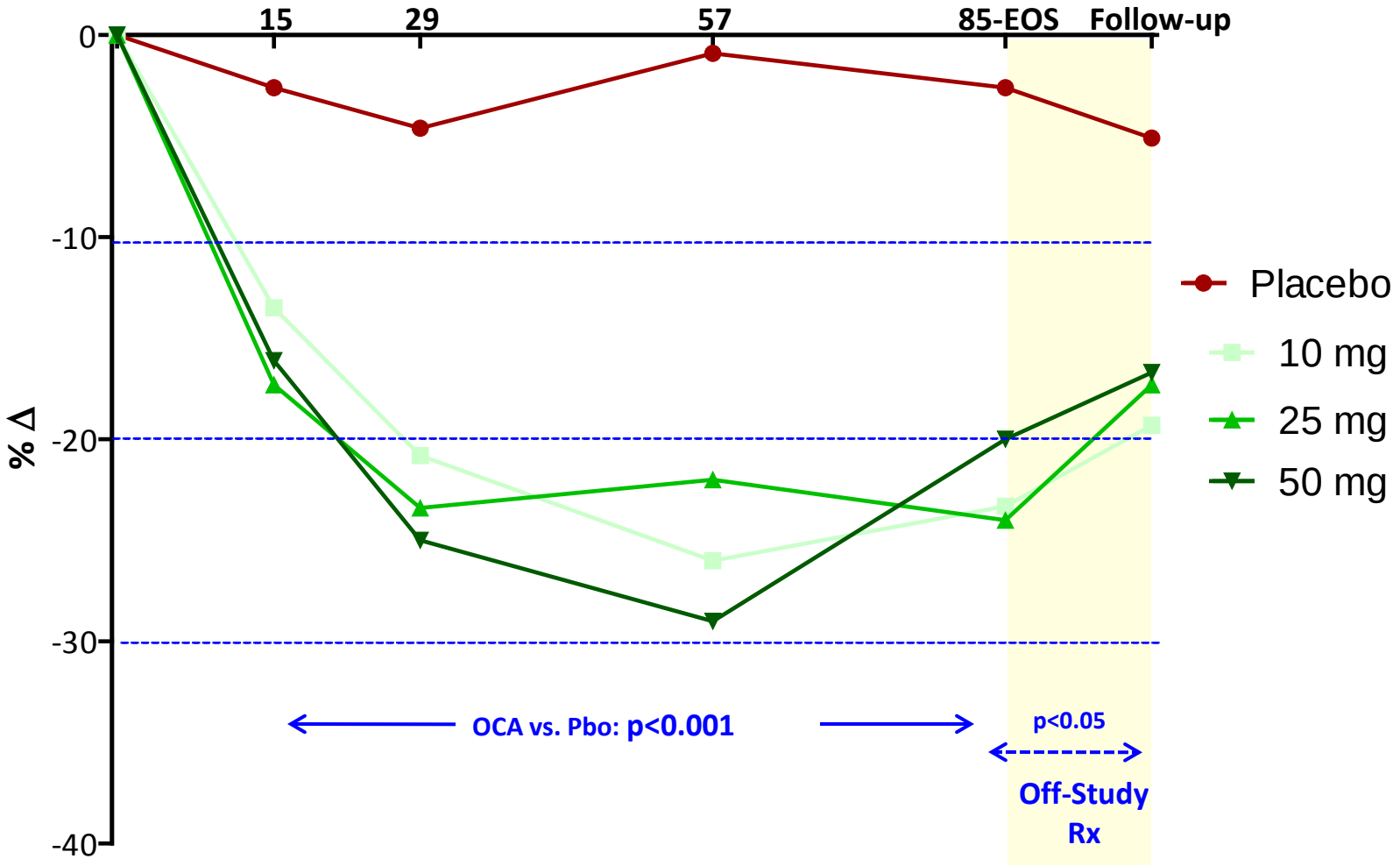
Pruritus as AE – Incidence by Dose



Dose Response Study Design – Addition to UDCA

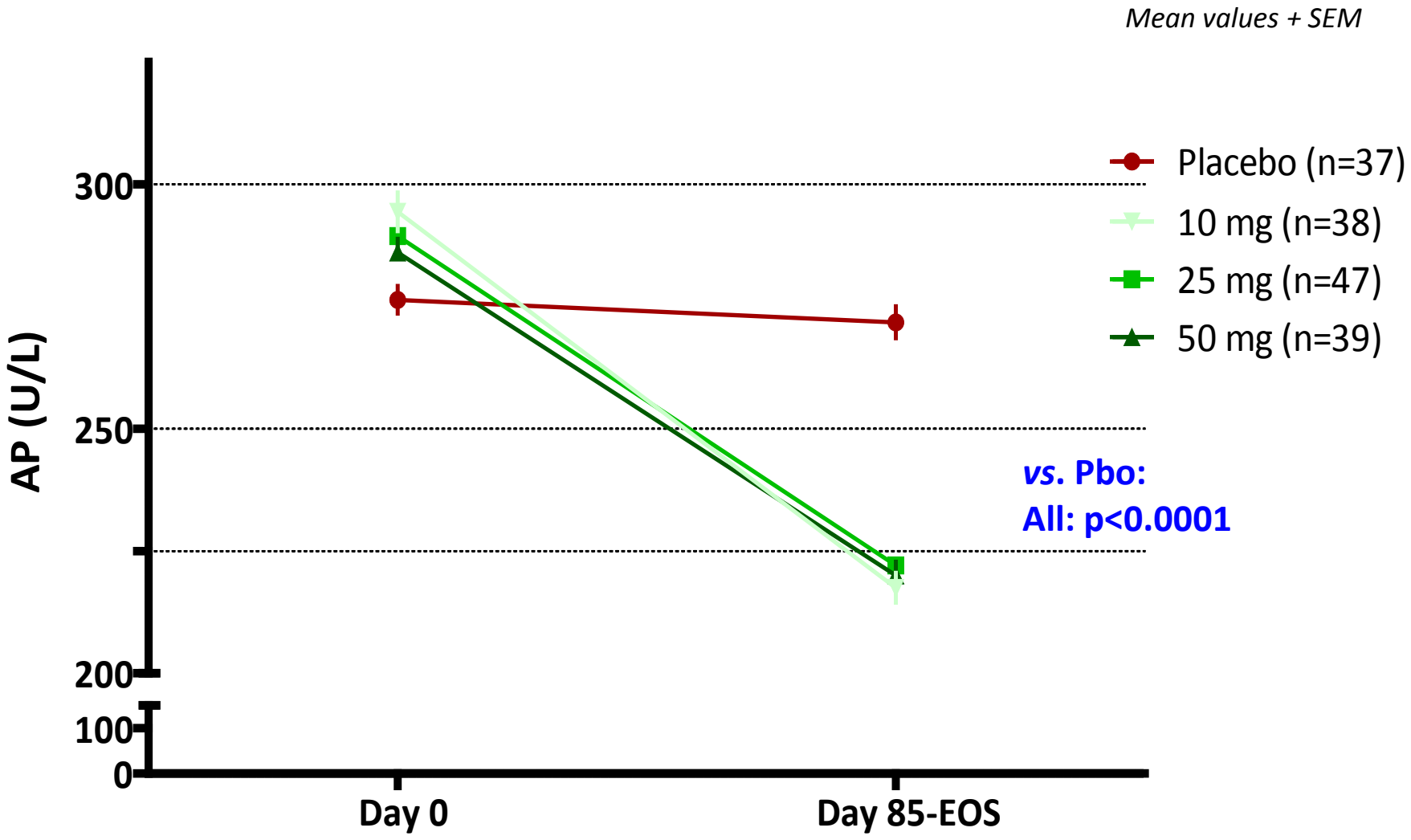


% Δ By Visit – Alkaline Phosphatase - ITT



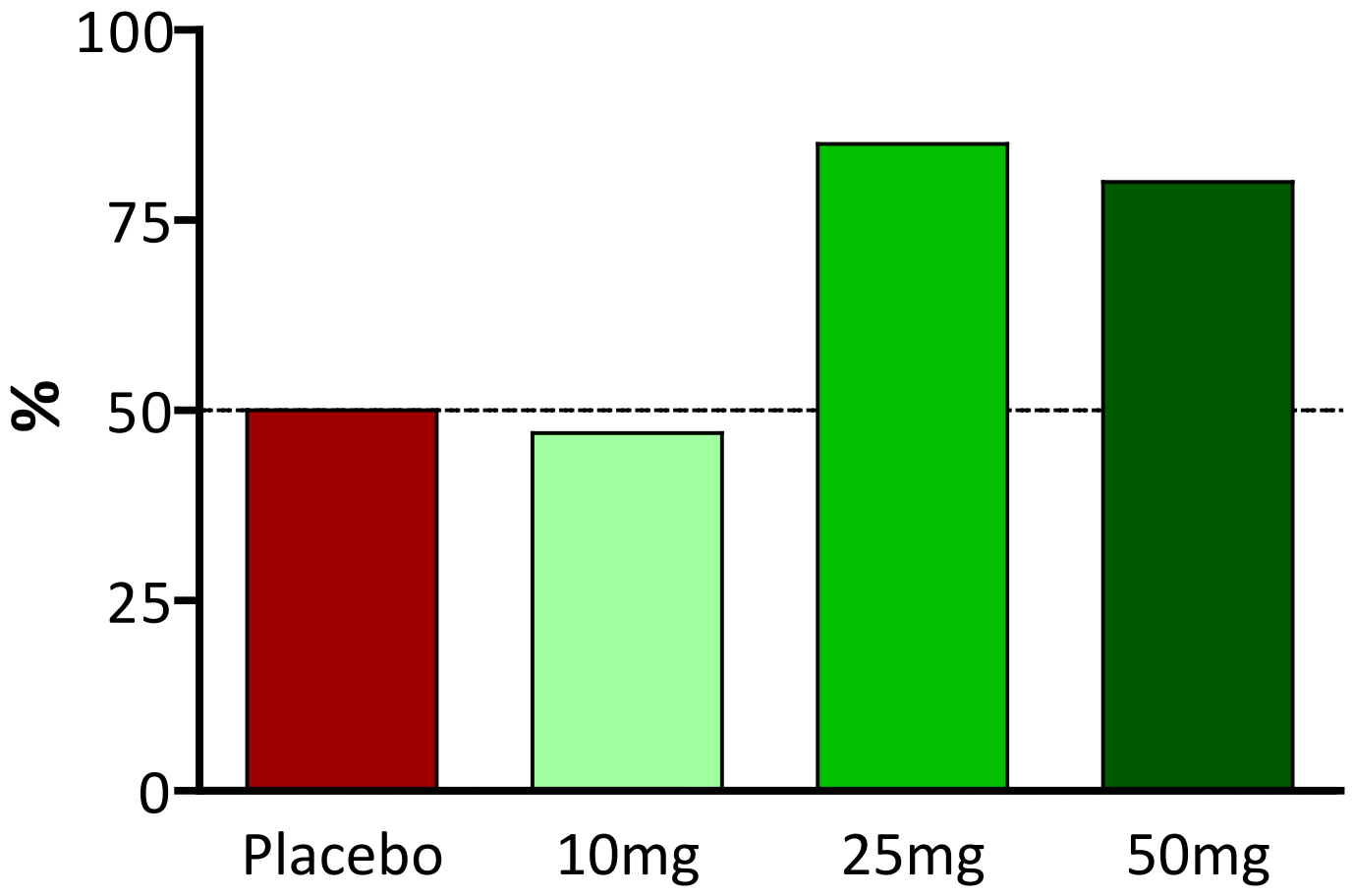
Hepatology 2010; 52(4); 357A

Alkaline Phosphatase



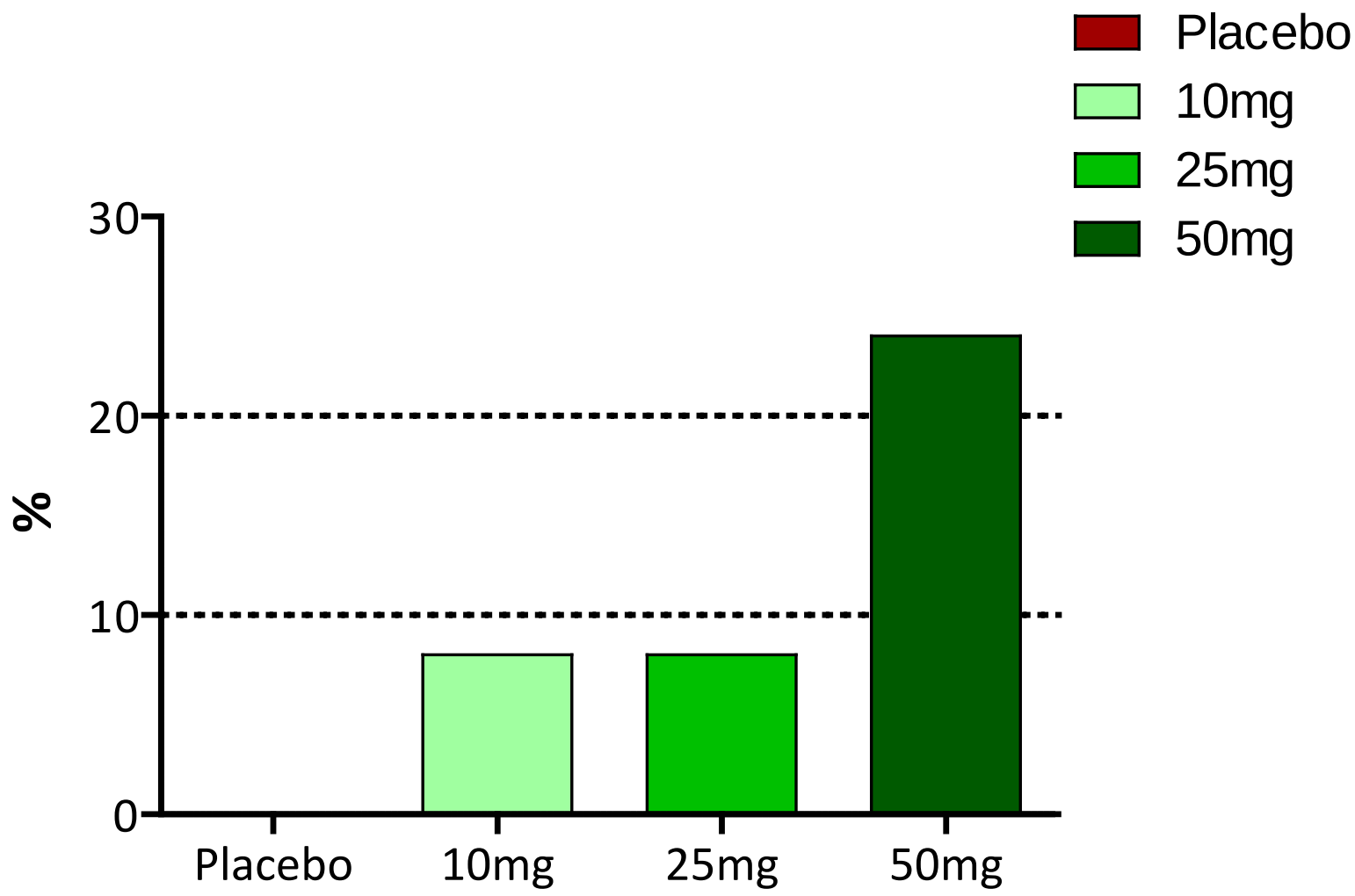
Hepatology 2010; 52(4); 357A

Pruritus as AE – Incidence by Dose



Hepatology 2010; 52(4); 357A

Pruritus - Discontinuations



Hepatology 2010; 52(4); 357A

Can Stem Cell Transplantation Replace Whole Organ Transplantation ?

Mark A. Zern, M.D.

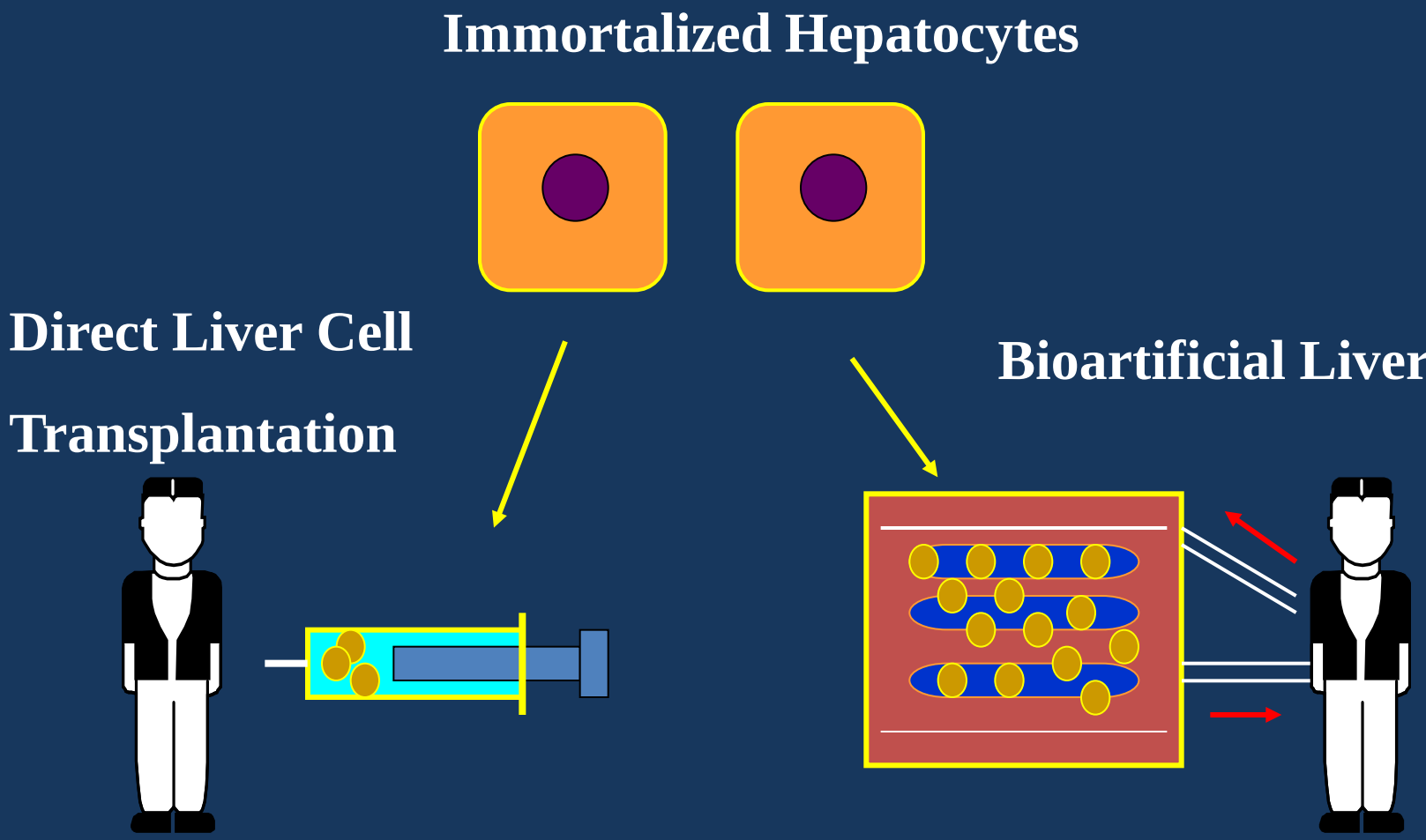
Professor of Medicine

Fred and Pat Anderson Family Professor of Transplant Research

Director, Transplant Research Program

UC Davis Medical Center

Cell Lines Can be Utilized in Vivo or in a BAL



Differentiation Protocol

hES
C

Induction of DE
(Nodal/Activin A)

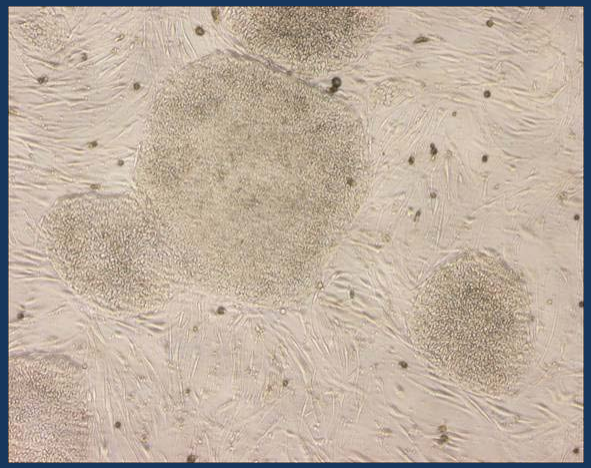
no serum

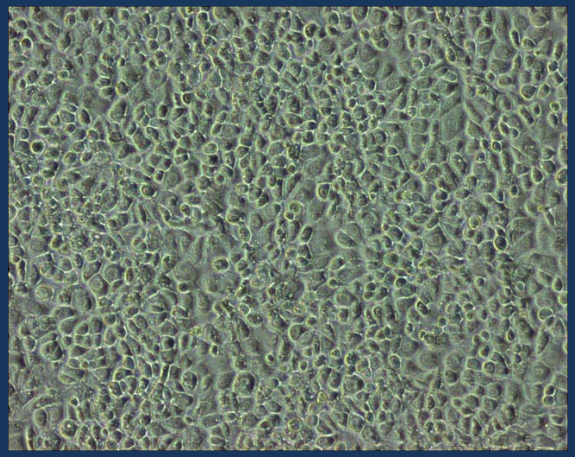
low serum

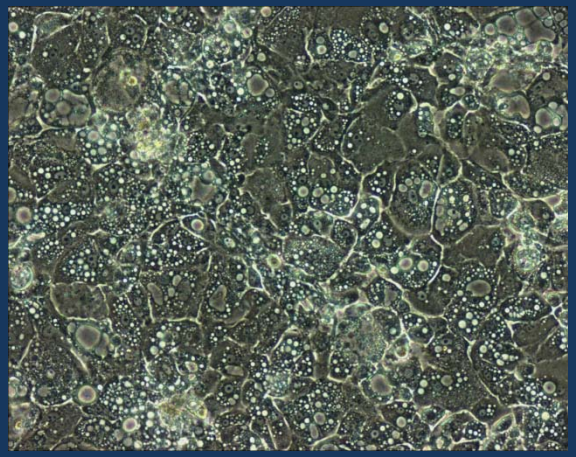
Differentiation/maturation

FGF4, HGF,
BMP2/4
10-14d

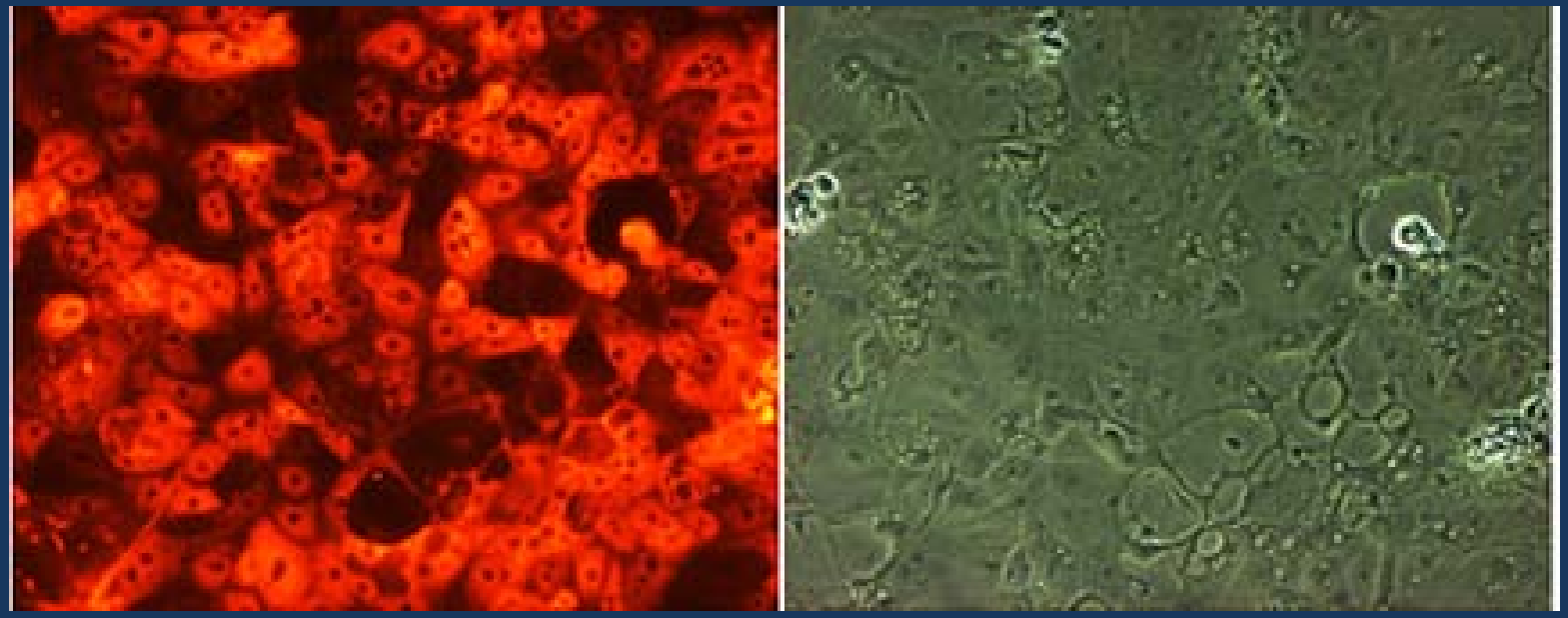
FGF4, HGF
OM
until use



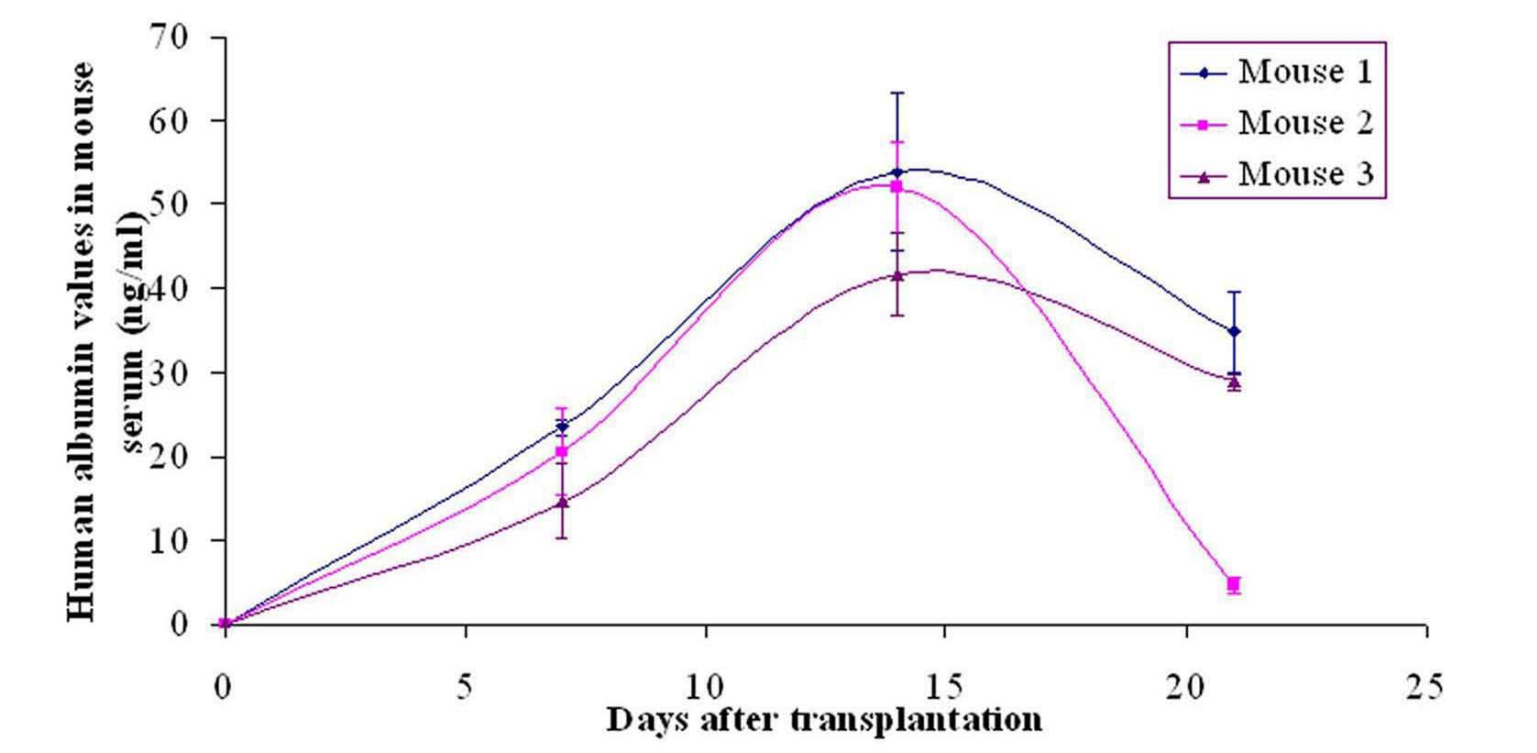




Albumin expression in human iPSC-derived hepatocytes



Serum Levels of Human Albumin in Transplanted Mouse

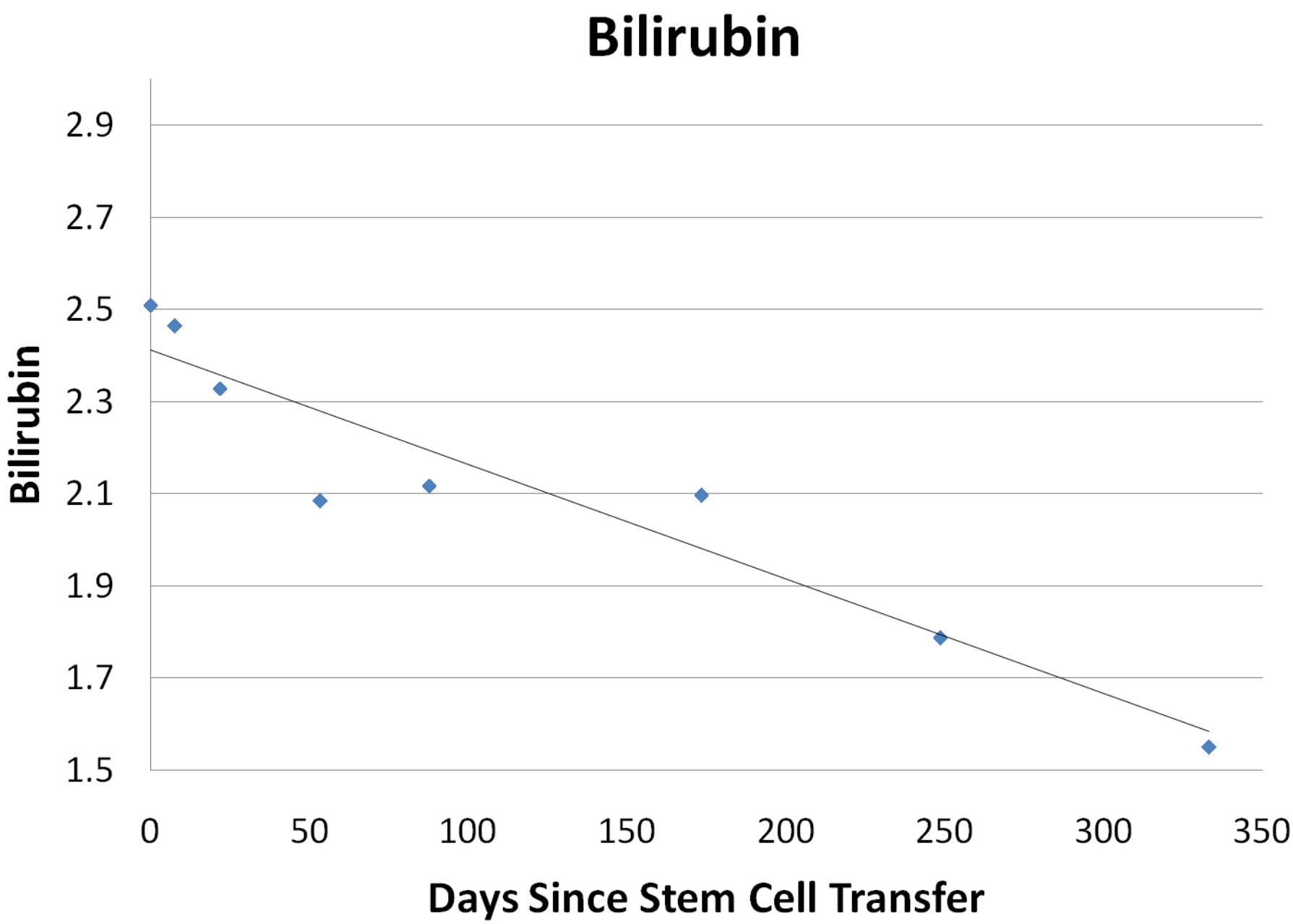


Adult Bone Marrow-Derived Stem Cell Therapy In Egyptian Patients with Chronic Liver Disease

Hosny Salama and Abdel Zekry- Egypt
Nagy Habib - UK
Elizabeth Huttinger, Cheryly Vigen, Wendy Burke, Omar Alfi, Mark A. Zern, -US

Clinical Study

- 57 patients with end-stage liver disease, mostly HCV, receive autologous CD34+ stem cells that have been amplified and differentiated towards hepatocytes in culture, then reinfused by portal veins or hepatic arteries. All followed for at least 26 weeks.


Bilirubin
2.9
2.7
2.5
2.3
2.1
1.9
1.7
1.5
Bilirubin
0
50
100
150
200
250
300
350
Days Since Stem Cell Transfer

Can Liver Cell Transplantation Replace Whole Organ Transplantation?

Certainly not in the near future,

But with continued research….

There are real possibilities on the horizon


TAKE TWO STEM CELLS AND CALL ME IN THE MORNING.
STAYSKAL
TAMPA TRIBUNE