

St. Veiter Gastroenterologen-Gespräche
Chronische Entzündung in der GE, Hepatologie & Rheumatologie
3. Juli 2009

Entzdgs.-Mechanismen & Therapieansätze bei Immunologischen Hepatopathien

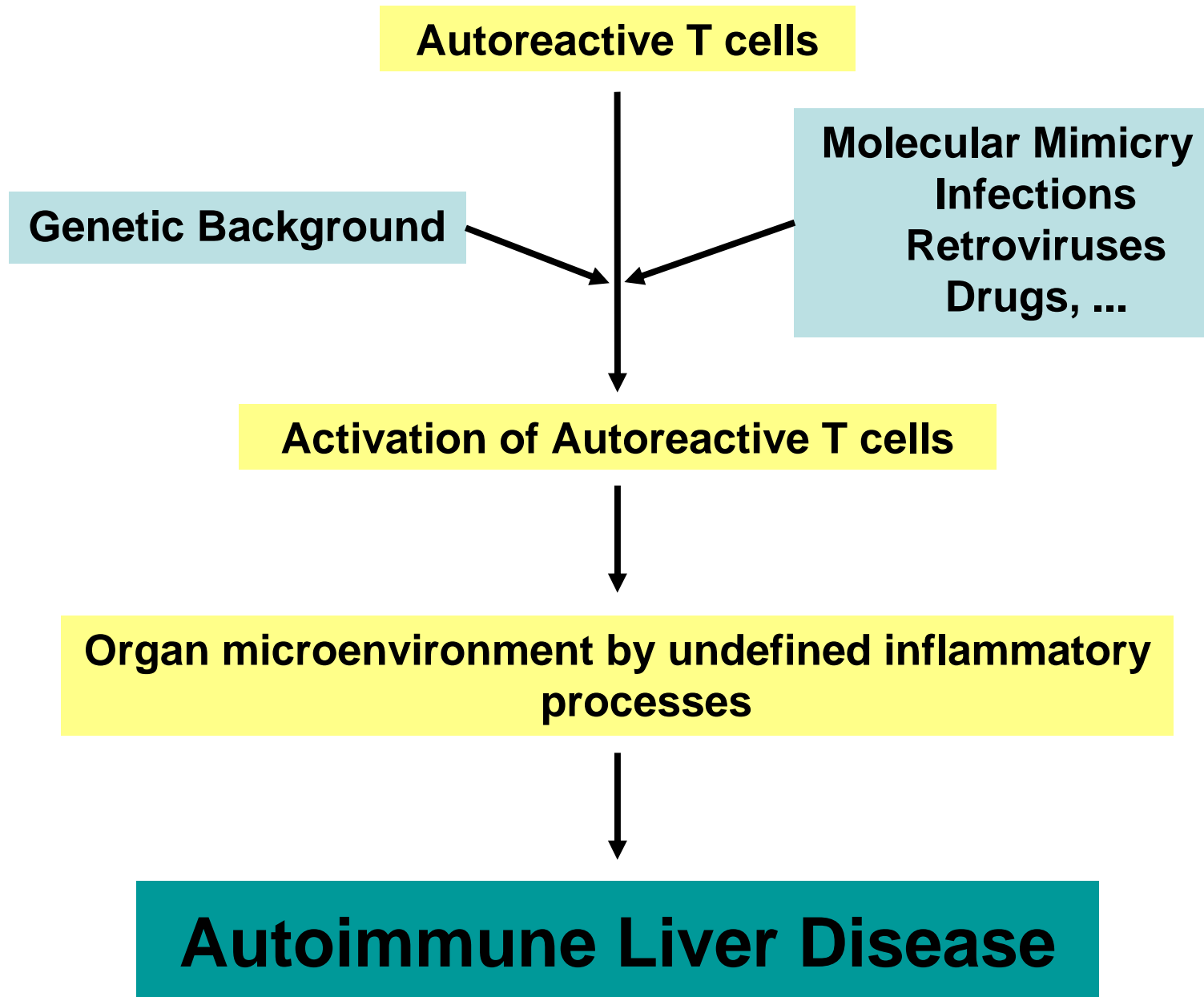
Michael Trauner
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Gastroenterologie und Hepatologie
Univ. Klinik für Innere Medizin



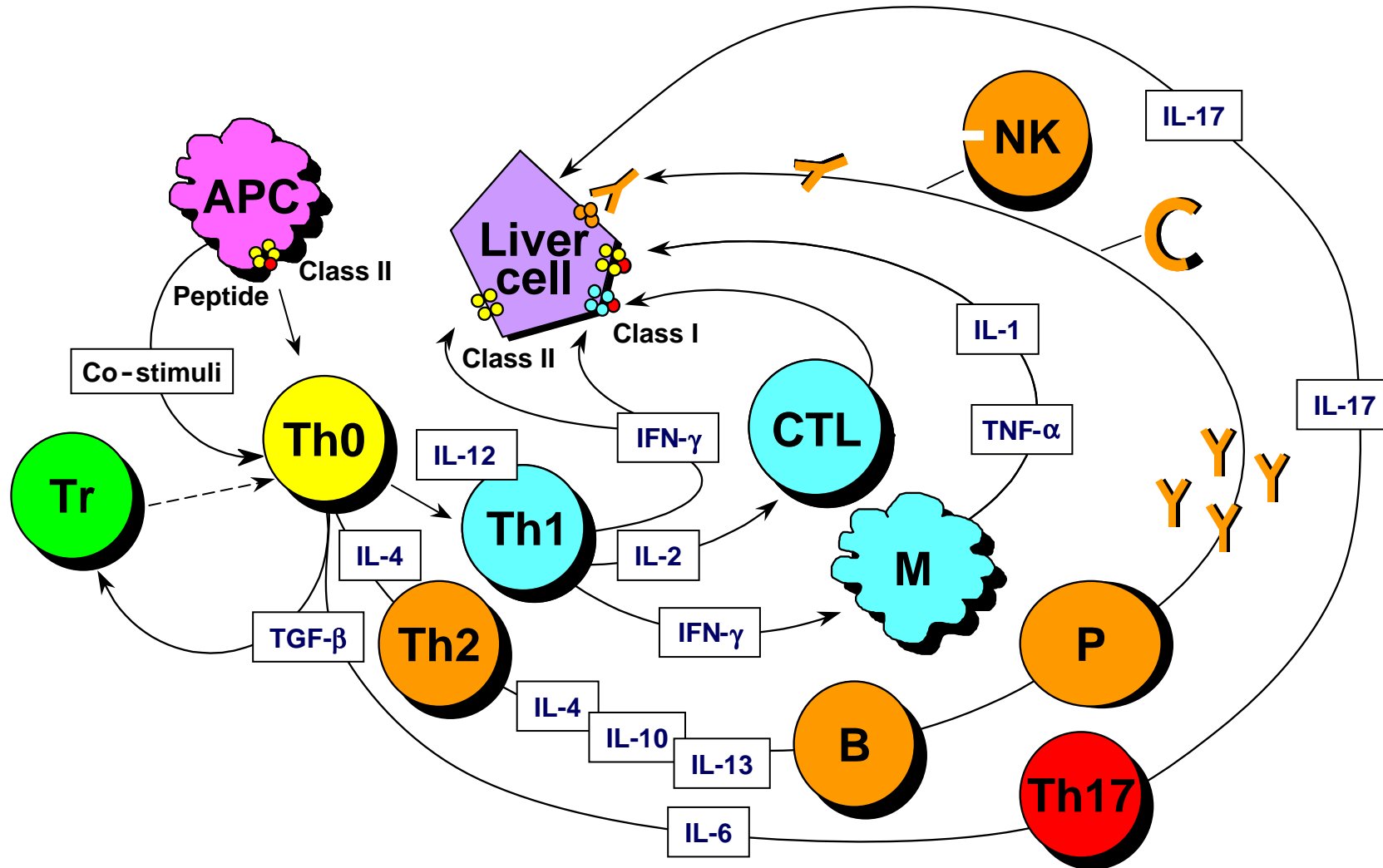
Immunologische Hepatopathien

- „Klassische“ (Auto)Immun-Hepatopathien
 - AIH (Präv. $17 / 10^5$)
 - PBC ($15-30 / 10^5$)
 - PSC ($9 / 10^5$)
- Andere H. mit (Auto)Immunphänomenen
 - Med. (DILI)
 - HCV, HDV, (HBV)
 - A₁AT-Mangel
 - (N)ASH

+ Extrahepatische
Autoimmun-KH



Autoimmun-Attacke bei AIH



Therapie der AIH

- Induktion der Remission

Standard Therapie:

- Steroide
- Azathioprin

80-90%

Remission

10-20%

Non-
Responder



Diagnose, Compliance?

Therapeutische Alternativen

- | | |
|--------------------|---|
| - Cyclosporin | Alvares et al., <i>J Hepatol</i> 1999 |
| - FK 506 | Van Thiel et al., <i>Am J Gastro</i> 1995 |
| - Mycophenolat/MMF | Richardson et al., <i>J Hepatol</i> 2000 |
| - Cyclophosphamid | Kanzler et al., <i>Z Gastroenterol</i> 1997 |
| - Rapamycin | Kerkar et al., <i>Am J Transplant</i> 2005 |
| - Budesonid | Wiegand et al., <i>Liver Int</i> 2005 |

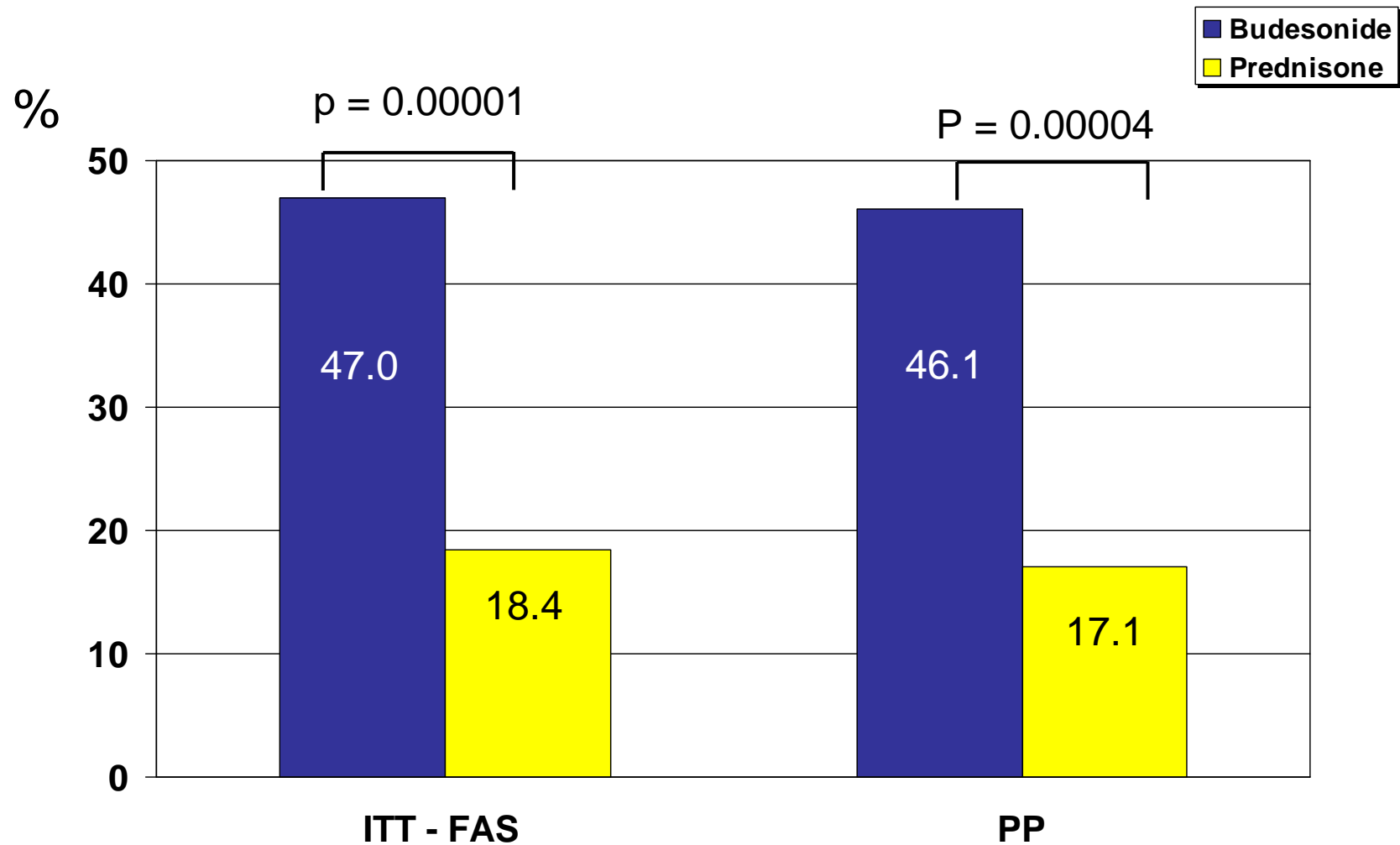
Budesonide & Azathioprine for AIH

Final Results of a Multicenter International Trial

- Prospective, multi-centre, multinational study
- Randomised, double-blind, double-dummy, active-controlled, two-arm parallel-group study (n=203)

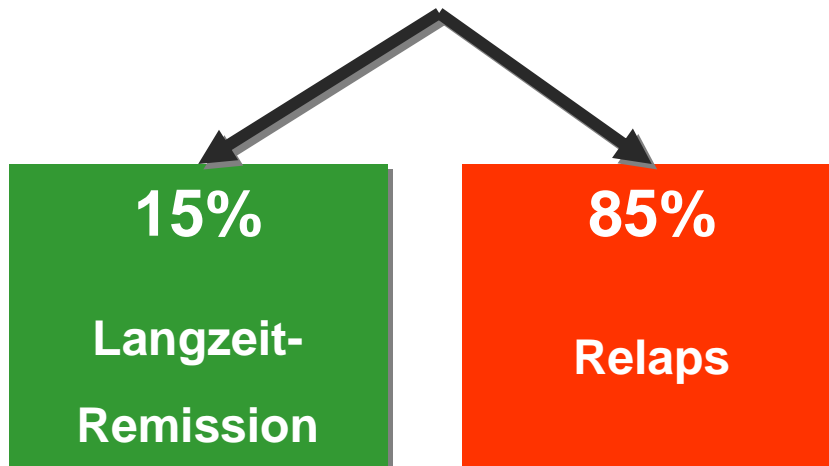
	Month 1				Month 2				Months 3-6			
	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8				
Arm 1	Prednisone											
	40 mg/d ----->				30 mg/d 25 mg/d 20 mg/d 15 mg/d				10 mg/d ----->			
	40 mg/d -----> 30 mg/d 25 mg/d				20 mg/d 15 mg/d 10 mg/d ----->							
Arm 2	Azathioprine											
	1-2 mg/kg/d ----->											
Arm 2	Budesonide											
	3 mg TID -----> 3 mg TID, upon biochemical remission 3 mg BID ----->											
	Azathioprine											
1-2 mg/kg/d ----->												

Complete Response Rates at 6 Months



Therapie der AIH

- Induktion der Remission (Non-Responder)
- Remissions-Erhaltung (Relapser, Dauer?)



Langzeittherapie:

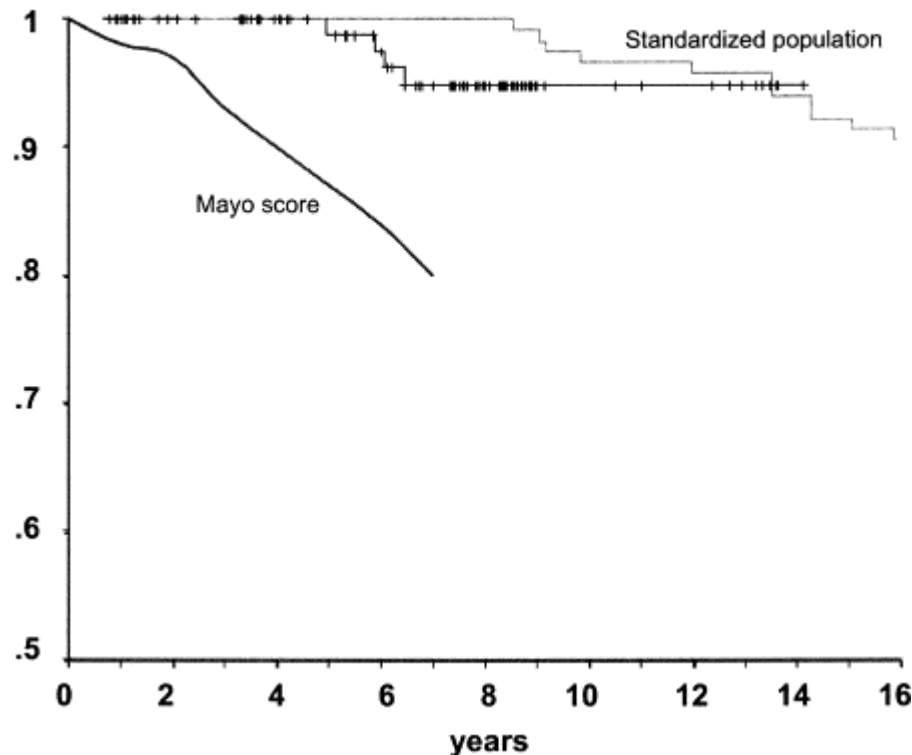
Azathioprin 1-2 mg/kg
Prednis(ol)on 5 – 15 mg
Budesonid ??? 1-2 x 3 mg

‘Dare to Relapse’

Exzellente Prognose bei PBC PatientInnen mit Biochemischem Ansprechen auf UDCA

Responder (AP-40%)

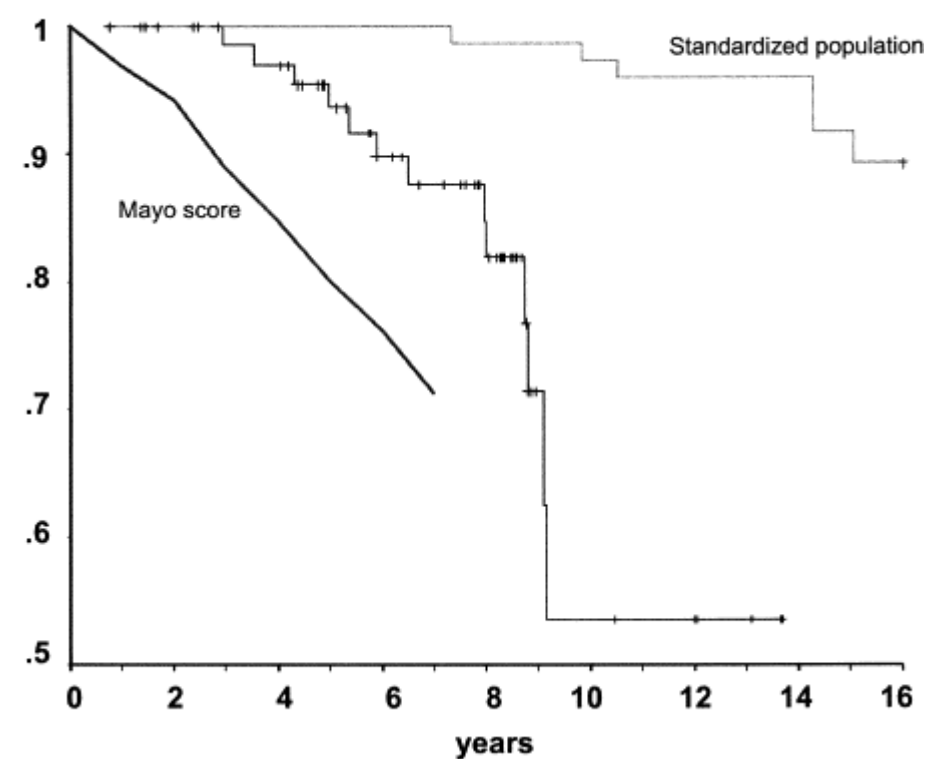
Survival



Non-Responder

33-61%

Survival



Pathogenese und Therapieansätze bei PBC

Anti-Retroviral? Antibiotika?

Immunolog. Gallengangsschaden

Anti-CD20 ↓ (Rituximab)?

Verstärkung des Gallengangsschaden durch Gallensäuren

Cholestase mit Retention von Gallensäuren in Hepatozyten

Nekrose, Apoptose, Fibrose, Zirrhose

Leberversagen

Tamoxifen?
Raloxifen?

Fibrate?
Statine?

~~Methotrexat
CSA, MMF
Thalidomid, Sulindac
Azathioprin
Predniso(lo)n~~
Budesonid 6-9 mg/d

Kombinationstherapie

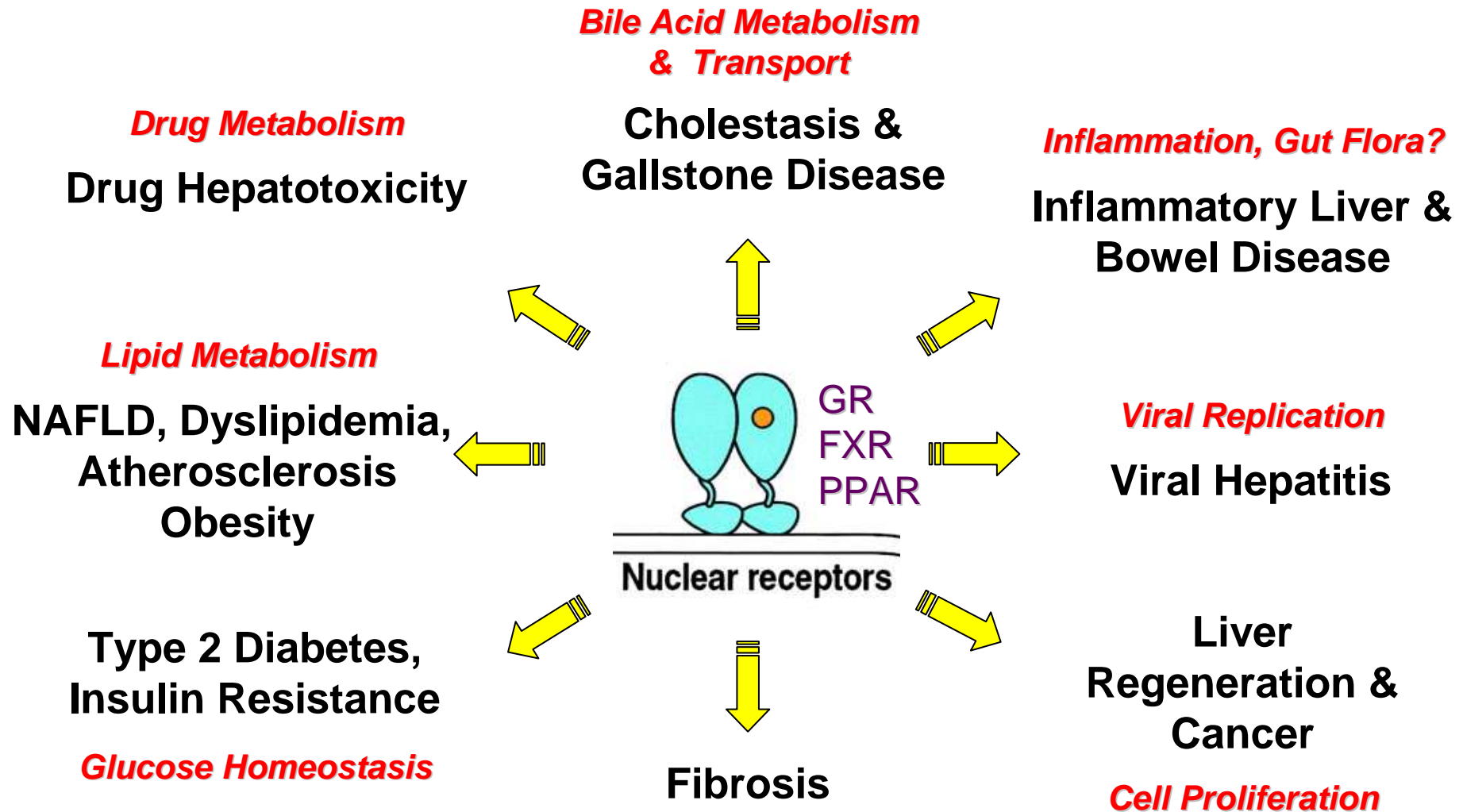
Ursodeoxycholsäure (UDCA) 13-15 mg/kg/d

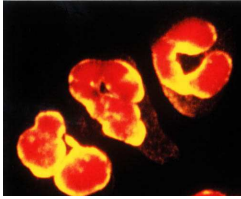
~~Colchicin, Silymarin
D- Penicillamin~~

LTx

*Rezente Übersichten:
Paumgartner & Pusi;
Silveira & Lindor
Clinics Liver Dis 2008*

Nuclear Receptors at the Crossroads of Metabolism, Inflammation & Regeneration





Immunological Mechanisms

Atypical pANCA
CD4-pos. Infiltrates
Polymorphismen
(HLA, non-HLA)

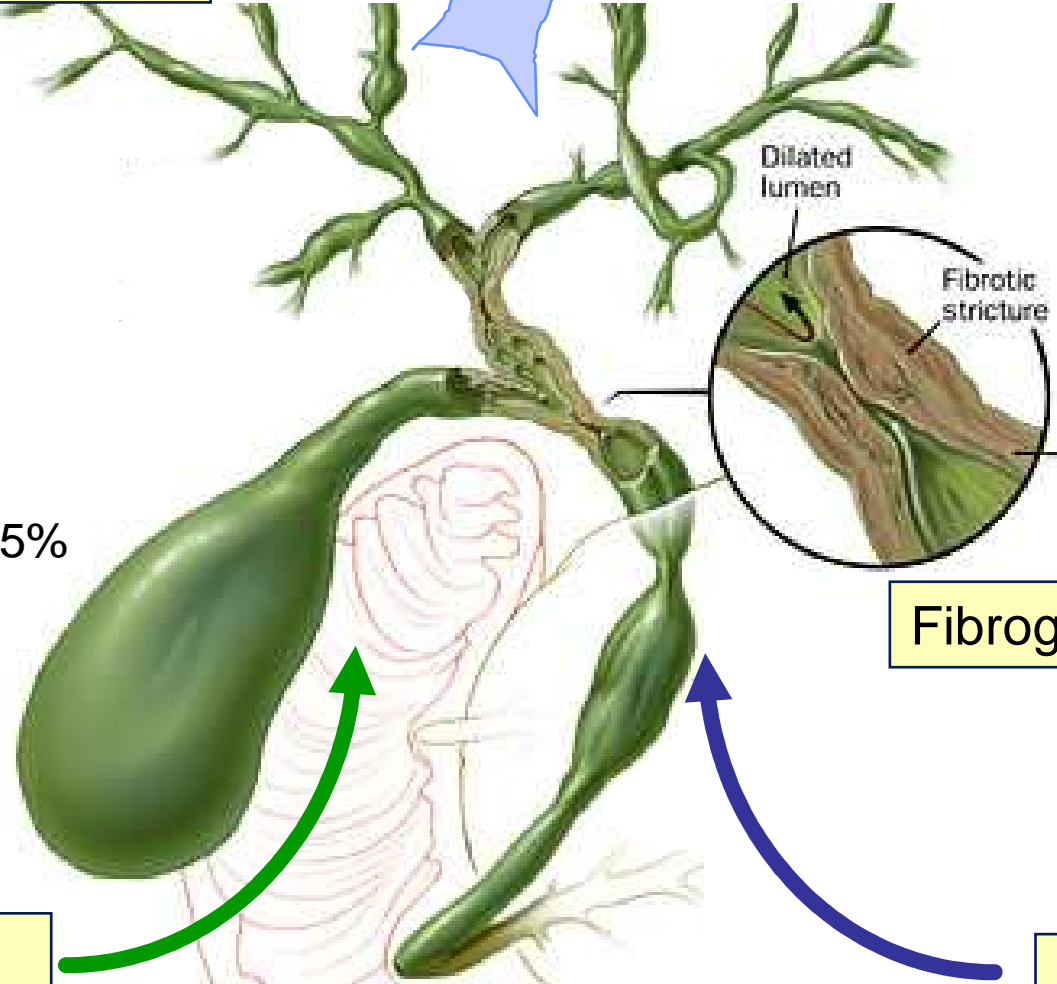


Cytokines

CFTR, MDR3
PXR/SXR

Transport Defects

Toxic Bile



4-7% ↔
↔ ~75%



Intestinal Translocation

PAMPs (LPS...)



Fibrogenesis

Ischemia

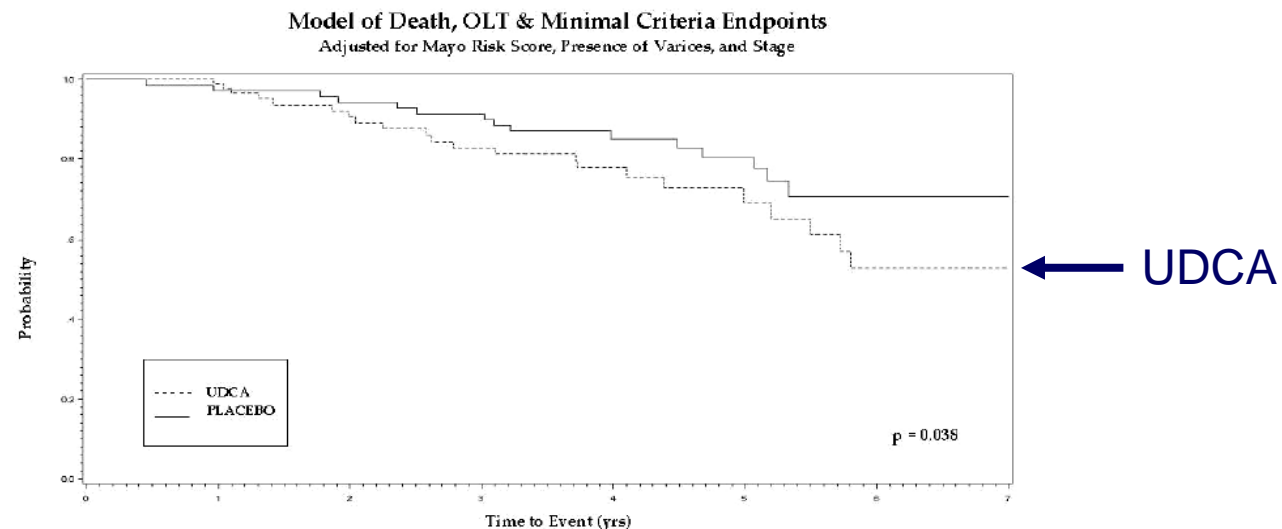
PSC as Immune-mediated Inflammatory "Disease"

PSC: Pathomechanismen → Rx

- Immunologisch → ~~Immunsuppressiva~~
- „Gut-derived“ → ~~Rx d. CED, ABx~~
- Vaskulär → Angiogenese?
- Toxische Galle → UDCA?

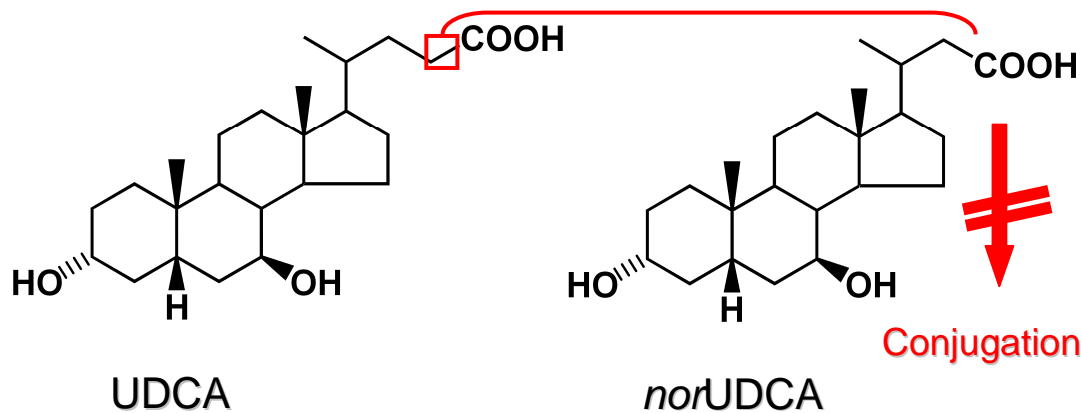
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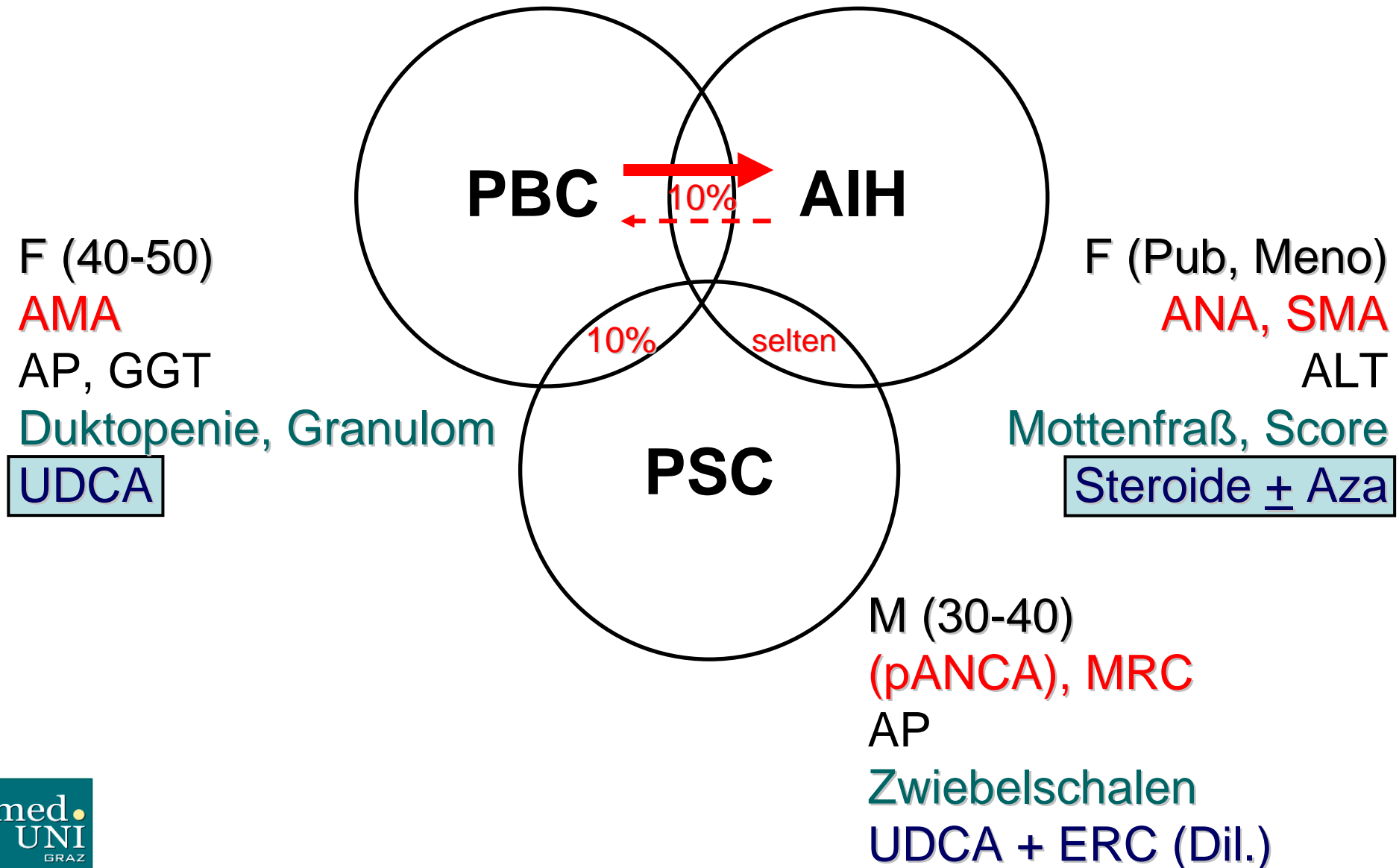
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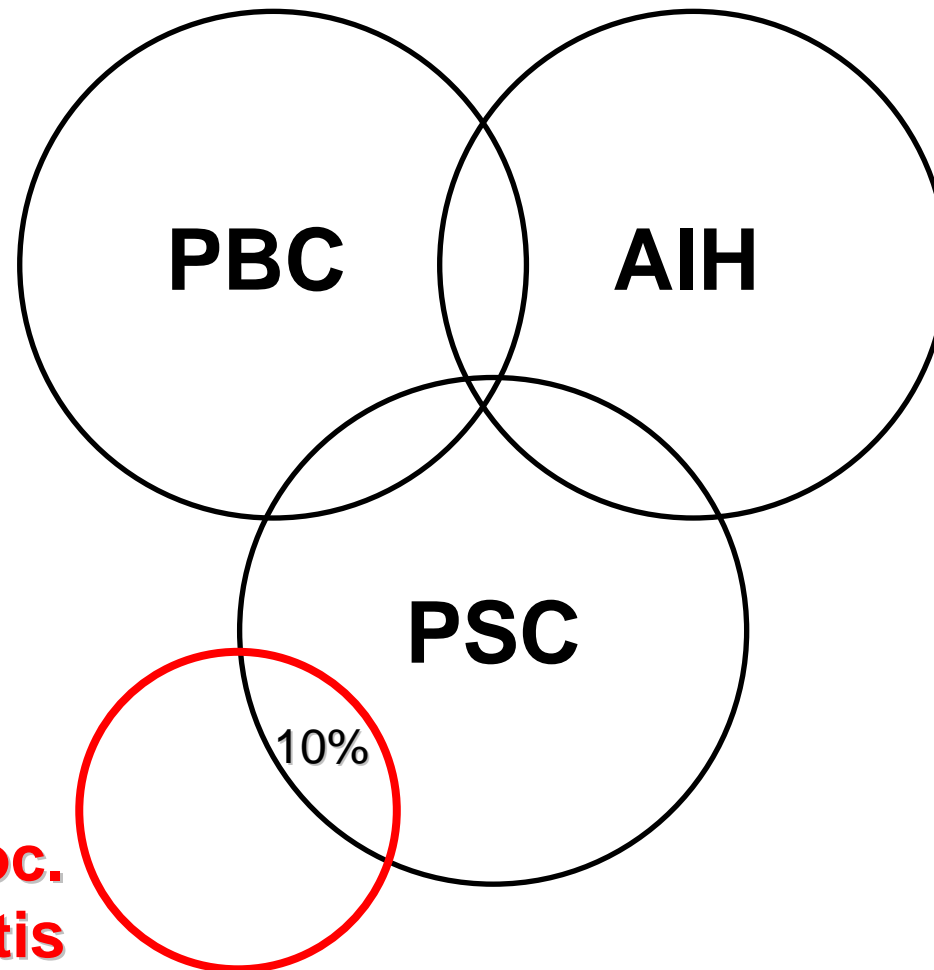


Phase 1	2009
Phase 2	2010
Phase 3	2012

Overlap-Syndrome



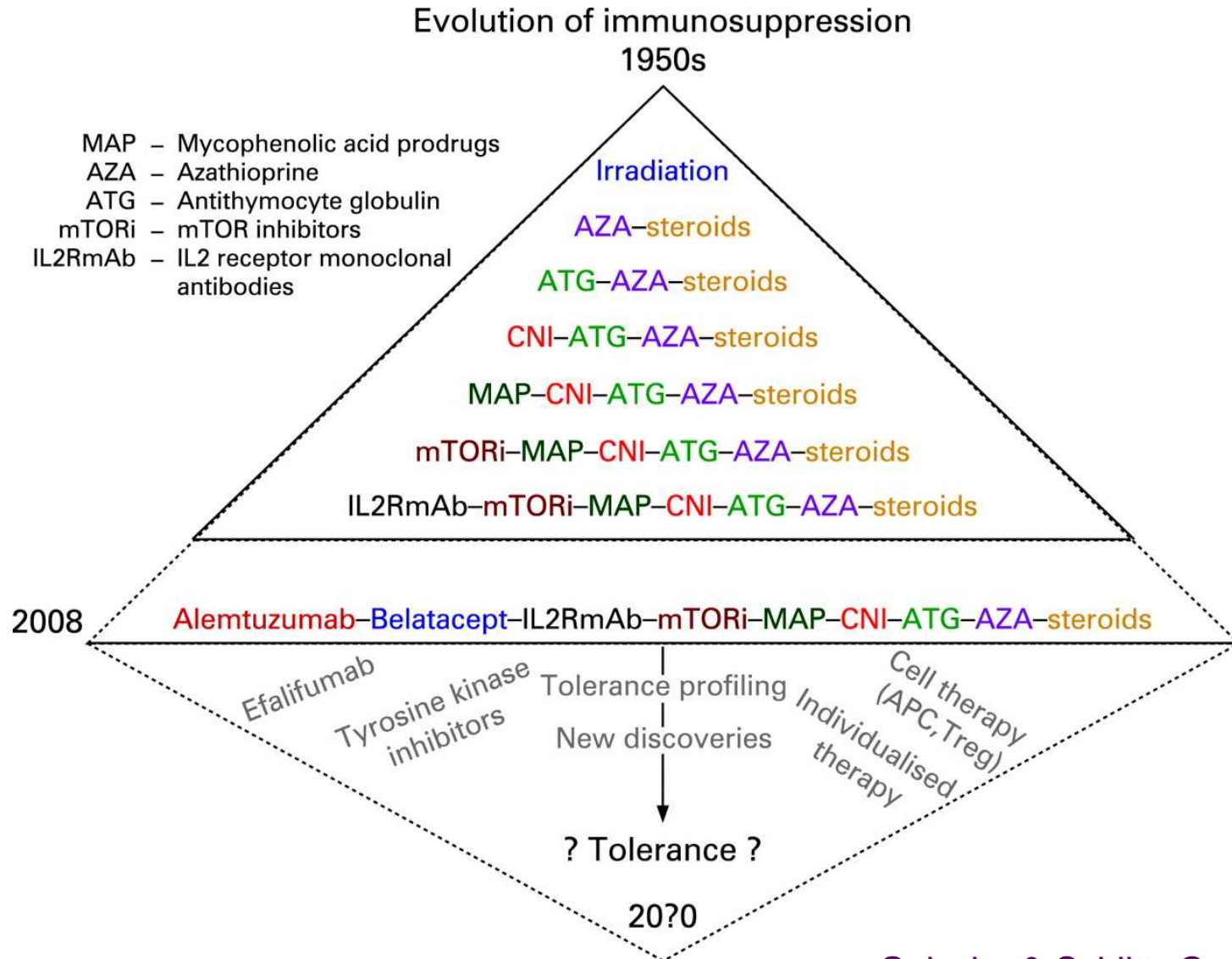
Overlap-Syndrom



**IgG4-assoc.
Cholangitis**

Autoimmunpancreatitis
Steroide

Entwicklung der Immunsuppression bei Lebertransplantation (LTX)



Rezidiv nach LTx → Rx

- AIH (~20%) → Prednisolon + Aza
- PBC (~20%) → UDCA
- PSC (~20%) → ERCP, UDCA?

Zusammenfassung

- Hepatologischer Zugang konservativ
- AIH: Standardtherapie effektiv (NW!) *
- PBC, PSC: Immunintervention zu spät?
 - Pathogenese nach wie vor unklar
- Endpunkte (Survival Benefit) – hohe Latte
- Biologicals bei RA / CED + Leber-KH?
- EASL CPG (PBC, PSC, IAC, Overlaps) **

* ÖGGH Konsensus 2007

** *J Hepatol* 2009; 51: 237

http://www.easl.ch/easl_cpg.asp

**Danke für Ihre
Aufmerksamkeit!**

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