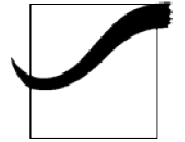




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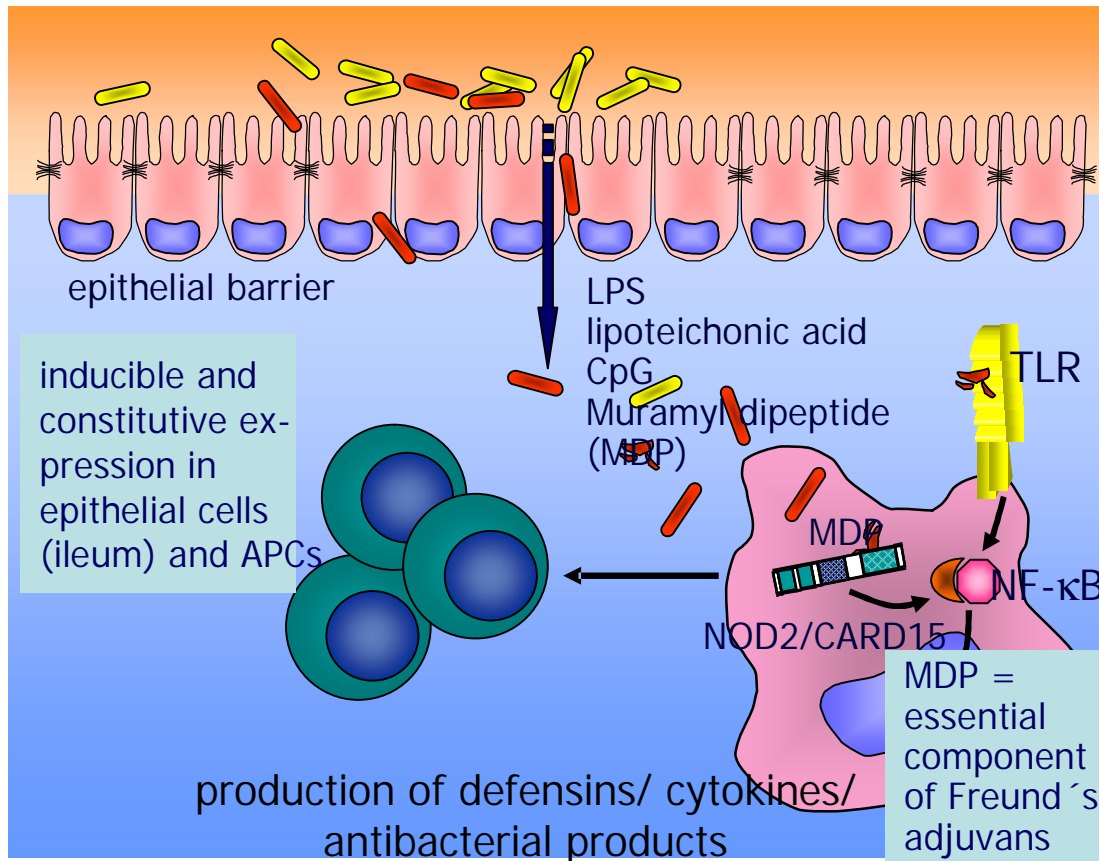
KLINIKUM

Department of Internal Medicine I, University of Regensburg

Role of NOD2/CARD15 for oxidative burst reaction and NF- κ B activation in intestinal macrophages

Gerhard Rogler, MD, PhD
Department of Internal Medicine I
University of Regensburg

NOD2/CARD15 is a susceptibility factor for Crohn's disease



- Variations (SNPs) in the **NOD2/CARD15** gene cause a **4-fold** (heterozygous) or **40-fold** risk (homozygous) to develop Crohn's disease

(Hugot et al; Ogura et al: Nature 2001)

- **NOD2/CARD15** protein: **intracellular sensor** for muramyl-dipeptide (MDP); induces **NF-κB** activation in **epithelial cells** (Paneth cells) and **macrophages** (Nunez et al; Gastroenterology, 2003)

- **NOD2/CARD15** variants associated with early onset of disease, involvement of the terminal ileum and fibrostenotic behavior

Open questions

- NOD2/CARD15 variations cause loss of function and reduced NF- κ B activation in transfection and in vitro experiments – intestinal macrophages show increased NF- κ B activation in Crohn's disease → conflicting data!

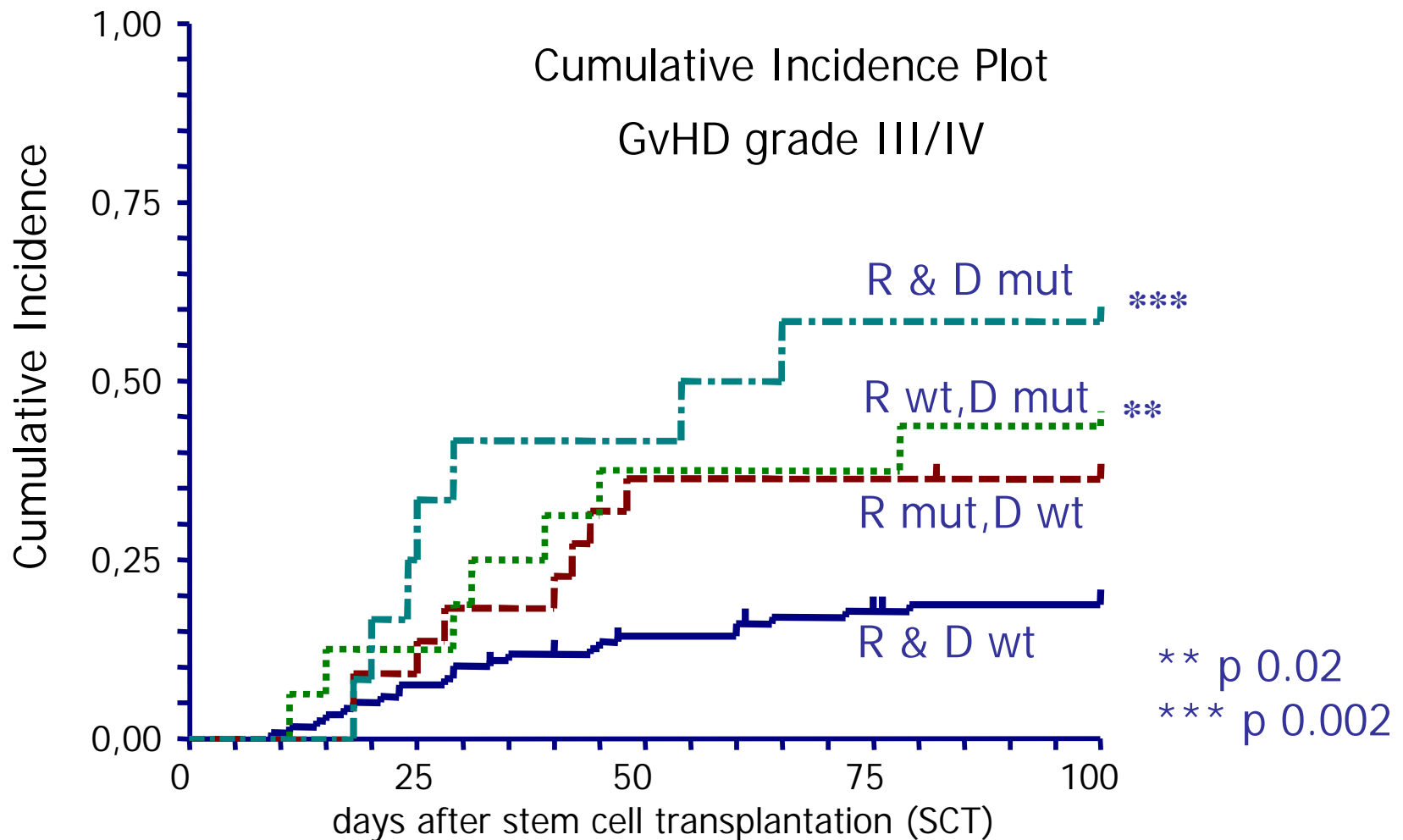
(Rogler et al; Gastroenterology, 1998)

- Do NOD2/CARD15 variants only play a role in Crohn's disease? Can other diseases involving NOD2/CARD15 malfunction contribute to the understanding of Crohn's disease?
- Are NOD2/CARD15 variants followed by decreased or increased cell reactivity in vivo (in humans)?

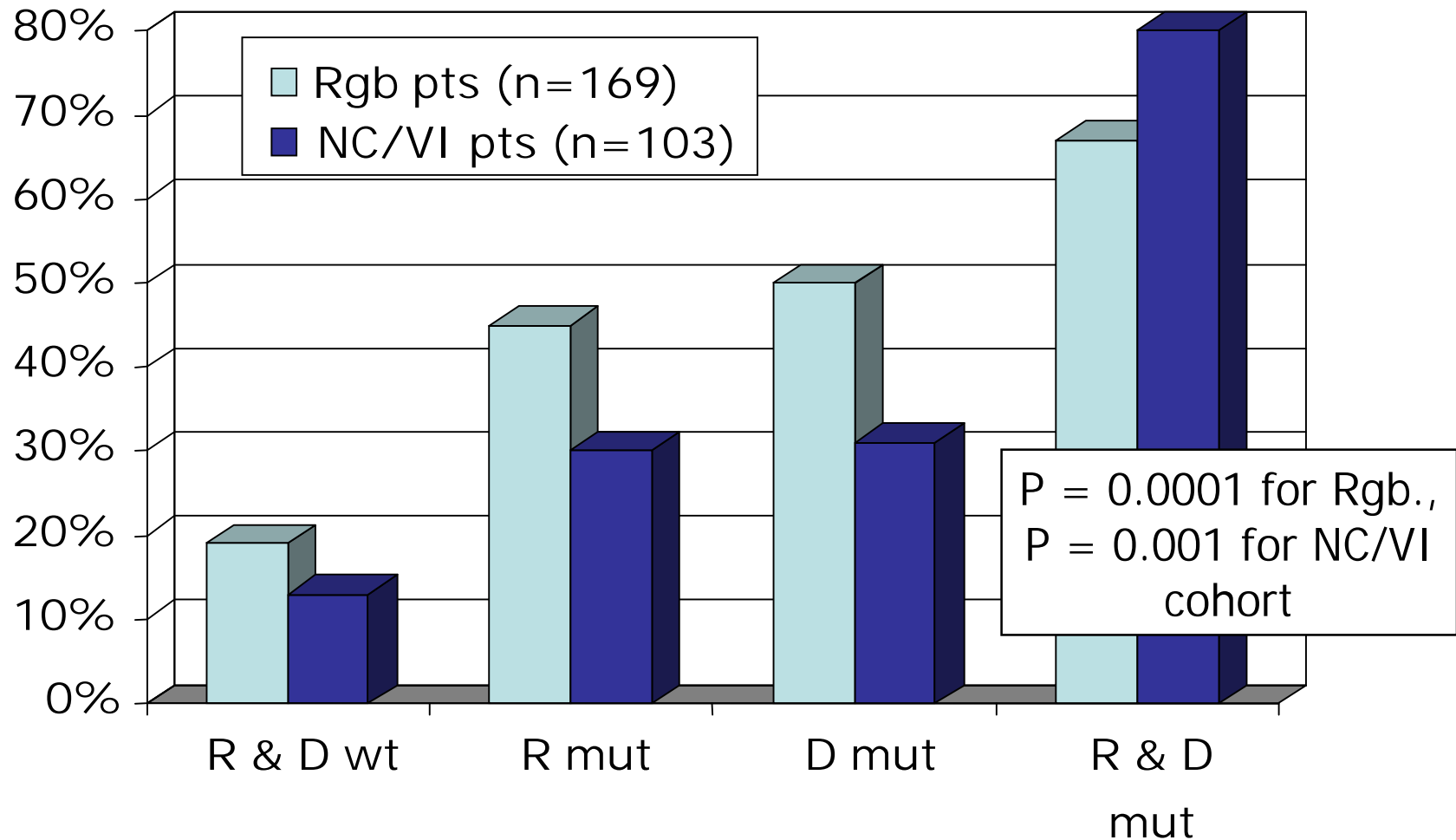
Rationale for the study of GVHD after stem-cell transplantation

- Van Bekkum (1974):
 - Role of intestinal flora – mice grown under germfree conditions are protected from severe GvHD
- Hill, Ferrara (1996/2000):
 - Protection from gut damage (e.g. by IL-11, KGF...) prevents cytokine release and severe GvHD
- Gerbitz (2004):
 - Lactobacilli reduce gut pathology, GvHD mortality and splenic T cell expansion

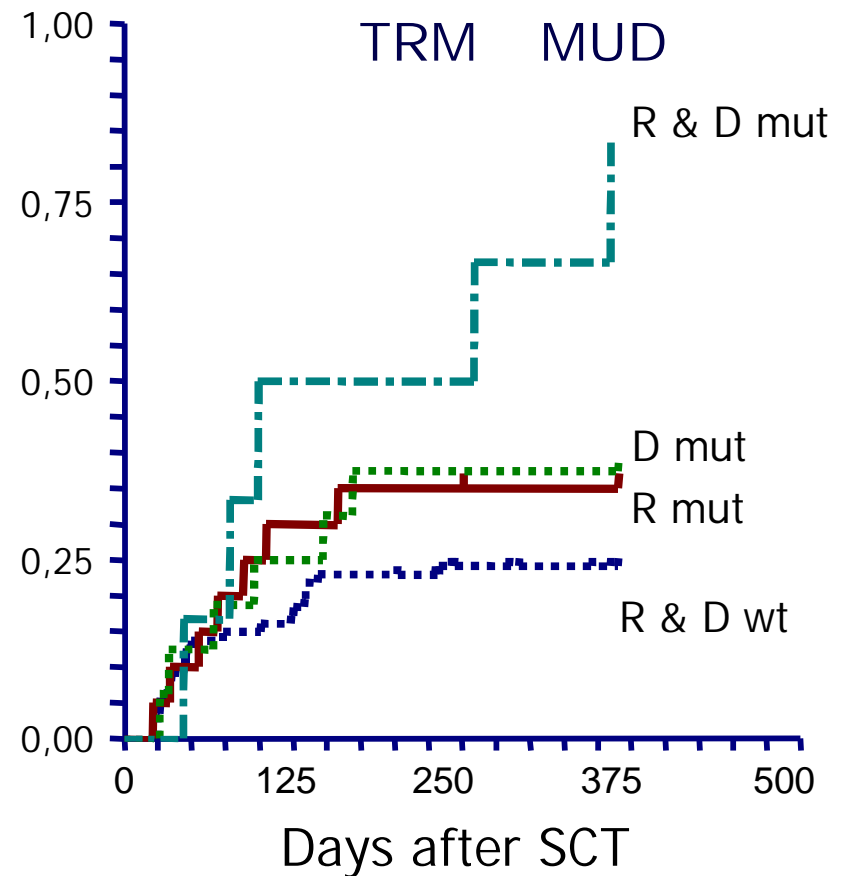
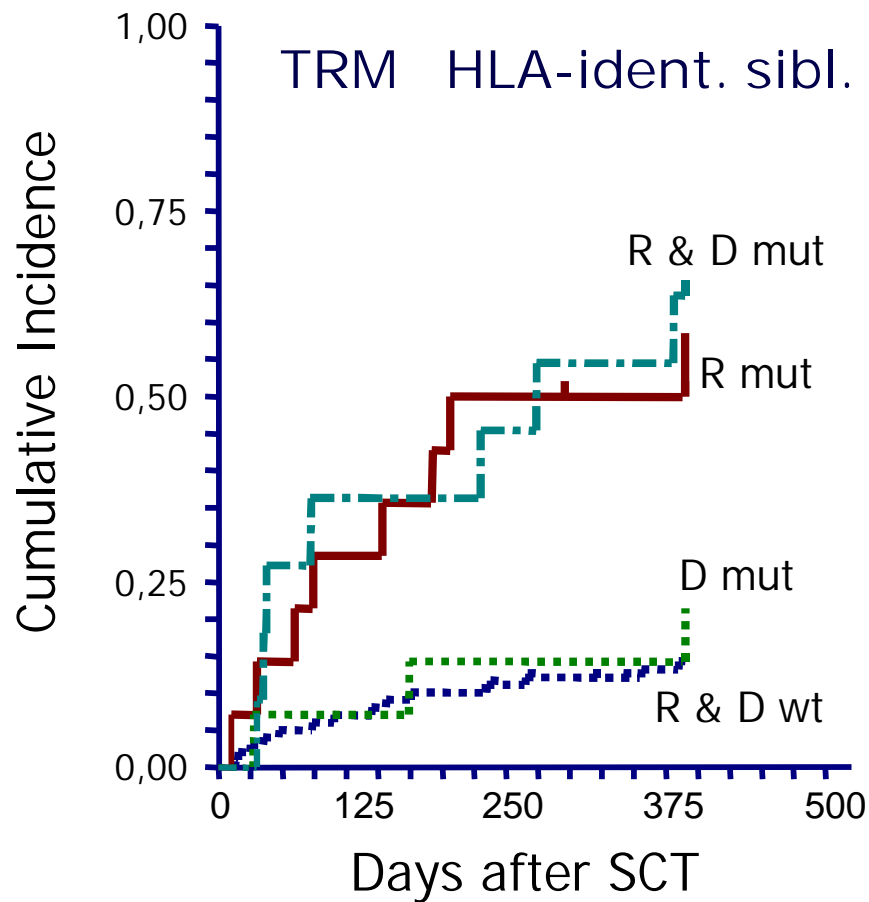
CARD15/NOD2 mutations correlate with severe GvHD – Regensburg cohort



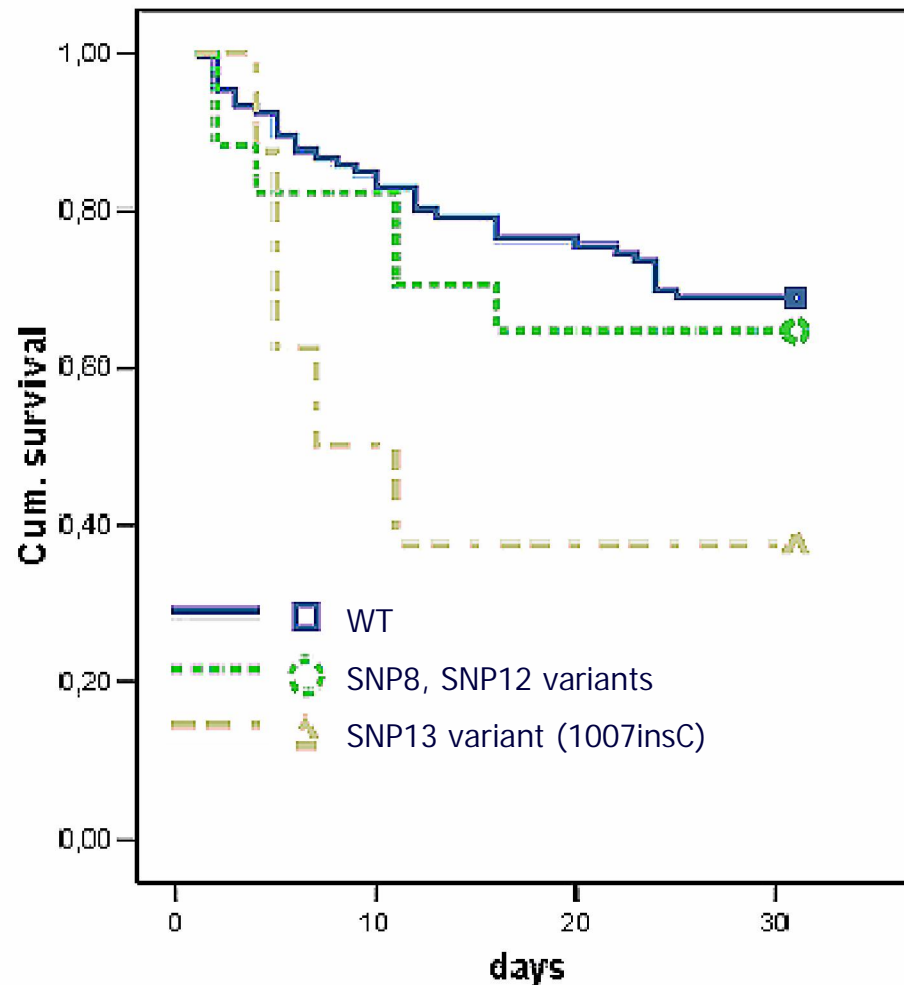
GvHD and NOD2/CARD15 in both cohorts



TRM - Different role of recipient vs. donor SNPs in HLA-identical sibl. vs. matched unrelated donors (MUD)

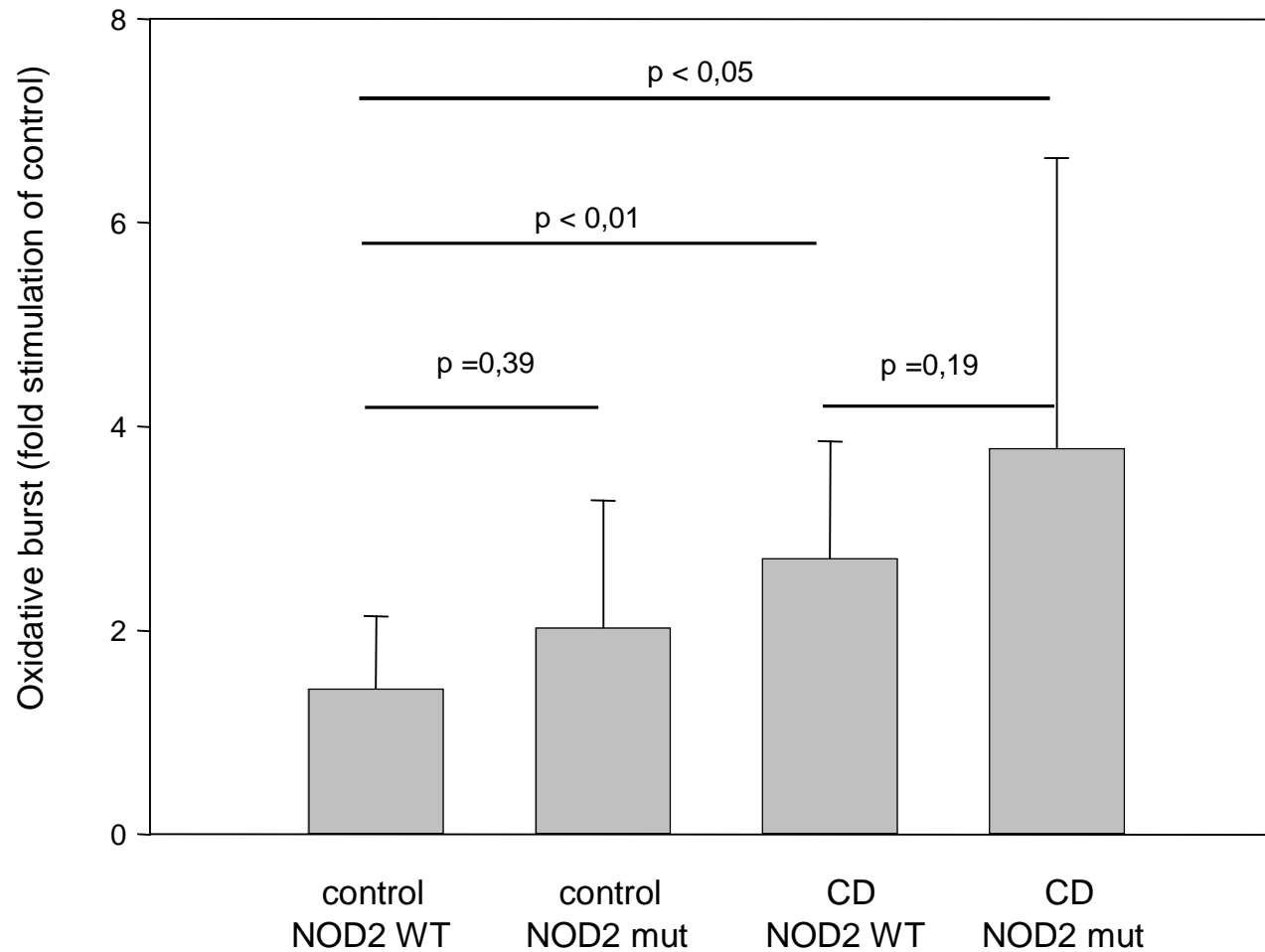


Association of NOD2/CARD15 genotype with early mortality during sepsis

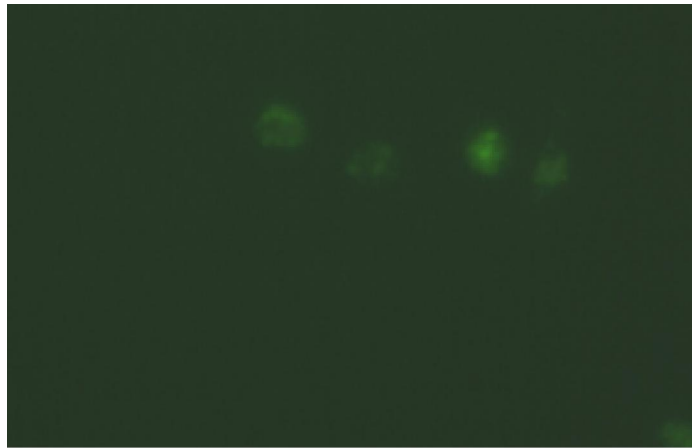


- cohort of 132 consecutive patients
- sepsis associated mortality (SRM, day 30) increased in patients with NOD2/CARD15 variants (42% versus 31%)
- SRM highest (57%) in 8 patients with 1007insC variant (SNP13, $p < 0.05$)
- independent risk factor for SRM

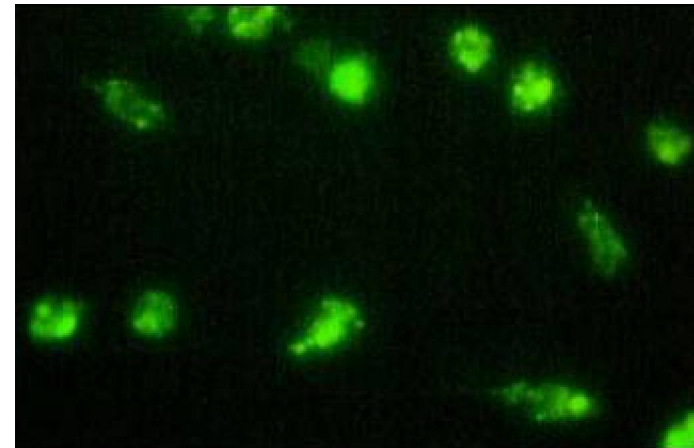
NOD2/CARD15 variants may cause an increase in oxidative burst reaction in IMACs



NF- κ B activation in IMACs as demonstrated by reporter plasmid micro-injection



WT



1007insC



Conclusion: Role of NOD2/CARD15 during intestinal inflammation

- NOD2/CARD15 SNPs in both, recipient and donor cells contribute to an dysregulated inflammatory response in SCT
 - Cells possibly involved:
 - Recipient: IEC, intestinal APCs
 - Donor: APCs (intestinal macrophages, DCs)
- CD and gastrointestinal GvHD might be considered as a consequence of a dysregulated response against intestinal bacteria
- NOD2/CARD15 variants and ineffective bacterial recognition may be associated with increased mortality
- Intestinal macrophages bearing NOD2/CARD15 variants show increased NF- κ B activation and oxidative burst reaction

Coworkers:

Univ. of Regensburg, Dept of Intern.Med.I:

- J Brenmoehl, H Herfarth, J Scholmerich

Univ. of Regensburg, Intern. Med. I, Haemat/Oncol.:

- E Holler, G Eissner, J Hahn, M Kreuz, H Bremm, R Andreesen

Thank you for your attention!

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- JP Wild (Dept of Pathology), J Marienhagen

Transeurope partners:

- Univ. of Newcastle upon Tyne:
AM Dickinson, G Jackson
- AKH Vienna:
H Greinix, F Fischer