

A possible role for regulatory T-cells in survival differences between HP positive and HP negative gastric cancer patients after curative tumor resection



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Gastric cancer

- Poor prognosis even after curative resection
- Predictive factors for survival
 - Depth of invasion (pT)
 - Lymph node metastasis (pN)
 - expression of metalloproteinases, cathepsin D, VEGF, erbB-2, CEA

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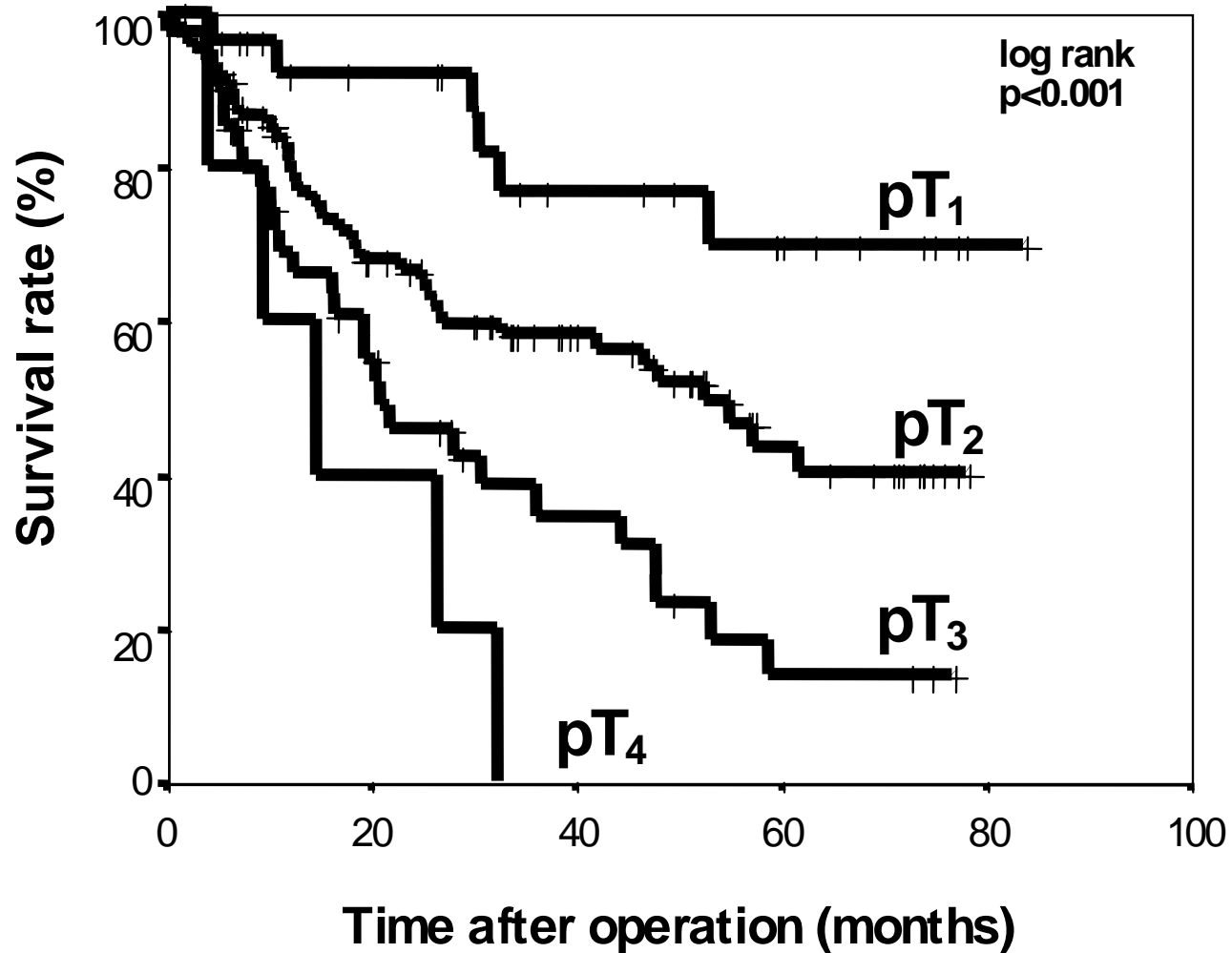
Helicobacter pylori

- Gram-negative helical shaped bacterium
- Correlation with induction of gastritis and peptic ulcer
- Role in the development of gastric cancer unclear
 - An *H.p.* negative subgroup of gastric cancer patients exists
 - No differences in expression patterns of oncogenes and tumor suppressor genes

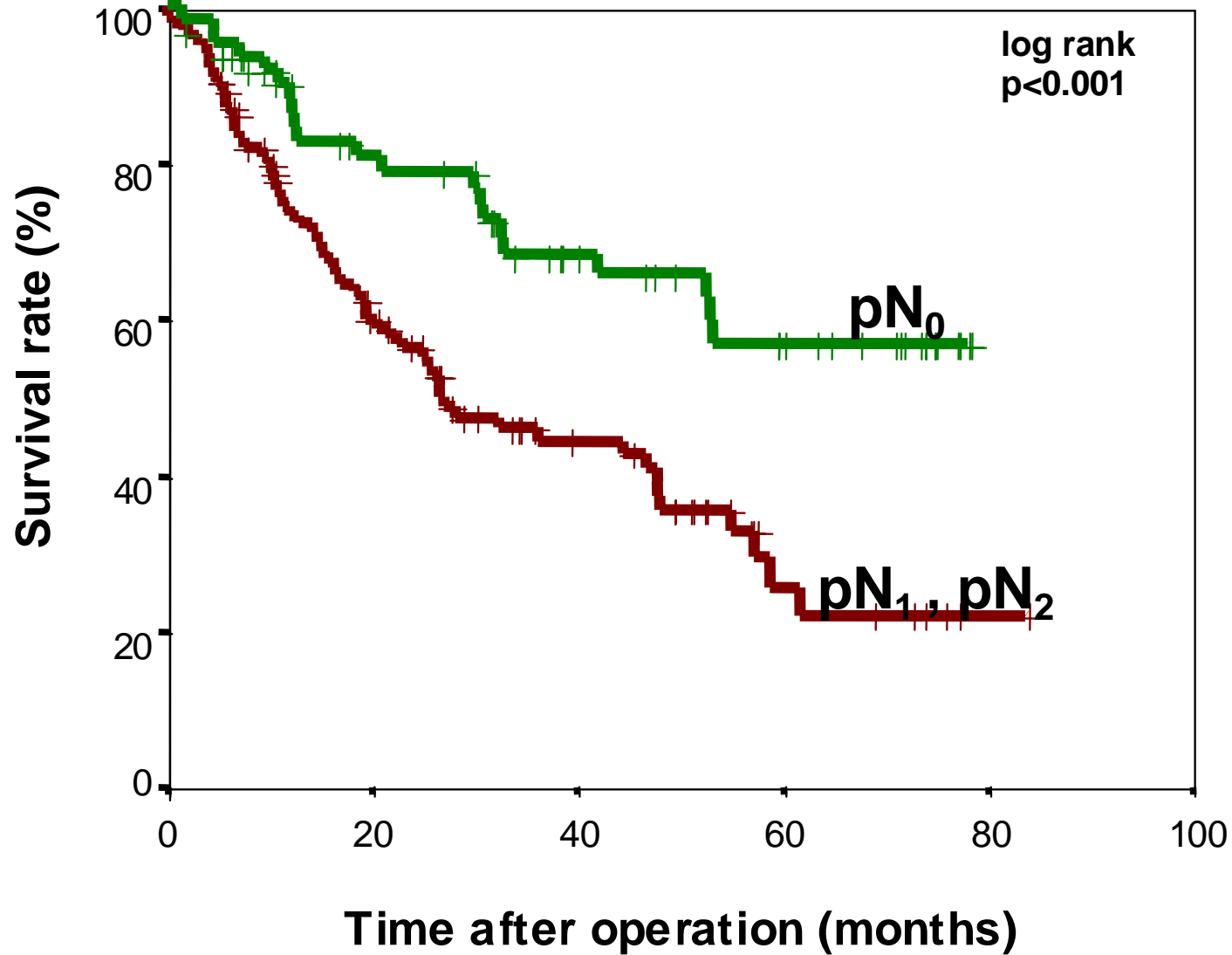
Clinical Study

- Follow-up of 166 patients between 1992 and 2004 with gastric cancer who underwent curative gastrectomy
 - 125 HP⁺ patients
 - 41 HP⁻ patients
- Preoperative *Helicobacter pylori* status was examined with bacterial culture, histology and serology

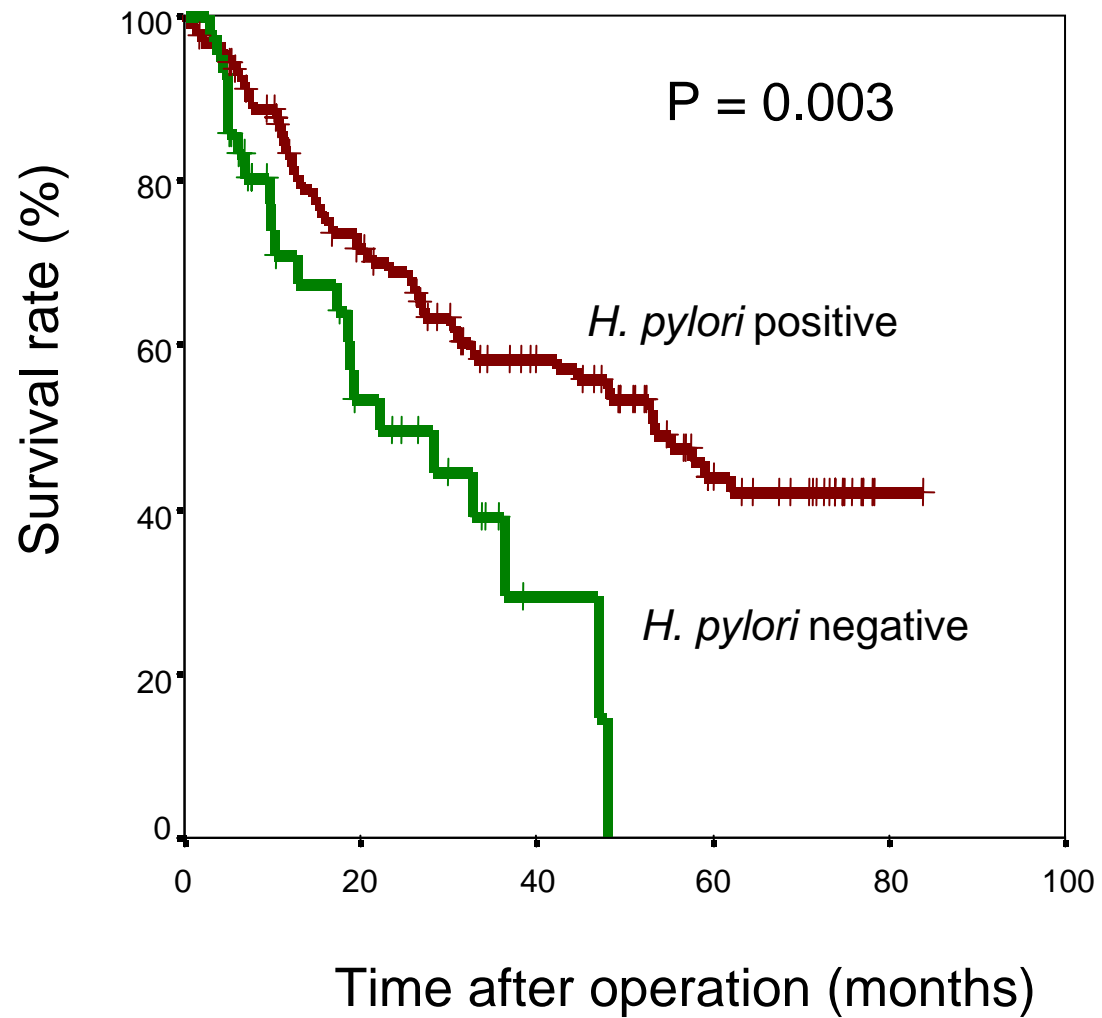
Survival after curative gastrectomy stratified by “pT-stage”



Survival after curative gastrectomy stratified by “pT-stage”



Survival after curative resection



Hypothesis

H.p. promotes the generation of a tumor-specific type 1 response

Aruga et al., J. Immunol. 1997

Hu et al., J. Immunol. 1998

Dudley et al., Science 2002

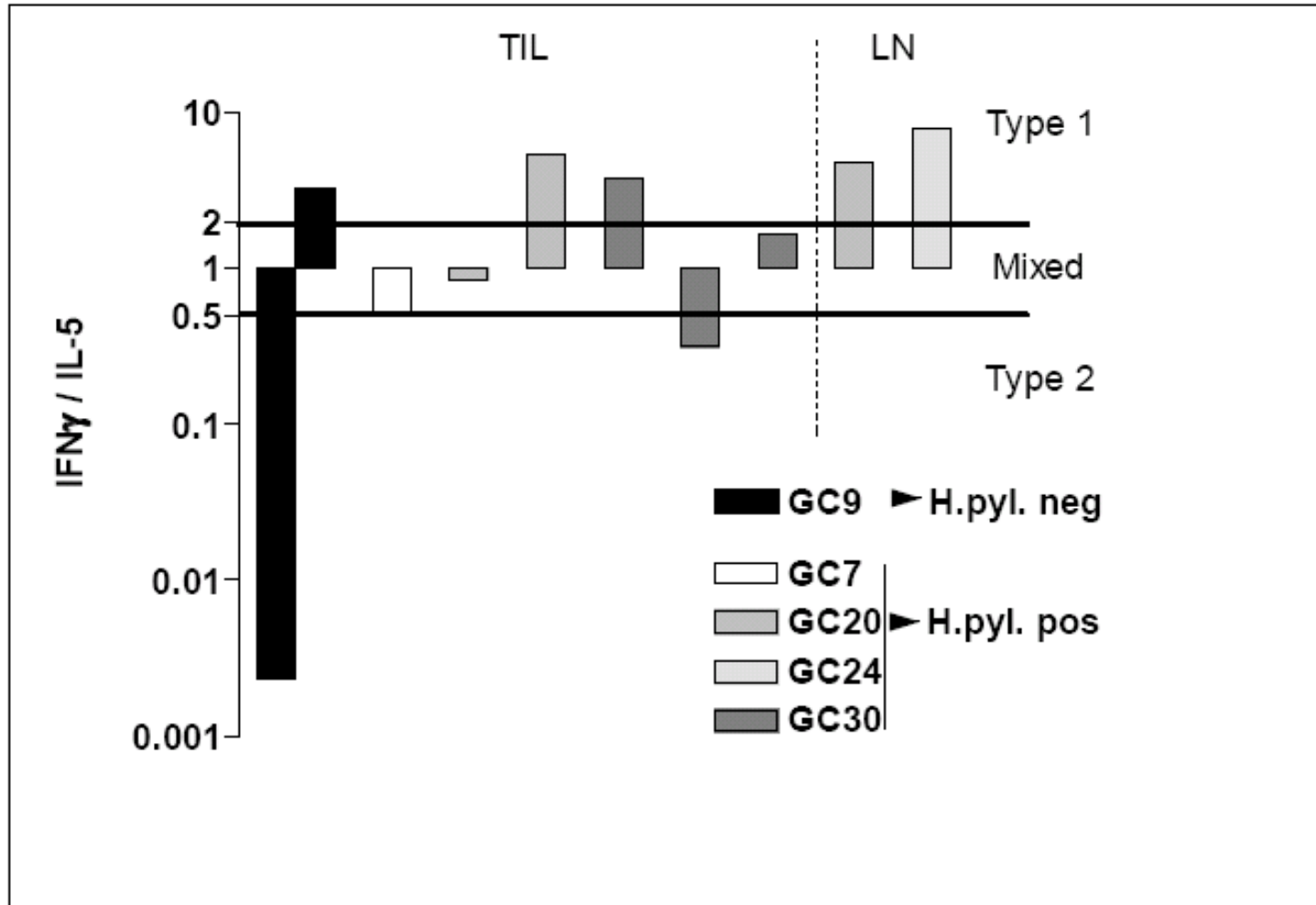
Background

H.p. induces a type 1 immune response in the stomach mucosa

Bamford et al., Gastroenterol. 1998

Luzza et al., Dig. Liver Dis. 2001

Tumor specific cytokine release of TIL cloids from Hp+ and Hp- gastric cancer patients

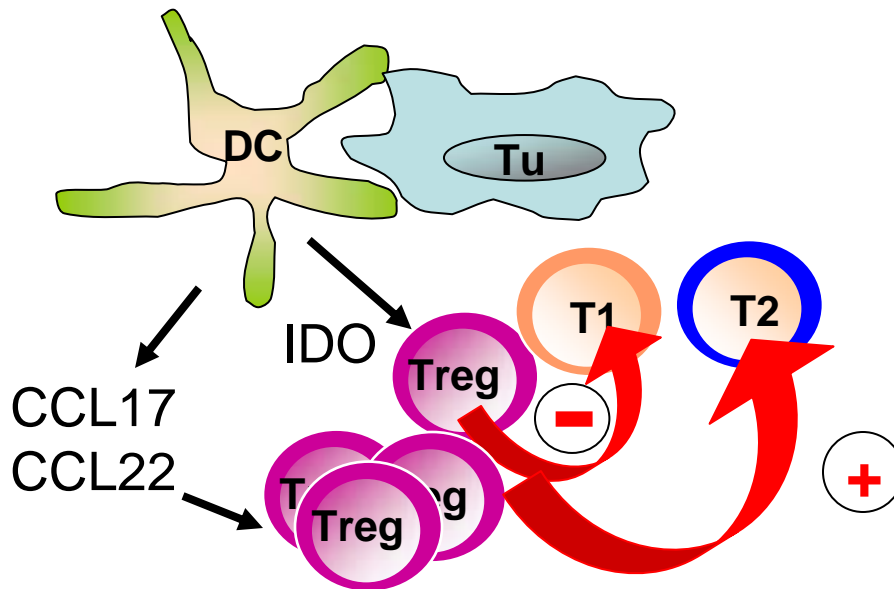


Hypothesis

H. pylori

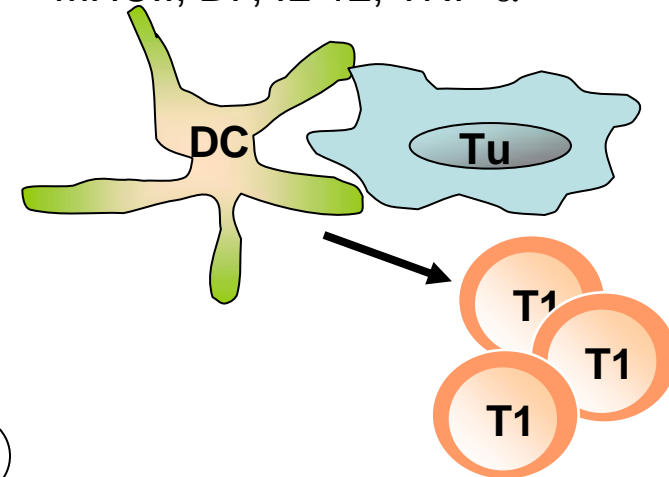


Immature DC



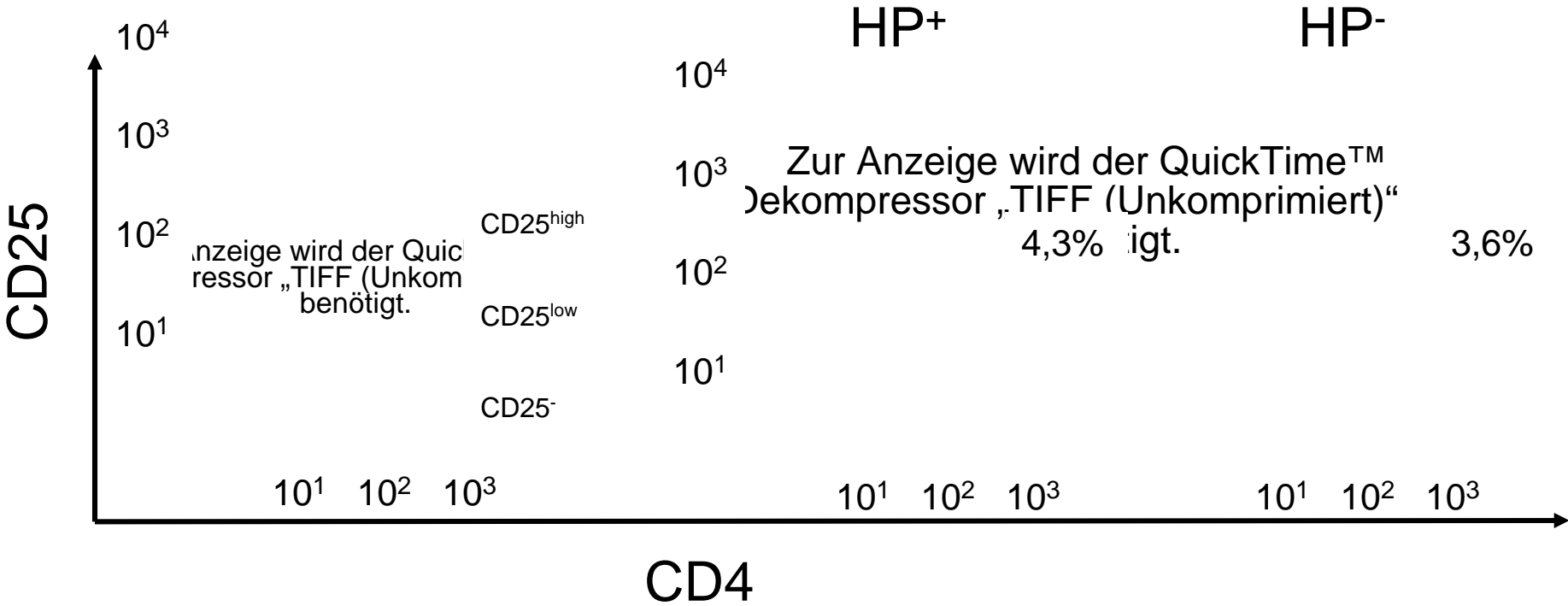
Mature DC

CD83, CD208
MHCII, B7, IL-12, TNF- α



Distribution of T cells in the peripheral blood

CD4 CD25^{high} cells in the peripheral blood of gastric cancer patients



CD4⁺ CD25^{high} cells in the peripheral blood of gastric cancer patients (FACS)

% CD3⁺CD4⁺CD25^{high} cells

P=0.5268

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HP⁺ PBMC

HP⁻ PBMC

CD4⁺ CD62L^{high} cells in the peripheral blood of gastric cancer patients (FACS)

%CD4⁺ CD62L⁺ T cells

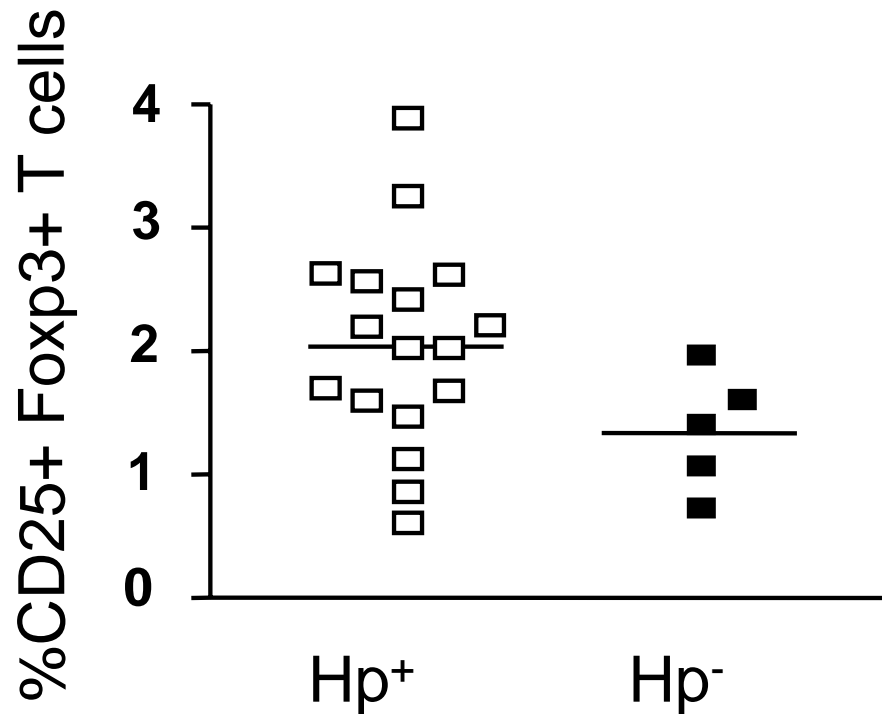
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Hp⁺

Hp⁻

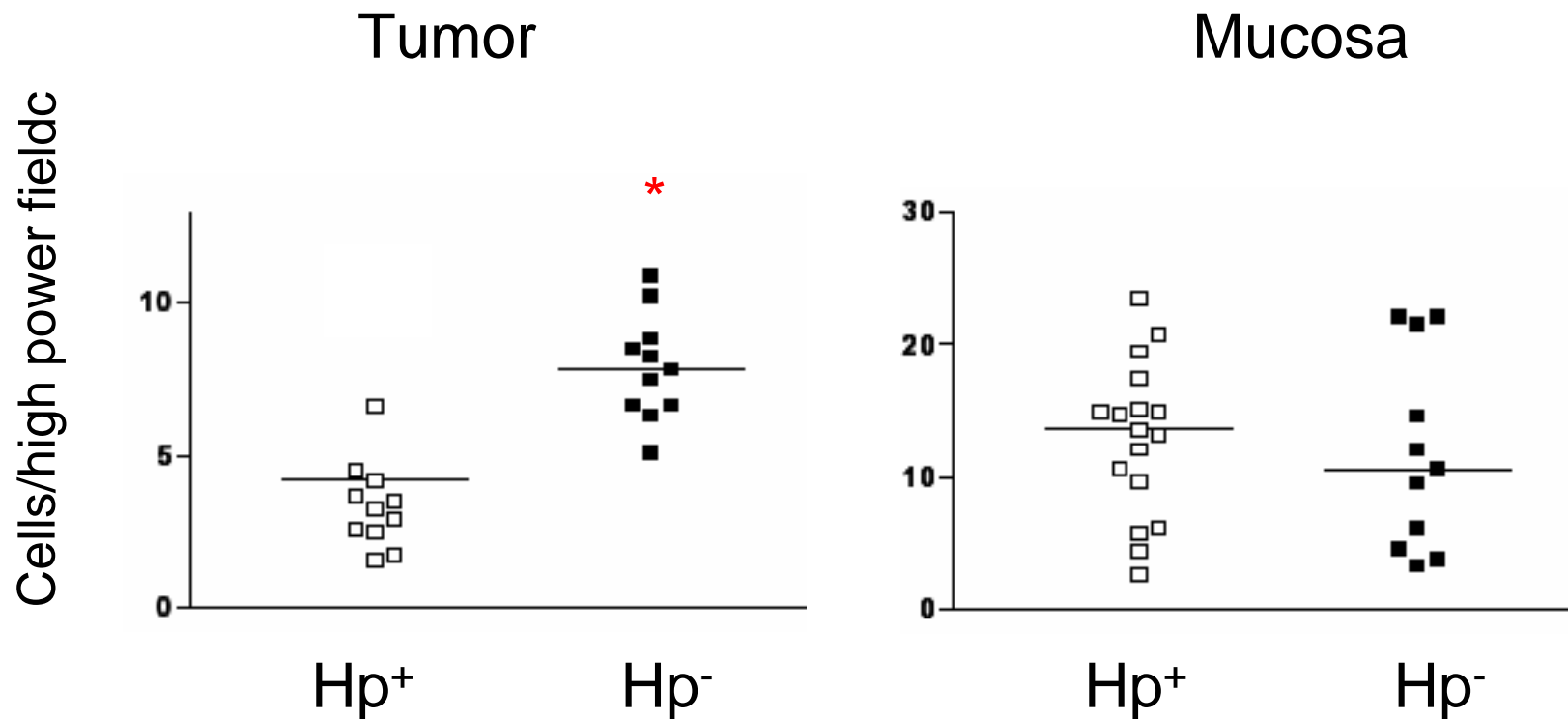
*

CD4⁺CD25⁺FoxP3⁺ cells in peripheral blood of gastric cancer patients (FACS)



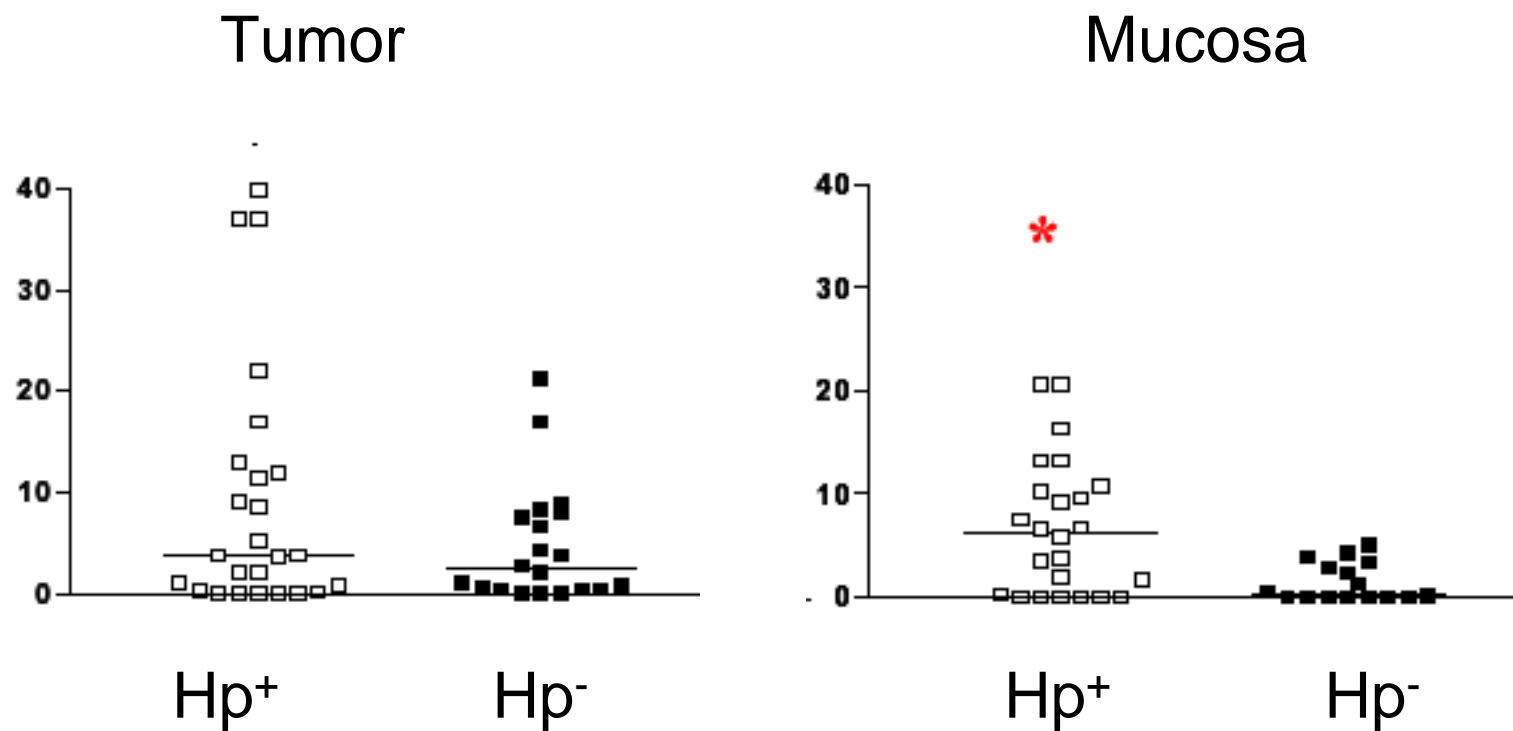
Distribution of T-cells in gastric tumor

CD8 cells in tumor tissue (Histochemistry)



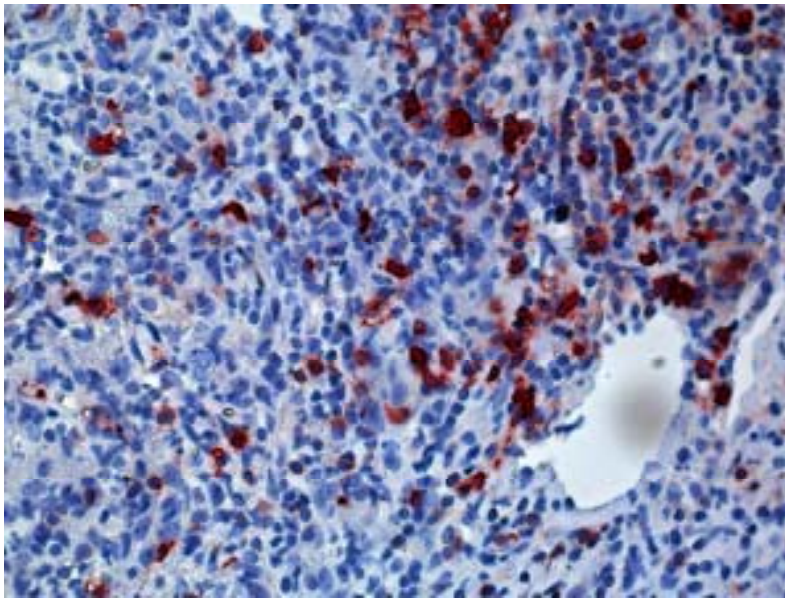
CD4 cells in tumor tissue (Histochemistry)

Cells/high power fieldc

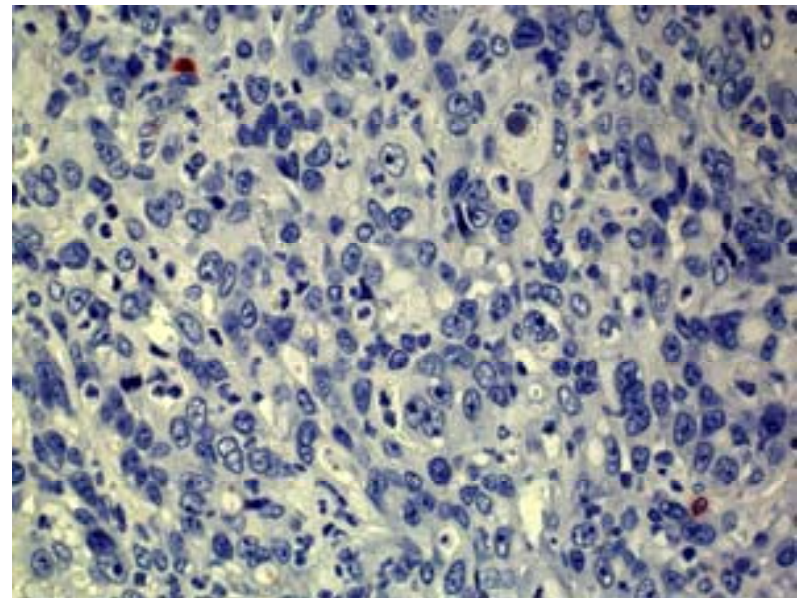


OX40 expression in gastric cancer

OX40 Hp⁻ gastric cancer (400x)



OX40 Hp⁺ gastric cancer (400x)



CD4⁺CD25⁺ cells in tumor tissue (FACS)

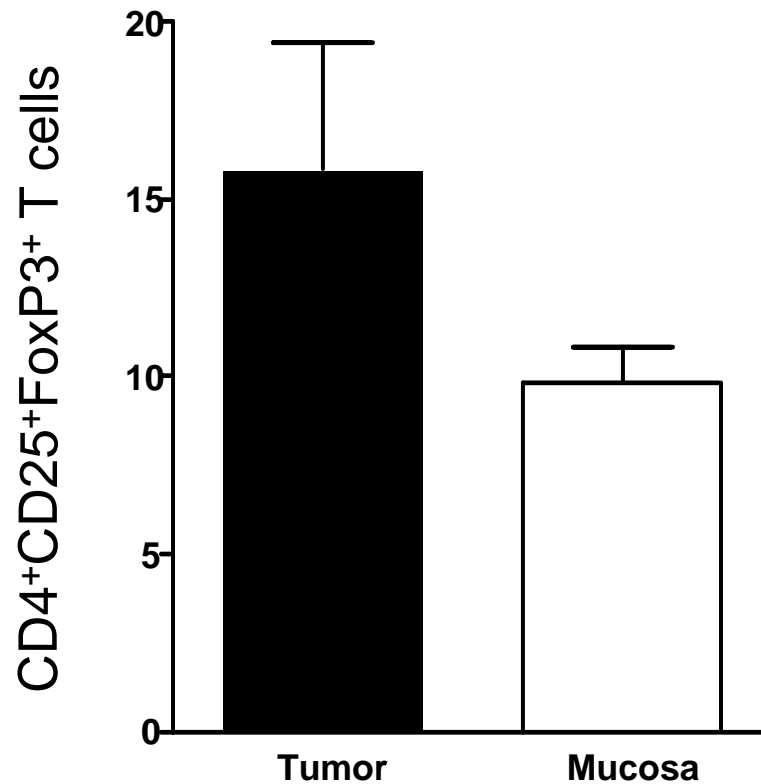
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Freshly isolated T cells from tumor and tumor free mucosa (FACS)



FoxP3 expression in gastric cancer (FoxP3 copies/ 10^6 copies 18SrRNA)

* *

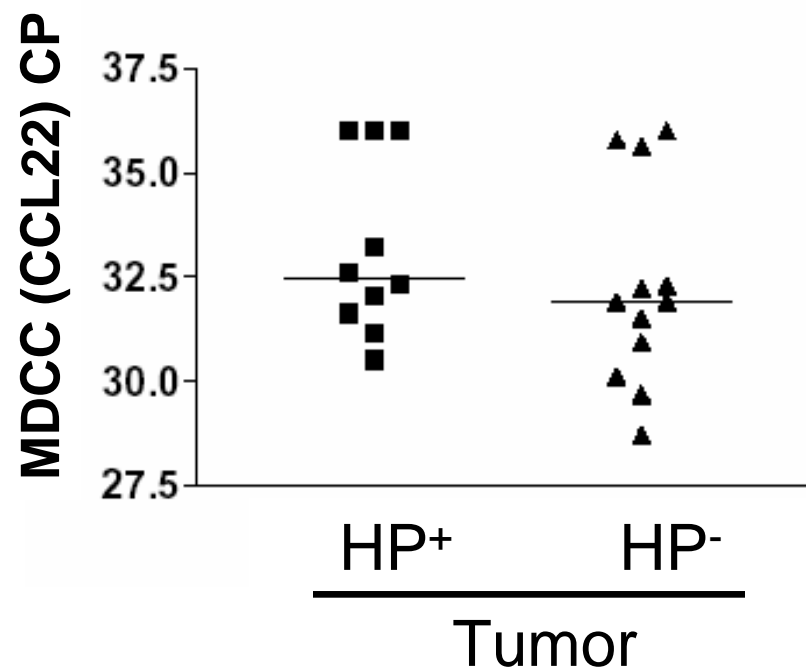
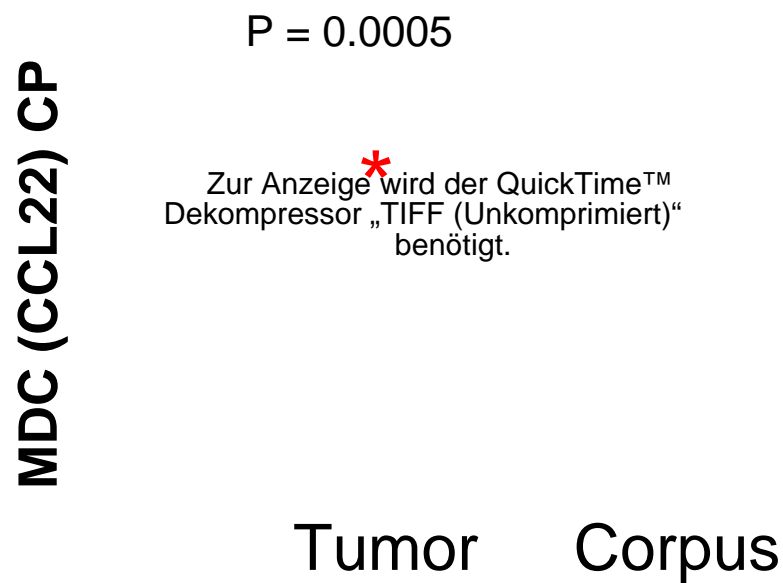
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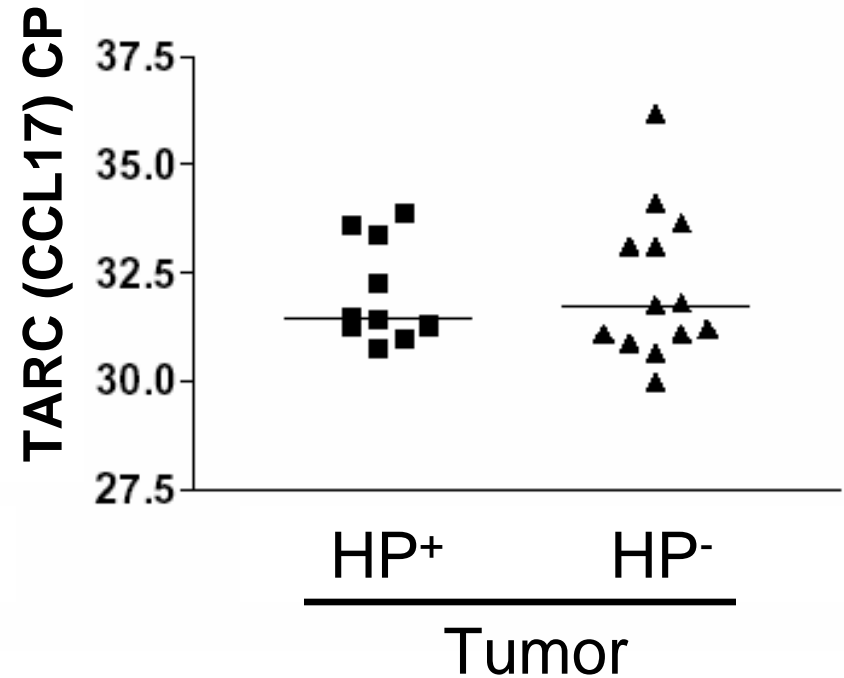
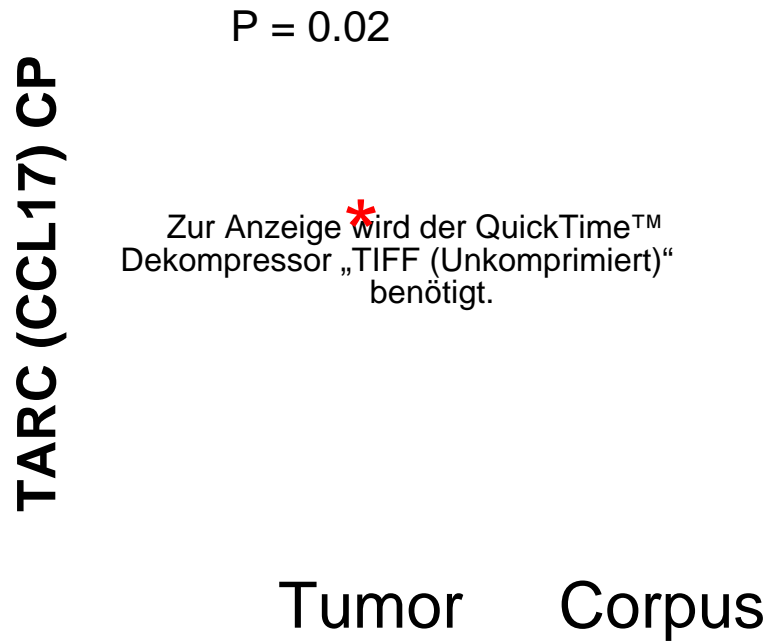
Chemotaxis of Treg

- CD4+CD25+Treg express the chemokine receptor
 - CCR4
 - CCR8
- Response to the chemokines
 - MDC (CCL22) macrophage derived chemokine
 - TARC (CCL17) thymus and activation regulated chemokine
 - vMIP1, virokinine
 - CCL1

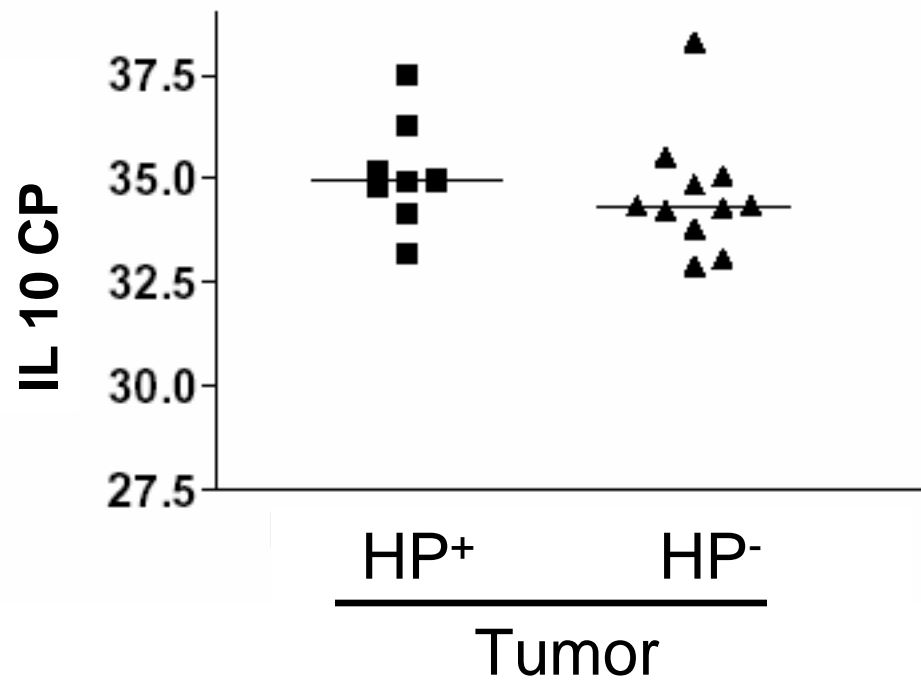
MDC (CCL22) expression in gastric cancer of HP⁺/HP⁻ patients (PCR)



TARC (CCL17) expression in gastric cancer and tumor free mucosa (PCR)



IL-10 expression in gastric cancer of HP⁺ and HP⁻ patients (PCR)



IL-17 expression in gastric cancer of HP⁺ and HP⁻ patients (PCR)

IL 17 CP

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Tumor

Corpus

Conclusion

- Tumor specific T cells can be isolated from HP⁺ and HP⁻ gastric cancer patients
- There are significantly more CD4⁺CD25⁺T cells in the tumor tissue than in tumor free mucosa
- A significantly higher FoxP3 expression and more CD4⁺CD25⁺FoxP3⁺ T cells are found in HP⁻ gastric cancer patients than in HP⁺ patients



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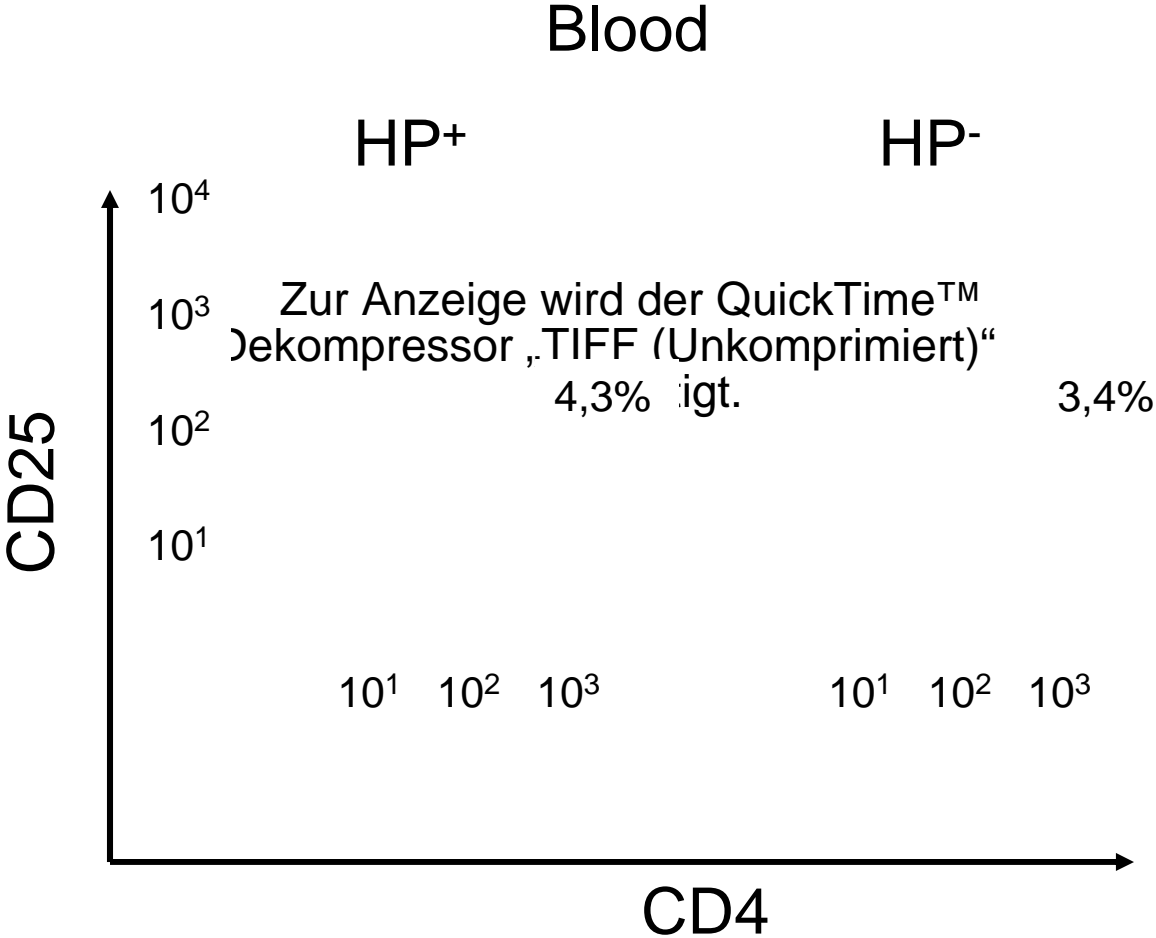
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Ox40 expression in tumor tissue

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CD4 CD25^{high} cells in the peripheral blood of gastric cancer patients



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