UniversitätsKlinikum Heidelberg

dkfz. GERMAN CANCER RESEARCH CENTER IN THE HELMHOLTZ ASSOCIATION

# Die Tumorzelle und ihre Umgebung: Immunsystem und Stroma – neue therapeutische Möglichkeiten

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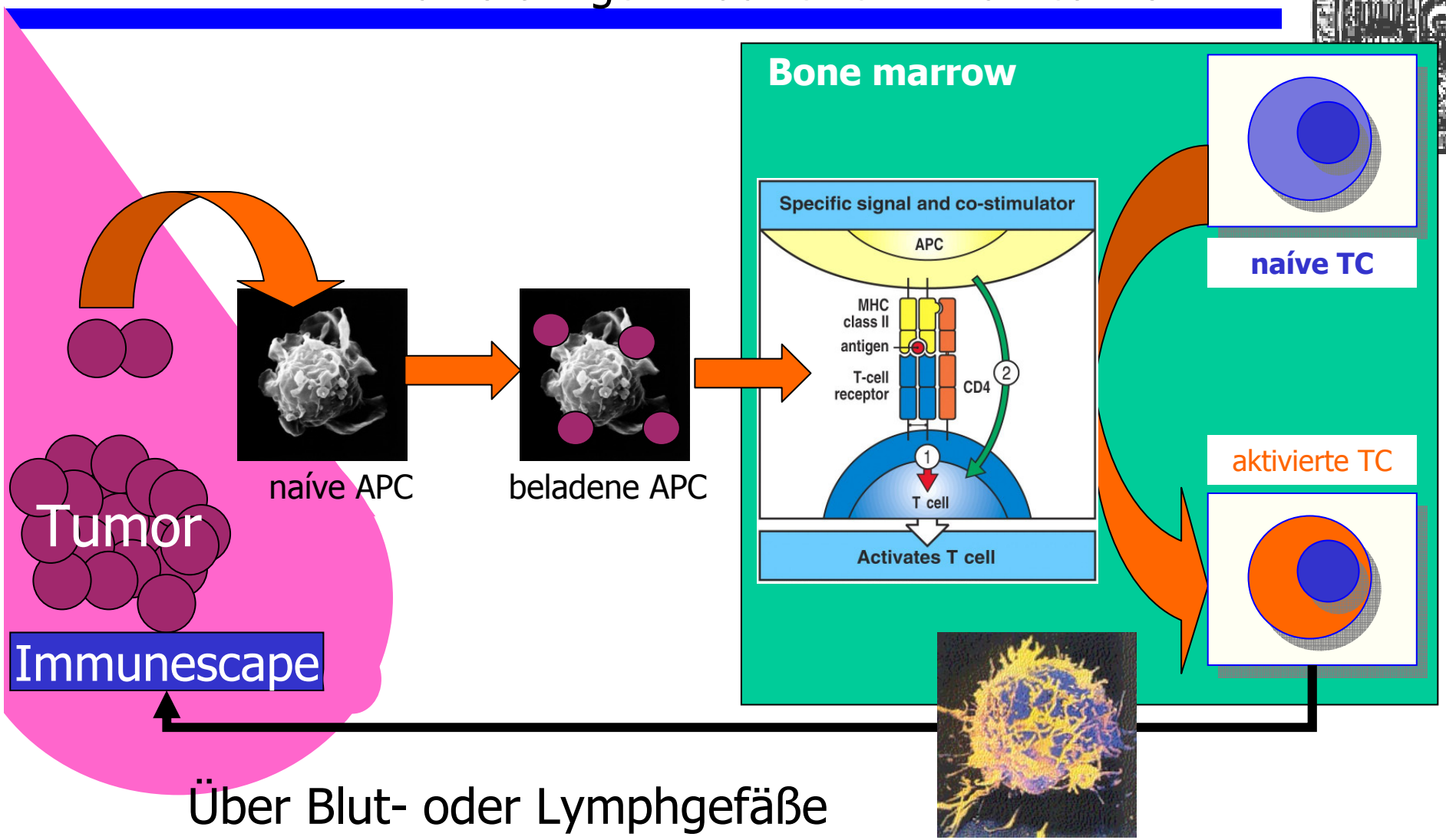
# Zelluläres Immunsystem

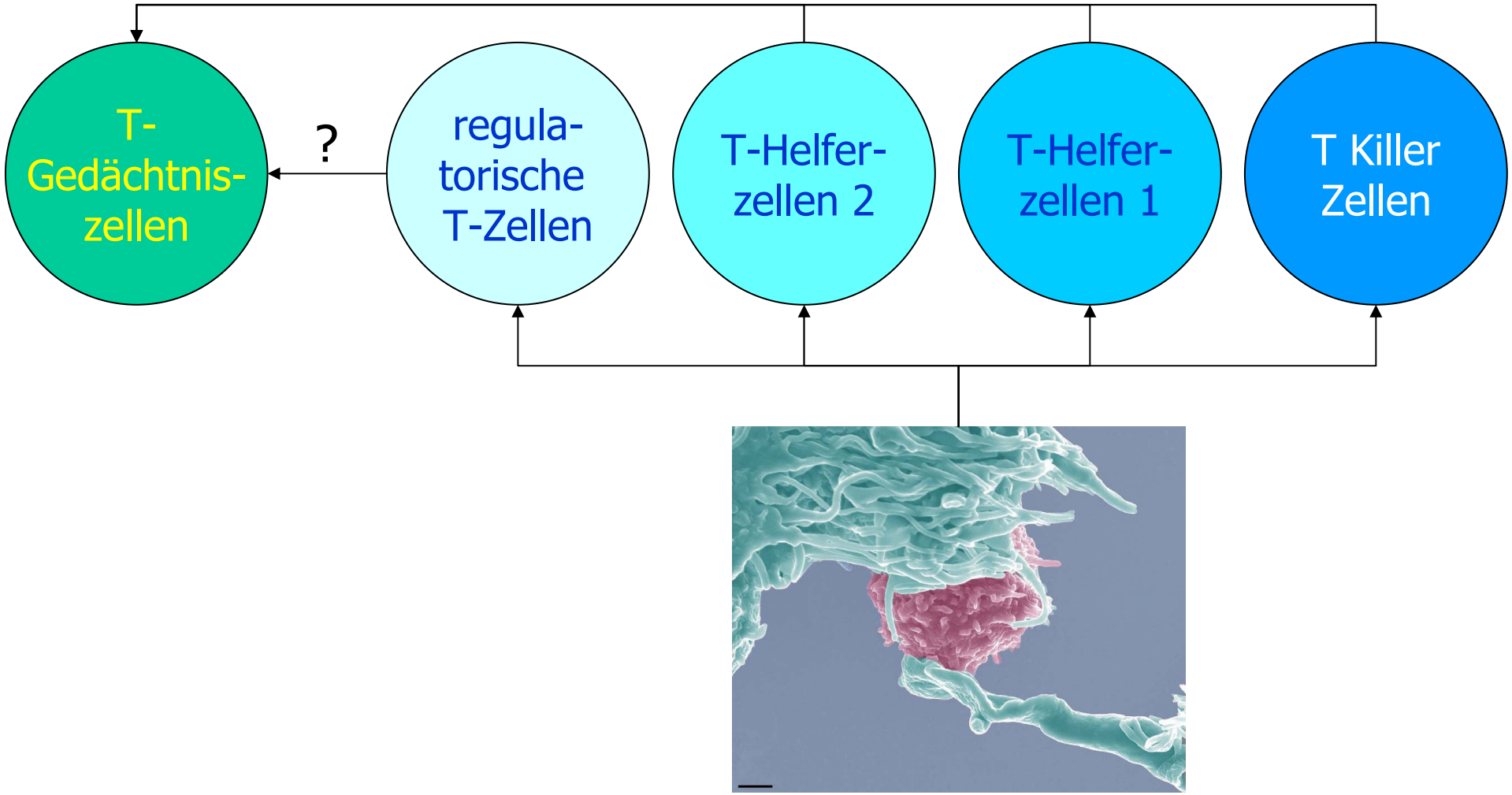
## Tumorantigen induzierte Immunreaktion




Über Blut- oder Lymphgefäße

# Zelluläres Immunsystem

## T-Zellen Subgruppen



# Werden Mammakarzinome immunologisch erkannt?

# Tumorreaktive T-Gedächtniszellen

| Bisher nachgewiesen | n tested | TAA-reactive | | tetramer positive |
|---|---|---|---|---|
| | | IFN - Elispot | Kill | |
| breast cancer | >200 | 40 % | +++ | 77% |
| pancreatic carcinoma | 60 | 100 % | +++ | n.d. |
| multiple myeloma | 90 | 42 % | +++ | 33% |
| malignant melanoma | 40 | 20 % | n.d. | n.d. |
| glioblastoma | 50 | 40 % | n.d. | n.d. |
| head and neck cancer | 70 | 30% | + | n.d. |
| colorectal carcinoma | 40 | 30% | n.d. | n.d. |
| | 540 | | | |

*Cancer Res., 2006, Ann. of Surgery, in press, Blood, 2005, 105:2132-4 , Cancer Res., 2005, 65:10079-87, J. Clin. Oncol., 2004, 27:1141-9, Cancer Res., 2004, 64:8057-61, Nat. Med., 2001, 7:452-8*

# Immunologisch aktive MaCa-Genotypen

„Precise definitions of the specific subtypes of immune cells in the tumor can be accomplished from microarray data. ... The LCK metagene actually separates the ER-negative tumors into better or worse prognosis!"

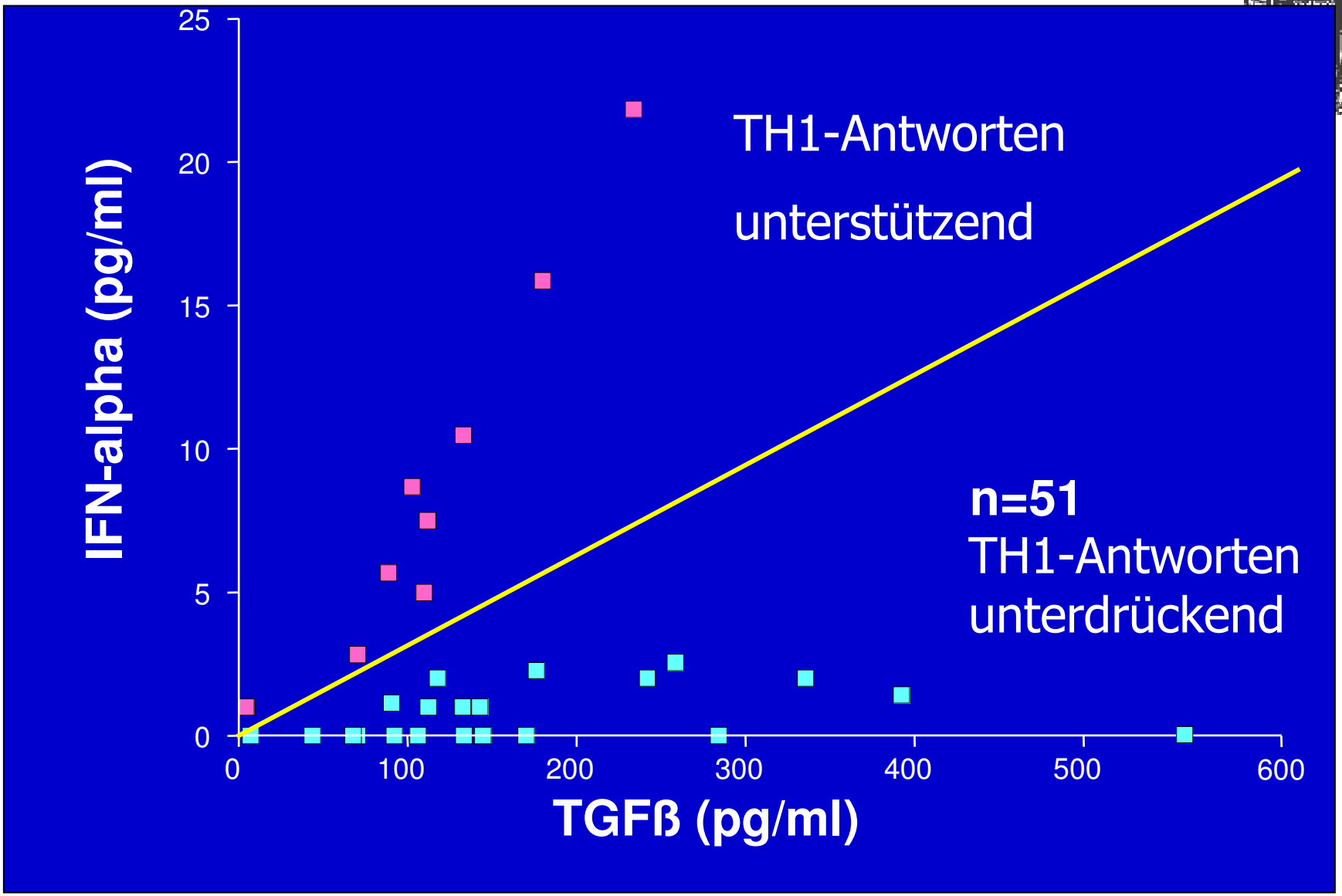
Rody, Holtrich, Kaufmann et al; Breast Canc Res, 2009

„Thus, we could show in three cohorts of untreated, node negative BC patients that the humoral immune system plays a pivotal role in metastasis-free survival of carcinomas of the breast."

Schmidt, Böhm, Gehrmann et al; Canc Res, 2008

# Aktivierung oder Suppression von TH1-Antworten

## Expression von TGF-ß1 and IFN-α

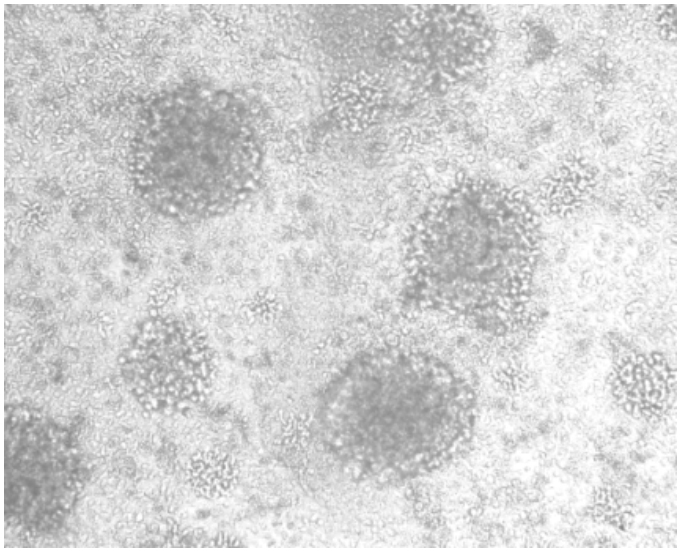


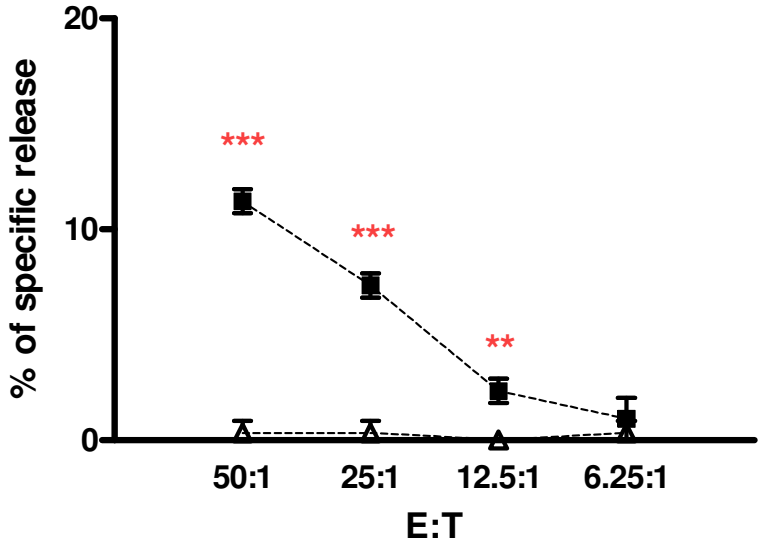

Schütz, Domschke, Cancer Research 2009

**Warum sind Immunantworten bei einigen Patientinnen scheinbar unterdrückt?**

# Fox P3$^{+}$ CD 25$^{+}$ Regulatorische T-Zellen

## Hemmung der Effektorzellen

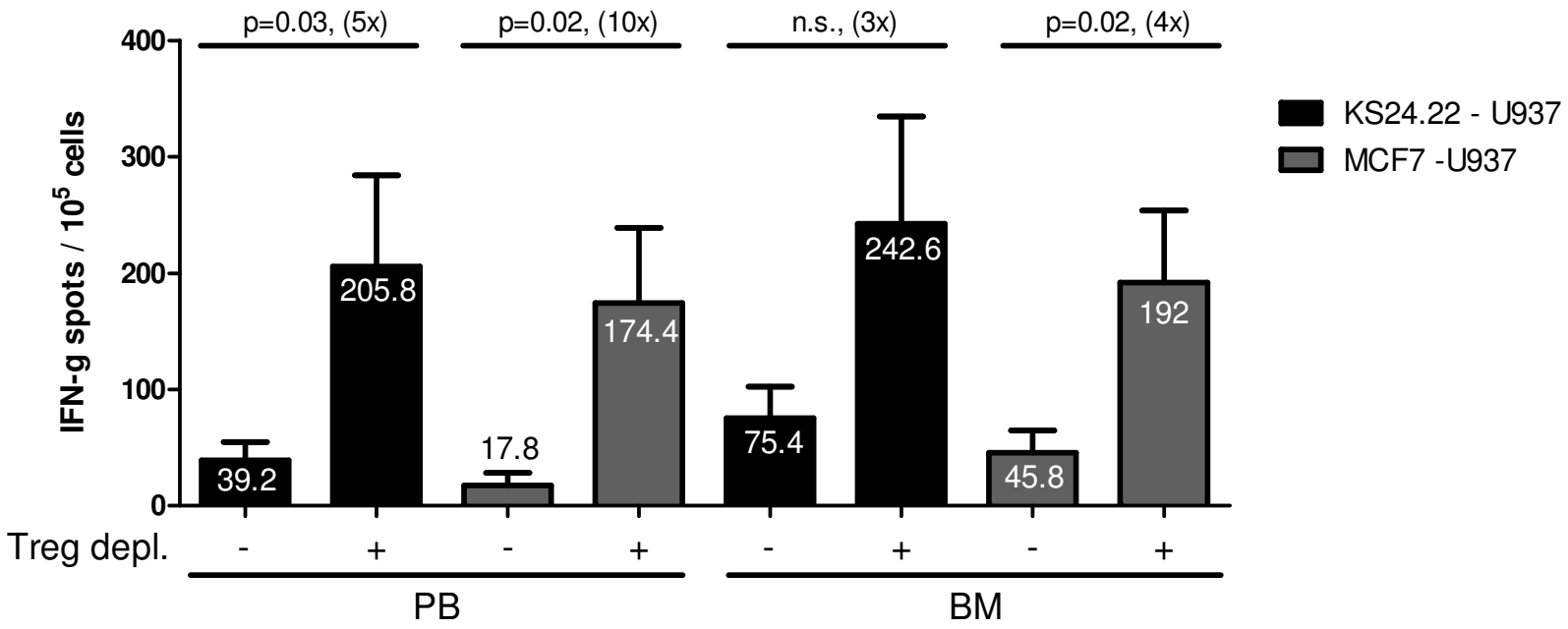





Schütz, Gi, submitted

# T reg inhibieren tumorspezifische TC-Antworten

## in PB und BM - Tumorzellinien

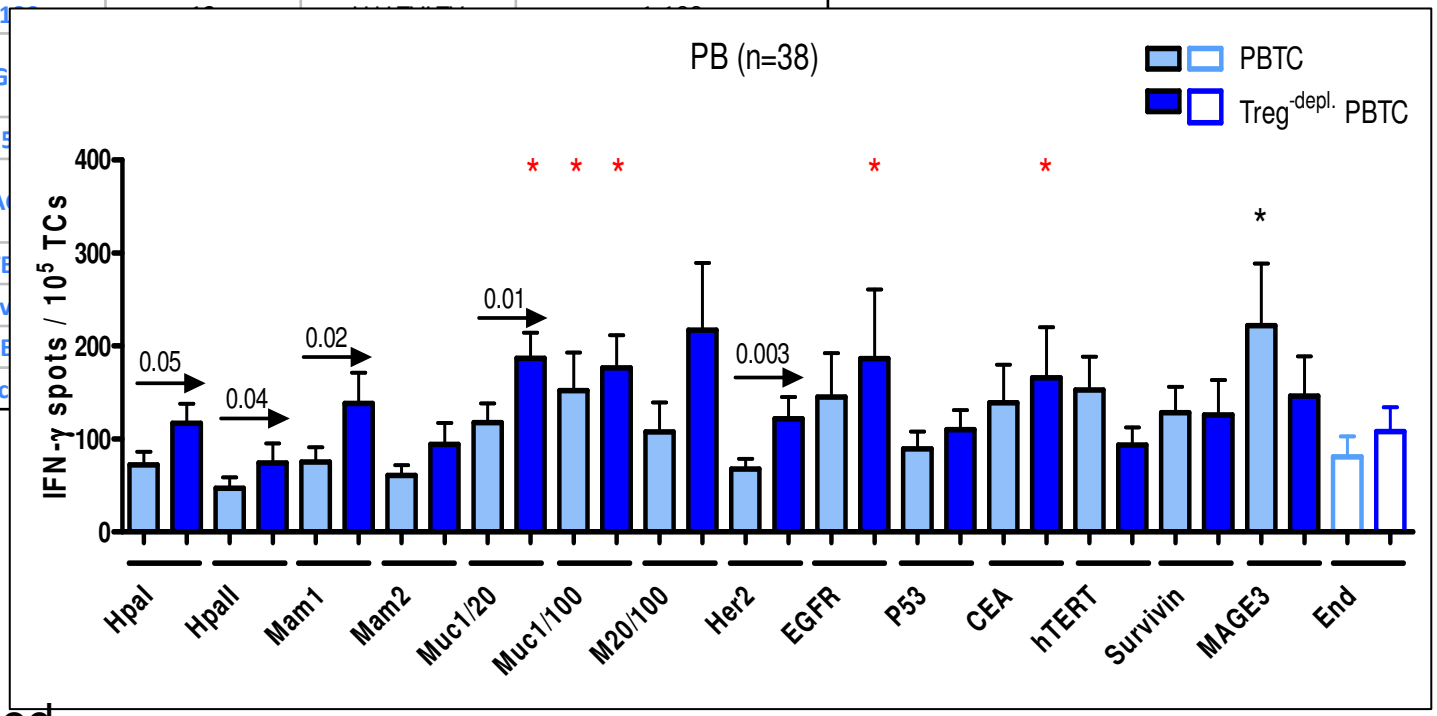



Schütz, Gi, submitted

# T reg inhibieren tumorspezifische TC-Antworten

## in PB und BM (Polypeptide)

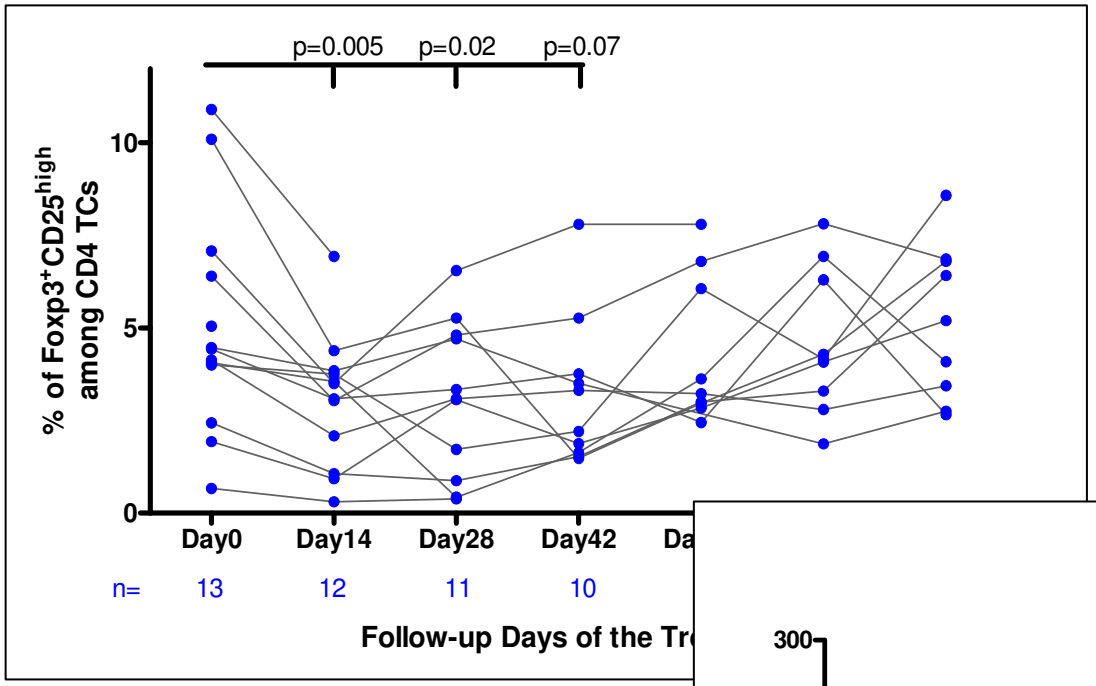
| TAA and control | abbreviation | start position of nonamer in amino acid sequence | HLA-A*0201 – restricted-peptide sequence | Designed polypeptide position in amino acid sequence |
|---|---|---|---|---|
| Heparanase | HpaI | 16 | LLLGPLGPL | 1-50 |
| Heparanase | HpaII | 183 | DLIFGLNAL | 163-212 |
| Mammaglobin A | Mam1 | 4 | LMVLMLAAL | 4-56 |
| Mammaglobin A | Mam2 | 66<br>83 | FLNQTDETL<br>LIYDSSLCDL | 41-92 |
| Her2/neu | Her2/neu | 369 | KIFGSLAFL | 351-384 |
| Mucin-1 tandem repeat | M20 | 9 | STAPPAHGV | 137-157 |
| Mucin-1 signal sequence | M1 | | | |
| Epidermal growth factor receptor | EG | | | |
| p53 | p5 | | | |
| Melanoma asscociated antigen-3 | MA | | | |
| Human telomerase | hTE | | | |
| Survivin | Surv | | | |
| Carcinoembryonic Antigen | CE | | | |
| Human immunoglobulin | IgG / c | | | |

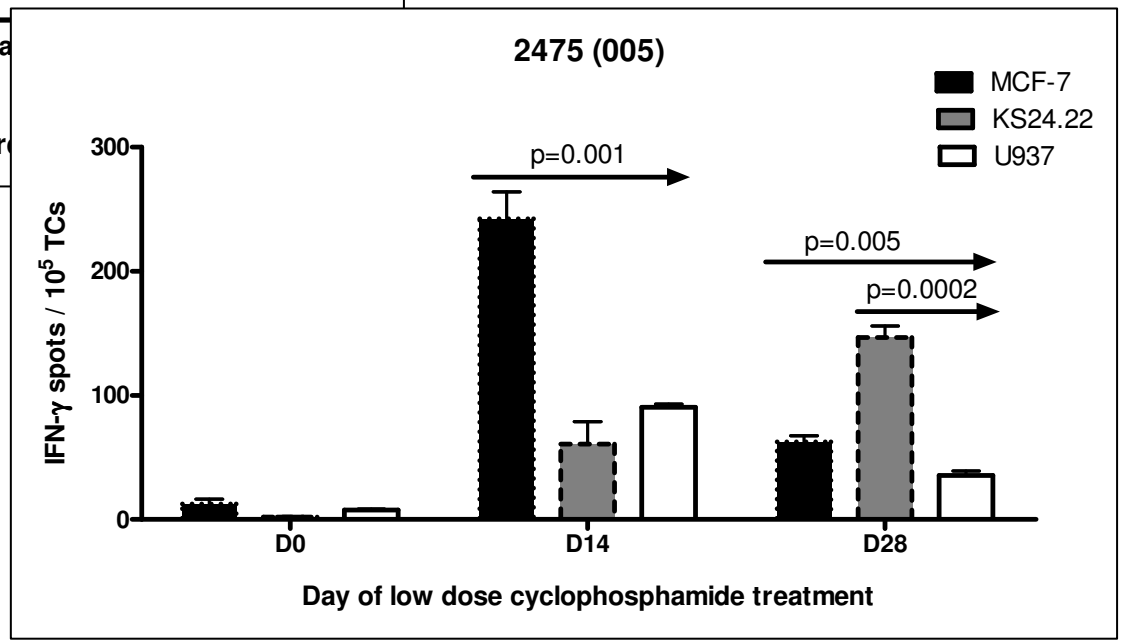



Schütz, Gi, submitted

# Klinische Bedeutung von T reg Inhibition

## Metronomisches Cyclophosphamid in MBC



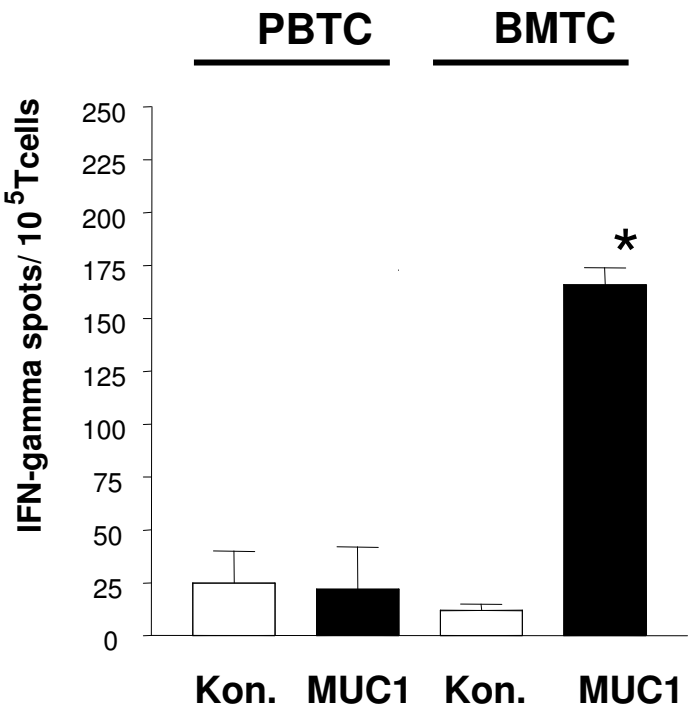

Schütz, Gi, submitted

**Haben tumorantigen-reaktive T-Gedächtniszellen des KM eine tumorlytische Kapazität?**

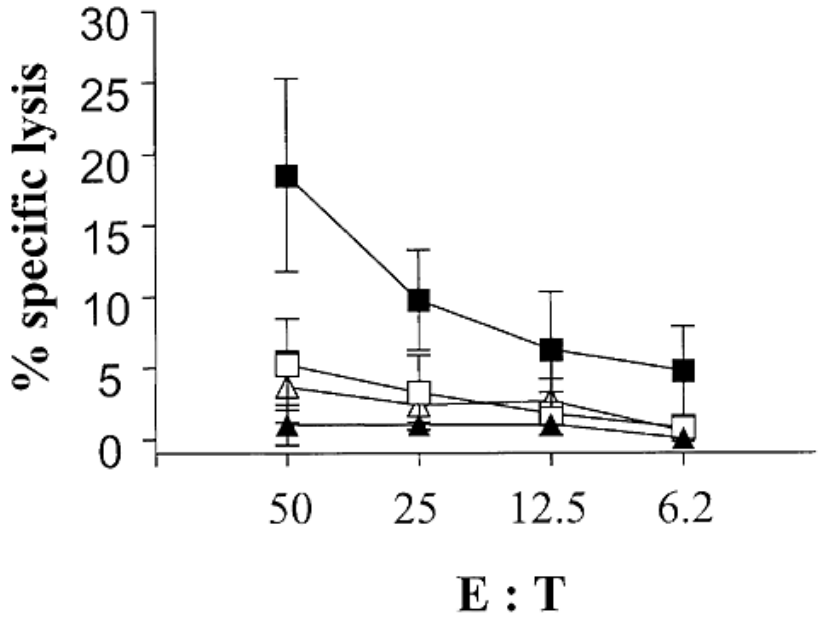
# Tumorantigen-reaktive TMC des KM von BC

## Funktionelle Kapazität

**IFN-γ Sekretion**




**Zytotoxizität**

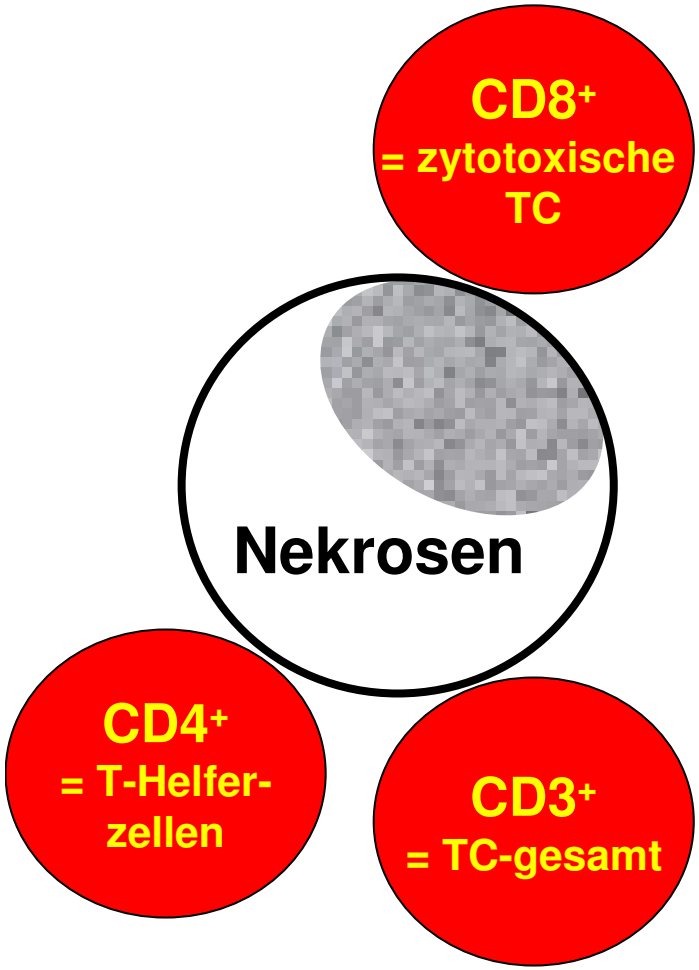


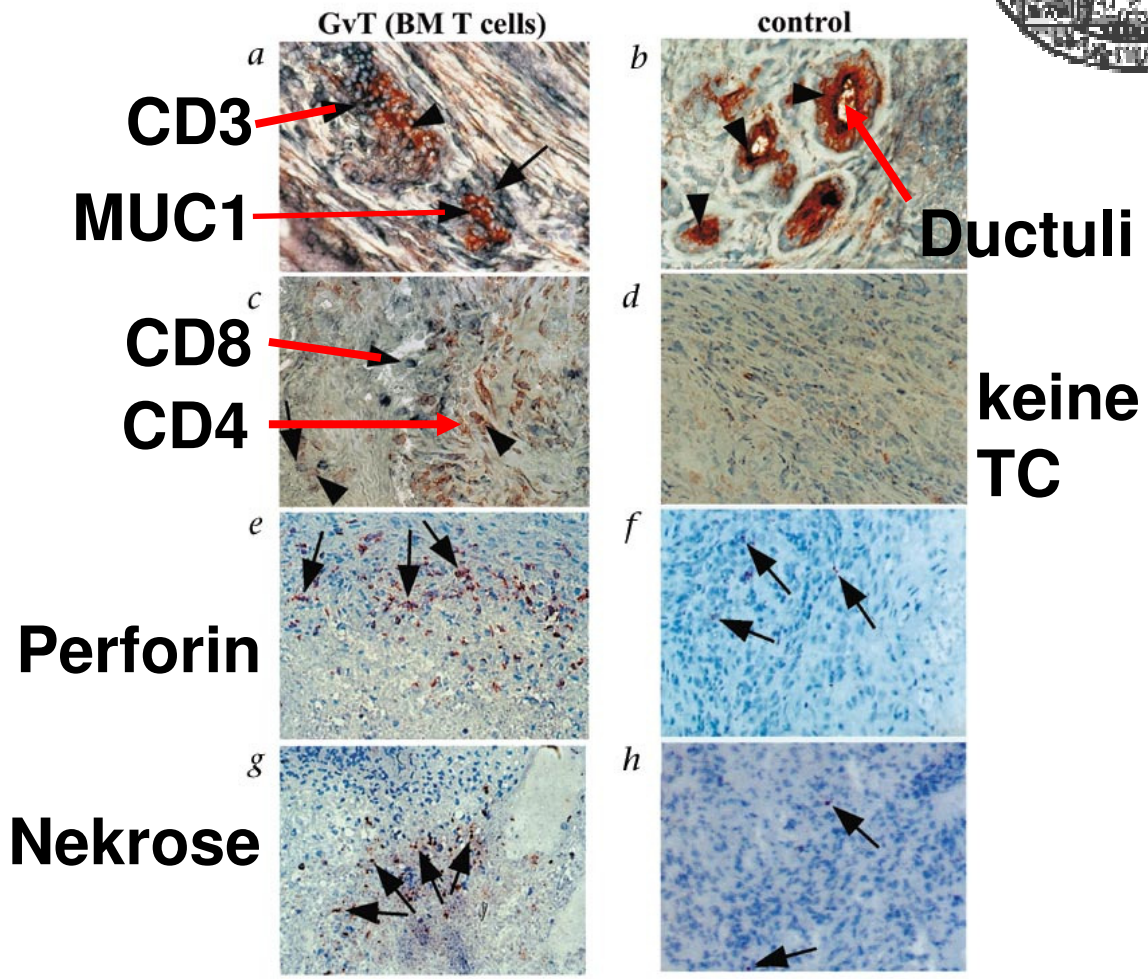

*J. Clin. Invest. , 2004, 114:67-76.*

*Nat. Med., 2001, 7:452-8*

# Reaktivierte T-Gedächtniszellen

## Histologische Tumorabstossung



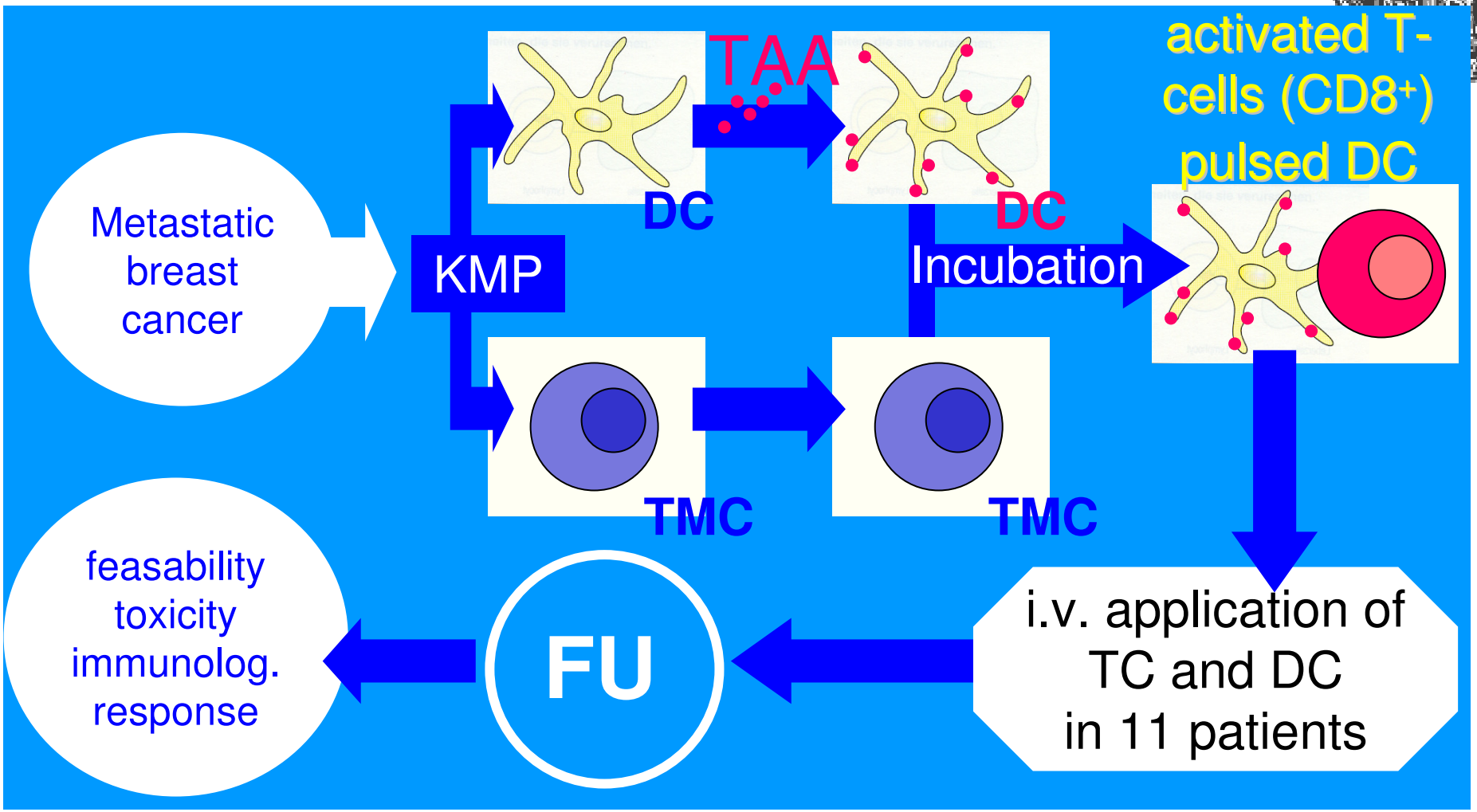




*Feuerer et al, Nature Medicine, 2001, 7:452-8*

**Können tumor-reaktive T-Gedächtniszellen des KM therapeutisch beim Menschen eingesetzt werden?**

# Zelluläre Immuntherapie mit TC & DC

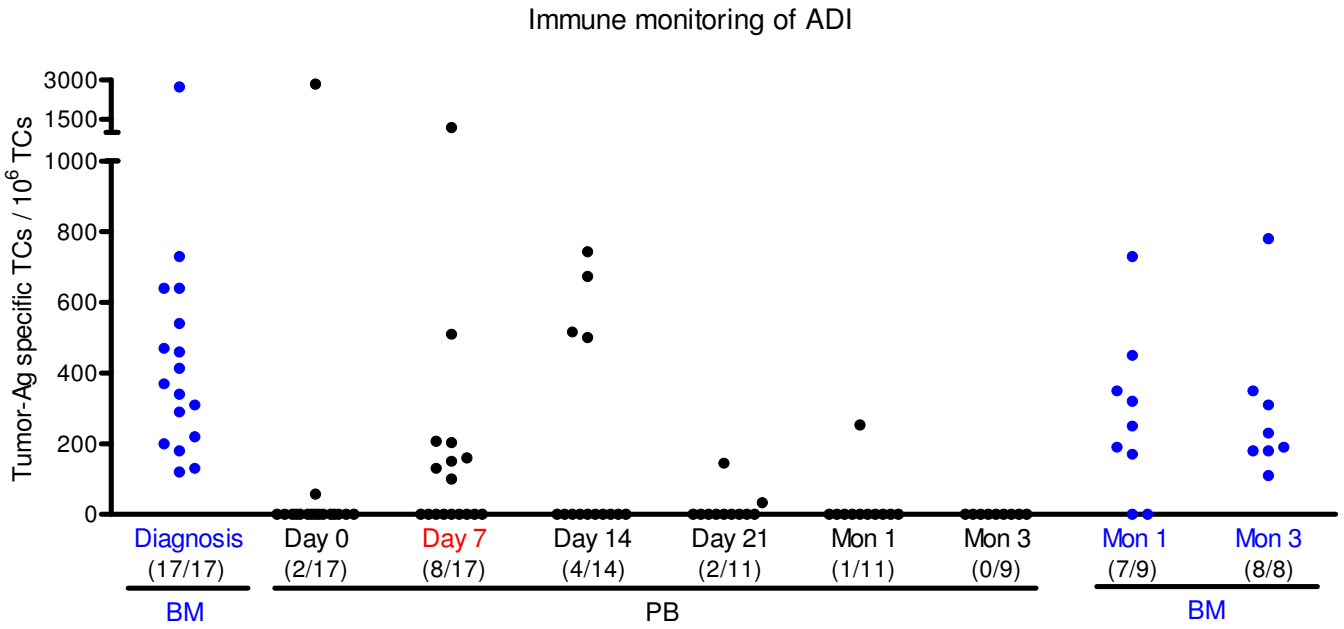
## Studiendesign Phase 1




Schütz et al., Immunotherapie 2008

# De-novo Detektion tumor-reaktiver T-Zellen

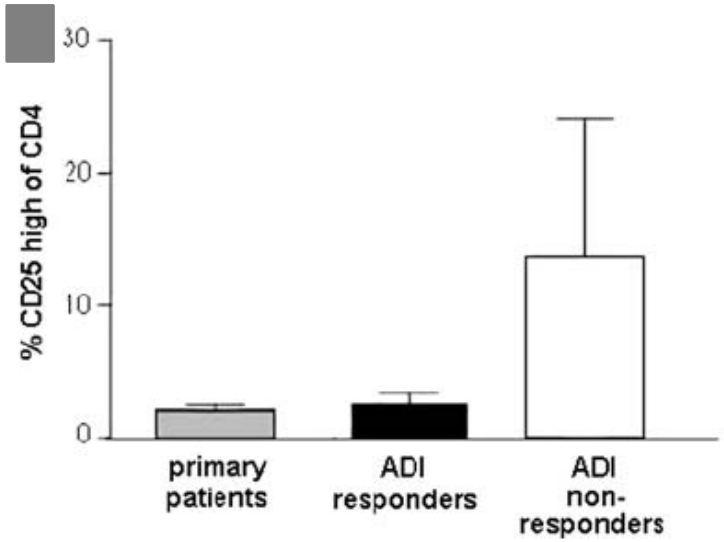
## 7 Tage nach ADI bei 50% der Patientinnen




Schütz et al., Immunotherapy 2008

# Zelluläre Immuntherapie
## Phase 1 – T regs

Treg presence (% CD25$^{+}$)

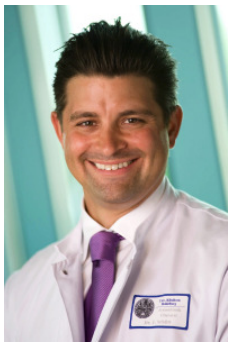


# Zusammenfassung

## Immunologische Interaktionen

- MaCa-Zellen werden immunologisch erkannt
- Tregs unterdrücken Immunreaktionen
- Depletion von Tregs ist möglich
- CD45R0 CD8+ T-Zellen können therapeutisch genutzt werden

DEUTSCHES KREBSFORSCHUNGSZENTRUM IN DER HELMHOLTZ-GEMEINSCHAFT



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# Vielen Dank

# für

# Ihre Aufmerksamkeit!

Ihr Florian Schütz