

# Multiples Myelom

## Forschung

PD Dr. med. Markus Munder

III. Medizinische Klinik (Hämatologie, Internistische Onkologie & Pneumologie)

Universitätsmedizin Mainz

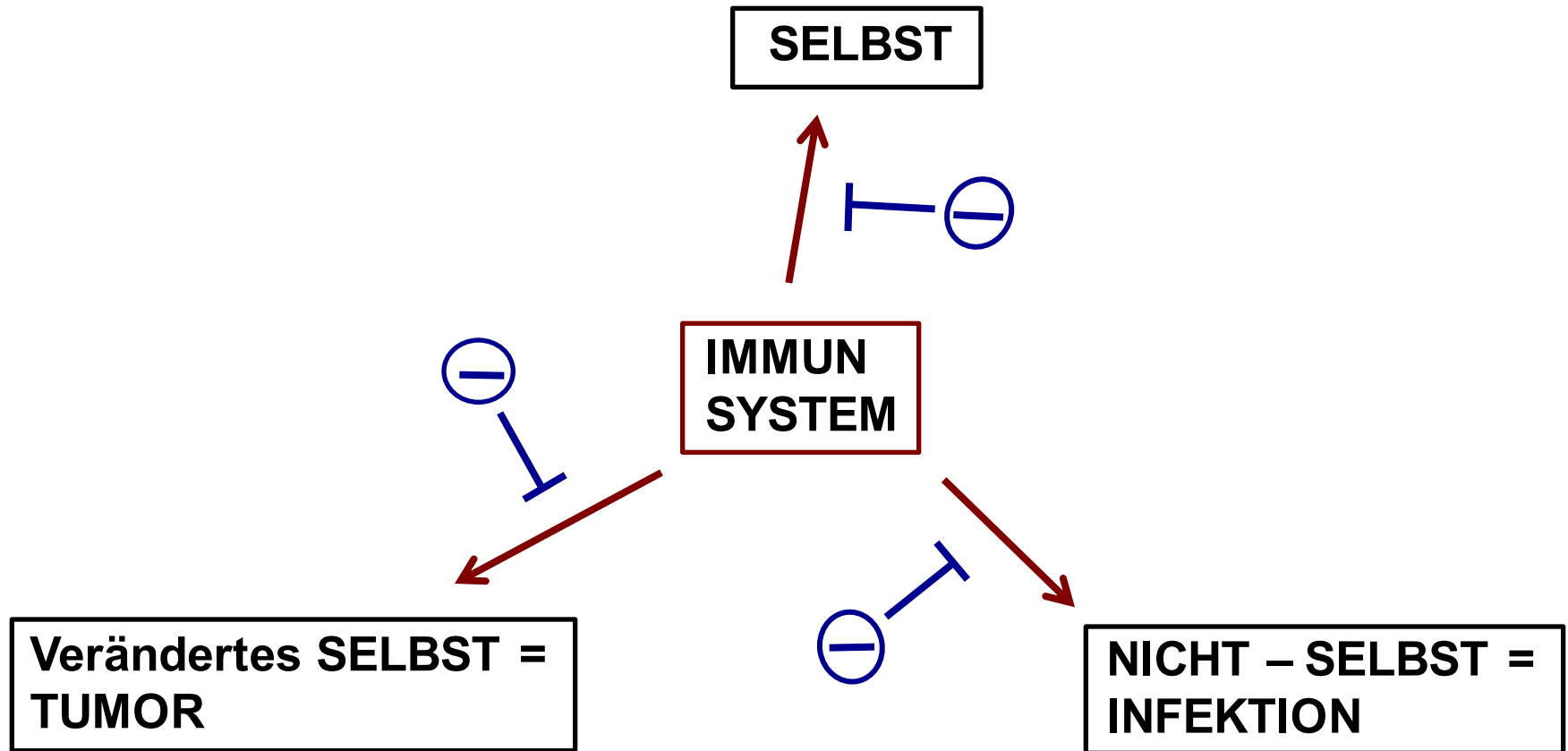
LHRM / Rüsselsheim 28.4.2016

## AGENDA

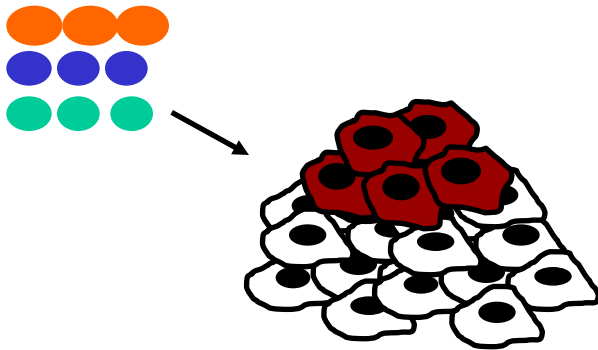
- Forschung global: Immuntherapie
- Forschung lokal: Arginin !!!
  - Immuntherapie
  - Arginin-Transporter von Myelomzellen: neue therapeutische Zielstrukturen ?
  - Metabolische Therapie: Induktion von Zellstress

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- **Forschung lokal: Arginin !!!**
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# Immunüberwachung



**Paul Ehrlich**  
(1854-1915)

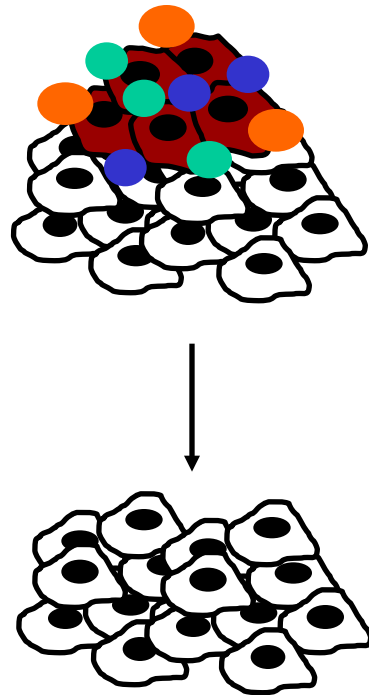


**Frank Macfarlane  
Burnet**  
(1899-1985)



**Lewis Thomas**  
(1913-1993)

# Immunüberwachung



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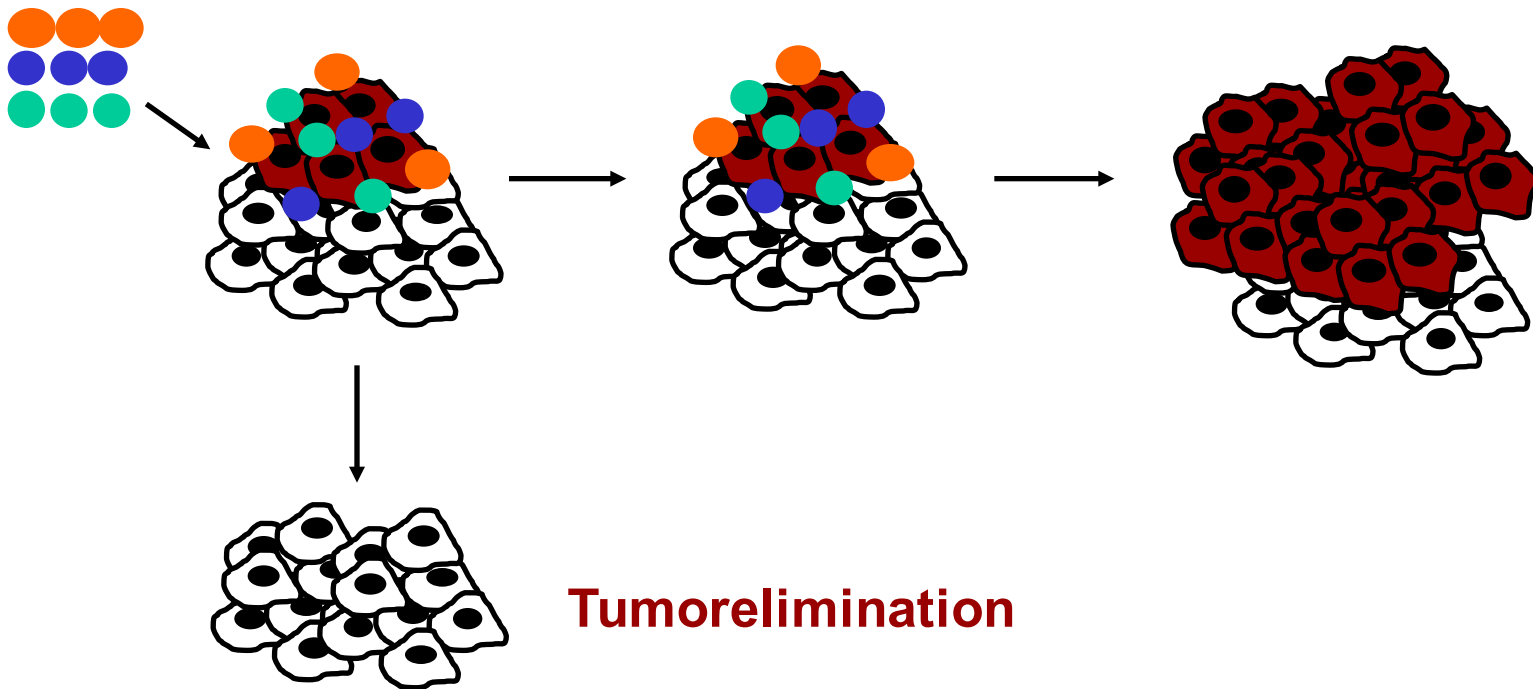


**Lewis Thomas**  
(1913-1993)

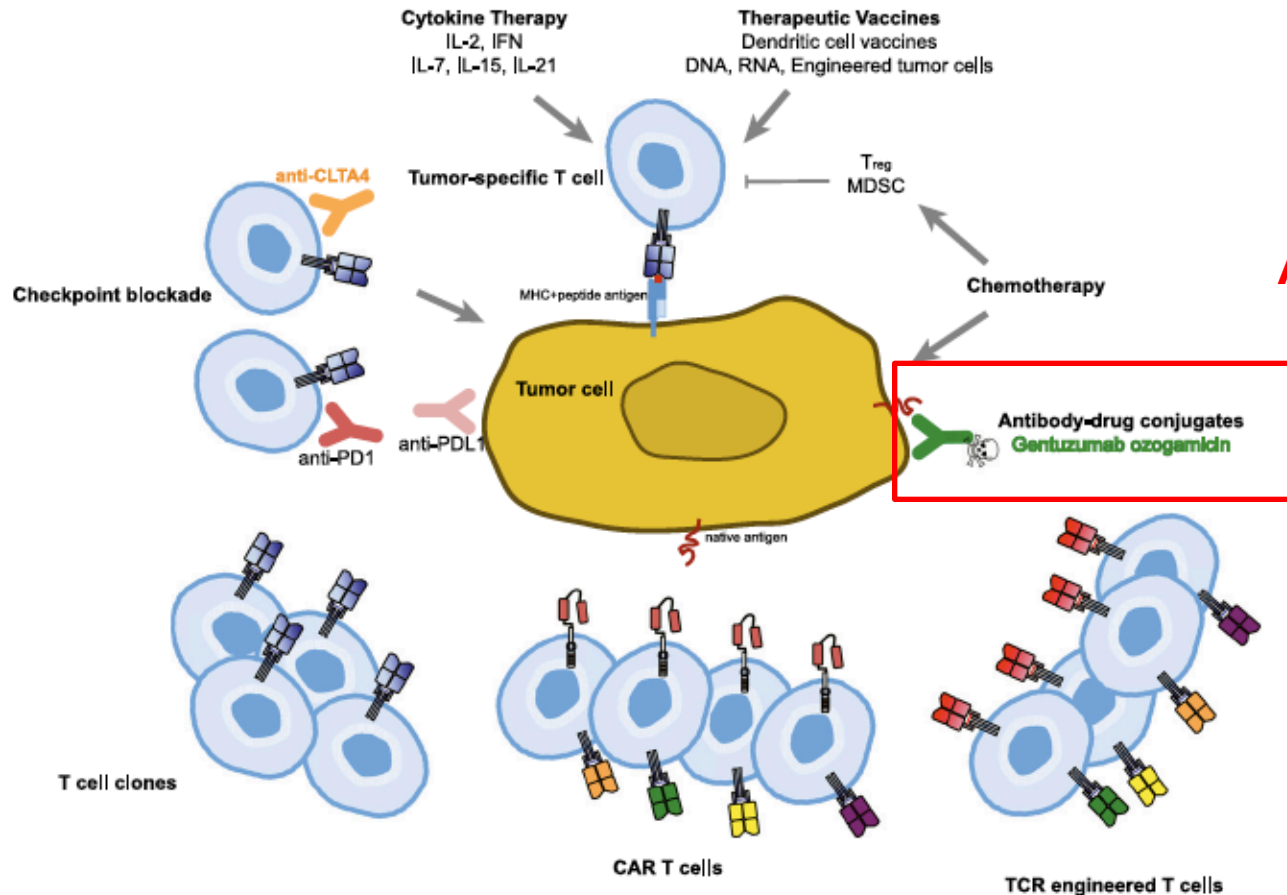
**Immunüberwachung**

**Gleichgewicht**

**Tumorwachstum**

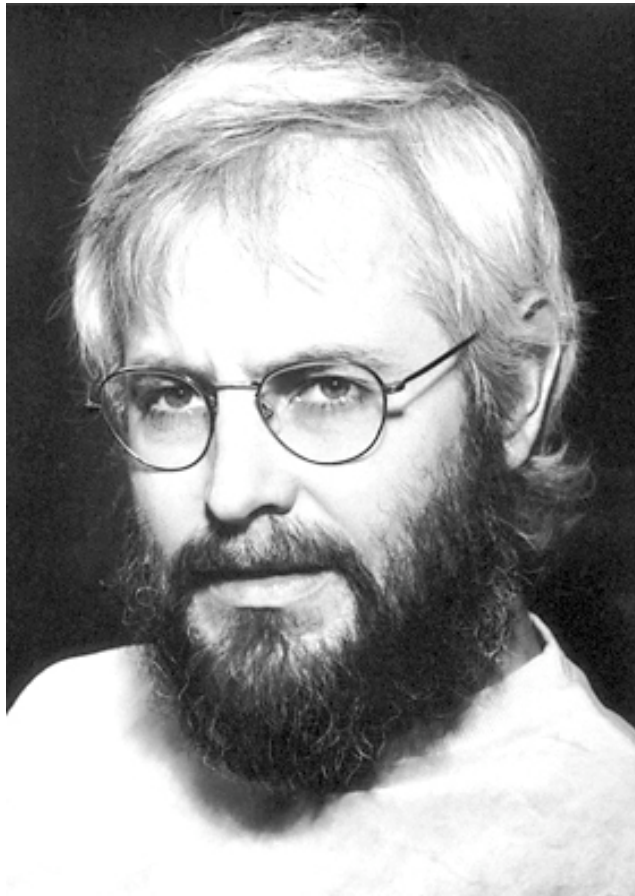


# Verstärkung der Immunantwort gegen Krebszellen





## Georges Köhler



(1946-1995)

**1984 Medizin-Nobelpreis**

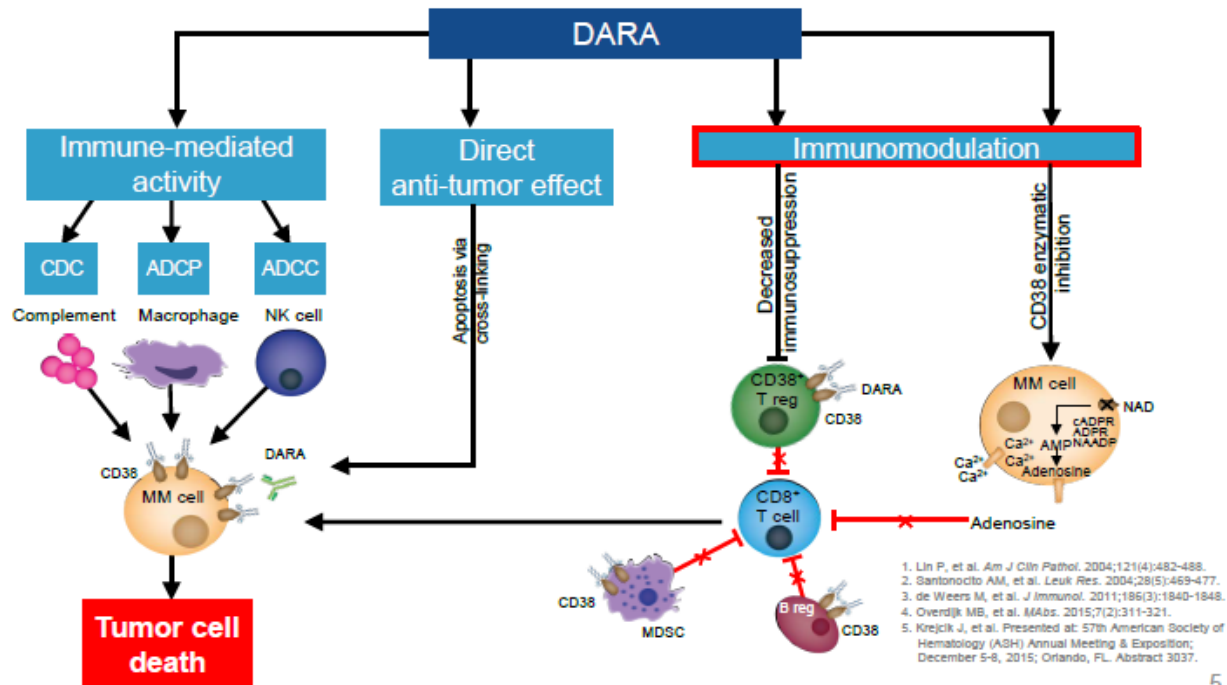
## Verstärkung der Immunantwort gegen Krebszellen

**Daratumumab: anti-CD38**

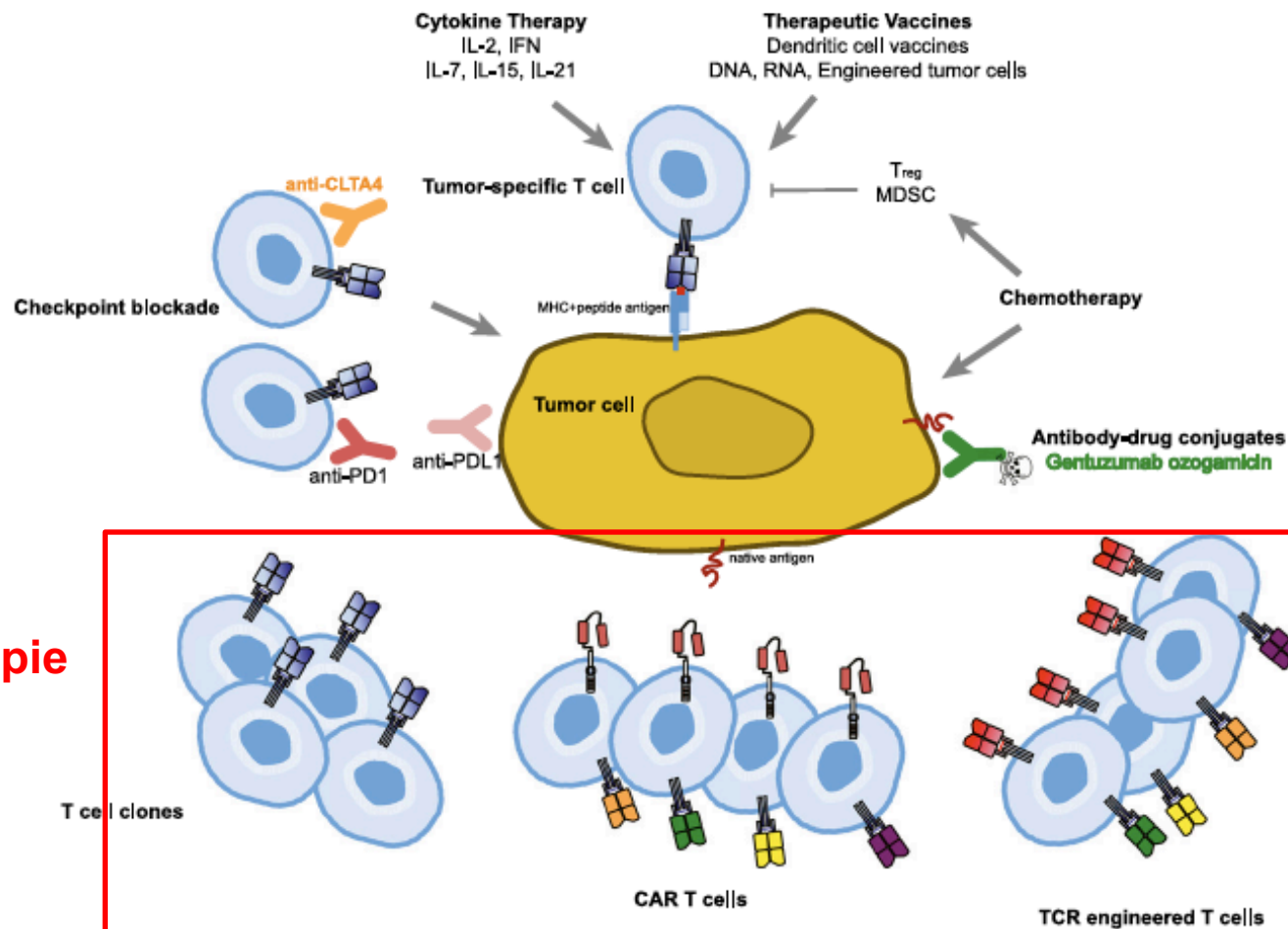
**Elotuzumab: anti-SLAMF7**

# Verstärkung der Immunantwort gegen Krebszellen: Antikörper

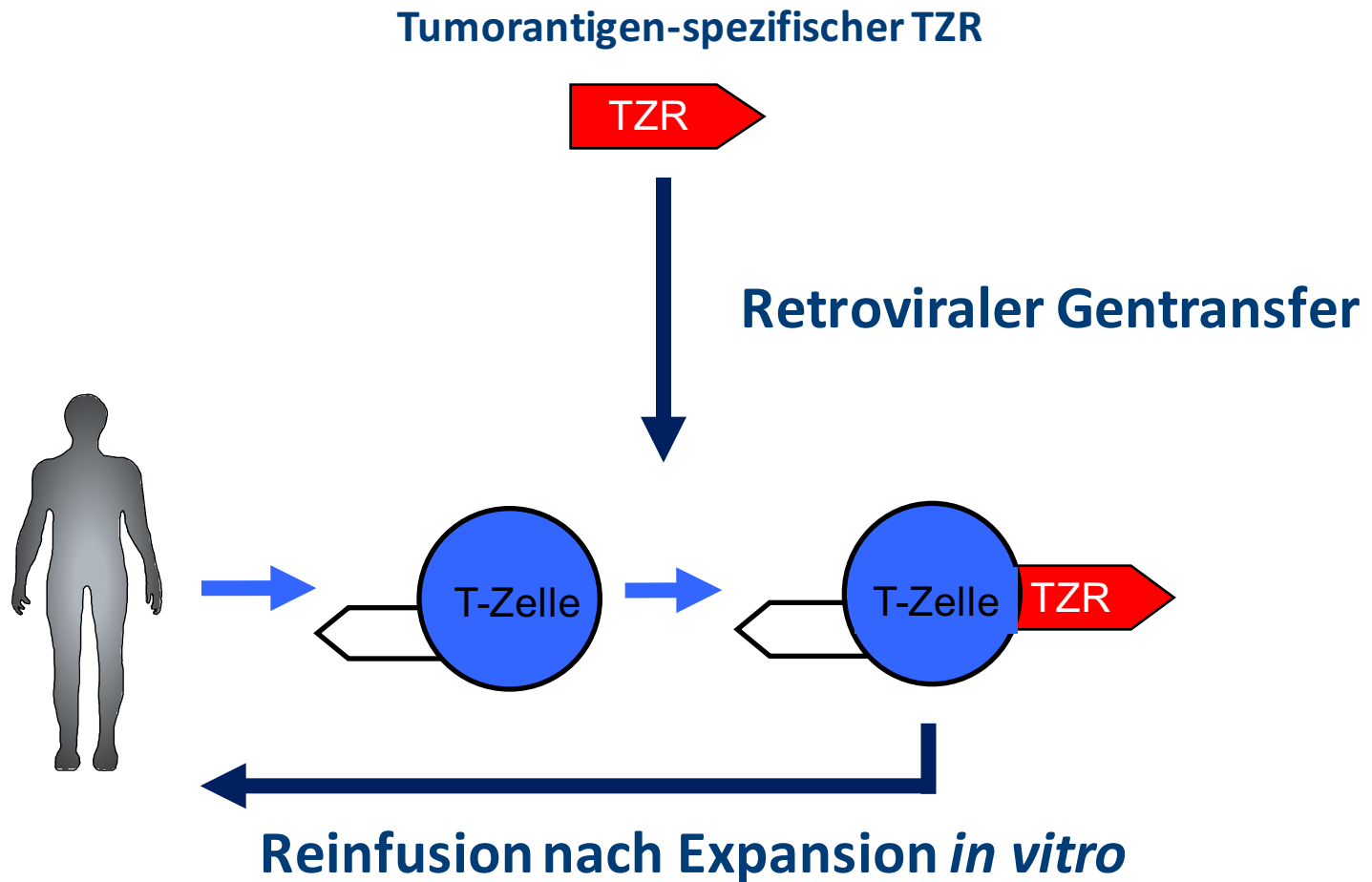
## Daratumumab: Vielfältige Wirkmechanismen



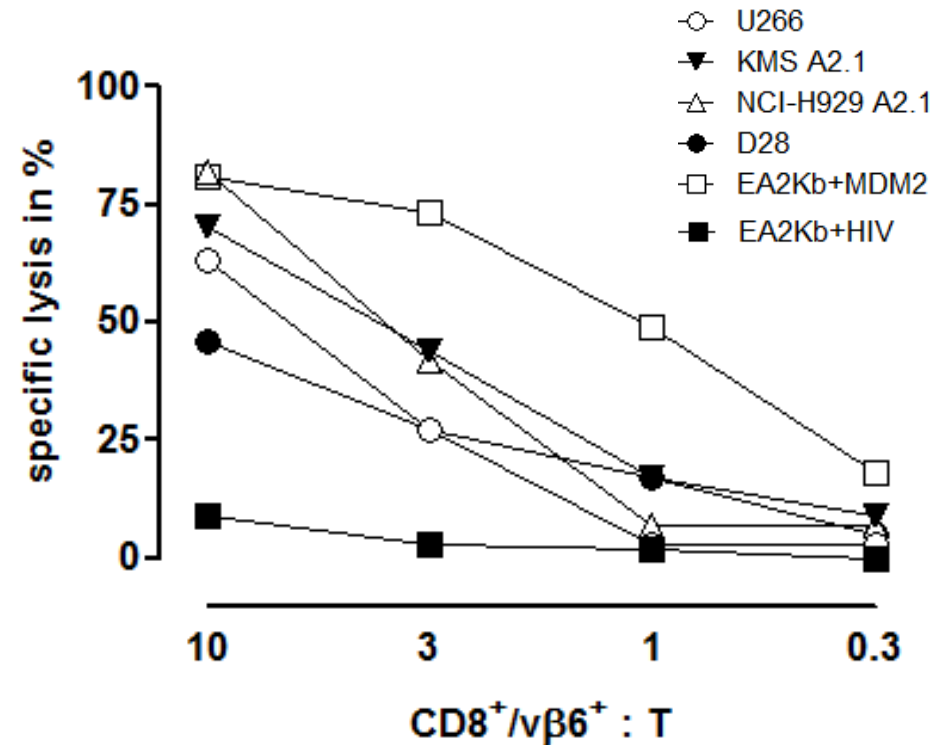
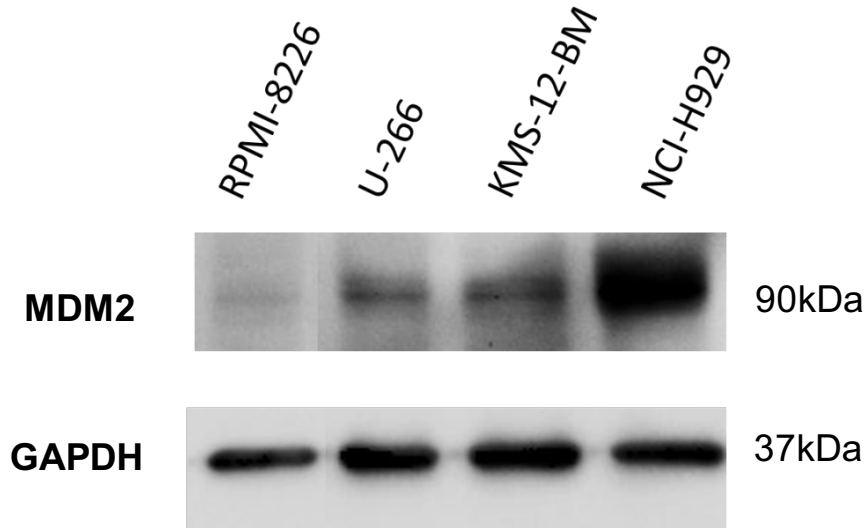
# Verstärkung der Immunantwort gegen Krebszellen



# Adoptive Immuntherapie



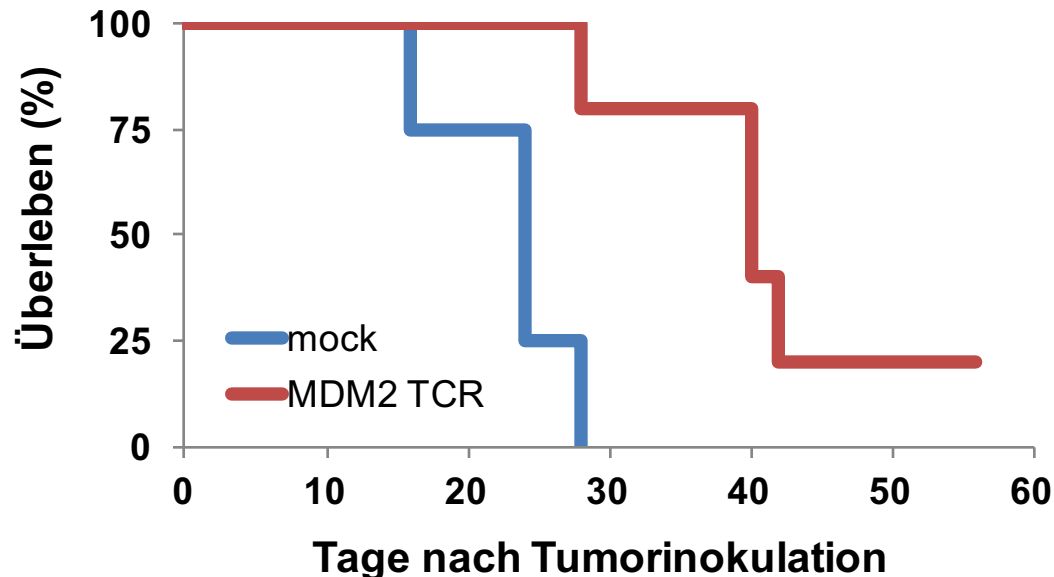
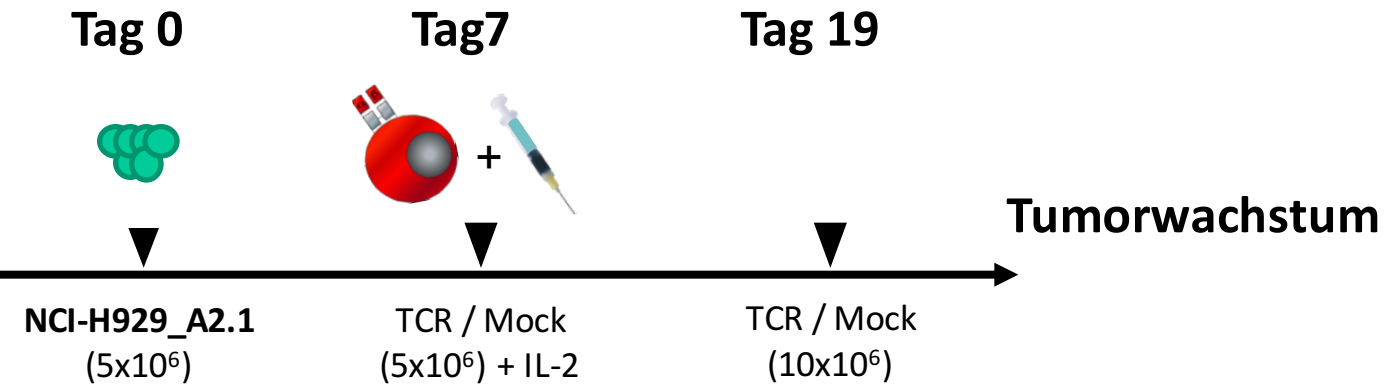
# Myelomzell-Erkennung und Abtötung: MDM2 als Zielstruktur Zellkultur



# Myelomzell-Erkennung und Abtötung: MDM2 als Zielstruktur Tiermodell



NSG



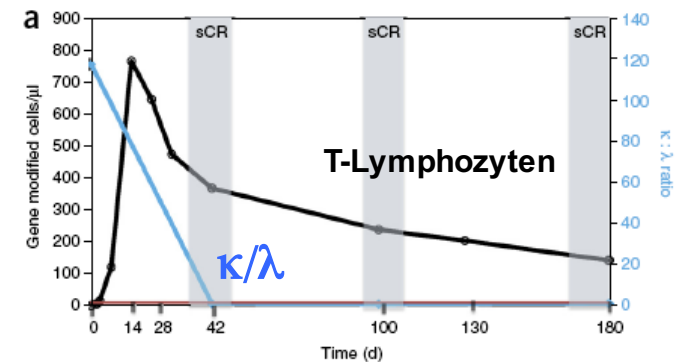
# Zelluläre Therapie beim Multiplen Myelom

## NY-ESO-1-specific TCR-engineered T cells mediate sustained antigen-specific antitumor effects in myeloma

Aaron P Rapoport<sup>1,8</sup>, Edward A Stadtmauer<sup>2,8</sup>, Gwendolyn K Binder-Scholl<sup>3,8</sup>, Olga Goloubeva<sup>1,4</sup>, Dan T Vogl<sup>2</sup>, Simon F Lacey<sup>2,5</sup>, Ashraf Z Badros<sup>1</sup>, Alfred Garfall<sup>2</sup>, Brendan Weiss<sup>2</sup>, Jeffrey Finklestein<sup>4,5</sup>, Irina Kulikovskaya<sup>2,5</sup>, Sanjoy K Sinha<sup>6</sup>, Shari Kronsberg<sup>1,4</sup>, Minnal Gupta<sup>2,5</sup>, Sarah Bond<sup>7</sup>, Luca Melchiorri<sup>3</sup>, Joanna E Brewer<sup>3</sup>, Alan D Bennett<sup>3</sup>, Andrew B Gerry<sup>3</sup>, Nicholas J Pumphrey<sup>3</sup>, Daniel Williams<sup>3</sup>, Helen K Tayton-Martin<sup>3</sup>, Lilliam Ribeiro<sup>3</sup>, Tom Holdich<sup>3</sup>, Saul Yanovich<sup>1</sup>, Nancy Hardy<sup>1</sup>, Jean Yared<sup>1</sup>, Naseem Kerr<sup>5</sup>, Sunita Philip<sup>1</sup>, Sandra Westphal<sup>1</sup>, Don L Siegel<sup>2,5</sup>, Bruce L Levine<sup>2,5</sup>, Bent K Jakobsen<sup>3</sup>, Michael Kalos<sup>2,5,8</sup> & Carl H June<sup>2,5</sup>

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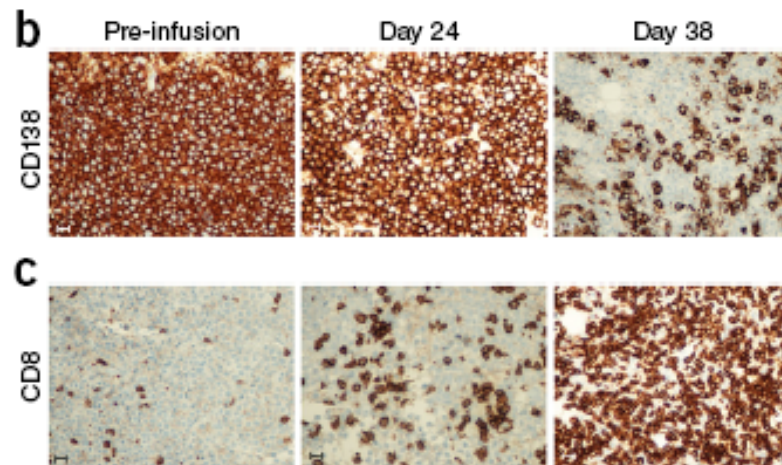
### Blut



Knochenmark

Myelomzellen

T-Lymphozyten





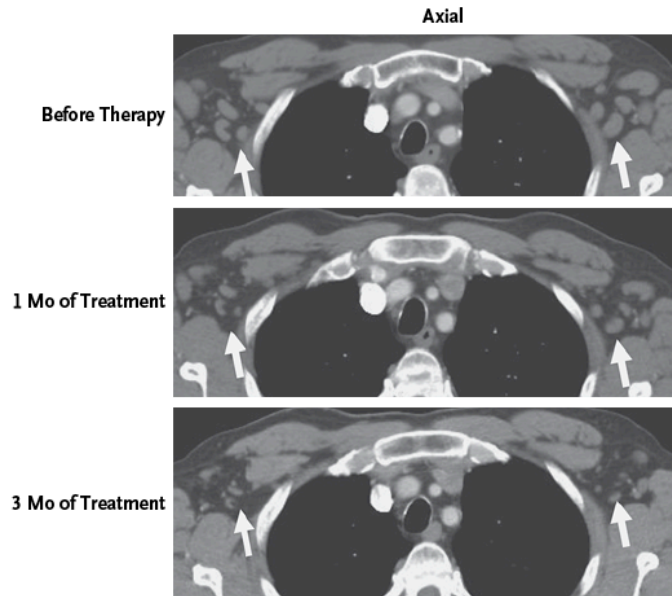
# Verstärkung der Immunantwort gegen Krebszellen

## CAR T Zellen

### Chimeric Antigen Receptor–Modified T Cells in Chronic Lymphoid Leukemia

David L. Porter, M.D., Bruce L. Levine, Ph.D., Michael Kalos, Ph.D., Adam Bagg, M.D., and Carl H. June, M.D.

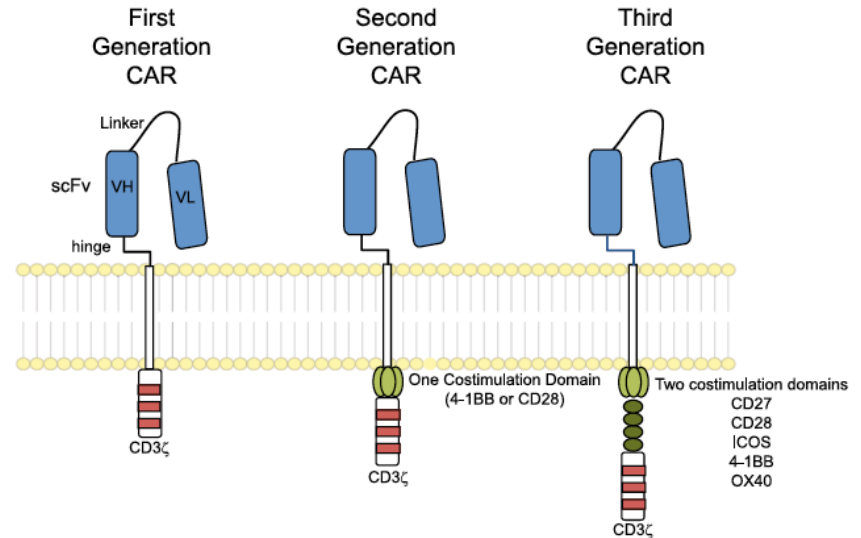
N Engl J Med 2011;365:725-33.



### Antibody-modified T cells: CARs take the front seat for hematologic malignancies

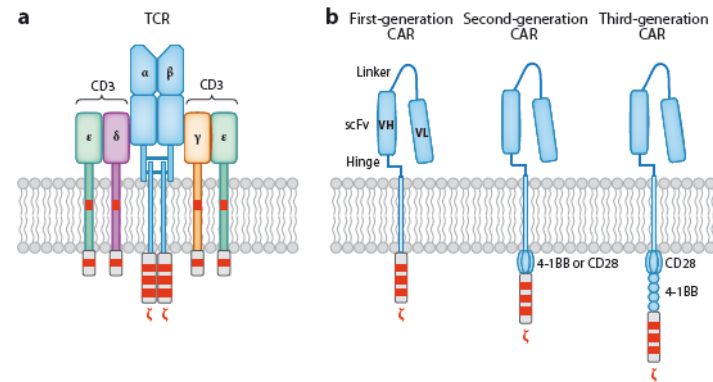
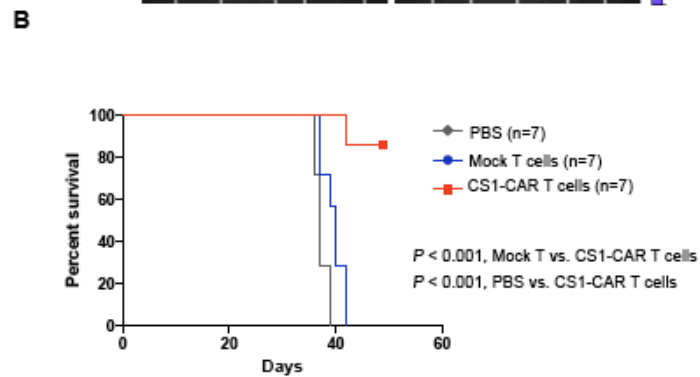
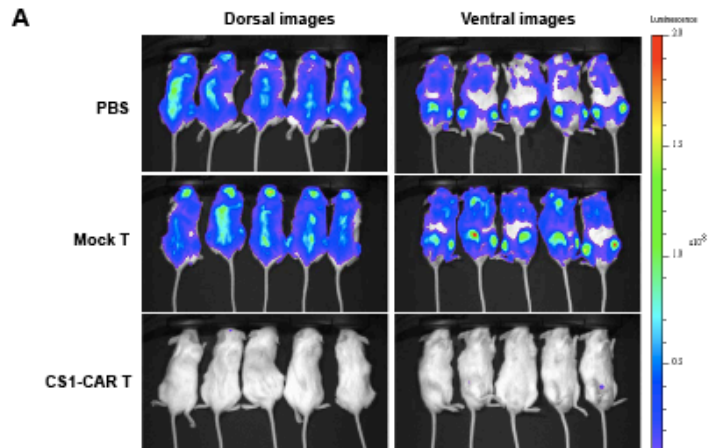
Marcela V. Maus,<sup>1,2</sup> Stephan A. Grupp,<sup>1,3,4</sup> David L. Porter,<sup>1,2</sup> and Carl H. June<sup>1,5</sup>

BLOOD, 24 APRIL 2014 • VOLUME 123, NUMBER 17



# CAR T-Zellen

Figure 6



## Clinical Cancer Research

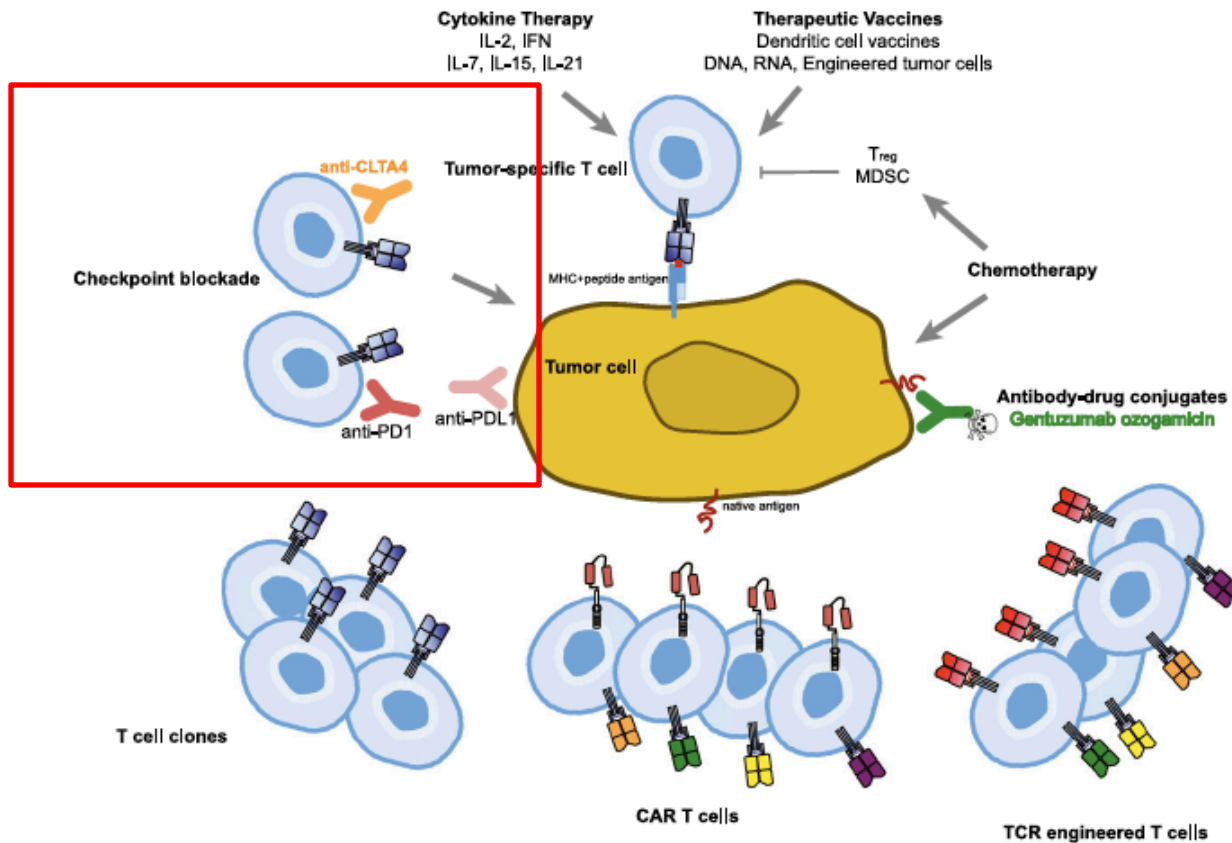
### Genetic Modification of T Cells Redirected towards CS1 Enhances Eradication of Myeloma Cells

Jianhong Chu, Shun He, Youcai Deng, et al.

Clin Cancer Res. Published OnlineFirst March 27, 2014.

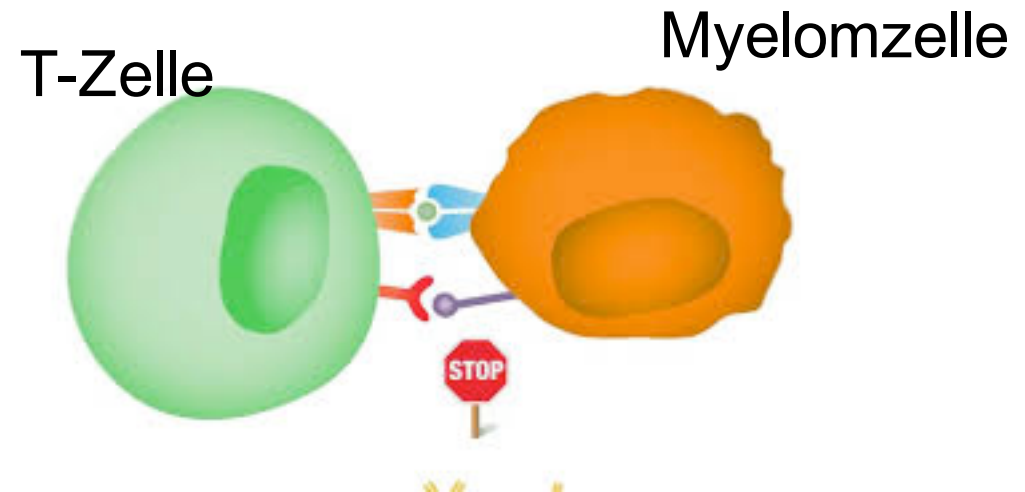
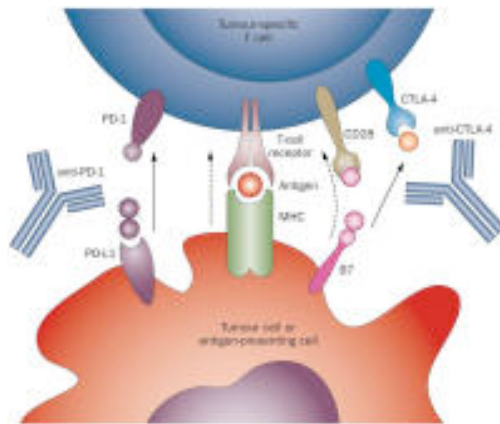
# Verstärkung der Immunantwort gegen Krebszellen

## Checkpoint Inhibitoren: Lösen der Bremse des körpereigenen Immunsystems



## Verstärkung der Immunantwort gegen Krebszellen

### Checkpoint Inhibitoren: Lösen der Bremse des körpereigenen Immunsystems



<http://www.lymphomation.org/-news-immune-therapy.htm>

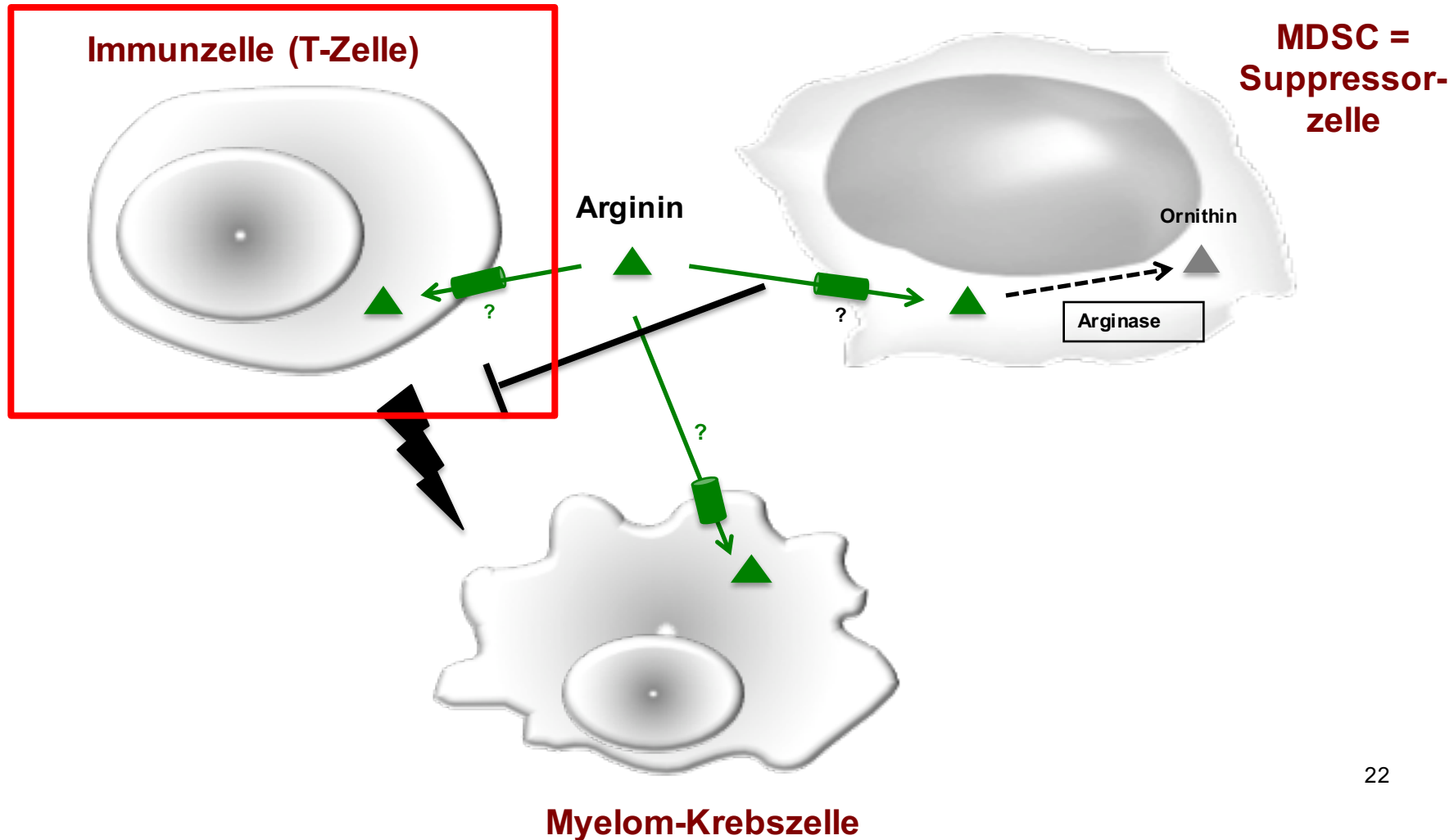
**Ipilimumab**  
**Nivolumab**  
**Pembrolizumab**  
**Durvalumab**

.....

## AGENDA

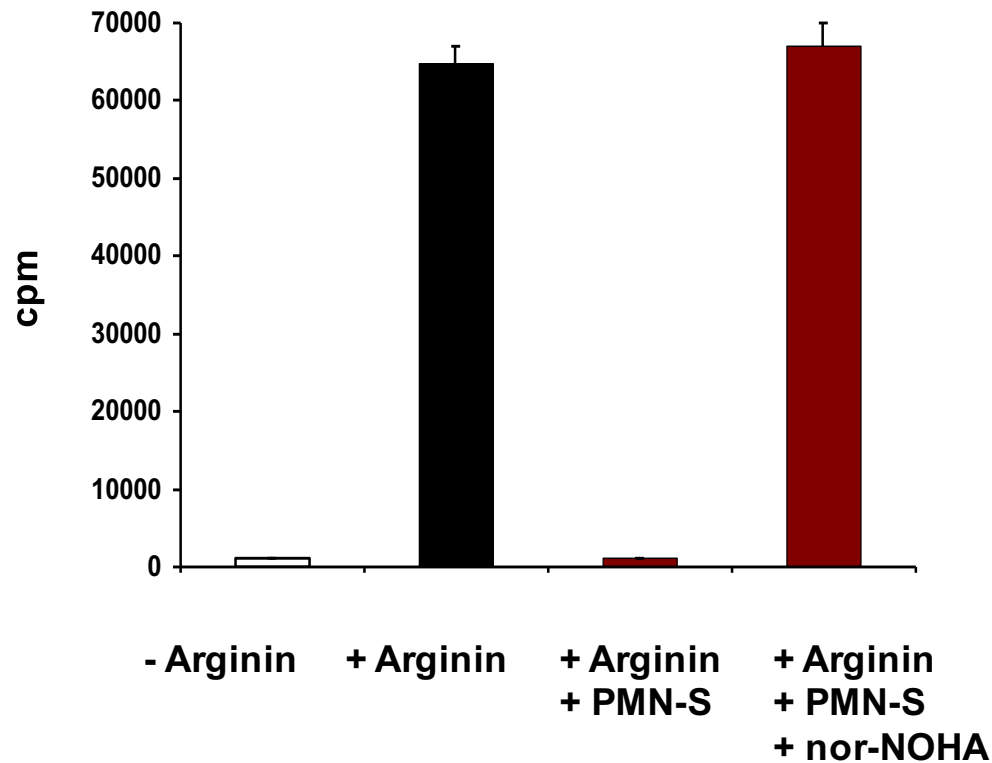
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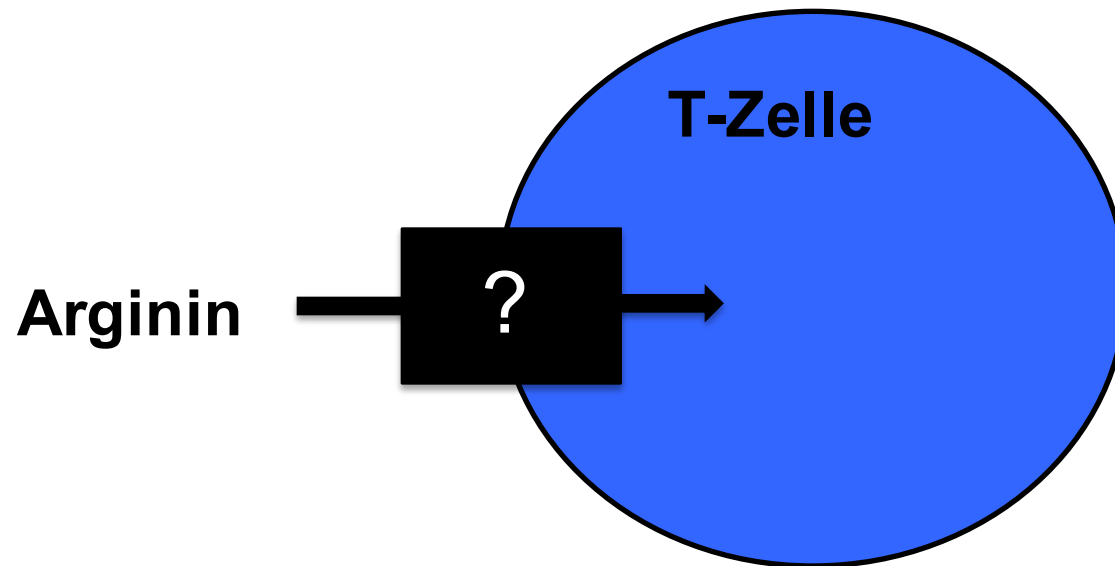
## Kampf um die Aminosäure Arginin !



# T Zellen benötigen Arginin !

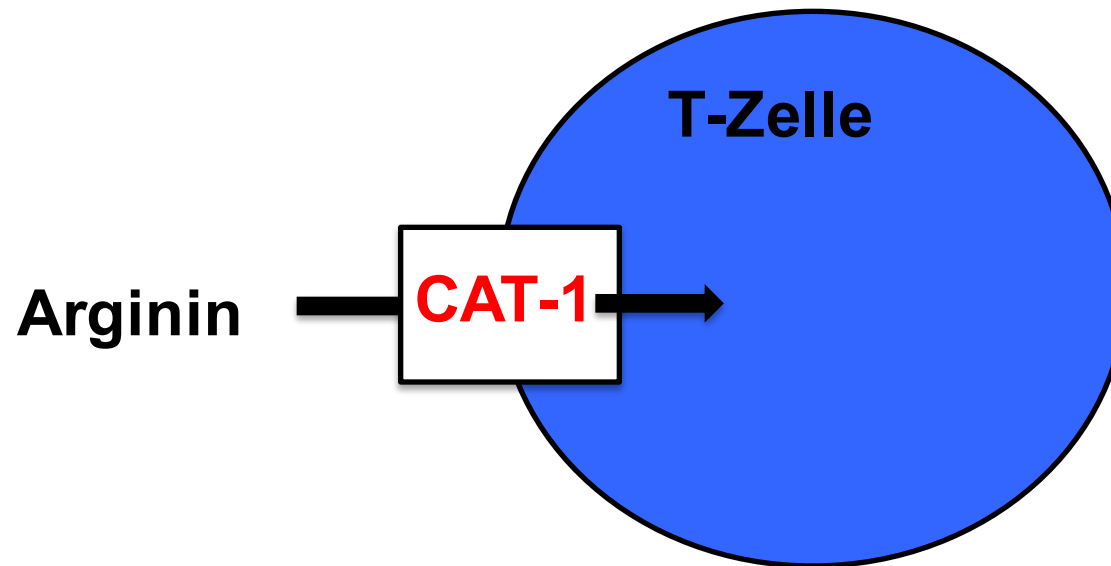
## Zellteilung



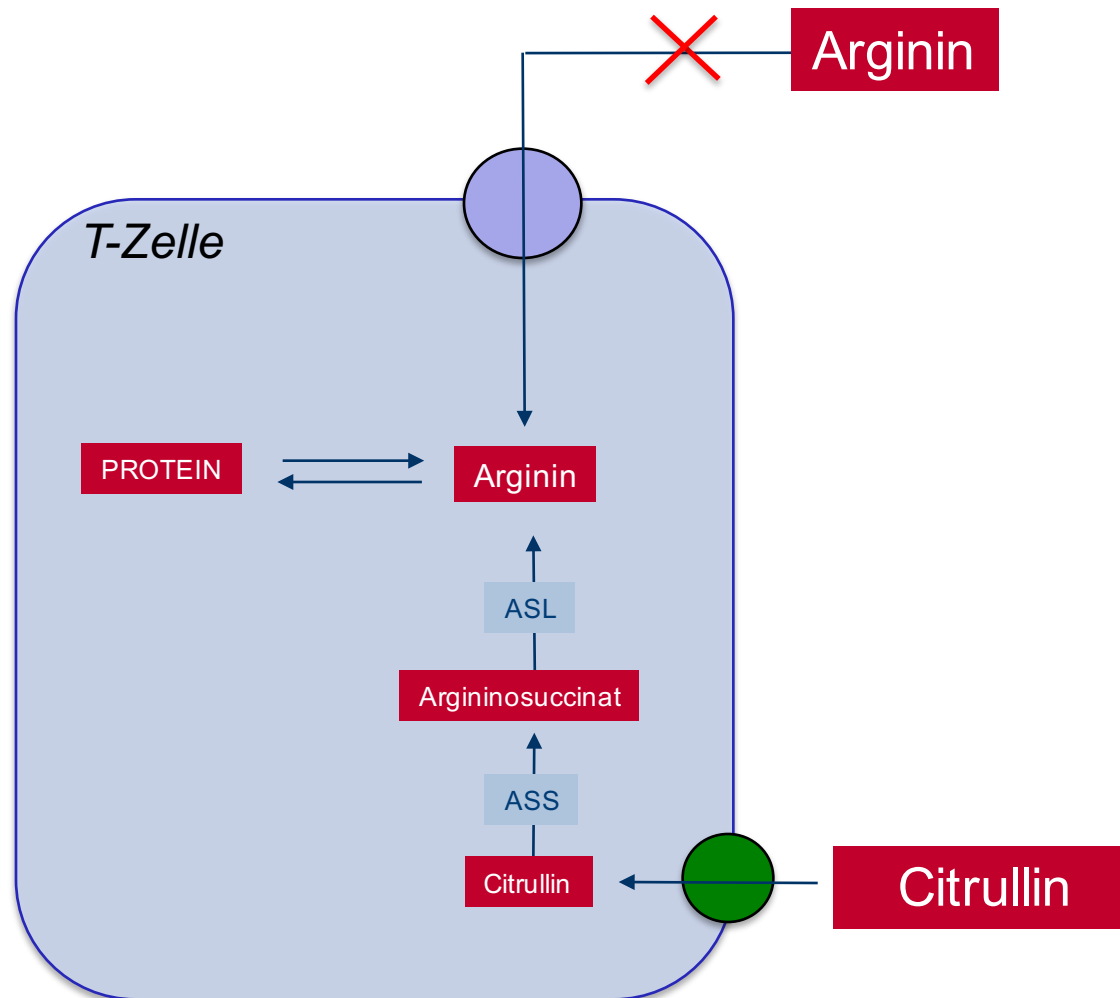




## CAT-1 = der Arginintransporter humaner T-Zellen

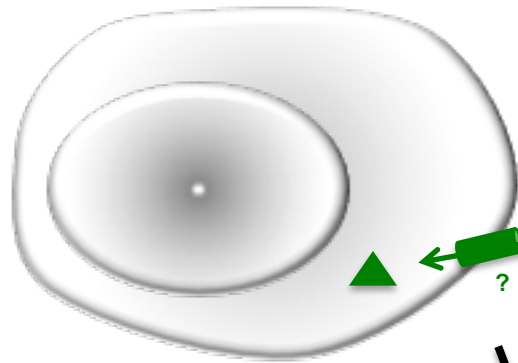


## T-Zell Aktivierung ohne Arginin ist möglich: CITRULLIN !

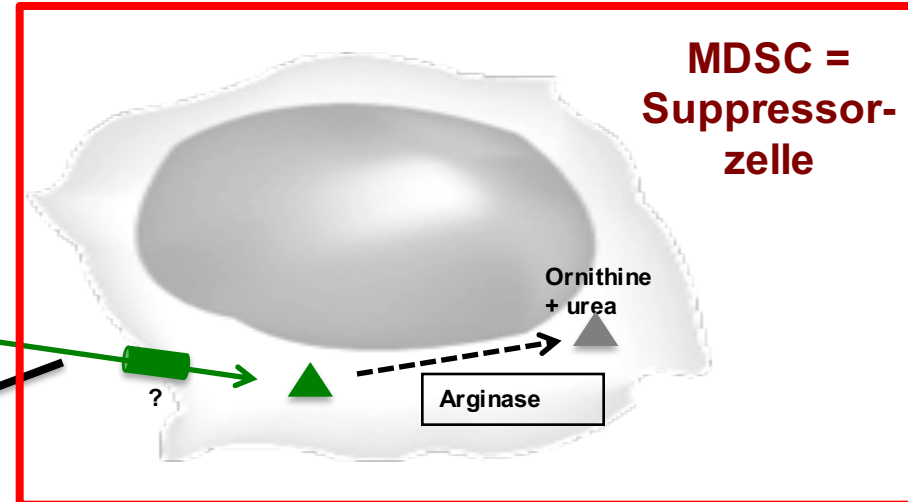


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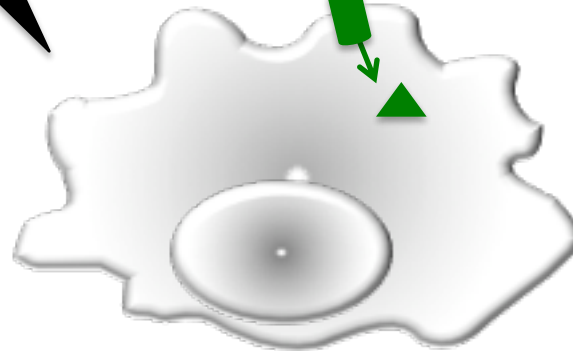
Immunzelle (T-Zelle)



Arginin

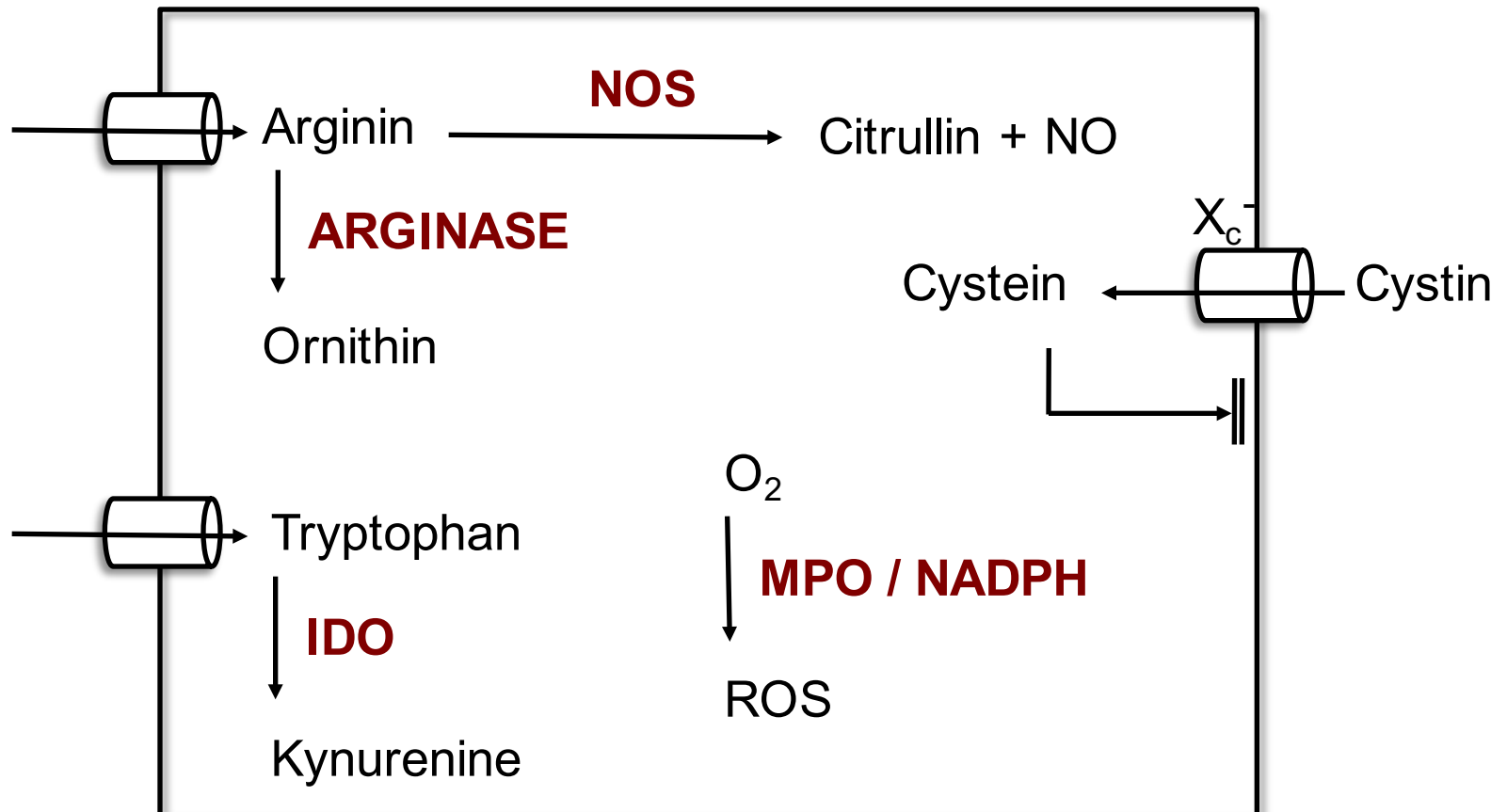


MDSC =  
Suppressor-  
zelle

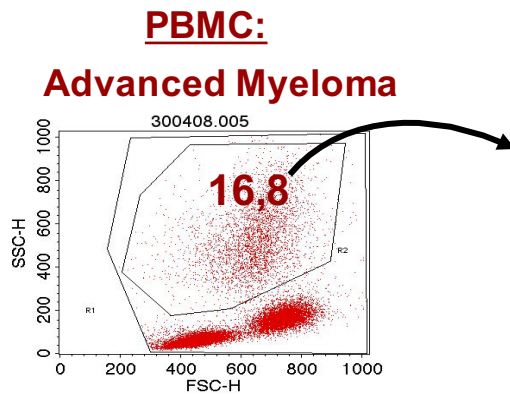


Myelom-Krebszelle

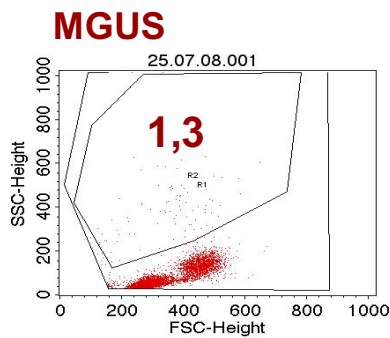
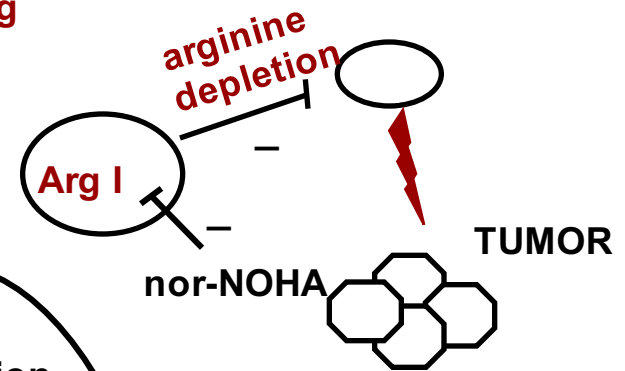
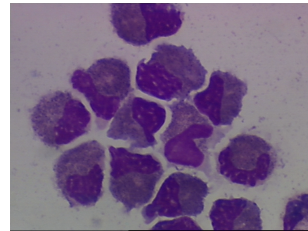
# Myeloische Suppressorzellen



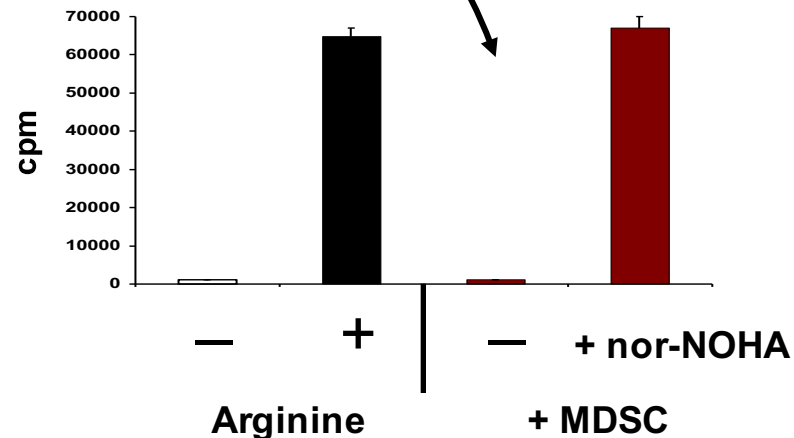
# Myeloid derived suppressor cells (MDSC)



Arginase: 1555 mU/mg



T cell proliferation

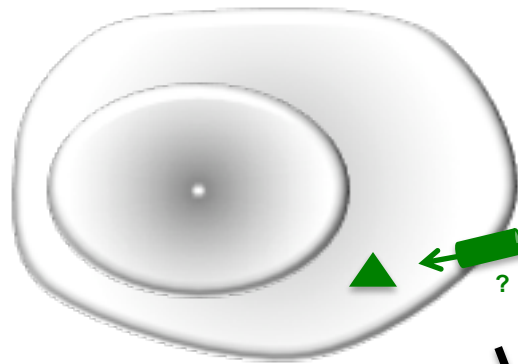


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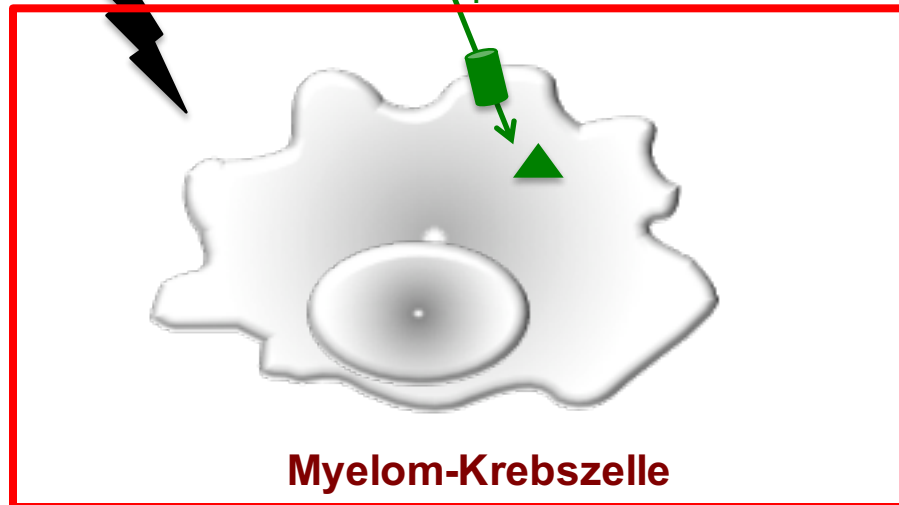
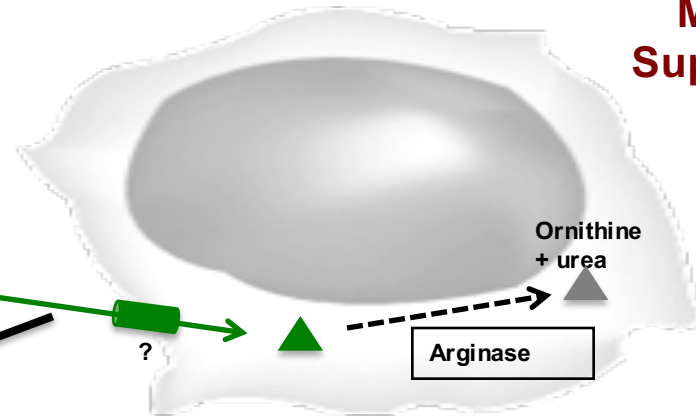
# Kampf um die Aminosäure Arginin !

Immunzelle (T/NK)



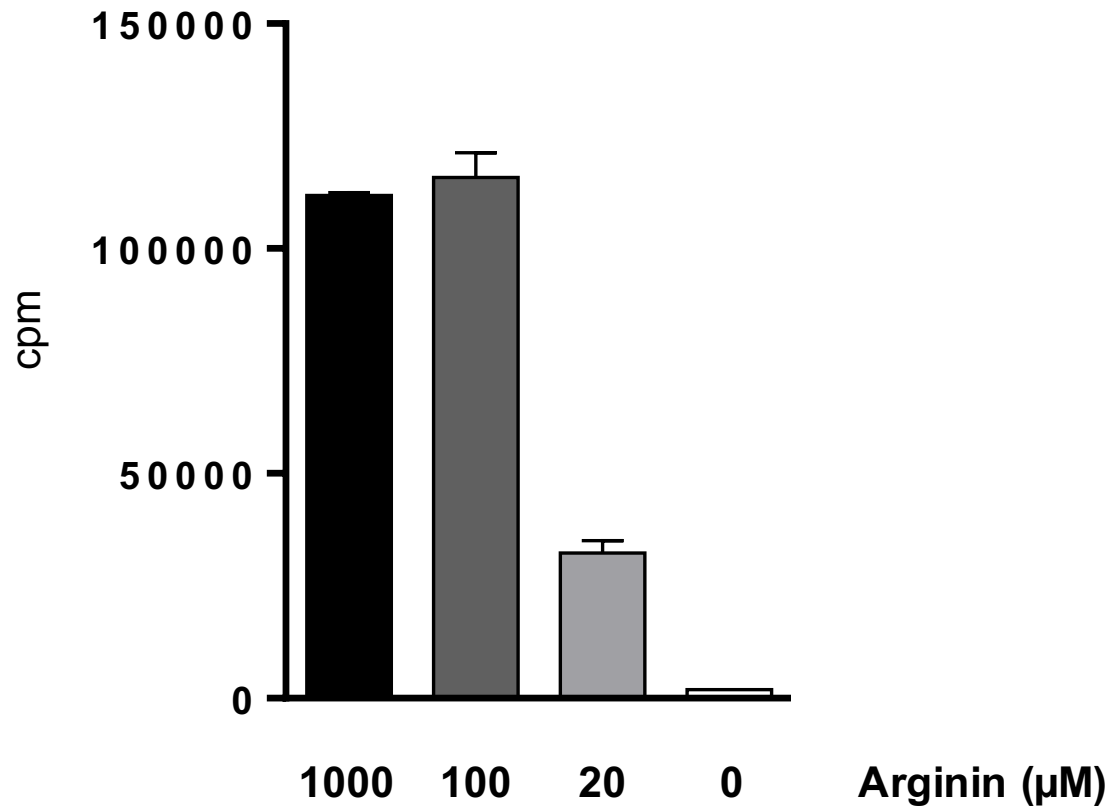
Arginin

MDSC =  
Suppressor-  
zelle



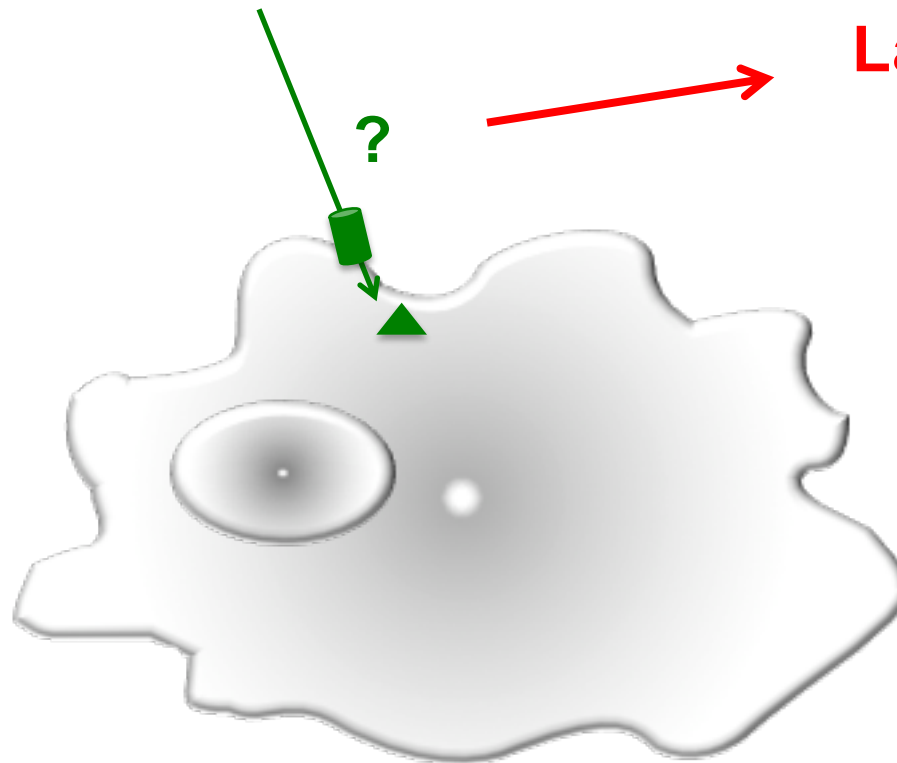
Myelom-Krebszelle

## Ohne Arginin kein Tumorzellwachstum !





▲ Arginin



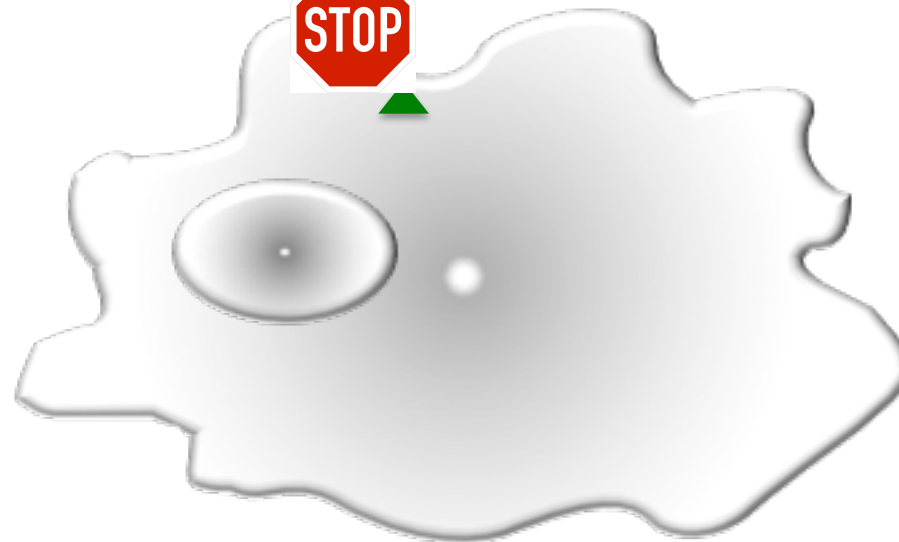
Lara Kürzer

Myelom-Krebszelle

▲ Arginin

CAT-1

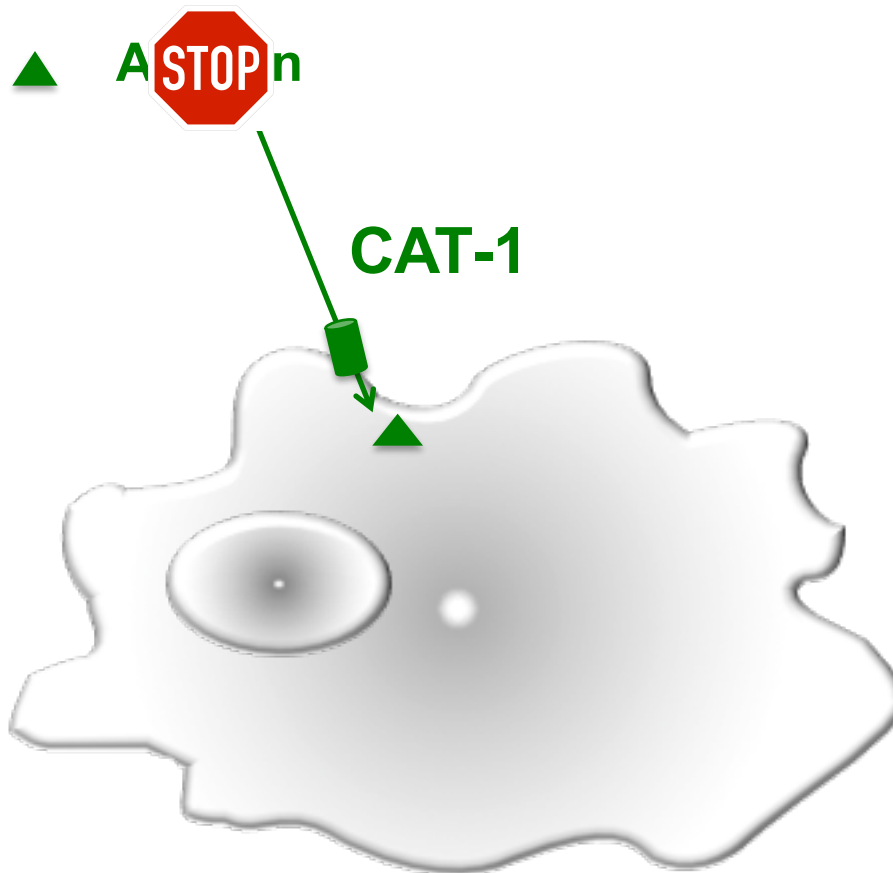
STOP



**Myelom-Krebszelle**

## AGENDA

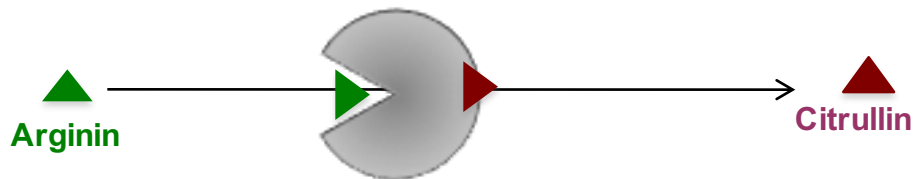
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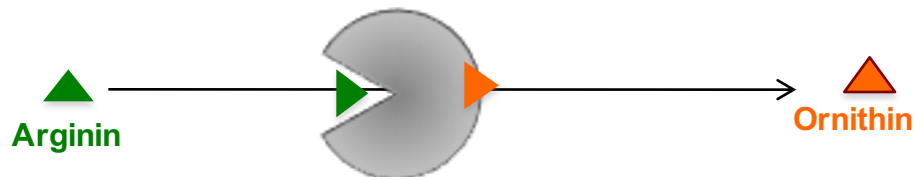
**Myelom-Krebszelle**

## Arginine depletion as novel anti-tumor strategy

### Arginin Deiminase (ADI)

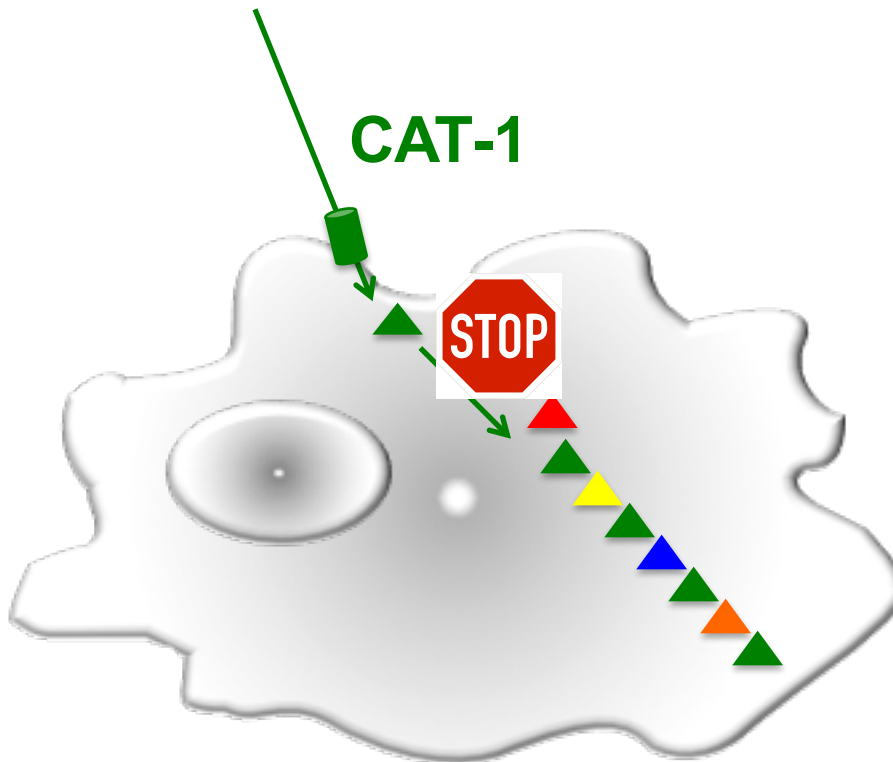


### Arginase



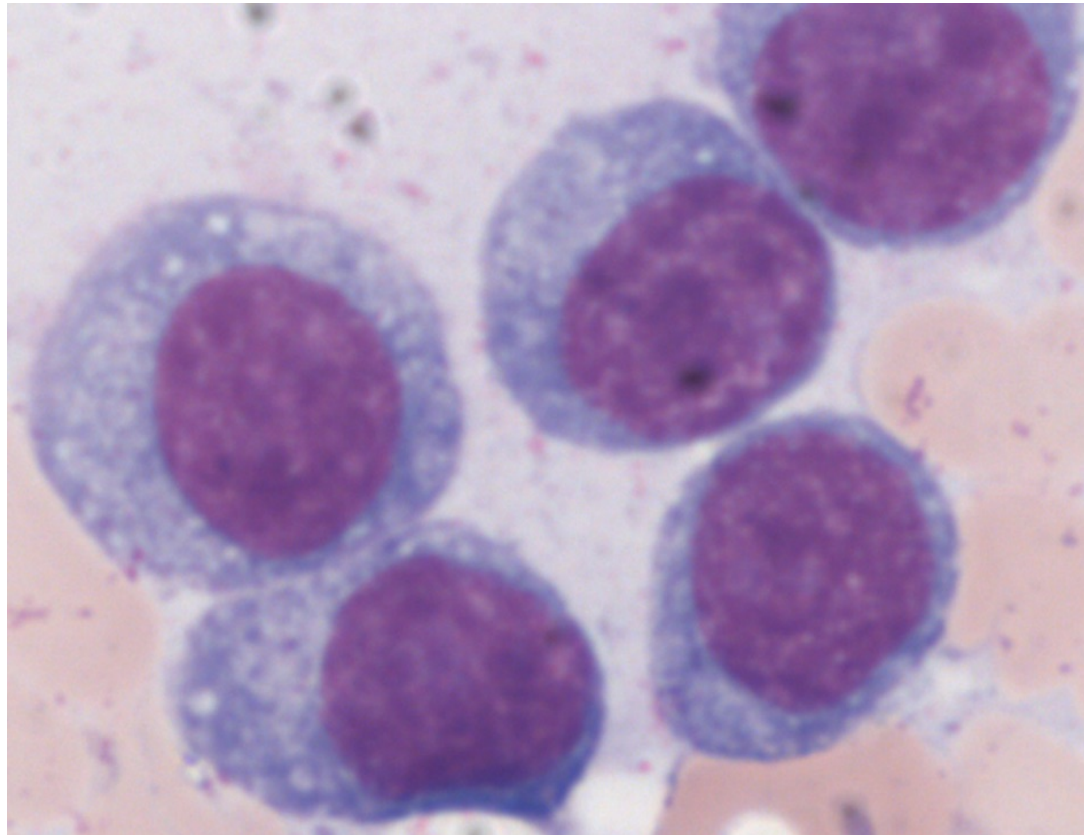
▲ Arginin

CAT-1

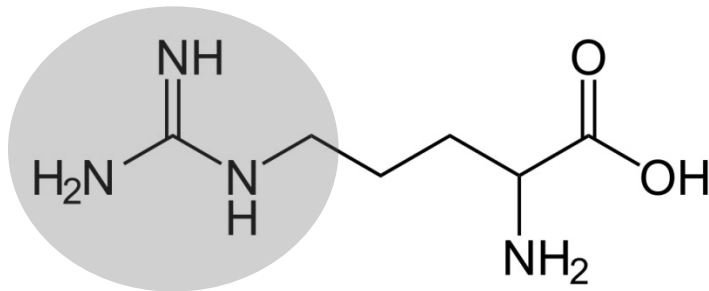


**Myelom-Krebszelle**

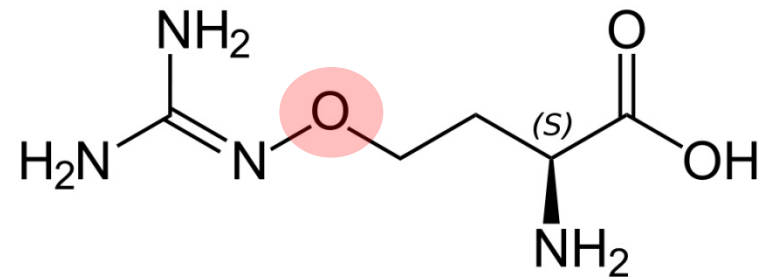
## Myelomzellen = Eiweißproduzenten !!



# Canavanin



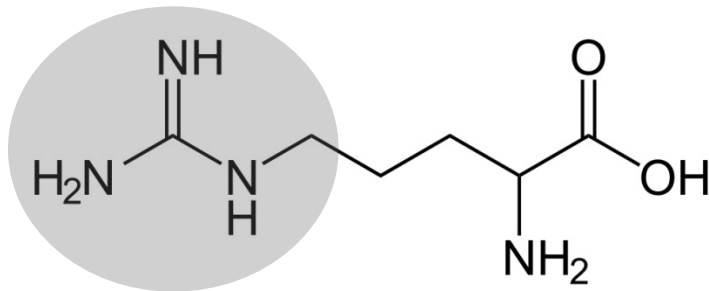
**Arginin**



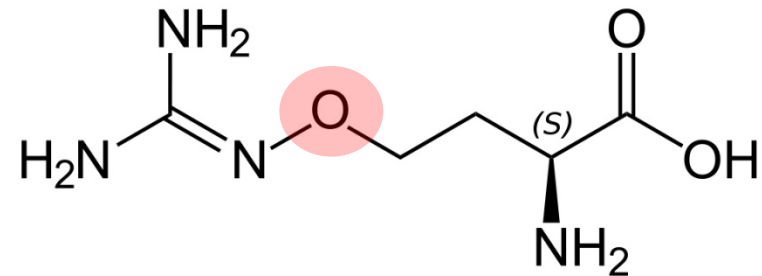
**Canavanin**



# Canavanin



Arginin

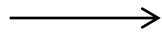


Canavanin



## Proteinfehlfaltung = STRESS

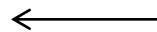
**Protein-  
fehlfaltung**



**UPR (Unfolded protein response)**



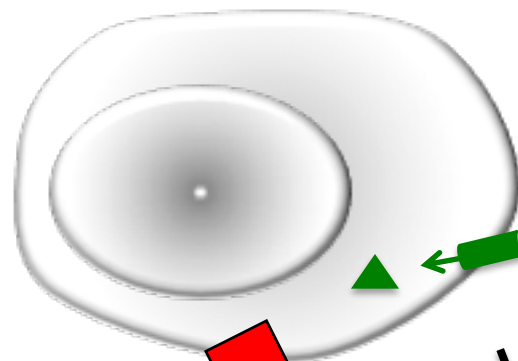
**Zelltod**



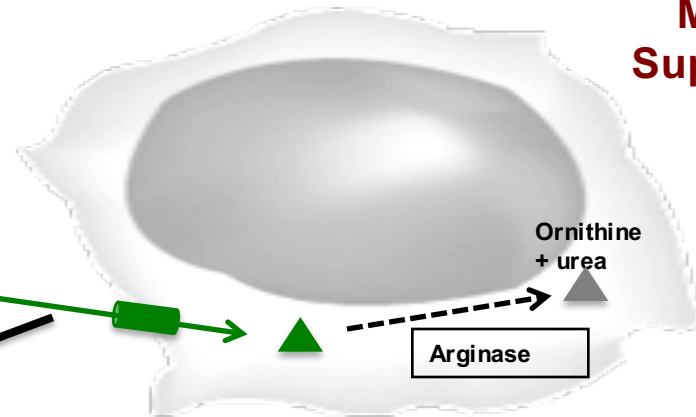
**Überleben**

## Kombinationsstrategie gegen die Myelomzelle

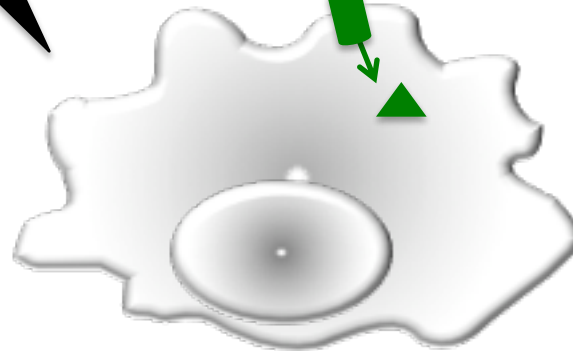
Immunzelle (T/NK)



Arginin



MDSC =  
Suppressor-  
zelle



Myelom-Krebszelle

## Acknowledgements

### AG Munder

- Alexander Desuki
- **Björn Jacobi**
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- Katharina Schneider
- Vanessa Schnitzius
- Rebecca Seidl
- Lea Ströher
- Jose Hadi Sutanto
- Janine Tappe

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- **Ellen Closs**
- Alice Habermeier
- Susanne Muther
- Johanna Rupp
- **Anke Werner**

### AG Theobald

- Eva Amann
- Edite Antunes
- Hakim Echchannaoui
- Matthias Theobald



**Stiftung Rheinland Pfalz  
für Innovation**



Vielen Dank  
für Ihre Aufmerksamkeit!

Kontakt:

PD Dr. med. Markus Munder

Oberarzt

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