Immuntherapie - neue Wege in der Krankenversorgung

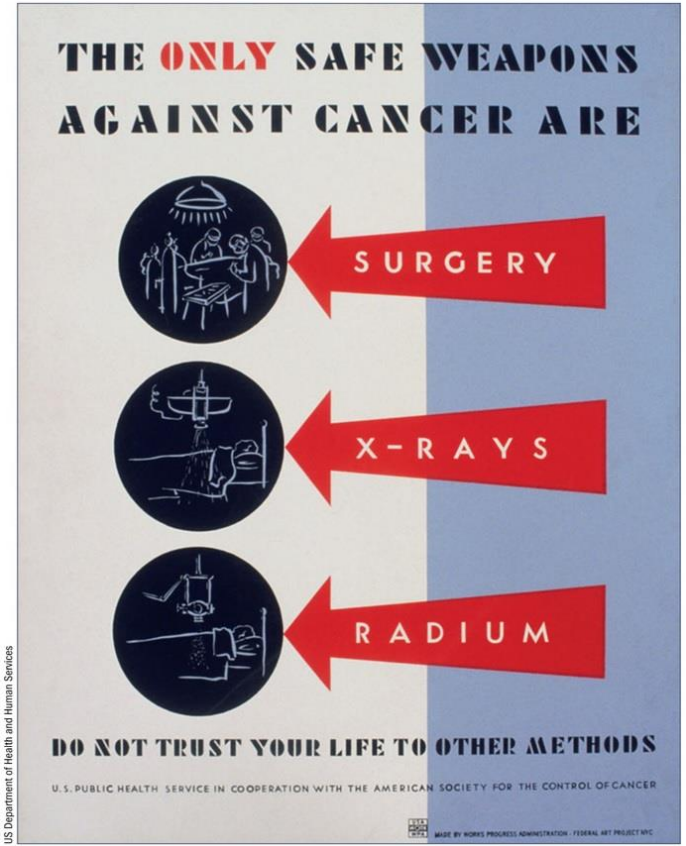
Prof. Dr. med. Niels Halama

Potentielle Interessenkonflikte

- Ehemaliger Arbeitgeber (Uniklinikum Heidelberg) erhält Forschungsförderung von Bristol-Myers Squibb (BMS)
- Vortragstätigkeit: Merck KgA Darmstadt // Beratertätigkeit (DKFZ): Roche Ltd
- Patente für „immune cell quantification for stratification of patients (solid tumor diseases)“
- Patente für die Verwendung von CCR5i bei soliden Tumoren
- Patente für die Anwendung von onkolytischen Viren und zellulären Therapien bei soliden Tumoren
- Mitgründer und Anteilseigner der CRO Organisation (Navitect Bio GmbH)

Beteiligte Einrichtungen

Therapie von Tumorerkrankungen

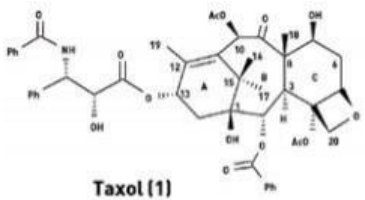


…also alles ganz einfach?

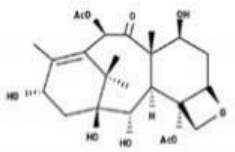
Was wird am häufigsten verwendet?

Wie funktioniert eine Chemotherapie…?

Zellgifte im Einsatz…



Taxol (1)

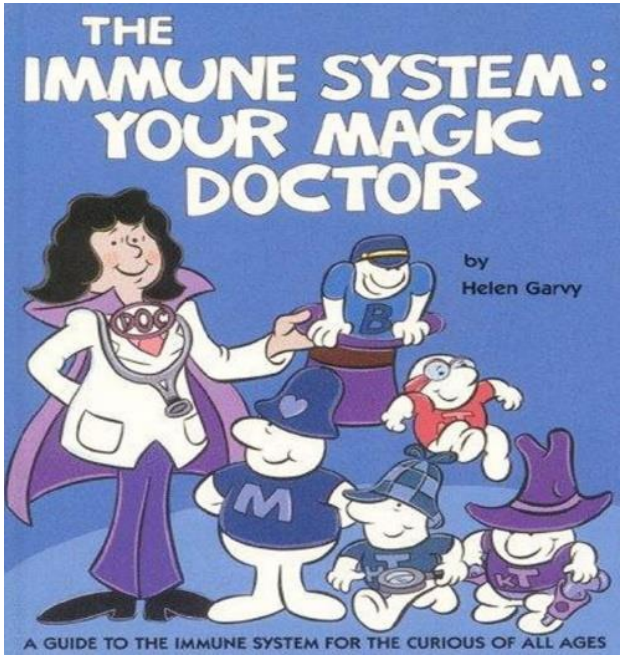


Baccatin III (2)

Chemotherapie und die Wirkung auf Tumorzellen

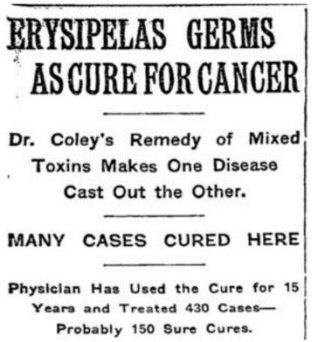
… Fortsetzung folgt…

Und jetzt die Immuntherapie…



Die Verbindung von Entzündung und Tumorbekämpfung…

„Die beiden deutschen Ärzte Wilhelm Busch 1868 und Friedrich Fehleisen 1882 waren die Ersten, die absichtlich Tumorpatienten mit einem Erysipel infizierten und darunter eine Tumorverkleinerung beobachteten (Busch, 1868; Fehleisen, 1882).“



ERYSIPELAS GERMS AS CURE FOR CANCER

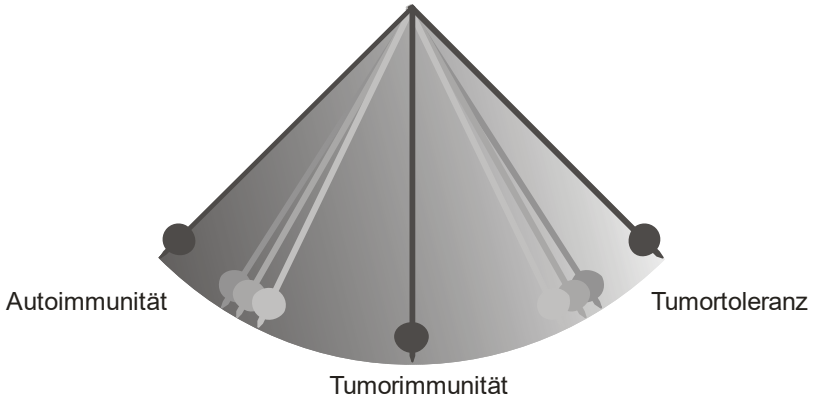
Dr. Coley's Remedy of Mixed Toxins Makes One Disease Cast Out the Other.

MANY CASES CURED HERE

Physician Has Used the Cure for 15 Years and Treated 430 Cases— Probably 150 Sure Cures.

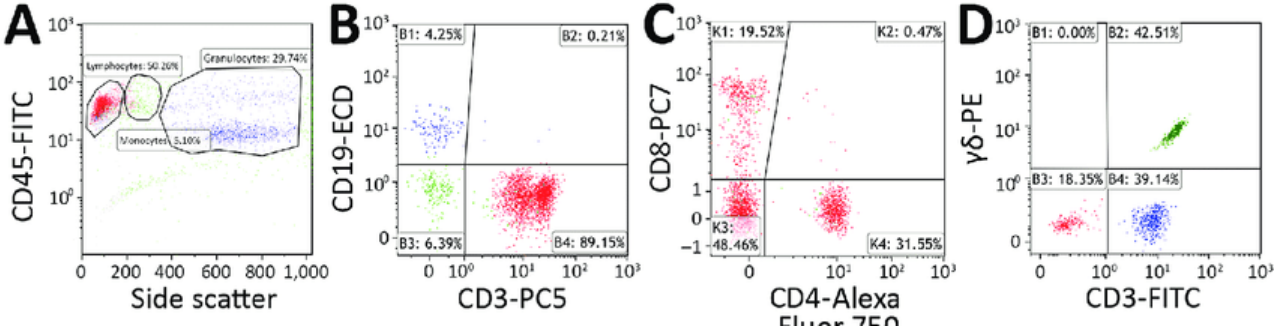
Auszug “The New York Times”, 1908

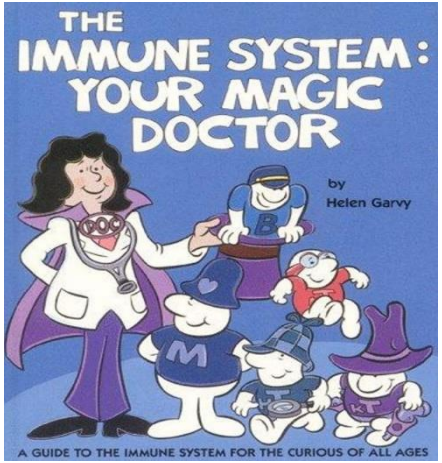
Immuntherapien: was ist das Ziel…?



Immunsystem:
ein System mit verschiedenen Ansatzpunkten

Das Immunsystem



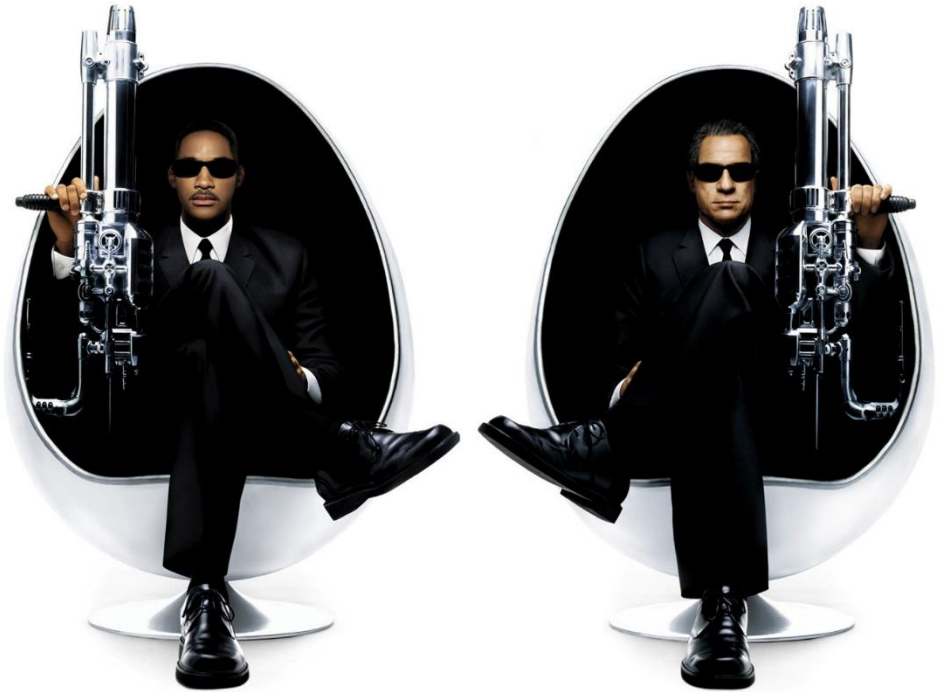


Welche Funktionen hat das Immunsystem?

Funktion:
Erkennung von „nicht-selbst“ versus „selbst“
(Bakterien, Viren, Tumorzellen…)

Quelle: 21st Century FOX

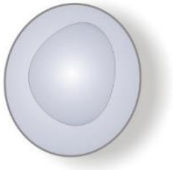
Zwei verknüpfte Systeme: angeborenes und adaptives

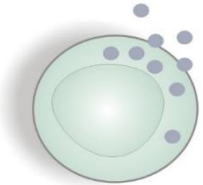


Source: 21st Century FOX

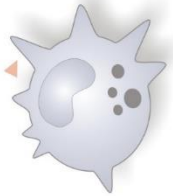
Wiederholung: formale Elemente der Immunantwort

Zelluläre Immunität:
Immunzellen (T-,B-, NK Zellen, Makrophagen usw.)





Spezifische Abwehr („adaptive immune response"):
Gegen spezifische Infektionen oder Ziele gerichtet

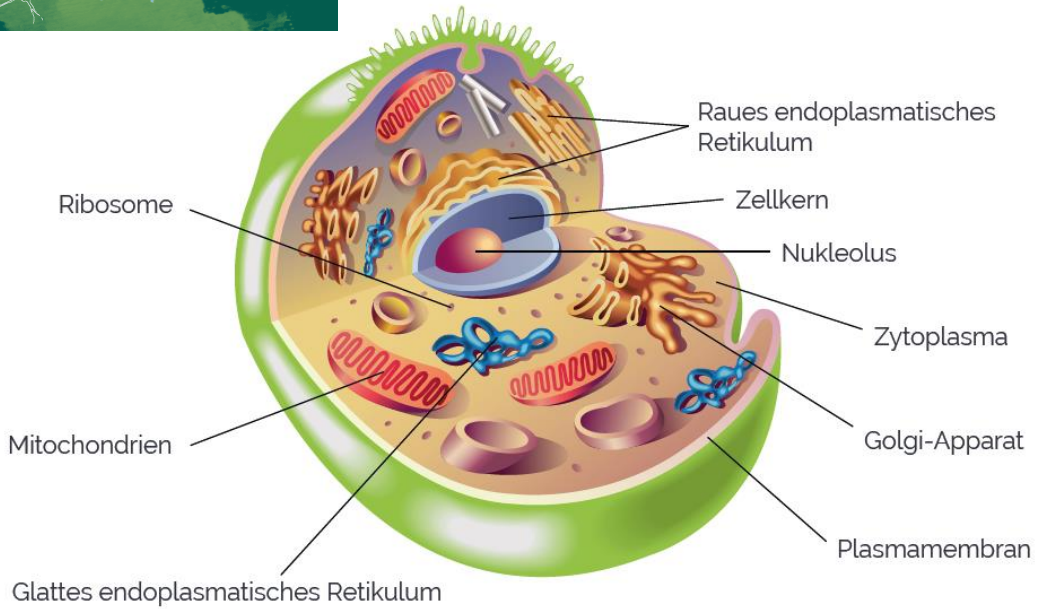


Azelluläre Immunität:
humorale („Serum") Elemente wie Komplement, Antikörper etc.

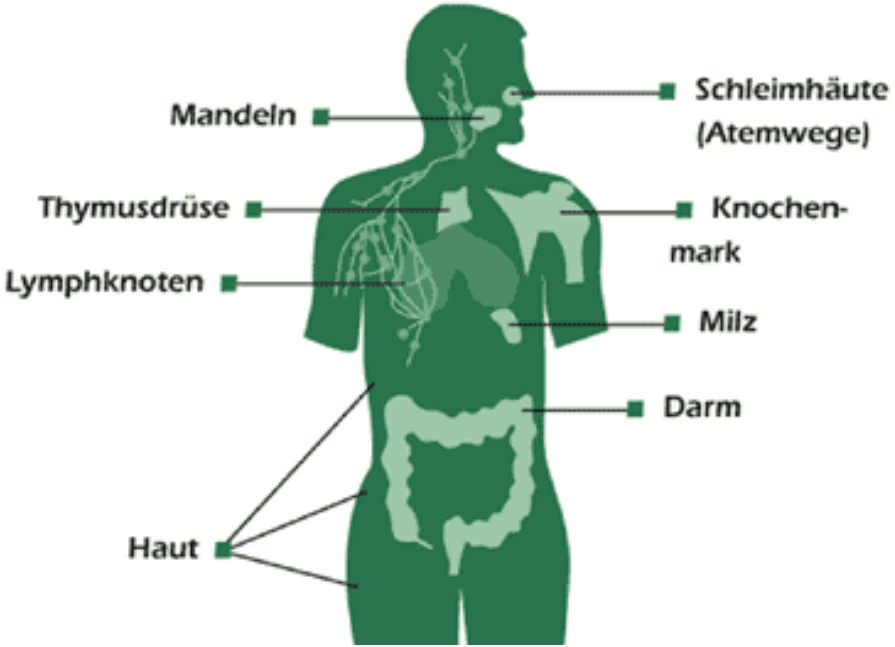
Unspezifische Abwehr:
Gerichtet gegen „nicht-selbst"

Kurzes Interludium…

=„Funktionseinheit“

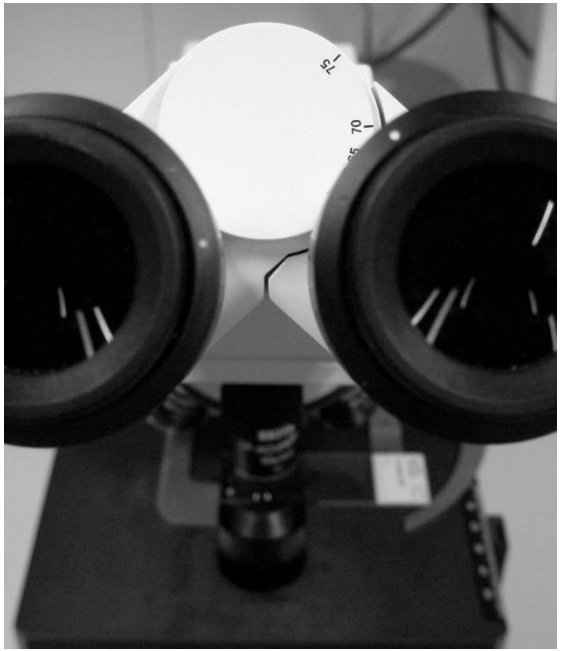


Wo ist das Immunsystem?



…also überall.

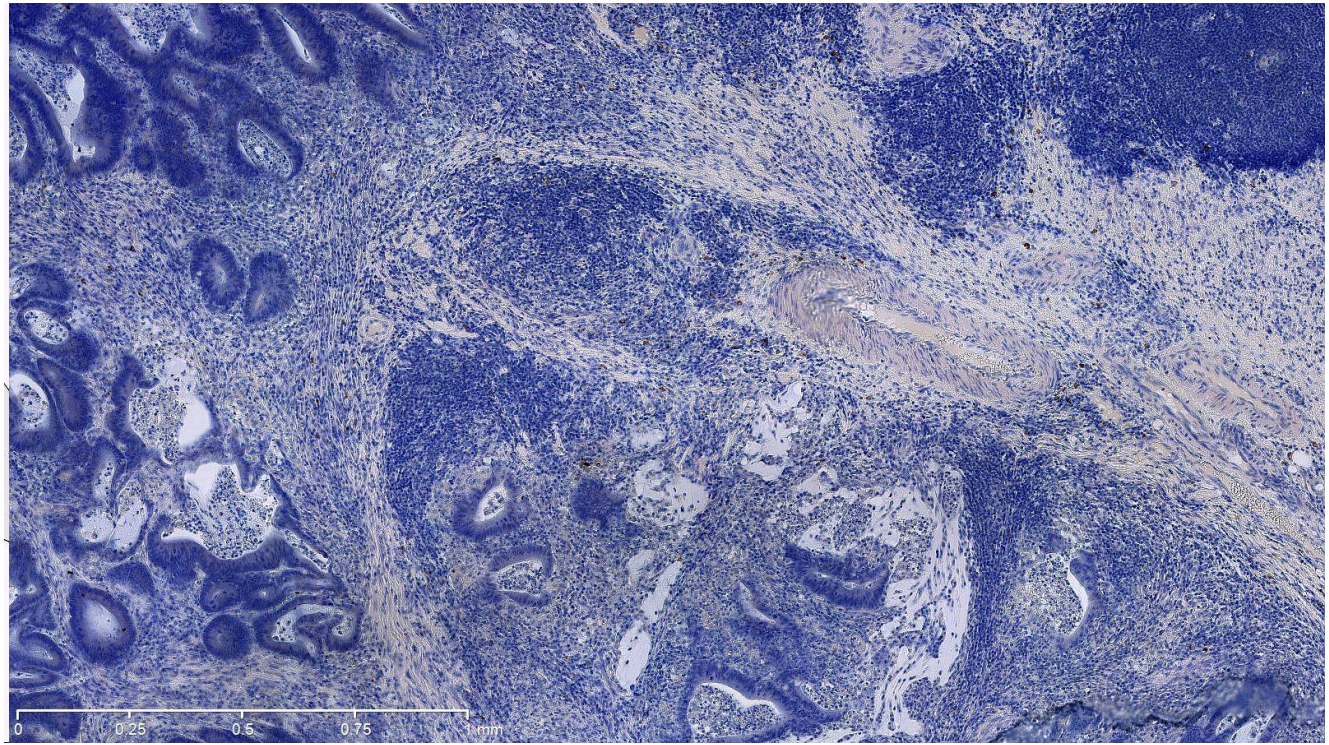
Ein tiefer Blick…



…durch das Mikroskop.

Und ein Blick auf die dunkle Seite des Mondes…

Die lokale immunologische



Aber wenn man über „Immunogenität“ reden will…

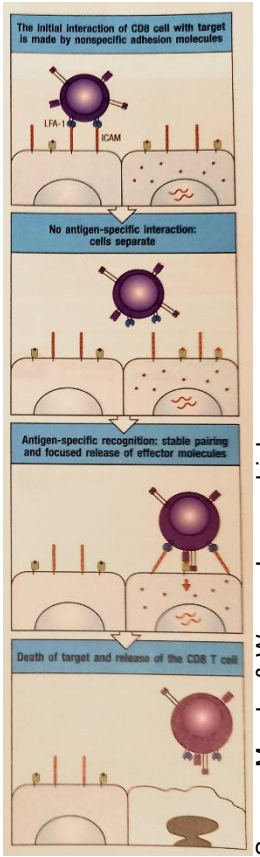
…muss man doch verstehen…

…aus was diese „lokale immunologische Tumormikroumgebung“ besteht…?

Eine kurze Wiederholung: welche Immunzellen…?

Zytotoxische T Zellen

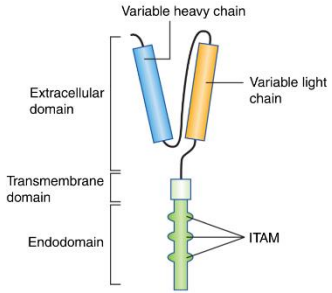
Effektor T Zelle
(CD3+ CD8+)



Source: Murphy & Weaver Immunobiology

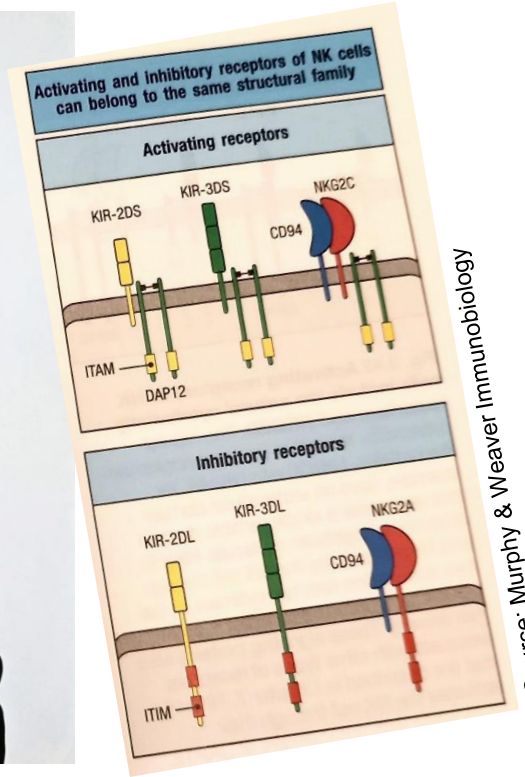
Source: toys‘r‘us

CAR T cell
(chimeric antigen receptor)



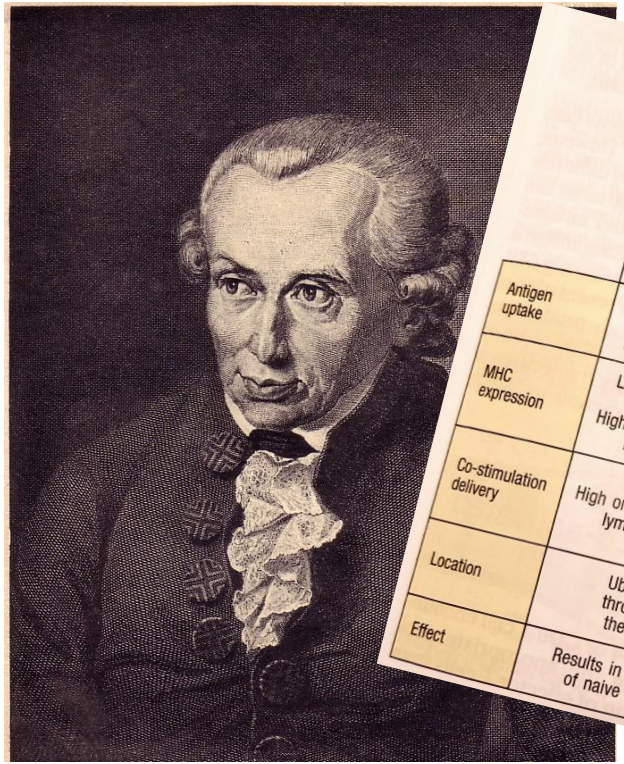
Tokarew et al. BJC 2018

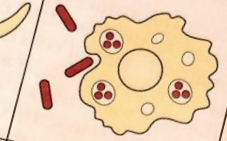
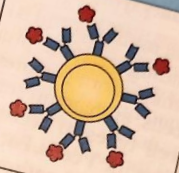
Natürliche Killerzellen (NK Zellen)



Source: Murphy & Weaver Immunobiology

Dendritische / Antigen-präsentierende Zellen

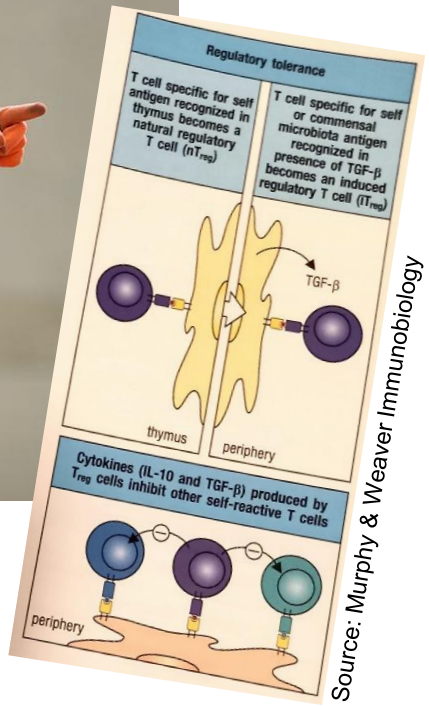


	Dendritic cells	Macrophages	B cells
			
Antigen uptake	+++ Macropinocytosis and phagocytosis by tissue dendritic cells	+++ Macropinocytosis +++ Phagocytosis	Antigen-specific receptor (Ig) ++++
MHC expression	Low on tissue-resident dendritic cells High on dendritic cells in lymphoid tissues	Inducible by bacteria and cytokines – to +++	Constitutive Increases on activation +++ to ++++
Co-stimulation delivery	Inducible High on dendritic cells in lymphoid tissues ++++	Inducible – to +++	Inducible – to +++
Location	Ubiquitous throughout the body	Lymphoid tissue Connective tissue Body cavities	Lymphoid tissue Peripheral blood
Effect	Results in activation of naive T cells	Results in activation of macrophages	Results in delivery of help to B cell

Source: Murphy & Weaver Immunobiology

Regulatorische Zellen

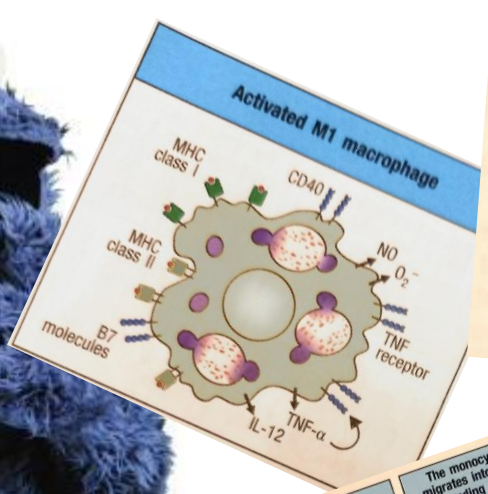
FOXP3+ et al.

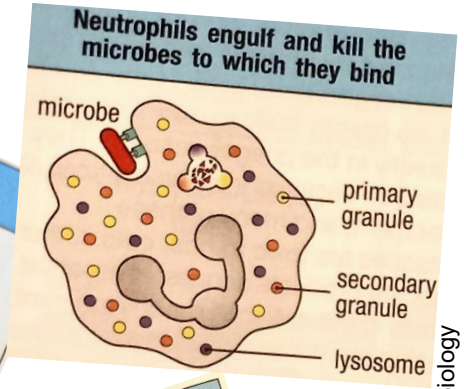


Source: Murphy & Weaver Immunobiology

Makrophagen und andere myeloide Zellen

Phagozytierende Zellen

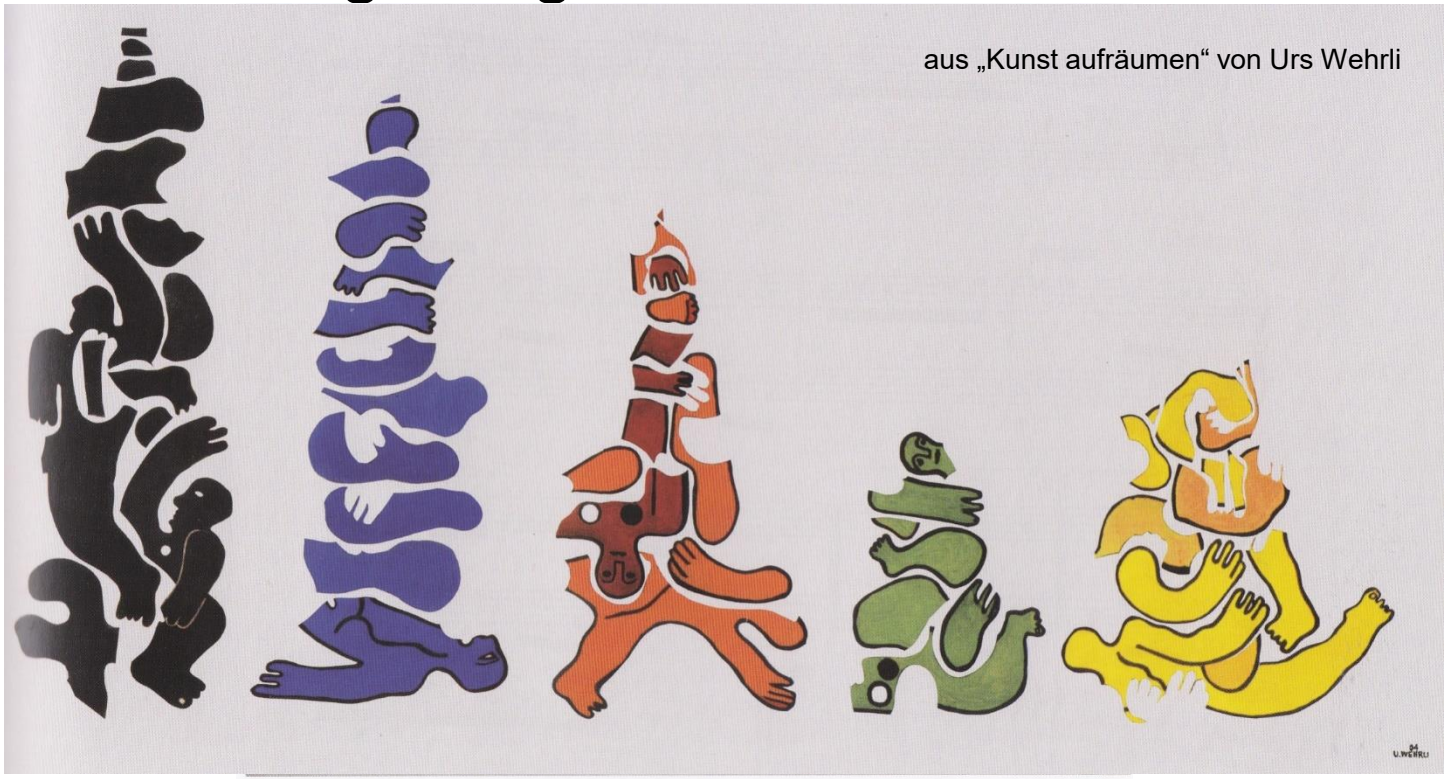




Source: Murphy & Weaver Immunobiology

Und natürlich auch: das stromale Kompartment mit Cytokeratinen und Fibroblasten und Matrix und und und…

Die Vermessung der Elemente in der Mikroumgebung…



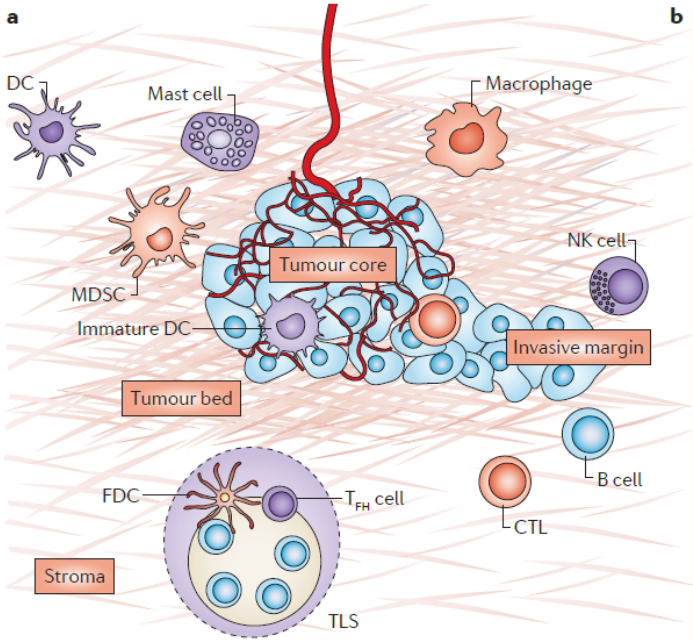
„Plongers“ von F. Leger

Nach einer Idee von Christine Falk

Das größere Bild…

Komplexität…

Der immunologische Kontext



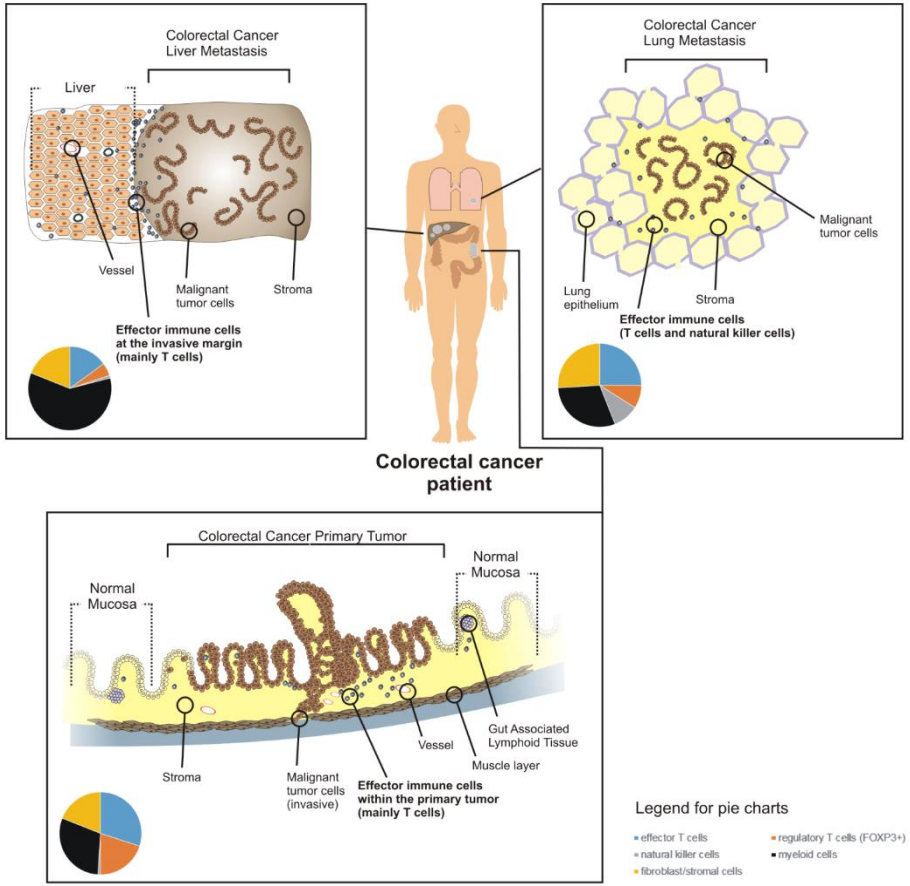
b

Immune contexture	Parameters: positive association with survival
Type	CTLs ($CD3^+CD8^+$)
	Memory T cells ($CD45RO^+$)
Location	Core of the tumour
	Invasive margin
Density	Number of cells per mm^2: 1, 10, 100, 1,000, 10,000 — $CD3^+_{CT}$, $CD3^+_{IM}$, $CD8^+_{CT}$, $CD8^+_{IM}$, $CD45RO^+_{CT}$, $CD45RO^+_{IM}$
Functional orientation	T_H1 cell-associated factors (IFNγ, IL-12, T-bet and IRF1)
	Cytotoxic factors (granzymes, perforin and granulysin)
	Chemokines (CX3CL1, CXCL9, CXCL10, CCL5 and CCL2)
	T_H17 cells, T_{Reg} cells and T_H2 cells have a variable effect on survival, depending on tumour type
TLS	Presence and quality

Figure 1 | **The immune contexture. a** | Tumour anatomy showing the features of the immune contexture, including the tumour core, the invasive margin, tertiary lymphoid structures (TLS) and the tumour microenvironment. The distribution of different immune cells is also shown. **b** | Table depicting the parameters of the immune contexture that predict a good prognosis. CT, core of the tumour; CTL, cytotoxic T lymphocyte; DC, dendritic cell; FDC, follicular dendritic cell; IFNγ, interferon-γ; IL-12, interleukin-12; IM, invasive margin; IRF1, interferon regulatory factor 1; MDSC, myeloid-derived suppressor cell; NK cell, natural killer cell; T_H, T helper; T_{Reg} cell, regulatory T cell.

microenvironment / contexture → prognosis

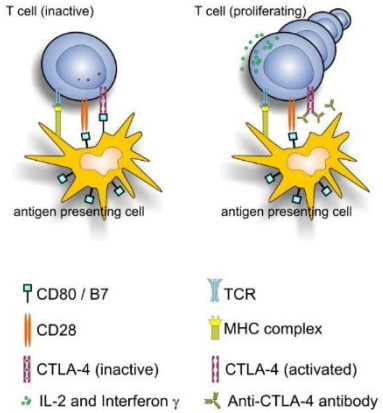
Fridman et al. Nature Reviews Cancer 2012



Halama et al. Oncoimmunology 2012
Keim et al. Oncoimmunology 2013
Kather & Halama. Br J Cancer 2018

from Elliot Erwitt „snaps“

Wie sprechen Immunzellen miteinander…?



Rezeptoren, Cytokine & Chemokine…

Welche „Wörter“ hat denn die Sprache?

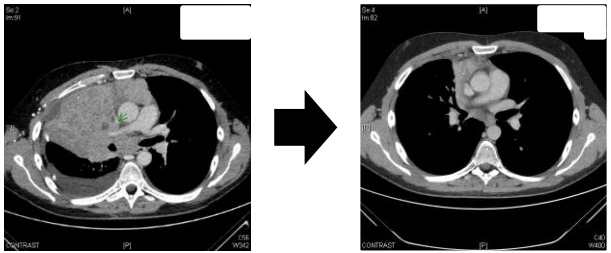
…ein paar prominente Beispiele…

Interferon-γ

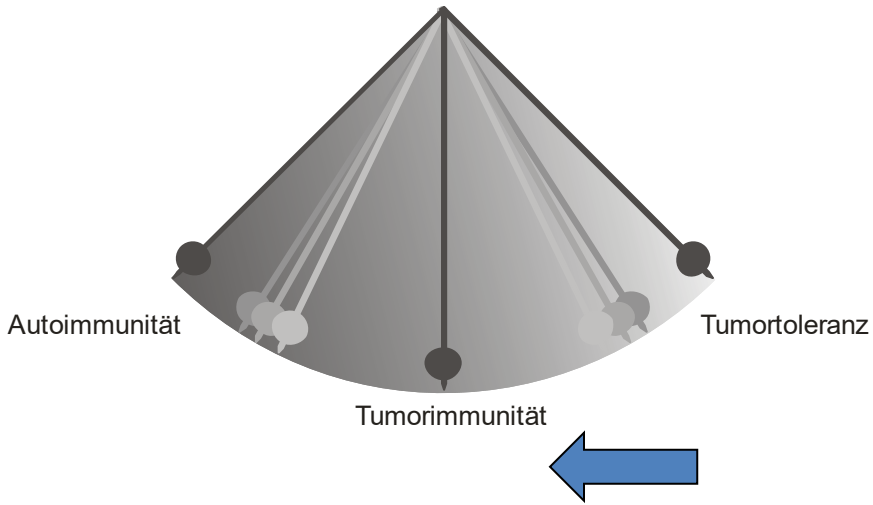
Zusammen ergibt sich also…

+

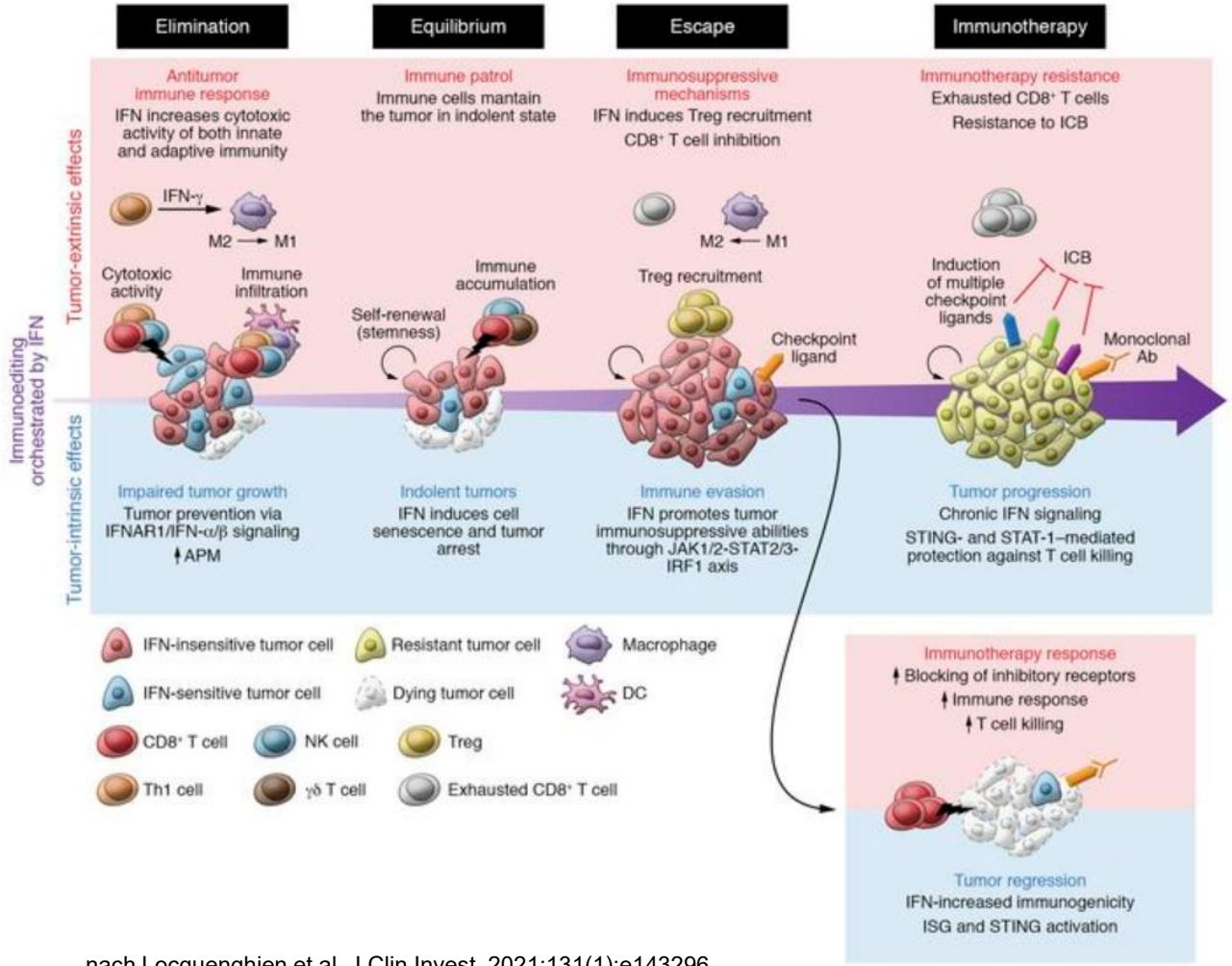
=



Therapieerfolg



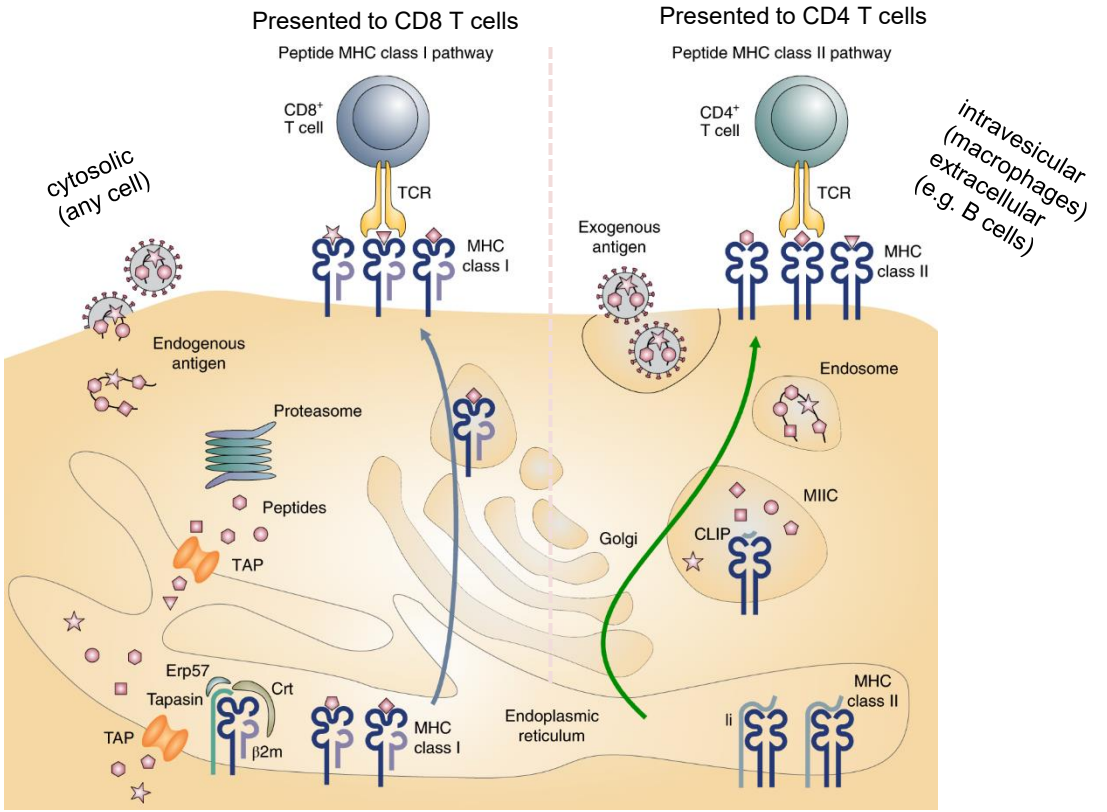
aus Halama et al.



Dynamik

nach Locquenghien et al. J Clin Invest. 2021;131(1):e143296.

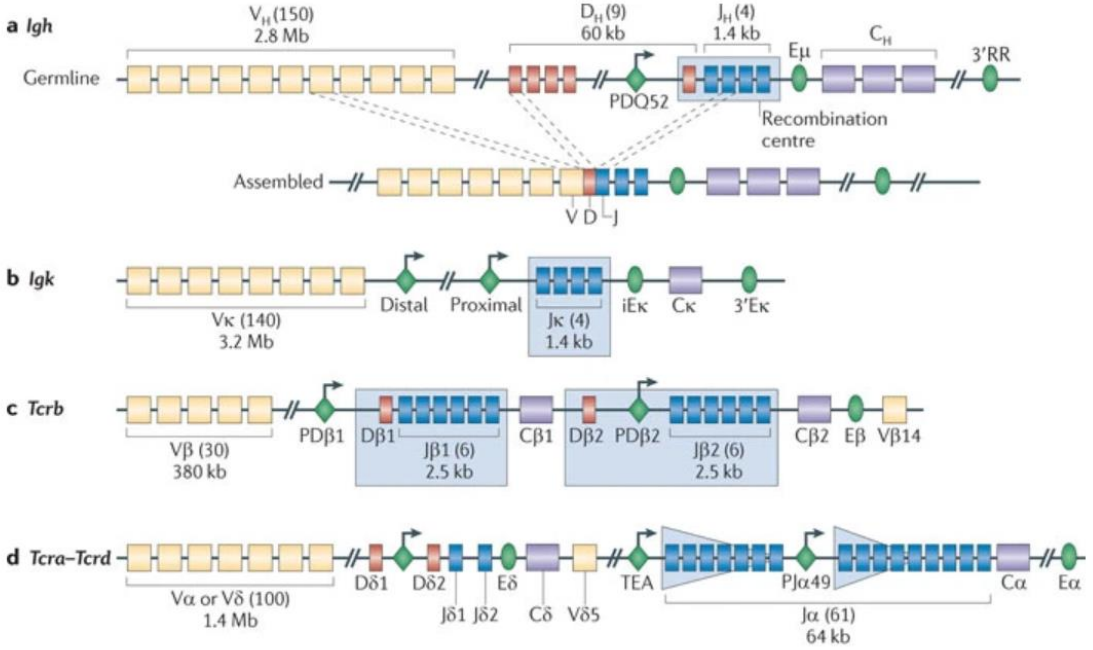
Technik: erkennen von “selbst” und “nicht-selbst” via MHC (major histocompatibility complex)



Purcell et al. Nature Protocols 2019

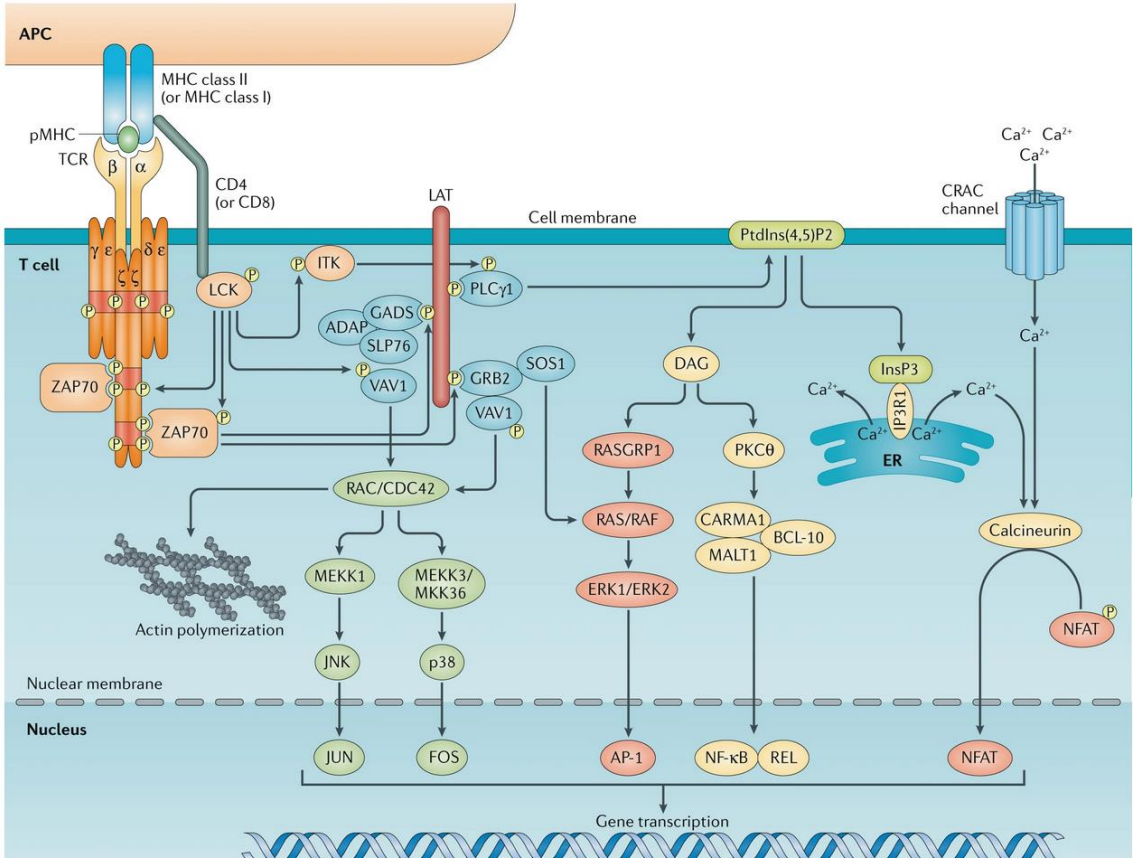
„Immunreaktion“ aus dem Blickwinkel der T Zelle…

Arming the T cell: der T Zellrezeptor



[Schatz et al. Nature Reviews Immunology](#) 2011

T Zell Rezeptor Signalling: Pathways



Gaud et al. Nature Reviews Immunology 2018

Was ist das ideale Tumorantigen?

- Protein eines mutierten Gens (e.g. Onkogen oder Tumorsuppressor)
- Überexprimiert oder abberante Expression
- Tumorantigene durch onkogene Viren
- Onkofetale Antigene (e.g. CEA)
- Veränderte Oberflächen-Glykolipipde oder Glykoproteine
- …

Was ist das ideale Zielantigen?

„The neoepitope: An epitope which the immune system has not encountered before (e.g. under non-tumor conditions). Therefore it is not subject to tolerance mechanisms of the immune system.”

Was wird überhaupt erkannt?

The response of autologous T cells to a human melanoma is dominated by mutated neoantigens

Volker Lennerz[†], Martina Fatho[†], Chiara Gentilini[‡], Roy A. Frye[§], Alexander Lifke[†], Dorothea Ferel[†], Catherine Wölfel[†], Christoph Huber[†], and Thomas Wölfel[†¶]

[†]Department of Medicine, Hematology/Oncology, Johannes Gutenberg University, Langenbeckstrasse 1, D-55101 Mainz, Germany; [‡]Department of Medicine, Hematology/Oncology, University of Leipzig, Liebigstrasse 22, D-04103 Leipzig, Germany; and [§]Department of Pathology, Veterans Affairs Medical Center, University Drive C, Pittsburgh, PA 15240

Edited by Lloyd J. Old, Ludwig Institute for Cancer Research, New York, NY, and approved September 12, 2005 (received for review January 6, 2005)

Our understanding of pathways leading to antitumor immunity may depend on an undistorted knowledge of the primary antigenic targets of patients' autologous T cell responses. In the melanoma model derived from patient DT, we applied cryopreserved short-term autologous mixed lymphocyte–tumor cell cultures (MLTCs) in combination with an IFN-γ enzyme-linked immunospot (ELISPOT) assay to cDNA expression screening. We identified three previously unknown peptides processed from melanosomal proteins tyrosinase (presented by HLA-A*2601 and -B*3801) and gp100 (presented by HLA-B*07021) and five neoantigens generated by somatic point mutations in the patient's melanoma. The mutations were found in the genes SIRT2, GPNMB, SNRP116, SNRPD1, and RBAF600. Peptides containing the mutated residues were presented by HLA-A*03011, -B*07021, and -B*3801. Mutation-induced functional impairment was so far demonstrated for SIRT2. Within antigens detected with highly selected clonal T cells does not adequately reflect the situation *in vivo*.

We modified the cDNA expression cloning of tumor antigens by applying cryopreserved, multispecific mixed lymphocyte–tumor cell cultures (MLTCs) in addition to clonal T cells. In the example of a long-term surviving melanoma patient with metastatic disease, we identified eight antigens, three of which were previously unknown peptide antigens processed from structurally unaltered melanosomal proteins, and five of which were neoantigens generated by somatic mutations in tumor cells. T cells reactive with mutated peptides clearly predominated in independent MLTCs.

Materials and Methods

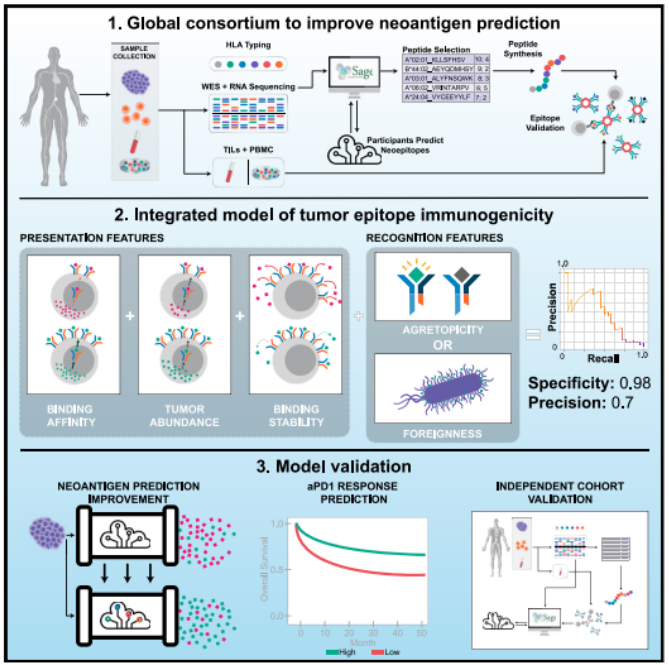
Supporting Information. For further details, see Figs. 7–10 and Tables 2–5, which are published as supporting information on the

Die Suche läuft…

Cell

Key Parameters of Tumor Epitope Immunogenicity Revealed Through a Consortium Approach Improve Neoantigen Prediction

Graphical Abstract



Authors

Daniel K. Wells, Marit M. van Buuren, Kristen K. Dang, ..., Ton N. Schumacher, Pia Kvistborg, Nadine A. Defranoux

Correspondence

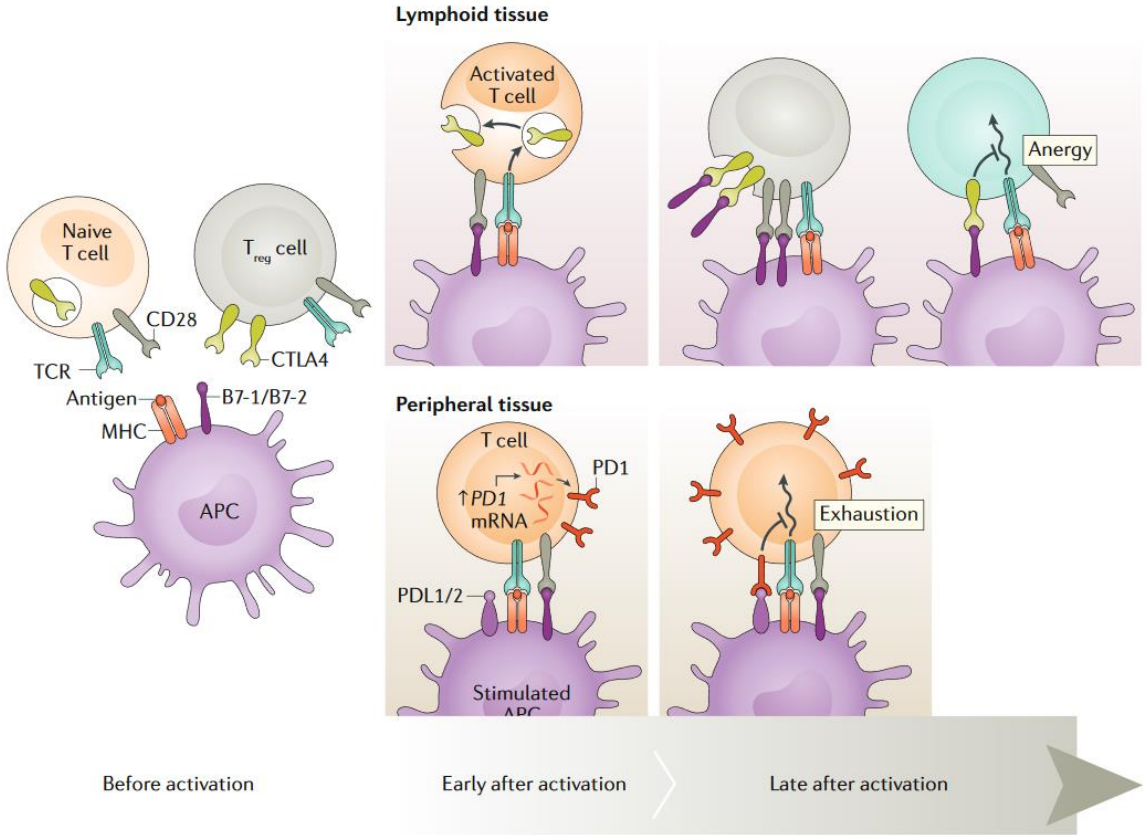
dwells@parkerici.org (D.K.W.), ndefranoux@parkerici.org (N.A.D.)

In Brief

Genomic tumor sequencing data with matched measurements of tumor epitope immunogenicity allows for insights into the governing parameters of epitope immunogenicity and generation of models for effective neoantigen prediction.

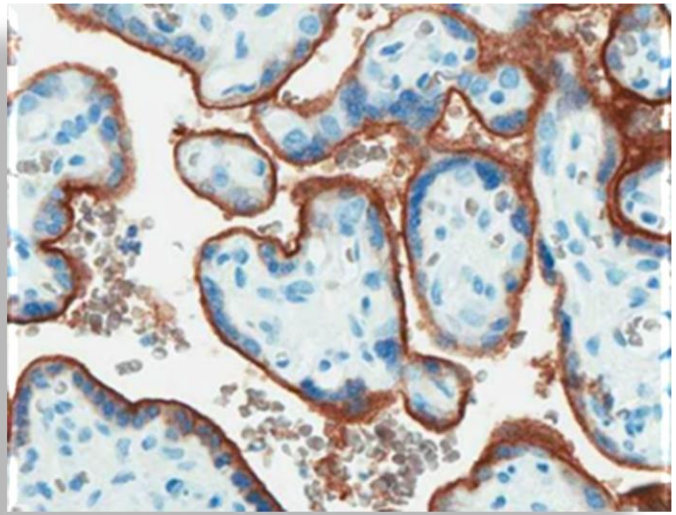

SPIEGLEIN, SPIEGLEIN, AN DER WAND, WER IST DIE SCHÖNSTE IM GANZEN LAND?
HMM. DAS IST IN DIESEN TAGEN SCHWER ZU SAGEN...
FEIGE
-DEBESTE-

Inhibitory receptor pathways: Schutz vor Überaktivierung

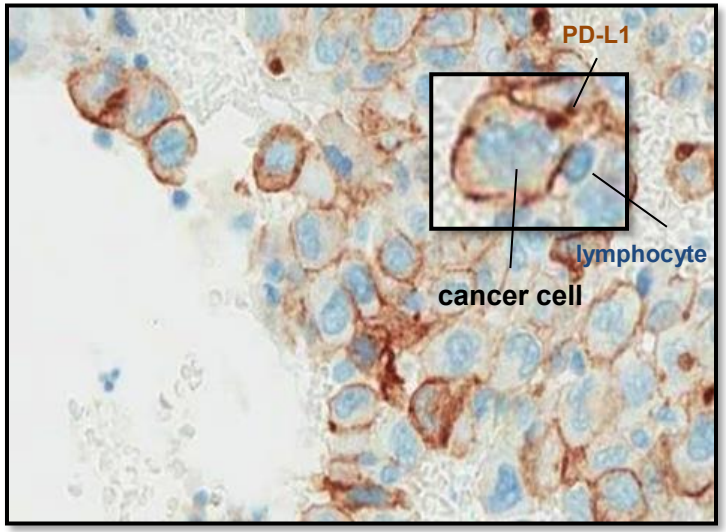


Waldmann et al. Nat Rev Immunol 2020

PD-L1 findet sich in…



Plazenta

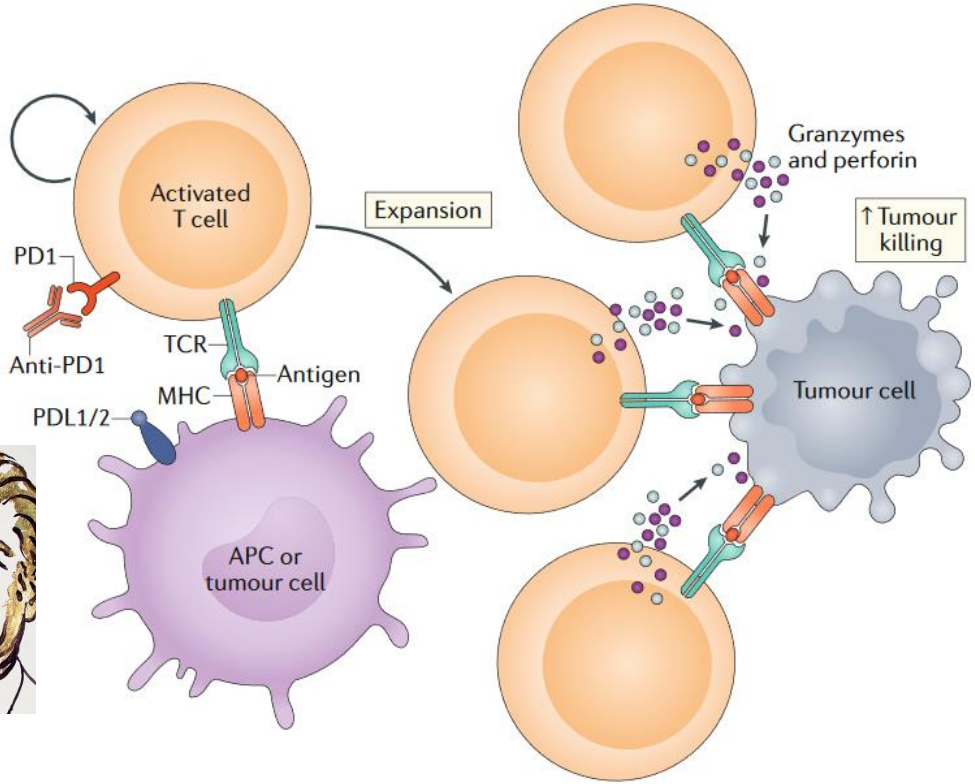


Tumorgewebe

source: John Powderly 2022

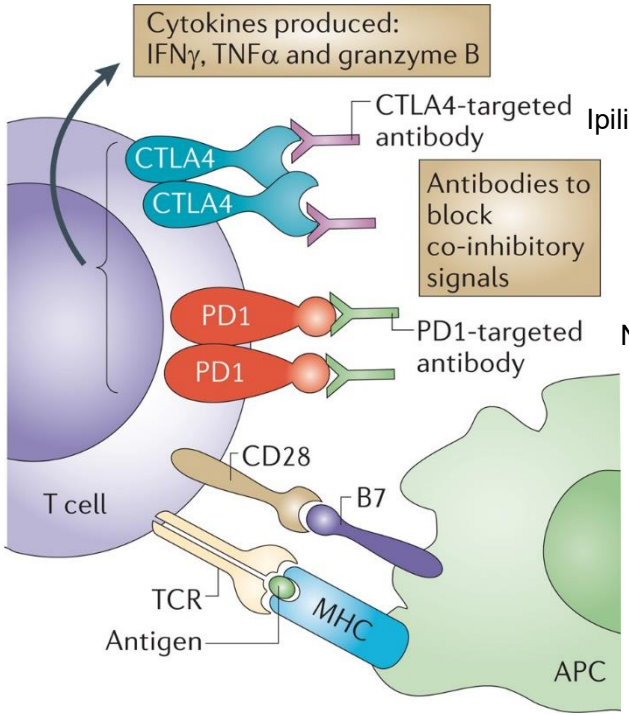
Das berühmte Beispiel…

James P Allison and Tasuku Honjo



Waldmann et al. Nat Rev Immunol 2020

Checkpoint-Inhibition



Sharma et al. Nat Rev Cancer. 2011

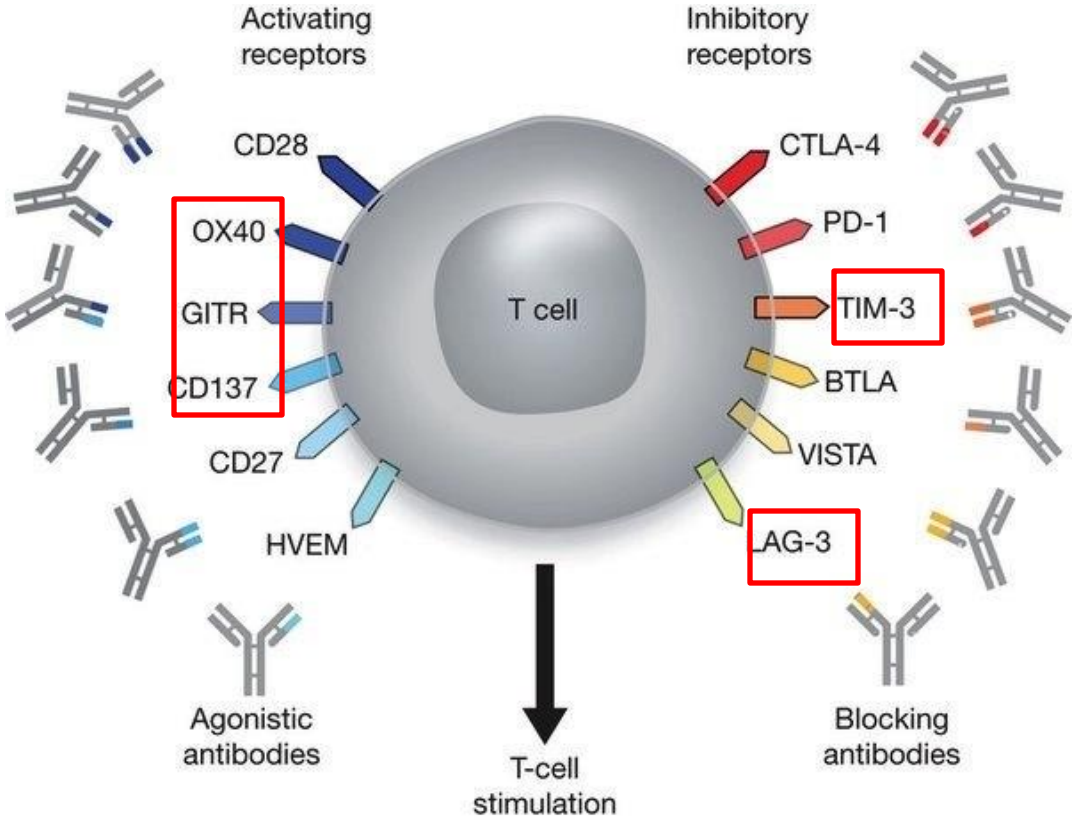
Checkpoint-Inhibition: „Auftauen“ der Immunantwort…

(from: StarWars: Han Solo frozen in carbonit)

Und noch mehr Signalkaskaden in T Zellen…

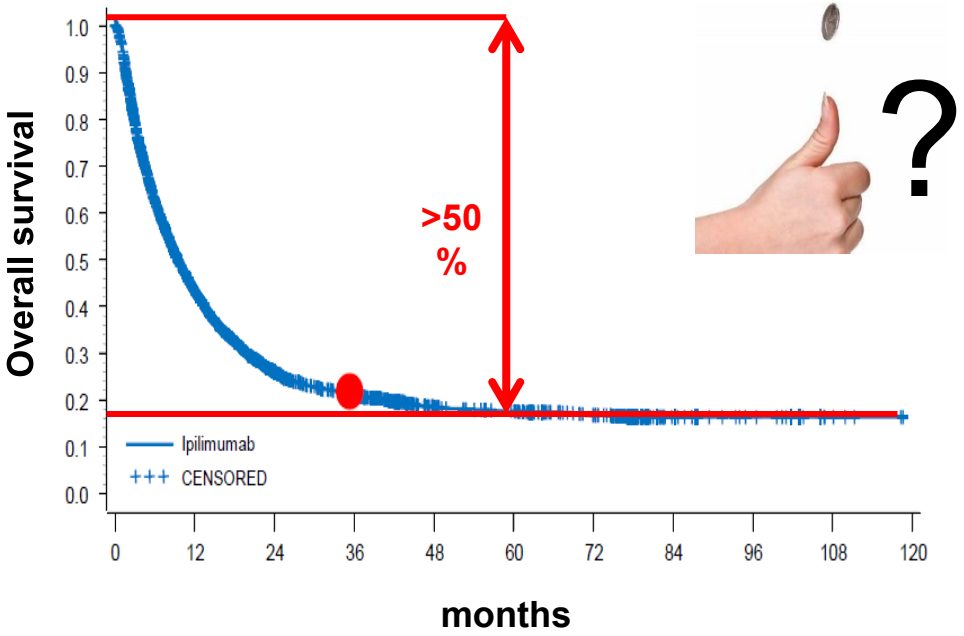
Turning up The Activating

Blocking the Inhibiting



Adapted from Mellman *et al.* Nature, 2011

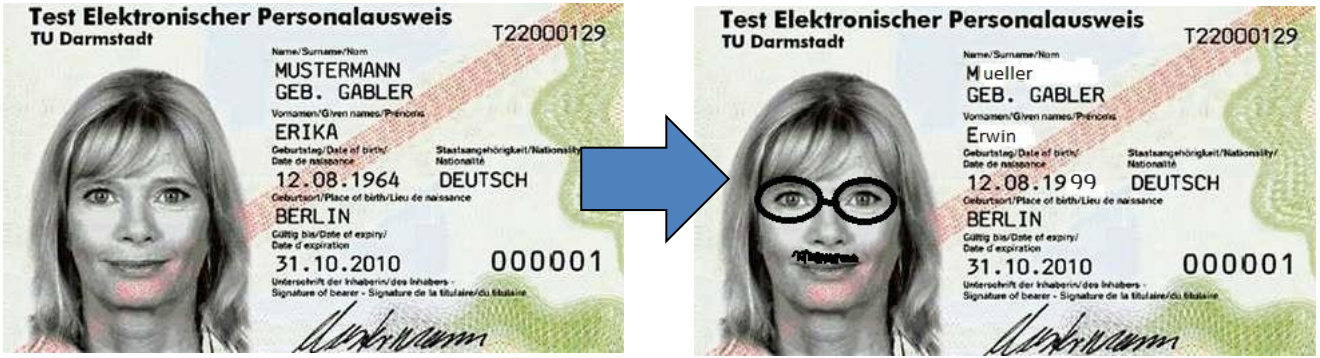
Immuntherapie



Adapted from Schadendorf et al., ESMO 2013

Tumorimmunogenität und Immunreaktionen: ein komplexes Gebiet

Resistenzmechanismen 1



„Failed recognition / antigen masking / mimicry“
Bsp. via HLA Regulation, „unsichtbare“ Klone

Resistenzmechanismen 2

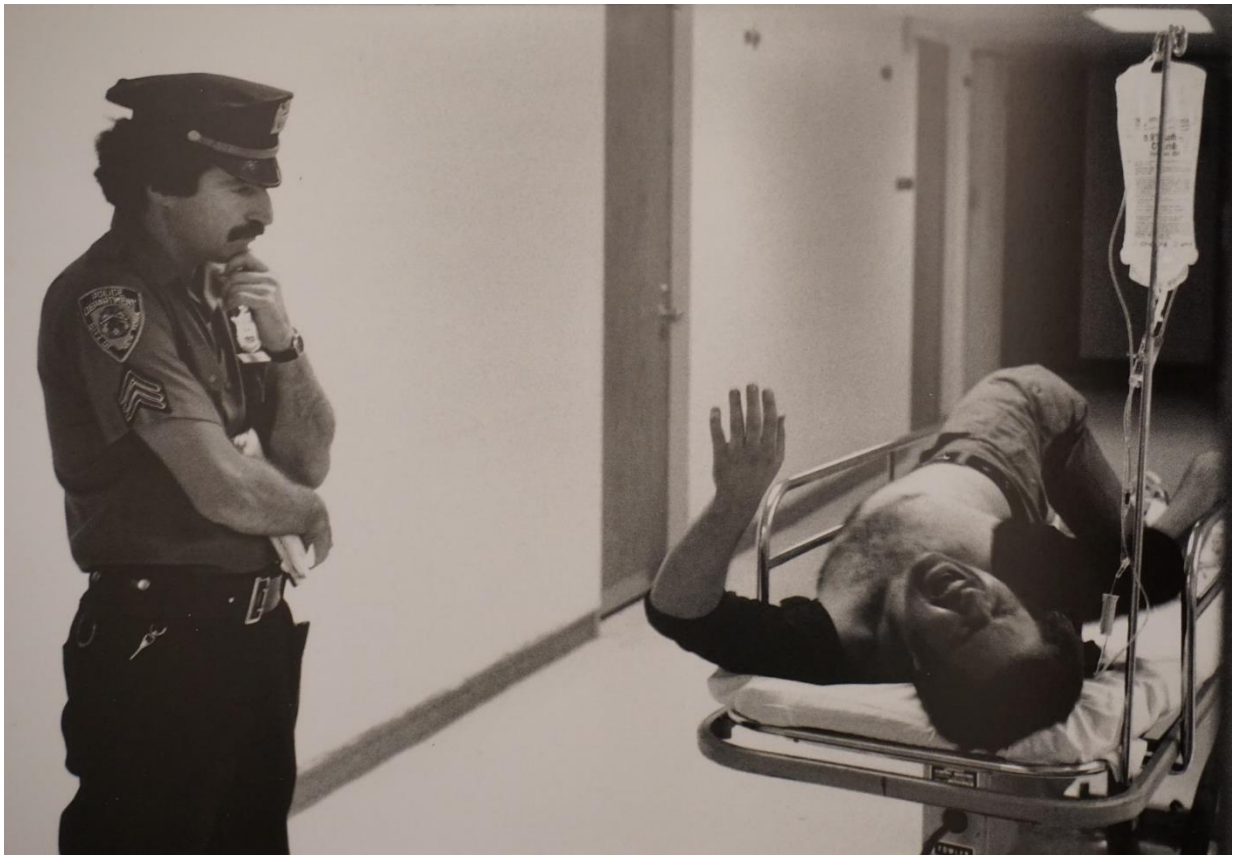


Image by Leonard Freed

Anergie

(= Effektorzellen inaktiviert)

e.g. metabolic anergy, absent co-stimulating signals

Resistenzmechanismen 3

Image by Lee Friedlander

In die Irre führen…
(= „away from tumor“ <aft>)
e.g. „invasive margin“

Resistenzmechanismen 4

Image by Leonard Freed

Unrecognized tumor or effector T cells activated with false target
e.g. CEA expression on immune cells / „fratricide“

Resistenzmechanismen 5

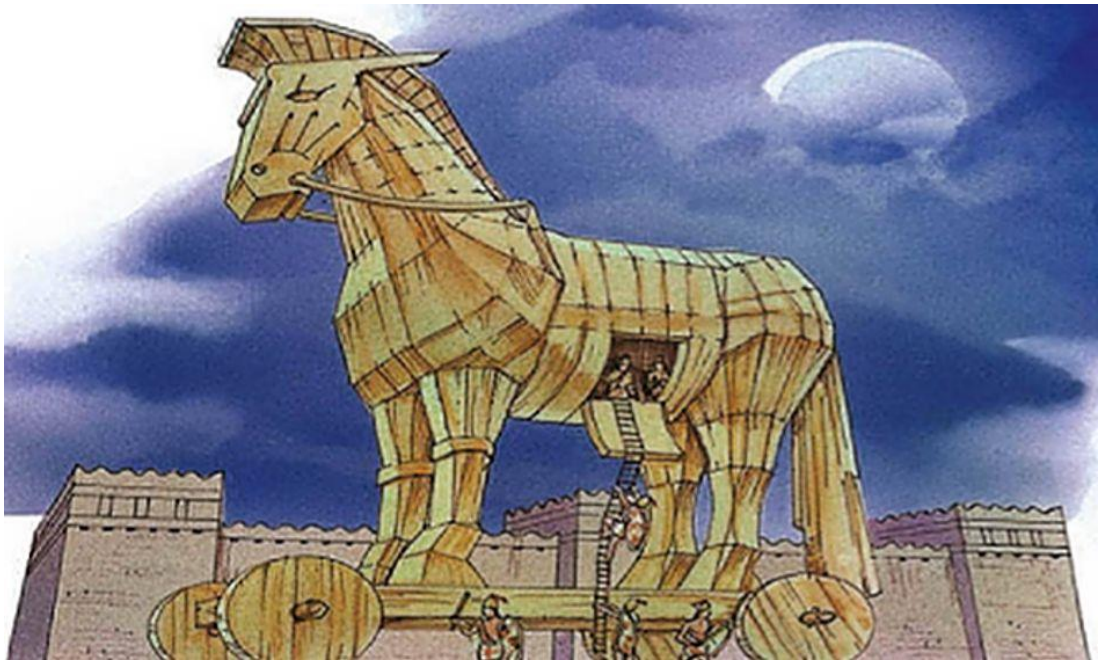


Image by outschool.com

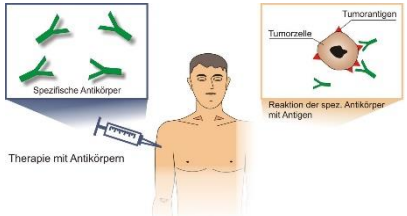
Abwehrmechanismen übernehmen

Bsp. CCL5-CCR5

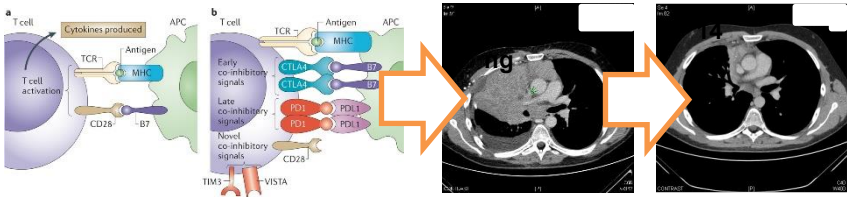
Mehr Informationen unter…

Wie lässt sich die Tumorimmunogenität in der Klinik verbessern?

Konzepte…

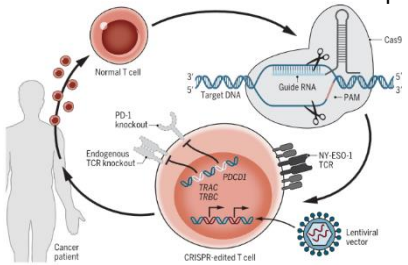


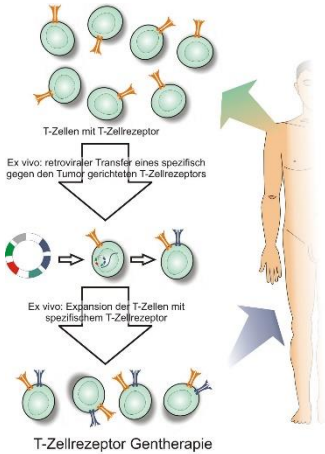
Antikörper-basierte Therapien

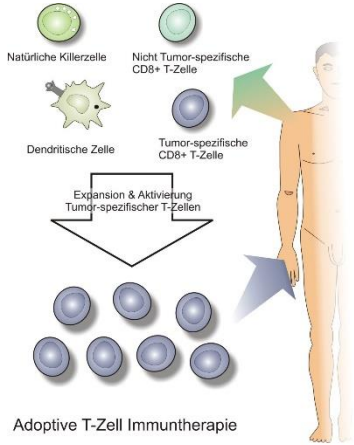


Checkpoint-Inhibitoren

Genschere für zelluläre Immuntherapie



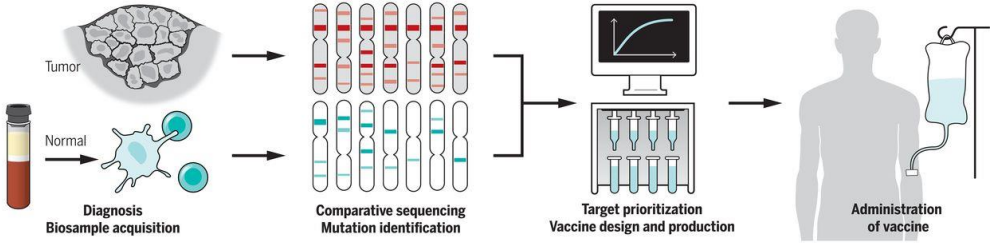




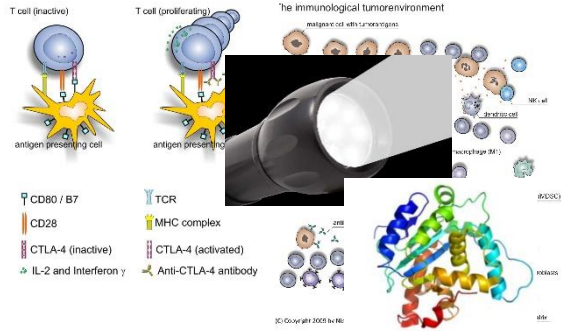
Zelluläre Immuntherapien

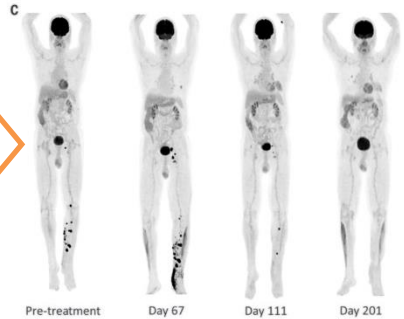
Und nochmal Konzepte…

mRNA-basierte personalisierte Impfung & Therapie

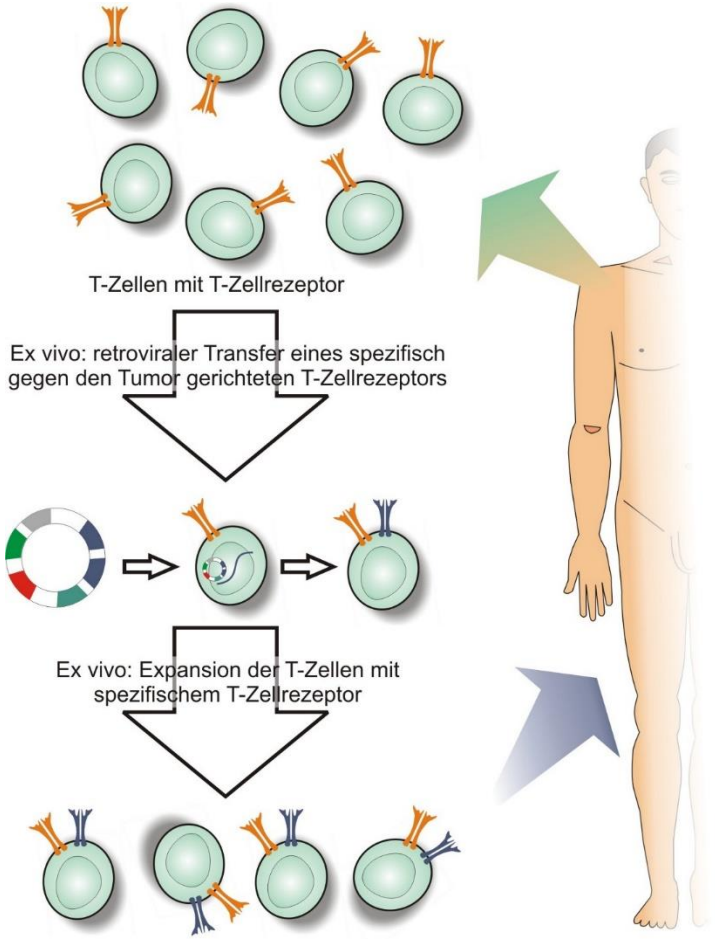


Modulation der Mikroumgebung: Virotherapie, Mikrobiom & angeborenes Immunsystem





Und mit dem geeigneten Antigen…?

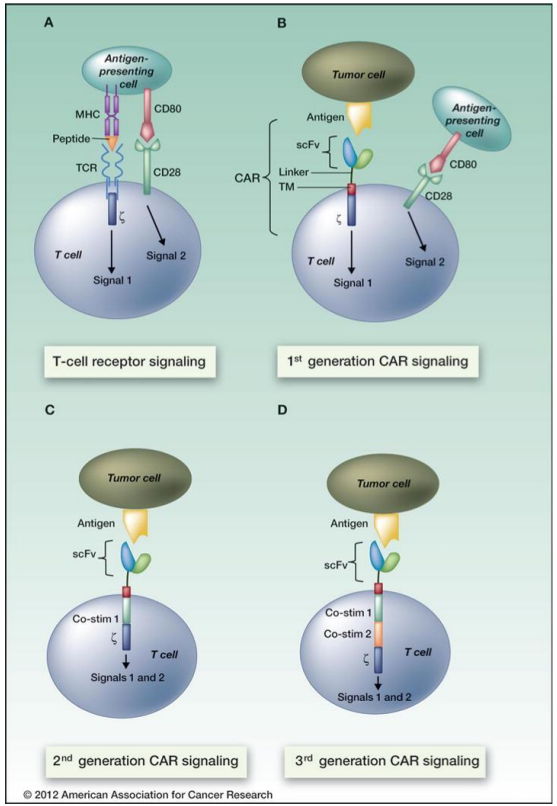


T-Zellrezeptor Gentherapie

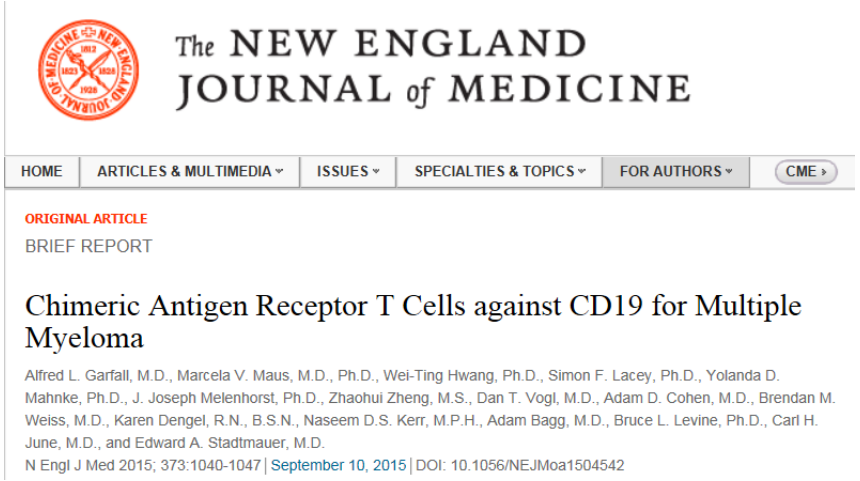
Beispiele:
chimeric antigen receptor CAR Therapie als derzeit prominentestes Beispiel, etc…

aus Halama et al. 2012

Chimeric antigen receptor (CAR)



Lee et al. Clin Cancer Res 2012



The NEW ENGLAND JOURNAL of MEDICINE

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ORIGINAL ARTICLE

BRIEF REPORT

Chimeric Antigen Receptor T Cells against CD19 for Multiple Myeloma

Alfred L. Garfall, M.D., Marcela V. Maus, M.D., Ph.D., Wei-Ting Hwang, Ph.D., Simon F. Lacey, Ph.D., Yolanda D. Mahnke, Ph.D., J. Joseph Melenhorst, Ph.D., Zhaohui Zheng, M.S., Dan T. Vogl, M.D., Adam D. Cohen, M.D., Brendan M. Weiss, M.D., Karen Dengel, R.N., B.S.N., Naseem D.S. Kerr, M.P.H., Adam Bagg, M.D., Bruce L. Levine, Ph.D., Carl H. June, M.D., and Edward A. Stadtmauer, M.D.

N Engl J Med 2015; 373:1040-1047 | September 10, 2015 | DOI: 10.1056/NEJMoa1504542

A patient with refractory multiple myeloma received an infusion of CTL019 cells, a cellular therapy consisting of autologous T cells transduced with an anti-CD19 chimeric antigen receptor, after myeloablative chemotherapy (melphalan, 140 mg per square meter of body-surface area) and autologous stem-cell transplantation. Four years earlier, autologous transplantation with a higher melphalan dose (200 mg per square meter) had induced only a partial, transient response. Autologous transplantation followed by treatment with CTL019 cells led to a complete response with no evidence of progression and no measurable serum or urine monoclonal protein at the most recent evaluation, 12 months after treatment. This response was achieved despite the absence of CD19 expression in 99.95% of the patient's neoplastic plasma cells.

Nobelpreis 2020 in Chemie

© Nobel Media. Ill. Niklas Elmehed.

Emmanuelle Charpentier

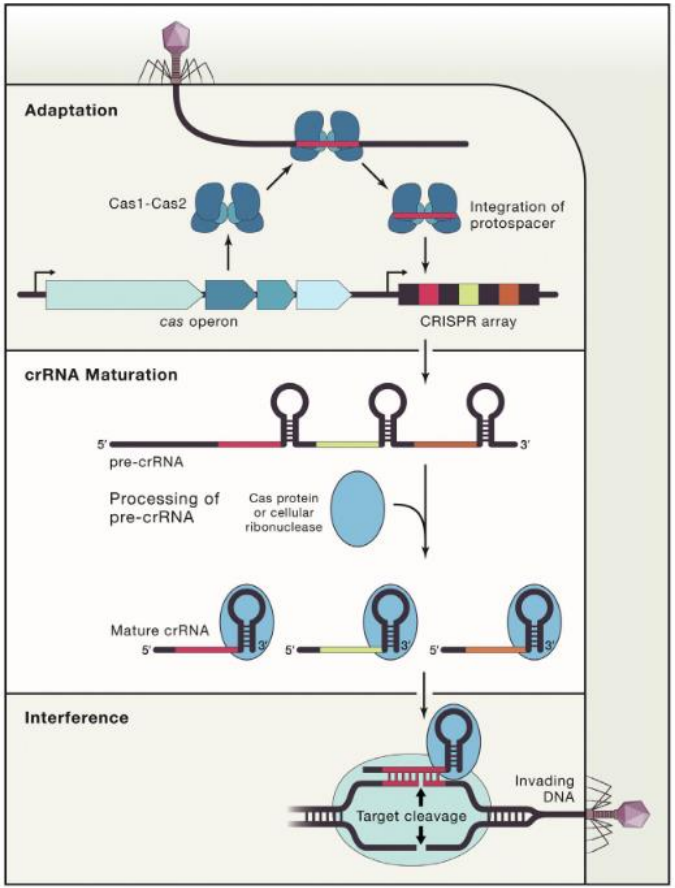
Prize share: 1/2

© Nobel Media. Ill. Niklas Elmehed.

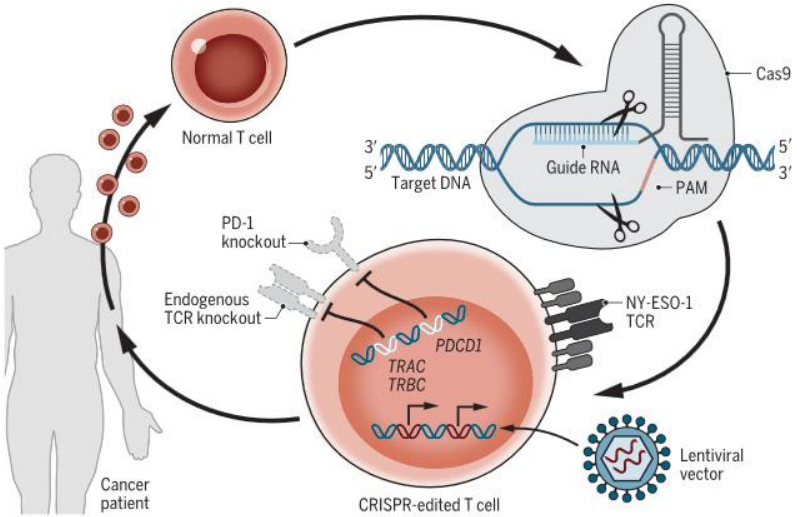
Jennifer A. Doudna

Prize share: 1/2

CRISPR/CAS


Adaptation
Cas1-Cas2
Integration of protospacer
cas operon
CRISPR array
crRNA Maturation
5'
3'
pre-crRNA
Processing of pre-crRNA
Cas protein or cellular ribonuclease
Mature crRNA
Interference
Invading DNA
Target cleavage

Neuer Ansatz…

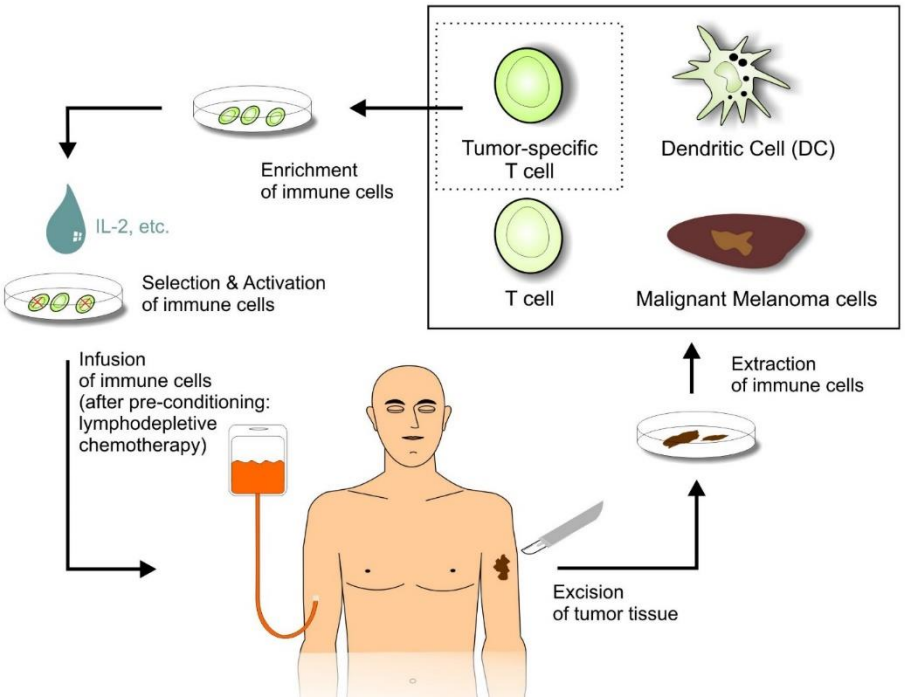


CRISPR-Cas9 engineering of T cells in cancer patients. T cells (center) were isolated from the blood of a patient with cancer. CRISPR-Cas9 ribonuclear protein complexes loaded with three sgRNAs were electroporated into the normal T cells, resulting in gene editing of the *TRAC*, *TRBC1*, *TRBC2*, and *PDCD1* (encoding PD-1) loci. The cells were then transduced with a lentiviral vector to express a TCR specific for the cancer-testis antigens NY-ESO-1 and LAGE-1 (right). The engineered T cells were then returned to the patient by intravenous infusion, and patients were monitored to determine safety and feasibility. PAM, protospacer adjacent motif.

Stadtmauer *et al.*, *Science* **367**, 1001 (2020) 28 February 2020

Und mit dem geeigneten Antigen…?

Adoptiver T Zell Transfer

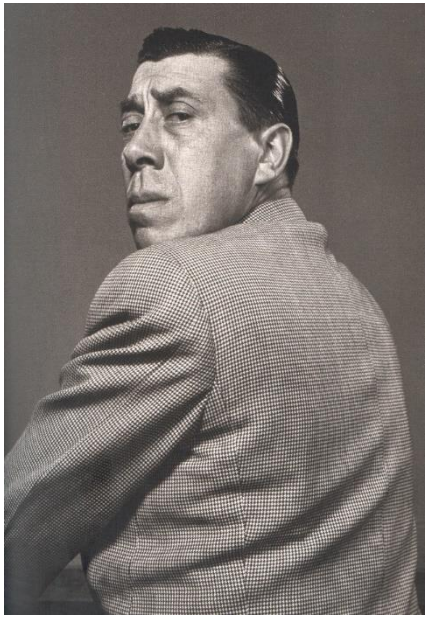


Halama et al. J Oncology 2010

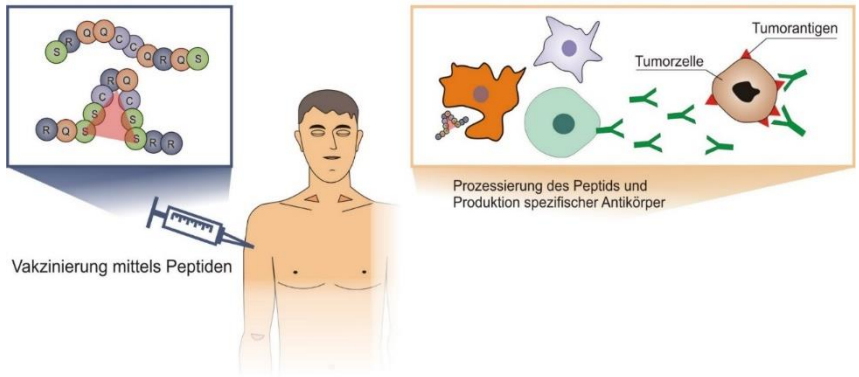
Zelluläre Therapien bei soliden Tumoren bisher…

…zeigt keine anhaltenden Effekte.

(Noch kurz warten…es geht aber weiter!)

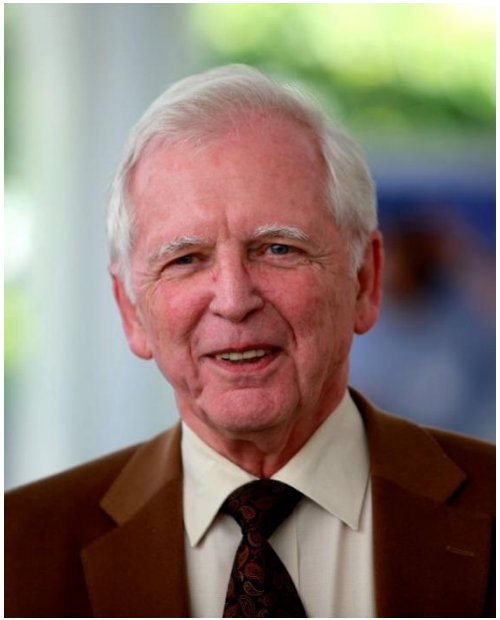


Quelle: Halsman, „The Frenchman“



Impfungen mit Proteinen / Peptiden: Myeloma GVAX (Phase I/II)…

Achtung:
präventive Impfung vs therapeutische Impfung!



source: dkfz

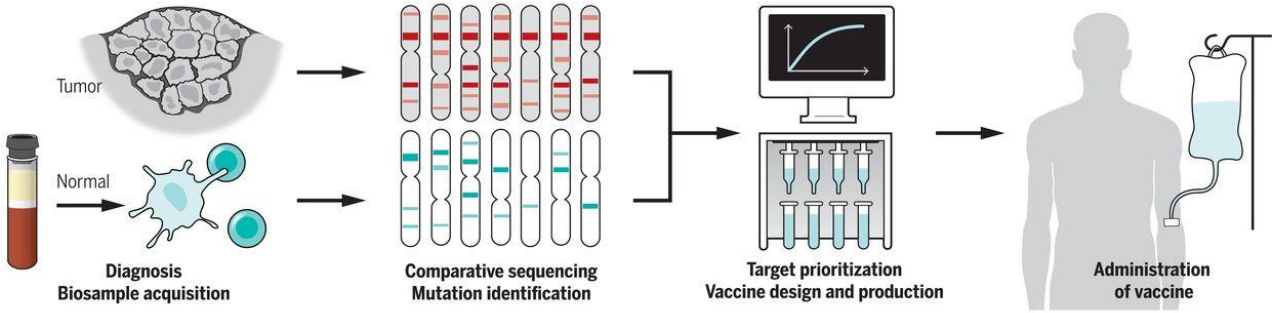
dkfz. DEUTSCHES KREBSFORSCHUNGSZENTRUM IN DER HELMHOLTZ-GEMEINSCHAFT

Mehr Informationen unter…

Deutscher Krebspreis 2019

Kategorie translationale Krebsforschung

Prof. Dr. Ugur Sahin



Personalisierte Tumorvakzine

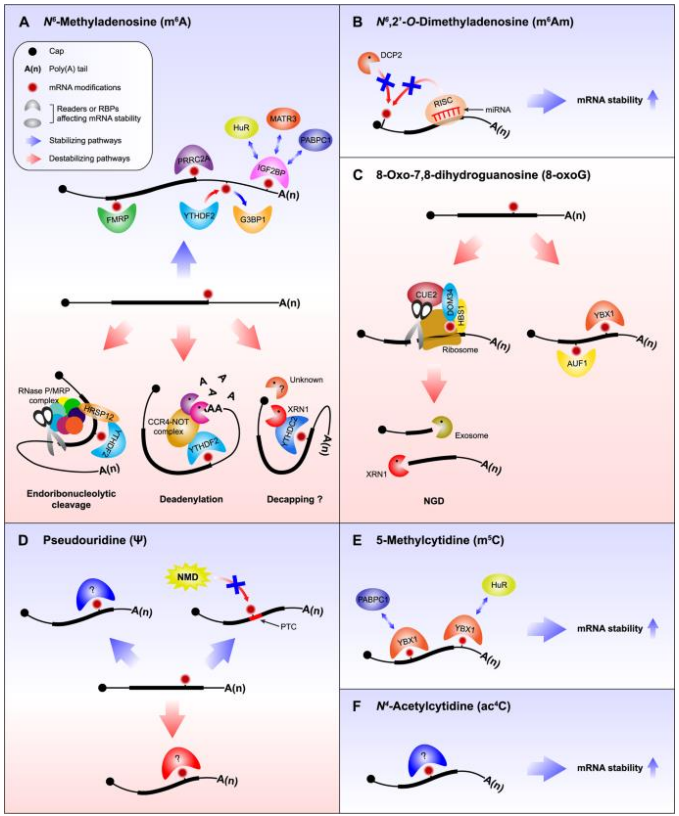
dkfz. DEUTSCHES KREBSFORSCHUNGSZENTRUM IN DER HELMHOLTZ-GEMEINSCHAFT

Schnelle Entschlüsselung des Erbguts

source: Uroforum

Wo liegen die Unterschiede zwischen dem Tumorerbgut und dem Erbgut der gesunden Zellen…?

source: www.ratefux.de



source: nature.com
source: iStockphote

mRNA…
…modifizieren und einpacken (und die Haltbarkeit erhöhen)

dkfz. DEUTSCHES KREBSFORSCHUNGSZENTRUM IN DER HELMHOLTZ-GEMEINSCHAFT

The Nobel Prize in Physiology or Medicine 2023

Ill. Niklas Elmehed © Nobel Prize Outreach

Katalin Karikó

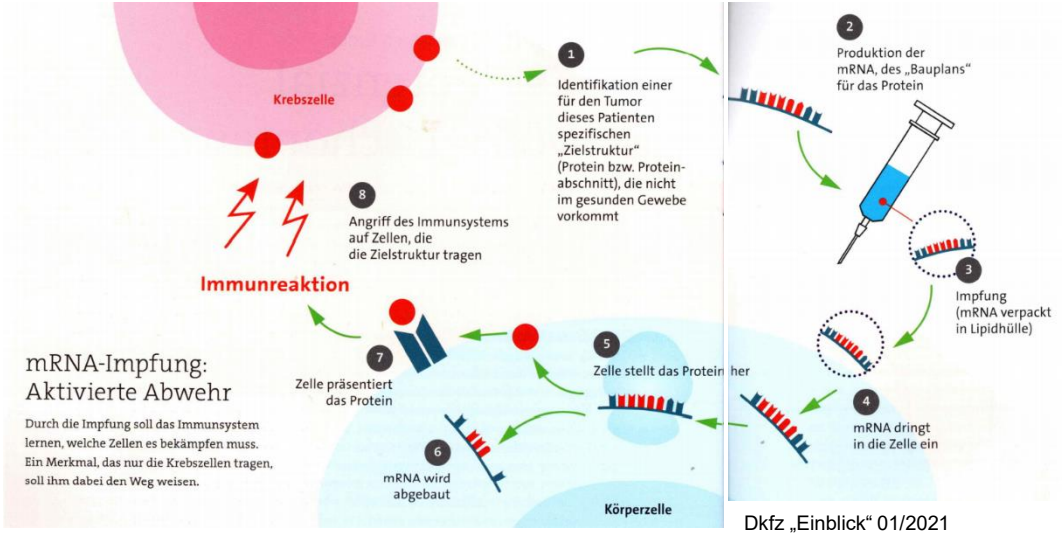
Prize share: 1/2

Ill. Niklas Elmehed © Nobel Prize Outreach

Drew Weissman

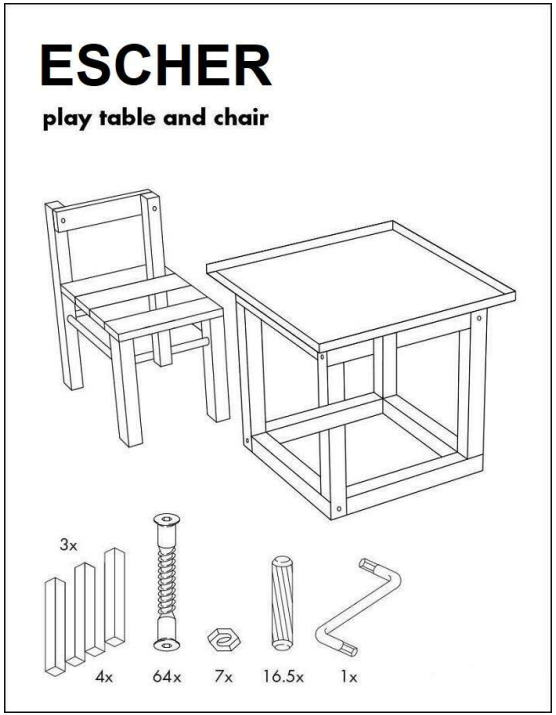
Prize share: 1/2

Personalisierte
Impfung gegen den Tumor

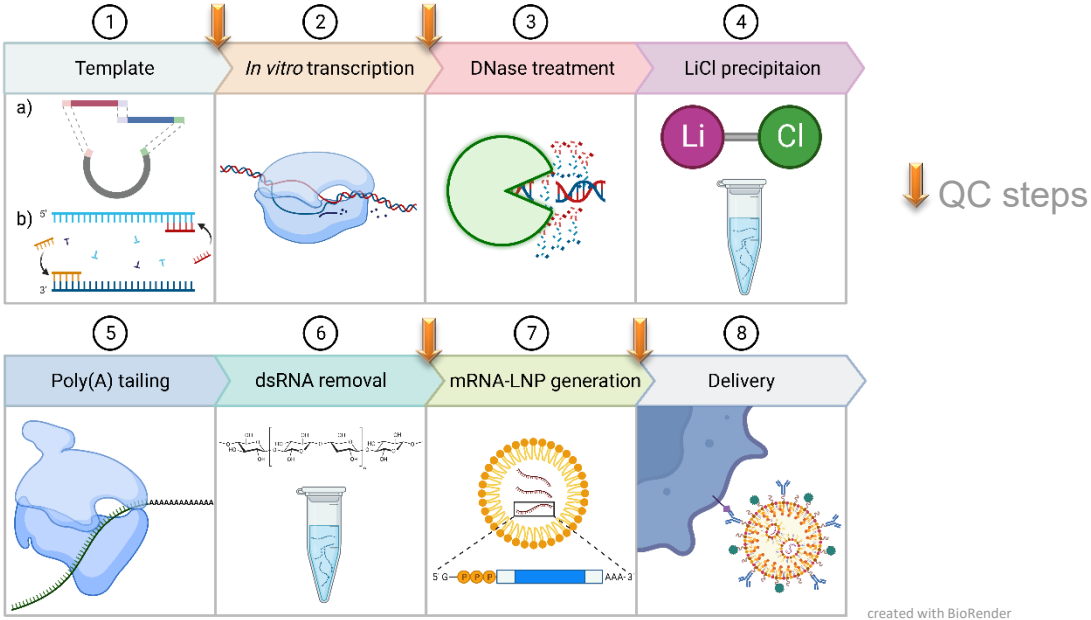


Dkfz „Einblick“ 01/2021

Wie wird die mRNA Vakzine „zusammengebaut“?



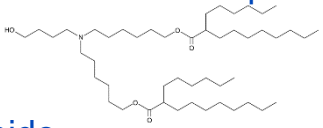
Arbeitsschritte (Schema)



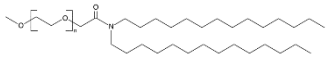
Erstellt von Jannis Wißfeld (HI-TRON)

Lipid Nanoparticle Formulation (LNF)

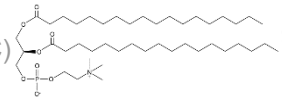
- **Ionisierte cationische Lipide**
  - ALC-0315



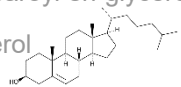
- **PEG Lipide**
  - ALC-0159



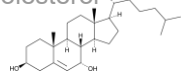
- **Rahmen-/Strukturelle Lipide**
  - 1,2-Distearoyl-sn-glycero-3-PC (DSPC)



  - Cholesterol

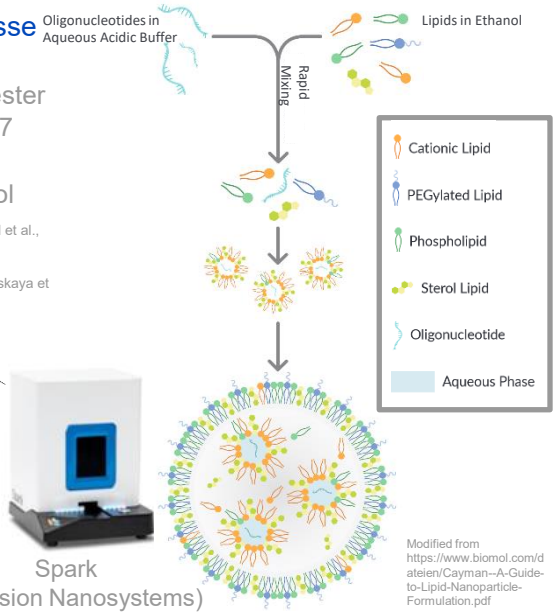


  - 7α-hydroxy cholesterol



Chemical structures from biomol.com

- **Molare Verhältnisse**
  - ALC-315:ALC-0159:DSPC:Cholesterol 46.3:1.6:9.4:42.7
  - Cholesterol:7α-hydroxy cholesterol 75:25 or 50:50 (Patel et al., 2022)
  - N:P ratio 6-15 (Gretskaya et al., 2023)

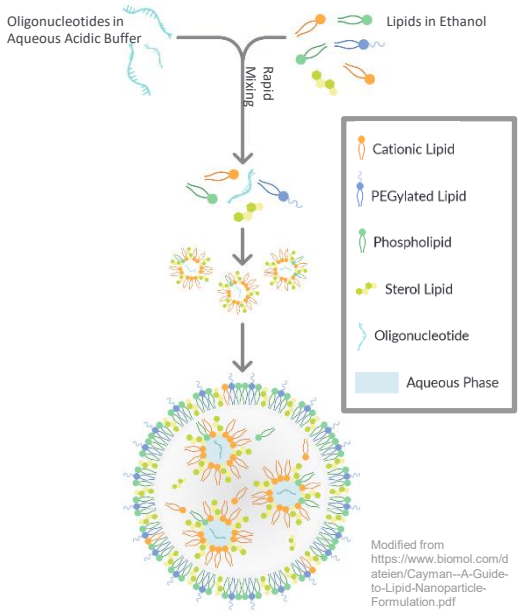


Spark
(Precision Nanosystems)

Modified from https://www.biomol.com/dateien/Cayman--A-Guide-to-Lipid-Nanoparticle-Formulation.pdf

Erstellt von Jannis Wißfeld (HI-TRON)

Lipid nanoparticle formulation - Qualitätskontrollen



Erstellt von Jannis Wißfeld (HI-TRON)

QC Analysen

- Encapsulation efficiency
  - Ribogreen Assay
- LNP Größe und Heterogenität
  - Dynamic light scattering
- LNP Partikelladung
  - Zeta Potential Analyzer

Quelle: Christoph Niemann

Was kostet das ganze denn…?

- Checkpoint Inhibitoren liegen bei Kosten von bis zu 250.000 Euro pro Quartal
- Zelluläre Therapien liegen bei Kosten von 0.5-1.5 Millionen Euro pro einmalige Anwendung
- mRNA basierte Therapien haben noch keine Kostenschätzung…

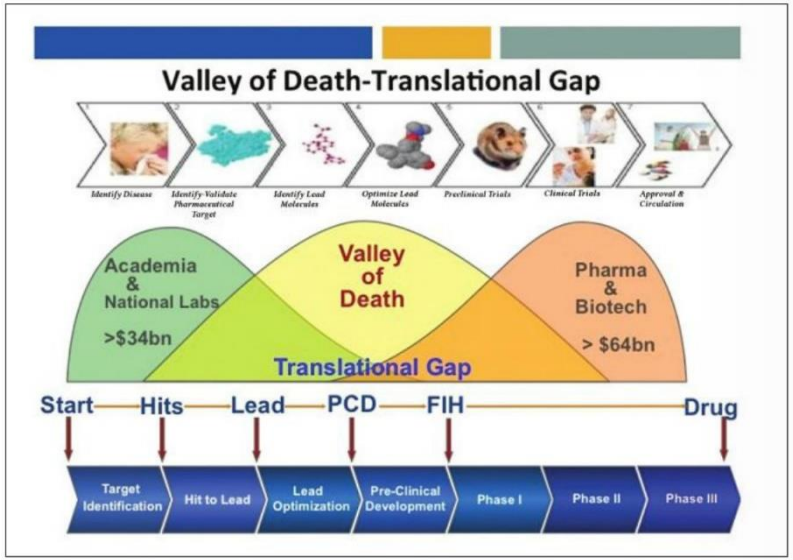


Figure 8 The map of valley of death-translational gap

https://www.ddw-online.com/translational-chemical-biology-gap-assessment-for-advancing-drug-discovery-development-and-precision-medicine-1031-201612/

Entwicklungskosten neues Medikament: typischerweise mehr als 100 Millionen Euro…

Und in der Klinik…?

mRNA Impfung in der Onkologie

Individualised neoantigen therapy mRNA-4157 (V940) plus pembrolizumab versus pembrolizumab monotherapy in resected melanoma (KEYNOTE-942): a randomised, phase 2b study

Jeffrey S Weber, Matteo S Carlino, Adnan Khattak, Tarek Meniawy, George Ansstas, Matthew H Taylor, Kevin B Kim, Meredith McKean, Georgina V Long, Ryan J Sullivan, Mark Faries, Thuy T Tran, C Lance Cowey, Andrew Pecora, Montaser Shaheen, Jennifer Segar, Theresa Medina, Victoria Atkinson, Geoffrey T Gibney, Jason J Luke, Sajeve Thomas, Elizabeth I Buchbinder, Jane A Healy, Mo Huang, Manju Morrissey, Igor Feldman, Vasudha Sehgal, Celine Robert-Tissot, Peijie Hou, Lili Zhu, Michelle Brown, Praveen Aanur, Robert S Meehan, Tal Zaks**

Lancet 2024; 403: 632–44

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See Comment page 590

*Contributed equally to the scientific inquiry, design, and execution of the study

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Summary

Background Checkpoint inhibitors are standard adjuvant treatment for stage IIB–IV resected melanoma, but many patients recur. Our study aimed to evaluate whether mRNA-4157 (V940), a novel mRNA-based individualised neoantigen therapy, combined with pembrolizumab, improved recurrence-free survival and distant metastasis-free survival versus pembrolizumab monotherapy in resected high-risk melanoma.

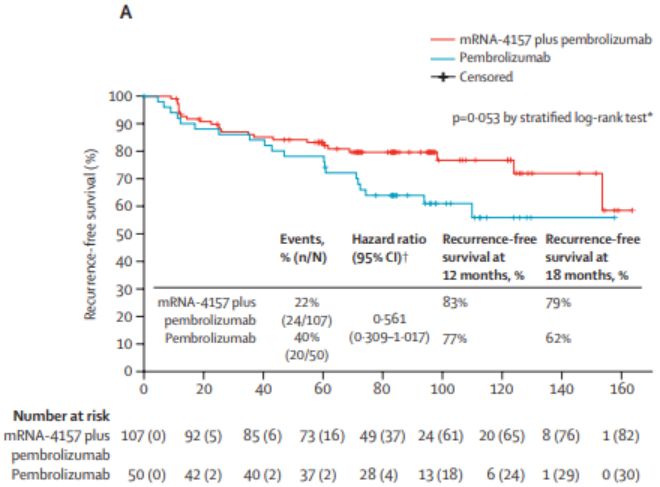
Methods We did an open-label, randomised, phase 2b, adjuvant study of mRNA-4157 plus pembrolizumab versus pembrolizumab monotherapy in patients, enrolled from sites in the USA and Australia, with completely resected high-risk cutaneous melanoma. Patients with completely resected melanoma (stage IIIB–IV) were assigned 2:1 to receive open-label mRNA-4157 plus pembrolizumab or pembrolizumab monotherapy. mRNA-4157 was administered intramuscularly (maximum nine doses) and pembrolizumab intravenously (maximum 18 doses) in 3-week cycles. The primary endpoint was recurrence-free survival in the intention-to-treat population. This ongoing trial is registered at ClinicalTrials.gov, NCT03897881.

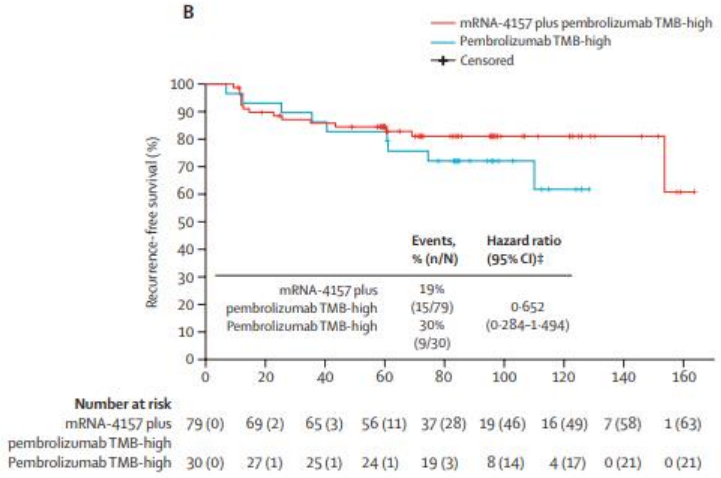
Findings From July 18, 2019, to Sept 30, 2021, 157 patients were assigned to mRNA-4157 plus pembrolizumab combination therapy (n=107) or pembrolizumab monotherapy (n=50); median follow-up was 23 months and 24 months, respectively. Recurrence-free survival was longer with combination versus monotherapy (hazard ratio [HR] for recurrence or death, 0·561 [95% CI 0·309–1·017]; two-sided p=0·053), with lower recurrence or death event rate (24 [22%] of 107 *vs* 20 [40%] of 50); 18-month recurrence-free survival was 79% (95% CI 69·0–85·6) versus 62% (46·9–74·3). Most treatment-related adverse events were grade 1–2. Grade ≥3 treatment-related adverse events occurred in 25% of patients in the combination group and 18% of patients in the monotherapy group, with no mRNA-4157-related grade 4–5 events. Immune-mediated adverse event frequency was similar for the combination (37 [36%]) and monotherapy (18 [36%]) groups.

Interpretation Adjuvant mRNA-4157 plus pembrolizumab prolonged recurrence-free survival versus pembrolizumab monotherapy in patients with resected high-risk melanoma and showed a manageable safety profile. These results provide evidence that an mRNA-based individualised neoantigen therapy might be beneficial in the adjuvant setting.

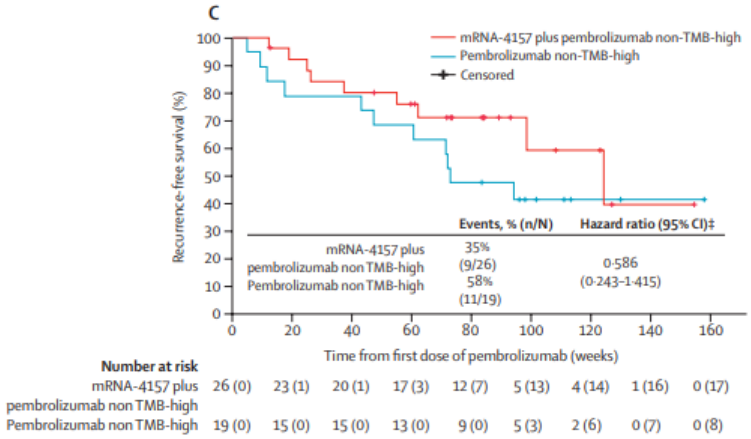
Funding Moderna in collaboration with Merck Sharp & Dohme, a subsidiary of Merck & Co, Rahway, NJ, USA.

mRNA Impfung in der Onkologie…

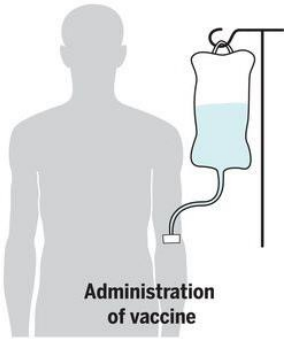




mRNA Impfung in der Onkologie…

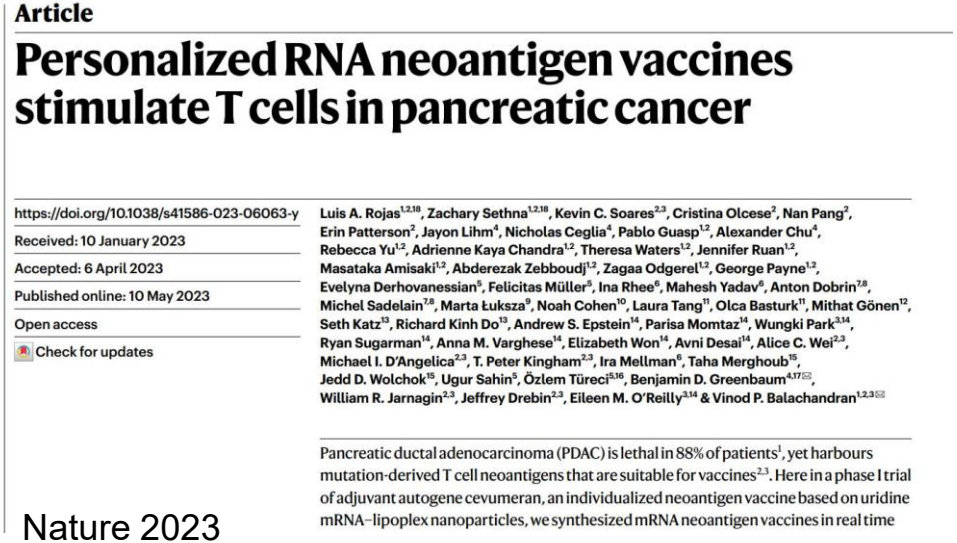


mRNA Impfung in der Onkologie: wo stehen wir konzeptionell?



Mehr Informationen unter…

Neue Aspekte der mRNA Impfung in der Onkologie…



Article

Personalized RNA neoantigen vaccines stimulate T cells in pancreatic cancer

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Check for updates

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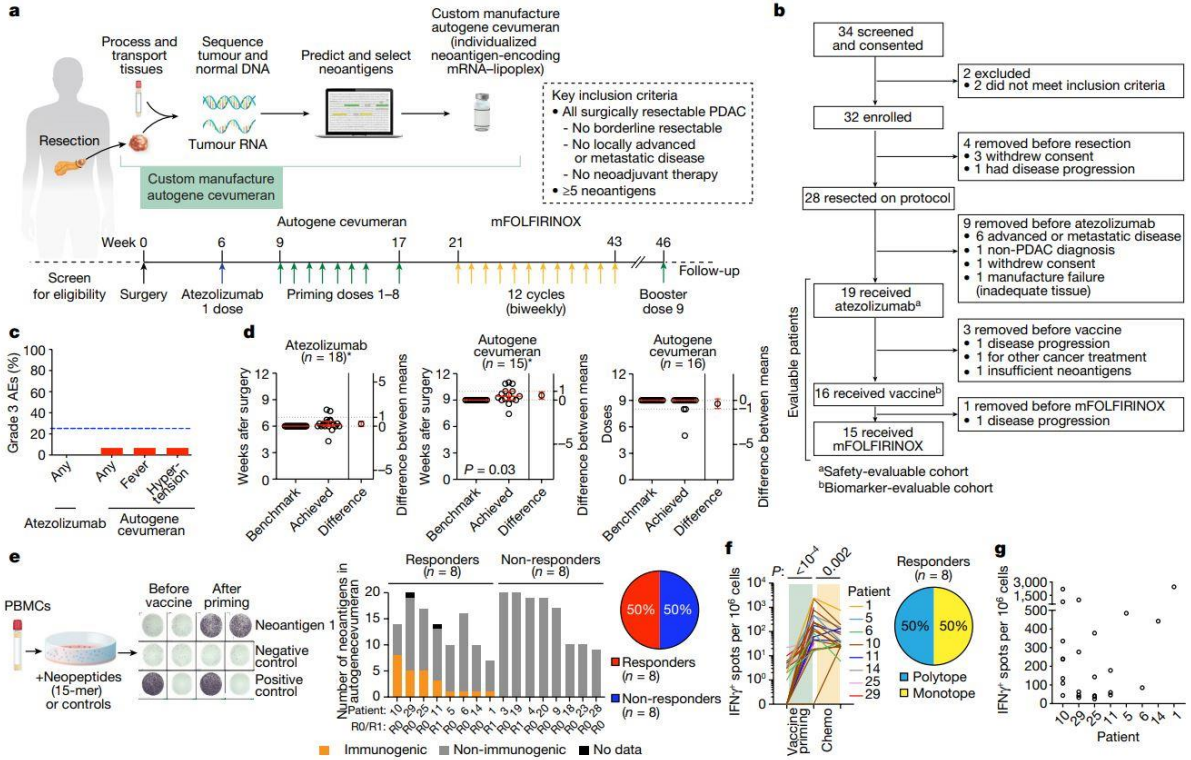
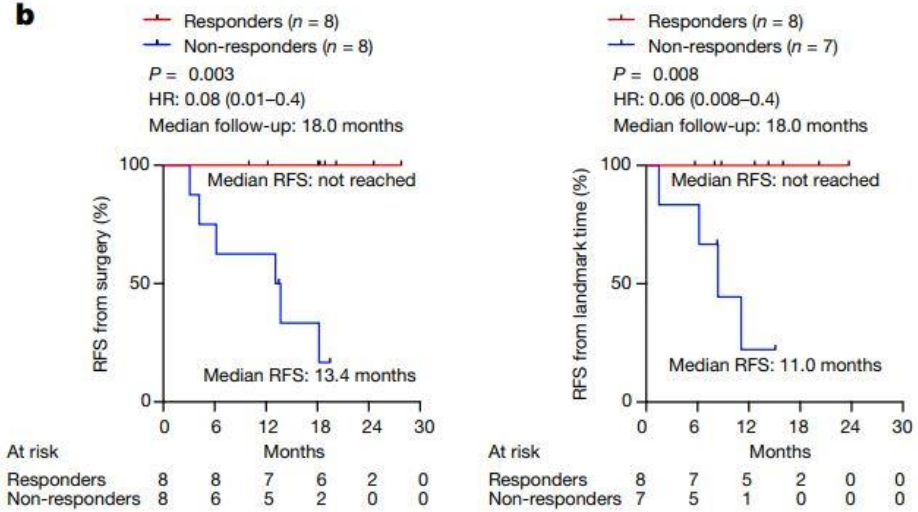
Pancreatic ductal adenocarcinoma (PDAC) is lethal in 88% of patients[1], yet harbours mutation-derived T cell neoantigens that are suitable for vaccines[2,3]. Here in a phase I trial of adjuvant autogene cevumeran, an individualized neoantigen vaccine based on uridine mRNA–lipoplex nanoparticles, we synthesized mRNA neoantigen vaccines in real time

Nature 2023

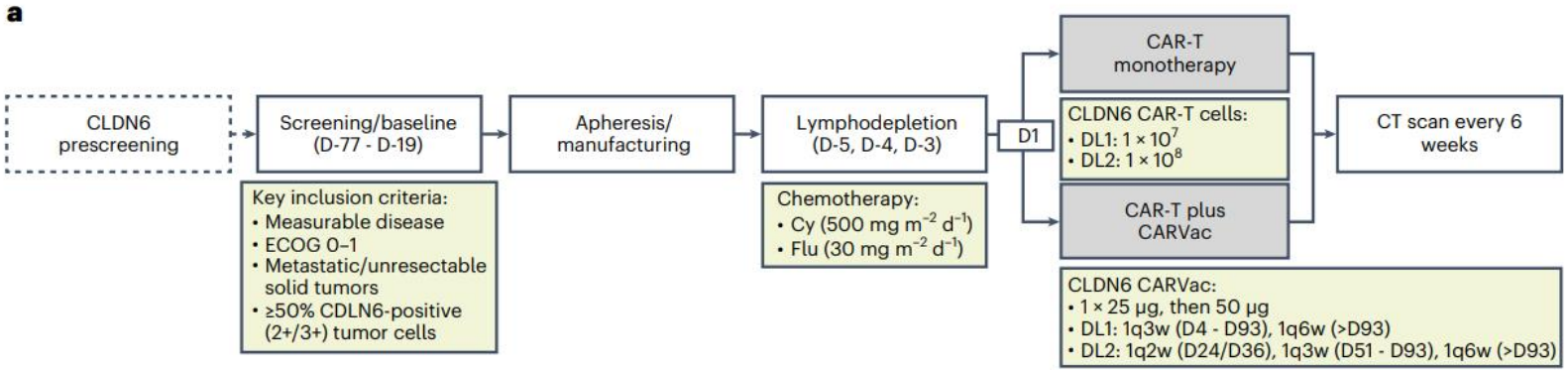

a
Process and transport tissues
Sequence tumour and normal DNA
Predict and select neoantigens
Custom manufacture autogene cevumeran (individualized neoantigen-encoding mRNA–lipoplex)
Resection
Tumour RNA
Custom manufacture autogene cevumeran
Key inclusion criteria
• All surgically resectable PDAC
- No borderline resectable
- No locally advanced or metastatic disease
- No neoadjuvant therapy
• ≥5 neoantigens
Autogene cevumeran
mFOLFIRINOX
Week 0
6
9
17
21
43
46
Follow-up
Screen for eligibility
Surgery
Atezolizumab 1 dose
Priming doses 1–8
12 cycles (biweekly)
Booster dose 9
b
34 screened and consented
2 excluded
• 2 did not meet inclusion criteria
32 enrolled
4 removed before resection
• 3 withdrew consent
• 1 had disease progression
28 resected on protocol
9 removed before atezolizumab
• 6 advanced or metastatic disease
• 1 non-PDAC diagnosis
• 1 withdrew consent
• 1 manufacture failure (inadequate tissue)
19 received atezolizumab[a]
3 removed before vaccine
• 1 disease progression
• 1 for other cancer treatment
• 1 insufficient neoantigens
16 received vaccine[b]
1 removed before mFOLFIRINOX
• 1 disease progression
15 received mFOLFIRINOX
Evaluable patients
[a]Safety-evaluable cohort
[b]Biomarker-evaluable cohort
c
Grade 3 AEs (%)
Any
Any
Fever
Hyper-tension
Atezolizumab
Autogene cevumeran
d
Atezolizumab (n = 18)*
Autogene cevumeran (n = 15)*
Autogene cevumeran (n = 16)
Weeks after surgery
Doses
Difference between means
P = 0.03
Benchmark
Achieved
Difference
e
PBMCs
+Neopeptides (15-mer) or controls
Before vaccine
After priming
Neoantigen 1
Negative control
Positive control
Responders (n = 8)
Non-responders (n = 8)
Number of neoantigens in autogenecevumeran
Patient:
R0/R1:
50%
Responders (n = 8)
Non-responders (n = 8)
Immunogenic
Non-immunogenic
No data
f
P:
<10⁻⁴
0.002
IFNγ⁺ spots per 10⁶ cells
Patient
Vaccine priming
Chemo
Responders (n = 8)
Polytope
Monotope
g
IFNγ⁺ spots per 10⁶ cells
Patient

Hope…made in Germany

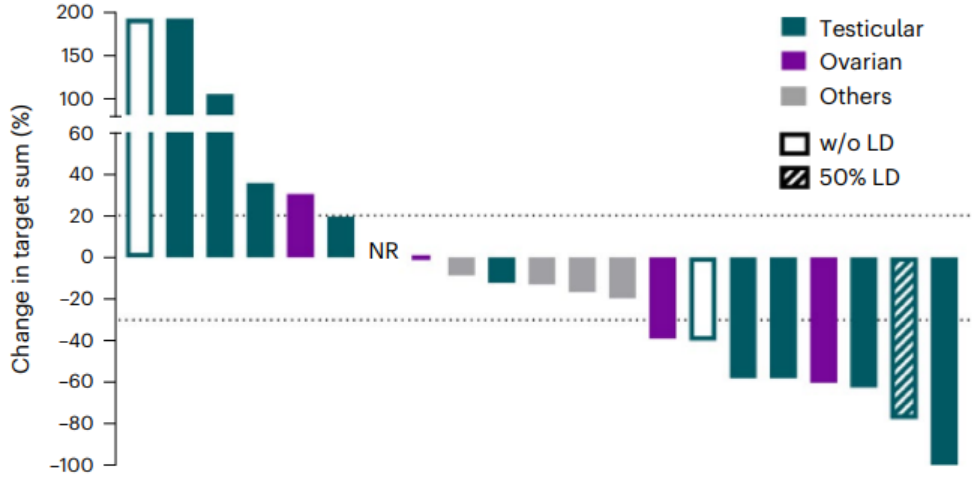


mRNA als Werkzeug…

Kombinierte Behandlung: mRNA Impfung plus zelluläre Therapien



Mackensen et al. Nature Medicine 11-2023



CAR-T dose	DL2	DL2	DL1	DL1	DL2	DL2	DL1	DL1	DL2	DL2	DL2	DL2	DL1	DL2	DL2	DL1	DL2	DL2	DL2	DL2	DL2
LD dose (%)	0	100	100	100	100	100	100	100	100	100	100	100	100	100	0	100	100	100	100	50	100
CARVac	+	+	+	–	–	+	+	–	–	+	–	–	–	+	+	+	–	+	+	+	–
Crossover	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	+	–	–	–	–
Redosing	–	–	–	+	–	–	–	+	–	–	–	–	–	–	–	+	+	–	+	–	–
Best response	PD	PD	PD	PD	PD	SD	PD	SD	SD	SD	SD	SD	SD	uPR	PD	cPR	cPR	cPR	uPR	cPR	CR
PD before ACT	NE	+	+	+	+	NE	+	NE	–	–	NE	NE	NE	NE	–	+	–	NE	–	NE	+
PFS, days	46	42	38	46	49	72	29	162	85	NR	87	126	81	79	44	154	119	120	79	289	NR

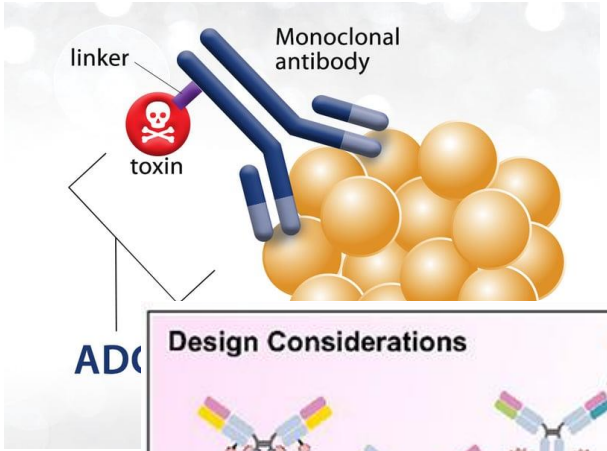
Mackensen et al. Nature Medicine 11-2023

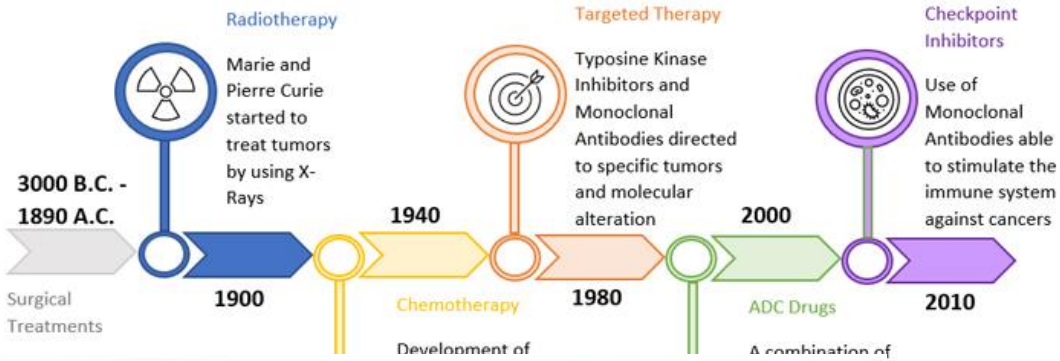
Neue Möglichkeiten mit…

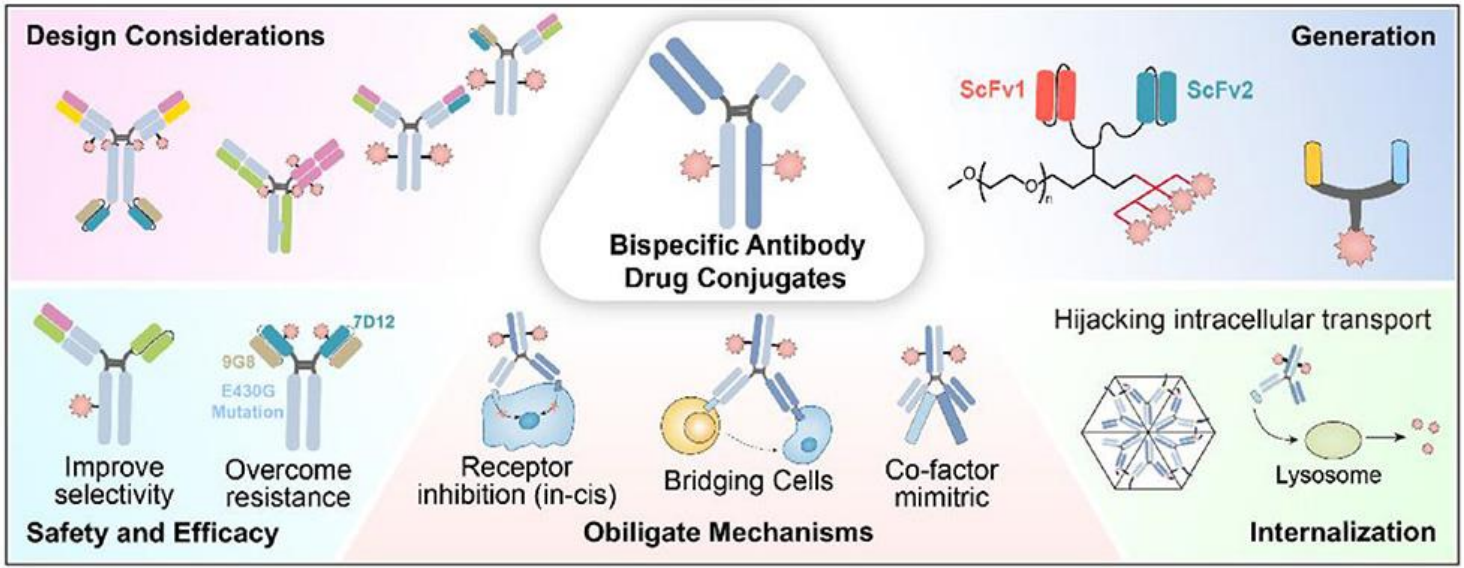
…Effekten von zellulärer Therapie bei soliden Tumoren!

Source: www.phoenixnewtimes.com

Die Ära der Kombinationstherapien…





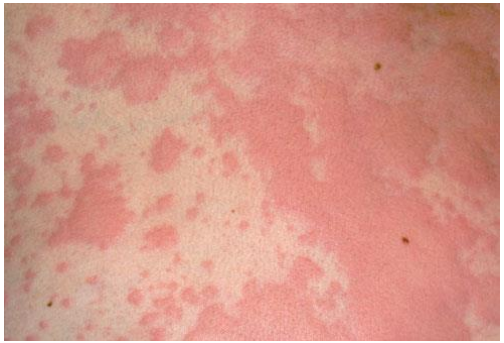


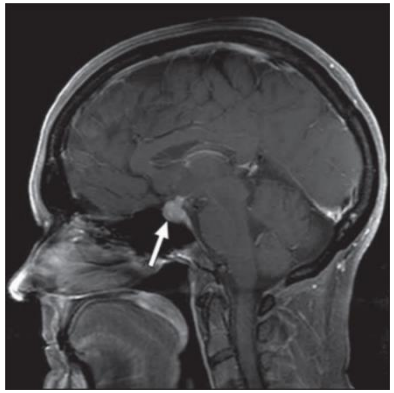
Anti-tumorale Immunantwort…aber zuviel ist zuviel!

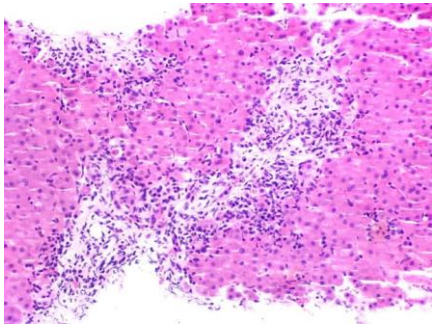
Setting fire to the rain…

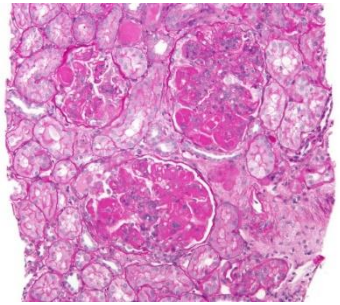
Aus „Evidence“ Mandel & Sultan 1972

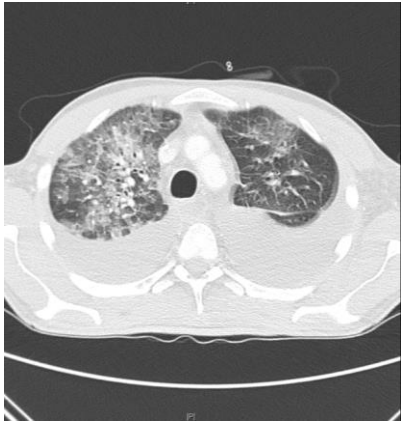
irSAEs = immune related severe adverse events











Folie von J. Krauss zur Verfügung gestellt

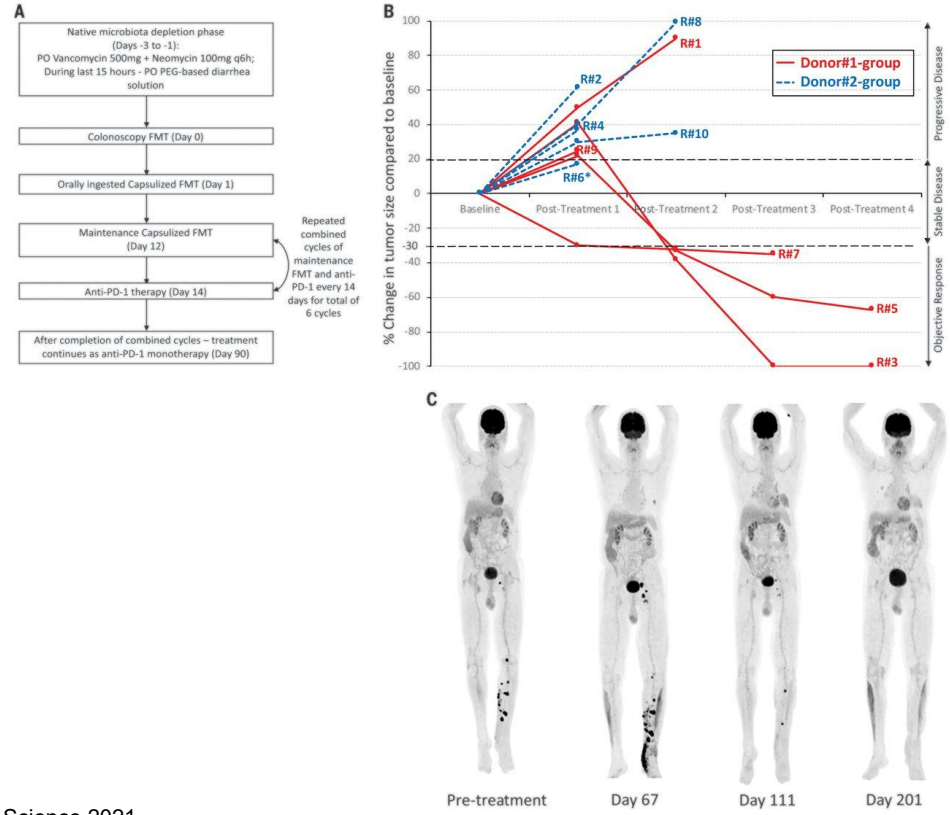
Ein kleiner Ausblick…Tumorimmunogenität & Co

Immunmodulation der Tumormikroumgebung

Das Mikrobiom…

„The future is now“ microbiome…

Immunmodulation „at it‘s finest“…



Baruch et al. Science 2021

Aber auch das…

Neulich in *Nature*…

Article

SARS-CoV-2 mRNA vaccines sensitize tumours to immune checkpoint blockade

https://doi.org/10.1038/s41586-025-09655-y

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Adam J. Grippin[1,29], Christiano Marconi[2,29], Sage Copling[3,29], Nan Li[1,29], Chen Braun[1], Cole Woody[1], Elliana Young[4], Priti Gupta[1], Min Wang[1], Annette Wu[1], Seong Dong Jeong[5,6], Dhruvkumar Soni[2], Frances Weidert[2], Chao Xie[2], Eden Goldenberg[2], Andrew Kim[3], Chong Zhao[2], Anna DeVries[2], Paul Castillo[2,7], Rishabh Lohray[8], Michael K. Rooney[1], Benjamin R. Schrank[1], Yifan Wang[1], Yifan Ma[1], Enoch Chang[1], Ramez Kouzy[1], Kyle Dyson[9], Jordan Jafarnia[3], Nina Nariman[3], Gregory Gladish[10], Jacob New[11], Ada Argueta[1], Diana Amaya[1], Nagheme Thomas[2], Andria Doty[2], Joe Chen[1], Nikhil Copling[12], Gabriel Alatrash[1], Julie Simon[13], Alicia Bea Davies[13], William Dennis[1], Richard Liang[1], Jeff Lewis[14], Xiong Wei[14], Waree Rinsurongkawong[14], Ara A. Vaporciyan[15], Andrew Johns[16], D3CODE Team[17]*, Jack Lee[18], Ji-Hyun Lee[19], Ryan Sun[18], Padmanee Sharma[16,20,21], Hai Tran[14], Jianjun Zhang[14], Don L. Gibbons[14], Jennifer Wargo[13], Betty Y. S. Kim[5,6], John V. Heymach[14], Hector R. Mendez-Gomez[2], Wen Jiang[1], Elias J. Sayour[2,7,30] & Steven H. Lin[1,30]

Immune checkpoint inhibitors (ICIs) extend survival in many patients with cancer but are ineffective in patients without pre-existing immunity[1–9]. Although personalized mRNA cancer vaccines sensitize tumours to ICIs by directing immune attacks against preselected antigens, personalized vaccines are limited by complex and time-intensive manufacturing processes[10–14]. Here we show that mRNA vaccines targeting SARS-CoV-2 also sensitize tumours to ICIs. In preclinical models, SARS-CoV-2 mRNA vaccines led

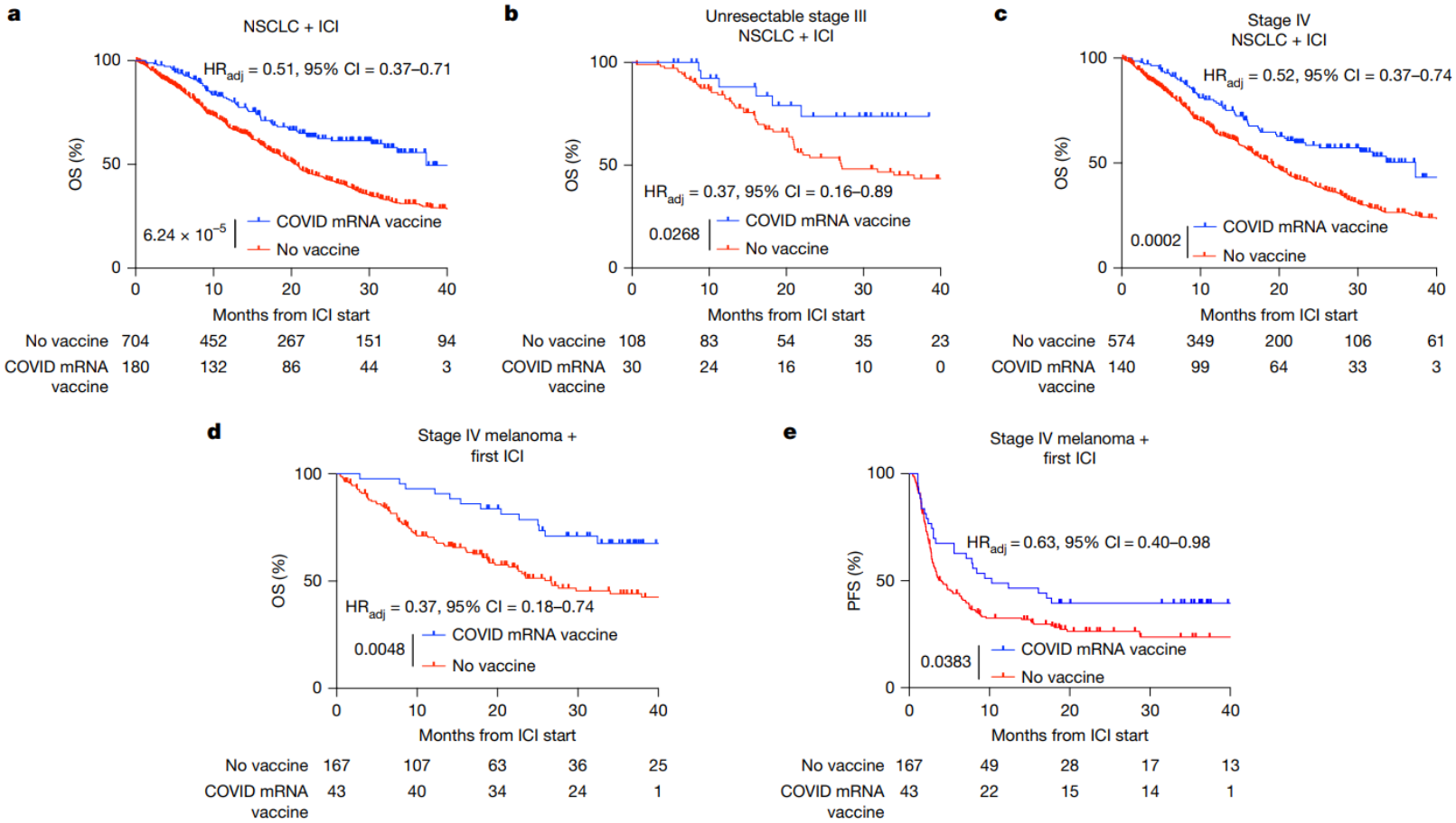

Fig. 1 | COVID-19 mRNA vaccines are associated with improved survival in patients with NSCLC or metastatic melanoma receiving immunotherapy. stage IV NSCLC (**c**) and patients with metastatic melanoma (**d** and **e**). *P* values and HR$_{adj}$ were calculated using two-sided Cox proportional hazards regression

„Off the shelf“ versus personalisierte Impfungen?

Neue Wege in der Immuntherapie…

Danksagungen

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Darjus Tschaharganeh

Translational Immunotherapy
www.dkfz.de/en/translationale-immuntherapie/

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