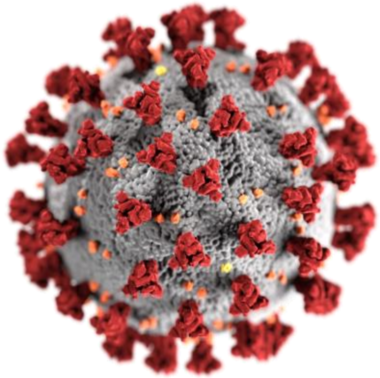
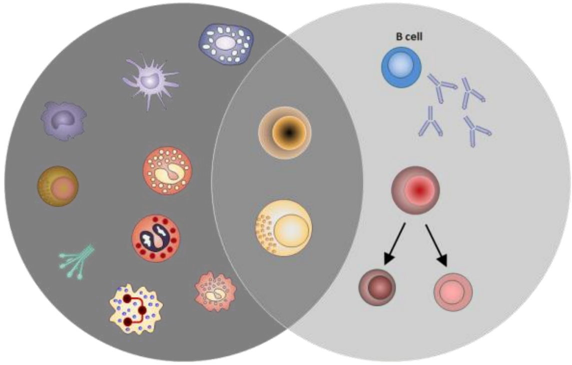


SARS-CoV2

und das

Immunsystem



Ralf Georg Meyer
Klinik für Innere Medizin II

Dortmunder Centrum für
ZELLTRANSPLANTATION
Eine gemeinsame Einrichtung von
St.-Johannes-Hospital & Klinikum Dortmund gGmbH

St.-Johannes-Hospital
Schwerpunktkrankenhaus
Kath. St.-Johannes-Gesellschaft Dortmund gGmbH

Agenda

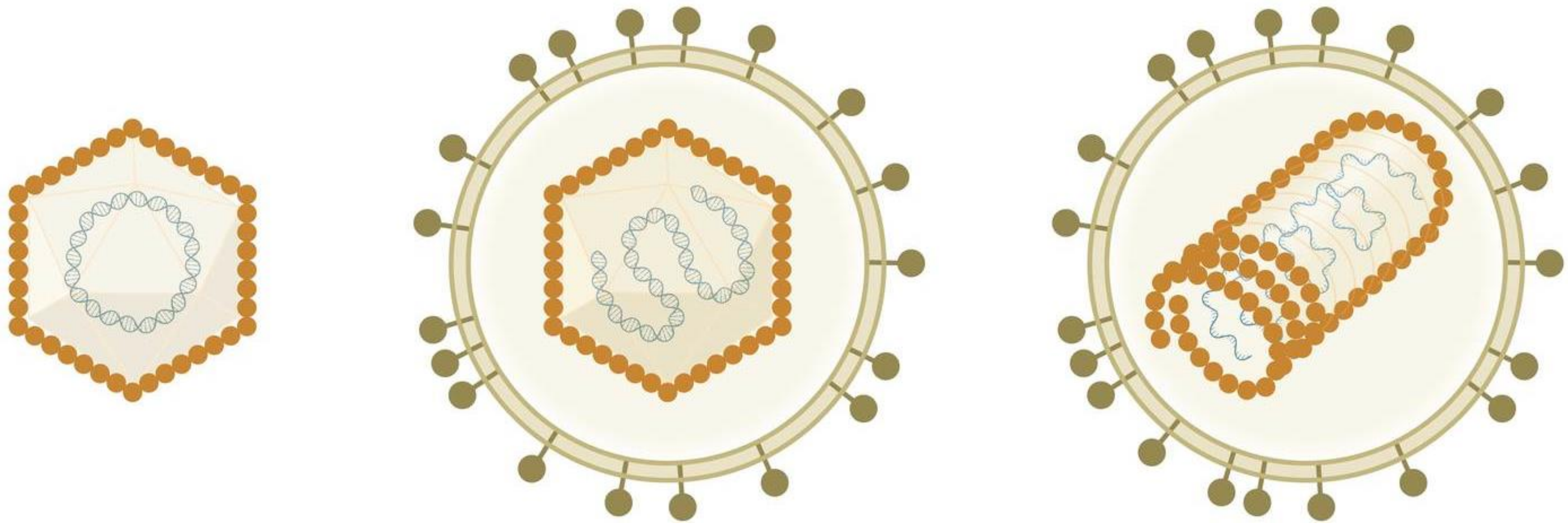
- Einführung

- Was macht das Immunsystem mit SARS-CoV2?

  …….... und umgekehrt

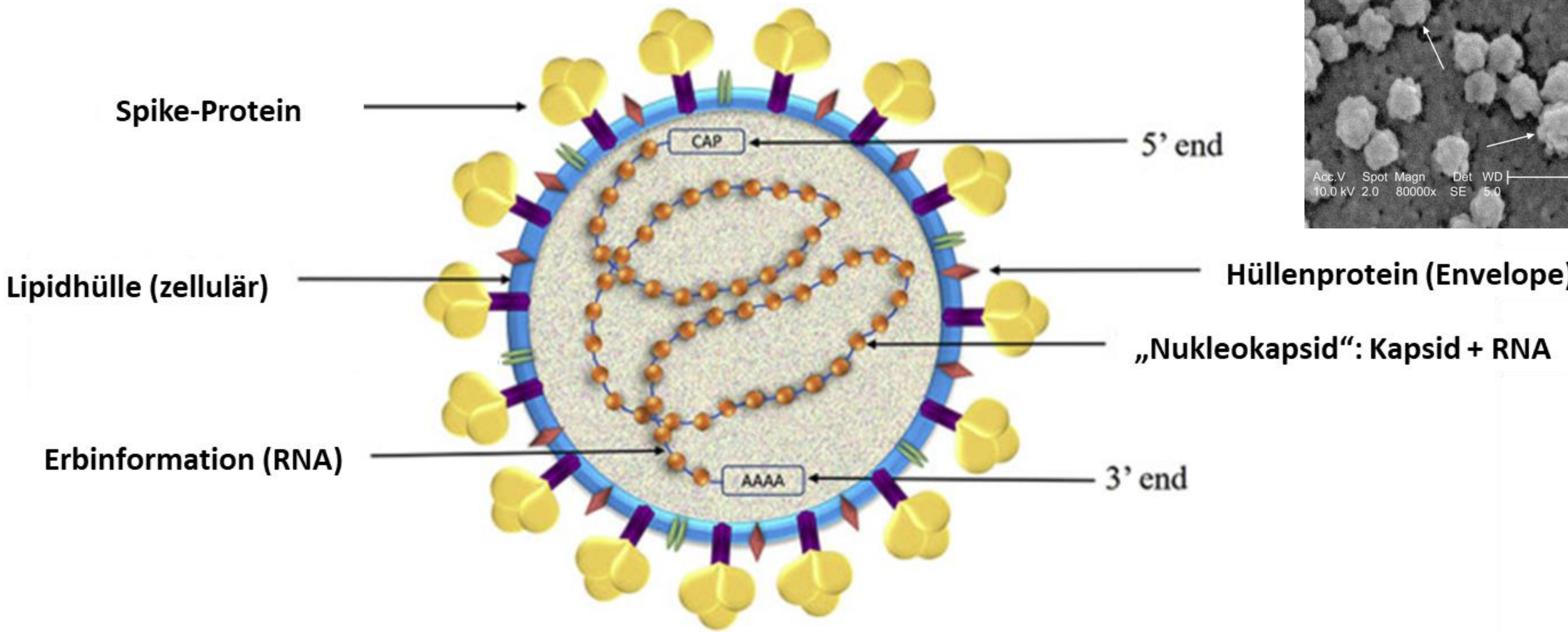
- (Wie) hilft das Immunsystem in der Pandemie?

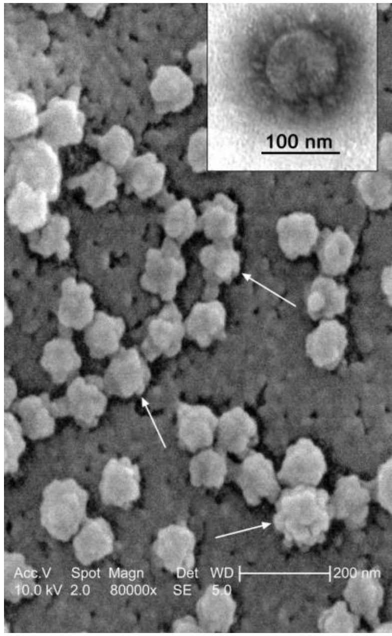
Was sind Viren?



Quelle: © AMBOSS GmbH, Berlin und Köln, Germany

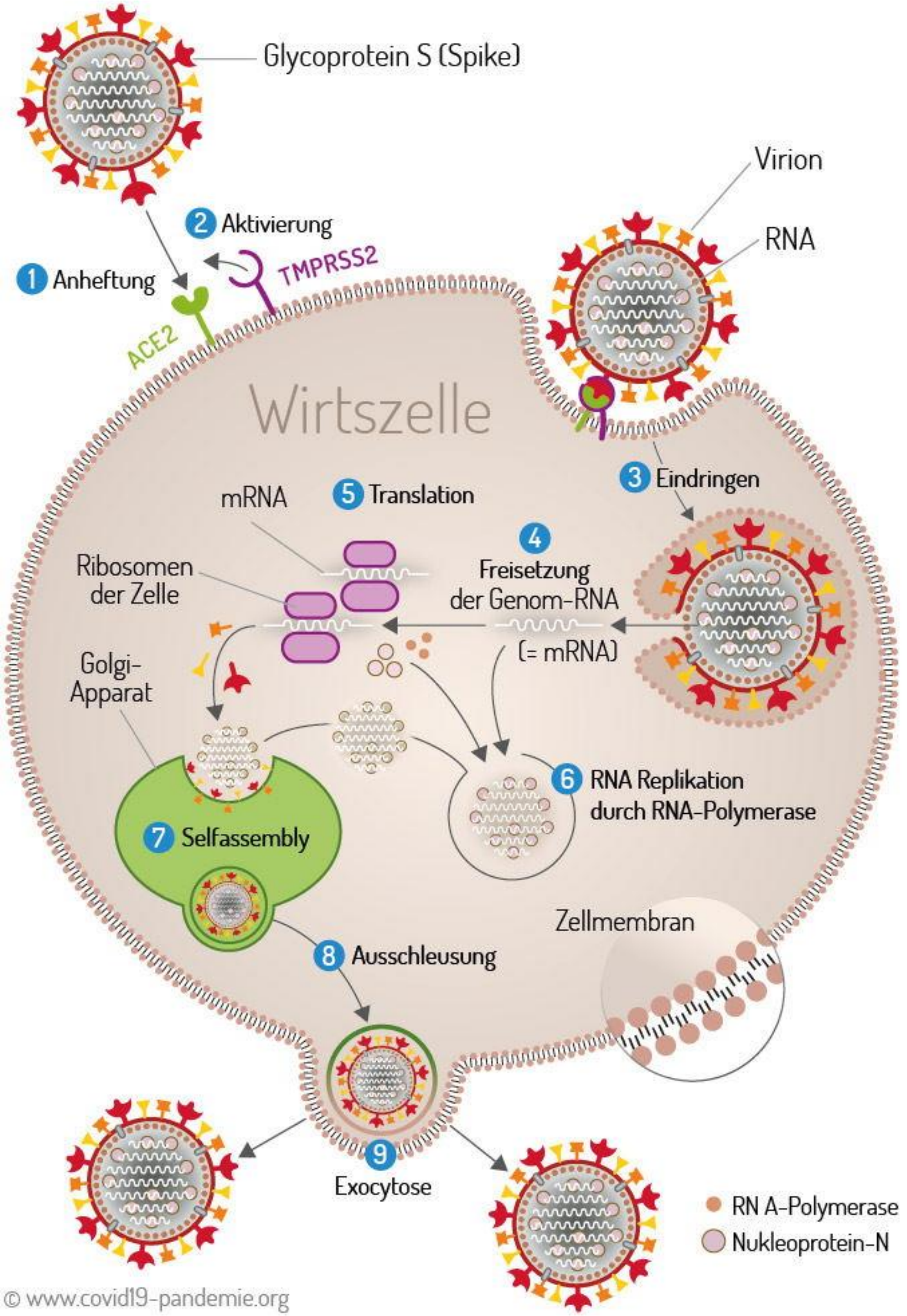
SARS-CoV2





Satarker & Nampoothiri, Arch Med Res 2020; Novotny et al. PLoS Med 2006

Der Viruszyklus von SARS-CoV2



Dietmar Schäffer, covid19-pandemie.org

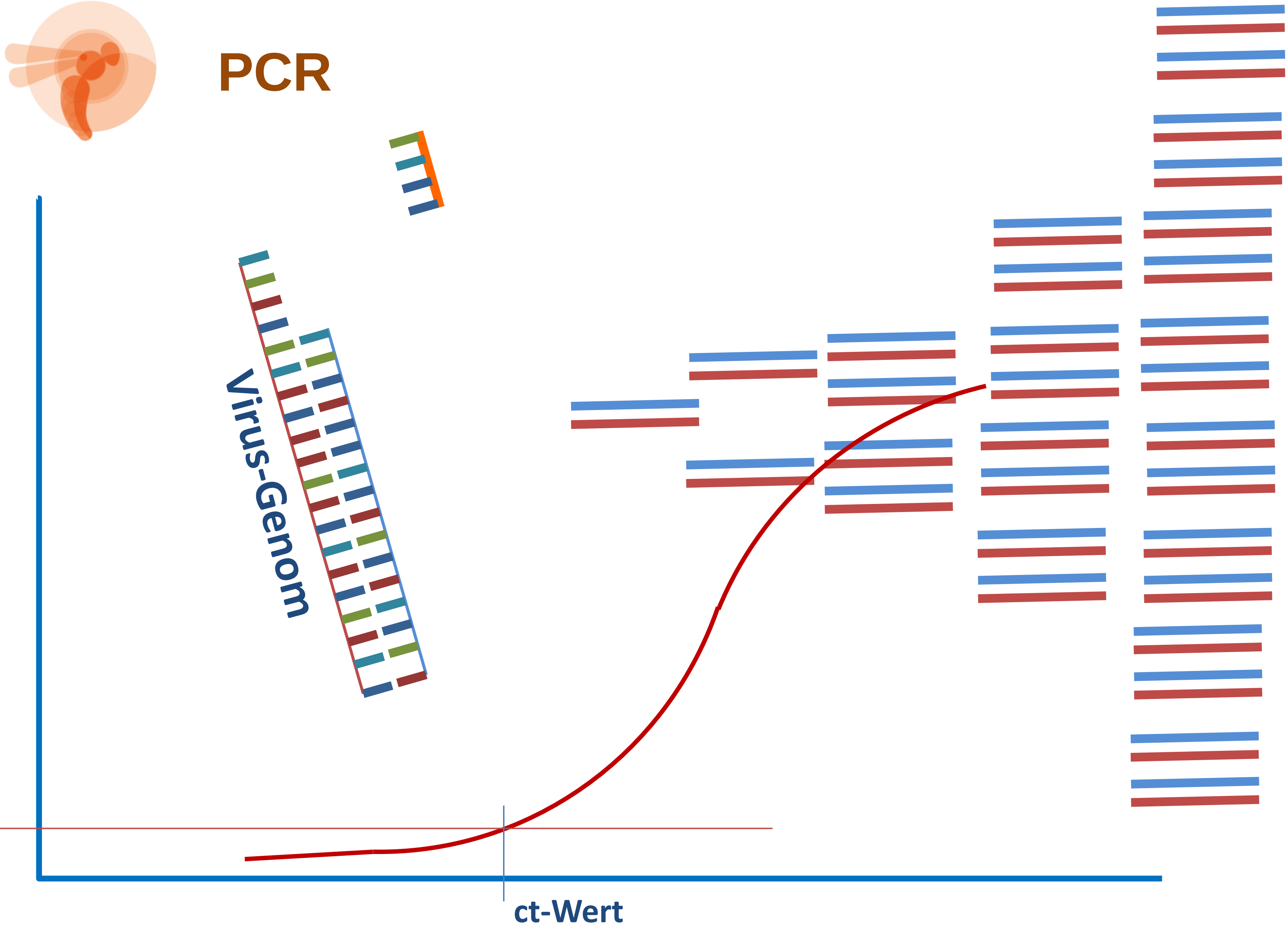
Wie misst man Viren?

- Nachweis Viruspartikel („Antigen-Test“)

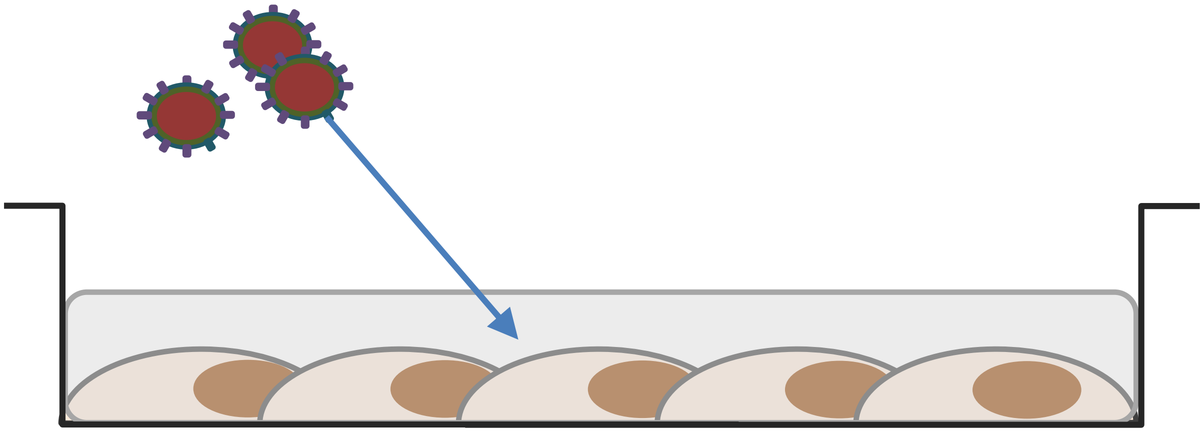
- Virus-Genom („PCR“)

- Nachweis der Infektiosität („Plaque-Test“)

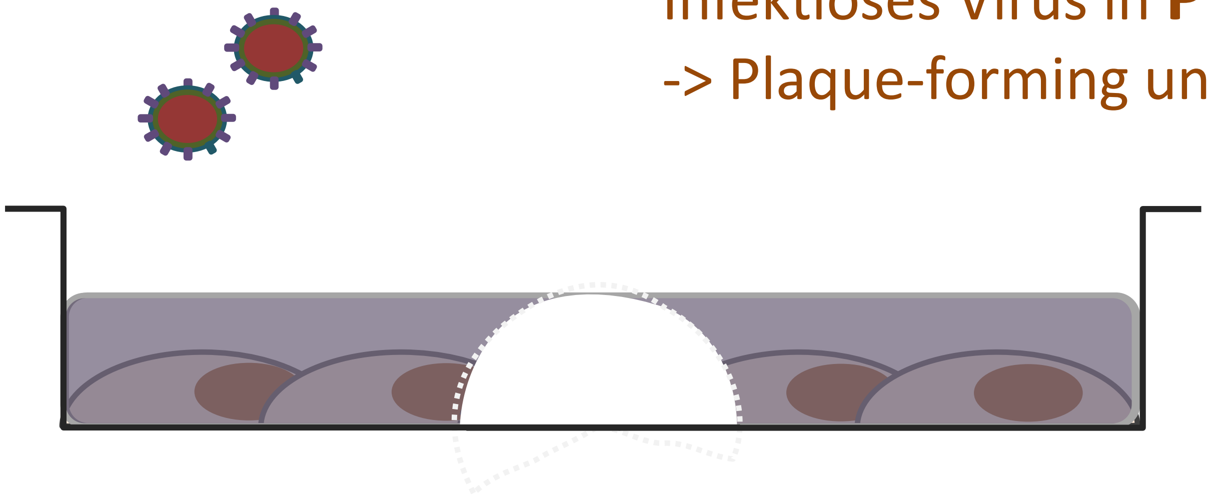
PCR



Plaque-Test



Plaque-Test

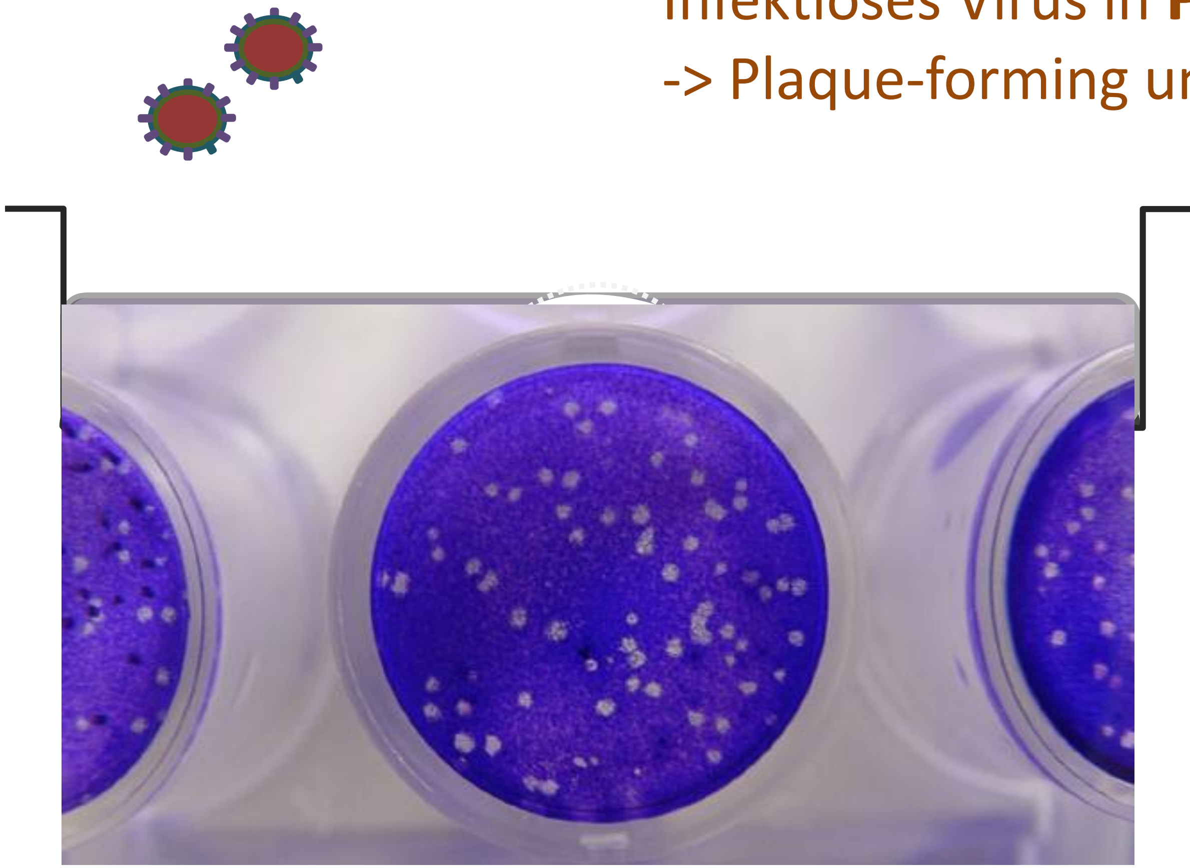


Infektiöses Virus in **PFU**/ml
-> Plaque-forming unit

Plaque-Test

Infektiöses Virus in **PFU**/ml

-> Plaque-forming unit



Y tambe, CC BY-SA 3.0 via Wikimedia Commons

Take home 1

- Viren und viraler Infektionszyklus
- PCR und ct-Wert
- Plaque-Test und pfu

Das Immunsystem

	Angeboren *(schnell)*	**Erworben** = lernend/adaptiv *(langsam, spezifisch)*
Gelöste Faktoren		
Zellen		

Gelöste Faktoren
Zellen

Das Immunsystem

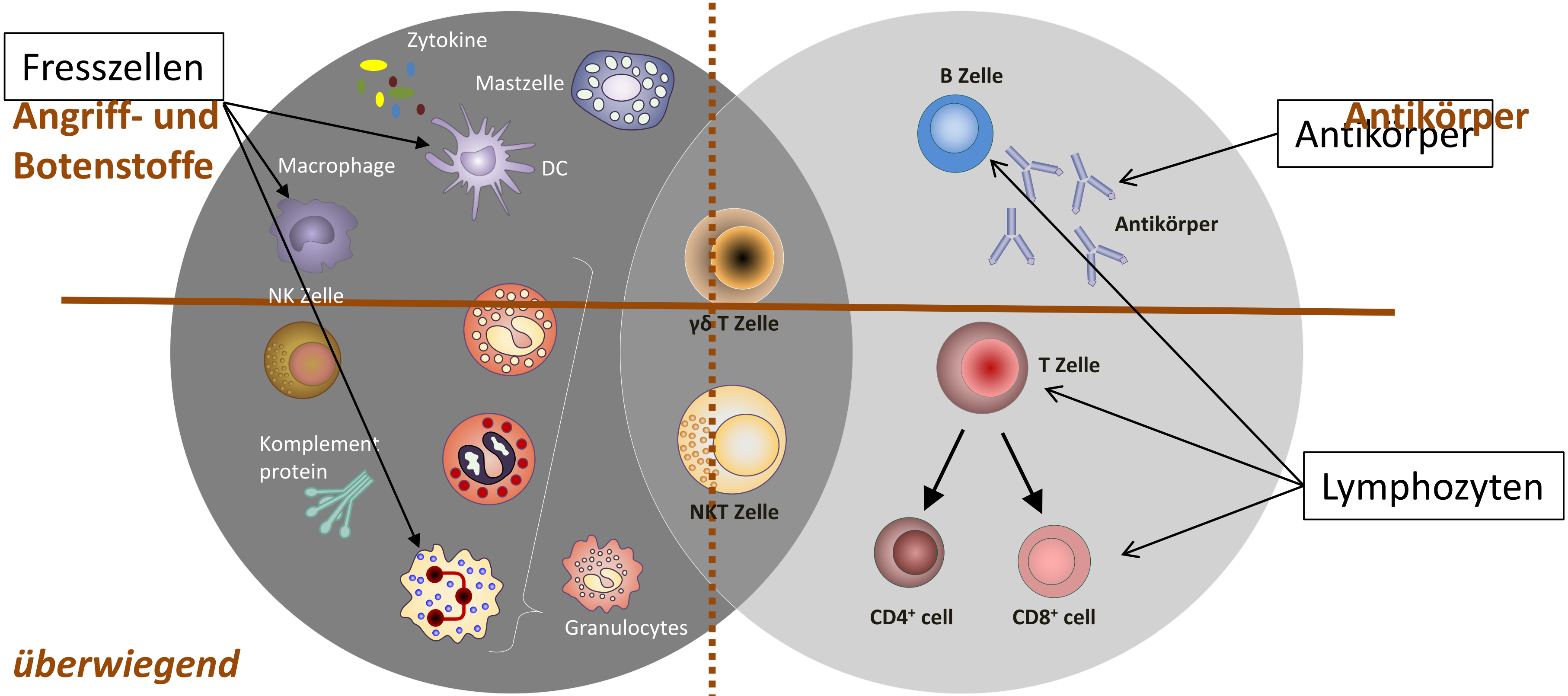
Angeboren *(schnell)*

Erworben = lernend/adaptiv *(langsam, spezifisch)*

Gelöste Faktoren

Angriff- und Botenstoffe

Antikörper



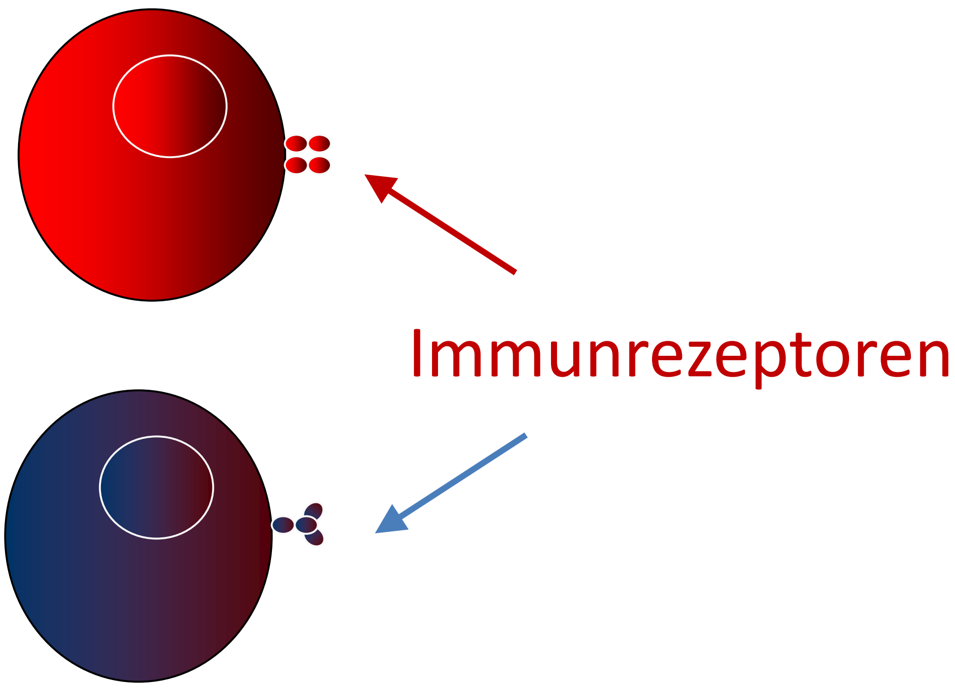
Zellen

überwiegend **Fresszellen**

Lymphozyten

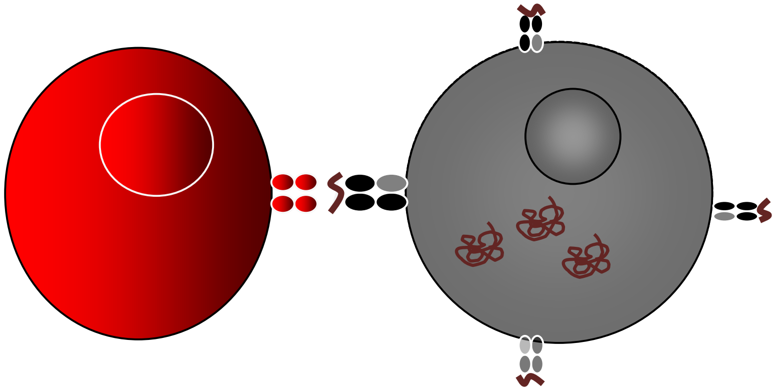
Das adaptive Immunsystems

Lymphozyten:

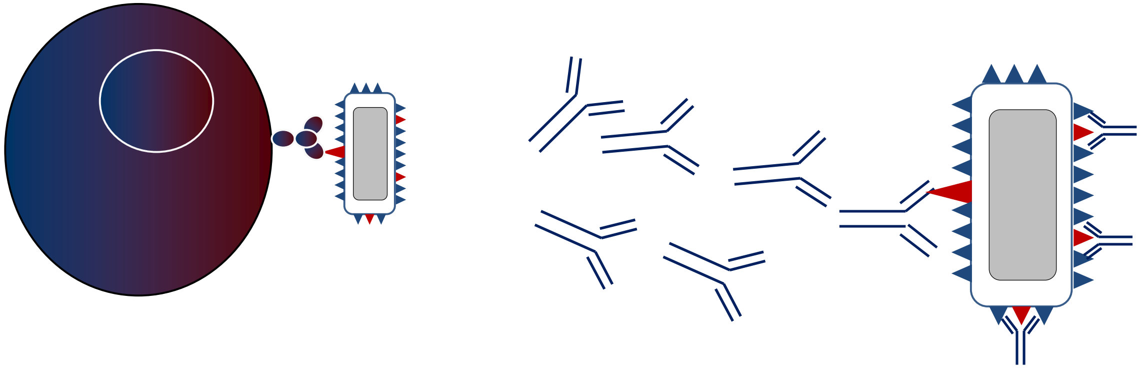


Das adaptive Immunsystem

- Lymphozyten

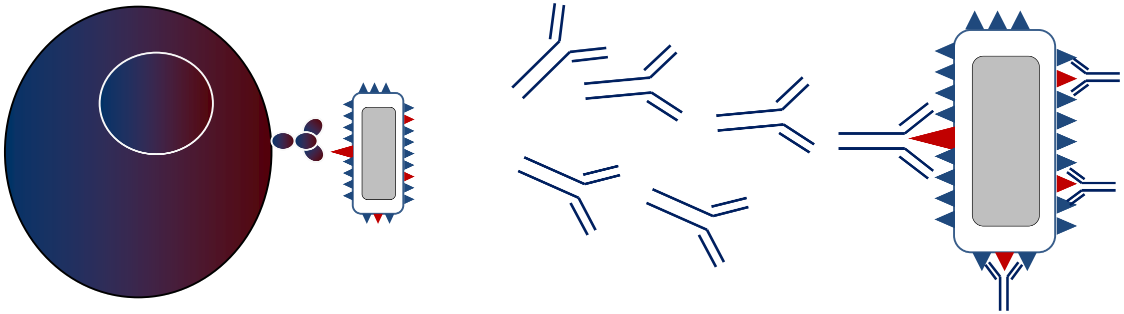


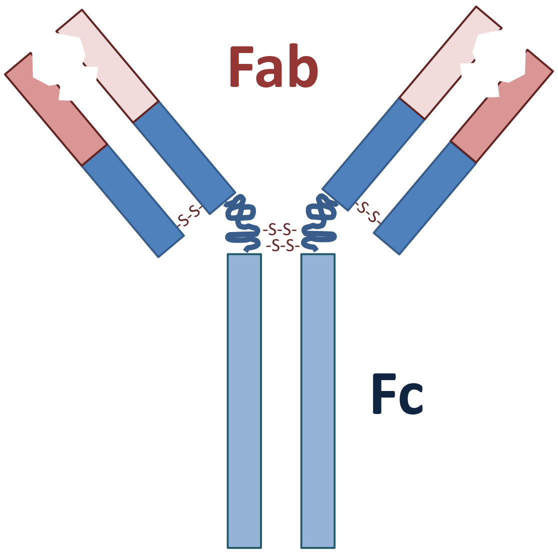
T-Lymphozyten
- *Zellzerstörung*
- *Regulation*

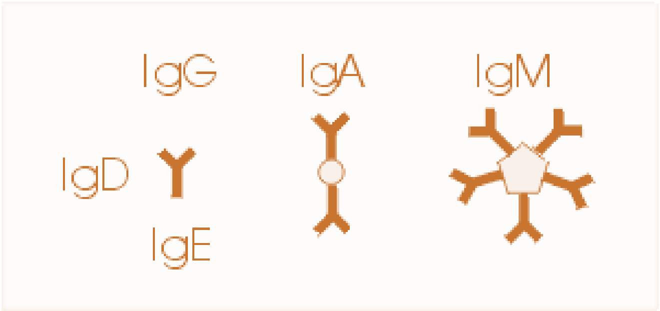


B-Lymphozyten
- *Antikörper*
- *Regulation*

Was sind Antikörper?

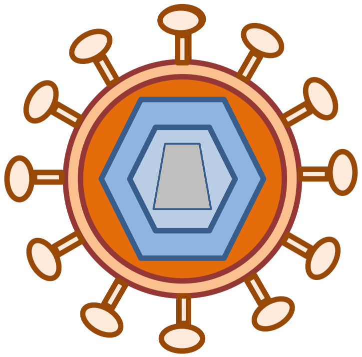


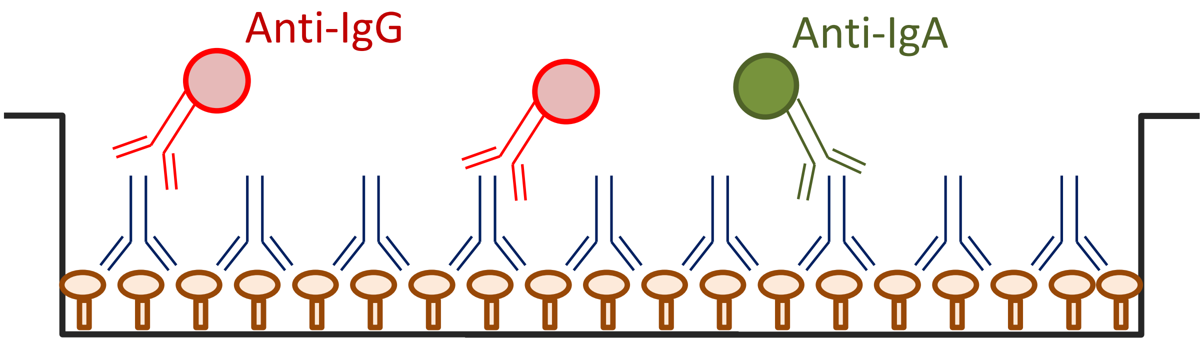




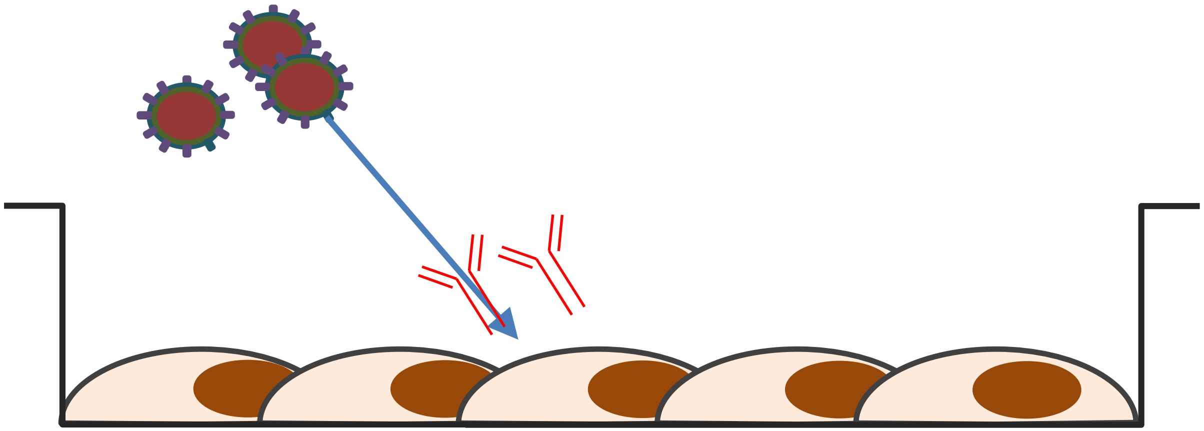
Wie misst man Antikörper?

Der „ELISA“

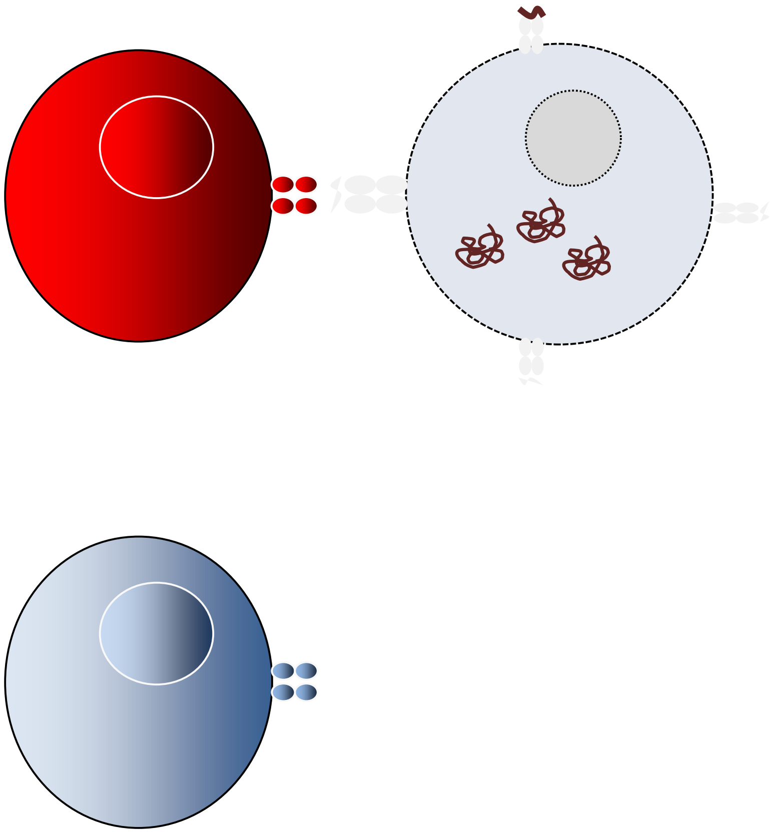




Neutralisierende Antikörper



T-Lymphozyten

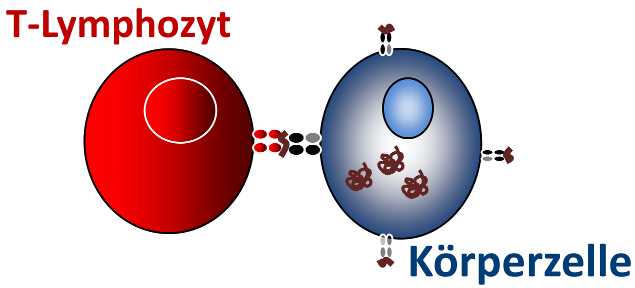


CD8-positive T-Zellen

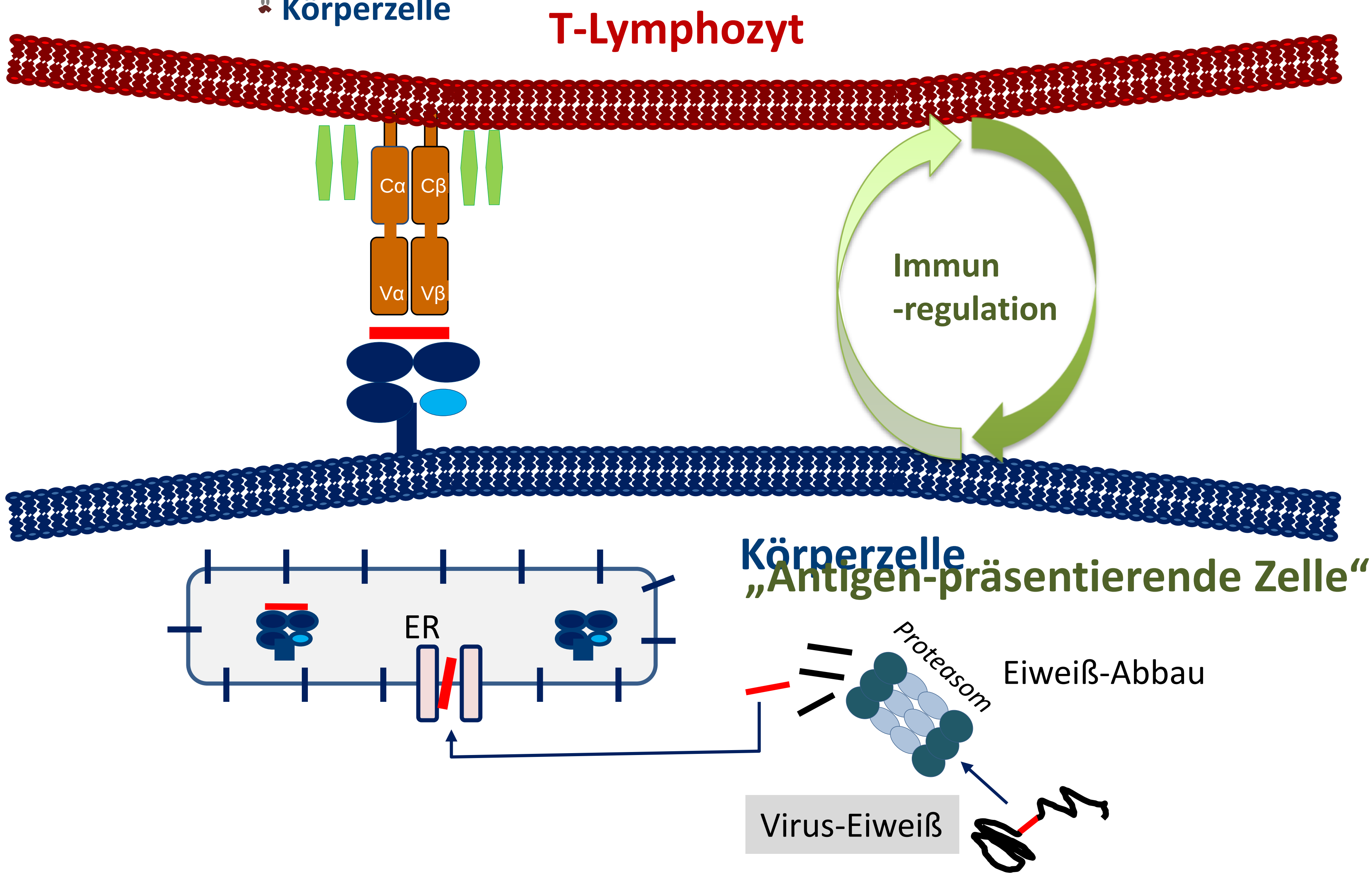
- *Killerzellen*

CD4-positive T-Zellen

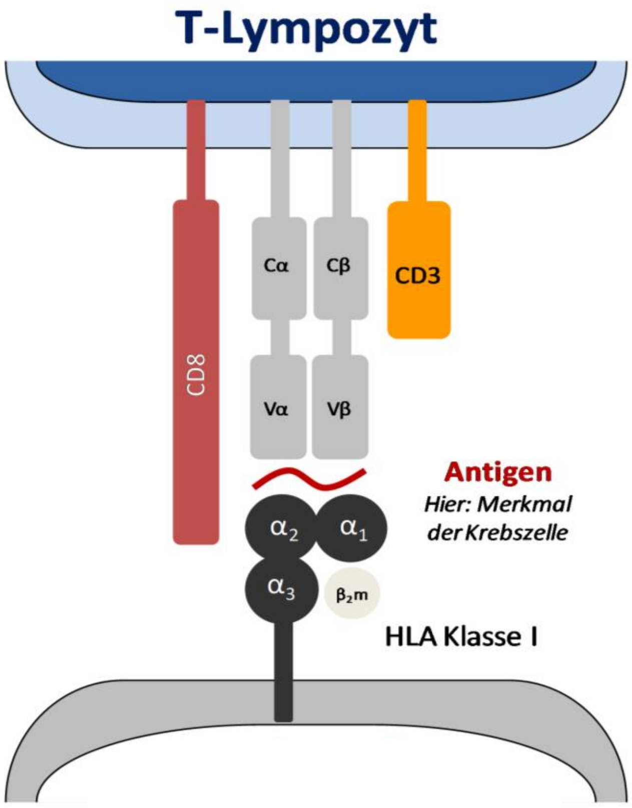
- *Helferzellen*
- *Regulatoren*

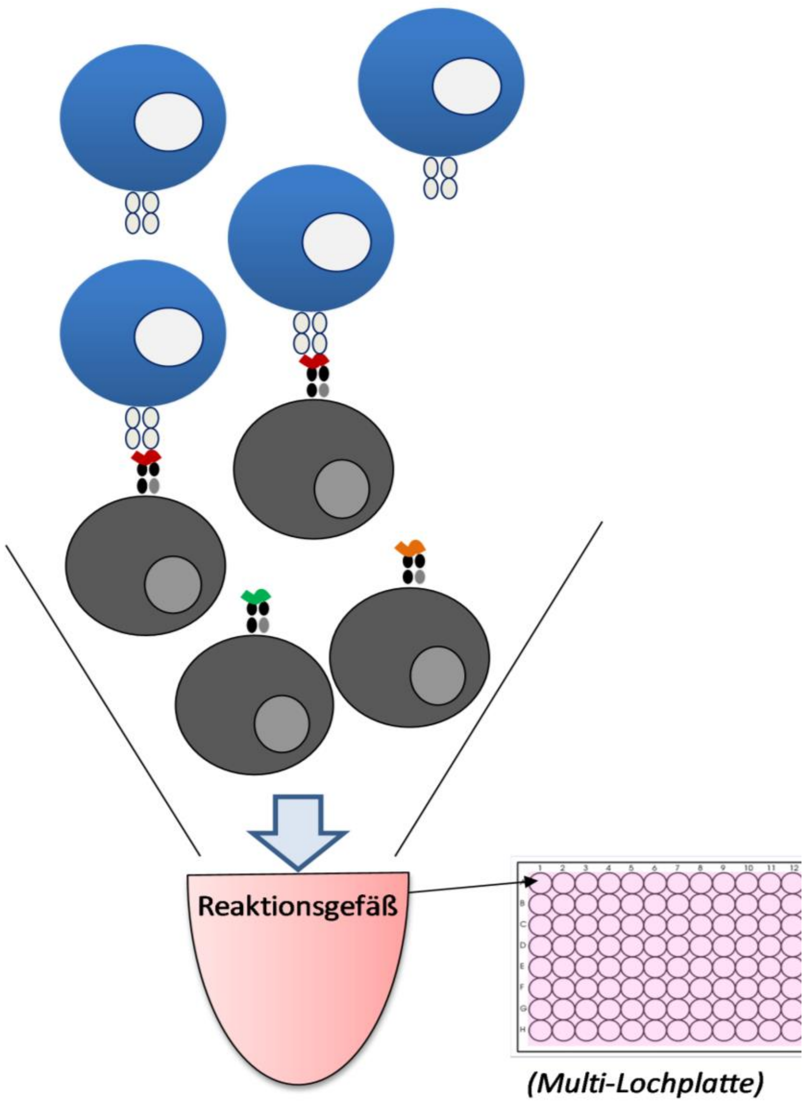


Wie erkennen T-Lymphozyten?

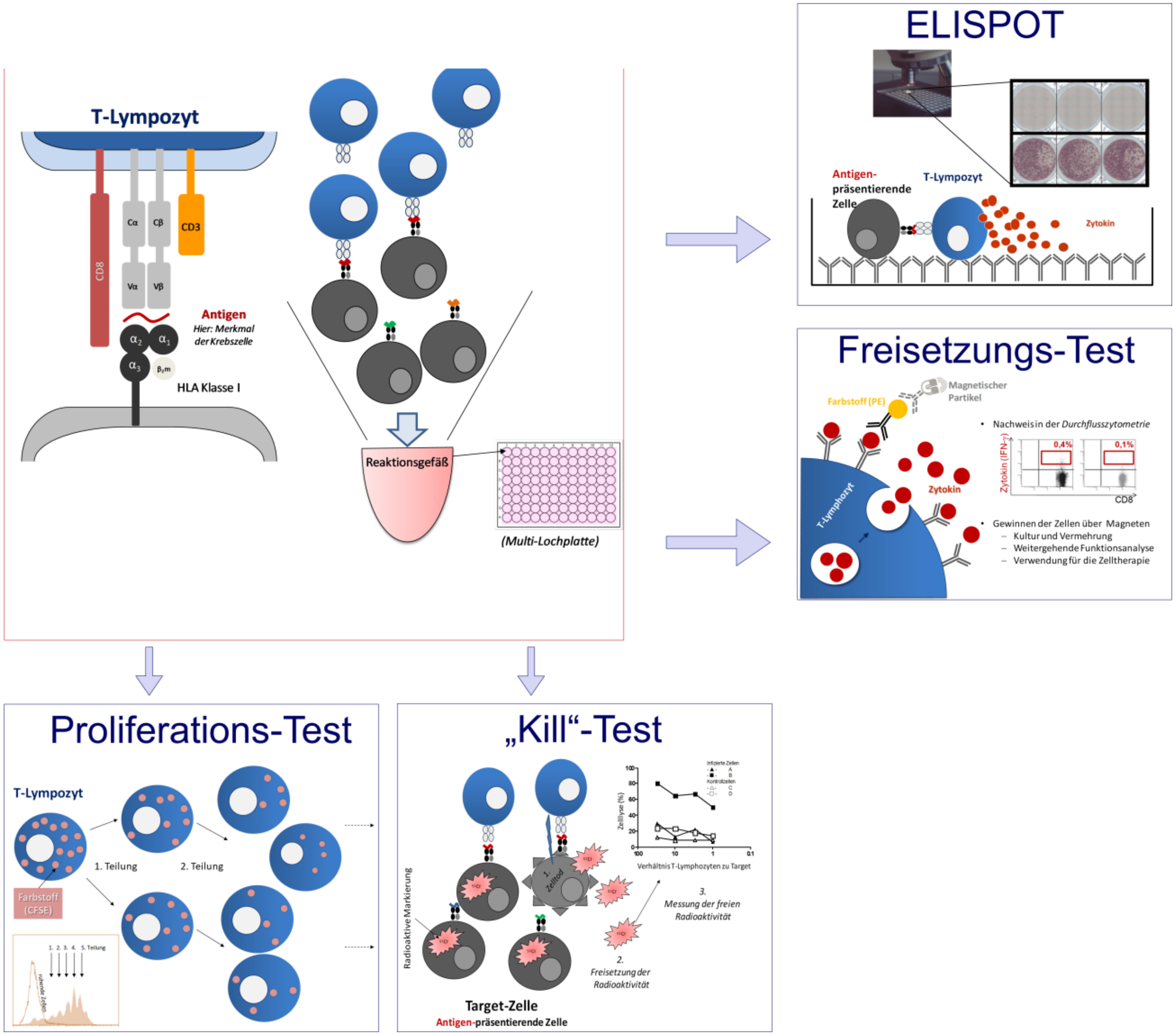


Messung einer T-Zellantwort





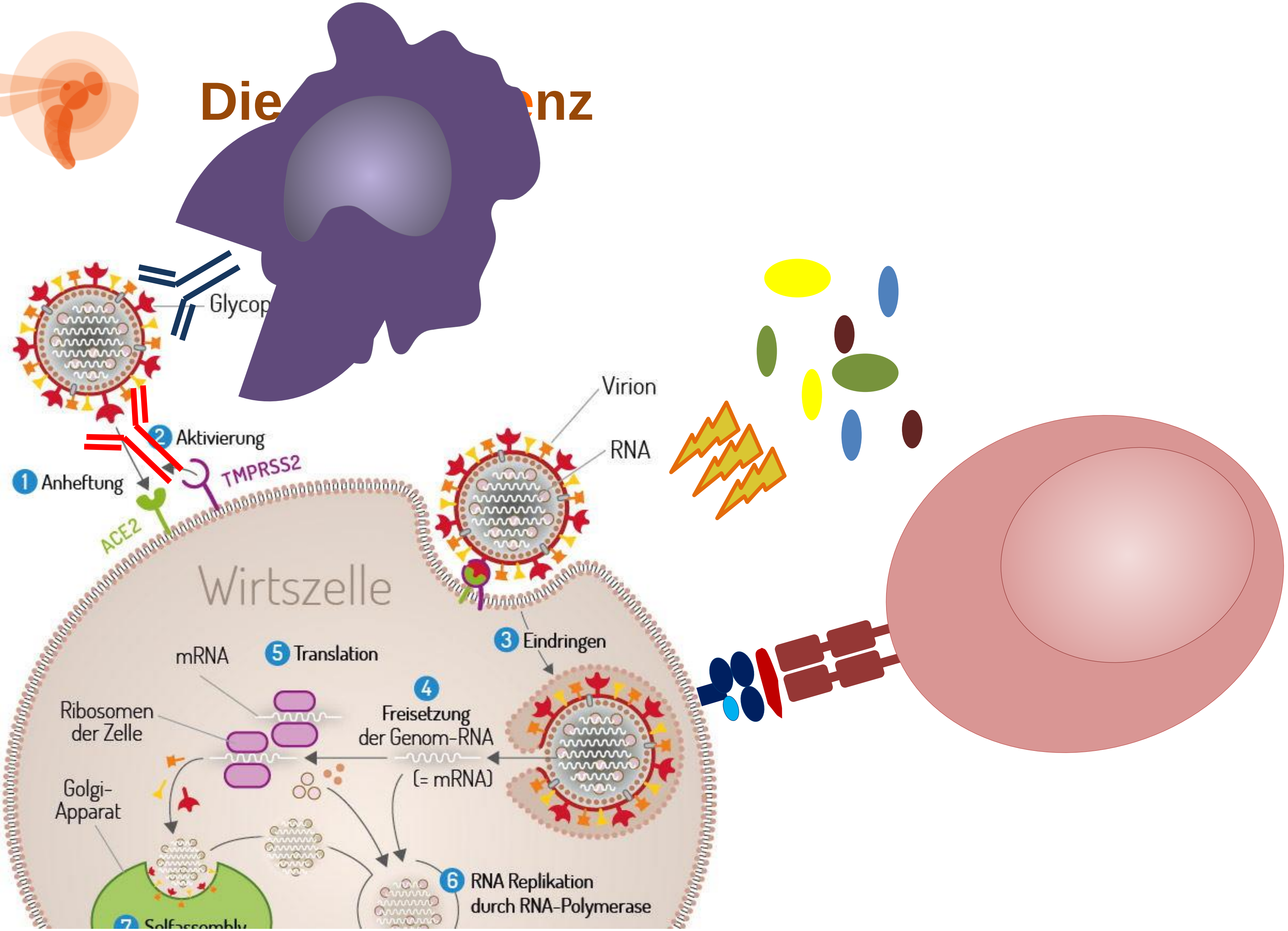
Messung einer T-Zellantwort



Take home 2

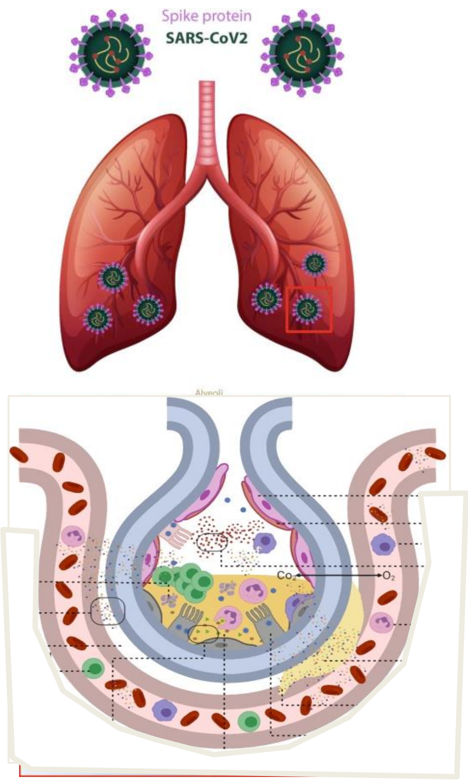
- Angeborenes und erworbenes Immunsystem
- ELISA und Neutralisationstest
- T-Zell-Funktionstests und Multimer-Färbung

Die ... enz


Glycop
Virion
RNA
2 Aktivierung
TMPRSS2
1 Anheftung
ACE2
Wirtszelle
3 Eindringen
mRNA
5 Translation
4
Freisetzung
der Genom-RNA
(= mRNA)
Ribosomen
der Zelle
Golgi-
Apparat
6 RNA Replikation
durch RNA-Polymerase

Die Ambivalenz

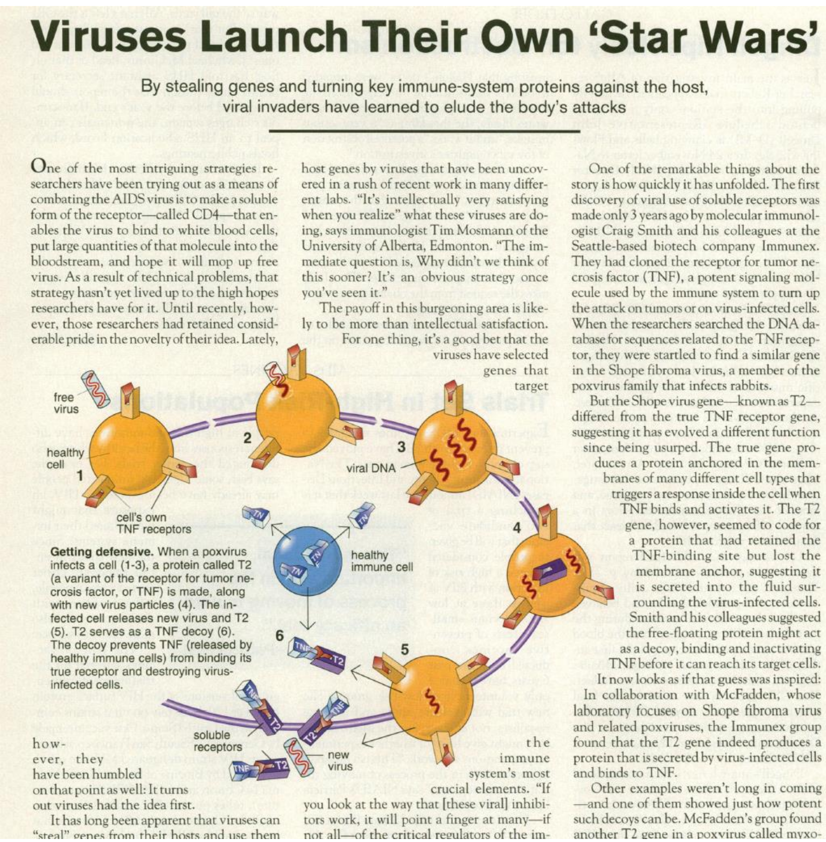
Immun-Effektoren führen zu…



- Gewebezerstörung
- „weißer Lunge“
- Gerinnungs-Überaktivierung

Ebrahimi Int Immunopharmacol 2020, Mathews-Vaehese Immunobiology 2020,
Song Nature Comm. 2020, Bloch J Clin Invest 2020

„The Virus strikes back“



Viruses Launch Their Own 'Star Wars'

By stealing genes and turning key immune-system proteins against the host, viral invaders have learned to elude the body's attacks

One of the most intriguing strategies researchers have been trying out as a means of combating the AIDS virus is to make a soluble form of the receptor—called CD4—that enables the virus to bind to white blood cells, put large quantities of that molecule into the bloodstream, and hope it will mop up free virus. As a result of technical problems, that strategy hasn't yet lived up to the high hopes researchers have for it. Until recently, however, those researchers had retained considerable pride in the novelty of their idea. Lately, however, they have been humbled on that point as well: It turns out viruses had the idea first.

It has long been apparent that viruses can "steal" genes from their hosts and use them

host genes by viruses that have been uncovered in a rush of recent work in many different labs. "It's intellectually very satisfying when you realize" what these viruses are doing, says immunologist Tim Mosmann of the University of Alberta, Edmonton. "The immediate question is, Why didn't we think of this sooner? It's an obvious strategy once you've seen it."

The payoff in this burgeoning area is likely to be more than intellectual satisfaction. For one thing, it's a good bet that the viruses have selected genes that target the immune system's most crucial elements. "If you look at the way that [these viral] inhibitors work, it will point a finger at many—if not all—of the critical regulators of the im-

One of the remarkable things about the story is how quickly it has unfolded. The first discovery of viral use of soluble receptors was made only 3 years ago by molecular immunologist Craig Smith and his colleagues at the Seattle-based biotech company Immunex. They had cloned the receptor for tumor necrosis factor (TNF), a potent signaling molecule used by the immune system to turn up the attack on tumors or on virus-infected cells. When the researchers searched the DNA database for sequences related to the TNF receptor, they were startled to find a similar gene in the Shope fibroma virus, a member of the poxvirus family that infects rabbits.

But the Shope virus gene—known as T2—differed from the true TNF receptor gene, suggesting it has evolved a different function since being usurped. The true gene produces a protein anchored in the membranes of many different cell types that triggers a response inside the cell when TNF binds and activates it. The T2 gene, however, seemed to code for a protein that had retained the TNF-binding site but lost the membrane anchor, suggesting it is secreted into the fluid surrounding the virus-infected cells. Smith and his colleagues suggested the free-floating protein might act as a decoy, binding and inactivating TNF before it can reach its target cells.

It now looks as if that guess was inspired: In collaboration with McFadden, whose laboratory focuses on Shope fibroma virus and related poxviruses, the Immunex group found that the T2 gene indeed produces a protein that is secreted by virus-infected cells and binds to TNF.

Other examples weren't long in coming—and one of them showed just how potent such decoys can be. McFadden's group found another T2 gene in a poxvirus called myxo-

Getting defensive. When a poxvirus infects a cell (1-3), a protein called T2 (a variant of the receptor for tumor necrosis factor, or TNF) is made, along with new virus particles (4). The infected cell releases new virus and T2 (5). T2 serves as a TNF decoy (6). The decoy prevents TNF (released by healthy immune cells) from binding its true receptor and destroying virus-infected cells.

SARS-CoV2

- Induziert „Lymphopenie“
- Infiziert Immunzellen
- Stört immunologische Organe
- Nutzt immunologische Effekte

Baringa Science 1992 - Mathews-Vaehese Immunobiology 2020

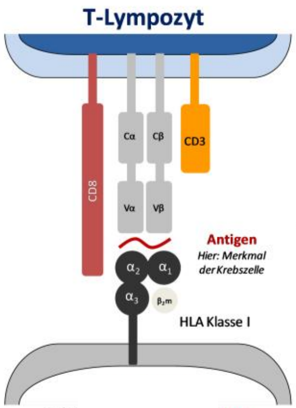
Take home 3

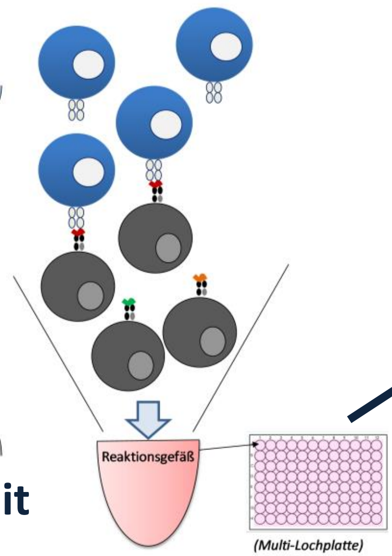
- Immunologische Effekte gegen SARS-CoV2

- COVID-19 ist u.A. ein „colateral damage“

- SARS-CoV2 versucht, dem Immunsystem auszuweichen

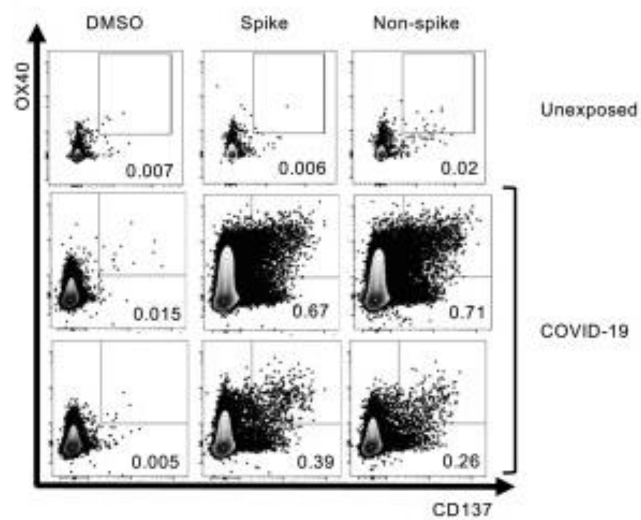
Infektion führt zu zellulärer Immunität





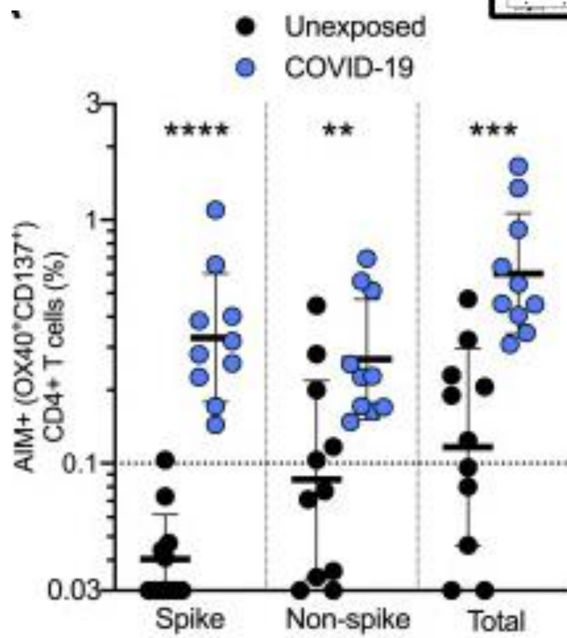
Detektion von Aktivierungmarkern

- CD137
- OX40



Stimulation mit

- Spike-Protein
- allem anderen (Non-Spike)

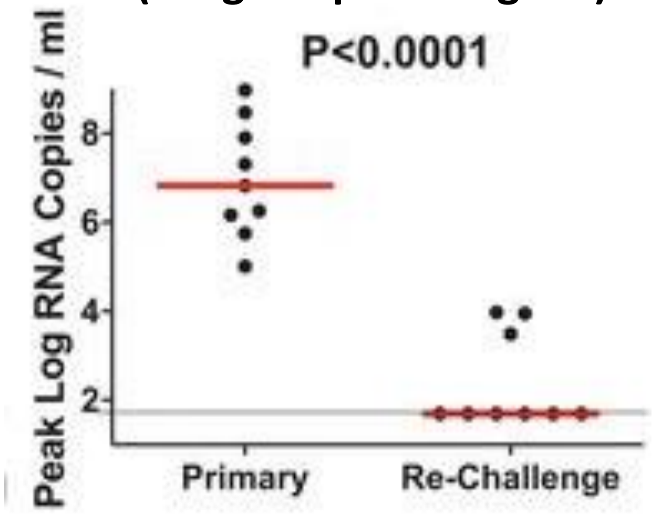


Grifoni Cell 2020

Erstinfektion schützt vor 2. Infektion

- Menschenaffen: wurden nach 35 Tagen erneut mit SARS-CoV2 infiziert

Virus-PCR In der „BAL“ (Lungen-Spülflüssigkeit)



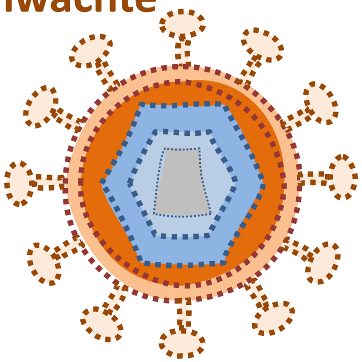
- 3 Virusdosen

Immunität schützt wahrscheinl. vor Infektiosität

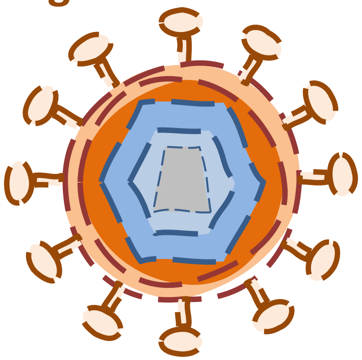
Chandrashekar Science 2020

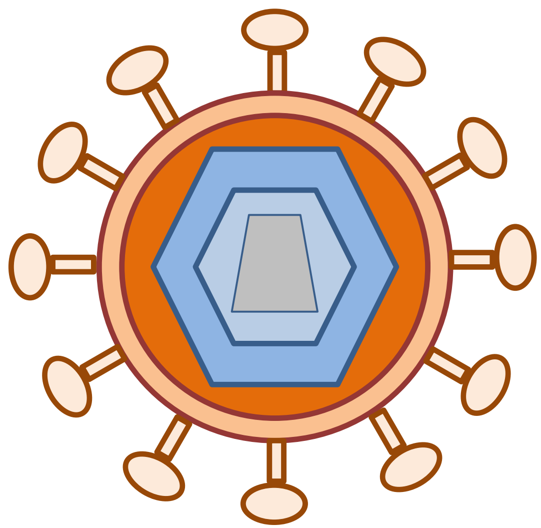
Mögliche Ansätze für Impfungen

Abgeschwächte Viren

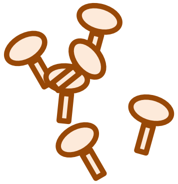


Abgetötete Viren

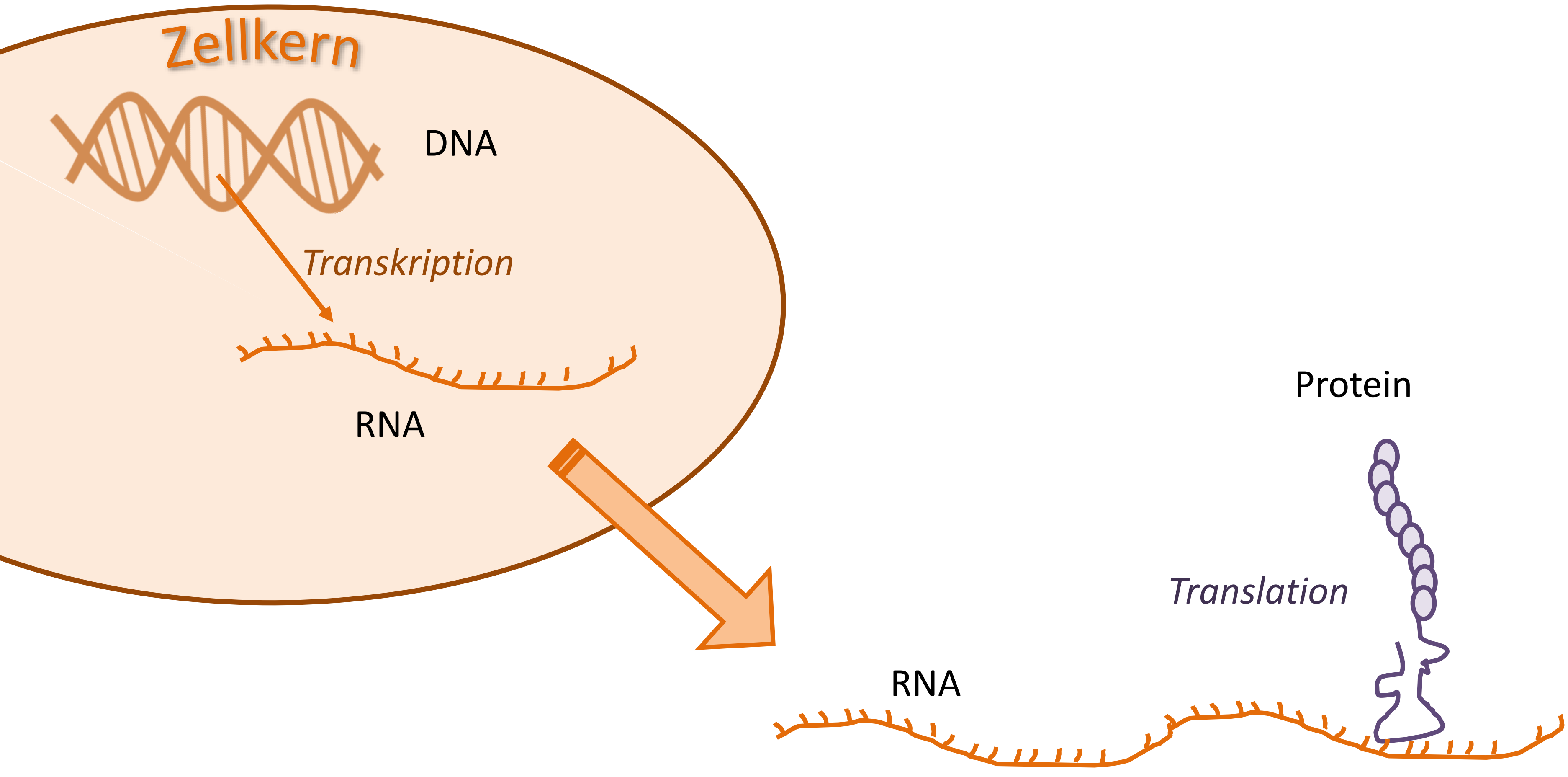




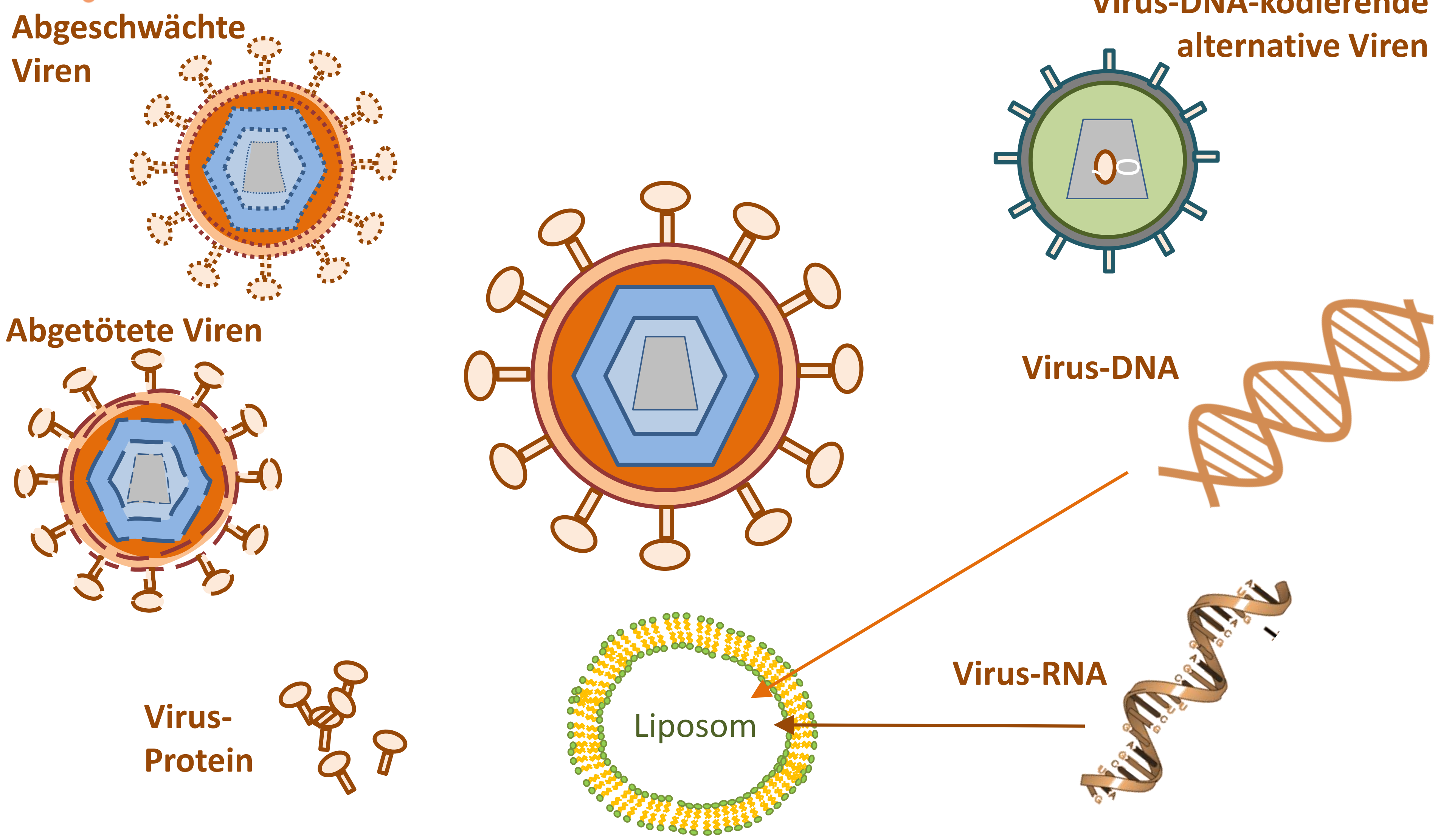
Virus-Protein



Exkurs: Protein (*Eiweiß*)-Biosynthese



Mögliche Ansätze für Impfungen



Aktuelle Impfstudien

Curevac (Tübingen, D)

AstraZeneca (Oxford, UK)

Moderna (NIH, MA, USA)

BioNTech (Mainz, D)

„Sputnik V“, Gamaleya (RUS)

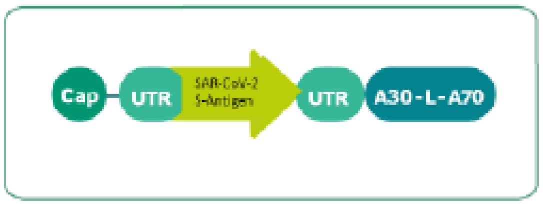
Poland Lancet 2020

Institut / Firma	Teilnehmer	Impfstoff	Land
Phase 1 Studie			
Inovio		DNA	USA
Genexine		DNA	South Korea
Academy of Military Sciences; Suzhou Abogen Biosciences; Walvax Biotechnology		mRNA	China
ReiThera; Lazzaro Spallanzani National Institute for Infectious Diseases		Gorilla-Adenovirus	Italy
Clover Pharmaceuticals; Dynavax Technologies		Protein	..
Vaxine		Protein	Australia
Medicago; GSK; Dynavax Technologies		Virus-like particle	USA
University of Queensland; CSL		Proteine	Australia
Kentucky Bioprocessing		Pflanzenvektor (?)	USA
Medigen; Dynavax Technologies		Protein	Taiwan
Adimmune		Protein	Taiwan
West China Hospital of Sichuan University		Protein	China
Sanofi; GSK		Protein	..
Merck; Pasteur Institute		Masern-Virus	France
Research Institute for Biological Safety Problems		Inaktiviertes Virus	Kazakhstan
Themis; Merck; University of Pittsburgh Center for Vaccine Research		Vesicular-Stomatitis -Virus	Belgium; France
Symvivo		Oral	USA; Canada
Phase 1 und 2 Studien			
Imperial College London; Morningside Ventures		Selbst-amplifi.RNA	UK
AnGes; Osaka University; Takara Bio		DNA	Japan
Arcturus; Duke-NUS Medical School		mRNA	Singapore
Johnson & Johnson; Beth Israel Deaconess Medical Center		Adenovirus	USA
Novavax		Nanoparticle	USA; South Africa
Finlay Vaccine Institute		Protein	Cuba
Vector Institute		Peptide	Russia
Bharat Biotech; Indian Council of Medical Research; National Institute of Virology		Inaktiviertes Virus	India
Anhui Zhifei Longcom Biopharmaceutical; Institute of Microbiology of the Chinese Academy of Sciences		Protein	China
Zydus Cadila		DNA	India
Curevac		mRNA	Germany, Belgium
Phase 3 Studien			
AstraZeneca; University of Oxford	30000	Chimpansen-Adenovirus	UK; India; Brazil, South Africa; USA
Moderna; National Institutes of Health	30000	RNA	USA
Pfizer; BioNTech	44000	RNA	USA
Janssen Pharmaceutical	60000	Adenovirus serotype 26	Nord- und Südamerika, Philippinen, Südafrika, Ukraine
Gamaleya National Research Centre for Epidemiology and Microbiology; Academy of Military Medical Sciences	40000	Adenovirus Serotype 5 und 26	Russia
CanSino Biologics; Academy of Military Medical Sciences	40000	Adenovirus Serotype 5	China; Pakistan
Sinovac Biotech	9000	Inaktiviertes Virus	Brazil; Indonesia
Sinopharm; Wuhan Institute of Biological Products	21000	Inaktiviertes Virus	United Arab Emirates; Bahrain; Peru; Morocco; Argentina; Jordan
Sinopharm; Beijing Institute of Biological Products	5000	Inaktiviertes Virus	United Arab Emirates

mRNA-Vakzine am Beispiel der BIONTECH

Vakzine-Strategien aus der Forschung zu *Krebs-Impfung*

Uridine mRNA (uRNA)[1]



Rationale

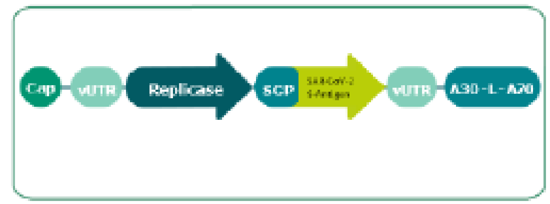
- 2 Impfungen notwendig
- Starke Immunstimulation (Adjuvans-Effekt)
- Deutliche AK-Antwort
- CD8 > CD4 T-Zellen

Nucleoside-modified mRNA (modRNA)[2]

Rationale

- 2 Impfungen notwendig
- Weniger starke Stimulation (Adjuvans-Effekt)
- Sehr starke AK-Antwort
- CD4 > CD8 T-Zellen

Self-amplifying mRNA (saRNA)[3]



Rationale

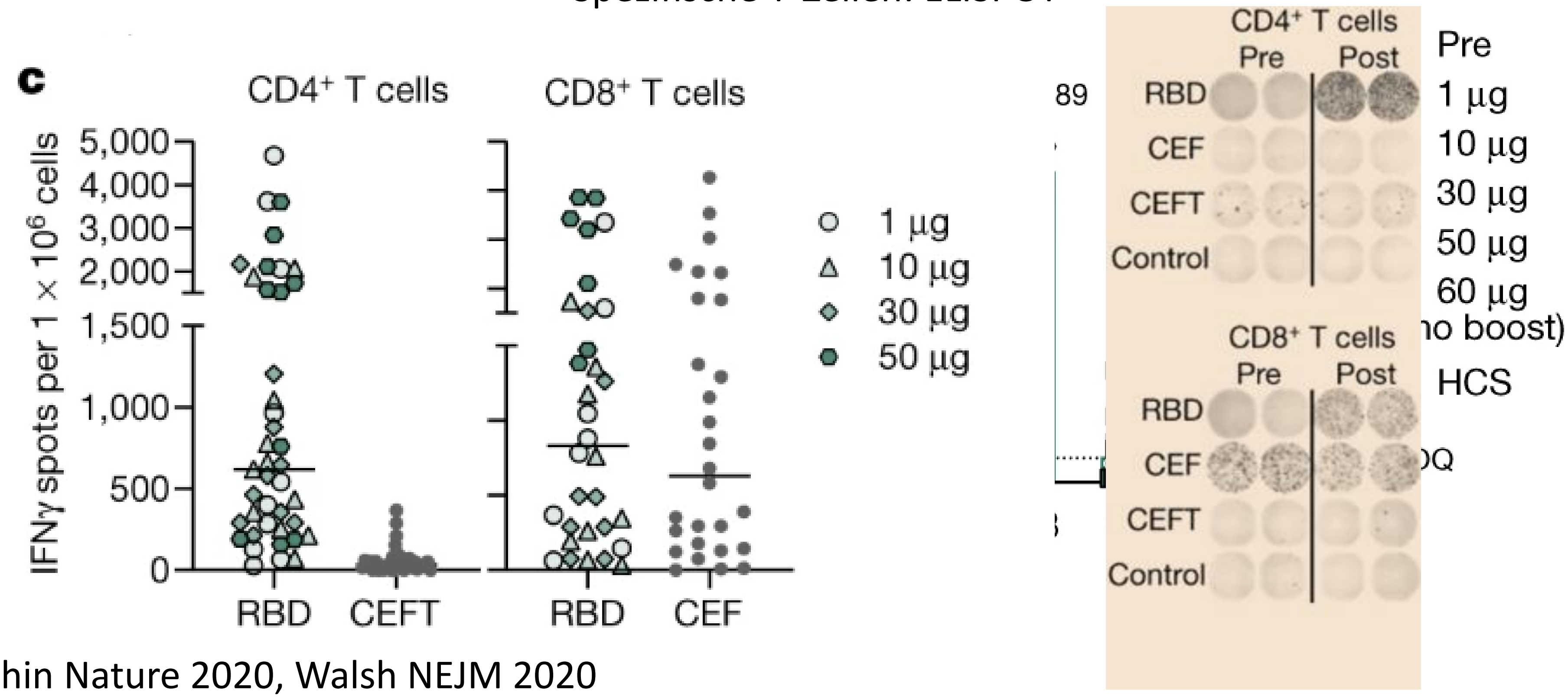
- Nur 1 Impfung notwendig
- Anhaltender Effek
- Sehr starke AK-Antwort
- Starke CD4 und CD8 T-Zellantwort
- Niedrige Dosis notwendig (ca. 1/60)

[1] Kreiter et al., Nature 2015, Kranz, Diken et al., Nature, 2016, Sahin et al., Nature 2017, Reinhard et al., Science 2020
[2] Pardi et al., Nature, 2017, Pardi et al., Mol Ther 2019, [3] Vogel et al., Mol. Ther 2018, Moyo et al., Mol Ther 2019

Immunität nach BNT162b1

- Impfung gegen das Spike Protein (RBD)

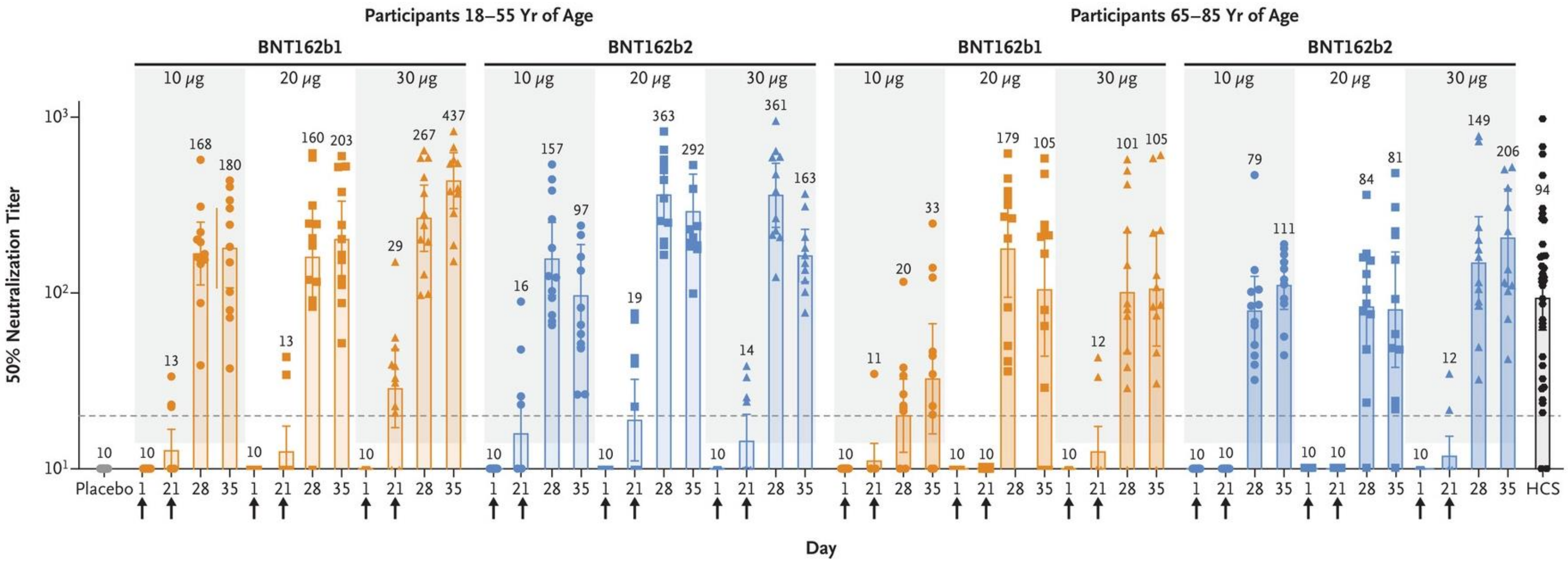
Spezifische T-Zellen: ELISPOT



Sahin Nature 2020, Walsh NEJM 2020

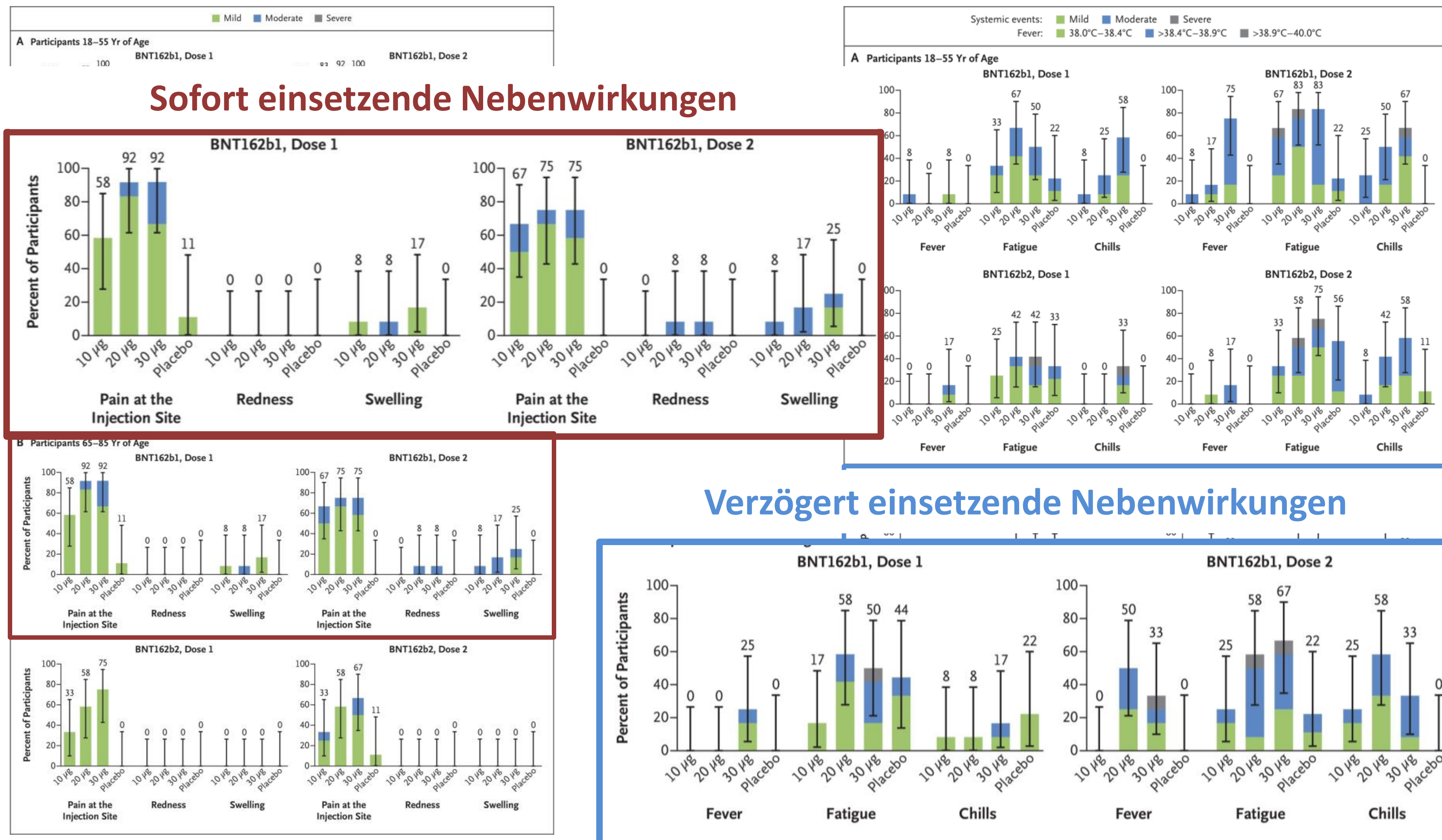
Impferfolg von BNT162b1und b2

- 195 Patienten wurden 2 x geimpft
- 2 Kohorten (18-55 und 56 bis 85 Jahre)



Sahin Nature 2020, Walsh NEJM 2020

Nebenwirkungen BNT162b1und b2



Sahin Nature 2020, Walsh NEJM 2020

Der Moderna-RNA-Impfstoff „mRNA1273“

- Impfstoff ist auch eine mRNA des Spike-Proteins
- Immunologische Ergebnisse bei älteren

  Patienten 56-70 und > 70 Jahre
- Effektivät bei Menschenaffen

Corbett NEJM 2020, Anderson NEJM 2020

Der Moderna-RNA-Impfstoff „mRNA-1273“

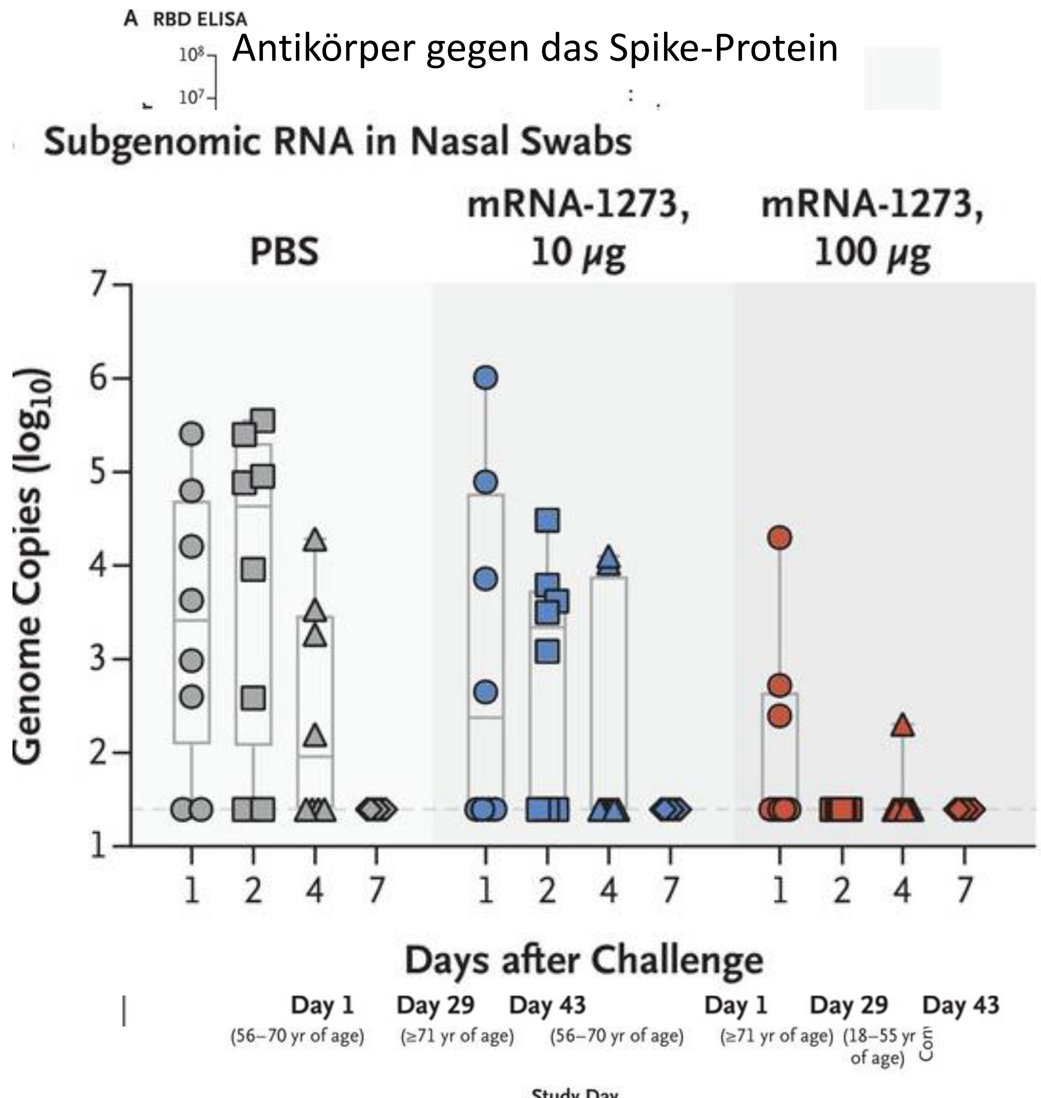
ELISA + Neutralisation

T-Zell-Stimulation

Messung von intrazellulären Botenstoffen / Zytokinen

„klinische“ Effektivität

Virus-Clearance bei geimpften Menschenaffen

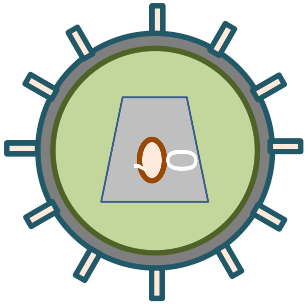


Corbett NEJM 2020, Anderson NEJM 2020

Der „AstraZeneca“ Impfstoff AZD1222

- Ein Affen-Adenovirus trägt die Erbinformation für das Spike-Protein
- Die Impfung ist eine echte Infektion
- Das Virus (AZD1222)

ChAdOx1-nCOV19



clinicaltrials.gov: NCT04516746

Take home 3

SARS-CoV2…

- induziert eine starke Reaktion des Immunsystems
- hinterlässt eine humorale und zelluläre Immunität

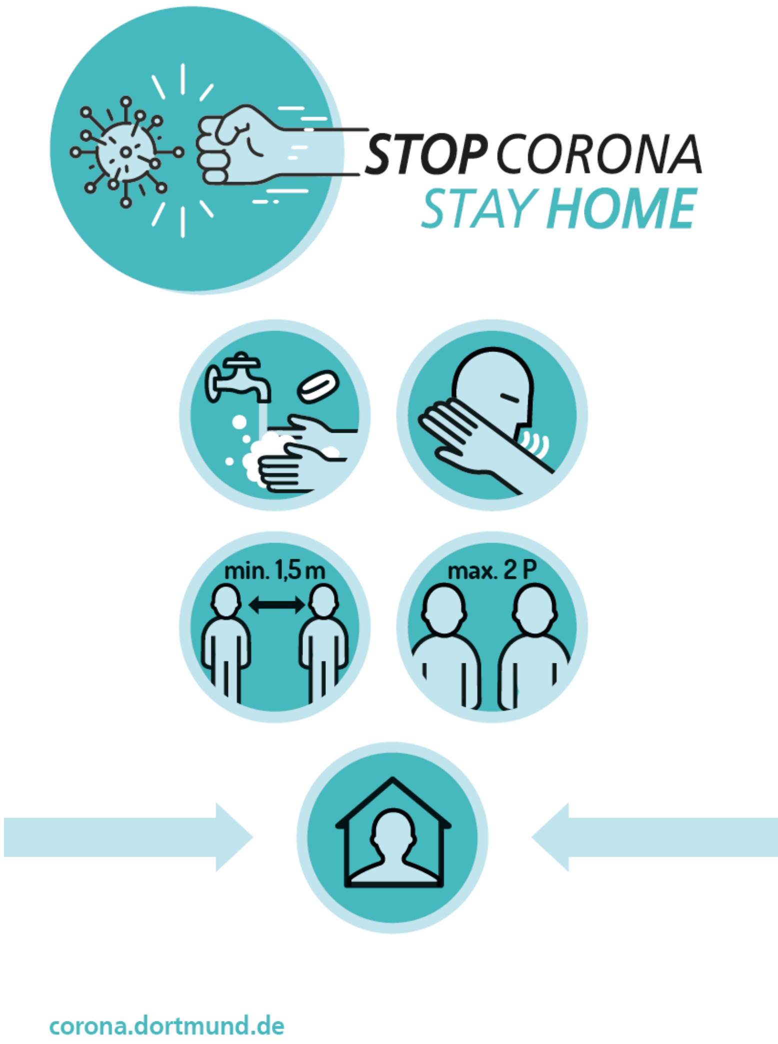
Die Immunität gegen SARS-CoV2…

- ist protektiv
- wird durch *RNA-* und *adenovirale* Impfstoffe induziert

Bleiben Sie gesund!

Bleiben Sie wachsam!

Bleiben Sie vernünftig!



…. und lassen Sie sich impfen!!

St.-Johannes-Hospital

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