

# Deutschland und die Pandemie: COVID-19 Erfahrungen aus der Klinik



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## Disclosures: Peter Bader

- Research Grants: Neovii, Riemsler, Medac (Institution).
- Advisory Board: Novartis, Cellgene, Amgen, Medac, Servier (Institution).
- Speakers Bureau: Miltenyi, Jazz, Riemsler, Novartis, Amgen (Institution).
- Medac: Patent and Royalties.

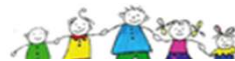




# Agenda

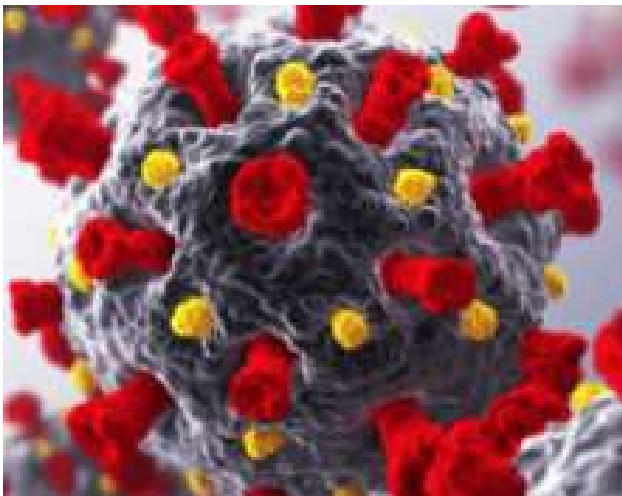
- Entwicklung der Pandemie in Deutschland
- Virus und Krankheitsdefinitionen
- Klinische Symptomatik
- Pathophysiologie
- Infektionswege
- Diagnostik
- Verlaufsformen
- Dr. Neb: klinische Behandlung auf der Intensivstation
- Mesenchymale Stromazellen
- Geplante klinische Studie





27. Januar 2020

Das Coronavirus hat Deutschland erreicht. Ein Mann aus dem Landkreis Starnberg in Bayern hat sich infiziert, erklärte ein Sprecher des Gesundheitsministeriums in München. Er wurde isoliert, wird medizinisch versorgt und befindet sich klinisch in einem guten Zustand. Das Risiko für eine Ausbreitung des Virus in Deutschland ist aber nach wie vor gering.



“

Es war zu erwarten, dass das Virus auch Deutschland erreicht. Der Fall aus Bayern zeigt aber, dass wir gut darauf vorbereitet sind. Die Gefahr für die Gesundheit der Menschen in Deutschland durch die neue Atemwegserkrankung aus China bleibt nach Einschätzung des RKI weiterhin gering.

– Bundesgesundheitsminister Jens Spahn





31. Januar 2020

Rund 100 Personen werden voraussichtlich am 1. Februar 2020 aus Wuhan nach Deutschland zurückkehren. Die Rückkehrer sind symptomfrei gestartet. Als Vorsichtsmaßnahme und um sie und weitere Menschen zu schützen, werden sie in einer Unterkunft in Germersheim in Rheinland-Pfalz zwölf bis 15 Tage lang isoliert.

“

Wenn man mir in zwei Wochen vorwirft, übertrieben vorsichtig gewesen zu sein, bin ich zufrieden - denn dann hat sich alles gut entwickelt.

— Bundesgesundheitsminister Jens Spahn





# It will be gone by April.....

<https://www.youtube.com/watch?v=bYFnfoJHiVc>

## Coronavirus

This article is more than 2 months old

### Six months of Trump's Covid denials: 'It'll go away ... It's fading'

Trump repeats his promise that the virus will disappear as US passes another somber milestone of 150,000 confirmed deaths

Ed Pilkington in New York

@edpilkington

Wed 29 Jul 2020 22:27 BST



1.573



▲ Trump's changing reactions to coronavirus: from calm to closing borders – video report

Six months of coronavirus in the US, six months of Trump denials.

As the US passed another somber landmark, with more than 150,000 confirmed deaths from Covid-19, the grim toll stands in stark contrast to Donald Trump's repeated promise that under his leadership the disease would simply disappear.

Here are some of his starkest statements on the topic:

#### 20 January: 'We have it under control'

On 20 January the US recorded its **first case** of coronavirus. Two days later Trump told **CNBC**: "It's one person coming in from China. We have it under





# COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU)

## Global Cases

# 40.433.853

Cases by Country/Region/Sovereignty

8,215,578	US
7,597,063	India
5,250,727	Brazil
1,406,667	Russia
1,002,662	Argentina
974,449	Spain
965,883	Colombia
952,600	France
868,675	Peru
854,926	Mexico
744,122	United Kingdom
705,254	South Africa
534,631	Iran
493,305	Chile
430,678	Iraq
423,578	Italy
391,586	Bangladesh
377,068	Germany
368,842	Indonesia



[Cumulative Cases](#) | 
 [Active Cases](#) | 
 [Incidence Rate](#) | 
 [Case-Fatality Ratio](#) | 
 [Testing Rate](#)

# 189

countries/regions

Lancet Inf Dis Article: [Here](#). Mobile Version: [Here](#). Data sources: [Full list](#). Downloadable database: [GitHub](#), [Feature Layer](#).  
 Lead by [JHU CSSE](#). Technical Support: [Esri Living Atlas team](#) and [JHU APL](#). Financial Support: [JHU](#), [NSF](#), [Bloomberg Philanthropies](#) and [Stavros Niarchos Foundation](#). Resource support: [Slack](#), [Github](#) and [AWS](#).  
 Click [here](#) to **donate** to the CSSE dashboard team, and other JHU COVID-19 Research Efforts. [FAQ](#). Read more in

Last Updated at (M/D/YYYY)  
**10/20/2020, 12:24 nachm.**

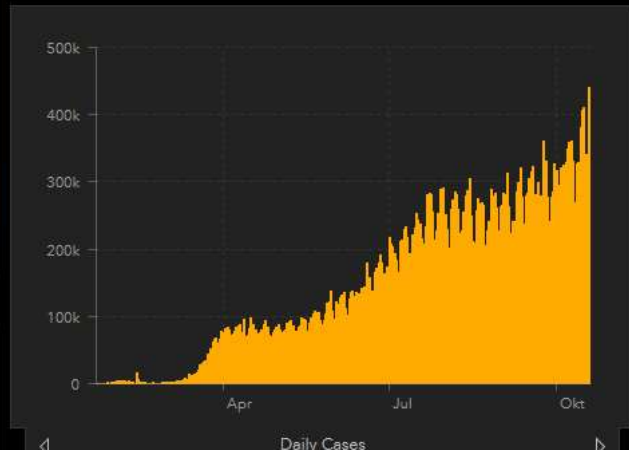
## Global Deaths

# 1.118.681

220,134 deaths	US
154,176 deaths	Brazil
115,197 deaths	India
86,338 deaths	Mexico
43,816 deaths	United Kingdom
36,616 deaths	Italy
33,992 deaths	Spain
33,759 deaths	Peru

## US State Level Deaths, Recovered

33,366 deaths, <b>78,442</b> recovered	New York US
17,481 deaths, <b>729,762</b> recovered	Texas US
16,992 deaths, <b>recovered</b>	California US
16,214 deaths, <b>35,944</b> recovered	New Jersey US
16,021 deaths, <b>recovered</b>	Florida US
9,753 deaths, <b>118,892</b> recovered	Massachusetts US
9,496 deaths, <b>recovered</b>	Illinois US





# Spiegel online 20.10.2020

## Corona-Pandemie >

### **"Es ist absehbar, dass das System implodiert"**

Wer meint, sich mit dem Coronavirus infiziert zu haben, meldet sich oft bei seiner Hausärztin. Wie gehen Praxen damit um? Der SPIEGEL hat bundesweit nachgefragt. Aufgezeichnet von Nike Laurenz



## +++ News-Update +++

### **Hunderte Touristen müssen Berchtesgadener Land verlassen**

Im Landkreis Berchtesgaden gelten strikte Ausgangsbeschränkungen. Zahlreiche Feriengäste wurden aufgefordert, abzureisen. Und: Die Region Hannover führt eine Maskenpflicht in Unternehmen ein. Der Überblick.

## Corona-Politik

### **Spahn verteidigt geplante Verlängerung seiner Sonderrechte**

Jens Spahn will seine Sonderbefugnisse in der Corona-Bekämpfung verlängern lassen - und sorgt damit für Unmut bei den Abgeordneten des Bundestags. Nun hat der Gesundheitsminister sich an die Kritiker gewandt.

## Klopapier-Hersteller

### **"Es wird keine Unterversorgung geben"**

Und täglich grüßt... der Hamster: Mancher fühlt sich bei den steigenden Corona-Zahlen ans Frühjahr erinnert und will Klopapier auf Vorrat kaufen. Ein Produzent beruhigt nun - das sei nicht nötig.



## Pro-Asyl-Experte über getrennte Familien

### **"Wenn Corona wieder alles lahmlegt, ist das eine Katastrophe"**

Karim Alwasiti von der Menschenrechtsorganisation Pro Asyl erklärt, was die Pandemie für Flüchtlingsfamilien bedeutet. Ein Interview von Katrin Elger



▶ 04:43

## Corona-Langzeitschäden

### **"Ich vergesse alles"**

Schmerzen, Antriebslosigkeit, Gedächtnisverlust: Auch Wochen nach einer Corona-Infektion fühlen sich viele Patienten krank. Thomas Thielen in der Reha-Klinik Heiligendamm ist einer von ihnen. Ein Video von Birgit Groß "Ich vergesse alles"

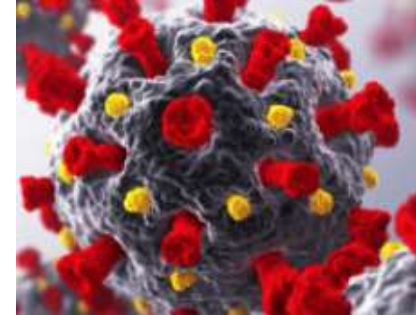






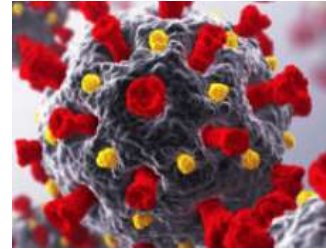
# Definitionen am 11. Februar 2020

- Virus:
  - International Committee on Taxonomy of Viruses (ICTV):
    - Severe Acute Respiratory Syndrome Corona Virus type2 = SARS-CoV2
  
- Krankheit:
  - WHO: SARS-Cov-2 verursacht:
    - Corona Virus Disease 2019 = COVID 19



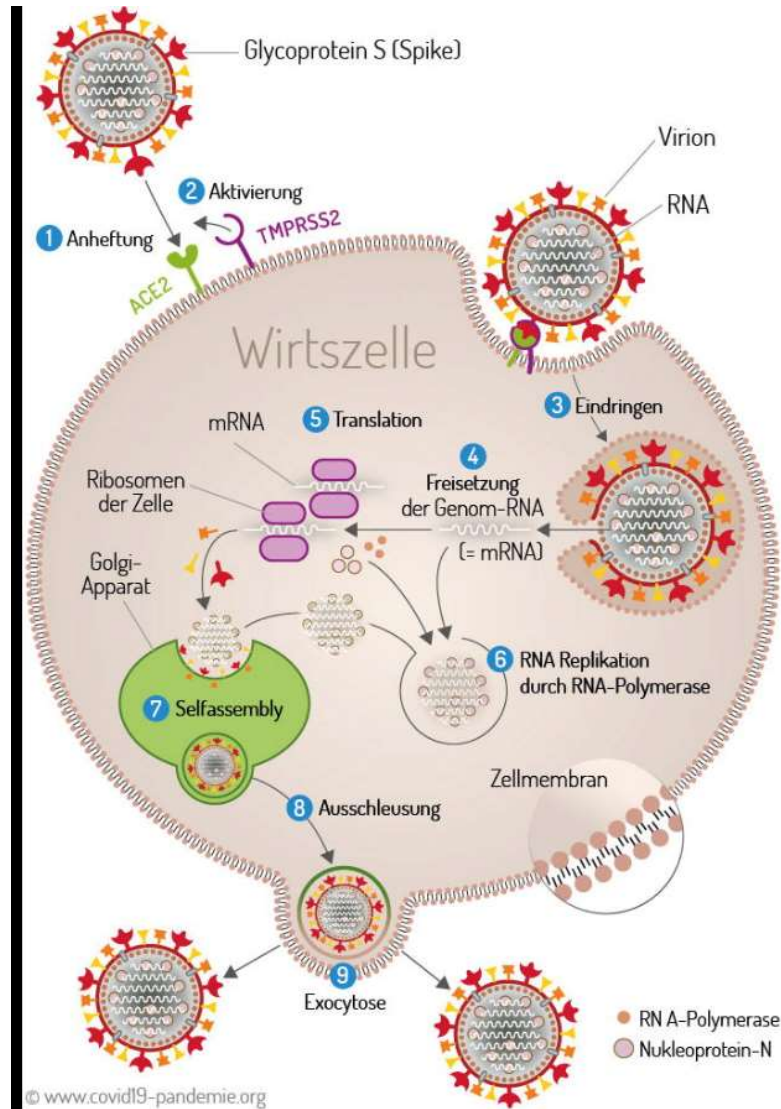


# Definitionen



- Verbreitung der Corona Viren:
  - Vögeln und Säugetiere, Mensch
  - Können sehr leicht das Wirtsspektrum erweitern und die Artengrenze überspringen
  - Sieben Corona Virus Spezies sind bekannt (Alphacoronaviren und Betacoronaviren:
    - Middle East Respiratory Syndrome MERS-CoV, SARS-Cov-1 und SARS-CoV-2 sind erst vor kurzer Zeit vom Tier auf den Menschen übergegangen
  - SARS-CoV-2 ist ein neues Corona Virus, erst Anfang 2020 identifiziert
  - RNA Viren: Haben ein Einzelstrang-RNA-Genom







## Häufigste Symptome: COVID 19

- Fieber
- Trockener Husten (38%)
- Husten (45%)
- Schnupfen (20%)
- Müdigkeit
- **Seltenere Symptome:**
- Gliederschmerzen, Halsschmerzen
- Durchfall
- Bindehautentzündung
- Kopfschmerzen
- Verlust des Geschmacks- oder Geruchssinns (15%)
- Verfärbung an Fingern oder Zehen oder Hautausschlag
- Schwere Symptome:
- Atembeschwerden oder Kurzatmigkeit (3%)
- Schmerzen oder Druckgefühl im Brustbereich
- Verlust der Sprach- oder Bewegungsfähigkeit







# Symptome

## COVID -19, ERKÄLTUNG & GRIPPE - DIE WICHTIGSTEN UNTERSCHIEDE

Symptome	Coronavirus	Erkältung	Grippe
Fieber	häufig	selten	häufig
Müdigkeit	manchmal	manchmal	häufig
Husten	häufig*	wenig	häufig*
Niesen	nein	häufig	nein
Gliederschmerzen	manchmal	häufig	häufig
Schnupfen	selten	häufig	manchmal
Halsschmerzen	manchmal	häufig	manchmal
Kopfweg	manchmal	selten	häufig
Kurzatmigkeit	manchmal	nein	nein





## Anzeichen, Symptome und der medizinische Bedarf



### Übertragung

Mensch-zu-Mensch  
über respiratorische  
Sekrete und Aerosole



### Inkubation

Zwischen 2-14 Tagen  
(Median 5 Tage)



### Leitsymptome

Fieber, respiratorische  
Symptome (Husten),  
Durchfall, Erbrechen,  
Kopfschmerzen, Glieder-  
schmerzen, Geruchs-  
verlust



### Klinische Ausprägung

asymptomatische  
Infektion, leichte  
Erkrankung, Lungen-  
entzündung oder  
tödliche Erkrankung



### Klinischer Verlauf

Kann eine schwere  
Organschädigung  
(Lunge, Herz, Gefäße,  
Niere, Nervensystem)  
verursachen, besonders  
bei multimorbiden und  
älteren Patienten

Früherkennung  
infizierter Patienten

Tieferes Verständnis des  
Infektionsgeschehens  
und der Infektiosität

Erkennen des  
Krankheitsverlaufs

Individuelle  
Entscheidung der  
Therapieform und  
frühzeitiges Eingreifen  
bei Komplikationen

Tieferes Verständnis von  
Organkomplikationen



# Übertragung

- Das Coronavirus SARS-CoV-2 wird im normalen gesellschaftlichen Umgang in der Bevölkerung hauptsächlich über virushaltige Partikel übertragen
  - Husten und Niesen sowie beim Atmen und Sprechen
    - Tröpfchen und kleinere Aerosole
    - größere Tröpfchen sinken schneller zu Boden
    - Aerosole auch über längere Zeit in der Luft schweben und sich in geschlossenen Räumen verteilen
  - Beim Atmen und Sprechen, vor allem bei höherer Lautstärke, werden Aerosole ausgeschieden
  - Beim Husten und Niesen entstehen zusätzlich deutlich mehr Tröpfchen





# Diagnose

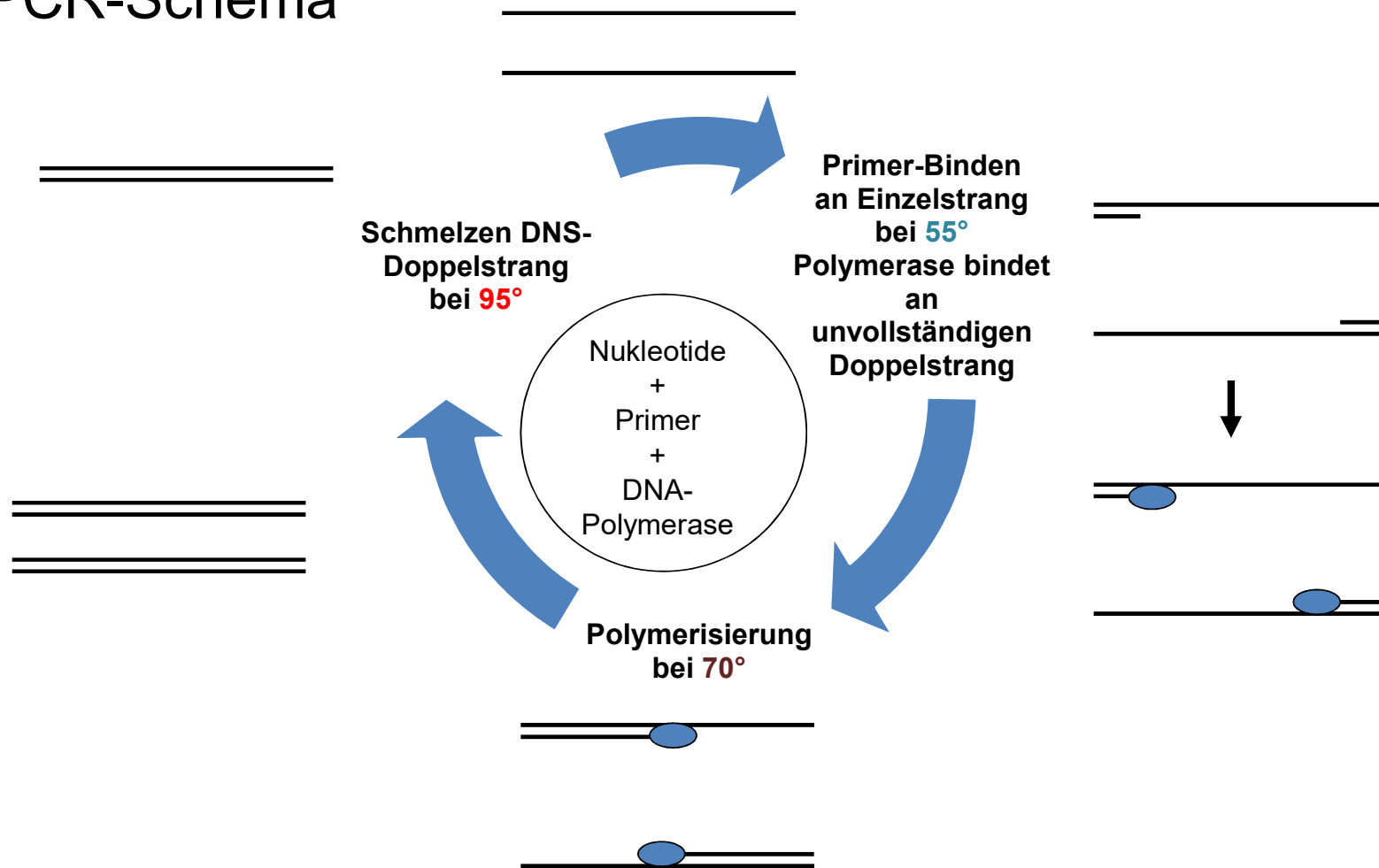
- Klinischer Verdacht
- Labor - Diagnose
  - Polymerase Kettenreaktion (PCR) zum Nachweis von Virus DNA oder RNA
  - Antigen Nachweis mittels monoklonaler Antikörper





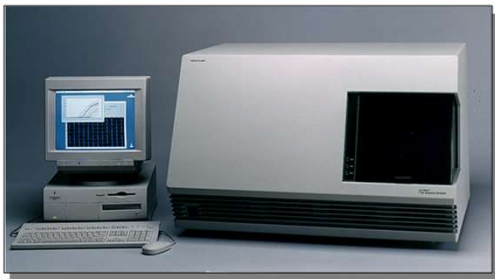
# Polymerase Kettenreaktion – Vermehrung von DNA

## PCR-Schema

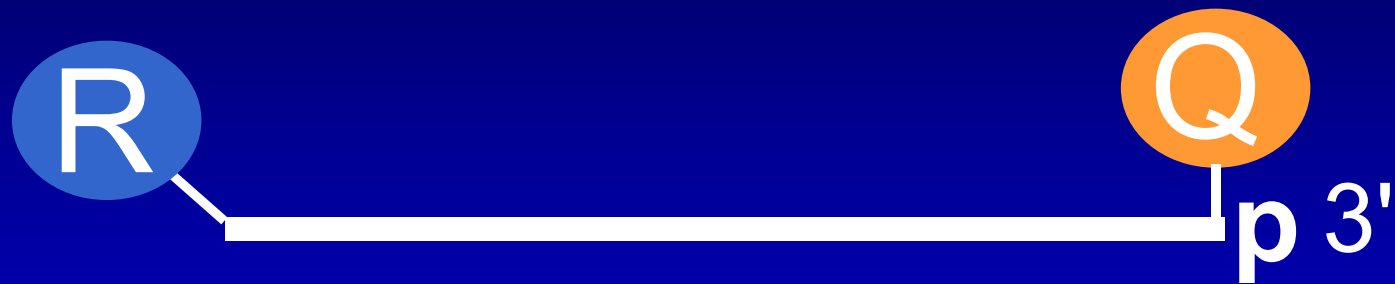


# Quantitative PCR mit Hilfe der TaqMan<sup>®</sup> -Technology heute Real time PCR

ABI PRISM™ 7700  
Sequence Detection System



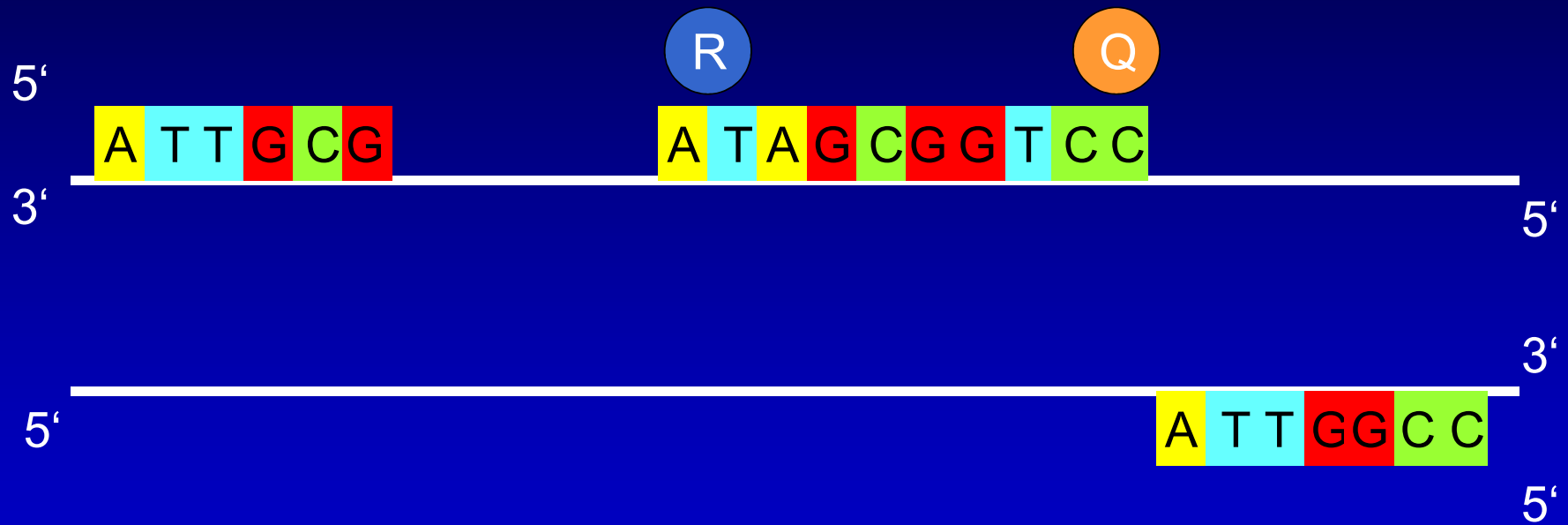
# Fluorogene TaqMan<sup>®</sup> -Sonde



R = Reporter

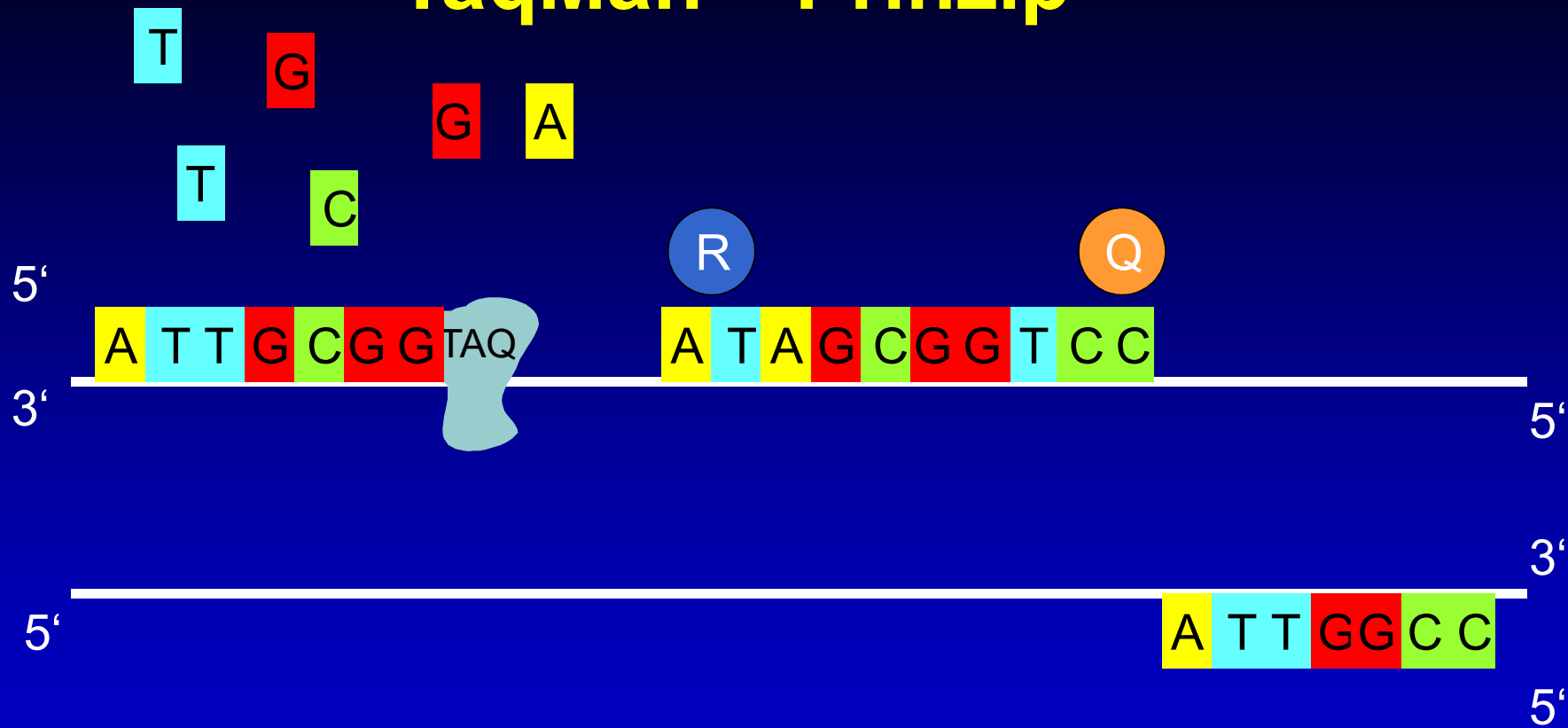
Q = Quencher

# TaqMan<sup>®</sup> -Prinzip

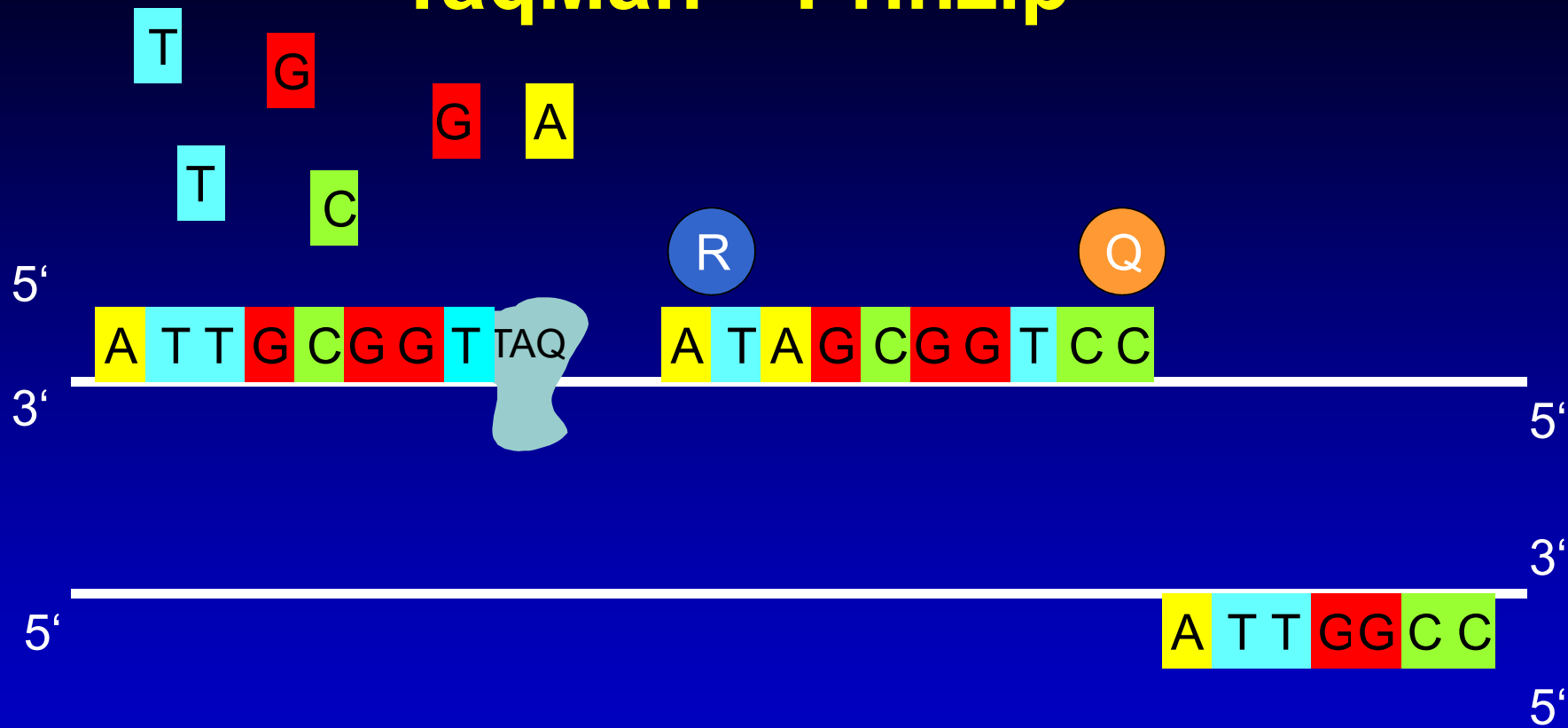




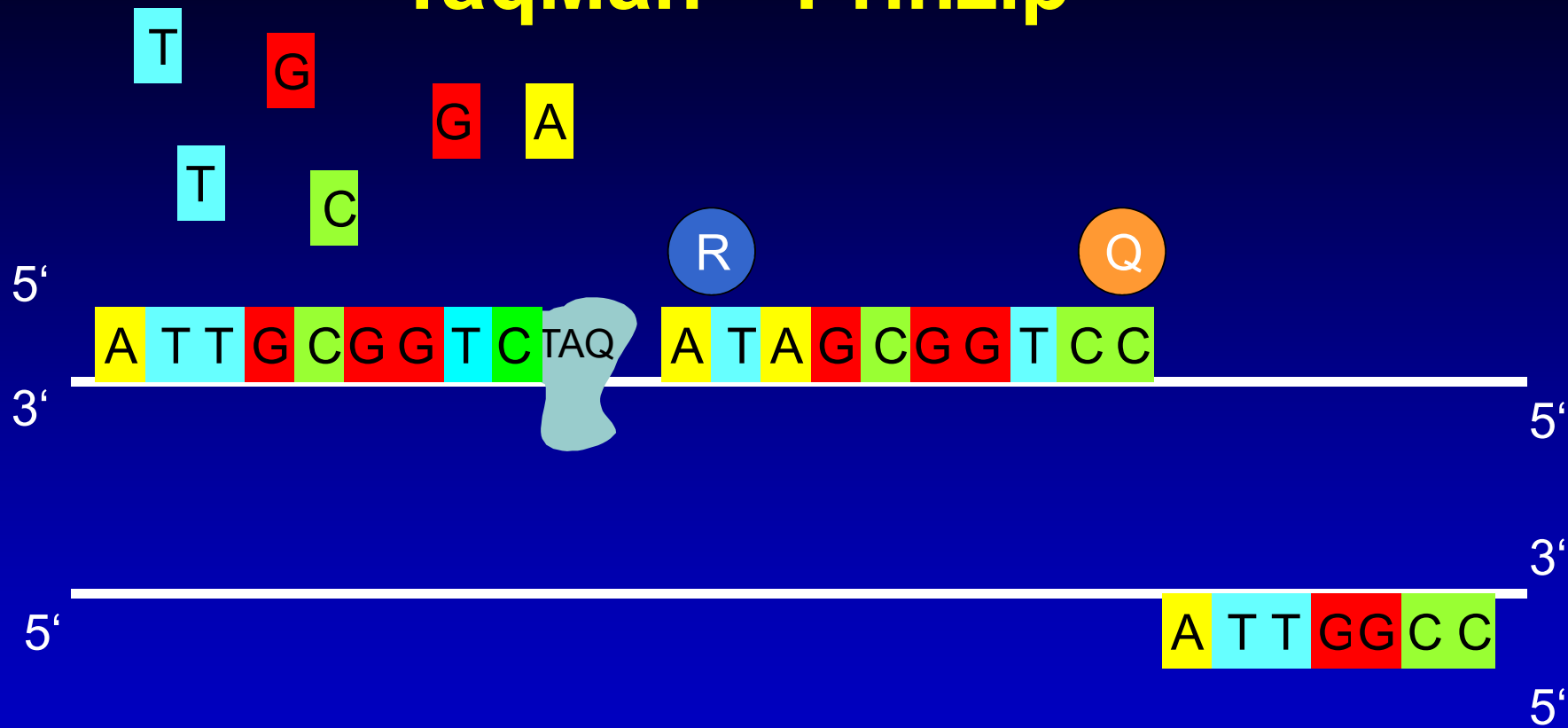
# TaqMan<sup>®</sup> -Prinzip



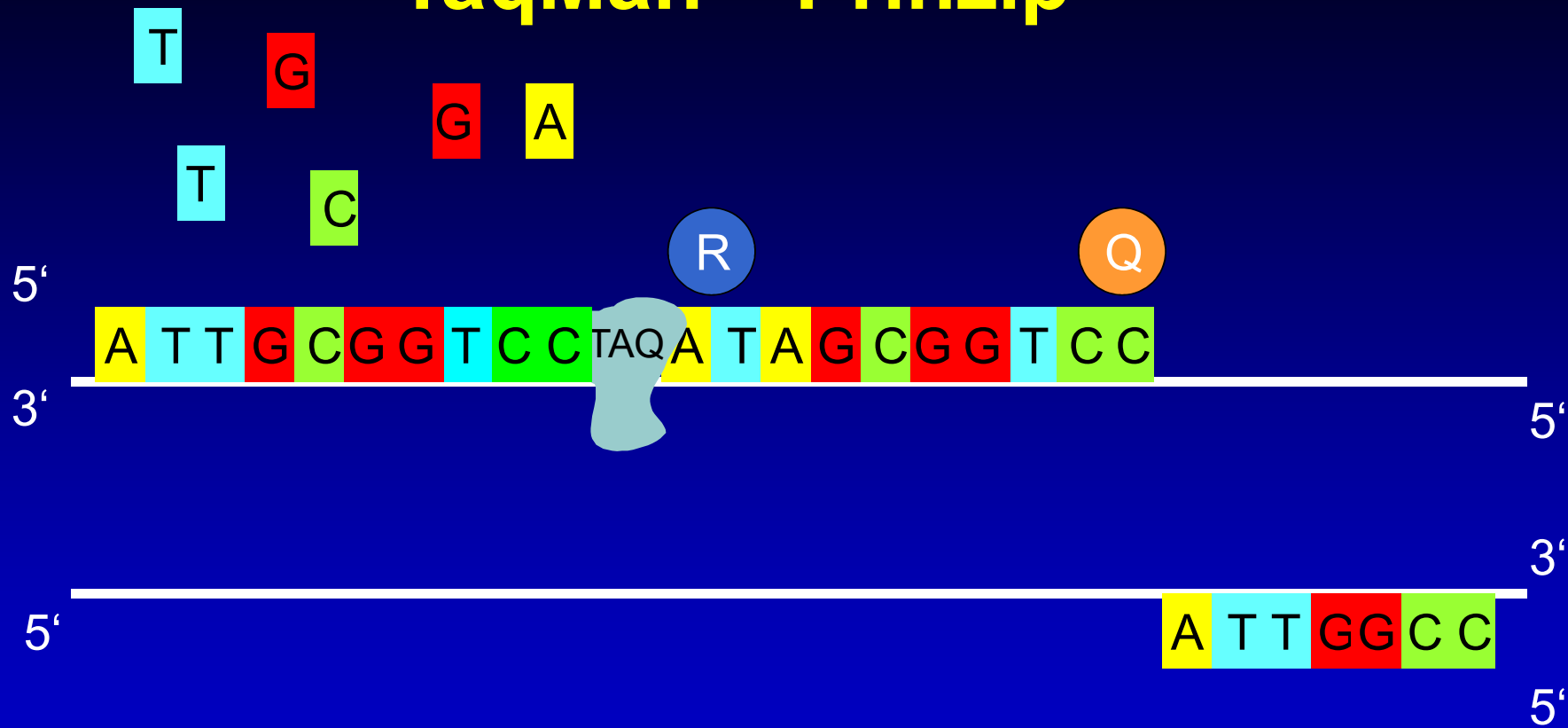
# TaqMan<sup>®</sup> -Prinzip



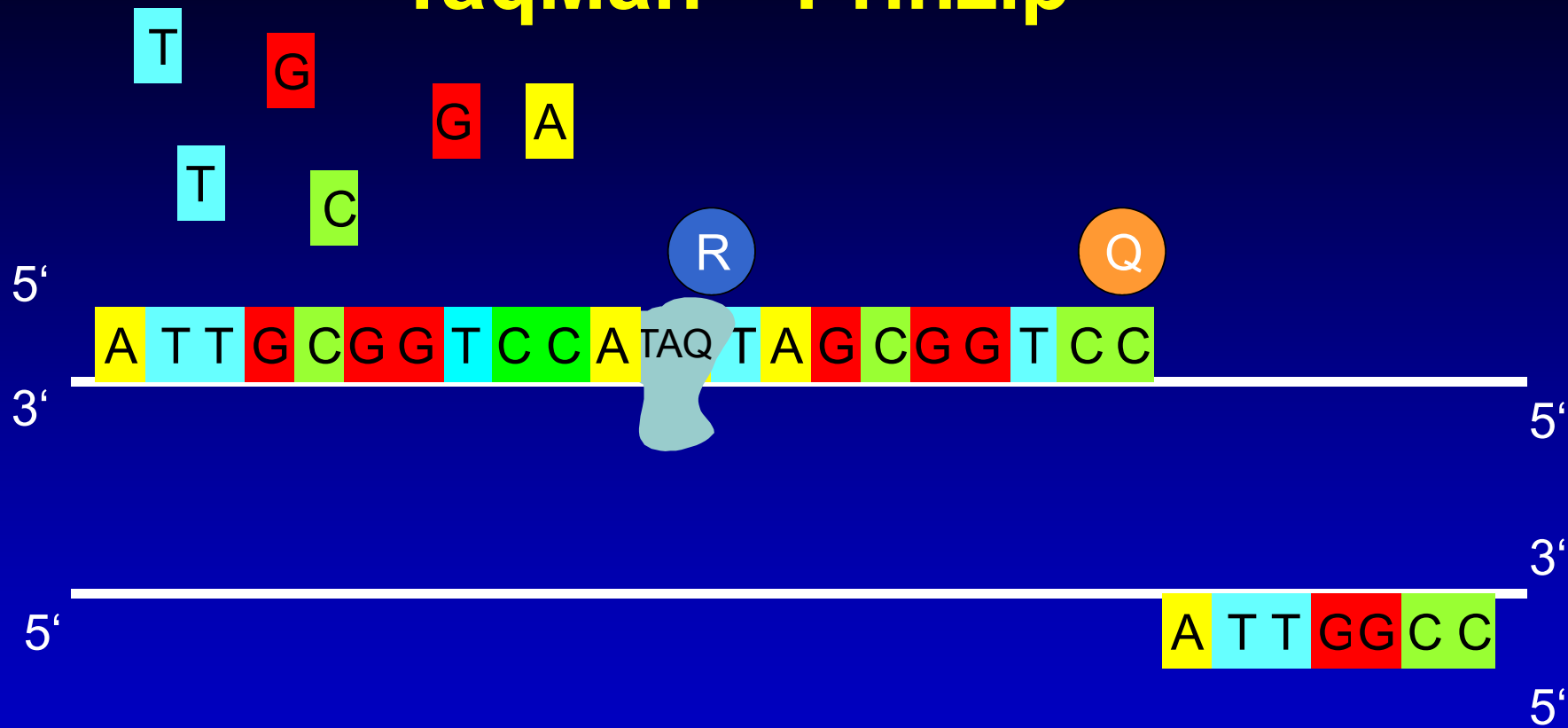
# TaqMan<sup>®</sup> -Prinzip



# TaqMan<sup>®</sup> -Prinzip

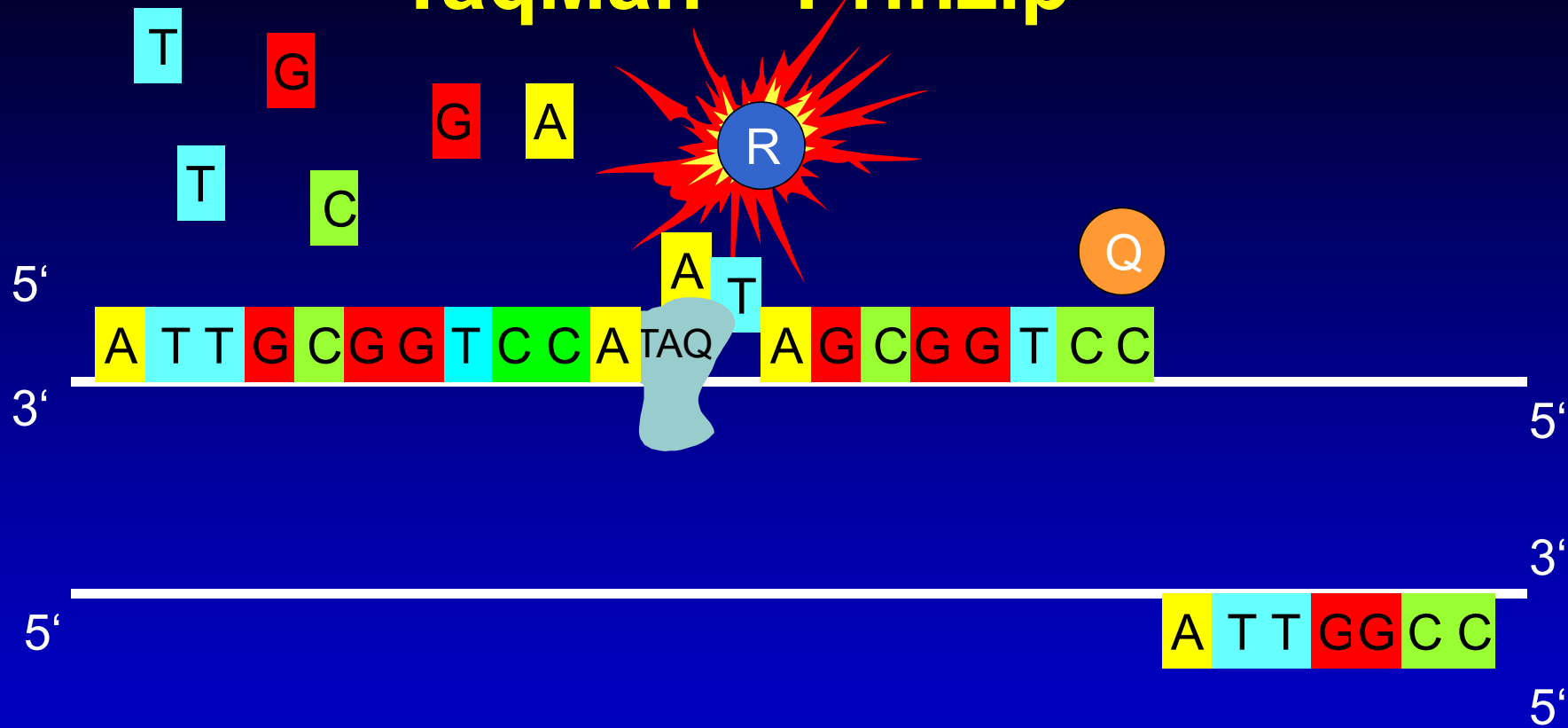


# TaqMan<sup>®</sup> -Prinzip

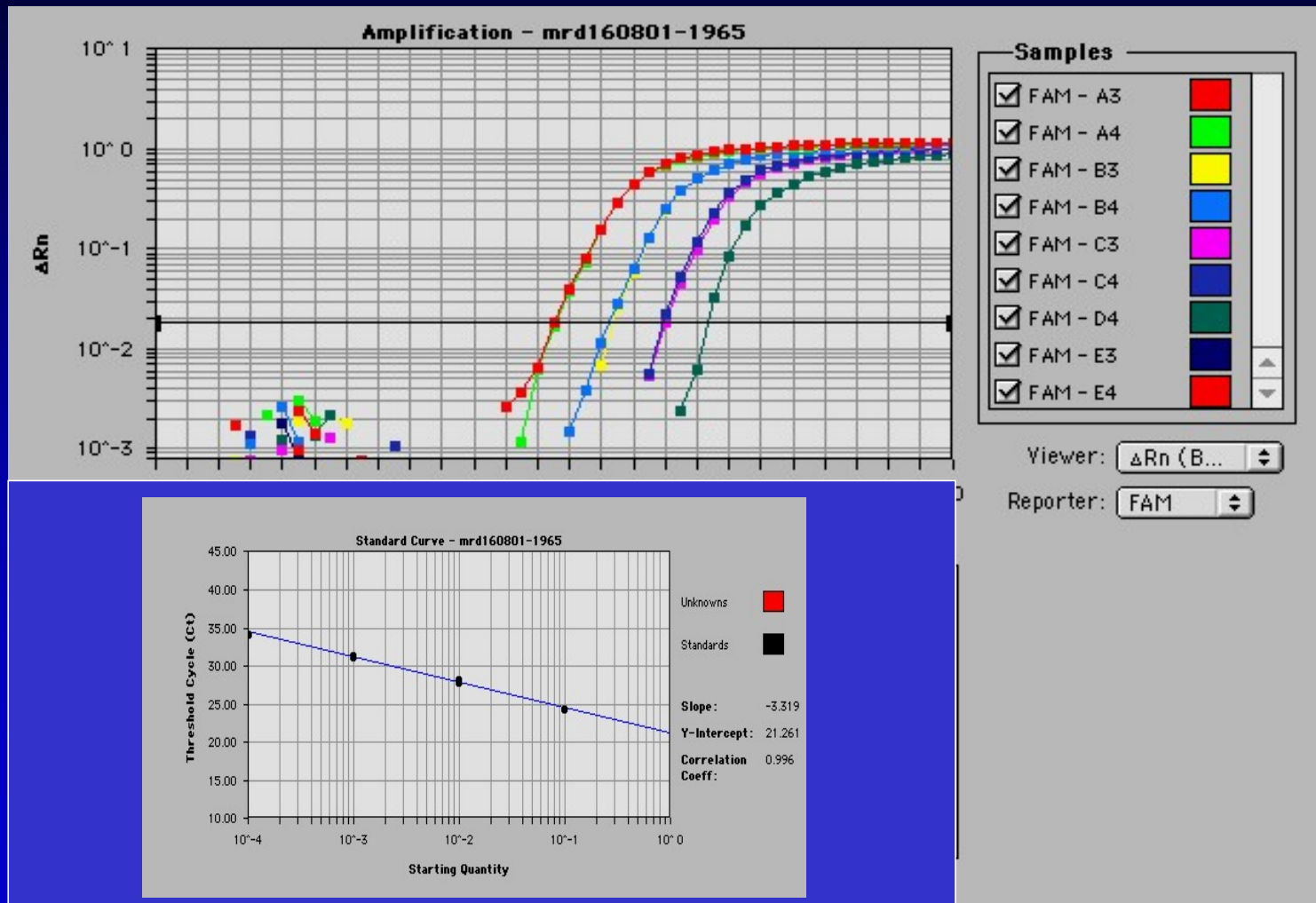




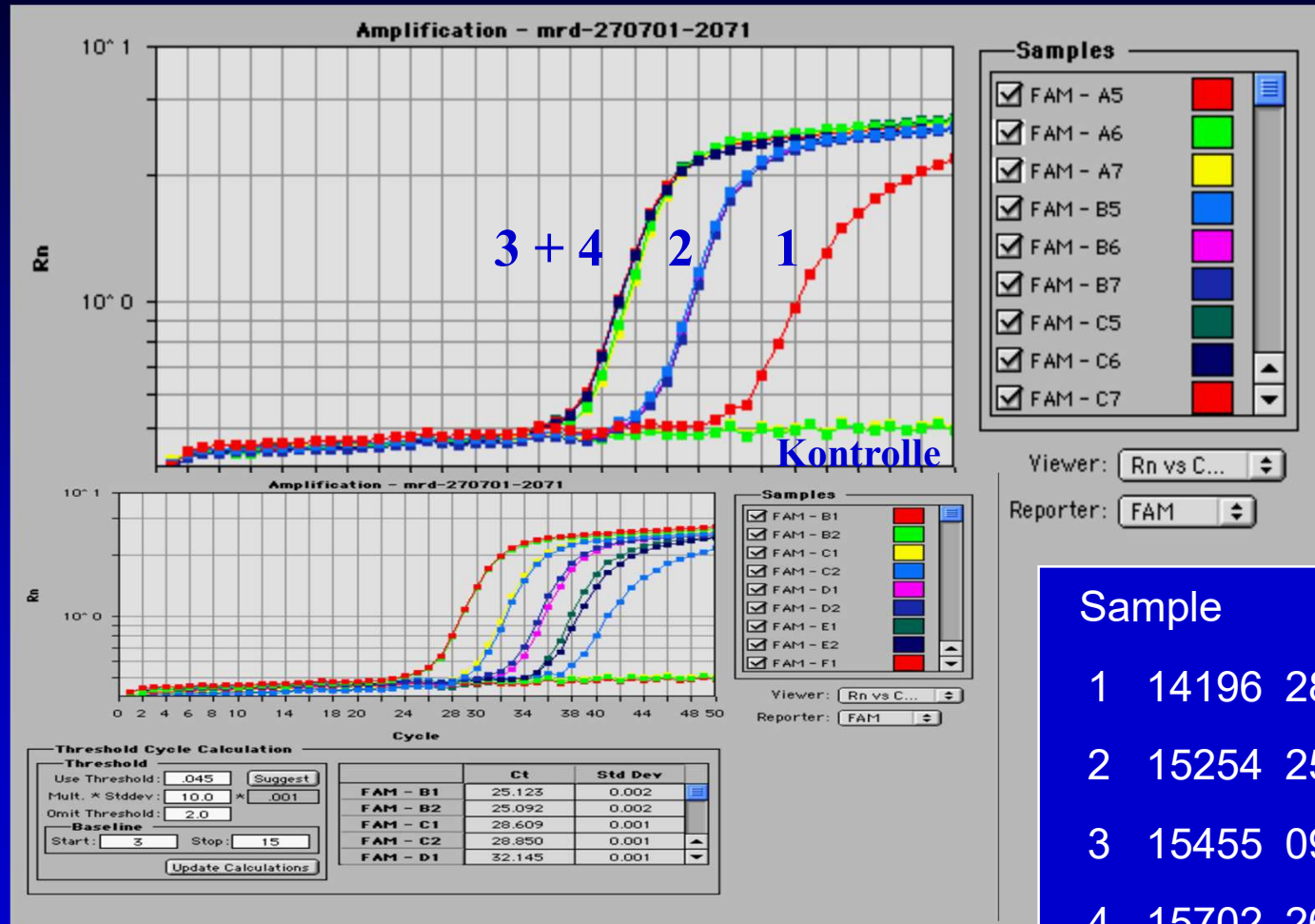
# TaqMan<sup>®</sup> -Prinzip



# Real Time PCR - Standardkurve



# Patient UPN 2071



Sample	Date	MRD
1	14196 28.03.01	1.6 x 10 <sup>-5</sup>
2	15254 25.06.01	3.6 x 10 <sup>-3</sup>
3	15455 09.07.01	2.1 x 10 <sup>-1</sup>
4	15702 26.07.01	2.3 x 10 <sup>-1</sup>



# Moderne PCR Maschinen in Großumsatzlaboren

*In kürzester Zeit zum Ergebnis*



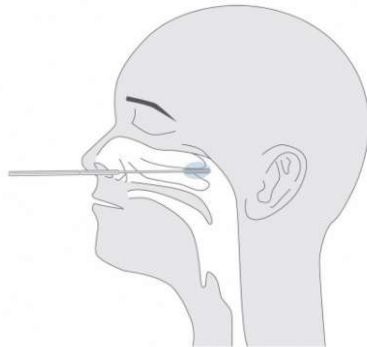
Die ersten Ergebnisse für ein Batch von 96 Tests liefern die **cobas**<sup>®</sup> 6800 und **cobas**<sup>®</sup> 8800 Systeme bereits innerhalb von 3,5 Stunden. Die nachfolgenden Batches mit je 96 Ergebnissen sind beim **cobas**<sup>®</sup> 6800 System nach je 90 Minuten und beim **cobas**<sup>®</sup> 8800 System nach je 30 Minuten fertiggestellt. Mit der minimalen Hands-on-Time und der sehr einfachen Bedienung liefern Ihnen die **cobas**<sup>®</sup> Systeme verlässliche Ergebnisse in der sehr kurzer Zeit.



# Antigen Nachweis der Fa. Roche

Handhabung - in 4 Schritten zum Ergebnis

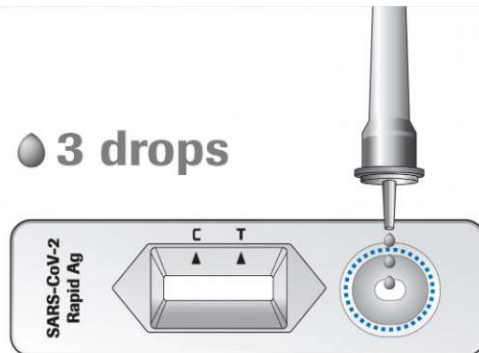
**1. Abstrich entnehmen**



Ein Abstrich wird durch das medizinische Fachpersonal aus dem Nasen-Rachen-Raum entnommen.

Handhabung - in 4 Schritten zum Ergebnis

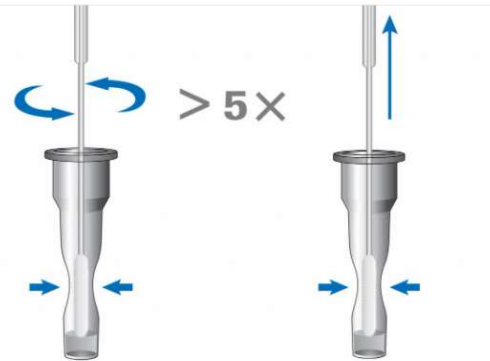
**3. Auftragung der gelösten Probe**



Drei Tropfen der zu testenden Probe werden auf den vorgesehene Reagenzträger aufgetragen.

Handhabung - in 4 Schritten zum Ergebnis

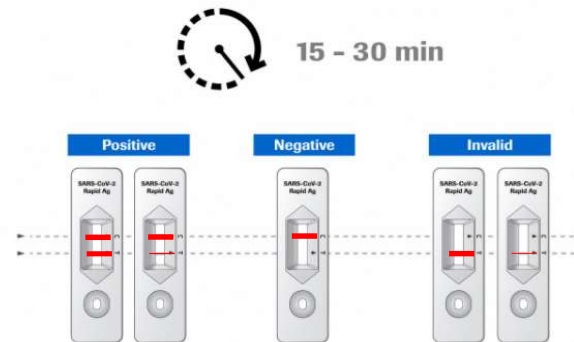
**2. Lösen der Probe im Extraktionspuffer**



Die Probe wird durch mindestens 5 mal Rotationsdrehung im Extraktionspuffer gelöst. Anschließend kann das Teststäbchen wieder entnommen werden.

Handhabung - in 4 Schritten zum Ergebnis

**4. Ergebnis ablesen**



Das Ergebnis kann nach 15 bis 30 Minuten abgelesen werden.

Für ein validiertes Ergebnis muss sich die Kontrolllinie "C" bilden. Das Ergebnis ist positiv, sobald sich die Testlinie "T" färbt. Ein negatives Ergebnis liegt vor, sofern sich keine Bande für die Testlinie bildet.

*Spezifikationen*

Assay Format	Lateral flow test / Im
Test Type	Qualitative
Instrument	Gerätfrei
Probenmaterial	Nasopharyngeal
Ziel Antigen	Nucleocapsid (N)
Auslesezeit	15-30 Minuten*
Spezifität	99,68%
Sensitivität	96,52%
Lagertemperatur	2-30°C





# Verlaufsformen der Erkrankung

**Tabelle 1.** Klinische Klassifikation der COVID-19 Infektion (adaptiert nach [WHO Clinical Guidance](#))

Klassifikation	Definition	Symptome
Leichte Erkrankung	Keine Pneumonie	
Moderate Erkrankung	Pneumonie	Keine Symptome einer schweren Pneumonie
Schwere Erkrankung	Schwere Pneumonie	definiert durch Fieber und beidseitige Lungeninfiltrate und entweder Atemfrequenz > 30/min, schwere Luftnot oder SpO2 <90-94 % bei Raumluft,
Kritische Erkrankung	ARDS	
Kritische Erkrankung	Hyperinflammation	klinisches Bild einer Sepsis, bzw. eines septischen Schocks mit Multiorganversagen





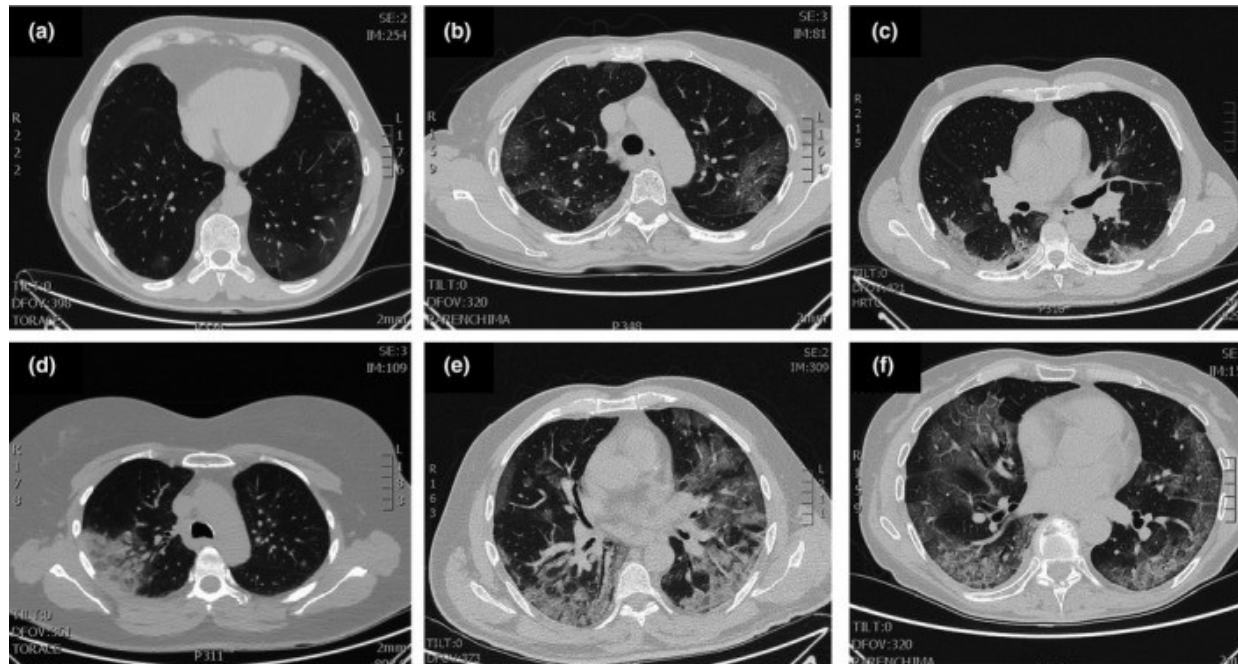
# Der kritisch Kranke

- Einblick in einen „typischen“ intensivmedizinischen COVID-19 Verlauf





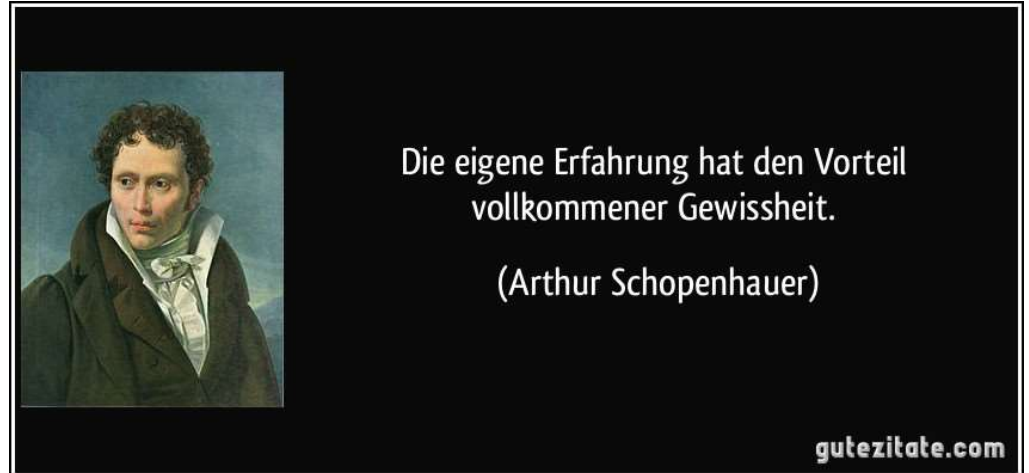
# Verlauf der „Lungentzündung“





## Der klinische Verlauf

- Symptombeginn
- (ca. 1 Woche)
- Probleme beim Atmen
- (ca. 1 Woche)
- Aufnahme im Krankenhaus
- (ca. 1 Woche)
- Künstliche Beatmung erforderlich
- Verschlechterung kein muss
- Ende = Lungenfibrose?







## Wer erkrankt schwer?

Risiken:

1. männliches Geschlecht
2. Übergewicht
3. Arterielle Hypertonie (Bluthochdruck)
4. Genetische Komponente (Blutgruppensystem,...)
5. Diabetes mellitus







# Visite am Krankenbett





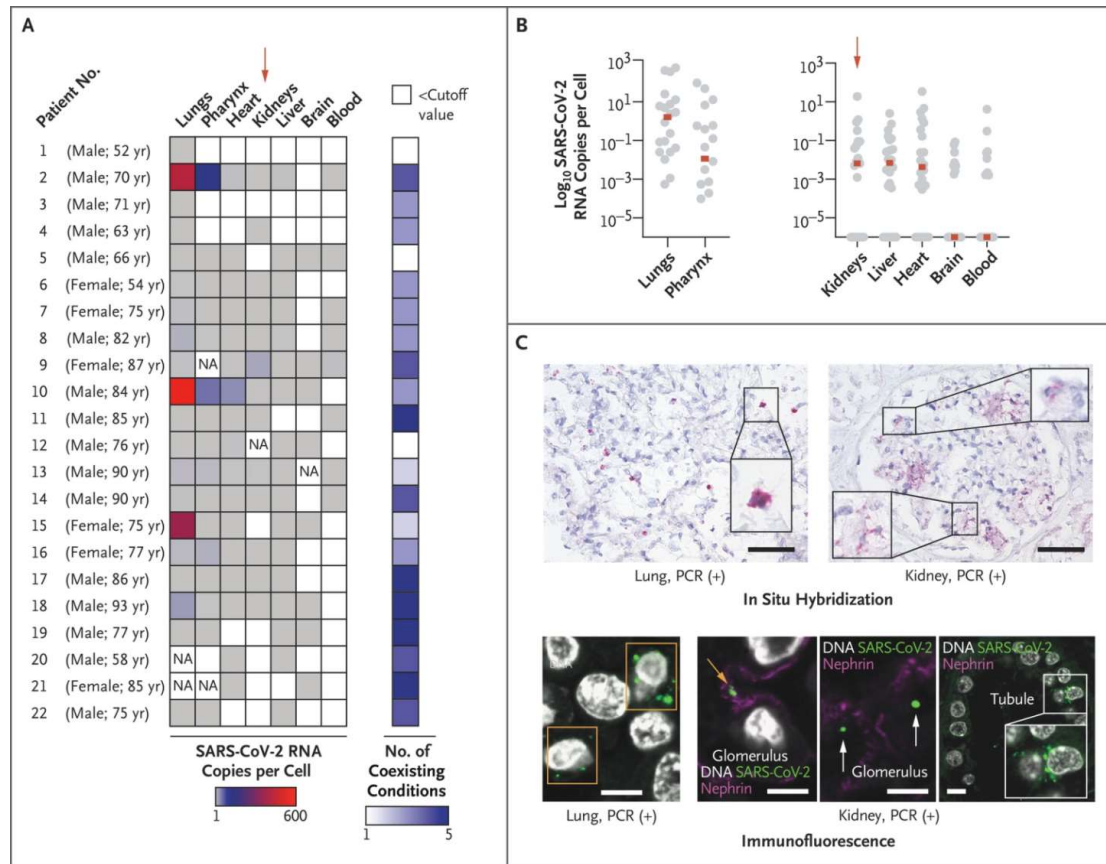
## Laboruntersuchung

- Kein Laborwert erlaubt bisher die Identifizierung für einen schweren Verlauf!
- Lymphozytenzahl reduziert
- Entzündungszeichen erhöht
- Leberwerte, Nierenwerte, Herzenzyme erhöht



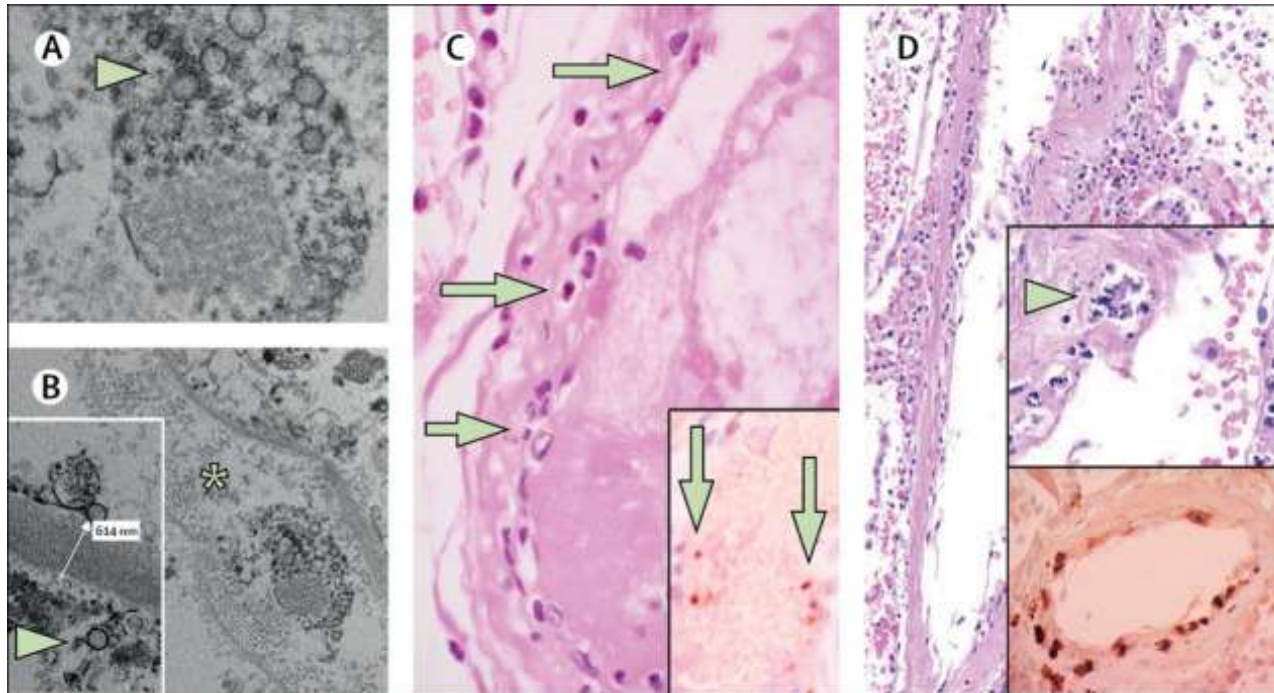


# Multiorganbeteiligung?





# Anderer Zusammenhang?







# Endothelitis/Endothelialitis

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19

Maximilian Ackermann, M.D., Stijn E. Verleden, Ph.D., Mark Kuehnel, Ph.D., Axel Haverich, M.D., Tobias Welte, M.D., Florian Laenger, M.D., Arno Vanstapel, Ph.D., Christopher Werlein, M.D., Helge Stark, Ph.D., Alexandar Tzankov, M.D., William W. Li, M.D., Vincent W. Li, M.D., Steven J. Mentzer, M.D., and Danny Jonigk, M.D.

ABSTRACT

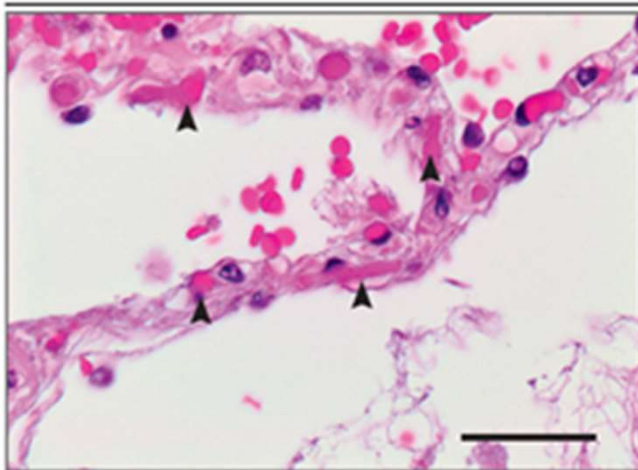
### BACKGROUND

Progressive respiratory failure is the primary cause of death in the coronavirus disease 2019 (Covid-19) pandemic. Despite widespread interest in the pathophysiology of the disease, relatively little is known about the associated morphologic and molecular changes in the peripheral lung of patients who die from Covid-19.

### METHODS

We examined 7 lungs obtained during autopsy from patients who died from Covid-19 and compared them with 7 lungs obtained during autopsy from patients who died from acute respiratory distress syndrome (ARDS) secondary to influenza A(H1N1)

From the Institute of Pathology and Department of Molecular Pathology, Helios University Clinic Wuppertal, University of Witten–Herdecke, Wuppertal (M.A.), the Institute of Functional and Clinical Anatomy, University Medical Center of the Johannes Gutenberg University Mainz, Mainz (M.A.), the Institute of Pathology (M.K., F.L., C.W., H.S., D.J.), the Department of Cardiothoracic, Transplantation, and Vascular Surgery (A.H.), and the Clin-



**Figure 2.** Microthrombi in the Interalveolar Septa of a Lung from a Patient Who Died from Covid-19.

The interalveolar septum of this patient (Patient 4 in Table S1A in the Supplementary Appendix) shows slightly expanded alveolar walls with multiple fibrinous microthrombi (arrowheads) in the alveolar capillaries. Extravasated erythrocytes and a loose network of fibrin can be seen in the intraalveolar space (hematoxylin–eosin staining; the scale bar corresponds to 50  $\mu$ m).







# Gefäßentzündung bedeutet was?

Kawasaki-ähnliches Syndrom

## New York rätselt über tödliche Kinderkrankheit

Stand: 11.05.2020 13:08 Uhr

Nach Fällen in Europa sind nun auch bei Kindern in USA ungewöhnlich schwere Erkrankungen festgestellt worden. Symptome sind heftige Entzündungen. Noch ist unklar, ob ein Zusammenhang mit dem Coronavirus besteht.

Von Antje Passenheim, ARD-Studio New York

In New York sind mindestens 38 Jungen und Mädchen an einem unbekanntem Syndrom erkrankt. Drei Kinder starben im Bundesstaat New York: ein Fünfjähriger, ein Grundschüler und ein Jugendlicher. Außerdem gebe es im Bundesstaat rund 50 weitere Verdachtsfälle, teilten die Behörden mit.

Bei der Krankheit sind verschiedene Körperteile von Entzündungen betroffen, ausgelöst offenbar durch eine übertriebene Immunreaktion. Zu den Symptomen zählen anhaltendes Fieber, Ausschlag, Bauchschmerzen und Erbrechen. "Und diese fügen dem Körper Schaden zu", erläuterte Bürgermeister Bill de Blasio. Er rief alle Eltern auf, deren Kinder unter beschriebenen Beschwerden litten, sofort ärztliche Hilfe zu suchen.

**Corona-Krise in New York**  
**Erst das Virus, dann die Armut**  
Eine halbe Million Menschen in New York hat...

KORRESPONDENTIN

Antje Passenheim, WDR

Aktuelle Meldungen zum Coronavirus  
Hier finden Sie eine Übersicht aller Berichte von tagesschau.de zum Coronavirus. | mehr

CHRONIK ZUR CORONAKRISE



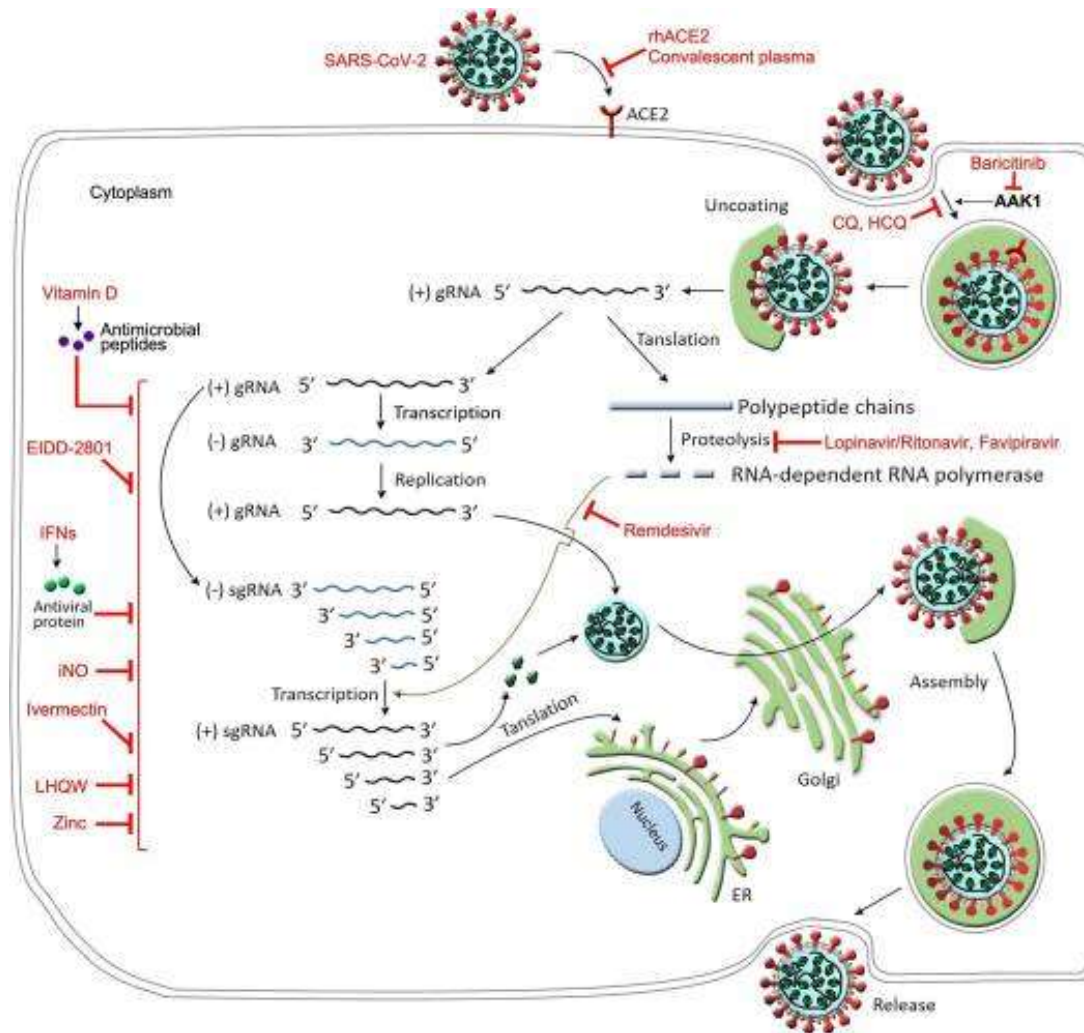


# Was können wir dagegen tun?





# Was können wir ursächlich dagegen tun?







# Medikamente gegen das Virus

ORIGINAL ARTICLE

## A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19

D.R. Boulware, M.F. Pullen, A.S. Bangdiwala, K.A. Pastick, S.M. Lofgren, E.C. Okafor, C.P. Skipper, A.A. Nascene, M.R. Nicol, M. Abassi, N.W. Engen, M.P. Cheng, D. LaBar, S.A. Lother, L.J. MacKenzie, G. Drobot, N. Marten, R. Zarychanski, L.E. Kelly, I.S. Schwartz, E.G. McDonald, R. Rajasingham, T.C. Lee, and K.H. Hullsiek

ABSTRACT

BACKGROUND

Coronavirus disease 2019 (Covid-19) occurs after exposure to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). For persons who are exposed, the standard of care is observation and quarantine. Whether hydroxychloroquine can prevent symptomatic infection after SARS-CoV-2 exposure is unknown.

METHODS

We conducted a randomized, double-blind, placebo-controlled trial across the United States and parts of Canada testing hydroxychloroquine as postexposure prophylaxis. We enrolled adults who had household or occupational exposure to someone with confirmed Covid-19 at a distance of less than 6 ft for more than 10 minutes while wearing neither a face mask nor an eye shield (high-risk exposure) or while wearing a face mask but no eye shield (moderate-risk exposure). Within 4 days after exposure, we randomly assigned participants to receive either placebo or hydroxychloroquine (800 mg once, followed by 600 mg in 6 to 8 hours, then 600 mg daily for 4 additional days). The primary outcome was the incidence of either laboratory-confirmed Covid-19 or illness compatible with Covid-19 within 14 days.

RESULTS

We enrolled 821 asymptomatic participants. Overall, 87.6% of the participants (719 of 821) reported a high-risk exposure to a confirmed Covid-19 contact. The incidence of new illness compatible with Covid-19 did not differ significantly between participants receiving hydroxychloroquine (49 of 414 [11.8%]) and those receiving placebo (58 of 407 [14.3%]); the absolute difference was -2.4 percentage points (95% confidence interval, -7.0 to 2.2; P=0.35). Side effects were more common with hydroxychloroquine than with placebo (40.1% vs. 16.8%), but no serious adverse reactions were reported.

CONCLUSIONS

After high-risk or moderate-risk exposure to Covid-19, hydroxychloroquine did not prevent illness compatible with Covid-19 or confirmed infection when used as postexposure prophylaxis within 4 days after exposure. (Funded by David Baszucki and Jan Ellison Baszucki and others; ClinicalTrials.gov number, NCT04308668.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Boulware at the University of Minnesota, 689 23rd Ave., Minneapolis, MN 55455, or at [boulw001@umn.edu](mailto:boulw001@umn.edu).

This article was published on June 3, 2020, at [NEJM.org](http://NEJM.org).

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## The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

MAY 7, 2020

VOL. 382 NO. 19

## A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19

B. Cao, Y. Wang, D. Wen, W. Liu, Jingli Wang, G. Fan, L. Ruan, B. Song, Y. Cai, M. Wei, X. Li, J. Xia, N. Chen, J. Xiang, T. Yu, T. Bai, X. Xie, L. Zhang, C. Li, Y. Yuan, H. Chen, Huadong Li, H. Huang, S. Tu, F. Gong, Y. Liu, Y. Wei, C. Dong, F. Zhou, X. Gu, J. Xu, Z. Liu, Y. Zhang, Hui Li, L. Shang, K. Wang, K. Li, X. Zhou, X. Dong, Z. Qu, S. Lu, X. Hu, S. Ruan, S. Luo, J. Wu, L. Peng, F. Cheng, L. Pan, J. Zou, C. Jia, Juan Wang, X. Liu, S. Wang, X. Wu, Q. Ge, J. He, H. Zhan, F. Qiu, L. Guo, C. Huang, T. Jaki, F.G. Hayden, P.W. Horby, D. Zhang, and C. Wang

ABSTRACT

BACKGROUND

No therapeutics have yet been proven effective for the treatment of severe illness caused by SARS-CoV-2.

METHODS

We conducted a randomized, controlled, open-label trial involving hospitalized adult patients with confirmed SARS-CoV-2 infection, which causes the respiratory illness Covid-19, and an oxygen saturation (Sao<sub>2</sub>) of 94% or less while they were breathing ambient air or a ratio of the partial pressure of oxygen (Pao<sub>2</sub>) to the fraction of inspired oxygen (Fio<sub>2</sub>) of less than 300 mm Hg. Patients were randomly assigned in a 1:1 ratio to receive either lopinavir-ritonavir (400 mg and 300 mg, respectively) twice a day for 14 days, in addition to standard care, or standard care alone. The primary end point was the time to clinical improvement, defined as the time from randomization to either an improvement of two points on a seven-category ordinal scale or discharge from the hospital, whichever came first.

RESULTS

A total of 199 patients with laboratory-confirmed SARS-CoV-2 infection underwent randomization; 99 were assigned to the lopinavir-ritonavir group, and 100 to the standard-care group. Treatment with lopinavir-ritonavir was not associated with a difference from standard care in the time to clinical improvement (hazard ratio for clinical improvement, 1.31; 95% confidence interval [CI], 0.95 to 1.80). Mortality at 28 days was similar in the lopinavir-ritonavir group and the standard-care group (19.2% vs. 25.0%; difference, -5.8 percentage points; 95% CI, -17.3 to 5.7). The percentages of patients with detectable viral RNA at various time points were similar. In a modified intention-to-treat analysis, lopinavir-ritonavir led to a median time to clinical improvement that was shorter by 1 day than that observed with standard care (hazard ratio, 1.39; 95% CI, 1.00 to 1.91). Gastrointestinal adverse events were more common in the lopinavir-ritonavir group, but serious adverse events were more common in the standard-care group. Lopinavir-ritonavir treatment was stopped early in 13 patients (13.8%) because of adverse events.

CONCLUSIONS

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Cao at [caobin\\_bem@163.com](mailto:caobin_bem@163.com), or to Dr. C. Wang at [cwh-birm@263.net](mailto:cwh-birm@263.net), or to Dr. D. Zhang at [181386398@qq.com](mailto:181386398@qq.com).

Drs. Cao, Y. Wang, Wen, W. Liu, Jingli Wang, Fan, L. Ruan, Song, Cai, and M. Wei and Drs. D. Zhang and C. Wang contributed equally to this article.

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# Bestes antivirales Medikament?!

THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Remdesivir for the Treatment of Covid-19 — Preliminary Report

J.H. Beigel, K.M. Tomashek, L.E. Dodd, A.K. Mehta, B.S. Zingman, A.C. Kalil, E. Hohmann, H.Y. Chu, A. Luetkemeyer, S. Kline, D. Lopez de Castilla, R.W. Finberg, K. Dierberg, V. Tapson, L. Hsieh, T.F. Patterson, R. Paredes, D.A. Sweeney, W.R. Short, G. Touloumi, D.C. Lye, N. Ohmagari, M. Oh, G.M. Ruiz-Palacios, T. Benfield, G. Fätkenheuer, M.G. Kortepeter, R.L. Atmar, C.B. Creech, J. Lundgren, A.G. Babiker, S. Pett, J.D. Neaton, T.H. Burgess, T. Bonnett, M. Green, M. Makowski, A. Osinusi, S. Nayak, and H.C. Lane, for the ACTT-1 Study Group Members\*

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ABSTRACT

**BACKGROUND**  
Although several therapeutic agents have been evaluated for the treatment of coronavirus disease 2019 (Covid-19), none have yet been shown to be efficacious.

**METHODS**  
We conducted a double-blind, randomized, placebo-controlled trial of intravenous remdesivir in adults hospitalized with Covid-19 with evidence of lower respiratory tract involvement. Patients were randomly assigned to receive either remdesivir (200 mg loading dose on day 1, followed by 100 mg daily for up to 9 additional days) or placebo for up to 10 days. The primary outcome was the time to recovery, defined by either discharge from the hospital or hospitalization for infection-control purposes only.

**RESULTS**  
A total of 1063 patients underwent randomization. The data and safety monitoring board recommended early unblinding of the results on the basis of findings from an analysis that showed shortened time to recovery in the remdesivir group. Preliminary results from the 1059 patients (538 assigned to remdesivir and 521 to placebo) with data available after randomization indicated that those who received remdesivir had a median recovery time of 11 days (95% confidence interval [CI], 9 to 12), as compared with 15 days (95% CI, 13 to 19) in those who received placebo (rate ratio for recovery, 1.32; 95% CI, 1.12 to 1.55;  $P < 0.001$ ). The Kaplan-Meier estimates of mortality by 14 days were 7.1% with remdesivir and 11.9% with placebo (hazard ratio for death, 0.70; 95% CI, 0.47 to 1.04). Serious adverse events were reported for 114 of the 541 patients in the remdesivir group who underwent randomization (21.1%) and 141 of the 522 patients in the placebo group who underwent randomization (27.0%).

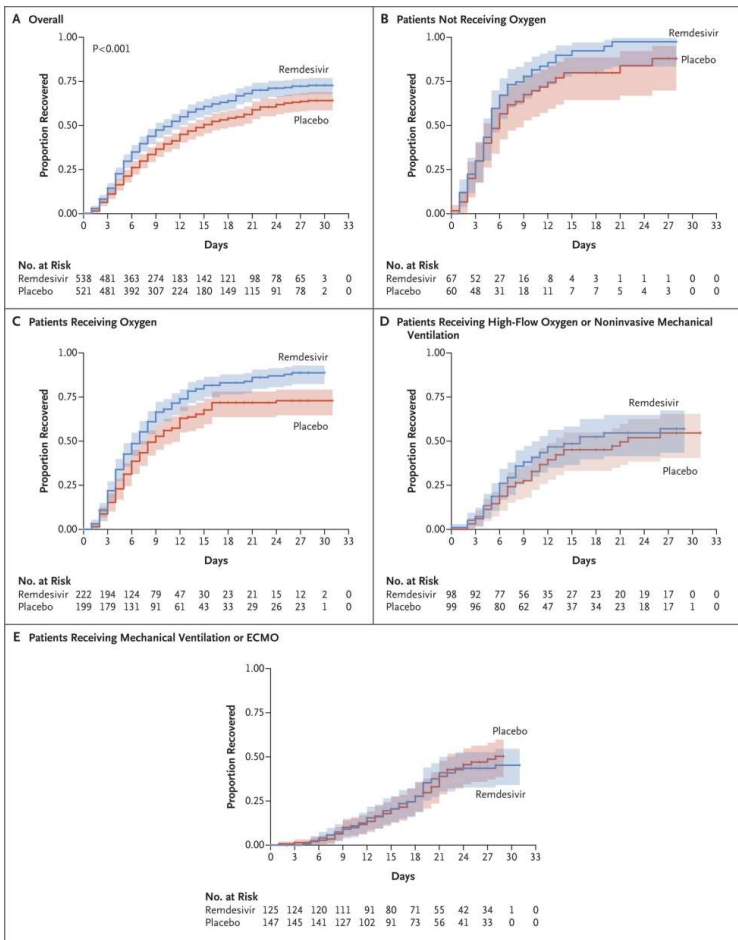
**CONCLUSIONS**

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Beigel at the National Institute of Allergy and Infectious Diseases, National Institutes of Health, 5601 Fishers Ln., Rm. 7E60, MSC 9826, Rockville, MD 20892-9826, or at [beigel@niaid.nih.gov](mailto:beigel@niaid.nih.gov).

\*A complete list of members of the ACTT-1 Study Group is provided in the Supplementary Appendix, available at [NEJM.org](https://www.nejm.org).

This article was published on May 22, 2020, at [NEJM.org](https://www.nejm.org).

DOI: 10.1056/NEJMoa2007764  
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# Medikamente gegen Endothelitis?

ORIGINAL ARTICLE

## Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report

The RECOVERY Collaborative Group\*

ABSTRACT

**BACKGROUND**

Coronavirus disease 2019 (Covid-19) is associated with diffuse lung damage. Glucocorticoids may modulate inflammation-mediated lung injury and thereby reduce progression to respiratory failure and death.

**METHODS**

In this controlled, open-label trial comparing a range of possible treatments in patients who were hospitalized with Covid-19, we randomly assigned patients to receive oral or intravenous dexamethasone (at a dose of 6 mg once daily) for up to 10 days or to receive usual care alone. The primary outcome was 28-day mortality. Here, we report the preliminary results of this comparison.

**RESULTS**

A total of 2104 patients were assigned to receive dexamethasone and 4321 to receive usual care. Overall, 482 patients (22.9%) in the dexamethasone group and 1110 patients (25.7%) in the usual care group died within 28 days after randomization (age-adjusted rate ratio, 0.83; 95% confidence interval [CI], 0.75 to 0.93;  $P < 0.001$ ). The proportional and absolute between-group differences in mortality varied considerably according to the level of respiratory support that the patients were receiving at the time of randomization. In the dexamethasone group, the incidence of death was lower than that in the usual care group among patients receiving invasive mechanical ventilation (29.3% vs. 41.4%; rate ratio, 0.64; 95% CI, 0.51 to 0.81) and among those receiving oxygen without invasive mechanical ventilation (23.3% vs. 26.2%; rate ratio, 0.82; 95% CI, 0.72 to 0.94) but not among those who were receiving no respiratory support at randomization (17.8% vs. 14.0%; rate ratio, 1.19; 95% CI, 0.91 to 1.55).

**CONCLUSIONS**

In patients hospitalized with Covid-19, the use of dexamethasone resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone at randomization but not among those receiving no respiratory support. (Funded by the Medical Research Council and National Institute for Health Research and others; RECOVERY ClinicalTrials.gov number, NCT04381936; ISRCTN number, 50189673.)

The members of the writing committee (Peter Horby, F.R.C.P., Wei Shen Lim, F.R.C.P., Jonathan R. Emberson, Ph.D., Marion Mafham, M.D., Jennifer L. Bell, M.Sc., Louise Linsell, D.Phil., Natalie Staplin, Ph.D., Christopher Brightling, F.Med. Sci., Andrew Ustianowski, Ph.D., Einas Elmahi, M.Phil., Benjamin Prudon, F.R.C.P., Christopher Green, D.Phil., Timothy Felton, Ph.D., David Chadwick, Ph.D., Kanchan Rege, F.R.C.Path., Christopher Fegan, M.D., Lucy C. Chappell, Ph.D., Saul N. Faust, F.R.C.P.C.H., Thomas Jaki, Ph.D., Katie Jeffery, Ph.D., Alan Montgomery, Ph.D., Kathryn Rowan, Ph.D., Edmund Juszcak, M.Sc., J. Kenneth Bailie, M.D., Ph.D., Richard Haynes, D.M., and Martin J. Landray, Ph.D.) assume responsibility for the overall content and integrity of this article.

The affiliations of the members of the writing committee are listed in the Appendix. Address reprint requests to Drs. Horby and Landray at RECOVERY Central Coordinating Office, Richard Doll Bldg., Old Road Campus, Roosevelt Drive, Oxford OX3 7LF, United Kingdom, or at [recoverytrial@ndph.ox.ac.uk](mailto:recoverytrial@ndph.ox.ac.uk).

\*A complete list of collaborators in the RECOVERY trial is provided in the Supplementary Appendix, available at [NEJM.org](http://NEJM.org).

Drs. Horby, Lim, and Emberson and Drs. Haynes and Landray contributed equally to this article.

This article was published on July 17, 2020, at [NEJM.org](http://NEJM.org).

DOI: 10.1056/NEJMoa2021436

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# MSC in the treatment of severe COVID-19 Disease?

The NEW ENGLAND JOURNAL of MEDICINE

## SARS-CoV-2:

- Novel infection
- Hyperinflammation
- Cytokine storm
- Capillary leakage
- Endothelitis
- ARDS
- Multi-organ failure

## CORRESPONDENCE

### Covid-19 in Immune-Mediated Inflammatory Diseases — Case Series from New York

**TO THE EDITOR:** Data on Covid-19 in patients with immune-mediated inflammatory disease who have received anticytokine biologics, other immunomodulatory therapies, or both on a long-term basis are scarce. Trials to assess the efficacy of antirheumatic therapies such as hydroxychloroquine<sup>1</sup> and anticytokine therapies such as interleukin-6 inhibitors<sup>2</sup> to improve outcomes in patients with Covid-19 are ongoing. The rationale for their use is that worse outcomes (i.e., hospitalization, ventilation, or death) may be related to a proinflammatory cytokine storm.<sup>3,4</sup>

Here, we report a prospective case series in-

tients. Although the distribution of diagnoses of immune-mediated inflammatory diseases was similar in the ambulatory group and the hospitalized group, a higher percentage of admitted patients had rheumatoid arthritis. As compared with the ambulatory patients, more of the patients for whom hospitalization was warranted had coexisting hypertension, diabetes, or chronic obstructive pulmonary disease.

The percentage of patients who were receiving biologics or JAK inhibitors at baseline was higher among the ambulatory patients than among the hospitalized patients (55 of 72 pa-



M. Mehra et al.:  
NEJM: 2020, May 4



# Mesenchymale Stromazellen

- Erstbeschreibung durch Friedenstein
- Aus dem Mesoderm
- Haben die Fähigkeit sich in Zellen der drei Keimblätter zu differenzieren
  
- Erstbeschreibung 1968 im Knochenmark
  - Elognierte Zellen, die in der Zellkultur Zellklone bilden können
  - Fibroblasten-ähnlich, multipotent

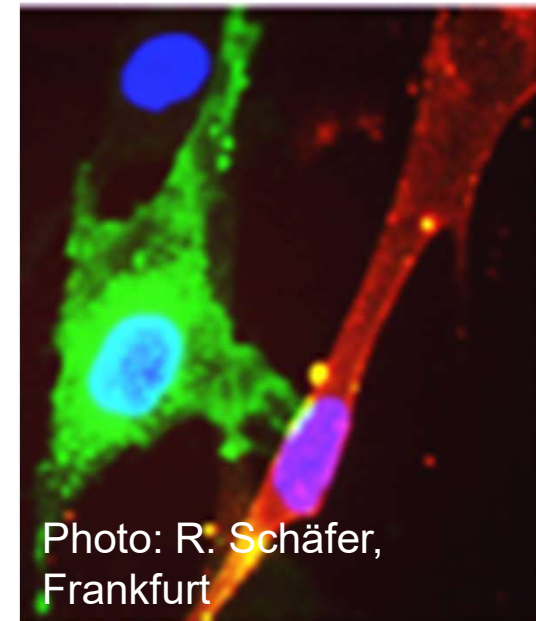
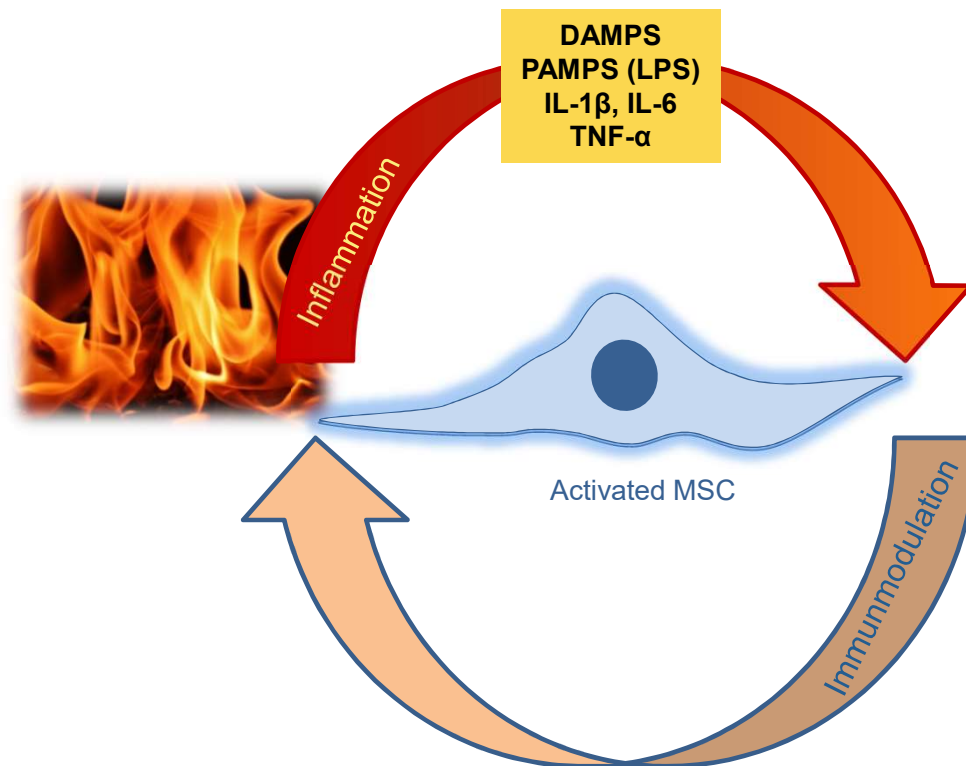


Photo: R. Schäfer,  
Frankfurt



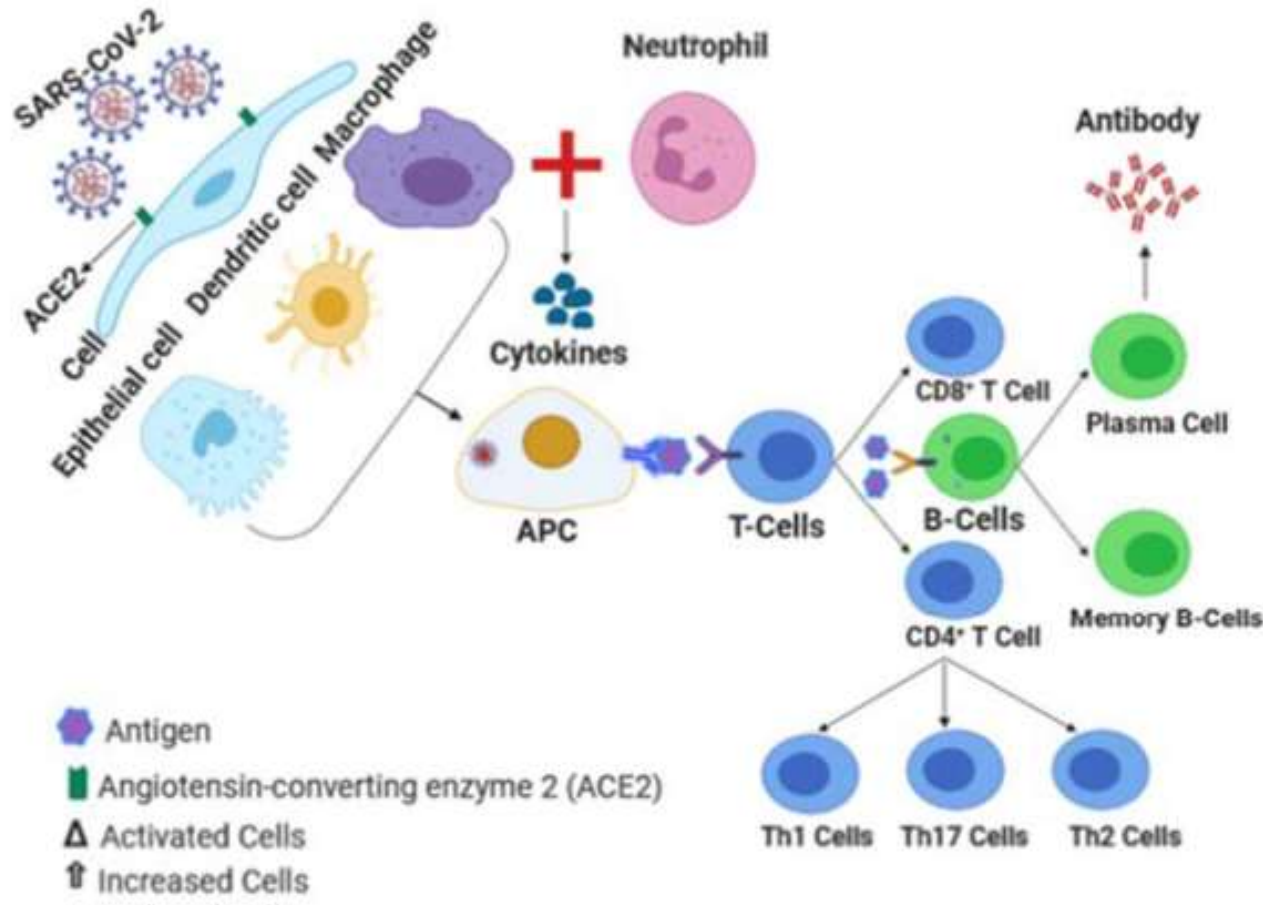


# Homeostasis des Immunsystems





Stem Cell Rev and Rep (2020) 16:427–433



**Mild-to-Moderate phase:**

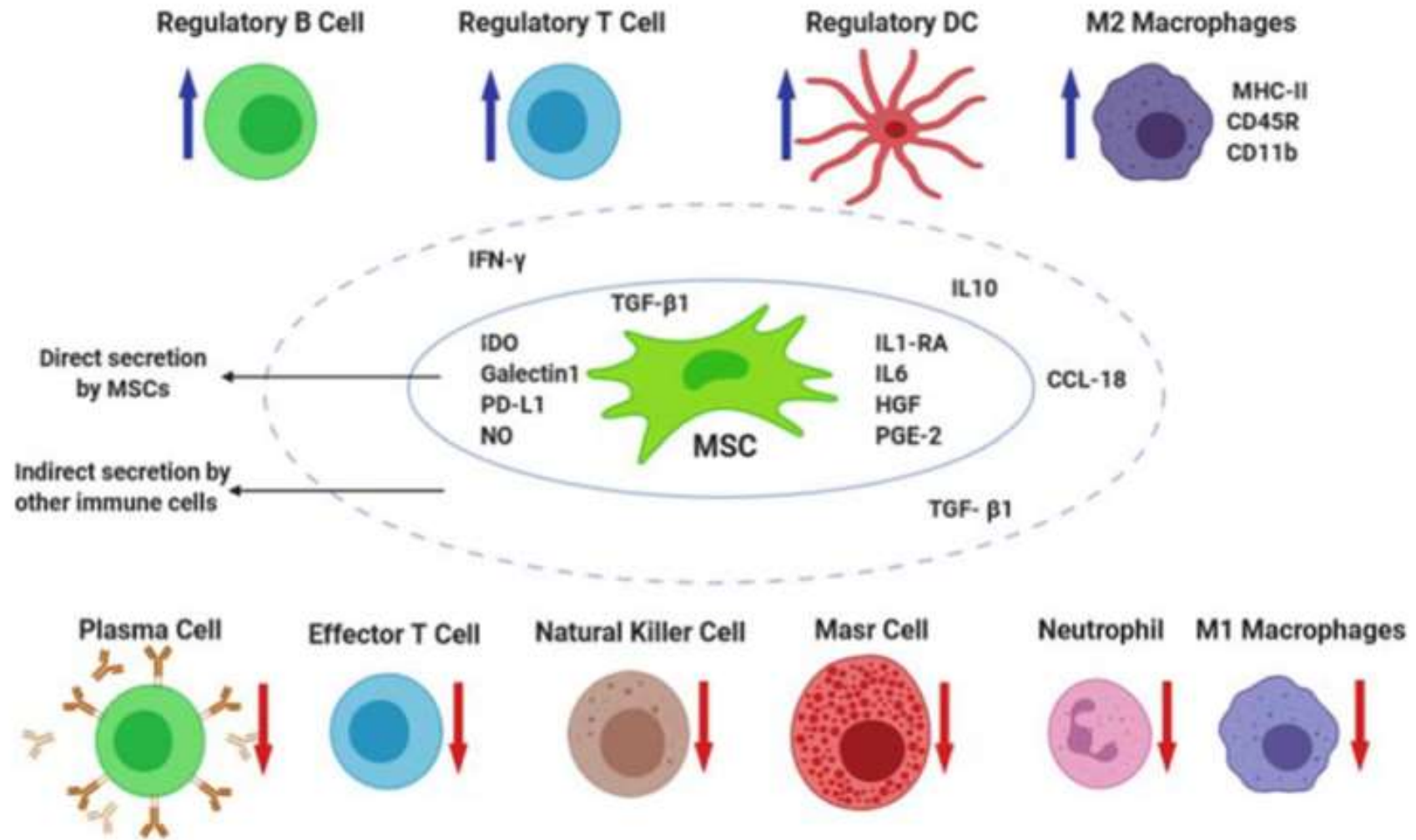
- ↑ Antibody-secreting cells (ASCs)
- ↑ Follicular helper T cells (TFH cells)
- ↑ CD4<sup>+</sup> T cells and CD8<sup>+</sup> T cells
- Δ CD4<sup>+</sup> T cells and CD8<sup>+</sup> T cells
- ↑ Immunoglobulin M (IgM) antibodies
- ↑ Immunoglobulin G (IgG) antibodies

**Acute phase:**

- ↓ lymphocytes (lymphopenia)
- ↑ IL-2, IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP-1A, and TNFα
- Δ neutrophils and monocytes/macrophages
- Δ Specific Th1/Th17
- Δ Plasma cells
- ↓ CD4<sup>+</sup> T cells and CD8<sup>+</sup> T cells
- Cytokine storm











# MSC in der Behandlung der schweren COVID-19 Erkrankung?

**Aging and Disease**

[www.aginganddisease.org](http://www.aginganddisease.org)

Volume 11, Number 2; 216-228, April 2020

<http://dx.doi.org/10.14336/AD.2020.0228>

Original Article

## **Transplantation of ACE2<sup>-</sup> Mesenchymal Stem Cells Improves the Outcome of Patients with COVID-19 Pneumonia**

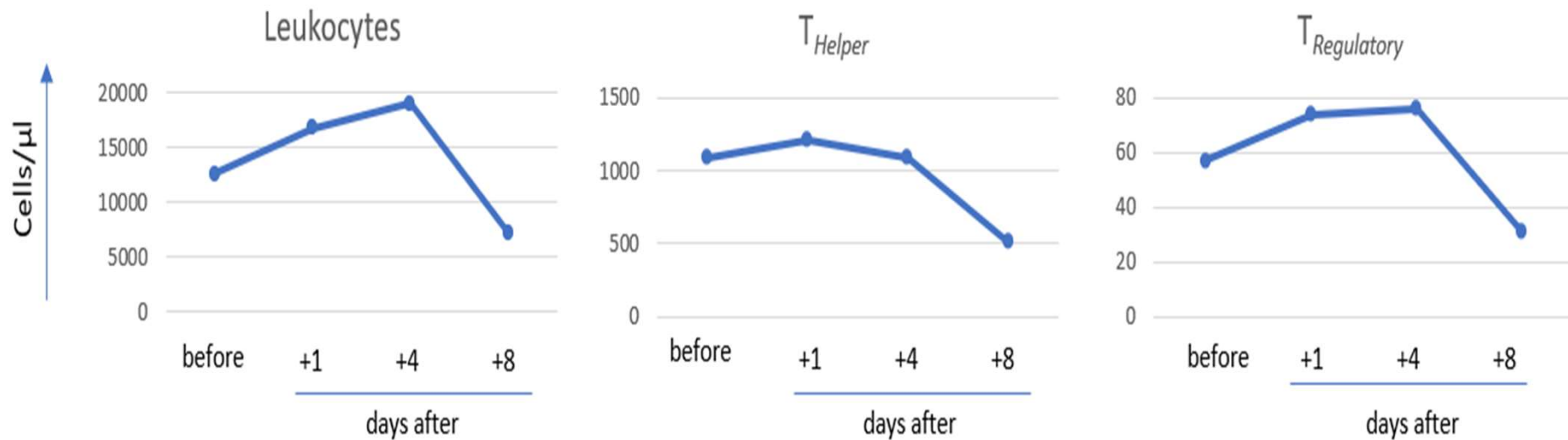
**Zikuan Leng<sup>1,5,#</sup>, Rongjia Zhu<sup>2,#</sup>, Wei Hou<sup>3,#</sup>, Yingmei Feng<sup>3,#</sup>, Yanlei Yang<sup>4</sup>, Qin Han<sup>2</sup>, Guangliang Shan<sup>2</sup>, Fanyan Meng<sup>1</sup>, Dongshu Du<sup>1</sup>, Shihua Wang<sup>2</sup>, Junfen Fan<sup>2</sup>, Wenjing Wang<sup>3</sup>, Luchan Deng<sup>2</sup>, Hongbo Shi<sup>3</sup>, Hongjun Li<sup>3</sup>, Zhongjie Hu<sup>3</sup>, Fengchun Zhang<sup>4</sup>, Jinming Gao<sup>4</sup>, Hongjian Liu<sup>5\*</sup>, Xiaoxia Li<sup>6</sup>, Yangyang Zhao<sup>2</sup>, Kan Yin<sup>6</sup>, Xijing He<sup>7</sup>, Zhengchao Gao<sup>7</sup>, Yibin Wang<sup>7</sup>, Bo Yang<sup>8</sup>, Ronghua Jin<sup>3\*</sup>, Iliia Stambler<sup>9,10,11</sup>, Lee Wei Lim<sup>9,10,12</sup>, Huanxing Su<sup>9,10,13</sup>, Alexey Moskalev<sup>9,10,14</sup>, Antonio Cano<sup>9,10,15</sup>, Sasanka Chakrabarti<sup>16</sup>, Kyung-Jin Min<sup>9,10,17</sup>, Georgina Ellison-Hughes<sup>9,10,18</sup>, Calogero Caruso<sup>9,10,19</sup>, Kunlin Jin<sup>9,10,20\*</sup>, Robert Chunhua Zhao<sup>1,2,9,10\*</sup>**

<sup>1</sup>School of Life Sciences, Shanghai University, Shanghai, China. <sup>2</sup>Institute of Basic Medical Sciences Chinese Academy of Medical Sciences, School of Basic Medicine Peking Union Medical College, Beijing, China. <sup>3</sup>Beijing YouAn Hospital, Capital Medical University, Beijing, China. <sup>4</sup>Department of Rheumatology and Clinical Immunology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union





**The first patient who received MSC was a 29 year old female patient** with a body weight of 120 kg. She developed first signs of Covid-19 disease on April 1<sup>st</sup> with fever and malaise. On April 5<sup>th</sup>, she required intubation and mechanical ventilation. Due to controllable inflammation she continued to deteriorate and progressed to require extracorporeal mechanical oxygenation (ECMO) on April 13<sup>th</sup>. In this desperate situation and with informed consent by her family, she received one dose of Obnitix® on April 20<sup>th</sup>.



Clinical signs of inflammation with leukocytosis, elevated CRP, IL-6 and PCT as well as HLA-DR activated cytotoxic CD8 T-cells.

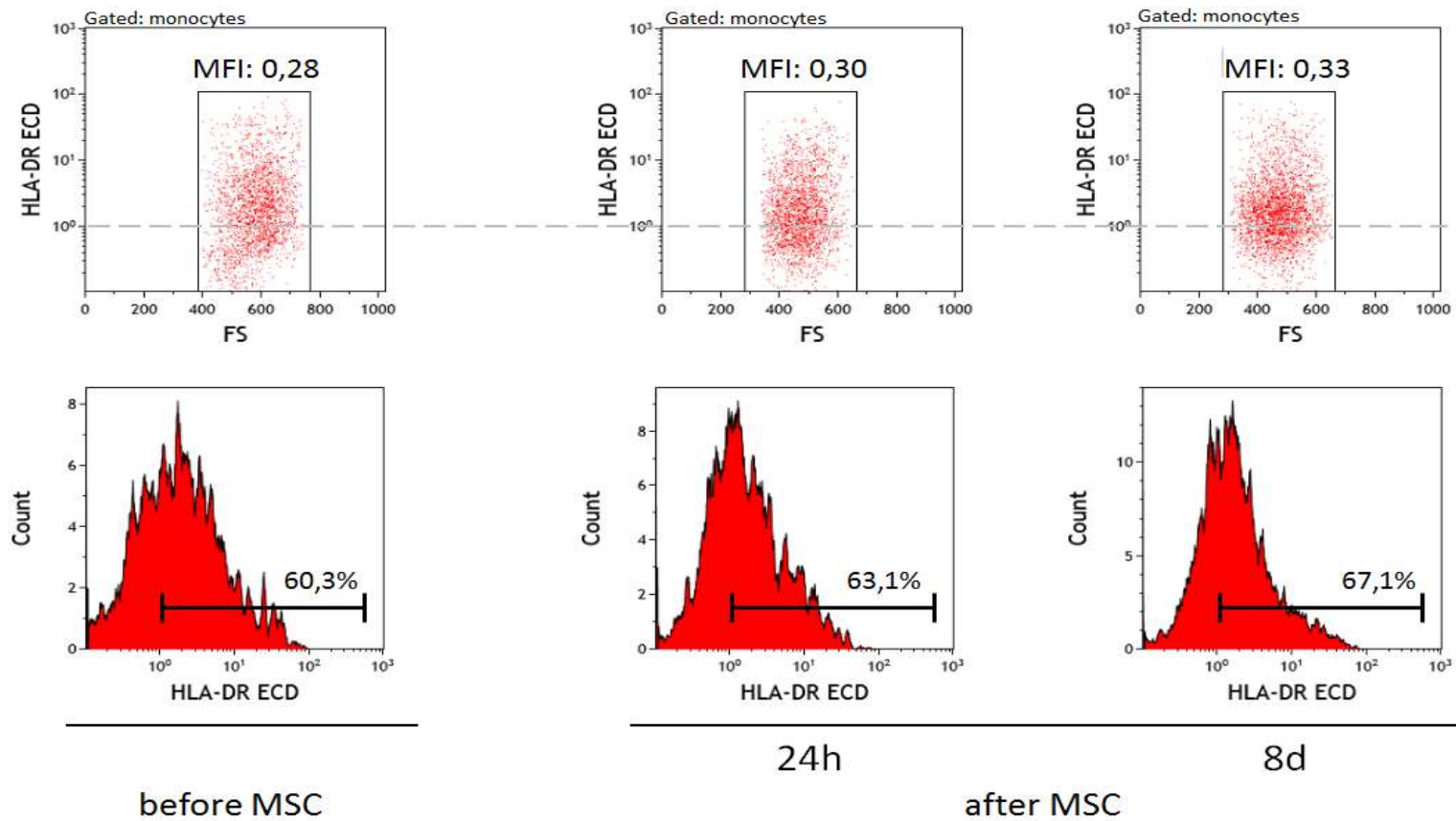
After transfusion of one dose of MSC, the patient's regulatory CD4 T cells temporarily increased, concurrent to a reduction of activated T-cells.





## Analysis of HLA-DR expression on monocytes

In patients suffering from bacterial sepsis, a long lasting decline of HLA-DR expression was related to poor survival. Therefore, we investigated HLA-DR activation on monocytes. HLA-DR expression on monocytes 24h and eight days following Obnitix® application indicating effective immune modulation of Obnitix®.





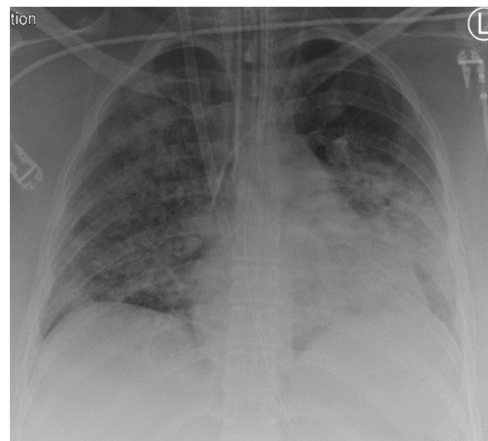
Both ECMO support could be steadily reduced the patient lungs took continuously over oxygen saturation. ECMO support could be terminated one week later on April 28<sup>th</sup>.



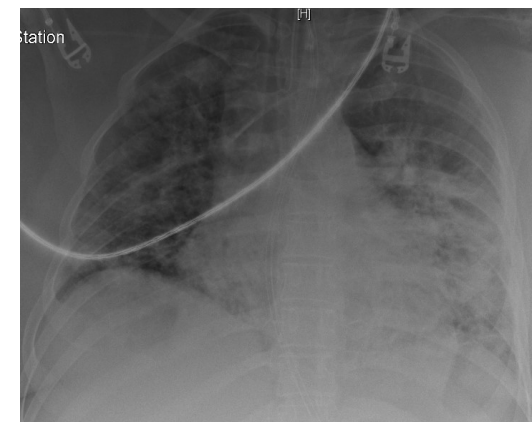
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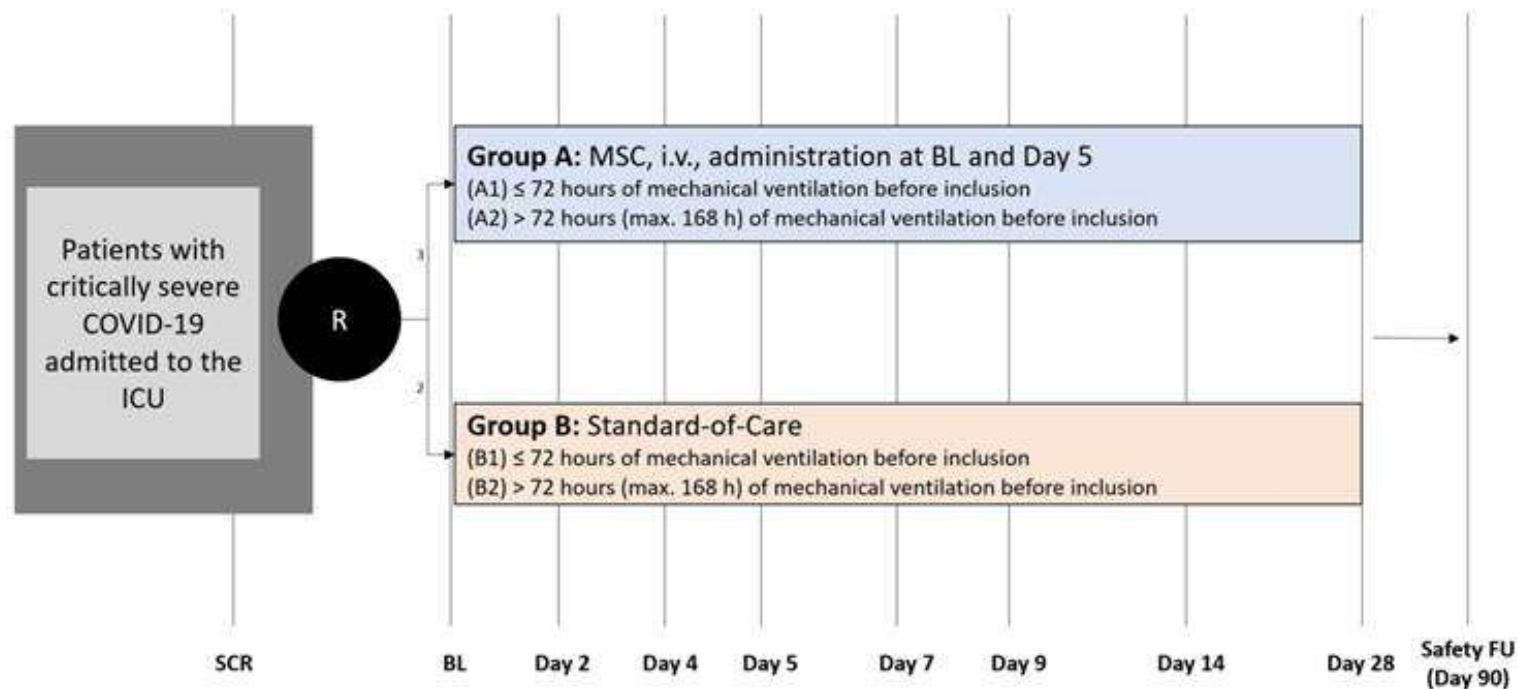


30.04.2020





# Flow-Chart: MSC Study and Critically Ill COVID-19 Patients



## Gefördert durch:

Else Kröner-Fresenius-Stiftung zusammen mit Stefan Quandt, J2xU-Stiftung und der Barbara und Wilfried Mohr-Stiftung mit insgesamt 1,45 Millionen Euro (EKFS: 700.000 €) finanziert







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