Canlı Atenüe Aşılar

‘Gelişen Teknoloji’

Dr. Süda TEKİN
Koç Üniversitesi Tıp Fakültesi
İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Anabilim Dalı

19.02.2022

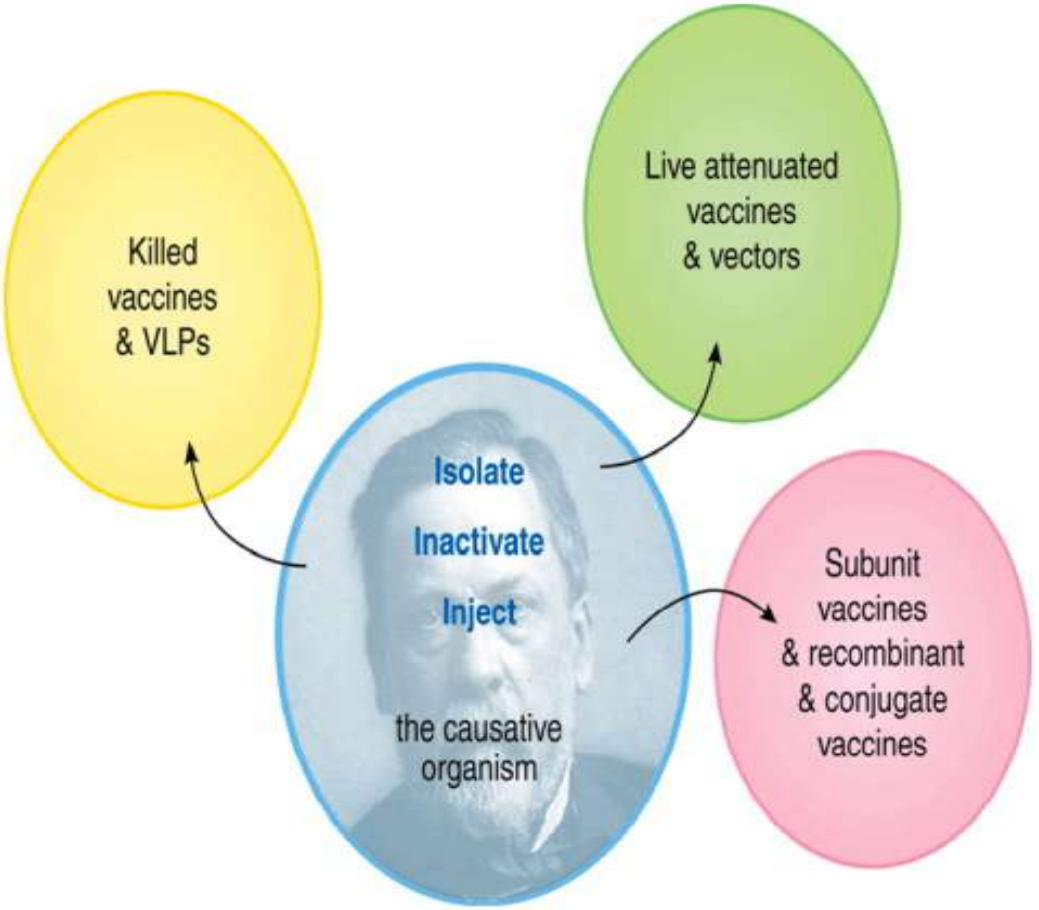
Neler Konuşulacak?

- **Aşılar**
  - ✓ Genel bakış
  - ✓ Canlı aşı avantaj/dezavantaj
- **Aşı geliştirme teknolojileri**
  - ✓ Canlı atenüe aşılar
  - ✓ Canlı atenüe olmayanlar
- **Soru & Katkı**

Louis Pasteur
FRS

Photograph by Nadar

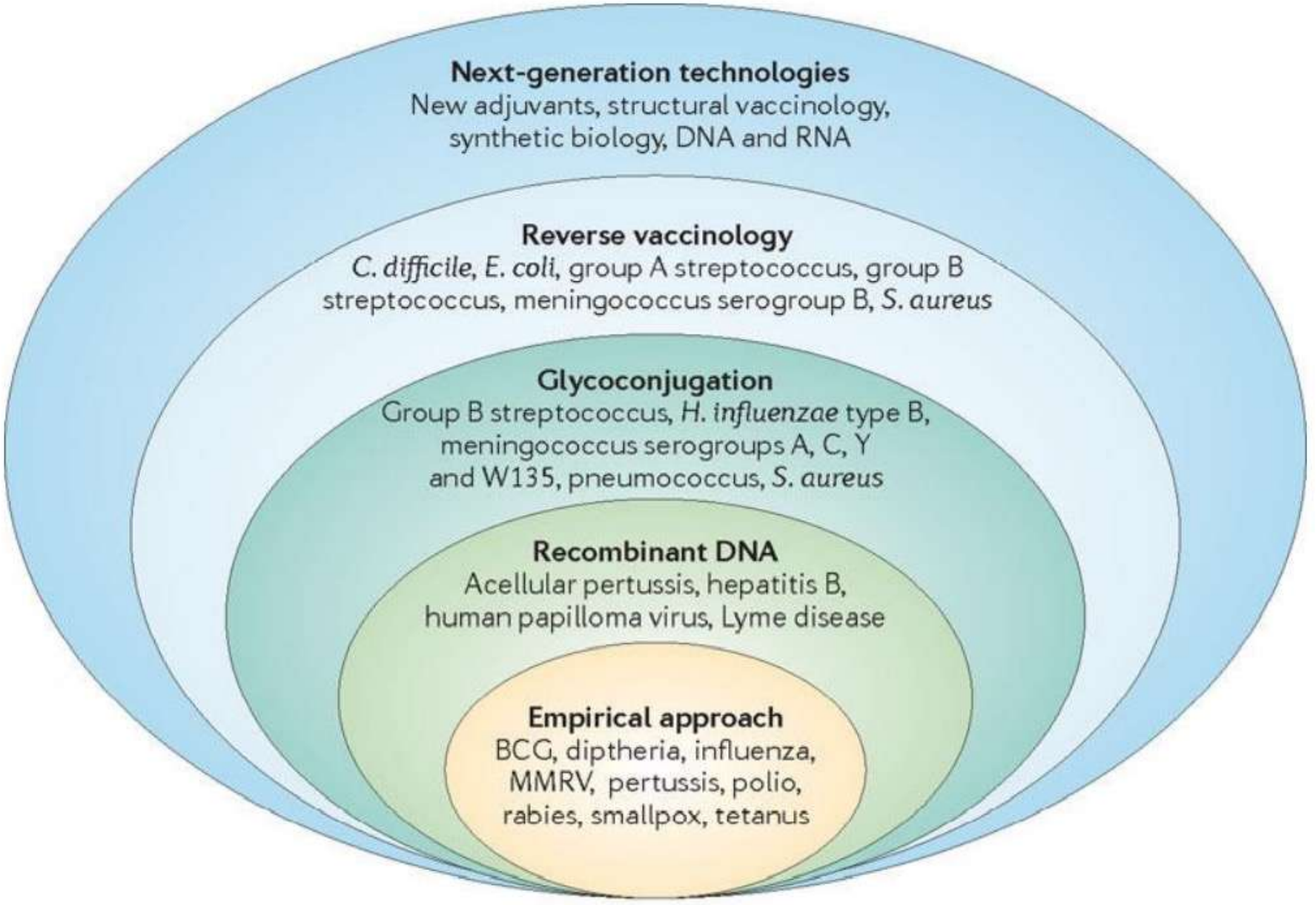
Born	27 December 1822 Dole, Jura, France
Died	28 September 1895 (aged 72) Marnes-la-Coquette, France
Nationality	French
Education	Mathematics,[1] Docteur ès Sciences (Chemical Physics)[2]
Alma mater	École Normale Supérieure University of Paris
Known for	Created the first vaccines for rabies Cholera vaccine[3] Anthrax vaccines Pasteurization



Aşı hedeflenen mikroorganizma

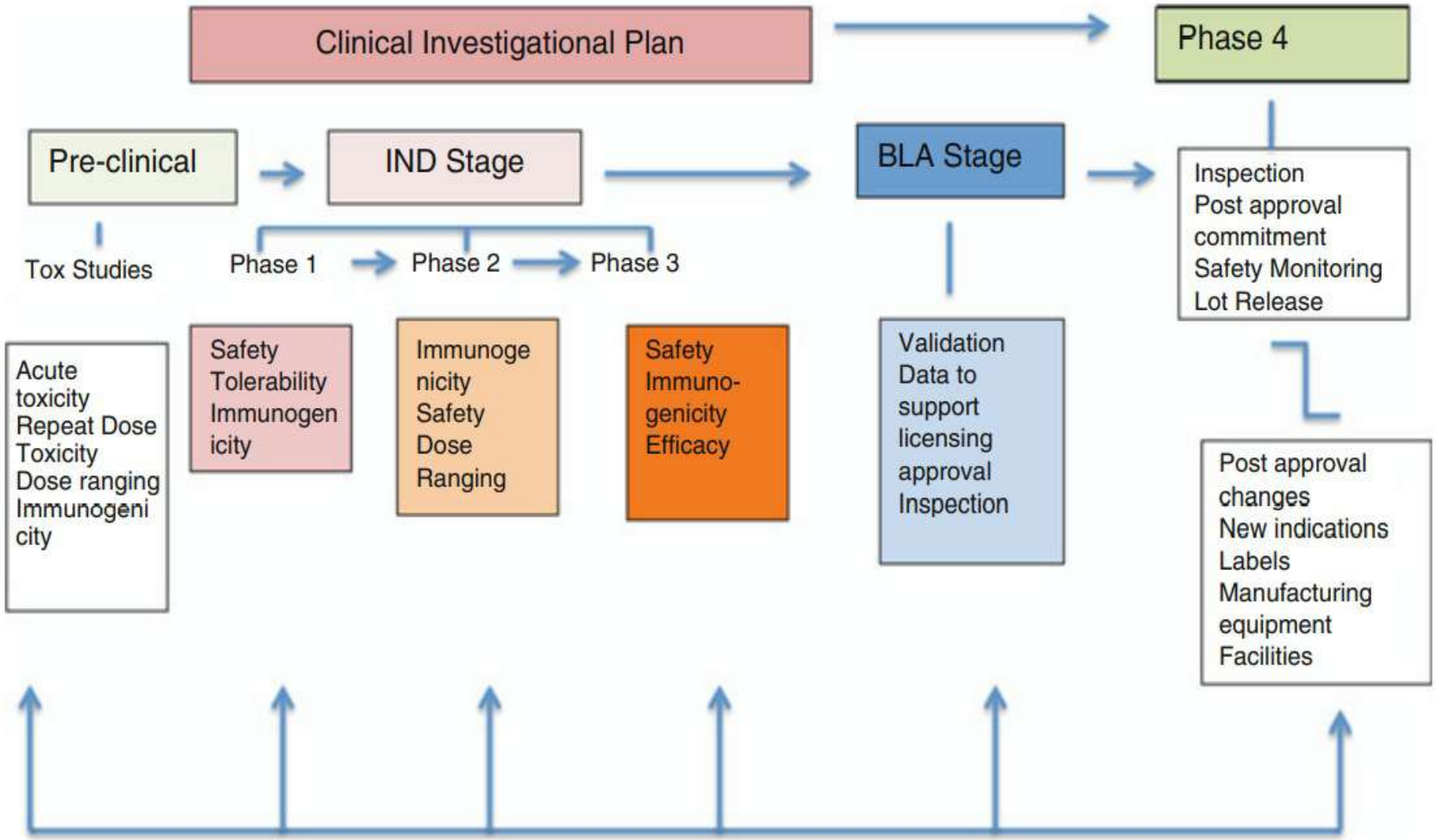
- İzole et
- İnaktive et
- Enjekte et

Aşılama Teknolojileri



Nature Reviews | Immunology

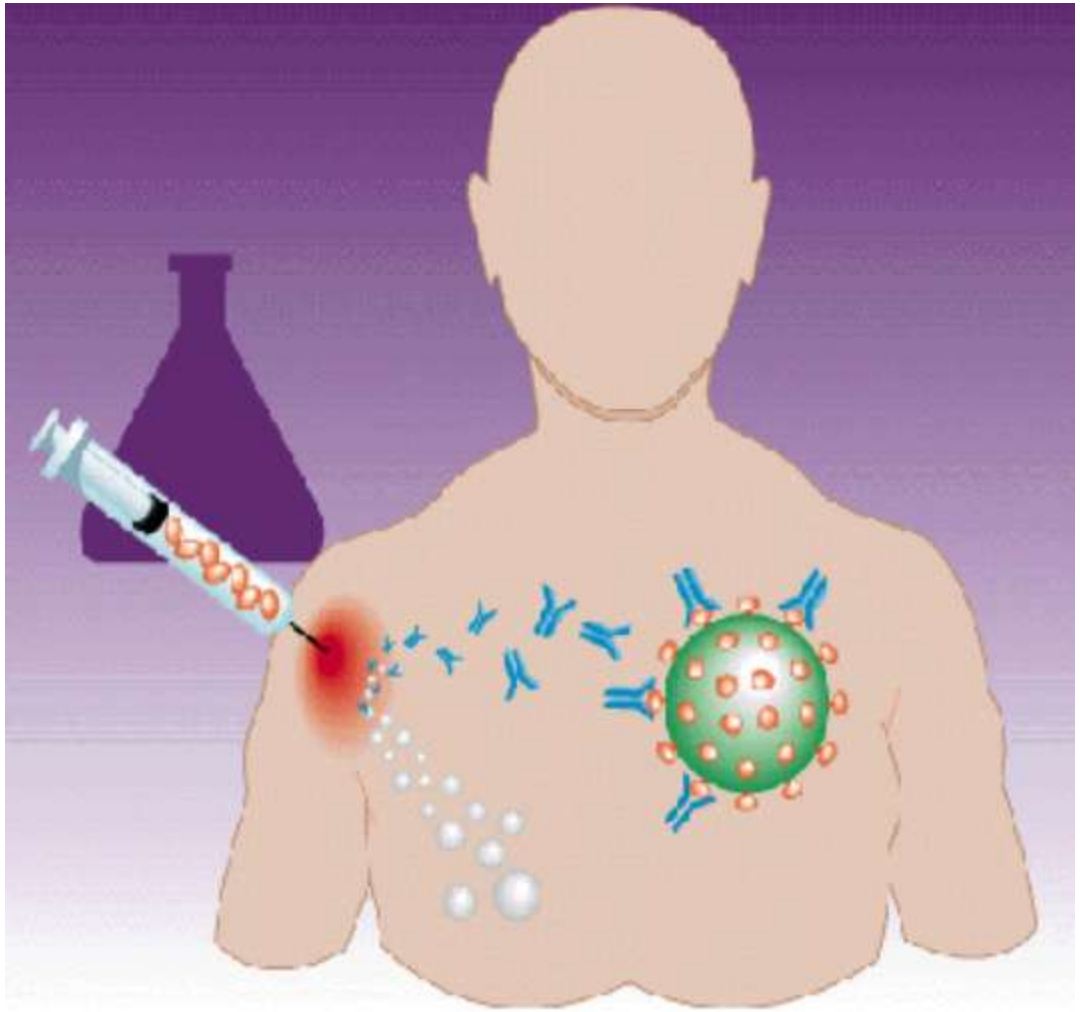
Aşı Geliştirme Aşamaları



Adv Biochem Eng Biotechnol. 2020; 171: 155-88.

Bir aşıda bulunması gereken ideal özellikler

- ✓ Etkin
- ✓ Stabil
- ✓ Ucuz
- ✓ Güvenli
- ✓ Erişilebilir

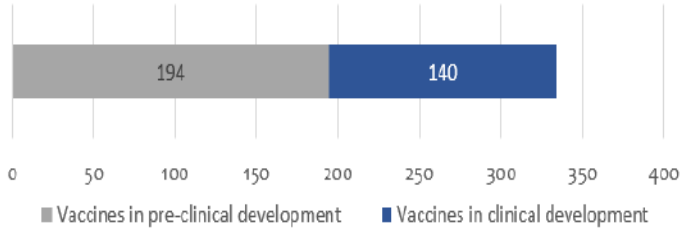


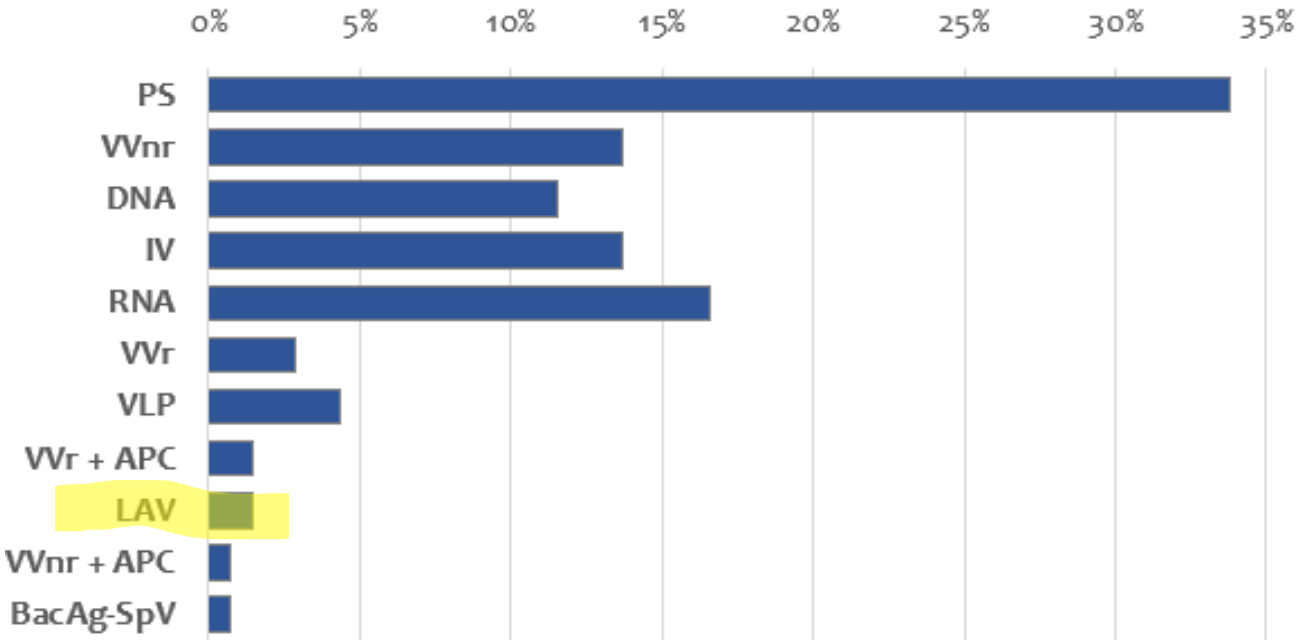
COVID-19 - Landscape of novel coronavirus candidate vaccine development worldwide

21 Ocak 2022 Cuma

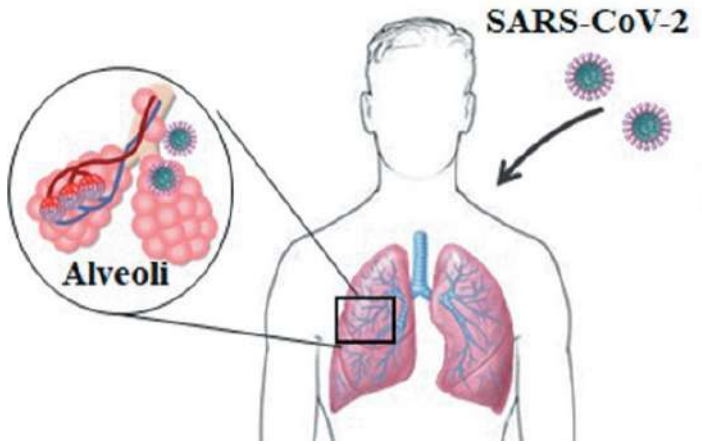
Summary Information on Vaccine Products in Clinical Development

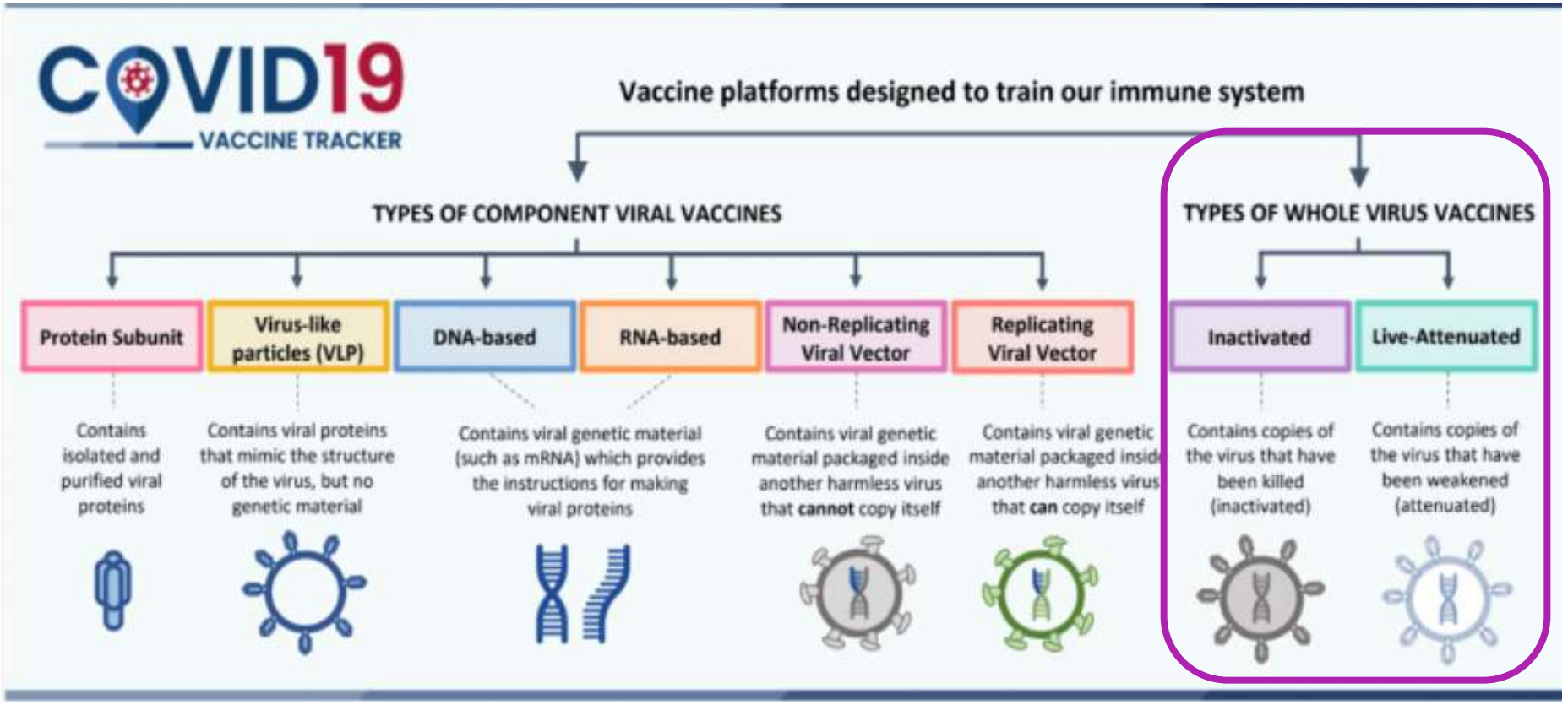
1. - Number of vaccines in clinical development	140
2. - Number of vaccines in pre-clinical development	194





World Health Organization





Expert Review of Vaccines. 2021; 20: 23-44.

COVID19 VACCINE TRACKER

WORLD HEALTH ORGANIZATION (WHO)

Last Updated 9 February 2022.

RNA

Moderna

Spikevax

Protein Subunit

Novavax

Nuvaxovid

Protein Subunit

Serum Institute of India

COVOVAX

Inactivated

Sinovac

CoronaVac

RNA

Pfizer/BioNTech

Comirnaty

Non Replicating Viral Vector

Janssen (Johnson & Johnson)

Ad26.COV2.S

Non Replicating Viral Vector

Oxford/AstraZeneca

Vaxzevria

Non Replicating Viral Vector

Serum Institute of India

Covishield

Inactivated

Bharat Biotech

Covaxin

Inactivated

Sinopharm (Beijing)

Covilo

REVIEW

COVID-19 vaccine: where are we now and where should we go?

Saman Soleimanpour[a,b] and Atieh Yaghoubi[a,b]

COVID-19'a yönelik aşıların geliştirme stratejileri;

- Canlı-zayıflatılmış
- mRNA temelli aşılar
- DNA aşıları
- İnaktif aşılar
- Vektör temelli aşılar

LAV	Live attenuated virus	Codon deoptimized live attenuated vaccines	SARS-CoV2		Mehmet Ali Aydinlar University / Acibadem Labmed Healt
LAV	Live attenuated virus	Codon deoptimized live attenuated vaccines	SARS-CoV2		Indian Immunologicals Ltd/Griffith University
LABV	Live attenuated bacterial vector	Live attenuated bacterial (Pertussis) Vector	SARS-CoV2		Institut Pasteur Lille, Inserm
LABV	Live attenuated bacterial vector	Live attenuated bacterial vector	SARS-CoV2		ALtraBio, TheRex

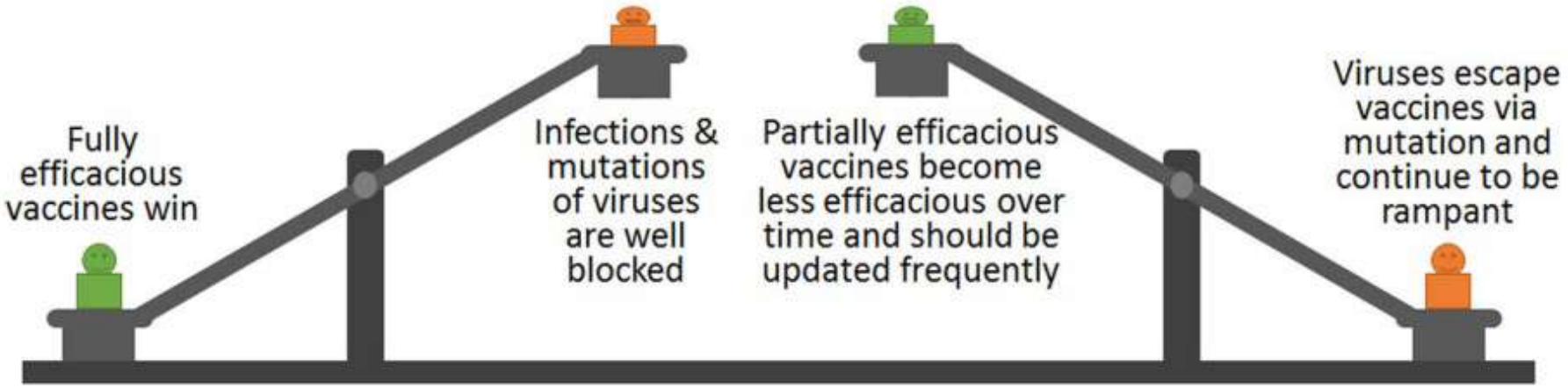
Expert Review of Vaccines. 2021; 20: 23-44.

Should the world collaborate imminently to develop neglected live-attenuated vaccines for COVID-19?

Ji-Ming Chen

J Med Virol. 2022; 94: 82–7.

Uzun vadede SARS-CoV-2 ve aşılar arasındaki olası tahterevalli oyunu



COVID-19 aşıları arasında **mRNA temelli** olanlar en etkili **ancak**;

✓Yeni varyantlarla birlikte koruyuculuk ~%91'den ~66'ya geriledi

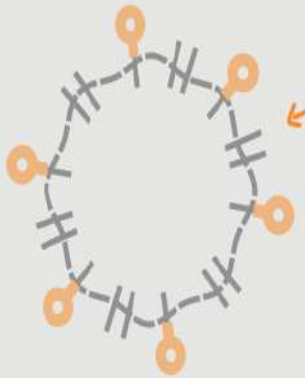
✓Zamanla koruyuculuk azalmakta / **ek doz** ihtiyacı

Types of SARS-CoV-2 vaccines for COVID-19

Attenuated vaccines

British Society for immunology

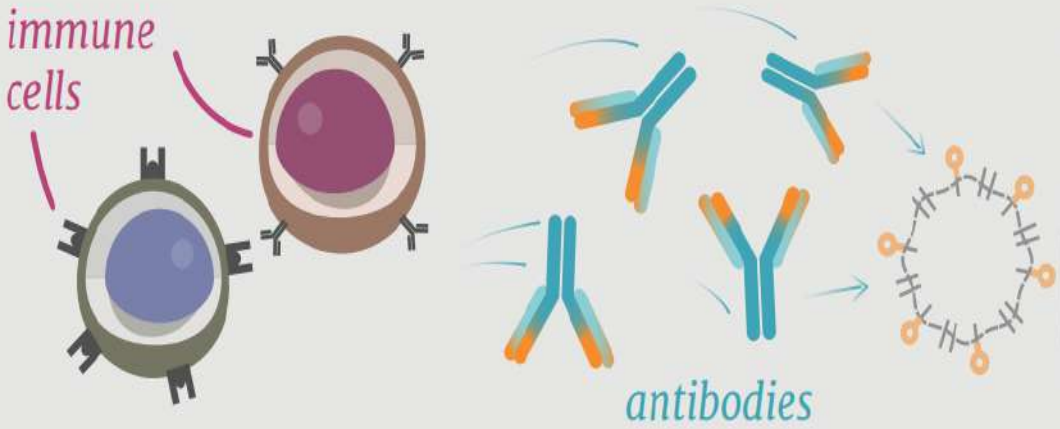
www.immunology.org



Contain **weakened SARS-CoV-2 virus**.

The weakened virus is recognised by the immune system to trigger a response without causing illness.

This response builds immune memory, so your body can fight off SARS-CoV-2 in future.



Considerations

A well-known approach which requires time and extensive testing.

The immune response resembles the natural infection.

Examples in human use for other disease

Oral Polio vaccine

In clinical trials for COVID-19

Codagenix

Canlı-atenüe COVID-19 Aşılarının Avantajları

✓ ‘M**esihle**r’ gibi, çok daha fazla viral hastalığın **elimine/eradike** olmasını sağladılar (19 infeksiyondan 11’inde KKK, OPV vb.)

✓ LAV’lar diğer aşılardan farklı endojen antijenlerle hem **hümoral** bağışıklığı hem de **hücresel bağışıklığı** uyararak çok daha **etkili** olabilir.

✓ LAV **maliyeti düşüktür** (Örn. OPV aşısı İPV’den~% 85.9 ucuzdur ve OPV için 10*5 virus gerekli İPV için 10*10) Herkese **eşit** ve **yeterli** üretim olabilir.

✓ LAV’lar, diğer aşıların **güvenlik risklerini** ortadan kaldırabilir (taşıyıcı ajanların yan etkisi gibi).

✓ LAV’lar **yüksek etkinlikleriyle** infeksiyonu güçlü **bloke** edebilir aşı kaçışını veya virülans arttırıcı **mutasyonlarını inhibe** ederler

J Med Virol. 2022; 94: 82–7.

Canlı-attenüe COVID-19 Aşılarının Dezavantajları

- ✓ LAV’lar, **invitro üretmeye uygun değil**, ama SARS-CoV-2 **hücre kültüründe** iyi çoğalır
- ✓ **Güvenli** LAV tohum (**seed**) elde etmek zordur
- ✓ LAV’lar, iletim yoluyla insanlarda **virülanslarına geri** dönebilirler
- ✓ **İmmün süprese** konakta **patojenik** olabilir
- ✓ LAV’lar ve vahşi tip viruslar arasındaki rekombinasyonla **yeni varyantlar** oluşur
- ✓ LAV'ler diğer patojenik viruslarla **kirlenebilir**

J Med Virol. 2022; 94: 82–7.

COVID-19'a yönelik aşıların geliştirme stratejileri

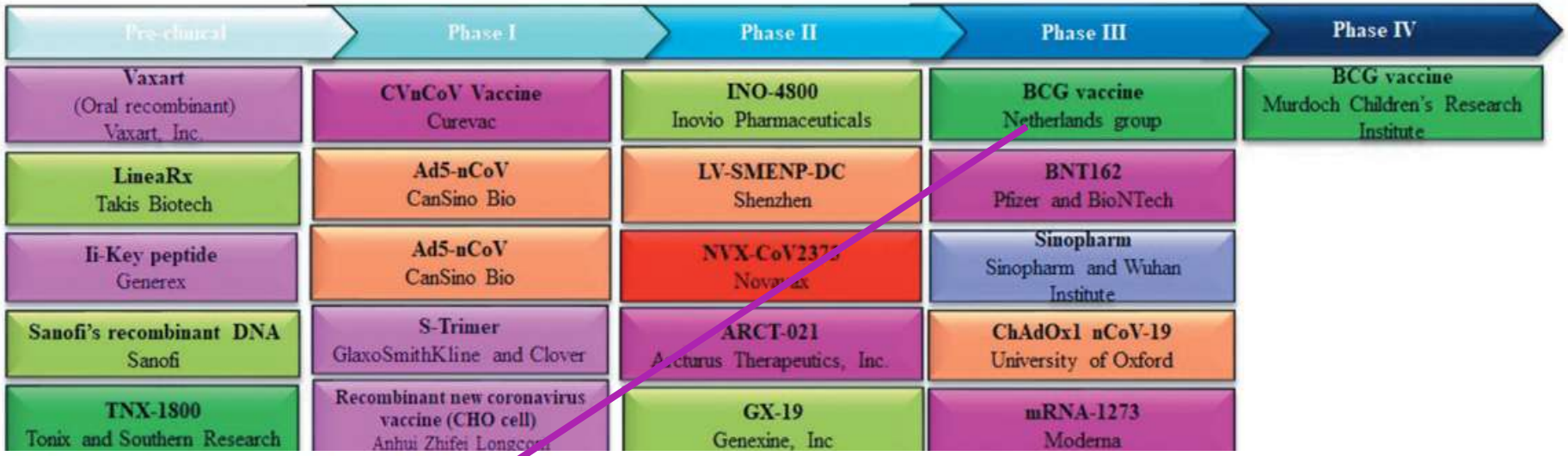


Table 2. COVID-19 vaccine candidates tested in clinical trials.

Platform	Candidate	Description	Clinical trial	Mechanism of immune stimulation	Company
Live-attenuated	BCG vaccine	Repurposing the BCG vaccine live-attenuated vaccine for COVID-19	Phase II/III	Inducing an innate immune response; Production pro-inflammatory cytokines (IL-1β, TNF and IL-6)	Research group of Netherlands
	BCG vaccine	The BRACE trial to repurposing the BCG vaccine live-attenuated vaccine for SARS-CoV-2.	Phase IV	Inducing an innate immune response; Production pro-inflammatory cytokines (IL-1β, TNF and IL-6)	Murdoch Children's Research Institute

Expert Review of Vaccines. 2021; 20: 23-44.

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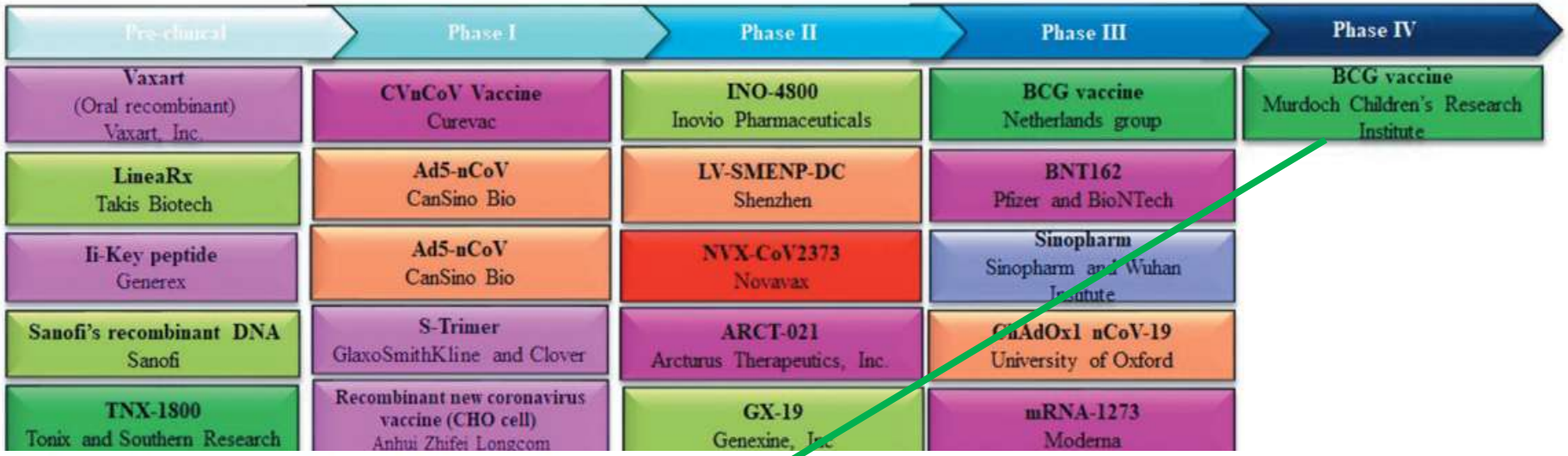

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Expert Review of Vaccines. 2021; 20: 23-44.

BCG temelli canlı-atenüe COVID-19 aşısı Murdoch Children's Research Institute ve Research Group of Netherlands

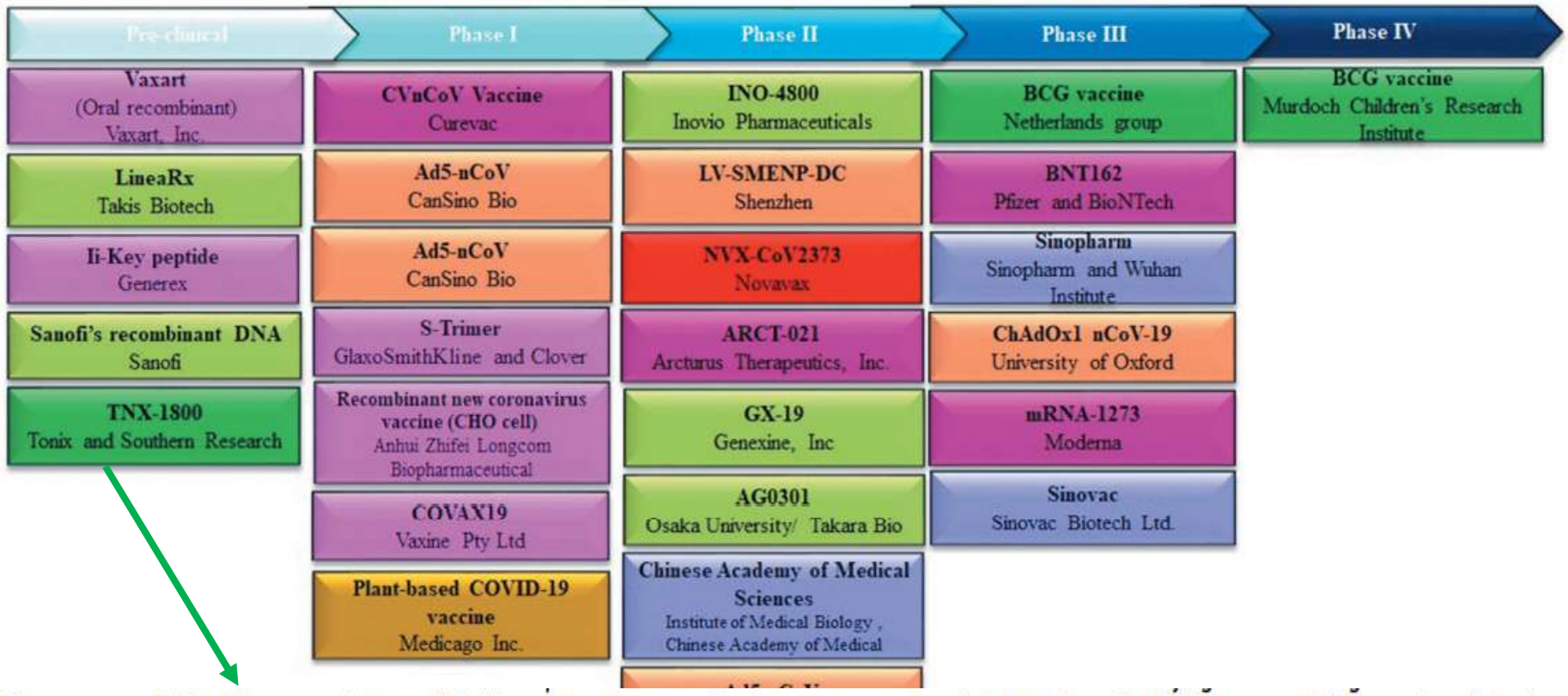
- Phase III ***BRACE trial*** on 4170 healthcare workers in hospitals in Australia (**NCT04327206**).
- Phase III ***BCG-CORONA trial***, which aimed to identify the effect of BCG vaccination on 1500 healthcare workers to receive the BCG vaccine or placebo in the Netherlands (**NCT04328441**).
- Phase **IV** trial of this candidate, on 1800 participants

The primary results of this trial are expected in **November 2021** (**NCT04348370**).

BCG Vaccine for Health Care Workers as Defense Against COVID 19 (BADAS)

Expert Review of Vaccines. 2021; 20: 23-44.

COVID-19'a yönelik aşıların geliştirme stratejileri



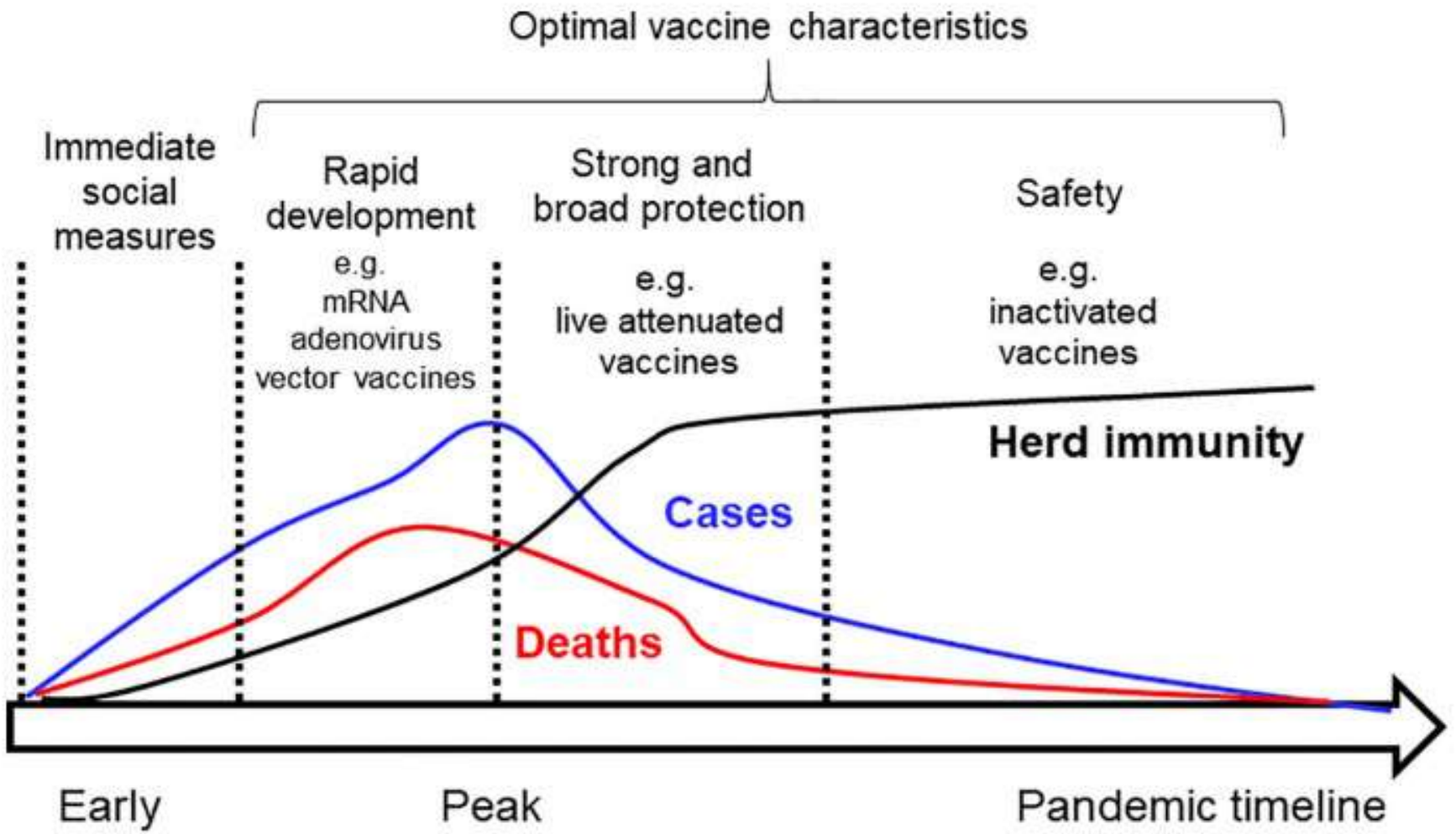
Expert Review of Vaccines. 2021; 20: 23-44.

Review

Could live attenuated vaccines better control COVID-19?

Shinya Okamura [a,b], Hirotaka Ebina [a,b,c,*]

Vaccine



Vaccine. 2021; 39: 5719-26.

Review

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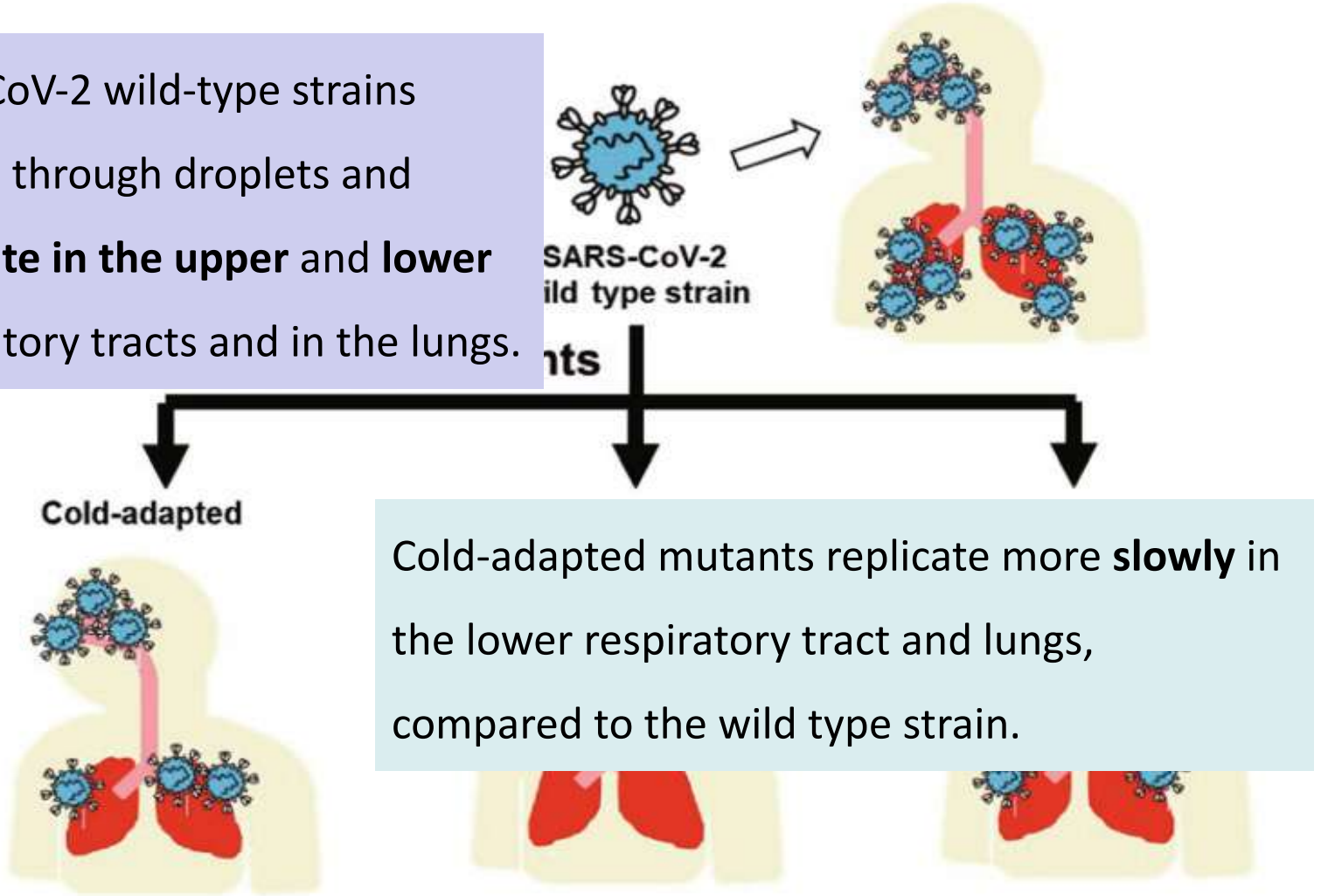
Vaccine

SARS-CoV-2 wild-type strains spread through droplets and **replicate in the upper** and **lower** respiratory tracts and in the lungs.



Cold-adapted mutants replicate more **slowly** in the lower respiratory tract and lungs, compared to the wild type strain.

Vaccine. 2021; 39: 5719-26.

Review

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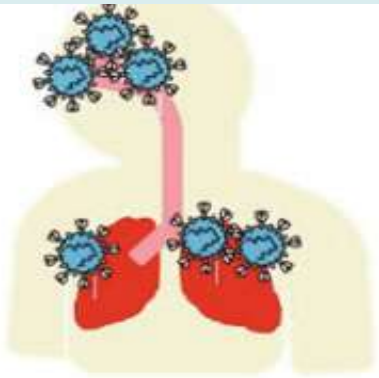
Vaccine

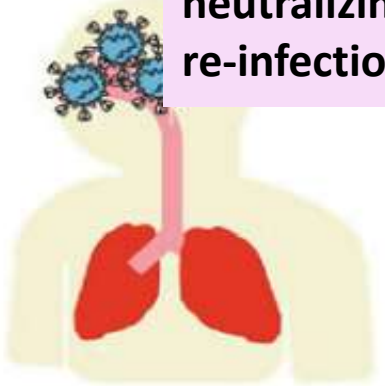
Temperature-sensitive (**TS**) mutants, which could replicate at **low temperatures** (32-34 C) but showed impaired proliferation at 37 C

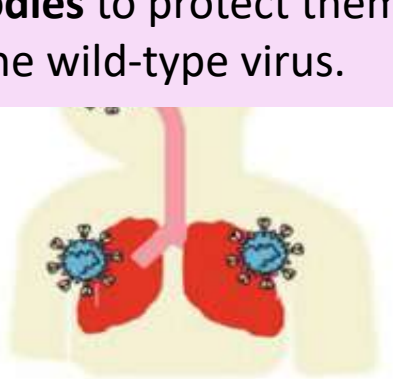
This phenotype is similar to **live attenuated influenza** vaccine

TS mutants showed **lower pathogenicity** than the wild type parent strain in Syrian hamsters. A similar amount of virus in nasal wash specimens from TS- or wild type-infected hamsters, but the virus titer was significantly **lower in the lungs of TS-infected** hamsters than in those of wild type-infected hamsters.

TS-infected hamsters generated **sufficient neutralizing antibodies** to protect them from **re-infection** with the wild-type virus.







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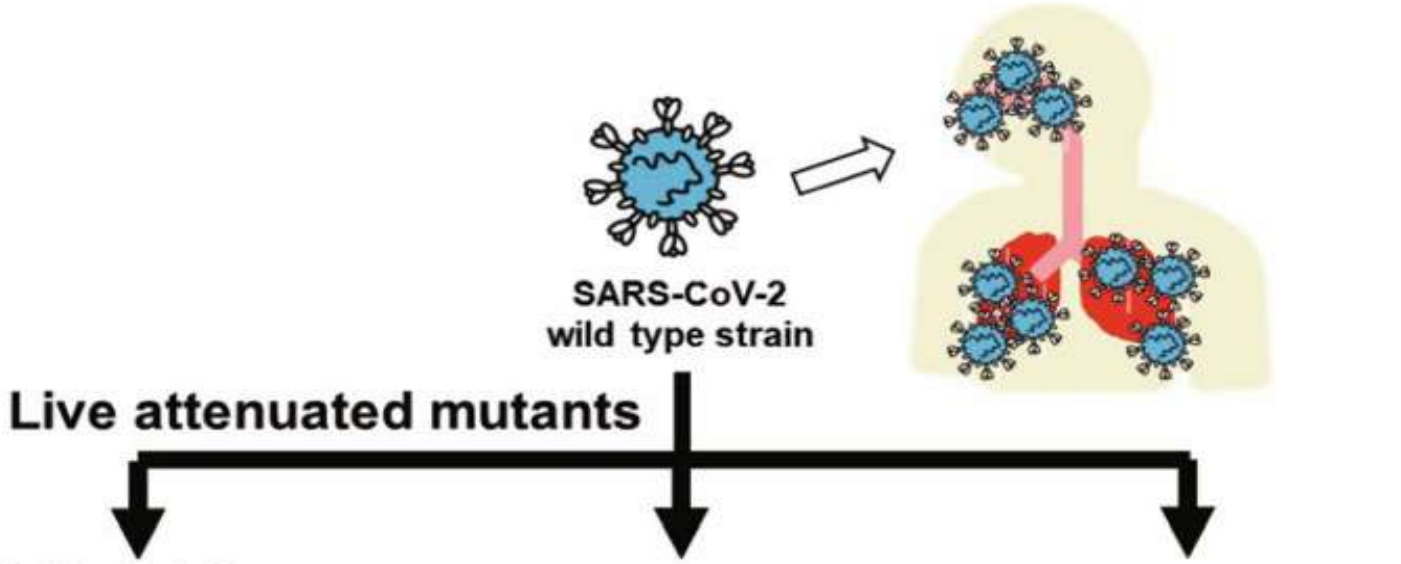
Vaccine



Codon de-optimized mutants show **lower proliferation** rates than the wild type strain, at any location.

Recently, codon de-optimization has been used as a **tool to attenuate** viruses

Vaccine. 2021; 39: 5719-26.

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Vaccine

CODAGENIX Inc. **codon de-optimized** SARS-CoV-2 strain

- Canlı atenüe SARS CoV-2 suşlarının intranazal uygulanması, varyant suşlar tarafından infeksiyonu önleyebilen **IgA üretimini** uyarabilir.
- Canlı influenza aşısı, intranazal yoldan uygulanan, **soğuğa adapte edilmiş** bir suş, **IgA** salgılanmasını ve **CD8+ T** hücre tepkisini indükler

- Şu anda kullanılan **mRNA aşıları** ve **adenovirus vektörlü** aşılar sadece **spike** proteinini kodlar
- Sadece bu viral antijene karşı bağışıklık tepkisini sınırlar.
- **Canlı atenüe** aşılar, birkaç hastalığa karşı bağışıklığı indükleyebilir
- Koruma şansını arttırır.

Vaccine. 2021; 39: 5719-26.

Review

Could live attenuated vaccines better control COVID-19?

Shinya Okamura [a,b], Hirotaka Ebina [a,b,c,*]

- Canlı atenüe aşılar **güçlü aşı modaliteleri** içinde en yaygın olanlardır
- Ancak en ciddi **sorun**, aşılama sonrası **mutasyonlar** nedeniyle virusun toksik ve infekte özelliklerini geri kazanmalarıdır
- Bu soruna olası bir çözüm, TS'den sorumlu ***nsp3*** ve ***nsp14*** gibi genlerin ters genetik yöntemi **BAC DNA** ve **CPER** yöntemlerle aşı suşunun düzenlenmesidir
- Burun boşluğundaki atenüe aşı suşlarının çoğalmasına bağlı **advers reaksiyonlar** değerlendirilmelidir.
- SARS-CoV-2 infeksiyonu **indüklenmesi** ve **sitokin fırtınası**, **tromboz** ile ilişkilendirilmiş

Vaccine. 2021; 39: 5719-26.

Article

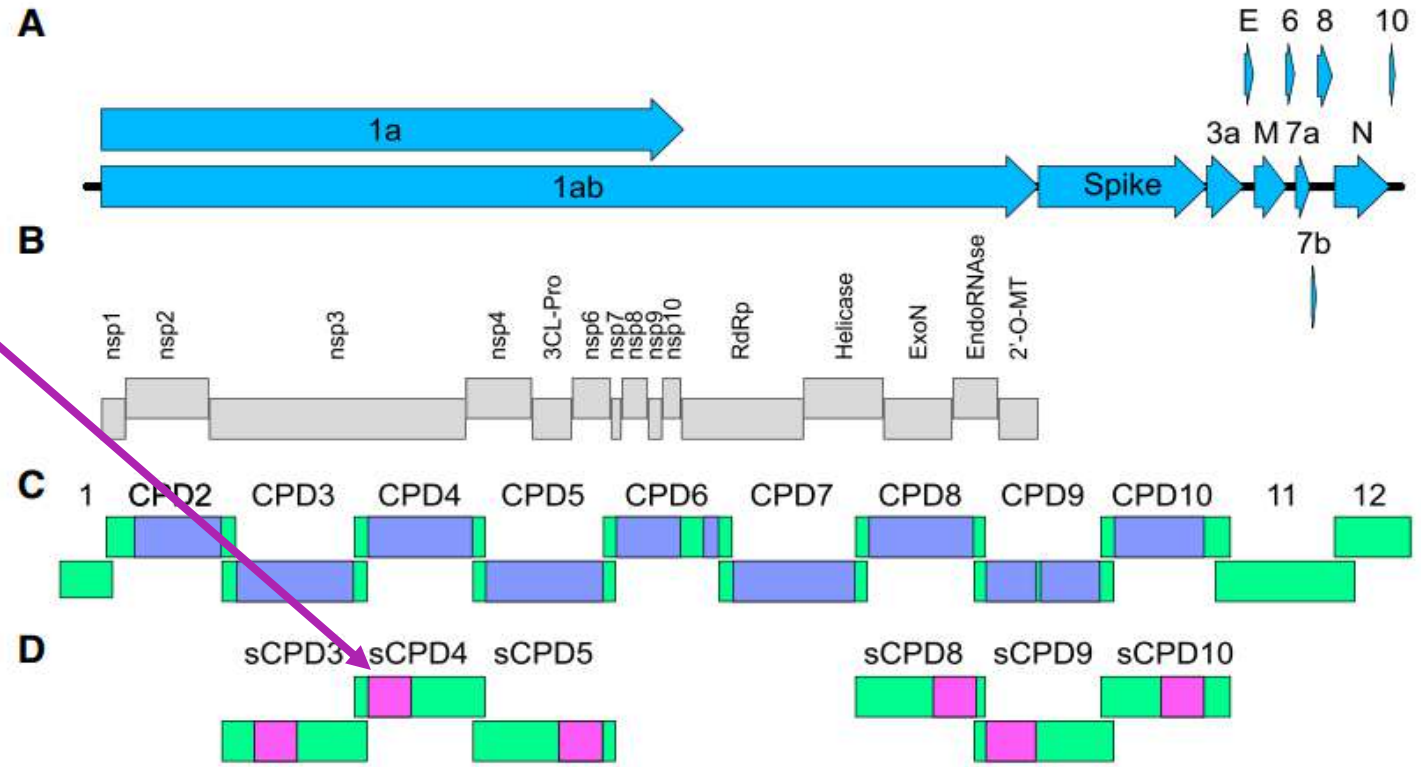
Development of safe and highly protective live-attenuated SARS-CoV-2 vaccine candidates by genome recoding

Jakob Trimpert,[1] Kristina Dietert,[2,3] Theresa C. Firsching,[2] Nadine Ebert,[4,5] Tran Thi Nhu Thao,[4,5,6] Daria Vladimirova,[1] Susanne Kaufer,[1] Fabien Labroussaa,[5,7] Azza Abdelgawad,[1] Andelé Conradie,[1] Thomas Höfler,[1] Julia M. Adler,[1] Luca D. Bertzbach,[1,9] Joerg Jores,[5,7] Achim D. Gruber,[2] Volker Thiel,[4,5] Nikolaus Osterrieder,[1,8] and Dusan Kunec[1,10,*]

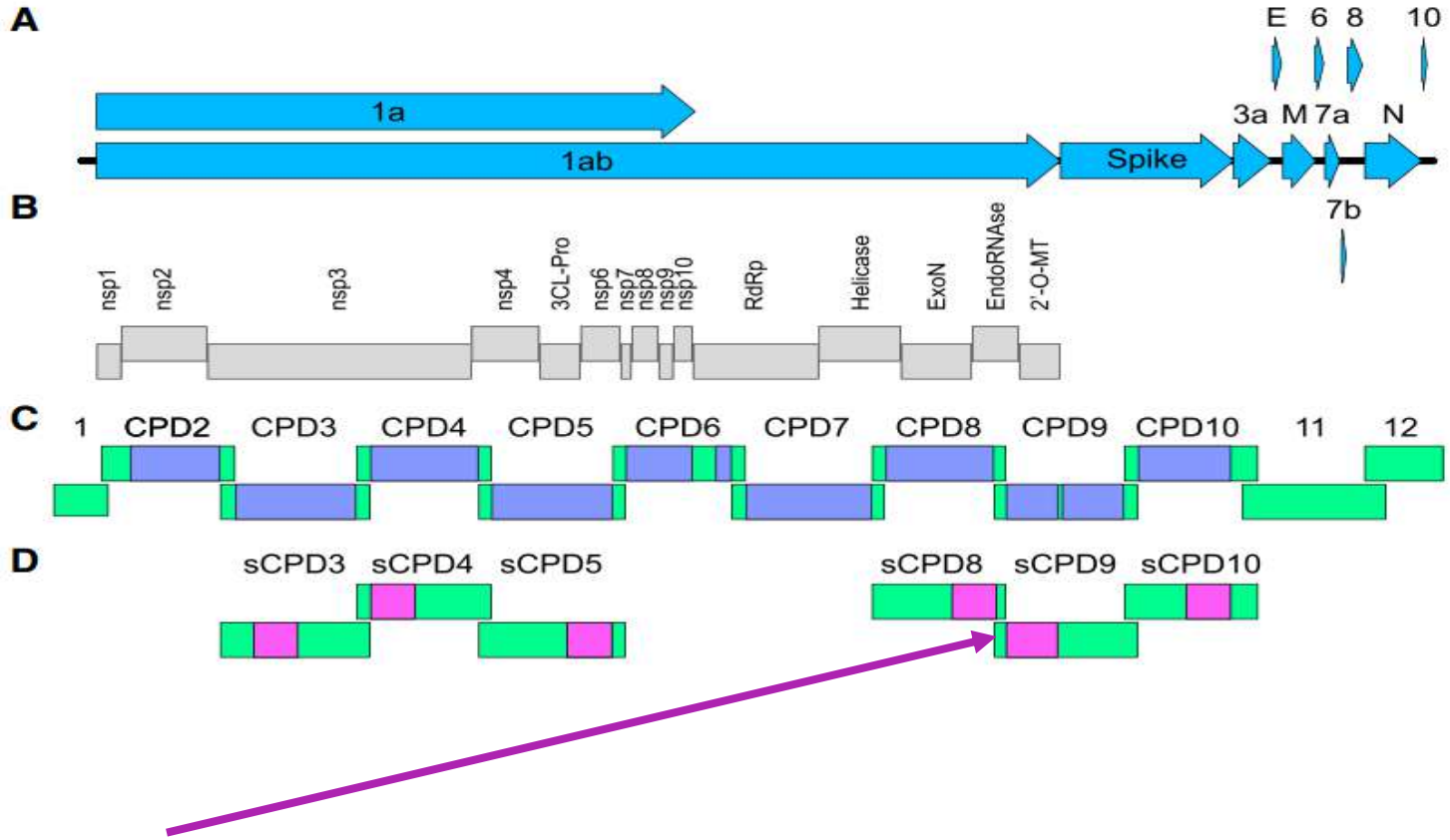
[1]Institut für Virologie, Freie Universität Berlin, Berlin, Germany

Kodon çiftin yeniden optimizasyonu (**Codon Pair deoptimization CPD**)

(Aslında 2008'de çalışılan teknoloji)



Trimpert et al, *Cell Reports*. 2021; 36: 09493, August 3.



- Kaydedilmiş viruslar, ataları kadar verimli genlerden protein üretemezler
- Konağın **doğal ve adaptif yollarla** vahşi tip virus infeksiyonunu kontrol etmesini sağlar

Trimpert et al, *Cell Reports*. 2021; 36: 09493, August 3.

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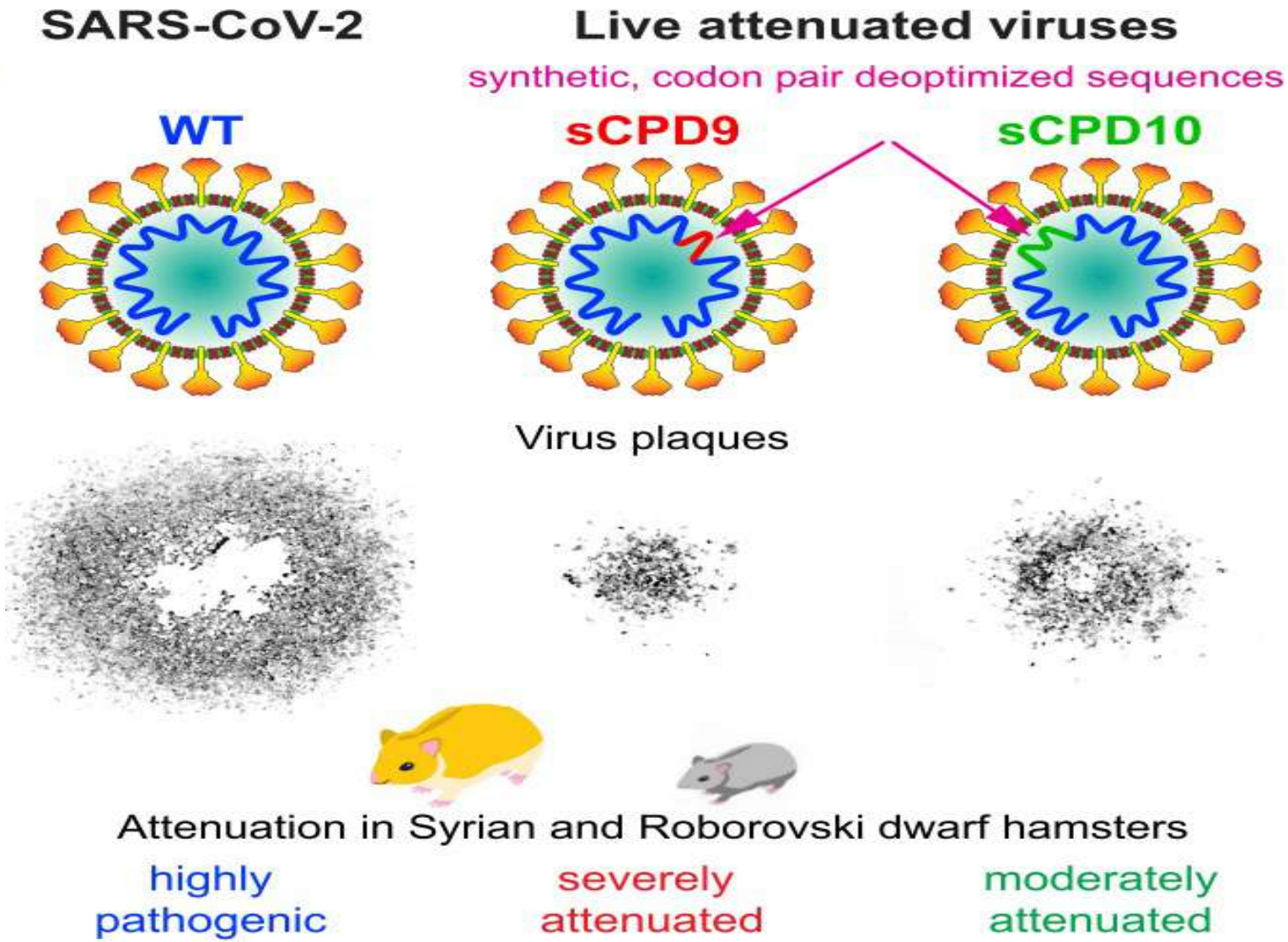

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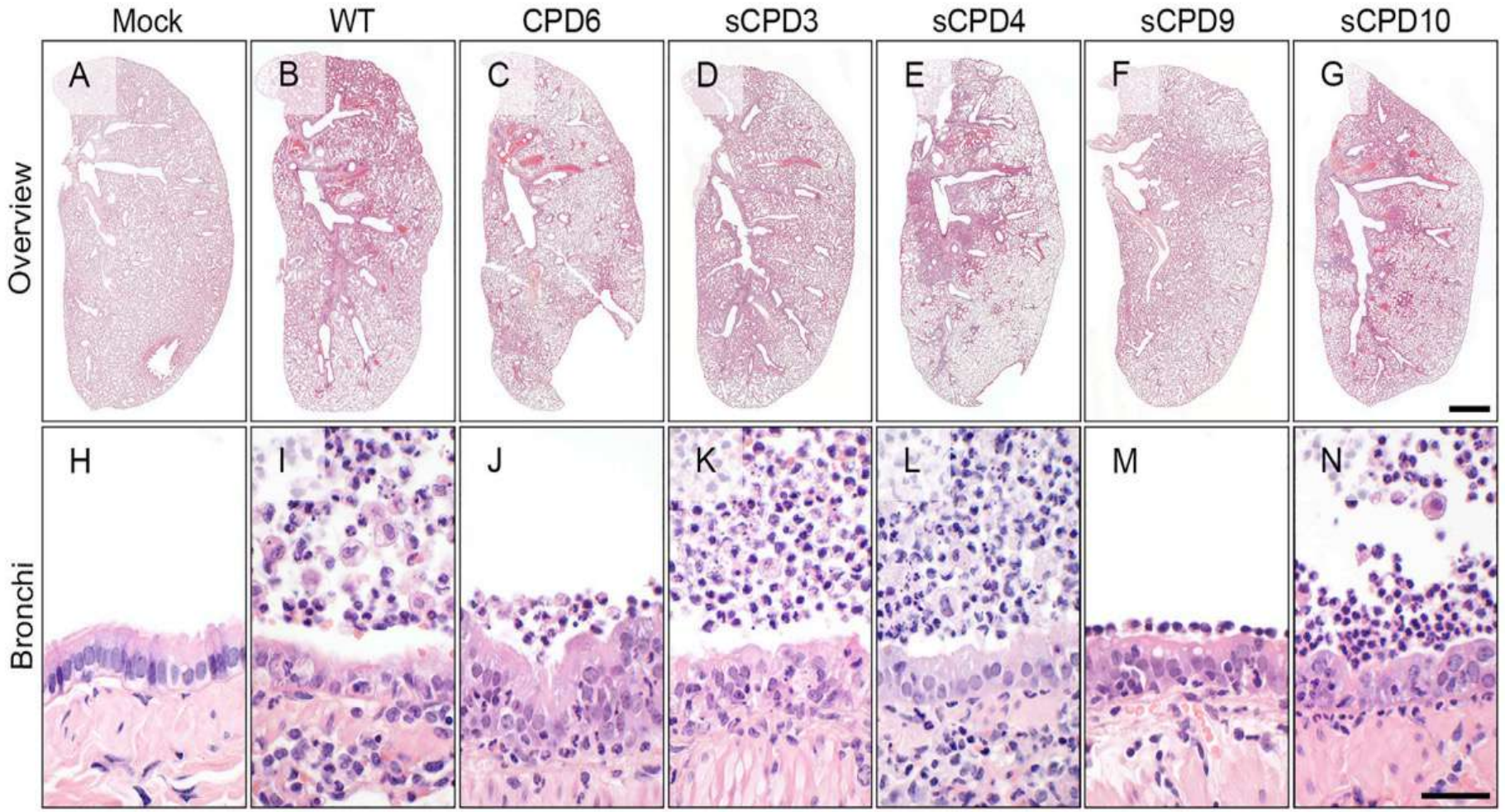
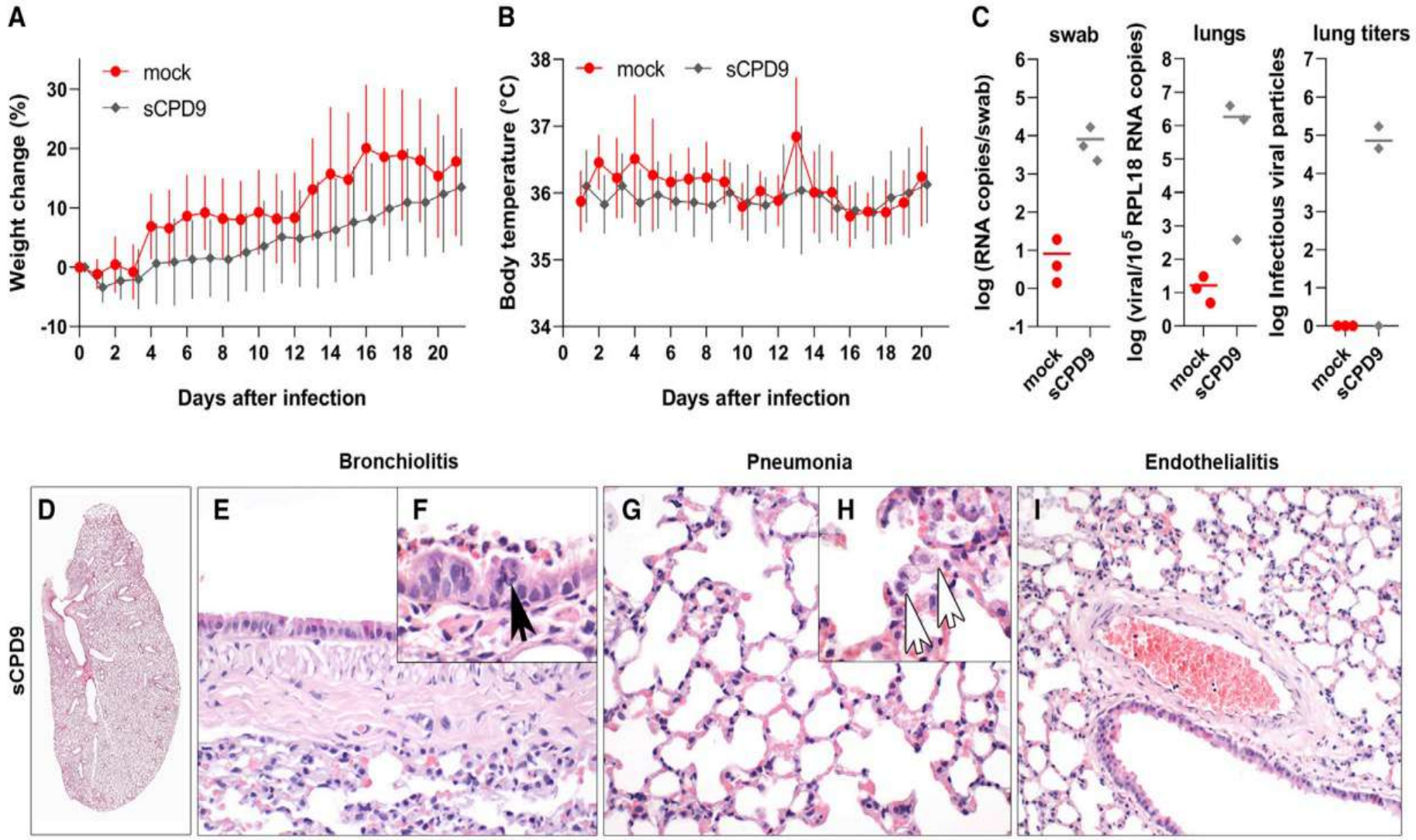


Figure 4. Lung histopathology of infected Syrian hamsters 3 days after vaccination

Representative whole cross-sectional scans of left lung lobes (upper row, A–G) and micrographs of bronchial epithelium (bottom row, H–N) of formalin-fixed, paraffin embedded, hematoxylin and eosin-stained tissues. Hamsters were either mock-vaccinated (Mock), infected with SARS-CoV-2 (WT) or vaccinated with viruses CPD6, sCPD3, sCPD4, sCPD9, or sCPD10. Bars: 1 mm (A–G) or 100 μm (H–N).

Trimpert et al, *Cell Reports*. 2021; 36: 09493, August 3.

Recoded SARS-CoV-2 mutant sCPD9s is strongly attenuated in Roborovski dwarf hamsters



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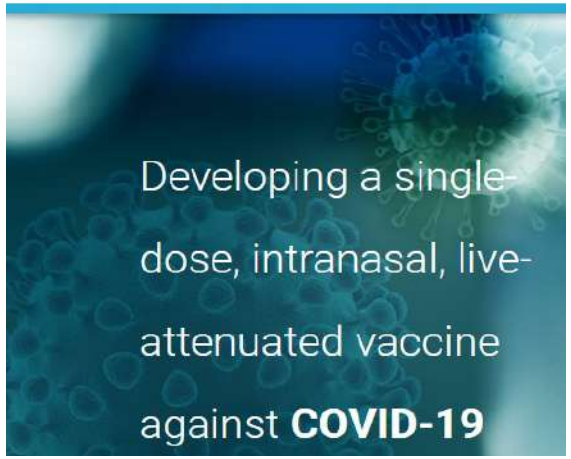
[1]Institut für Virologie, Freie Universität Berlin, Berlin, Germany

Sonuçta;

- Canlı atenüe aşı adayları yeniden **SARS-CoV-2 genomunun yeniden kodlanmasıyla** oluşturulmakta
- Önde gelen aşı adayı **sCPD9** fiilen **apatojenik**tir
- Hamsterlerde **klinik kötüleşme olmadan** immün sistemi uyarabilmiş
- iki hamster türünde **sCPD9** ile aşılama, güçlü **nötralize edici antikor** ortaya çıkarmıştır
- Tek bir **burun içi damlacık aşısı** hamsterlerde sterilizan bağışıklığı sağlamaktadır

Trimpert et al, *Cell Reports*. 2021; 36: 09493, August 3.

CODAGENIX TECHNOL



1. Recode

2. Synthesize

3. Transfect

4. Recover

Codagenix's computer-based algorithm to introduce hundreds of silent mutations into the genome to use codon pairs that are underrepresented in human cells

48-60 days to begin clinical lot manufacturing

COVI-VAC (codenamed **CDX-005**) is a COVID-19 vaccine developed by Codagenix, Inc. In **December 2020**

On September 29, 2021, **Codagenix** presented positive **phase 1** data for COVI-VAC at **IDWEEK 2021**.

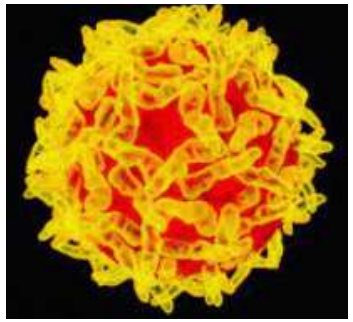
✓**COVI-VAC** iyi tolere edilmekte

✓Ciddi bir **yan etkisi yoktur**

✓**İntranasal** aşı **immünojenik**, etkin ve virusun nazal replikasyonunu engellemekte

✓Nazal **saçılım çok düşük**

Yellow fever 17D (YF17D)



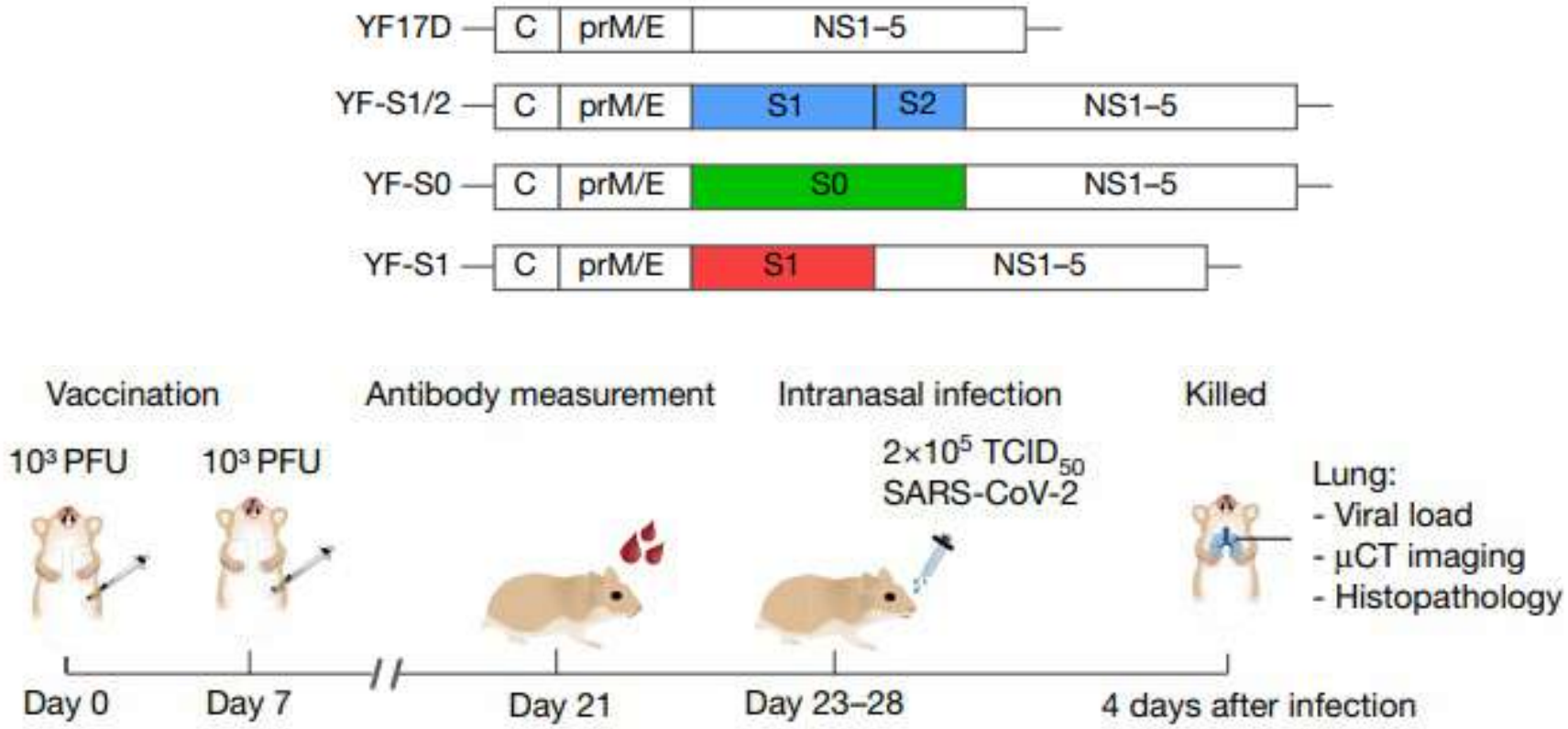
A single-dose live-attenuated YF17D vectored SARS-CoV-2 vaccine candidate

- ✓ **YF17D, canlı** zayıflatılmış **küçük pozitif** polariteli **RNA virusu**
- ✓ **Sınırlı vektör kapasitesine sahip** viral poliproteindeki yabancı antijenleri tolere edebiliyor
- ✓ **YF17D** aşısı **hümoral** ve **hücresel bağışıklığı uyaran** geniş işlevi var
- ✓ Tek **bir aşı** dozundan sonra yaşam boyu koruma sağlamakta
- ✓ **YF17D 'omurga' vektör** olarak kullanarak ***Japon ensefaliti*** ve ***Deng ateşi*** aşılarında kullanılmış

Nature. 2021; 590: 320-35.

A single-dose live-attenuated YF17D vectored SARS-CoV-2 vaccine candidate

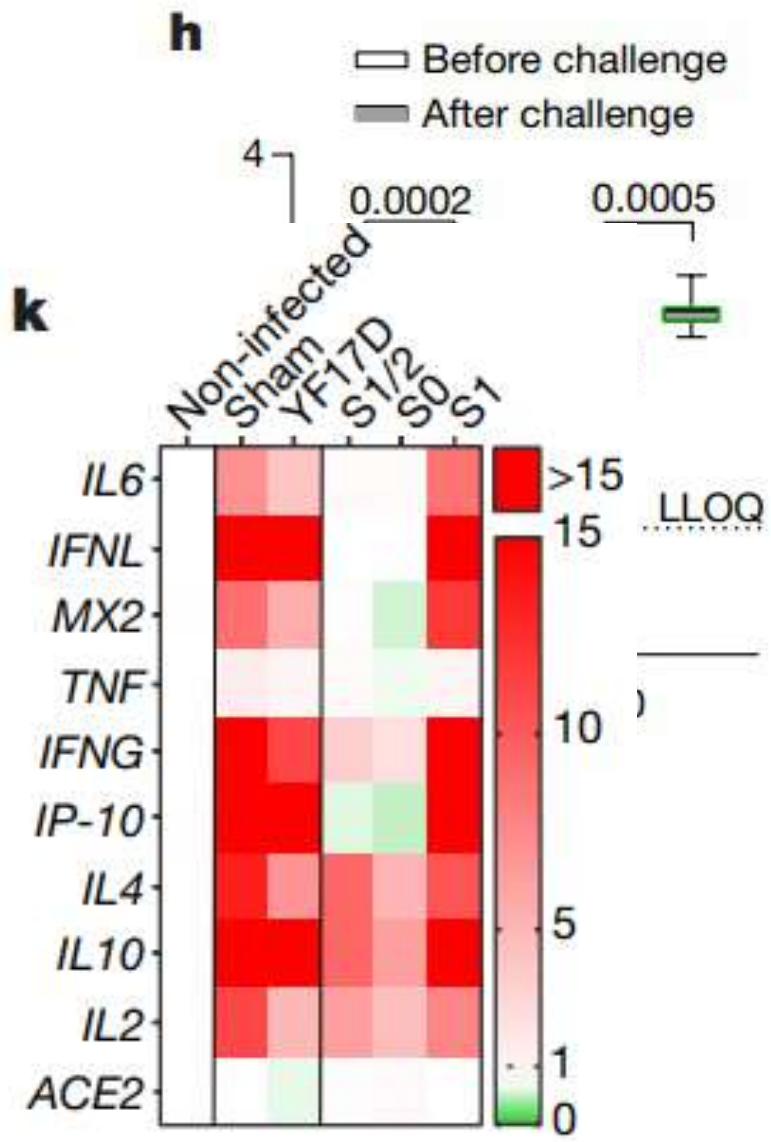
YF17D-temelli aşı (**YF-S**)
S protein of SARS-CoV-2 -> **S1** and **S2** subunits

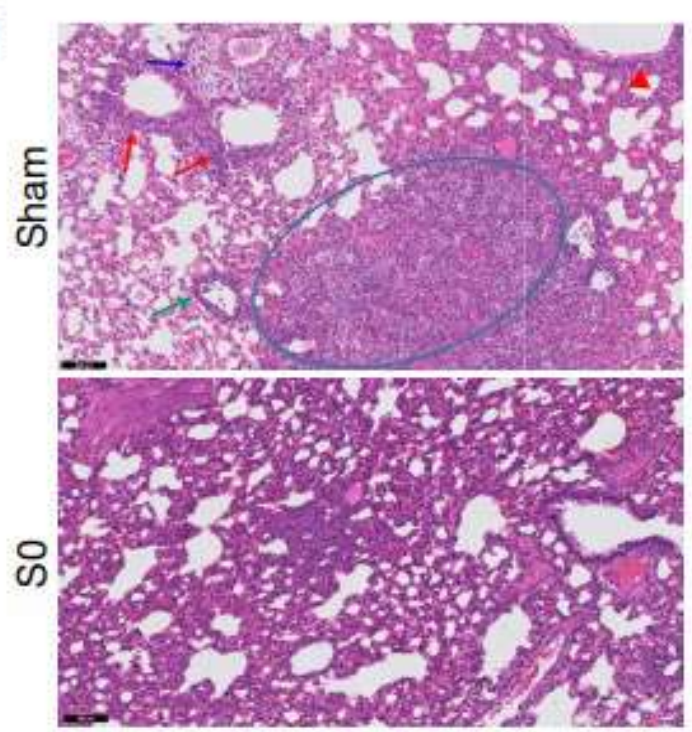


Syrian hamsters were immunized **twice intraperitoneally**

Nature. 2021; 590: 320-35.

A single-dose live-attenuated YF17D vectored SARS-CoV-2 vaccine candidate





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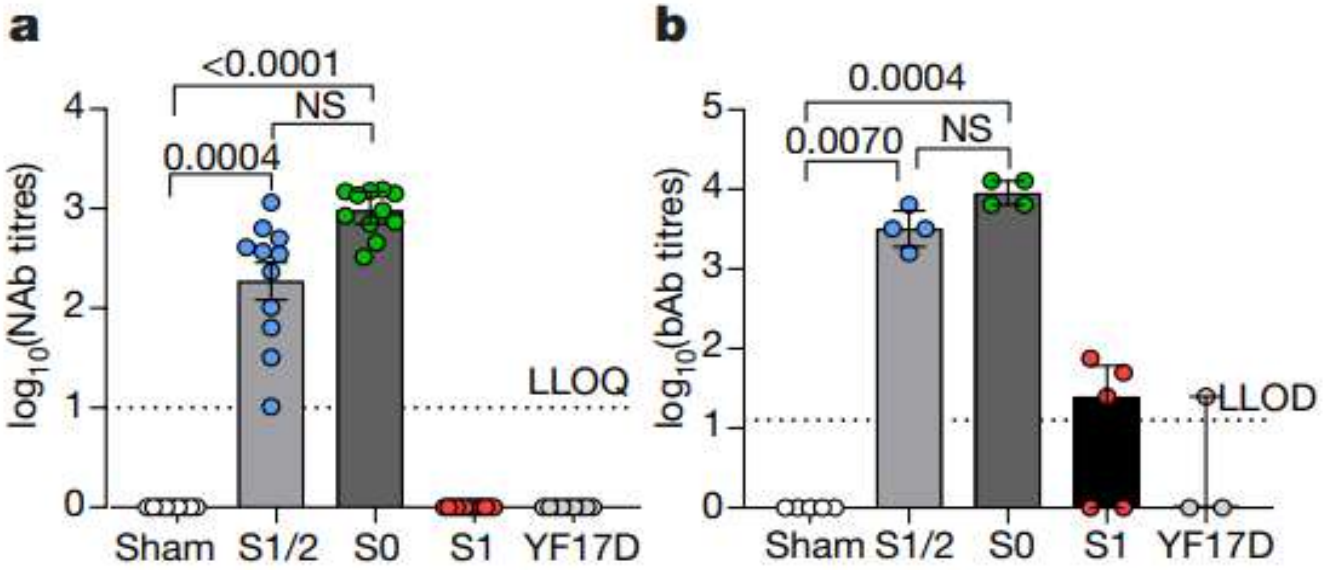
A single-dose live-attenuated YF17D vectored SARS-CoV-2 vaccine candidate



Sonuçta;

- **YF-S0 has an excellent safety** profile and induces **high levels** of SARS-CoV-2 **neutralizing antibodies** in hamsters (*Mesocricetus auratus*), mice (*Mus musculus*) and cynomolgus macaques (*Macaca fascicularis*)
- Concomitantly—**protective** immunity against **yellow fever virus**
- **Humoral** immünite **T helper 1** üzerinden kazanılmakta ve tek doz koruyucu

Nature. 2021; 590: 320-35.

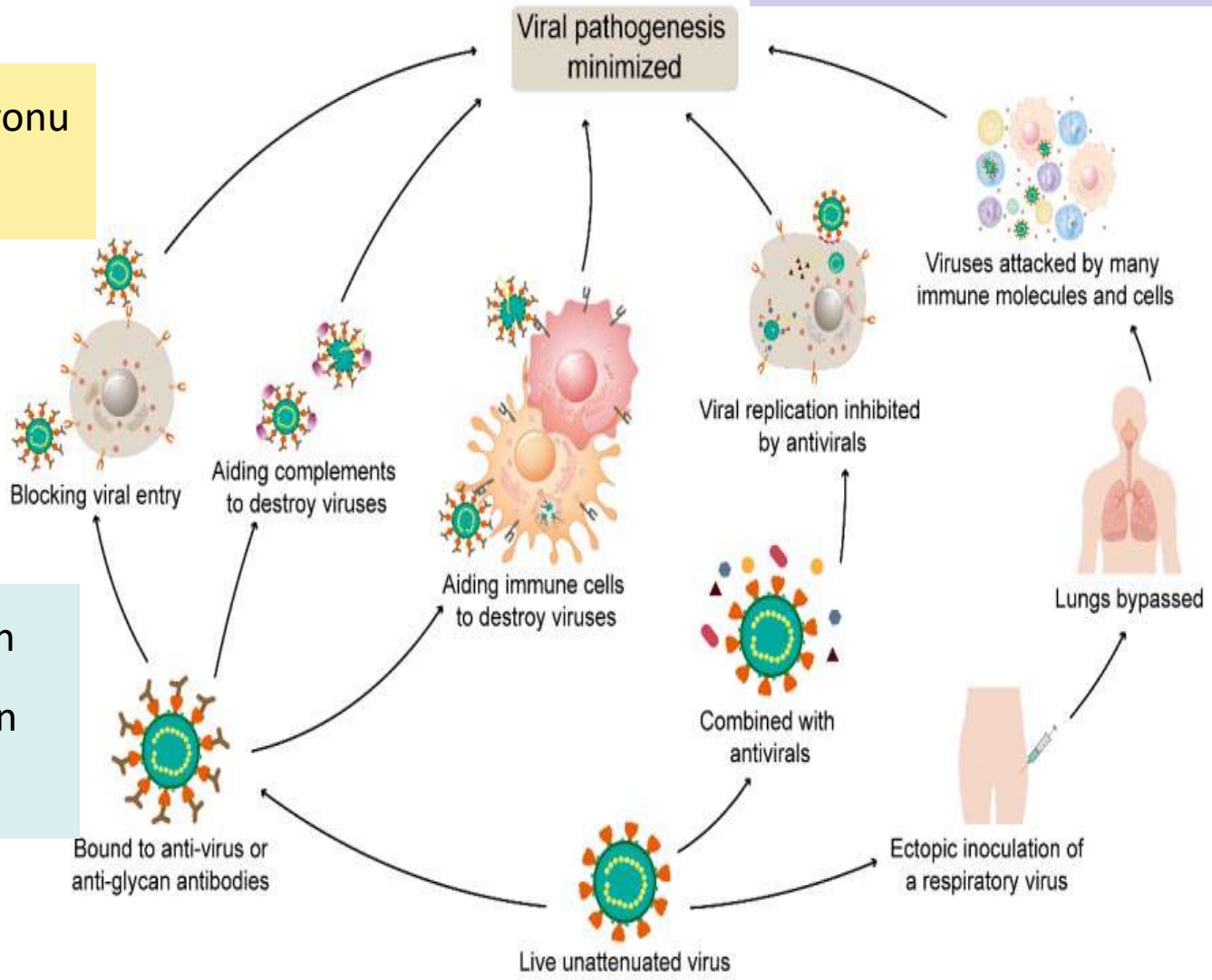
Live unattenuated vaccines for controlling viral diseases, including COVID-19

Ji-Ming Chen [1]

Viral patogenezi yavaşlatır

LUV'lar viral replikasyonu inhibe eder

Kazanılmış bağışıklığın yükselmesi için zaman kazanılır



J Med Virol. 2021; 93(4): 1943-9.

Live unattenuated vaccines for controlling viral diseases, including COVID-19

Ji-Ming Chen [1]

- ✓ **Yüksek güvenlikli**; (Antivirus ab) AVA LUV'ler daha güvenlidir, çünkü canlı virus her zaman nötralize edici ile bağlıdır (kelepçeli ve zincirli insanlar gibi) **immün yetmezliği** olanlarda da kullanılabilir.
- ✓ **Yüksek etkinlikte**
- ✓ **Yüksek geliştirme hızı**

Virusun zayıflatılması için ek yüke gerek yok veya patojenik **reversiyon izlenmiyor**.

Sonuçta **LUV**'lar, nötralize edici **anti-virus antikorların**, doğal **anti-glikan antikorların**, antikor olmayan **antivirallerin** seçici kullanımı ve ektopik aşılama ile oldukça güvenli olabileceği kanısındayız.

J Med Virol. 2021; 93(4): 1943-9.

Sonuç olarak;

✓ Canlı aşılar hastalığın **elimine/eradikasyonunda** daha etkilidirler

✓ Diğer aşılardan farklı endojen antijenlerle hem **hümoral** bağışıklığı hem de **hücresel bağışıklığı** uyararak çok daha **etkili** olabilir.

✓ Aşı **maliyeti düşüktür, p**andeminin bitirilmesinde **etkin** rol oynayabilir

✓ Yüksek etkinlikleriyle infeksiyonu güçlü bloke edebilir **aşı kaçışını** veya virülans arttırıcı **mutasyonlarını inhibe** ederler

✓ İnsanlarda **virülanslarına geri dönebilmeleri** ve immün süprese konakta **patojenik** olabilmeleri dezavantajlarıdır

✓ Aşılara herkesin **hakkıdır** ve **eşit erişilebilirlik** sağlanmalıdır.

Doğayla barışık birlikte sağlıkla yaşamak mümkün…