

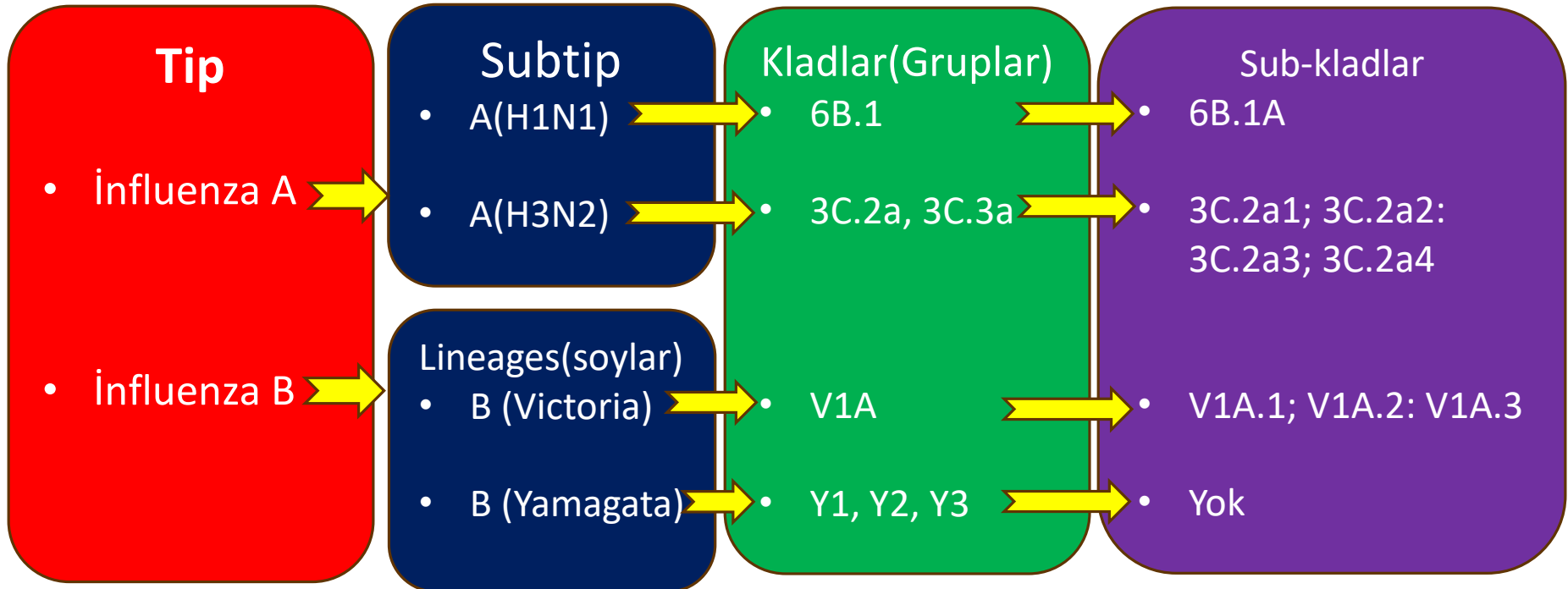
# İnfluenza Aşılarında Yeni Ne Var? Ufukta Neler Var?

Dr. Ali Acar

Bayındır Söğütözü Hastanesi

Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji

# Mevsimsel influenza virüsleri

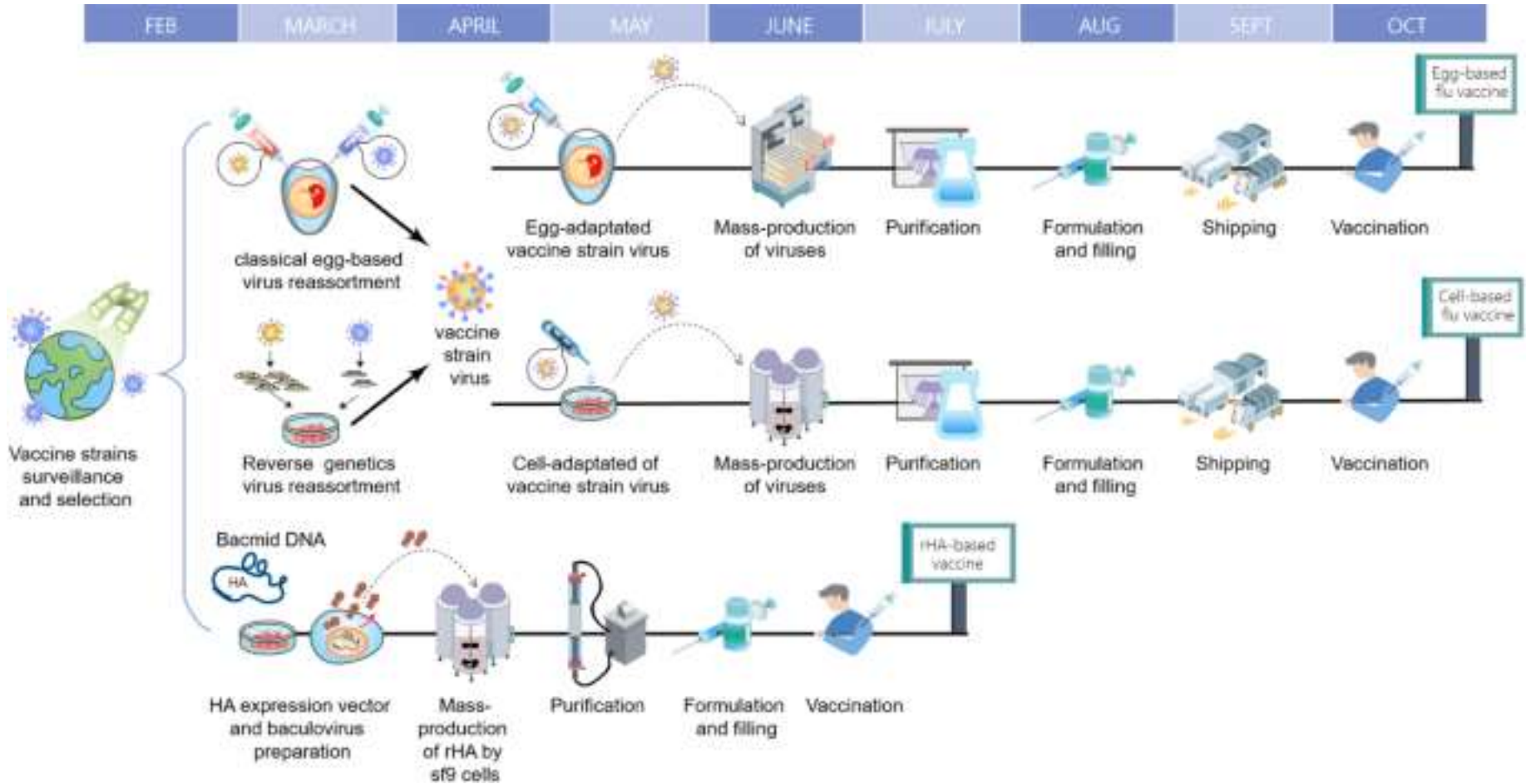


# Influenza Aşıları

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- Yumurta bazlı aşı-1950
  - İnaktive aşı
  - Canlı zayıflatılmış aşı
- Hücre kültür bazlı aşı : 2012 FDA
  - İnaktive aşı
- Rekombinant aşı: 2013 FDA
  - Aday aşı virüsüne ihtiyaç yok
  - Sentetik olarak oluşturulur
  - HA geni – baculovirus ile kombine edilir (rekombinant baculovirus)
  - RV konak hücre hattına girdiğinde HA sentezi talimatı verir

# Günümüzde aşı üretimi



# 2023-2024 Aşı Suşları

## Kuadrivalan yumurta bazlı

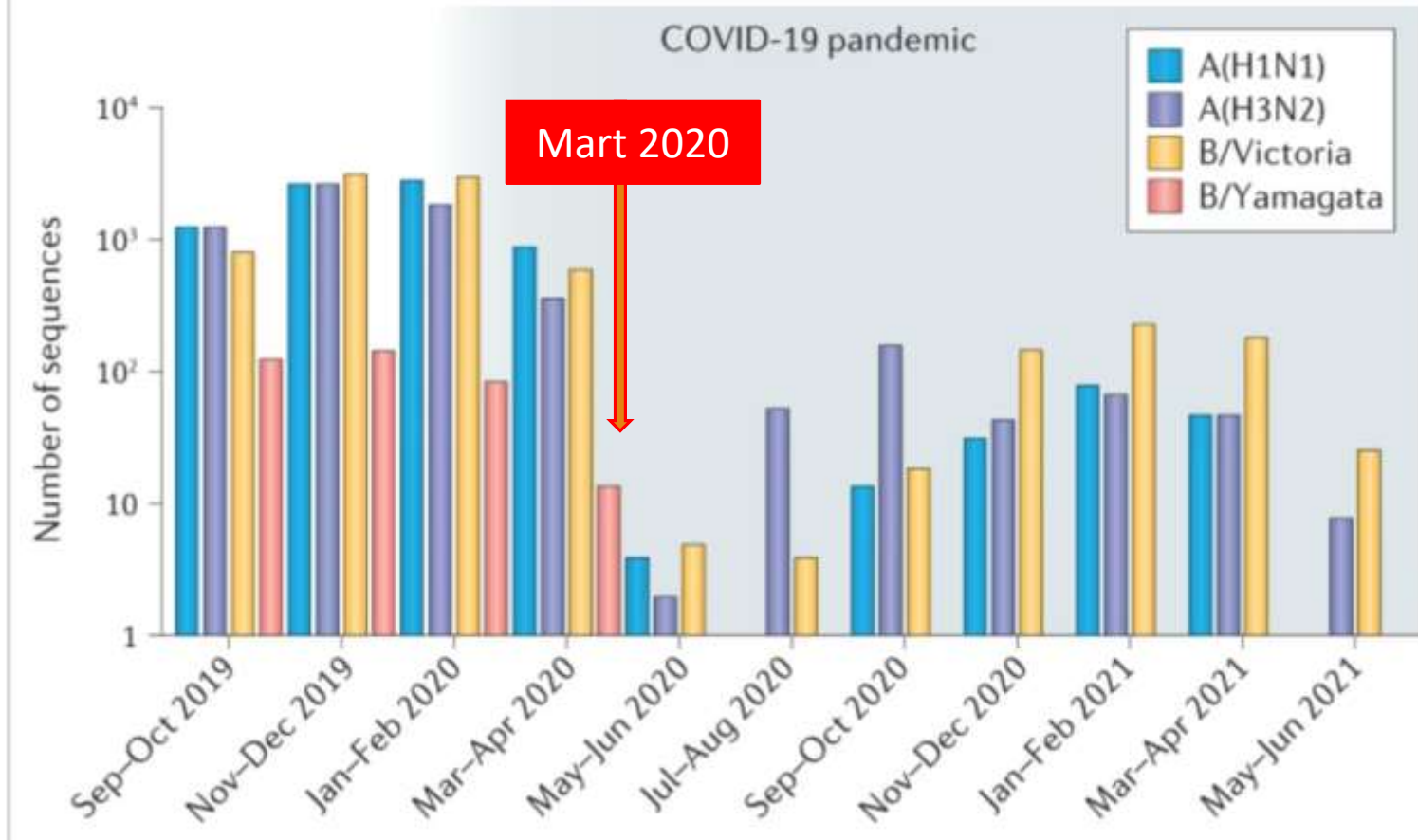
- H1N1 = A/Victoria/4897/2022; hafif değişiklik A/Victoria/2570/2019
- H3N2 = A/Darwin/9/2021; hafif değişiklik A/Darwin/6/2021
- B Victoria = B/Austria/1359417/2021; Değişiklik yok
- B Yamagata = B/Phuket/3073/2013; Değişiklik yok

## Kuadrivalan hücre veya rekombinant

- H1N1 pdm09 = A/Wisconsin/67/2022; hafif değişiklik A/Wisconsin/588/2019
- H3N2 = A/Darwin/6/2021; Değişiklik yok
- B Victoria = B/Austria/1359417/2021; Değişiklik yok
- B Yamagata = B/Phuket/3073/2013; Değişiklik yok

# B/Yamagata eredike edildi ?

**Fig. 1: Circulation of influenza viruses before and during the COVID-19 pandemic.**



# 2024-2025 Aşı Suşları

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## Yumurta bazlı aşı

- H1N1= A/Victoria/4897/2022 (H1N1)pdm09-like virus;
- H3N2= A/Thailand/8/2022 (H3N2)-like virus;
- B Victoria=B/Austria/1359417/2021 -like virus.

## Hücre kültürü veya rekombinat bazlı aşı

- H1N1 pdm09=A/Wisconsin/67/2022-like virus
- H3N2= A/Massachusetts/18/2022 -like virus
- B Victoria= a B/Austria/1359417/2021-like virus.

# DSÖ Küresel Grip Gözetim ve Müdahale Sistemi (GISRS)

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# Grip aşısını iyileştirme çabalarının uzun vadeli hedefi nedir?

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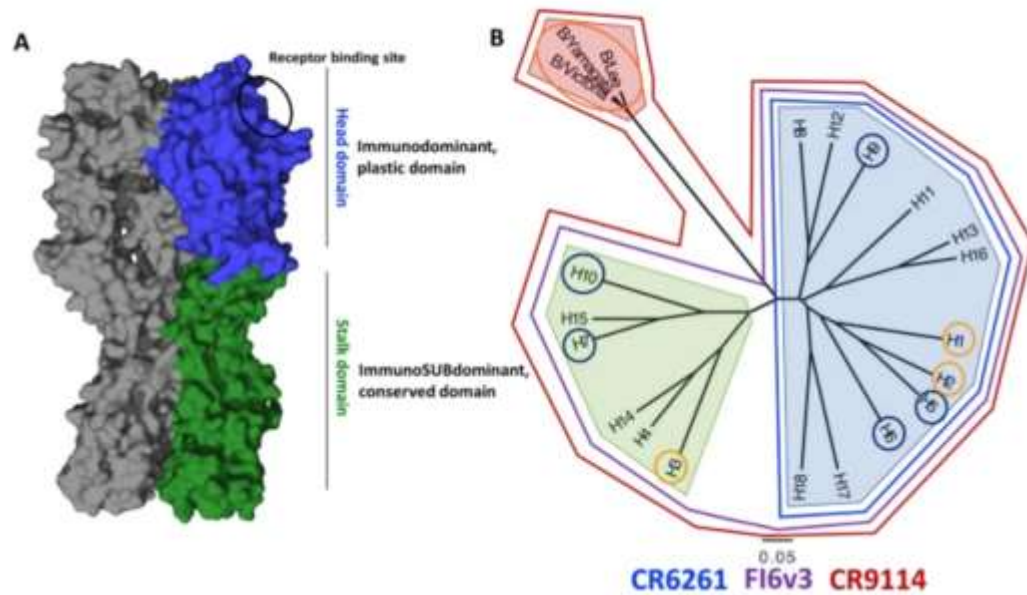
## □ Yeni Aşı Teknolojileri:

- Yumurta bazlı grip aşısı üretim yöntemlerine olan bağımlılığı azaltmak,
- Yeni grip salgınlarına ve pandemilerine daha hızlı yanıt vermek için kullanılacak daha **yeni aşı üretim teknolojilerini** benimsemek

- **Evrensel Grip Aşısı:** Hem mevsimsel hem de yeni (olası pandemik) olmak üzere geniş bir grip virüsü yelpazesine karşı **güvenli, etkili ve uzun süreli bağışıklık** (yani, birden fazla grip mevsimi süren bağışıklık) sağlayacak tek bir grip aşısının **"evrensel grip aşısı"** geliştirilmesi

# HA kuyruk kısmı aşı hedefi olabilir

Figure 1



## Anti-Stalk mAb

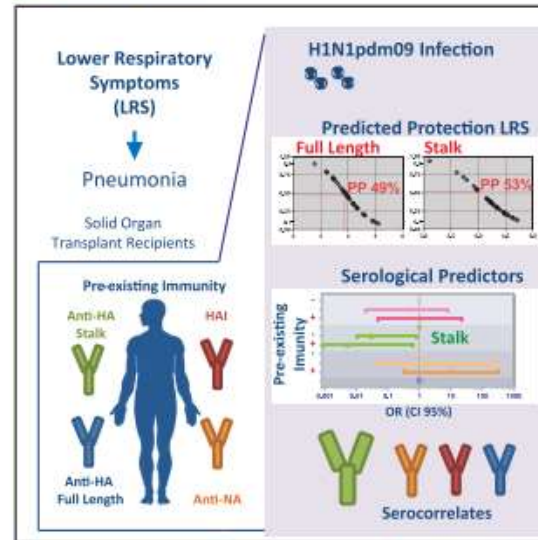
- CR6261 (pan-grup 1 mAb),
- FI6v3 (pan-influenza A mAb)
- CR9114 (pan-influenza A ve B mAb)

Ericka Kirkpatrick. The influenza virus hemagglutinin head evolves faster than the stalk domain. *Nature. Sci Rep* **8**, 10432 (2018).

HA k

# Pre-existing Hemagglutinin Stalk Antibodies Correlate with Protection of Lower Respiratory Symptoms in Flu-Infected Transplant Patients

## Graphical Abstract



## Authors

Teresa Aydillo, Alba Escalera, Shirin Strohmeier, ..., Florian Krammer, Adolfo García-Sastre, Elisa Cordero

## Correspondence

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## In Brief

Aydillo et al. identify lower respiratory symptoms (LRSs) as a predictor of influenza pneumonia in a cohort of transplant recipients. When pre-existing immunity was characterized, the levels of anti-HA stalk antibodies correlated independently with protection from lower respiratory infection.

## Highlights

- Solid organ transplant recipients (SOTRs) had low levels of HAI antibodies at baseline
- SOTRs have high levels of pre-existing, broadly cross-reactive anti-HA stalk antibodies
- Anti-HA stalk antibodies correlate with lack of lower respiratory symptoms in SOTRs
- Presence of lower respiratory symptoms is associated with influenza pneumonia



Aydillo et al., 2020, Cell Reports Medicine 1, 100130  
November 17, 2020 © 2020 The Authors.  
<https://doi.org/10.1016/j.xcrm.2020.100130>





Global Funders Consortium For  
Universal Influenza Vaccine  
Development

<https://unifluvac.org/>

Evrensel Grip Aşısı  
Geliştirilmesi için Küresel  
Fon Sağlayıcılar  
Konsorsiyumu -2017



## Evrensel Grip Aşısı Teknolojileri

### TRACKER



PRECLINICAL	PHASE 1	PHASE 2	PHASE 3	APPROVED
Platform: Influenza virus-based				
<b>14</b> Vaccines in Preclinical	<b>2</b> Vaccines in Phase 1	<b>3</b> Vaccines in Phase 2	<b>0</b> Vaccines in Phase 3	<b>0</b> Vaccines in Approved
<div style="border: 1px solid #ccc; padding: 2px; margin-bottom: 5px;"> <small>DEV</small> Beijing Institute of ...  <small>NAME</small> RSM2eFP spore vaccine         </div> <div style="border: 1px solid #ccc; padding: 2px; margin-bottom: 5px;"> <small>DEV</small> Chinese Academy of Sciences ...  <small>NAME</small> PROTAC         </div> <div style="border: 1px solid #ccc; padding: 2px; margin-bottom: 5px;"> <small>DEV</small> Gamma Vaccines (Australia)  <small>NAME</small> GammaFlu         </div> <div style="border: 1px solid #ccc; padding: 2px; margin-bottom: 5px;"> <small>DEV</small> Georgia State University (US)  <small>NAME</small> NAe-HA and M2e-HA         </div> <div style="border: 1px solid #ccc; padding: 2px; margin-bottom: 5px;"> <small>DEV</small> Icahn School of Medicine at ...  <small>NAME</small> Mosaic HA-based whole ...         </div> <div style="border: 1px solid #ccc; padding: 2px; margin-bottom: 5px;"> <small>DEV</small> Icahn School of Medicine at ...  <small>NAME</small> ΔN S1 virus         </div> <div style="border: 1px solid #ccc; padding: 2px; margin-bottom: 5px;"> <small>DEV</small> Institute of Experimental ...  <small>NAME</small> LAIV-4M2e         </div> <div style="border: 1px solid #ccc; padding: 2px; margin-bottom: 5px;"> <small>DEV</small> Institute of Experimental ...  <small>NAME</small> Reassortant LAIV with ...         </div> <div style="border: 1px solid #ccc; padding: 2px; margin-bottom: 5px;"> <small>DEV</small> University of Georgia (US)  <small>NAME</small> H1, H3 COBRA IIV         </div> <div style="border: 1px solid #ccc; padding: 2px; margin-bottom: 5px;"> <small>DEV</small> University of Georgia (US)  <small>NAME</small> RAM-IGIP         </div> <div style="border: 1px solid #ccc; padding: 2px; margin-bottom: 5px;"> <small>DEV</small> University of Hong Kong (Hong ...  <small>NAME</small> α-1,3-GT         </div> <div style="border: 1px solid #ccc; padding: 2px;"> <small>DEV</small> University of Oxford (UK)  <small>NAME</small> S-FLU         </div>	<div style="border: 1px solid #ccc; border-radius: 10px; padding: 10px; margin-bottom: 10px;"> <small>DEVELOPER</small>  <b>Codagenix (US)</b>  <small>NAME</small>  <b>CodaVax</b>  <small>STATUS:</small> Active         </div> <div style="border: 1px solid #ccc; border-radius: 10px; padding: 10px;"> <small>DEVELOPER</small>  <b>National Institute of Allergy and Infectious ...</b>  <small>NAME</small>  <b>BPL-1357</b>  <small>STATUS:</small> Active         </div>	<div style="border: 1px solid #ccc; border-radius: 10px; padding: 10px; margin-bottom: 10px;"> <small>DEVELOPER</small>  <b>FluGen (US)</b>  <small>NAME</small>  <b>M2SR</b>  <small>STATUS:</small> Active         </div> <div style="border: 1px solid #ccc; border-radius: 10px; padding: 10px; margin-bottom: 10px;"> <small>DEVELOPER</small>  <b>Icahn School of Medicine at Mount Sinai (US)</b>  <small>NAME</small>  <b>Chimeric HA constructs</b>  <small>STATUS:</small> Active         </div> <div style="border: 1px solid #ccc; border-radius: 10px; padding: 10px;"> <small>DEVELOPER</small>  <b>Vivaldi Biosciences (US)</b>  <small>NAME</small>  <b>deltaFLU</b>  <small>STATUS:</small> Active         </div>		

Platform: Nucleic acid-based

**28** Vaccines  
in Preclinical

DEV	BioNTech (Germany)
NAME	ta-RNA, sa-RNA
DEV	Chinese Academy of Sciences ...
NAME	mHAs
DEV	Chinese Academy of Sciences ...
NAME	Optimized M2e DNA ...
DEV	Chinese PLA General Hospital ...
NAME	HA, NP, and 3M2e mRNA
DEV	Georgia State University (US)
NAME	cGAMP-adjuvanted ...
DEV	Georgia State University (US)
NAME	mRNA LNP prime and ...
DEV	Ghent University (Belgium)
NAME	NP mRNA
DEV	Greenlight Biosciences (US)
NAME	Quadrivalent HA mRNA
DEV	GSK (US)
NAME	SAM-GM-CSF + SAM-NP
DEV	Imperial College London ...
NAME	dbDNA-encoded NA
DEV	Imperial College London ...
NAME	pABOL-formulated saRNA ...
DEV	Jilin University (China)
NAME	HA-F DNA vaccine
DEV	Merck & Co. (US)
NAME	mRNA/LNP vaccine
DEV	National Engineering ...
NAME	H1c-mRNA-LNP
DEV	National Institute for Public Health
NAME	

**6** Vaccines  
in Phase 1

DEVELOPER	Arcturus Therapeutics (US) CSL Seqirus (US)
NAME	sa-RNA (ARCT-2138)
STATUS:	Active
DEVELOPER	CSL Seqirus (US)
NAME	sa-mRNA (SQ012)
STATUS:	Active
DEVELOPER	Moderna (US)
NAME	mRNA-1230
STATUS:	Active
DEVELOPER	National Institute of Allergy and Infectious ...
NAME	DCVC H1 HA mRNA-LNP
STATUS:	Active
DEVELOPER	National Institute of Allergy and Infectious ...
NAME	VRC H1ssF_3928 mRNA-LNP
STATUS:	Active

**5** Vaccines  
in Phase 2

DEVELOPER	GSK (US) CureVac (Germany)
NAME	Multivalent Modified mRNA
STATUS:	Active
DEVELOPER	Moderna (US)
NAME	mRNA-1011 and mRNA-1012
STATUS:	Active
DEVELOPER	Moderna (US)
NAME	mRNA-1020 and mRNA-1030
STATUS:	Active
DEVELOPER	Pfizer (US)
NAME	saRNA
STATUS:	Active
DEVELOPER	Sanofi Pasteur (US)
NAME	mRNA constructs
STATUS:	Active

**4** Vaccines  
in Phase 3

DEVELOPER	Moderna (US)
NAME	mRNA-1010
STATUS:	Active
DEVELOPER	Moderna (US)
NAME	mRNA-1083
STATUS:	Active
DEVELOPER	Pfizer (US)
NAME	Modified mRNA vaccine
STATUS:	Active
DEVELOPER	Pfizer (US) BioNTech (Germany)
NAME	modRNA-based combination
STATUS:	Active

**0** Vaccines  
in Approved

Platform: Non-VLP nanoparticles

**42** Vaccines  
in Preclinical

DEV	Agricultural Research, ...
NAME	M2e/CpG-ODN/TMC
DEV	California Institute of ...
NAME	HA trimers
DEV	Chinese Academy of Sciences ...
NAME	3M2e-rHF nanoparticle
DEV	Chinese Academy of Sciences ...
NAME	NM2e@DDAB/PLA ...
DEV	Fudan University (China)
NAME	M2e-based ...
DEV	Georgia Institute of ...
NAME	Self-assembled protein ...
DEV	Georgia State University (US)
NAME	Double-layered protein ...
DEV	Georgia State University (US)
NAME	HA/GP nanoparticles
DEV	Georgia State University (US)
NAME	ISCOMs/MPLA-adjuvanted ...
DEV	Griffith University ...
NAME	Liposomal peptide ...
DEV	Huazhong Agricultural ...
NAME	3M2e-T4 nanoparticle
DEV	Huazhong Agricultural ...
NAME	Mini-HA-LS Nano-vaccine
DEV	Indian Institute of Science ...
NAME	Adjuvanted ...

**4** Vaccines  
in Phase 1

DEVELOPER	Emergent BioSolutions (US)
NAME	EBS-UFV-001 (UFluA)
STATUS:	Active
DEVELOPER	National Institute of Allergy and Infectious ...
NAME	FluMos self-assembling nanoparticle
STATUS:	Active
DEVELOPER	National Institute of Allergy and Infectious ...
NAME	HA2 HA-ferritin nanoparticle
STATUS:	Active
DEVELOPER	National Institute of Allergy and Infectious ...
NAME	Stabilized headless HA stem nanoparticles
STATUS:	Active

**1** Vaccines  
in Phase 2

DEVELOPER	Osivax (France)
NAME	OVX836
STATUS:	Active

**2** Vaccines  
in Phase 3

DEVELOPER	Novavax (US)
NAME	CIC Vaccine
STATUS:	Active
DEVELOPER	Novavax (US) Emergent BioSolutions (US)
NAME	Nano-Flu (qNIV)
STATUS:	Active

**0** Vaccines  
in Approved

Platform: Recombinant proteins

**39** Vaccines  
in Preclinical

- DEV Academia Sinica (Taiwan)  
NAME cHA<sub>mG</sub>
- DEV Chinese Academy of Sciences ...  
NAME M2e-CRM<sub>197</sub> conjugates
- DEV Chinese Academy of Sciences ...  
NAME NMHC
- DEV Chongqing Medical University ...  
NAME rM2e-ΔPly
- DEV Duke University (US)  
NAME S<sub>bmut</sub> HA
- DEV Georgia State University (US)  
NAME M2e-H3 stalk
- DEV Ghent University (Belgium)  
NAME rNA antigens
- DEV Helmholtz Centre for ...  
NAME rNP plus BPPcysMPEG
- DEV Icahn School of Medicine at ...  
NAME Mosaic and Chimeric HA
- DEV Icahn School of Medicine at ...  
NAME N2-MPP
- DEV Korea Research Institute of ...  
NAME 3M2e-3HA2-NP chimeric ...
- DEV Korea Research Institute of ...  
NAME nM2Pr

**1** Vaccines  
in Phase 1

DEVELOPER  
**Sumitomo Pharma (Japan)  
National Institutes of  
Biomedical Innovation, ...**  
NAME  
**fH1/DSP-0546LP**  
STATUS: Active

**3** Vaccines  
in Phase 2

DEVELOPER  
**ConserV Bioscience (UK)  
Imutex (UK)**  
NAME  
**FLU-v**  
STATUS: Active

DEVELOPER  
**Janssen Vaccines and  
Prevention, J&J  
(Netherlands)**  
NAME  
**G1 mHA**  
STATUS: Active

DEVELOPER  
**Immune Targeting Systems  
(Altimmune) (UK)**  
NAME  
**FP-01.1**  
STATUS: Inactive

**1** Vaccines  
in Phase 3

DEVELOPER  
**BiondVax Pharmaceuticals  
(Israel)**  
NAME  
**Multimeric-001 (M-001)**  
STATUS: Inactive

**0** Vaccines  
in Approved



Platform: **Virus-like particles (VLP)**

**28** Vaccines  
in Preclinical

**2** Vaccines  
in Phase 1

**0** Vaccines  
in Phase 2

**1** Vaccines  
in Phase 3

**0** Vaccines  
in Approved

DEV Auburn University (US)  
NAME NA2 VLP

DEV Chinese Academy of Sciences ...  
NAME HBc VLPs

DEV Emory University (US)  
NAME Hybrid fusion protein ...

DEV Georgia Institute of ...  
NAME Inverted HA VLP

DEV Georgia State University (US)  
NAME HA-VLP-Cyt

DEV Georgia State University (US)  
NAME HA/M1 VLP

DEV Georgia State University (US)  
NAME m-cNA-M2e VLP

DEV Georgia State University (US)  
NAME M2e5x VLP (multiple ...

DEV Georgia State University (US)  
NAME N1 VLP

DEVELOPER  
**Russian Academy of Sciences (Russia)**  
**VA Pharma (Russia)**  
NAME  
**HBc-4M2eh (Uniflu)**

DEVELOPER  
**Ghent University (Belgium)**  
**Sanofi Pasteur (US)**  
NAME  
**M2e-based VLPs (ACAM-FluA)**  
STATUS: Inactive

DEVELOPER  
**Medicago (Canada)**  
NAME  
**Quadrivalent VLP (QVLP)**  
STATUS: Inactive

Platform: Virus-vectored

**25** Vaccines  
in Preclinical

- DEV** Blue Water Biotech (US)  
**NAME** BWV-101
- DEV** China CDC (China)  
**NAME** RVJ-4M2eNP
- DEV** Emergent BioSolutions (US)  
**NAME** MVA-vectored vaccines
- DEV** Ewha Womans University (Korea)  
**NAME** rAd/NP + rAd/HA-M2e
- DEV** Federal Medical-Biological ...  
**NAME** rMVA-k1-k2
- DEV** Food and Drug Administration ...  
**NAME** A/NP+M2-rAd
- DEV** Fudan University (China)  
**NAME** AdC68-CR9114
- DEV** German Center of Infection ...  
**NAME** MVA-NP
- DEV** Health Canada (Canada)  
**NAME** rAd-HA2
- DEV** Icahn School of Medicine at ...  
**NAME** Ad-5-H1
- DEV** Icahn School of Medicine at ...  
**NAME** ChAdOx1 NP+M1 prime, ...
- DEV** Jilin University (China)  
**NAME** rAd-NP-M2e-GFP

**2** Vaccines  
in Phase 1

**DEVELOPER**  
Jenner Institute, University of Oxford (UK)  
**NAME**  
ChAdOx1 NP+M1 and MVA NP+M1 in heterologous prime-boost regimens

**STATUS:** Inactive

**DEVELOPER**  
National Institute of Allergy and Infectious ...  
**NAME**  
Ad4-H5-VTN

**STATUS:** Inactive

**3** Vaccines  
in Phase 2

**DEVELOPER**  
Vaxart (US)  
**NAME**  
VXA-A1.1 oral tablet

**STATUS:** Active

**DEVELOPER**  
Altimmune (US)  
**NAME**  
NasoVAX

**STATUS:** Inactive

**DEVELOPER**  
Barinthus Biotherapeutics (UK)  
**NAME**  
MVA-NP+M1 (VTP-100)

**STATUS:** Inactive

**0** Vaccines  
in Phase 3

**0** Vaccines  
in Approved

PHASE 2	PHASE 3	APPROVED
m: Influenza virus-based		
3 Vaccines in Phase 2	0 Vaccines in Phase 3	0 Vaccines in Approved
<p>DEVELOPER FluGen (US)</p> <p>NAME M2SR</p> <p>STATUS: Active</p>		
<p>DEVELOPER Icahn School of Medicine at Mount Sinai (US)</p> <p>NAME Chimeric HA constructs</p> <p>STATUS: Active</p>		
<p>DEVELOPER Vivaldi Biosciences (US)</p> <p>NAME deltaFLU</p> <p>STATUS: Active</p>		

# FluGen (US)

**Platform kategori:** Influenza virüs tabanlı

**Aşı Platform:** Live-attenuated influenza virus (LAIV) /M2 ion kanalı defisitli tek replikasyonlu aşı virüsü

**Uygulama:** Intranasal

**AdjuVan:** yok

**Durum:** aktif – geliştirilme aşamasında

**-Hayvan çalışması:** M2SR, vahşi tip influenza virüsünün tek bir replikasyon döngüsünü taklit eder, ancak bulaşıcı bir virüs üretilmez, bu da hayvan modellerinde geniş spektrumlu koruma sağlar

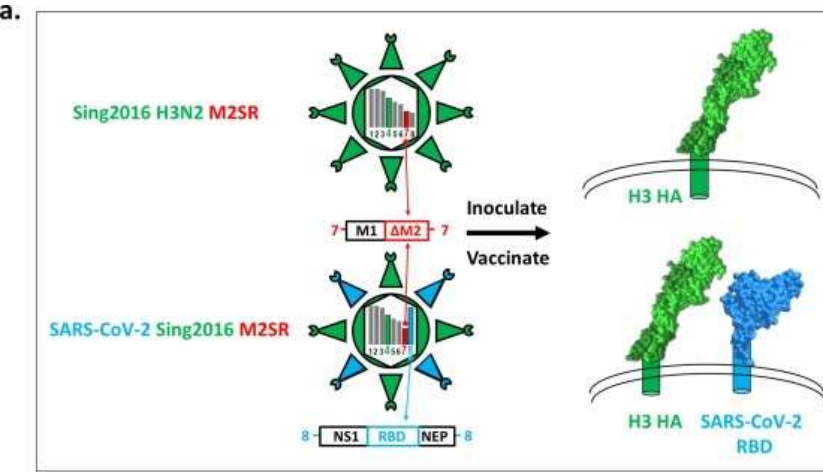
**Quad M2SR aşı** korunmuş HA kuyruk epitoplara çapraz reaktivite geliştirir, aşı içeriğinde olmayan suşlarda dahil multivalan koruma sağlar *Lindsay Hill-Batorski. Vaccines 2023*

- (Faz1b): Güvenli, tolare edilebilir >6 ay koruyucu Ab sağlamakta.
  - (Faz 2a): Intranasal **M2SR (M2-Deficient Single Replication)** H3N2 Influenza aşısı yetişkinlerde güçlü serum ve mukozal Ab
- Joseph Eiden.The Journal of Infectious Diseases® 2023;227:103–12*

# Kombine bivalent influenza / SARS-CoV-2 (COVID-19) aşısının klinik öncesi gelişimi devam ediyor



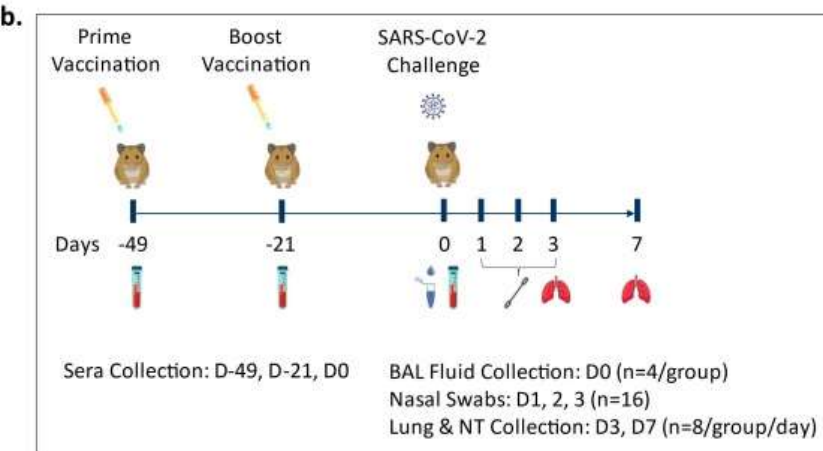
Vaccine  
Volume 42, Issue 11, 19 April 2024, Pages 2770-2780



Mucosal immunization with dual influenza/COVID-19 single-replication virus vector protects hamsters from SARS-CoV-2 challenge

- **Intranazal M2SR SARS-CoV-2**, SARS-CoV-2 infeksiyonuna karşı koruma sağlamada IM-adjuvanlanmış inaktif tam virüs aşısından daha etkili
- Çapraz reaktif mukozal antikorlara ek olarak Wuhan ve Omicron SARS-CoV-2 virüslerine karşı nötralize edici serum antikorları ortaya çıkardı.
- H3N2 M2SR influenza aşısına benzer şekilde influenzaya karşı serum HAI ve mukozal antikor tepkileri üretti.

- Hem influenzaya hem de COVID'e karşı koruma sağlama potansiyeline sahip



PHASE 2	PHASE 3	APPROVED
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m: Influenza virus-based

**3** Vaccines in Phase 2

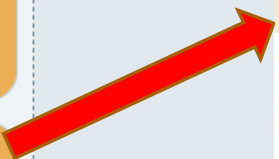
**0** Vaccines in Phase 3

DEVELOPER  
FluGen (US)  
NAME  
M2SR  
STATUS: Active

DEVELOPER  
Icahn School of Medicine at Mount Sinai (US)  
NAME  
Chimeric HA constructs  
STATUS: Active

DEVELOPER  
Vivaldi Biosciences (US)  
NAME  
deltaFLU  
STATUS: Active

**Platform Category:** Influenza virus-based  
**Vaccine Platform:** Chimeric HA (cHA)  
**Delivery Mechanism:** Intranasal  
**Adjuvant:** Aluminum salts: ASO3A  
**R&D Status:** Active  
*Currently in development*



## A chimeric haemagglutinin-based universal influenza virus vaccine boosts human cellular immune responses directed towards the conserved haemagglutinin stalk domain and the viral nucleoprotein

Carly M. Bliss,<sup>1,2</sup> Raffael Nachbagauer,<sup>3,4</sup> Chiara Mariottini,<sup>5,6</sup> Frans Cuevas,<sup>7</sup> Jodi Feser,<sup>8</sup> Abdi Naficy,<sup>9,10</sup> David I. Bernstein,<sup>11</sup> Jeffrey Guptill,<sup>1,2</sup> Emmanuel B. Walter,<sup>3</sup> Francesco Berlanda-Scorza,<sup>12</sup> Bruce L. Innis,<sup>6</sup> Adolfo Garcia-Sastre,<sup>13,14,15</sup> Peter Palese,<sup>16</sup> Florian Krammer,<sup>17,18</sup> and Lynda Coughlan<sup>19,20\*</sup>

**Background** The development of a universal influenza virus vaccine, to protect against both seasonal and pandemic influenza A viruses, is a long-standing public health goal. The conserved stalk domain of haemagglutinin (HA) is a promising vaccine target. However, the stalk is immunosubdominant. As such, innovative approaches are required to elicit robust immunity against this domain. In a previously reported observer-blind, randomised placebo-controlled phase I trial (NCT03300050), immunisation regimens using chimeric HA (cHA)-based immunogens formulated as inactivated influenza vaccines (IIV) +/- AS03 adjuvant, or live attenuated influenza vaccines (LAIV), elicited durable HA stalk-specific antibodies with broad reactivity. In this study, we sought to determine if these vaccines could also boost T cell responses against HA stalk, and nucleoprotein (NP).

**Methods** We measured interferon- $\gamma$  (IFN- $\gamma$ ) responses by Enzyme-Linked ImmunoSpot (ELISpot) assay at baseline, seven days post-prime, pre-boost and seven days post-boost following heterologous prime:boost regimens of LAIV and/or adjuvanted/unadjuvanted IIV-cHA vaccines.

**Findings** Our findings demonstrate that immunisation with adjuvanted cHA-based IIVs boost HA stalk-specific and NP-specific T cell responses in humans. To date, it has been unclear if HA stalk-specific T cells can be boosted in humans by HA-stalk focused universal vaccines. Therefore, our study will provide valuable insights for the design of future studies to determine the precise role of HA stalk-specific T cells in broad protection.

**Interpretation** Considering that cHA-based vaccines also elicit stalk-specific antibodies, these data support the further clinical advancement of cHA-based universal influenza vaccine candidates.

PHASE 2	PHASE 3	APPROVED
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m: Influenza virus-based

**3** Vaccines  
in Phase 2

**0** Vaccines  
in Phase 3

DEVELOPER  
FluGen (US)  
NAME  
M2SR

STATUS: Active

DEVELOPER  
Icahn School of Medicine at  
Mount Sinai (US)  
NAME  
Chimeric HA constructs

STATUS: Active

DEVELOPER  
Vivaldi Biosciences (US)  
NAME  
deltaFLU

STATUS: Active

**Platform Category:** Influenza virus-based

**Vaccine Platform:** Chimeric HA (cHA)

**Delivery Mechanism:** Intranasal

**Adjuvant:** Aluminum salts: ASO3A

**R&D Status:** Active

*Currently in development*

**A chimeric haemagglutinin-based universal influenza virus vaccine boosts human cellular immune responses directed towards the conserved haemagglutinin stalk domain and the viral nucleoprotein**

*Carly M. Bliss,<sup>1,2</sup> Raffael Nachbagauer,<sup>3,4</sup> Chiara Mariottini,<sup>5,6</sup> Frans Cuevas,<sup>7</sup> Jodi Feser,<sup>8</sup> Abdi Naficy,<sup>9,10</sup> David I. Bernstein,<sup>11</sup> Jeffrey Guptill,<sup>1,2</sup> Emmanuel B. Walter,<sup>3</sup> Francesco Berlanda-Scorza,<sup>12</sup> Bruce L. Innis,<sup>6</sup> Adolfo Garcia-Sastre,<sup>13,14,15</sup> Peter Palese,<sup>16</sup> Florian Krammer,<sup>17,18</sup> and Lynda Coughlan,<sup>19,20\*</sup>*

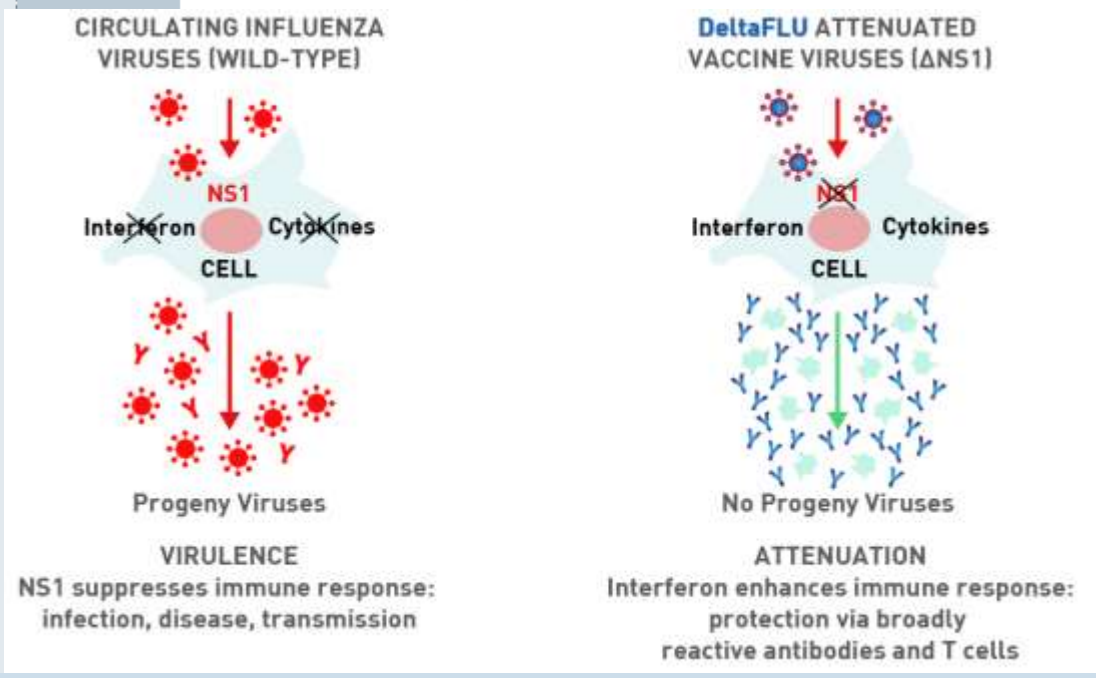
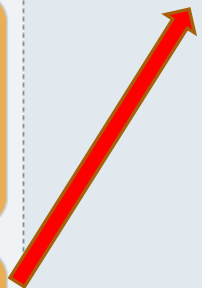
- **Faz-1:** Kimerik HA temelli inaktive (adjuvanlı – ASO3/adjuvansız) aşı, veya canlı aşuların geniş reaktiveli ve uzun süreli HA kuyruk spesifik Ab geliştirdiği gösterilmiştir.
- **Faz-2:** HA kuyruk ve NP karşı T-hücre yanıtı araştırıldı
- cHA bazlı IIVs, insanda **stalk (kuyruk) spesifik ve NP-spesifik T hücre yanıtı oluşturmakta.**
- cHA üniversal aşı adayı

clinical advancement of cHA-based universal influenza vaccine candidates.

PHASE 2	PHASE 3
m: Influenza virus-based	
<b>3</b> Vaccines in Phase 2	<b>0</b> Vaccines in Phase 3
<p>DEVELOPER FluGen (US)</p> <p>NAME M2SR</p> <p>STATUS: Active</p>	
<p>DEVELOPER Icahn School of Medicine at Mount Sinai (US)</p> <p>NAME Chimeric HA constructs</p> <p>STATUS: Active</p>	
<p>DEVELOPER Vivaldi Biosciences (US)</p> <p>NAME deltaFLU</p> <p>STATUS: Active</p>	

Avrupa Birliği, Vivaldi Biosciences ve önde gelen akademik ve endüstri ortaklarından oluşan bir konsorsiyum olan FLUniversal aracılığıyla **DeltaFLU** evrensel grip aşısının klinik gelişimini finanse ediyor.

**Delta Flu** influenza **NS1 genin** delesyonuna dayalı klinik geliştirme aşmasındaki tek aşı.  
Virülans genin çıkartılması atenüasyon, hızlı etki, IFN indüksiyonu

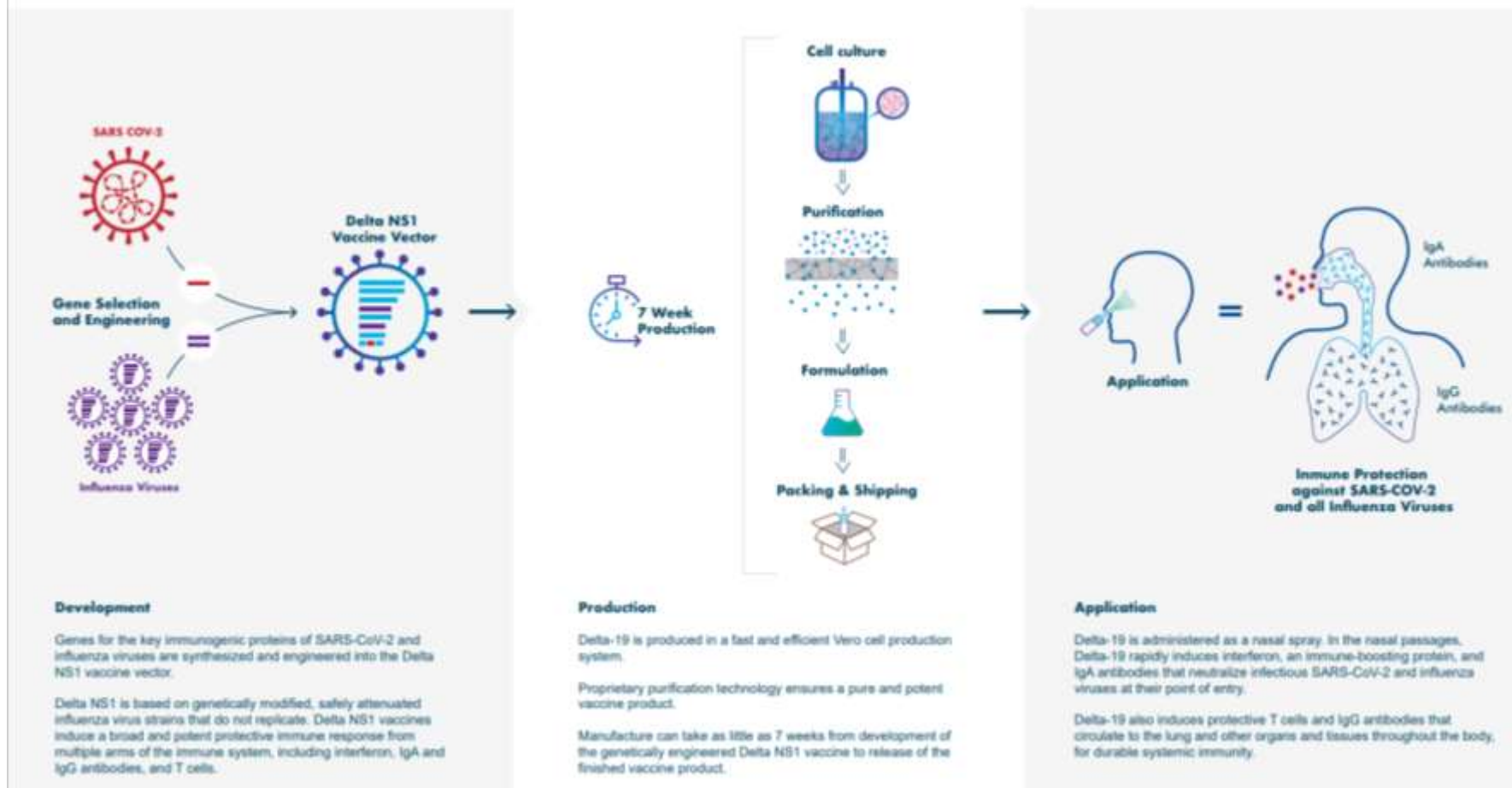


**Platform Category:** Influenza virus-based  
**Vaccine Platform:** Replication-deficient LAIV  
**Delivery Mechanism:** Intranasal  
**Adjuvant:** Self-adjuvanted  
**R&D Status:** Active  
*Currently in development*

Rathnasinghe, R. Interferon mediated prophylactic protection against respiratory viruses conferred by a prototype live attenuated influenza virus vaccine lacking non-structural protein 1. Nature Scientific Reports. 2021.

# Delta-19 (SARS-CoV-2 (COVID-19) + evrensel influenza) kombinasyon aşısı klinik öncesi geliştirme aşamasında.

## Covid-19 + Universal Influenza Combination Vaccine



[Vivaldi Delta-19 Website](#), [Delta-19 Infographic](#), [Press release 7-13-2022](#); [Press release 7-13-2022](#); [Press release 11-29-2021](#); [Press release 10-6-2021](#); [Press release 11-23-2020](#)



Platform: Nucleic acid-based

**28** Vaccines  
in Preclinical

DEV	BioNTech (Germany)
NAME	ta-RNA, sa-RNA
DEV	Chinese Academy of Sciences ...
NAME	mHAs
DEV	Chinese Academy of Sciences ...
NAME	Optimized M2e DNA ...
DEV	Chinese PLA General Hospital ...
NAME	HA, NP, and 3M2e mRNA
DEV	Georgia State University (US)
NAME	cGAMP-adjuvanted ...
DEV	Georgia State University (US)
NAME	mRNA LNP prime and ...
DEV	Ghent University (Belgium)
NAME	NP mRNA
DEV	Greenlight Biosciences (US)
NAME	Quadrivalent HA mRNA
DEV	GSK (US)
NAME	SAM-GM-CSF + SAM-NP
DEV	Imperial College London ...
NAME	dbDNA-encoded NA
DEV	Imperial College London ...
NAME	pABOL-formulated saRNA ...
DEV	Jilin University (China)
NAME	HA-F DNA vaccine
DEV	Merck & Co. (US)
NAME	mRNA/LNP vaccine
DEV	National Engineering ...
NAME	H1c-mRNA-LNP
DEV	National Institute for Public Health
NAME	

**6** Vaccines  
in Phase 1

DEVELOPER	Arcturus Therapeutics (US) CSL Seqirus (US)
NAME	sa-RNA (ARCT-2138)
STATUS:	Active
DEVELOPER	CSL Seqirus (US)
NAME	sa-mRNA (SQ012)
STATUS:	Active
DEVELOPER	Moderna (US)
NAME	mRNA-1230
STATUS:	Active
DEVELOPER	National Institute of Allergy and Infectious ...
NAME	DCVC H1 HA mRNA-LNP
STATUS:	Active
DEVELOPER	National Institute of Allergy and Infectious ...
NAME	VRC H1ssF_3928 mRNA-LNP
STATUS:	Active

**5** Vaccines  
in Phase 2

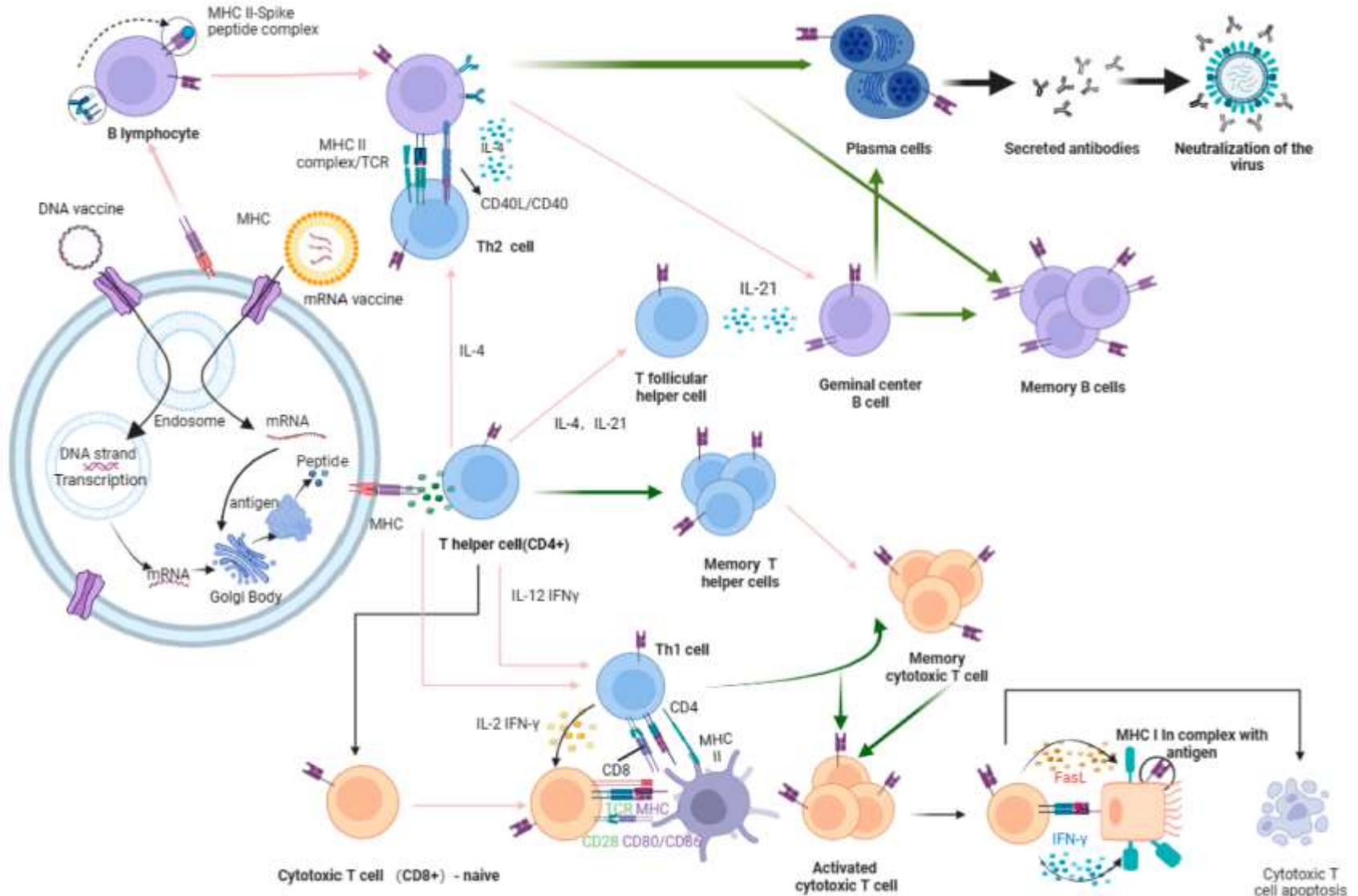
DEVELOPER	GSK (US) CureVac (Germany)
NAME	Multivalent Modified mRNA
STATUS:	Active
DEVELOPER	Moderna (US)
NAME	mRNA-1011 and mRNA-1012
STATUS:	Active
DEVELOPER	Moderna (US)
NAME	mRNA-1020 and mRNA-1030
STATUS:	Active
DEVELOPER	Pfizer (US)
NAME	saRNA
STATUS:	Active
DEVELOPER	Sanofi Pasteur (US)
NAME	mRNA constructs
STATUS:	Active

**4** Vaccines  
in Phase 3

DEVELOPER	Moderna (US)
NAME	mRNA-1010
STATUS:	Active
DEVELOPER	Moderna (US)
NAME	mRNA-1083
STATUS:	Active
DEVELOPER	Pfizer (US)
NAME	Modified mRNA vaccine
STATUS:	Active
DEVELOPER	Pfizer (US) BioNTech (Germany)
NAME	modRNA-based combination
STATUS:	Active

**0** Vaccines  
in Approved

# Nükleik Asit Temelli Aşı Etki Mekanizması



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## NEWS RELEASES

Monday, May 15, 2023

# Clinical trial of mRNA universal influenza vaccine candidate begins

# Moderna (US) mRNA-1010

## Moderna's Respiratory Vaccines (Pipeline 1/3)

Modality	Program	ID #	Preclinical development	Phase 1	Phase 2	Phase 3	Commercial	Moderna rights	
Adults	COVID-19 vaccine	Spikevax®						Worldwide	
		mRNA-1283	Next generation (2-5 °C)					Worldwide	
	Flu vaccine	mRNA-1010						Worldwide	
		mRNA-1020						Worldwide	
		mRNA-1030						Worldwide	
		mRNA-1011						Worldwide	
		mRNA-1012						Worldwide	
		mRNA-1345						Worldwide	
	Older adults RSV vaccine	mRNA-1345						Worldwide	
	Flu + COVID vaccine	mRNA-1083						Worldwide	
	Flu + COVID + RSV vaccine	mRNA-1230						Worldwide	
	Flu + RSV vaccine	mRNA-1045						Worldwide	
Infectious disease vaccines	Endemic HCoV vaccine	mRNA-1287						Worldwide	
	Pandemic Flu	mRNA-1018						Worldwide	
	RSV + hMPV vaccine	mRNA-1365						Worldwide	
	Adolescents & Pediatrics	COVID-19 vaccine (adolescents)	mRNA-1273.815	TeenCOVE					Worldwide
		COVID-19 vaccine (pediatrics)	mRNA-1273.815	KidCOVE					Worldwide
		Pediatric RSV vaccine	mRNA-1345						Worldwide



Infectious disease vaccines

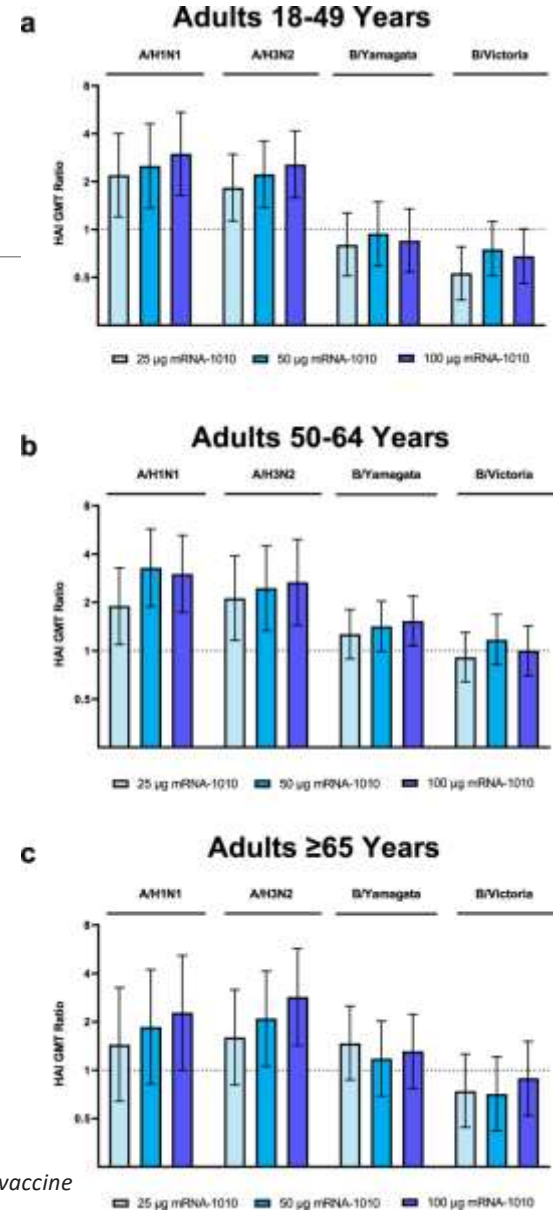
Adolescents & Pediatrics

# Moderna (US) mRNA-1010

- Modifiye edilmiş mRNA tabanlı lipid nanopartikül aşı adayı mRNA-1010 (3. fazda),
- 4 mevsimsel influenza suşundan (A/H1N1, A/H3N2 ve B/Yamagata ve B/Victoria soyları) HA antijenleri içeren dördümlü bir formülasyon

■ 10 -15 Kasım 2021;  $\geq 18$  yaşlarındaki toplam 501 katılımcı,

- tek doz Afluria (IIV) (n = 53) veya mRNA-1010 (25  $\mu$ g, n = 152; 50  $\mu$ g, n = 149; 100  $\mu$ g, n = 147) almak üzere rastgele atandı
- mRNA-1010 (25  $\mu$ g, 50  $\mu$ g veya 100  $\mu$ g), influenza A ve B suşları için standart doz inaktif mevsimsel influenza aşısından daha yüksek HAI titreleri ortaya çıkardı

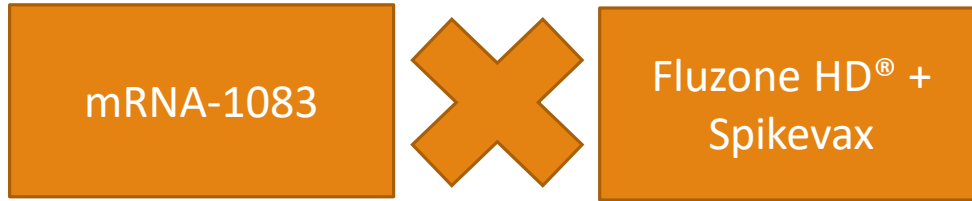


Lee, I. T. Safety and immunogenicity of a phase 1/2 randomized clinical trial of a quadrivalent, mRNA-based seasonal influenza vaccine (mRNA-1010) in healthy adults: interim analysis. *Nat Commun* **14**, 3631 (2023).

# Moderna (US)

## mRNA-1083 (influenza + COVID19 aşısı)

- mRNA-1083, Moderna'nın mevsimsel influenza aşı adayı mRNA-1010 ve Moderna'nın yeni nesil COVID-19 aşı adayı mRNA-1283'ün bileşenlerinden oluşmaktadır.
- >65 yaş ve 18-64 yaş / 40 000



Her iki yaş kohortunda da mRNA-1083, üç influenza virüsü suşuna (H1N1, H3N2 ve B/Victoria) ve SARS-CoV-2'ye karşı **istatistiksel olarak anlamlı derecede daha yüksek** bağışıklık tepkileri ortaya çıkarmıştır.

Kabul edilebilir bir tolere edilebilirlik ve güvenlik profili gösterdi. Yan etkilerin çoğu şiddette 1 veya 2. derecedeydi ve denemede kullanılan lisanslı aşılarla tutarlıydı. En sık YE enjeksiyon bölgesinde ağrı, yorgunluk, miyalji ve baş ağrısıydı.

([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT06097273) Identifier: [NCT06097273](https://clinicaltrials.gov/ct2/show/study/NCT06097273))

# Pfizer (US) BioNTech (Germany) modRNA-based combination

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- SARS-CoV-2'nin *vahşi tip spike proteinini ve Omicron BA.4/BA.5 alt varyantlarının spike proteinini* kodlayan mRNA suşlarının yanı sıra **dört farklı influenza suşunun hemaglütininini** kodlayan mRNA iplikçiklerini içeren kombine mRNA SARS-CoV-2 (COVID-19) ve influenza aşısı.
- Faz 3 randomize, gözlemci körlemesine çalışma
  - Güvenliği, tolere edilebilirliği ve immünojenisitesi
  - 18 - 64 yaş arası 8.000'den fazla yetişkin
- **Sonuç:**
  - Karşılaştırma aşularına kıyasla daha yüksek influenza A yanıtları ve karşılaştırılabilir COVID-19 yanıtları **elde edilmesine rağmen, influenza B suşuna karşı birincil immünojenisite hedeflerinden biri olan non-inferiorite hedefini karşılamamıştır.**
  - *Gözden geçiriliyor* ➤ ([ClinicalTrials.gov](https://clinicaltrials.gov) NCT06178991)

Platform: Non-VLP nanoparticles

**42** Vaccines  
in Preclinical

DEV	Agricultural Research, ...
NAME	M2e/CpG-ODN/TMC
DEV	California Institute of ...
NAME	HA trimers
DEV	Chinese Academy of Sciences ...
NAME	3M2e-rHF nanoparticle
DEV	Chinese Academy of Sciences ...
NAME	NM2e@DDAB/PLA ...
DEV	Fudan University (China)
NAME	M2e-based ...
DEV	Georgia Institute of ...
NAME	Self-assembled protein ...
DEV	Georgia State University (US)
NAME	Double-layered protein ...
DEV	Georgia State University (US)
NAME	HA/GP nanoparticles
DEV	Georgia State University (US)
NAME	ISCOMs/MPLA-adjuvanted ...
DEV	Griffith University ...
NAME	Liposomal peptide ...
DEV	Huazhong Agricultural ...
NAME	3M2e-T4 nanoparticle
DEV	Huazhong Agricultural ...
NAME	Mini-HA-LS Nano-vaccine
DEV	Indian Institute of Science ...
NAME	Adjuvanted ...

**4** Vaccines  
in Phase 1

DEVELOPER	Emergent BioSolutions (US)
NAME	EBS-UFV-001 (UFluA)
STATUS:	Active
DEVELOPER	National Institute of Allergy and Infectious ...
NAME	FluMos self-assembling nanoparticle
STATUS:	Active
DEVELOPER	National Institute of Allergy and Infectious ...
NAME	HA2 HA-ferritin nanoparticle
STATUS:	Active
DEVELOPER	National Institute of Allergy and Infectious ...
NAME	Stabilized headless HA stem nanoparticles
STATUS:	Active

**1** Vaccines  
in Phase 2

DEVELOPER	Osivax (France)
NAME	OVX836
STATUS:	Active

**2** Vaccines  
in Phase 3

DEVELOPER	Novavax (US)
NAME	CIC Vaccine
STATUS:	Active
DEVELOPER	Novavax (US) Emergent BioSolutions (US)
NAME	Nano-Flu (qNIV)
STATUS:	Active

**0** Vaccines  
in Approved









# Platform: Non-VLP nanoparticles

## Novavax (US)

### NAME: CIC Vaccine

## Core vaccine products and pipeline

### Significant opportunities for future development

Disease	Product	Preclinical	Phase 1	Phase 2	Phase 3	Authorized
<b>Novavax Clinical-Stage</b>						
Coronavirus	Novavax COVID-19 Vaccine <sup>1</sup>					
Combination Vaccines	COVID / Influenza					
<b>Partnered Clinical-Stage</b>						
Malaria	R21/Matrix-M adjuvant <sup>2</sup>					

1. Authorized in select geographies under trade names Novavax COVID-19 Vaccine, Adjuvanted; Covavax™; and Nuvaxovid™, and authorized in the U.S. under trade name, Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula); Ongoing post-authorization Phase 3 strain change trial.
2. Authorized in Ghana, Nigeria, and Burkina Faso; Commercialized by Serum Institute of India; Granted prequalification by the WHO.



# Novavax nanopartikül M-adjuvan platformu (6 basamaktan oluşur)

- 1- Hedef gen bölgesinin tespiti (immün yanıtı uyaracak Ag sentezleyecek) ve **Baculovirus** içerisine insersiyonu
- 2- Baculovirus **Sf9 hücre** enfeksiyonu,
- 3- BV içerisindeki rekombinant gen Sf9 hücre nükleusuna girer ve mRNA transkripsiyonu olur
- 4- Sf9 hücreleri rekombinant antijenleri kodlayan mRNA'ları translate eder
- 5- Sf9 hücre yüzeyinde rekombinant antijenler toplanır, saflaştırılır ve **nanopartikül bir kor** ile sarılır
- 6- Rekombinant antijen içeren nanopartiküller **Matriks-M adjuvanıyla** birleştirilir

# Platform: Non-VLP nanoparticles Novavax (US) NAME: CIC Vaccine

## Kombinasyon qNIV/CoV2373 aşısı – hayvan çalışması

- Influenza A ve B suşlarına karşı yüksek titrede influenza HA inhibisyonu (HAI) ve nötralize edici antikorlar üretir.
- SARS-CoV-2 spike proteininin hACE2 reseptörüne bağlanmasını engelleyen antikorlar ortaya çıkarmıştır.
- qNIV/CoV2373 aşısı ile aşılanan ve SARS-CoV-2 ile enfekte edilen **hamsterler** kilo kaybına karşı korunmuş ve viral pnömoni kanıtı olmaksızın üst ve alt solunum yollarında **SARS-CoV-2 replikasyonu görülmemiş**
- qNIV/CoV2373 kombinasyon aşısının mevsimsel influenza ve CoVID-19 karşı etkinliğini desteklemekte

*Combination Respiratory Vaccine Containing Recombinant SARS-CoV-2 Spike and Quadrivalent Seasonal Influenza Hemagglutinin Nanoparticles with Matrix-M Adjuvant. bioRxiv 2021.05.05.442782; doi: <https://doi.org/10.1101/2021.05.05.442782>*

# Sonuç

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- Geniş ve kalıcı koruma sağlayan evrensel bir influenza aşısının geliştirilmesi, halk sağlığı ve pandemi hazırlığının uzun vadeli bir hedefi
- Etkili bir aşı için:
  - Korunmuş bölgelerin daha iyi tespiti
  - Korunmuş bölgelere eklenmiş multivalan antijenleri içeren kimerik formülasyon
  - Etkili adjuvanlarla birlikte kullanım
  - Hem hücresel hem de humoral yanıt oluşturabilme kabiliyeti
- mRNA aşı platformu, suş eşleşmelerini iyileştirebilme, çok değerlikli antijenleri veya korunmuş antijenleri içine alarak ve daha geniş humoral ve güçlü hücresel bağışıklık tepkilerini indükleyebilme kapasitesiyle üniversal aşı için en önemli aday
- COVID19 + infleunza aşıları ön plana çıkabilir