Harnessing the Immune System to Prevent Cancer: Basic Immunologic Mechanisms & Their Application to Clinical Trials of Vaccines

Part 2: The Vaccines

Barbara K. Dunn
NCI/Division of Cancer Prevention
August 3, 2020
Harnessing the Immune System to Prevent Cancer: Basic Immunologic Mechanisms and Therapeutic Approaches that are Relevant to Cancer Prevention

I. Basic immunologic mechanisms

II. Application to prevention & treatment of cancer

   1. Antibodies: as drugs
   2. Vaccines: general principles & your vaccine trials & more…

      I) Vaccines to prevent cancers caused by infectious agents

      II) Vaccines to prevent non-infection associated cancer (directed toward tumor associated antigens)
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   "active immunity"
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KEY COMPONENTS OF VACCINES

the specific component: the Antigen

- Peptide-long vs short

the nonspecific component: the Adjuvant

Adjuvants = agents added to vaccine formulations that enhance the immunogenicity of antigens in vivo

Epitope (antigenic determinant) = the part of an antigen that is recognized by the immune system (antibodies, B cells, T cells); main immunogenic part of the vaccine

VLP

Pentamer of a protein

Cell-based vaccines

Antigen comes from the thing you want to destroy: cancer cell, pathogen

Vaccines - “active immunity”
Adaptive Immune System
Vaccines - “active immunity”
Adaptive Immune System

KEY COMPONENTS OF VACCINES

the specific component:

the Antigen/Epitope

Pentamer of a protein

Peptide-long vs short

Genetic vaccines:
• DNA (encodes a protein)
• RNA vaccines

• Viral vector

the nonspecific component:

the Adjuvant

Platform technology
Vaccines - “active immunity”
Adaptive Immune System

KEY COMPONENTS OF VACCINES

the specific component: the Antigen

the nonspecific component: the Adjuvant

Antigen

Platform

Endpoints:
1) Safety
2) Reactogenicity
3) Immunogenicity:
   - seroconversion: Ab
   - neutralization: Ab
   - CD4, CD8 Tcell

Antigen comes from the thing you want to destroy: cancer cell, pathogen
Vaccines - “active immunity”
Adaptive Immune System

KEY COMPONENTS OF VACCINES

the specific component:

the Antigen

Epitope (antigenic determinant) = the part of an antigen that is recognized by the immune system (antibodies, B cells, T cells)

Peptide-long vs short Pentamer of a protein

the nonspecific component:

the Adjuvant

Adjuvant non-specific stimulation to immune system = INNATE

How do we pick the antigen/epitope to target?

- Non-specific Immuno-Modulators = INNATE only
Harnessing the Immune System to Prevent Cancer: Basic Immunologic Mechanisms and Therapeutic Approaches that are Relevant to Cancer Prevention

I. Overview: Context of immunologic mechanisms: Elicits a specific response from the body’s own immune system:

**Focus on the Antigen!**

II. Structure/physical components and hierarchy of the immune system

I. How immunologic mechanisms are used in medical interventions to treat and prevent cancer

1. Antibodies as drugs “passive immunity”

2. Vaccines: general principles & your vaccine trials
   - I) Vaccines to prevent cancers caused by infectious agents
   - II) Vaccines to prevent non-infection associated cancer (directed toward tumor associated antigens)
Vaccines to prevent cancers caused by infectious agents

Targets a specific antigen = ADAPTIVE

How do we pick the antigen/epitope to target?

The infectious agent is FOREIGN/NON-SELF → pick the antigen from this!
example of antigen(s) derived from infectious agents, HBV, HCV
Vaccines to prevent cancers caused by infectious agents

Pathogenesis of Hepatitis B Virus-Associated Cancer

Infects **350-400 million people** (5% world population)

**Chronic HBV Carriers - incidence of HCC** (hepatocellular carcinoma) ranges from 70% to 90% and nearly 100% in children

Chronic HBV infection and high HBV DNA levels are a strong predictor for cirrhosis and HCC (irrespective of other viral and biochemical factors)

Viral exposure $\rightarrow$ Viral infection $\rightarrow$ Chronic Viral infection $\rightarrow$ Precancer conditions $\rightarrow$ Liver Cancer

Prophylactic vaccine
Focus on the Antigen!

**HBV Vaccines**  
*(hepatitis B virus)*

**HBV vaccine** – **FIRST** vaccine in humans for cancer prevention **(1981)**

-the **Antigen**: hepatitis B surface antigen *(HBsAg)* = a viral envelope protein

- **Pre-exposure prophylaxis/prophylactic vaccine**
- Vaccination with **hepatitis B surface antigen** *(HBsAg)* = a viral envelope protein – made from recombinant DNA, produced in yeast
- Recombivax HB (Merck), Engerix-B (GSK), Elovac B (Human Biologicals Institute, Genevac B (Serum Institute), Shanvac B, etc.

How do we pick the antigen/epitope to target?  
The infectious agent is FOREIGN/NON-SELF → pick the antigen from this!
Infection associated cancer

chronic HCV infection

d example of antigen(s) derived from infectious agent, HCV

no preventive vaccine for HCV
Vaccines to prevent cancers caused by infectious agents

Pathogenesis of Virus-Associated Cancer

*Therapeutic* from an infectious disease standpoint; actually *prophylactic* from a cancer standpoint

Vaccines
No **therapeutic** vaccine for HCV and HBV

**WHY VACCINE FAILURE?** IMPAIRED T CELL RESPONSES

**CHRONIC HCV INFECTIONS**

- Increased number of Tregs
- High IL-10 secretion

**immunoediting**
Phase I Trial of a Therapeutic DNA Vaccine for Chronic Hepatitis C Virus (HCV) Infection

Prior to discussing protocol entry with the participant, call the CPN Registration Office (507-284-4130) between 8:00 a.m. and 4:30 p.m. Central Time Monday through Friday to insure that a place on the protocol is open to the participant.

Study Population (maximum n=32)
Male and female participants with chronic genotype 1 HCV infection with plasma HCV RNA >10,000 IU/ml, who are not currently receiving HCV treatment and not in acute clinical need for HCV treatment, have no documented evidence of cancer, cirrhosis, or extensive bridging fibrosis (Metavir 2, 3, 4), are not HIV-infected, have no other immune-compromising illness or receiving immune-suppressing medications, are not HBV-infected.

Baseline (maximum n=up to 32)
Informed Consent

Pre-Registration (maximum n=up to 32 with a 5% ineligibility rate to obtain 30 eligible for study)
- History and physical
- Laboratory studies

Registration/Sequential Dose Level Assignment
(maximum n=30 for a 20% non-evaluable rate to obtain 24 evaluable for primary endpoint)
Participants will be enrolled in cohorts of 3. See Section 7.3 for details.

Vaccine administration at Day 0, Week 4 (+/-3 days), Week 12 (+/-3 days), and Week 24(+/-7 days)
INO-8000 (6 mg) alone (dose level 0) (starting dose)
INO-8000 (6 mg) with INO-9012 (0.3 mg, dose level 1)
INO-8000 (6 mg) with INO-9012 (1.0 mg, dose level 2)
INO-8000 (6 mg) with INO-9012 (3.0 mg, dose level 3)
(Note: INO-8000 is the HCV antigen DNA; INO-9012 is the IL-12 adjuvant DNA. The HCV DNA vaccine is the combination of INO-8000 alone or in combination with INO-9012.)

1° Endpoint: safety, AEs; immunogenicity: change HCV-specific IFN-Ɣ (wk 26)
Translational Endpoints: virologic response (decrease in HCV RNA level)

Expansion Cohort

Additional participants will be randomized across all dose levels that are deemed safe until 24 participants are treated.

DNA plasmid vaccine platform

HCV genotype 1a/1b consensus DNA vaccine: encoding HCV NS3, NS4A; NS4B, NS5A
Day 0; Weeks 4, 12, 24

Therapeutic HCV vaccine
Infection associated cancer
Antigen
NS3 NS4B NS5a
HPV Vaccines

example of antigen(s) derived from infectious agent, HPV
human papilloma virus - >100 strains:
Some cause cancer - 14 high risk
Some cause warts

Causes:
~100% of cervical cancers
+ head and neck cancers
anal cancers

L1 differs among strains
Vaccines to prevent cancers caused by infectious agents

**HPV VACCINES (HUMAN PAPILLOMAVIRUS)**

Prophylactic (3 FDA Approved HPV vaccines)

- **the Antigen**: virus-like particles (VLP) from major capsid proteins L1 = strain specific

  - Bivalent/Quadrivalent subunit vaccines
    - (HPV 16 and 18 – 70% of cervical cancers)
    - (HPV 6 and 11 – majority of genital warts)

Vaccines 98% effective preventing high-grade cervical lesions

- **Nonavalent** vaccine (V503, Merck) (FDA approval Dec 2014)

  - HPV 6/11/16/18/31/33/45/52/58 – Gardasil 9®
  - Bivalent (HPV 16 and 18) (Xiamen Innovax Biotech Co)

  (China: approved Jan 2, 2020) - Cecolin

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Cervarix® (GSK-bivalent)

Gardasil® (Merck-quadrivalent)

The infectious agent is FOREIGN/NON-SELF → pick the antigen from this!

How do we pick the antigen/epitope to target?
Vaccines to prevent cancers caused by infectious agents

Pathogenesis of HPV-Associated Cancer
& Vaccines to Prevent Cervical Cancer

Viral exposure → Viral infection → Chronic Viral infection → Precancer conditions → Cervical Cancer

Prophylactic vaccine

Cervarix: HPV 16, 18
Gardasil: HPV 16, 18, 6, 11
Gardasil 9: HPV 6/11/16/18/31/33/45/52/58

Lasker-DeBakey Clinical Medical Research Award: John Schiller & Douglas Lowy
Infection associated cancer
Transplant Vaccine
example of antigen(s) derived from infectious agent, HPV
Vaccines to prevent cancers caused by infectious agents

HPV – HUMAN PAPILLOMAVIRUS

Adult solid organ transplant recipients

Immunosuppression

Increased risk of developing several malignancies, especially causally linked to carcinogenic HPV infection:

- Squamous cell carcinoma of: anogenital region
  - [vulva, cervix, penis, vagina]
- naso/oropharynx

Engels 2011 JAMA 306:1891
SCHEMA: Immunogenicity of Nonavalent HPV Vaccine Administered Prior To Renal Transplantation in Adults: A Prospective, Single-Arm, Multi-Center Clinical Trial

Adults planning renal transplant ↓
Gardasil® 9 HPV ≥1 dose L1 VLP ↓
30 days prior to transplantation ↓
1° Objective: immunogenicity: HPV type-specific seroconversion at 12 months post-tx
Control Infectious Agent(s)
Vaccines – prophylactic / therapeutic
Antiviral therapy

Control Infection

Prevent Cancer
Harnessing the Immune System to Prevent Cancer: Basic Immunologic Mechanisms and Therapeutic Approaches that are Relevant to Cancer Prevention

I. Overview of these immunologic mechanisms

II. Structure/physical components of the immune system

III. How immunologic mechanisms are used in medical interventions to treat and prevent cancer

1. Antibodies as drugs --- “passive immunity”

2. Vaccines: general principles – “active immunity”

   I. Vaccines to prevent cancers caused by infectious agents

   II. Vaccines to prevent non-infection associated cancer (directed toward tumor associated antigens)
Vaccines to prevent cancers not caused by infectious agents

Selection of appropriate antigen in non-infection-associated cancers, the antigens are modified normal antigens, taken from cancer cells.

Concern is:
We do not want the immune system to attack the normal cells (don’t want toxicity),
We only want the immune system to attack the cancer cells, which have modified normal antigens.

There is a table on the left:

<table>
<thead>
<tr>
<th>Targets a specific antigen</th>
<th>How do we pick the antigen/epitope to target?</th>
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<tbody>
<tr>
<td>= ADAPTIVE</td>
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</table>

The antigen is from ALTERED SELF cells → tolerance = self vs non-self!
Vaccines to prevent non-infection associated cancer: the Antigen Mechanism of Tumor Antigen:

- Tumor Associated Antigens (TAAs)/ neoantigens → “self”- antigens or normal cellular proteins that become immunogenic during the malignant process

- Mechanisms by which normal cell protein becomes aberrant in cancer (“abnormal-self”)

1- acquisition of mutations (melanoma antigen MAGE1)

2- overexpression of cancer associated proteins (breast cancer HER2/NEU)

3- post-translational modifications (abnormal glycosylation (colon cancer antigen MUC-1))
Non-infection associated cancer

Colorectal Cancer Vaccine

eexample of antigen with abnormal
post-translational modification
Muc1 Expression in Cancers: Normal Muc1

Mucins = large glycoproteins:

O-linked carbohydrates/
Oligosaccharides:
Glycosylated MUC1

Immunohistochemical analysis of paraffin-embedded human colon carcinoma, using MUC1 (VU4H5) Mouse mAb.

Colorectal Cancer - MUC-1
Colorectal Cancer - MUC-1

Cancer-Associated Mucins

Normal MUC-1 Mucin

- Basal Expression in normal ductal epithelial cells:
  - Pancreas, Breast, Lung, Gastrointestinal tract

MUC-1 Cancer Mucin

- Overexpressed & aberrantly glycosylated in most adenocarcinomas, inflammatory diseases, e.g. inflammatory bowel disease (IBD)

O-linked oligosaccharides

Tumor-associated antigen:
Post-translational modification

Exposed core peptide targeted by BLP25 Liposome vaccine

Cell Surface plasma membrane
Vaccination against MUC1 prevents the development of dysplasia and CACC. (A) Percentage of untreated (n=13) and adjuvant treated (n=9) mice with dysplasia at 16 weeks of age.

\[ \text{TnMUC1: 100-mer peptide (five tandem repeats of 20–amino acid sequence)} \]

Untreated mice—many tumors
Randomized, Double-Blind, Placebo-Controlled Trial of MUC1 Vaccine in Patients with Newly Diagnosed Advanced Adenomas

Target population:
- Male and female participants between 40 and 70 years of age
- Recent diagnosis (within 1 year) of ≥1 advanced adenoma defined as: an adenoma ≥ 1 cm in size, or with villous or tubulovillous histology, or with high-grade (or severe) dysplasia.
- Informed Consent

Endpoints: immunogenicity – adenoma recurrence

≥ 1 advanced adenoma

MUC1 vaccine (peptide) placebo

weeks 0, 2, 10, 53

Endpoints:
- Immunogenicity: IgG anti-MUC1 antibody titer
- Week156- adenoma recurrence

Endpoints:  immunogenicity – adenoma recurrence
Non-infection associated cancer

Breast Cancer Vaccines

despite examples of antigen that is overexpressed in cancer
Breast Cancer - **HER2/NEU, IGF1R, IGFBP-2**

3 antigens **overexpressed** in breast cancer

- Overexpressed DCIS, ER-
- **HER2**
- **EGF, EFG, TGF α**
- **HB-EGF, AR, EPR, β-cellulin**
- **IGFBP-2**
- Overexpressed in hyperplasia/DCIS
- LUMINAL: ER+

- **IGFIR**
- Overexpressed in hyperplasia/DCIS
- LUMINAL AND TN: ER-HER2-
Breast Cancer - HER2/NEU, IGF1R, IGFBP-2-positive
BREAST CANCER IMMUNOPREVENTION
TARGETING [ HER2/NEU + IGF1R + IGFBP-2 ]

Vaccination to prevent disease onset

1. Interferon-γ secreting cells
ELISPOT assay

2. Tumor-free

3. Survival

- Overexpressed DCIS, ER-
- HER2+

- Overexpressed in hyperplasia/DCIS
- LUMINAL AND TN: ER-HER2

- Overexpressed in hyperplasia/DCIS
- LUMINAL: ER+

- Hyperplasia-DCIS-IDC
- neu, IGFBP-2, IGF-IR high, ER low, PTEN low
- Resistant to chemotherapy, neuMoAb

- Tri-antigen 8 epitope vaccine 100% homology

Data courtesy of Dr. Mary Disis (CADRG/PREVENT Cancer Program)

Vaccinated at 18 weeks, n=15/group

Park et al Ca Res, 2008; Cecil et al, 2011
**MDACC2014-04-02**

**VADIS 1/BREAST**

**SCHEMA**

VADIS Trial: Phase II trial of the Nelipepimut-S Peptide Vaccine in Women with DCIS of the Breast

Pre- or post-menopausal women with DCIS on core biopsy

Baseline Testing/Prestudy Evaluation (within 30 days prior to randomization)
Screening visit informed consent, registration, screening for eligibility including HLA typing, cardiac evaluation

Randomization
Eligibility confirmation (the trial is limited to HLA-A2 positive participants), randomization

<table>
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<tr>
<th>Nenvax™ (nelipepimut-S+ GM-CSF); 32 randomized / 27 evaluable</th>
<th>GM-CSF alone (Control); 16 randomized / 13 evaluable</th>
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</table>

**Intervention:**

- Vaccine 1 (day 0)
  - Blood draw
- Vaccine 2 (day 14 +/- 3 days)
- Surgery (day 28 +/- 5 days)

**DCIS on CORE Bx**

↓

VADIS (Nelipepimut-S Peptide vaccine: HER2 9aa)

↓

3 monthly vaccinations

↓

1° Endpoint: safety

2° Endpoint: immunogenicity: Th1, Th2

---

**UWI2014-03-01**

**WOKVAC/Breast**

**SCHEMA**

A Phase I Trial of the Safety and Immunogenicity of a DNA Plasmid Based Vaccine (WOKVAC) Encoding Epitopes Derived From Three Breast Cancer Antigens (IGFBP-2, HER2, and IGF-1R) in Patients with Breast Cancer

Patients with non-metastatic, node positive, HER2 negative breast cancer that is in remission and defined as no evidence of disease (NED). Patients must have a good performance status, be at least 28 days from last cytotoxic chemotherapy and/or radiotherapy and 28 days from any use of systemic steroids.

Baseline Visit:

- Physical examination, baseline symptom assessments, ECHO/MUGA, and Clinical Labs

Sequential assignment to one of three dose arms:

- Arm 1: WOKVAC (150 mcg) with Sargramostim (rhuGM-CSF) (100 mcg)
- Arm 2: WOKVAC (300 mcg) with Sargramostim (rhuGM-CSF) (100 mcg)
- Arm 3: WOKVAC (600 mcg) with Sargramostim (rhuGM-CSF) (100 mcg)

First Vaccination Visit:

non-metastatic node+ HER2neg NED (in remission)

↓

WOKVAC (DNA plasmid-based vaccine: IGFBP-2, HER2, IGF-1R)

↓

3 monthly vaccinations

↓

1° Endpoint: safety

2° Endpoint: immunogenicity: Th1, Th2

Primary Endpoint:

Safety as assessed by NCI CTCAE v. 4.0.
SUM UP: NON-INFECTION ASSOCIATED CANCER PREVENTION

Vaccines – target a TAA

↓
↓
↓
↓

Prevent Cancer

The antigen derives from an altered cellular protein/TAA/neoantigen – Concern about “self” versus “non-self”
Evaluate vaccines in the states of:

"minimal residual disease"
and Cancer Prevention: Why?

Vaccination early in disease process:

→ **Intact** immune system (**active immunity**)

→ Permissive microenvironment

→ Pre-cancers are smaller lesions

→ Immune mechanisms in early lesions involve CD4+T<sub>H</sub>, IFNγ, Antibodies & Cytotoxic T-Lymphocytes (**CTL**) that fight cancer

**Why are vaccines more promising in cancer prevention (vs treatment)?**

**Immunoediting**
Vaccines - “active immunity”
Adaptive Immune System

KEY COMPONENTS OF VACCINES

the specific component:
the Antigen/Epitope

- Peptide
  - long vs short

- Pentamer of a protein

- Genetic vaccines:
  - DNA (encodes a protein)
  - RNA vaccines
  - Viral vector

the nonspecific component:
the Adjuvant

- Adjuvants = agents added to vaccine formulations that enhance the immunogenicity of antigens in vivo

Vaccines - Genetic vaccines:
- DNA (encodes a protein)
- RNA vaccines
- Viral vector

Viral-like Protein/VLP

Cell-based vaccines

Platform technology
Vaccines - “active immunity”
Adaptive Immune System

KEY COMPONENTS OF VACCINES

the specific component: the Antigen

Epitope (antigenic determinant) = the part of an antigen that is recognized by the (innate) immune system (antibodies, B cells, T cells), main immunogenic part of the vaccine

Pentamer of a protein

Cell-based vaccines

Viral vector

the nonspecific component: the Adjuvant

Adjuvants = agents added to vaccine formulations that enhance the immunogenicity of antigens in vivo
Although all the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) proteins are potential drug targets, some are likely to be more easy to find a drug against, in part because they play principal roles in the viral lifecycle and also lack human protein homologues. Examples include the spike glycoprotein, the papain-like protease, the chymotrypsin-like main protease, and the RNA-dependent RNA polymerase. A list of the Worldwide Protein Data Bank identifiers of the structures shown is provided in the Supplementary Appendix, available with the full text of this article at NEJM.org. ACE2 denotes angiotensin-converting enzyme 2, NSP nonstructural protein, ORF open reading frame, and RdRP RNA-dependent RNA polymerase.

Parks, Smith, How to Discover Antiviral Drugs Quickly N Engl J Med (June 4, 2020); 382:2261
Schematic representation of the novel SARS-CoV-2 viral capsid. The coronavirus spike (S) protein mediates membrane fusion by binding to cellular receptors. S spike binds cell’s receptor for angiotensin-converting enzyme (ACE2) and mediates virus entry into cell.

Amawi et al. Therapeutic Delivery (May 2020)
Developing Covid-19 Vaccines at Pandemic Speed
Lurie et al.
NEJM Mar 30, 2020

ALL PHASES of VACCINE CANDIDATES FOR COVID-19

### Technology

<table>
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<td>Tulane University</td>
</tr>
</tbody>
</table>

* Attributes refer to general attributes of the platform, and assessments are not intended as inferences about a particular candidate. NIAID denotes National Institute of Allergy and Infectious Diseases, and WRAIR Walter Reed Army Institute of Research.
### ALL PHASES of VACCINE CANDIDATES FOR COVID-19

### Main Categories of Vaccine Platforms
(summarized by Dr. Anthony Fauci, July 31 during congressional testimony)

- **Nucleic acid (DNA, RNA)**
- **Peptide (protein)**
- **Modified virus**

### Developing Covid-19 Vaccines at Pandemic Speed

Lurie et al.

NEJM Mar 30, 2020

---

**Table: Vaccine Platforms, Their Attributes, and the Status of Vaccine Candidates.**

<table>
<thead>
<tr>
<th>Technology</th>
<th>Single Dose</th>
<th>Licensed Platform</th>
<th>Speed</th>
<th>Current Scale</th>
<th>Candidates in Preclinical Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA</td>
<td>No</td>
<td>No</td>
<td>Fast</td>
<td>Medium</td>
<td>Takis/Applied DNA Sciences/Evvivax Zydus Cadila</td>
</tr>
<tr>
<td>Inactivated</td>
<td>No</td>
<td>Yes</td>
<td>Medium</td>
<td>Medium to high</td>
<td>Sinovac, Phase 1 (NCT04352608) Inactivated Beijing Institute of Biological Sciences/Wuhan Institute of Biological Sciences, Phase 1 (ChiCTR20000031809)</td>
</tr>
<tr>
<td>Live attenuated</td>
<td>Yes</td>
<td>Yes</td>
<td>Slow</td>
<td>High</td>
<td>Codagenix/Serum Institute of India</td>
</tr>
<tr>
<td>Nonreplicating vector</td>
<td>Yes</td>
<td>No</td>
<td>Medium</td>
<td>High</td>
<td>GeoVax/BravoVax Janssen Pharmaceutical Companies, Alimmune</td>
</tr>
<tr>
<td>Nucleic acid (DNA, RNA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fudan University/Shanghai JiaTong University/RNACore Biopharma, China CDC/Tongji University/Stermina, Arcturus/Duke-NUS, Imperial College London Curevac, BioNTech/Pfizer</td>
</tr>
<tr>
<td>Peptide (protein)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Moderna/NIAID (NCT04283461) University of Pittsburgh, University of Saskatchewan, ImmunoPrecise, MIGAL Galilee Research Institute, Doherty Institute, Tulane University</td>
</tr>
</tbody>
</table>

*Attributes refer to general attributes of the platform, and assessments are not intended as inferences about a particular candidate. NIAID denotes National Institute of Allergy and Infectious Diseases, and WRAIR Walter Reed Army Institute of Research.*
CD4 vs CD8 and $T_H1$ vs $T_H2$

Syndrome of vaccine-enhanced respiratory disease $\neq$ Covid-cytokine storm,
Multisystem Inflammatory Syndrome—children
Operation Warp Speed (goal: 300mil doses)

Where Fed Govt/HHS has put its $$:

March 30 – HHS $$456mil → Johnson & Johnson /Janssion → Phase I
April 16 – HHS $$483mil → Moderna/NIAID → [NEJM July 14 → Phase I]
May 21 – HHS $$1.2bil → AstraZeneca/Oxford → [Lancet July 20 → Phase I/II] Phase III (~this summer)
July 7 - HHS $$1.6bil → Novavax (Gaithersberg)
July 22-Fed Govt $$1.95bil → Pfizer/BioNTech 100mil doses
July 31-Fed Govt $$2.1bil → Sanofi/GSK 100mil doses
An mRNA Vaccine against SARS-CoV-2 — Preliminary Report


**phase I, dose-escalation, open-label trial**

45 healthy adults

\[ n=15 \quad n=15 \quad n=15 \]

\[ 25\mu g \rightarrow 100\mu g \rightarrow 250\mu g \]

\[ \downarrow \quad \downarrow \quad \downarrow \quad 1^{st} \text{ Day 1} \]

\[ \downarrow \quad \downarrow \quad \downarrow \quad 2^{nd} \text{ Day 29} \]

**mRNA-1273**

lipid nanoparticle encapsulated mRNA

SARS-CoV2 spike (**S**-2**P**) glycoprotein

**Day 57:**

**immunogenicity:**

ELISA: Receptor binding assay \( \rightarrow \rightarrow \rightarrow \rightarrow \) seroconversion: IgG vs **S**-2**P**

PsVNA: neutralization assay; PRNT: plaque reduction \( \rightarrow \rightarrow \rightarrow \rightarrow \)

(+responses: CD4/Th1-humans; CD8,CD4/Th1-mice)

**safety:** adverse event (local, systemic)

**reactogenicity:** (short-term immunologic adverse reactions)

---

(Moderna/NIAID)

Jan 10: genome posted
Mar 11: WHO:pandemic
First-in-human trial
Mar.16: 1\textsuperscript{st} vacc. pt.
July 14: **Interim** analysis:
No serious toxicity
#2>#1, 250μg>lower
Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial


**Phase I / II, single(pt)-blind RCT**

<table>
<thead>
<tr>
<th>1077 healthy (18-55y) adults</th>
<th>AZD1222/ ChAdOx1 nCoV-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:1 - ChAdOx1 nCoV-19:control</td>
<td>Chimpanzee adenovirus-vectored vaccine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5 × 10^{10} viral particles</th>
<th>↓</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day 0:</strong> 1st dose</td>
<td>↓</td>
</tr>
<tr>
<td><strong>Day 28:</strong> booster dose</td>
<td>↓</td>
</tr>
<tr>
<td>(n=10)</td>
<td></td>
</tr>
</tbody>
</table>

**Immunogenicity:**

- ELISA: seroconversion: anti-spike IgG (↑day 28→boost after 2nd dose)
- Live neutralizing antibody (↑day 28, boost); PRNT, MNA, Marburg VN
- Spike-specific T-cell responses (ELISpot:IFNɣ) (↑day 14)

**Safety:** no serious adverse event (+local, systemic AEs)

**Reactogenicity:** (short-term immunologic adverse reactions)

**Double Immunity:** humeral & cellular

(AstraZeneca/Oxford)

Jan 10: genome posted
Mar 11: WHO: pandemic
Phase I / II RCT
July 20: preliminary report
No serious toxicity
Double immunity

Jan 10: genome posted
Mar 11: WHO: pandemic
Phase I / II RCT
July 20: preliminary report
No serious toxicity
Double immunity
FURTHER VACCINE UPDATES

Ongoing: Phase II trial of **mRNA-1273** in 600 healthy adults, evaluating doses of 50 µg and 100 µg (ClinicalTrials.gov NCT04405076); **Moderna/NIAID**

July 22: **BioNTech/Pfizer** vaccine **BNT162b2** 30 µg (full-length spike mRNA); early data: +neutralizing Abs;

July 27 Phase IIb/III n=30,000

July 16: Oxford/ **AstraZeneca** ChAdOx1nCoV19(AZD1222) Phase I trial prelim: ↑antibodies + ↑killer T cells (Lancet July 20)

plan: ongoing PhII; 2-3wks ago (July) Phase III trial

Later in July 2020: Moderna & Pfizer & AstraZeneca: large trials

July 27: **Moderna/NIAID** (NEJM July 14): Phase III trial mRNA-1273 100 µg dose n=30,000: 1st patient

July 31: plan Sept: **Sanofi/GSK**: begin human testing
### Coronavirus Vaccine Tracker

**SARS-CoV-2 genome posted January 10, 2020**

#### June 10, 2020

<table>
<thead>
<tr>
<th>Phase</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRECLINICAL</td>
<td>125 +</td>
</tr>
<tr>
<td>PHASE I</td>
<td>7</td>
</tr>
<tr>
<td>PHASE II</td>
<td>7</td>
</tr>
<tr>
<td>PHASE III</td>
<td>1</td>
</tr>
<tr>
<td>APPROVAL</td>
<td>0</td>
</tr>
</tbody>
</table>

- Vaccines not yet in human trials
- Testing safety and dosage
- Expanded safety trials
- Large-scale efficacy test
- Vaccines approved for use

By [Jonathan Corum](https://nytimes.com) and [Carl Zimmer](https://nytimes.com), New York Times, June 10, 2020

#### August 3, 2020

<table>
<thead>
<tr>
<th>Phase</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRECLINICAL</td>
<td>140 +</td>
</tr>
<tr>
<td>PHASE I</td>
<td>18</td>
</tr>
<tr>
<td>PHASE II</td>
<td>12</td>
</tr>
<tr>
<td>PHASE III</td>
<td>6</td>
</tr>
<tr>
<td>APPROVAL</td>
<td>1</td>
</tr>
</tbody>
</table>

- Vaccines approved for limited use

HARNESSING THE IMMUNE SYSTEM TO PREVENT CANCER: VACCINES

DCP CANCER Immunoprevention
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TRI group

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