To address global public health threats by translating basic research discoveries into clinical advances
Community education, engagement, and participation
Training: students, residents, fellows, international investigators
Translational human immunology studies
Clinical trials of vaccines and treatments
www.hopeclinic.emory.edu
404-712-1371
The Hope Clinic Funding

• Human Immunology Project Consortium
• Cooperative Centers for Human Immunology
• Vaccine & Treatment Evaluation Unit
• HIV Prevention Trials Network
• HIV Vaccine Trials Network
• Emory Center for AIDS Research
• Antibacterial Resistance Leadership Group
• Vaccine Research Center
• Emerging Infections Program
• Centers for Diseases Control and Prevention
Conflict of Interest

• I receive funds from the following manufacturers to conduct research studies at Emory:
  • Sanofi Pasteur
  • Merck
  • Pfizer
  • Quidel
  • Eli Lilly

• I serve as the Hope Clinic PI for Moderna SARS-CoV-2 phase 1 and 3 vaccine trials

• I serve as the international co-Chair for the Sanofi Pasteur SARS-CoV-2 Phase 3 vaccine trial

• I serve on the advisory board for 1DaySooner (non profit organization advocating for human challenge trials)
Non Conflict of Interest
COVID-19 and SARS-CoV-2

Berlin et al. NEJM May, 15 2020
Natural Immunity to SARS-CoV-2

**Coronavirus infection**

The virus uses its surface spike protein to lock onto ACE2 receptors on the surface of human cells. Once inside, these cells translate the virus's RNA to produce more viruses.

1. Virus enters the body
2. Virus enters a cell
3. Virus fuses with vesicle and its RNA is released
4. Virus assembly
5. Virus release

**Immune response**

Specialized 'antigen-presenting cells' engulf the virus and display portions of it to activate T-helper cells. T-helper cells enable other immune responses. B cells make antibodies that can block the virus from infecting cells, as well as mark the virus for destruction. Cytotoxic T cells identify and destroy virus-infected cells.

Long-lived 'memory' B and T cells that recognize the virus can patrol the body for months or years, providing immunity.
Lessons Learned from Natural Immunity to SARS-CoV-2

• What is the desired element in a vaccine immune response?
• Is vaccine induced protection solely mediated by antibodies?
• What part of the virus should the vaccine candidate target?
• Does the virus mutate?

Korber et al., BioRxiv, May 2020.
Tillet et al., The Lancet, 2020.
To et al., Clinical Infectious Diseases, Aug 2020.
Long et al., Nature Medicine, 2020 Aug;26(8):1200-1204.
Suthar et al., Cell Rep Med, 2020 Jun 23; 1(3): 100040.
Grifoni et al., Cell, 2020. 181(7): p. 1489-1501.e15.
Arunachalam et al, Science, 2020 Sep 4;369(6508):1210-1220
Lessons Learned from Other Coronaviruses

• How long does the immune response last?
• Is there a concern for potential for vaccine-associated enhanced respiratory disease (VAERD)?

Tang et al., The Journal of Immunology, 2011. 186(12): p. 7264.
Modjarrad et al., Lancet Infect Dis 2019;19:1013-22.
Martin et al., Vaccine 2008;26:6338-43.
Kim et al., AM J of Epi 1969;89:422-34.
Ruckwardt et al., Immunity 2019;51:429-42.
Tseng et al., PLoS One 2012;7:e35421
Wang et al., ACS Infect Dis 2016;2:361-76.
Corbett et al., N Engl J Med 2020, Jul 28.
Lessons Learned from Challenge Models

- What is the correlate of protection?
- Will vaccine candidates protect against illness or infection in humans?
- Will vaccine candidates protect vulnerable populations?

Callow et al., Epidemiology and Infection, 1990. 105(2): p. 435-446.
Reed. Journal of Medical Virology, 1984. 13(2): p. 179-192.
Chandrashekar et al., Science, 2020. 369(6505): p. 812.

Lung bronchoalveolar lavage
Nasal swab
Coronavirus Vaccine Tracker

- **PHASE 1**: 29 Vaccines testing safety and dosage
- **PHASE 2**: 14 Vaccines in expanded safety trials
- **PHASE 3**: 11 Vaccines in large-scale efficacy tests
- **LIMITED**: 5 Vaccines approved for early or limited use
- **APPROVED**: 0 Vaccines approved for full use

Updated October 14, 2020
nytimes.com/vaccinetracker
Nucleic Acid Vaccines

Callaway. Nature, 2020; 580(7805):576-577
### mRNA 1273-Phase 1

**Phase 1 trial overview**

**Protocol Title**
Phase I, Open-Label, Dose-Ranging Study of the Safety and Immunogenicity of 2019-nCoV Vaccine (mRNA-1273) in Healthy Adults

**Population**
45 adults (18-55 years [mean 33]- 89% White)

| Study Groups   | Dosage (D0, D28) | ELISA (RBD) D57 | Live Virus PRNT (80) D43 | CD4 response D43 | CD8 response D43 |
|---------------|-----------------|----------------|--------------------------|------------------|------------------|
|               | 25 mcg          | 184,000        | 340                      | Th1>>>Th2        | ---              |
|               | 100 mcg         | 371,000        | 654                      | Th1>>>Th2        | minimal          |
|               | 250 mcg         | 582,000        | ND                       | ND               | ND               |
|               | Convalescent    | 38,000         | 158                      | ND               | ND               |

**Tolerability**
Most common: fatigue, chills, headache, myalgia, and pain at the injection site

**Safety**
More systemic reactogenicity after second dose. The group that received 250 mcg dose had three severe adverse events.
mRNA 1273-Phase 1

**Pseudovirus neutralization assay titers (ID50)**

Strong correlation between Live Virus and Pseudovirus assay results
mRNA BNT162b1-Phase1

**Phase 1 trial overview***

**Protocol Title**
Safety and immunogenicity of varying dose levels of BNT162b1 and BNT162b2.

**Population**
45 adults (18-55 years[mean 35]- 82% White)

| Study Groups | Dosage (D0, D21) | ELISA (RBD) D35 | Live Virus Neuts (80) D43 | CD4 response D43 | CD8 response D43 |
|--------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| 10 mcg       | 5,880           | 180             | ND              | ND              | ND              |
| 30 mcg       | 16,166          | 437             | ND              | ND              | ND              |
| 100 mcg      | ND              | ND              | ND              | ND              | ND              |
| Convalescent | 602             | 94              | ND              | ND              | ND              |

**Tolerability**
Most common: fever, fatigue, chills, headache, myalgia, and pain at the injection site.

**Safety**
Both the 10 and 30 mcg group showed 1 severe AE; the 100 mcg group showed 7 severe AEs.

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*Placebo controlled study*
Other Nucleic Acid Vaccine Candidates
Viral Vector Vaccines

- Replicating viral vector (such as weakened measles)
  - Coronavirus spike gene
  - Viral genes
  - Virus replicates
  - Antigen-presenting cell
  - Immune response

- Non-replicating viral vector (such as adenovirus)
  - Coronavirus spike gene
  - Viral genes (some inactive)

Callaway. Nature, 2020; 580(7805):576-577
Chimpanzee Ad ChAdOx1-Phase 1/2

Phase 1 trial overview

Protocol Title: Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomized controlled trial

Population: 1077 adults (18-55 [mean 35]; 50% male; 91% White)

Study Groups

| Dosage (D0, D28) | ELISA (Anti-S) D56 | Microneuts (80) D28,42 | IFNγ-ELISpot T cells D14,56 |
|-----------------|--------------------|------------------------|-----------------------------|
| 5E10 viral particles | 119 | 51 | 0.05-0.1% |
| Prime only, no second dose. | | | |
| 5E10 viral particles | 639 | 136 | 0.05-0.1% |
| Prime and boost* | | | |
| Convalescent | Similar range** | Similar range ** | NA |

Tolerability: Most common and lessened by prophylactic paracetamol: pain, feeling feverish, chills, muscle ache, headache, and malaise.

Safety: 16-18% reported a fever>38C- no SAE.

*Only 10 subjects received prime-boost **exact numbers not provided***Meningococcal conjugate vaccine (MenACWY) as comparative arm

Folegatti et al., Lancet 2020; 396:467–78
Adenovirus Ad5-Phase 2

| Protocol Title | Immunogenicity and safety of a recombinant adenovirus type-5-vectored COVID-19 vaccine in healthy adults aged 18 years or older: a randomised, double-blind, placebo-controlled, phase 2 trial |
|----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Population     | 508 adults (mean age 40; 50% male)                                                                                                                                                                  |
| Study Groups   | Dosage* (D0) | ELISA (RBD) D28 | Live Virus Neuts D28,42 | IFNγ-ELISpot T cells D14,56 |
|                | 1E11 viral particles | 571 | 18 | 90% |
|                | 5E10 viral particles | 657 | 20 | 88% |

| Tolerability   | Most common: fever, fatigue, headache and pain at the injection site | |

| Safety         | 9% of the 1E11 dosage group exhibited a grade 3 AE vs. 1% of the 5E10 dosage group. |

*Placebo controlled study

Half of the subjects had high levels of pre-existing Ab against Ad5 vector and had Ab response twice lower than those with low level pre-existing Ad5 Ab.
Adenovirus Ad26/Ad5- Phase 1/2

Phase 1 trial overview

**Protocol Title**
Safety and immunogenicity of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine in two formulations: two open, non-randomised phase 1/2 studies from Russia.

**Population**
76 adults (18-60 years [mean 27]; 70% male)

**Study Groups**

|                  | Dose* (D0, D21) | ELISA (RBD) D42 | Live Virus Neuts (50) D42 | CD4** Day 28 | CD8** Day 28 |
|------------------|----------------|-----------------|---------------------------|--------------|--------------|
| rAd26/rAd5-Frozen| 14,703         | 49              |                           | 2.5%         | 1.3%         |
| rAd26/rAd5-Lyophilised | 11,143    | 46              |                           | 1.3%         | 1.1%         |

**Tolerability**
Most common: injection site pain, hyperthermia, headache, asthenia and muscle and joint pain.

**Safety**
No grade 3 AEs were exhibited.

*10 × 10¹¹ viral particles with SARS-CoV-2 full-length glycoprotein S

*4 additional groups tested: rAd26 alone or rAd 5 alone – frozen or lyophilized

**T cell proliferation**
Adenovirus Ad26 Phase 1/2

| Phase 2 trial overview | COHORT 1A |
|------------------------|-----------|
| Protocol Title         | Safety and immunogenicity of the Ad26.COV2.S COVID-19 vaccine candidate: interim results of a phase 1/2a, double-blind, randomized, placebo-controlled trial. |
| Population             | Healthy adults 18-55 years old, median age of 34. |
| Study Groups           | Dosage (D0.56) | ELISA (D29) | Neuts (D29) | CD4/Th1 (D15) | TCD4/Th2 (D15) | CD8+ T (D15) |
|                        | 5E10 viral particles | 528 | 214 | 76% | negligible | 51% |
|                        | 1E11 viral particles | 695 | 243 | 83% | negligible | 64% |
| Tolerability           | Most common: injection site pain, fatigue, headache and myalgia. Fever in 19% (Grade 3 fever in 5%) - Grade 3 systemic AE in 11%. |
| Safety                 | No grade 4 AE. 2 SAE- No discontinuation from AE. |

Sadoff, Jerald et al., medRxiv 2020, September 25
Other Viral Vector Vaccine Candidates
Protein Based Vaccines

Callaway. Nature, 2020; 580(7805):576-577
## NVX-CoV2373-Phase 1/2

**Phase 1 trial overview**

Keech et al., NEJM 2020, Sep 2

### Protocol Title
Phase 1-2 Trial of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine

### Population
108 adults (mean age 31; 50% male; 79% white)

### Study Groups

| Dosage (D0, D21)          | ELISA (Anti-S) D35 | Live Virus Neuts (99) D35 | T Cell Response |
|---------------------------|-------------------|--------------------------|-----------------|
| 5 mcg + M1                | 63,160            | 3,906                    | Th1>>>Th2       |
| 25 mcg                    | 575               | 41                       | ---             |
| 25 mcg + M1 no second dose| 2,932             | 128                      | ND              |
| 25 mcg + M1               | 47,521            | 3,305                    | Th1>>>Th2       |
| Convalescent              | 8,344             | 983                      | ND              |

### Tolerability
Most common: pain and tenderness, fatigue, headache, myalgia, malaise.

### Safety
More systemic, more frequent severe AE after second vaccination.

*Placebo controlled study*
Other Protein Based Vaccine Candidates
Virus Vaccines
# Inactivated Whole Virus - Phase 1/2

## Phase 1 trial overview

**Protocol Title**  
Effect of an Inactivated Vaccine Against SARS-CoV-2 on Safety and Immunogenicity Outcomes

**Population**  
Triple-dose schedule: 96 adults (mean age 41; 60% female)  
Double-dose schedule: 224 adults (mean age 44; 64% female)

| Study Groups | Dosage (D0, D28, D56) | ELISA (whole virus) | Live Virus PRNT (50) | T Cell Response |
|--------------|-----------------------|---------------------|----------------------|----------------|
|              | 2.5 mcg               | 415                 | 316                  | ND             |
|              | 5 mcg                 | 349                 | 206                  | ND             |
|              | 10 mcg                | 311                 | 297                  | ND             |

| Dosage (D0,DX ) | ELISA (whole virus) | Live Virus PRNT (50) | T Cell Response |
|-----------------|---------------------|----------------------|----------------|
| 5 mcg (D0, D14) | 74                  | 121                  | ND             |
| 5 mcg (D0, D21) | 215                 | 247                  | ND             |

**Tolerability**  
Few reactogenicity events: pain and fever most common

**Safety**  
Good Profile

*14 days after last dose; **Alum as comparative arm*
Other Virus Vaccine Candidates
How Long Will a Vaccine Really Take?

By Stuart A. Thompson
April 30, 2020

Years and years, at minimum
The vaccine development process has typically taken a decade or longer.

| Vaccine Type                  | Time (years) |
|-------------------------------|--------------|
| Varicella                     | 28           |
| FluMist                       | 28           |
| Human papillomavirus          | 15           |
| Rotavirus                     | 15           |
| Pediatric combination         | 11           |
| Covid-19 goal                 | 18 months    |

Note: Rotavirus and HPV vaccines include time from filing of the first investigational new drug to approval. Source: “Plotkin’s Vaccines” (7th edition)

https://www.nytimes.com/interactive/2020/04/30/opinion/coronavirus-covid-vaccine.html
When Can We Expect a Vaccine?

WHERE WE ARE

Vaccine Development
- Identify viral target
- Pre-clinical vaccines

Efficacy & Toxicity
- Testing in animal models to ensure efficacy and non-toxicity

Clinical Trials
- Phases 1-3
- Receive regulatory approval
- Phase 4

YOU ARE HERE

REMAINING STEPS

Production & Distribution
- Mass-produce vaccine
- Distribute worldwide

Administration & Immunity
- Administer vaccine
- Await impact

Vaccine target (S-protein) was identified, various vaccine types spawned.

Initial safety testing for new vaccine technology was executed.

Animal model developed

Under normal circumstances, a vaccine can take 6-7 years to complete phases 1-4.

Mass production facilities and technology must be developed

Two vaccinations may be required for complete immunity.

Antibody response could be weak.

Protective immunity is realized one to two weeks after vaccination is complete.
MISSION: Deliver 300 million doses of safe and effective vaccine by 1 January 2021.

1. A typical 8-month process is accelerated by:
   - Creating vaccine candidates immediately after viral genome sequence is available.
   - Using vaccine platforms developed for other diseases.

2. A typical 42-month process is accelerated by:
   - Large scale Phase III clinical trials of 30,000 volunteers allowing for rapid collection and earlier analysis of safety and efficacy data of demographically diverse populations by the FDA, reducing the typical 12-month approval process to three months.
   - Two promising candidates began Phase III clinical trials in July, with others to follow quickly in upcoming months. Before beginning Phase III, candidates must show safety data from animal and human studies.
   - The U.S. Government funding at-risk, large-scale manufacturing of the most promising vaccine candidates during Phase III clinical trials to ensure any vaccine proven to be safe and effective is available immediately upon FDA Emergency Use Authorization (EUA) approval or licensure.

3. A typical 15-month process is accelerated by:
   - Planning for infrastructure and distribution before the vaccines are approved or authorized.
   - CDC leading distribution planning with DoD augmentation.

4. A typical 6-month process is accelerated by:
   - A tiered approach based on CDC recommended allocation methodology used as part of pandemic flu planning and the COVID-19 response will be used to determine vaccine distribution.

5. A typical 12-month FDA review for EUA approval or licensure is accelerated by:
   - Providing continuous safety and efficacy data collected in large Phase III clinical trials.

Legend:
- R&D + Preclinical Trials Vaccine Candidate/s Identified
- Phase I Clinical Trials
- Phase II Clinical Trials
- Phase III Clinical Trials
- Manufacturing
- Distribution
- **Moderna**: $1.5 billion for 100 million doses
  - Phase 3 began July 2020
- **Pfizer**: $1.95 billion for 100 million doses
  - Phase 2/3 began July 2020
- **AstraZeneca**: $1.2 billion to for 300 million doses
  - Phase 3 began September 2020 – currently on hold in the US
- **J&J (Janssen)**: $1 billion for 100 million doses
  - Started in September - currently on hold
- **Sanofi / GlaxoSmithKline**: $2.1 billion for 100 million doses
  - Anticipated to start later this fall
- **Novavax**: $1.6 billion for 100 million doses
  - Anticipated to start in the fall

Courtesy of Dr Colleen Kelley
Help Find a Vaccine for COVID-19

Volunteer Today

https://www.coronaviruspreventionnetwork.org/
Administration of COVID-19 vaccine will require a phased approach

- **Limited Doses Available**
  - Constrained supply
  - Cold chain & handling may require specialized equipment and high throughput
  - Highly targeted administration

- **Large Number of Doses Available**
  - Likely sufficient supply to meet demand
  - Additional vaccine products allow a wider range of administration locations
  - Broad administration network required (pharmacies, doctors offices, public health clinics, mobile clinics, FQHCs)
  - Focus on increasing access for critical populations

- **Continued Vaccination**
  - Sufficient supply to meet demand
  - Harness vaccine provider networks with proven ability to reach critical populations
  - Enhance series completion
The Amazing Team