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### **SARS-CoV-2 candidate vaccines - composition, mechanisms of action and stages of clinical development**

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Vaccines are the gold standard immuno-prophylaxis to prevent infectious diseases. Mass vaccination strategies have been successful, completely eradicating some human and animal infectious diseases such as smallpox and almost eliminating poliovirus. With the SARS-CoV-2 pandemic we observe an unseen effort of the scientific community and pharmacological industry to understand its immunopathology and to develop successful treatments and vaccines<sup>1</sup>. In December 2020, the first vaccine was approved in the UK and is awaiting approval in other countries. Several others are in the final stages of clinical trials so next months we will observe real-life results of the global vaccination strategy.

According to the World Health Organization, as of 11<sup>th</sup> December, there are 214 vaccines against SARS-CoV-2 in different stages of clinical development<sup>2</sup>. They can be divided in two groups: the classical technologies, successfully used in the marketed vaccines, and new formats which have not been approved yet. The most common route of vaccine delivery is intramuscular injection inducing strong priming of DCs. Vaccines using other administration routes are being developed and their different pharmacological processes and priming features should be elucidated<sup>3</sup>.

In the classical group, there are four different types of vaccines: subunit, inactivated, live attenuated and virus-like particles (VLP) vaccines. The subunit vaccines are composed of viral surface proteins formulated with adjuvants to elicit strong neutralizing antibody responses. Once injected, the proteins are engulfed by the antigen processing cells (APCs) and their epitopes are presented by MHC class II. A currently used subunit

vaccine is hepatitis B vaccine. Such vaccines have good safety and stability profile, however, the immune response created might be limited and booster strategies are often necessary. For SARS-CoV-2 there are two subunit vaccines in phase 2: the whole spike protein (Sanofi+GSK) or the receptor binding domain (Institute of Microbiology Chinese Academy of Science) (Table 1).

Inactivated vaccines are constituted by a virus treated physiochemically to inhibit its pathogenicity. An example is the inactivated polio vaccine (IPV). Upon injection, the inactivated viruses are engulfed by APCs and different epitopes are presented to the immune system. They also present good safety profile as the virus cannot cause disease; however, they need a booster strategy to create immune memory. The inactivated vaccines most advanced in clinical trials are being developed by Sinovac and Sinopharm.

Another technology are live attenuated vaccines. These vaccines contain viruses modified to hamper their replication and infection rate. An example is the oral polio vaccine (OPV). Such vaccines create mild viral infections with the consequent antiviral response, inducing strong immune memory responses not requiring reminders. Nevertheless, they can cause full-blown infection in immunocompromised patients. Furthermore, these viruses might revert and cause a disease<sup>4</sup>. As extensive knowledge about the virus is required, there are no attenuated SARS-CoV2 vaccines currently being tested.

VLPs are constituted by one or more viral proteins assembled into a particle without viral genetic material. As such, these viral particles do not cause a disease while having a better uptake profile and more efficient circulation to the lymph nodes. Thus, they produce stronger immune responses. A current example is the human papilloma virus vaccine. The main concerns include the dependence on the efficient expression platforms and stability. One VLP vaccine against SARS-CoV-2 by Medicago is currently in phase 3 of the clinical trial.

There have been new vaccination strategies in development in recent years, however none approved yet. As such, the infrastructure and logistics for their mass production and distribution (e.g. transportation and storage and the required temperature) need to be created or adapted. One new strategy are recombinant virus vaccines, composed of viral vectors containing proteins from the target virus. The advantage of this approach is nearly complete mimicking of natural viral infection, creating a strong immune response against it. However, the vector has a potential to revert and might be dangerous in immunocompromised patients. Some recombinant virus vaccines being currently tested include Astra Zeneca, Janssen, Cansino and Gamaleya Research Institute. All express the spike protein in different vectors: a chimpanzee adenovirus (ChAdOx),

human adenovirus type 26 (hAdv26), type 5 (hAdv5) or both, respectively. Some additional concerns include the possibility of lower immune priming in case someone has pre-existing immunity against the vector and possible recombination with other viral diseases. The first concern has been faced with a smart and personalized design. For example, using a virus that does not circulate in the target population (Janssen and Cansino use a vector that does not circulate extensively in Europe and Asia, respectively<sup>5,6</sup>), using two different viral vectors in the same formulation (Gamaleya Research Institute<sup>7</sup>) or using a viral vector that does not exist in humans (Astra/Zeneca<sup>8</sup>). Safety concerns of these vectors should be carefully addressed. Astra/Zeneca and Janssen had to temporarily stop their clinical trials due to unexpected adverse effects.

Other novel approaches are the RNA-based vaccines. These vaccines deliver RNA coding target viral proteins into human cells. Then, they will produce viral proteins and, if a polymerase is encoded, also replicate themselves. This way RNA-based vaccines mimic ongoing viral infection including toll-like receptors activation and IFN production. Such vaccines containing different versions of mRNA for the spike protein have been developed by Moderna, Curevac and Pfizer<sup>9</sup>. RNA-based vaccines are relatively inexpensive and easy to handle in case of mass production. Also, they are easier to modify than other approaches, if the naturally occurring virus significantly mutates. They should be safe in immunocompromised patients as the theoretical risk of infection is rather negligible. The disadvantages include the unknown efficacy of the delivery and the possibility of a short half-life of viral mRNA within the cell, which would reduce the creation of immune memory even in prime boost strategies.

In summary, due to the extensive scientific-industry collaborations the vaccine field is evolving at an unprecedented speed. Yet, to stop the pandemics equal access to the vaccine all over the world, limiting the costs of vaccines and logistics, close monitoring and reporting of adverse events are absolutely necessary. Development of a successful SARS-CoV-2 vaccine should not slow down the studies on the effective broader antiviral treatments. If not for SARS-CoV-2, we will need it for another coronavirus or an inevitably emerging virus X.

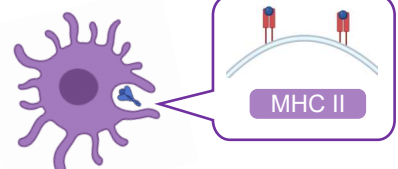
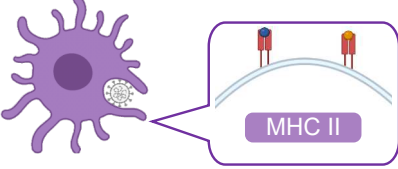
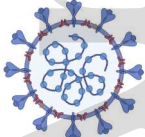
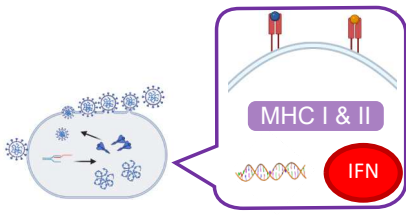
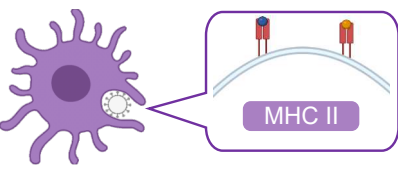
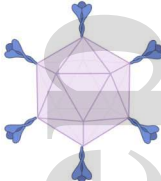
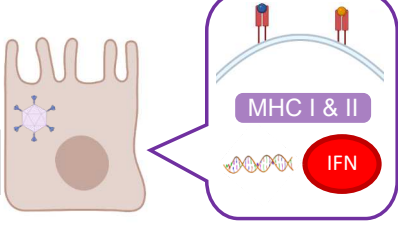
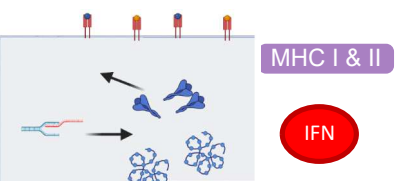
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Table caption

Table 1. Summary of the types, mechanism and examples of vaccines in development against SARS-CoV-2.  
Figures have been created using Biorender.com. Legend: CT= Clinical trial, IM=Intramuscular.

| Type of vaccine                                                                                                  | Mechanism                                                                           | Advantages & Disadvantages                                                                                                                                                                                                                | Existing examples                       | SARS-CoV 2 vaccines in clinical trials                                                                                                                                                                                                                                                                                                                |
|------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Subunit</b><br>               |    | <div> <div>✓ Do not cause disease</div> <div>✓ Very stable</div> <div>✗ Needs booster strategy</div> <div>✗ Short memory</div> </div>                                                                                                     | HBV                                     | Recombinant spike protein (Sanofi+GSK) IM CT II: NCT04537208<br><br>RBD dimer (Institute of Microbiology Chinese Academy of Science) IM CT II: NCT04466085                                                                                                                                                                                            |
| <b>Inactivated</b><br>           |    | <div> <div>✓ Do not cause disease</div> <div>✓ Very stable</div> <div>✗ Needs booster strategy</div> <div>✗ Short memory</div> </div>                                                                                                     | Inactivated polio vaccine (IPV)         | Inactivated virus (Sinovac) IM CT III: NCT04456595/ NCT04582344<br><br>Inactivated virus (Sinopharm) IM CT III: NCT04560881                                                                                                                                                                                                                           |
| <b>Live attenuated</b><br>       |    | <div> <div>✓ Mimic natural infection</div> <div>✓ Creates cross reactivity</div> <div>✗ Can revert and cause disease</div> <div>✗ Might be harmful in immunocompromised</div> </div>                                                      | Measles<br><br>Oral polio vaccine (OPV) | N/A                                                                                                                                                                                                                                                                                                                                                   |
| <b>Virus like particles</b><br> |   | <div> <div>✓ Increased uptake by lymph node</div> <div>✓ Do not cause disease</div> <div>✗ Dependant on efficient expression platform</div> <div>✗ Difficult to make VLP stable in long term</div> </div>                                 | Papillomavirus                          | Plant derived VLP (Medicago) IM CT III: NCT04450004                                                                                                                                                                                                                                                                                                   |
| <b>Recombinant viruses</b><br> |  | <div> <div>✓ Mimics natural infection</div> <div>✓ Strong memory</div> <div>✓ Cannot revert to natural disease</div> <div>✗ Pre-existent memory against vector lowers efficacy</div> <div>✗ Recombination with other viruses</div> </div> | N/A                                     | Spike protein in ChAdOx vector (Astra-Zeneca) IM CT III: NCT04516746/ NCT04540393<br><br>Spike protein in Ad26 vector (Janssen) IM CT III: NCT04505722/ NCT04614948<br><br>Spike protein in Ad5 vector (Cansino) IM CT III: NCT04526990/ NCT04540419<br><br>Spike protein in Ad26 & 5 vector (Gamaleya institute) IM CT III: NCT04530396/ NCT04564716 |
| <b>RNA vaccines</b><br>        |  | <div> <div>✓ Easy to modify</div> <div>✓ Do not cause disease</div> <div>✗ Short immune memory if not stable</div> <div>✗ Low immune priming if efficacy of delivery is low</div> </div>                                                  | N/A                                     | Spike protein mRNA (Moderna) IM CT III: NCT04470427<br><br>Spike protein mRNA (Pfizer) IM CT III: NCT04368728<br><br>Spike protein mRNA (Curevac) IM CT II: NCT04515147                                                                                                                                                                               |