ChAdOx1 S (recombinant) – Mechanism of Action

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ChAdOx1 S (recombinant) is a COVID-19 vaccine candidate that uses an established non-replicating chimpanzee adenovirus vector, ChAdOx1, and contains the genome that produces the full-length wild-type SARS-CoV-2 S protein in the pre-fusion conformation.3,5

**Summary**

- **ChAdOx1 S (recombinant)** is a COVID-19 vaccine candidate that was initially developed by the Jenner Institute at the University of Oxford.1
- It uses a non-replicating chimpanzee adenovirus vector, ChAdOx1, that contains a full-length wild-type SARS-CoV-2 S protein genome, with a tissue plasminogen activator leader sequence.2,3
- ChAdOx1 S (recombinant) is not a conventional live attenuated vaccine and does not contain live coronavirus. The replication-defective adenovirus is live but cannot multiply or spread throughout the body.4,6
- The recombinant adenovirus vector ChAdOx1 cannot cause an adenovirus or COVID-19 infection in the vaccinated individual.6
- Adenovirus vectors do not integrate into host genomes but stay as episomal DNA in the nucleus of host cells.7
- The host cell transcribes the DNA to mRNA and translates the mRNA into the S protein which is expressed in the pre-fusion conformation, on the surface of the cell and/or secreted from the cell.12,13
- Subsequently, neutralizing antibodies are formed, and T-cells are activated against the S protein of the SARS-CoV-2, priming the body to fight a subsequent SARS-CoV-2 infection if exposed.1

**ChAdOx1 S (recombinant)**

- **ChAdOx1 S (recombinant)** is a COVID-19 vaccine candidate that uses a replication-deficient chimpanzee viral vector based on a weakened version of a common cold virus (adenovirus) that causes infections in chimpanzees.1
- ChAdOx1 S (recombinant) contains the genetic material of the wild-type SARS-CoV-2 S protein.1
- ChAdOx1 S (recombinant) is not a conventional live attenuated vaccine and does not contain live coronavirus. The replication-defective adenovirus is live but cannot multiply or spread throughout the body.4,6
- After vaccination, the surface S protein is produced by the human cells, in the pre-fusion conformation, priming the immune system to attack the SARS-CoV-2 virus if it later infects the body.1,5
- The recombinant adenovirus vector ChAdOx1 was chosen because it generates a strong immune response and, since it is non-replicating, it cannot cause an adenovirus or COVID-19 infection in the vaccinated individual.8
- Previously used to develop vaccines against MERS, malaria, HIV, influenza, hepatitis C, tuberculosis, and Ebola, this platform has been extensively tested and shown to be well tolerated across a broad age range in humans, demonstrating a well-defined safety profile consistent with a tolerable vaccine.2,3,7
- Please refer to the following link for a visual representation: **ChAdOx1 S (recombinant) Animation**

**Adenoviral Vectors**

- Adenovirus-based vectors can transduce and deliver transgenes to various cell types, including replicating and quiescent cell populations, where they are used to transfer the genetic code
(transduce) to produce the target of interest. This is a critical requirement in gene therapy or vaccine development.\textsuperscript{7}

- Adenovirus vectors do not integrate into host genomes but stay as episomal DNA in the nucleus of host cells.\textsuperscript{7}
- Modern adenoviral vectors can take multiple gene cassettes, up to 36 kb of foreign DNA, making them suitable for delivering various gene sizes.\textsuperscript{7,8}
- Adenoviruses activate several innate immune signaling pathways resulting in the secretion of several proinflammatory cytokines. These proinflammatory cytokines allow for effective immune cell stimulation and result in the induction of robust adaptive humoral and cellular immune responses, including CD8+ CTL responses, which are critical to resolving viral infections.\textsuperscript{7}
- Transgene antigens carried by adenoviral vectors are presented to T-cells via MHC class I molecules, thereby inducing efficient and robust CTL responses. The CTLs efficiently recognize and kill virus-infected cells, intracellular pathogens, and cancerous cells.\textsuperscript{7}

**Step 1: Creating the Vaccine Platform (ChAdOx1)**

- Adenoviruses are potent inducers of both T-cell and antibody immune responses. They have been well-studied in both preclinical and clinical studies.\textsuperscript{9}
- The ChAdOx1 platform is derived from chimpanzee adenovirus and genetically engineered to deliver a specifically encoded antigenic genome.\textsuperscript{8,9}
  - Utilization of a ChAdOx1 platform avoids pre-existing anti-vector immunity in humans.\textsuperscript{6,9}
- The adenovirus has undergone genetic alterations rendering it unable to replicate (or revert) in humans.\textsuperscript{3,6}
- Extensive homologies and abundant chromosomal repeat elements present in the vector do not lead to the vector’s integration via homologous or homology-mediated mechanisms.\textsuperscript{8}

**Step 2: Expressing the Antigen SARS-CoV-2 S protein and receptor-binding domain**

- The structural surface glycoprotein, also known as the S protein, on the SARS-CoV-2 virus, recognizes and binds to angiotensin-converting enzyme (ACE) 2 receptors and aids in cell entry during infection in humans.\textsuperscript{10}
- The ChAdOx1 vector in the ChAdOx1 S (recombinant) vaccine contains the full-length SARS-CoV-2 S protein genome with a tPA leader sequence.\textsuperscript{3}
  - A tPA leader is a signaling peptide sequence that is inserted upstream of the encoded antigen (SARS-CoV-2 S protein genome).\textsuperscript{11}
  - tPA leader sequences have been shown to improve immunogenicity in similarly vectored vaccines (ChAdOx1 MERS), causing strong promotion of S protein expression.\textsuperscript{11}
- Once injected, the ChAdOx1 vector fuses with the host cell and releases its genetic contents; the genome for the SARS-CoV-2 S protein.\textsuperscript{1,3}
- The host cell transcribes the DNA to mRNA and translates the mRNA into the S Protein which is expressed on the surface of the cell and/or secreted from the cell in the wild type pre-fusion conformation.\textsuperscript{12,13}

**Step 3: Driving the Immune Response**

- The host immune system recognizes the S protein and mounts a B-cell (neutralizing antibodies) and T-cell response.\textsuperscript{1,3}
- Memory B-cells and T-cells are formed, priming the immune system to attack the SARS-CoV-2 during a subsequent infection to the virus.\textsuperscript{1,3}

**Abbreviations:**

- CD: cluster of differentiation; COVID-19: coronavirus disease 2019; CTL: cytotoxic T lymphocyte; ChAdOx1: chimpanzee adenovirus Oxford 1; DNA: deoxyribonucleic acid; Kb: kilobytes; MERS: middle east respiratory syndrome; MHC: major histocompatibility complex; mRNA: messenger ribonucleic acid; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; S protein: spike protein; tPA: tissue plasminogen activator.
The information in this response is intended to be a concise summation of representative clinical trial data, rather than being all-inclusive, so all available published literature may not be included.

**REFERENCE(S)**