

**THIRD PARTY OBSERVATIONS PURSUANT TO ARTICLE 115 EPC
BY MEDECINS DU MONDE
IN REGARD OF EP3901260 (EP21168938.5) IN THE NAME OF BIONTECH SE**

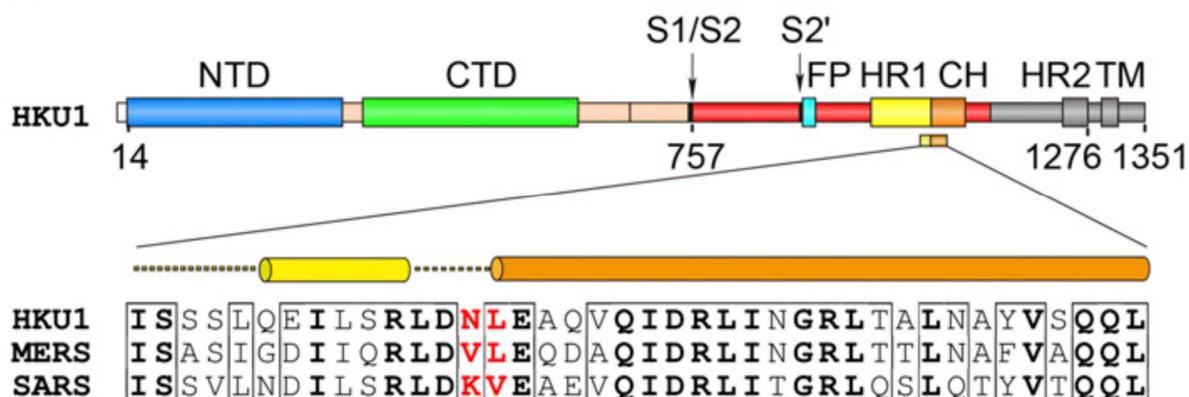
The claimed composition lacks an inventive step, as the inventors **directly applied** the teachings of previous academic works of Pallesen *et al.* (2017) and Pardi *et al.* (2019) to the sequence of SARS-CoV-2 which was publicly released on 13 January 2020 (https://www.ncbi.nlm.nih.gov/nuccore/NC_045512.1).

More specifically, starting from Hodgson (2020) (D1 in the examination proceedings) it would have been obvious for the person of skill in the art to provide alternative anti-COVID-19 mRNA vaccines to those mentioned in Table 2 (e.g. BioNTech and Moderna), expressing an amino acid sequence that comprises SEQ ID NO: 7 according to patent application EP21168938.5.

Indeed, Pallesen *et al.* (2017) teach that structure-based design was used to develop a generalizable strategy for retaining coronavirus S proteins in the antigenically optimal prefusion conformation and demonstrate that the engineered immunogen is able to elicit **high neutralizing antibody titers** against MERS-CoV.

The strategy involves replacing consecutive amino acids V1060 and L1061 of the S protein of MERS-CoV **by two prolines (2P)** (see page E7350, left column).

A



The position of the amino acids to be mutated to prolines is shown for MERS-CoV and SARS-CoV in the above Figure 1A.

Applying this strategy to the S protein of SARS-Cov-2 directly yields SEQ ID NO: 7.

We show below the alignments of the SARS-CoV-2 S protein from NC_045512.1 (Query) and SEQ ID NO: 7 (Sbjct) between amino acids 961 and 1020:

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Query  961  TLVKQLSSNFGAISSVLNDILSRLDKVEAEVQIDRLITGRLQSLQTYVTQQLIRAAEIRA 1020
                TLVKQLSSNFGAISSVLNDILSRLD  EAEVQIDRLITGRLQSLQTYVTQQLIRAAEIRA
Sbjct  961  TLVKQLSSNFGAISSVLNDILSRLDPEAEVQIDRLITGRLQSLQTYVTQQLIRAAEIRA 1020
  
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It can be readily seen that SEQ ID NO: 7 only differs from NC_045512.1 by the substitution of K986 and V987 by two prolines and that the position of the substituted amino acids corresponds exactly to that shown for SARS-CoV in the above-figure.

Accordingly, there was a clear incitation in the art to have SEQ ID NO: 7 expressed by the mRNA vaccine.

Moreover, Pardi *et al.* (2019) teach that intradermal anti-HIV vaccination with nucleoside-modified 1086C Env **mRNA-LNPs** elicited high levels of gp120-specific antibodies in rabbits and rhesus macaques.

As such, it would have been equally obvious to have SEQ ID NO: 7 expressed by a mRNA comprising N1-methyl-pseudouridine and formulated in LNPs comprising ionizable cationic lipid, phosphatidylcholine, cholesterol, and polyethylene glycol (PEG)-lipids as provided by Pardi *et al.* (2019) (see from page 42, right column, to page 43 left column) and initially described in WO2009127060 (see *e.g.* claims 14 and 17).