

Using the common cold virus as a naturally occurring vaccine to prevent COVID-19: Lessons from Edward Jenner

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ABSTRACT

Three recent papers published in Nature, Science and Cell, all present clear evidence that there is cross-reactive T-cell immunity between human coronaviruses (229E, NL63, OC43, and HKU1), linked with the common cold, and SARS-CoV-2, the causative agent of COVID-19. Can we use this information to design and build a new vaccine based on the less pathogenic, common cold coronaviruses, for the prevention of COVID-19? If we look at the history of medicine and vaccine development, from the point of view of Edward Jenner, the answer just might be yes.

Edward Jenner, was an English surgeon, who is credited with creating the first vaccine, in 1798, which was used to combat the Smallpox virus. Jenner employed the zoonotic Cowpox virus (as a live vaccine). Using the observation that milkmaids were somehow protected against Smallpox, he hypothesized that the pus from the milkmaid's skin blisters could be used as a vaccine to inoculate other people, to protect against Smallpox. His successful clinical trial, of 23 patients, ultimately led the English Parliament to pass the Vaccination Act in 1840, making vaccination a new public health policy. His approach was used all over the world and ultimately led to the eradication of Smallpox by the WHO (World Health Organization) in 1980, nearly 40 years ago.

What can we learn today from Jenner's observations that could be useful for designing a vaccine against SARS-CoV-2? Are there any less pathogenic viruses that could be used as a vaccine against SARS-CoV-2? The answer is probably yes.

For example, there are four human coronaviruses that are known to cause the common cold, namely 229E, NL63, OC43, and HKU1, which lead to mild upper respiratory infections (URI's) [1–4]. According to the CDC, their route of transmission appears to be similar

to SARS-CoV-2, but the onset of symptoms is quite mild in comparison. <https://www.cdc.gov/coronavirus/general-information.html>

All five viruses contain a viral spike glycoprotein (VSG), which is the main target of SARS-CoV-2 vaccine development world-wide.

One attractive hypothesis is that inoculation with the common cold coronavirus (229E, NL63, OC43, or HKU1) or, more likely, an attenuated version, could provide immunity against SARS-CoV-2. If that was the case, then we might already have a naturally-occurring vaccine at hand, that could soon be implemented, off the shelf.

To begin to test this hypothesis, we retrieved the protein sequences of the relevant viral spike glycoproteins from a variety of available databases, such as UniProt/FASTA, and analysed their shared protein sequence similarity and identity using BLASTP.

Table 1 summarizes the results of this brief analysis.

Based on this simple analysis, the viral spike glycoprotein of coronavirus OC43 appears to be the

Table 1. Protein sequence identity of the viral spike glycoproteins of SARS-Cov-2 and the common cold corona viruses (229E, NL63, OC43, or HKU1).

Common Cold VSG	SARS-Cov-2 VSG
229E	27.78%
NL6	31.27%
OC43	37.65%
HKU1	36.66%

most similar to that of SARS-CoV-2, with nearly 38% identity and up to 53% similarity (Figure 1). In fact, the viral spike glycoproteins of coronavirus OC43 and HKU1 are also quite similar to each other, sharing 64% identity (Figure 2). So, both OC43 and HKU1 would

possibly be good candidates for developing a potential vaccine to SARS-CoV-2.

Is there any clinical evidence to support these assertions?

Score	Expect	Method	Identities	Positives	Gaps	
464 bits(1195)	1e-145	Compositional matrix adjust.	285/760(38%)	410/760(53%)	43/760(5%)	
Query 528	KKSTNLVKNKCVNFNENGLTGTGVLTESNKKFL-PFQQFGRDIADTTDAVRDPQTLLEILD					586 SARS-CoV-2
Sbjct 611	K +T+++ CVN++ G+ G G+ E N + +Q D RD					OC43
Query 587	KANTDIILGVCVNYDLYGILGQGFIVEVNATYYNSWQNLLYDSNGNLYGFRDYIINRTFM					720 SARS-CoV-2
Sbjct 671	ITPCSGGGVSVITPGTNTSNQVAVLYQDVNCTEVPVAIHADQLTPTWRVYSTGSNVFQTR					OC43
Query 647	IRSCYSGRVSAAFHAN--SSEPALLFRNIKCNVFNNSLTRQLQPI-----NYFDSY					704 SARS-CoV-2
Sbjct 721	AGCLIGAEHVN--NSYECDIPIGAGICASYQTQTNSPRRARSVASQSI IAYTMSLGAENS					OC43
Query 705	GC++ A + + CD+ +G+G C Y RR+R + NS					758 SARS-CoV-2
Sbjct 777	LGCVVNAYNSTAISVQTCDLTVGSGYCVDYSKN---RRSRGAIITGYRFTNFPEPTVNS					OC43
Query 759	VAYSNN-----SIAIPTNFTISVTEILPVSMKTSTVDCMTYICGDSSTECNSLLQYGS					786 SARS-CoV-2
Sbjct 837	VNDLEPVGGLYEIQIPSEFTIGNMVEFIQTSSPKVTIDCAAFVCGDYAACKSQLVEYGS					OC43
Query 810	FCTQLNRALTGIAVEQDKNTQEVF-AQVKQIYKTPPIKDFGGFNFSQILPDP-----					809 SARS-CoV-2
Sbjct 897	FC +N LT + D +V + + + + +KD FN I P					OC43
Query 869	FCDNINAILTEVNELLDTTQLQVANSLMNGVTLSTKLKDGVNFNVDINFPVGLGCLGSE					868 SARS-CoV-2
Sbjct 957	-SKPSKRSFIEDLLFNKVTADAGFIKQYGDCLGDI AARDLICAQKFNGLTVLPPLLTDE					OC43
Query 929	SK S RS IEDLLF+KV L+D GF++ Y +C G RDLIC Q + G VLPPLL++					928 SARS-CoV-2
Sbjct 1013	CSKASSRSAIEDLLFDKVKLSDVGFVEAYNNTGGAEIRDLCVQSYKIGKVLPPLLSEN					OC43
Query 989	MIAQYTSALLAGTITSGWTFGAGAALQIPFAMQMAYRFRNGIGVTQNVLYENQKLIANQFN					988 SARS-CoV-2
Sbjct 1073	I+ YT A + ++ WT AG +PF + + YR NG+GVT +VL +NQKLIAN FN					OC43
Query 1049	QISGYTLAATSASLFPPTAAAG----VPPYLVNQRINGLVMTDVLSONQKLIANAFN					1012 SARS-CoV-2
Sbjct 1133	SAIGKIQDLSLSTASALGKLQDVVNQNAQALNTLVKQLSSNFGAISSVLDLILSRDLKVE					OC43
Query 1108	+A+ IQ+ +T SAL K+Q VVN NA+ALN L++QLS+ FGAIS+ L +ILSRDL +E					988 SARS-CoV-2
Sbjct 1193	NALYAIQEGFDATNSALVKIQAVVNANAEALNNLLQQLSNRFGAISASLQELILSRDLDALE					OC43
Query 1168	AEVQIDRLITGRLQSLQTYVTYVQQLIRAAEIRASANLAATKMSCEVLGQSKRVDFCGKGYH					1048 SARS-CoV-2
Sbjct 1253	AE QIDRLI GRL +L YV+QQL + ++ SA A K++ECV QS R++FCG G H					OC43
Query 1227	AEAQIDRLINGRLTALNAYVSQQLSDSTLVKFSAAQAMEKVNCEVKSSRINFCGNGNH					1132 SARS-CoV-2
Sbjct 1312	LMSFPQSAPHGVVFLHVTVYVPAQEKNFHTTAPAICHDG-KAHFPREGVFSNGTHWFVTQR					OC43
Query 1108	++S Q+AP+G+ F+H +YVP + +P +C G + P+ G FV+ W T					1107 SARS-CoV-2
Sbjct 1193	IISLVQNAPYGLYFIHFSYVPTKYVTVARVSPGLCIAGDRGIAPKSGYFVNVNNTWMTGS					OC43
Query 1168	NFYEPQIITTDNTFVSGNCDVVIGIVNNTVYDPLQPELDSFKEELDKYFKNHTSPDVDLG					1167 SARS-CoV-2
Sbjct 1253	+Y P+ IT +N V C V + + P L FKEELD++FKN TS DL					OC43
Query 1227	GYYYPEPITENNVMVSTCAVNYTKAPVMLNTSIPNLPDFKEELDQWFKNQTSVAPDLS					1252 SARS-CoV-2
Sbjct 1312	DISGINASVVNIQKEIDRLNEVAKNLNESLIDLQELGKYEQYIKWPWYIWLGF-IAGLIA					1226 SARS-CoV-2
Query 1227	+ IN + +++Q E++RL E K LN+S I+L+++G YE Y+KWPWY+WL +AG+					OC43
Sbjct 1312	-LDYINVTFLDLQVEMNRLQEAIKVLNQSINLNKDIGTYEYVYKWPWYVWLLICLAGVAM					1311 SARS-CoV-2
Query 1227	IVMVTIMLCCMTSCCSCLKGCSCGSCCKFDEDDSEPVLK					1266 SARS-CoV-2
Sbjct 1312	+V++ + CC SC K CG CC E V+K					OC43
Query 1227	LVLLFFICCTGCGTSCFK---KCGGCCDDYTGQELVIK					1348 SARS-CoV-2

Figure 1. Protein sequence alignments of the Viral Spike Glycoproteins (VSGs) from SARS-CoV-2 and the related Human Coronavirus OC43. Areas of high sequence homology are highlighted in color, which may represent potentially shared epitopes for immune recognition. Generated using the online program BLASTP, by pairwise sequence analysis.

Score	Expect	Method	Identities	Positives	Gaps	
1817 bits(4707)	0.0	Compositional matrix adjust.	883/1381(64%)	1079/1381(78%)	58/1381(4%)	
Query 1		MFLILLISLPTAFAVIGDLKCTSDNINDKDTGPPPISTDTVDVTNGLGTYYYVLDLRYVLT			60	OC43
Sbjct 1		MFLI+ I LPT AVIGD CT+ IND + P IS D VDV+ GLGTYYYL+RVYVLT			59	HKU1
Query 61		TLFLNGYYPTSGSTYRNMALKGSVLLSRLWFKPPFLSDFINGIFAKVKNKTKVIKDRVMYS			120	OC43
Sbjct 60		TLFLNGYYPTSGSTYRNMALKGSVLLSRLWFKPPFLSDFINGIFAKVKNKTKVIKDRVMYS			119	HKU1
Query 121		EFPAITIGSTFVNTSYVQVPTINSTQDGNKLGLEEVSVQYNMCEYPTQICHPNL			180	OC43
Sbjct 120		EFSTIVIGSVFVNTSYTVVQPH-----NGILEITACQYTMCEYPHTVCKSK-			166	HKU1
Query 181		GHRKELWHLDTGVVSCLYKRNFTYVDVNADLYLPHFYQEGGTFYAYFTDQVVTKFLFNV			240	OC43
Sbjct 167		GSRNESWHIDSSEPLCLFKNFTYVNSADWLYLPHFYQERGVFYAYADVGMPTTFLFSL			226	HKU1
Query 241		YLGMAISHYYVPLTCNS-----KLTLEYWVTPLTSRQYLLAFNQDGIIFNAEDCMSDF			294	OC43
Sbjct 227		YLG LSHYYVPLTCN+ TLEYWVTP+ RQYLL F++ G+I NA DC S F			286	HKU1
Query 295		MSEIKCKTQSIAPPTGVYELNGYTVQPIADVRRKPNLPCNIEAWLNDKSVSPPLNWER			354	OC43
Sbjct 287		LSEIQCKTQSFAPNTGVYDLSGFTVVKPVATVYRRIPNLPCDDIDNWLNNVSPPLNWER			346	HKU1
Query 355		KTFSNCFNMSLSMFIQADSFTCNNIDAAKIYGMCFSSITIDKFAIPNGRQVLDLQGLN			414	OC43
Sbjct 347		RIFSNCFNLSLTLRLVHVSFSCNLDKSKIFGSCFNISITVDKFAIPNRRRDDLLQGLS			406	HKU1
Query 415		GYLQSFNYRIDTTATSCQLYNLPAAVSVSRFNPSTWNKRFGFIEDSVFKPRPAGVLTN			474	OC43
Sbjct 407		GFLQSSNYKIDISSSCQLYSLPLVNVTTINNFNPSSWNRRYGF-----GSFNLS			457	HKU1
Query 475		HDVVYAQHCFAKPKNFCPC---KLNKSGCVSGPGKNGIGTCTPAGTNYLTCD-----			523	OC43
Sbjct 458		YDVVYSDHCFVNSDFPCADPSVNSCAKSKPPS---AICPAGTKYRHCDDLTLYVK			513	HKU1
Query 524		----NLCTPDPITFTGTQKSLVIGEHCSGLAVKSDYCG----GNSCTCRPQAF			575	OC43
Sbjct 514		NWCRCSCLPDPITSTYSPNTCPQKVVVIGIEHCPLGINEEKGCTQLNHSSCFSPDAFL			573	HKU1
Query 576		GWSADSCLOGDKCNIFANFILHDVNSGLTCTDLDQKANTDILGVCVNYDLYGILGQGIF			635	OC43
Sbjct 574		GWSFDSGISNRCNIFSNFIFNGINSGTCSNDLLYSNTEISTGVCVNYDLYGITGQGIF			633	HKU1
Query 636		VEVNATYYNSWQNLLYDSNGNLYGFRDYIINRTFMIRSCYSGRVSAAFHANSSEPALLFR			695	OC43
Sbjct 634		KEVSAAYYNNWQNLLYDSNGNIIGFKDFLTNKTYTILPCYSGRVSAAFYQNSSSPALLYR			693	HKU1
Query 696		NKCNVFNNSLTRLQPIYFDSYLGCVVNAVNSTAISVQTCDLTVGSGYCVDYD--KN			753	OC43
Sbjct 694		NLKCYSVLLN--ISFISQPF--YFDSYLGCVLNAVNLTSYVSSCDLRMGSGFCIDYALPSS			751	HKU1
Query 754		RRSRGAIITGYRFTNEPEFTVNSVNDLSEPVGGLYEIQIPSEFTIGNMVEFIQTSSPKVT			813	OC43
Sbjct 752		RRRRGISSPYRFVTFEFPNVSVNDSVETVGGFELIPIQIPNTFTIAGHEEFIQTSSPKVT			811	HKU1
Query 814		IDCAAFVCGDYAACKSQLVEYGSFCDNINAILTEVNELLDTTQLQVANSLMNGVTLSTKL			873	OC43
Sbjct 812		IDCSAFVCSNYAACHDLLSEYGTFCDNINSILNEVDLLDITQLQVANALMQGVTLSSNL			871	HKU1
Query 874		KDGVNFDVDDINFSPVLGCLGSECSKASSRSAIEDLLFDKVKLSDVGFVEAYNNCTGGAE			933	OC43
Sbjct 872		NTNLHSDVDNIDFKSLGLGSGQC--SSRSLEDDLLFNKVKLSDVGFVEAYNNCTGGSE			930	HKU1
Query 934		IRDLICVQSYKGIKVLPPLLSENQISGYTLAATSASLFPWPWAAAGVPPYLNQYRINGL			993	OC43
Sbjct 931		IRDLLCVQSFNGIKVLPILSETQISGYTTAATVAAMFPWAAAGVPPYLNQYRINGL			990	HKU1
Query 994		GVTMVLSQNKLIANAFNLYAIQEGFDATNSALVKIQAVVNANAALNLLQQLSNR			1053	OC43
Sbjct 991		GVTMVLSQNKLIANAFNLYAIQEGFDATNSALVKIQAVVNANAALNLLQQLSNR			1050	HKU1
Query 1054		FGAISASLQEILSRDLDAEAQIDRLINGRLTALNAYVSQQLSDTLVKFSAQAQMEKV			1113	OC43
Sbjct 1051		FGAISASLQEILSRDLDAEAQIDRLINGRLTALNAYVSQQLSDTLVKFSAQAQMEKV			1110	HKU1
Query 1114		NECVKSQSRINFCGNGNHIISLVQNPYGLYIFHFSYVPTKYVTARVSPGLCIAGDRGI			1173	OC43
Sbjct 1111		NECVKSQSRINFCGNGNHIISLVQNPYGLYIFHFSYVPTKYVTARVSPGLCIAGDRGI			1170	HKU1
Query 1174		APKSGYFVNVNNTWMTGSGYYPPEPIETENNVVMSTCAVNYTKAPYVMLNTSIPNLPDF			1233	OC43
Sbjct 1171		APKQGYFIKQNSWMTGSSYYPPEPISDKNVVFMNSCVNFTKAPFIYLNNSIPNLPDF			1230	HKU1
Query 1234		KEELDQWFKNQTSVAPDLSL--YINVTFLDLQVEMNRLQEAIKVLNQSYINLKDITGYEY			1292	OC43
Sbjct 1231		EAELSLSWFKNHTSIAPNLTFSHINATFLDLYEMNVIQESIKLSNSSFINLKEIGTYEM			1290	HKU1
Query 1293		YVKWPWYVWLLIICLAGVAMLVLLFFICCTCGCTSCFKKCGGCCDDYTGQELVIKTSHD			1352	OC43
Sbjct 1291		YVKWPWYVWLLIIVLFIIFLMLFFICCTCGCSACFSKCHNCDEYGGHDFVIRASHD			1350	HKU1
Query 1353		D 1353				
Sbjct 1351		D 1351				

Figure 2. Protein sequence alignments of the Viral Spike Glycoproteins (VSGs) from two related Human Coronaviruses, namely OC43 and HKU1. Note the high homology between OC43 and HKU1, with up to 78% similarity. Generated using the online program BLASTP, by pairwise sequence analysis. The same potentially shared epitopes, highlighted in color in Figure 1, are also highlighted here, for comparison.

Three recent papers published in Nature, Science and Cell have begun to look at the existence of cross-reactive immunity in a variety of patient populations, especially patients infected with the SARS-CoV-2 (with frank COVID-19 or asymptomatic) and uninfected patients. The results are all quite encouraging, directly demonstrating cross-reactive T-cell immunity between SARS-CoV-2 and the existing known human cold coronaviruses (229E, NL63, OC43, and HKU1) [5–7]. One of the papers also detected cross-reactive serum IgG as well.

These reports clearly provide tantalizing clinical evidence for the feasibility of using a human cold coronavirus, such as attenuated OC43 or HKU1, as a potential vaccine for the prevention of COVID-19. What would Edward Jenner suggest, if he was living today?

Further support for this idea has recently appeared in the popular press and was supported by data from the National Institutes of Health (NIH), because there is significant shared serological cross-reactivity between SARS-CoV-2, OC43 and HKU1 [8, 9].

Fortunately, two live coronaviruses, OC43 and 229E, associated with the common cold, are actually

commercially available from the American Type Culture Collection (ATCC), which could greatly facilitate their potential use in new, off-the-self, vaccine development.

<https://www.lgcstandards-atcc.org/products/all/VR-1558.aspx>

<https://www.lgcstandards-atcc.org/products/all/VR-740.aspx>

Moreover, the VSGs from OC43 and HKU1, may also be sufficient to convey cross-reactive immunity, when recombinantly-inserted in another non-pathogenic viral vector, specifically designed for live or attenuated vaccine immunizations (Figure 3).

Ultimately, this may be a safer approach, than using the VSG from SARS-CoV-2, which may have mild negative, or even pathogenic, side-effects. Only time will tell.

Nature may have already done the “experiment” or “clinical trial” for us, as so many people that are SARS-CoV-2 virus-positive, are asymptomatic and show evidence of cross-reactive immunity, to both SARS-CoV-2 and the common cold coronaviruses.

These findings have been independently confirmed now, in several different laboratories world-wide.

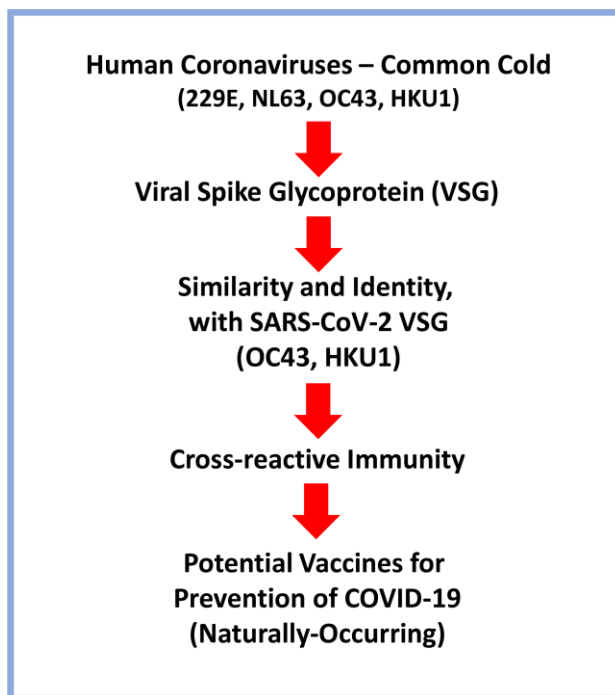


Figure 3. Schematic diagram summarizing the possible use of Human Coronaviruses that cause the common cold as naturally-occurring vaccines for targeting SARS-CoV-2 and preventing COVID-19. A brief flow-diagram is presented, outlining a vaccine development strategy.

UNIPROT accession numbers for 5 relevant protein sequences:

P0DTC2,
SPIKE_SARS2 Spike glycoprotein, Severe acute respiratory syndrome coronavirus 2

<https://www.uniprot.org/uniprot/P0DTC2.fasta>

Q6TUL7,
CVH22 Spike glycoprotein Human coronavirus 229E

<https://www.uniprot.org/uniprot/Q6TUL7.fasta>

Q6Q1S2,
SPIKE_CVHNL Spike glycoprotein Human coronavirus NL63

<https://www.uniprot.org/uniprot/Q6Q1S2.fasta>

P36334,
SPIKE_CVHOC Spike glycoprotein Human coronavirus OC43

<https://www.uniprot.org/uniprot/P36334.fasta>

Q0ZME7,
SPIKE_CVHN5 Spike glycoprotein Human coronavirus HKU1

<https://ebi10.uniprot.org/uniprot/Q0ZME7.fasta>

AUTHOR CONTRIBUTIONS

FS and MPL conceived the ideas presented, performed the protein sequence homology analysis and wrote the text of the article. MPL prepared the figures. Both authors edited and approved the final version of the article, prior to journal submission.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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Serologic cross-reactivity of SARS-CoV-2 with endemic and seasonal Betacoronaviruses. Version 1. medRxiv. Preprint. 2020.
<https://doi.org/10.1101/2020.06.22.20137695>

SUPPLEMENTARY MATERIALS

Note Added in Proof

After this *Perspective Article* was submitted for peer-review, another relevant paper appeared in the *British Medical Journal (BMJ)*, highlighting the role of human coronaviruses associated with the common cold in conferring cross-reactive immunity to SARS-CoV-2 in the world population.

<https://www.bmj.com/content/370/bmj.m3563.full>

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