

Twitter Thread by rubic3n



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Fondation Merieux

2017

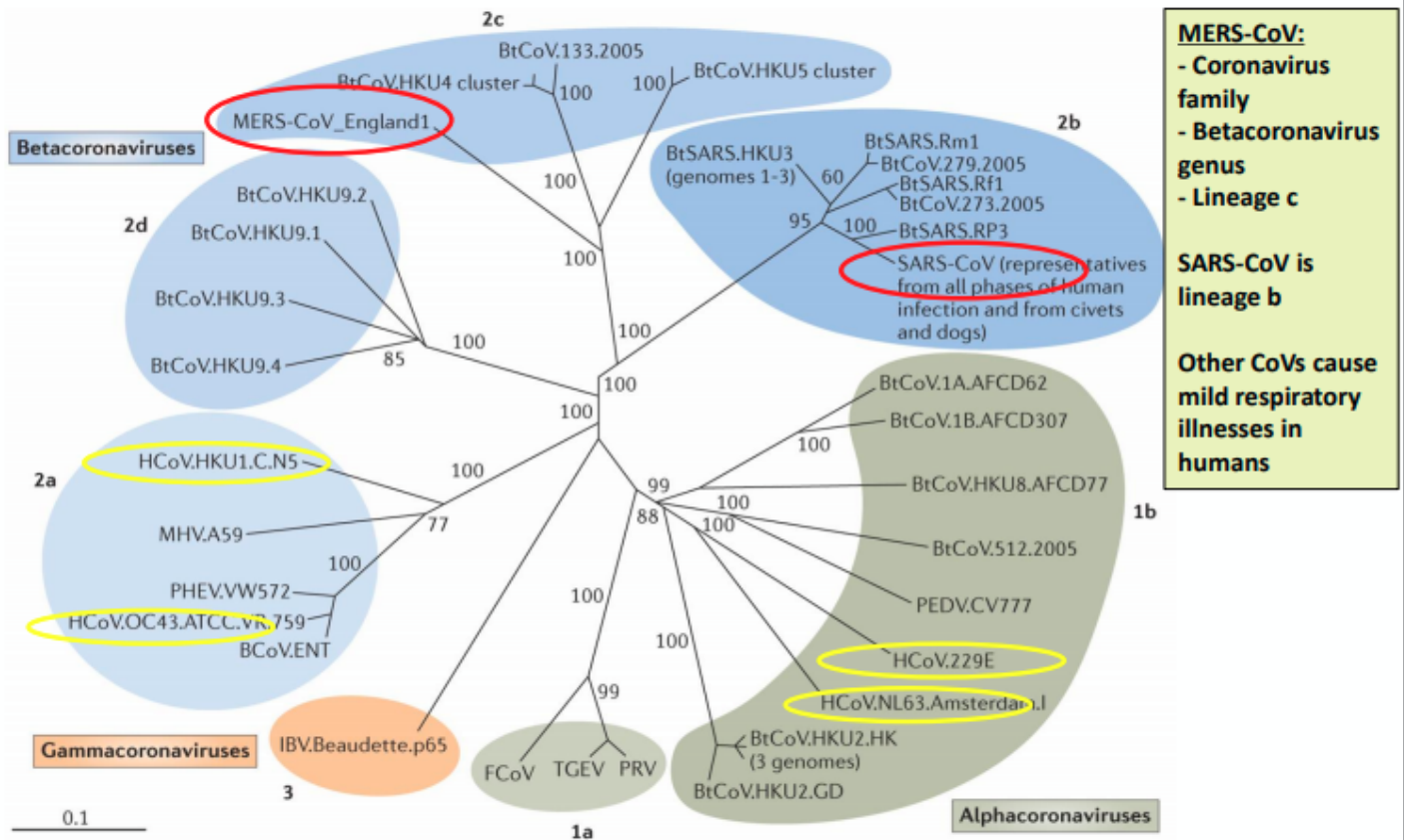
**Pushing the
CEPI Dialogue**

Excellent presentation to see, how they, including Bancel, had layed out the narrative.

Quess, what they had specifically included in their list of targeted viruses?

<https://t.co/J5FDe6W986>

MERS-CoV as a target EID vaccine



MERS-CoV:
 - Coronavirus family
 - Betacoronavirus genus
 - Lineage c

SARS-CoV is lineage b

Other CoVs cause mild respiratory illnesses in humans

Graham RL, Donaldson EF, Baric RS. Nat Rev Microbiol. 2013 Dec;11(12):836-48.

Nature Reviews | Microbiology



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CEPI

Almost basking about their list being more inclusive, more emergent viruses based.

<https://t.co/J5FDe6W986>

Priority pathogens

CEPI Initial List

Group 1: first choice for funding

- Chikungunya
- Coronaviruses (MERS)
- Filoviruses
- Rift Valley fever
- West Nile

Group 2: Additional choice for funding: Lassa, Nipah, Paratyphoid A, Plague

Group 3: Targets without candidate vaccines: Congo-Crimean hemorrhagic fever, severe fever with thrombocytopenia, Zika

WHO List

- Arenavirus hemorrhagic fevers (Lassa)
- Congo-Crimean hemorrhagic fever
- Filovirus diseases (Ebola, Marburg)
- MERS
- Other pathogenic coronaviruses (SARS)
- Nipah
- Rift valley fever
- Severe fever with thrombocytopenia syndrome
- Zika
- Disease X

15



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Narrative: "Look, what ZIKA has done to your populace. Nasty ZIKA."

How much of that ZIKA damage was actually related to a virus? Was there a computer guy, who had invested in mosquitos as a vector?

<https://t.co/J5FDe6W986>

Incentivizing vaccines for EIDs

Millions in Ebola funding, a casualty of Zika virus, may not be replenished

By DYLAN SCOTT / JUNE 1, 2016



Funding for neglected “tropical” diseases with and without Ebola, GHTC 2016



10

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What is the advances of a programme like CEPI.

And for who?

Let me translate: They want a coordinated vaccine production, with only one strong production pipeline, and solidly regulated pathways.

Provide the incentives for big pharma.

They've made it.

Challenges for EID vaccines

1

The pipeline is weak for most emerging infectious diseases characterized by lack of market incentives

2

Unilateral, uncoordinated government efforts to fund R&D preparedness are inefficient and unsustainable in addressing global epidemic risks

3

Clinical & regulatory pathways are not easily adaptable to epidemic contexts

4

Incentives are lacking to motivate greater industry engagement

12



Vision - look at nasty ZIKA, you surely do not want that

Mission - get the pipeline going of (only) the big ones

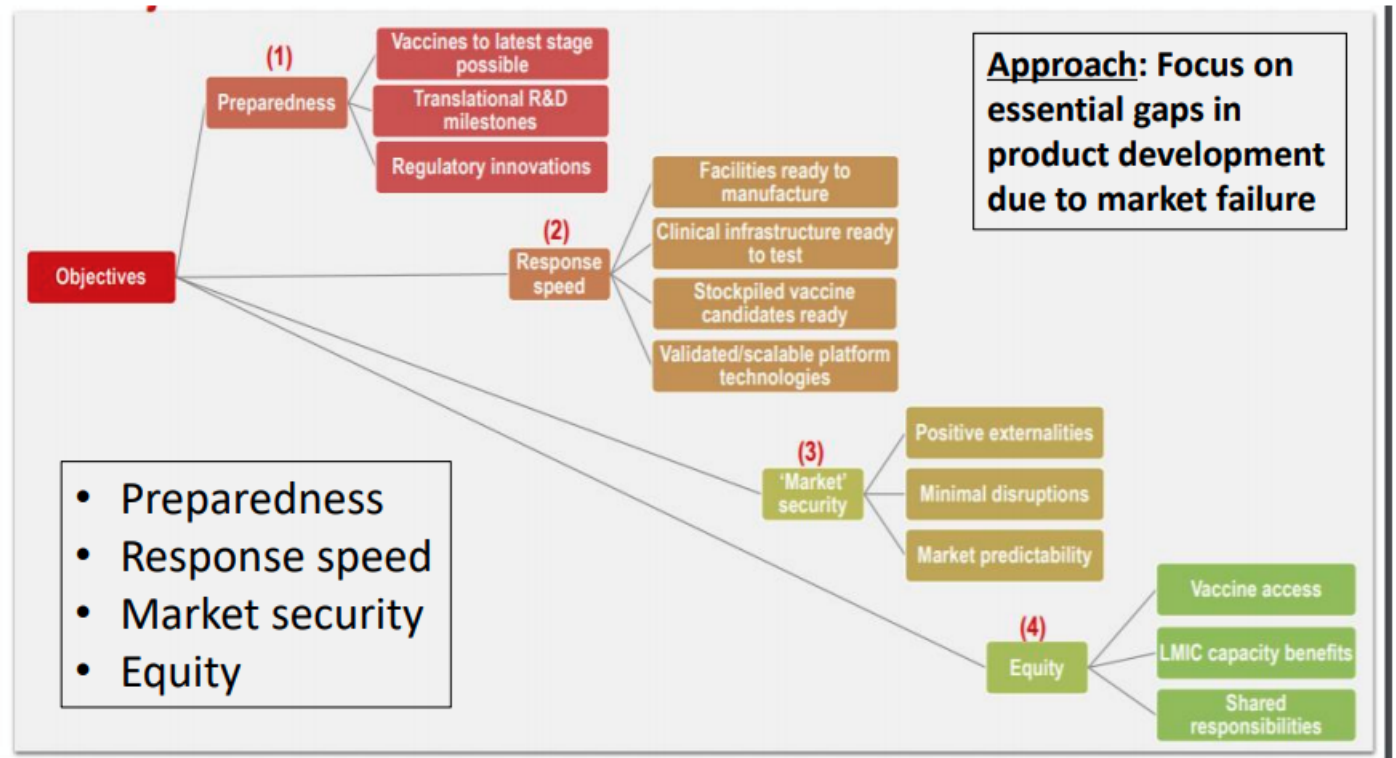
Scope - the anti-cancer platforms with their DNA, mRNA basis fit perfectly. They so far do not sell very well, but they could be recycled.

Correct me, if I am wrong.

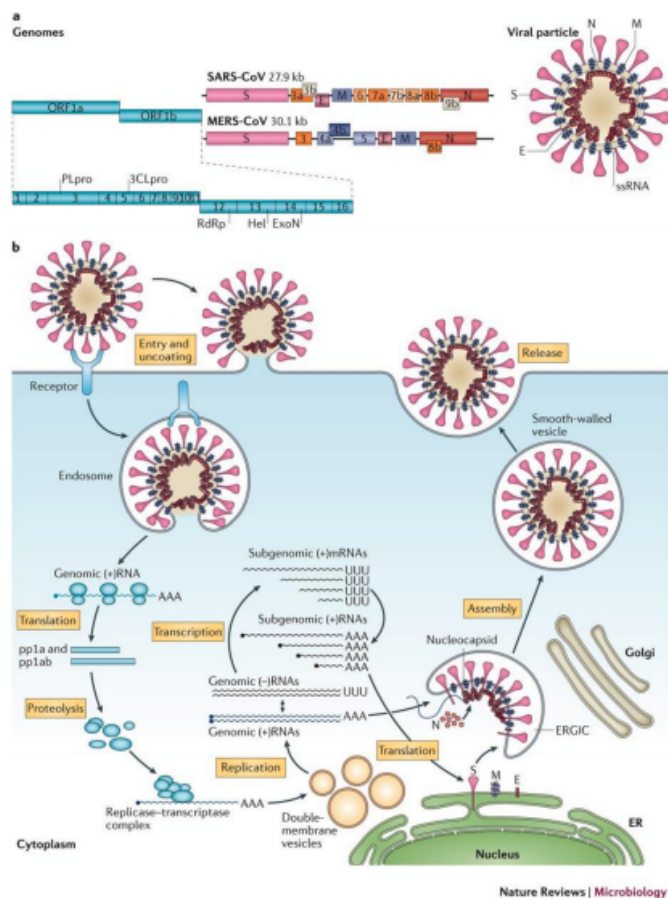
Vision	Vaccines can prevent outbreaks from becoming health, economic and humanitarian crises.
Mission	Prioritize, stimulate, finance and coordinate vaccine development against EIDs with epidemic potential, especially in cases where market incentives alone do not achieve this.
Scope	End-to-end approach to vaccine development 1. Advance EID vaccines through late preclinical studies to proof of concept and safety in humans, and 2. Develop platforms that can be rapidly deployed against known and unknown pathogens.

How to create your own market and exclude competitors right from the start.
Start even before the 'incident' - which will give you more advantage of your competitors.
'Booster' it. ZIKA, MERS?
Get people used to the forced vaccine narrative with measles?

Correct me, if I am wrong



MERS-CoV background



- 30 kb enveloped, single-stranded, positive-sense RNA virus
- 4 structural proteins: spike (S), envelope (E) matrix (M), nucleocapsid (N)
- S protein is primary target for neutralizing Abs during natural MERS-CoV infection
- S1 subunit contains **receptor-binding domain (RBD)**
- Host cell receptor for RBD is **dipeptidyl peptidase 4 (DPP4 or CD26)**

de Wit E et al. Nat Rev Microbiol. 2016 Aug;14(8):523-34.



MERS in Korea

Why not try it out and create some interesting PR pictures at the same time?

<https://t.co/hrCU2xVi3U>

MERS in Korea



- About 17,000 people quarantined
- Massive disruption
- Huge economic impact



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CEPI sales presentation

They were envisaging 3 different vaccines:

- quick response but not long lasting immunity
- long lasting immunity vaccines for specific groups of people
- vaccinating animals because of the animal reservoir.

ALL the markets

WHO MERS R&D roadmap and TPP

- Develop and license vaccine suitable for reactive use in outbreak settings with rapid onset of immunity
- Develop and license vaccine with long-term protection for administration to those at high ongoing risk of MERS-CoV such as healthcare workers and those working with potentially infected animals
- Dromedary camel vaccine: Develop and license a vaccine suitable for administration to camels to prevent transmission of MERS-CoV from animal reservoir to humans

Modjarrad et al, Nat Med 2016; 22:70

1

WHO R&D Blueprint <http://www.who.int/csr/research-and-development/en/>

24



Nicola Bidoli, let us just pretend, you were still around here.

MERS Vx trial run?

Can you spot Baculovirus, production in mice, sf9, VLP, full length S trimers here.

We can already spot Novavax here, doing a trial run.

I am sure, you would spot more.

<https://t.co/J5FDe6W986>

MERS-CoV vaccine pipeline (1)

Vaccine type	Vaccine name	Design	Animal immunogenicity	Animal protection	Stage of development	Sponsor/ Developer
DNA	GLS-5300	Plasmid DNA encoding full-length S; with electroporation	C57BL/6 mice, rhesus, camels	Rhesus	Phase I ongoing in the US	GeneOne/Inovio
Protein subunit	MERS-S	Nanoparticles of full-length S trimers; with Matrix-M adjuvant	BALB/c mice	Transduced mice	Preclinical; SAB-301 polyclonal Abs from transgenic cows in Phase I	Novavax
	MERS-CoV VLP	VLP of S, E, M in baculovirus/Sf9; with alum	Rhesus	-	Preclinical	Jiangsu Center, China
	S-RBD-Fc	S1-RBD subunit fused with human Fc; with various adjuvants	BALB/c mice, rabbits	Transduced mice	Preclinical	New York Blood Center; Fudan Univ; Central South Univ
	MERS-CoV rRBD	Truncated S1-RBD subunit; with alum	BALB/c mice, rhesus	Rhesus	Preclinical	China CDC
Heterologous prime-boost	S-DNA/S1 Protein	Plasmid DNA encoding full-length S (prime) + S1 subunit (boost)	BALB/c mice, rhesus	Rhesus	Preclinical	US NIH/VRC

MERS Vx trial run

More good old known here

Nice sandbox toy area. Look who is all at play.

German PEI in it as well with a Measles Vector.

Drosten with a DZIF minimal vector approach.

And also some recombinant.

The REAL GERM GAMES

Sandbox. Give it a try.

MERS-CoV vaccine pipeline (2)

Vaccine type	Vaccine name	Design	Animal immunogenicity	Animal protection	Stage of development	Sponsor/ Developer
Vector	MVA-S	MVA vector with full-length S	BALB/c mice, camels	Transduced mice, camels	Preclinical; Phase I planned in Germany	DZIF consortium
	ChAdOx1-MERS-S	Chimp adenovirus 3 with full-length S	Mice	Mice	Preclinical; Phase I planned in UK	Jenner Institute, UK
	MERS-S/MERS-solS	Measles vector with full-length S/solS	IFNAR -/- mice	Transduced mice	Preclinical	Paul Ehrlich Insitut; German Cent for Inf Res
	Ad5-S & Ad41-S	Human adenovirus vector with full-length S	BALB/c mice	-	Preclinical	China CDC
	GreMERSfi	Human adenovirus 5 vector with full-length S	Mice	-	Preclinical	Greffex
Live recombinant	rMERS-CoV-ΔE	Recombinant without E	-	-	Preclinical	Universidad Autonoma de Madrid

Oh, and look

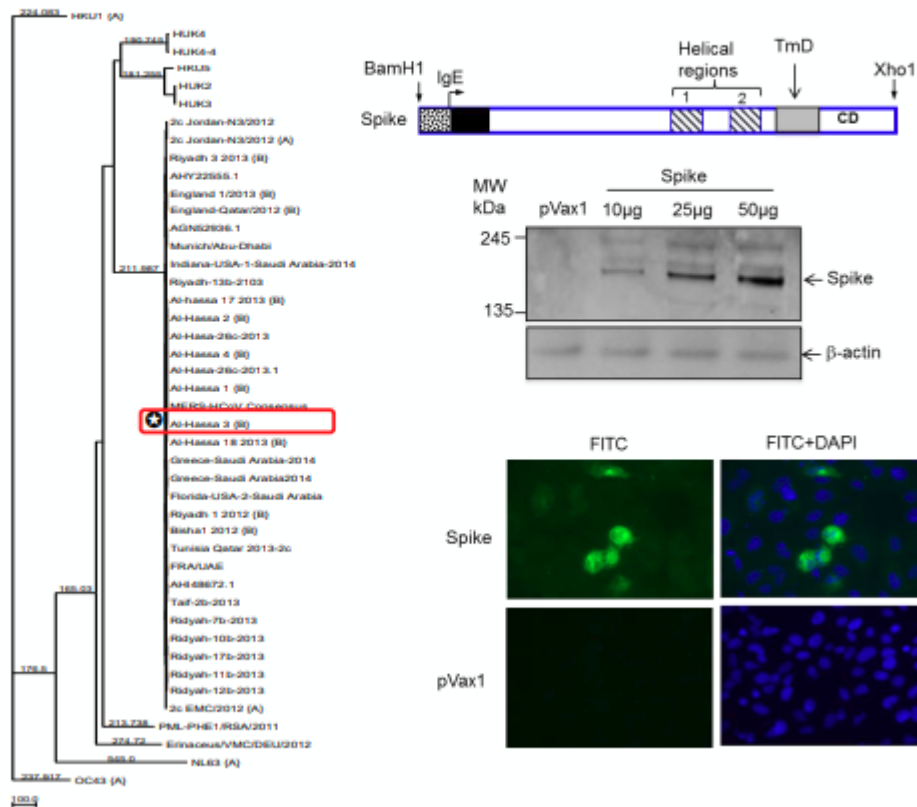
GeneOne Inovio is on board as well sailing the sandbox of a fading vx platform booster outbreak.

GeneOne/Inovio DNA vaccine

Most advanced candidate in development

pVax1 plasmid DNA coding full-length S glycoprotein using consensus sequence

Given with electroporation



27



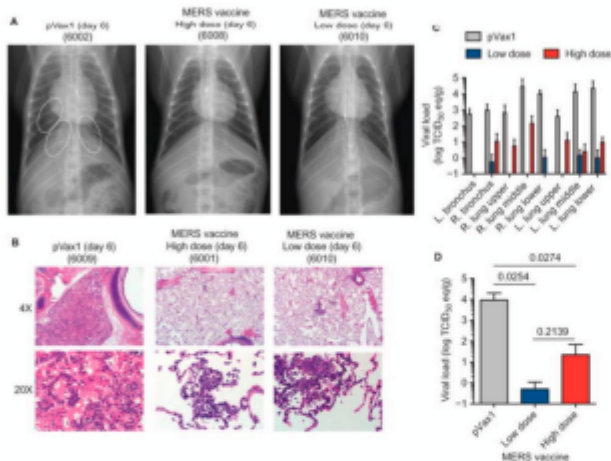
They knew what to look for - what makes a good immune response for a vaccine:
Antibodies and

Induction of strong T-cell immune responses

- Antigen specific CD4+ and CD8+
- Multiple epitopes recognized across length of S protein

Have they forgotten about cellular response now?

Rhesus immunogenicity and protection



- 12 rhesus macaques at control, low and high dose at 0, 3, 6 wks
- Challenged at 11 wks (4 wks after 3rd dose)
- Full protection by radiography

- Binding & neutralizing antibodies
 - Seroconversion and induction of strong MERS-CoV Spike specific bAb responses after single immunization
 - bAb titers: 10^4 - 10^5
 - nAb titers: 1:80-240 post dose 3
- Cellular immune responses
 - Induction of strong T-cell immune responses
 - Antigen specific CD4+ and CD8+
 - Multiple epitopes recognized across length of S protein

Muthumani K et al. Sci Transl Med. 2015 Aug 19;7(301):301ra132.



Human Trial MERS vax sandbox arena

They were even then working on a multi jab approach. Here they were looking at three jabs.

Dose 1: week 1

Dose 2: week 5

Dose 3: week 14

1 month, 3 months

75 people

Phase I first-in-human MERS vaccine trial

- Randomized, open-label trial of GeneOne MERS DNA vaccine (GLS-5300)
 - 75 healthy adults in 3 dose groups (0.67 mg, 2 mg, 6 mg)
 - Vaccinations at 0, 4 and 12 weeks administered by electroporation
- Primary objective
 - Safety up to 60 wks
- Secondary objectives
 - Immunogenicity
 - 1, 2, 3 and 4 wks after 1st dose
 - 2 wks after 2nd dose (i.e., at 6 wks)
 - 2 wks after 3rd dose (i.e., at 14 wks)
 - 3, 6 and 12 mos after 3rd dose (i.e., at 24, 36 and 60 wks)

Study update

- Fully enrolled
- All study visits completed
- Vaccine has been safe & well tolerated
- No Serious Adverse Events reported

Sponsor: GeneOne Life Science Inc.
PI: Kayvon Modjarrad MD
Clinical Trials Gov: NCT02670187

29



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"MERS-CoV vaccine landscape will change dramatically in near future"

Yes, mRNA was in the pipeline. Still restricted by the toxicity of the LNP (Moderna first major pipeline). Bancel moved on to Moderna.

<https://t.co/hsnNHePvRw>

- MERS-CoV vaccine landscape will change dramatically in near future
- CEPI grant results to be announced by end of 2017
- Accelerate pace of clinical development
- However, inherent challenges to EID vaccines



Up until very recently the LNP formulation had many problems, causing increasingly allergic reactions in test subjects with each dose. This was solved with their new PEG LNP formula, apparently.

Moderna co founder in a 2016 paper: pic.twitter.com/lxcEZgKH2n

— realism fan \u73b0\u5b9e\u4e3b\u4e49\u7231\u597d\u8005 (@realism_fan) October 7, 2021

Giuseppe Ciaramella | Chief Scientific Officer

Valera - fully owned by Moderna

Has certainly brought the LNP development further

<https://t.co/usCgynv5wU>

Complete history of Giuseppe Ciaramella stock trades at Beam Therapeutics

Date	Company	Insider	Transaction	Shares	Price per share	Total value	Shares after ⓘ	Source
29 Dec 2021	BEAM	Giuseppe Ciaramella President and CSO	Option	39,700	\$0.67	\$26,599	102,473	↗
22 Dec 2021	BEAM	Giuseppe Ciaramella President and CSO	Option	2,607	\$7.22	\$18,823	65,380	↗
20 Dec 2021	BEAM	Giuseppe Ciaramella President and CSO	Option	29,393	\$7.22	\$212,217	87,877	↗
17 Sep 2021	BEAM	Giuseppe Ciaramella President and CSO	Option	18,012	\$0.67	\$12,068	62,773	↗
28 Jun 2021	BEAM	Giuseppe Ciaramella President and CSO	Option	78,580	\$17.00	\$1,335,860	123,341	↗
5 Mar 2021	BEAM	Giuseppe Ciaramella President and CSO	Option	4,030	\$0.67	\$2,700	19,761	↗
30 Dec 2020	BEAM	Giuseppe Ciaramella President and CSO	Option	55,842	\$0.95	\$53,050	15,731	↗
30 Sep 2020	BEAM	Giuseppe Ciaramella President and CSO	Option	3,731	\$0.67	\$2,500	3,731	↗

A sight aside on
 MODERNA LNP and the 'competitive landscape of mRNA vaccines'
 Patents 069 435
 #Patents #435 & #069

<https://t.co/iAka69L1RO>

A sight aside on
 MODERNA LNP and the 'competitive landscape of mRNA vaccines'
 Part II
 Patents 069 435
 #Patents #435 & #069
<https://t.co/68QlxcsojH>

Another just aside

MODERNA patents
 Patents 069 435
 #Patents #435 & #069
 Lawyers
<https://t.co/sLMtQwd0i8>
<https://t.co/8dCSyAKJgd>
 Property Dispute
<https://t.co/saorrrZ8E1>
 Arbutus '19 article
<https://t.co/d1B0lbdWBm>
 Arbutus '20 article
<https://t.co/qbWjWBXY1I>

Back to the sandbox MERS approach
 They knew what they let themselves in for in 2017

Challenges for MERS-CoV human vaccines

- **Animal models not ideal**
 - Transduced mice, transgenic mice, rhesus, marmosets, camels
- **No immune correlate of protection in humans**
- **Protective immune response unclear**
 - Broad immune responses may be needed (high mutation rate of CoVs)
 - Cross-neutralizing Abs; T cells to multiple S epitopes
- **Scientific risks**
 - E.g., theoretical risk of enhancement
- **Difficulty in demonstrating efficacy in field**
 - Regulatory innovations

IVI is an International Organization dedicated to Global Health



Global Vaccine Research Institute

- HQ and labs at Seoul National University
- Field programs in 29 countries: Asia, Africa, Latin America
- 12 nationalities in workforce of ~130

OECD-recognized International Organization (not for profit)

- UNDP initiative
- First international organization in Korea (1997)
- 35 countries and WHO as state parties

