KnowGenix
sustainable strategies

KnowGenix *Insights*

No.5.May 2020

COVID 19 Vaccines and Therapies

Promise, Prospects, and Perils

COVID 19 Vaccines and Therapies: Promise, Prospects, and Perils

December 2019, will be remembered as one of the major milestones in human history, when a novel coronavirus pneumonia rose from the wet markets of Wuhan, China, where animal-to-human transmission transformed to human-to-human transmission. What followed was a catastrophic sequence of events enveloping global nations it stopped the wheels of global economy bringing it to a grinding halt.

The days that followed changed healthcare; industrial and societal systems in unimagined ways. Millions of views from experts, media and industry overwhelmed global communities. Even as the virus was heading towards peak levels the wheels of commerce chugged along offering survival plans in a Post Covid phase. While millions of dollars were committed to advanced research into therapies and vaccines, the more serious issues of starvation and nutrition emerged to pose further challenges. Debate rages on economic and psychological effects of lockdowns, large scale migration of labour, healthcare practices, malnutrition, efficacy and viability of vaccines in different geographies. In countries like India with low healthcare infrastructure the debate now ranges on how do we save our hospitals to save lives.

This discussion focuses on the promise of some of the most prospective vaccine and therapy platforms; the strategy of companies in fast tracking vaccine and therapies for COVID 19 and more importantly the perils in taking vaccines to the markets without insights into the inherent dynamics of vaccines and immune systems.

The rage of pathogens

While university labs and the industry have been announcing breakthroughs in new vaccines at a pandemic pace, the World Health Organization (WHO), the Centers for Disease Control and Prevention (CDC), and the FDA sounded a cautious note; that there are currently no medications or vaccines proven to be effective for the treatment or prevention of SARS-CoV-2.

Till date here are no specific therapies approved by the U.S. Food and Drug Administration (FDA) for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 COVID-19. Several agents are being used under clinical trial and compassionate use protocols based on *in vitro* activity (against SARS-CoV-2 or related viruses) and on limited clinical experience.

Coronaviruses (CoVs) are positive-sense, single-stranded RNA viruses of the family Coronaviridae (subfamily Coronavirinae) that infect a wide host range to produce diseases ranging from common cold to severe/fatal illnesses. The novel virus was initially named “2019-nCoV” which was changed to “SARS-CoV-2” by the Coronavirus Study Group (CSG) of International Committee on Taxonomy of Viruses (ICTV), since it was found to be the sister virus of severe acute respiratory syndrome coronavirus (SARS-CoV).1

Many nations are diverting their best efforts for the implementation of appropriate preventive and control strategies. Neither vaccines nor direct-acting antiviral drugs are available for

the treatment of human and animal coronavirus infections (1) . Many efforts have been directed to develop vaccines against human CoV infections in recent decades, but a limiting factor is the degree of cross-protection rendered by these vaccines due to their extensive sequence diversity (2)

Various vaccines, immunotherapeutics, and drug options have been explored during the recent threats of Zika, Ebola, and Nipah viruses6-8 as well as against previous CoVs including SARS- and MERS-CoVs. These valuable options can be exploited for their potency, efficacy, and safety along with expediting other ongoing research. There is a long list of anti-CoV agents, mostly preclinical compounds yet to be evaluated as anti-COVID-19 agents. Some of these agents are in phase III trials for COVID-19, including remdesivir, oseltamivir, ASC09F (HIV protease inhibitor), lopinavir, ritonavir, darunavir, and cobicistat.

While the following drugs were being discussed their efficacy has not been established.

1. Chloroquine – *In vitro* and limited clinical data suggest potential benefit.
2. Hydroxychloroquine – *In vitro* and limited clinical data suggest potential benefit.
3. Lopinavir; Ritonavir - Role in the treatment of COVID-19 is unclear. Preclinical data suggested potential benefit; however, more recent data has failed to confirm.
4. Remdesivir – Investigational and available only through expanded access and study protocols; several large clinical trials are underway. Remdesivir showed encouraging results among animals infected with two related coronaviruses, one responsible for severe acute respiratory syndrome (SARS) and another for causing Middle East respiratory syndrome (MERS).
5. Azithromycin – Used in some protocols based on theoretical mechanism and limited preliminary data as adjunct therapy.
6. Tocilizumab – Immunomodulating agent used in some protocols based on theoretical mechanism and limited preliminary data as adjunct therapy.
7. COVID-19 convalescent plasma – Investigational use is being studied.

The major therapeutic drugs: remdesivir, lopinavir/ritonavir are used alone or in combination with interferon-β, convalescent plasma, and mAbs. Nevertheless, before utilizing these drugs for COVID-19 pneumonia patients, clinical efficacy, and safety studies should be conducted.

Some potential treatments aren’t aimed at the coronavirus itself but instead will hopefully reduce some of the severe side effects the disease causes, like hyperinflammation and respiratory distress.

Notably, many of the proposed treatments have gone through U.S. Food and Drug Administration (FDA) approval for other uses or are currently going through that process, meaning the route to getting approved for a clinical trial to study their effects on COVID-19 patients is shorter and faster than it would be for a new drug.

Chase is on for the elusive COVID 19 vaccines

The chase was on for therapies and vaccines for the pharmaceutical and vaccine developers to fast track their pipelines for COVID 19. The frenzy of activities continues

unabated. While a few traditional drugs rose to offer some promise it was the holy grail of COVID 19 vaccine that fired the imagination.

The finding that SARS-CoV-2 is transmitted from infected individuals without symptoms together with its ability to cause pandemic disease within a period of weeks, suggests that control of this viral infection will be challenging without the prospect of a vaccine.

The major COVID 19 vaccine development programs revolve around : Whole Virus Vaccines; Sub unit vaccines and Nucleic acid vaccines.

Whole virus vaccines

a. Janssen (Johnson & Johnson) : Adenovirus-vectored vaccine using AdVac® and PER.C6® technology
b. Codagenix/Serum Institute of India: Live-attenuated vaccine

Subunit vaccines

a. University of Queensland/CEPI: Protein-based vaccine using Molecular Clamp platform
b. Novavax: Recombinant nanoparticle technology
c. Clover Bipharmaceuticals: S-trimer recombinant protein using Trimer-Tag technology
d. Baylor College of Medicine, Fudan University, New York Blood Center, Univ Texas Medical Branch: Coronavirus RBD protein-based vaccine
e. Vaxart: Ora recombinant protein vaccine using VAAST platform

Nucleic acid vaccines

a. Inovio/Beijing Advaccine Biotechnology Co./CEPI: DNA vaccine (INO-4800, based on INO-4700 MERS vaccine)
b. Moderna/NIH/CEPI : mRNA vaccine
c. CureVac/CEPI : mRNA vaccine

Since March 3rd week over 600 Companies, research labs and agencies have announced breakthrough vaccine innovations; most of them yet unsubstantiated. Some of the more promising ones are discussed below.

Moderna Therapeutics, a biotech company based in Cambridge, Mass., has shipped the first tbatches of its COVID-19 vaccine. The vaccine was created just 42 days after the genetic sequence of the COVID_19 virus, called SARS-CoV-2, was released by Chinese researchers in mid-January. The first vials were sent to the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH) in Bethesda, MD, which will ready the vaccine for human testing as early as April.

Moderna's vaccine against COVID-19 was developed in record time because it's based on a relatively new genetic method that does not require growing huge amounts of virus. Instead, the vaccine is packed with mRNA, the genetic material

that comes from DNA and makes proteins. Moderna loads its vaccine with mRNA that codes for the right coronavirus proteins which then get injected into the body. Immune cells in the lymph nodes can process that mRNA and start making the protein in just the right way for other immune cells to recognize and mark them for destruction.

RNA; LNP-encapsulated mRNA (mRNA 1273): The National Institute of Allergy and Infectious Diseases (NIAID) and Moderna's potential vaccine builds on research into the MERS virus. It's a messenger RNA or mRNA vaccine, where a bit of the virus's genetic material gets injected into your muscle. The role of mRNA is to carry genetic information from DNA needed to make proteins. The RNA is packaged in lipid nanoparticles (LNPs), to help effectively deliver it. The mRNA would deliver instructions to cells on how to make proteins to fight the virus. No RNA vaccines have even been approved for human use.

BioNTech and Pfizer Inc. have disclosed additional details of their collaboration to advance candidates from BioNTech's mRNA vaccine program, previously announced on March 17, 2020. The collaboration aims to rapidly advance multiple COVID-19 vaccine candidates into human clinical testing based on BioNTech's proprietary mRNA vaccine platforms, with the objective of ensuring rapid worldwide access to the vaccine, if approved. The collaboration will leverage Pfizer's broad expertise in vaccine research and development, regulatory capabilities, and global manufacturing and distribution network. BioNTech and Pfizer intend to initiate the first clinical trials as early as the end of April 2020, assuming regulatory clearance.

CanSino Biologics is testing a vaccine candidate in healthy adults, the first phase of clinical testing. In 2017, the company, collaborating with the Chinese Academy of Military Medical Sciences' Bioengineering Institute, developed an ebola vaccine. The potential COVID-19 vaccine, AD5-nCoV, is based on the same technology. It's a non-replicating viral vector, so it can infect cells but has been rendered incapable of multiplying. Johnson & Johnson is working on a similar type of vaccine, which will be ready for phase one trials in September.

Status of vaccine development

Coronaviruses caused SARS in the early 2000s and MERS in 2012. The two epidemics were contained before vaccines were created, but some work was started for both which is being leveraged by a few companies to find a vaccine for COVID-19. The Coalition for Epidemic Preparedness Innovations, or CEPI, is an organization helping to accelerate vaccine development. About 42 companies and academic institutions are searching for a COVID-19 vaccine; two in phase-1 clinical trials, and over 40 in preclinical development.

Vaccines for COVID 19 are based on multiple platforms and vaccine developers focus on specific platforms of their expertise. There are 2 candidates in Phase 1 (Table 1) and over 40 in pre-clinical state (Table 2)

Table 1: Candidate vaccines in clinical evaluation Phase 1

Platform	Type of candidate vaccine	Developer	Present status
Non-Replicating Viral Vector	Adenovirus Type 5 Vector	CanSino Biological Inc. and Beijing Institute of Biotechnology	Phase 1 ChiCTR2000030906
RNA	LNP-encapsulated mRNA	Moderna/NIAID	Phase 1 NCT04283461

Table 2: Candidates in Pre-clinical stage

Platform	Type of candidate vaccine	Developer	Present status
DNA	DNA plasmid vaccine Electroporation device	Inovio Pharmaceuticals	Pre-Clinical
DNA	DNA	Takis/Applied DNA Sciences/Evvivax	Pre-Clinical
DNA	DNA plasmid vaccine	Zydus Cadila	Pre-Clinical
Inactivated	Formaldehyde-inactivated + alum	Sinovac	Pre-Clinical
Live Attenuated Virus	Deoptimized live attanuated vaccines	Codagenix/Serum Institute of India	Pre-Clinical
Non-Replicating Viral Vector	MVA encoded VLP	GeoVax/BravoVax	Pre-Clinical
Non-Replicating Viral Vector	Ad26 (alone or with MVA boost)	Janssen Pharmaceutical Companies	Pre-Clinical
Non-Replicating Viral Vector	ChAdOx1	University of Oxford	Pre-Clinical
Non-Replicating Viral Vector	adenovirus-based NasoVAX expressing SARS2-CoV spike protein	Altimmune	Pre-Clinical
Non-Replicating Viral Vector	Ad5 S (GREVAX™ platform)	Greffex	Pre-Clinical
Non-Replicating Viral Vector	Oral Vaccine platform	Vaxart	Pre-Clinical
Protein Subunit	Drosophila S2 insect cell expression system VLPs	ExpreS2ion	Pre-Clinical

Protein Subunit	S protein	WRAIR/USAMRIID	Pre-Clinical
Protein Subunit	S-Trimer	Clover Biopharmaceuticals Inc./GSK	Pre-Clinical
Protein Subunit	Peptide	Vaxil Bio	Pre-Clinical
Protein Subunit	S protein	AJ Vaccines	Pre-Clinical
Protein Subunit	Ii-Key peptide	Generex/EpiVax	Pre-Clinical
Protein Subunit	S protein	EpiVax/Univ. of Georgia	Pre-Clinical
Protein Subunit	S protein (baculovirus production)	Sanofi Pasteur	Pre-Clinical
Protein Subunit	Full length S trimers/ nanoparticle + Matrix M	Novavax	Pre-Clinical
Protein Subunit	gp-96 backbone	Heat Biologics/Univ. Of Miami	Pre-Clinical
Protein Subunit	Molecular clamp stabilized Spike protein	University of Queensland/GSK	Pre-Clinical
Protein Subunit	S1 or RBD protein	Baylor College of Medicine	Pre-Clinical
Protein Subunit	Subunit protein, plant produced	iBio/CC-Pharming	Pre-Clinical
Protein Subunit	Subunit	VIDO-InterVac, University of Saskatchewan	Pre-Clinical
Protein Subunit	Adjuvanted microsphere peptide	University of Saskatchewan	Pre-Clinical
Replicating Viral Vector	Measles Vector	Zydus Cadila	Pre-Clinical
Replicating Viral Vector	Measles Vector	Institute Pasteur/Themis/Univ. of Pittsburg Center for Vaccine Research	Pre-Clinical
Replicating Viral Vector	Horsepox vector expressing S protein	Tonix Pharma/Southern Research	Pre-Clinical
RNA	LNP-encapsulated mRNA cocktail encoding VLP	Fudan University/ Shanghai JiaoTong University/RNACure Biopharma	Pre-Clinical
RNA	LNP-encapsulated mRNA encoding RBD	Fudan University/ Shanghai JiaoTong University/RNACure	Pre-Clinical

		Biopharma	
RNA	mRNA	China CDC/Tongji University/Stermina	Pre-Clinical
RNA	mRNA	Arcturus/Duke-NUS	Pre-Clinical
RNA	mRNA	BioNTech/Fosun Pharma/Pfizer	Pre-Clinical
RNA	saRNA	Imperial College London	Pre-Clinical
RNA	mRNA	Curevac	Pre-Clinical
VLP	Plant-derived VLP	Medicago Inc.	Pre-Clinical
Unknown	Unknown	University of Hong Kong	Pre-Clinical
Unknown	Unknown	ImmunoPrecise	Pre-Clinical
Unknown	Unknown	MIGAL Galilee Research Institute	Pre-Clinical
Unkno wn	Unknown	Doherty Institute	Pre-Clinical
Unknown	Unknown	Tulane University	Pre-Clinical

Source: WHO

Status of therapy development

Globally multiple therapies are being studied for COVID 19. Some of these therapy approaches and their status (3) is given in Table 3.

Table 3: COVID 19 Type of treatments and Status

Treatmment	**Developer Organization**	**Current Stage of Development**
ANTIBODIES		
Treatment (TAK-888; anti-SARSCoV-2 polyclonal hyperimmune globulin (H-IG), antibodies from recovered patients)	Takeda	Pre-clinical
Treatment (antibodies from mice; REGN3048-3051)	Regeneron	Pre-clinical
Treatment (antibody from recovered patients)	Celltrion	Pre-clinical
Treatment (anti-corona (COVID-19) IgG from recovered patients)	Kamada	Pre-clinical
Treatment (antibodies from recovered patients)	Vir Biotech/WuXi Biologics/Biogen	Pre-clinical
Treatment (antibodies from recovered US patient)	Lilly/Ab-Cellera (NIH Vaccines Research Ctr)	Pre-clinical
Treatment (Avastin (bevacizumab))	Numerous trials with Chinese research sponsors; Roche	Clinical
Treatment (PD-1 blocking antibody; Thymosin)	Southeast University, China	Clinical

Treatment (leronlimab (PRO 140), a CCR5 antagonist)	CytoDyn	Pre-clinical
Treatment (camrelizumab)	Southeast University, China	Clinical
Treatment (Kevzara (sarilumab))	Sanofi/Regeneron	Clinical
Treatment (Actemra (tocilizumab))	First People's Hospital of University of Science and Technology of China	Clinical
Treatment (antibodies)	ImmunoPrecise Antibodies	Pre-clinical
Treatment (antibodies)	AstraZeneca	Pre-clinical
ANTIVIRALS		
Treatment (Favilavir/Favipiravir/T-705/Avigan,licensed in Japan to treat influenza	Fujifilm Toyama Chemical/Zhejiang Hisun Pharmaceuticals numerous trials with Chinese research sponsors	Clinical
Treatment (Kaletra (lopinavir/ritonavir) and Aluvia)	AbbVie/Chinese hospital testing	Clinical
Treatment (remdesivir; investigational drug)	Gilead	Clinical and expanded access
Treatment (Prezcobix (darunavir/cobicistat); Janssen)	Chinese hospital testing	Clinical
Treatment (galidesivir)	BioCryst Pharmaceuricals	Pre-clinical
Treatment (ebastine; lopinavir; interferon alpha)	Wuhan Red Cross Hospital	Clinical
Treatment (Ganovo (danoprevir); ritonavir; interferon)	Numerous trials with Chinese research sponsors	Clinical
Treatment (Truvada; emtricitabine and tenofovir)	Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital	Clinical
Treatment (Arbidol; umifenovir) licensed in Russia and China for treatment of respiratory viral infections	Numerous trials with Chinese research sponsors	Clinical
Treatment (Xofluza (baloxavir marboxil), Roche)	The First Hospital Affiliated to Zhejiang University's Medical School	Clinical
Treatment (azvudine)	Henan Provincial People's Hospital	Clinical
CELL-BASED THERAPIES		
Treatment (PLX cell product, placenta-based cell therapy)	Pluristem Therapeutics/BIH Ctr for	Pre-clinical

	Regenerative Therapy/ Berlin Ctr for Advanced Therapies	
Treatment (mesenchymal stem cells)	Numerous trials with Chinese research sponsors	Clinical
Treatment (Ryoncil (remestemcel-L), allogenic mesenchymal stem cells)	Mesoblast	Pre-clinical
RNA BASED TREATMENTS		
Treatment (RNAi - testing 150 RNAis)	Sirnaomics	Pre-clinical
Treatment (siRNA candidates)	Vir Biotech/Alnylam Pharmaceuticals	Pre-clinical
Treatment (Ampligen; (rintatolimod))	AIM ImmunoTech/ National Institute of Infectious Diseases in Japan	Pre-clinical
SCANNING COMPOUNDS TO REPURPOSE		
Treatment (scanning library of anti-viral compounds)	Janssen Pharmaceutical Companies	Pre-clinical
Treatment (scanning compounds to repurpose)	Novartis	Pre-clinical
Treatment (scanning anti-viral compounds previously in development)	Pfizer	Pre-clinical
Treatment (scanning compounds to repurpose)	Merck	Pre-clinical
Treatment (repurposing antiviral drug candidates)	Materia Medica/Cyclica	Pre-clinical
Treatment (screening new drugs + library of antiviral compounds)	Enanta Pharmaceuticals	Pre-clinical
Treatment (screening drug compounds)	Southwest Research Institute	Pre-clinical
Treatment (scanning compounds to repurpose)	Takeda	Pre-clinical
OTHERS		
Treatment (washed microbiota transplantation)	The Second Hospital of Nanjing Medical University	Clinical
Treatment (corticosteroids)	Peking Union Medical College Hospital	Clinical
Treatment (hydroxychloroquine), antimalarial	Numerous trials with research sponsors in China; University of Minnesota; University of Oxford	Clinical

Treatment (Jakafi/jakavi (ruxolitinib))	Department of Hematology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology	Clinical
Treatment (PegIntron, Sylatron, IntronA)	Wuhan Jinyintan Hospital (Wuhan Infectious Diseases Hospital)	Clinical
Treatment (Novaferon, Nova) licensed in China for Hep B	The First Affiliated Hospital of Medical College of Zhejiang University	Clinical
Treatment (recombinant ACE2)	The First Affiliated Hospital of Guangzhou Medical University	Clinical
Treatment (Cerocal (ifenprodil), NP-120)	Algernon Pharmaceuticals	Pre-clinical
Treatment (APN01; recombinant soluble human Angiotensin Converting Enzyme 2)	University of British Columbia/Apeiron Biologics	Clinical
Treatment (Brilacidin, a defensin mimetic)	Innovation Pharmaceuticals	Pre-clinical
Treatment (BXT-25; glycoprotein)	Bioxytran	Pre-clinical
Treatment (peptides)	CEL-SCI	Pre-clinical
Treatment (ASC09)	Ascletis	Clinical
Treatment (Gilenya (fingolimod); Novartis)	First Affiliated Hospital of Fujian Medical University	Clinical
Treatment (unknown)	Mateon Therapeutics	Pre-clinical
Treatment (unknown)	NanoViricides	Pre-clinical
VACCINES		
Vaccine (DNA plasmid; INO-4800)	Inovio Pharmaceuticals/ Beijing Advaccine Biotechnology	Pre-clinical
Vaccine (DNA)	Takis/Applied DNA Sciences/Evvivax	Pre-clinical
Vaccine (DNA plasmid)	Zydus Cadila	Pre-clinical
Vaccine (deoptimized live attenuated virus)	Codagenix/Serum Institute of India	Pre-clinical
Vaccine (non replicating viral vector; MVA encoded VLP)	GeoVax/BravoVax	Pre-clinical
Vaccine (non replicating viral vector; Ad26 (alone or with MVA boost))	Janssen Pharmaceutical Companies/Beth Israel Deaconess Medical Center (BIDMC)	Pre-clinical
Vaccine (non replicating viral	University of Oxford	Pre-clinical

vector; ChAdOx1)		
Vaccine (non replicating viral vector; adenovirus based NasoVAX)	Altimmune	Pre-clinical
Vaccine (non replicating viral vector; Ad5 S (GREVAX™ platform))	Greffex	Pre-clinical
Vaccine (non replicating viral vector; Oral Vaccine platform)	Vaxart	Pre-clinical
Vaccine (non replicating viral vector; Viralvectored based)	CanSino Biologics	Pre-clinical
Vaccine (protein subunit; Drosophila S2 insect cell expression system VLPs)	ExpreS2ion	Pre-clinical
Vaccine (protein subunit; S protein)	WRAIR/USAMRIID	Pre-clinical
Vaccine (protein subunit; S trimer)	Clover Biopharmaceuticals Inc./GSK	Pre-clinical
Vaccine (protein subunit; Ii-Key peptide)	Generex/EpiVax	Pre-clinical
Vaccine (protein subunit; S protein)	EpiVax/Univ. of Georgia	Pre-clinical
Vaccine (protein subunit; S protein, baculovirus production)	Sanofi Pasteur	Pre-clinical
Vaccine (protein subunit; Full length S trimers/ nanoparticle + Matrix M)	Novavax	Pre-clinical
Vaccine (protein subunit; S protein clamp)	University of Queensland/GSK	Pre-clinical
Vaccine (protein subunit; S1 or RBD protein)	Baylor, New York Blood Center, Fudan University	Pre-clinical
Vaccine (protein subunit; Subunit protein, plant produced)	iBio/CC-Pharming	Pre-clinical
Vaccine (replicating viral vector; measles vector)	Zydus Cadila	Pre-clinical
Vaccine (replicating viral vector; measles vector)	Institute Pasteur	Pre-clinical
Vaccine (replicating viral vector; horsepox vector; TNX-1800)	Tonix Pharma/Southern Research	Pre-clinical
Vaccine (RNA; mRNA)	China CDC/Tongji University/Stermina	Pre-clinical
Vaccine (RNA; mRNA; mRNA 1273)	Moderna/NIAID	Pre-clinical
Vaccine (RNA; mRNA)	Arcturus/Duke-NUS	Pre-clinical
Vaccine (RNA; saRNA)	Imperial College London	Pre-clinical
Vaccine (RNA; mRNA)	Curevac	Pre-clinical
Vaccine (RNA)	RNACure Biopharma	Pre-clinical
Vaccine (RNA; BNT162)	BioNTech/Fosun	Pre-clinical

	Pharma/Pfizer	
Vaccine (unknown)	University of Pittsburgh	Pre-clinical
Vaccine (unknown)	University of Saskatchewan	Pre-clinical
Vaccine (unknown)	ImmunoPrecise	Pre-clinical
Vaccine (modified infectious bronchitis virus vaccine)	MIGAL Galilee Research Institute	Pre-clinical
Vaccine (unknown)	Doherty Institute	Pre-clinical
Vaccine (unknown)	Heat Biologics	Pre-clinical
Vaccine (unknown)	Tulane University	Pre-clinical
Vaccine (unknown)	ImmunoPrecise Antibodies	Pre-clinical
Vaccine (unknown)	AJ Vaccines	Pre-clinical

Vaccine development: Perils

As governments and industry increase the pressure on vaccine researchers to fast track vaccine development, it is vital for them to ensure that their target candidate des not lead to a counter productive and far more dangerous phenomenon known as immune system reaction known as immune enhancement (4).

In the past there have been instances where vaccines lead to immune systems malfunctions; hence it is important to validate if similar types of malfunctions do not occur in vaccines under development. Gaining insights into how immune system reacts not only with the pathogen but with vaccine itself is vital while developing a safe vaccine.

Through 60s to now tests of vaccines for respiratory syncytial virus; severe acute respiratory syndrome (SARS) have shown contrarian trends. Animals and human beings or people who received the vaccine and were later exposed to the virus developed more severe disease than those who had not been vaccinated (5).

The vaccine primed immune system, in certain cases, seemed to launch a unexpected response to the natural infection. This is also called immune enhancement and it may manifest in different ways such as antibody-dependent enhancement (ADE), a process in which a virus leverages antibodies to aid infection; or cell-based enhancement, a category that includes allergic inflammation caused by Th2 immunopathology.

Scientific debate is underway as to which, if any, of these phenomena—for which exact mechanisms remain unclear—could be at play with the novel coronavirus and just how they might affect the success of vaccine candidates. It is critical that animal experiments and human clinical trials of candidate vaccines for COVID-19, is subjected to very careful assessment of possible immune breakdown before taking it to markets. Risks arising from such immune compromise can be immense.

In summing up

There are no effective vaccines or specific antiviral drugs for COVID-19. Hence, the emphasis is to rely exclusively on enforcing strict preventive and control measures that minimize the risk of possible disease transmission. Results obtained from the recently

conducted in vitro study against COVID-19 are promising since the drugs remdesivir and chloroquine were found to be highly effective in controlling the infection.

Direct clinical trials can be conducted among the patients infected with COVID-19 since these drugs are being used for treating other diseases and have well-established safety profiles, making the further evaluation of these drugs much easier.

S protein is considered a key viral antigen for developing CoV vaccines, as shown in several preclinical studies. Although research is in progress to improve prevention, treatment, and control of COVID-19, the documented clinical data on different therapeutic approaches for CoVs are scarce. Most of the therapeutic options are based on previous experiences in treating SARS- and MERS-CoV.

Outbreaks happens once in a while and demand for vaccines last only for short time periods; a reason for the relative lack of interest among the pharmaceutical companies. By the time a new drug or vaccine is developed, there might not be any patients for clinical trials and also no meaningful market for newly discovered drugs.

There are now at least a half-dozen candidates, including live viruses, recombinant protein subunits, and nucleic acids that may ultimately offer promise as preventive vaccines against COVID-19. These will require additional manufacturing steps and formal toxicology testing before submitting a regulatory package to national regulatory agencies. Only then commencement of the clinical development, first with phase 1 clinical trials for safety and immunogenicity, and later, phase 2 and phase 3 trials for both safety and efficacy.

It must be kept in mind that a new major coronavirus epidemic has happened every decade in the twenty-first century—SARS in the 2000s, MERS in the 2010s, and now COVID-19. It is a global security priority to advance and stockpile coronavirus vaccines. This will need a funding mechanism to support their development, testing, and manufacture, and storage.

A global health initiative was launched late April 2020 by WHO, **Access to COVID-19 Tools (ACT) Accelerator**, will accelerate the development, production and deployment of safe and effective diagnostics, therapeutics and vaccines against COVID – making them accessible and affordable to all.

This pandemic is a clarion call for all to not only react but also prepare for the next coronavirus crossing from wild bats, primates and rodents into mammals. With vaccine researchers, epidemiologists, immunologists and the medical community being challenged as never before disruptive thinking is needed to come up with solutions hitherto never thought of.

References:

1. Kuldeep Dhama, Khan Sharun, Ruchi Tiwari, Maryam Dadar, Yashpal Singh Malik, Karam Pal Singh & Wanpen Chaicumpa (2020): COVID-19, an emerging coronavirus infection: advances and prospects in designing and developing

vaccines, immunotherapeutics, and therapeutics, Human Vaccines & Immunotherapeutics, DOI: 10.1080/21645515.2020.1735227
2. Graham RL, Donaldson EF, Baric RS. A decade after SARS: strategies for controlling emerging coronaviruses. Nat Rev Microbiol. 2013;11(12):836–48. doi:10.1038/nrmicro3143.
3. Source : Milken Institute COVID 19 Treatment and Vaccine Tracker; WHO list, March 2020
4. Lynne Peeples,www.pnas.org/cgi/doi/10.1073/pnas.2005456117
5. S. M. Tirado, K. J. Yoon, Antibody-dependent enhancement of virus infection and disease. Viral Immunol. 16, 69–86 (2003).

Author: R.Rajagopal