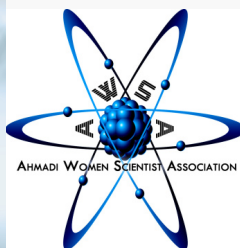




THE PROCESS OF SCIENCE FROM DISEASE TO DRUG DISCOVERY

Nusrat Sharif, PhD

Serving as President of Ahmadi Women Scientists
Association



Outline:

- Why choose a Scientific research career in drug discovery?
- What is drug discovery process for a disease?
- Stages in drug discovery
- Working for a pandemic drug
- Impact/Benefit of working for a large pharmaceutical company
- Hadhrat Khalifatul Masih V (atba) guidance



Why is drug discovery research interesting?



■ Imagine a career that touches the lives of the patients

- Direct benefit- new medical treatment which could be a new drug or a new medicinal product, showing a translation of basic research (idea or rationale) to medicine.
- Impact includes a “decrease in the severity of symptoms” & thereby an increase in quality of life or survival time.
- Collective benefits for society & community

■ Creativity, Challenge & Cutting Edge Science

- Majority of scientists are inspired to discover a new medicine. eg: imagine being the first chemist to synthesize an important treatment for Alzheimer, or the first biologist to champion a new therapeutic approach for cancer and see if it works?
- Resources for cutting edge science including latest developments in science and technology will be provided by the industry, allowing high impact research.
- New challenge & Creativity vs Repetitive work behaviours.



Drug discovery process for a disease

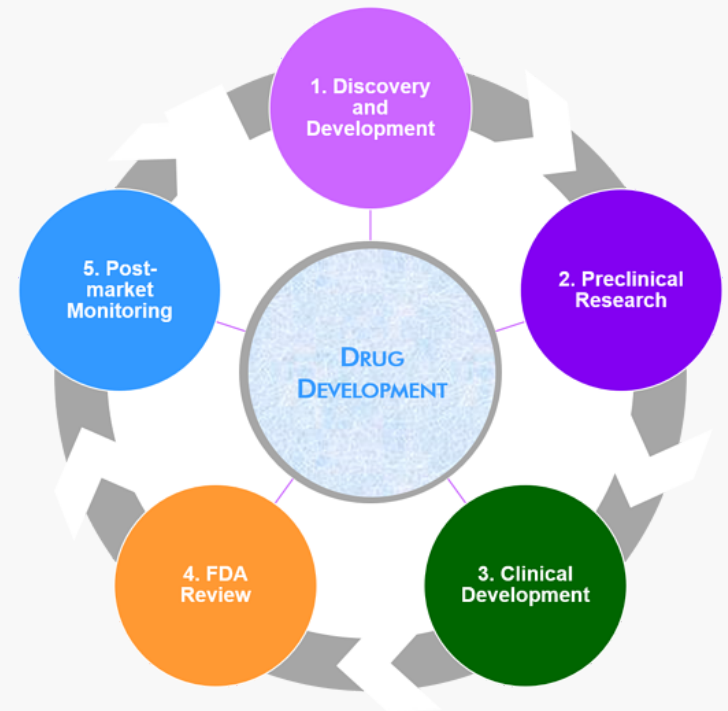
- Understanding of a human disease is essential at the molecular, biochemical and genetic level.
 - Eg: infectious disease or a chronic illness such as cardio-vascular disease, diabetes, cancer, rare genetic diseases such as sickle cell anemia, diseases of central nervous system or the immune system.
- Complexity of the disease plays an important role
 - Even though new information arises at breath-taking speed, yet we have not seen the greatest increase in medications that enter the market.
 - Our ability to translate or interpret results is lagging.
- Identifying a “disease target”
 - A target is a molecule or a pathway component (eg: an enzyme) that contributes to development of disease or its symptoms.
 - **Target Selection:** the decision to focus on finding an agent with a particular biological action that is anticipated to have therapeutic utility.



Stages in drug discovery & development

- Step 1: Discovery and Development
- Step 2: Preclinical Research
- Step 3: Clinical Development
- Step 4: FDA Review
- Step 5: FDA Post-market Safety Monitoring

- ❑ Every stage is defined by a milestone. Timelines must be maintained at each stage
- ❑ Discovering and bringing one new drug to the market takes an **average of 12** years of research and clinical development to commercialization.
- ❑ The cost is **\$500 million USD**



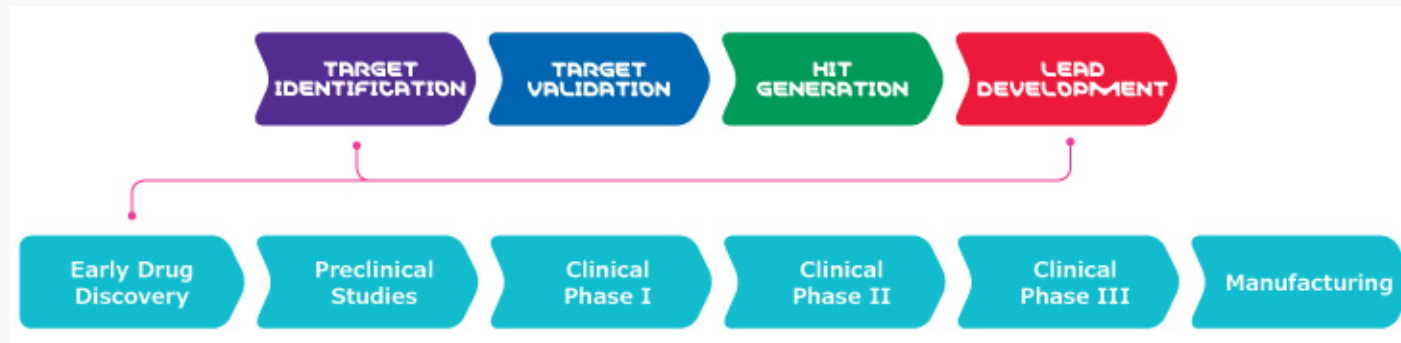
Teams

- ✓ Research Scientists- Industry
- ✓ Collaborative Scientists- Academia
- ✓ Medicinal Chemists
- ✓ Drug Pharmacology
- ✓ Drug Safety
- ✓ BioStatisticians
- ✓ Computational biologists
- ✓ Geneticists
- ✓ Medical Practitioners
- ✓ Marketing Pharmaceutical Practitioners
- ✓ Legal Attorneys



Target identification & validation-critical steps in early discovery phase

- ❑ Identifying a good target: A “good target” (RNA, gene or a protein) must be **druggable, efficacious (highly effective in its therapeutics) and safe**
- ❑ Target validation shows that a molecular target is **directly** involved in a disease process, so that blocking or modulating that target we must be able to see a therapeutic effect. Eg gene knock-down (siRNA) & knock-out (CRISPR)



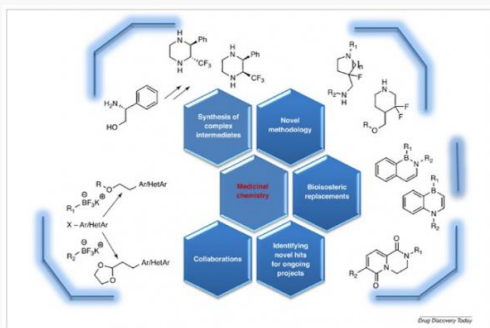
Hit generation & lead selection

❑ Hit is a **chemical compound** which has a desired activity in a compound screen.

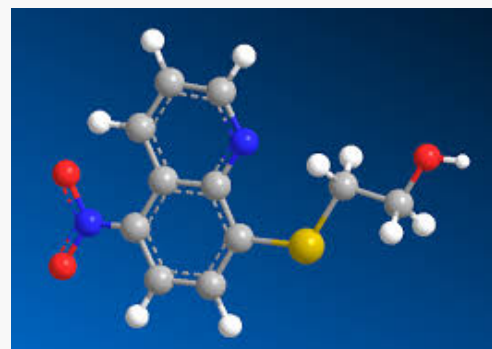
Main goal here is to identify molecules that interact with the target. Show positive effect in an assay. Not all Hits can be drugs, for eg: some Hits could have toxic effects.

❑ When does a hit become a **“lead compound”**?

- ✓ When a hit has the desired pharmacological structure.
- ✓ Structures can be optimized by a chemist to make a potential drug

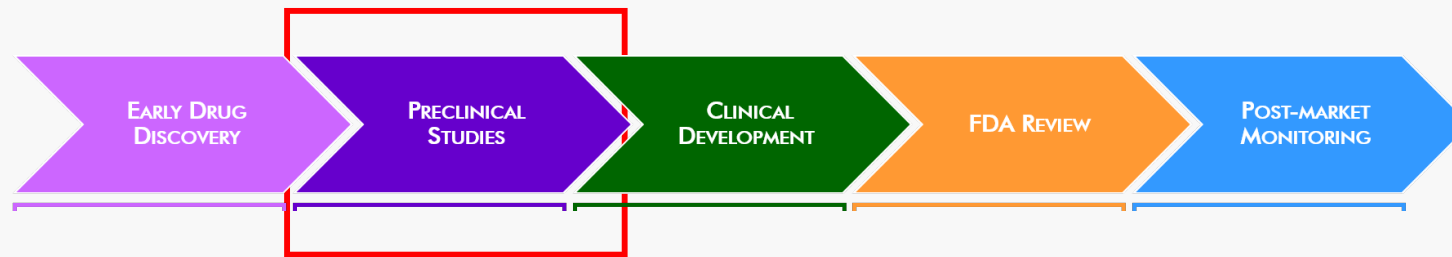


Hit generation- Medicinal chemistry



Lead compound

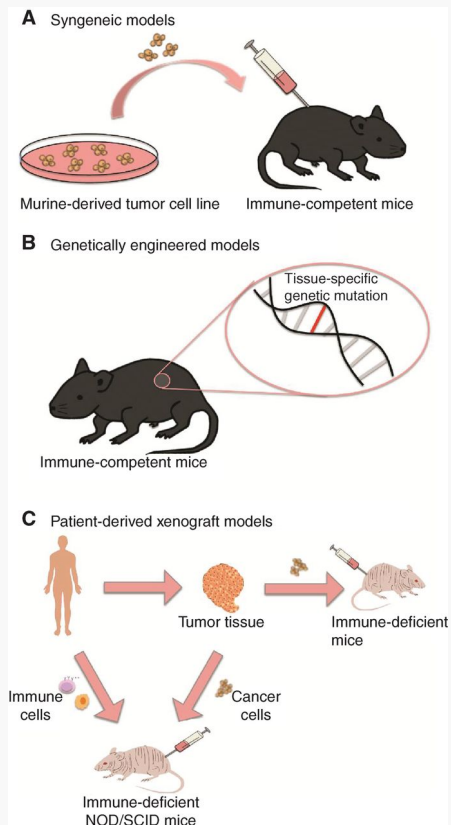
Pre-Clinical Studies



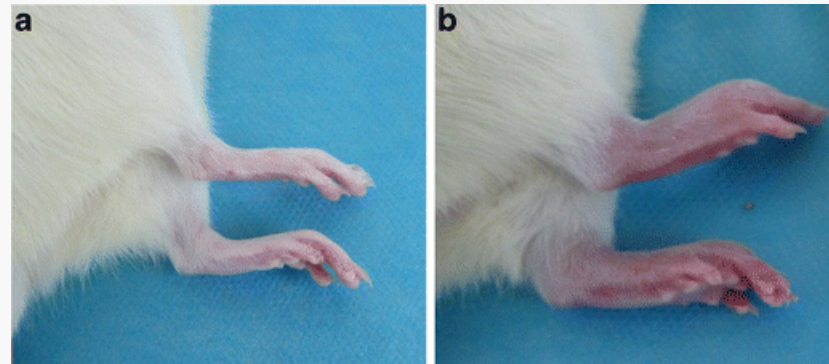
- Before testing in people, researchers must provide information on:
 - **Evidence of testing *in vivo*:** The potential drug works in a desired manner in animal models of disease
 - **Safety of the Drug:** Evidence that the drug is safe and not toxic to the animal

Pre-Clinical Animal Models of Disease

Mouse model of Cancer



Mouse model of Arthritis



Normal paws

Swollen paws in arthritic mice



Normal Hands



Patient with severe
Rheumatoid Arthritis

Safety studies: Critical for advancing a drug candidate to clinic

- Safety studies are highly critical aspect of Pre-Clinical research and a drug needs to be tested in animal studies for its safety profile
 - Hepatotoxicity (Liver)
 - Cardiovascular toxicity
 - General toxicity
 - Developmental & Pulmonary Safety
 - Reproductive Toxicity
 - CNS Safety

Dog, Rat, Guinea Pigs and Non human Primates will be used in these studies.

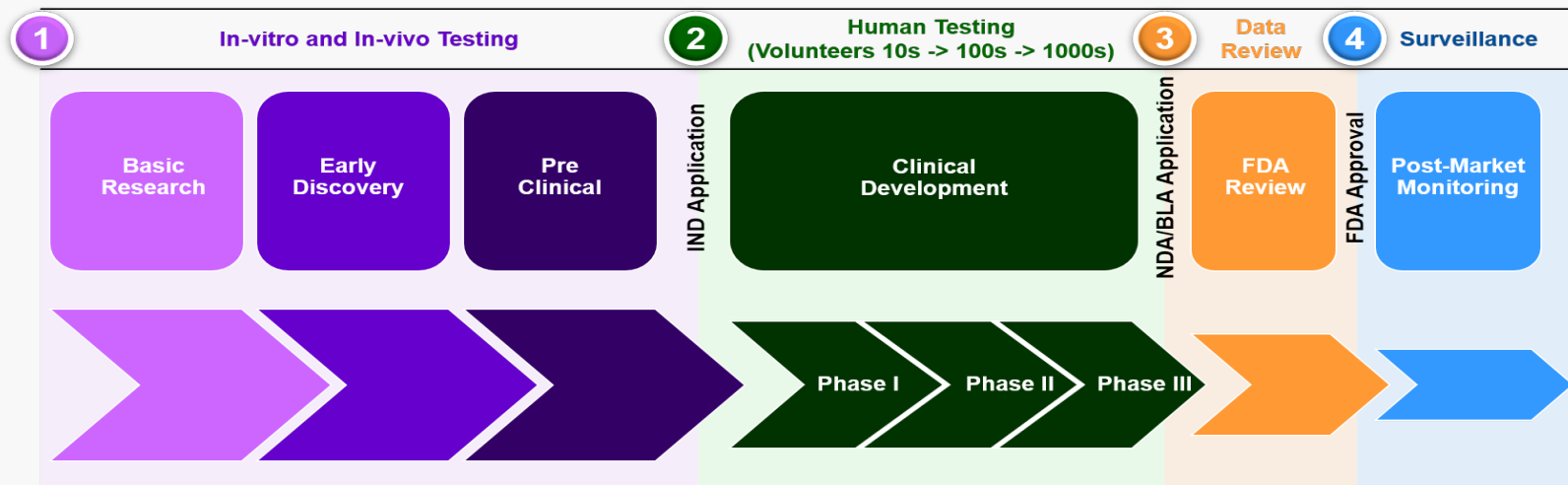


Did you know?

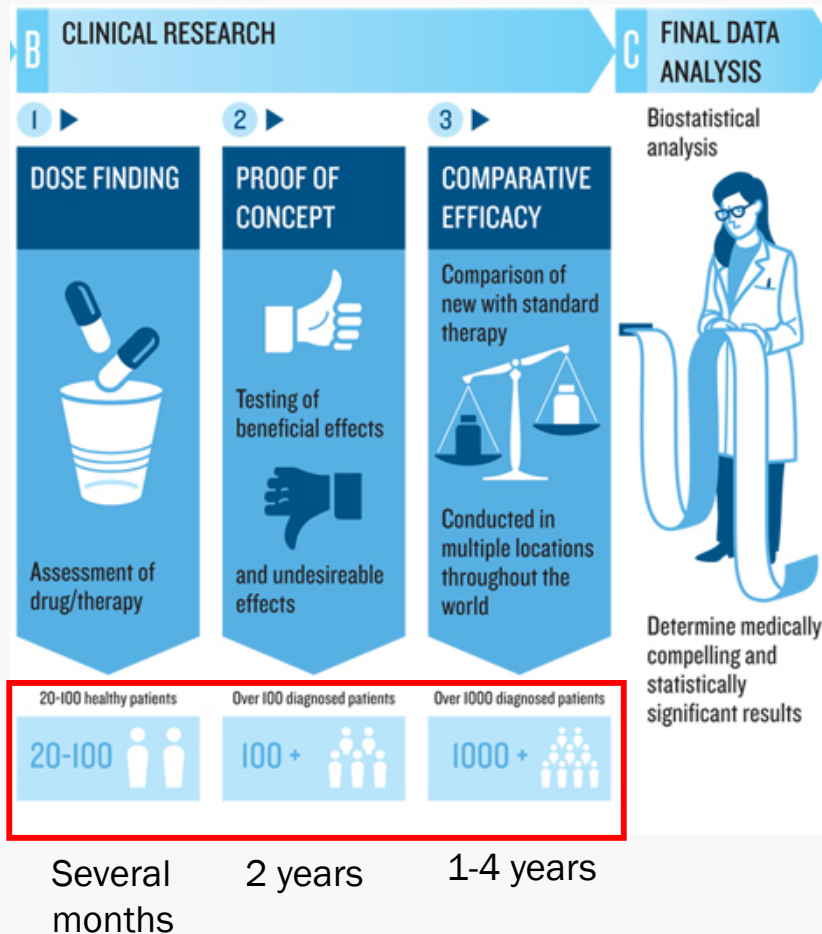
- ☐ Not every drug goes to the market !
- ☐ Statistics are that of 5000 compounds that show initial promise, 5 will go into human clinical trials and only one becomes an approved drug

Clinical Trials

- ✓ Effective (successful of producing a desired result)
- ✓ Safe
- ✓ Dose
- ✓ Within the budget



How do clinical trials work?



Phase I studies:

- Before testing in patients, a new medicine must be tested in healthy volunteers to see if the drug is well tolerated, and safe.
- Low doses of drug are used initially and if this is safe, move upward to determine optimal dose

Phase II studies:

- Assess drug safety & effectiveness in patients
- 100-500 patients
- May use a placebo or a standard drug previously used as treatment
- Adverse effects

Phase III studies:

- 1000+ Patients
- Long term effect of the drug
- Conducted to expand & confirm effectiveness, results from phase I & phase II
- Compare drug to standard therapies

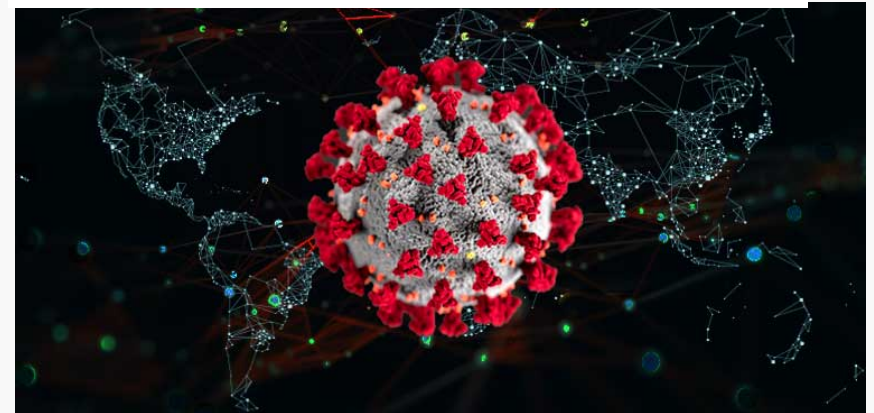
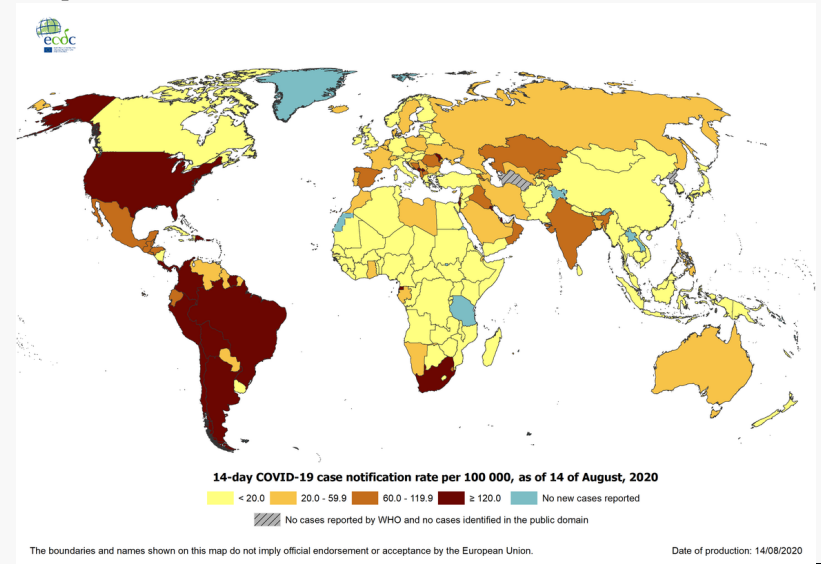
Regulatory Approval



- Based on the results from clinical trials, if the **benefits** of the drug outweigh the adverse effects, and criteria is met, **drug gets FDA approval.**
- Regulatory approval timeline:
 - may be **standard, fast track, breakthrough or accelerated.**
 - Standard takes a year
 - **Fast track, occur sooner (eg: approval for a pandemic drug)**

Covid 19: Urgent need for a pandemic vaccine

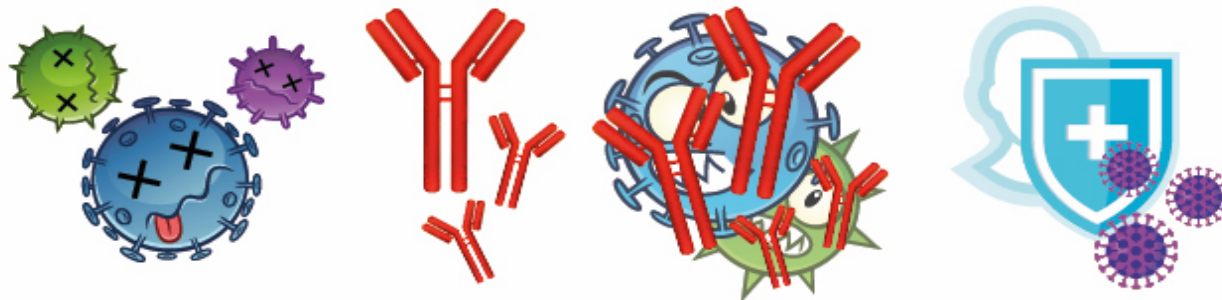
- ❖ Coronavirus (Covid 19) has caused unforeseen challenges across the world, there is a worldwide **urgent need of vaccine** to protect people from this global pandemic.
- ❖ The premise of any vaccine is to induce a long term immune memory in the form of B and T cells.
- ❖ Traditional vs Pandemic vaccines
- ❖ Finding a cure for the pandemic is a challenge, however, any pharmaceutical company that comes up with a vaccine that is **safe & protective**, will offer a potential cure.



Vaccines to the Rescue

- ❖ Help you develop immunity without getting sick first
- ❖ Made of same germs (virus & bacteria) that cause disease, but the germs in vaccine are killed so they don't make you sick.
- ❖ The immune system responds to the vaccine by making proteins called “antibodies”
- ❖ The antibodies destroy the vaccine germs, just as they would the disease germ
- ❖ If you are ever exposed to the real disease the antibodies are there to protect you

HOW VACCINES WORK



A weak or dead form of the germ is introduced

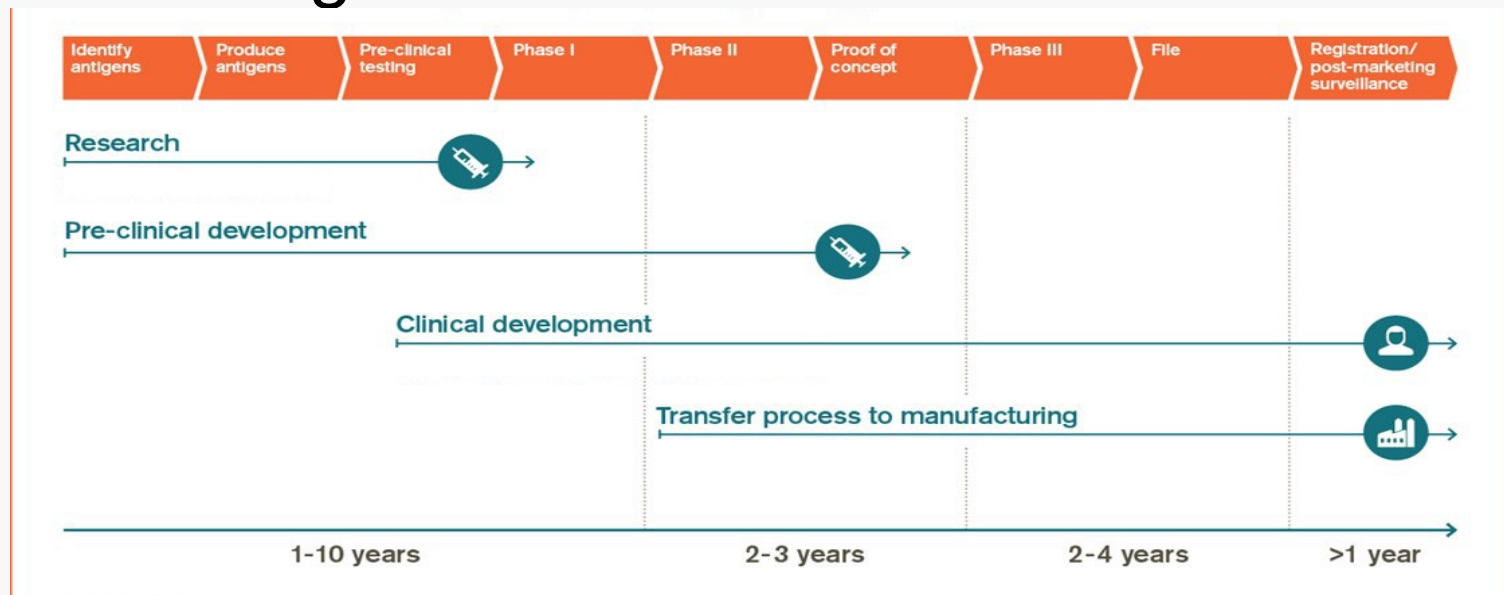


This sparks your immune response to develop antibodies that remember the germ



The antibodies fight off the germ if it invades again

Vaccine development is similar to that of other drugs



- ❑ **Early Research-** Identify the antigen that might help prevent disease
- ❑ **Pre-Clinical-** Testing in animals to determine whether there is an immune response, and selecting the dose
- ❑ **Phase I Clinical Trials:** 80-100, Test Safety and extent of Immune response in human
- ❑ **Phase II Clinical Trials:** Larger gp (100+), Safety & Dose, method of delivery
- ❑ **Phase III Clinical Trials:** very large gp(30-50,000) has a placebo gp. Age gps, Adverse effects

Traditional vs Coronavirus Pandemic



Traditional

- Lengthy & Expensive process
- Multiple candidates involved & several years.
- Involves a linear sequence of steps with multiple pauses for data analysis and manufacturing process checks

Pandemic

- Requires a Pandemic paradigm.
- Fast Start
- Multiple Steps executed in parallel before confirming a successful outcome of the previous step . For eg: phase 1 clinical trial may proceed in parallel with testing in animal models.
- Elevated Financial Risk



Forbes: June 16, 2020

THE NINE PHARMACEUTICAL COMPANIES AHEAD IN THE COVID-19 RACE					
COMPANY NAME	SYMBOL	COLLABORATION	TYPE OF VACCINE	STAGE OF CLINICAL TRIAL	COUNTRY OF ORIGIN
Johnson & Johnson	JNJ	Beth Israel Deaconess Medical Center, Biomedical Advanced Research and Development Authority (BARDA)	Version of the common cold virus to deliver a coronavirus pathogen into cells to prompt the immune system	Phase I	U.S.
Pfizer	PFE	BionTech	mRNA	Phase I	U.S./Germany
Moderna	MRNA	National Institute of Allergy and Infectious Diseases (NIAID), Lonza Ltd.	mRNA	Phase II	U.S.
AstraZeneca PLC	AZN	Oxford University	Combination of a weaker version of the common cold virus with some genetic material from SARS-CoV-2 virus	Phase II	U.K.
GlaxoSmithKline	GSK	Sanofi (SNY)	Combination of a technology that produces S protein found in SARS-CoV-2 with an immunological agent	Phase I	U.K./France
CanSino Biologics	6185 [Hong Kong]	Precision NanoSystems	1) Adenovirus type-5 vectored Covid-19 vaccine, 2) mRNA	Phase I	China
Sinovac	[private]	Dynavax [DVAX]	Combination of Sinovac's chemically inactivated SARS-CoV-2 vaccine candidate, with Dynavax's immunological agent	Phase I	China/U.S.
Novavax	NVAX	NA	Combination of S protein found in SARS-CoV-2 with the company's proprietary nanoparticle technology	Phase I	U.S.
Source: CFRA					

Russia's fast-track coronavirus vaccine draws outrage over safety- nature news Aug, 11, 2020

The immunization is the first approved for widespread use but could be dangerous because it hasn't been tested in large trials, say researchers.

Key questions by scientific community are:

- 1) Is Russia rushing to get this vaccine without adequate data?
- 2) Were the large trials to test safety and effective action (efficacy)?
 - Early data shows similar effect as other vaccine candidates
- 3) Report says that the phase III trials were yet to be completed**
 - ✓ No published protocol
 - ✓ How did the Regulation approve this vaccine ?

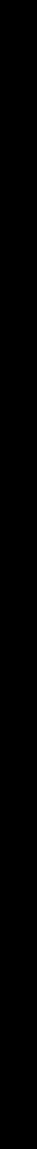
Considering your Research for benefit of humanity



“Whilst conducting research to answer questions that remain unsolved, an Ahmadi researcher must keep at the forefront of their mind that whatever has been created by Allah the Almighty has been made for the benefit of humanity.

“It should be their objective to uncover and derive the benefits and to ensure that whatever intellectual progress is made is for the betterment of mankind.”

Hadhrat Khalifatul Masih V (atba)



JazakAllah

Questions?!