James Cappola MD PhD

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Education/Academic Affiliations

- PhD Immunology/Microbiology – Rutgers University Waksman Institute of Microbiology
- MD – Esquela de Medicina UACJ- joint US program
- Internal Medicine – Cornell Medical School Affiliate Hospitals
- Former: Medical Director and Safety Officer at The Harvard Clinical Research Institute, Boston, MA

30 Years in Pharmaceutical Drug/Device Development/FDA affiliations

- Launch support of the first recombinant Hepatitis B vaccine (as Medical Director-Merck International)
- Launch support of Tipranavir for the treatment of AIDS (as Medical Director at Boehringer Ingelheim Pharmaceutical)
- Safety Officer at Harvard for a 22,000 patient outcomes study in post -cardiac STENT placement
- FDA liaison officer for the Cardio-Renal Division of the FDA
- Presently- consulting to biotech for global clinical studies:
  Trans Tech Pharma, Synteract HCR, NextGen, Quintiles, Esperion Therapeutics, Agios Pharma, QST Consultants, ChemoCentryx, Covance, BMS, World Wide Clinical Trials CRO, Trilliam Therapeutics, Nabriva Therapeutics

A Covid -19 "universal vaccine" and anti-cancer vaccines
new research in treatment of PTSD

i Jobs

Rutgers Univeristy

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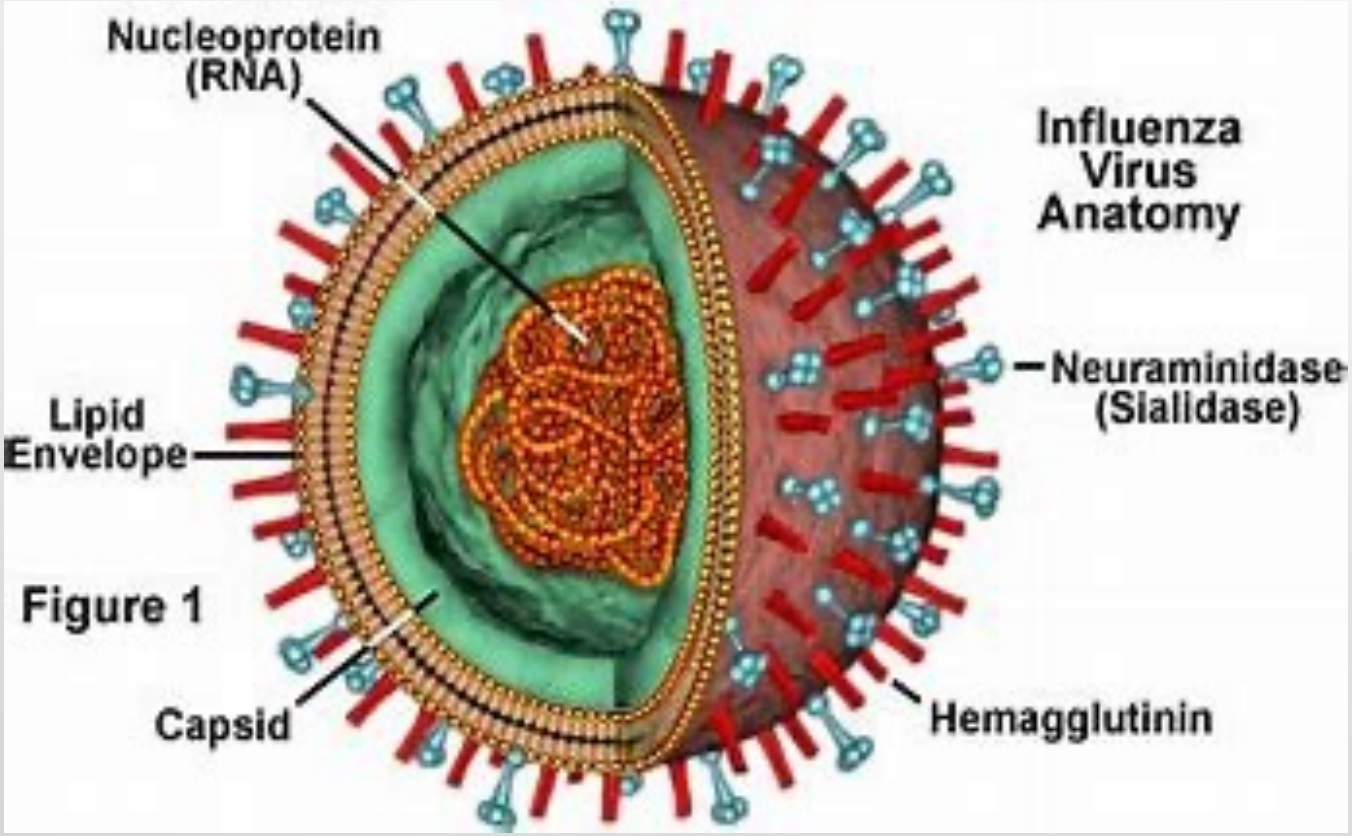
The Elusive Universal Influenza Vaccine – Are We Any Closer?

Development of "universal" vaccines- hemagglutinin antigen as target in influenza viruses



NIH begins first-in-human trial of a universal influenza vaccine candidate

- H1ssF_3928 is designed to teach the body to make protective immune responses against diverse influenza subtypes
- It displays part of hemagglutinin (HA), an influenza protein, on the surface of a microscopic nanoparticle made of nonhuman ferritin.
- The stem is more constant than the head among influenza strains, and thus less likely to need to be updated every season.

The vaccine technology refinement to attain a universal covid-19 vaccine

- At Duke University, virologists are targeting a particular part of the spike protein known as the receptor binding domain (RBD), as this region appears to have relatively little variation between different forms of the same coronavirus.
- "We designed our vaccine to focus the immune system on a site of vulnerability for the virus, which is the receptor binding domain," says Kevin Saunders, director of research at the Duke Human Vaccine Institute.
- "The RBD amino acid sequence is similar among viruses that belong to the same beta coronavirus group."

The vaccine technology refinement to attain a universal covid-19 vaccine

- The most exciting findings so far have come from the Walter Reed Army Institute of Research, who found that their vaccine has efficacy against a range of Covid-19 variants as well as the original Sars virus when tested in non-human primates.
- Readouts from a phase I trial are now expected imminently, with plans already underway for a larger phase II study later in 2022.

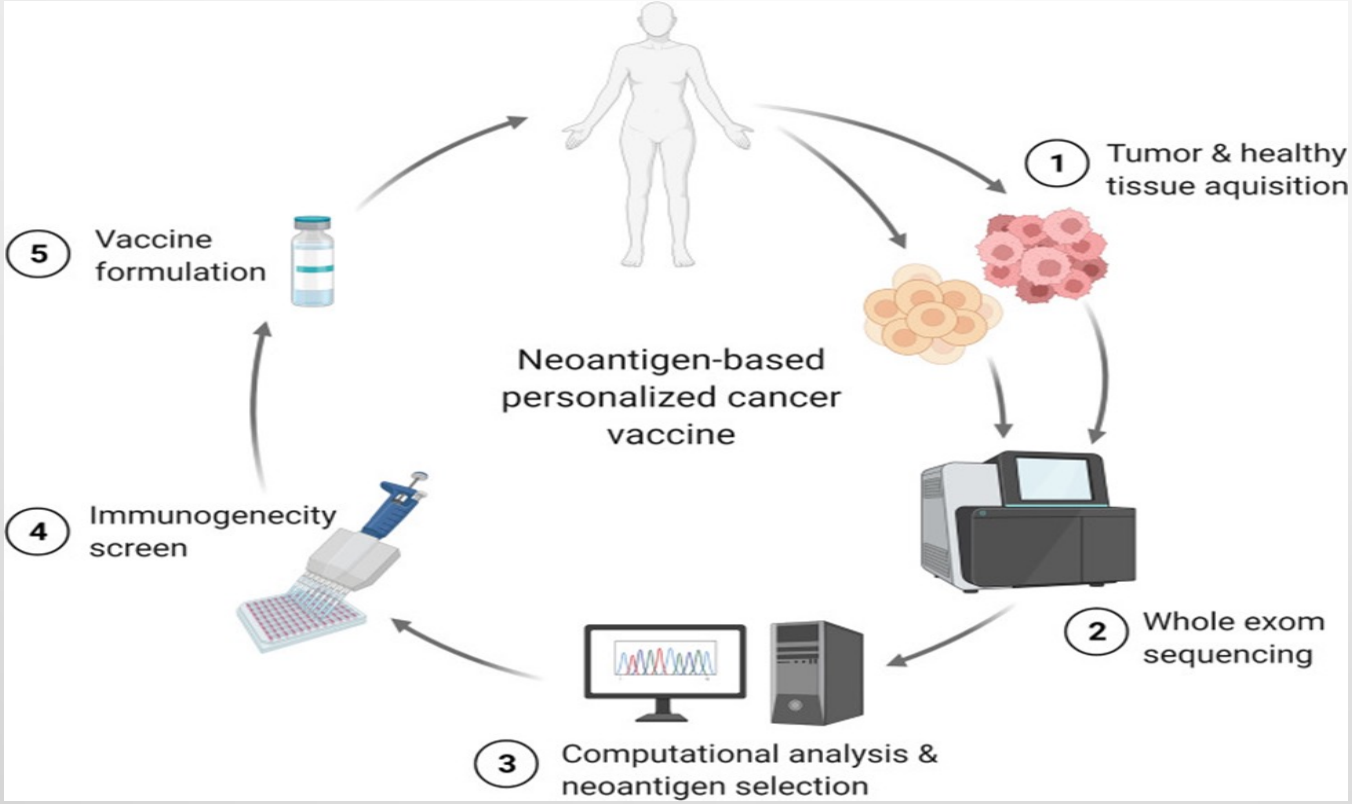
The approved vaccines for cancer prevention and therapy

Vaccine	Target antigen	Use	Cancer Type
Hepatitis B	Hepatitis B virus (HBV) surface antigen (HBsAg)	Preventative	Hepatocellular carcinoma caused by chronic HBV infection
Cervarix	L1 protein of Human papilloma virus (HPV) types 16 and 18	Preventative	HPV-associated cervical, oropharyngeal, anal, penile, and vulvovaginal cancers
Gardasil-4	L1 protein of HPV types 6, 11, 16, and 18	Preventative	HPV-associated cervical, oropharyngeal, anal, penile, and vulvovaginal cancers
Gardasil-9	L1 protein of HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58	Preventative	HPV-associated cervical, oropharyngeal, anal, penile, and vulvovaginal cancers
Bacillus Calmette-Guerin (BCG)	Non-pathogenic Mycobaterium bovis	Therapeutic	high-risk non-muscle-invasive bladder cancer (NMIBC)
Sipuleucel-T (Provenge)	Prostate acid phosphatase (PAP) protein	Therapeutic	Castration-resistant prostatic cancer

Personalized neoantigen-based cancer vaccine.

Neoantigens are recognized by whole exome sequencing of tumor genome and comparing it to the sequences from normal tissue.

Identified neoantigens are screened for immunogenicity and used in vaccine preparation to immunize the patient

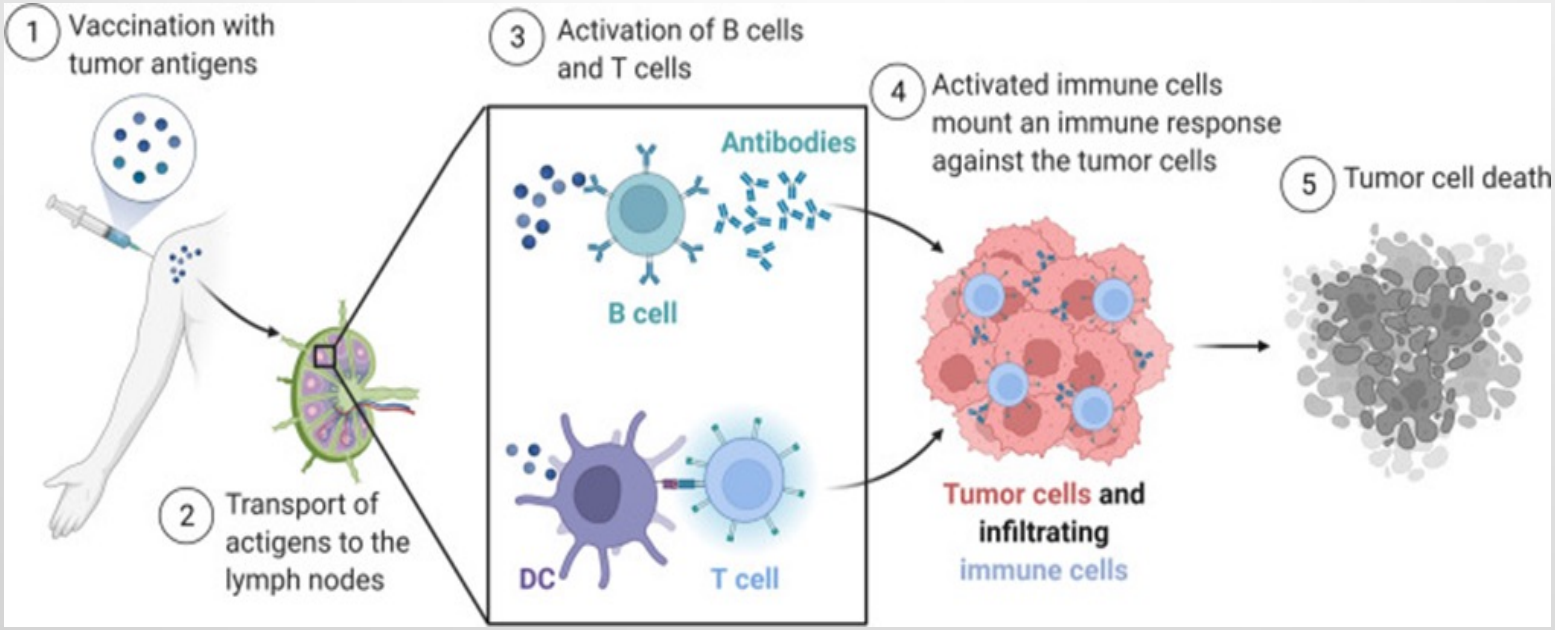


Cancer vaccine.

After vaccination, tumor antigens are carried to the lymph nodes, where they activate antigen-specific B and T cells.

B cells recognize antigens directly, while T cells are activated by dendritic cells (DC) which process and present antigen on MHC molecules.

Antibodies produced by activated B cells and activated effector T cells infiltrate tumors and induce tumor cell death



Review Cancer vaccines: past, present and future; a review article

Eddie Grimmett1 · Bayan Al-Share2 · Mohamad Basem Alkassab1 · Ryan Weng Zhou1 · Advait Desai1 · Mir Munir A. Rahim1 · Indryas Woldie1,2

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Cancer vaccines
for active specific immunotherapy approaches

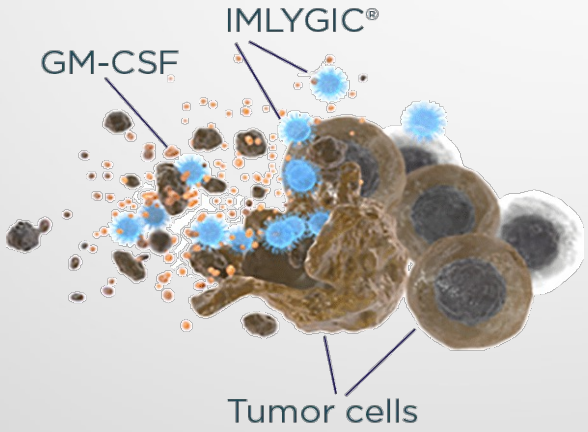
Are more properly referred to as 'active specific immunotherapy’
used to treat cancers rather than to prevent them

Melacine, hapten-treated autologous melanoma cells (M-Vax) is a whole cell lysate

- Regressions of metastatic nodules have been noted
- Controlled trials of **Melacine** indicate prolongation of survival in patients with resected stage IIB disease, particularly those with one or more of the following HLA class I alleles: HLA-A2 or -A28 (-A6802), HLA-B12, -44 or -45, and HLA-C3.
- A combination of interferon-alpha2b and **Melacine** appears to enhance the anti-tumor response in advanced (stage IV) disease, and is being tested in a large randomized controlled trial in resected stage III disease.

IMLYGIC® multiplies inside the tumor cells and triggers the immune system to fight the cancer

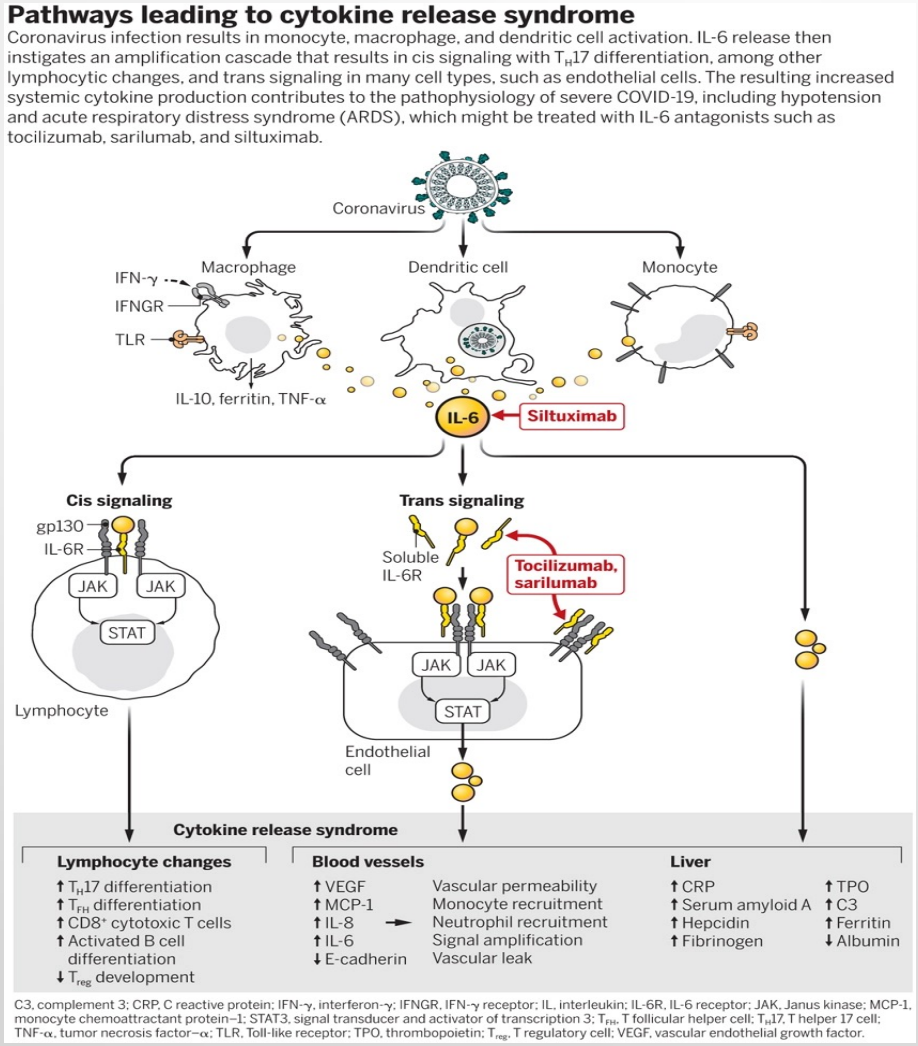
- It is based on herpes simplex virus type 1.
- Although this virus can infect both cancer and normal cells, normal cells are able to kill the virus while cancer cells cannot.



Cancer "Vaccine" Progress-
Talimogene laherparepvec - a biopharmaceutical acting like a vaccine to treat melanoma

- The first FDA-approved oncolytic virus therapy is talimogene laherparepvec (T-VEC, or Imlygic®).
- IMLYGIC is a genetically modified oncolytic viral therapy indicated for the local treatment of melanoma recurrent after initial surgery
- IMLYGIC has been genetically modified to replicate within tumors and to produce the immune stimulatory protein GM-CSF.
- IMLYGIC causes lysis of tumors, followed by release of tumor-derived antigens, which together with virally derived GM-CSF may promote an antitumor immune response.

Cytokine Release Syndrome



The Indaptus Inc Approach in oncology

- Their platform is based on the hypothesis that highly efficient anti-tumor immunotherapy will require safe activation of both innate and adaptive cellular immunity in both tumors and immune organs

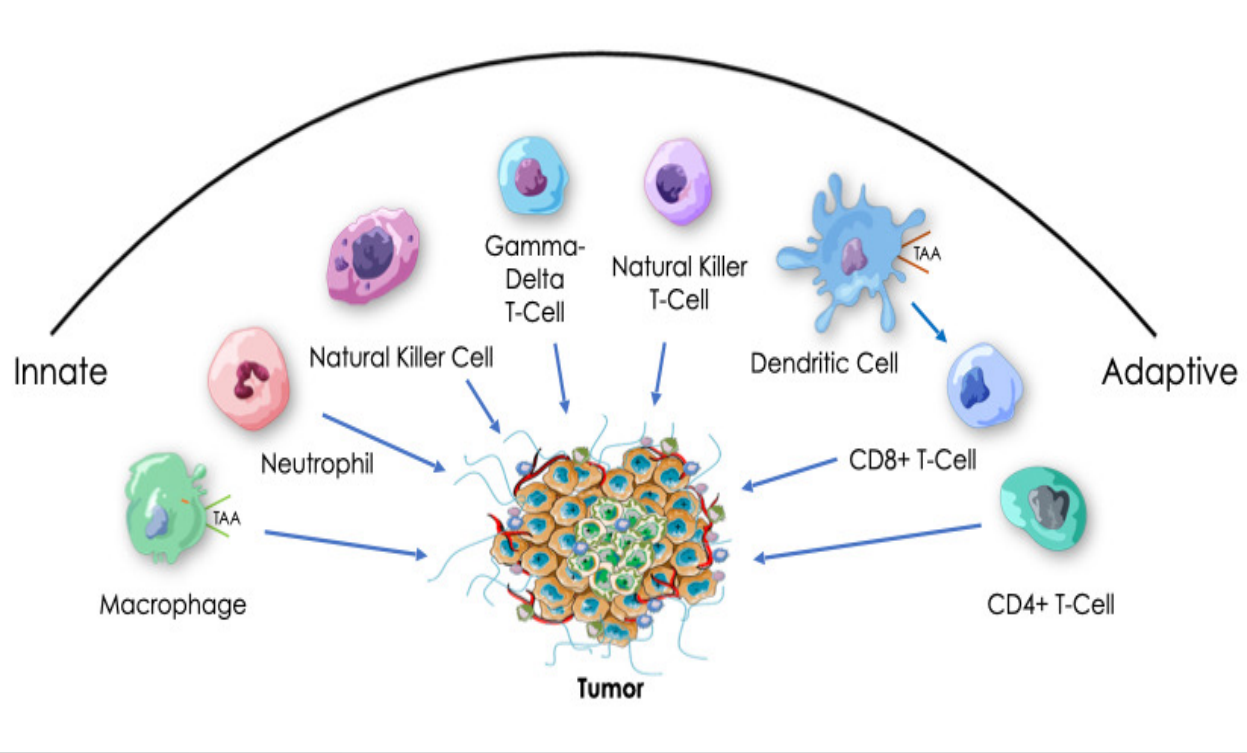
- that this might be achieved with a multi-targeted package of bacterial pathogen-associated molecular patterns (PAMPs), in the form of attenuated and killed, intact but non-pathogenic bacteria

Indaptus "decoy technology"

- Indaptus' Decoy technology is unique in its ability to mobilize both innate and adaptive anti-tumor immune pathways with systemic administration in pre-clinical tumor models
- at the same time not inducing sustained hallmarks of cytokine release syndromes in pre-clinical toxicology studies

The Indaptus approach

Goal: to safely and effectively activate both innate and adaptive cellular anti-tumor pathways by passively targeting both the tumor and immune organs.



Post-traumatic stress disorder (PTSD)

- Post-traumatic stress disorder (PTSD) is a debilitating and often chronic psychiatric disorder the develops following exposure to severe trauma
- PTSD is associated with intrusive memories, distressing dreams, dissociative reactions (such as flashbacks), avoidance of trauma stimuli, negative cognition and mood, increased arousal and irritability and clinically significant distress and impairment of functioning.
- Patients respond to these symptoms by avoidance of people, places or situations that may trigger memories of the traumatic event and develop symptoms similar to major depressive disorder (MDD), irritability, self-destructive behaviour, sleep disturbance and lack of concentration

Prevalence of PTSD

- Approximately 70% of the world population has been exposed to trauma, and of these 6-9% of trauma-exposed individuals develop PTSD
- Abdallah et al., 2019; Liriano et al., 2019).

PTSD and War

- **How Common Is PTSD Among Veterans?**
- The U.S. Department of Veterans Affairs reports that incidence of post-traumatic stress disorder among veteran varies depending on which conflict a service member was involved with.
- About 11 to 20 out of every 100 veterans (or between 11 and 20%) who served in operations Iraqi Freedom and Enduring Freedom have PTSD in a given year.
- About 12 out of every 100 Gulf War Veterans (or 12%) have PTSD in a given year.
- About 15 out of every 100 Vietnam veterans (15%) were currently diagnosed with PTSD when the most recent study of them (the National Vietnam Veteran Readjustment Study) was conducted in the late 1980s. It's believed that 30% of Vietnam veterans have had PTSD in their lifetime.

Treatment of PTSD

- Currently there are only two drugs have been approved by the FDA for the treatment of PTSD: paroxetine and sertraline, both of which are slow acting (taking weeks to months to cause an effect) serotonin reuptake inhibitor antidepressants.
- These drugs offer a treatment advantage as they have a low side effect rate; however, full remission of PTSD symptoms is not obtained (Abdallah et al., 2019; Liriano et al., 2019)
- SSRIs have been shown to have a 50-60% response rate and up to 30% remission rate with a high relapse rate (Jumaili et al., 2021).
- In addition, the SSRIs have minimal effects on synaptic remodelling and PTSD symptoms.

Experimental Approaches in the treatment of PTSD

- Ketamine, an N-methyl-d-aspartate (NMDA) receptor agonist, is classified as a rapid-acting antidepressant (RAAD), and based on the findings a conducted observational study, topical ketamine has been shown to take effect within minutes of administration.
- In animals, ketamine has shown to reverse stress-related synaptic loss/gain within 24 hours of administration, as well as atrophy of the inferior frontal gyrus observed in PTSD patients (Abdallah et al., 2019; Vargas et al., 2021).
- Similar findings have also been observed in humans suggesting a rapid structural and functional reversal of synaptic dysconnectivity within 24 hours of treatment

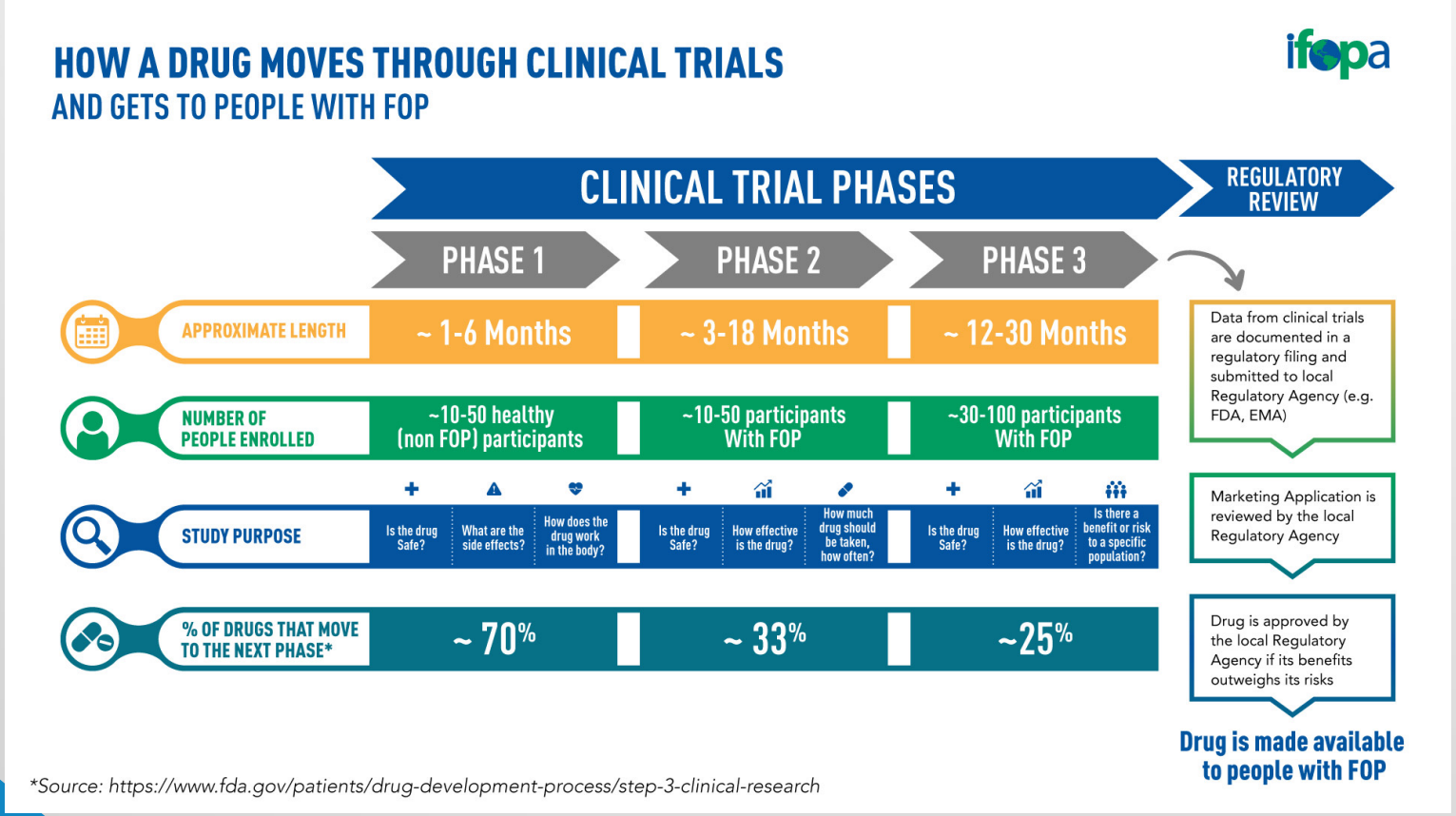
Mode of action of Ketamine

- Ketamine reverses the effects of chronic stress by promoting the rapid synthesis of proteins that promote synaptogenesis by restoring lost synaptic connections and increased spine density.
- This occurs through disinhibition of excitatory neurons in the medial prefrontal cortex (mPFC) via blockade of the NMDA receptors on inhibitory interneurons; this increased excitation leads to activation of downstream signalling cascades like mammalian target of rapamycin (mTOR) via Akt phosphorylation (Wright and Kabbaj, 2018).
- This prevents neuronal membrane depolarization that decreases the probability of neuronal firing, preventing further propagation of the neuronal signal, neurotransmitter release or downstream signalling mechanisms (Kokane et al., 2020).

Mode of action of Ketamine, cont

- Ketamine can also increase brain-derived neurotrophic factor (BDNF) protein translation, but in contrast to antidepressants which also impact BDNF signalling, ketamine does so in a rapid fashion after a single administration (Vargas et al., 2021).
- BDNF increases structural plasticity in neuronal populations and direct administration of BDNF into the rodent brain has shown to alleviate several depressive phenotypes, curb addiction and enhance fear extinction; PTSD impairs fear extinction.
- Blockage of BDNF signalling in the brain can block the behavioural effects of antidepressants.
- Ketamine modulates cortical neuron function by increasing dendritic spine and synapse density in the PFC.

Clinical Trial Phases
- for drug, biologic and device development



*Source: https://www.fda.gov/patients/drug-development-process/step-3-clinical-research

Rutgers Graduate and Medical School

Clinical Research Industrial Opportunities

- Project Management- MS, Pharm D, RN, PhD
- Data Management- MS, Pharm D, Math, PhD
- Safety Monitoring- MD, Pharm D, RN
- Clinical Monitoring- Pharm D, RN
- Medical Monitoring- MD, MD PhD
- Biostatistics – MS, PhD
- Regulatory Affairs -MD, PharmD, RN, MS, PhD