

# To Stop Spreading COVID Disease Completely, Only When We Know and Understand Very Well its Origin, How its Active Sites Analyze Nucleic Acids *in vivo* and How it Spreads? Then will be Easy to be Recovered

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## ABSTRACT

If we remove adenine and cytosine from the viral chain, then will prepare a vaccine containing TG nucleotides from virus and CA nucleotides from marine or from fruits origin, and will give it to the patient with increasing his immune efficiency, that will confirm the ability of neuron to produce antibodies and T-cells with lymphocytes associated protein CTLA4 which is the surface protein on T cells that has an inhibitory effect on the host immune reaction and prevent overreaction of the neuron to face that virus and will have the ability to resist. We can prepare vaccine with only thymine nucleotides from viruses than grow it with guanine and cytosine from fruits origin (orange and apple) to give the sequence TGC, or GTC, then bonded with Tyr-Gly-Gly-methionin we can use adenine from fruits origin as apple, or oranges but I prefer using that new chain containing only TvGfCf (that TV is thymine from virus, and Gf and Cf is guanine and cytosine from fruit origin). In case of using the vaccine for male we'll increase the cytosine, guanine and thymine (e.g., methionine bonded to phosphate gps), but for females would like to refer to increase the guanine and cytosine only more than tandem nucleotides. With adjusting the Phosphorylations in presence of ATPase and GTPase (GTP in proper % for reactivating brain and immune cells functions for facilitate the metabolic cycles for facing that virus dangers)+7-Methyl-guanosine-5'-( $\alpha$ -fluoro)-monophosphate carefully and in accurat %, that'll be able to act on coronaviruses successfully. Absolutely coronaviruses in most animal reservoirs. Those viruses don't like to depend on themselves but are depending on elements as vanadium that will help them entering lungs and digestive system to break nucleic acids and biological molecules *in vivo* then will be easy to destroy immune cells.

So, if we can remove A and G nucleotides from viruses chains (because the most dangerous nucleotides in viruses sequences are A and C then G), with enough proper phosphorylations through using GTPase and its substrates (which are mainly for brain reactivation), so it'll be best success for reservival patients. Also, reactivate main Leu-enkephalin cycles in patient's brain which has this sequence Tyr-Gly-Gly-Phe-Leu, with increasing proper phosphorylation carefully will start to save patients through increasing proper metabolic cycles for the benefit of the 1st steps of increasing immunity strength. Also, please never treat that virus with any drug can cause decompositions. The Photo Reactivating Enzyme (PRE) is an enzyme that repairs DNA damage caused by ultraviolet radiation. The enzyme is found in a variety of species and body tissues. Actually that enzyme is activated by phosphorylations that damaged DNA, so there is no problem for that enz because like what happened just the presence of phosphate gps then will be able to repair nucleic acids again. Now, pyrimidine metabolic process is so imp for enzyme synthesis, for T-cells formation and for immune effectiveness. Furthermore, there are sufficient differences between corresponding enzymes of pyrimidine metabolism, in mainly human body from the viruses that the pyrimidine and purine belongs to viruses will try to isolate the main original pyrimidine from activities in the favor of virus's nucleic acids. But pyrimidine control metabolic process in the favor of their purines.

**Keywords:** COVID; Disease; Nucleic acids; T-cells

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## INTRODUCTION

The effects of vanadium on animals and human are: Irritation of lungs, throat inflammation, damage to nervous system, bleeding of liver and kidneys, stomach inflammation, severe trembling and nose bleeds and throat pains, paralyses and weakening those symptoms are the same symptoms of the COVID-19 disease. Do you think vanadium is the main source of COVID-19 disease? Do the increasing of vanadium in soil, in water and in atmosphere as a source of feeding for microorganisms will cause cove problems. Will some microbes when will be feeded on those biological molecules containing vanadium or their living depending on presence of vanadium will cause effective fast and danger diseases. If so, do those microbes will act on productive system and digestive system including intestine through their so effective oxidative positive bonds.

Also, do you think that their dangers will depend on %of those vanadium mol bonds to viral biological chain, and depend on the number of their effective positive bonding energy that acting on human genes? Most reptiles and animals live in the area where vanadium is available are suffer from vanadium oxidative molecules and also Their female placenta stores these molecules as well, and when some human eats and feed on them (as some countries are eating those animals), those mol will transmitted in molecules in form of microbes and so dangerous viruses [1].

## LITERATURE REVIEW

ATP is involved in the development of synaptic transmission and contributes to the establishment of functional neuronal networks in the developing brain, and in all tissues cells. Additionally, several purinergic receptors (spanning from adenosine to P2X and P2Y receptor subtypes) are differentially expressed by neural stem cells, depending on their maturation stage, and their activation tightly regulates cell proliferation and differentiation to neurons or glial cells, as well as their correct colonization of the developing telencephalon. Purines perform many important functions in cells, being the formation of the monomeric precursors of nucleic acids DNA and RNA but under control of their pyrimidines molecules which are their thymines.

Purines which also contribute to modulate energy metabolism and signal transduction are structural components of some coenzymes and have been shown to play important roles in the physiology of platelets, muscles and neurotransmission. I would like to close all doors for viral purines that will not be used by patient neuron cells *in vivo*, that the only purines will be used *vivo* by neurons will be the neuron main purines. Many enzymes are involved in the conversion of the two purine nucleic acids, adenine and guanine, to Adenosine

Monophosphate (AMP), and to Guanosine Monophosphate (GMP) (and I believe that every purine has their own pyrimidine which are controlling their metabolic processes), so i need that steps of formation AMP and GMP in the pathological cases to activate and run neuron metabolic cycles, but you have to be sure to reduce deaminase cycles to reduce completely uric acid formation [2].

Also, by increasing acetolactate synthase (with its substrate) which is catalytic enzyme involved in the biosynthesis of various amino acids, to start to activate acetylcholine synthesis and cycles and therefore will stimulate the enkephalin pentapeptides which is involved in regulating nociception through antigen resynthesis and nucleic acids systems with T-cells synthesis in the human body, and the Leu pentapeptides functions which are so imp for heart activities. Then phosphatase in a careful limiting %, and transaminases enzyme will help to run most of metabolic cycles in all patient body. Note, when we want to increase GMP so I recommend this molecule: 7-Methyl-guanosine-5'-( $\alpha$ -fluoro)-monophosphate. That the presence of fluorine in biological mol will ensure the facilitating and flexibility of blood flow that will remove any blood clotting if found in arteries and filaments *vivo*. Also, I need to sure the synthesis of CoA and acetyl *in vivo* for brain and all neuron functions, phosphate acetyltransferase are acetyl-CoA and phosphate, whereas its two products are CoA and acetyl phosphate.

In case of Cov infection, we can carefully put patients in safety areas from virus effects during recoveries and then will start to activitie brain acetylcholine cycles with enkephalin cycles for strengthen brain activities and immune cells: Acetyl-coa-CpG-Tyr-Gly-Gly-Phe-Leu and malonyl CoA-CpG-Tyr-Gly-Gly-Phe-Leu. Then treat their respiratory TTF-1 cDNA and polypeptide and MUC 1 to 5 CpG-Leu-Phe-Gly-Gly-Tyr. Then carefully you can start or increase the % from the selected antibiotic antibiotic as ATP drug (e.g., tenofovir ATP drug), then their immune first, tropomyosin and G-actin are main for pain and inflammation sensations, that mainly are contained ATPase in grooves and the tropomyosin has several intermolecular contacts in the overlap region, which consist of ionic hydrophobic and non-polar interaction and contain many methionine in their alpha isoforms. (Note: Many of the methionine residues interacting between the dimers are selenomethionine, which are used here to help migrate, connect and transfer sensation to neuron cells and brain.

Now, if we'll understand very well, how we'll be able to activate brain, then it will be easy to solve any disease problems. Leu pentapeptide will be used as t-RNAs during sending massages from brain to neurons or can be used for tRNAs synthesis for feeding neuron cells in the presence of acetylcholine functions and effects for antigen synthesis which for T-cells and for living cells [3].

Protection and triggering, for healthy successful translations for accelerate brain sending answering but meth pentapeptides for inner cells synthesis and histidine coding and transcriptions for fast tissue synthesis CAC and CAT. Notice, the most effective and useful nucleotide used for resending messages to brain, for GTPase functions and for lipid metabolism is Guanine. Methionine is involved in tropomyosin, in G actin, in T-cells synthesis and in most of proinflammatory treatment by neuron cells. In pentapeptides first'll lead to disappearance of pentapeptides in brain activities, deficiency in pain sensations, deficiency in T-cells synthesis and will lead to cirrhosis and also, the % of deficiency in Gly in the presence of Tyr will affect on T cells synthesis that may will be formed but not be active to face viruses, and the cells antigen will not be active to protect cells and to perform healthy metabolic translations, with their permeability through cells membranes and filtrations for the benefit of the living cell. Met (ATG) pentapeptides is imp for cells proliferations and connection to mast cells along with other pro-inflammatory cytokines with all tissues. SIRP- $\alpha$  receptors have a cytoplasmic tail that includes several Immunoreceptor Tyrosine-Based Inhibitory Motifs (ITIMs). Phosphorylation of the tyrosines in these motifs leads to the recruitment and activation of tyrosine phosphatases SHP-1 and SHP-2 [4].

Also the SIRP- $\alpha$  receptors which have a tyrosine cytoplasmic tail encoded by leu pentapeptides which is companion to met pentapeptides in brain then through mRNA and tRNAs synthesis through translations then transcriptions, cell proliferation started. Leu pentapeptides are the main for antigen synthesis for covering and protecting cell by the active SIRP- $\alpha$  receptors which have a cytoplasmic tyr tail. The activation of acetylcholine in human brain in the availabilities of GTP and proper percentage of ATP will lead to activate pentapeptides for feeding cells and resynthesizes their active antigen that will lead to increase immune efficiency. Notice, we've to increase heart efficiency too through increasing immune efficiency that I notice [5].

Heart muscles thickness due to increasing in positive molecules including  $Ca^{2+}$  can deactivate tyr cytoplasmic tail which characterized in heart cells epithelial cells membranes and antigen, that cytoplasmic Tyr tail responsible for eliminating the inner cell biological products and when that part which is the cytoplasmic tyr tail disrupted, so the accumulations of cell cycles products will begin to be accumulated leading to tumor, muscle swelling, stiffness, constriction, and diastole, which in the future leads to increasing in sclerosis to stop the movement of heart muscles, so we've to help heart cells to reform antigen cytoplasmic Tyr tail to be able to perform their regular activities during re-strengthen the immune cells functions. Now, GGC-Gly is imp for neuron for supporting mRNAs for all functions. But this code "GGA-Gly" in neuron mRNA is for necessary message for rebuilding cells and tissue function. But, this code "GGG-Gly" is for resupply and support 2<sup>nd</sup> DNA strand with guanine which is so imp for all females, for lipid metabolism, for enzymes synthesis, and for rebuilding cells in liver tissues, heart muscles, pancreas can in proper flexibilities for performing their proper functions [6].

Both pentapeptides in brain "CTC, CTA- Leu", and "methionine GTG", at time of facing viruse both pentapeptides will start their most functions in equal % to form their mRNAs for sending messages to neuron and living cells to face problems anode for T-cells synthesis, but at time of fear not both pentapeptides will be active but the Meth pentapeptides will be active more than Leu pentapeptides to give mostly His CAC to build only tissues more than T-cells synthesis, and may so many problems will begin due to decreasing in tRNAs synthesis and decreasing in translations processes that will lead to arteriosclerosis and blockage of the arteries and enlarged heart muscle, as well as the incomplete the formation of healthy living cell, where it will be formed with an imbalance in the antigen and its functions as well. I would like to give mention that the first steps for viruses to attack living cells *in vivo* are to attack their tRNAs then attack their pathways *in vivo* [7].

Let us discuss and understand carefully the tRNAs and their functions and their origins too. The types of tRNA can be classified based on their amino acid that carries, giving rise to 20 different tRNAs. Alternatively, they can also be grouped based on their anticodon. There are 64 possible codons arising from a combination of four nucleotides. A codon is found in the coding 1<sup>st</sup> strand of double-stranded DNA and in the (single-stranded) mRNA. The anticodon is found in the 2<sup>nd</sup> double DNA strand and in tRNA that is the part of the supplement and complementary to that base-pairs codon (on the mRNA) in order to bring the appropriate amino acid to the ribosome to be added to the growing peptide chain. Ribosomal Ribonucleic Acid (rRNA) is the RNA component of ribosomes that originated from 1<sup>st</sup> DNA strand specific codon that will specify its main function within living cells that will form distinguish tissue and that rRNA is the molecular machines for analysing catalyzing protein synthesis through generating its own tRNAs and its own mRNA. Ribosomal RNA are transcribed in the nucleus, at specific structures called nucleoli. These are dense, spherical shapes that form rounded genetic coding sites for rRNA that specify its main general function. In eukaryotic cells, tRNA are made by a specific proteins that will be able to reads their DNA code and makes an short or long RNA code copies, or pre-tRNA depending on the composition of feeded protein and biological chain [8].

That process is sometimes called the suppling with the available feeded codes then available removing and gaining nucleotides started till full transcription occurred for making specific tRNA that will move to its living cells for translations across antigen protective sheet for referring inner cells to restart generating necessary rRNAs and imp enzymes for their metabolic cycles inside and outside cells, some processes done by RNA polymerase III. Pre-tRNA are processed once they leave the nucleus.

Activation of tRNAs depends on the source and origin of cytosine and other nucleotides in biological molecules. The binding of an amino acid code or specific nucleotides to an tRNA acceptor stem occurs as a result of a two-step process: The enzyme binds ATP to the amino acid to form an amino acid AMP complex linked by a high energy bond (PP released, and phosphorylate act on tRNAs cytosine residues that will increase

mobility to reach and bind with amino acids codes in biological chains [9].

The tRNAs levels vary widely among human tissues and coordinate according to the properties of their cognate amino acids. Whether codon usage fine tunes mRNA translation in mammals remains controversial, with recent papers suggesting that production of proteins in specific Gene Ontological (GO) pathways can be regulated by actively modifying the codon and anticodon pools in different cellular conditions. When HIV infects vital cells in the human immune system, such as helper T cells (specifically CD4<sup>+</sup> T cells, macrophages, and dendritic cells, HIV infection leads to low levels of CD4<sup>+</sup> T cells through a number of mechanisms, including pyroptosis of abortively infected T cells, apoptosis of uninfected bystander cells, direct viral killing of infected cells, and killing of infected CD4<sup>+</sup> T cells by CD8<sup>+</sup> cytotoxic lymphocytes that recognize infected cells. When CD4<sup>+</sup> T cell numbers decline below a critical level, cell-mediated immunity is lost, and the body becomes progressively more susceptible to opportunistic infections, leading to the development of disease. Now, when viruses chain codes are containing binding energy more than tRNAs stored bonding energy so will be able to lysis tRNAs thus will lysis antigen then infection occurs, but when tRNAs will be able to lysis the foreign bodies including viruses so will directed them after binding to metabolic cycles for preparing for translations across antigen and cell membrane for inner cells cycles. Also, ppGpp negatively impacts ribosome assembly affecting growth and antimicrobial tolerance in Gram-positive bacteria [10].

Aminoacylation of trna with phosphorylation is sometimes called "charging" or "loading" the tRNA with the amino acid. Once the tRNA is charged, a ribosome can transfer the amino acid from the tRNA onto a growing peptide, according to the genetic code. Aminoacyl tRNA therefore plays an important role in RNA translation, the expression of genes to create proteins. Also, aminoacyl-tRNA synthetase (aaRS or ARS), "phosphorylation of glutamyl-prolyl tRNA synthetase by cyclin-dependent kinase 5 dictates. Also, phosphorylation of many aminoacyl tRNA synthetases (AARSs) has been recognized for decades. phosphorylation is essential for performance of diverse noncanonical functions of AARSs unrelated to protein synthesis [11].

Stimulus-dependent phosphorylation of EPRS is essential for its release from the parental multi-aminoacyl tRNA synthetase complex (MSC), for binding to other GAIT complex proteins, and for regulating the binding to target mRNAs. Importantly, phosphorylation is the common driving force for the context- and stimulus-dependent release, and non-canonical activity, of other AARSs residing in the MSC, for example, lysyl tRNA synthetase (KARS).

The antiviral drugs are supposed to fight off viral infections or fight off foreign bodies effects, usually by attacking the viruses, but if that antiviral molecules will affect on tRNAs in some tissues *in vivo* so will give a danger revers results. In spring, most organisms want to live back after cold and frozen winter e.g., plants that their growth depend on many microorganisms, that some viruses contain and produce high energy molecules when are attack human nose cells and lungs, then the respiratory

genes with lower energy bonds will begin to be attracted to viral chains and results will be breaking most of low energy bonds by viral effects then the fluid will be drawn from the nose until the nose flows. At that point, the body should be supported to rebuild the missing amino acids in their nucleic acids quickly otherwise mutations will begin to start in tissues, and the main blood cycles will fail, then the deposition in the blood vessels and blockage of the arteries will occur and the prevention of blood to reach the heart will occur, and then death will be the result [12].

Certain viruses depend in the activity of certain elements, such as vanadium, that when entering the body of an animal or human, their activities will aided the activity of the virus to break amino acids down. In that case, the virus has to be stopped immediately through feeding body with the mission of nucleic acids, then increasing the water % in the blood until these elements will soluble and leave the body easily (if are water soluble).

Some viruses are positive senses that are spherical or pleomorphic enveloped particles containing single stranded (positive sense) RNA associated with a nucleoprotein within a capsid comprised of matrix protein. In the treatment against those viruses it is imp to use relatively more active negative molecules in antiviral drugs that will affect on viruses without effects on cells and their essential metabolic cycles, and in the same time drugs can increase immune efficiency "as 7-Methylguanosine-5'-( $\alpha$ -fluoro)-monophosphate" which has healthy active negative bonds in its biological molecule structure [13].

So, my suggestion for treating many respiratory health problems and their viruses is to preparing these active gene chain with its carrier helper motor as active fluoro CoA (Its main function is to deliver the acetyl group to the citric acid cycle, and activate brain function). But, For building tissues after surgeries tyr, glu, meth "1", cys, asp, ser, gly, gly, meth "2" with fluoroacetyl CoA. Notice in case of old ages Meth "1" has to be removed "to decrease the sulfur bonded with methionine that are responsible for increasing the time of tissues synthesis with some molecules can be precipitate in arteries and veins", with slightly more in fluoro CoA concentration "that presence of fluorine will help in blood fluidity and reducing blood clotting". Do you think vanadium is the main source of Cov. Do increasing of vanadium in soil, plants and atmosphere can cause the Cov problems? Will some microbes when feeded on those biological molecules containing or depending on presence of vanadium will cause effective fast diseases as will act from productive system with intestine through its so effective oxidative bonds and their dangers will depend on % of those vanadium mol bonds and the number of their effective bonding energy that acting on human genes. Is fluorine can reduce or stop the vanadium harms effects on liver, on kidney that reflect strong effects on respiratory cells, heart and immune functions. Now, most reptiles and animals in the places where vanadium is available are suffer from vanadium oxidative molecules and Their female placenta stores these molecules as well, and if human eats them, those mol will transmitted in molecules in form of microbes and so dangerous viruses [14].

## DISCUSSION

I'm thinking that to stop that virus, first increase blood flow by increasing ATP+GTP+fluoro acetyl CoA for a period of 24 hours. Then treat with active fluoro methyl guanosine monophosphat with aglutathione transferase containing 5-fluorotryptophan or fluorocytosin (that usually used for colon infections and some cancers). I'm concerning on fluorinated molecules as their functions is anticoagulation that will help increasing blood fluidity that will start to run against gravity to feed brain and heart. Also, the ACh diffuses within synaptic cleft and activates acetylcholine receptors (AChRs). For Acetylcholine (ACn) activities with pentapeptides cycles resynthesis. Notice both have fluorine used as carrier and activate ACn transmitting across neuron. I expect that that virus start first in reproductive system in males and females (in placenta) then will start to spread first attracting and distroy most of biological genes from liver and kidneys. And I expect that is a kind of viruses that vanadium dependent, that's why is having the same effect as vanadium and that will be discovered by X-rays [15].

## CONCLUSION

Its main function is to deliver acetyl grp to citric acid cycle, and activate brain immune function, also it has been proven that the effect of G-CSF on peripheral blood progenitor cell mobilization will lead to increasing in CD34 cell counts and white cells increased too, but blood platelets decreased due to increasing tRNA for accelerating translations and transcriptions cycles to be ready to face any danger. Coronavirus (Cov) today has very active hydroxide bonds. Molecules may also bonded to rare positive elements, that so thirsty to attract most of effective genes from respiratory system and heart. Cov breaks most of the molecules bonds to give unknown micro molecules which are not eligible for doing any metabolic cycle *in vivo*. Coronaviruses (Cov) contain bonding energy in their molecules more than triple active bonds in its biological molecules. So i believe that the increasing phosphorylations in control with what I wrote previously will limit that viral activity and saturate their thirsty ffor acting on nucleic acids, and will force that viral molecules to follow catabolic cycles to be broken to defined short molecules that will be used by immune cells.

## REFERENCES

- Whitby FG, Phillips GN Jr. Crystal structure of tropomyosin at 7 angstroms resolution. *Proteins*. 2000;38(1):49-59.
- Clayton JE, Sammons MR, Stark BC, Hodges AR, Lord M. Differential regulation of unconventional fission yeast myosins via the actin track. *Curr Biol*. 2010;20(16):1423-1431.
- Stark BC, Sladewski TE, Pollard LW, Lord M. Tropomyosin and myosin-II cellular levels promote actomyosin ring assembly in fission yeast. *Mol Biol Cell*. 2010;21(6):989-1000.
- Cho NH, Shaw JE, Karuranga S, Huang Y, da Rocha Fernandes JD, Ohlrogge AW, et al. IDF diabetes atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. *J Diabetes Res*. 2018;138:271-281.
- Banerjee J, Dhas Y, Mishra N. Middle-aged indians with type 2 diabetes are at higher risk of biological ageing with special reference to serum CDKN2A. *J Diabetes Res*. 2020.
- Anjana RM, Deepa M, Pradeepa R, Mahanta J, Narain K, Das HK, et al. Prevalence of diabetes and prediabetes in 15 states of India: Results from the ICMR-INDIAB population-based cross-sectional study. *Lancet Diabetes Endocrinol*. 2017;5(8):585-596.
- Rajadhyaksha V. Managing diabetes patients in India: Is the future more bitter or less sweet? *Clin Res*. 2018;9(1):1.
- Gujral UP, Pradeepa R, Weber MB, Narayan KV, Mohan V. Type 2 diabetes in South Asians: Similarities and differences with white Caucasian and other populations. *Ann Acad Sci*. 2013;1281(1): 51-63.
- DeFronzo RA, Hompesch M, Kasichayanula S, Liu X, Hong Y, Pfister M, et al. Characterization of renal glucose reabsorption in response to dapagliflozin in healthy subjects and subjects with type 2 diabetes. *Diabetes Care*. 2000;36(10):3169-3176.
- Gerich JE. Role of the kidney in normal glucose homeostasis and in the hyperglycaemia of diabetes mellitus: Therapeutic implications. *Diabet Med*. 2010;27(2):136-142.
- Vallon V, Platt KA, Cunard R, Schroth J, Whaley J, Thomson SC, et al. SGLT2 mediates glucose reabsorption in the early proximal tubule. *J Am Soc Nephrol*. 2011;22(1):104-112.
- Bailey CJ, Iqbal N, Tjoen C, List JF. Dapagliflozin monotherapy in drug-naive patients with diabetes: A randomized-controlled trial of low-dose range. *Diabetes Obes Metab*. 2012;14(10):951-959.
- Kaku K, Kiyosue A, Inoue S, Ueda N, Tokudome T, Yang J, et al. Efficacy and safety of dapagliflozin monotherapy in Japanese patients with type 2 diabetes inadequately controlled by diet and exercise. *Diabetes Obes Metab*. 2014;16(11):1102-1110.
- Ji L, Ma J, Li H, Mansfield TA, Tjoen CL, Iqbal N, et al. Dapagliflozin as monotherapy in drug-naive Asian patients with type 2 diabetes mellitus: A randomized, blinded, prospective phase III study. *Clin Ther*. 2014;36(1):84-100.
- Ferrannini E, Ramos SJ, Salsali A, Tang W, List JF. Dapagliflozin monotherapy in type 2 diabetic patients with inadequate glycemic control by diet and exercise: A randomized, double-blind, placebo-controlled, phase 3 trial. *Diabetes Care*. 2010;33(10):2217-2224.