How Nanotherapy Fails SARS-CoV-2: The BI(G)MED Experience
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ABSTRACT
While the Sars-CoV-2 epidemics seems to rebound more and more despite the massive vaccination surveys that prove not only moderately efficacy but more deleterious effects than expected, the need for an effective treatment against the coronavirus is imperatively needed. In this article we present such a treatment, based on empirical clinical observations. The goal of this treatment is to give hope to as many patients as possible for the existence of an effective and safe treatment without any side effect.

Keywords
SARS-CoV 2, Nanotherapy, Ultra-low doses, Epigenetic regulation, Prevention.

Introduction
We all know that the pandemic caused by SARS-CoV-2 has shaken the medical world as never before. Currently, the health situation is still not under control in most Western countries; the results seem to be better in Asia at the cost of very great sacrifices made by the native populations.

Officially, no progress has been made in terms of therapeutics, with a few trials of molecules, sometimes known for a long time for their anti-infectious properties, more or less quickly dropped.

Since the beginning of the epidemic, the medical and scientific community has relied on the implementation of an anti-SARS-CoV-2 vaccination conducted according to different methodological procedures, most of the time with minimal follow-up.

Currently the effectiveness of the various vaccines is highly questioned by the emergence of variants, which are probably the consequence of the inability of the vaccine substances to completely block the progression and spread of the virus. Consecutively fears of a new epidemic expansion with its corresponding major socioeconomic problems increase and require an adapted and efficient response from virology experts worldwide.

Methods
General Principles of BI(G)MED
This is both a diagnostic and therapeutic method based on a global and biomimetic approach of the immunogenetic mechanisms of the cell, in order to obtain a restoration of the disturbed self-regulation processes. To this end, the BI(G)MED will attempt on the one hand to promote deregulated immunogenetic mechanisms in a global and multi-scale approach as in the Systems Biology approach and, on the other hand to restore the homeostatic balance at the genomic, epigenomic, proteomic and metabolic levels (Figure 1).

To this purpose, the BI(G)MED will use the various molecules involved in the regulation of these biological mechanisms at ultra-low doses to comply with the principle of biomimicry.
In a recent paper, EJ Calabrese & J Giordano describe evidence establishing that ultra-low doses of diverse chemical agents at concentrations from $10^{-18}$ to $10^{-24}$ mol.L$^{-1}$ (e.g., approaching and/or less than 1 atom or molecule of a substance by cell based on Avogadro’s constant $6.022\times10^{23}$ mol$^{-1}$) are able to engage receptor and intracellular signaling systems to provide reproducible effects in a variety of species, from unicellular organisms to humans [2]. The authors describe multiple experimental studies showing that only one or very few molecules are needed to activate a cell and/or entire organism via cascade(s) of amplification mechanisms and processes. For example, ultra-low dose ligand exposure was able to activate by about 50% both an individual cell, and ~3000 to 25,000 neighboring cells on average.

Such activation of cells and whole organisms typically displayed “hormetic-biphasic dose responses” [3], which explain one of the important reasons for the success of BI(G)MED, namely "the reversal of action of a molecule according to dilution/concentration" (Figure 2).

This law of classical pharmacology argues that low dilutions have a rather activating effect which is reversed as the dilutions increase.

Another important point is the use of dynamized dilutions, whose effectiveness is a fundamental element of the impact of our remedies on the regulation mechanisms. Their mechanism of action relies on the principles of ab initio Molecular Dynamics, which describe the molecular speed up resulting from the interactions between used molecules and their aqueous substrate [4,5] (Figure 3).

**SARS-Cov-2 & BI(G)MED**

This pharmaceutical product includes several molecules belonging to the SARS-Cov-2 viral genome as well as to its epigenome and transcriptome, identified for their important role in the regulation of essential mechanisms involved in the pathogenicity of the virus. At the genomic level [6,7], the formula contains the main ORFs of the genes involved in the replication of the viral RNA molecule, in particular ORFs 1a, 1b, 6 & 8, whose gene-silencing we will be obtained with the help of very high dynamic dilutions ranging from $10^{-12}$ to $10^{-18}$ mol.L$^{-1}$. We will obtain in the same way a gene-silencing of the protein S gene in order to prevent its *de novo* synthesis.
Regarding epigenomic regulation, it exclusively concerns the one related to RNA interference [8-10] allowing both a post-transcriptional inhibition of viral mRNA and a modulation of various immune responses, also involving microRNAs used in low activating dilutions ranging from $10^{-5}$ to $10^{-7}$ mol.L$^{-1}$.

The therapeutic use of the proteome will of course concern not only the major proteins of the virus but also a large number of proteins linked to the host cell as well as to certain immunocompetent cells.

At the viral level, it is first and foremost the now famous membrane protein S and its numerous variants that are regularly updated, but also the membrane protein N and several non-structural proteins of the virus, which all represent major components of our remedy [11-13].

At the cellular level, it is above all the proteins corresponding to the entry points of the virus into the host cell, including the ACE and TMPRSS2 molecules, as well as the furin molecule responsible for a large part of the virulence of the virus, which will be blocked using high inhibitory dilutions [14,15].

Concerning the implementation of the molecules involved in the immune reaction, it appears to be very contrasted between the inhibition of the main pro-inflammatory cytokines with well-known devastating effects [16-21], and the activation of molecules capable either of detecting the virus such as certain TLRs and RLRs or of promoting the apoptosis of infected cells such as Caspases [22].

We thus obtain a formula close to the one presented in Table 1.

Table 1: COROVIR/REG composition.

| Component                             | Dilution |
|---------------------------------------|----------|
| CoV replicase gene ORF 1a             | $1 \times 10^{-18}$ mol |
| CoV replicase gene ORF 1b             | "        |
| CoV replicase gene ORF 6              | "        |
| CoV N protein                         | "        |
| CoV S protein & gene                  | "        |
| CoV S protein D614G                   | "        |
| CoV S protein N501Y .....              | "        |
| Furin                                 | "        |
| hACE2 protein + gene                  | "        |
| TMPRSS2                               | "        |
| IL-6                                  | "        |
| TNF-α                                 | "        |
| miR-146-5p .....                       | "        |
| TLR3                                  | $1 \times 10^{-5}$ mol |
| TRIF                                  | "        |
| RIG-1                                 | "        |
| IL-18                                 | "        |
| miR-198                               | "        |
| miR-761 .....                          | "        |

To prepare the ultra-low doses we use the traditional dilution/dynamization methods of the European Pharmacopoeia to obtain xylitol globules impregnated with the active molecules of the formula, which will soon be replaced by second generation liposomal nanovectors [23].

**Results**

COROVIR/REG has proven to be extremely effective as a preventive agent in the context of the SARS-CoV-2 pandemic. More than 10,000 patients have been treated with this product, and the feedback we have received so far confirms that only two patients have nevertheless developed a mild to moderate infection.

Another aspect of the problem concerns the "long COVID syndrome", which according to a publication in the journal "Pathogens" last June and signed by JE Gold & al, involves EBV as a co-factor of SARS-CoV-2 in this chronic disabling pathology. In fact, their results clearly show a correlation between the amount of EBV EA-D IgG and the occurrence of long COVID symptoms [24].

These authors concluded their work as following “many long COVID symptoms may not be a direct result of the SARS-CoV-2 virus but may be the result of COVID-19 inflammation-induced EBV reactivation”.

In this respect, BI(G)MED has been able to demonstrate for a long time the efficacy of our products - that is the association of the FORMULA-VIRUSREG with the FORMULA-EBV-REG/MIR - to treat and neutralize this particularly harmful virus.

**Conclusion**

BI(G)MED, while not triggering any adverse effects, achieves the presupposed objectives of
- having a preventive effect on SARS-CoV-2
- controlling acute infections
- not only preventing but also overcoming long-term reactions.

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