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The Bio Immune(G)ene Medicine or How to Use a Maximum of Molecular Resources of the Cell for Therapeutic Purposes

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Abstract

At a time when emerging concepts capable of revolutionizing old medical paradigms are flourishing, such as systems biology, integrative medicine or personalized medicine, it is of the utmost interest to observe how such concepts can be applied in the context of a therapeutic method that is both innovative and devoid of any undesirable effect, because it simply seeks to play a regulatory role. The aim of this method called Bio Immune(G)ene MEDicine (BI(G)MED) is to make the best use of all the molecular resources available to the cell to restore the homeostasis of the latter at its various levels of genome, epigenome, transcriptome, proteome and metabolome. To achieve this goal, it is of course essential to use means borrowed to nanobiotechnologies to ensure a high efficiency of the molecules made available to the cells to facilitate their self-regulation thanks to a therapeutic model essentially based on true biomimicry. The description of one or the other clinical case will show how this method can be effective in polypathologies, sometimes very advanced and often recurrent, without ever harming the patient elsewhere.

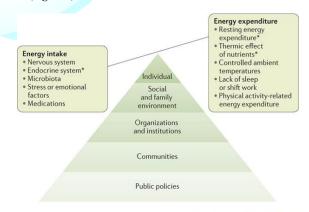
Keywords: Personalised medicine, Systems biology, Cell regulation, Nanotherapy, miRNAs. **Abbreviations:** BI(G)MED-Bio Immune(G)ene MEDicine, PBC- Primary Biliary Cirrhosis, SSc- Systemic Sclerosis, ENT infection- Ear, Nose and Throat infections.

Introduction

In recent years, new concepts have emerged that have led to changes in the way the sick individual and the context of his disease are approached. This began with a broader approach to the disease process, which in some way lost its status as an inalienable state that can only partially and temporarily be remedied. The disease has thus become a dynamic phenomenon involved in a succession of pathological states more or less reversible depending on their greater or lesser interactivity. In that sense, it has been recently written by DG Limbaugh that "one can conceive of cases where simultaneous disorders prevent each other from being, in any traditional sense, actually harmful" [1].

On even broader bases, the concept of "One Health" has developed in recent years, which requires breaking down the interdisciplinary barriers that still separate human and veterinary medicine from ecological, evolutionary, and environmental sciences [2]. On the same way appeared the concepts of personalized medicine, precision medicine, integrative medicine or P4 medicine, all interconnected by the concept of globality and interactivity and using increasingly powerful tools. It should be noted at the outset that all these concepts, which are relatively close to the others, share the same concern, which is to take on as effectively as possible the major challenge represented by the exponential development of chronic diseases throughout the world. In 2011, we could find following definition of personalized medicine in U.S. News: "Personalized medicine is a young but rapidly

advancing field of healthcare that is informed by each person's unique clinical, genetic, genomic, and environmental information." Because these factors are different for every person, "the nature of diseases—including their onset, their course, and how they might respond to drugs or other interventions—is as individual as the people who have them (Figure 1)."



Nature Reviews | Disease Primers

Figure 1: Key factors involved in the regulation of energy balance [3].



Personalized medicine is about making the treatment as individualized as the disease. It involves identifying genetic, genomic, and clinical information that allows accurate predictions to be made about a person's susceptibility of developing disease, the course of disease, and its response to treatment [4-6] (**Figure 2**).

New Paradigm Shift in Treatment

Transitioning From the 'one-size-fits-all' to 'precision medicine' model with multi-level patient stratification.

One-size-fitsall
Medicine

Patients are grouped by:
Disease Sudrypes
Disease Sudr

Figure 2: Frost and Sullivan: new paradigm shift in treatment.

In order for personalized medicine to be used effectively by healthcare providers and their patients, these findings must be translated into precise diagnostic tests and targeted therapies (**Figure 3**). Specific advantages that personalized medicine may offer patients and clinicians include:

- · Ability to make more informed medical decisions
- Higher probability of desired outcomes thanks to better-targeted therapies
- · Reduced healthcare costs
- Reduced probability of negative side effects
- Focus on prevention and prediction of disease rather than reaction to it
- · Earlier disease intervention than what has been possible in the past

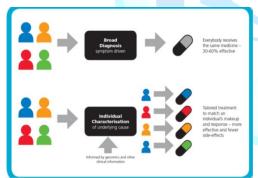


Figure 3: Personalized medicine and treatment, NHS explanation document.

The four 'P's of personalized medicine have thus given birth to P4 medicine, a term coined by David Galas and Leroy Hood from the Institute for Systems Biology (ISB) in Seattle, and based on four references: Predictive, Preventive, Personalized and Participatory [7,8]. The conceptual matrix at the origin of all these evolutions of medical thinking remains this of "systems biology" with its central components that are genetically programmed networks (circuits) within cells and networks of cells [9].

Prediction and prevention of disease

Using genomic technologies and other diagnostics, we will be able to identify people most at risk of disease even before the onset of their symptoms. Earlier detection will open up the prospect of new treatment options and support people to make informed lifestyle choices.

More precise diagnoses thanks to the knowledge of each individual's complex molecular and cellular processes, informed by other clinical and diagnostic information define the so-called Precision Medicine [10] (Figure 4).



Figure 4: Personalized and precision medicine.

Targeted and personalized interventions

We are already beginning to see the development of simple point of care tests, based on genomic knowledge, which enable clinicians in a wide variety of settings to identify the best therapy. Variants in our genetic code can also be used to predict the potential for adverse drug reactions [11]. The ability for a clinician to discuss with their patients about information on individual genomic characteristics, lifestyle and environmental factors, and interpret personal data from wearable technology will drive a new type of conversation, that might lead patients to consider preventive measures with the idea that patients should play a decisive role in their own healthcare by actively controlling their health status and participating in the decision-making process regarding their treatments [12].

Material and Methods

The Bio Immune(G)ene Medicine, so-called BI(G)MED, is first and foremost a method combining predictive diagnosis as well as biomimetic and personalized treatment (**Figure 5**). To try to achieve this objective, there is currently a very fruitful concept, that of "systems biology", aiming at a global approach of biological phenomena.

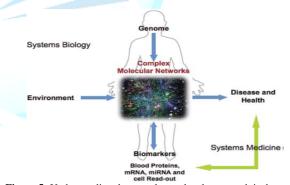


Figure 5: Understanding the complex molecular network is the center of systems biology and systems medicine [13].

Systems biology employs a holistic approach to study all components and interactions in the network of DNA (genes), RNA, proteins and biochemical reactions within a cell or an organism. This concept of "systems biology" corresponds entirely to the approach of human diseases that we have been using for many years in the framework of BI(G)MED, and that we are able to translate at both the diagnostic and therapeutic level. At the diagnostic level, we have a very efficient overview of the cellular immune system thanks to the lymphocyte phenotyping, which is not only an important tool for the diagnosis of hematological and immunological disorders, but also a means of fine-tuning cellular immune status and drawing predictive conclusions [13-15] (Figure 6).

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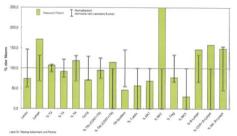


Figure 6: Example of a lymphocyte phenotyping.

To appreciate the humoral mediated immune system, we use the protein profile, which allows us to measure several types of humoral immune responses that are both complementary and interactive [16] (**Figure 7**).



Figure 7: Example of a protein profile.

Thanks to these two types of investigations, which are essential for us, we can direct the biological diagnosis more specifically towards parameters related to microbiology, oncology, allergy, autoimmunity or metabolism (**Figure 8**). The therapeutic goal of the BI(G)MED is therefore to make the best use of all the molecular resources available in the cell to restore its homeostasis at the different genomic, epigenomic, transcriptomic, proteomic and metabolomic levels [16].



Figure 8: Systems biology of asthma and allergic diseases: a multiscale approach [17].

To achieve this goal, it is necessary to use means borrowed to nanobiotechnologies, to ensure a very efficient transport of molecules made available to the cells, so as to facilitate their self-regulation through a truly biomimetic treatment. Usually the BI(G)MED uses nanovectors with a xylitol base [18], carrying molecules of all types at ultra-low concentrations (1g x10⁻⁴ until 1g x10⁻¹⁰ Mol). These small globules must be dissolved in the oral cavity as in all sub-lingual immunotherapies, from where the molecular information will be transmitted to the target organ via the lymphatic network. These molecules can be fragments of DNA and RNA (among these will be found mainly microRNAs as epigenetic regulators), transcription factors, all kinds of molecules involved in the various cell signalling pathways, but also cytokines and enzymes such as kinases. All together are included in formulas in ultra-low doses [19]; all are therefore at concentrations similar to those observed in the cell physiology, making them unlikely to trigger unwanted side reactions.

In this way we can progressively regulate most of the disturbed molecular pathways in one or more given pathologies according to the general rule of our kind of treatment: from the gene to the whole cell [20,21].

Results

The results obtained with this method will be presented through three case reports.

Primary Biliary Cirrhosis (PBC) and Systemic Sclerosis (SSc)

This is a 67-year-old woman at the time of her first consultation in 2003, by which a Primary Biliary Cirrhosis (PBC) and a Systemic Sclerosis (SSc) were recently discovered on the occasion of pericarditis associated with pleural effusion. At this time, biology shows the usual abnormalities for this type of pathology, namely increased antinuclear and in particular anti-centromere antibodies; it is the same with regard to anti-mitochondrial antibodies. It is also interesting to note the viral reactivations concerning EBV, CMV and Parvovirus B19, which will follow the patient in a very irregular way during all the coming years.

The diagnosis is confirmed by tissue biopsies, and the patient wants to stop the immediate corticosteroid therapy, while agreeing to continue a treatment with ursodeoxycholic acid, which she never interrupted. For this reason, we initiated a treatment with BI(G)MED essentially oriented towards the regulation of the autoimmunity processes and the neutralization of the various reactivated viruses mentioned above. The clinical evolution has shown a remarkable stability even if it has been complicated by various accidents such as:

- The early development of a xerostomia, itself causing recurrent problems of periodontal diseases and dental infections at the origin of numerous local treatments
- The accidental discovery in 2010 of a ductal adenocarcinoma of the left breast requiring a lumpectomy followed by the establishment of an appropriate BI(G)MED-immunogenetic regulation
- The sudden appearance in 2014 of an autoimmune thrombocytopenia following osteosynthesis after traumatic wrist fracture and needing the establishment of an additional regulatory treatment to stabilize platelets between 30 and 40 thousand
- The occurrence in 2017 of several episodes of bacterial pulmonary infections which each time required the use of appropriate antibiotic therapy

Despite all these health disorders, that adjustments at the level of the BI(G)MED nanotherapy have each time contributed to rebalance, the patient has preserved until now a very stable condition and a biological state hardly evolutive, where the various parameters alternately normalize and then degrade again more or less. PBC and SSc remained perfectly stabilized during all these years.

Waldenström's macroglobulinemia

The second example is that of a 53-year-old woman at the time of her first consultation in 2012, by which a Waldenström's macroglobulinemia was discovered a few months ago in the course of investigations carried out following multiple recurrent ENT (Ear, Nose and Throat) infections.

The first biological parameters corroborate a triple monoclonal peak estimated at $13.42\ g/l$ and including:

- · IgG kappa
- IgA kappa
- IgM kappa

Associated with a positive Bence-Jones proteinuria and an increased value of thymidine kinase by 10.2 U/L. After approximately eighteen months of a BI(G)MED sublingual regulatory nanotherapy, the triple

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monoclonal peak had decreased to 3.3 g/L, Bence-Jones proteinuria had disappeared, and thymidine kinase was normal to 5.0 U/L. In addition, the patient had not had the least ENT infections during the previous winter. From that time on, no pejorative developments have been reported.

Waldenström disease and sclerosing cholangitis

A third and final example concerns a 55-year-old man at his first consultation for Waldenström disease and sclerosing cholangitis discovered the previous year. Otherwise an ulcerative colitis has been known since the age of 22 and is regularly treated by mesalazine.

At this time, its clinical condition is not bad, but the biological parameters show the typical disturbances of the diagnosed diseases with:

- Increased levels of liver enzymes
- IgM greatly increased
- Positive p-ANCA

There is also a reactivation of Parvovirus B19. The patient followed for a year and a half a regulatory treatment of BI(G)MED nanotherapy while continuing his regular intake (but at a very reduced dosage) of mesalazine and ursodesoxycholic acid, and results in biological parameters almost normalized among those initially disturbed.

Discussion

This brief description of three clinical examples drawn from a daily medical practice make it possible to demonstrate the therapeutic interest and effectiveness of resorting to the regulating potential of the cell itself, the only one able to rebalance a disturbed mode of functioning, when the needed molecular information is provided to it. It turns out that this regulatory capacity is as greater as the molecular resources used by the cell for this purpose of global regulation are made available by means of ultra-low doses of nanotherapeutic compounds administered sublingually. This observation does not exclude that other types of nanocarriers could be considered in the near future.

Conclusion

- Different medical concepts have emerged in recent years all based on globality and interactivity
- Personalized medicine (also named precision medicine) individualizes the disease and consequently the treatment that must regulate it
- The best way to achieve this goal is probably to use the molecular resources of the cell itself, and direct them towards a return to cellular homeostasis through a regulatory treatment.
- The BI(G)MED is suitable for this regulatory process in the form
 of a sublingual nanotherapy, whose efficiency is confirmed in
 very variable clinical situations.

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