Open Access Maced J Med Sci **electronic publication ahead of print,**
published on August 30, 2019 as https://doi.org/10.3889/oamjms.2019.775

ID Design Press, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences.
https://doi.org/10.3889/oamjms.2019.775
eISSN: 1857-9655
Global Dermatology

Clinical Applications of System Regulation Medicine

Massimo Fioranelli[1*], Alireza Sepehri[1], Maria Grazia Roccia[1], Cota Linda[1], Chiara Rossi[1], Amos Dawodo[1], Petar Vojvodic[2], Jacopo Lotti[1], Victoria Barygina[3], Aleksandra Vojvodic[4], Uwe Wollina[5], Michael Tirant[6], Thuong Nguyen Van[7], Torello Lotti[8]

[1]Department of Nuclear Physics, Sub-nuclear and Radiation, G. Marconi University, Rome, Italy; [2]Clinic for Psychiatric Disorders "Dr. Laza Lazarevic", Belgrade, Serbia; [3]Department of Biomedical Experimental and Clinical Sciences, University of Florence, Florence, Italy; [4]Department of Dermatology and Venereology, Military Medical Academy, Belgrade, Serbia; [5]Department of Dermatology and Allergology, Städtisches Klinikum Dresden, Dresden, Germany; [6]G. Marconi University, Rome, Italy; [7]Vietnam National Hospital of Dermatology and Venereology, Hanoi, Vietnam; [8]Department of Dermatology, University of G. Marconi, Rome, Italy

Citation: Fioranelli M, Sepehri A, Roccia MG, Linda C, Rossi C, Dawodo A, Vojvodic P, Lotti J, Barygina V, Vojvodic A, Wollina U, Tirant M, Nguyen Van T, Lotti T. Clinical Applications of System Regulation Medicine. Open Access Maced J Med Sci. https://doi.org/10.3889/oamjms.2019.775

Keywords: Bioregulatory Systems Medicine; Preclinical; Networks

***Correspondence:** Massimo Fioranelli. Department of Nuclear Physics, Sub-nuclear and Radiation, G. Marconi University, Rome, Italy. E-mail: massimo.fioranelli@gmail.com

Received: 16-Jul-2019; **Revised:** 04-Aug-2019; **Accepted:** 05-Aug-2019; **Online first:** 14-Sep-2019

Funding: This research did not receive any financial support

Competing Interests: The authors have declared that no competing interests exist

Abstract

Increasing incidence and poor outcome of chronic non-communicable diseases in western population would require a paradigm shift in the treatments. Guidelines-based medical approaches continue to be the standard rule in clinical practice, although only less than 15% of them are based on high-quality research. For each person who benefits from the 10 best-selling drugs in the USA, a number between 4 and 25 has no one beneficial effect.

The reductionist linear medicine method does not offer solutions in the non-manifest preclinical stage of the disease when it would still be possible to reverse the pathological progression and the axiom "a drug, a target, a symptom" are still inconclusive. Needs additional tools to address these challenges.

System Medicine considers the disease as a dysregulation of the biological networks that changes throughout the evolution of the pathological process and with the comorbidities development. The strength of the networks indicates their ability to withstand dysregulations during the perturbation phases, returning to the state of stability. The treatment of dysregulated networks before the symptomatological manifestation emerges offers the possibility of treating and preventing pathologies in the preclinical phase and potentially reversing the pathological process, stopping it or preventing comorbidities. Furthermore, treating shared networks instead of individual phenotypic symptoms can reduce drug use, offering a solution to the problem of ineffective drug use.

Introduction

The reductionist linear medicine has undoubtedly contributed to the prolongation of the life expectancy of the western population, but, as far as chronic non-communicable diseases are concerned, it presents some problems that require a paradigm shift in the treatments currently in use.

The progressive ageing of the population and the increase in environmental pollution are conditions capable to profoundly influencing the health status of the population.

The management of non-communicable diseases, the ageing of the population and the progressive environmental pollution, pose new and complex problems, difficult to be solved by the current health organisation, also due to the economic sustainability of the care [1], [2], [3].

The incidence of complex non-communicable diseases, such as type II diabetes, cardiovascular diseases (growing exponentially), atopic dermatitis and cancer, increases with age, but the most worrying fact is that it is also increasing in the pediatric population [4], [5], [6], [7], [8].

Also, regarding transmissible pathologies, there are new challenges related to the increasing resistance of microbes to antibiotics and to the limited number of new drugs being developed [9], [10], [11].

Guidelines-based medical approaches continue to be the rule in clinical practice, although only less than 15% of them are based on high-quality

research. Although this type of (statistical) approach can be profitable in the general population, it becomes unsuccessful when compared to the genetic, epigenetic and environmental characteristics of the individual subject [4]. The result is excessive healthcare spending compared to poor results. The annual cost of ineffective treatments in the US would be $ 350 billion, while the development of new linear drugs costs $ 1 billion for each formulation, with an additional impact on the cost of health care [12].

In research on the 10 best-selling drugs in the USA, it was found that, for each person who benefits from one of these treatments, a number between 4 and 25 has none [13].

Another study showed that the use of prescription drugs has drastically increased among the elderly population during an observation period of 12 years and, in particular, the number of patients taking more than 5 drugs has increased from 12.8% at 39.0% from 1988 to 2010, identifying a population considered particularly fragile [14].

Usually, in chronic conditions, Western Medicine treats the symptomatic manifestations of the disease (e.g. hypertension or hypercholesterolemia) and often can identify patients at risk in advance. However, this method does not offer solutions in the non-manifest preclinical stage of the disease, when it would still be possible to reverse the pathological progression, correcting underlying causes [12], [13], [14], [15].

It, therefore, appears clear that the need for additional tools to address these challenges. For this reason, more and more frequently, System Medicine is proposed as a useful tool [16], [17], [18], [19], in particular in terms of different view and approach to the disease, unfortunately even more in theory than in practice, because the alternatives to the axiom "a drug, a target, a symptom" are still struggling to get ahead.

The Bioregulatory System Medicine (BrSM), the subsequent evolution of Systems Medicine, aims to bridge this gap through the use of low dose medicines with precise, targeted and synergistic bioregulatory capacities. These are medicines composed of different therapeutic nuclei (multi-component) with an effect on as many different targets (multi-target) and a favourable safety profile [20], [82]. Based on a correct evaluation of the patient's clinical history, recognition of its characteristics specific and at the stage of progression of the pathology, the BrSM directs the choices of therapeutic strategy, allowing a more complete and systematic approach to the patient.

Systems Medicine

Biological systems have some aspects in common, including self-organisation, intrinsic stability, robustness and resilience [12], [15], [21].

Self-organisation is one of the fundamental characteristics of Systems Medicine and takes up the so-called autopoiesis of the school of Santiago de Francisco Varela and Humberto Maturana [21], [22].

The complexity of the human body is considered as a set of interconnected networks, composed of genome, molecules, cells, organs, going beyond, up to the environment surrounding the organism and to the networks created by individuals in societies [4], [12].

The disease is considered a dysregulation of the networks, linked to different perturbations or disturbances that act by jeopardising stability and functionality [23], [24], [25].

The networks go through phases of dysregulation long before the recognisable pathology divides, and before any structural symptoms or alterations appear.

Stability is another intrinsic characteristic of complex systems, and in living organisms, it is ensured by self-regulation to maintain homeostasis.

The networks are organised in functional modules to protect the system from global collapse, and robustness (i.e. the ability of systems to resist, without modification, to perturbations) allows the system to defend itself against elements of disturbance and destabilisation [15], [26].

Finally, resilience indicates the ability of the system to withstand disturbances by adapting to it to guarantee the function of the system itself.

These characteristics can be exploited in the clinical approach and the BrSM aims at this goal, placing as the main goal of the therapy the support to the organism self-regulation system to re-establish a normal state of homeostasis or, if this is not possible, a state of optimal compensation, reducing the use of drugs as much as possible [20].

In practice, numerous distinctive aspects differentiate the Systems Medicine from the linear reductionist approach [4], [16], [81].

The use of targeted drug therapies that target only one point of the network, as happens in reductionist medicine, has been questioned. If the interrelations of the target are not taken into account, in fact, one risks unintentionally causing the opposite effect. For example, the use of statins could increase atherosclerosis due to the depletion of coenzyme Q10 and vitamin K2, 25 or the use of non-steroidal anti-inflammatory drugs in acute inflammation has an anti-inflammatory effect, but also tends to block the

production of prostaglandins (PG) E2, necessary for the activation of lipid mediators responsible for resolving inflammation and triggering the repair and restoration processes of tissue physiology [28], [29], [30].

The recognition of the role of the dysregulation of biological networks in the evolution of pathologies not only offers opportunities for their management but also questions the current diagnostic procedure, based on a fixed number of biomarkers that are interpreted only after the onset of clinical symptoms [31], [32]. This different approach to the patient, called Network Medicine, has many advantages [12].

According to this more current reference model, in the diagnosis phase we tend to recognize dynamic patterns in network dysregulations rather than resort to isolated and immutable biomarkers over time and, in particular, in the approach to the progressive evolution of the pathology, such patterns contribute to the definition of an individualized vision for each patient [17], [33], [34].

In 2008 Fuite et al., showed him that, through the analysis of a genomic network in patients with chronic fatigue syndrome, it was possible to identify an alteration in the interrelation of the immune system, adrenocorticotropic hormone, and thyroid [35].

More recently, recognition of specific patterns in patients with systemic sclerosis has allowed physicians to predict prognosis and contributed to the definition of therapy [36].

To examine and visualise these complex networks to define their patterns, the so-called "-*omics*" technologies are used: genomics, epigenomics, proteomics, metabolomics and microbiomics, up to the most recent exposomics [10], [19], [37]. It appears very promising, in this panorama, also the alterations of the parameters of bio-impedance metre that involve the analysis of the systems [38].

The reductionist approach tends largely to ignore environmental influences, but starting from the revolutionary article by Christopher Wild, who introduced the term esposoma in 2005, this concept has taken on a prominent role in the systems approach [10], [39], [40], [41].

The concept of exposome indicates the list of all the chemical substances to which a subject has been and including environmental, food or work-related, endogenous biochemical substances formed by normal metabolic processes, and by inflammation, oxidative stress, lipid peroxidation and infections, as well as other natural metabolic processes, such as alteration of the intestinal microbiome [41]. These exhibits affect all networks and in particular the epigenetic one.

The omics technologies are also ideally useful for investigating the effects of multicomponent / multitarget drugs with bioregulation properties, as they would allow clarifying the effects effects [42] better.

In summary, System Medicine considers the disease as a dysregulation of the biological networks that changes throughout the evolution of the pathological process and with the development of comorbidities. The strength of the networks indicates their ability to withstand dysregulations during the perturbation phases, returning to the state of stability or guaranteeing the best possible stability through compensation mechanisms [5], [24], [43], [44].

The treatment of dysregulated networks before the symptomatological manifestation emerges offers the possibility of treating and preventing pathologies in the preclinical phase and potentially reversing the pathological process, stopping it or preventing comorbidities [15].

Furthermore, treating shared networks instead of individual phenotypic symptoms can reduce drug use, offering a solution to the problem of ineffective drug use [4].

Systems Bioregulation Medicine

The conceptual pillar of BrSM is a therapeutic approach that aims to treat the networks dysregulations of underlying pathology by supporting self-regulation networks, to promote the restoration of physiological homeostatic conditions of networks or the achievement of a state of equilibrium [20].

The dysregulation of the networks is the initial phase of the pathological evolution, preceding the symptomatological manifestation; it follows an advantageous overall therapeutic intervention and directed to the dysregulation as a whole, instead of on the single symptomatological manifestations of each disease.

Complex non-communicable diseases often share dysregulations of the inflammatory and metabolic networks. During evolution, these same networks have evolved to address a wide variety of circumstances. At the same time, however, it must be considered that this characteristic of flexibility also makes them more vulnerable to dysregulation. The regulation of these networks is based on relatively primitive self-regulation processes and is often overwhelmed by incongruous lifestyles and by increasingly unfavourable conditions of environmental pollution to which modern man is exposed [45], [46].

The Nervous and Endocrine Systems maintain a systemic homeostatic state, while the local homeostatic circuits regulate the state and integrity of cell and tissue networks. However, when homeostatic mechanisms are not sufficient, the inflammatory

process is triggered in order to maintain or restore balance. Several authors define this process as homeostatic inflammation (or physiological inflammation [47], [48].

The inflammatory response of the organism and its effects on it in the acute phase play a fundamental role in the model of BrSM. The inflammations that persist can potentially cause alterations of the cellular microenvironment and progressively lead to structural tissue damage, up to their degeneration [45], [49]. In BrSM the inflammatory response is used as a substitute in clinical decision making.

The vision of inflammation as a static process that ends with the elimination of its mediators has changed a lot in recent years. Today inflammation is considered an active process. As is often observed in homeostatic mechanisms, it is the initial mechanism itself that also determines its end. Among the main protagonists is PGE2, which is not only responsible for most of the symptoms associated with acute inflammation, but also plays a fundamental role in the activation of the so-called mediators favouring the resolution of the inflammatory process [26], [27].

Drugs developed linearly, such as non-steroidal anti-inflammatory drugs, whose main target is cyclo-oxygenase 2, have an anti-inflammatory action, but can at the same time prevent the resolution of the problem by forcibly suppressing PGE2 [28].

It has recently been shown that the multi-component drug *Traumeel* has a different mechanism of action in the context of the inflamed tissue and a modulation effect on PGE2 and on specialised prorisolutive mediators that can favour a more physiological resolution of the process [50], [51].

Individualised treatments

In their pioneering article, Ahn et al., they also outlined the future of System Medicine in clinical practice [52].

The applications-*omics* bode well for a revolution in the approach to the diagnosis and individualisation of patients based on risk, stage of the disease and possible response to treatment. However, the costs and degree of innovation currently prevent the use of these tools as a routine medical practice. This means that doctors must continue to rely on classical methods to selectively choose the therapy of their patients.

The path starts from the collection of the anamnesis, in which the aspects related to genetics and exposome deserve special attention. The patient's prenatal history has the same importance as post-birth events, as many stress factors, such as maternal psychological stress and exposure to environmental xenobiotics, have a fundamental impact on the patient's responses in the later stages of life. This is often mediated by epigenetic alterations [53], [54], [55].

Work and leisure activities can be indicative of possible exposures and stress factors.

Genetic and genomic markers are often suggestive of possible risks; by way of example, single nucleotide polymorphisms may represent a risk factor, for example in the known association between homocysteine metabolism disorders and cardiovascular diseases [56]; another example is the risk assessment tests for breast cancer [57]. Genomics and metabolomics are also used in clinical practice to predict treatment responses [58].

This is also useful for the probabilistic forecasts cited by Ahn.

The biomarkers and algorithms currently used to diagnose pathologies in terms of phenotypic results (e.g. erythrocyte sedimentation rate, high-sensitivity C-reactive protein and complete blood count) should be used appropriately for clinical decisions.

The treatment based on the progression of the disease and in particular on the recognition of preclinical stages will remain difficult to apply until the sciences-omics and Networks Medicine become part of the common practice.

In BrSM, the effect of the inflammatory response on the microenvironment is used as a substitute / in addition to the sciences-*omics* available for the interpretation of clinical decisions. Unlike what was thought in the past, the microenvironment has the possibility to reverse the structural alterations, provided that the cell membrane has not been damaged.

In the BrSM there is, therefore, a dynamic attitude in the prescription, which will be based on the degree of progression of the patient's pathology.

To further individualize the treatment, the patient's exposure and microbiome are considered and, consequently, the use of appropriate draining and detoxifying medicines and the insertion of certain probiotic strains, often specific for each pathological process (eg Bifidobacterium PBL1 in the metabolic syndrome or Bifidobacterium lactis CECT 8145, Bifidobacterium longum CECT 7347, and Lactobacillus casei CECT 9104 in atopic dermatitis) [59], [80].

Change in therapy paradigm

In the "one drug, one target, one symptom" approach, pharmacological treatment is often symptomatic or aimed at treating phenotypic results secondary to dysregulation. These are static treatments, and patients often take the same therapies for long periods.

Supporting the self-regulation system, the BrSM aims to re-establish a state of health or compensation, and this means that often, once this result is achieved, the patient no longer needs drugs or needs only in limited quantities. This requires careful assessments of disease progression and good monitoring. In the case of advanced phenotypic alterations, drug treatment is frequently the only option available. Obviously, this also applies to diseases in which there is no possibility of regulation, for example in the case of ablation of an organ, and, in these cases, replacement therapy must be taken for life.

Low dose drugs effects

This characteristic does not exclusively refer to the attempt to reduce the use of drugs to the minimum necessary, which can be the result of better individualisation of the patient or improvement of the state of health through the achievement of optimal self-regulation.

The hormetic effects of the substances are the subject of constant research [60]. The hormesis seems to have positive consequences on the resilience of the organism, in particular through the so-called mitormesis [slight mitochondrial damage can induce a hormetic response (mitormesis) that promotes compensatory adaptive processes] [61], [62], [63].

Some authors have specifically cited the hormetic effects that increase adaptive responses through the exposure of natural phytotherapeutic substances (xenormes) [64].

This is a concept that requires further research but could be a plausible hypothesis to explain how some substances in reduced concentrations exert bioregulation effects.

The low naltrexone dose, which has been discussed earlier, is a good example of how a drug to conventional doses, developed with a specific purpose, can also be used for other purposes. It is able, at this lower dosage, to generate bioregulatory effects. This also happens for other preparations with bioregulation properties: for example, the medicinal product *Lymphomyosot*, originally developed for lymphatic pathology, has subsequently shown that it can also be usefully used for wound healing [65].

Since-*omic* technologies allow the analysis of large groups of data on multitarget actions; the identification of alternative applications of drugs is destined to grow over time.

Synergistic treatments

To achieve bioregulation in dysregulations involving more than one network or different functional modules of a network, it may be necessary to resort to a combination of several drugs (treatments).

This is a common approach in the BrSM, in particular for chronic diseases, in which with the development of comorbidities we are witnessing the subsequent dysregulation of further networks.

Chronic diseases seem to have in common the main dysregulation of certain networks [66], [67], [83]. These include the network inflammatory, the network metabolic, the network energy-mobile, and network neuroendocrine.

The chronic dysregulation of the networks also puts a strain on the processes of self-regulation. It is, therefore, necessary to add cofactors to optimise the efficient operation of enzymes, for example, since they can run out if they are not reintegrated over time. The patient's nutritional status must be carefully considered and, about it, deficient cofactors will be established according to specific needs.

As mentioned above, some pharmacological therapies also lead to the depletion of cofactors that are fundamental for self-regulation (e.g. coenzyme Q 10 and vitamin K2 in statin-based therapies) [25]. Missing cofactors must be adequately replenished and, if bioregulation allows it, the patient must gradually reduce and then stop therapy.

Recently the efficacy of a combination of two drugs with bioregulatory properties and their synergistic effects in the treatment of knee osteoarthritis (Arnica comp. + Zeel T) has been demonstrated [68], [69], [70].

"Space - sensitive" treatments: administration of drugs in specific locations

As can be seen from the bioregulation model, the microenvironment plays a fundamental role in the therapeutic approach of the BrSM. In numerous

publications, it is argued that connective tissue is an organ with interconnecting properties [71], [72]. A recent publication in *Nature* even speaks of interstitial spaces containing fluidly plastic structures previously not characterised, emphasising the fundamental function of this important tissue and introducing for it the most correct classification of the organ [73].

Drugs can be administered directly in this organ through infiltration techniques at specific points. In fact, injection into the acupuncture points is frequent in the BrSM approach [74], [75], [76], [77]. Intradermal injections are also used in Aesthetic Medicine, similarly to infiltration in the corresponding dermatomes to act on the internal organs [78], [79].

Conclusions

In the current context, medical personnel are exposed to numerous challenges, which require new tools to respond to patients' needs.

The Systems Medicine approach is making headway in clinical practice as a solution for improving patient management; however, the reference paradigm of conventional therapies "a target, a drug" is proving not entirely suitable.

System Medicine applications, such as BrSM, aim to remedy the shortcomings of the conventional approach, using complex multicomponent drugs, to obtain regulatory effects on multiple targets.

The BrSM complies with the fundamental criteria that distinguish the Systems Medicine approach, but the clear therapeutic objective is the support of patient self-regulation networks. This approach can be associated with "linear drugs" based on the specific needs of patients. Applying these different approaches at the same time, we will witness the birth of a single Medicine: the one that responds to the specific patient's needs at a specific time.

References

1. Cesario A, Cazzola M, Lauro D, Frustaci A, Neri M. A systems medicine clinical platform for understanding and managing non-communicable diseases. Curr Pharm Des. 2014; 20(38):5945-5956. https://doi.org/10.2174/1381612820666140314130449 PMid:24641232

2. Bland JS, Minich DM, Eck BM. A Systems Medicine approach: translating emerging science into individualized wellness. Adv Med. 2017; 2017:1718957. https://doi.org/10.1155/2017/1718957 PMid:29164177 PMCid:PMC5661085

3. Kramer F, Just S, Zeller T. New perspectives: Systems Medicine in cardiovascular disease. BMC Syst Biol. 2018; 12(1):1-13. https://doi.org/10.1186/s12918-018-0579-5 PMid:29699591 PMCid:PMC5921396

4. Trachana K, Bargaje R, Glusman G, Price ND, Huang S, Hood LE. Taking Systems Medicine to heart. Circ Res. 2018; 122(9):1276-1289. https://doi.org/10.1161/CIRCRESAHA.117.310999 PMid:29700072 PMCid:PMC5926821

5. Peters U, Dixon AE, Forno E. Obesity and asthma. J Allergy Clin Immunol. 2018; 141(4):1169-1179. https://doi.org/10.1016/j.jaci.2018.02.004 PMid:29627041 PMCid:PMC5973542

6. Faienza MF, Wang DQH, Fruhbeck G, Garruti G, Portincasa P. The dangerous link between childhood and adulthood predictors of obesity and metabolic syndrome. Intern Emerg Med. 2016; 11(2):175-182. https://doi.org/10.1007/s11739-015-1382-6 PMid:26758061

7. Nutten S. Atopic dermatitis: global epidemiology and risk factors. Ann Nutr Metab. 2015; 66(1):8-16. https://doi.org/10.1159/000370220 PMid:25925336

8. Isaevska E, Manasievska M, Alessi D, et al. Cancer incidence rates and trends among children and adolescents in Piedmont, 1967-2011. PLoS One. 2017; 12(7):e0181805. https://doi.org/10.1371/journal.pone.0181805 PMid:28742150 PMCid:PMC5524393

9. Courvalin P. Why is antibiotic resistance a deadly emerging disease? Clin Microbiol Infect. 2016; 22(5):405-407. https://doi.org/10.1016/j.cmi.2016.01.012 PMid:26806259

10. Turner MC, Vineis P, Seleiro E, et al. EXPOsOMICS: final policy workshop and stakeholder consultation. BMC Public Health. 2018; 18(1):260. https://doi.org/10.1186/s12889-018-5160-z PMid:29448939 PMCid:PMC5815236

11. Frieri M, Kumar K, Boutin A. Antibiotic resistance. J Infect Public Health. 2017; 10(4):369-378. https://doi.org/10.1016/j.jiph.2016.08.007 PMid:27616769

12. Gustafsson M, Nestor CE, Zhang H, et al. Modules, networks and systems medicine for understanding disease and aiding diagnosis. Genome Med. 2014; 6(10):82. https://doi.org/10.1186/s13073-014-0082-6 PMid:25473422 PMCid:PMC4254417

13. Schork NJ. Time for one-person trials. Nature. 2015; 520:609-610. https://doi.org/10.1038/520609a PMid:25925459

14. Charlesworth CJ, Smit E, Lee DSH, Alramadhan F, Odden MC. Polypharmacy among adults aged 65 years and older in the United States: 1988-2010. J Gerontol A Biol Sci Med Sci. 2015; 70(8):989-995. https://doi.org/10.1093/gerona/glv013 PMid:25733718 PMCid:PMC4573668

15. Hu JX, Thomas CE, Brunak S. Network biology concepts in complex disease comorbidities. Nat Rev Genet. 2016; 17(10):615-629. https://doi.org/10.1038/nrg.2016.87 PMid:27498692

16. Ahn AC, Tewari M, Poon C-S, Phillips RS. The limits of reductionism in medicine: could systems biology offer an alternative? PLoS Med. 2006; 3(6):e208. https://doi.org/10.1371/journal.pmed.0030208 PMid:16681415 PMCid:PMC1459480

17. Cardinal-Fernàndez P, Nin N, Ruiz-Cabello J, Lorente JA. Systems Medicine: a new approach to clinical practice. Arch Bronconeumol (English Ed). 2014; 50(10):444-451. https://doi.org/10.1016/j.arbr.2014.09.001

18. Apweiler R, Beissbarth T, Berthold MR, et al. Whither Systems Medicine? Exp Mol Med. 2018; 50(3):e453. https://doi.org/10.1038/emm.2017.290 PMid:29497170 PMCid:PMC5898894

19. Fiandaca MS, Mapstone M, Connors E, et al. Systems healthcare: a holistic paradigm for tomorrow. BMC Syst Biol. 2017; 11(1):1-17. https://doi.org/10.1186/s12918-017-0521-2 PMid:29258513 PMCid:PMC5738174

20. Goldman AW, Burmeister Y, Cesnulevicius K, et al. Bioregulatory Systems Medicine: an innovative approach to integrating the science of molecular networks, inflammation, and

systems biology with the patient's autoregulatory capacity? Front Physiol. 2015; 6:225. https://doi.org/10.3389/fphys.2015.00225 PMid:26347656 PMCid:PMC4541032

21 Varela FJ, Maturana HR, Uribe RB. Autopoiesis: the organization of living systems, characterization and a model. Biosystems. 1974; 5:187-196. https://doi.org/10.1016/0303-2647(74)90031-8

22 Varela FJ, Shear J. First-person methodologies: what, why, how? Journal of Consciousness Studies. 1999; 6(2-3):1-14.

23. Barabàsi A. Emergence of scaling in random networks. Science. 1999; 286(5439):509- 512. https://doi.org/10.1126/science.286.5439.509 PMid:10521342

24. Barabàsi A-L, Gulbahce N, Loscalzo J. Network medicine: a network-based approach to human disease. Nat Rev Genet. 2011; 12(1):56-68. https://doi.org/10.1038/nrg2918 PMid:21164525 PMCid:PMC3140052

25. Uriarte SM, Rane MJ, Luerman GC, et al. Granule exocytosis contributes to priming and activation of the human neutrophil respiratory burst. J Immunol. 2011; 187(1):391-400. https://doi.org/10.4049/jimmunol.1003112 PMid:21642540 PMCid:PMC3582343

26. Whitacre JM. Biological robustness: paradigms, mechanisms, and systems principles. Front Genet. 2012; 3:67. https://doi.org/10.3389/fgene.2012.00067 PMid:22593762 PMCid:PMC3350086

27. Okuyama H, Langsjoen PH, Hamazaki T, et al. Statins stimulate atherosclerosis and heart failure: pharmacological mechanisms. Expert Rev Clin Pharmacol. 2015; 8(2):189-199. https://doi.org/10.1586/17512433.2015.1011125 PMid:25655639

28. Serhan CN, Levy BD. Resolvins in inflammation: emergence of the pro-resolving superfamily of mediators. J Clin Invest. May 2018. https://doi.org/10.1172/JCI97943 PMid:29757195 PMCid:PMC6025982

29. Ricciotti E, FitzGerald GA. Prostaglandins and inflammation. Arterioscler Thromb Vase Biol. 2011; 31 (5):986-1000. https://doi.org/10.1161/ATVBAHA.110.207449 PMid:21508345 PMCid:PMC3081099

30. Dakin SG, Dudhia J, Smith RKW. Resolving an inflammatory concept: the importance of inflammation and resolution in tendinopathy. Vet Immunol Immunopathol. 2014; 158(3-4):121-127. https://doi.org/10.1016/j.vetimm.2014.01.007 PMid:24556326 PMCid:PMC3991845

31. Cesario A, Auffray C, Russo P, Hood L. P4 medicine needs P4 education. Curr Pharm Des. 2014; 20(38):6071-6072. https://doi.org/10.2174/1381612820666140314145445 PMid:24641231

32. van Bon L, Affandi AJ, Broen J, et al. Proteome-wide analysis and CXCL4 as a biomarker in systemic sclerosis. N Engl J Med. 2014; 370(5):433-443. https://doi.org/10.1056/NEJMoa1114576 PMid:24350901 PMCid:PMC4040466

33. Buchman TG. The community of the self. Nature. 2002; 420(6912):246-251. https://doi.org/10.1038/nature01260 PMid:12432410

34. Buchman TG. Cardiovascular variability as a measure of inflammation. Crit Care Med. 2014; 42(8):1964. https://doi.org/10.1097/CCM.0000000000000460 PMid:25029145

35. Fuite J, Vernon SD, Broderick G. Neuroendocrine and immune network re-modeling in chronic fatigue syndrome: an exploratory analysis. Genomics. 2008; 92(6):393-399. https://doi.org/10.1016/j.ygeno.2008.08.008 PMid:18775774

36. Dobrota R, Mihai C, Distler O. Personalized medicine in systemic sclerosis: facts and promises. Curr Rheumatol Rep. 2014; 16(6):425. https://doi.org/10.1007/s11926-014-0425-8 PMid:24752884

37. Barko PC, McMichael MA, Swanson KS, Williams DA. The gastrointestinal microbiome: a review. J Vet Intern Med. 2018; 32(1):9-25. https://doi.org/10.1111/jvim.14875 PMid:29171095 PMCid:PMC5787212

38. Chrousos GP. Stress and disorders of the stress system. Nature reviews endocrinology. 2009; 5(7):374-381. https://doi.org/10.1038/nrendo.2009.106 PMid:19488073

39. Escher Bl, Hackermuller J, Polte T, et al. From the exposome to mechanistic understanding of chemical-induced adverse effects. Environ Int. 2017; 99:97-106. https://doi.org/10.1016/j.envint.2016.11.029 PMid:27939949 PMCid:PMC6116522

40. Miller GW, Jones DP. The nature of nurture: refining the definition of the exposome. Toxicol Sci. 2014; 137(1):1-2. https://doi.org/10.1093/toxsci/kft251 PMid:24213143 PMCid:PMC3871934

41. Nakamura J, Mutlu E, Sharma V, et al. The endogenous exposome. DNA Repair (Amst). 2014; 19:3-13. https://doi.org/10.1016/j.dnarep.2014.03.031 PMid:24767943 PMCid:PMC4097170

42. St Laurent G, Seilheimer B, Tackett M, et al. Deep sequencing transcriptome analysis of murine wound healing: effects of a multicomponent, multitarget natural product therapy-Tr14. Front Mol Biosci. 2017; 4(August):1-12. https://doi.org/10.3389/fmolb.2017.00057 PMid:28879183 PMCid:PMC5572416

43. Kitano H. Violations of robustness trade-offs. Mol Syst Biol. 2010; 6:384. https://doi.org/10.1038/msb.2010.40 PMid:20571533 PMCid:PMC2913402

44. Kitano H. Biological robustness in complex host-pathogen systems. Prog Drug Res. 2007; 64(239):239-263. https://doi.org/10.1007/978-3-7643-7567-6_10 PMid:17195478

45. Kotas ME, Medzhitov R. Homeostasis, inflammation and disease susceptibility. Cell. 2015; 160(5):816-827. https://doi.org/10.1016/j.cell.2015.02.010 PMid:25723161 PMCid:PMC4369762

46. Stearns SC, Medzhitov R. Evolutionary Medicine. Oxford, UK: Oxford University Press; 2016.

47. Cheng LE, Locksley RM. Allergic inflammation: innately homeostatic. Cold Spring Harb Perspect Biol. 2014; 7(3):a016352. https://doi.org/10.1101/cshperspect.a016352 PMid:25414367 PMCid:PMC4355269

48. Miyake K, Kaisho T. Homeostatic inflammation in innate immunity. Curr Opin Immunol. 2014; 30(10):85-90. https://doi.org/10.1016/j.coi.2014.08.003 PMid:25190609

49. Chovatiya R, Medzhitov R. Stress, inflammation, and defense of homeostasis. Mol Cell. 2014; 54(2):281-288. https://doi.org/10.1016/j.molcel.2014.03.030 PMid:24766892 PMCid:PMC4048989

50. St Laurent G, Toma I, Seilheimer B, et al. Differential effects of Tr14 versus diclofenac on COX/LOX pathways revealed by RNASeq. Ann Rheum Dis. 2018; 77(2):238-239. https://doi.org/10.1136/annrheumdis-2018-eular.3779

51. St Laurent G, Toma I, Tackett M, et al. Differential effects of Tr14 versus diclofenac on pro-resolving lipid mediators revealed by RNASeq. Ann Rheum Dis. 2018; 77(2):1237-1238. https://doi.org/10.1136/annrheumdis-2018-eular.3789

52. Ahn AC, Tewari M, Poon C-S, Phillips RS. The clinical applications of a systems approach. PLoS Med. 2006; 3(7):e209. https://doi.org/10.1371/journal.pmed.0030209 PMid:16683861 PMCid:PMC1459481

53. Marciniak A, Patro-Matysza J, Kimber-Trojnar Z, Marciniak B, Oleszczuk J, Leszczyhska-Gorzelak B. Fetal programming of the metabolic syndrome. Taiwan J Obstet Gynecol. 2017; 56(2): 133-138. https://doi.org/10.1016/j.tjog.2017.01.001 PMid:28420495

54. Perera F, Herbstman J. Prenatal environmental exposures, epigenetics, and disease. Reprod Toxicol. 2011; 31(3):363-373. https://doi.org/10.1016/j.reprotox.2010.12.055 PMid:21256208 PMCid:PMC3171169

55. Jiménez-Chillarón JC, Nijland MJ, Ascensào AA, et al. Back to the future: transgenerational transmission of xenobiotic-induced epigenetic remodeling. Epigenetics. 2015; 10(4):259-273. https://doi.org/10.1080/15592294.2015.1020267 PMid:25774863

PMCid:PMC4622959

56. Sun K, Song J, Liu K, et al. Associations between homocysteine metabolism related SNPs and carotid intima-media thickness: a Chinese sib pair study. J Thromb Thrombolysis. 2017; 43(3):401-410. https://doi.org/10.1007/s11239-016-1449-x PMid:27822905 PMCid:PMC5337241

57. Thompson ER, Rowley SM, Li N, et al. Panel testing for familial breast cancer: calibrating the tension between research and clinical care. J Clin Oncol. 2016; 34(13):1455-1459. https://doi.org/10.1200/JCO.2015.63.7454 PMid:26786923

58. Monte AA, Brocker C, Nebert DW, Gonzalez FJ, Thompson DC, Vasiliou V. Improved drug therapy: triangulating phenomics with genomics and metabolomics. Hum Genomics. 2014; 8(1):1-9. https://doi.org/10.1186/s40246-014-0016-9 PMid:25181945 PMCid:PMC4445687

59. Navarro-López V, Ramirez-Boscà A, Ramón-Vidal D, et al. Effect of oral administration of a mixture of probiotic strains on SCORAD Index and use of topical steroids in young patients with moderate atopic dermatitis: a randomized clinical trial. JAMA Dermatol. 2018; 154(1):37-43. https://doi.org/10.1001/jamadermatol.2017.3647 PMid:29117309 PMCid:PMC5833582

60. Calabrese EJ. Hormesis: from mainstream to therapy. J Cell Commun Signal. 2014; 8(4):289-291. https://doi.org/10.1007/s12079-014-0255-5 PMid:25366126 PMCid:PMC4390802

61. Yun J, Finkel T. Mitohormesis. Cell Metab. 2014; 19(5):757-766. https://doi.org/10.1016/j.cmet.2014.01.011 PMid:24561260 PMCid:PMC4016106

62. Srivastava S. The mitochondrial basis of aging and age-related disorders. Genes (Basel). 2017; 8(12). https://doi.org/10.3390/genes8120398 PMid:29257072 PMCid:PMC5748716

63. Barbour JA, Turner N. Mitochondrial stress signaling promotes cellular adaptations. Int J Cell Biol. 2014; 2014. https://doi.org/10.1155/2014/156020 PMid:24587804 PMCid:PMC3920668

64. Kim S-A, Lee Y-M, Choi J-Y, Jacobs DR, Lee D-H. Evolutionarily adapted hormesisinducing stressors can be a practical solution to mitigate harmful effects of chronic exposure to low dose chemical mixtures. Environ Pollut. 2018; 233:725-734. https://doi.org/10.1016/j.envpol.2017.10.124 PMid:29126094

65. Keim AP, Slis JR, Mendez U, et al. The multicomponent medication Lymphomyosot improves the outcome of experimental lymphedema. Lymphat Res Biol. 2013; 11(2):81-92. https://doi.org/10.1089/lrb.2012.0024 PMid:23725444 PMCid:PMC3696932

66. van Ommen B, Wopereis S, van Empelen P, et al. From diabetes care to diabetes cure: the integration of systems biology, eHealth, and behavioral change. Front Endocrinol (Lausanne). 2018; 8:381. https://doi.org/10.3389/fendo.2017.00381 PMid:29403436 PMCid:PMC5786854

67. Stroeve JHM, van Wietmarschen H, Kremer BHA, van Ommen B, Wopereis S. Phenotypic flexibility as a measure of health: the optimal nutritional stress response test. Genes Nutr. 2015; 10(3):459. https://doi.org/10.1007/s12263-015-0459-1 PMid:25896408 PMCid:PMC4404421

68. Lozada C, del Rio E, Reitberg D, Smith R, Kahn C, Moskowitz RW. A multi-center double-blind, randomized, controlled trial (db-RCT) to evaluate the effectiveness and safety of co-administered Traumeel® (Tr14) and Zeel® (Ze14) intra-articular (IA) injections versus IA placebo in patients with moderate-to-severe pain ass. Arthritis Rheum. 2014; 66(Suppl):S1266. https://doi.org/10.1136/annrheumdis-2015-eular.4268

69. Lozada C, del Rio E, Reitberg DP, Smith R, Moskowitz RW. Risk-benefit of coadministered Traumeel® (Tr14) and Zeel® (Ze14) intra-articular (IA) injections in patients with moderate-to-severe pain associated with OA of the knee (OAK) (THU0441). Ann Rheum Dis. 2015; 74(2):4268. https://doi.org/10.1136/annrheumdis-2015-eular.4268

70. Lozada CJ, del Rio E, Reitberg DP, Smith RA, Kahn CB, Moskowitz RW. A doubleblind, randomized, saline-controlled study of the efficacy and safety of co-administered intra-articular injections of Tr14 and Ze14 for treatment of painful osteoarthritis of the knee: the MOZArT trial. Eur J Integr Med. 2017; 13:54-63. https://doi.org/10.1016/j.eujim.2017.07.005

doi: 10.101 6/j.eujim.201 7.07.005.

71. Langevin HM. Connective tissue: a body-wide signaling network? Med Hypotheses. 2006; 66(6):1074-1077. https://doi.org/10.1016/j.mehy.2005.12.032 PMid:16483726

72. Oschman JL. Charge transfer in the living matrix. J Bodyw Mov Ther. 2009; 13(3):215-228. https://doi.org/10.1016/j.jbmt.2008.06.005 PMid:19524846

73. Benias PC, Wells RG, Sackey-Aboagye B, et al. Structure and distribution of an unrecognized interstitium in human tissues. Sci Rep. 2018; 8(1):1-8. https://doi.org/10.1038/s41598-018-23062-6 PMid:29588511 PMCid:PMC5869738

74. Langevin HM, Yandow J a. Relationship of acupuncture points and meridians to connective tissue planes. Anat Rec. 2002; 269(6):257-265. https://doi.org/10.1002/ar.10185 PMid:12467083

75. Kersschot J. Biopuncture: The Management of Common Orthopedic and Sports Disorders. Thieme; 2014 May 14.

76. Frase W, Bauer G. Moderne Homöosiniatrie. Baden-Baden, Germany: Aurelia, 2002.

77. Ben-Yakir S. Primary evaluation of homeopathic remedies injected via acupuncture points to reduce chronic high somatic cell counts in modern dairy farms. J Biomed Ther. 2004; (Fall):13-15.

78. Bossy J. Morphological data concerning the acupuncture points and channel network. Acupuncture & electro-therapeutics research. 1984; 9(2):79-106. https://doi.org/10.3727/036012984816714758 PMid:6148847

79. Bredikhin A V, Bredikhin KA, Chekha OA. New organ representation areas localized between front & back of the human neck and body their potential application to metameric acupuncture. Acupunct Electrother Res. 2016; 41(3-4):199-205. https://doi.org/10.3727/036012917X14831065080050

80. Roccia MG, Fioranelli M, Lotti T. Dermatol Ther. Obesity, psoriasis, and microbiota: an unexplored dangerous connection? J Biol Regul Homeost Agents. 2015. https://doi.org/10.1111/dth.12218 PMid:25731602

81. França K, Castillo DE, Roccia MG, Lotti T, Wollina U, Fioranelli M. Psychoneurocutaneous medicine: past, present and future. Wien Med Wochenschr. 2017. https://doi.org/10.1007/s10354-017-0573-3 PMid:28616665

82. Fioranelli M, Del Prete M, Aracena JC, Roccia MG, Dal Lin C, Tomella C. Integrative Cardiology. Editor: Massimo Fioranelli. Low-Dose Therapy for the Treatment of Low-Grade Chronic Inflammation. Springer International Switzerland, 2017. https://doi.org/10.1007/978-3-319-40010-5_3 PMid:28801812

83. Fioranelli M, Roccia MG, Lotti T. Coronary blood flow and psoriasis. Dermatol Ther. 2017. https://doi.org/10.1111/dth.12471 PMid:28211598