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Commentary

Normalization of Vital Functions of Pathological Cells and Tissues By Key Mechanisms of Cell Adaptation and Reprogramming

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Many decades have passed since the discovery of stem cells in 1908 by the Russian histologist Alexander Maximov [1] and the beginning of serious study of stem cells in 1961 by Canadian scientists James Till and Ernest McCulloch [2]. Unfortunately, there has been little success in developing therapeutic applications for stem cells.

Fully pluripotent potent human stem cells hold the sophisticated genetic guidelines for producing over 200 different cell types. A particular therapeutic application requires directing stem cells towards a single plan of construction of one type of tissue specific progenitor cells which may satisfy a patient's needs, for example, hepatocytes for a patient who has a hepatic impairment. This approach necessitates successfully mimicking all of the complicated biochemical, biophysical, and other mechanisms that normally occur during differentiation of cells during the ultra-rapid processes of embryonic and fetal development. Attempts to stimulate these processes in the research and clinical settings may be significantly hampered by the fantastic speeds at which the majority of biochemical processes work and by the extremely complex pattern of events underlying activity in cellular matrixes.

For example, during the ninth month of human pregnancy, the average fetal cell division rate may reach 20,000 cells per second. Replication of DNA over that time period requires an assembly rate exceeding 208,000 nucleotides per second. Amazingly, that DNA replication is accomplished with an average of only 1 error per billion nucleotides [3]. The control of physiologically appropriate cell division, differentiation, and tissue and organ formation is highly orchestrated, involving a complicated hierarchy of vital processes about which we know very little. We suggest that artificial stimulators designed to control developmental strategies of stem cells will never replace the natural biochemical machinery responsible for complex and precise construction of multichannel routes of embryogenesis. We suggest that a mechanism of reversion was evolutionally developed in multi-celled organisms for regenerative response to external irritation. It is clear, that irritated cells can not rush "headlong" at the enemy factor. Instead, they have to take time to estimate the dangerous condition and reply correctly to the damaging factor. We believe that the regeneration process starts from a flash-like scanning of past experience and then retrieval of the right information necessary for a protective response. Cell and tissue defense mechanisms have been thoroughly developed over a long-term period of evolution of particular species, therefore amazingly fast reversion to the past must be a very important part of adaptation and regeneration. The phenomenon of rapid reading of reprogramming information is precious not only for defensive adaptation but also for long-term processes such as aging and pathological diseases.

As an alternative to introducing artificially induced stem cells as a means of therapy for a specific disease state, we propose using a native signaling system, which allows reversing the terminally differentiated pathological or aging cells towards a younger and healthier state.

The existence of the reprogramming signaling system in amphibian oocytes of the African frog *Xenopus laevis* was demonstrated for the first time in the work of Professor John Gurdon (UK) in 1968 using co-culture of frog oocyte extracts with adult human cells [4]. Dr. Gurdon demonstrated that an extremely small proportion (0.01%) were reprogrammed into cells resembling human embryonic stem cells. Since the efficiency of regression of human cells using *Xenopus* oocyte extracts was so low, this first discovery of native reprogramming machinery made by Dr. Gurdon did not get it's due continuation. However, the existence of this natural reprogramming potential, although very feasible, was still there: the human cells were reprogrammed into progenitor state and this phenomenon was initiated and directed by an evolutionarily older species such as frogs, known to exist hundreds of millions of years before humans.

The basis of our therapeutic concept lies in the possibility of reverting somatic cells affected by aging and pathology into

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younger and normally functioning states. Cell regression is attained using patented technology that stimulates key mechanisms of reprogramming and adaptation used by species of amphibians and other lower organisms, which after amputation are able to regenerate the missing parts of the body in perfect structure and function.

During the development of our proposed therapy, we considered why the reprogramming observed by Professor Gurdon is not observed in the case when the whole frog oocytes (rather than frog oocyte extracts) are placed in one testing tube with human cells. The reprogramming potential releases only when oocytes are destroyed during the preparation of the extract. Obviously, a simple answer suggests itself – the mechanisms and tools of cell reprogramming, are contained within the *Xenopus* oocyte, inside a tough and selective cell membrane.

We also thought about why the efficiency of reprogramming previously observed with the frog oocyte extracts was so low. We believe that this is a result of separation of protoplasm of a frog oocyte (ooplasm) from its nuclear component, which in the process destroys genetically predetermined and sophisticated biochemical machinery responsible for processes of normal regeneration and adaptation.

We sought a method which, in our opinion, could facilitate the release of the reprogramming potential in a pure, unaffected way, i.e., without violation of oocyte integrity. We anticipated the existence of some natural trigger, which have to be parental or adequate stimuli for activation of *Xenopus* eggs. This trigger should not be reckoned today among the simple bioactive preparations and artificial conditions created in the experiments by scientists, but, should lay somewhere in the antiquity and hidden behind million of years of evolution among the mechanisms of archebiosis, and, more specifically, among parameters of the primitive atmosphere present on our planet during its early stages of biological exuberance.

As a result of intensive research studies carried out at Bio quark Inc. within the recent four years, we identified the some of the main parameters of this trigger. We patented its composition and applied successfully the new activators for stimulation of *Xenopus* oocytes. During special incubation process, post-activated frog oocytes release a very powerful reprogramming potential in the form of emission of semio-chemical signaling into the environment.

This concept offered by Bio quark Inc. is supported by experiments, both in-vitro and in-vivo animal models, and also in preliminary studies on human subjects. We discovered that co-electroporating different types of human cells (both pathological and healthy) with *Xenopus laevis* oocytes, may reprogram them to induced multipotent stem cells (iPSC), including the following differentiated cells: BJ (Normal Foreskin Fibroblasts); HPA (human pre-adipocytes – precursors of fat cells); Human Lymphocytes; MCB-cells (human Mononuclear cord blood cells); Human Buccal Mucosa cells (oral epithelium); and human bone marrow stromal cells (BMSC) [5].

Co-electroporation also normalized two types of human cancer cells: HeLa (cervical carcinoma) and MCF-7 (breast adenocarcinoma). In a week of exposure of cultured medium containing cancer cells with Bioquantine™ ooplasm extract, the uncontrolled growth of cancer cells was completely stopped.[5]

We collected a liquid mixture of intra- and extra-oocyte phases of the process in the form of a combinatorial extract (Bioquantine™) which we suggest may contain reprogramming components from both phases of oocyte semio-chemical emission.

The consistency with which the co-electroporation process reprograms different human somatic cell lines can highlight the complicated relict and unique composition of the semio-chemical signal emitted by *Xenopus* and utilized by experimental human cells inside an electroporation chamber.

This interpretation lead to our decision to test Bio quantine™ on animal models followed by first-in-human studies on volunteer patients. Both types of studies focused on known types of pathologies. Bioquantine™ extract showed potential in animal models as a treatment for a wide range of conditions including melanoma, traumatic brain injury, and skin wrinkling [6]. The recent exploratory human studies observed beneficial changes with Bioquantine™ therapy in a small group of patients with a variety of disorders [7]. A patient with CKD due to polycystic kidney disease showed volumetric improvement along with reduction in the number of renal cysts and decreases in plasma creatinine. A patient with CKD related to hypertension and type 2 diabetes also demonstrated decreases in plasma creatinine. This patient, who had been dependent on dialysis at study entry, was able to go for longer periods between dialysis to the point where he did not require dialysis. A patient with type 2 diabetes and inadequate glycemic control on standard oral therapy showed normalization of fasting blood glucose. A patient with hypothyroidism achieved normalization of thyroid function. A patient with pydoderma gangrenosum demonstrated considerable reduction in number of sites affected by cutaneous ulcerations with mucopurulent or hemorrhagic exudates and reduction in recurrences. Three patients with spinal cord injuries had regeneration and reconstruction of spinal cord along all entire length of lesion as visualized using magnetic resonance imaging along with considerable improvement in sensation and walking ability and coordination of movement. A patient with metastatic breast cancer showed substantial decreases in cancer-related biomarkers and improvement in body weight and vital signs. These results indicate that Bioquantine™ may be safe and well tolerated for extended study in humans, and that it has potential therapeutic activity including restoration of renal function, glycemic control, and thyroid function, dermatologic healing, spinal cord regeneration, and anti-breast cancer activity.

We propose that the mechanism of action of Bioquantine™ in these various diseases derives from its unique, combinatorial reprogramming properties. The striking consistency with which Bioquantine™ reprograms different human somatic cells may be connected to an ability to activate dormant regenerative genes that have been retained through human evolution from the early proto-amphibians. Otherwise, human cells would not be able to respond to the reprogramming semio-chemical signals emitted by

activated amphibian eggs. In other words, we believe that in the absence of adequate stimulation and molecular and biochemical instructions to activate dormant regenerative genes, regression and re-differentiation of pathological human and animal cells into a healthier state becomes impossible.

These encouraging results may open a wide opportunity for application of Bioquantine™ bio-products in human therapies. Introduction of Bioquantine™ bio-products into the current healthcare system could set off a new trend in contemporary medicine. We have termed it Reprogramming Based Medicine (RBM), which in the future will utilize the reprogramming potential of patient's own sick cells via reactivation of its dormant regeneration genes.

We acknowledge that our investigations are in a very preliminary stage, and that we may never achieve a full understanding of the processes taking place RBM, but it would be a mistake to let this lack of knowledge hinder further research into developing this therapeutic modality.

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