**magma13 Technology**
**Summary of Biological Findings**

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Dear Dr Cortella,

Approaching the end of the year, I am sending you an update on the state of the research, and a summary of the latest scientific evidence that has emerged on magma13.

As I have already written to you in previous reports, the field of medicine concerning human beings has long been stranded within two main approaches: therapy and diagnosis, with solutions to diseased states essentially revolving around therapy. Nevertheless, according to the definition provided by the World Health Organization in 1946, an individual's health is not only characterized by the absence of disease but also by the presence of wellbeing: *"Health is a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity".*

Within this context, Wellbeing science, emerges as a "legally protected wellness", distinguishing itself from Wellness, which refers to the wellness that individuals may seek in their own way or may not seek at all. Adhering to a modern concept of Life Extension, we aim at preserving the finest biophysical dynamics at the level of both the somatic and the stem cells residing in all tissues of the human body, under coherent physiological states, as well as within the context of hostile conditions, such as ischemia, hypoxia, oxidative stress, pathological aging, and inflammation. In these cases, it is not a matter of implementing strategies that reprogram the tissue resident stem cells, making them capable to exploit processes that would never otherwise be accomplished. It is rather an issue of being able to maintain those basic physiological and spontaneous reparative properties of stem cells residing in every tissue of the human body, which would be compromised by the hostile conditions mentioned above.

More than three years ago, I was introduced to your Swiss technology named magma13, through our INBB lab, in a scientific research project that aimed at validating the effects of this technology on human somatic and stem cells. To date, the results have been more than outstanding.

The way you described magma13 technology, as an innovative, non-invasive technology designed to afford unprecedented non-invasive wellbeing responses, harnessing our endogenous biophysical and biochemical circuitries to boost our regenerative and rejuvenation potential, and induce self-healing patterns when and where they are mostly needed, in light of all the experimental data, seems to be validated with the scientific evidence to date. We have extensively tested this through the effects of different magma13 formulations *in vitro* in different populations of human somatic and stem cells, including control comparisons.

We first exposed to magma13 human neural cells (the electric impulse-conducting, and neurotransmitter-releasing cells) and human glial cells (cells that provide physical/metabolic support and communication networking to neurons), inside a thorough replica of the magma13 Regeneration Room, previously shown to achieve remarkable anti-inflammatory, pain-suppressing responses, and recovery in joint mobility and flexibility, as well as proprioceptive/postural stabilization and spine balance *in vivo* in humans. During each treatment, the magma13 chamber was placed inside a cell culture incubator, under controlled atmosphere, temperature, and humidity conditions. The exposure of neural and glial cells resulted in the differential expression of genes responsible for the ability of mechano-sensing and modulation of cellular ionic and electric currents, including TMEM63A, TRPV4, KCNK2, PIEZO2. The observation that inside the magma13 chamber neuronal and glial cells exhibited different transcriptional responses in the investigated genes (i.e. some of the overexpressed genes in one cell type resulted to be downregulated in the other) indicates the ability of magma13 to finely modulate the neuronal and glial repertoire to adapt to fundamental physical and biophysical stimuli such as mechanical, electrical, electromagnetic (also light radiation) and chemical signals. The same exposure in the magma13 chamber induced a marked increase in the protein expression of acetylated β-III tubulin in both neuronal and glial human cells. This finding is rewarding since acetylated tubulin is an essential building block in microtubule dynamics and adaptogenic responses in all cells, including neural cells, up to the point that an overexpression of acetylated β-III tubulin is currently regarded as a marker for neurogenesis and neuronal stability, and maintenance of neuronal identity. In neuronal cells, magma13 also elicited an increase in the phosphorylated active form of HSP27, an essential protein that confers cellular resistance to adverse environmental changes of any type, thus enhancing cellular resilience. This effect was also associated with an increase in the protein expression of the active form of P53, a molecule that has been referred to as the "guardian of human genome".

In human mesenchymal stem cells (hMSCs), a stem cell type that is currently being applied in multiple clinical contexts of regenerative medicine, magma13 was found to significantly inhibit the transcription of a number of crucial genes (Pax3, SPARC, TNC, COL3A1, PIEZO), whose expression can either counteract stem cell commitment and differentiation, or be involved in pathological (stem) cell dynamics, including degenerative diseases onset and progression. Noteworthy, hMSC exposure to magma13 within the regeneration chamber resulted into a marked reduction in the protein expression of Focal Adhesion Kinase (FAK), and Fibronectin (FN). While these two components of the extracellular matrix (ECM) are relevant during the embryonic development, in the adulthood their activation has a crucial role in the onset and progression of several human pathophysiological processes, including fibrosis, skeletal diseases, vascular pathologies and severe inflammation. Thus, their inhibition in adult hMSCs gives a clear indication of the ability of magma13 of providing a safe cell-to-cell connectedness environment, preserving the physiological cellular dynamics and stability.

Notably, the downregulation of several ECM components, including fibronectin, has now been identified as potential therapeutic strategy in various severe diseases. Compounding the multifaceted repertoire of useful cellular responses induced by magma13 is the finding that it elicited a massive translocation of the phosphorylated, active form of P53 inside the stem cell nucleus. This observation shows that P53, one of the most effective controllers of deranged cell behavior and proliferation, was effectively translocated in the subcellular compartment (nucleus) that represents the final target destination for its transcriptional regulation to occur. This effect was paralleled by a concomitant overall subcellular redistribution patterning in F-actin, showing a whirlpool-like pattern in magma 13-exposed hMSCs, when compared with the disordered distribution in control unexposed cells. This observation is of major interest, since when F-actin undergoes defined vortex/whirlpool-like self-assembly, the whole cytoskeleton acquires features of connectedness, with F-actin itself acting as a major propeller in the formation of cell signaling networks, including mitochondrial and exosome trafficking, thus enhancing the rescuing potential in stem cells. The nuclear translocation of P53 was associated with a decrease in the hMSC expression of P21. In particular, P21 increase can be assumed as an indicator of the parallel level of MSC senescence. Thus, the nuclear translocation of P53, together with a decrease in P21 expression indicate that magma13 elicited an environment that suppresses cellular derangement

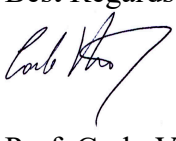
(nuclear P53 translocation), without a concomitant risk for stem cell senescence. The possibility that magma13 may oppose stem cell senescence is particularly intriguing, since while we age throughout our lifespan, not only the somatic but the tissue-resident stem cell population in our body also age, with a progressive decline in our self-healing potential. In this regard, magma13 was found to suppress the stem cell expression of a number of aging-associated/-promoting factors. In particular, magma13 inhibited hMSC expression of α-smooth muscle actin (α-SMA), a well-documented marker of somatic and stem cell aging, as well as of tissue fibrosis and stiffness, two major determinants of multi-organ failure. Moreover, hMSC exposure to magma13 inhibited the expression of vimentin. While α-SMA expression is associated with inflammation and tissue derangement, the expression of vimentin, a type III intermediate filament, besides being a well-established marker for (stem) cell aging, has been shown to play a causal role in inflammatory processes, by activating crucial steps in the *inflammasome* dynamics, leading to the secretion of major pro-inflammatory cytokines. The anti-inflammatory and anti-aging effect of magma13 on human stem cells was further supported by the observation that it also downregulated the expression of BIP, a molecule that plays a major role in tissue derangement owing to the activation of both inflammatory and senescence processes.

In a separate set of experiments, we aimed at investigating whether a minimal amount of magma13, as that incorporated inside the "magma13 Seed" technology (total seed weight is 12 g with 0.8 g of active principle) may still be able to elicit a protective anti-aging effect on human dermal hMSCs. This hMSC population that was chosen based upon the miniaturized wearable features of magma13 Seeds, used in contact with the skin, mainly as a pendant around the neck or as a bracelet. hMSCs were cultured inside a cell culture incubator, under controlled atmosphere, temperature and humidity conditions, and exposed to magma13, with each single seed placed in contact, but outside the Petri dishes in which hMSCs were grown. Under these experimental conditions, Seed exposure elicited an interesting trend towards a wound healing *in vitro*. This approach estimates the extent of closure by cell migration and proliferation of a mechanically scratched area in the stem cell culture, representing a commonly accepted *in vitro* model representative of wound healing paths *in vivo*.

Even more intriguingly, magma13 Seeds induced a remarkable increase in the protein expression of the active phosphorylated form of ATM/ATR kinases. This finding is particularly relevant. In fact, the ATM/ATR pathway is highly expressed in embryonic stem cells, when they need to become more resistant to the detrimental consequences of their inherent genomic instability and susceptibility to DNA damage. ATM and ATR kinase are key sensors of DNA double strands breaks and activate downstream signaling pathways involved in DNA repair mechanisms, following DNA breaks and damages induced by various stressors, including oxidative stress and chronic inflammation. The same pathway activated by hMSC exposure to magma13 Seeds has been found indispensable for the long-term maintenance and self-renewal in stem cells, as well as in their descendant adult, terminally differentiated cells. To make the implication of this finding even more intriguing, the ATM/ATR pathway is crucial in promoting somatic and stem cell longevity and resistance to ageing processes, and has been found to be required for telomere elongation, a major hallmark in anti-aging strategies.

Thus, even a minimally traceable amount of magma13 technology is capable of modulating essential dynamics in our stem cell biology, including those responsible for anti-aging, anti-inflammatory, and wound healing responses.

Best Regards



Prof. Carlo Ventura
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