SOLS

magma13 Research | Brief Summary

Characterization of physical/biophysical effects elicited by magma13

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Consiglio Nazionale delle Ricerche

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Characterization of physical/biophysical effects elicited by MAGMA13 in human somatic cells, Mesenchymal Stem Cells (hMSCs) and induced Pluripotent Stem Cells (iPS).

Proposing institution:
Istituto Nazionale di Biostrutture e Biosistemi (INBB- Interuniversitary Consortium / www.inbb.it)

Location of the Feasibility Study:
National Laboratory of Molecular Biology and Stem Cell Bioengineering
National Institute of Biostructures and Biosystems (INBB)
"Innovation Accelerators", Research Area of the CNR, Via Piero Gobetti 101, 40129 Bologna.

Scientific Director:
Prof. Carlo Ventura
Chief of the National Laboratory of Molecular Biology and Stem Cell Bioengineering of the INBB.

Full Professor of Molecular Biology, School of Medicine of the University of Bologna,

Scientific members: Riccardo Tassinari Ph,D.; Claudia Cavallini Ph.D.; Valentina Taglioli Ph.D. ; Dr. Martina Marcuzzi (Medical Bio technology Degree, Ph.D. Student fully committed to the project).

Timeframe: December 2020 - January 2022

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Disclaimer:

The following is a brief summary of the research study “Characterization of physical/biophysical effects elicited by MAGMA13 in human somatic cells, Mesenchymal Stem Cells (hMSCs) and induced Pluripotent Stem Cells (iPS).” conducted at the National Laboratory of Molecular Biology and Stem Cell Bioengineering - National Institute of Biostructures and Biosystems (INBB) "Innovation Accelerators", Research Area of the CNR, Via Piero Gobetti 101, 40129 Bologna, conducted under Scientific Director Professor Carlo Ventura from December 2020 - January 2022.

The research was conducted as part of a preliminary feasibility study into the effects of magma13 on human somatic and stem cells. Additional and continuous studies are currently being pursued to further explore the mechanisms of the observed effects, as well as replicate the research over variable periods of time and magma13 exposure. The results of this study have not yet been reviewed by any outside research, health or medical authorities.

The information provided in this summary is not designed to provide medical advice and is for general education purposes only.

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Observed Effects in magma13 Feasibility Study Included:

Enhanced Cellular Regeneration

Increased Cellular Resistance to Adverse Environmental Change

Improved Gene and Protein Expression

Promotion of Anti-Aging Factors / Decrease in Cellular Senescence

Anti-Inflammation Effects

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Somatic and Stem Cells

All body cells of an organism, apart from reproductive cells, are somatic cells.

The feasibility study looked at **Neural** and **Glial** cells.

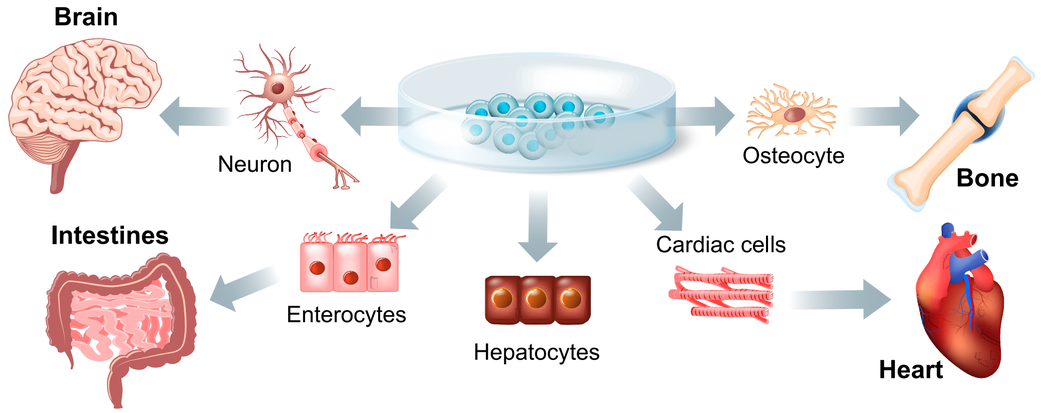
Neural Cells are neuronal cells or the impulse-conducting cells that constitute the brain, spinal column, and nerves.

Glial cells are cells which are non-neuronal and are located within the central nervous system and the peripheral nervous system that provide physical and metabolic support to neurons, including neuronal insulation and communication, and nutrient and waste transport.

Stem cells are cells with the potential to develop into many different types of cells in the body. They serve as a repair and regenerative system for the body.

The type of stem cells used in the feasibility study were harvested from adipose (fat) tissue.

Stem cells are different from other cells in the body in that they: 1) can divide and **renew themselves over a long time**; 2) **are not yet specialized**, so they cannot do specific functions in the body; and 3) **have the potential to become specialized cells**, such as muscle cells, blood cells, and brain cells

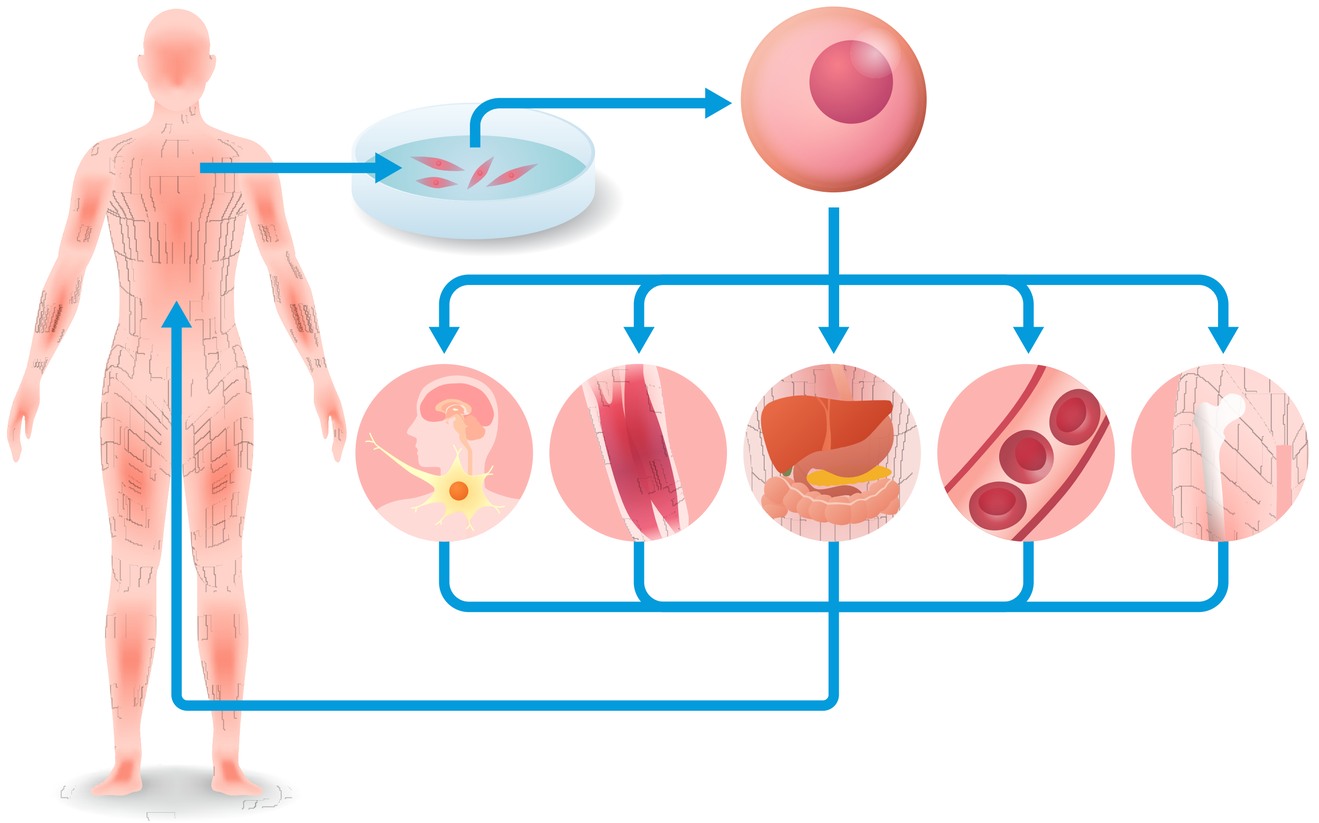


Enhanced Cellular Regeneration

Regeneration is the natural process of replacing or restoring aging, damaged or missing cells, tissues and organs.

Our cells are naturally designed to regenerate and keep us optimally functioning. However, at times because of our genetic make-up, altered protein expression, exposure to detrimental environmental factors or simply time, our cells lose their vitality, and can lose reiterative ability and even turn towards pathologic cell growth.

Scientists are studying regeneration for its huge potential uses in health and wellbeing, such as treating a variety of injuries and diseases, as well as its link to the human aging process.



Enhanced Cellular Regeneration Somatic Cells

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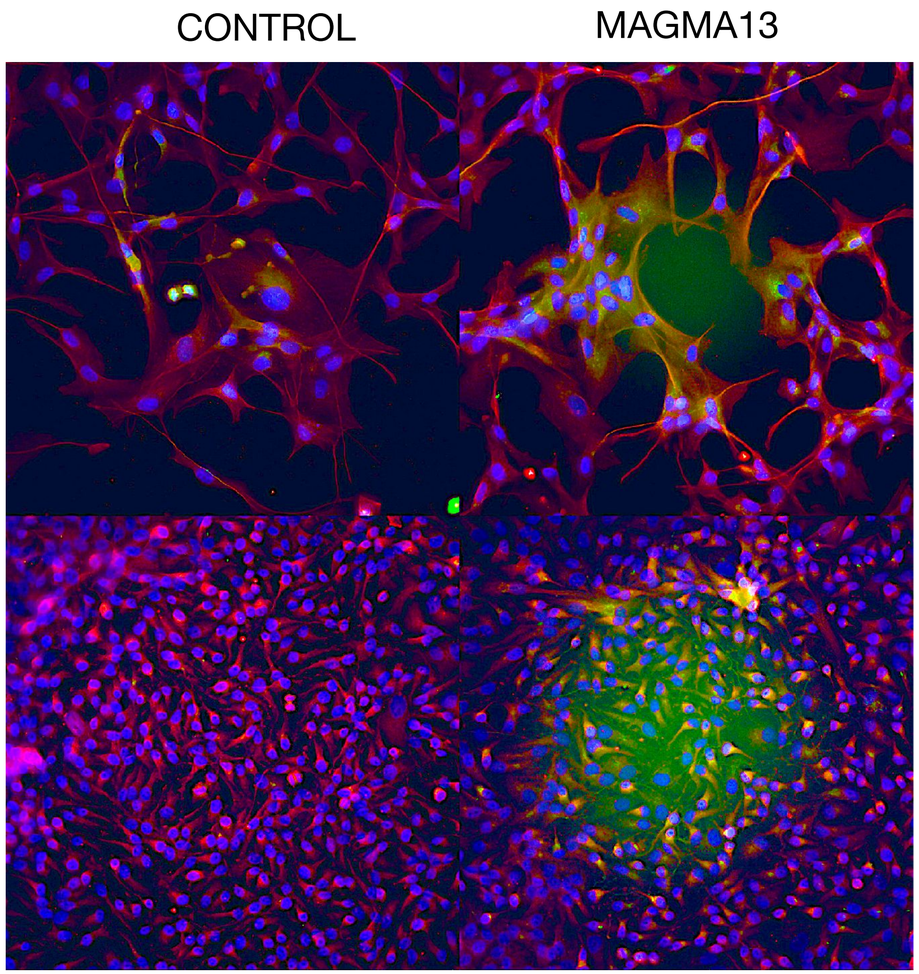

Tubulin is a protein that combines into long chains or filaments that form microtubules, hollow polymers fibers which serve as a skeletal system for living cells. **Microtubules** (polymers of Tubulin) are essential components of the cytoskeleton and behave like a bioelectronic circuit capable of giving and receiving signals (electrical and luminous), maintaining the healthy structure of the cell and intracellular transport inside the cell.

The degree of acetylation and deacetylation are a useful tool to evaluate tubulin stability in order to investigate cellular response to physical and chemical stimuli. **Following Magma13 exposure, an evident increase in the acetylated tubulin signal was detected.**

Tubulin Expression (immunofluorescence analysis)

Enhanced Cellular Regeneration
Somatic Cells

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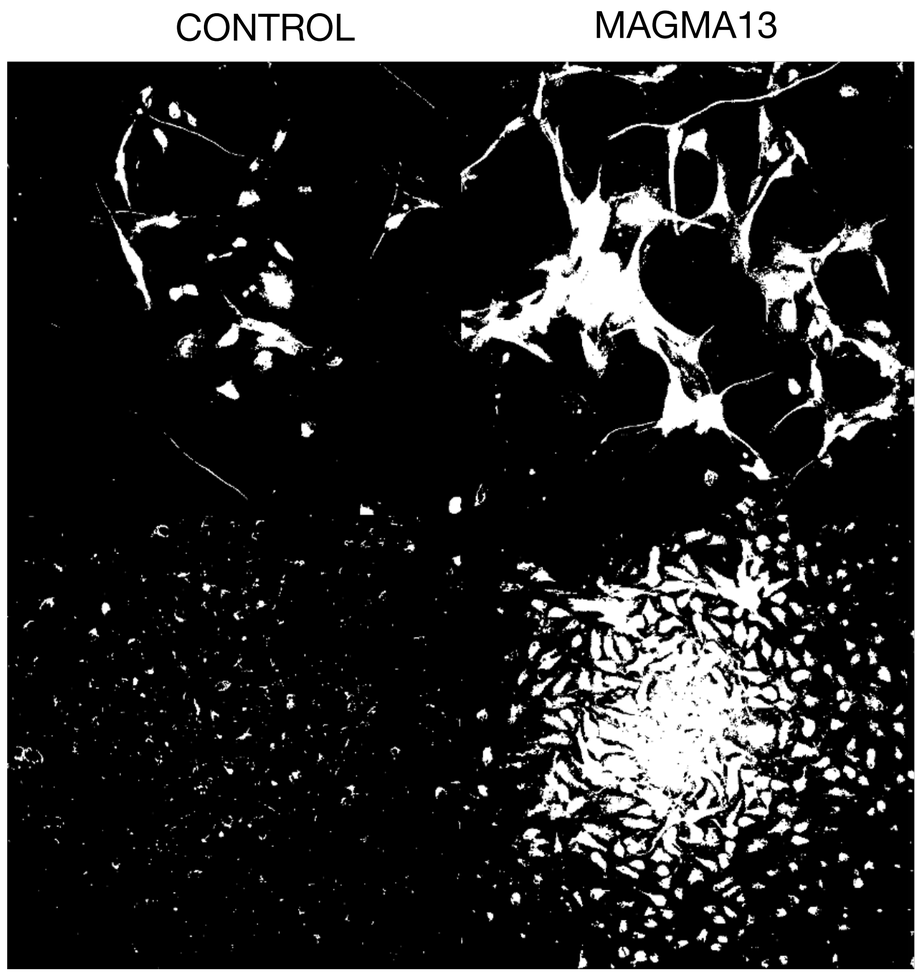

βIIITubulin is an element of tubulin found almost exclusively in neurons. It is expressed in healthy neuronal cells, and is used as a **marker of neurogenesis and neuronal stability, protection, maintenance of neuronal identity**.

A remarkable expression of βIIITubulin was only seen following MAGMA13 exposure.

Tubulin Distribution (Monofocal enhancement with dark contrast)

Enhanced Cellular Regeneration Stem Cells

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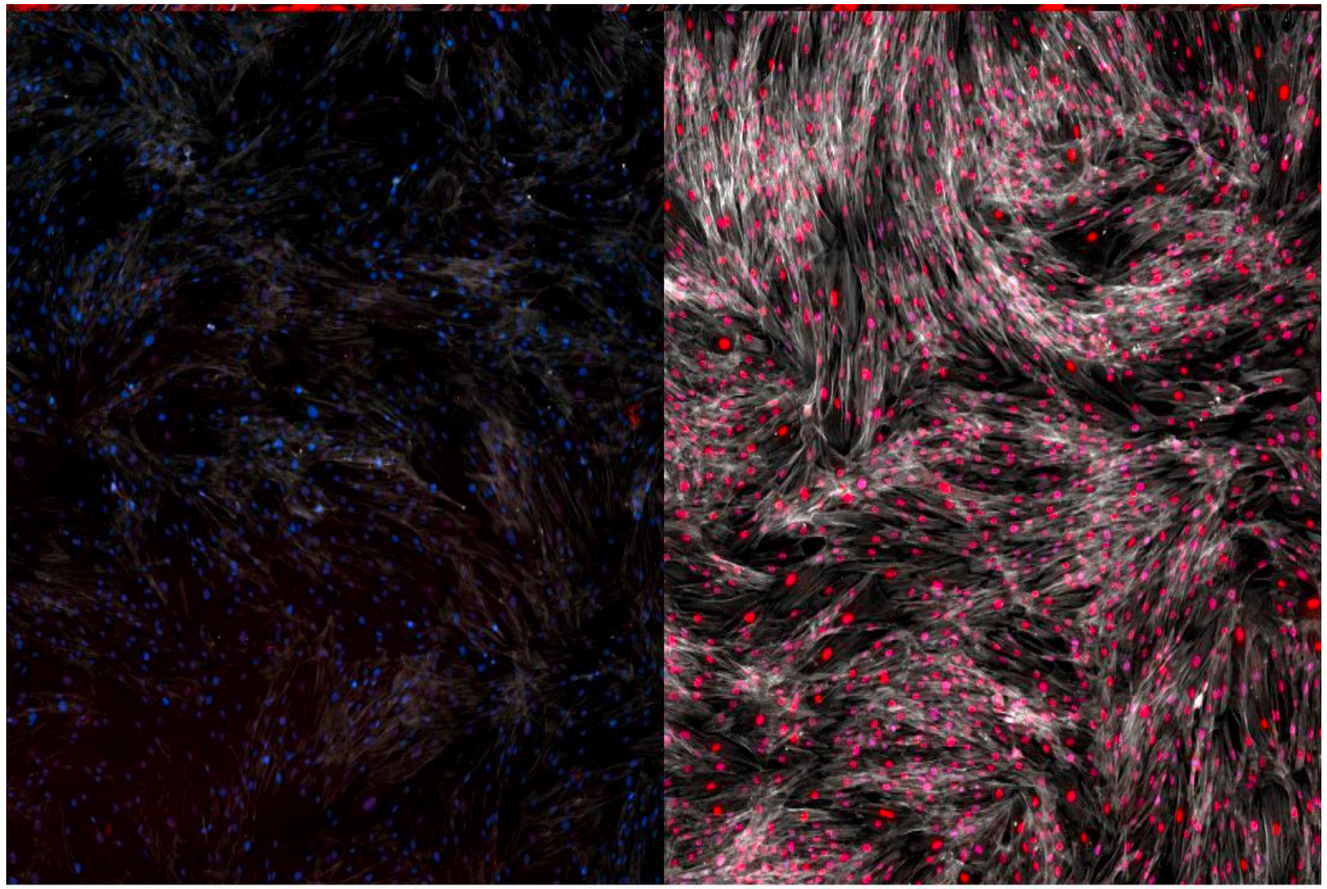
CONTROL

MAGMA13



P53 regulates cell division by keeping cells from growing and dividing (proliferating) too fast or in an uncontrolled way. It is the genome's major protector and a key factor for cell anti-derangement.

The Expression of the Active phospho-P53 (p-P53) and F-Actin in hMSCs that had been exposed to control (Left) and magma13 (Right) SOLS chamber is **really remarkable and unprecedented** in any other experiments ever conducted before by this laboratory.

When F-actin undergoes defined vortex/whirlpool-like self-assembly, the whole cytoskeleton acquires features of connectedness. **On the whole, these data indicate that this was associated with significant cytoskeletal reprogramming and with features of enhanced cell polarity and regeneration.**

Expression of phospho-53P53 (p-P53) and F-Actin in hMSCs

Enhanced Cellular Regeneration
Stem Cells

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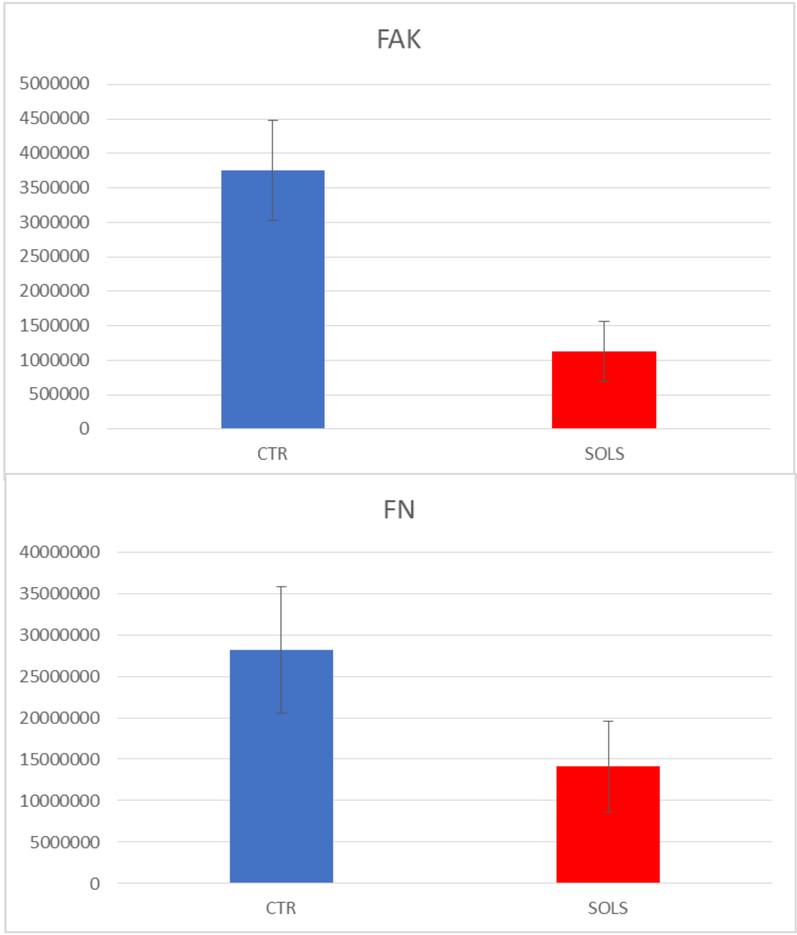
hMSC exposure to MAGMA13 resulted in **a remarkable inhibition in the expression of two critical players in tissue and cellular derangement: Focal Adhesion Kinase (FAK), a major regulator of cellular adhesion, and Fibronectin (FN), an essential conductor involved in pathophysiological processes and fibrosis in cell/cell and cell/ECM (extra Cellular Matrix) interaction**.

The current experimental data provided significant evidence that **MAGMA13 is capable of modulating a number of essential determinants in stem cell biology. In particular, MAGMA13 elicited a down-regulatory action on the expression of genes and proteins that have been clearly reported to hamper stem cell lineage commitment, and that promote detrimental tissue derangement**.

As with the gene down-regulation, these will be further investigated to more fully understand the dimensions of its contributive factors.

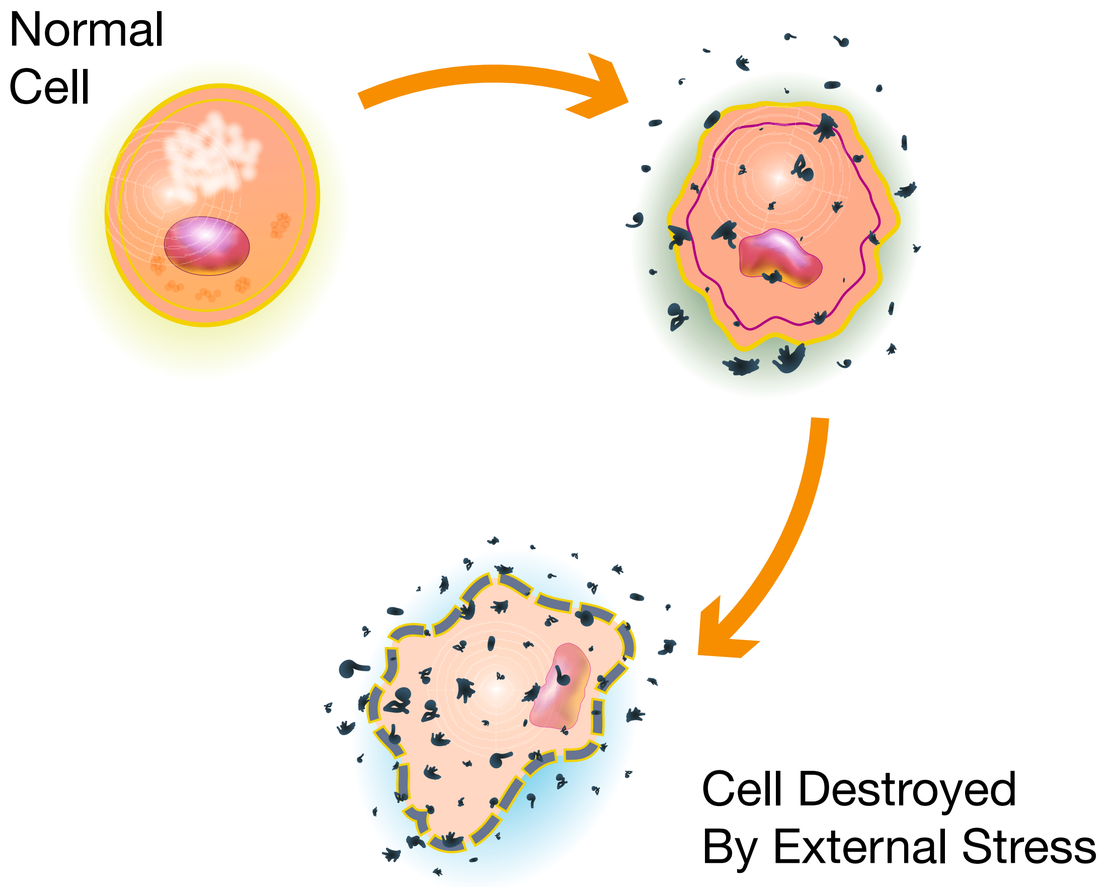


Increased Cellular Resistance to Adverse Environmental Change

Cells are embedded with mechanisms that help them resist being damaged by environmental stresses.

We call this process homeostasis, and it helps maintain stable internal conditions in a changing environment. Individual cells, as well as organisms, must maintain homeostasis in order to live.

When cells become overly stressed by external factors, they can malfunction or even mutate. We want our cells to be strong and be able to resist these factors, and if needed adapt, but in a healthy and dynamic manner.



Increased Cellular Resistance to Adverse Environmental Change

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Neuronal and glial cells express complex adaptive mechanisms to the cellular environment itself but also to stimuli coming from the external environment. We investigated whether MAGMA13 can modulate expression of genes that are related to the ability of mechano-sensing and modulation of cellular ionic and electrical currents, looking at the expression of genes in their ability to adapt to physical and biophysical stimuli such as mechanical, electrical, electromagnetic (also light radiation) and chemical signals.

magma13 appears to be capable of imparting modulatory and adaptogenic behaviors in a coherent way.

Increased Cellular Resistance to Adverse Environmental Change

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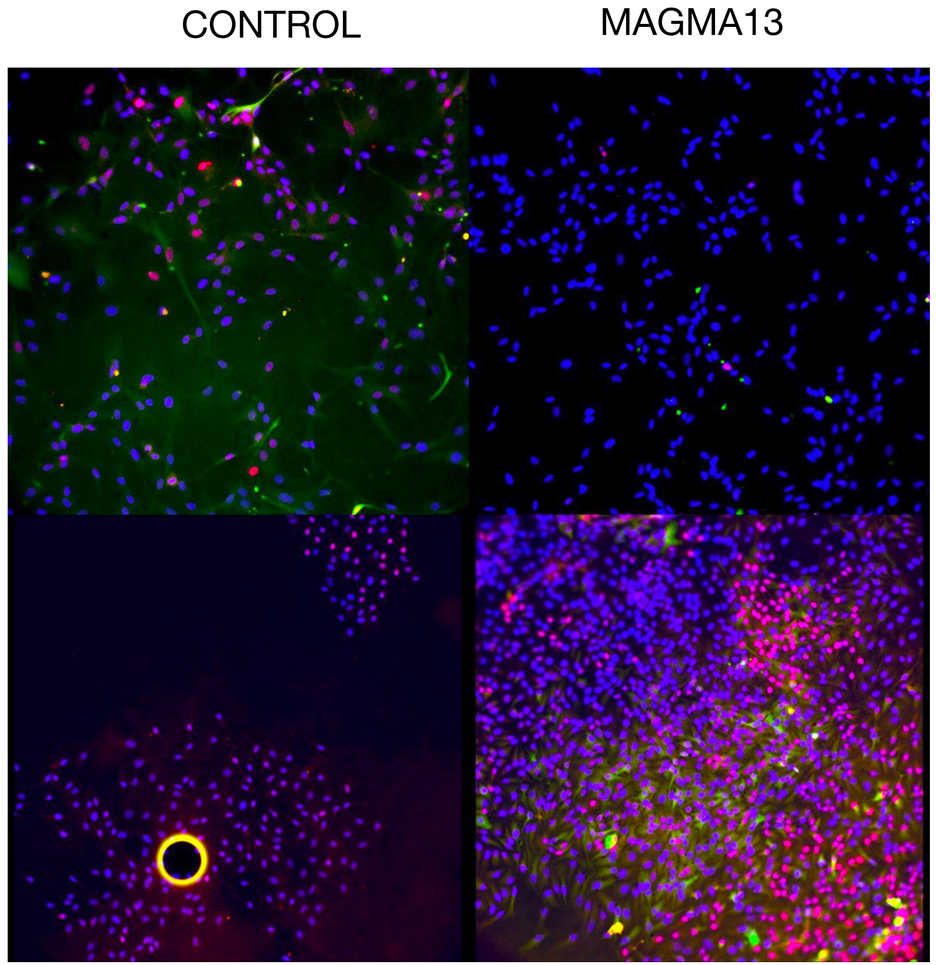

In response to stress, the **Phospho-HSP27** (Heat-shock protein) expression increases several-fold to confer **cellular resistance** to the adverse environmental change of any type and confer cellular resilience.

In magma13-treated glial cells, P27 as well as p-HSP27 were downregulated. Glial elements are generally a population involved in cellular connectomics and networking thus subjected to adaptive challenging. **The observed downregulation may reflect the capability of magma13 to decrease cell susceptibility to both endogenous and exogenous stressogens**.

Phospho-HSP27 and P27 Expression (immunofluorescence analysis)

Increased Cellular Resistance to Adverse Environmental Change

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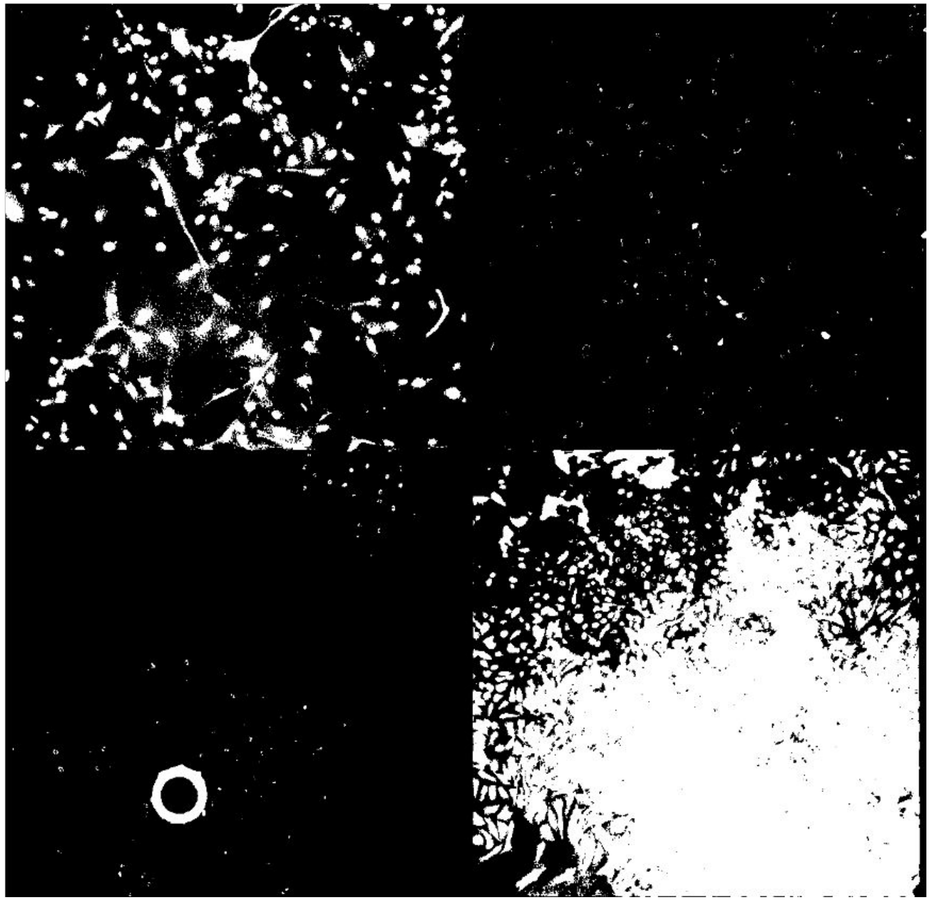
CONTROL MAGMA13

glial **U-87MG** cells

neural **AF** cells



Amazingly enough, the effect was completely opposite in neural AF cells, where both P27 and pP27 were dramatically enhanced by magma13.

Such an effect is consonant with the higher susceptibility of neurons to multiple stressors, and it may be viewed as a remarkable protective action supporting the acquirement of a stemness-like condition and enhanced neurogenic performances.

Phospho-HSP27 and P27 Distribution (Monofocal enhancement with dark contrast)

Increased Cellular Resistance to Adverse Environmental Change

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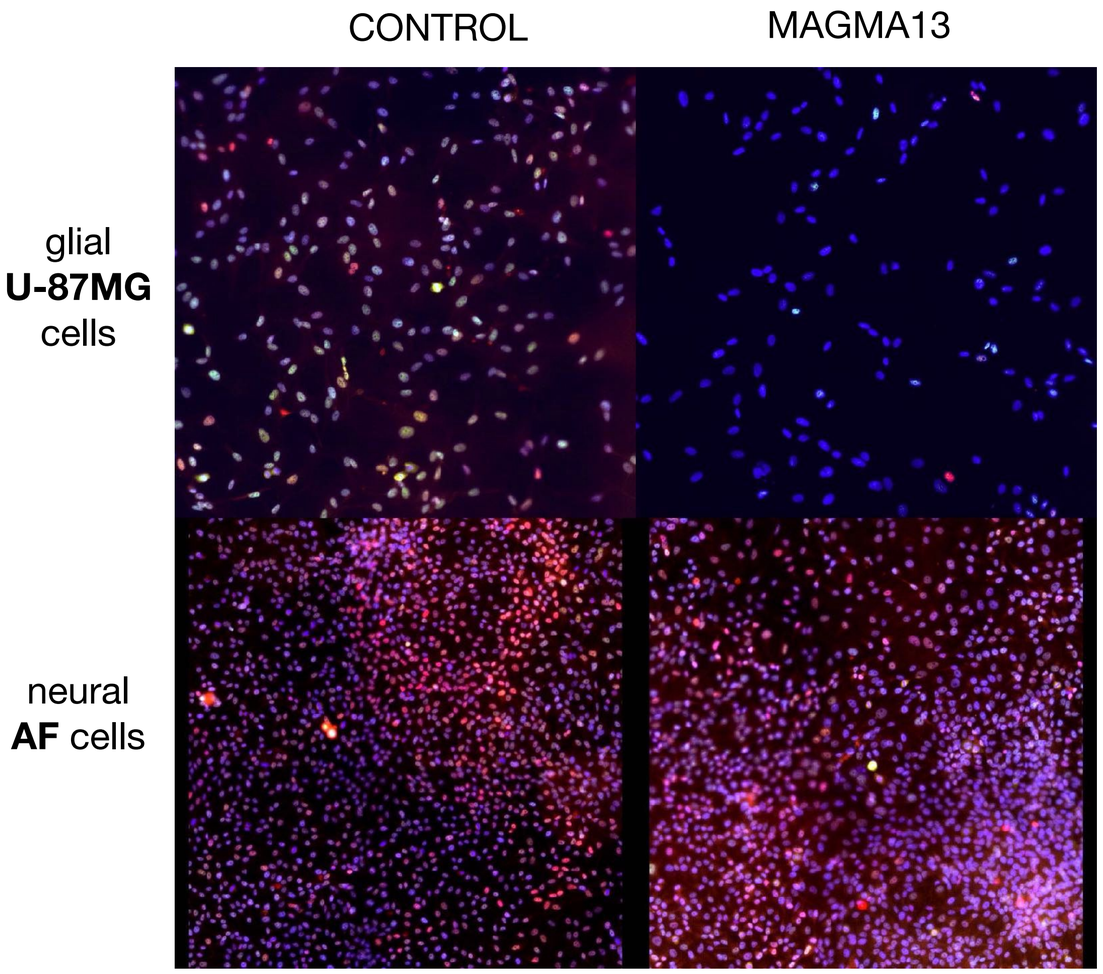

P53/pP53 Expression, regulates cell division by keeping cells from growing and dividing (proliferating) too fast or in an uncontrolled way. It is the genome's major protector and cell anti-derangement key factor. Mirroring the adaptogenic effects elicited by magma13 on pP27 expression in glial and neuronal cells,

Magma13 treated glial cells displayed a substantial downregulation in pP53 expression.

Conversely, neuronal cells treated in MAGMA13 chamber displayed an over-expression response. Such an effect is consonant with the higher susceptibility of neurons to multiple stressors, and it may be viewed as a remarkable protective action and enhanced neurogenic performances.

P53 and pP53 Expression (immunofluorescence analysis)

Increased Cellular Resistance to Adverse Environmental Change

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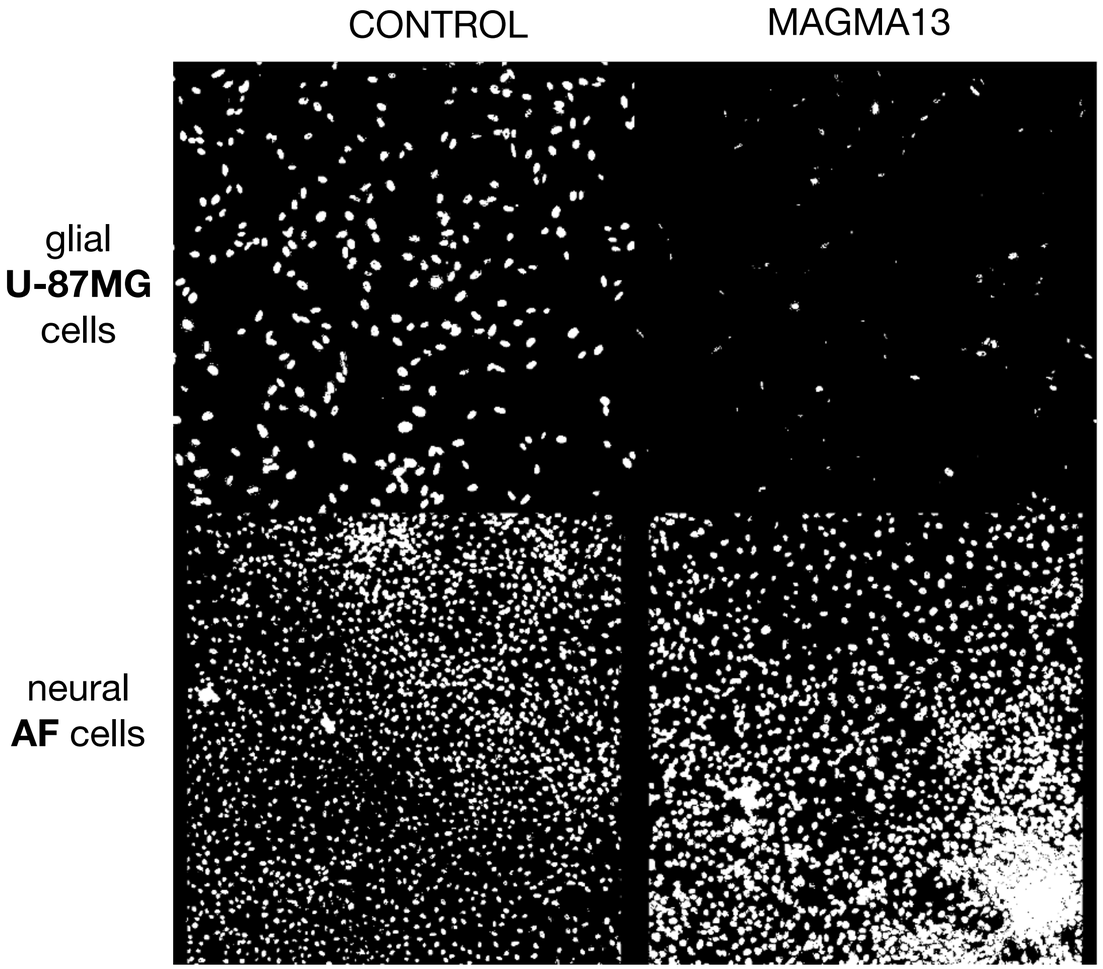

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P53 and pP53 Distribution (Monofocal enhancement with dark contrast)

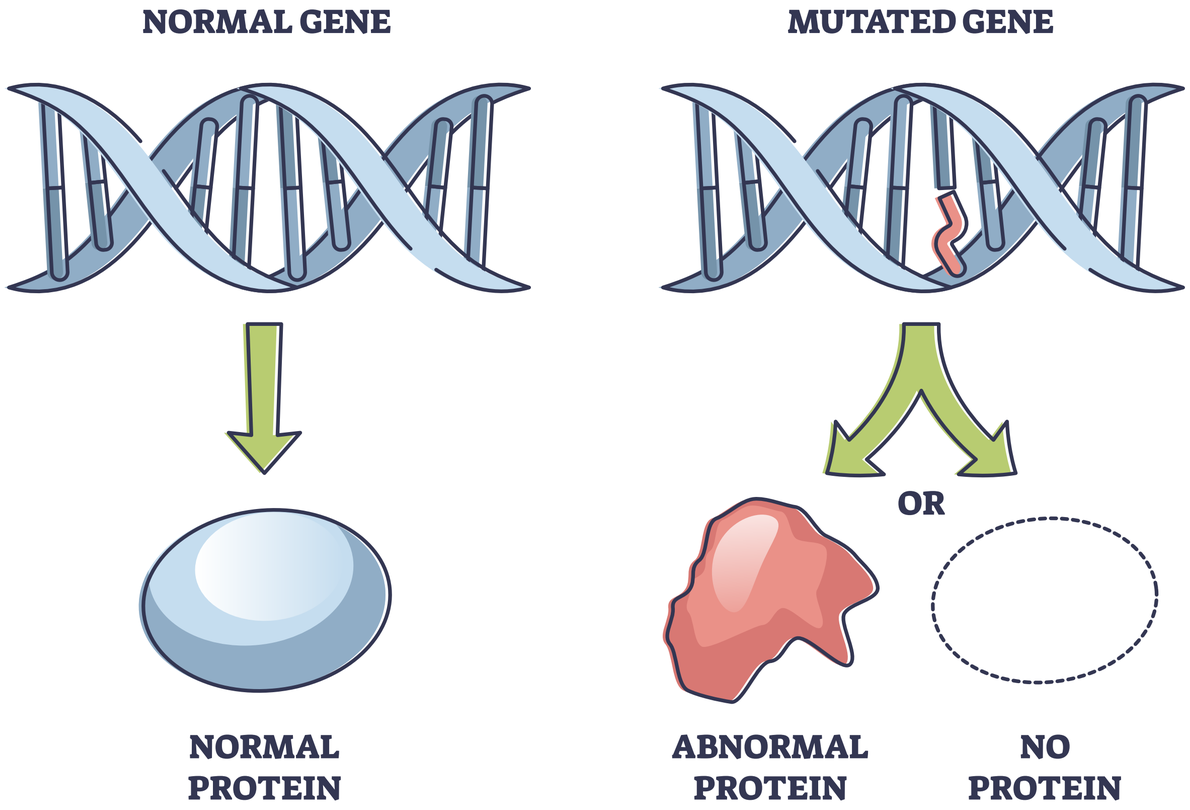
Improved Gene and Protein Expression

Gene expression is the process the cell uses to produce the molecule it needs by reading the genetic code written in DNA.

In the genome is an organism's complete set of genetic instructions. Each genome contains all of the information needed to build that organism and allow it to grow and develop.

To do this, the cell interprets the genetic code, and for each group of three letters it adds one of the 20 different amino acids that are the basic units needed to build proteins.

These proteins are the functional units of our bodies and it is critical that they be coherently produced and replicated.



Improved Gene and Protein Expression Somatic Cells

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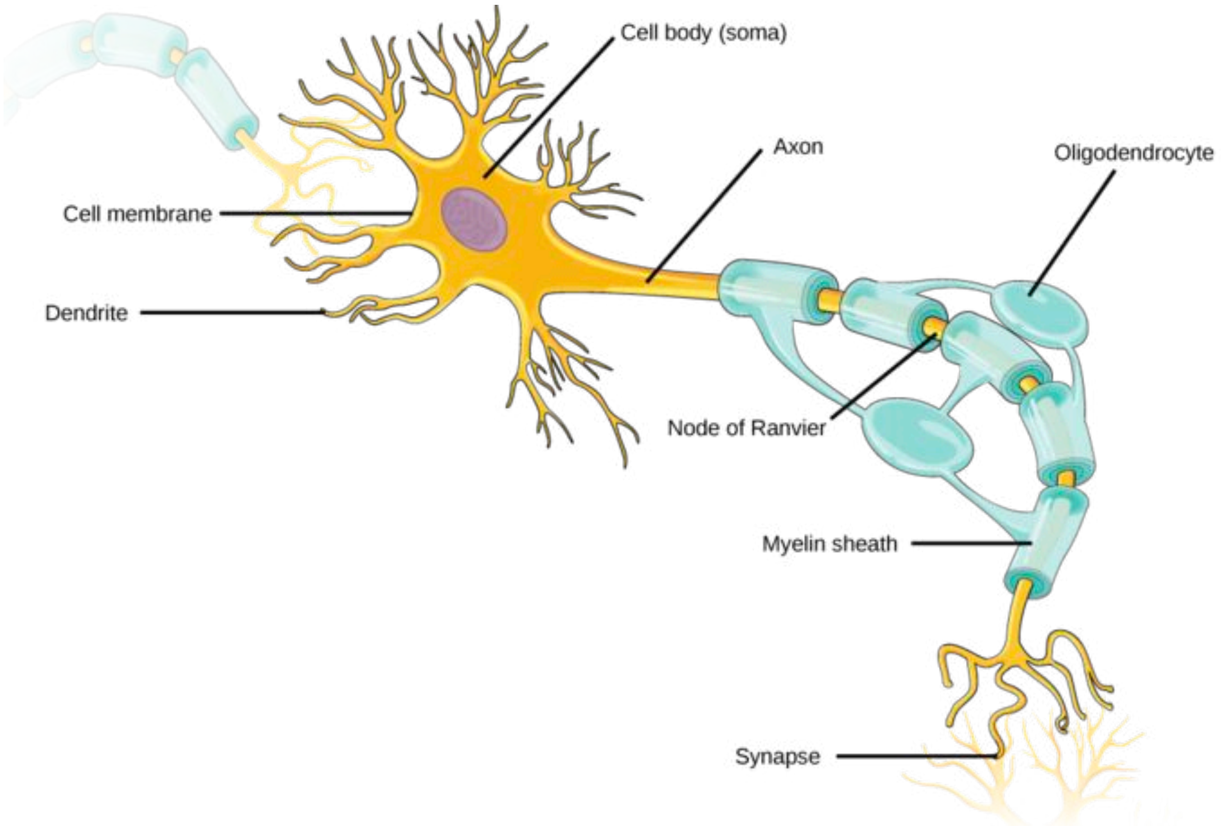
Research performed with Neural and Glial cells.

The modulation in gene expression in cells exposed to MAGMA13 was very noticeable.

Different responses were observed mediated by MAGMA13 exposure in the two cell lines, demonstrating how the same signal can lead different behaviours, also in cell similar for lineage specification.

The findings indicate the capability of MAGMA13 to exert multifaceted, selected, and cell specific actions.



Improved Gene and Protein Expression Somatic Cells

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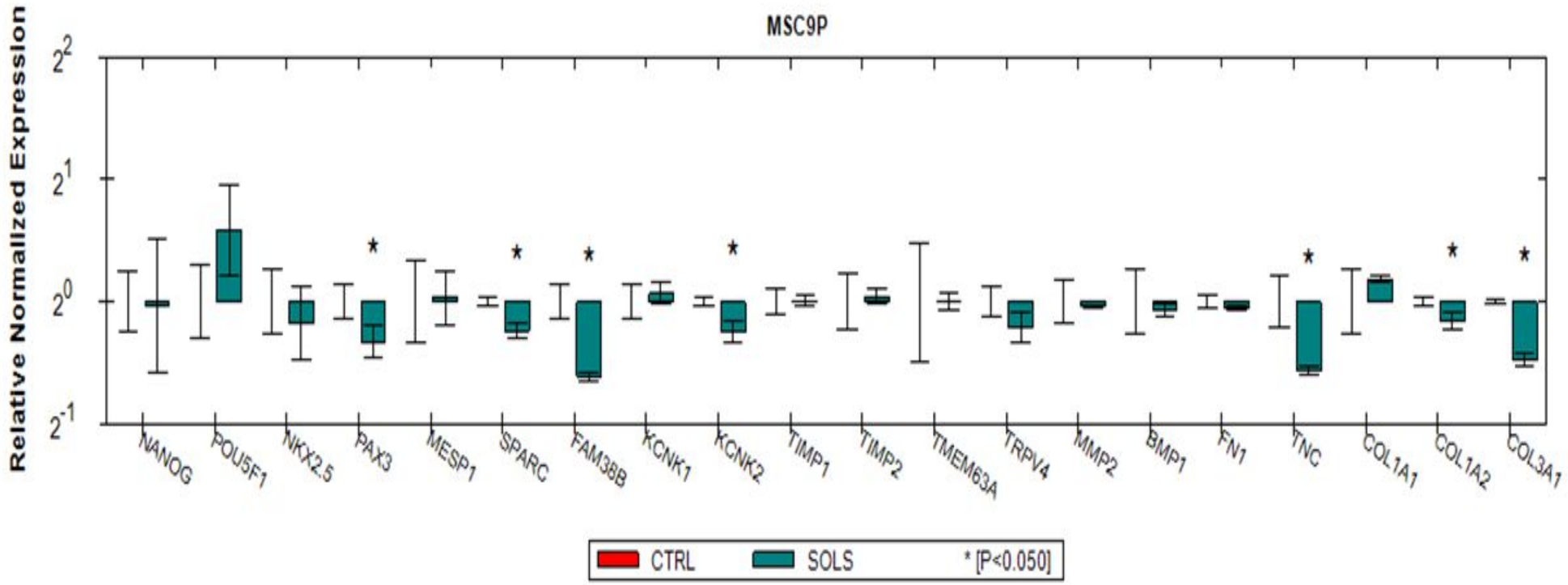
Protein expression was surprisingly influenced by the presence or absence of MAGMA13. **These findings indicate the capability of Magma13 to exert multifaceted, selected, and cell specific actions. Given the current experimental findings and replicates the results are quite robust. Magma13 really acted as fine tuner of crucial determinants and conductors of cellular homeostasis and fate. It afforded a significant induction of signaling related to the ability of cells to cope with environmental stressors, and promoted patterning associated with the onset of stemness-like features**. Similar effects are usually observed only when cells are exposed to major pharmaceutical or therapeutic chemical agents, or to physical energies, improving cellular dynamics as it has been demonstrated following the exposure to mechanical oscillations, and specific electromagnetic fields.

Intriguingly **the reported findings did not involve any adverse effect on cellular vitality**. **On the contrary, magma13 elicited the gene and protein expression of molecules protecting cells from major stressing and adverse reactions.**

Improved Gene and Protein Expression Stem Cells



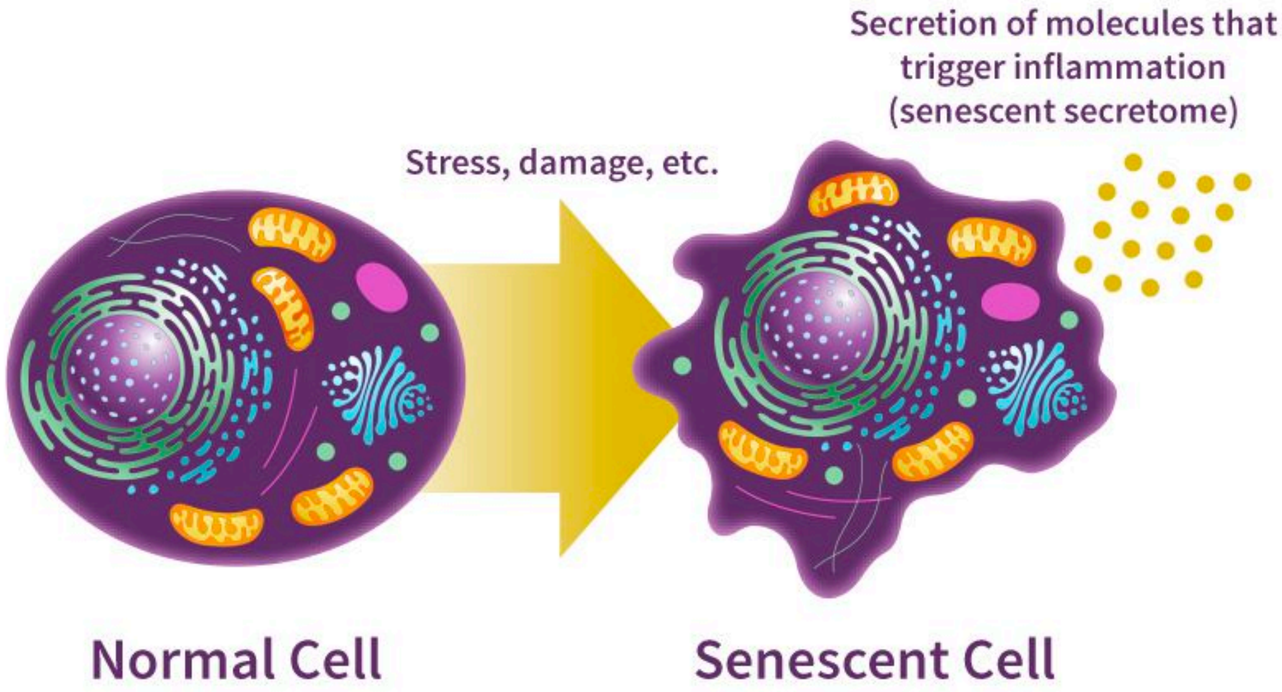
PAX3
SPARC
TNC
COL1A2
COL3A1
PIEZO (FAM38B)
KCNK2
TREK-1

hMSC exposure to MAGMA13 was found to significantly inhibit the transcription of a number of crucial genes, whose expression can either counteract stem cell commitment and differentiation, or be involved in pathological (stem) cell dynamics, including severe disease onset and progression.

Promotion of Anti-Aging Factors
Decrease in Cellular Senescence

Senescence or biological aging is the gradual deterioration of functional characteristics in living organisms.

Cellular senescence is defined by permanent cell cycle arrest. Senescent cells accumulate with age and contribute to the normal aging process as well as age-related disorders. The link between senescence, aging, and age-related pathologies, including cancer, neurodegeneration, and metabolic and cardiovascular diseases is widely studied.



Promotion of Anti-Aging Factors Decrease in Cellular Senescence

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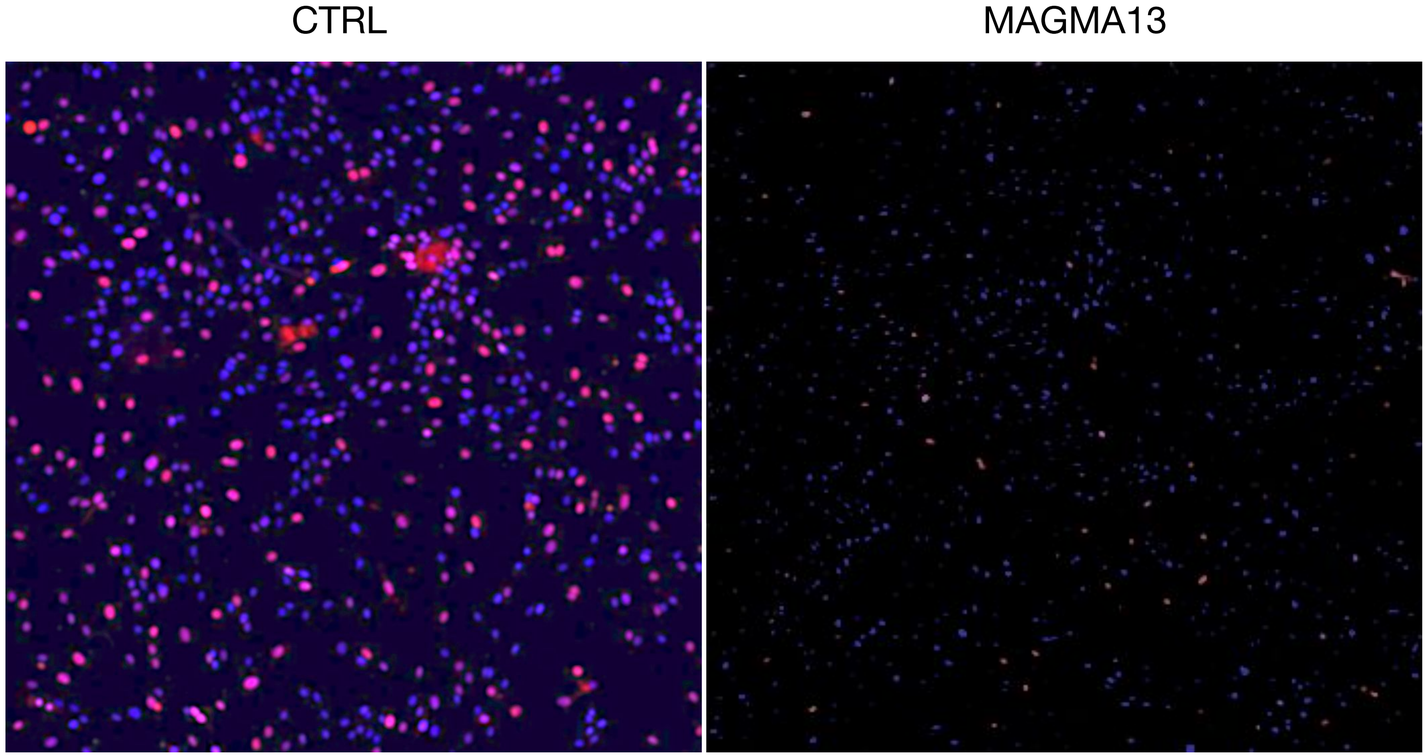
The study observed a downregulation of P21 in MAGMA13 exposed hMSCs. This cellular derangement suppression player is overexpressed in cells and stem cells undergoing aging. In particular, P21 increase can be assumed as an indicator of the parallel level of MSC senescence.

This finding, considered within the context of a p-P53 overexpression, with a concomitant E-Cadherin downregulation, and the absence of an effect on RB expression, further corroborates the evidence that MAGMA13 may selectively counteract hMSC aging, without creating a risky, pro-oncogenic environment, as it may occur in “forced” anti-senescence strategies.



P21 Expression in hMSCS (immunofluorescence analysis)

Promotion of Anti-Aging Factors Decrease in Cellular Senescence

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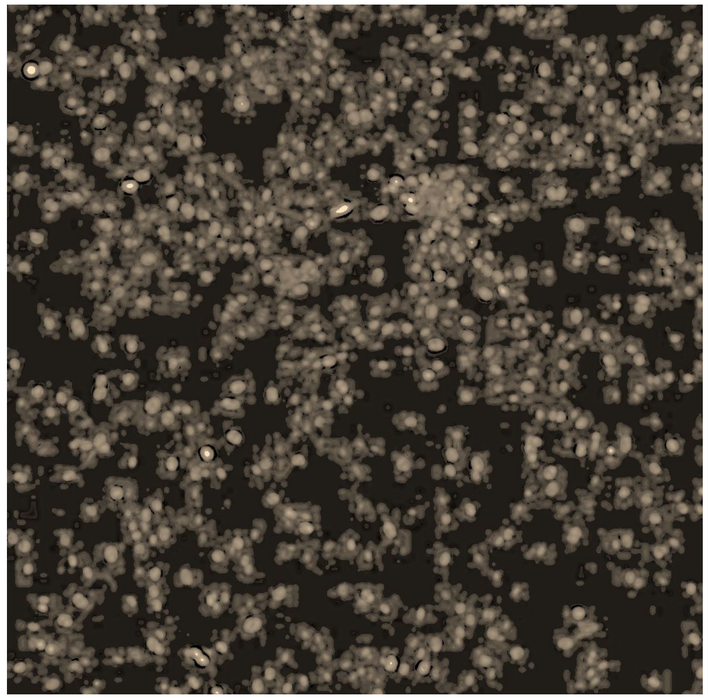


MAGMA13

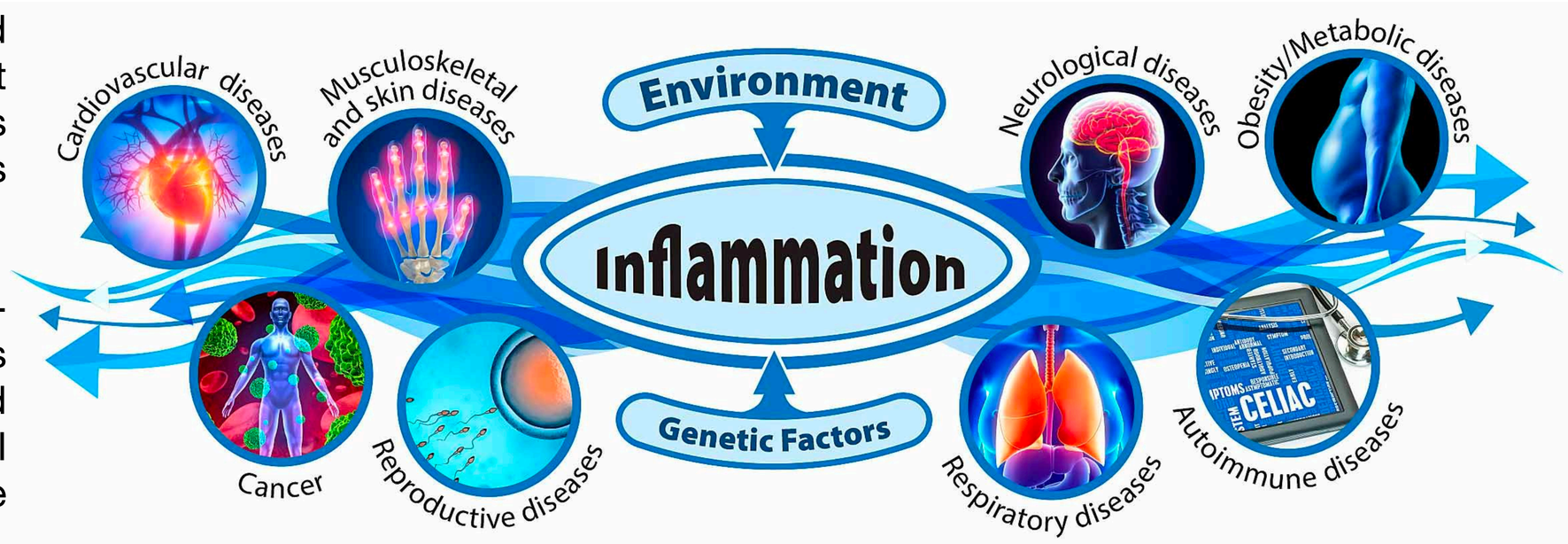
P21 Distribution in hMSCS (Monofocal enhancement with dark contrast)

Anti-Inflammation Effects

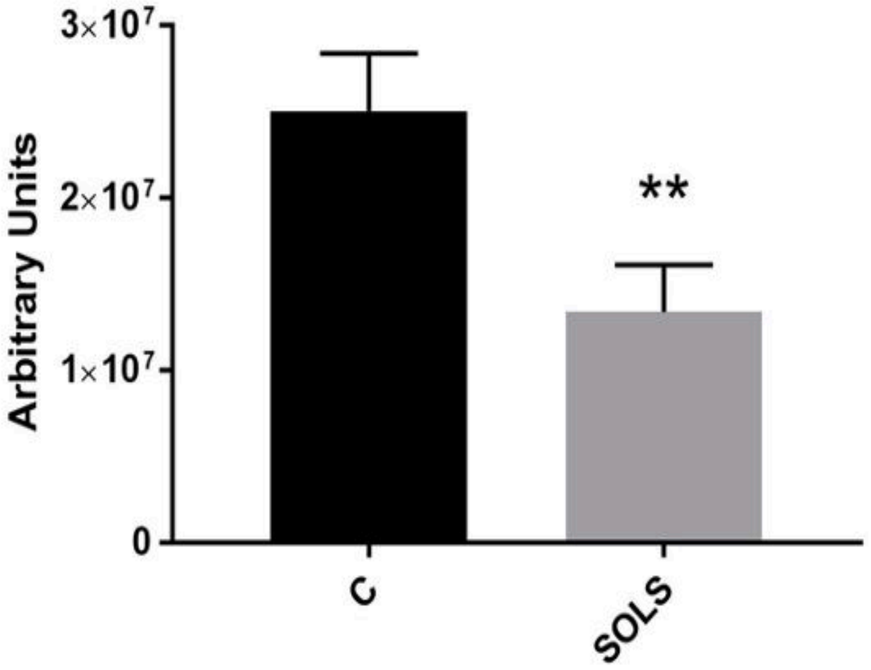
Cellular inflammation is an inflammatory process which occurs on a basic, cellular level. Inflammation is a normal process that occurs in the body, and is designed for acute situations, to aid in the healing of tissue. However, when this inflammation becomes on-going it can cause the damage and death of cells to occur, which may eventually lead to a pathological or disease process.

It has been well established through decades of research that chronic inflammation is associated with many diseases and conditions.

It is also known that chronic, low-grade inflammation also develops with age (Inflamm-aging) and may contribute to clinical manifestations of other age related pathologies.



Establishing an Anti-Aging and Anti-Inflammatory Profile



Western Blot analysis of α-SMA expression in control (C) and MAGMA13 exposed (SOLS) hMSCs (n = 6 form six different independent samples).

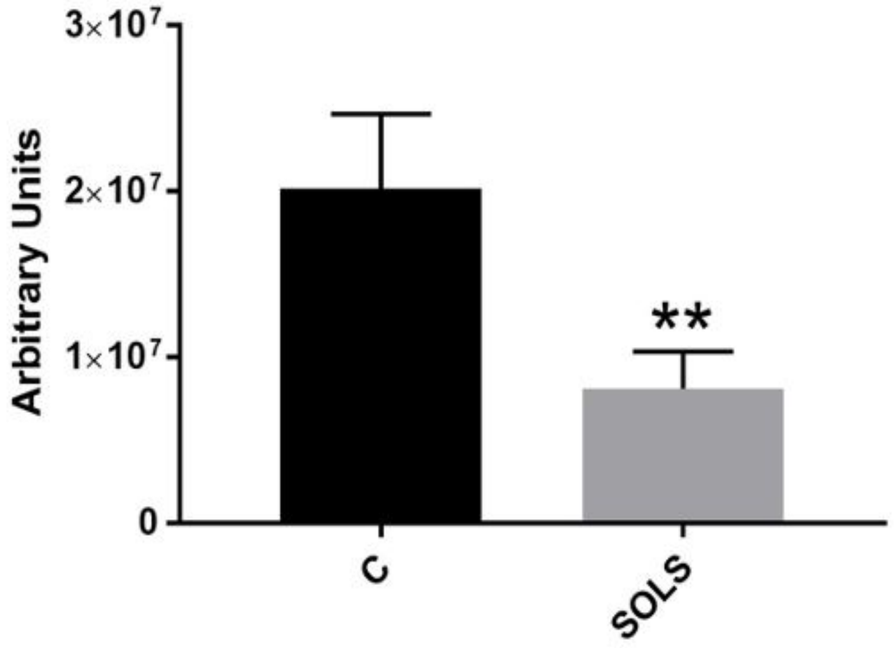
There is compelling and growing evidence that **α-SMA (Alpha-Smooth Muscle Actin)** expression represents an affordable marker of cell and stem cell aging, as well as of tissue fibrosis/derangement/stiffness and degenerative diseases.

Moreover, α-SMA overexpression correlates with **telomere** shortening in the activation of senescent processes.

There is also mounting evidence that relates increased α-SMA expression to tissue remodeling (fibrosis and failure) and inflammation.

We found that MAGMA13 was able to afford a highly significant ($p<0.001$) reduction in α-SMA expression of exposed hMSCs, as shown by Western blot analysis. The downregulatory action was consistently observed throughout all the experiments.

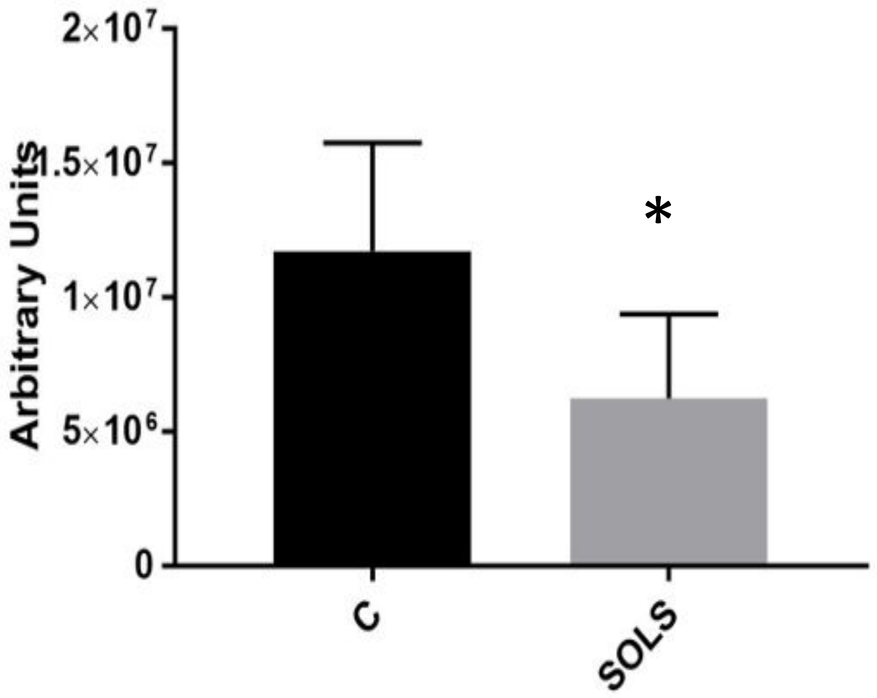
Establishing an Anti-Aging and Anti-Inflammatory Profile



Western Blot analysis of Vimentin expression in control (C) and MAGMA13-exposed (SOLS) hMSCs (n = 6). (n = 6 form six different independent samples).

A major finding from the experimental observation of the present report is that hMSC exposure to MAGMA13 consistently and remarkably afforded a down-regulation in **vimentin resulting in more than a 2-fold decrease in target protein expression in exposed, as compared to unexposed hMSCs.** 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 the inflammatory processes. Vimentin, has been shown to activate crucial patterning in the *inflammasome* dynamics, leading to the secretion of major pro-inflammatory cytokines.

Establishing an Anti-Aging and Anti-Inflammatory Profile



Western Blot analysis of BiP expression in control (C) and MAGMA13-exposed (SOLS) hMSCs (n = 6). (n = 6 form six different independent samples).

Compounding the anti-inflammatory potential of MAGMA13, hMSC exposure to this compound elicited a decrease in **BiP (Binding immunoglobulin protein)** expression, as compared to control unexposed cells. This supports the results from the second part of this feasibility study, where we provided evidence that MAGMA13 remarkably decreased TNC gene expression. The ability of MAGMA13 to downregulate both TNC and a-SMA expression places the action elicited by this compound within a wider context of anti-inflammatory/anti-degenerative actions.

Establishing an Anti-Aging and Anti-Inflammatory Profile

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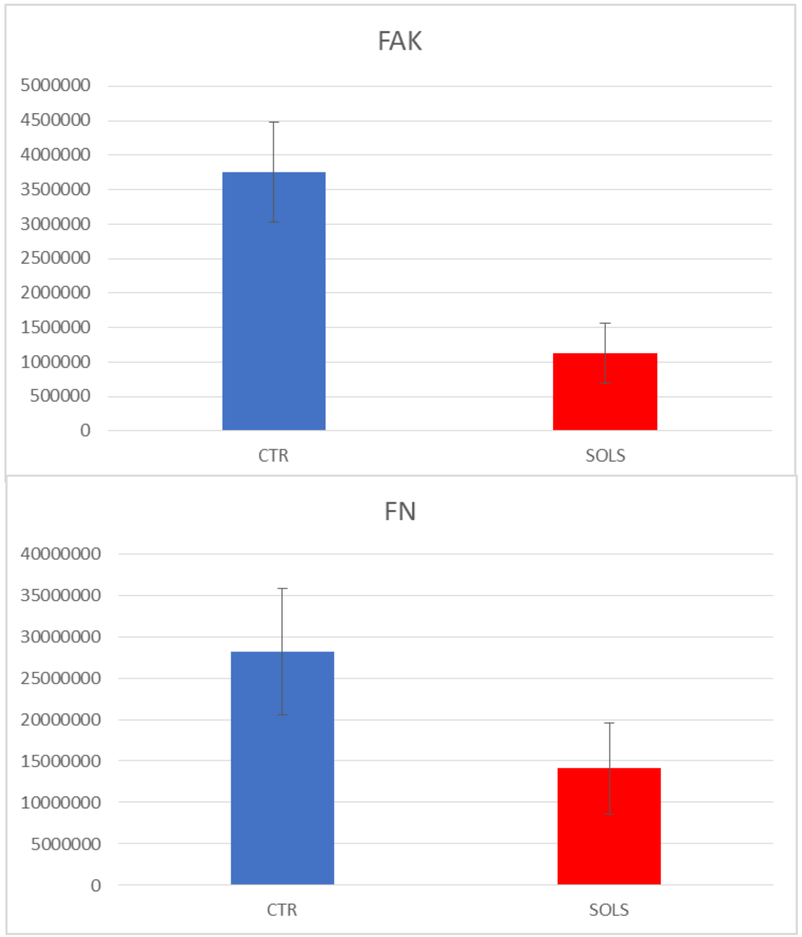
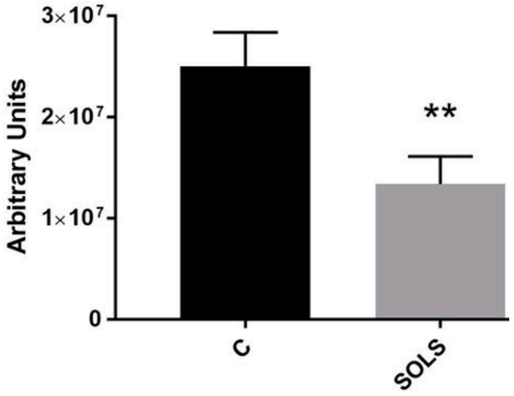
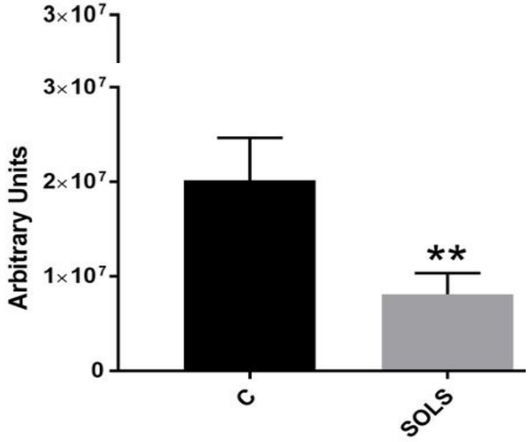
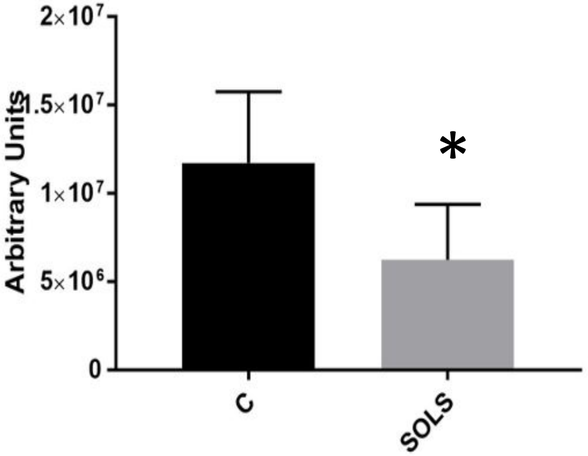




α-SMA expression



Vimentin expression



BiP expression

Conclusions of feasibility study

The current findings are the completion of the whole feasibility study. All the experiments provide compelling evidence that MAGMA13 is able to promote a profound modulation of gene and protein expression in human neural, glial and stem cells orchestrating essential signaling responsible for the optimization of cellular homeostasis, viability, stemness features, and favorable adaptogenic patterning. Moreover, magma13 proved to be effective in maximizing the expression of cellular armamentarium responsible for protection against detrimental endogenous, as well as exogenous stressors. MAGMA13 elicited a consistent reprogramming in the subcellular organization of F-actin, generating whirlpool/vortices-like patterning that have been associated with the recruitment of the cytoskeleton in the optimization of cell polarity, and the activation of cell-to-cell physical connectedness and communication. Notably, MAGMA13 downregulated the expression of players that have been unequivocally associated with aging, inflammation and tissue degeneration, such players behaving both as essential markers or causative conductors in tissue inflammation, remodeling (scarring) and aging. As demonstrated in the study, MAGMA13 did not exert these actions with loss to any cellular viability.

Final report feasibility study
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