

Evaluation and Licensing Opportunities

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Patent Literature

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GHEM: Conditioning Cells for Regeneration

A novel method for conditioning stem cells and producing a regenerative phenotype

Advanced culture medium formulation enhances the regenerative and proliferative capacity of ageing cells

Stem cells are a functionally heterogeneous population of undifferentiated cells that play a crucial role in tissue maintenance and regeneration. This is largely attributed to their ability to secrete bioactive factors that preserve cellular function within their local microenvironment, a property that has significant potential for the treatment and prevention of disease. Consequently, research into stem cell biology has accelerated over the past decade, leading to numerous applications across the pharmaceutical and biotechnology sectors. However, ageing represents a major limitation to both stem cell function and therapeutic utility. Ageing is characterised by the progressive accumulation of cellular damage resulting from environmental and physiological stressors, including chronic inflammation, altered intercellular communication, mitochondrial dysfunction, and cellular senescence. Cellular senescence, in particular, is marked by an irreversible arrest of cell-cycle progression, leading to impaired proliferation and diminished tissue regenerative capacity. Improving our understanding of the mechanisms that drive, maintain, or potentially modulate the senescent state is therefore essential for restoring stem cell function and enhancing their therapeutic potential.

Despite significant progress in the field, therapeutic approaches targeting cellular senescence remain constrained by limited efficacy, high production costs, and manufacturing complexity. The development of more effective and economically viable strategies is therefore essential to advance the translation of anti-ageing therapies into clinical practice. Ideally, these interventions would induce a regenerative cellular phenotype, restoring tissue homeostasis and producing durable therapeutic outcomes.

Dr Andrés Caicedo and researchers at Universidad San Francisco de Quito (USFQ, Quito, Ecuador) have developed **GHEM** (**G**rowth **H**ormone, **E**pinephrine, **M**itochondria), a novel patent-pending three-step priming strategy to enhance the regenerative capacity of mesenchymal stem cells (MSCs) and generate a cell-free conditioned medium with potential regenerative applications. This *in vitro* system involves the conditioning of MSCs with factors that emulate a young system's response to damage signals in cells. This has been optimised to include the following established stimuli in three sequential steps:

1. Growth factor (growth hormone)
2. Epinephrine (emergency stimulus)
3. Artificial mitochondrial transfer (metabolic activity enhancer)



GHEM induces the release of a secretome of bioactive factors that may promote tissue repair and rejuvenation by combating processes of cellular decline, including inflammation, mitochondrial dysfunction, and senescence. This occurs by enhancing the proliferative capacity of the treated cells directly, but may also indirectly cause the treated cells to secrete regenerative substances that may further aid the rejuvenation process.

Promising preliminary results support GHEM

Laboratory research undertaken at USFQ has yielded encouraging preliminary findings that demonstrate the potential of GHEM technology. As shown in **Figure 1**, the treatment of MSCs with GHEM causes a suppression of mitochondrial activity. This is typically indicative of a shift in metabolic profile within cells and suggests that this three-step priming strategy is capable of altering the intrinsic metabolic properties of MSCs. This is particularly relevant since metabolism plays a critical role in the immunomodulatory properties of MSCs, as reviewed by Li and colleagues (Li, Dai and Li, 2023). In this case, the observed shift has been shown to provide MSCs with a more glycolytic profile exhibiting better immunoregulatory and regenerative activity in various diseases (Liu *et al.*, 2019).

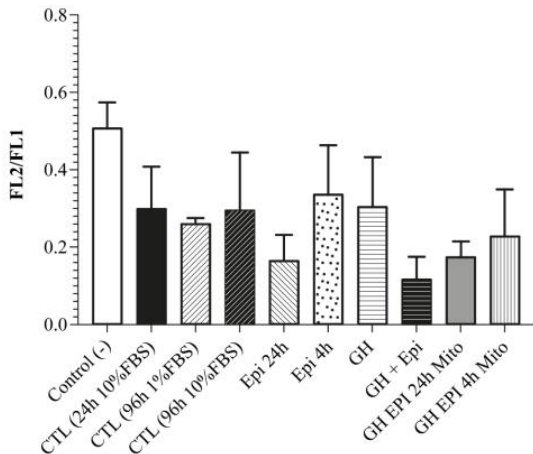


Figure 1. Mitochondrial activity is suppressed in mesenchymal stem cells treated with GHEM. Mitochondrial membrane potential assessed by flow cytometry following JC1 staining (mitochondrial membrane potential dye), FL2/FL1 represents the proportion of red JC1 stained mitochondria compared to green FL1 (inactive mitochondria). GH EPI 24h Mito and GH EPI 4h Mito conditions both exhibit reduced mitochondrial activity compared to appropriate non-GHEM treated controls.

This is further supported through assessment of cellular senescence in human fibroblasts treated with GHEM. The stimuli are shown to significantly reduce detected senescence levels (**Figure 2**), illustrating the potential that GHEM has to influence cellular processes associated with ageing. P21 and P53, two central regulators of the cellular senescence pathway, are also shown to be downregulated in response to GHEM stimulation. Together, these findings suggest that GHEM reduces cellular stress and senescence induction which may be contributing to improved fibroblast viability and function.

Since the GHEM method utilises an artificial mitochondrial transfer in MSCs, Andrés Caicedo and colleagues sought to determine the presence of membranous structures in the secreted conditioned media. Such structures have been shown to facilitate the transfer of mitochondria into donor cells, including tunnelling nanotubes (TNTs), dendrites and microvesicles. For instance, MSCs are reported to transfer mitochondria to damaged neural cells via TNTs to facilitate tissue repair (Babenko *et al.*, 2018), whilst MSCs also extrude mitochondria in MVs when under oxidative stress for uptake by macrophages to enhance their bioenergetics (Phinney *et al.*, 2015). Here, as depicted in **Figure 3**, no DNA-containing structures were detected in the media prior to lysis however after there was an increased presence of DNA-containing structures in media conditioned with GHEM. Although the assay could not directly determine vesicle release, the results are noteworthy as they may indicate secretion of such structures with potential regenerative implications for cells exposed to GHEM conditioned media.

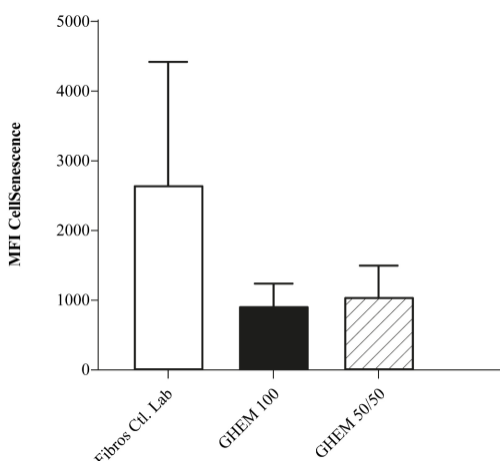


Figure 2. Human fibroblasts exhibit reduced senescence in 100% and 50% GHEM treated conditions. "CellSenescence™" marker quantified in fibroblasts treated with 100% GHEM or 50% GHEM plus 50% fresh medium. Senescence-marker intensity was assessed by flow cytometry.

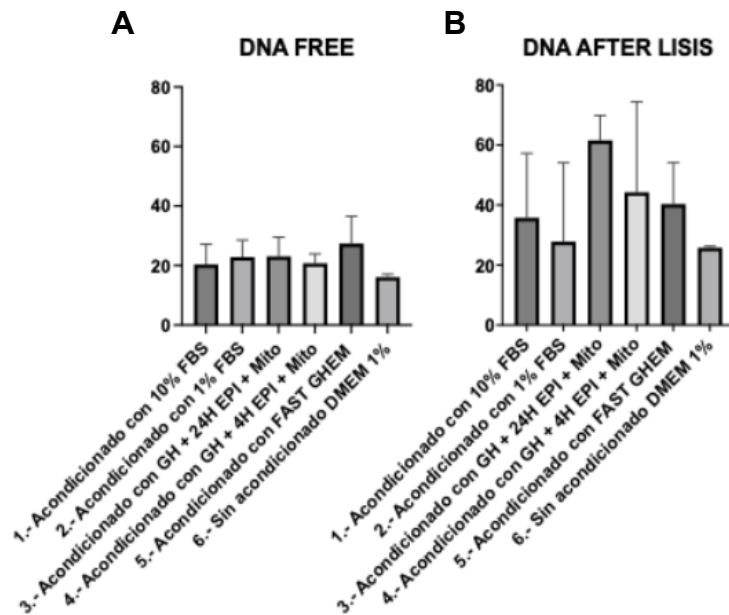


Figure 3. Increased presence of membranous structures with genetic material in GHEM conditioned media. Spectrophotometry and fluorometry assessed the presence of DNA containing structures within GHEM conditioned media after 48hr compared to non-treated control media. A) Free genetic material was absent prior to lysis buffer treatment. B) DNA release was detected following lysis. Significantly increased presence of membranous structures, potentially including extracellular vesicles, loaded with genetic material in media conditioned with GHEM relative to non-GHEM treated media.

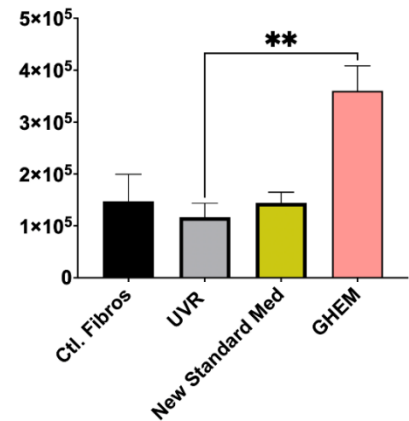


Figure 4. GHEM treated fibroblasts exhibit an enhanced proliferative capacity. Cell viability was determined in fibroblasts treated with GHEM for 48hr compared to appropriate controls.

Fibroblast viability was also investigated to compare the proliferative capacity of fibroblasts treated with GHEM, control media or exposure to ultraviolet radiation for 5 minutes (**Figure 4**). Notably, GHEM stimulation triggered significant proliferation of fibroblasts compared to the appropriate control conditions.

Taken together, the preliminary results suggest that factors secreted into the medium can influence cellular characteristics associated with ageing phenotype in target cell types, instead supporting cell proliferation and metabolic function. This is mediated, at least in part, through the attenuation of molecular signals associated with cellular ageing and P21-induced senescence, resulting in reduced cellular senescence and potential regenerative effect on the target cells.

Key benefits

- As a potential cell-free therapy GHEM could directly address the underlying cause of disease rather than simply alleviating the symptoms, acting as a form of personalised regenerative medicine
- The first methodology employing mitochondrial transfer to condition a MSC secretome with potential bioenergetic effect on the target cells
- Proliferative effects on dermal and epidermal cell lines, including following UV radiation exposure, highlighting its potential for applications in skin repair and rejuvenation
- GHEM provides a potential alternative approach to conventional stem-cell therapies, without requiring direct cell transplantation.
- Ability to potentially produce GHEM conditioned media cost-effectively as scale
- GHEM conditioned media itself can also be lyophilized for extended storage period and potentially more easily transported than live cells

Potential applications

- Cosmetics: e.g. as a serum topically applied to the skin to support tissue repair or rejuvenation
- Regenerative medicine: e.g. a treatment given orally or topically, i.e. for wound healing or stimulating hair growth

Cells conditioned using this method offer the potential for use in therapeutic applications, as well as in the production of enriched media that may promote tissue repair or rejuvenation in human subjects.

The USFQ GHEM technology is the subject of patent applications filed by USFQ. For more information or licensing interest, please contact PBL.