17 November 2020

ASX Code: MXC

Further successful results from cannabinoid treatment of glioblastoma progresses MGC Pharma towards clinical trials

ASX RELEASE

Key Highlights:

- Pre-clinical *in-vitro* research program into the use of cannabinoids in the treatment of glioblastoma delivers further successful results
- The research is specifically focused on the use of CBD (Cannabidiol) and CBG (Cannabigerol) in glioblastoma treatment following previous positive results in April 2020
- The formulations and data are key intellectual property owned by MGC Pharma
- Results are from an additional 18 patient tumour samples demonstrate the efficacy of MGC Pharma's proprietary CBD:CBG formulation in differing ratios
- The CBD:CBG formulation acted effectively in producing a cytotoxic effect on glioblastoma (GBM) cell viability by encouraging cell death (apoptosis) for GBM cells
- CBD is demonstrated to inhibit the tumours' viability and CBG is more efficient in setting off the cascade of biological processes leading to the apoptosis of glioblastoma cells
- Results also found combined cannabinoids were advantageous *vs* single treatment, recent investigations revealed the efficient formulations of CBD and CBG treatment effectively trigger a cytotoxic effect on GBM cells viability, leading to their killing effects
- The study demonstrates the additive effect between the ingredients, supporting the strategy of compounded products and the silver blanket methodology by Dr. Jonathan Grunfeld
- Most important are novel findings that CBG, the non-psycho-active cannabinoid has been poorly investigated so far as it has already shown in low doses to inhibit the invasion of GBM cells and GBM stem cells (GSC). The latter are known as the root of the disease progression and highly resistant to standard therapies
- MGC Pharma's research team reports that for the first time, increasing concentrations of CBG is efficiently setting off the cascade of biological processes leading to the apoptosis of the GSCs, opening new avenues for adjuvant therapies for this fatal type of tumour
- MGC Pharma and NIB will now move forward towards pre-clinical *in-vivo* studies, firstly on animals using the zebra fish model with the development of cannabinoids and curcumin nanoparticles formulation, and then to rodent studies and clinical trials in humans

MGC Pharmaceuticals Ltd (ASX: MXC, 'MGC Pharma' or 'the Company'), a European based bio-pharma company specialising in the production and development of phytocannabinoid-derived medicines, is pleased to announce further successful results from its ongoing-pre clinical research program focused on evaluating cannabinoid formulations in the development of a treatment of the most aggressive and therapeutically resistant brain tumour, glioblastoma ('GBM').

The pre-clinical *in-vitro* research program is being conducted in collaboration with the National Institute of Biology ('NIB') and the Neurosurgery Department at the University Medical Centre in Ljubljana, Slovenia and these results are from an additional 18 patient tumour samples collected between January and August 2020.

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The Results

We report here for the first time that CBG exerts a superior effect in impairing the major hallmarks of glioblastoma progression, i.e. fast proliferation and invasion, and particularly enhancing glioblastoma cell death. Moreover, CBG can destroy therapy-resistant glioblastoma stem cells, which are the root of cancer development and extremely resistant to various treatments of this lethal cancer. CBG should present a new yet unexplored modality of glioblastoma therapy that could replace Tetrahydrocannabinol (THC) as a more acceptable add-on or adjuvant treatment strategy. See Annexure A for additional information on the results.

The 18 samples (14 GBM lines and 4 GSC primary cultures) were successfully grown and tested. Frozen tissues and paraffin-embedded tissue sections deposited in national Gliobank also included comprehensive patients' clinical and molecular data on relevant GBM biomarkers. These included the 3 key receptors' mRNA status, CB1, TRPV1 and GRP55. GRP55 will be correlated to the patients' in-vitro GBM response to reveal their possible relevance in directing their adjuvant treatment by CBD/CBG formulations.

These results show that the use of CBD and CBG double the cytotoxic effect on glioblastoma cells. While CBD inhibits the tumours viability, CBG is more efficient in setting off the cascade of biological processes leading to the specific apoptosis pathways in glioblastoma cells. This is significantly more effective in glioblastoma stem cells – GSC's.

These results together with previously announced results (refer ASX release 22 April 2020), significantly progress the Company as they demonstrated efficacy of its new formulations in the treatment of glioblastoma, in particular the stem cells lines is considered to be this critical target in oncology therapy research.

This research will make the drug development and registration process streamlined and the program will be able to progress into a clinical trial. The cannabinoid formulations used in this collaborative research program are proprietary and are core to the intellectual property of MGC Pharmaceuticals.

Research into the treatment of glioblastoma using cannabinoids

The objective of the preclinical *in-vitro* research is to develop formulations to define the protocols for clinical trials for the treatment of high-grade brain tumours, i.e. glioblastoma, with cannabinoids. Glioblastoma is the most common primary brain cancer in adults accounting for approximately 75% of malignant brain tumors and one of the deadliest types of solid cancer overall. Survival rates after a diagnosis – 1 year – 38%, 2 years – 16%, 3 years – 9%, 4 years – 6%[1].

As early relapses are unavoidable despite standard-of-care treatment, the cannabinoids THC and CBD alone or in combination have been suggested as a combined treatment strategy for glioblastomas. However, the known psychoactive effects of THC hamper the medical applications of cannabinoids in general. Therefore, nontoxic CBG has been recently tested in some carcinomas and has exhibited anti-tumour properties.

Next steps

Following the completion of this testing phase, MGC Pharma in collaboration with NIB will design and develop a program to continue testing on animals using a zebrafish (ZF) model with the development of a cannabinoids and curcumin nanoparticles formulation. The Company is also planning rodent studies and a Phase II clinical trial in humans with submissions expected to be made in May 2021.

There are several advantageous features of the ZF brain tumour model, which represents *in vivo* brain environment that is highly analogous to higher animals and humans. This allows to screen for glioblastoma progression and for the drug effects on these tumours. The emerging ZF model(s) also facilitate nanomedicine formulation design and optimization prior to the rodent studies, needed for entry to Clinical Trials (Stieber et al. *Adv. drug delivery Reviews*, 2019, 152; Vittori et al., *Histochem Cytochem*., 2015, 63).

[1] Source: https://www.healio.com/news/hematology-oncology/20190703/despite-incremental-progress-longterm-survival-rates-have-not-budged-in-glioblastoma

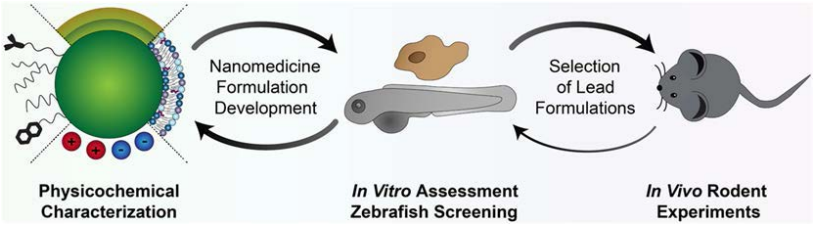

Image: *The ZF model offers imaging modalities, availability of genetic tools and disease/tumour models used for various applications in nanomedicine development. Additionally, as the whole experimental pipeline, including transplantation, drug exposure, and evaluation, can be performed in zebrafish embryos younger than 5 -11 days.*

Research program background

One of the general aims of the MGC Pharma research project is to develop formulations and to define the protocols for the treatment of high-grade brain tumours (glioblastoma) with glioblastoma stem cell antagonists, also including cannabinoids alone or as adjuvant therapeutics *in-vitro* with the goal of *in-vivo* translation to clinics. Further, the aim of this report was to assess the influence of natural cannabinoids THC, CBD and CBG on cell viability and apoptosis and testing if there is a correlation of cannabinoid receptors gene expression in the primary glioblastoma cells and glioblastoma cancer stem cells (GSC), derived from patients *vs* standard cell lines.

A key highlight of the research included the investigation of synergistic effects that compound-cannabinoid formulations may have on glioblastoma stem cells, as opposed to possible inferior efficacy associated with the use of single-cannabinoid preparations.

Roby Zomer, Co-founder and Managing Director of MGC Pharma, commented: "The results we have seen in our pre-clinical work on glioblastoma have continued to be very encouraging. We are constantly learning more about the therapeutic benefits of medicinal cannabinoids in the treatment of a number of medical conditions and are pleased to report that the Company will now begin preparations for the next stage of clinical trial work on glioblastoma."

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About MGC Pharma

MGC Pharmaceuticals Ltd (ASX: MXC) is a European based bio-pharma company developing and supplying affordable standardised phytocannabinoid derived medicines to patients globally. The Company's founders were key figures in the global medical cannabis industry and the core business strategy is to develop and supply high quality phytocannabinoid derived medicines for the growing demand in the medical markets in Europe, North America and Australasia. MGC Pharma has a robust product offering targeting two widespread medical conditions – epilepsy and dementia – and has further products in the development pipeline.

Employing its 'Nature to Medicine' strategy, MGC Pharma has partnered with renowned institutions and academia to optimise cultivation and the development of targeted phytocannabinoid derived medicines products prior to production in the Company's EU-GMP Certified manufacturing facility.

MGC Pharma has a number of research collaborations with world renowned academic institutions, and including recent research highlighting the positive impact of using specific phytocannabinoid formulations developed by MGC Pharma in the treatment of glioblastoma, the most aggressive and so far therapeutically resistant primary brain tumour.

MGC Pharma has a growing patient base in Australia, the UK and Brazil and has a global distribution footprint via an extensive network of commercial partners meaning that it is poised to supply the global market.

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ANNEXURE A

Additional information on the Results

Various ratios of MGC Pharma's cannabinoid formulations (THC, CBD and CBG) were tested on the nine GBM lines from patients' glioblastoma samples. These formulations were tested for cytotoxicity (viability) inhibition to define the optimum ratio of different cannabinoids.

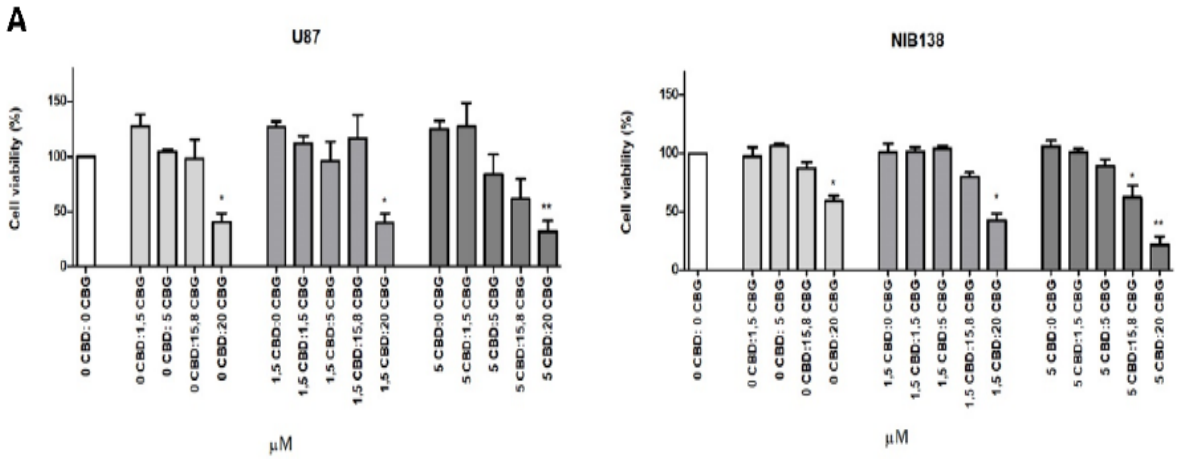
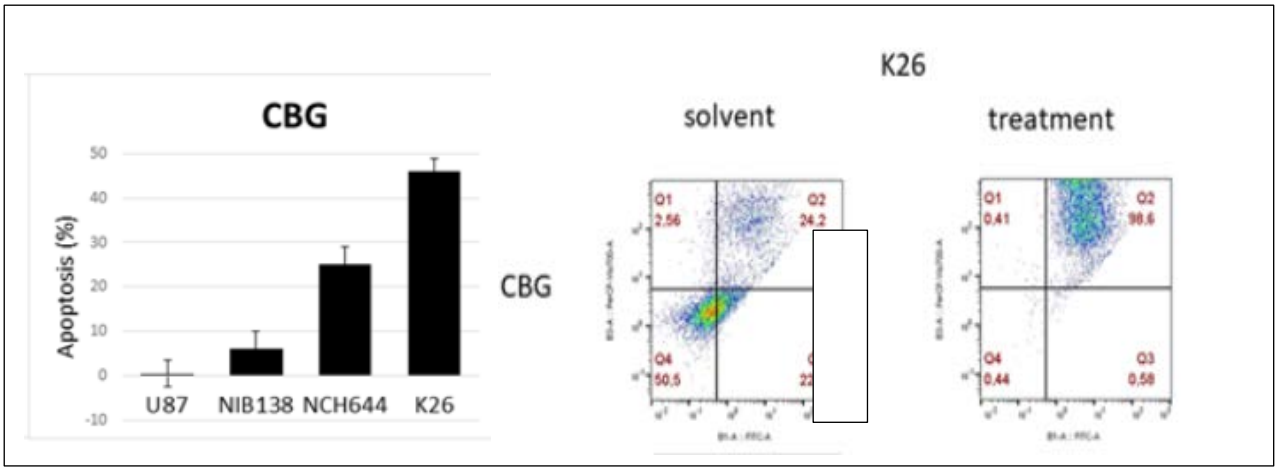


Figure 1. *The effects of combined CBD and CBG on the viability of primary glioblastoma (GB) cells (The efficacy of combined CBD and CBG treatment was tested on cell lines U8 and NIB138, The viability was determined by MTT assay after 48 h of single treatment, White bars represent the untreated controls, and the grey and black bars represent treatments with fixed concentrations of CBD (1.5 and 5 µM) increasing concentrations of CBG(0–20 µM) were added. Error bars represent mean ± S.E.M. (*p < 0.05, **p < 0.01, ***p < 0.001; one-way Anova test). Three biological and three technical repeats were performed. Vehicle comprised ≤ 0.4% (v/v) DMSO for CBD and 0.24% (v/v) ethanol for CBG. (B) The combination responses were determined as factor of inhibitory concentration (FIC) values between CBD and CBG.*

The CBG is more effectively inducing death rate of patients derived glioblastoma stem cells, NCH644 and K26 than that of differentiated GBM cells U87 and NIB 138 cells, at the concentrations where the viability of the cells is 50 % inhibited. This suggests that GSC are highly sensitive to CBG induced cell death. Lower panels demonstrate that GBM cell apoptosis pathways are involving proteolytic activation of the enzyme caspase 3, translocating to the nucleus, where this enzyme is assisting DNA degradation, resulting cell death.



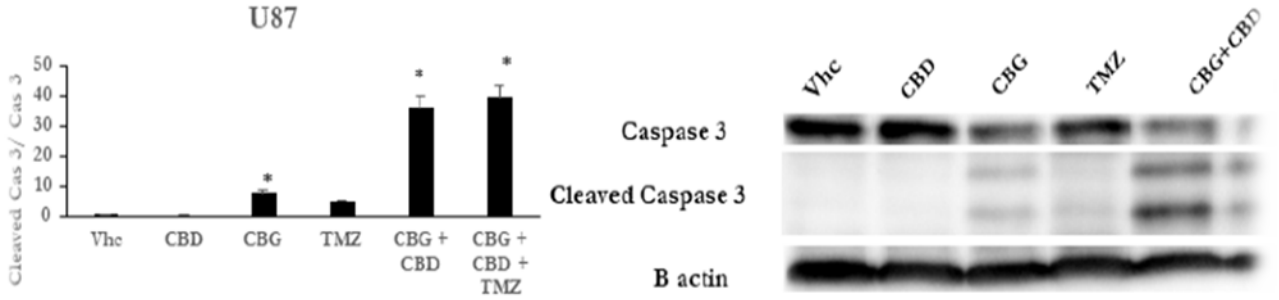


Figure 2. Upper left panel: *The cells were treated at IC50 concentrations of CBG viability inhibition for 48 hours and labelled with Annexin V-FITC and propidium iodide for apoptosis analyses by flow cytometry.* ***(A)*** *The graphs represent the percentage of cells in early and late apoptosis after cannabinoid treatment (mean ± S.E.M.).* ***(B)*** *Flow cytometry analysis of apoptosis in GSC line K26 (right) after CBG treatment. Most K26 cells after treatment were in the late apoptotic state.*

Lower panel *shows that CBG induces caspase-3 cleavage in GB cell line U87. Western blot analysis and densitometric quantification of caspase-3 protein levels. Caspase-3 densitometric values were normalized to B actin, which was used as a loading control. Cleaved caspase-3 densitometric values were normalized to caspase-3. Representative blots are depicted, and three separate experiments were performed. *p < 0.05 treated vs untreated cells*