

Successful research results for MGC cannabinoid formulation on one of the most aggressive cancers, glioblastoma

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MGC Pharmaceuticals Ltd (ASX: MXC, 'MGC' or 'the Company'), a European based 'Seed to Medicine' bio-pharma company specialising in the production and development of phytocannabinoid-derived medicines, is pleased to announce successful research results from the ongoing pre-clinical research program that supports and directs novel cannabinoid formulations in the development of treatment for glioblastoma multiforme ('**GBM**'), the most aggressive, and so far therapeutically resistant, primary brain tumour.

This 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. These results, from the ongoing research program as originally announced to the ASX on 24 July and 29 July 2019, deliver another significant step for the Company as it continues its research to pioneer the use of cannabinoid compounds for effective treatment on cancerous cells.

The cannabinoid formulations used in this collaborative research program are proprietary and are core to the intellectual property of MGC Pharmaceuticals.

Key Highlights

- This pre-clinical research focuses on the development of cannabinoid formulations specifically tailored for the effective treatment of high-grade brain tumours
- Recent data from NIB, conducted on 14 additional GBM tumour tissue samples, support and direct novel cannabinoid formulations in the treatment of glioblastoma
- Results to date on brain tissue samples from a total of 24 patients (including the 10 patients reported on in July 2019) confirm that the cannabinoid preparations can successfully inhibit tumour cell viability and cause a significant percentage of glioblastoma cells to undergo "programmed cell death" i.e. apoptosis, after a short time following application
- Results supporting the multi compound cannabinoid formulations (the "**small entourage**") are more effective than single cannabinoid preparations and importantly are the intellectual property of MGC Pharmaceuticals
- Importantly, MGC cannabinoid formulations are shown to be able to target glioblastoma stem cells that are considered to be the "roots" of the disease and the critical target in oncology therapy
- The study has introduced the use of CBG (Cannabigerol), an additional non-intoxicating cannabinoid as an anti-cancer agent; CBG is enriched in younger cannabis plants and demonstrates therapeutic characteristics
- New research data has shown adding CBG to CBD can 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 apoptosis of glioblastoma cells
- Effective power of CBG and CBD shown to induce apoptosis is sufficient without a need for THC, thus enabling the development of a therapeutic intervention devoid of psychotropic effects
- Research also shows CBG termination effects specifically on glioblastoma stem cells, which tend to be extremely resistant to irradiation and chemotherapy treatments

MGC Pharma – NIB Glioblastoma Cancer Study Introducing CBG to Formulation

The updated MGC Pharma – NIB Reporting Study research (**‘the Study’**) published by NIB has introduced the use of Cannabigerol (CBG) to effectively treat glioblastoma. 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 (GB), with cannabinoids.

CBG is a less recognized cannabinoid compared to Tetrahydrocannabinol (THC) and Cannabidiol (CBD), which has been in research and development for a variety of different cancers, including glioblastoma. CBG is one of the less investigated naturally occurring phytocannabinoids, which possesses promising therapeutic features and is devoid of undesirable psychotropic effects which characterize some of the other members of this family of active molecules.

As the majority of preclinical and animal research (Velasco, 2019, rev in Abrams, 2019) and all the Clinical Trials (ACTRN12617001287325, NCT03529448) to date, including the MGC/NIB previous research, are focused on THC:CBD ratios, the wider clinical application of these preparations is hindered due to the psychotropic effects of THC. This often limits the clinical use of THC and CBD mixtures in glioblastoma patients as many will already present with adverse neuropsychiatric symptoms such as impaired cognition. Consequently, recent clinical practice tends to be restricted to the use of CBD alone, despite its apparent minimal impact on survival (Likar, 2019). Furthermore, the exclusive use of CBD is currently subject to critical evaluation in the context of oncology, due to the posited immunosuppressive effect which has been suggested to hinder the natural immune response to the presence of the tumours and thus interfere with their therapy. Hence the contemporary preference is to moderate the doses of CBD to the extent possible, while still retaining its desirable effects.

The MGC research team is now seeking to address these issues, by adding CBG to CBD to avoid the immunological side effects of the latter, while enhancing its desirable impact on the viability of the glioblastoma cells in conjunction with the previously reported effect of CBD (GB cells; Figure 1 and 2). We have not only tested the standard cell lines (e.g. U87-MG) but also a panel of 14 patient-derived cancer cells, which were established from fresh patient’s tumour sample and tested for their sensitivity of CBD and CBG mixtures in 1.0-100 µMolar range.

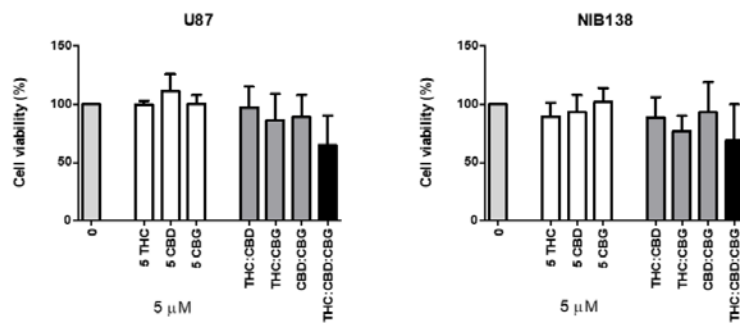


Figure 1: Cell viability of U87 line and NIB138 GB cells after CBD, THC and CBG combination treatments, this represents mono controlled group for the cannabinoids’ matrix research

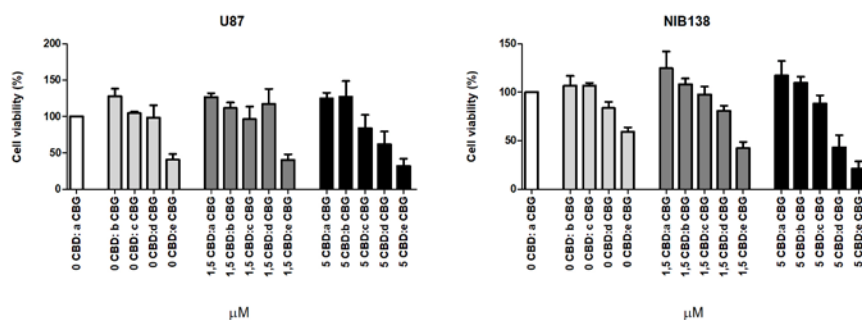


Figure 2: Shows cell viability inhibition of model GB cell line U87 and NIB138 GB cells after CBD^M and CBG^M combination treatments. Solvent control comprised of solvent dimethyl sulfoxide and ethanol was compared to each of the mono ingredients.

Below, we show results demonstrating that CBG is also affecting the survival of glioblastoma stem cells. This observation is of importance since these are the cells that tend to survive the initial treatment and then multiply and lead to tumour recurrence. Although these cells lines are extremely resistant to irradiation and chemotherapy, they appear to be sensitive to CBG, as shown in our experiments which demonstrated the death of one third of the cells which were exposed to a milieu with a concentration of circa 50 μ Molar of CBG. The resistance of cancer stem cells to CBD/THC has been previously reported by MGC (on 24 and 29 July 2019) and suggested in a few published reports (Dimitru, 2019).

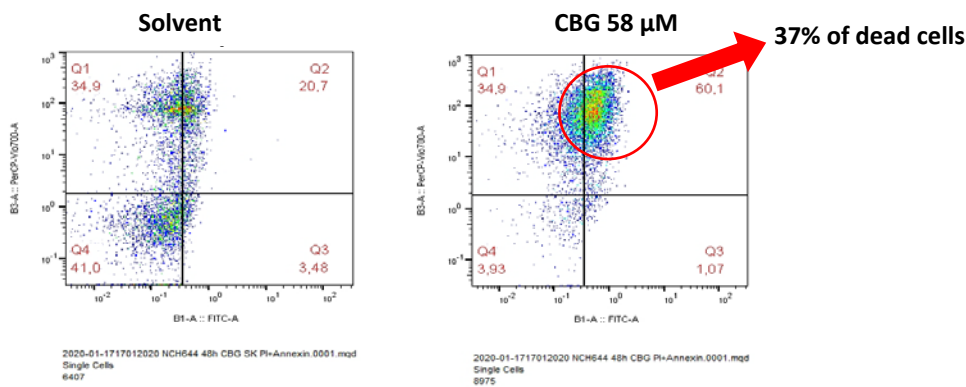


Figure 3: shows that a Glioblastoma stem cells line (top right: NCH644 cells) 48h after addition of 58 μ Mol of CBG, 37 % of the cells were dead

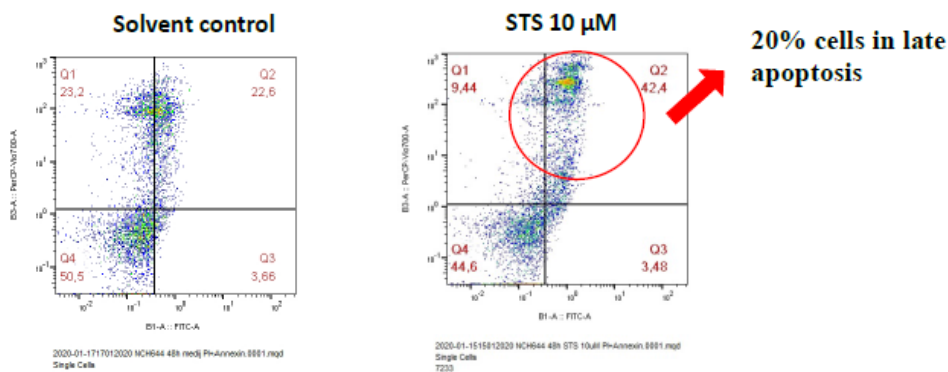


Figure 4: Staurosporine (STS; Sigma-Aldrich) treatment (10 μ M, 4h) served as a positive control for apoptosis. NCH644 cells were cultured with STS (10 μ M) for 4h, stained with Annexin V conjugated to FITC and followed by staining with PI and analyzed by flow cytometry using the MACSQuant[®] Analyzer. Ethanol was analyzed as solvent control. 20% of the cells were in late apoptosis

Research Program Background

To initiate the study in 2019, the research, which is covered by the approval of the National Ethical Committee of Slovenia at the Ministry of Health of the Republic of Slovenia, was issued for the wider scope of Slovenia-Italy INTERREG Project TRASGLIOMA. This is coordinated by Medical Faculty of University of Ljubljana, Prof. Radovan Komel, where NIB (Prof. Tamara T. Lah), is the key partner, responsible for holding and managing the brain tumour bank GLIOBANK. One of the general aims of the 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, with MGC supports also including cannabinoids alone or as adjuvant therapeutics *in-vitro* with the goal of *in-vivo* translation to clinics. The aim of this further 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 (GB) cells and GB cancer stem cells (GSC), derived from patients vs standard cell lines.

Individualized, informed treatment of patients is an emerging trend in medicine and the work for this research included testing cannabinoid preparations in compositions that can be adjusted to individual patients. In this instance it involves the testing of fresh tumour tissues, obtained from patients after therapeutic surgical removal of the tumour, to determine the optimal cannabinoid preparation for the effective treatment of the remaining cancer - either alone or in combination with the chemotherapeutic temozolomide that is used in the patients with a suitable epigenetic set-up.

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 inferior efficacy associated with the use of single-cannabinoid preparations.

Program Next Steps

Following this study, pre-clinical studies will continue *in-vitro*, using a four-dimensional matrix designed to find the most efficient cannabinoid preparation. This will guide the company in determining the content of cannabinoids and their ratios in its pursuit of the most efficient formula purposed to inhibit the viability of patients-derived glioblastoma cells and/or their stem cells. Subsequently this will assist us to move to Clinical Studies through Phase I and potentially Phase II, at which time the results will be reviewed by an ethics committee. Based on the information yielded by the platform that this pre-clinical study is setting up, it is expected that clinical laboratories will be able to determine the optimum cannabinoid composition to be administered to individual patients during (postoperative) adjuvant therapy *in vivo*, in a random clinical (RTC) study. Based on the response of the patient derived glioblastoma cells and stem cells, it should be possible to offer the oncologist a rational basis for selecting combinations of cannabinoids intended to reduce the tumour volume.

To take the project a step further towards approval of clinical studies in humans a study for further consolidation of individualized recommendation of cannabinoid formulations is proposed as follows: it is designed to produce data on the basis of a matrix of patient-tumour response *in-vitro* to particular formulations/dose and identification of cannabinoid receptors. This would employ methods of direct transplantation of the patient-derived tumour cells (xenograft) into animal brain. Following the tumour growth *in-vivo*, cannabis formulations will be identified based on the results of their application alone and in the combination with standard therapy for glioblastoma. To assist with medical agency approval of use of the formulations for human studies tumour volume (MRI) and survival rate would be measured.

Roby Zomer, Co-founder and Managing Director of MGC Pharma, commented: “These are further exciting results for the cannabinoid research programs that our Company is pioneering. Further research, using the *in-vitro* diagnostic platform on a glioblastoma patient’s tumour cells will focus on the most effective CBG and CBD combination doses and doses of cannabinoids to approach individualized, informed treatment of patients, avoiding unwanted effects of THC. These formulations are core to the intellectual property and the intrinsic value we are developing for our Company and our shareholders.”

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About MGC Pharma

MGC Pharmaceuticals Ltd (ASX: MXC, OTCQB: MGCLF) 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 'Seed 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 recent research conducted in collaboration with the National Institute of Biology and University Medical Centre Ljubljana, highlighted the positive impact of using specific phytocannabinoid formulations 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, Brazil and Ireland and has a global distribution footprint via an extensive network of commercial partners meaning that it is poised to supply the global market. In order to meet the demands of becoming a key global supplier the company is constructing a large scale GMP state of the art facility in Malta.

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