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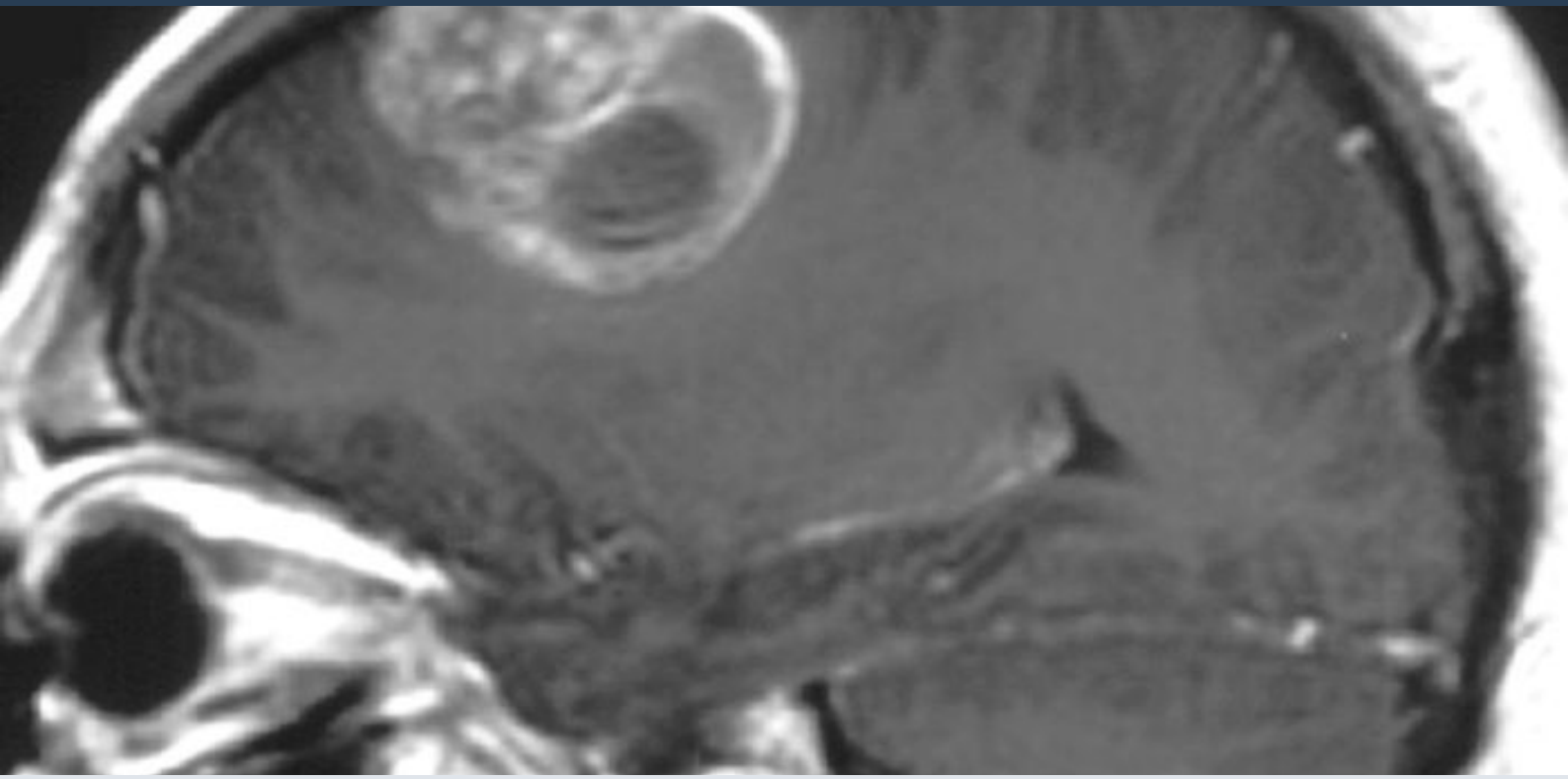
Next-generation Temozolomide: Repair Resistance DNA-Targeted Anti-cancer Agents with Broader Spectrum Activity

Three novel TMZ analogues that possess in vitro anti-tumour activity superior to TMZ in GBM and colorectal carcinoma



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IP Status

Patented

Seeking

Licensing, Seeking investment, Development partner

About **University of Nottingham**

The University of Nottingham produces world-changing research by focussing on the problems and challenges that affect societies and people on a wide scale. More than 80% of Nottingham research is ranked in the highest categories ‘world-leading’ or ‘internationally excellent’.

Background

Glioblastoma multiforme (GBM; grade IV astrocytoma) is the most prevalent and aggressive adult primary brain tumour. Standard of care includes surgery, radiotherapy and adjuvant cytotoxic therapy temozolomide (TMZ), conferring a median survival time of 14.6 months. The therapeutic benefit of TMZ depends on its ability to damage DNA and trigger the death of tumour cells. Although TMZ offers some hope to GBM patients, a best 5-year survival rate of 9.8% is achieved.

Tech Overview

A key limitation of TMZ is the repair of TMZ-induced DNA damage by the DNA damage repair protein methylguanine-DNA methyl transferase (MGMT) or by deficient mismatch repair (MMR) which are associated with inherent and acquired resistance to TMZ treatment. This not only limits effective therapy in the majority of GBM patients (~47%) but also restricts TMZ's utility to a very small number of other tumour-types.

Nottingham researchers have synthesised three novel N3-propargyl, C8-substituted TMZ analogues which overcome MGMT+/MMR resistance and possess *in vitro* anti-tumour activity superior to TMZ in GBM and colorectal carcinoma (CRC) cell lines. DMPK package expected autumn 2017.

New variants based on the TMZ bicyclic scaffold are also being synthesised with key alterations in two positions:

- 3-position: anti-tumour activity
- 8-position: pharmaceutical properties

Benefits

Academics at the University of Nottingham are developing a successor molecule to TMZ that:

- Has an activity profile at least equivalent to TMZ in TMZ-sensitive tumours
- Is active in TMZ-resistant tumours, by overcoming MGMT-mediated resistance.
- Retains other favourable pharmaceutical characteristics of TMZ (Orally available so can be used on out-patient basis, acceptable side effect profile)

Applications

The intended application is as an improved treatment for Glioblastoma particularly for tumours that display MGMT mediated resistance, both innate and acquired.

Opportunity

The University is seeking partners for further preclinical and clinical investigations with view to licensing or investment.

Patents

- The compounds are covered by granted patents entitled “3-substituted-8-substituted-3H-Imidazo[5, 1-D] [1,2,3,5]Tetrazin-4-One Compounds And Their Use” in the US (US9024018) and Europe (EP2445915).