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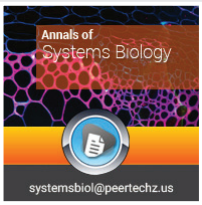

LIFE SCIENCES GROUP

ANNALS OF Systems Biology OPEN ACCESS JOURNAL

ISSN: 2692-4765 DOI: https://dx.doi.org/10.17352/asb

Opinion

The potential use of O^6-Benzylguanine, and O^6-Methylguanine for the treatment of Alzheimer's Disease, and T. brucei group trypanosomes infections

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Received: 01 August, 2022
Accepted: 12 August, 2022
Published: 13 August, 2022

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Very recently we had published a paper entitled 'The Potential Development Sulfonylhydrazines for the Treatment of Alzheimer's Disease' [1]. Our paper was a development from an observation by others from 1997, where a remarkable remission in Dementia was observed in cancer patients following treatment with the chemotherapeutic agent BCNU (Carmustine, 1,3-Bis(2-chloroethyl)-1-nitrosourea) [2].

Our laboratory had considerable experience in the synthesis, development and evaluation of chemotherapeutic agents [3]; our aims were to produce less toxic, and more highly effective agents by selectively generating the efficacious electrophiles (or functional analogues thereof), while minimizing the production of unwanted reactive species. The nitrosourea BCNU generates a wide range of reactive electrophiles including species that 2-chloroethylate, 2-hydroxyethylate, vinylate, aminoethylate, and carbamoylate biomolecules including targets in DNA. The species that 2-chloroethylate the O-6 position of DNA guanine are responsible for the anticancer activity of BNCU, while the other species largely contribute to the toxicity of BCNU. Unlike the nitrosoureas, our sulfonylhydrazine drugs possess substantial design flexibility and tolerance for structural modification [3]. This flexibility allows the synthesis of agents, which generate individual or combinations of identical or similar electrophiles to those produced by the nitrosoureas [1]. Exploiting this flexibility we developed the anticancer agent 101m [4] which exhibited a therapeutic index (LD_{50}/ED_{50}) against L1210 leukemia in female CD_2F_1 mice [5] that is more than double the value of the best of over 300 nitrosoureas tested [6,7]. We reasoned that this same strategy could be used to produce a superior anti-Alzheimer's agent, that possibly even lacks any major toxicity depending upon which reactive species was found to be responsible for the anti-Alzheimer's activity [1]. Unfortunately our laboratory was closed down in 2016 and all work on this project ceased.

Very recently (June 30th 2022) MGMT (O^6-methylguanine-DNA methyltransferase) expression was linked to a lower risk of developing Alzheimer's disease [8]. On reading this I immediately realized that MGMT activity elevation was the action caused by BCNU that resulted in its anti-dementia/anti-Alzheimer's activity. MGMT is the major defense mechanism against the species that O-6 alkylate DNA guanine [9]. Furthermore, MGMT expression is induced 2-3 fold in response to the alkylation of the O-6 position of DNA guanine [10]. MGMT is a suicide enzyme that can only repair a single DNA lesion per MGMT molecule [11], and the spent enzyme results in the stimulation of MGMT expression [10]. This would imply that relatively low toxicity methylating sulfonylhydrazines, or the clinically approved anticancer agent temozolomide, would have anti-dementia/anti-Alzheimer's activity. However, an even better approach would be to use low doses of a nontoxic MGMT inhibitor, such as O^6-Benzylguanine, or O^6-Methylguanine, to induce MGMT activity. These agents are

Citation: Penketh PG, Baumann RP, Shyam K (2022) The potential use of O^6-Benzylguanine, and O^6-Methylguanine for the treatment of Alzheimer's Disease, and T. brucei group trypanosomes infections. Ann Syst Biol 5(1): 010-011. DOI: https://dx.doi.org/10.17352/asb.000018

non-toxic [12] in the absence of co-treatment with agents that alkylate the O-6 position of DNA guanine [12]. These MGMT inhibitors would generate spent MGMT from MGMT, inducing 2-3 fold higher MGMT levels [10]. This would be analogous to a little sun exposure to build up sunburn resistance. If a patient was treated with a very low dose of O^6-Benzylguanine or O^6-Methylguanine (optimized to maximized de novo MGMT synthesis) this would elevate the MGMT levels (and give rise to an anti-Alzheimer's effect) but in the absence of any significant toxicity [12]. The speculative mechanism by which methylating/alkylating agents give rise to anti-dementia/anti-Alzheimer's activity, likely relates to a hormetic like response [13]. In the hormetic response the stress caused by actual, or perceived, damage to a cell results in the activation of cellular repair and maintenance programs. We suspect that the generation of spent MGMT acts as a measure of cellular damage by cells, and turns on programs resulting in repair, maintenance, and differentiation.

Furthermore, O^6-Benzylguanine or O^6-Methylguanine could potentially have another very interesting application; 35 years ago we observed that methylating sulfonylhydrazines, and agents such as temozolomide induced terminal differentiation in bloodstream T. brucei group trypanosomes [14,15]. We recently published a small review on this topic [16]. If this methylating agent action was also activated by a similar spent MGMT mediated mechanism, O^6-Benzylguanine or O^6-Methylguanine could potentially be low toxicity trypanocidal agents, working by the induction of terminal differentiation.

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