Results: We observed a significant decline in cell proliferation after treatment with γ-secretase inhibitors, and in combination with RT and temozolomide. In addition, we observed a comprehensive targeting of Notch pathway, both at canonical and non-canonical levels. All these phenotypic effects were augmented with a synergy of these inhibitors with both RT and temozolomide. Lastly, we observed context-specific effects of targeting Notch receptors on cell proliferation, invasion, EMT, and their cross-talk with other radioresistance pathways.
Conclusion: Targeting notch pathway modulates the vital cellular processes that are implicated in the tumorigenesis of the gliomas. All these endeavors may lead to better treatment outcomes for the patients. Further studies to authenticate the druggability of notch effectors and their interacting partners should be investigated to determine if this combinatorial targeting could be used to design personalized therapeutic interventions for GBM patients.
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Ionizing Irradiation Mitigator GS-Nitroxide (JP4-039) is Deliverable in an I.M. Formulation Suitable for Self-Administration

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Purpose/Objective(s): Effective mitigation of ionizing irradiation toxicity in the civilian or military setting must be rapidly deployable in a formulation suitable for self-administration. The mitochondrial targeted GS-nitroxide (JP4-039) has been demonstrated to be highly effective in total body irradiation (TBI) mitigation in animal models (Rwigema, IJROBP, 80(3): 860-869, 2011, Goff, In Vivo, 25: 315-324, 2011, Steinman, Radiation Research, 189(1): 68-83, 2018), and is effective when delivered as late as 72 h after TBI. The drug has been shown to mitigate ionizing irradiation damage to the bone marrow and the gastrointestinal tract, and it is effective in organ specific (partial body) irradiation protection and mitigation (Berhane, Radiation Research, 182: 35-49, 2014, Shinde, Radiation Research, 185: 134-150, 2016). JP4-039 has also been shown to be effective for mitigation and treatment of beta irradiation (fallout) skin damage (Brand, J Investigative Derm, 137(3): 576-586, 2017). Pharmacokinetics (PK) experiments demonstrated clearance of JP4-039 after I.V. administration with a half-life of 10 min when administered I.V. (Christner, J Pharm & Biomed Analysis, S0731-7085(17): 32605-5, 2017).
Materials/Methods: We evaluated the feasibility of intra-muscular injection of JP4-039 in each of three commercially available formulations (Captisol, 2-hydroxypropyl-B-cyclodextrin (Cyclodextrin), and Miglyol-812-N). C57BL/6J male and female mice received the LD50/30 TBI dose of 9.25 Gy, and 24 h later were administered 10 mg/kg JP4-039 in 100 μmL I.M. formulation.
Results: Significant radiation mitigation was demonstrated when JP4-039 was administered in each formulation (Table) (n=12 per group). There was no significant mitigation seen in mice given each formulation alone (n=12 per group).
Conclusion: Satisfactory stability of JP4-039 in the most straightforward formulation using Miglyol-812-N was observed at room temperature, and this must now be assessed over a wide range of temperatures and storage intervals. The effectiveness in I.M. administration makes JP4-039 suitable for both civilian and military applications.

Abstract SU_40_2393; Table 1

Survival Increase After Total Body Irradiation (TBI)	
Formulation	LD50/30 Survival Increase at Day 30 After 9.25 Gy
Miglyol-812-N/JP4-039	p = 0.0088
Cyclodextrin/JP4-039	p = 0.0015
Captisol/JP4-039	p = 0.0247

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The Impact of Tianeptine in the Prevention of Radiation-Induced Neurogenesis Inhibition

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Purpose/Objective(s): Cranial radiotherapy (RT) is a frequently used treatment option, but its neurocognitive side effects emerge as a serious problem. Radiation inhibits hippocampal neurogenesis by induction of apoptosis and by decreasing the proliferation in the hippocampus. Tianeptine is an antidepressant drug and has been shown to induce hippocampal neurogenesis by reducing apoptosis and by providing a protective effect on proinflammatory cytokines. We aimed to demonstrate the effect of tianeptine on the inhibition of hippocampal neurogenesis and the apoptosis due to RT.
Materials/Methods: Fifty six Wistar Albino rats were divided into 4 groups consisting of a control (n = 14), tianeptine (n = 14), RT (n = 14) and tianeptine + RT (n = 14) groups. Tianeptine and RT+tianeptine groups were administered tianeptine by oral gavage 3 weeks before the first sacrification and until day 120. Groups consisting of RT protocols received 10 Gy cranial RT. Hippocampal samples from the rats in each group were collected at 5^{th} hour (early effects) and 120^{th} day (late effects) after the RT. Morphological and immunohistochemical examinations were performed to detect cell proliferation with Ki67, apoptosis with TUNEL and immature neurons with doublecortin (DCX) selective antibody.
Results: At 5^{th}-hour post-RT, there was no statistically significant difference between the RT+tianeptine and the RT groups in terms of Ki-67(+) cell counts ($p = 0.246$). Ki67(+) cell count in the RT group was reduced compared with the control group ($p<0.001$). The difference in the number of DCX(+) cells between RT and RT+tianeptine groups was not statistically significant ($p = 0.39$). In the RT group, however, the number of DCX(+) cells was lower than the control group ($p <0.001$). In the RT group, more TUNEL (+) cells were observed than RT+tianeptine and the other groups, and the difference was statistically significant ($p <0.001$). There was no statistically significant difference between groups in terms of Ki67(+) cell counts at 120 days post-RT ($p = 0.1$). The number of DCX (+) cells in the RT group was lower than the control group ($p <0.001$), but there was no statistically significant difference in the number of DCX (+) cells between RT and RT+tianeptine groups ($p = 1$). In the RT group, more TUNEL (+) cells were observed than RT+tianeptine and the other groups, and it was statistically significant ($p <0.001$).
Conclusion: To the best of our knowledge, this is the first study in the literature examines the effect of tianeptine on neurogenesis induction observed in hippocampus due to RT. Our study showed that there is an increase in hippocampal apoptosis and a decrease in neurogenesis due to RT. Tianeptine reduced RT-induced apoptosis but did not have a statistically significant effect on neurogenesis. However, we believe that the effect of tianeptine on neurogenesis may be more pronounced in lower doses of cranial RT because of the fact that it has relieved inhibition of neurogenesis following 10 Gy cranial RT.
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