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Letters to the Editor

Targeting tyrosine receptor kinase B in gliomas

We read with great interest the recent article by Ni et al.[1] on the role of the tyrosine receptor kinase B (TrkB) as a drug target for the treatment of astrocytomas. Among central nervous system tumors, astrocytomas are the most frequent type of glioma, and grade IV astrocytoma (also called glioblastoma) is the most aggressive type of primary brain cancer. As pointed out by the authors, signaling triggered by TrkB, which is activated by its endogenous ligand, the neurotrophin brain-derived neurotrophic factor (BDNF), plays a crucial role in normal development and plasticity of the central nervous system,[2] but increasing evidence also indicates a role for BDNF/TrkB upregulation in different types of cancer.[3,4] By systematically screening a library of human tyrosine kinases for their oncogenic potential in astrocytoma formation and then characterizing functional features and molecular mechanisms associated with TrkB-induced oncogenesis, Ni et al. have provided compelling findings indicating that TrkB can play a role in astrocytoma formation.[1]

It is worth pointing out that previous studies not cited by Ni et al.[1] had already identified an increase in TrkB expression in both low-grade astrocytoma and glioblastoma,[5,6] and a role for TrkB signaling in the growth of gliomas and other types of brain tumors or peripheral tumors of possible neural origin has been previously proposed. For example, BDNF-induced activation of TrkB increases the viability of brain-tumor stem cells (BTSCs) isolated from gliomas through activation of the extracellular-regulated kinase (ERK) and Akt pathways, whereas TrkB knockdown or pharmacological inhibition reduces BTSC growth and BDNF-dependent ERK activation.[7] Another recent study has suggested that glioma growth may be regulated by TrkB expressed in exosomes.[8] We have recently provided evidence for a potential role of TrkB inhibition as a strategy to reduce cell proliferation and potentiate the effects of chemotherapy in medulloblastoma[9] and Ewing sarcoma.[10]

In order to investigate the antitumor effects of pharmacological inhibition of TrkB-associated signaling, Ni et al. used the compounds AZD1480, a janus kinase (JAK) inhibitor, and RXDX-101, which nonselectively inhibit different members of the Trk receptor family (TrkA, TrkB, and TrkC), C-ros oncogene 1 (ROS1), and the anaplastic lymphoma kinase (ALK).[1] Thus, they did not assess the effects of selective TrkB blockade, and

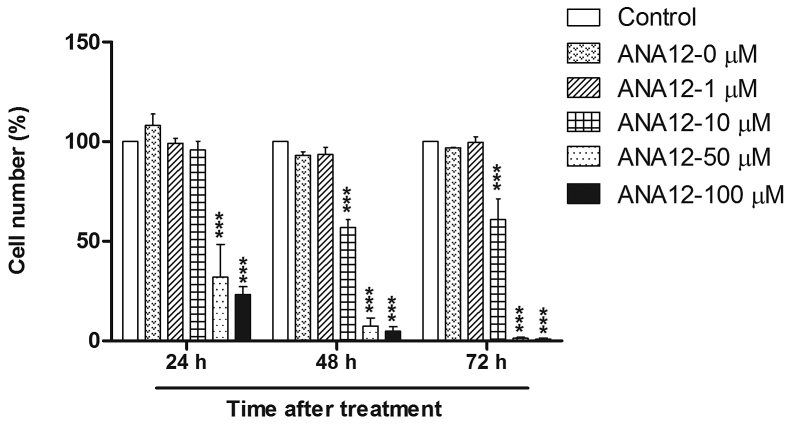

Fig. 1 Selective tyrosine receptor kinase B (TrkB) inhibition reduces the viability of human glioma cells. A172 cells obtained from the American Type Culture Collection (Rockville, Maryland) were cultured in Dulbecco's modified Eagle's medium (DMEM) low glucose supplemented with 10 % (v/v) fetal bovine serum (FBS) and 1% (v/v) penicillin/streptomycin. Cells were incubated in a humidified atmosphere of 5 % CO_2 at 37 °C, were seeded at a density of 5 x 10^3 cells/well in 96-well plates and allowed to grow for 24 hours. The medium was replaced for treatments with increasing concentrations of ANA-12 (1, 10, 50, or 100 μM). Control cells were exposed to vehicle (dimethylsulfoxide, [DMSO], 1.6 %) alone, and cells in the ANA-12 0 μM group were not exposed to either vehicle or drug as an additional control showing that the vehicle had no effect by itself. Cell viability was assessed by trypan blue cell counting 24, 48, and 72 hours after treatment. Data normalized to control cells are presented as means ± SEM and represent 2 independent experiments performed in quadruplicate; *** $P < .001$ compared with control cells exposed to vehicle alone (2-way ANOVA followed by Bonferroni's post hoc tests). All experimental procedures were approved by the institutional research ethics committee (GPPG HCPA number 1406–22).

the effects they observed could be influenced by inhibition of other types of Trk receptors or signaling molecules downstream of Trk. We have recently started a series of experiments aiming to verify whether specific TrkB inhibition reduces glioma cell proliferation using ANA-12, a small-molecule selective TrkB antagonist. Our first results showed that ANA-12 effectively and dose-dependently reduces the viability of a human glioblastoma cell line with almost complete disappearance of cultured cells 72 hours after treatment (Fig. 1). Therefore, selective TrkB inhibition might prove to be an effective experimental therapeutic strategy, possibly with fewer off-target toxicities compared with multitarget drugs in patients with astrocytomas harboring oncogenic TrkB.

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GlioVis data portal for visualization and analysis of brain tumor expression datasets

We are currently living in the "genomic era." In the last decade, high-throughput genomic analyses have generated massive quantities of data that can be used to explore gene function in specific biological settings. In the field of cancer research, studies performed in a variety of laboratories and by a number of large-scale projects, like The Cancer Genome Atlas (TCGA, http://cancergenome.nih.gov/, accessed October 31, 2016) and the International Cancer Genome Consortium (ICGC),[1] have given researchers an unparalleled amount of information on many different tumors through several platforms such as: mRNA expression arrays, comparative genomic hybridization arrays, DNA methylation arrays, exome sequencing, RNA sequencing, reverse protein phase arrays, and clinical parameters.[2] Consolidating these data