Editorial

Rogue one: another faction of the Wnt empire implicated in assisting GBM progression

Riasat Ahsan, Shivani Baisiwala, Atique U. Ahmed

The Department of Neurological Surgery, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA

Correspondence to: Atique U. Ahmed. The Department of Neurological Surgery, Feinberg School of Medicine, Northwestern University, 303 East Superior Street, Chicago, IL 60611, USA. Email: atique.ahmed@northwestern.edu.

Comment on: Hu B, Wang Q, Wang YA, *et al.* Epigenetic Activation of WNT5A Drives Glioblastoma Stem Cell Differentiation and Invasive Growth. Cell 2016;167:1281-95.e18.

Abstract: It remains incumbent on researchers to conceive novel treatments for the most common primary malignancy of the brain in adults, glioblastoma multiforme (GBM), as the standard of care for patients today fails to yield a median survival beyond two years following diagnosis. Recent studies have tended towards appreciating the cellular heterogeneity of GBM tumors, focusing on the subpopulation of highly plastic glioblastoma stem cells (GSCs). In the November 2016 issue of *Cell*, Hu and colleagues developed a *de nova* GBM model derived from immortalized neural stem cells and, using this model, they demonstrated that GSCs can generate $CD133^{+}/CD144^{+}$ cells with endothelial cell-like characteristics. Contrasts between the epigenetic state and gene expression level before and after oncogenic transformation of this utilized *de novo* model for GBM implicated WNT5A, which has been previously shown to play a role in endothelial cell proliferation and migration via non-canonical Wnt signaling, as a mediator of the process. The transdifferentiation was accompanied by alterations in the histone marks at the gene loci of WNT5A, and its transcription factors PAX6 and DXL5. The authors hypothesize that activation of AKT, an aberration of the RTK/PTEN/PI3K pathway observed in the majority of GBM cases, triggers these epigenetic changes causing WNT5A expression. This phenomenon is of obvious clinical significance, as it provides an insight into how GBM may circumvent therapies targeting angiogenesis to achieve the neovascularization required to sustain invasive growth. The unveiling of this atypical differentiation process also raises questions about its interaction with the radiotherapy and chemotherapy commonly used to counter GBM progression. Here, we review the recent efforts to understand the complex mechanisms behind the plasticity of GSCs.

Keywords: Glioblastoma; cellular plasticity; glioma stem cell (GSC); vascular mimicry; WNT5A; GCS-derived endothelial-like cells

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A diagnosis of glioblastoma multiforme (GBM), currently entails a dire prognosis: notorious for its potent propensity to spread across the encompassing brain parenchyma and the near omnipresence of recurrence, GBM has held on to its throne as one of the most lethal malignancies with a relentless tenacity over the decades, despite advances in diagnostic techniques and the advent of aggressive multimodality treatment regimens (1,2). The median survival of patients remains dismal, less than two years, defying even three-pronged therapies with surgical resection, radiotherapy, and chemotherapy (3). A heterogeneous tapestry of different cell types comprises this primary brain tumor, giving it the latter part of its name, multiforme (4). In addition to the transformed astrocytes

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from which GBM is derived, and the endothelial cells associated with its characteristically rich vascularization, there exists a distinct cohort of undifferentiated multipotent cells ensconced within the tumor (5). It is theorized that these quasi-stem cells drive the distinctive features of GBM, such as multimodality therapeutic resistance, invasiveness, neoangiogenesis, vasculogenic mimicry and recurrence, which render attempts to treat it a veritable quagmire (6,7). According to the Cancer Stem Cell (CSC) hypothesis, these Glioma Stem Cells (GSCs) are maintained as a niche within the tumor, similar to tissue-specific somatic stem cells (8).

In the November 2016 issue of *Cell*, Hu *et al.* illuminate some of the aberrations in GSCs compared to neural stem/progenitor cells (NSCs); the latter play a pivotal role in the normal embryonic development of the nervous system, differentiating into neurons and supporting glial, and some persisting to become adult stem cells (9,10). GSCs show marked similarities to NSCs: both express stem cell markers, the capacity to self-renew, that is to maintain the undifferentiated state through numerous rounds of cell division, and the potency to differentiate into multiple lineages (10). Indeed, studies have implicated transformed NSCs as an origin of malignant astrocytomas (11). In addition to the characteristic features mentioned earlier, these stem cell-like properties bestow upon GSCs a robust potential for tumor initiation. In contrast to NSCs however, GSCs have been documented to undergo trans-differentiation, suggesting an inability to commit to a final differentiated state, which could confer the volatility required to withstand multiple therapeutic stresses and its concomitant selection pressures (12,13). It seems increasingly likely that these GSCs, whose markedly enhanced plasticity enables them to evade and adapt to the initial round of treatment that may succeed in shrinking the primary tumor, drive GBM's recurrence with radio- and chemoresistance (14,15). Hence, the elucidation of what sets these GSCs apart is of paramount importance and a worthwhile avenue for research. To that end, the authors established a *de novo* GBM model derived from human NSCs (hNSCs) that would allow for the detection of genes possibly contributing to the anomalous developmental plasticity of GSCs (*Figure 1*). These hNSCs were transduced to overexpress the proto-oncogene c-Myc, in order to immortalize them for ease of culture *in vitro* (16). c-Myc is robustly overexpressed in many cancers, including GBM (2), and the hNSCs employed demonstrated many of the properties shared between NSCs and GSCs. The hNSCs were oncogenically transformed by lentiviral co-transduction of a mutant form of p53 (p53DN), which exerts a dominant-negative effect on the tumor suppressor function of wild-type p53, and a lipidated, constitutively active variant of the serine/threonine kinase, AKT. This approach yielded an ideal model to investigate GSCs, due to the parallels between GSCs and NSCs. Furthermore, the transductions with p53DN and N-myristolated AKT (myr-Akt) served to emulate the deregulation of TP53-ARF-MDM2 and PTEN-PI3K-AKT pathways respectively, as seen in the majority of GBM cases (17,18). The loss of p53 function, which compromises the G1 to S phase checkpoint and negates cell cycle arrest in response to DNA damage, combine with the enhanced activity of AKT and c-Myc overexpression to drive gliomagenesis, by enabling cells to evade apoptosis, accumulate mutations, proliferate and indefinitely postpone terminal differentiation. Only doubly infected hNSCs (p53DN-AKT-hNSCs), expressing both p53DN and myr-AKT, exhibited anchorage-independent growth, a hallmark of carcinogenesis, as evidenced by the formation of colonies in soft agar. These p53DN-AKT-hNSCs readily formed tumors with classical GBM features following intracranial injection in immunocompromised mice, unlike both of the singly transduced hNSCs expressing either p53DN or myr-AKT. In order to control for the innate sequence non-specificity of lentiviral integrase (19) and any other biases introduced by the line of hNSCs from which their model was derived, the authors transduced c-Myc, p53DN and myr-AKT simultaneously in a different primary human NSC line, which demonstrated similar tumorigenic potential following intracranial injection in mice, hence confirming the reproducibility of their *de novo* model for GBM.

The tumors derived from p53DN-AKT-hNSCs evidently induced the formation of glioma stem cells (iGSCs), evidenced by their abilities to trigger tumor reformation and differentiate into glial and neuronal linages, albeit likely retaining the capacity for opportunistic self-renewal and transdifferentiation. Of more intrigue, however, is what differentiates GSCs from their non-malignant counterparts, that is the ability of the former to give rise to endothelial cells (ECs), a testament to the aberrantly heightened plasticity of GSCs compared to NSCs. This is of particular clinical relevance as evidence suggests that when patients are treated with therapies targeting angiogenesis, such as VEGF-inhibitors like bevacizumab, GBM tumors compensate by increased differentiation of GSCs to ECs (20,21). The neovascularization of GBM feeds the exponential growth

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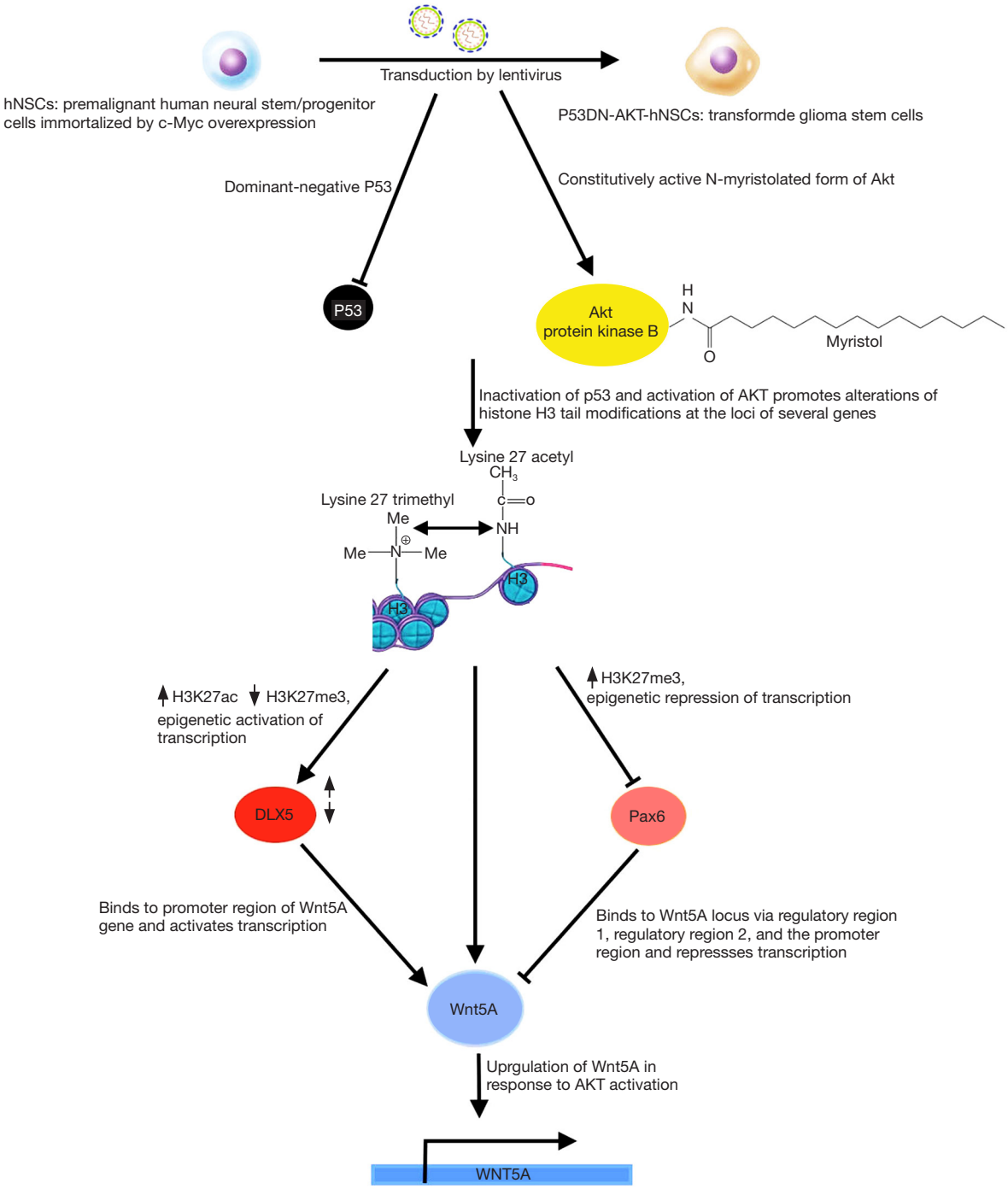

Figure 1 The activation of AKT stimulates a switch in histone modifications at the locus of the Wnt5a gene from repressive H3K27 trimethylation to activating H3K27 acetylation. This is mirrored at the gene locus of its transcriptional activator DLX5. Contrastingly, the histones at the promoter of Pax6, a transcription factor that downregulates Wnt5a, gained repressive H3K27me3 marks. These epigenetic alterations have the net effect of increasing Wnt5a expression in induced glioma stem cells compared to their parental human neural stem/progenitor cells.

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of the tumor and its invasiveness, therefore representing an attractive target for novel therapies. If the mechanism behind the generation of GCS-derived endothelial-like cells (GdECs), which most likely contributes to the pathogenesis of GBM, were to be delineated, novel therapies could be devised, which, in conjunction with existing anti-angiogenic chemotherapies, could impede neovascularization and hence halt tumorigenesis. To that end, the authors compared differences in gene expression between the parental NSCs and the iGSCs. In order to narrow their search for the culprits contributing to the stemness of their oncogene-induced model, the authors used bioinformatics, first identifying signaling pathways involved in stem cells using the Molecular Signatures Database (MSigDB), which they used to guide their transcriptomic gene set enrichment analysis (GSEA) that revealed a statistically significant upregulation of EC signaling following oncogenic induction (22). Genome-wide chromatin immunoprecipitation sequencing (Chip-seq) was utilized to detect epigenetic changes by revealing the post-translational modification states of the N-terminal Lysine of H3 histone proteins at the loci of genes of interest. This showed the epigenetic the activation of EC signaling, as many genes involved in the pathway showed a dynamic switch from repressive H3K27 trimethylation (me3) to activating H3K27 acetylation (ac) (23). These prompted the authors to confirm the expression of EC phenotypes by iGSCs, such as the expression of the EC markers VE-Cadherin (CD-144) and PECAM-1 (CD31), using fluorescence-activated cell sorting (FACs) and fluorescent acetylated-low density lipoprotein (Dil-AcLDL) uptake under NSC and EC culture conditions respectively. 12.8% and 5.8% of these p53DN-AKT-hNSC derived iGSCs expressed CD144 and CD31 respectively, along with other classical EC markers and functional features, like increased uptake of acetylated-LDL. With FACSs analysis revealing the co-expression of CD144 with the stem cell marker CD133 and EC formation *in vivo* in tumors, these findings together confirm the presence of GdECs derived from this *de novo* model (24).

In order to home in on exactly what transpired to elicit this differentiation, the authors focused on genes associated with high AKT activity, given the correlation of high AKT activation with poor prognosis, and of course, the central role of constitutive AKT activation in the oncogenic transformation of their model. The intersection of genes associated with high AKT activity and the genes that were epigenetically activated upon transformation of their model narrowed the list of culprits down to only eight genes. Individual knockdowns of each of these eight genes by RNA interference in $CD133^+/CD144^+$ p53DN-AKT-NSCs strongly implicated WNT5A as a driver of the process. This suspicion was bolstered using the WNT5A antagonist, BOX5, which markedly reduced the proportion of $CD133^+/CD144^+$ p53DN-AKT-NSCs and their EC-like property of tubular network formation. Furthermore, complimentary to the activating alterations in the gene locus of WNT5A were similar changes at the locus of its transcriptional activator, DLX5, which was shown to have a DNA binding motif specific to the promoter region of the *WNT5A* gene. On the other hand, PAX6, which also possesses a DNA binding site specific for regulatory regions of the WNT5A gene but represses transcription had contrary, repressive histone mark alterations. Doubtlessly, these had the combined effect of activating WNT expression.

WNT5A is a lipid-modified secreted glycoprotein that serves as a ligand of the Wnt signal transduction pathway, which has long been associated with carcinogenesis. The normal functions of the Wnt pathway are critical during embryogenesis and include promoting rapid cell proliferation, with members of the pathway being widely expressed in mouse cleavage stage embryos. It goes without saying that loss of regulation of this pathway has a strong potential to cause cancer. However, there are a variety of Wnt signaling pathways with a plethora of often opposing functions. While the canonical Wnt signaling pathway is dependent on β-catenin and has been and implicated in many cancers (25), including gliomas (26,27), and is even correlated with worse prognoses (28), this is likely not involved in the process of GdEC formation: WNT5A is a typical non-canonical Wnt ligand and, curiously enough, inhibition of canonical Wnt signaling is one of its known properties (17). This highlights a glaring paradox in the role of WNT5A in tumor progression, as previous research has shown the canonical pathway to be intimately involved in stem/progenitor cells and cancer stem cells alike. There is no evidence to suggest that WNT5A hinders GBM's formation of stem cells, and on the contrary, immunohistochemical and transcriptomic analysis of paired primary/recurrent GBM patient samples reveal WNT5A to be consistently upregulated in recurrent tumors, with a symmetric increase in the incidence of GdECs. As recurrent tumors are well known to be more plastic and comprised of a higher proportion of GSCs (29), this hints that WNT5A is functioning through a different, as yet unidentified pathway, which has no effect on the

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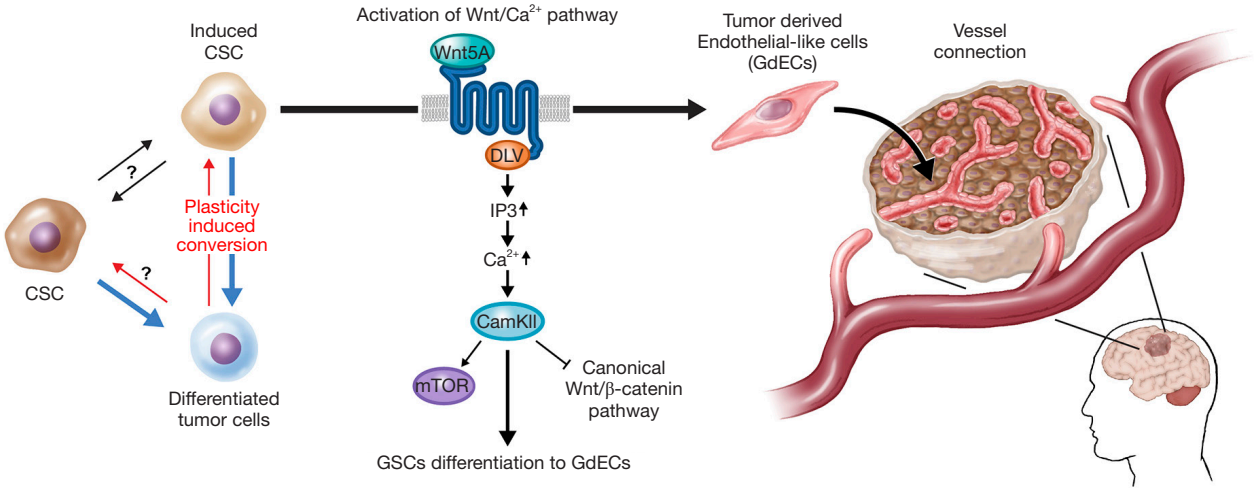

Figure 2 Glioblastoma stem cells are characterized by self-renewal, the potential for specialization to multiple lineages and aberrant transdifferentiation. Wnt5A expression most likely activates the Wnt/Ca^{2+} pathway via autocrine signalling, leading to their differentiation into endothelial-like cells. The lineage reprograming capacity of these cells remains a mystery. Will they respond to drugs targeting their endothelial-like phenotypes by going back to an undifferentiated state or switching their lineage? To what extent are the hallmarks of cancer stem cells preserved in these endothelial-like cells?

canonical Wnt signaling. It could also mean that GSCs simply upregulate β-catenin expression to offset the effect of WNT5A. The authors to not delve into which particular Wnt signaling WNT5A invokes in this context, but Cheng *et al.* demonstrated that WNT5A regulates endothelial cell proliferation and migration during angiogenesis by activating the Ca^{+}/calmodulin-dependent protein kinase II (30), and it is reasonable to assume that something similar is occurring here.

WNT5A is secreted before binding to an extracellular domain of its G-protein coupled receptor, frizzled, which in turn activates the cytoplasmic protein disheveled that relays the signal to downstream effectors of the pathway, which in this context leads to an increase in cytosolic Ca^{+} concentrations and the activation of the mTOR/S6K pathway (31). Hence, it may mediate its effect in an autocrine or paracrine manner. WNT5A is robustly epigenetically activated in $CD133^{+}$/$CD144^{+}$ cells sorted from p53DN-AKT-NSCs, hinting towards an autocrine mode of action. It would be interesting to see which of the iGSCs express the receptor for WNT5A to reveal whether or not paracrine signaling also plays a role. Paracrine signaling certainly plays a role in the recruitment of host ECs by GdECs, something the authors also accuse WNT5A of enabling in this context. This recruitment, they say, forms a vascular-like niche, which is reminiscent of the generation of vascular pericytes by GSCs reported by Lin Cheng and colleagues, making it quite possible that WNT5A plays a role in the latter phenomenon as well (30).

The standard of care for GBM today involves maximal surgical resection followed by radiotherapy and chemotherapy in the form of the DNA alkylating agent temozolomide (32). It remains to be seen how the process of WNT5A mediated GSC differentiation to EC is affected by stress form these therapies. Of particular interest is the extent to which GdECs retain the stemness of their progenitors. Given its known inhibition of the canonical Wnt pathway, which helps in the maintenance of the GSC pool, WNT5A may favor transdifferentiation at the expense of GSC's multipotency and self-renewal (*Figure 2*). The transdifferentiation capacity of GSCs, which could help it evade therapies targeting the Wnt pathway, can be understood by lineage tracing experiments: by utilizing the Cre-lox system, for example, a reporter system can be established to reveal the fate of $CD133^{+}$/$CD144^{+}$ cells in real time under conditions of different therapeutic stresses. Likewise, similar fate-mapping experiments can give a detailed depiction of GSC evolution *in vivo*, something that remains to be accomplished for GBM in a clinical setting.

The CRISPR-Cas9 system of introducing indels into the genome in a sequence-specific manner has emerged from its infancy and is currently a powerful tool that can be used to perform a genome-wide screen with commercially available functional genetic single RNA (sgRNA) libraries (33).

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This can create knockout mutations in almost all human genes and may be used to reveal genes whose loss of function mutations contribute to the transition of GSCs to EC-like cells. This can be done by analyzing the sgRNA populations by reverse-transcriptase quantitate PCR to reveal which sequences from the original library are enriched in the EC-like cells compared to the GSCs from which they originate, following transduction of the latter by the gene encoding the Cas-9 protein and the sgRNA library. Often, this kind of an assay will have hits for many genes besides those that are known oncogenic drivers. This *de novo* approach of identifying culprit mutations compliment the bioinformatics-guided approach utilized by the authors to arrive at WNT5A.

Baoli Hu and colleagues have presented extensive data that leaves no room for doubt about WNT5A's aid to tumor neovascularization in GBM patients, including compelling evidence that GdECs are indeed incorporated into host blood vessels. Even though they do not pinpoint the source of host ECs, their proposed model for a vascular-like niche spurring GBM's breach of the surrounding brain tissue and recurrence, is supported by an increase of WNT5A expression in peritumoral regions compared to their matched intratumoral counterparts from clinical samples. However, the finer mechanistic details of WNT5A induced differentiation of GSCs to GdECs, and the maintenance of peritumoral satellite lesions are yet to be revealed. It is important for the exact pathways by which these processes come about to be elucidated in their entirety, as this will reveal all the essential components that could potentially be targeted by novel drugs, alleviating the challenge of designing drugs that must overcome the blood-brain barrier.

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Footnote

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