Navitoclax

ABT-263, also known by its generic name navitoclax, is a small molecule drug that was developed as an inhibitor of B-cell lymphoma 2 (Bcl-2) family proteins. Bcl-2 family proteins play a crucial role in regulating apoptosis (programmed cell death). ABT-263/navitoclax specifically inhibits Bcl-2, Bcl-xL, and Bcl-w, which are anti-apoptotic proteins that help cancer cells evade programmed cell death.

Here are some key points about ABT-263/navitoclax:

Mechanism of Action: ABT-263/navitoclax works by binding to Bcl-2, Bcl-xL, and Bcl-w proteins, preventing them from inhibiting apoptosis. This mechanism allows cancer cells to undergo programmed cell death, which is an essential process for preventing the survival and proliferation of cancer cells.

Clinical Applications: ABT-263/navitoclax has been investigated for its potential in treating various types of cancer, including lymphomas and solid tumors. It has shown promise in preclinical studies and early-phase clinical trials.

Limitations: While ABT-263/navitoclax has demonstrated efficacy in some cases, its use is associated with thrombocytopenia (low platelet count). This side effect is due to the inhibition of Bcl-xL, which is also important for platelet survival. The thrombocytopenia limits the dose that can be administered, and strategies to address this limitation are under investigation.

Development: Navitoclax was developed by Abbott Laboratories (now AbbVie). It has undergone various clinical trials to assess its safety and efficacy in different types of cancer.

Combination Therapies: Researchers are exploring combination therapies to enhance the effectiveness of ABT-263/navitoclax while minimizing its side effects. Combining it with other targeted therapies or conventional chemotherapeutic agents is an area of active investigation.

Navitoclax in neurosurgery

- Senescent Endothelial Cells in Cerebral Microcirculation Are Key Drivers of Age-Related Blood-Brain Barrier Disruption, Microvascular Rarefaction, and Neurovascular Coupling Impairment in Mice
- Genome-wide CRISPR-Cas9 screens identify BCL family members as modulators of response to regorafenib in experimental glioma
- Analysis of cuproptosis-related genes in prognosis and immune infiltration in grade 4 diffuse gliomas
- OGDH and Bcl-xL loss causes synthetic lethality in glioblastoma
- Preventing spontaneous cerebral microhemorrhages in aging mice: a novel approach targeting cellular senescence with ABT263/navitoclax
- Elimination of senescent cells by treatment with Navitoclax/ABT263 reverses whole brain irradiation-induced blood-brain barrier disruption in the mouse brain
- Silencing of the MEG3 gene promoted anti-cancer activity and drug sensitivity in glioma
- Accelerated cerebromicrovascular senescence contributes to cognitive decline in a mouse model of paclitaxel (Taxol)-induced chemobrain

Emerging evidence from both clinical and preclinical studies underscores the role of aging in potentiating the detrimental effects of hypertension on cerebral microhemorrhages (CMHs, or cerebral microbleeds). CMHs progressively impair neuronal function and contribute to the development of vascular cognitive impairment and dementia. There is growing evidence showing accumulation of senescent cells within the cerebral microvasculature during aging, which detrimentally affects cerebromicrovascular function and overall brain health. Faakye et al. postulated that this build-up of senescent cells renders the aged cerebral microvasculature more vulnerable, and consequently, more susceptible to CMHs. To investigate the role of cellular senescence in CMHs' pathogenesis, they subjected aged mice, both with and without pre-treatment with the senolytic agent ABT263/Navitoclax, and young control mice to hypertension via angiotensin-II and L-NAME administration. The aged cohort exhibited a markedly earlier onset, heightened incidence, and exacerbated neurological consequences of CMHs compared to their younger counterparts. This was evidenced through neurological examinations, gait analysis, and histological assessments of CMHs in brain sections. Notably, the senolytic pre-treatment wielded considerable cerebromicrovascular protection, effectively delaying the onset, mitigating the incidence, and diminishing the severity of CMHs. These findings hint at the potential of senolytic interventions as a viable therapeutic avenue to preempt or alleviate the consequences of CMHs linked to aging, by counteracting the deleterious effects of senescence on brain microvasculature [1)]

Gulej et al. aimed to test the hypothesis that Whole brain radiotherapy induces endothelial senescence, contributing to chronic blood-brain barrier disruption (BBB) and microvascular rarefaction. To accomplish this, they utilized transgenic p16-3MR mice, which enable the identification and selective elimination of senescent cells. These mice were subjected to a clinically relevant fractionated WBI protocol (5 Gy twice weekly for 4 weeks), and cranial windows were applied to both WBI-treated and control mice. Quantitative assessment of BBB permeability and capillary density was performed using two-photon microscopy at the 6-month post-irradiation time point. The presence of senescent microvascular endothelial cells was assessed by imaging flow cytometry, immunolabeling, and single-cell RNA-sequencing (scRNA-seq). WBI induced endothelial senescence, which associated with chronic BBB disruption and a trend for decreased microvascular density in the mouse cortex. In order to investigate the cause-and-effect relationship between WBI-induced senescence and microvascular injury, senescent cells were selectively removed from animals subjected to WBI treatment using Navitoclax/ABT263, a well-known senolytic drug. This intervention was carried out at the 3-month post-WBI time point. In WBI-treated mice, Navitoclax/ABT263 effectively eliminated senescent endothelial cells, which was associated with decreased BBB permeability and a trend for increased cortical capillarization. Our findings provide additional preclinical evidence that senolytic treatment approaches may be developed for prevention of the side effects of WBI [2)]

1)
Faakye J, Nyúl-Tóth Á, Muranyi M, Gulej R, Csik B, Shanmugarama S, Tarantini S, Negri S, Prodan C, Mukli P, Yabluchanskiy A, Conley S, Toth P, Csiszar A, Ungvari Z. Preventing spontaneous cerebral microhemorrhages in aging mice: a novel approach targeting cellular senescence with ABT263/navitoclax. Geroscience. 2023 Dec 4. doi: 10.1007/s11357-023-01024-9. Epub ahead of print. PMID: 38044400.
2)
Gulej R, Nyúl-Tóth Á, Ahire C, DelFavero J, Balasubramanian P, Kiss T, Tarantini S, Benyo Z, Pacher P, Csik B, Yabluchanskiy A, Mukli P, Kuan-Celarier A, Krizbai IA, Campisi J, Sonntag WE, Csiszar A, Ungvari

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