biosynthetic pathways were primarily in focus at the beginning of antimetabolite era. The first metabolic pathway modulated in oncology and virology was one-carbon metabolism. This pathway targets folate, which acts as a single-carbon donor critical for purine ring formation [2].

Endogenous purine nucleosides are involved in essential cellular processes such as DNA and RNA synthesis, cell signaling, enzyme regulation and metabolism [3]. Their synthetic, chemically modified analogs have been developed to mimic physiological molecules and exploit cellular metabolism. The analogs can be incorporated into DNA or RNA and inhibit cancer cell and virus replication. In addition to their incorporation into nucleic acids, purine nucleoside analogs can interact with and inhibit essential enzymes such as DNA and RNA polymerases, kinases, ribonucleotide reductase, DNA methyltransferases and purine nucleoside phosphorylase [3].

Gertrude Elion and George Hitchings, Nobel Prize Laureates for Physiology and Medicine in 1988 [4-6], developed 6-Mercaptopurine (6-MP) that was shown to induce complete, albeit temporary, remissions of acute leukemia in children when very few other treatment options were available. 6-MP was approved by the US Food and Drug Administration for this indication in 1953, two years after its first synthesis.

The classic antimetabolite strategy provided the basis for chemotherapy regimens that are still used today. Obvious limitation when nucleotide pathways are generally targeted is the lack of a sufficient therapeutic window. Selectivity towards cancer cells remains a huge problem. Therefore, achieving selectivity by modulating nucleotide pathways is the major aim in the future research in this field [4].

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Some of purine nucleoside analogues are used against viral infection, which primarily does not attack central nervous system (CNS), but is linked to neuroinflammation and cognitive impairment [7-10]. Therefore, therapeutic
action achieved in anti-viral treatment could be partially due to alleviation of neuroinflammation [9]. In addition, apart from viruses and cancer cells, some of purine nucleoside analogues also target different cell types of immune system [11-13]. In the context of the foregoing and the fact that purine nucleoside analogues have ability to readily pass blood-brain barrier [14,15], administration of these substances expanded into neuropathological conditions associated with neuroinflammation.

Herein, we describe the anticancer and neuroprotective action of certain purine nucleoside analogs initially developed as anticancer and antiviral drugs (Figure 1). A better understanding of their mechanism of action may provide the basis for the development of new compounds and contribute to the rational development of synergistic combinations with other drugs that have different and/or complementary mechanisms of action.

2 Mechanism of action of purine nucleoside analogs

Purine nucleoside analogs enter cells through specific nucleoside transporters: concentrative and equilibrative nucleoside transporters [16]. Organic ion transporters as well as peptide transporters could be also involved in the cellular and viral uptake of certain analogs [17]. Once inside the cell, the nucleoside analog undergoes an initial rate-limiting phosphorylation step by a nucleoside kinase, which leads to the production of a monophosphate metabolite. A second phosphorylation step is then performed by nucleoside monophosphate kinase, and the third phosphorylation step is performed by nucleoside diphosphate kinase. Triphosphates can be incorporated in nucleic acids, in competition with endogenous nucleoside-triphosphates, or they can inhibit DNA and RNA synthesis by inhibiting essential enzymes such as polymerases [3]. In addition, ribonucleotide reductase M1 (RRM1), a key enzyme involved in nucleotide metabolism, can be inhibited both by diphosphorylated and triphosphorylated analogs. Catabolic enzymes may reduce the amount of active metabolites, including deaminases and 5'-nucleotidases [3].

The incorporation into DNA may terminate the chain elongation, accumulate the mutations or induce DNA strand breaks and eventually lead to the apoptosis [18].

Nucleotide analogs compete with physiological nucleotides during the initiation and extension of DNA or RNA chains by cellular polymerases. The incorporation of the analogs is dependent on the affinity of polymerases for nucleotides [3]. Chain termination is observed with anticancer nucleotide analogs that possess the 3’ hydroxyl group (such as deoxyguanosine derivatives), and the recognition of the nucleotide as foreign seems to be responsible for this effect [3].

![Figure 1. Chemical structure of purine nucleoside analogs with anticancer properties (a) 6-thioguanosine and (b) sulfinosine derived from 6-thioguanosine; and neuroprotective properties (c) ribavirin and (d) tiazofurin.](image)
The sustained chain elongation after their incorporation into DNA or RNA may induce mismatching that leads to mutagenesis in human cells and viruses [19]. Although beneficial for the destruction of viruses, this is a serious obstacle for purine nucleoside usage in anticancer therapy.

However, purine nucleoside analogs may induce apoptosis of cancer cells. The exact mechanism is still not clearly understood [18]. Nucleoside analogs generally cause a block in the S phase of the cell cycle due to the incorporation of their corresponding nucleotides in DNA chain. In contrast to other analogs, purine nucleoside analogs act both in the mitotic and quiescent cell cycle phases as the recognition of the inadequate nucleotides in DNA takes place only after second replication of the cell treated with purine nucleoside analog [3]. Therefore, they are commonly combined with DNA poisoning agents, such as alkylating or platinum compounds, as they both inhibit DNA repair [3].

### 3 Purine nucleoside analogs in anticancer research

#### 3.1 Recently approved drugs and/or in clinical trials

There are only few FDA- and European Medicines Agency (EMA) - approved cytotoxic nucleoside analogs that are derivatives of deoxyadenosine or deoxyguanosine [20]. In the last few years, three deoxyadenosine have been approved for the treatment of lymphoid malignancies and other hematological disorders: cladribine or 2-chlorodeoxyadenosine (2-CdA), fludarabine and pentostatin. 2-CdA and fludarabine are also active in the treatment of acute myeloid leukemia [21, 22]. Recently novel adenosine analog clofarabine has been introduced into clinical trials. It has been approved for the treatment of refractory patients with acute lymphoblastic leukemia and lymphoblastic lymphoma [23].

8-amino-adenosine that inhibits transcription and depletes adenosine-triphosphate (ATP) was in preclinical development [24, 25], while 8-chloro-adenosine was in phase I clinical trials [26]. Both 8-chloro-adenosine and 8-amino-adenosine decrease RNA synthesis and induce cell death by decreasing the intracellular concentration of ATP [24]. 8-amino-adenosine induces a decrease in both RNA and DNA synthesis, whereas 8-chloro-adenosine preferentially decreases mRNA synthesis [25]. 8-chloro-adenosine also inhibits the polymerization of actin and the activity of topoisomerase II [27, 28].

Controversial results have been obtained with cyclic nucleotide 8-chloro-cAMP that has been redrawn from Phase II clinical trials. Its action could be explained by modulation of protein kinase A activity [29] or through the conversion to its active nucleoside metabolite 8-chloro-adenosine [26, 30]. 8-chloro-cAMP was shown to exert cytotoxic effect in a broad range of human cancer cell lines [31], disturb cell cycle kinetics and induce apoptosis in glioma and neuroblastoma cell lines [32, 33].

Very important findings indicated 8-Cl-cAMP as potent multidrug resistance reversal agent [34]. Pretreatment with 8-Cl-cAMP improved the sensitivity to doxorubicin (DOX) more than verapamil (VER), the standard modulator of MDR. The increased accumulation of DOX observed after 8-Cl-cAMP treatment resembled the results obtained with VER. Even more, 8-Cl-cAMP considerably decreased mdr1 expression [34].

Nelarabine is a guanosine analog in which the hydrogen of the hydroxide group at the 6-position of the guanine ring is substituted by a methoxy group [35]. Nelarabine is more water soluble pro-drug of 9-β-Darabinofuranosyl-guanine (Ara-G) [36]. The Ara-G competes with endogenous deoxyxynucleosides for incorporation into DNA by DNA polymerases. This results in inhibition of DNA synthesis and initiation of apoptosis [37].

#### 3.2 Thiopurines

Particularly important group of the purine nucleoside analogs represents analogs with oxidized sulfur at the C6 position. These compounds are known as thiopurines and their main representatives are 6-MP and 6-thioguanine (6-TG), clinically approved derivatives of hypoxantine and guanine, respectively [4]. Together with azathioprine (AZA), which is modified 6-MP, these thiopurines are used as immunomodulators in the treatment of inflammatory diseases [38-40], as well as anticancer agents, applied primarily in the treatment of acute leukemia [41, 42]. 6-MP and 6-TG act as antimetabolites and exert their cytotoxic effect by interfering with purine metabolism. They are converted into the thioguanine nucleotides that compete with standard nucleotides and incorporate into DNA and RNA [43]. These false nucleotides are further targets for action of the mismatch repair (MMR) system [44]. Thiopurines can also lead to purine starvation by interfering with de novo purine synthesis [4].

Polymorphisms in enzymes involved in purine metabolism as well as alterations in components of DNA repair system and multidrug resistant associated proteins influence thiopurine cytotoxicity and can...
lead to development of resistance to these drugs [45]. Moreover, prolonged treatment with thiopurines can lead to undesired side effects such as increased incidence of malignancies [46]. Therefore, chemists were encouraged to develop new nucleoside analogs, which would have fewer side effects, better solubility and greater selectivity than 6-MP and 6-TG, and which could also successfully overcome resistance to 6-MP and 6-TG.

### 3.3 Sulfinosine, a derivative of 6-thioguanosine

In 1990, a great number of new purine nucleosides were synthesized and tested for their antileukemic activity in mice. Sulfinosine or SF ([R,S]-2-amino-9-β-D-ribofuranosylpurine-6-sulfinamide) was one of the most efficient newly synthesized compounds which was selected for further anticancer research. It is a thiopurine analog derived from 6-thioguanosine by amination with chloramine solution and subsequent oxidation [47]. First preclinical testing showed that SF was active against six solid tumors (glioma, sarcoma, melanoma, mammary and two colon carcinomas) and four strains of experimental leukemia, being more water soluble, dose and time dependent and having more cumulative effect than its precursor [48]. Most importantly, it was shown to be efficient against tumors resistant to other nucleoside analogs and cytotoxic drugs. SF was further used to synthesize other sulfur-containing cytotoxic drugs but they were not as effective as SF itself [49; 50].

SF inhibits cancer cell growth, at least partially, by the incorporation of its phosphorylated derivative into DNA. The metabolic conversion of SF into its corresponding nucleotide-monophosphate derivative is more complex than that of other thiopurines. Since SF utilizes different metabolic pathways for its intracellular activation, SF treatment does not induce resistance in cancer cells [51-53].

After a decade of stagnation in SF research, studies on its anticancer activity were continued in 2002. Initially, this drug was shown to be effective against lung cancer, both non-small cell lung carcinoma (NSCLC) and small cell lung carcinoma (SCLC) cell lines in micromolar concentrations [54]. In this study SF was proved to disturb cell cycle kinetics and arrest cells in G2M phase further leading to extensive apoptosis. Additionally, SF was observed to exert cytotoxicity against neuroblastoma cells in a similar manner, also causing accumulation of cells in G2M phase and cell death by apoptosis [33]. Moreover, its antineoplastic activity against neuroblastomas was enhanced when combined with another cyclic purine nucleotide analog, 8-Cl-cAMP. Most notably, SF was nontoxic for normal cells (HaCaT), showing selectivity towards cancer cells [55].

A significant property of SF is its almost equal anticancer activity on both drug sensitive and their resistant counterparts with the overexpression of major multidrug resistant protein P-glycoprotein (P-gp). It can be successfully used to overcome multidrug resistance in NSCLC and glioma cell lines, either alone or in combination with other antineoplastic agents [34, 55-57]. Namely, SF efficiently inhibited cell growth, downregulated mdr1 and topo IIa gene expression and arrested cell cycle in S and G2M phase (Figure 2). These effects are even more pronounced and synergistic when SF was applied simultaneously with DOX or curcumin on resistant NSCLC cells [34, 57]. SF was also capable to induce apoptosis in p53-independent manner and to increase cellular autophagy [55]. Additionally, pretreatments with SF, either alone or with verapamil, could efficiently sensitise multidrug resistant cells to DOX treatment [34, 55, 58]. Treatment with SF prior to DOX, similarly to simultaneous treatment, efficiently reduced cell viability, decreased mdr1 and topo IIa gene expression and disturbed cell cycle kinetics in multidrug resistant cells [34, 58]. SF pretreatment increased DOX accumulation, similarly to non-competitive P-gp inhibitor tariquidar and even more than verapamil, a representative of first generation of P-gp competitive inhibitors [34, 55, 58]. This purine nucleoside analog was proved to exert its antiangiogenic potential by modulating VEGF secretion and reducing its expression [55]. Additionally, it decreased the expression of HIF-1α, which was argued to be responsible for the anti-P-gp and anti-VEGF effects of SF [55].

The cellular redox environment is a delicate balance between the levels of reactive oxygen species (i.e., superoxide and hydrogen peroxide) and the antioxidant system that scavenges them (i.e., glutathione/glutathione peroxidase and thioredoxin/peroxiredoxin pathways) [59]. SF was capable to disturb significantly the redox balance in cancer cells (Figure 2). Namely, it was found that the mechanism of SF action against resistant tumors is essentially attributed to the significant depletion of glutathione (GSH) [55, 58]. Such effect on the cellular detoxification system is expected, since it was previously observed that SF readily and rapidly forms adducts with sulfhydryl compounds (GSH and cysteine) both in vivo and in vitro [51-53]. Furthermore, SF was shown to increase reactive oxygen species (ROS) and to inhibit the expression of key enzymes involved in GSH synthesis and cell detoxification, gamma glutamyl-cysteine-synthetase (γGCS) and glutathione-S-transferase π (gst-π) [55, 57]. The
alteration of \textit{gst-\pi} expression was even more pronounced when resistant cells were co-treated with SF and curcumin [57].

Although poorly studied, purine nucleoside analog SF possesses unique anticancer effects. It depletes GSH and reverses multidrug resistant phenotypes through inhibition of P-gp expression and activity (Figure 2). The mechanisms beyond these effects are modification of redox status and HIF-1\(\alpha\) regulation. These results rationalize the use of SF alone or in combination with conventional anticancer agents.

3.4 IMPDH inhibitors

Ribavirin and tiazofurin are N-glycosyl and C-glycosyl purine nucleosides, respectively, both inhibitors of inosine 5’-monophosphate dehydrogenase (IMPDH, EC 1.1.1.205), a key enzyme of \textit{de novo} guanosine-5’-triphosphate (GTP) biosynthesis (Figure 3). Inhibition of IMPDH lowers the cellular guanine nucleotide concentration and as a consequence interruption of GTP-dependent cellular processes occurs, which could result in antiviral, anticancer or immunosuppressive activity[60]. It should be noted that ribavirin and tiazofurin achieve most of their biological action through their active metabolites. Ribavirin is metabolized to ribavirin-monophosphate, -diphosphate and –triphosphate and tiazofurin into tiazole-4-carboxamide adenine dinucleotide.

Since IMPDH was recognized as an enzyme linked with proliferation and malignancy [61], ribavirin and tiazofurin activity against numerous cancer cell lines was proved. Both compounds reached Phase II of clinical trials against leukemia [62, 63]. Patients with bcr-abl positive acute myelogenous leukemia and chronic myelogenous leukemia in blast crisis treated with tiazofurin achieved transient hematologic responses [63]. Chemotherapy of leukemia with tiazofurin is based on the inhibition of IMPDH enzyme since it was shown that up-regulation of this enzyme together with the p210 bcr-abl gene rearrangement is a feature of chronic myelogenous leukemia [64]. Ribavirin also showed encouraging activity against M4/M5 subtypes of acute myelogenous leukemia.
Unlike tiazofurin, the chemotherapeutic target of ribavirin is not IMPDH. It entails acting on another molecule - the eukaryotic translation initiation factor eIF4E, which is shown to be elevated in M4/M5 acute myelogenous leukemia [66] that could be blocked by ribavirin [67]. These results indicated that ribavirin and tiazofurin are good candidates for combination treatments with already established antileukemia therapeutics.

In vitro studies showed considerable antiglioma and antiangiogenic activity of tiazofurin [68, 69].

### 4 Purine nucleoside analogs in neuroinflammation

From the time when ribavirin was synthesized in 1972 as broad spectrum antiviral agent, its clinical application was limited against two infections, one caused by Hepatitis C virus (HCV) and the other by Respiratory syncytial virus (RSV) [70-75]. In the treatment of chronic HCV infection, it is necessary to emphasize that the ribavirin is administered in combination with other approved therapies (e.g. peginterferon alfa-2a), since it was not effective as monotherapy. Although ribavirin antiviral activity is well known, the precise mechanism that lies underneath is not yet fully elucidated, probably because ribavirin does not universally act on all viruses; its actions are rather virus specific and also depend on the type of infected cell [76]. Ribavirin antiviral activity depends on its interaction with viral RNA polymerases that lead to inhibition of viral replication or to error catastrophe incident, although it is not excluded that in certain cases the antiviral effect can be achieved via inhibition of IMPDH [76]. Since tiazofurin is known only as potent and selective IMPDH inhibitor this could be the reason why tiazofurin has a narrower circle of action when it comes to viruses compared to ribavirin [77, 78].

#### 4.1 Experimental autoimmune encephalomyelitis

Recent studies repositioned ribavirin and tiazofurin in the field of neuroinflammation, more precisely, to animal model of multiple sclerosis – experimental autoimmune encephalomyelitis (EAE). How did it come to these investigations? The first important fact was that ribavirin...
has the capacity to enter the CNS, where it demonstrated antiviral activity against several RNA viruses responsible for neurological damage in humans and animals [79-81]. In addition, ribavirin entry in the brain is enhanced by neuroinflammation, due to disrupted blood brain barrier (BBB)[15]. Likewise, tiazofurin has ability to cross the BBB [14, 82]. The second important fact was that IMPDH inhibitors exhibit immunosuppressive actions [83, 84]. In addition, it was shown that ribavirin inhibits proliferation of human peripheral blood lymphocytes and preserves Th1 cytokine production [85], but inhibits Th2 cytokine response in viral-induced macrophages [11].

Potential immunosuppressive actions of ribavirin and tiazofurin, together with the ability to enter the CNS, have encouraged research of these drugs in the EAE, which started a decade ago. Both drugs proved to be efficient in the amelioration of disease severity regardless of whether they were administrated from inductive (day 0) or effective phase (day 7) of EAE [86, 87]. Since this neurodegenerative disorder implies disturbance of balance between the immune system and the CNS, these beneficial effects of ribavirin and tiazofurin raised question: which system of these two is their main target?

Stosic-Grujicic et al. placed effects of tiazofurin outside the CNS, demonstrating that this drug manly affects the immune branch of disease, through interaction with encephalitogenic T-cells [87]. However, the well known anti-proliferative action of tiazofurin in malignancy was not confirmed on autoreactive T-cells in EAE. Based on reduced intensity of adhesion interactions between mononuclear cells isolated from tiazofurin treated animals recorded in vitro and reduced mononuclear cell infiltration in the spinal cord of tiazofurin treated rats, it was concluded that this drug interferes with adhesive interaction between encephalitogenic T-cells and endothelial cells of brain vasculature, and thus prevents lymphocytes to enter into the CNS. An explanation of aforementioned has been found in the inhibition of IMPDH. The inhibition of IMPDH enzyme leads to a depletion of cellular GTP pool and several studies on lymphocytes and monocytes with other IMPDH inhibitors have shown that lack of GTP suppresses glycosylation of adhesion molecules on these cells and thus prevents their binding function [83]. Therefore, it was concluded that this may be the reason why tiazofurin induced favorable disease outcome.

The first study on the role of ribavirin in EAE was published a year later with a focus on histopathological changes within the CNS [80]. Namely, ribavirin induced general reduction of inflammatory infiltrates (CD4+ and CD8+ T cells as well as macrophages, monocytes and granulocytes), prevented demyelination and decreased microgliosis in spinal cord of diseased animals. Nevertheless, as for the tiazofurin, explanation for attenuated histological signs in spinal cord of EAE animals was also found in preventing lymphocyte recruitment into the target tissue, a process linked to interference with adhesion interactions between cells. The concept that nucleoside analogs operate mainly outside of the CNS in EAE pathology was further confirmed by the study of Lavrnja et al. in 2008 [88]. It was shown that aside from limiting the entrance of autoreactive T-cells into the CNS, ribavirin also substantially reduced levels of proinflammatory cytokines (IFN-γ, IL 1-β and TNF-α) produced by immune cells in draining lymph node in initial phase of EAE. Consequently, expression of IFN-γ, IL1-β and TNF-α was down-regulated in the spinal cord tissue at the pick and the end of disease.

Several studies exploited the fact that ribavirin and tiazofurin inhibit IMPDH via their active metabolites through binding to the enzyme at different sites and trialed them in combination therapy [89-91]. Indeed, it was shown that combination therapy was more effective in suppression of the ongoing disease, than each drug used alone.

4.2 Modulation of glial cell response

The effect of ribavirin and tiazofurin was also studied on glial cells obtained from rat CNS. It was shown that ribavirin reduced the number of reactive astrocytes in the white and grey matter of the spinal cord, probably via affecting proliferation of these cells [92]. These data are consistent with our previous reports showing that ribavirin down-regulates the process of reactive astrogliosis and postpones glial scarring after adult brain injury, even after the cessation of treatment [93, 94]. Apart of its effects on GTP biosynthesis pathway, ribavirin was shown to affect the ERK/MAPK signaling pathway that is known to be essential for the induction and maintenance of reactive astroglial phenotypes. Namely, Pekovic et al. revealed that ribavirin attenuates ERK1/2 expression around the lesion site and hypothesized that down-regulation of ERK-MAPK signaling pathway underlies the inhibition of reactive astrogliosis in the rat forebrain following stab injury [94]. Besides, in EAE, ribavirin together with tiazofurin, polarized morphology of microglia and astrocytes to a less activated state, that indicated attenuation of inflammation in the spinal cord [92, 95]. Certainly, the modulation of glial cell response during EAE may be due to preventing infiltration of immune cells in the CNS. However, the fact that ribavirin regulated glial fibrillary acidic protein,
vimentin and TNF-α expression at the mRNA level in spinal cord tissue indicated that they might act on the other side of the BBB (i.e. within the CNS) [92].

In addition, the theory that they can operate within the CNS has been further strengthened by the study of their effect on cultured microglia cells, specifically in in vitro model of neuroinflammation [96, 97]. Ribavirin and tiazofurin modulated the activity of immune-stimulated microglia in a complex manner inducing both anti- and pro-inflammatory effects. Anti-inflammatory modulation of microglia activity included a reduction in cell viability and NO level, suppression of the activated morphological profile of microglia, reduction in TNF-α and IL-6 release, as well as an increase in IL-10 secretion. Conversely, enhanced release of IL-1β represented pro-inflammatory property of ribavirin and tiazofurin [96, 97]. These results could be placed into the context of ribavirin use as antiviral agent and tiazofurin as an anticancer drug. Since HCV virus could activate microglial cells, which may induce irreversible neurological damage [98, 99], there is a possibility that part of ribavirin therapeutic action achieved in HCV treatment could be due to its effect on microglial cells. Tiazofurin anticancer activity was demonstrated on various neoplastic cells, including glioma cell lines [68, 100]. Since microglia cells could be significant for progression or suppression of glioma [101], the fact that tiazofurin affects both of these cell types makes this drug interesting for future surveys that investigate interactions of microglial and glioma cells.

In general, although ribavirin and tiazofurin have capacity to interact with cells of immune system, as well as with cells of the CNS, they affect more powerfully immune branch of EAE, probably because immune cells are more sensitive to IMPDH inhibition (Figure 4).

4.3 Potential of purine nucleoside analogs for medicinal usage

Besides their role in oncology and virology, some analogs have been used in various other indications such as immunosuppression (azathioprine, a derivative of 6-MP), neuroprotection and cardioprotection [92, 95, 102]. Interestingly, several purine nucleoside analogs have undergone drug repurposing. For example, ribavirin that was initially approved as antiviral agents has shown promising antileukemia properties [66]. Similarly, certain anticancer analogs have been found to possess antiviral or antibacterial properties. In some instances, agents (ribavirin and tiazofurin) have been repositioned to non-viral and non-cancer indications such as neurodegenerative diseases or brain injuries [86, 87, 94].

In the case of anticancer purine nucleoside analogs, approved compounds remain largely limited to hematological malignancies [20]. Their potential in the therapy of solid malignancies is not sufficiently explored. Therefore, this field would greatly benefit from an improved knowledge about the role of purine nucleoside analogs in cancer metabolism and chemoresistance. According to our results, patients with incurable neurodegenerative diseases and chemoresistant gliomas may both benefit from therapy based on purine nucleoside analogs. Although the idea to use purine (as well as pyrimidine)
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analogs is old, it should not be underestimated. These drugs certainly deserve to be more exploited as therapeutic agents.

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