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Multimodal molecular imaging has recently attracted much attention due to its advantages in disease diagnostics. Within this context, we have demonstrated a new paradigm for multimodal bioimaging based on amino acids-anchored ultrasmall lanthanide-doped GdVO₄ nanoprobes. To develop effective contrast agents for medical imaging, the amino acids-anchored ultrasmall lanthanide-doped GdVO₄ nanocastings were a promising candidate as multimodal contrast agents and would bring more opportunities for biological and medical applications with further modification.

1. Introduction

Along with the rapid development in nanotechnology and bioengineering, significant attention has been focused on developing disease diagnostic nanoprobes using modern imaging modalities, such as optical, ultrasound, magnetic resonance imaging (MRI), X-ray computed tomography (CT), positron emission tomography (PET), and photoacoustic tomography (PAT). Among the various nanoparticulate contrast agents, the lanthanide-doped Gd³⁺-containing nanoparticles have shown prominent potential in biomedical field. Owing to the superior characteristics such as long luminescence lifetime, narrow emission band widths, high resistance to photobleaching, the lanthanide-doped Gd³⁺-containing inorganic nanoparticles have become promising alternative to organic fluorophores and quantum dots for application in photoluminescent bioimaging. Additionally, Gd³⁺ ions, with unpaired f electrons are paramagnetic and have been used as contrast agents for MR imaging. Moreover, because of their relatively larger K-edge value and higher X-ray mass absorption coefficient, Gd³⁺-doped nanocastings have been used as more excellent CT contrast agents than routinely used small iodinated molecules. Given above, lanthanide-doped Gd³⁺-containing nanoparticles would be applied as nanoprobes for multimodal imaging, combining CT, MRI and PL imaging, combining provided advantages of high temporal resolution and relatively high sensitivity. In particular, for application to in vivo bioimaging, there were some rigorous requirements for bioprobes, such as small size (<10 nm), metabolism and biocompatibility. However, the formation of monodispersed sub-10 nm lanthanide-doped nanoparticles was generally based on high temperature thermal decomposition methods, which makes the hydrophobic ligands remain on the surface of nanoparticles. Therefore, for the biocompatible and practical utility, these as-prepared nanogents always need to be functionalized with biocompatible molecules through complicated synthesis routes, time-consuming experimental techniques, and stringent synthetic conditions such as layer-by-layer method, post-modification of ion complex, as well as ligand exchange route. Generally, several amphiphilic polymer materials have been chosen for surface coating and assembly with nanoparticles to form hydrophobic inner layer. In this way, the hydrophobic inner layer would restrict water exchange, reduce the r1 relaxivity and weaken contrast effect. Accordingly, fabrication of ultrasmall, metabolizable and biocompatible multimodal contrast agents via simple methods and achieving superior contrast effect are very challenging but highly desirable.

In recent years, as a new bottom-up solution chemistry method to design and manipulate desired structures, biomolecule-assisted synthetic routes have attracted much attention. Various biomolecules, such as DNA, proteins, peptides, and enzyme, have been exploited to become extremely favorable scaffolds for the fabrication of various nanoparticles, which have shown potential in catalysis, biosensing, clinical diagnosis and therapy, et al. Taking advantage of biomolecular complexation, functional nanostructures can be prepared without additional complex modification. Additionally, biomolecule-assisted synthetic nanoparticles possess a large number of functional groups anchoring on their surface to enable solubility/dispersibility in various solvents. These functional groups can also allow flexible covalent chemistry for linkage with target molecules. More
significantly, biomolecule-capped nanoparticles have shown low toxicity and high biocompatibility for biomedical applications.

Herein, we demonstrated a new paradigm for multimodal bioimaging based on amino acids-anchored ultrasmall lanthanide-doped GdVO₄ nanoprobes. In merit of special metal-cation complexation and abundant functional groups, these amino acids-anchored nanoprobes would show high colloidal stability and excellent dispersibility in different media. Additionally, due to typical paramagnetic behavior, high X-ray mass absorption coefficient and strong fluorescence, these nanoprobes would provide a unique opportunity to develop multifunctional probes for MRI, CT and luminescence imaging. More importantly, the small size and biomolecule coatings would endow the nanoprobes with the effective metabolism and high biocompatibility, which is the emphasis on moving this contrast agent closer to the clinical setting.

2. Experimental section

2.1. Reagents and materials

All chemicals were of analytical grade and used directly without further purification. Gadolinium (III) nitrate hexahydrate (Gd(NO₃)₃·6H₂O), europium(III) nitrate hexahydrate (Eu(NO₃)₃·6H₂O), sodium orthovanadate (Na₃VO₄), aminoacetic acid (NH₂CH₂COOH) were purchased from Aladdin. Dehydrated ethanol was purchased from Beijing Chemicals (Beijing, China). Water throughout all experiments was obtained by using a Milli-Q water system.

2.2. Synthesis of amino acids-capped GdVO₄: Eu³⁺ nanocastings

Gd(NO₃)₃·6H₂O (0.2616 g), Eu(NO₃)₃·5H₂O (0.0136 g), and aminoacetic acid (0.16 g) were dissolved in 20 mL of distilled water. 20 mL of an aqueous Na₃VO₄ solution (0.1122 g) was added to the above aqueous solution under magnetic stirring for about 10 min at room temperature. The resulting reaction mixture (40 mL) was transferred to a Teflon-lined stainless steel autoclave and treated at desired temperature in the range of 180–350 °C for 20 h, and then cooled naturally to room temperature. The obtained product was centrifugated, washed several times by water and ethanol, and dried at 60 °C for 2 h.

2.3. Leaching study of Gd³⁺ ions from the nanoparticles

10 mL of GdVO₄: Eu³⁺ nanoparticles solution (1 mg/mL) was taken into a dialysis bag (50 kD cut-off) and dialyzed against physiological saline with 10% fetal bovine serum under stirring. Taking 0.5 mL of above physiological saline out one week later and inductively coupled plasma mass spectrometry (ICP-MS) was applied to determine the content of Gd³⁺ ions.

2.4. Cell cultures

A549 cells, HEK-293 cells and HeLa cells were supplied by ATCC (American Type Culture Collection). Cells were cultured in Dulbecco’s modified Eagle’s medium (DMEM) containing penicillin (100 U/mL), streptomycin (100 μg/mL), and 10% fetal bovine serum (FBS) in a humidified incubator at 37 °C and 5% CO₂. Cells were harvested by the use of trypsin and were resuspended in fresh complete medium before plating.

2.5. In vitro cytotoxicity studies

MTT reduction assays were carried out to quantify the cytotoxicity of GdVO₄: Eu³⁺ nanocastings. In a typical procedure, cells (A549 and HEK-293 cell lines) were cultured in 96-well plates as a density of 5000 per well for 12 h to allow the cells to attach. Subsequently, serial dilutions of different nanoparticles formulations were added to the culture medium. At the end of the incubation time, the medium containing nanoparticles were removed, and cell samples were treated with MTT for another 4 h, which was followed by the addition of dimethyl sulfoxide (DMSO) to dissolve the formazan crystals. Bio-Rad model-680 microplate reader was applied to measure the absorbance at a wavelength of 570 nm (corrected for background absorbance at 630 nm). Six replicates were done for each treatment group and percent viability was normalized to cell viability in the absence of nanoparticles.

2.6. Cellular modality and observation

To observe morphological changes of cells, a typical experiment, A549 and HEK-293 cells with a density of 2 × 10⁵ were placed in a 24-well plate for 4 h to allow the cells to attach. After the cells were washed twice by cool phosphate-buffered saline (PBS), nanoparticles (200 μg/mL) were added to the cell culture medium. After incubating for 48 h, the cells were washed again with PBS several times to remove the remaining nanoparticles, and then observed under an Olympus BX-51 optical system microscopy upon white light. Pictures were then taken with an Olympus digital camera.

2.7. In vitro hemolysis assay

The hemolysis assay experiments were carried out as an important factor to evaluate the in vitro biocompatibility. Human blood samples stabilized by EDTA were obtained from the local hospital. Firstly, 1 mL of blood sample was added to 2 mL of PBS, and then red blood cells (RBCs) were isolated from serum by centrifugation at 8,000 rpm for 10 min. After being washed five times with 5 mL of PBS solution, the purified blood was diluted to 1/10 of its volume with PBS solution. 0.2 mL of diluted RBC suspension was then mixed with (a) 0.8 mL of PBS as a negative control, (b) 0.8 mL of D. I. water as a positive control, and (c) 0.8 mL of GdVO₄: Eu³⁺ nanoparticle suspensions at concentrations ranging from 0 to 200 μg mL⁻¹. Then all the mixtures were vortexed and kept at room temperature for 3 h. Finally, the mixtures were centrifuged at 8,000 rpm for 5 min, the absorbance of supernatants at 541 nm was determined by a JASCO V-550 UV-vis spectroscopy. The percent hemolysis of RBCs was calculated as follows: percent hemolysis = [(sample absorbance – negative control absorbance) / (positive control absorbance – negative control absorbance)] × 100.

2.8. In vitro phosphorescence imaging

HeLa cells were incubated with GdVO₄: Eu³⁺ nanoparticles (100 μg/mL) for 4 h, and were washed with phosphate buffer saline (PBS) three times and being resupplied with fresh DMEM. Phosphorescence images were collected. The cell samples were then examined by an Olympus BX-51 optical system microscopy. Pictures were taken with an Olympus digital camera.

2.9. Animal administration

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Wistar rats and Kunming mice were purchased from Medical Experimental Animal Center of Jilin University (Changchun, China). All animal procedures were in accord with the guidelines of the Institutional Animal Care and Use Committee.

2.10. In vitro and in vivo CT imaging

For in vitro CT imaging, GdVO₄: Eu³⁺ nanoparticles and lobitiridol were dispersed in PBS buffer solution at concentrations ranging from 0 to 100 mM. For in vivo CT imaging, the rat was first anesthetized by intraperitoneal injection of chloral hydrate solution (10 wt%), and then 1 mL of GdVO₄: Eu³⁺ nanoparticles solution (25 mM) were injected intravenously into rat, respectively. The rat was imaged repeatedly up to 60 min. CT images were collected using a JL U.A NO.2 HOSP Philips iCT 256 slice scanner, imaging parameters were as follows: thickness, 0.9 mm; pitch, 0.99; 120 KVP, 300 mA; field of view, 350 mm; gantry rotation time, 0.5 s; table speed, 158.9 mm/s.

2.11. In vitro and in vivo MR imaging

For in vitro T₁-weighted MR imaging, dilutions of GdVO₄: Eu³⁺ nanoparticles in PBS buffer solution containing 1% agarose with expected different concentrations as contrast agent were placed in 20 nanoparticles in PBS buffer solution containing 1% agarose with thickness and stained with hematoxylin and eosin (H&E).

2.12. Biodistribution assays

To study the tissue distribution for GdVO₄: Eu³⁺ nanoparticles, the organs (heart, liver, spleen, lung, and kidneys) were surgically removed from above two groups (control and test groups). 50 liquid was subjected to ICP-MS analysis.

2.13. Hematology studies

GdVO₄: Eu³⁺ nanoparticles (5 mg/kg) was injected via the tail vein into five healthy Kunming mice in each group, other five mice were used as the untreated controls. 30 days after injection, mice in each group were respectively sacrificed to collect blood (0.8 mL) for serum biochemistry assay and complete blood panel test. 30 days after injection, mice in each group were respectively sacrificed to collect blood (0.8 mL) for serum biochemistry assay and complete blood panel test.

2.14. Histologic analysis

For histologic studies, mice were sacrificed for 30 days after administration. The tissues (heart, spleen, liver, lung, and kidney) were collected from above two groups (control and test groups). The ex vivo organs were immersed in a buffered solution of 4% paraformaldehyde for 2-3 days, dehydrated and treated for inclusion in paraffin. The specimen was sectioned serially at 4 mm thickness and stained with hematoxylin and eosin (H&E).

2.15. Statistical analysis

All data were expressed in this article as mean result ± standard deviation (SD). All figures shown in this article were obtained from three independent experiments with similar results. The statistical analysis was performed by using Origin 8.0 software.

2.16. Characterization

Transmission electron microscope (TEM) measurements were carried out on a JEOL JEM-2010EX transmission electron microscope with a tungsten filament at an accelerating voltage of 200 kV. Energy-dispersive X-ray spectrometer (EDS) was employed for approximate elemental analyses. The samples were prepared by placing a drop of prepared solution on the surface of a copper grid and dried at room temperature. The crystalline structures of the as-prepared samples were evaluated by X-ray diffraction (XRD) analysis on a Rigaku-Dmax 2500 diffractometer by using CuKα radiation (λ = 0.15405 nm). The operation voltage and current were kept at 40 kV and 40 mA. The surface composition of the samples and binding energy were determined by X-ray photoelectron spectroscopy (XPS, Perkin Elmer PHI 5600). FT-IR analyses were carried out on a Bruker Vertex 70 FT-IR Spectrometer.
scattering (DLS) (Fig. S1b). The diameters of as-prepared amino acids-anchored GdVO₄:Eu³⁺ based on DLS became larger than the size observed from TEM images due to the swell in aqueous solution. High-resolution TEM images suggested that the nanoparticle was a single crystal with an interplanar spacing of 0.30 nm, which corresponds to the separation between the (200) lattice planes of tetragonal GdVO₄ (Fig. 1b). The elemental dispersive spectrum (EDS) evidenced the existence of all expected elements (Gd, Eu, V, O and N) in the as-prepared nanoparticles (Fig. 1c). All of the diffraction peaks’ positions and intensities for the as-prepared nanoparticles in the X-ray diffraction (XRD) pattern (Fig. 1d) were in good agreement with the reference data (JCPDS: 17-0260). In addition, carboxylic groups were observed from the Fourier transform infrared (FTIR) spectrum, which demonstrated that amino acids were anchored on the surface of the nanoparticles (Fig. S2). The amount of amino acids on the nanoparticles, as evaluated by TGA analysis, was approximately 6.20% (Fig. S3). Due to the present of hydrophilic ligands on their surface, the well-designed products were stable and dispersible in various solutions including PBS, FBS, and DMEM, which was important for further biomedical application (Fig. S4).

To evaluate the potential application of amino acids-capped GdVO₄:Eu³⁺ nanoparticles as multimodal bioimaging probes, the toxicity of nanomaterials were firstly investigated. Leaching of free Gd ions from materials could cause high toxicity towards natural organs and tissue, such as nephrogenic systemic fibrosis (NSF), thereby long-term dialysis experiments against solution were initially studied. The result revealed that no significant leakage of Gd⁴⁺ was measured through inductively coupled plasma mass spectrometry (ICP-MS) even after a week, which was benefit from the functional groups (amines and carbonyls) interacted with the metal ions.

Having established the excellent dispersibility and stability of the amino acids-anchored GdVO₄:Eu³⁺ nanocastings in solution, we next performed methyl thiazolyl tetrazolium (MTT) assay to evaluate their cytotoxicity with A549 cells and HEK 293 cells, which determined their feasibility for potential bioimaging applications. After incubation with increasing amounts of GdVO₄:Eu³⁺ nanoparticles for 24 h, neither the cell viability nor proliferation in A549 cells and HEK 293 cells were hindered. Even at a relatively high dose of nanoparticles (1000 μg/mL), the cell viability still remained above 90% (Fig. 2a). Morphological changes in living cells affected by GdVO₄:Eu³⁺ were also investigated using microscope (Fig. 2b). Microscope images illustrated no obvious difference in the cell morphology between treated and control groups. In vitro hemolytic assay was usually applied to investigate the interaction between nanomaterials and blood components. As shown in Fig. 2c, nearly no signal around 541 nm was detected upon the maximal experimental concentration (200 μg/mL), indicating the extremely low hemolysis of amino acids-capped GdVO₄:Eu³⁺ nanocastings. On the basis of these results, it could be inferred that amino acids-capped GdVO₄:Eu³⁺ nanocastings was biocompatible and nearly nontoxic to live cells, which implied that they could serve as a secure contrast agent for bioimaging.

Compared with organic luminophores, phosphorescent lanthanide-doped complexes as probes have attracted increasing interest due to their advantageous photophysical properties, such as large Stoke’s shifts for easy separation of excitation and emission, high photostability, and long emission-lifetimes.
GdVO$_4$:Eu$^{3+}$ nanoparticles can be used as a novel phosphorescent probe for cellular imaging. As shown in Fig. 3c, after HeLa cells were incubated with GdVO$_4$:Eu$^{3+}$ nanoparticles (100 $\mu$g/mL) for 2 h at 37 °C, bright red luminescence signals (red color) inside cells were observed. This result demonstrated that amino acids-capped GdVO$_4$:Eu$^{3+}$ nanoparticles can be used as a novel phosphorescent probe for the cellular imaging.

**Fig. 4** (a) In vitro CT images of GdVO$_4$:Eu$^{3+}$ nanoparticles and iobitridol with different concentrations. (b) CT values (HU) of GdVO$_4$:Eu$^{3+}$ nanoparticles and iobitridol as a function of the agent concentrations at 120 KVp. (c-e) In vivo CT coronal view images of a rat after intravenous injection of 1 mL 25 mM GdVO$_4$:Eu$^{3+}$ nanoparticles solution at timed intervals. (c) Heart and liver. (e) Spleen and kidney. (d, f) The corresponding 3D renderings of in vivo CT images.

Owing to high X-ray mass attenuation coefficient (3.11 cm$^2$ g$^{-1}$ at 100 keV) and large K-edge energy (50.2 keV), Gd-based nanostructures hold great promise as CT contrast agents. To investigate the in vitro CT contrast efficacy, we compared the X-ray absorption of amino acids-capped GdVO$_4$:Eu$^{3+}$ nanoparticles to that of iobitridol, a routinely used clinical CT contrast agent (Fig. 4a). The Hounsfield units (HU) values varied linearly as a function of the each agent concentration (Fig. 4b). Notably, at equivalent concentrations, the measured HU value of amino acids-capped GdVO$_4$:Eu$^{3+}$ nanoparticles was significantly enhanced compared to iobitridol due to the fact that the attenuation coefficient of Gd was larger than that of I (1.94 cm$^2$ g$^{-1}$ at 100 keV). Moreover, lanthanides usually gave high HU value at clinical voltage because of their high atomic number and suitable K-edge locating within the higher energy region of clinical X-ray spectrum. Therefore, our well-prepared nanoparticles showed greatly superior to previous reported Au-, Ta-, and W-based nanoparticle contrast agents.

Encouraged by their high CT contrast performance of in vitro experiment, we further evaluated the feasibility of as-prepared nanoparticles as a CT contrast agent in vivo. We tested the whole-body CT imaging by intravenous injection of nanoparticles and discussed the biodistribution of contrast agents tracked by X-ray CT technique at timed intervals. As shown in Fig. 4c and 4d, we could observe clear contrast enhancement in liver at an early time (10 min) and a gradual accumulation in the liver as time progressed. Remarkably, even after 1 h, the HU value of the liver was still higher than other surrounding tissues. This feature of the long-lasting liver contrast enhancement was mainly ascribed to the fact that more nanoparticles could be accumulated by macrophages and hepatocytes. These results indicated that our imaging nanoprobe was beneficial in potential clinical applications because of its highly stability and excellent contrast performance.

Simultaneously, because the Gd in GdVO$_4$:Eu$^{3+}$ nanoparticles can accelerate longitudinal ($T_1$) relaxation of water protons, the nanoparticles showed greatly superior to previous reported Au-, Ta-, and W-based nanoparticle contrast agents. 

To verify the MRI effectiveness of nanoprobes, an in vitro $T_1$-weighted MR imaging was conducted on a 1.5 T Siemens Magnetom Trio system. As illustrated in Fig. 5a, a positive enhancement for MR signal was observed for all the tubes comparing to water. Moreover, with the increase of GdVO$_4$:Eu$^{3+}$ nanoparticles concentration, $T_1$-weighted MR imaging intensity substantially brightened, demonstrating it could serve as an efficient $T_1$-weighted MR contrast agent. The specific relaxivity values ($r_1$) calculated from the slope of the concentration-dependent relaxation rate was 1.88 mmol$^{-1}$s$^{-1}$, which was comparable to the values of previous Gd-based $T_1$ contrast agents (Fig. 5b).
Additionally, the application of MR imaging in vivo for small animals was also demonstrated by the rat after intravenous injection with 1 mL 10 mM GdVO$_4$:Eu$^{3+}$ nanoparticles. The pre-contrast and post-contrast $T_1$-weighted MR imaging were recorded at the beginning, and after 10 min, 30 min, and 60 min following injection with nanoparticles. It was worth noting that the nanoparticles could induce an efficient positive-contrast enhancement in liver along with the passing of time (Fig. 5c), which was consistent with our CT imaging results. These results suggested that the as-prepared nanoparticles could be desirable contrast agents for MR imaging.

With the excellent multifunctional imaging performance of amino acids-capped GdVO$_4$:Eu$^{3+}$ nanoparticles, detailed toxicity in vivo must be well investigated before they are translated into the clinic. As shown in Fig. 6a, nearly no GdVO$_4$:Eu$^{3+}$ nanoparticles retained in the mice body at one month after administration of a single dose, indicating the effective time-dependent metabolism process. In order to know the pathway of the GdVO$_4$:Eu$^{3+}$ nanoparticles clearance from the mice body, the accurate biodistribution of the contrast agent in the main organs (heart, liver, spleen, lung, kidneys, and intestine) was measured as a function of time and detected through ICP-MS analysis. As shown in Fig. 6b, markedly decreasing signals of Gd$^{3+}$ contents in all organs were observed due to the stepwise clearance of nanoparticles from mice body. Furthermore, Gd content measurements in mice excretions (feces and urine) after intravenous injection showed that the contrast agent was possibly excreted via metabolism (Fig. S6).

![Fig. 6](image)

**Fig. 6** (a) Whole body clearance of GdVO$_4$:Eu$^{3+}$ nanoparticles in mice at different timed intervals. (b) Time-dependent biodistribution of GdVO$_4$:Eu$^{3+}$ nanoparticles in mice. (c) Histological changes of the mice 30 days after a single-dose intravenous injection of GdVO$_4$:Eu$^{3+}$ nanoparticles. These organs are stained with H&E and observed under a light microscope. Error bars were based on standard deviation of 5 mice per group.

To further determine whether GdVO$_4$:Eu$^{3+}$ nanoparticles caused any adverse effects or disease during its retention in the mice bodies, we next investigated the long-term toxicity through body weight measurement, histological assessment and hematological analysis. The fluctuation in body weight is a useful indicator for studying the toxicity effects. As shown in Fig. S7, body weight of the test group increased slightly in a pattern similar to that of the control group. Straightforward behavior observation over 30 days also indicated that there were no obvious signals of toxicity. Additionally, histological assessment was performed on the tissues obtained from the susceptible organs (heart, liver, spleen, lung, and kidney) to assess signs of potential toxicity. As shown in Fig. 6c, no tissue damage or any other harmful effect associated with the administration of the contrast agents was observed compared with those of the control group (Fig. S8). For hematological analysis and blood biochemical assay, there was nearly no difference between these two groups one month after intravenous injection (Table S1). Based on above results, it indicated that amino acids-assisted GdVO$_4$:Eu$^{3+}$ nanoparticles showed promise as a multimodal contrast agent for applications in biological medicine because of their eminent safety.

4. Conclusions

In summary, ultrasmall GdVO$_4$:Eu$^{3+}$ nanoparticles were successfully synthesized by amino acids-assisted approach and used as a new platform for MRI/CT/phosphorescence multimodal imaging. Amino acids endowed nanoparticles with high colloidal stability and excellent dispersibility. Additionally, toxicity studies results revealed the excellent biocompatibility of GdVO$_4$:Eu$^{3+}$ nanoparticles, indicating the feasibilities for bioimaging. The property of phosphorescence, which possessed the strong red light emission, enhanced the high signal-to-noise ratio of cellular imaging. Moreover, Gd in amino acids-capped GdVO$_4$:Eu$^{3+}$ nanoparticles endowed the nanoparticles with high longitudinal relaxivity and the nanoparticles were suitable for $T_1$-weighted MR imaging. Notably, by virtue of a high X-ray absorption coefficient and a high content of gadolinium, the well-prepared nanoparticles provided a higher contrast efficacy than routine iodine-based agents in clinic. More importantly, the study of pharmacokinetics, biodistribution, and in vivo toxicity demonstrated the nanoparticles possessed effective metabolism and high biocompatibility. With the superior stability, high biocompatibility, effective metabolism and excellent contrast performance, amino acids-capped GdVO$_4$:Eu$^{3+}$ nanocastings were a promising candidate as in vivo multimodal contrast agents and would bring more opportunities for biological and medical applications with further modification.

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