Magnetofection™ *In vivo*

INSTRUCTION MANUAL

Magnetofection™ In vivo Kits

In vivo PolyMag
In vivo DogtorMag
In vivo ViroMag







In vivo Magnetofection™

Instruction Manual

In vivo Magnetofection™ is an original, simple and efficient method to transfect target cells/tissue *in vivo*.

List of *In vivo* Magnetofection™ kits

Catalog Number	Product	Volume	Number of injections	Suitable for
IV-KC30210	<i>In vivo</i> PolyMag Starting kit ¹	500 μL	5-50 injections	500 µg
IV-KC30220	<i>In vivo</i> DogtorMag Starting kit ²	500 μL <i>In vivo</i> Dogtor + 500 μL <i>In vivo</i> CombiMag	5-50 injections	500 µg
IV-KC30230	<i>In vivo</i> ViroMag Starting kit ³	250 μL	10-25 injections	1-2 x 10 ⁷ pfu
IV-PN30500	<i>In vivo</i> PolyMag 500	500 μL	5-50 injections	500 μg DNA
IV-PN31000	<i>In vivo</i> PolyMag 1000	1000 μL	10-100 injections	1000 μg DNA
IV-DM30500	<i>In vivo</i> DogtorMag 500	500 μL <i>In vivo</i> Dogtor + 500 μL <i>In vivo</i> CombiMag	5-50 injections	500 μg DNA
IV-DM31000	<i>In vivo</i> DogtorMag 1000	1000 μL <i>In vivo</i> Dogtor + 1000 μL <i>In vivo</i> CombiMag	10-100 injections	1000 μg DNA
IV-VM30250	<i>In vivo</i> ViroMag 250	250 μL	10-25 injections	1-2 x 10 ⁷ pfu
IV-VM30500	<i>In vivo</i> ViroMag 500	500 μL	20-50 injections	2.5-5 x 10 ⁷ pfu
IV-MAG1	Magnets set ⁴	1	/	/
IV-MAG2	Square magnets set⁵	1	/	/
IV-MAG3	Cylinder magnets set ⁶	1	/	/

¹ contains 1 vial of *In vivo* PolyMag and a Magnets set

² contains 1 vial of *In vivo* Dogtor, *In vivo* CombiMag and a Magnets set

 $^{^{3}}$ contains 1 vial of *In vivo* ViroMag and a Magnets set

⁴ contains 1 extra small cylinder (ø 2 mm), 1 small cylinder (ø 5 mm), 1 cylinder (ø 10 mm) and 1 square (18x18 mm) magnets

⁵ contains 4 square magnets (18x18 mm)

⁶ contains 4 extra small cylinder (ø 2 mm), 4 small cylinder (ø 5 mm), 4 cylinder (ø 10 mm) magnets

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1. Technology

1.1. Description

Congratulations on your purchase of the *In vivo* Magnetofection™ reagent!

In vivo Magnetofection[™] is a rapid, simple and highly efficient method especially dedicated to transfect and/or transduce target cells/tissue *in vivo*. This original system combines magnetic nanoparticles and nucleic acid vectors that will be retained after injection at the magnetically targeted site. In this way, targeted delivery minimizes systemic distribution, decreases gene vectors inactivation and reduces toxicity. Furthermore, the magnetic forces enhance the uptake of magnetic nanoparticles by the target tissue, and thus improve the efficiency of transfection/transduction. This allows decreasing the required process time of delivery to few minutes which is crucial for improvement of *in vivo* nucleic acid delivery (principally in stringent conditions, refer to results for more information). All *In vivo* Magnetofection[™] reagents have been especially designed by our R&D team to meet in vivo grade quality (reagents performed under high manufacturing and quality standards and tested by strict quality controls).

In vivo Magnetofection™ main advantages in comparison to standard procedures:

- 1. Increased transfection/transduction efficiency
- 2. Targeted process (magnetically-driven)
- 3. Reduction of the systemic dissemination of vectors during injection
- 4. Reduction of the vector doses (nucleic acid, virus...)
- 5. Work under non permissive conditions (hypothermia, physiological flow conditions)
- 6. Penetration of the vector into tissues
- 7. Minimized toxicity
- 8. Universal suitable for all nucleic acids or viral vectors

In vivo Magnetofection™ magnetic nanoparticles are non-toxic, biodegradable and totally biocompatible. The toxicity of iron oxide-based magnetic nanoparticles has been extensively studied due to their widespread use in medical imaging such as MRI, cell tracking and hyperthermia or cancer therapies as well as their use in diagnosis and cell purification. The amount of iron oxide required for nucleic acid delivery is far below the doses inducing toxicity. The iron oxide contained in Magnetofection™ nanoparticles has been shown to degrade through natural iron metabolism pathway (for review, Gupta and Gupta, 2005; Laurent *et al.*, 2011; Plank *et al.*, 2011).

1.2. Available Reagents

OZ Biosciences offers three types of ready-to-use *In vivo* Magnetofection™ reagents:

- 1. *In vivo* PolyMag is a cationic polymer-based magnetic nanoparticles formulation. It can be used with any nucleic acid (plasmid DNA, antisense oligonucleotides, mRNA, shRNA and siRNA...)
- 2. *In vivo* **DogtorMag** is a cationic lipid-based magnetic nanoparticles formulation. It associates *In vivo* **DogtorMag**, a specific cationic lipid, and **CombiMag** magnetic nanoparticles. This reagent is suitable for any nucleic acid (plasmid DNA, antisense oligonucleotides, mRNA, shRNA and siRNA...)
- 3. *In vivo* ViroMag is an optimized nanoparticles formulation dedicated to viral vectors. It is particularly suitable for Lentiviral/Retroviral, Adenoviral and Adeno-Associated Viral (AAV) vectors.

1.3. Kit Contents, Stability and Storage

Kit contents differ according to the components and volumes:

1. In vivo PolyMag.

- 1 tube containing 500 μL of *In vivo* PolyMag suitable for 5 to 50 injections
- 1 tube containing 1 mL of *In vivo* PolyMag suitable for 10 to 100 injections

2. In vivo DogtorMag.

- 1 tube containing 500 μL of *In vivo* CombiMag and 1 tube containing 500 μL of *In vivo* Dogtor suitable for 5 to 50 injections
- 1 tube containing 1 mL of *In vivo* CombiMag and 1 tube containing 1 mL of *In vivo* Dogtor suitable for 10 to 100 injections

3. In vivo ViroMag.

- 1 tube containing 250 μL of *In vivo* ViroMag suitable for 10 to 25 injections
- 1 tube containing 500 μL of *In vivo* ViroMag suitable for 20 to 50 injections

Stability, Storage and shipping conditions:

Storage: Upon receipt and for long-term use, store all tubes at the indicated storage conditions.

- In vivo PolyMag: store at +4°C
- In vivo DogtorMag: store at -20°C and In vivo CombiMag: store at + 4°C
- In vivo ViroMag: store at +4°C
- Do not freeze the nanoparticles
- Do not add anything to the stock solution of magnetic particles

<u>Stability</u>: Magnetofection[™] kits are stable for at least 18 months at the recommended storage temperature.

Shipping condition: room temperature.

Magnets manipulation:

- Manipulate carefully the magnets. Danger of injury by strong magnetic attraction of ferromagnetic materials
- Keep away from electronic devices and magnetic storage devices
- Persons with cardiac pacemakers should not work with these magnets

2. Applications

2.1. Nucleic acids and vectors

In vivo Magnetofection has been developed for in vivo targeted transfection of various types of nucleic acids such as DNA, RNA, oligonucleotides (In vivo PolyMag / In vivo DogtorMag) or transduction with any viral vectors (In vivo ViroMag). DNA/nanoparticles or virus/nanoparticles can be easily administrated through

various injection routes such as systemic administration (intravenous, intra-artery) or local administration (intraperitoneal, intratumoral, intracerebroventricular, intramuscular).

The instructions given hereunder represent protocols that were successfully applied in several studies. Nevertheless, optimal conditions vary depending on the nucleic acid, viral vector, animal model, administration route and the target organ. Therefore, use the Table 1 as a starting point for DNA amount and volume of injection in mouse and rats and Table 3 for viral vectors amount.

Notes:

- Nucleic acids should be as pure as possible, endotoxins free and prepare in water
- For the complexes preparation and injection, prefer saline buffer (HBS, PBS, normal saline, Ringer's solution) or glucose 5% solution.

Table 1: Suggested amount of nucleic acid and volume of injection in mouse (20 g) and rat (250 g)

		Mouse	
Route of injection	Amount of nucleic acid	Total volume of injection according to animal weight	Site of injection
Intravenous	40 µg	200 μL (10-25 μL/g)	Tail vein
Intramuscular	10 to 100 µg	100 μL (50 μL x 2 sites of injection)	Caudal tigh
Subcutaneous	10 µg	200 μL (10-40 μL/g)	Scruff
Intraperitoneal	100 µg	400 μL (20 μL/g)	Lower Ventral Quadrants
Intratumoral	10 to 50 µg	100 μL (0.5 μL/mm³)	Tumor
Intracerebroventricular	0.5 μg	2 μL	Brain ventricle
		Rat	
Route of injection	Amount of nucleic acid	Total volume of injection	Site of injection
Intravenous	150 µg	2.5 mL (10-20 μL/g)	Tail vein, saphenous vein
Intramuscular	50 to 300 μg	300 μL (100 μL x 3 sites of injection)	Triceps, Quadriceps, Gluteals
Intramuscular Subcutaneous	50 to 300 μg 5 to 10 μg		· · · · · · · · · · · · · · · · · · ·
		300 μL (100 μL x 3 sites of injection)	Triceps, Quadriceps, Gluteals
Subcutaneous	5 to 10 µg	300 μL (100 μL x 3 sites of injection) 1.25 mL (5-10 μL/g)	Triceps, Quadriceps, Gluteals Scruff, Back, Abdomen

Suggested volume of reagent:

- *In vivo* PolyMag: 1 μL per μg of DNA.
- In vivo DogtorMag and In vivo CombiMag: 1 μL each per μg of DNA.
- In vivo ViroMag: 10 to 20 μL per 1x10⁶ infectious viral particles.

2.2. Magnets

Several kinds of magnets are provided with the *In vivo* Magnetofection[™] kit; use Table 2 to choose the best one adapted to your application.

Table 2: Examples of use of magnets:

Kind of magnet	Tissue
Extra Small Cylinder	Brain area
2 mm (diameter) x 5 mm (height)	 Endothelial cells
	Small tumors
	 Lymph node
	Ovary
	Adrenal gland
Small Cylinder	Subcutaneous tumors
5 mm (diameter) x 5 mm (height)	Salivary gland
	Brain
Cylinder	Subcutaneous tumors
10 mm x 5 mm (height)	 Pancreas
	• Spleen
Square	Large organs
17 mm (length) x 17 mm (length)	Large tumor
x 5mm (height)	Muscle
	• Lung
	Skin flap

OZ Biosciences is currently proposing only those magnets. If you need specific magnet in terms of shape and size, please contact our technical service for obtaining fundamental properties of the magnet to purchase.

3.2 Protocols

3.1. In vivo PolyMag

Please refer to **Table 1** to determine the required amount of DNA as well as volume injection. The DNA, *In vivo* PolyMag and saline solutions should be at room temperature. We recommend using **1** µL of *In vivo* **PolyMag per µg of DNA**.

1. Reagents preparation.

a. *In vivo PolyMag*. Before each use, vortex *In vivo* PolyMag vial. Add the required volume of *In vivo* PolyMag (according to DNA amount needed) to a sterile microtube.

Note: For DNA doses of less than 1 μ g, pre-dilute an aliquot of *In vivo* PolyMag reagent with deionized water only, and use the volume required for your DNA dose. Discard the diluted *In vivo* PolyMag after use.

b. *DNA solution*. Dilute DNA in the final injection volume in a sterile vial (subtract the *In vivo* PolyMag volume).

Note: The final concentration of DNA should not exceed 0.5 mg/mL.

2. **Complexes formation**. Add the DNA solution to the *In vivo* PolyMag and mix immediately by pipetting up and down. Incubate the complexes for 20 min at room temperature.

3. Injection.

- a. Place the magnet on your targeted tissue
- b. Slowly inject the complexes
- c. Let the magnet stand from 5 min to 1 h (see section 3.4 and Table 4)

Notes for intracerebroventricular or intra tumoral injections: Place the magnet few seconds after the complexes injection. Dye *e.g.* Fast Green FCF can be added to the complexes solution for a better monitoring of the injection.

4. **Monitor gene expression** at the appropriate time point.

Important notes:

- Do not inject more than 1 mL of In vivo PolyMag per animal.
- Do not inject complexes if precipitate has formed

3.2. In vivo DogtorMag

Please refer to **Table 1** to determine the required amount of DNA as well as volume injection. The DNA, *In vivo* CombiMag, *In vivo* DogtorMag reagents and saline solutions should be at room temperature. We recommend using **1 μL of** *In vivo* **DogtorMag and 1 μL of** *In vivo* **CombiMag per μg of DNA**.

1. Reagents preparation.

a. *DNA solution*. Dilute DNA in half of the injection volume in a sterile vial (subtract the *In vivo* CombiMag volume).

Note: The final DNA concentration should not exceed 0.5 mg/mL. Dilute DNA in saline buffer (HBS, PBS, normal saline, Ringer's solution) or glucose 5% solution.

b. *In vivo DogtorMag solution*. Gently mix the reagent before use. Dilute *In vivo* DogtorMag in half of the injection volume. Incubate for 5 minutes at room temperature.

c. In vivo CombiMag reagent. Vortex the reagent before each use. Use 1 µL of CombiMag / µg DNA. Add the In vivo CombiMag reagent directly into a tube (do not dilute with any solution).

Note: For DNA doses of less than 1 µg pre-dilute an aliquot of *In vivo* CombiMag reagent with deionized water only and use the volume required for your DNA dose. Discard the diluted *In vivo* CombiMag after use.

2. **Complexes formation**. Combine the DNA solution with the Dogtor solution. Mix gently and incubate 5 min at RT. Combine the DNA/ *In vivo* DogtorMag mixture with the *In vivo* CombiMag reagent. Mix gently and incubate for 20 minutes at room temperature.

3. Injection.

- a. Place the magnet on your targeted tissue
- b. Slowly inject the complexes
- c. Let the magnet stand from 5 min to 1 h (see Table 6)

Notes for intracerebroventricular or intra tumoral injections: Place the magnet few seconds after complexes injection. Dye *e.g.* Fast Green FCF can be added to the complexes solution for a better monitoring of the injection.

4. **Monitor gene expression** at the appropriate time point.

Important notes:

- Do not inject more than 1 mL of *In vivo* CombiMag per animal.
- Do not inject complexes if precipitate has formed

Note: Magnetofectamine[™] (MTX0750) has also been successfully tested *in vivo*. Please contact our technical support team at <u>tech@ozbiosciences.com</u> for more details.

3.3. In vivo ViroMag

Determine the required injection volume according to the **Table 1**. The amount of virus you need to inject is closely correlated to your viral preparation, the route of injection, the target tissue and your preliminary *in vitro* studies. **Table 3** indicates a starting point for your protocol optimization. The *In vivo* ViroMag and saline solutions should be at room temperature. You may use **10 to 20 µL of** *In vivo* ViroMag per 1x10⁶ infectious viral particles. Do not exceed recommended volumes for injection.

Table 3: Suggested quantity of viral particles and *In vivo* ViroMag injected per mouse

Virus type	Viral particles titer (pfu)	<i>In vivo</i> ViroMag quantity (μL)
Adenovirus	1x10 ⁶ to 5x10 ⁸	10-20
AAV	1x10 ⁶ to 1x10 ¹⁰	10-20
Lentivirus	1x10 ⁶ to 5x10 ⁸	10-20

1. **Reagents preparation**. Immediately before use, vortex *In vivo* ViroMag vial. Add suitable amount of *In vivo* ViroMag to a sterile microtube

Note: If required *In vivo* ViroMag can be diluted with deionized water only. Discard the diluted *In vivo* ViroMag after use.

2. **Complexes formation**. Add your virus preparation to the tube containing the *In vivo* ViroMag reagent and mix immediately by pipetting up & down. Incubate 15-30 min at room temperature.

3. Injection.

- a. Place the magnet on your targeted tissue
- b. Slowly inject the complexes
- c. Let the magnet stand from 5 min to 1 h (see Table 6)

Notes for intracerebroventricular or intratumoral injections: Place the magnet few seconds after complexes injection. Dye *e.g.* Fast Green FCF can be added to the complexes solution for a better monitoring of the injection.

4. **Monitor gene expression** at the appropriate time point.

Important notes:

- Do not inject more than 1 mL of *In vivo* ViroMag per animal.
- Do not inject complexes if precipitate has formed

3.4. Magnetic incubation

The magnetic incubation time depends on the animal and the targeted tissue:

- for tumor, from 20 min (mouse, rat) to 1 hour (hamster, cat)
- for endothelial cells, from 5 to 20 min for mouse and rat, from 20 min to 1 h for rabbit or pig
- for peripheral tissue (e.g. stomach, gut, heart), 20 min
- for intracerebroventricular injection, 5 min

See **Table 4**, for other magnetic incubation times depending on target tissue, route of injection and magnet type.

Table 4: Suggested magnetic incubation time for various tissue

Target tissue	Route of injection	Kind of magnet	Magnetic incubation
Tumor	Intravenous, Intra-arterial, Intratumoral	All kind	20 min to 1 h
Endothelial cells	Intravenous, Intra-arterial	Extra small Cylinder	5 min to 1 h
Heart	Intra-arterial	Cylinder	20 min
Liver	Intravenous	Cylinder, Square	10 min
Lung	Intravenous	Square	10 min
Pancreas	Intrapancreatic	Cylinder	20 min
Kidney	Intraperitoneal	Cylinder, Square	20 min
Gut	llea lumen	All kind	20 min
Stomach	Stomach lumen	Cylinder, Square	20 min
Brain	Intraventricular	Small Cylinder	5 min

Notes:

- For long incubation time, (*e.g.* intratumoral injection), the magnet could be attached to the animal using adhesive tape in order to create a strong magnetic field in the area of the injection.
- Magnets can be easily handled with any magnetic surgical instruments (forceps, clamps, needle holders).
- Magnets can be sterilized by heat (steam sterilization or dry heat sterilization) or chemical means (ethanol 70%).

4. Appendix

4.1 Quality Controls

To assure the performance of each lot of *In vivo* PolyMag, *In vivo* DogtorMag, *In vivo* CombiMag and *In vivo* ViroMag produced, we qualify each component using rigorous standards. The following *in vitro* assays are conducted to qualify the function, quality and activity of each kit component.

Specification	Standard Quality Controls	
Sterility	Thioglycolate assay. Absence of fungal and bacterial contamination shall be obtained for 14 days.	
Biological Activity	<i>In vitro</i> transfection or infection efficiency. Every lot shall have an acceptance specification of > 80% of the activity of the reference lot.	
Magnetic nanoparticles	 Quality and size homogeneity of the magnetic nanoparticles. Stability of the magnetic nanoparticles formulations. 	
In vivo grade	Endotoxin Quantification. Endotoxins level shall be < 0.1 EU/mL for every lot.	

4.2. Troubleshooting

Problems	omments and Suggestions	
Low efficiency	Nucleic acid amount. Use different quantity of DNA transfection reagent / nucleic acid ratio.	A or siRNA with the recommended
	Magnetofection reagent / nucleic acid ratio. Optim varying the volume of reagent (<i>In vivo</i> PolyMag or <i>In</i> per µg of DNA.	-
	DNA quality. Nucleic acids should be as pure as pose phenol, ethanol) and endotoxins free. It must be "tra	
	Viral particles quality. Ensure that the ratio total/infect	tious particles number is correct
	Expression cassette . Make sure that the transgene is the expression cassette (promoter, terminator) is su	•
	Route of Injection . In order to improve your transfer injection close to your target tissue; <i>e.g.</i> inject your supplying artery (use the same quantity as intraveneraterial manipulations enhance the risk of thrombosis) together with magnet application.	vector intra-arterially into the tissue ous administration, be careful, intra-
	Medium used for preparing transfection complexe normal saline, Ringer's solution) or 5% glucose during	
	Injection volume. Optimize the volume of injection to	your application.
	Speed of injection. DNA expression could be deper your speed of injection to your target tissue.	ndent on the injection speed, adapt
	- Transfection reagent temperature. Reagents must vortexed prior to use.	t be at room temperature and be
	 Old transfection reagent / DNA complexes. The tra must be freshly prepared every time. Complexes pre hours can be aggregated. 	_ ·
	P-Incubation time. Optimal time range between transferomoter, expression product, etc. Transfection efficiency analyzing the gene product.	

Toxicity	1- Concentration of transfection reagent / nucleic acid too high. Decrease the amount of nucleic acid / reagent complexes injected by lowering the nucleic acid amount or the transfection reagent concentration. Complexes aggregation can cause some toxicity; prepare them freshly and never inject complexes where precipitate has formed.
	2- DNA quality - Presence of contaminants. Ensure that nucleic acid is pure, contaminant-free and endotoxin-free.
Precipitate formation	1- Concentration of transfection reagent / nucleic acid too high. Decrease the amount of nucleic acid / reagent complexes injected by lowering the nucleic acid amount or the transfection reagent concentration. Complexes aggregation can cause some toxicity; prepare them freshly and never inject complexes where precipitate has formed.
	2- DNA quality - Presence of contaminants. Ensure that nucleic acid is pure, contaminant-free and endotoxin-free. Prefer water than buffer (TE, Tris-CI) for your DNA preparation.
	3- Injection solution. Prefer 5% glucose (final concentration) than saline buffer (HBS, PBS, normal saline, Ringer's solution).

4.3. Bibliographic references

Please refer to the results sheet and to our website for a more comprehensive list of bibliographic reference.

- **Gupta A.K and Gupta M** 2005 Synthesis and surface engineering of iron oxide nanoparticles for biomedical applications. *Biomaterials*. 26:3995-4021.
- Laurent N, Sapet C, Le Gourrierec L, Bertosio E and Zelphati O 2011 Nucleic acid delivery nanoparticles : the Magnetofection™ technology. *Therapeutic Delivery*. 2:471:482.
- **Plank C, Zelphati O, Mykhaylyk O**. 2011 Magnetically enhanced nucleic acid delivery. Ten years of magnetofection-progress and prospects. *Adv Drug Deliv Rev.* 63:1300-1331

5. Related Products

Description

MAGNETOFECTION TECHNOLOGY

Super Magnetic Plate (standard size for all cell culture support)

Mega Magnetic plate (mega size to hold 4 culture dishes at one time)

Transfection reagents:

PolyMag Neo (for all nucleic acids)

Magnetofectamine™ (for all nucleic acids)

NeuroMag (dedicated for neurons)

SilenceMag (for siRNA application)

Transfection enhancer:

CombiMag (to improve any transfection reagent efficiency)

Viral Transduction enhancers:

ViroMag (to optimize viral transduction)

ViroMag R/L (specific for Retrovirus and Lentivirus)

AdenoMag (for Adenoviruses)

LIPOFECTION TECHNOLOGY (LIPID-BASED)

Lullaby (siRNA transfection reagent)

DreamFect Gold (Transfection reagent for all types of nucleic acids)

VeroFect (for Vero cells)

FlyFectin (for Insect cells)

i-MICST TECHNOLOGY

Viro-MICST (to transduce directly on magnetic cell purification columns)

3D TRANSFECTION TECHNOLOGY

3Dfect (for scaffolds culture) / 3DfectIN (for hydrogels culture)

RECOMBINANT PROTEIN PRODUCTION

HYPE-5 Transfection Kit (for High Yield Protein Expression)

PROTEIN DELIVERY SYSTEMS

Ab-DeliverIN (delivery reagent for antibodies)

Pro-DeliverIN (delivery reagent for protein in vivo and in vitro)

PLASMIDS PVECTOZ

pVectOZ-LacZ / pVectOZ-SEAP / pVectOZ-GFP / pVectOZ-Luciferase

ASSAY KITS

Bradford – Protein Assay Kit

MTT cell proliferation kit

SEAP Assay kit

β-Galactosidase assay kits (CPRG/ONPG)

BIOCHEMICALS

D-Luciferin, K^+ and Na^+ 1g

X-Gal powder 1g / G-418, Sulfate 1g

6. Purchaser Notification

Limited License

The purchase of this product grants the purchaser a non-transferable, non-exclusive license to use the kit and/or its separate and included components (as listed in section 1, Kit Contents). This reagent is intended **for in-house research only** by the buyer. Such use is limited to the purposes described in the product manual. In addition, research only use means that this kit and all of its contents are excluded, without limitation, from resale, repackaging, or use for the making or selling of any commercial product or service without the written approval of OZ Biosciences.

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