FlashRNA®: A GAME CHANGING RNA THERAPY FOR REGENERATIVE MEDICINE

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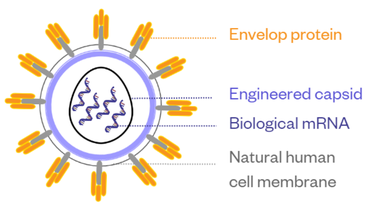
A. FlashRNA® for RNA therapy

Cell & Gene therapy approaches show that there is no universal delivery technology for all therapeutic strategies. Compared to DNA-based therapeutics, **RNA therapies** are expected to be more versatile, cover a broad range of applications with minimal regulatory concerns and thus address a large variety of diseases. The technology targets applications in which a **transient expression** is safer to stimulate a cellular process, to perform gene edition or to commit cells into a specific pathway.

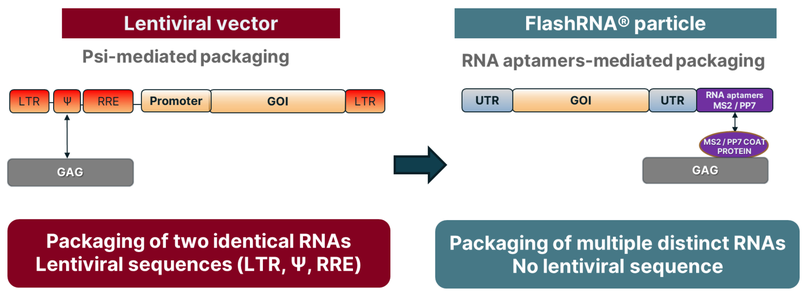
What is FlashRNA® ?



Prel *et al.* Mol Ther Methods Clin Dev. 2015

FlashRNA® is a bacteriophage-lentivirus chimera :

- ✓ efficiently and safely delivering **multiple RNA species** that are **rapidly bioavailable**
- ✓ leading to **a fast and short-term protein expression** in the target cells
- ✓ developed for **coding and non-coding RNAs**, and **gene editing systems**



B. FlashRNA® for regenerative medicine

BROAD RANGE OF APPLICATIONS

FlashRNA® is a cutting-edge RNA delivery system suitable for **all kinds of RNA therapy** applications such as :

GENE EDITING · REGENERATIVE MEDICINE · IMMUNOTHERAPY

As an example, this technology is fitted for **Regenerative medicine applied to single & multifactorial pathologies** paving the way for innovative therapies.

SECONDARY LYMPHEDEMA CLINICAL CONTEXT

Lymphedema is a lymphatic vascular system disorder characterized by:

- impaired lymphatic return and swelling of the extremities
- accumulation of undrained interstitial fluid/lymph.

It can occur after cancer surgery and lymph node removal. Indeed, 10-15% of women develop arm secondary lymphedema after surviving breast cancer. There is no curative treatment for lymphedema.

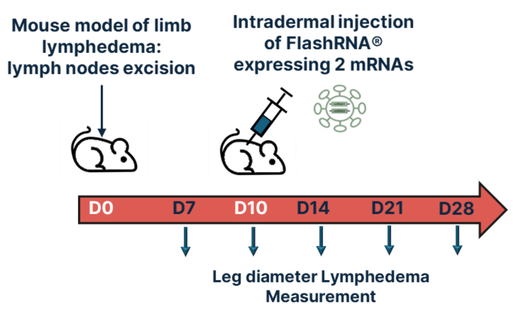
Theralymph clinical program's main objective is to establish a multiple gene therapy for secondary lymphedema, based on the transient expression of two factors allowing the restoration of a normal lymphatic function. FlashRNA® will be used to deliver the two therapeutic RNAs by intra-dermal injections.

THERALYMPH · HORIZON 2020 · Hôpitaux de Toulouse

C. An RNA Therapy for Secondary Lymphedema

LYMPHEDEMA MOUSE MODEL

Secondary lymphedema is induced in mice by mastectomy of the 2nd mammary gland, associated with brachial and axially lymphadenectomy. FlashRNA® is intra-dermally injected in limb at day 10.

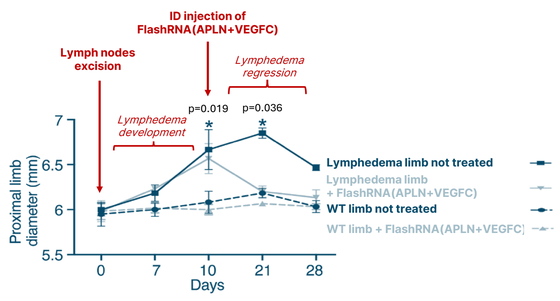


Natural regression of the pathology occurs after 21/28 days in mice.

Creff J. *et al*. EMBO Mol Med. 2024

PRE-CLINICAL RESULTS

FlashRNA® reduces lymphedema and inhibits swelling



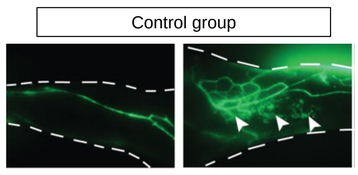
Measure of the size of healthy and diseased limbs over time (p-values are calculated using a two-way ANOVA test)

Lymphedema swelling reversion was observed from 1 day after FlashRNA® (APLN / VEGFC) treatment.
The complete regression was obtained 11 days post-injection despite the transient expression of the 2 transgenes.

FlashRNA® restores lymphatic vessels and suppresses dermal backflow

Lymphographies of treated and untreated limbs of control and lymphedema mice at day 14 post-surgery

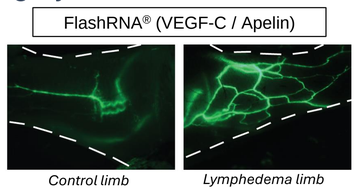
Control group



Control limb *Lymphedema limb*

After lymph nodes resection, mice exhibit a reduction of lymphatic drainage associated with visible dermal backflow (arrows)

FlashRNA® (VEGF-C / Apelin)



Control limb *Lymphedema limb*

14 days post-surgery lymphatic vessels are restored and dermal backflow is suppressed (well defined vessels)

No adverse immune responses with FlashRNA®

Confidential data, soon to be published

PRE-GMP BATCH RESULTS

Dose determination of FlashRNA®

Confidential data, soon to be published

D. Conclusion

FlashRNA® packages **biological RNAs of human origin**, without any lentiviral sequence.
FlashRNA® can deliver **multiple RNAs.**
FlashRNA® does **not** lead to **adverse immune responses.**
Transduction by FlashRNA® does **not** result in **GMO generation.**

It combines the efficient delivery of lentiviral vectors with the safety of RNA delivery since it enables **highly efficient transfer** and **transient expression:**

- ✓ FlashRNA® particles display a very large tropism thanks to **VSV-G pseudotyping.**
- ✓ **All cell types** can be efficiently transduced by FlashRNA® without altering cell viability nor phenotype.

The FlashRNA® properties, associated with FlashBioSolutions' **lentiviral production platform** compliant with the **cGMPs**, offer additional safety considerations making it a versatile and safe mean for human therapy.

Based on these positive pre-clinical results, **a first-in-human phase I/IIa clinical trial** using **dual RNA delivery by FlashRNA®** will be conducted **in 2025** on patients who developed lymphedema after breast cancer surgery (Sponsor: Toulouse University Hospital, France).

Furthermore, FlashRNA®, as an RNA delivery tool, can be used for a broad range of applications, such as **gene editing** (Mianné et al. 2022) and **vaccination/immunotherapy applications** for both infectiology and oncology purposes.

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