

TARGETING uPARAP TO TREAT SECONDARY LYMPHEDEMA

THE PATHOLOGY: SECONDARY LYMPHEDEMA

Secondary lymphedema (SL) affects a substantial and growing patient population worldwide, often following surgery, radiation therapy (especially in cancer treatment), infections, or trauma.

This chronic condition results from damage to the lymphatic system, leading to oedema, skin complications and progressive loss of function.

Among the 2.3 million women diagnosed with breast cancer each year worldwide, up to 25% will acquire debilitating SL, as are those treated for prostate, ovarian, and head and neck cancers.

NO AVAILABLE PHARMACOLOGICAL TREATMENT

Current patient care is limited to bandaging and limb compression to manage symptoms. No targeted pharmacological treatment exists to relieve, prevent or cure secondary lymphedema, underlining the urgent unmet need for an effective solution.

uPARAP AS A NEW TARGET

uPARAP (Mrc2 gene) is an endocytic receptor involved in fibrosis and lymphangiogenesis. uPARAP is implicated in extracellular matrix remodeling, a key process driving the development and progression of secondary lymphedema.

Two models were used to study the effects of uPARAP inhibition on SL attenuation: 1/ a preclinical mouse model of SL applied to uPARAP Knockout mice and 2/ an in vitro model of lymphatic endothelial cells downregulated for uPARAP.

⇒ uPARAP deficiency **mitigated several key pathological features of SL** including hindlimb swelling, epidermal thickening, as well as the accumulation of adipocytes.

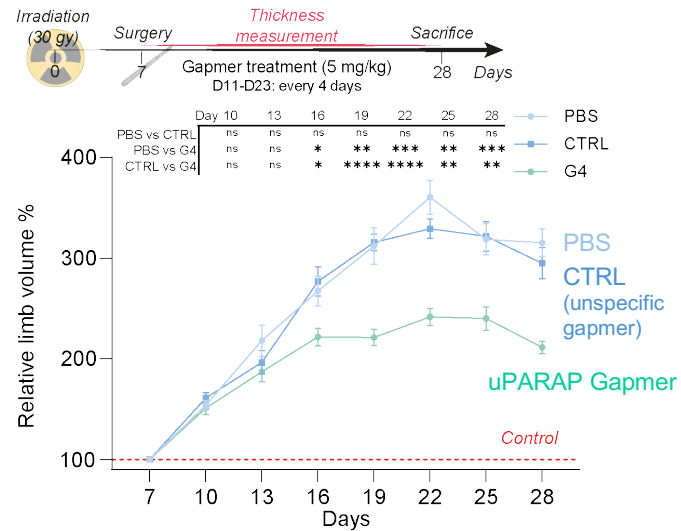
⇒ The absence of uPARAP expression induced a **beneficial formation of functional lymphatic vasculature** that attenuated lymphedema through a cell junction-based mechanism.

uPARAP INHIBITION: A NOVEL THERAPEUTIC PATHWAY

We developed **gapmer oligonucleotides targeting the uPARAP mRNA**, to silence its expression and reduce secondary lymphedema. Gapmers were injected in the mouse model of SL, resulting in a **significant reduction in lymphedema volume by 30–40%**, without affecting mice survival.

This volume reduction was associated with a decrease in adipose tissue density and a significant remodelling of the lymphatic network.

uPARAP Gapmer Injections Reduces Limb Swelling in SL Mice



Timeline of SL induction in WT mice treated with a gapmer (G4) targeting uPARAP (n=8), a negative control gapmer (CTRL; n=8), or PBS (n=8). The graph corresponds to the follow-up of the relative volume of the limb (percentage of control limb volume; dotted line=100%). Data are means ± SEM.

KEY ACHIEVEMENTS

- Remodeling of lymphatic vasculature in the absence of uPARAP
- Reducing lymphedema by 30–40% with Gapmer injection

KEY COMPETITIVE ADVANTAGES

- Mastering a preclinical secondary lymphedema model
- Reducing secondary lymphedema by targeting its pathophysiology
- A novel therapeutic pathway
- Move from palliative to curative care

KEY PUBLICATION

Gucciardo F. *et al.*, Circulation, 2025, Volume151, Issue19, 1412-1429.

INTELLECTUAL PROPERTY

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PARTNERSHIP SOUGHT

License and/or Collaboration Agreement to develop uPARAP gapmers and take them into the clinic