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| <b>Current Stage</b>              | Resubmission received                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <b>Title</b>                      | Nucleoside-Modified VEGFC mRNA Induces Organ-Specific Lymphatic Growth and Reverses Experimental Lymphedema                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
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| <b>Contributing Authors</b>       | Dr Dániel Szőke , Dr Gábor Kovács , Ms Eva Kemecei , Laszlo Balint , Kitti Ajtay , Petra Aradi , Andrea Styevkone Dinnyes , Barbara Mui , Ying Tam , Thomas Madden , Professor Katalin Karikó , Raghu Kataru , Dr Michael Hope , Professor Drew Weissman , Babak Mehrara , Dr Norbert Pardi                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <b>Authorship</b>                 | Yes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>Abstract</b>                   | Lack or dysfunction of the lymphatics leads to secondary lymphedema formation that seriously reduces the function of the affected organs and results in degradation of quality of life. Currently, there is no definitive treatment option for lymphedema. Here, we utilized nucleoside-modified mRNA encapsulated in lipid nanoparticles (LNPs) encoding murine Vascular Endothelial Growth Factor C (VEGFC) to stimulate lymphatic growth and function and reduce lymphedema in mouse models. We demonstrated that administration of a single low dose of VEGFC mRNA-LNPs induced durable, organ-specific lymphatic growth and formation of a functional lymphatic network. Importantly, VEGFC mRNA-LNP treatment reversed experimental lymphedema by restoring lymphatic function without inducing any obvious adverse events. Collectively, we present a novel application of the nucleoside-modified mRNA-LNP platform, describe a model for identifying the organ-specific physiological and pathophysiological roles of the lymphatics, and propose an efficient and safe treatment option that may serve as a novel therapeutic tool to reduce lymphedema.                                                                                                                                                                                                                                                                                                                                                                   |
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| <b>Subject Terms</b>              | Biological sciences/Biotechnology/Nucleic-acid therapeutics<br>Biological sciences/Developmental biology/Lymphangiogenesis<br>Health sciences/Medical research/Preclinical research                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>Show Author Information</b>    | Allow Reviewers to see Author information.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <b>Competing interests policy</b> | <b>Yes</b> there is potential Competing Interest.<br><br>In accordance with the University of Pennsylvania policies and procedures and our ethical obligations as researchers, we report that Katalin Karikó and Drew Weissman are named on patents that describe the use of nucleoside-modified mRNA as a platform to deliver therapeutic proteins. Drew Weissman and Norbert Pardi are also named on a patent describing the use of modified mRNA in lipid nanoparticles. We have disclosed those interests fully to the University of Pennsylvania, and we have in place an approved plan for managing any potential conflicts arising from licensing of our patents. No competing interests from other authors have been reported.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |

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| <b>Transparent peer review</b>   | Yes, I do want to participate in transparent peer review                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |

## Manuscript Items

1. Author Cover Letter [PDF \(321KB\)](#)
2. "Response to Referees Letter" [PDF \(512KB\)](#)
3. Merged File containing manuscript text and 17 Figure files. [PDF \(310843KB\)](#)
  - a. Article File [PDF \(120381KB\)](#)
  - b. Szoke et al. Figure 1 [PDF \(182KB\)](#)
  - c. Szoke et al. Figure 2 [PDF \(14349KB\)](#)
  - d. Szoke et al. Figure 3 [PDF \(4022KB\)](#)
  - e. Szoke et al. Figure 4 [PDF \(15222KB\)](#)
  - f. Szoke et al. Figure 5 [PDF \(26445KB\)](#)
  - g. Szoke et al. Figure 6 [PDF \(16635KB\)](#)
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  - q. Szoke et al. Suppl. Figure 5 [PDF \(7350KB\)](#)
  - r. Szoke et al. Suppl. Figure 6 [PDF \(5758KB\)](#)
4. Video - Szoke et al Suppl video 1 [Video \(71KB\)](#)
5. Video - Szoke et al Suppl video 2 [Video \(139KB\)](#)
6. Szoke et al VEGFC mRNA-LNP source data file [Supplementary Dataset \(535KB\)](#)
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