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Sustained-Release 9-*cis* Retinoic Acid Pellets for the Prevention of Postsurgical Lymphedema

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Purpose: Lymphedema is a disfiguring disease affecting over 250 million people worldwide. Nine-*cis* retinoic acid (9-*cis* RA) has recently been shown to limit postsurgical lymphedema and is already approved for clinical use in the US and UK for other conditions. Previous animal studies have tested 9-*cis* RA in intraperitoneal injection form, which has poor translatability to future clinical trials. The purpose of this study is to investigate the pro-lymphangiogenic effects of 9-*cis* RA contained within a single-use depot pellet drug delivery system in a clinically relevant mouse lymphedema model.

Methods: Hindlimb lymphedema was induced in 18 mice via combined lymphatic injury, consisting of inguinal and popliteal lymphadenectomy followed by irradiation. Animals were split into 2 groups: 1) the treatment group received pellets containing 9-*cis* RA, 2) the control group received placebo pellets. Pellets were placed within the surgical wound intraoperatively, with experimental pellets resulting in sustained drug release. Paw thickness was measured weekly for 6 weeks and normalized by calculating percent change relative to the unaffected paw. Lymphatic drainage was measured at postoperative week 6 via indocyanine green (ICG) lymphography.

Results: Compared to control animals, significantly less paw swelling was observed in 9-*cis* RA-treated animals at postoperative weeks 3 (7% change, $P<0.05$), 4 (12% change, $P<0.001$), 5 (9% change, $P<0.001$), and 6 (11% change, $P<0.001$). No significant difference in paw thickness was observed within the treatment group over time, indicating reduced lymphedema progression. 9-*cis* RA-treated animals had significantly faster lymphatic drainage than control animals as measured by ICG clearance ($P<0.05$).

Conclusion: Animals treated with 9-*cis* RA pellets at the time of surgery demonstrate significantly less paw swelling the first 6 weeks after lymphatic injury and faster lymphatic drainage compared to control animals. In conclusion, we demonstrate that single-use 9-*cis* RA pellets have favorable properties in limiting postsurgical lymphedema.