ONCOIMMUNOLOGY
2025, VOL. 14, NO. 1, 2510998
https://doi.org/10.1080/2162402X.2025.2510998

Taylor & Francis
Taylor & Francis Group

Routing immunomodulatory cytokine-encoded mRNAs to the omentum: turning an enemy into an ally in peritoneal metastasis

Leire Arrizabalaga[a,b], Ignacio Melero[a,b,c,d,e], Pedro Berraondo[a,b,c,e], and Fernando Aranda[a,b]

[a]Program of Immunology and Immunotherapy, Cima Universidad de Navarra, Cancer Center Clínica Universidad de Navarra (CCUN), Pamplona, Spain; [b]Navarra Institute for Health Research (IDISNA), Pamplona, Spain; [c]Department of Oncology, Clínica Universidad de Navarra, Cancer Center Clínica Universidad de Navarra (CCUN), Pamplona, Spain; [d]Nuffield Department of Medicine and Oxford Center for Immuno-Oncology, University of Oxford, Oxford, UK; [e]Centro de Investigación Biomédica en Red de Cáncer (CIBERONC), Madrid, Spain

ABSTRACT

Peritoneal metastases remain a significant clinical challenge owing to the immunosuppressive nature of the omentum, which serves as a protective niche for disseminated tumor cells. Our recent study explored the targeted delivery of immunomodulatory cytokine-encoded mRNAs to the omentum, aiming to shift its role from a tumor-supportive site to an immune-activating ally. Our findings highlight the potential of cytokine mRNA delivery as a novel and safe immunotherapeutic strategy for peritoneal metastases.

ARTICLE HISTORY
Received 17 March 2025
Revised 7 May 2025
Accepted 14 May 2025

KEYWORDS
mRNA; peritoneal carcinomatosis; locoregional immunotherapy; omentum

Peritoneal carcinomatosis is an advanced manifestation of cancer characterized by the dissemination of malignant cells within the peritoneal cavity. Primary tumors that can metastasize to the peritoneal cavity include gastrointestinal cancers such as gastric, colorectal, and appendiceal tumors, as well as gynecologic malignancies such as ovarian and endometrial cancer.[1] This condition is particularly challenging because it is usually diagnosed in the late stages and due to the limited effectiveness of available therapeutic options, such as systemic chemotherapy, which is often hindered by severe side effects and poor response in these advanced cases.[2] In light of this, locoregional immunotherapy has emerged as a promising alternative, given its potential to increase therapeutic efficacy locally, while reducing the systemic toxicity associated with conventional treatments. Previous investigations into immunotherapy delivered via intraperitoneal infusion represent a shift in the treatment paradigm for peritoneal carcinomatosis.[3] In this context, peritoneal metastases usually begin in the omentum. The omentum is recognized as the "*policeman of the abdomen*" which contains functional aggregates of different immune cells called "milky spots",[4] contributing to crucial peritoneal immunity by collecting antigens, toxins, and pathogens from the peritoneal cavity. Notwithstanding, in view of this paradox, our hypothesis highlights the omentum as a "*key player*" in the antitumor response against peritoneal metastases. In this regard, previous findings from our group have revealed that viral vectors[5] and tumor antigen-specific T cells[6] act mainly in the omentum when administered intraperitoneally, as opposed to other routes. This phenomenon activates the endogenous immune response of the omentum to induce antitumor responses in the areas of peritoneal carcinomatosis, which also have a systemic impact to eliminate distant tumors.[5] In line with this, we have demonstrated that locoregional immunotherapy strategies that are targeted to the omentum are a promising preclinical approach translatable to treat patients with peritoneal carcinomatosis.

More recently, we explored the potential of a cationic polymer/lipid-based transfection system for the intraperitoneal delivery of mRNA, aiming to induce an effector immune response in the omentum. In this study, the delivery system is shown to be highly efficient at promoting localized luciferase expression in the omentum following the intraperitoneal administration of mRNA complexes. One of the most relevant findings is that the delivery route minimizes systemic impact.[7] A particularly interesting aspect of this study was the identification of macrophages as the key cells involved in the uptake and expression of mRNA complexes. Depletion of macrophages in murine models resulted in a significant reduction in luciferase reporter expression in the omentum, suggesting that these phagocytes play crucial roles in the delivery and translation of mRNAs within the microenvironment surrounding the tumor.

These findings align with previous research highlighting the role of macrophages in immune responses against tumors and in the regulation of efficient immunotherapies. To evaluate the therapeutic potential of this strategy, as a proof-of-concept, we introduced mRNA encoding interleukin-12 (IL12), an immunostimulatory cytokine known for its ability to promote effective $CD4^+$ and $CD8^+$ T-cell responses against tumors. The results in murine models revealed a significant improvement in the survival of animals treated with mRNA-IL12; furthermore, these animals acquired immune memory, as demonstrated by subsequent tumor rechallenge. In addition, mRNA-IL12 was able not only to control tumor growth in the short

CONTACT Fernando Aranda faranda@unav.es Program of Immunology and Immunotherapy, Cima Universidad de Navarra, Cancer Center Clínica Universidad de Navarra (CCUN), Avenue de Pío XII, 55, Pamplona 31008, Navarr

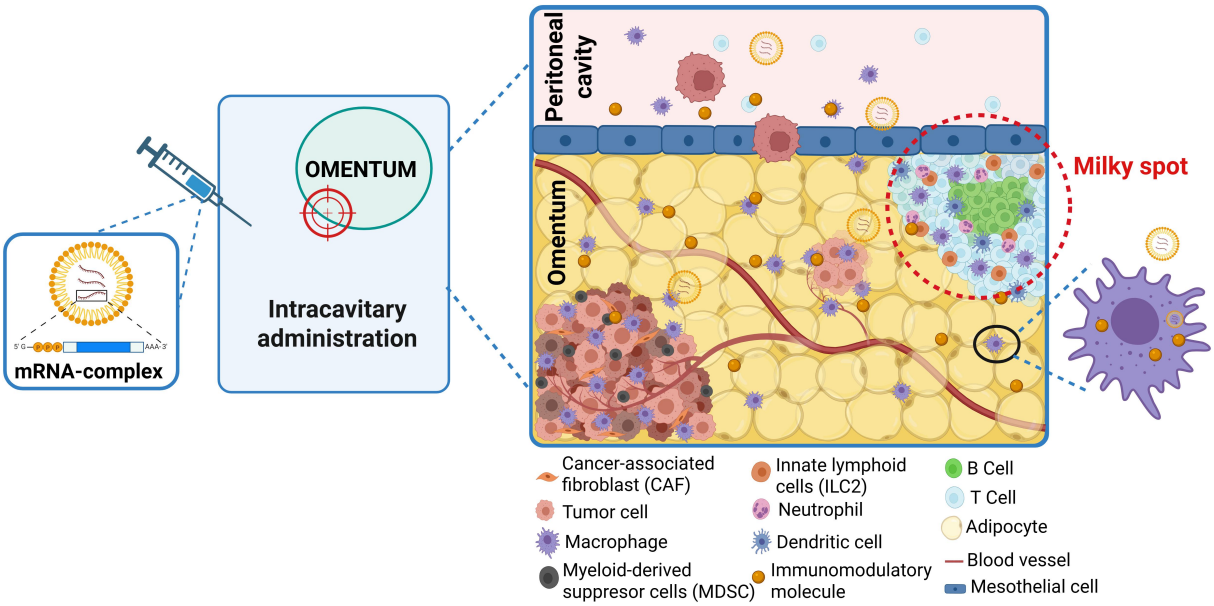

Figure 1. Targeting the omentum for immunomodulatory mRNA therapy in peritoneal metastases. This schematic illustrates the strategy for the intracavitary administration of immunomodulatory cytokine-encoded mRNA complexes to the omentum. The mRNA is encapsulated in lipid-based carriers and delivered via intraperitoneal injection. Upon reaching the omentum, the mRNA complexes are taken up by immune cells, particularly macrophages, leading to localized expression of immunomodulatory molecules. This approach aims to shift the omentum from an immunosuppressive niche to an immune-activating site, promoting an antitumor response while minimizing systemic toxicity.

term but also offer long-term protection against recurrence. We observed an increased proliferation of effector T cells and a reduction in suppressive myeloid populations within the tumor microenvironment. Hence, our results support the hypothesis that the intraperitoneal delivery of mRNA-IL12 could reprogram the immune environment to favor an effective antitumor response[7] (Figure 1).

While preclinical results are promising, translating this approach to human clinical trials requires thorough validation of the safety and efficacy of the mRNA delivery system, as well as optimal dosing and administration regimens. Additionally, the complexity of the human tumor microenvironment, which may differ significantly from that of murine models, is a determining factor in the adaptability and success of this strategy. Nevertheless, mRNA technology has proven to be flexible and scalable, suggesting that therapies based on this platform could be quickly developed to treat various types of cancer sharing peritoneal carcinomatosis as an advanced manifestation.

In conclusion, the findings from the studies conducted by our group on this subject introduce a new paradigm for treating peritoneal carcinomatosis. Locoregional treatment focuses on enhancing the mechanism of action of immunotherapy in the complex intraperitoneal tumor environment. This can be achieved by targeting the omentum, which is typically the tissue most affected by peritoneal metastases. Various immunomodulatory strategies have demonstrated their ability to induce changes in the tumor microenvironment, resulting in significant improvements in survival and the development of immune memory. Specifically, mRNA-based therapies have the potential to revolutionize the treatment of challenging tumors with local and intracavity approaches.[8,9] Although our findings have been demonstrated with TransIT®, which is not approved for clinical use, they provide a compelling proof-of-concept. Future studies should explore clinically translatable mRNA delivery systems, such as lipid nanoparticles (LNPs) already in clinical development, to evaluate whether similar tropism and immune activation in the omentum can be achieved. The advantages of our approach include the targeted activation of immune responses at the site of peritoneal metastases, the potential for inducing durable immune memory, and reduced systemic toxicity compared to systemic treatments. However, there are important caveats that must be acknowledged. The murine peritoneal environment differs from that of humans in complexity and scale, and our preclinical models may not fully capture the immune suppressive networks present in human disease. Moreover, macrophage involvement, while promising, may be modulated differently in clinical settings due to patient heterogeneity and comorbidities.

Moving forward, we aim to address several open questions. How might different mRNA-encoded cytokines, or combinations thereof, modulate the omental microenvironment? Can this strategy be integrated with adoptive cell therapies or checkpoint inhibitors for synergistic effects? And importantly, what biomarkers might predict responsiveness or resistance to omentum-targeted mRNA immunotherapy?

In summary, the intraperitoneal delivery of immunostimulatory mRNAs represents a promising strategy for reprogramming the immune microenvironment of the omentum. By converting this immunosuppressive niche into an immune-activating compartment, we hope to establish a platform for less toxic and more effective therapies against peritoneal

carcinomatosis. Continued research into optimizing delivery, understanding the underlying immune mechanisms, and ensuring clinical translatability will be key to advancing this approach from bench to bedside.

Acknowledgement

L.A., P.B., and F.A. were responsible for the conceptualization, supervision, validation, visualization, and writing the manuscript. I. M. performs conceptualization, supervision, validation and visualization.

Disclosure statement

I.M. reports receiving commercial research grants from AstraZeneca, BMS, Highlight Therapeutics, Alligator, Pfizer, Genmab, Catalym and Roche; has received speakers bureau honoraria from MSD; and is a consultant or advisory board member for BMS, Roche, AstraZeneca, Genmab, Pharmamar, F-Star, Bioncotech, Bayer, Numab, Pieris, Gossamer, Alligator and Catalym. The rest of authors have no conflicts of interest to declare.

Funding

Authors are supported by Hookipa Pharma Inc., Instituto de Salud Carlos III [PI22/00147 and PI23/00203], cofunded by the European Union, Caja de Rural de Navarra, and Gobierno de Navarra Proyecto ARNMUNE Ref.: 0011-1411-2023-000032. L.A. is the recipient of an FPU grant from The Spanish Ministry of Education and Professional training [FPU21/00042]. This work is supported by ERC grant [RIPECROP, 101142365]. Funded by the European Union. Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union or the European Research Council Executive Agency. Neither the European Union nor the granting authority can be held responsible for them.

ORCID

Ignacio Melero http://orcid.org/0000-0002-1360-348X
Pedro Berraondo http://orcid.org/0000-0001-7410-1865
Fernando Aranda http://orcid.org/0000-0002-9364-474X

Author contributions

CRediT: **Leire Arrizabalaga:** Conceptualization, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing; **Ignacio Melero:** Conceptualization, Supervision, Validation, Visualization; **Pedro Berraondo:** Conceptualization, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing; **Fernando Aranda:** Conceptualization, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Data availability statement

No data were generated in this work.

References

1. Coccolini F, Gheza F, Lotti M, Virzi S, Iusco D, Ghermandi C, Melotti R, Baiocchi G, Giulini SM, Ansaloni L, Catena F. Peritoneal carcinomatosis. World J Gastroenterol. 2013;19(41):6979–6994. doi: 10.3748/wjg.v19.i41.6979.
2. Galassi C, Chan TA, Vitale I, Galluzzi L. The hallmarks of cancer immune evasion. Cancer Cell. 2024;42(11):1825–1863. doi: 10.1016/j.ccell.2024.09.010.
3. Katz SC, Point GR, Cunetta M, Thorn M, Guha P, Espat NJ, Boutros C, Hanna N, Junghans RP. Regional CAR-T cell infusions for peritoneal carcinomatosis are superior to systemic delivery. Cancer Gene Ther. 2016;23(5):142–148. doi: 10.1038/cgt.2016.14.
4. Beelen RH. Role of omental milky spots in the local immune response. Lancet. 1992;339(8794):689. doi: 10.1016/0140-6736(92)90857-Y.
5. Bella Á, Arrizabalaga L, Di Trani CA, Gonzalez-Gomariz J, Gomar C, Russo-Cabrera JS, Olivera I, Cirella A, Fernandez-Sendin M, Alvarez M, et al. Intraperitoneal administration of a modified vaccinia virus Ankara confers single-chain interleukin-12 expression to the omentum and achieves immune-mediated efficacy against peritoneal carcinomatosis. J For Immunotherapy Cancer. 2023;11(11):e006702. doi: 10.1136/jitc-2023-006702.
6. Di Trani CA, Cirella A, Arrizabalaga L, Bella Á, Fernandez-Sendin M, Russo-Cabrera JS, Gomar C, Olivera I, Bolaños E, González-Gomariz J, et al. Intracavitary adoptive transfer of IL-12 mRNA-engineered tumor-specific CD8 + T cells eradicates peritoneal metastases in mouse models. Oncoimmunology. 2023;12(1):2147317. doi: 10.1080/2162402X.2022.2147317.
7. Arrizabalaga L, Di Trani CA, Fernandez-Sendin M, Bella Á, Russo-Cabrera JS, Gomar C, Ardaiz N, Belsue V, González-Gomariz J, Zalba S, et al. Intraperitoneal administration of mRNA encoding interleukin-12 for immunotherapy in peritoneal carcinomatosis. J Nanobiotechnol. 2025;23(1):113. doi: 10.1186/s12951-025-03196-2.
8. Pastor F, Berraondo P, Etxeberria I, Frederick J, Sahin U, Gilboa E, Melero I. An RNA toolbox for cancer immunotherapy. Nat Rev Drug Discov. 2018;17(10):751–767. doi: 10.1038/nrd.2018.132.
9. Shariati M, Zhang H, Van de Sande L, Descamps B, Vanhove C, Willaert W, Ceelen W, De Smedt SC, Remaut K. High pressure nebulization (PIPAC) versus injection for the intraperitoneal administration of mRNA complexes. Pharm Res. 2019;36(9):126. doi: 10.1007/s11095-019-2646-z.