PNRR Missione 4, Componente 2, Investimento 1.4 "Potenziamento strutture di ricerca e creazione di "campioni nazionali di R&S" su alcune Key Enabling Technologies"
Iniziativa finanziata dall'Unione europea –- NextGenerationEU.
National Center for Gene Therapy and Drugs based on RNA Technology
Sviluppo di terapia genica e farmaci con tecnologia a RNA
Codice progetto MUR: **CN00000041** – CUP UNINA: **E63C22000940007**

Doctorate of National Interest

RNA THERAPEUTICS AND GENE THERAPY

SELECT ONE OF THE FOLLOWING RESEARCH AREA:

☐ **Mechanisms of Diseases and Drug Target Identification**

☒ **Design and Delivery of New Gene Therapy and RNA-Based Medicines**

☐ **Validation and Safety In Preclinical and Clinical Studies**

LOCATION OF THE RESEARCH ACTIVITY (INSTITUTION/DEPARTMENT):

UNINA/DICMAPI

TUTOR: P. L. Maffettone, Concetta Di Natale

PROPOSED RESEARCH ACTIVITIES (max 300 words):

The poor response of Triple negative breast cancer (TNBC) patient against classical polychemotherapy has led to scientific community to develop novel effective anticancer therapeutics [1]. Different anticancer therapeutics, such as nano/micro-particles or polymeric microneedle-based therapies could represent the future of cancer therapy being able to facilitate the local and controlled delivery of the therapeutic agents at the tumor region[2, 3]. The delivery of DNA, RNA, proteins, or antibodies through the skin is, indeed, extremely difficult due to the presence of the stratum corneum which restricts the application to lipophilic drugs with relatively low molecular weight. To overcome these limitations, microneedle (MN) patches, consisting of micro/miniature-sized needles, could be a promising tool to perforate the stratum corneum and to release drugs and proteins into the dermis following a non-invasive route. In this context we propose our project based on the development of a novel drug delivery system based on polymeric microneedles (MNs)

within their body poly(lactic-co-glycolic acid) (PLGA)-nanoparticles (nPs) loaded Pembrolizumab (a very sensitive checkpoint inhibitor) and mRNA-4359 (mRNA vaccine candidate that acts by targeting indoleamine 2,3 dioxygenase (IDO) and programmed death-ligand 1 (PD-L1) antigen). In the recent years, immunotherapy, has been shown to prolong the survival in other solid tumors representing a promising strategy also for TNBC[4]. Additionally, the combination of mRNAs with immunotherapy compounds may further amplify this anti-tumor immunostimulatory effect, resulting in superior clinical outcomes. This combination is already under development by Moderna and Merck company for TNBC vaccine [5]. The nPS embedded MNs will be fabricated to improve drug penetration and diffusion, enhancing Pembrolizumab and mRNA-4359 effects. We will the electro-drawing approach for MN fabrication, while drug loaded nPs will be synthesized by microfluidic techniques. 4T1 tumor bearing BALB/c mice will be used for in vivo experiments to test the immunogenic power of our final system.

References

1. Marra, A. and G. Curigliano, *Adjuvant and Neoadjuvant Treatment of Triple-Negative Breast Cancer With Chemotherapy.* The Cancer Journal, 2021. **27**(1): p. 41-49.
2. Pérez-Herrero, E. and A. Fernández-Medarde, *Advanced targeted therapies in cancer: Drug nanocarriers, the future of chemotherapy.* European journal of pharmaceutics and biopharmaceutics, 2015. **93**: p. 52-79.
3. Wei, G., et al., *Recent progress in nanomedicine for enhanced cancer chemotherapy*. Theranostics, 2021. **11**(13): p. 6370.
4. Stagg, J. and B. Allard, Immunotherapeutic approaches in triple-negative breast cancer: latest research and clinical prospects. Therapeutic advances in medical oncology, 2013. 5(3): p. 169-181.
5. https://classic.clinicaltrials.gov/ct2/show/NCT05533697