European School of Molecular Medicine

RESEARCH ACTIVITY SHEET

2025 PhD selections

YOUR DETAILS

* Name & Surname: Manuel Albanese

* Affiliation INGM

PHD PROJECT DETAILS

* Title of the proposed project

Engineered Extracellular Vesicles for personalized leukemia therapy

* Short description of the project (up to 300 words)

The ideal cancer treatment effectively and specifically targets cancer cells, limiting possible side effects. Extracellular vesicles (EVs) are promising carriers of anti-cancer drugs to achieve high efficacy and specificity. However, two main problems are currently limiting the use of EVs for therapy: low cargo delivery of EVs into target cells and low enrichment of the therapeutic protein of interest into EVs. We hypothesize that, if *ad hoc* engineered, EVs can be loaded with any cargo protein and re-directed against any specific target cell.
This project aims at generating a platform of engineered EVs (eEVs) with multiple features to specifically target different cancer cells. Acute lymphocytic leukemia (ALL) will be selected proof-of-concept model to test our hypothesis. To monitor EV cargo delivery into target cells, we recently established a novel EV fusion assay. eEVs selected by fusion assay to be able to enter ALL and CLL will then be loaded with CRISPR/Cas9 ribonucleoproteins that carry guide RNAs to specifically target leukemia-specific genomic alterations.
We will generate a list of eEVs that will cover specificity for ALL from different patients. eEVs will first be challenged against *in vitro* and *ex vivo* models of leukemia to improve EVs delivery and anti-tumor effector function. Additionally, the most effective anti-ALL eEVs will be validated *in vivo* in an ALL patient-derived xenograft (PDX) model. Once established, the platform will consist of a combination of eEVs with different targeting/fusogenic machineries and Cas9-gRNAs, capable of targeting different genomic alterations in a tumor and patient-specific manner.

This novel therapeutic approach is going to revolutionize current cancer treatments. eEVs will provide a completely personalized and precise therapeutic option to replace or be combined with already available treatments.

* Indicate the main research area for the project described above Molecular Theraphy

If needed indicate a second research area for the project described above Cancer Biology

* Provide up to 3 key words for project:

CRISPR, Extracellular vesicles, Leukemia

YOUR LABORATORY ACTIVITIES DETAILS

* Main topic/s of the lab

Gene editing-based technologies and therapies in cancer and infectious diseases

* Short description of the lab activity (up to 500 words)

The central focus of our research is the development and adaptation of cutting-edge gene editing technologies for both fundamental laboratory investigations and translational therapeutic applications. We are dedicated to establishing innovative therapeutic interventions for a range of diseases, employing two complementary strategies: (i) the engineering of extracellular vesicles for efficient and targeted delivery of gene editing tools, and (ii) the precise manipulation of human lymphocyte activation and effector mechanisms to potentiate next-generation lymphocyte-based immunotherapies.

* Recent bibliography (max 5 references)

- Autoantibody-enhanced, CD32-driven trogocytosis creates functional plasticity of immune cells and is hijacked by HIV-1 to infect resting CD4 T cells.
  Albanese M, Chen HR, Gapp M, Muenchhoff M, Yang H-H, Peterhoff D, Hoffmann K, Xiao Q, Ruhle A, Ambiel I, Schneider S, Mejías-Pérez E, Stern M, Wratil PR, Hofmann K, Amann L, Jocham L, Fuchs T, Ulivi AF, Besson-Girard S, Weidlich S, Schneider J, Spinner C, Sutter K, Dittmer U, Humpe A, Baumeister P, Wieser A, Rothenfusser S, Bogner J, Roider J, Knolle P, Hengel H, Wagner R, Laketa V, Fackler O, Keppler O.
  Cell Reports Medicine 2024, Volume 5, Issue 4, 16 April 2024, 101483.
- Rapid, efficient and activation-neutral gene editing of polyclonal primary human resting CD4+ T cells allows complex functional analyses.
  Albanese M, Ruhle A, Mittermaier J, Mejías-Pérez E, Gapp M, Linder A, Schmacke NA, Hofmann K, Hennrich AA, Levy DN, Humpe A, Conzelmann KK, Hornung V, Fackler OT, Keppler OT.
  Nature Methods 2022. doi: 10.1038/s41592-021-01328-8.
- Three exposures to the spike protein of SARS-CoV-2 by either infection or vaccination elicit superior neutralizing immunity to all variants of concern.
  Wratil PR, Stern M, Priller A, Willmann A, Almanzar G, Vogel E, Feuerherd M, Cheng CC, Yazici S, Christa C, Jeske S, Lupoli G, Vogt T, Albanese M, Mejías-Pérez E, Bauernfried S, Graf N, Mijocevic H, Vu M, Tinnefeld K, Wettengel J, Hoffmann D, Muenchhoff M, Daechert C, Mairhofer H, Krebs S, Fingerle V, Graf A, Steininger P, Blum H, Hornung V, Liebl B, Überla K, Prelog M, Knolle P, Keppler OT, Protzer U.
  Nature Medicine 2022. doi: 10.1038/s41591-022-01715-4.
- MicroRNAs are minor constituents of extracellular vesicles that are rarely delivered to target cells.
  Albanese M, Chen YA, Hüls C, Gärtner K, Tagawa T, Mejias-Perez E, Keppler O, Göbel C, Zeidler R, Shein M, Schütz A, Hammerschmidt W. ***PLoS Genetics 2021. doi: 10.1371/journal.pgen.1009951.***
- Highly efficient CRISPR-Cas9-mediated gene knockout in primary human B cells for functional genetic studies of Epstein-Barr virus infection.
  Akidil E, Albanese M, Buschle A, Ruhle A, Keppler OT, Hammerschmidt W.
  PLoS Pathog. 2021. doi: 10.1371/journal.ppat.1009117.

* Group composition: total members, and roles distribution (PhD, postdoc, technician, etc.)

Total Lab members 5: 1 Technician, 2 postdocs, 1 predoc, and 1 master student. Currently hiring 1 lab manager and 1 postdoc.

Institutional page link

https://ingm.org/en/albanese-lab-eng/

Lab website link, if any

https://albaneselab.unimi.it/

Social media links, if any

If you prepare a video to promote your lab/project, please include the link below