Oncogenesis and Antitumour Drugs

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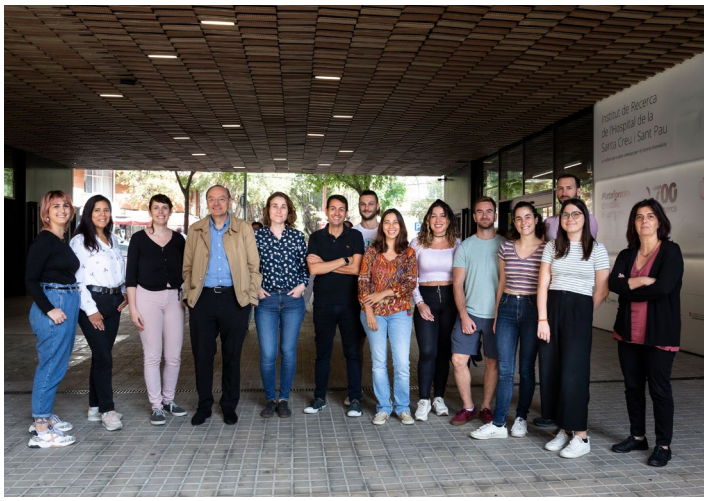

DESCRIPTION

We are developing targeted protein-based nanoparticles and nanoconjugates to selectively ablate cancer stem cells, or cancer associated fibroblasts, and inhibitors of Immune checkpoints to improve current treatment of solid (colorectal, head and neck) and hematological (DLBCL, AML) neoplasias. We also generate immunosuppressed and immunocompetent, subcutaneous, or orthotopic, cancer mouse models to preclinically evaluate the anticancer effect and the associated toxicity of these nanomedicines and their combination for clinical translation and industrial transference.

MAIN LINES OF RESEARCH

- To develop a humanized nanoconjugate of auristatin directed to leukemic stem cells for the treatment of Acute Myeloid Leukemia. Within this line, the activity of the nanoconjugate is being evaluated in new animal models derived from patient samples (PDX) and humanized murine models. We are also studying the ability of the nanoconjugate to activate the immune system and the possible synergies of its combination with other precision drugs. Isolda Casanova.
- To design and develop protein nanodrugs for the treatment of cancer. This line seeks to offer innovative therapeutic proposals based on rational design and development of active targeted protein nanoparticles for the selective delivery of therapeutic protein domains or conjugated antitumor drugs to tumor cells. Ugutz Unzueta.
- To develop and preclinical validation of tumor microenvironment targeted nanoparticles. This

research line aims to target cancer-associated fibroblasts within solid tumors to reprogram the tumor microenvironment to reduce cancer cell aggressiveness and block metastatic dissemination. Lorena Alba.

- Induction of local tumor pyroptosis, by administration of nanotoxins, to turn cold solid tumors into immune-hot ones, to achieve T cell cancer tissue infiltration, activation of anticancer immunity, and the search for synergistic activity by its combination with Checkpoint inhibitors and T Cell Receptor Agonists to reverse immune exhaustion. Ramon Mangues.

SCIENTIFIC CHALLENGES

- To develop nanomedicines to define preclinical protocols to achieve effective immunogenic activity against solid tumors, which are currently resistant to Immunotherapy.
- To develop new protein nanoconjugates for targeted delivery of antitumor drugs with innovative mechanisms of action for the treatment of tumors resistant to common drugs.
- To develop efficient protein nanovehicles for the targeted delivery of therapeutic nucleic acids to tumor cells in vivo as an alternative to viral vectors.
- To develop protein nanopharmaceuticals for the activation of the immune system against cancer as a more effective nano-immuno-oncology approach than current treatments.
- To develop targeted-nanotherapy to reprogram the tumor microenvironment to enhance their antitumor role.

ACTIVE GRANTS

- Alba Castellon, Lorena. Cancer-Associated Fibroblast-Targeted Nanoparticles to Improve Antimetastatic Therapy in Colorectal Cancer. POSTDOC AECC 2020. Asociación Española Contra el Cáncer (AECC). Duration: 2020-2025. 170.000,00 €.
- Mangues Bafalluy, Ramon. Eliminación selectiva de células madre de cáncer de colon mediante nanopartículas inductoras de poro, inflamación crónica e immunidad antineoplásica (IMMUNO-FIRING). PI21/00150. Instituto de Salud Carlos III (ISCIII). Duration: 2022-2024. 244.420,00 €.
- Mangues Bafalluy, Ramon. New protein-based nanodrugs for the development of targeted tumor-agnostic therapy. CPP2021-008946. Ministerio de Ciencia e Innovación (MICINN). Duration: 2022-2025. 439.367,01 €.
- Unzueta Elorza, Ugutz. Conjugación dirigida de nanomedicinas proteicas inteligentes para la mejora de la terapia selectiva del cáncer metastasico de colon. PI20/00400. Instituto de Salud Carlos III (ISCIII). Duration: 2021-2023. 171.820,00 €.

GRANTS AWARDED

- Mangues Bafalluy, Ramon. Oncogenesis and Antitumour Drugs. 2021 SGR 01140. Agència de Gestió d'Ajuts Universitaris i de Recerca (AGAUR). Duration: 2022-2024. 60.000 €.
- Unzueta Elorza, Ugutz. Eliminación selectiva de células madre metastásicas del cáncer colorrectal por bloqueo de la RNA polimerasa II. PI23/00318. Instituto de Salud Carlos III (ISCIII). Duration: 2023-2026. 230.000,00 €

DOCTORAL THESES DEFENDED

- López Laguna, Héctor. Simple biochemistry for complex protein-based materials. 31/03/2023. Universitat Autònoma de Barcelona. Supervisors: Villaverde Corrales, Antonio; Vázquez Gómez, Esther; Unzueta Elorza, Ugutz. http://hdl.handle.net/10803/690077.
- Núñez Amela, Yáiza. Nanopartícules dirigides a cèl·lules mare CXCR4+ per al tractament de la leucèmia mieloide aguda. 12/04/2023. Universitat de Barcelona. Supervisors: Mangues Bafalluy, Ramon; Casanova Rigat, Isolda; Cascante i Serratosa, Marta. http://hdl.handle.net/10803/688200.
- Voltà Durán, Eric. Exploring and exploiting multi-domain recombinant proteins as targeted nanomedical tools. 12/09/2023. Universitat Autònoma de Barcelona. Supervisors: Unzueta Elorza, Ugutz; Villaverde Corrales, Antonio; Vázquez Gómez, Esther.

SCIENTIFIC PRODUCTION

- Álamo P, Parladé E, Favaro MTP, Gallardo A, Mendoza R, Ferreira LCS, Roher N, Mangues R, Villaverde A, Vázquez E. Probing the Biosafety of Implantable Artificial Secretory Granules for the Sustained Release of Bioactive Proteins.

ACS Applied Materials & Interfaces. 2023; 15(33) DOI:10.1021/acsami.3c08643. PMID:37614001. IF:9,500 (Q1/2D). Document type: Article.

- López H, Rueda A, Martínez C, Sánchez L, Carratalá JV, Atienza J, Parladé E, Sánchez JM, Serna N, Voltà E, Ferrer N, Reverter D, Mangues R, Villaverde A, Vázquez E, Unzueta U. Biofabrication of Self-Assembling Covalent Protein Nanoparticles through Histidine-Templated Cysteine Coupling. ACS Sustainable Chemistry & Engineering. 2023; 11(10)DOI:10.1021/acssuschemeng.2c06635. IF:8,400 (Q1/1D). Document type: Article.
- Martinez C, Alba L, Carrasco LI, Serna N, Imedio L, Gallardo A, Casanova I, Unzueta U, Vazquez E, Mangues R, Villaverde A. Lymphocyte infiltration and antitumoral effect promoted by cytotoxic inflammatory proteins formulated as self-assembling, protein-only nanoparticles. BIOMEDICINE & PHARMACOTHERAPY. 2023; 164:114976. DOI:10.1016/j.biopha.2023.114976. PMID:37276641. IF:7,500 (Q1/1D). Document type: Article.
- Medina E, García A, Gallardo A, Álamo P, Alba L, Unzueta U, Villaverde A, Vázquez E, Casanova I, Mangues R. Potent Anticancer Activity of CXCR4-Targeted Nanostructured Toxins in Aggressive Endometrial Cancer Models. Cancers. 2023; 15(1):85. DOI:10.3390/cancers15010085. PMID:36612081. IF:5,200 (Q2/3D). Document type: Article.
- Nunez Y, García A, Falgas A, Serna N, Sánchez L, Garrido A, Sierra J, Gallardo A, Unzueta U, Vazquez E, Villaverde A, Mangues R, Casanova I. T22-PE24-H6 Nanotoxin Selectively Kills CXCR4-High Expressing AML Patient Cells In Vitro and Potently Blocks Dissemination In Vivo. Pharmaceutics. 2023; 15(3):727. DOI:10.3390/pharmaceutics15030727. PMID:36986589. IF:5,400 (Q1/2D). Document type: Article.
- Parladé E, Sánchez JM, López H, Unzueta U, Villaverde A, Vázquez E. Protein features instruct the secretion dynamics from metal-supported synthetic amyloids. INTERNATIONAL JOURNAL OF BIOLOGICAL MACROMOLECULES. 2023; 250:126164. DOI:10.1016/j.ijbiomac.2023.126164. PMID:37549767. IF:8,200 (Q1/1D). Document type: Article.
- Rueda A, Mendoza JI, Alba L, Parladé E, Voltà E, Paez D, Aviño A, Eritja R, Vázquez E, Villaverde A, Mangues R, Unzueta U. Site-directed cysteine coupling of disulfide-containing non-antibody carrier proteins (THIOCAPs). Science China-Materials. 2023; 66(10)DOI:10.1007/s40843-023-2571-6. IF:8,100 (Q1/3D). Document type: Article.
- Serna N, López H, Aceituno P, Rojas M, Parladé E, Voltà E, Martínez C, Sánchez JM, Di A, Carratalá JV, Livieri AL, Ferrer N, Vázquez E, Unzueta U, Roher N, Villaverde A. Efficient Delivery of Antimicrobial Peptides in an Innovative, Slow-Release Pharmacological Formulation. Pharmaceutics. 2023; 15(11):2632. DOI:10.3390/pharmaceutics15112632. PMID:38004610. IF:5,400 (Q1/2D). Document type: Article.
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