

TRANSFORMATION AND METASTASIS GROUP

Eva González Suárez
Group Leader

Research Scientists
Patricia González, María Jiménez,
Gema Pérez



Post-Doctoral Fellows
Sara Lázaro (April-August), Angélica
Santiago (since April)

Graduate Students
Alexandra Barranco, Marina Císcar
(until September), Alejandro Collado,
Jaime Redondo, Andrea Vethencourt
(Clinical Oncologist at *ICO/IDIBELL*,
Barcelona, Spain)

Undergraduate Student
Pedro Luis Echevarria (until
February)

Technicians
Lucía de Andrés (since April), Víctor
López, Sergi Velasco (until
September) (PEJ, CAM)*

**Plan de Empleo Joven de la Comunidad de
Madrid* (Youth Employment Plan,
Community of Madrid)

Students in Practice
Pablo Blanco (February-July)
(Master's Thesis, *UAM*, Madrid,
Spain), Isabel Jiménez (Jan.-July)
(Master's Thesis, *UCM*, Madrid,

Spain), Teresa Martí (Jan.-July)
(*AECC* Traineeship and BS Thesis,
Univ. Francisco de Vitoria, Spain)

Visiting Scientists
Emilia Brizzi (June-July) (Pathology
resident, *Hospital La Paz*, Madrid,
Spain), Marta Matas (Sept.-Nov.)
(*Althaia, Xarxa Assistencial
Universitària de Manresa*, Spain)

OVERVIEW

Tumours exploit and manipulate for their benefit the same mechanisms that regulate homeostasis in healthy tissue. In the Transformation and Metastasis Group, we aim to understand normal mammary gland development and the key events that lead to tumour initiation, progression, and metastasis in order to identify novel therapeutic targets to combat breast cancer. We use complementary tools, including primary cell cultures and organoids, lineage tracing mouse models, and clinical samples with the goal of translating basic knowledge into clinically relevant findings.

“Analyses of clinical samples and functional experiments in patient-derived xenografts demonstrate that RANK protein expression in tumour cells is associated with poor survival in ER negative breast cancer, and its inhibition improves chemotherapy response.”

RESEARCH HIGHLIGHTS

RANK is a poor prognosis marker and a therapeutic target in ER-negative postmenopausal breast cancer

Despite strong preclinical data, the therapeutic benefit of denosumab in breast cancer, beyond the bone, is unclear. Aiming to select patients who may benefit from denosumab, we analysed RANK and RANKL expression in more than 2000 breast tumours (777 oestrogen receptor-negative, ER⁻) from 4 independent cohorts. RANK expression was more frequent in ER⁻ tumours, where it associated with poor outcome and poor response to chemotherapy. In patient-derived orthoxenografts (PDXs) of ER⁻ breast cancer, RANKL inhibition reduced tumour cell proliferation and stemness, regulated tumour immunity and metabolism, and improved response to chemotherapy.

Intriguingly, RANK expression was associated with poor prognosis in postmenopausal breast cancer patients, activation of NFκB signalling, and modulation of immune and metabolic pathways, suggesting that RANK signalling increases after menopause. Indeed, RANKL inhibition showed greater therapeutic benefit in ER⁻ breast cancer PDXs under postmenopausal conditions. Our results demonstrate that RANK expression is an independent biomarker of poor prognosis in postmenopausal patients with ER⁻ breast cancer and support the therapeutic benefit of RANK pathway inhibitors in breast cancer patients with RANK⁺ ER⁻ tumours after menopause (FIGURE 1).

Luminal Rank loss decreases cell fitness leading to basal cell bipotency in parous mammary glands

Rank signalling is a known regulator of mammary gland homeostasis, being critical for stem cell maintenance and epithelial cell differentiation. Although the Rank receptor is highly expressed by basal cells and luminal progenitors, its role in each individual cell lineage remains unclear. By combining temporal/lineage specific *Rank* genetic deletion with lineage tracing techniques, we found that loss of luminal Rank leads to aberrant alveolar-like differentiation in virgin mammary glands, reminiscent of pregnancy, and an increase in hormone-sensing luminal population (PR/Rankl-positive cells). During a first pregnancy, Rank-deleted luminal cells are unable to produce milk and expand following successive pregnancies. This results in a “tissue-damage like” scenario in the developing alveoli leading to basal bipotency and the replacement of “unfit luminal cells” by Rank-proficient cells to restore lactation. Transcriptomic analysis and functional assays point to a dual role for luminal Rank signalling in the control of protein translation. In the virgin mammary gland, Rank-depleted luminal cells show aberrant expression of lactogenic genes and increased protein synthesis. This aberrant differentiation exhausts the protein synthesis capability of the parous Rank-depleted luminal cells, making them unable to cope with the high translational demands required for milk production upon pregnancy. Consequently, basal bipotency is awakened through the activation of Rank/NF-κB signalling in basal parous cells of the alveoli in successive pregnancies to restore lactation and tissue homeostasis (FIGURE 2). ■

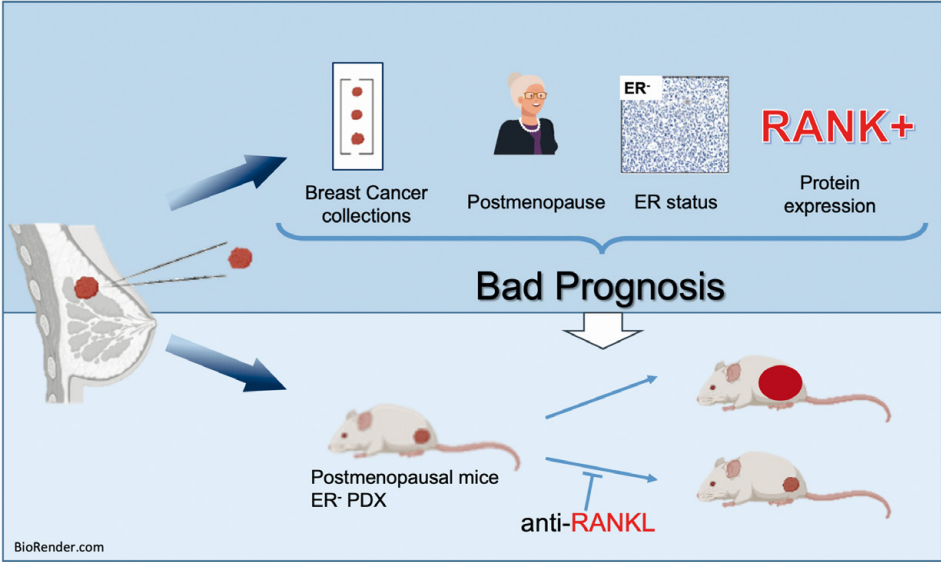


FIGURE 1

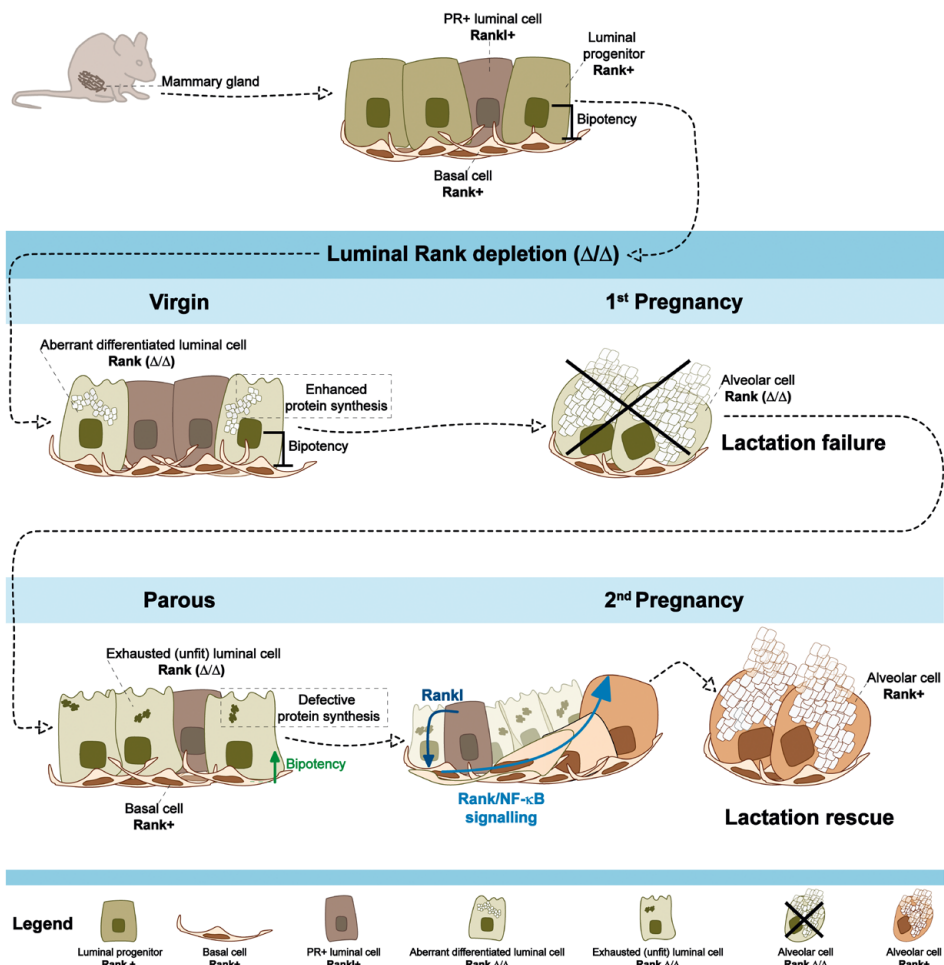


FIGURE 2

PUBLICATION

- Vethencourt A, Trinidad EM., Petit A., Soler Monso MT, Gomez Aleza C, Urruticochea A, Garcia-Tejedor A, Guma Martinez A, Obadia V, Vazquez S, Villanueva R, Fernandez A, Cejuela M, Penabad R, Stradella A, Gil-Gil M, Pernas S, Gonzalez-Suarez E, Falo C (2022). First results of the randomized window of opportunity clinical trial D-Biomark: immunomodulatory effect of denosumab in early breast cancer. *Cancer Res* 82 (4_Supplement), P2-10-P2-08-10.
- AWARDS AND RECOGNITION

- Invited Speaker, Basel Breast Consortium annual meeting on “Personalized breast cancer treatments”, November 2022, Basel, Switzerland.
- Forum Participant, Forbeck Forum “Aneuploidy in cancer development, prognosis and treatment”, April 2022, Lago Maggiore, Italy.
- Alejandro Collado: Selected oral presentation, Gordon Conference in Mammary Gland Biology 2022, Barga, Italy.

- Selected oral presentation, Workshop “Fat sensing and the brain control of puberty. 2022. Baeza, Spain.
- Alexandra Barranco: ECI Best Poster Award 2022, The European Congress of Immunology.
- Jaime Redondo: Selected oral presentation, annual meeting of the Spanish Cell Senescence Network, September 2022, Valencia, Spain.