Haematology represents one of the most “hot topics” areas in cancer of the last 5 years, due to society’s growing interest in the immunology that drives one of the biggest discoveries of the 21st century, immunotherapy. In addition, haematology has been gaining traction because of the interest in applying peripheral blood analysis to determine the diagnosis and prognosis of multiple cancers and diseases, and in emerging promising cutting-edge technology such as liquid biopsy, a method currently used to measure minimal residual disease (MRD).

The Haematological Malignancies Clinical Research Unit focuses on 2 research areas: 1) novel immunotherapies against cancer and, more specifically, NK-CAR technology; and 2) the development and improvement of liquid biopsy protocols through next-generation-sequencing.

Moreover, our group investigates the molecular mechanisms of haematological malignancies and then uses the identified molecules and markers (e.g., PIEZO1, HNRNPK) to develop mouse models of the disease that could be exploited therapeutically.

“Our results showed that it was feasible to genetically modify Natural Killer (NK) cells from patients and to safely express CAR-NKG2D, as well as the efficacy of these cells against multiple myeloma.”

RESEARCH HIGHLIGHTS

**NKG2D-CAR-transduced natural killer cells efficiently target multiple myeloma**

CAR-T-cell therapy is the most common genetically modified cell-based immunotherapy. However, CAR-T therapy usually has high toxicity. In contrast, CAR-NK cells may exert less toxicity. To explore this, we analysed the antitumour activity of activated and expanded NK cells (NKA€) and CD45RA- T cells from multiple myeloma (MM) patients that were engineered to express an NKG2D-based CAR. Although memory T cells were more stably transduced, CAR-NKAE cells exhibited greater in vitro cytotoxicity against MM cells, while showing minimal activity against healthy cells. In vivo, CAR-NKAE cells mediated highly efficient abrogation of MM growth, with 25% of the treated mice remaining disease free. Overall, these results demonstrate that it is feasible to modify autologous NKA€ cells from MM patients. They also show that it is possible to genetically modify NK cells from patients and to safely express CAR-NKG2D, as well as the efficacy of these cells against multiple myeloma.

Making clinical decisions based on measurable residual disease (MRD) improves the outcome in multiple myeloma

The use of MRD results to make clinical decisions in MM has been underexplored to date. In our study of 400 MM patients,
achieved MIRD negativity at any point was associated with improved progression free survival (PFS). In addition, patients in whom a treatment change was made showed prolonged PFS, in comparison with patients in whom MIRD results were not acted upon. In patients with positive MIRD during maintenance, a clinical decision (either intensification or change of therapy) resulted in better PFS compared to patients in whom no adjustment was made. Therefore, we find that MIRD is useful in guiding clinical decisions during initial therapy and has a positive impact on PFS in MM patients.

Many studies over the last 20 years have investigated the role of mitochondrial alterations in carcinoma. However, in the status of the mitochondria in MM and its implication in the pathogenesis of the disease remain unclear. Our results showed increased mitochondria (DNA content, gene expression, and activity) during the progression of MM. Mechanistically, OXPHOS metabolism was raised by regulation of increased MYC. We tested the efficacy of the mitochondrial inhibitor tagitoxin to overcome MM proliferation. In vivo and in vitro therapeutic targeting using the mitochondrial inhibitor tagitoxin showed promising efficacy and cytotoxicity in monotherapy and in combination with the MM frontline treatment bortezomib. Thus, we identified a new vulnerability in multiple myeloma and provided a novel alternative for MYC inhibition by targeting mitochondrial oxidative activity, as an indirect mechanism to avoid MM proliferation.

**Figure 1** (Kaplan-Meier survival curves showing the impact of making clinical decisions based on MIRD. (A) PFS from the first MRD data point, comparing patients who did vs. did not adjust their therapy based on MIRD with those for whom no change in therapy was made. (B) PFS according to adjustment or no adjustment (maintenance or discontinuation [maintenance or transplant]) vs. no change in therapy. (C) PFS according to positive patients, beginning a new therapy or intensifying their therapy vs. no change in therapy.)

**Figure 2** (Kaplan-Meier survival curves showing the impact of making clinical decisions based on MIRD. (A) PFS from the first MRD data point, comparing patients who did vs. did not adjust their therapy based on MIRD with those for whom no change in therapy was made. (B) PFS according to adjustment or no adjustment (maintenance or discontinuation [maintenance or transplant]) vs. no change in therapy. (C) PFS according to positive patients, beginning a new therapy or intensifying their therapy vs. no change in therapy.)

**Publications**

- Sánchez J, Martinez R, Sanda A, Hernandez-Martin HF, de la Rubia J, Jinkim K, Caballero V, Palomero L, Sanchez-Pina J, Bargay J, Malatos YF, Borrich D, Reseg J, San Miguel JP, Leblanc JA, Jaramillo E, (Grupo Español de Melanomas). (2021). Clinimetics PTM (Kaplan-Meier survival curves showing the impact of making clinical decisions based on MIRD. (A) PFS from the first MRD data point, comparing patients who did vs. did not adjust their therapy based on MIRD with those for whom no change in therapy was made. (B) PFS according to adjustment or no adjustment (maintenance or discontinuation [maintenance or transplant]) vs. no change in therapy. (C) PFS according to positive patients, beginning a new therapy or intensifying their therapy vs. no change in therapy.)