

Since the 1990's, we have conducted clinical trials of gene modified T cells. Chimeric antigen receptor (CAR) T cells independent of HLA and targeting CD19 on B cells leukemias and lymphomas have induced durable complete responses in patients who are relapsed or refractory to all other available treatments. New designs for genetically modified T cells include switches and potency enhancements that will be required for targeting solid tumors. In one such approach, a decoy receptor is inserted into CAR T cells to thwart a tumor immunosuppressive mechanism. Another improvement shortens ex vivo manufacturing, along with the addition of an anti-tumor cytokine to increase in vivo potency. Determining the critical quality attributes, dose, potency, and anticipating pharmacokinetics of a living, dividing drug presents unique challenges. Improving patient access to advanced cell and gene therapies entails not only on scientific progress in targeting, gene modification and cellular manipulation, but also on meeting automation, engineering, clinical site onboarding, and health policy challenges.

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FROM ALLOGENIC TRANSPLANTATION TO PRECISION IMMUNE THERAPY

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Allogeneic stem cell transplantation (ASCT) represents a model for immune cellular therapy leading to Immune Precision Medicine. *The pioneers* Georges Mathé in Paris and E. Donall Thomas (Nobel Prize in 1990) in Cooperstown, New York, pioneered ASCT in the clinical field. In 1958, the first 4 survivors were seen in patients after accidental exposure to lethal or near lethal dose of TBI, in Paris. However, they were subsequently shown to have autologous recovery. Understanding of ABMT immune support begun in 1954 with 1980 Nobel Prize Jean Dausset. The first ABMTs were performed in severe combined immunodeficiencies with the first success observed in 1968 (syngeneic donor), followed in 1973 by unrelated donor ABMT in London. This was also the time of the initiation of registries. *Development time in hematological malignancies* The first success of ABMT in acute leukemia was observed in 1976 in Seattle with a related donor and in 1976 with an unrelated donor. Thereafter, the evolution will take place within the framework of the risk-benefit balance with reduction of the intensity of the conditioning regimen, the graft versus leukemia (GVL)/graft versus host disease (GVH) balance and the donor extension with umbilical cord blood and more recently the haplo-identical allogeneic ASTC. Autologous SCT was introduced at the beginning of the 80s to amplify reduction in tumor mass, particularly in lymphoid malignancies. *Stem cell transplantation as an immune therapy platform* Whatever the autologous or allogeneic context, the

hematopoietic SCT is an exceptional platform for combining, modulating immunotherapy. In an allogeneic context, by modifying lymphocyte subpopulations, such as the supply of cytotoxic T-cells, the modulation of Tregs, the addition or activation of NK cells have an impact on GVH/GVL balance. The enhancement of anti-tumor cytotoxicity can be brought about using monoclonal antibodies (moAb), the addition of cancer vaccines. In an autologous context, there are some windows of opportunity, in the aplasia period due to the accessibility to stressed cancer cells, and cytokine burst approximately at D15, to add cell-drugs such as NK, $\gamma\delta$ T-cells or anti-cancer moAbs, or to associate chimeric antigen receptor (CAR) immune cells such as CAR-NK, as well as immune checkpoint inhibitors depending on the risks. This paves the way for a real dynamic personalized medicine and should cause the methodology for developing these therapeutic strategies to be rethought. Obtaining an optimization of the clinical efficiency which must be preceded by a reflection of biological efficiency can be helped by mathematical models or AI. We have thus developed a mathematical model for the optimization of the use of anti-IL-6. There is a modeling of use of cytotoxic cells. In cellular therapy, the concept of cell-drugs orients towards non-MHC dependent allogeneic cells such as NK and $\gamma\delta$ T-cells, as well as obtaining them in large batches to reduce production costs. We are entering a new medical era, with new notions such as dynamic, globalized vision, the use of new tools resulting from the digital revolution, new targeted therapies, immunotherapy, the combination of strategies for better efficiency: the Immune Precision Medicine.

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EUROPEAN EXPERIENCE FROM BARCELONA – IN-HOUSE PREPARATION AND CLINICAL RESULTS

XIII EHO 2022 / CELLULAR THERAPY: CAR T-CELLS IN HEMATOLOGICAL MALIGNANCIES

Manel Juan & a team of more than 200 professional

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ARI-0001 [systematically named Varnimcabtagene autoleucel (var-cel), a second generation anti-CD19 chimeric antigen receptor (CAR) T-cell] granted local use authorization (under the rule of “hospital exemption”, HE) by the AEMPS (Spanish drug agency = *Agencia Española de Medicamentos y Productos Sanitarios*) and just a little more than half-year ago (December 2021) PRIME (Priority Medicine) designation by the EMA (*European Medicines Agency*) for patients >25 years old with relapsed or refractory (R/R) B cell acute lymphoblastic leukaemia (B-ALL). The authorization is based on the results of a phase 1 clinical trial (NCT03144583), but additional patients (already reimbursed by Spanish Health System), new clinical trials or compassionate uses with ARI-0001, have been produced and infused in our Hospital Clínic de Barcelona or our