gene in bone marrow stem cells, 1,2 resulting in disruption to glycosylphosphatidylinositol (GPI) biosynthesis, 3. Among the deficient proteins are the complement regulatory proteinsCD55 andCD59, resulting in increased complement sensitivity of PNH cells, intravascular hemolysis, promotion of inflammatory mediators, and systemic hemoglobin release4 . Patients with PNH can present with multisystemic clinical manifestations due to intravascular hemolysis, thrombosis and bone marrow failure5 . Symptoms are therefore often non-specific, ranging from loss of vision (due to retinal thrombosis), headache and nausea/vomiting (due to cerebral thrombosis), pulmonary hypertension (due to pulmonary embolism), anaemia, through to pain and swelling in the lower extremities (due to deep vein thrombosis), renal failure and other symptoms affecting different systems6 . Thromboembolism is the most common cause of mortality in patients with PNH and accounts for approximately 40% to 67% of deaths of which the cause is known. Further, 29% to 44% of patients with PNH have been reported to have at least 1 thromboembolic event during the course of their disease, although the reason(s) a thrombotic event may suddenly occur remains an enigma7,8,9. Platelet activation, complementmediated hemolysis, impaired nitric oxide (NO) bioavailability, impairment of the fibrinolytic system, and inflammatory mediators are all proposed mechanisms and thought to be responsible for the increased thrombotic risk in patients with PNH. Multiple factors are likely to contribute to any one thrombotic event in patients with PNH. 10 Therapeutic strategies include terminal complement blockade and bone marrow transplantation. Eculizumab, a monoclonal antibody complement inhibitor, is highly effective and the only licensed therapy for PNH.11 The therapeutic anti-C5 antibody eculizumab (Soliris, Alexion) has proven effective in controlling intravascular hemolysis in vivo, leading to remarkable clinical benefit in a majority of PNH patients.12,13 Yet, persistent C3 activation occurring during eculizumab treatment may lead to progressive deposition of C3 fragments on affected erythrocytes and subsequent C3-mediated extravascular hemolysis, possibly limiting the hematologic benefit of anti-C5 treatment.14,15 Thus, upstream inhibition of the complement cascade seems an appropriate strategy to improve the results of current complement-targeted treatment.16,17

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Sp11

HOW WE (WILL) TREAT PNH?

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Clinical signs arising from intravascular hemolysis, hemolysis-related transfusions and thrombosis are indications for treatment initiation in paroxysmal nocturnal hemoglobinuria (PNH), whereas clone size *per se* is not. Eculizumab prevents intravascular hemolysis and reduces significantly thromboembolic risk resulting in a five-year overall survival of >90%. Hemoglobin value, LDH and reticulocyte count are used to define treatment response. Residual intravascular hemolysis is mainly caused by an incomplete C5 blockage and can lead to continuous low–grade hemolysis or transient breakthrough hemolysis episodes in 10-15% of PNH patients. Additional complement–amplifying conditions such as infections, surgery or pregnancy may overcome efficient therapeutic levels of Eculizumab and therefore require dose adjustments. *C3–mediated extra–vascular hemolysis* represents the main reason for residual anemia during anti–C5 treatment. Patients with an inherited C5-variant lack response to Eculizumab and have been directed (in past) towards allogeneic HSCT. Transplantation has an overall mortality of up to 30%, with a higher risk in patients with previous thrombosis. A plethora of novel therapeutic agents are reported to impact on both; residual intravascular hemolysis and C3–mediated extra–vascular hemolysis. The new C5 inhibitor Ravalizumab with an eight–week i.v. dosing interval showed non-inferiority to Eculizumab. Crovalimab, binding on the single missense C5 heterozygous mutation is injected s.c. monthly; two large phase III trials are ongoing as add on- and mono-therapy. Others, such as Pozelimab, injected subcutaneously on a weekly basis after an initial IV loading dose or Tesidolumab are still under current investigation. Currently investigated proximal inhibitors are acting towards: (i) the C3 complement; (ii) complement factor D or (iii) the complement factor B. They are aiming in particular to prevent C3–mediated extra–vascular hemolysis. Pegcetacoplan is a PEGylated version of compstatin which binds to C3 and is injected s.c. in monotherapy 4 weeks after initial concomitant therapy with Eculizumab. In a recent phase III trial, pegcetacoplan showed superiority to eculizumab in hemoglobin change from baseline and is now approved by the FDA for patients with PNH who are either treatment–naive or switching from anti–C5 monoclonal antibodies. Danicopan is an oral first–in–class factor D complement alternative pathway inhibitor and decreased significantly transfusion requirement, as shown in a phase II trial (phase III ongoing). BCX9930, another FD inhibitor in early development is given orally and demonstrated initial clinical efficacy both as add–on therapy in patients with inadequate response to eculizumab as well as in monotherapy in treatment–naive patients. In conclusion, novel proximal and distal complement inhibitors with different application modalities, in part as add-on or monotherapy seem to improve significantly intra- and extra–vascular hemolysis in PNH, resulting in a better hematological benefit. Before choosing specific treatment, hematologists have to assess hemolysis, thrombosis and patients‘ bone marrow function. Future studies will help to explore long-term efficacy and safety of these novel agents.

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Sp12

THE THEN, NOW, & FUTURE OF ENGINEERED T-CELL THERAPEUTICS FOR HUMAN APPLICATION

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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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Sp13

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 ASCCT 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 allogenic 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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Sp14

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

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

Manel Juan & a team of more than 200 professional

Servei d'Immunologia. Hospital Clínic de Barcelona (HCB). Plataforma de Hospital Sant Juan de Déu-HCB. Barcelona – Spain

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 Medicinamentos y Productos Sanitarios*) and just a little more than half-year ago (December 2021) PRIME (*Priority Medicine*) designation by the EMA (*European Mediciness 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