ABSTRACTS SELECTED FOR ORAL COMMUNICATION

Presentation number: OC0-TM 60 Abstract number: ABS-90-ISABS-2024

CAR-T-ONCOLYTIC VIRUS COMBINATIONS – EXPLOITING THE ENDOGENOUS T-CELL RECEPTOR (TCR) FOR ENHANCED THERAPY

Appleton Elizabeth[4,1], Liseth Olivia[1], Patrikeev Anton[4], Sangsuwannukul Thanich[1], Kendall Benjamin[1], Webb Mason[1], van Vloten Jacob[1], Evgin Laura[4], Tonne Jason[1], Thompson Jill[1], Metko Muriel[1], Moore Madelyn[1], Chiriboga Yerovi Maria[1], Kottke Tim[1], Diaz Rosa[1], Rizk Soha[1], Coffey Matt[2], Loghmani Houra[2], Melcher Alan[3], Parney Ian[1], McNiven Mark[1], Monga Satdarshan[6], Borad Mitesh[5], Roberts Lewis[1], Vile Richard[1]

[1]Mayo Clinic, Rochester, MN, United States of America; [2]Oncolytics Biotec, Inc., Calgary, Canada; [3]The Institute of Cancer Research, London, United Kingdom of Great Britain and Northern Ireland; [4]BC Cancer Research Institute, Vancouver, Canada; [5]Mayo Clinic, Phoenix, AZ, United States of America; [6]University of Pittsburgh, Pittsburgh, PA, United States of America

eliapp@ceh.ac.uk

The efficacy of chimeric antigen receptor (CAR) T-cell therapy in solid tumours faces hurdles such as poor expansion and persistence, insufficient trafficking, and T-cell dysfunction within the tumour microenvironment (TME). Oncolytic viruses (OVs) are viruses engineered specifically to replicate in and kill tumour cells, with capacity to inflame the TME to favor effective cell therapy. We observed that treatment with both OV and CAR-T cells generated a population of dual specific (DS) CAR T cells in which the DS CAR-T recognized onco-viral epitopes through their endogenous T-Cell Receptors. These DS CAR-T cells were significantly more therapeutically effective *in vivo* than conventional CAR-T cells, with enhanced trafficking, infiltration, and persistence. Single-cell RNA/TCR sequencing of FACS sorted tumour-infiltrating CD8 CAR-T demonstrated that cytotoxic-effector gene expression was enriched in CAR-T clusters with clonally expanded endogenous TCRs. CAR-T expanded with viral-specificity were shown to have a proliferative advantage over those with non-viral TCRs, with a favorable differentiation profile and altered trajectory. This highlights the importance of the endogenous TCR in the profile and function of CAR-T cells within solid tumors, with potential for exploitation of viral immunity for therapeutic benefit. Clinical development of this approach is now underway.

Keywords: CAR T cells, Oncolytic Viruses, Immuno-oncology, Immune Checkpoint Inhibition, Solid tumours

Presentation number: OC1-TM Abstract number: ABS-28-ISABS-2024

EXPANDING A PERSONALIZATION ALGORITHM FOR PREDICTING INDIVIDUAL RESPONSE TO IMMUNOTHERAPY IN PATIENTS WITH ADVANCED MELANOMA

Sakarovitch Diane[1], **Kogan Yuri**[1], Vico-Alonso Cristina[2], Burlak Kateryna[2], Mar Victoria[2], Agur Zvia[1]

[1]Institute for Medical BioMathematics, Bney Ataroth, Israel; [2]Monash University, Melbourne, Australia

yuri@imbm.org

Immune checkpoint inhibitors have brought an unprecedented improvement in the treatment of advanced cancers. Yet, the overall response rate to these drugs is below 50%, and predictive tools for selecting responsive patients are still urgently needed. Previously, we have developed an algorithm for predicting the response of patients with advanced melanoma to pembrolizumab (Tsur et al 2019, J. Translational Medicine). This algorithm was based on a mechanistic mathematical model for the effect of immunotherapy on the interactions of the immune system and melanoma tumors. We used clinical data of 54 patients from Israel and Germany to develop and initially validate this algorithm for the ability to predict individual time to progression, with reasonable accuracy (Cohen's kappa=0.489 for predicting the time interval of progression). In the present work we aim at validating the algorithm by an independent patient population from the Victorian Melanoma Service at Monash University, Australia. The original algorithm failed to satisfactorily generalize to the new data. This can be attributed to batch effect (patients from a different origin, a different period, or treated in a different health system). To expand the applicability of our algorithm, we trained and validated it by the entire patient cohort from the three different sources, applying an improved statistical and modeling methodology, and using a more advanced machine learning approach. This resulted in a new algorithm with comparable accuracy. In this work we demonstrate how an intricate predictive algorithm, involving statistical and mechanistic dynamical models can be sequentially improved by fine-tuning and testing on additional clinical data. Our goal is to develop a flexible framework for providing reliable quantitative response predictions (e.g., the time to radiological progression) for newly admitted patients, which will become an informative tool aiding clinicians in their decision making.

Keywords: checkpoint inhibitors, immunotherapy, melanoma, personalization, predictive model

Presentation number: OC2-TM Abstract number: ABS-106-ISABS-2024

EXPERIENCE WITH GENOMIC MATCHMAKING: ENHANCING DIAGNOSTIC EFFICACY AND NEW GENE-DISEASE DISCOVERIES IN NGS DIAGNOSTICS FOR RARE DISEASES

Golob Barbara, Maver Aleš, Bergant Gaber, Hodžić Alenka, Višnjar Tanja, Peterlin Borut

Clinical Institute of Genomic Medicine, University Medical Centre Ljubljana, Ljubljana, Slovenia

barbara.golob@kclj.si

In our efforts to enhance diagnostic efficacy and discover new gene-disease associations, we have incorporated genomic matchmaking. We present the outcomes of genomic matchmaking as an integrated component of extended analysis in NGS diagnostics at the Clinical Institute for Genomic Medicine in Ljubljana, Slovenia, emphasizing its impact on diagnostic yield and the discovery of new gene- disease associations. Material and methods: We conducted a retrospective analysis of candidate variants identified during extended whole exome and genome sequencing, which were submitted to the matchmaking nodes GeneMatcher (genematcher.org) and PhenomeCentral (phenomecentral.org) between 2017 and 2024. The analysis focused on the purpose of submission (whether for new gene- disease discovery or reclassification of variants of uncertain significance (VUS)), the number of matches and active submissions, as well as the final outcomes, including the number of publications and successfully diagnosed patients. Between 2017 and 2024, we submitted a total of 260 candidate variants based on our interpretation decision tree. The majority of these submissions (n=234, 90%) were aimed at new gene-disease discovery, while the remaining (n=26, 10%) involved candidate variants in genes with known gene-phenotype associations, observed in patients with discrepant phenotypes or for VUS reclassification. We successfully matched 31 new genes and 5 VUS, resulting in 9 publications and diagnoses for 32 patients, achieving a diagnostic yield of 12.3%. Currently, 107 submissions are still active. Our findings underscore the importance of data sharing and collaborative efforts through genomic matchmaking in maximizing the potential of NGS technologies for rare disease clinical setting.

Keywords: genomic matchmaking, diagnostic efficacy, new gene-disease associations, NGS Diagnostics, variant interpretation

Presentation number: OC3-TM Abstract number: ABS-124-ISABS-2024

VITAMIN D AND THYROID FUNCTION: A MENDELIAN RANDOMIZATION STUDY

Pleić Nikolina, Babić Leko Mirjana, Gunjača Ivana, Zemunik Tatijana

University of Split, School of Medicine, Department of Biology and Human Genetics, Split, Croatia

npleic@mefst.hr

Numerous organs, including the thyroid gland, depend on vitamin D to function normally. Low serum 25- hydroxyvitamin D [25(OH)D] levels may contribute to various thyroid disorders; however, the causal relationship remains unclear. Using a Mendelian randomization (MR) approach we investigated the causal effect of serum 25(OH)D concentration on the indicators of thyroid function. We conducted a two-sample MR analysis utilizing summary data from the most extensive genome-wide association studies (GWAS) of serum 25(OH)D concentration (n=443,734 and 417,580), thyroid-stimulating hormone (TSH, n=271,040), free thyroxine (fT4, n=119,120), free triiodothyronine (fT3, n=59,061), total triiodothyronine (TT3, n=15,829), as well as thyroid peroxidase antibody levels and positivity (TPOAb, n=12,353 and n=18,297), low TSH (n=153,241), high TSH (n=141,549), autoimmune hypothyroidism (n=287,247) and autoimmune hyperthyroidism (n=257,552). The primary analysis was conducted using the multiplicative random-effects inverse variance weighted (IVW) method. The weighted mode, weighted median, MR-Egger, MR-PRESSO, and Causal Analysis Using Summary Effect estimates (CAUSE) were used in the sensitivity analysis. Our analysis showed a causal effect of 25(OH) D concentration on the risk of high TSH. Each 1 SD increase in serum 25(OH)D concentration was associated with a 12% decrease in the risk of high TSH (p=0.02). Additionally, we found a causal effect of 25(OH)D concentration on autoimmune hypothyroidism. Specifically, each 1 SD increase in serum 25(OH)D concentration was associated with a 16.34% decrease in the risk of autoimmune hypothyroidism (p=0.02). Our results support a causal effect that was negative in the direction across all methods used, meaning that higher genetically predicted vitamin D concentration possibly lowers the odds of having high TSH or autoimmune hypothyroidism. Other thyroid parameters were not causally influenced by vitamin D serum concentration.

Keywords: thyroid, mendelian randomization, gwas, causal, vitamin D

Presentation number: OC4-TM Abstract number: ABS-148-ISABS-2024

PRECISION MEDICINE APPROACH TO CELL THERAPY IN HEART FAILURE

Frljak Sabina, Poglajen Gregor, Zemljic Gregor, Cerar Andraz, **Vrtovec Bojan**

UMC Ljubljana, Slovenia, Ljubljana, Slovenia

bojan.vrtovec@gmail.com

The goal of the study was to develop a personalized cell therapy approach to be used as a clinical management in patients with chronic heart failure. Materials and Methods. In the derivation part of the study, we analyzed the dataset from 5 cell therapy clinical trials conducted at UMC Ljubljana, enrolling a total of 240 patients with chronic heart failure. We performed machine learning analysis to define individual patient profiles with most clinical benefits after cell therapy. Patient profiles were then used as inclusion criteria in the validation part of the study. In the validation study, CD34+ stem cells were mobilized by 5-day stimulation with filgrastim, collected with apheresis and immunoselection and injected transendocardialy. Patients were followed 1 year after cell therapy. Results. In the derivation part we identified nonischemic heart failure etiology, lower NT-proBNP levels, transendocardial cell injection, and lower end-diastolic volume (LVEDV) as independent predictors of favorable response to cell therapy. Using these criteria in the validation part of the study, we enrolled 30 patients (male: 93%), aged 51±13 years, with LVEF of 28.4±5.0%, LVEDV of 224±46 mL, and NT-proBNP of 1231±1708 pg/mL. At 1 year after cell therapy, we found a significant improvement in LVEF (+10.5±7.8%, P<0.001), a decrease in NT-proBNP (-530±1430 pg/mL, P=0.001), and an improvement in exercise capacity, measured as 6-minute walk test distance (+31±58 m, P=0.01). An improvement of LVEF >5% was present in 24/30 (80%) of patients, and a concomitant improvement in LVEF, NT-proBNP, and exercise capacity was present in 18/30 (60%) of patients. Conclusions. The use of strategies based on informing target individuals with the highest likelihood of regenerative response may significantly improve the clinical efficacy of cell therapy in chronic heart failure patients.

Keywords: cell therapy, heart failure, clinical response

Presentation number: OC5-FG Abstract number: ABS-28-ISABS-2024

SARMATIAN GOTH OR GOTHIC SARMATIAN? FORENSICS SHEDS LIGHT ON SURPRISING IRON AGE BURIAL

Diepenbroek Marta[1], Lehn Christine[1], Hyrchała Anna[2,3], Bartecki Bartłomiej[2], Bayer Birgit[1], Anslinger Katja[1], Niezabitowska-Wiśniewska Barbara[4], Lorkiewicz-Muszyńska Dorota[5,6]

[1]Institute of Legal Medicine, the Ludwig Maximilian University of Munich, Munich, Germany; [2]Rev. Stanisław Staszic Museum in Hrubieszów, Hrubieszów, Poland; [3]Doctoral School of Humanities and Art, Lublin, Poland; [4]Institute of Archaeology, Maria Curie-Skłodowska University, Lublin, Poland; [5]Department of Forensic Medicine, Poznań University of Medical Sciences, Poznań, Poland; [6]Department of Forensic Medicine, Collegium Medicum, University of Zielona Góra, Zielona Góra, Poland

marta.diepenbroek@med.uni-muenchen.de

In 2017 during excavations in Gródek (south-eastern Poland) a few Iron Age burials were revealed. This area has been of interest to archaeologists since the 1970s following the discovery of a Gothic settlement and cemetery in the area. One grave from 2017 was particularly special. The site of the discovery of the burial as well as some artifacts attributed it to the local Gothic culture. However, the way the woman was laid in the grave and the necklace she was wearing were unusual for the Goths, but popular among the Sarmatians. An extended anthropological assessment of the remains, including a facial approximation by a forensic specialist was ordered. During the research, the idea emerged to enhance this analysis with a genetic prediction of the woman's physical appearance and also to use forensics to gain further insight into her biogeographic ancestry. DNA was extracted from the pars petrosa in a dedicated bone lab using the modified Dabney method. Three independent extracts were submitted to forensic DNA phenotyping using the Ion AmpliSeq™ PhenoTrivium Panel, which includes over 200 SNPs associated with phenotype and ancestry. Additionally, the mitogenome was analyzed using the Precision ID mtDNA Whole Genome Panel. Sequencing of the DNA libraries was performed on the Ion S5 System. Stable isotope analysis was conducted in addition to genetic testing. To gain insights into different stages of the woman's life, a tooth, a rib, and a fragment of humerus were tested. The forensic BGA analysis placed the individual among modern Europeans with no evidence of admixture, closest to the northwestern European populations. This aligns with the predicted physical characteristics of blue eyes, light blonde hair, and fair skin. Isotopic analysis suggests that the woman did not migrate during her lifetime. These findings support rather the hypothesis of a burial from the local community that interacted with and was influenced by outside cultures, including the Sarmatians.

Keywords: HIrisPlex-S; forensic DNA phenotyping; BGA; Goths; Sarmatians

Presentation number: OC6-AG Abstract number: ABS-33-ISABS-2024

GENETIC HISTORIES OF MEDIEVAL SICILIAN INDIVIDUALS

Monnereau Aurore[1,2], Carver Martin[1], Molinari Alessandra[3], Speller Camilla[4], Wales Nathan[1]

[1]BioArCh, University of York, York, United Kingdom of Great Britain and Northern Ireland; [2]Globe Institute, University of Copenhagen, Copenhagen, Denmark; [3]Università degli Studi di Roma Tor Vergata, Rome, Italy; [4]University of British Columbia, Vancouver, Canada

amrm500@york.ac.uk

The Mediterranean area, at the crossroads of three different continents, has attracted not only diverse cultures but also a diversity of people, thus witnessing multiple changes, conquests, colonization, the rise and fall of several civilizations, kingdoms. From Antiquity to the Middle Ages, written sources testify to historic events of these periods, however, the impact of those changes on the biological heritage of the southern Italian population as well as on social and biological interactions between different communities under these circumstances remains unclear. Ancient DNA analysis on medieval individuals from Sicily was performed. This project followed state-of-the-art methods for ancient DNA research, including extensive measures in the laboratory to avoid contamination, recovery of DNA from dense bones, preparation of double-stranded DNA libraries, and evaluation of authenticity criteria, including deamination patterns and contamination estimates using Schmutzi and ANGSD software. 118 samples were analyzed, however, only samples showing characteristic ancient DNA patterns, no contamination, no first-degree relationships and at least 10,000 SNPs underwent further analyses. A total of 44 samples passed those criteria. The results revealed that during the Middle Ages, the Islamic conquest was not exclusively responsible for the presence of North African and sub-Saharan ancestry, nor was a massive population replacement observed. Finally, the whole study provided an opportunity to document the genetic diversity during a period that has not yet been extensively studied.

Keywords: ancient DNA, Sicily, Middle Ages