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ORAL ABSTRACTS

803.EMERGING TOOLS, TECHNIQUES AND ARTIFICIAL INTELLIGENCE IN HEMATOLOGY

Endogenous Retroviral Elements Constitute a Promising Vaccine Antigen Source for Haematological Malignancies

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Introduction

Immunotherapy has revolutionized modern cancer treatment, both within the fields of solid and haematology malignancies. The recent success of checkpoint inhibitor (CPI) therapies (e.g., aPD-1, aCTLA-4) in so called "high" tumour mutational burden (TMB) cancers, such as melanoma and lung cancer (Alexandrov et al. Nature 2013), have found only limited transferability to the haematological setting outside classical Hodgkins lymphoma (Pianko et al. Cancer J. 2018). Recently, the effect of CPIs in high TMB cancers has been further augmented by the combination of CPIs with personalized cancer vaccines (PCVs) in patients with resectable melanoma (NCT03897881). However, recent progress in the identification of novel alternative antigen targets, besides classical missense mutations targeted by PCVs, provides hope for the targeting of haematological cancers with low TMB by immunotherapy-based treatments such as PCVs or even precision-based cancer vaccines. Such sources include endogenous retroviral elements (ERVs) (Saini et al. Nat Commun. 2020), structural rearrangements (Robbe et al. Nat Gen 2022), or activation of transposon elements (Wolf et al. Nat Rev Nephrol. 2023). To investigate the applicability of such approaches in a haematological setting, prospective datasets curated from the database of Genotypes and Phenotypes (dbGaP) and in-house developed antigen prediction platforms, were employed.

Methods

Data was downloaded from dbGAP and missense mutations (SNVs, INDELs) were determined either from datasets (firehose, TCGA), when available, or through GATK-Mutect2. ERVs were identified using an in-house developed platform (ObsERV), as previously described (Garde et al. BioRxiv 2023). Simulated PCVs were designed for seven selected patients covering high/low TMB and ERV burdens from datasets pertaining to Acute Myeloid Leukaemia (AML), Acute Lymphoblastic Leukaemia (ALL), Multiple Myeloma (MM), Diffuse Large B Cell Lymphoma (DLBCL) and Chronic Lymphocytic Leukaemia (CLL) using in-house platforms PIONEER (neo-epitope identification and ranking for PCV design) and/or ObsERV. PIONEER ranking was based on MHC class I and II ligand propensity, epitope expression level, clonality and tumour specificity Cut-off for inclusion of "efficacious" neoepitopes were based on PIONEER ranking from a recent Phase 1 clinical trial (Mørk et al. ASCO 2023-9551). Due to the high degree of ERV conservation amongst patients within each haematological indications, a precision-based approach was attempted relying on MHC I/II ligand propensity prediction and epitope combination for optimal patient coverage (HLA haplotype) - a similar machine learning approach was proven useful for viral vaccine design (Persson et al Front. Immunol. 2023). Shared vaccines were designed based on HLA frequencies in the human population, which was then applied to the dataset of each patient. The resulting patient specific coverage was then used to compute the total coverage for a given indication.

Results and Discussion

We found a high presence of ERVs in several haematological malignancies suggesting the potential application of PCVs in these indications, relying on this antigen source (Fig 1A). The combination of missense mutations and ERV sources allowed PCVs to be designed for six of seven patients on average for AML, CLL, and MM compared to only three of seven on average with missense mutations alone. The high level of ERV expression in AML, CLL, and ALL allowed for the generation of vaccines

based on shared antigens within each indication. The resulting vaccines had an average coverage, with at least three epitopes, for 84% of AML, 45% of ALL and 35% of CLL patients. In comparison, a missense mutation approach, for the highest TMB cancer (melanoma) would result in only 2.6 % patient coverage with three epitopes. We believe that these findings suggest a novel approach to the treatment of haematological malignancies, either through a PCVs approach, combining multiple sources of antigens, or a precision-based approach with "warehouse" HLA haplotype-specific vaccines for a given indication. This may allow for treatment regimens with greater treatment effect, more durable response, and improved quality of life in indications with a high unmet medical need such as AML and CLL.

Disclosures Thygesen: *Evaxion Biotech:* Current Employment, Current equity holder in publicly-traded company. **Klausen:** *Evaxion Biotech:* Current Employment, Current equity holder in publicly-traded company. **Thuesen:** *Evaxion Biotech:* Current Employment, Current equity holder in publicly-traded company. **Garde:** *Evaxion Biotech:* Current Employment, Current equity holder in publicly-traded company. **Jespersen:** *Evaxion Biotech:* Current Employment, Current equity holder in publicly-traded company. **Grønbæk:** *Kirsten Grønbæk received research support from Janssen and is on the advisory board of Nanexa and GSK.:* Consultancy, Research Funding. **Kringelum:** *Evaxion Biotech:* Current Employment, Current equity holder in publicly-traded company. **Bundgård Sørensen:** *Evaxion Biotech:* Current Employment, Current equity holder in publicly-traded company.

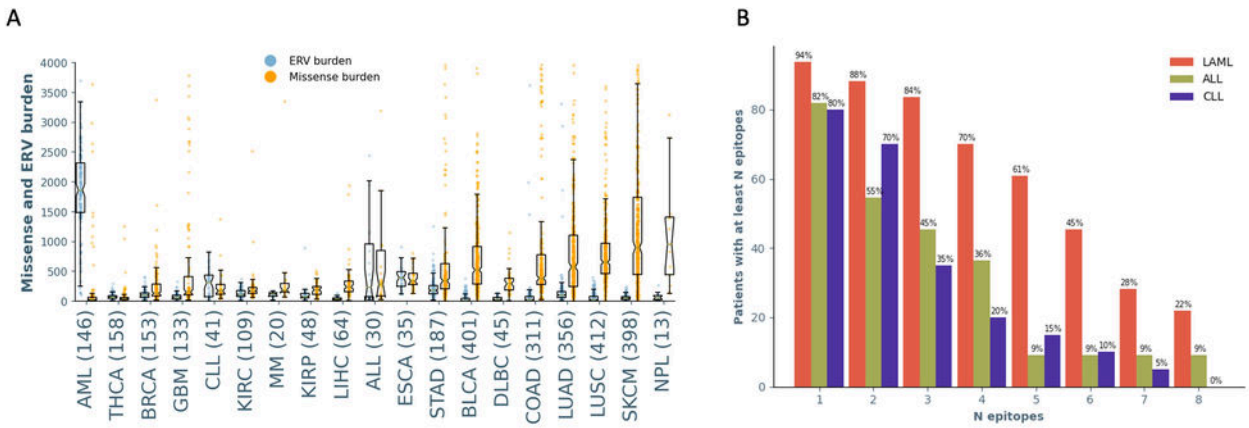

Figure 1. A) Predicted availability of antigen targets based on patient sequencing data sets (WXS, mRNAseq) from the dbGAP database (number of patients analysed). **B)** The possibility of generating three "shared/precision" based vaccine for each of CLL, AML and ALL based on ERV antigen sources. N epitopes denotes the number of epitopes that are shared for the percentage of patients analysed for the three given indications.

Figure 1

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