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Identification of a new target population for ibrutininb treatment

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INTRODUCTION

B-cell acute lymphoblastic leukaemia (B-ALL) is a clonal malignant disease that is characterised by the accumulation of genetically damaged precursors of B lineage lymphocytes. This lineage of ALL affects immature B-cells, suppressing normal haematopoiesis and affecting the ability of healthy immature B-cells to differentiate and mature into functional B and plasma cells. Like all leukaemias, ALL rapidly spreads throughout the body making localised treatments of little benefit. In addition, most ALL patients will achieve first remission but experience high relapse rates with long term disease free survival ranging from 15 – 45% depending on patient age.

Immunotherapy is currently used to treat ALL patients through allogeneic haematopoietic stem cell transplant and can improve overall survival for patients to 27-65%. To boost the graft versus host effect, and maximise the chances of successful transplantation of the donor stem cells, patients are given donor leukocyte infusions to support the graft. However, over one third of patients will still relapse and the mortality rates associated with SCTs remain high.

Despite the potential of existing therapies, new treatments targets are needed to further enhance survival rates for patients with adult B-ALL.

We used sero-profiling for the first time to directly compare sera samples from presentation adult B-ALL patients with age- and sex-matched healthy volunteer (HV) sera and identify differentially sero-recognised antigens for further study.

AIMS

- To identify antigens recognised by antibodies in adult B-ALL sera at disease diagnosis.
- To provide novel insights into the biology underlying B-ALL at the earliest stages of disease presentation, before treatment.
- To identify a new target patient population for existing, promising, immunotherapy treatment.

METHOD

We performed antibody specific profiling on sera samples from nine adult B-ALL patients and nine age and sex-matched healthy donor controls. Signals from 9,000 peptides were analysed on the ProScanArray using ProtoArray® Prospector v5.2 software. The mean value and standard deviation of each signal was calculated to produce a z-score and the most promising antigens identified.

RESULTS

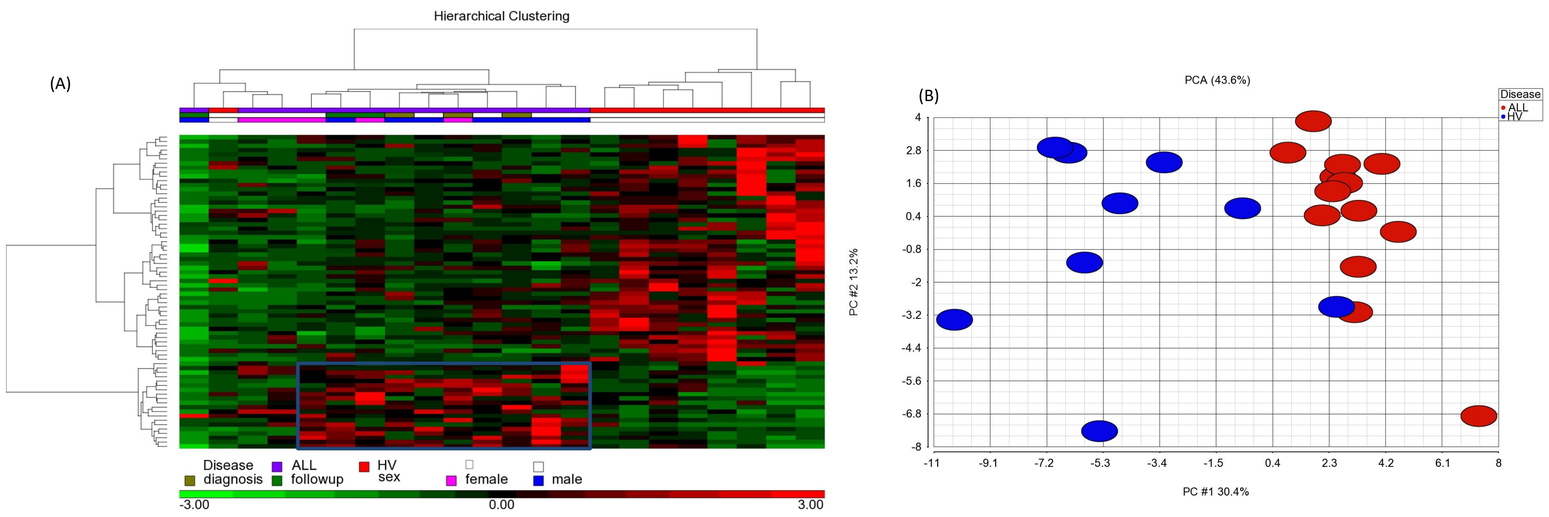

Fig 1. Immunoprofiling using sera from adult B-ALL patients and HVs. (A) Hierarchal Clustering of proteins shows that adult B-ALL and HV samples may be differentiated based on antibody recognition of antigens and that antigen recognition to adult B-ALL sera (blue box) may be less heterogeneous than previously thought; (B) PCA evidences the distinctness of features of samples from HVs (blue circles) and patient samples (red circles) bar one HV sample.

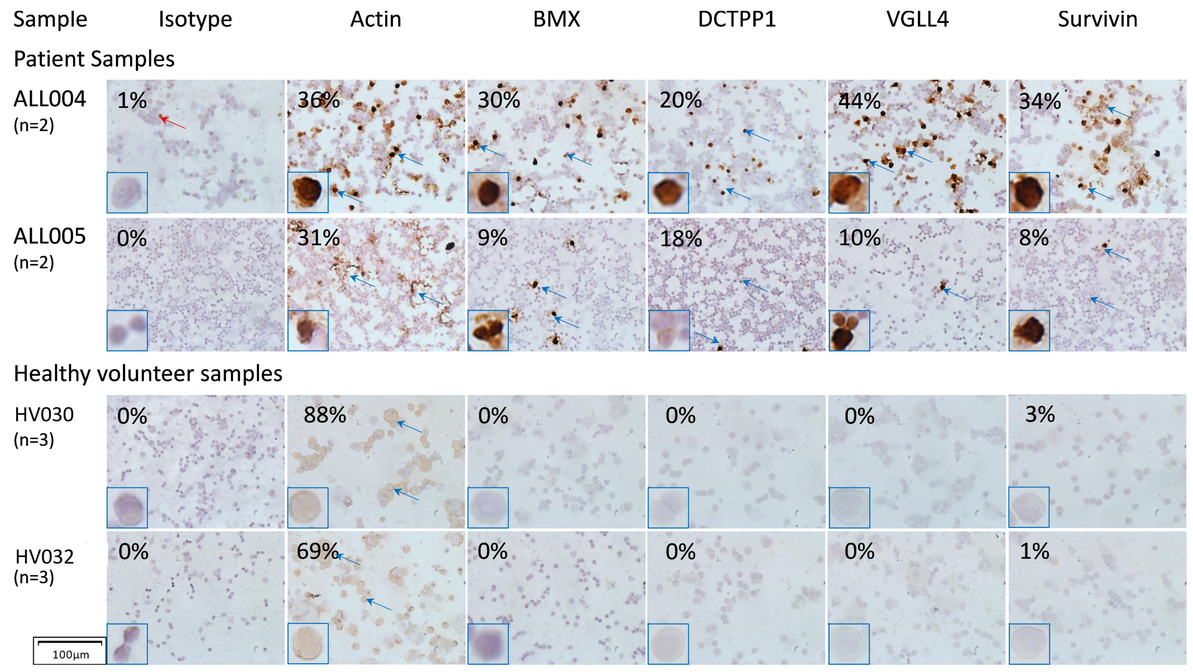

Fig 2. Immunolabelling detected the expression of the prioritised antigens in primary adult B-ALL patient samples. Blue arrows (and brown precipitation) shows patient and HV samples immunolabelled for expression of BMX, DCTPP1, survivin and VGLL4. Actin acted as the positive control while two isotype matched antibodies were used as negative controls. Percentages shown are the averages of positively stained cells of the 'n' independent experiments. Blue squares contain one-cell-zoom pictures from the original picture (scale bar is 100 µm). All pictures were taken at 400x magnification.

CONCLUSIONS

We have previously shown that survivin is frequently transcribed and translated in B-ALL patient samples but not healthy donors[2] providing a new target for immunotherapy strategies targeting this sub-set of patients.

In this study we have found that BMX was frequently recognised by sera from patients with adult B-ALL but was not transcribed differently between patients and HVs. However BMX protein was overexpressed[3] indicating it may be a target for drugs such as ibrutinib that act on the Bruton's Tyrosine Kinase pathway. As ibrutinib is already in clinical trials for mature B-cell disorders such as small lymphocytic lymphoma and mantle cell lymphoma, a case could be made that drugs such as ibrutinib could be used to target pre-BCR signalling in adults with B-ALL in future clinical trials.

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