MDX-124, a novel anti-ANXA1 antibody, has significant anti-cancer activity in preclinical models of osteosarcoma

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BACKGROUND

Osteosarcoma (OS) is a rare primary cancer of the bone characterised by its aggressive nature, strong invasiveness, rapid disease progression and high mortality rate. As patient outcomes have stagnated in the last 40 years, there remains a high unmet clinical need for novel targeted therapies to treat OS. Annexin-A1 (ANXA1), a 37 kDa phospholipid-binding protein, is overexpressed in several cancers, with high expression correlating with poor patient outcomes, tumour growth and metastatic spread[1-5]. Emerging gene expression data suggest annexin-A1 is a novel therapeutic target in OS[6]. MDX-124 is a first-in-class humanised antibody targeting annexin-A1 which is currently being evaluated in a Phase Ib clinical trial (ATTAINMENT). It has been shown previously to exert anti-cancer activity by reducing cancer cell growth, inhibiting migration and inducing antibody-dependent cell-mediated cytotoxicity[7-9]. Here we present data demonstrating efficacy of MDX-124 in preclinical OS models.

METHODS

TARGET EXPRESSION: ANXA1 gene and protein expression in OS samples were assessed via RNA-seq and immunohistochemistry respectively. ANXA1 protein expression in OS cell lines was evaluated via imaging flow cytometry, where multispectral images of OS cells in brightfield, green (ANXA1 via MDX-124) and red (nuclear staining via DRAQ5) were captured and analysed. Cellular localisation of ANXA1 was determined using Ideas™ imaging analysis software.

CELL VIABILITY ASSAYS: A panel of OS cancer cell lines ($1x10^6$ cells) were incubated for 72 h with IgG isotype control (0-10 μM) or MDX-124 (0-10 μM). Cell viability was measured via MTT assay. Data are presented as the mean of 3 independent experiments. Statistical significance was calculated using an unpaired t-test (GraphPad Prism 10).

CELL CYCLE ANALYSIS: A panel of OS cancer cell lines ($1x10^6$ cells) were incubated for 24 h with MDX-124 (25 μM). Cells were harvested and labeled with Cytophase violet dye (8 μM) before incubation at 37°C for 30 min. Flow cytometry was conducted using a CytoFLEX LX and analysed with FlowJo™ software to quantify the percentage of cells in each cell cycle phase (G1, S and G2).

MIGRATION ASSAY: A panel of OS cancer cell lines ($1x10^6$ cells) were pre-treated with MDX-124 (0 μM – 50 μM) for 1 h and transferred into 8 μM pore transwell plates for 24 h incubation. Migrated and non-migrated cells were harvested and counted using flow cytometry. Statistical significance was calculated using a 2-way ANOVA with Tukey's multiple comparison correction (GraphPad Prism 10).

RESULTS

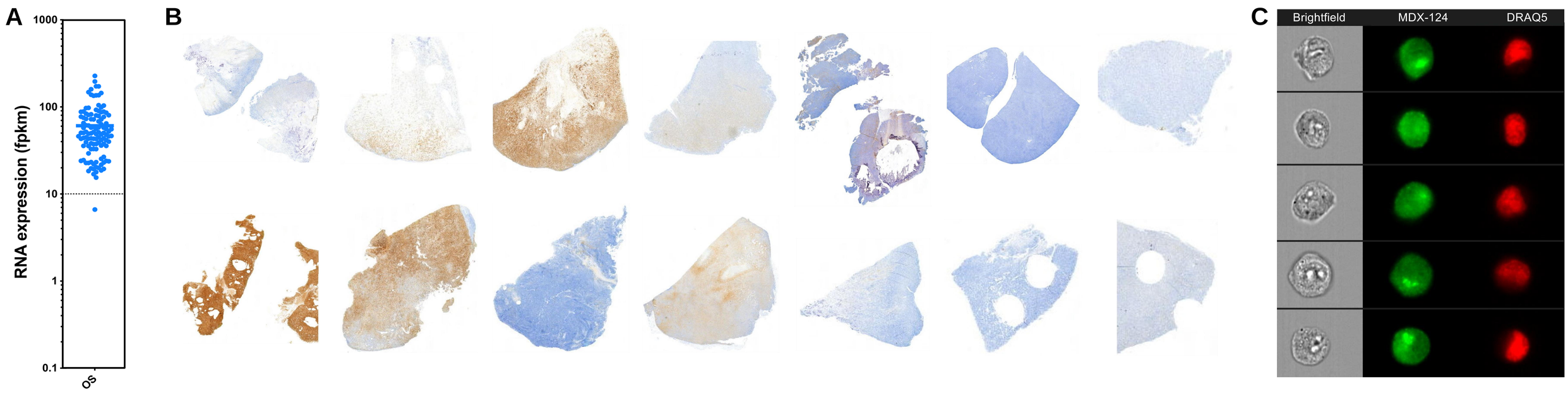
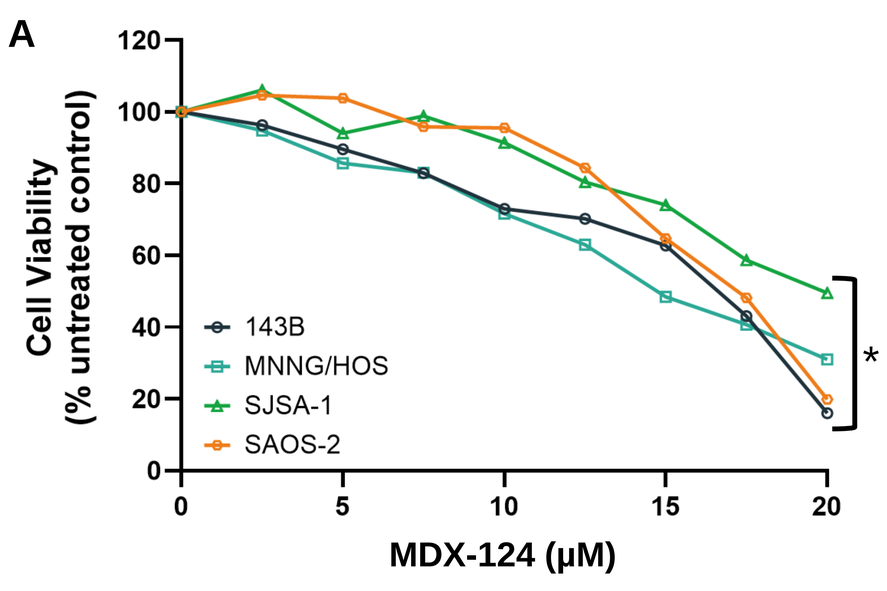


Figure 1. ANXA1 is highly expressed in OS tumour samples. (A) ANXA1 RNA expression in OS patient samples from the Pediatric Cancer Genome Project (PCGP) database. **(B)** OS xenograft samples from the St Jude Children's Hospital depository were high (9/14), medium (3/14) or negative (2/14) for ANXA1 expression. **(C)** ANXA1 was found to be highly expressed by all OS cell lines with expression observed in nuclear, cytoplasmic and membranal compartments (representative data showing 143B cells).



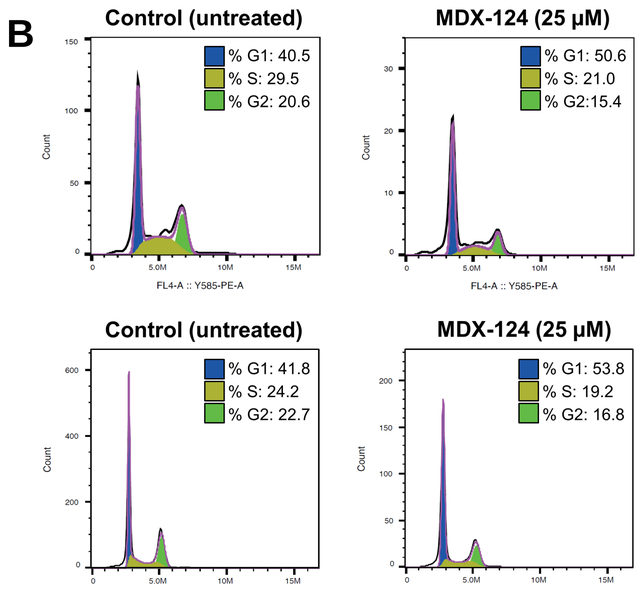


Figure 2. MDX-124 treatment reduces the viability of annexin-A1 expressing OS cell viability via cell cycle arrest. (A) 143B, MNNG/HOS, SJSA-1 and SAOS-2 OS cells had significantly reduced viability when exposed to MDX-124 vs an IgG1 isotype control. **(B)** MDX-124 incubation with OS cell lines SAOS-2 (upper) and SJSA-1 (lower) significantly decreased the proportion of cells in S and G2 phases and increased cells in G1 phase versus untreated controls (representative data).

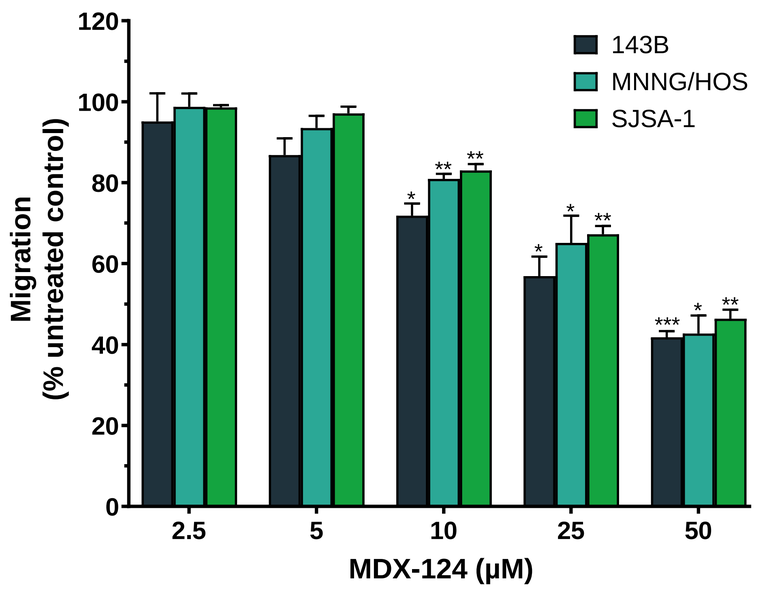


Figure 3. MDX-124 significantly inhibits OS cell migration. 143B, MNNG/HOS and SJSA-1 cells all displayed a reduced migratory capacity in a dose dependent manner when exposed to MDX-124.

CONCLUSIONS

MDX-124 targets extracellular forms of ANXA1 preventing the activation of FPR1/2 to reduce cancer progression. MDX-124 has been shown to have anti-tumour activity in several preclinical models of OS. Additional studies are ongoing to further evaluate the efficacy of MDX-124 in OS. Medannex plans to initiate a Phase Ib study of MDX-124 in paediatric OS in late 2025.

MORE INFORMATION

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