Targeting Myeloid-Derived Suppressor Cells (MDSCs) to Restore Antitumor Immunity in Non–Small Cell Lung Cancer (NSCLC) via SRC Family Kinase Inhibition with NXP900

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Introduction

Despite therapeutic advances, non–small cell lung cancer (NSCLC) demonstrates poor survival outcomes, with global 5-year rates of only ~ 16 - 19%[1]. The tumor microenvironment (TME) critically influences NSCLC prognosis and treatment response through immune contexture (cell type, density, and spatial location). Elevated $CD4^+$ and $CD8^+$ T-cell tumor infiltration correlates with improved survival. Contrastingly, increased myeloid-derived suppressor cells (MDSCs) promote immune evasion, angiogenesis, and metastasis[2]. NXP900 (a.k.a eCF506) is a highly potent and selective SRC family kinase (SFK) inhibitor (IC_{50} of 0.47 nM against YES1) that locks SFKs in their inactive "closed" conformation (type 1.5), inhibiting both enzymatic and scaffolding activities of SFKs. Cancer models exhibiting hippo pathway modulators such as FAT1 or NF2 mutation or loss are associated with increased sensitivity to NXP900 *in vitro* and tumor growth inhibition and regression *in vivo*[3]. Given MDSC dependence on SFKs and YAP/TAZ signaling required for immunosuppressive function, we hypothesized that NXP900 may suppress MDSCs, thereby reversing immune suppression, and enhance antitumor immunity in NSCLC.

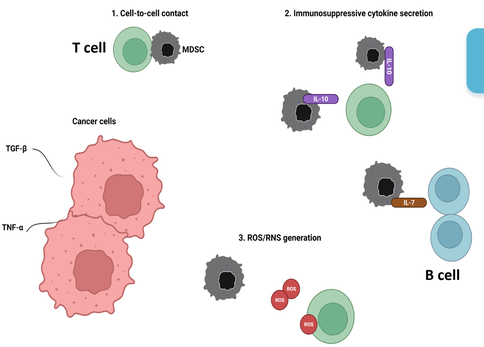

Figure 1. Myeloid-derived suppressor cells immunosuppressive mechanisms.
MDSCs use several different mechanisms to suppress immune cells including 1. Cell-to-cell contact 2 – immunosuppressive cytokine secretion (affecting T cell – green and B cell -blue functionality) and 3 – ROS/RNS generation. PMN-MDSCs preferentially utilize reactive oxygen species and arginase 1 to perform immunosuppression, meanwhile M-MDSCs apply nitric oxide, expression of immune regulatory molecules (PD-L1) and secretion of immunosuppressive cytokines such as IL-7 and IL-10.

Validation of induced-MDSCs

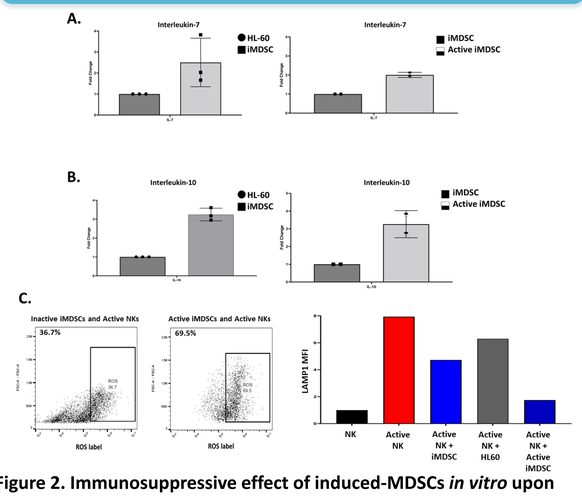

Figure 2. Immunosuppressive effect of induced-MDSCs *in vitro* upon Natural Killer cells.
Phenotypic validation of induced-myeloid-derived suppressor cells using production of immunosuppressive cytokines used by MDSCs to suppress T cells, B cells and NK cells. **A - B.** Assessment of IL-7 and IL-10 production in iMDSCs, activated iMDSCs and HL-60 cells via RT-PCR. **C.** ROS assay detection of hydroxyl, peroxyl, or other reactive oxygen species in live cells under co-culture conditions via flow cytometry, demonstrating basal and active induced-MDSCs, and active NK cells (**36.7% vs 69.5%).** Median MFI of LAMP1 NK degranulation marker demonstrated. n = 3.

High immune cell populations predict survival in NSCLC

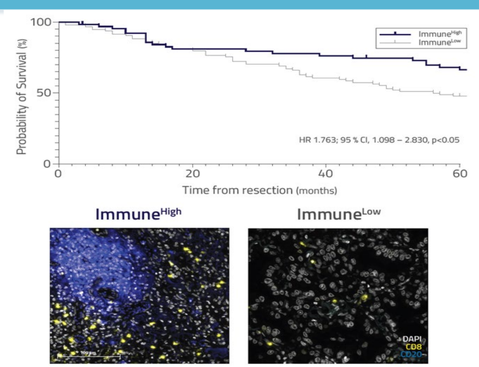

Figure 3. High immune cell populations in NSCLC TME associated with improved OS.
Kaplan-Meier curves for survival of 162 treatment-naïve patients with early-stage lung adenocarcinoma over 5 years. Patients were stratified for TME immune cell populations. $Immune_{High}$ n=64, $Immune_{Low}$ n = 98. $Immune_{High}$ vs $Immune_{Low}$ 5-year survival 66% vs 48% ($p<0.05$).

Myeloid-derived suppressor cells in the NSCLC TME

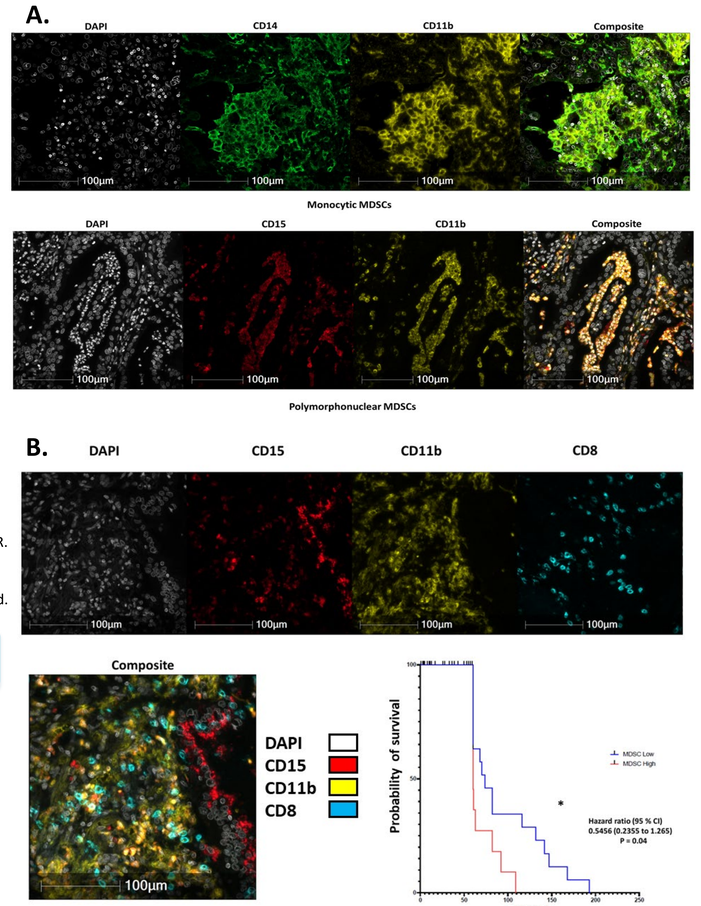

Figure 4. Myeloid-derived suppressor cells in the human NSCLC TME

A. Monocytic and polymorphonuclear MDSC subtypes within the TME. Four fluorescence channels illustrating the expression of DAPI (white), CD11b (yellow), CD14 (green) and CD15 (red), individually. mIF staining of two ROI's demonstrating monocytic MDSCs (CD11b+CD14+CD15-) and polymorphonuclear MDSCs (CD11b+CD14−CD15+) - DAPI (applied as a nuclear counterstain). **B. Cytotoxic T cell immunosuppression by polymorphonuclear MDSCs via cell-to-cell contact.** Representative example of multiplex immunofluorescence of a ROI showing cell-to-cell contact between PMN-MDSCs and CD8+ cytotoxic T cells. Associations between low and high PMN-MDSC populations across sub-cohort. Total PMN-MDSC populations normalised by paired population of cancer cells within the TME before generating survival plot. Statistical significance was assessed using the log-rank test (Mantel-Cox). ($p^*<0.05$, $p^{**}<0.01$). n=60.

NXP900 inhibits MDSC proliferation and nuclear YAP1 localization

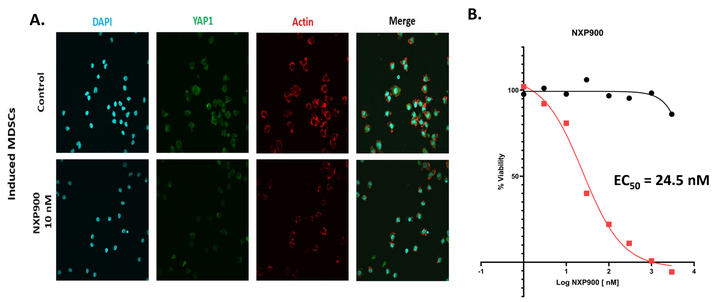

Figure 5. Study of iMDSC proliferation and YAP1 localization after treatment with NXP900.
A. Immunofluorescent confocal imaging study of YAP1 localization in induced-MDSCs, NXP900 at 10 nM for 24-hours (x60). **B.** Dose-dependent curve of induced-MDSCs cells treated with NXP900 for 72-hours (n=3).

Conclusions

- **High tumor immune infiltration predicts overall survival in NSCLC patients, however, patient immune response is hindered by immunosuppressive cells within the TME.**
- **These findings identify MDSCs as a key immunosuppressive driver of prognostic significance in NSCLC.**
- **NXP900 currently in a Phase 1b study (NCT05873686) including in NSCLC patients with YES1 and FAT1 genomic alterations, effectively suppresses MDSC viability and YAP1 signaling *in vitro*, supporting its potential as a novel therapy in NSCLC.**

Acknowledgements and Contacts

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