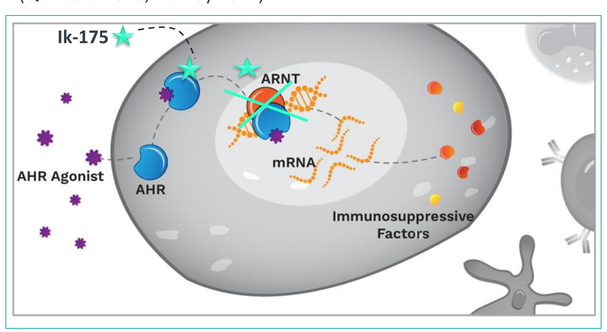
Computational Biology and Tissue-based Approaches to Inform Indication Selection for a Novel AHR Inhibitor

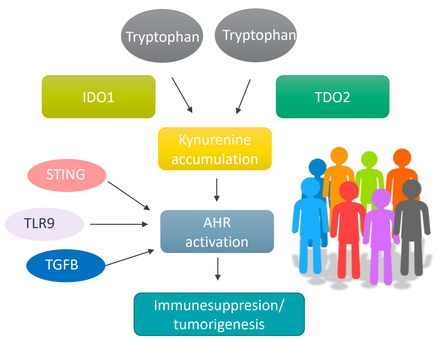
Abstract #15472
Poster #93

Marta Sanchez-Martin, Lei Wang, Karen McGovern, Jeffrey Ecsedy, X. Michelle Zhang
Ikena Oncology, Inc. Boston, MA 02210

Background: Aryl Hydrocarbon Receptor (AHR) is a ligand-activated transcription factor that regulates the activities of multiple innate and adaptive immune cell types. Various exogenous and endogenous ligands such as kynurenine bind to AHR and subsequently ARNT (AHR nuclear transportation) driving AHR nuclear translocation and transcriptional activation, leading to an immunosuppressive tumor microenvironment (Quintana 2013; Murray 2014).

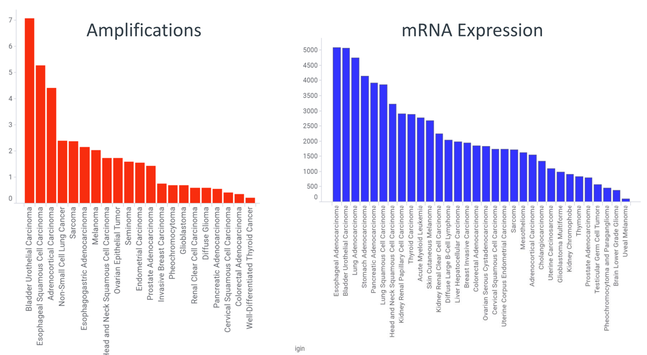


AHR activation is implicated in tumor development in multiple cancer types. In addition, high levels of serum kynurenine are associated with resistance to checkpoint inhibitors (Li 2019). To overcome AHR-mediated immunosuppression in cancers, we developed a selective oral AHR inhibitor IK-175 and took a combined computational and tissue-based approach to select cancer indications for its clinical development.



The aim of this work is to identify tumor indications dependent on AHR signaling based on computational and tissue analyses and define patient selection strategies to evaluate AHR inhibition in cancers.

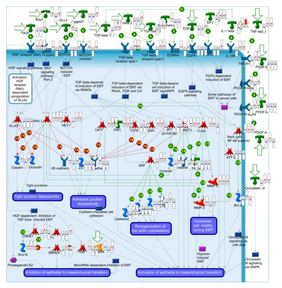
Genomic profiling of solid and hematological cancers from TCGA and Project GENIE demonstrated bladder cancer as the tumor type with the highest prevalence of AHR amplification and the second highest of AHR expression



Ranking of tumor types from TCGA and Project GENIE by frequency of copy number gains (left) and mRNA expression level (right) of AHR gene.

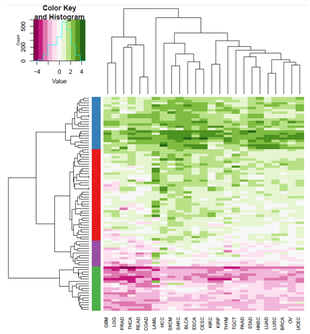
AHR signature analysis demonstrated bladder cancer as the tumor type with higher pathway activation

List of AHR interactors by pathway analysis with MetaCORE

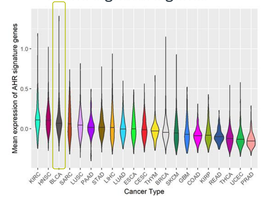


Clarivate™

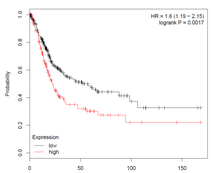
Modulation of AHR target gene expression across tumor types



Tumor types by mean expression of the signature genes



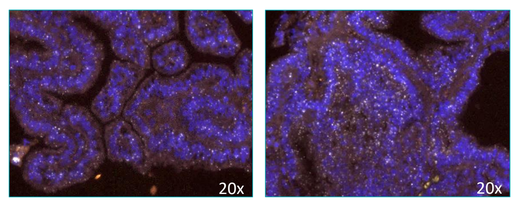
AHR signature correlation with Overall survival in bladder cancer



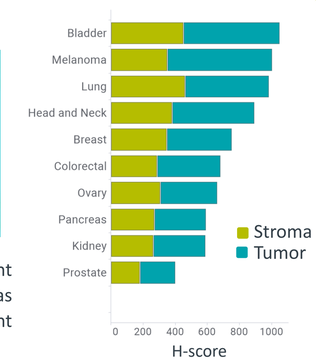
A proprietary gene signature of AHR activation was developed integrating literature, pathway analysis using MetaCore (Clarivate™) RNAseq and nanostring data from PBMC, T-cells, and cell lines upon AHR inhibition. Transcriptional analysis of the TCGA data using this signature demonstrated high expression of AHR and AHR signature genes in bladder cancer, suggesting increased pathway activity in bladder cancer relative to other cancer types (top 25%). High mean AHR signature gene expression was also associated with worse overall survival in the TCGA bladder cancer cohort (patients were divided by mean expression of signature genes; top 50% vs lowest 50%).

RNAScope analysis of AHR transcripts in tumor and stromal cells from 10 tumor types demonstrated bladder cancer is the tumor type with higher AHR expression

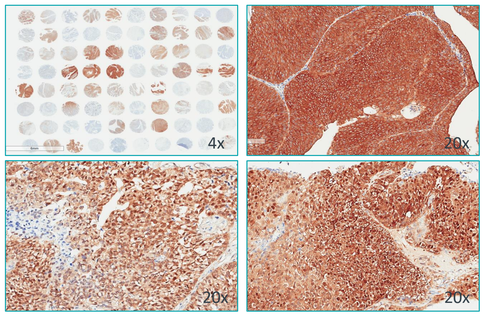
AHR transcripts in Bladder cancer (white)

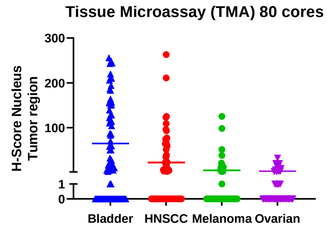


RNAscope analysis of a tissue microarray containing 10 different tumor types (11 cores per tumor type) revealed bladder cancer has the highest expression of AHR transcripts in the tumor compartment (white dots in the images).



Bladder cancer is the tumor type with highest nuclear AHR protein expression in the tumor region across all cancers evaluated





A newly developed IHC assay was used to assess nuclear localization of AHR protein as an indicator of pathway activation. Computational scoring of 4 TMAs from different indications demonstrated bladder cancer as the tumor type with the largest number of high AHR nuclear H-scores.

Conclusions

In summary, we demonstrated high prevalence of nuclear AHR protein expression, AHR gene amplification and target gene expression in bladder cancer, suggesting aberrant AHR activation may play an important role in the progression of this tumor type. This study provides rationale for therapeutic targeting of AHR in bladder cancer patients. Ikena is currently evaluating the anti-tumor activity of IK-175 as a single agent and in combination with nivolumab in bladder cancer in a Phase 1a/1b clinical study (NCT04200963).

correspondence to: msanchez-martin@ikenaoncology.com