1304 ROBUST MACHINE LEARNING (ML) APPROACH FOR SCREENING MICROBIOME ECOSYSTEM THERAPIES (MET) DRUG CANDIDATES IN COMBINATION WITH IMMUNE CHECKPOINT INHIBITORS

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Background Studies for the last 8 years have connected gut microbiome composition to ICI efficacy in cancer therapy, including pilot studies[1] [2] demonstrating that FMT from responders to non-responders can improve response rates. However, interstudy inconsistencies were observed in microbiome signature findings[3] also confirmed when reprocessing internally raw data from multiple studies. It remains critical to tackle this heterogeneity to learn from stable patterns and develop a robust and reliable drug candidate screening algorithm.

Hence, MaaT Pharma developed an AI framework to train models from microbiota Whole Metagenome Sequencing (WMS) datasets that predict the responder status to ICIs. We focused on performance and robustness, which was achieved by monitoring the *AUC* as a standard approach, and *precision* to control for false positive rate and to emphasize the positive classification criticality in a drug candidate selection approach.

Methods We collected baseline WMS datasets from 10 cohorts in 3 ICI indications: melanoma, non-small cell lung cancer and renal cell carcinoma, along with clinical evaluation of ICI treatment. Those datasets were processed by gutPrint® *MgRunner* software, before being included in the AI framework. About 70 experiments were conducted within a Leave-One-Dataset-Out cross-validation scheme. Various factors such as taxonomic or functional inputs, dataset bias correction, data augmentation approaches, ML algorithms and data representation methods, were tested to select the top ones.

Finally, a model was refit with the best performing parameters on the entire dataset, and applied to score MaaT Pharma mono-donor and healthy-pooled-donors-derived drug substances (DS).

Results The best performing experiment provided models based on the XGBoost algorithm with AUCs ranging from 0.52 to 0.73 depending on the left-out cohort (average AUC = 0.65), and a precision that ranges between 0.55 and 0.81 (average precision = 0.65). Those results outperform melanoma-centered study with a comparable method.[4] Despite the diverse data sources and indications, the multi-indication approach surpassed the mono-indication (melanoma) training approach for predictions related to melanoma patients. Considering the scoring of DS derived from healthy donors, 73% of mono-donors and 91% of healthy-pooled-donors-derived DS were classified as 'Responder-like'.

Conclusions Present study highlights the significance of dataset size in ICI microbiota models and presents a methodology to enhance the performances of a multi-cohort-based ML approach. Conditioned to the performances we obtained, the healthy-pooled-donors-derived DS harbor a considerable ratio (91%) of 'ICI Responder-like', significantly higher than the mono-donor stools (73%) suggesting that pooled ecosystems from healthy donors could better convert ICI-non responders into responders.

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