Abstracts

1085 INNATE IMMUNE ACTIVATION BY MICROTUBULE DESTABILIZING AGENTS ENHANCES THEIR EFFICACY IN VIVO, AS PREDICTED BY MACHINE LEARNING ANALYSES OF HUMAN PBMC TREATED WITH A LARGE, BIOACTIVE COMPOUND LIBRARY

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Background Chemotherapies are first-line cancer treatments, often preceding immunotherapies, but their impacts on immune responses are poorly understood. Drug discovery pipelines typically must choose between large library screens with simple readouts or small, targeted compound sets for more complex mechanistic investigation. Spring’s Immune Compass uses machine learning (ML) analyses of high-content cell paint images and secreted protein profiles to simultaneously screen full compound libraries while acquiring complex functional details for each compound.

Methods 10,000+ bioactive compounds were screened in human PBMC using Spring’s Immune Compass platform. Compounds were compared to benchmark controls and identified as immune potentiators for further study as vaccine adjuvants, innate agonists, and cancer immunotherapies, among others.1 Microtubule destabilizing agents (MDAs) Taltobulin (oral) and Verubulin (intravenous) were further explored in MC38 and EG7.OVA C57BL/6 mouse syngeneic tumor models at Charles River Labs.

Results Here, we show that an established class of chemotherapeutics, MDAs, were identified in our screen as having immunostimulatory functions based on their similarity to approved adjuvant AS03 and pro-inflammatory cytokine profiles. Screening data, particularly IL-1b secretion, was used to prioritize specific MDAs for further study. We confirmed in vitro that Verubulin and Taltobulin activate human monocyte-derived dendritic cells, as shown for approved MDAs like Colchicine and Vinblastine.2–4 Further, these drugs, especially Taltobulin, reduce tumor size and prolong survival (figure 1). These effects were not due exclusively to cytotoxicity, as benefits of Taltobulin treatment continued without additional doses in EG7 tumor-cleared mice upon tumor rechallenge on the opposite flank. In RAG2-/- immunodeficient mice, initial EG7 tumor clearance after Taltobulin administration was similar to wildtype C57BL/6, but maintenance of tumor regression and survival were impaired, suggesting that these long term effects are immune-mediated.

Conclusions These data demonstrate the power of coupling ML analysis with high-throughput, high dimensional library screens to identify multiple functional classes of novel drug candidates simultaneously. Using this approach, Spring identified the immunostimulatory potential of the MDA family, directly selected top candidates, and designed in vivo experiments that demonstrated the significance of MDA mediated immune stimulation. These effects are likely due to improved DC activation,5–6 but future studies are needed to confirm. Our results support further study of the benefits of MDAs in combination with immunotherapies, like checkpoint inhibitors, that require strong anti-tumor immune memory. In particular, Taltobulin shows promise as an MDA with both strong tumor cytotoxic effects and durable immune memory generation with minimal toxicity.

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REFERENCES

Ethics Approval All procedures were conducted in accordance with the Institutional Animal Care and Use Committee of Charles River Labs, under IACUC No. 1033.

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Abstract 1085 Figure 1 Microtubule destabilizing agents (MDAs) Taltobulin and Verubulin slow tumor growth and improve survival in EG7.OVA model