Machine Learning to extract, standardize, and analyze interactions from drug and biologic applications reviewed by FDA.

Results Using Regulatory Foresight, we discovered (a) the major topics of interest and concerns of the FDA, (b) the commonalities and differences in topics between the individual ICIs, (c) the evolution of topics from the oldest to the most recently approved ICI, and (d) the unaddressed topics in official FDA guidance documents.

Conclusions This work successfully uncovers regulatory requirements in the development of immune checkpoint inhibitors using AI algorithms in order for sponsors to (a) optimize strategies for development of new drugs, (b) better understand regulatory expectations, and (c) adequately prepare for meetings and submissions to regulatory agencies. In addition this work discovers the current gaps in official FDA guidance documents so that they may be adequately addressed in future versions.

REFERENCES

- Jardim DL, de Melo Gagliato D, Kurzrock R. Lessons From the Development of the Immune Checkpoint Inhibitors in Oncology. *Integr Cancer Ther* 2018;**17**(4):1012–1015. doi:10.1177/1534735418801524
- Ferrara R, Pilotto S, Caccese M, *et al*. Do immune checkpoint inhibitors need new studies methodology?. *J Thorac Dis* 2018;**10**(Suppl 13):S1564–S1580. doi:10.21037/jtd.2018.01.131
- 'Impact Story: Determining the Clinical Benefit of Treatment Beyond Progression with Immune Checkpoint Inhibitors' US FDA Regulatory Science Impact Story. Accessed on the 26th of July 2020: <https://www.fda.gov/drugs/regulatory-science-action/impact-story-determining-clinical-benefit-treatment-beyond-progression-immune-checkpoint-inhibitors>
- 'Clinical trial endpoints for the approval of cancer drugs and biologics' Guidance for industry. US Department of Health and Human Services, FDA, Oncology Center of Excellence, CDER, CBER. December 2018
- Gong, J., Chehrizi-Raffle, A., Reddi, S. *et al*. Development of PD-1 and PD-L1 inhibitors as a form of cancer immunotherapy: a comprehensive review of registration trials and future considerations. *J. Immunotherapy cancer* 2018;**6**:8. <https://doi.org/10.1186/s40425-018-0316-z>
- Vaddepally RK, Kharel P, Pandey R, Garje R, Chandra AB. Review of Indications of FDA-Approved immune checkpoint inhibitors per NCCN guidelines with the level of evidence. *Cancers (Basel)* 2020;**12**(3):738. Published 2020 Mar 20. doi:10.3390/cancers12030738
- PD1/PD-L1 Landscape. Cancer Research Institute. Accessed on the 26th of July 2020. <https://www.cancerresearch.org/scientists/immuno-oncology-landscape/pd-1-pd-l1-landscape>
- Immuno-Oncology Landscape. Cancer Research Institute. Accessed on the 26th of July 2020. <https://www.cancerresearch.org/scientists/immuno-oncology-landscape>

<http://dx.doi.org/10.1136/jitc-2020-SITC2020.0666>

667

INTEGRATED MOLECULAR CHARACTERIZATION AND THERAPEUTIC VULNERABILITIES OF NEURALLY PROGRAMMED TUMORS ACROSS 33 HUMAN INDICATIONS

Yasin Senbabaoglu*, Aslihan Calviello, Guadalupe Munoz, Richard Bourgon, Shannon Turley, Christine Mousson. *Genentech, South San Francisco, CA, USA*

Background Neuroendocrine tumors (NETs) can arise from neuroendocrine stem cells de novo, or from tumors that develop lineage plasticity and undergo neuroendocrine transformation. De novo NETs are generally immune desert, and thus are refractory to single agent immune checkpoint inhibitors (ICIs) such as monoclonal antibodies against PD1, PDL1 and CTLA4. Transformed NETs also present a clinical challenge as there is no established therapeutic approach for these tumors. Despite the high unmet medical need, our understanding of the molecular characteristics and microenvironment of both de novo and transformed NETs remains largely incomplete.

Methods Here, we develop a machine learning-based classifier NEPTUNE (NEurally Programmed Tumor Prediction Engine) to identify neurally programmed (neuroendocrine-like or neural crest embryonic origin) tumors across 33 different human cancers and more than 10000 treatment-naive tumors, and study their molecular and immune microenvironment characteristics.

Results We find that neurally programmed (NEP) patient tumors are characterized by low lymphocyte and myeloid cell infiltration, p53 and RB1 functional loss, chromosome arm level aneuploidy, genome-doubling, loss of REST-mediated transcriptional repression, and enrichment in NRAS mutations. Similar to neuroendocrine indications, NEP tumors exhibit two major variants: 1) well-differentiated low-proliferating, and 2) poorly-differentiated high-proliferating; with the latter being substantially more prevalent in humans and significantly more aggressive in terms of survival and time to metastasis. We find evidence that BAF complexes and de-repression of Polycomb repressive complex 2 (PRC2) targets may play roles in the neural programming of particularly poorly differentiated NEP tumors. NEP tumors also exhibit characteristics of lineage plasticity such as EMT/stem-like phenotype as well as activation of MYCN and SOX family transcription factors. These observations suggest that lineage plasticity is not restricted to the post-therapy setting, but can be seen in treatment-naive primary tumors as well. In vitro, NEP tumor lines are most sensitive to NAMPT inhibitors, which may be due to low NAD biosynthesis enzyme expression and/or low NAD metabolite levels. Unbiased metabolite analysis also reveals that NEP tumors may be sensitive to inhibition of certain components in pyrimidine biosynthesis and urea cycle pathways. Further, we find in a pancreatic cancer metabolomic dataset that N-acetyl-aspartate and/or its synthesizing enzyme NAT8L may have potential as diagnostic biomarkers for NEP tumors.

Conclusions Our study sheds light on previously underexplored aspects of neuroendocrine tumors; defines and characterizes the novel class of neurally programmed tumors; and provides a collection of evidence to guide clinical trial design and clinical care for these tumors.

<http://dx.doi.org/10.1136/jitc-2020-SITC2020.0667>

668

A TOOLKIT FOR THE QUANTITATIVE ANALYSIS OF THE SPATIAL DISTRIBUTION OF CELLS OF THE TUMOR IMMUNE MICROENVIRONMENT

¹Anna Trigos*, ²Tianpei Yang, ¹Yuzhou Feng, ²Volkan Ozcuban, ¹Maria Doyle, ¹Anu Pasam, ¹Nikolce Kocovski, ¹Angela Pizzolla, ¹Yu-Kuan Huang, ³Greg Bass, ¹Simon Keam, ⁴Terrence Speed, ¹Paul Neeson, ¹Shahneen Sandhu, ¹David Goode. ¹Peter MacCallum Cancer Centre, Melbourne, Australia; ²The University of Melbourne, Melbourne, Australia; ³CSL, Melbourne, Australia; ⁴Walter and Eliza Hall Institute, Melbourne, Australia

Background Spatial technologies that query the location of cells in tissues such as multiplex immunohistochemistry and spatial transcriptomics are gaining popularity and are likely to become commonplace. The resulting data often includes the X, Y coordinates of millions of cells, cell phenotypes and marker or gene expression levels. In cancer, the spatial location of lymphocytes has been linked to prognosis and response to immunotherapy. While these advances have been exciting for the field, the methods currently being used are still coarse, making us severely underpowered in our ability to extract quantifiable information. Appropriate

Conclusions SPIAT is compatible with multiplex immunohistochemistry, spatial transcriptomics and data generated from other spatial platforms, and continues to be actively developed. We expect SPIAT to become a user-friendly and speedy go-to package for the spatial analysis of cells in tissues, as well as promote the use of quantitative metrics in the spatial analysis of the tumor immune microenvironment.

1. Tianpei Yang, Volkan Ozcoban, Anu Pasam, Nikolce Kocovski, Angela Pizzolla, Yu-Kuan Huang, Greg Bass, Simon P. Keam, Paul J. Neeson, Shahneen K. Sandhu, David L. Goode, Anna S. Trigos. SPIAT: An R package for the Spatial Image Analysis of Cells in Tissues. *BioRxiv* doi: <https://doi.org/10.1101/2020.05.28.122614>

669 COMPUTATIONAL ANALYSIS OF MUTUAL FEEDBACK REGULATIONS BETWEEN IDO1 AND PD-L1

Background PD-L1 is a validated biomarker for anti-PD-1/PD-L1 therapies and its expression can be regulated by IDO1, and vice versa IDO1 can regulate PD-L1 expression indirectly through various signaling pathways. Concurrent inhibition of IDO1 and PD-1/PD-L1 may have enhanced anti-tumor effects. **Methods** In this study, computational models were established to identify factors involved in interactions between these two therapeutic targets. Abstracts published on IDO1, PD-1, PD-L1, anti-PD1/PD-L1 were downloaded from PubMed, and analyzed by natural language processing and text mining. The information on interactions among gene, compound/therapy, cell/animal model, pathway and disease was extracted. Two gene networks, IDO1->PD-L1 and PD-L1->IDO1, were constructed (figures 1 and 2, respectively).

Conclusions As the network analyses revealed, IDO1 and PD-L1 are involved in complex mutual feedback regulations. Inhibition of IDO1 could either up- or down-regulate PD-L1, and enhance or reduce efficacy of anti-PD-1/PD-L1. The factors involved in the mutual feedback regulations could serve as biomarkers to determine and monitor the efficacy of combining IDO1 and PD-1/PD-L1 inhibitors, as well as additional therapeutic targets. The literature-based modeling approach facilitates the development of combination strategies especially when the experimental evident is lacking.

A401