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Combining Multiplexed Ion Beam Imaging (MIBI) with Convolutional Neural Networks to accurately segment cells in human tissue

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Background
Multiplexed imaging is a rapidly growing field that promises to substantially increase the number of proteins that can be imaged simultaneously. We have developed Multiplexed Ion Beam Imaging by Time of Flight (MIBI-TOF), which uses elemental reporters conjugated to primary antibodies that are then quantified using a time of flight mass-spectrometer. This technique allows for more than 40 distinct proteins to visualized at once in the same clinical samples. This has already yielded significant insights into the interactions and relationships between the many different immune cell populations present in the tumor microenvironment. However, one of the remaining challenges in analyzing such data is accurately determining target protein expression values for each cell in the image. This requires the precise delineation of boundaries between cells that are often tightly packed next to one another. Current methods to address this challenge largely rely on DNA intensity to make these splits, and are thus mostly limited to nuclear segmentation.
Methods
We have developed a novel convolutional neural network to perform whole-cell segmentation from multiplexed imaging data. Rather than relying only on DNA signal, we use a panel of morphological markers. Our method integrates the information from these distinct proteins, allowing it to segment large cancer cells, small lymphocytes, and normal epithelium at the same time without requiring fine-tuning or manual adjustment.
Results
By combining our novel imaging platform with new computational tools, we are able to achieve extremely accurate segmentation of whole cells in tissue. Our approach compares favorably with many of the currently used tools for segmentation. We show that our improvements in accuracy come both from our novel imaging approach as well as algorithmic advances. We perform significantly better than traditional machine learning algorithms trained on the same dataset. Additionally, we show that our algorithm can be trained to identify cells across a range of cancer histologies and disease grades.
Conclusions
We have developed a robust and accurate approach to whole-cell segmentation in human tissues. We show the superiority over this method over current state of the art algorithms. The accurate segmentation generated by our approach will enable the analysis of complex tissue architectures with highly overlapping cell types, and will help to advance our understanding of the interactions between cell types in the diseased state.

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Model-based meta-analysis of the exposure-response and clinical efficacy across approved anti-PD(L)1 agents

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Background
The objective of this model-based meta-analysis is to characterize the exposure-response (overall response rate [ORR]) across approved anti-PD(L)1 agents (nivolumab, pembrolizumab, atezolizumab, avelumab and durvalumab) to quantify the effect of drug, patient and trial characteristics on ORR, and assess the-relationship between ORR and efficacy outcomes such as 6-month progression-free survival (PFS) and 12-month overall survival (OS).
Methods
A clinical outcomes database was generated using published data for anti-PD(L)1 agents through March 2018. Reported exposures following Cycle 1 were normalized by the potency of the anti-PD(L)1 agents using respective IC50 values. Exposure-response (ORR) analysis was conducted using bayesian mixed effects modeling (R software), and included weighting by the number of subjects in each trial arm. Tumor type, number of prior therapies, ECOG performance, line of treatment, region, age, and gender were evaluated as model covariates. Impact of PD-L1 expression cut-off values was assessed to estimate the effect of PD-L1 expression on ORR. Correlation analyses were conducted between ORR, 6-month PFS and 12-month OS.
Results
Clinical data from 56 trials in approximately 11,000 subjects, and approximately 45 trials in 9,000 subjects across approved anti-PD(L)1s was included for the exposure-response and correlation analyses, respectively. A log-transformed linear model best described the flat exposure-response relationship, with tumor type as the most significant covariate ($p < 0.001$): the predicted ORR across the agents at approved dose ranges was 22% (95% CI: 16 – 30%) in non-small cell lung cancer. ORR appeared to increase by approximately 8 - 12% with greater PD-L1 expression (≥5% and ≥10% cut-offs respectively). ORR was correlated with 6-month PFS and 12-month OS (correlation coefficient, r = 0.6-0.7), and indicated a significant effect of tumor type on the correlation.
Conclusions
The model-based meta-analysis of exposure-response shows similar ORR depending on tumor type, across anti-PD(L)1s at the approved clinical doses. Improved efficacy was predicted with greater (i.e. ≥ 5%) PD-L1 expression.

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Artificial intelligence-based tumor purity assessment of digitized histology samples in multiple tumor types from clinical trials of nivolumab

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Background
Tumor purity (TP) estimation is routinely performed for whole exome sequencing (WES) analysis to ensure signal is derived from cancer cells and not from other cells in the tumor microenvironment. Low TP has been shown to impact assessment of immunotherapy-related biomarkers including tumor mutational burden (TMB) [1]. While several methodologies exist to estimate TP by WES, a majority of studies do not compare against pathologist estimation, the gold standard. In this study, we utilize artificial-intelligence (AI)-based image analysis to estimate TP, and further benchmark two methodologies of TP estimation on WES against pathologist and AI estimates across 1509 pretreatment samples from patients with melanoma, non-small cell lung cancer, small cell lung cancer, or urothelial carcinoma enrolled in clinical trials of nivolumab.
Methods
To assess TP by WES, paired tumor-normal samples were processed by Sentieon [2] or Strelka [3] somatic variant callers with subsequent SciClone [4] tumor heterogeneity analysis. For comparison, we evaluated corresponding serial tumor sections of hematoxylin and eosin (H&E) and immunohistochemistry (IHC) digitized images for TP. A subset of H&E slides were read by pathologists, while scanned IHC images were read by deep-learning algorithms on the PathAI platform (Boston, MA) for each tumor type, to distinguish cancer cells from immune and other non-cancerous cell types based on morphology.