Artificial Intelligence to Support Mass Spectrometry Imaging Analysis in Drug Discovery

Rima Ait-Belkacem[1], Fabien Pamelard[1], Lauranne Poncelet[1], Manon Beuque[1], Gaël Picard de Muller[1], David Bonnel[1] and Jonathan Stauber[2]

[1]*ImaBiotech SAS, Parc Eurasanté, Loos, France;* [2]*ImaBiotech Corp, Billerica, Boston, USA*

Introduction

Growing tools and techniques development in drug discovery field needs to be accompanied with an efficient process of choosing the drug candidate, by using the vast tranches of available data to provide actionable insights for assessing drug target exposure and engagement. There are a number of ways that statistics come out to play in data science, which can be extremely helpful for interpreting data and producing results. Machine learning or IA algorithms are a part of data science. Here, we choose some of them to improve the precision of delimiting drug and biomarker localizations and to decrease the time to define this histological localization. We finally automatically quantified and scored drug to biomarker co-localization to assess efficacy at cellular level.

Methods

Target exposure scoring: targeted MSI and immunohistochemistry (IHC) staining were performed together to target the drug and enzyme histological localization, respectively in serial tissue sections.
Target engagement scoring: targeted MSI and immunohistochemistry (IHC) staining were performed to measure substrate and product changes in parallel to the drug and enzyme localization.
Then, different targeted segmentations using color-based algorithms were applied (K-Means clustering, CIELAB analysis + Nearest Neighbor Classification etc) for an automatic creation of ROIs related to the drug or enzyme presence. After MSI acquisition and signal/pixels extraction, a correlation matrix was performed in order to assess and to score the drug/enzyme and the product/substrate co-localization and co-concentration for target exposure and engagement, respectively.

Results

For drugs targeting enzymes, the most straightforward target engagement assay is substrate and product changes measurement. IA was used to identify histological ROIs and to co-localize and quantify drugs, enzymes and biomarkers (product and substrate) in particular sub-structures of the tissue. Training and test sets were used during:
First, an immunostaining based segmentation algorithm (based on the brown color of colorimetric reaction) was developed for the enzyme expression. It allowed identifying 2 regions based on the staining density: A (+++) and B (+) for high and low enzyme expression levels, respectively. Then, drug molecular signal and absolute quantities were assessed (obtained using QMSI). From this image is automatically the ratio of intensity/quantity and immunostaining density.
Second, a pixel intensity based segmentation algorithm (based on the class integration compared to the threshold) was developed for the molecular image. It allowed identifying 2 regions based on the molecular signal: A (+++) and B (+) for high and low drug level, respectively. Product and substrate molecular signals and absolute quantities were assessed, automatically extracted and a ratio of intensities or quantities was automatically calculated for each pixel of each region by the software.
It provided a higher histological definition capacity allowing calculating a percent of exposed drug with and without the presence of its target, but also a percent of target engagement based on the product/substrate enzyme ratio. This confirmed that the drug reached its specific enzymatic molecular target. As exposure at the site of action and to its specific target were identified as the most important factors for success in drug discovery and the design of chemical probes, these results showed and confirmed the high contribution of MSI to provide simultaneous readouts of on-target and off-target activity.

Novel aspect

Artificial intelligence to improve drug exposure and engagement scoring in heterogeneous tissues under Mass Spectrometry Imaging