Maastricht University

Systems biology approaches applied in mass spectrometry imaging

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CHAPTER 7

Valorization

Over the last decade, more attention has been paid to knowledge transfer, research valorization and societal impact of academic research. In other words, the focus has shifted to the ability to translate theoretical scientific knowledge into practice by making the knowledge suitable and available for economic or societal utilization. Also, the exchange of valuable knowledge, experience and resources through public-private partnerships is a large, integral part of scientific valorization. The following paragraphs discuss the valorization aspects of my journey as a doctoral researcher.

7.1 Scientific impact

Across my thesis I have given several examples on how data from MSI can be integrated with: (a) open public datasets (The Cancer Genome Atlas, *chapter 6*), (b) other open-source softwares (QuPath, *chapter 4*) and commercial algorithms (*chapter 3*), and (c) curated databases (Lipid pathways, *chapter 5*). Within the MSI field, the presented efforts are among the first proposed strategies to integrate publicly available data sources with MSI datasets. The proposed workflows for integration of several omics datasets with histological staining and clinical data will be of great value to the broader scientific community, since as many different fields deal with data from diverse sources. The majority of the studies presented in this thesis are published in open scientific journals and thus are available in public data repositories to enable fellow researchers and industrial entities to benefit from them for their own purposes. Hopefully, sharing large molecular data as well as data handling algorithms will bring us one step closer to understanding the complex biology of disease.

In addition to the generation of novel integration workflows, our data demonstrates the potential of MSI technology as a discovery tool with extraordinary clinical impact. For example, in *chapter 5*, we showed that the steatosis lipid fingerprint identified by MALDI-MSI had high predictive accuracy, demonstrating potential use for clinical applications. We revealed that tissue context enabled by spatial molecular analysis is imperative to good classification performance. The insights generated by this study provide researchers, as well as clinical chemists, with awareness of the importance of tissue context when assessing tissue specimens, possibly resulting in the design

of novel improved diagnostic strategies that take the spatial information into account.

The last chapter (*chapter 6*) demonstrates that molecular pathology delivered by MALDI-MSI is an innovative discovery tool. MALDI-MSI provides chemical sensitivity and specificity combined with spatial analysis of tissue sections which leads to research opportunities with unprecedented translational potential. Here, MALDI-MSI combined with deep pathology analysis enabled extensive evaluation of N-glycosylation patterns in metastatic BC. We possessed a unique single-patient tissue microarray sample set that allowed us to study N-glycosylation changes of BC cells as they metastasized from primary tumor to different metastatic sites. The potential of MSI technology to identify novel therapeutic targets, validate novel diagnostic assays and enhance our basic biochemical understanding of disease processes is clearly demonstrated by this study. The presented study allows the cancer research community to significantly enhance our basic understanding of BC metastasis. The N-glycan signatures of the metastatic BC patient cohort presented in our study need to be further validated and if confirmed, could drive the development of novel diagnostic screening panels allowing early detection of metastasis progression based on MSI data. New treatment strategies could be derived from the obtained knowledge. Deepening our understanding of how metastatic tumors continue to resist and evade therapy could eventually lead to better treatment options. Better treatment options would save lives, provide a better quality of life for cancer patients, and result in more cost-effective healthcare. Lastly, rapid autopsy programs, which are the source of unique patient sample sets similar to the single-patient TMAs used in our metastatic breast cancer study, solely rely on the trust and motivation of patients who are fighting terminal diseases, and their open-minded and big-hearted personalities that support our research. Thanks to their sacrifice we now better understand this aggressive disease. It is also thanks to the legacy of these women who have suffered and lost their lives due to metastatic BC, that we learn about novel therapeutic targets that may help future generations suffering from the same disease. Therefore, I would like to express special thanks to all of the patients and families whose selfless generosity made this research possible.

7.2 Commercial impact

Throughout my PhD projects, I have worked with several industrial partners such as Icometrix (Belgium), Molecular Horizon (Italy), and Bruker Daltonics (Germany). While every setting was slightly different, the ultimate goal was the same - the development of functional, user-friendly tools for smarter and comprehensive data analysis and interpretation of MALDI-MSI data. With the team of Icometrix (Belgium), we used their algorithm originally developed for magnetic resonance imaging data analysis and re-purposed the algorithm to fit MSI and histology needs. Together with Molecular Horizon (Italy) I had the pleasure to co-develop a new MSI data processing, visualization and data identification software. Our fruitful collaboration ensured that the MSI community now has a new, powerful, user-friendly, vendor-neutral all-in-one software solution. Furthermore, the LipostarMSI software is the only software to date that can automatically read and process data-dependent analysis imaging datasets and thus provide accurate MS/MS-based lipid identifications from MSI experiments. Lastly, the data processing workflows and integrations strategies that we developed throughout my PhD journey were also shared with one of the main MSI instrumentation and software vendors - Bruker Daltonics (Germany). Based on this open partnership and feedback, Bruker Daltonics now incorporated the QuPath import function within their SCiLs software to allow for easier histology annotation transfer from histology images to MSI datasets.

Working in these public-private partnership allowed for exchange of experience, knowledge and insight from both perspectives. While, I could provide in-depth knowledge on the current state of the MSI field and share my customer's/users's point of view, the industrial partners provided valuable resources and expertise in product development and tailor-made solutions. By developing such necessary tools, we created intellectual property value for the scientific MSI community, which can now directly benefit from advanced data analysis platform and thus enhance their research. In addition, these developments also create revenue for the industrial partners should they choose to market these software packages.

Lastly, thanks to the broad background and multidisciplinary experience with which my PhD journey has provided me, I learned to speak and translate between the different languages of medicine, biology, chemistry, and data analysis, as well as business and management. I came to realize that I firmly believe in the strengths and complements of interdisciplinary research, and

that fundamental research must be translated to a functional product/solution. As such knowledge transfer, idea generation and stimulation within diverse multi-cultural and interdisciplinary settings has appealed to me. Therefore, during my PhD I volunteered to become a part of the organization committee for Life science with Industry workshops co-organized by NWO (De Nederlandse Organisatie voor Wetenschappelijk Onderzoek) and the Lorentz Center. In this initiative, we have helped life sciences companies to find innovative solutions to challenging and commercially important scientific problems by having a multidisciplinary team of motivated young scientists (PhDs and postdocs) in the life sciences tackle a specific R&D problem within a week. The workshop has aimed to stimulate cooperation between academia and industry. It has made young scientists aware of societal expectations and needs in relation to research and its application by stakeholders, such as the industry or governmental agencies. For me it was an extraordinary experience that allowed me to see scientific research output put into a business context. It stimulated me to further educate myself in business and management and it helped shape the path of my future career.

7.3 Societal impact

In the last part I would like to discuss the digital molecular revolution in pathology and the potential role of MSI. Despite the advances in technology, pathology has remained a field where the majority of work is performed manually and interpreted by human experts, which leads to subjectivity and lengthy processes. Also, it results in overworked pathologists and thus higher medical costs. Novel high-throughput scanning platforms and digital pathology tools are being developed for routine use in pathology. Such a digital revolution could enhance learning, sharing and re-examination of the clinical data among expert pathologist from any location, and thus ultimately lead to the discovery of new clinico-pathological entities that are relevant to patients' prognoses and treatments. The work presented in *chapter 4* demonstrates that with the current developments, the combination of digital pathology and MSI technology delivers tools that enable rapid, accurate and tailored pathological and molecular tissue assessment. The currently proposed digital pathology platforms offer traditional

immunohistochemistry as well as hyperspectral/multispectral imaging integrated into one platform. With the work presented in *chapter 4* it is easy to imagine that MSI could become part of such modern molecular pathology platforms. Additionally, unlike traditional histology and immunohistochemistry, MSI offers sensitive and specific multiplexed detection of several hundreds of unique molecules including lipids and N-glycans that are impossible to separate and detect by other technologies. Augmenting digital pathology platforms with information delivered by MSI would enable the establishment of disease specific molecular profiles. This could lead, for instance, to disease specific lipid panels (*chapter 5*) or to specific N-glycan panels to monitor cancer progression and response to treatment (*chapter 6*). Having both high-quality, high-resolution histology and molecular data together could present to the evaluating pathologist an already altered metabolic profile in regions that appear histologically normal and hence facilitate timely measures preventing further disease development. By providing histological as well as molecular information of the cells within tissue, these digital molecular pathology platforms could lead to improved clinical guidelines based on new biomedical insights enabling personalized diagnostics. Moreover, the automation of the annotation process could accelerate the work of a pathologist and hence lead to improved time and cost management. Should these platforms be implemented on a larger scale, this could lead to a nationwide sharing and learning from the data, e.g. for consultation purposes or to mine the data for novel biomedical insights. Furthermore, digitization of molecular pathology would enable healthcare to be more objective though united and standardized measures and reporting, which would reduce the time needed to examine each case. Ultimately, this could shorten the duration and improve the quality of a patient‘s journey from diagnosis to treatment, yielding better more cost-effective patient care.