Maastricht University

Spatial omics to quantitatively study tissue heterogeneity

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Chapter 5

Impact

This PhD thesis describes diverse research topics where public and private partnerships are employed to obtain relevant scientific impacts. In this chapter, the direct/short-term impact of the results in this thesis on science and society are discussed. In particular the economic impact for companies directly involved in the newly developed spatial omics workflow. The advantages of a new quantitative approach with potential applications in pharmaceutical research and application are discussed in detail. The long-term impact of this work improved understanding and scientific insights on diseases that will translate to *in fine* patient care. Finally, I will discuss and expand the potential applications of my work to various fields.

Scientific impact

The work described in this thesis is a major step forward in establishing a link between spatial information in biological tissue specimens and omics approaches. When combined, these provide comprehensive local molecular information on quantities and identities of hundreds to thousands of molecules. In **chapter 2**, two different technologies, MSI and LC-MS, are brought together by creating an open-source computer program that enables the transfer of spatial molecular information from MSI to a laser microdissection system with an accuracy at the single-cell level. Indeed, mass spectrometry imaging has spread as a great analytical tool employed in more and more different research areas such as pharmaceutical industries, biomedical research, biomarker discoveries, fundamental research, or art. The conscious choice to use an open source approach intends to increase the scientific availability of this approach and could augment its impact across a wide range of research fields.

During my PhD, I also worked on one of the most important topics in MSI; quantitative MSI. While regular MSI is now well established and constitutes a powerful tool in biomedical research, quantitative MSI is still controversial due to technical challenges. In **chapter 4**, a multi-label per pixel quantitation method in mass spectrometry imaging is described that could provide quantitative information at a single-cell level. Here, the endogenous peptide of the histone H4 protein in colon pig tissue is successfully quantified. This protein was used as proof of principle for our novel strategy but could easily be disseminated for the quantification of small molecules, peptides, or

proteins. One interesting application would be the quantitative study of antibodies, a growing class of biopharmaceuticals with a major impact in oncology, immunology, and chronic inflammatory diseases.

Economic impact

The in-house script developed and employed in **chapters 2** and **3** will be now integrated into commercial data analysis software such as Scils Lab (Bruker, Germany) or LipostarMSI (Molecular Horizon, Perugia, Italy) or be used as a free tool and could constitute a pipeline daily applied in research centers. In this research, I developed this workflow on three distinct instruments that enable, MSI, laser microdissection, and LC-MS respectively. I performed the MSI experiment on a Synapt G2-Si (Waters, England) and the LC-MS analysis with a Q-exactive Orbitrap (Thermo Fisher Scientific, USA). In **chapter 3**, I simplified the developed pipeline to be compatible with a single state-of-the-art MSI instrument in collaboration with Bruker Daltonics. Bruker Daltonics is one of the leading companies in MS based molecular imaging research and develops high-performance scientific instruments with high analytical value. This public-private collaboration allowed me to gain knowledge about instrumentation specificities of a newly developed instrument and share my insight for the implementation of this pipeline. As part of the knowledge dissemination, the newly developed TimsTof flex (Bruker, Germany), a mass spectrometer equipped with a dual-source: a MALDI (Matrix-Assisted Laser Desorption and ionization) source and an ESI (electrospray) source was used to evaluate the innovative protocols developed in this thesis. This mass spectrometer enables to perform rapid experiments with high-speed and high sensitivity. Bruker now refers to this workflow as MALDI Guided SpatialOMx ® on their official website and is available to any scientist in the world that is interested in cellular processes and disease progression. This pipeline could be applied to any type of heterogeneous materials and constitutes the next-generation method for in-situ characterization of tissue.As a result of this collaboration, a paper was published (**Chapter 3** of this thesis) in addition to an application note (https://www.bruker.com/en/applications/academia-life-science/imaging/maldi-imaging/SpatialOMx.html) and finally, grant support

materials. The impact of this scientific endeavor is demonstrated to go beyond merely publishing papers.

Societal impact

In this paragraph, the translational aspects of my work are discussed in a clinical context. In the second part, I would like to speculate and discuss the future possible applications of my research in a broader perspective.

As shown in **chapter 3**, I highlighted intratumor heterogeneity in breast tumor tissue sections. Intratumor heterogeneity refers to a mix of cells with different genetic and non-genetic molecular profiles. This has an impact on the disease outcome of the patient including prognosis, response to chemotherapy, or relapse. Therefore, the investigation of intratumor heterogeneity is of utmost interest for the scientific community to better understand the evolution of cancer. A label-free approach to reveal intra-tumor heterogeneity by MSI as shown in this thesis has the ability to improve prognostics and predictive accuracy of disease phenotypes by allowing physicians to better analyze positive effects of therapies while minimizing deleterious side effects. Moreover, a spatial multi-omics approach developed in this thesis with really high throughput capabilities developed in the future would be compatible in a clinically relevant timeframe and will constitute a great tool possibly implemented into already existing molecular pathology tools.

While a global picture is needed to better understand disease processes, a more targeted approach is sometimes required. **Chapter 4** offers a novel approach that could help pharmaceutical industries to investigate the efficacy or the toxicity of their developed drugs. For instance, as stated in "next generation antibody drugs: the pursuit of the 'high-hanging fuit'", antibodies are the most growing drug class that have a major impact on human health, such as oncology, autoimmunity, and chronic inflammatory diseases. My research in **chapter 4** could help to better understand their mechanisms of action and could extend their therapeutic applications.

Medical treatment is going towards personalized medicine for the best possible outcomes. However, this new approach relies on scientific breakthroughs to diagnose how individual molecular and genetic profiles influence certain diseases. Therefore, scientific research and technology

improvement have a direct impact on clinical research and *in fine* on patient care.

My PhD was executed in a life sciences context with a focus on biomedical research and clinical settings. However, my work has a wide range of potential applications that are not directly related to health sciences. In the food industry, MSI has gained interest in the past decade and thus potential applications for my newly developed workflow. Indeed, it is of utmost interest to identify and visualize the distribution of molecular food components to improve quality, food safety and, nutritional content. For instance, this workflow could help to study and identify micronutrients such as vitamins or minerals, endogenous toxins, or exogenous contaminants in plants. This in addition to the evaluation of conventional molecular classes such as lipids, metabolites, and proteins.

The study of biofilm and complex microbial could also be a potential application of my research. Indeed, understanding the chemical processes involved in microbial communities could help to elucidate antibiotic resistance that would allow the development of new treatment approaches. This could also enable to better understand the effect of climate change on these microbiomes and understand the changing environmental challenges impacting agriculture and bioenergy.

The impact of our research associated with high-quality education and open science are essential to resolve societal challenges. This impact results from the professional interaction of academics with society in order to contribute outside the field of science. The complexity resides in the assessment of this impact. Indeed, it is difficult to observe the effect of our fundamental research on a short- mid- or long-term timescale that results in applications. Maastricht University defines the impact of education and research into three different categories: output which is the direct profit (public presentations, graduation of students, softwares etc…), outcome which corresponds to mid-term effect (patents, impact on policy design etc…), societal and economic (results of output and outcome such as adopted policy, influencing local, regional and national politics etc…). Regarding the work in this thesis, the impact is, for now, a direct output with scientific publications, public presentations,

computer tools and it will be used for use and dissemination of research results both within and outside academia.