Unravelling the role of signal transduction pathways in high-grade serous carcinogenesis

Valorisation

Valorisation entails the process of creating value out of knowledge, by making knowledge suitable and available for economic or societal use.[1] New insight from scientific research might contribute to solutions for the societal challenges of today and tomorrow. With this thesis, we aim to improve the implementation of targeted treatment strategies for ovarian cancer patients by stratification based on a novel method measuring signal transduction pathway (STP) activity. This chapter describes the scientific and societal impact of the results and conclusions of this thesis.

From bench to bedside: translation of laboratory results to the clinic

The process of cancer development is characterized by complex and dynamic mechanisms of action.[2] One of the major challenges of today is to interpret the enormous amount of information on cancer biology and use it to develop successful treatment strategies. While the growing number of targeted drugs makes it challenging for physicians to choose the optimal treatment, as physicians are generally not trained to interpret molecular information. In this thesis, we demonstrate that results from translational research, in which we aim to understand the differences in STP activity between healthy and malignant cells, can be translated to the clinic as potential targets for therapeutic strategies. Moreover, with an alternative approach, we show that it is possible to map the pathway activity profile of a tumour sample and easily interpret the results to a 0-100 scale. Our cut-off values help to discriminate between normal and aberrant STP activity and could guide physicians to define potentially tumour-promoting STPs for treatment decision-making strategies. With our research, we demonstrate that collaboration between basic researchers, physicians and the industry could support the translation of laboratory findings into clinically applicable therapeutics.

The right treatment to the right patient

Cancer treatment is a major global burden and health spending on cancer keeps increasing each year. In the Netherlands, the total cost of cancer care was 10,163 million euros in 2018.[3] Especially for patients with recurrent or metastatic cancer, costly chemotherapeutics and targeted drugs are used as treatment options, often with limited effect on survival and quality of life.[4] To ensure affordable health care in the coming decades, we must focus on treatment optimization and improve diagnostic testing to help identify patients who do and do not respond well to particular treatments. With reliable biomarkers for response prediction, we could reduce the number of suboptimal therapies and thereby contain the health care cost. In this thesis, we investigate several possible targeted treatment options for ovarian cancer patients and demonstrate effectiveness in a small proportion of the

patients. Unfortunately, our results show that current biomarkers (e.g. immunohistochemical protein expression and evaluation of genomic alterations) have low predictive value on therapy response, indicating that the activation state of a signalling pathway cannot simply be inferred from changes in protein expression patterns or genomic alterations. With our research, we attempt to create scientific awareness for the functional phenotype of STP activity in tumour cells to enhance the search for more accurate predictive biomarkers. We expect that our results can motivate others to accomplish *phenotype*-guided profiling strategies and design innovative clinical trials to improve the biomarker-drug matching process for cancer patients.

Drug rediscovery: the use of old drugs for new therapeutic purposes

Drug development is a high-cost and time-consuming process. Currently, the time needed to develop a new drug for cancer treatment can take up to 15 years and only 7% of the drugs entering phase I clinical trials will ultimately receive approval.[5,6] Drug rediscovery is a strategy to identify effectiveness of existing drugs in new indications and offers rapid implementation of potential therapeutic strategies in a cost-effective manner.[7] Particularly, the use of generic drugs whose patents have expired could significantly reduce health care cost. The individual chapters of this thesis resulted in the development of the STAPOVER study, a study to match ovarian cancer patients to off-label treatment with existing targeted drugs. The study aims to alleviate the shortage of effective cancer drugs by applying functional STP activity as response prediction biomarker. Furthermore, the use of trusted drugs brings additional benefit to patients by the well-known toxicity profile, and thereby, minimisation of side effects will help maintain quality of life of cancer patients. Our hope is that the results of the STAPOVER study will stimulate health insurance companies, governmental agencies, and the industry to further support drug rediscovery initiatives in order to increase the societal impact and lower the burden of healthcare cost.

Conclusion

Health care faces increasingly complex challenges with the increasing rise of cancer incidence along with unsustainable cost. This thesis contributes to the implementation of targeted treatment strategies by elucidating ovarian cancer behaviour on a molecular level, investigating the therapeutic value of current biomarkers for targeted therapy, and improving patient stratification methods to allocate patients to effective therapies.

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