Valorisation

Knowledge valorisation is described as ‘the process of creating value from knowledge, by making knowledge suitable and/or available for social (and/or economic) use and by making knowledge suitable for translation into competitive products, services, processes and new commercial activities’.

(definition taken from the report of the National Valorisation Committee, Leonie van Drooge, Rens Vandeberg et al., Waardevol: Indicatoren voor Valorisatie. Den Haag, Rathenau Instituut, 2011).

Introduction

The global burden of human cancer worldwide is rapidly growing and is predicted to become the single leading cause of death in every country of the world in the 21st century. According to the latest release of the Global Cancer Observatory (GCO, GLOBOCAN 2018), it is estimated that there have been 18.1 million new cancer cases and 9.6 million cancer deaths in 2018.1 As we progress and improve our understanding of the epidemiology of cancers, the multitude of cancer-causing variables increases which captures the extraordinary diversity of this challenging disease. Due to research initiatives that are attempting to increase our understanding, preventative measures and novel processes and services are increasingly developed to tackle this conundrum. This section is dedicated to scientifically valorizing the research result of the current thesis and should be viewed through a biomedical scope.

Fundamental research relevance

The ‘publish and/or perish’ era we are currently participating in, results in minor appreciation for the fundamental understanding of diseased mechanisms and focusses excessively on clinical applicability. When viewed historically, great advances in medicine and biomedical science are the collective achievement of thousands by scientists for whom the primary goal was to understand fundamental mechanisms of biology. Funding institutions and project managers aiming primarily at swift results, preferring observing to understanding, often neglect this concept. As a result, we start to observe less and less and creativity is replaced by productivity. In chordoma, understanding the molecular processes responsible for tumor growth, cell and molecular heterogeneity and treatment resilience, are pivotal in the quest for finding a potential target for disease prediction and therapy. In order to provide insight into the majority of molecular data available we have published a comprehensive review of these molecules in our second chapter. One of the interesting mechanisms discussed is “chromothripsis”. A phenomenon deemed responsible for the chromosomal instability often witnessed in chordoma cells.2 Investigating viral involvement in chordoma was a rational follow up as it is stated to relate to chromothripsis.3 In chapter 7, we therefore studied
the presence of oncogenic viruses in healthy and tumorous tissue derived from chordoma patients. The observation indicates a potential involvement of primarily parvovirus B19 in the disease, broadening the scope of potential biomarkers for potential clinical application.

Clinical relevance
The body of work in this dissertation has the primary focus to increase the scientific understanding of the tumor’s biological behavior and to help unravel the complex heterogeneity that accompanies clinical research in chordoma. The essential foundation of clinical management of all patients, right after communicating the diagnosis, is guidance of patients during the disease course. For most physicians, a vigorous challenge lies within this aspect of care where patients, after processing the devastating diagnosis, generally inquire about the prognosis in order to assess their expected quality of life for the remainder of their life. For many experienced physicians the main dilemma lies within the vast heterogeneity of the prognosis. This complexity is, amongst others, primarily derived from the often-observed distinct treatment sequence and, more likely, biological predisposition. Identifying biological substances (biomarkers) that relate to a specific disease state, susceptibility to treatment or outcome often capture this biological tendency for a malignant or benign outcome. It should therefore come to no surprise that hunt on biomarkers in current biomedical research is one of the leading subjects. Discovered biomarkers in other cancers (e.g. glioma) are utilized to enhance the diagnosis and moreover to predict treatment outcome and prognosis. In the design of the study reported on in chapter 6 the authors set out to investigate clinical and molecular markers related to worse outcome. As displayed, were patient characteristics are not reliable markers for the prediction of disease course, molecular markers p53 and CDK4 are related to a more malignant disease course. As we were the first to report on the expression of CDK4 in chordoma and its relation to worse prognosis, it is interesting to note that recently, this negative association has been validated in a larger cohort of 75 patients further cementing this claim.4 Currently, a clinical trial using a CDK4 inhibitor, Palbociclib, is recruiting patients with advanced disease in chordoma. As this typical “from bench to bedside” exemplifies an increase of clinically relevant experiments performed today, one must note that often these single biomarker based research initiatives often fail to be reproduced in other datasets as important aspects, such as dose-response are often overlooked. Identifying a set of biomarkers often results in a more comprehensive understanding of the diseases state.

And so, the authors of this thesis in chapter have set out to investigate a more diverse set of proteins (proteome) with its relation to different chordoma like tissues. With the previously mentioned notochordal proposed origin and closely related chondrosarcoma’s, a comparative study design was implemented. Data of such a design yielded significant findings, not included in this thesis, with a potential to serve clinical biomarkers.

However, computational analysis using algorithms to examine large sets of data with respect to certain clinical aspects bear the risk of overlooking the vulnerability of overfitting the
data. This occurs when a multitude of potential predictive biomarkers are applied to differentiate a small number of outcome events. The apparent risk of failure to reproduce such findings with other clinical dataset remains a difficult problem.

A socio-economic perspective

As the incidence of cancer is increasing, a substantial socio-economic burden arises as, according to the World Health Organization (WHO) healthcare associated costs rising when plotted against per capita GDP. Latest indications (2018, CBS) indicate a weight of approximately 100 billion euro in the Netherlands, where most of the spending is made in the insured spectrum (Zorgverzekeringswet). Consideration on allocation of health care resources are based largely on cost-effectiveness analysis in which terms as quality-adjusted life-year (QALY) are the mainstay. Applying QALY’s in decision support for allocation in cancer treatment are shown to contain important limitations. However, the high cost of (novel) cancer treatments on society is increasing and will become unaffordable, making further progression of the current standard impossible. Most of these costs in oncology are attributed to the high price of cancer drugs and the overuse of drugs in anticancer treatment regiments. Potent solutions to this problem have been proposed, with the most potent being a shift towards treatments tailored specifically to the genetic makeup of an individual’s tumor. This way expenditure of (new) anticancer drugs that confer only a minor level of clinical benefit are eliminated.

In chordoma, standard primary treatment regimen for patients lacks any drug therapy, as chordomas are deemed unresponsive to conventional chemotherapy. Due to this limitation, a significant proportion of treated patients have a propensity to show tumor recurrence. Although recent treatment guidelines on this, frequently observed, recurrent growth of the tumor do reserve the possibility of implementing targeted therapy in the form of anticancer drugs in advanced disease, the scientific evidence favoring such a treatment remains limited. Reasons for this predicament are the relatively low incidence of chordoma and the heterogenic markup of the patient characteristics and cell pathophysiology. High costs, as a result of efforts of medical oncologists to treat patients with advanced disease and subsequent morbidity accompanying such a treatment, would be substantially diminished if tumor recurrence and implementation and accuracy of a patient tailored approach in advanced disease could be predicted.

In this thesis, chapter 5 is dedicated to discovering potential biomarkers in the tumor cells of chordoma and chondrosarcoma patients. By comparing tumor protein lysates of primary tumor of patients with no recurrence and primary tumor of patients with recurrent disease, we were able to identify a spectrum of phosphorylated kinases that are indicative of recurrent disease. Two of the more frequently proposed antidrug therapies in chordoma Imatinib and Nilotinib hold promise by targeting these biological factors. Although these findings require validation in a larger cohort, applying these biomarkers will benefit opti-
mization of individual health care for chordoma patients and minimize disease burden for the general population by reducing unnecessary treatments and their related morbidities.

**From proprietary data to a collective effect and future perspective**

As quoted by Isaac Newton (1642-1727): “If I have seen further than others, it is by standing upon the shoulders of giants”, it is only with the help of previous research that we gain our insights in the underlying mechanism of the diseased process. For this to continue, it is imperative that scientist, as much as possible, confirm to the notion of shared knowledge to enable synergistic research. In this thesis, two research articles are dedicated to aiding future chordoma research endeavors by informing the reading on how to perform certain procedures. In chapter 3, the authors illustrate how to isolate human notochordal tissue with the help of laser captured microdissection. Here, advice and procedural strategies on extraction of tissue from human fetuses, with a gestation of 9, 11 and 13 weeks, are discussed. This is relevant for chordoma research, as this tissue is proposed to be essential in the etiology of this tumor. A growing body of studies performed on the etiology of chordoma will therefore benefit from this detailed description.

Similarly, observation of trends toward increased investigation of the proteome in cancer research, has instigated our initiative to publish the methodology we have applied to research the chordoma proteome. Although the results of this final study are outside of the scope of this thesis, the promising outcome supports a more frequent use of this field of research.

As the title of the current manuscript already implies and recent standards in clinical care are progressively leaning towards the use of molecular biomarkers to guide our understanding and management of the disease. The author expects that single biomarker-based study designs will be replaced by a broader set of biomarkers derived from an integrated assessment of the disease state (e.g. genomics, transcriptomics, proteomics as well as metabolomics and nutriomics) plotted against a well-documented clinical databases. This large datasets, “Big Data”, when balanced and validated accordingly, diminish concerns about clinical and statistical validity that hinder their application and will provide the clinician and patients with increased knowledge on how to improve the quality of life.
References