

CAIX

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Valorization addendum

This thesis describes the potential of increasing the efficacy of standard treatment modalities, such as chemo- and radiotherapy, through inhibition or targeting of carbonic anhydrase IX (CAIX). The main aim of this thesis was the development and evaluation of compounds targeting the hypoxic tumor microenvironment to decrease normal tissue side-effects of currently clinically used anti-cancer chemotherapeutic agents. Developing new anti-cancer therapies however remains challenging, since cancer is an extremely heterogeneous disease consisting of distorted versions of a person's own cells. Nevertheless, the increase in cancer incidence has a severe socio-economic impact and the development of novel anti-cancer therapies therefore remains essential. In this valorization addendum the societal benefit of targeting CAIX expression in cancer is evaluated.

CLINICAL RELEVANCE

The heterogeneity of cancer requires personalized medicine, which consists of treatment options specifically tailored for each individual patient's needs. Many studies aim to identify biomarkers to predict treatment response and to stratify patients based on their sensitivity to a certain treatment. One such a biomarker might be CAIX as its expression is highly tumor-specific and is generally associated with a worse prognosis for cancer patients (Chapter 2). Clinical evaluation of CAIX expression in tumors may therefore prove beneficial for patient stratification; although the specific treatments best suited for this type of stratification remain to be identified. An interesting approach to evaluate tumoral CAIX expression levels is by using PET imaging with specific CAIX targeting PET tracers that are currently being developed. This non-invasive method of visualizing CAIX expression might also be promising for the detection and diagnosis of early malignant lesions in patients.

In addition, CAIX has been implicated in several carcinogenic processes (e.g. invasion and migration), but the clinical benefit of using CAIX inhibitors in patients remains to be investigated. The CAIX inhibitors described in this thesis (Chapter 3, 4, 5 and 6) will unlikely be implemented in clinical practice due to limited efficacy, but an alternative CAIX inhibitor (i.e. SLC-0111) is currently under investigation in a phase I clinical trial to evaluate its safety for use in patients. The results of this clinical trial however are not yet available and will provide data on safety and some insights into the efficacy of CAIX inhibitors in patients. Prior to implementing CAIX inhibitors in clinical practice, their interactions with standard treatment modalities need to be investigated in detail, since unexpected adverse effects may occur, as described in this thesis (Chapter 3) where the efficacy of doxorubicin decreased in combination with CAIX inhibitor treatment in one of the investigated tumor models.

The CAIX targeting molecules may also be utilized in clinical practice as a carrier to deliver cytotoxic compounds towards CAIX expressing tumor cells (e.g. the dual-targeting concept described in Chapter 4, 5 and 6). It is hypothesized that such an ap-

proach would decrease normal tissue side-effects, thereby allowing dose escalation in the tumor and enhancement of overall treatment efficacy. Even though dual-targeting compounds (Chapter 6) in general showed no preference for CAIX expressing cells, the tumor-specific and extracellular expression of CAIX continues to make it a promising target for drug delivery using alternative approaches.

GAIN FOR SOCIETY

Improving the efficacy of anti-cancer treatment through targeting CAIX will also be beneficial for society in general. Firstly, the use of tumoral CAIX expression as a biomarker (Chapter 2) may select treatment-sensitive patient populations. This type of personalized medicine will lead to a general increase in treatment efficacy as the non-responsive patient population may be treated with alternative more effective therapies, which eventually will decrease the overall treatment costs. Secondly, treatment costs may also decrease when normal tissue side-effects caused by anti-cancer therapy can be reduced, e.g. via targeting cytotoxic drugs towards CAIX expressing tumor cells. In general, any benefit in cancer treatment has the potential to be a gain for society as it can decrease treatment costs and prolong patient's survival.

IMPROVEMENT IN HEALTH CARE

Even though tumoral CAIX expression is hypothesized to be suited for theragnostic purposes, single CAIX inhibitor treatment may not be sufficiently potent enough to significantly improve health care (Chapter 3, 4, and 5). Nevertheless definitive conclusions regarding the efficacy of single CAIX inhibitor treatment can only be drawn after completing multiple clinical trials, for which the CAIX inhibitor SLC-0111 is a likely candidate that is currently being evaluated in a Phase I clinical trial. The extracellular and tumor-specific CAIX expression in tumors might also be alternatively exploited by designing a method for specific drug delivery to those regions (Chapter 6). Such an approach is expected to improve health care as patients will experience less toxic side-effects that otherwise may require additional interventions. Alternatively, CAIX inhibitors may modulate the efficacy of standard treatment options, although rigorous validation is required before clinical implementation (Chapter 3). Taken together both these methods can potentially increase the therapeutic window of anti-cancer therapy and thereby result in an improvement in the health care of cancer patients.

In addition, CAIX expression is tumor-specific and has prognostic value in a wide variety of cancer types (Chapter 2). The expression levels of CAIX could therefore be an excellent biomarker for patient selection, although the relevant therapies remain to be identified. Patient selection improves health care when it can prevent treating unre-

sponsive patients who would otherwise experience the side-effects of treatment without the therapeutic gain. Furthermore, CAIX may also be of diagnostic importance when it is proven to identify malignant lesions, e.g. via PET imaging. Early detection of these malignant lesions, e.g. by implementing CAIX visualization in screening programs, can be a great improvement in health care, since diagnosis and treatment can start earlier thereby increasing the patient's chance of survival.

NOVELTY OF THE CONCEPT

The application of CAIX as either a biomarker or a therapeutic target in cancer is not novel. Studies investigating the prognostic value of CAIX exponentially increased after the identification of a hypoxia-responsive element (HRE) in its promotor region in 2001. A wide variety in protocols and patient populations were however used in these studies and this thesis is therefore the first summarizing all available data regarding the tumoral CAIX expression and its association with prognosis (Chapter 2). The clinical application of this finding however remains to be elucidated and requires a standardized quantification method for evaluating the levels of CAIX expression.

Furthermore, CAIX has long been hypothesized to be a valuable therapeutic target due to its tumor-specific expression and its involvement in maintaining the pH balance of tumor cells. In addition, CAIX has been implicated in several other carcinogenic processes (e.g. proliferation, migration, and invasion). In general, however, the efficacy of CAIX inhibitors varies greatly (Chapter 3, 4, 5 and 6) and single CAIX inhibitor treatment may therefore not be potent enough to exert a significant effect on tumor cells. This thesis therefore focused on the potential of CAIX inhibitors to modulate the efficacy of standard treatment modalities, i.e. chemo- and radiotherapy (Chapter 3, 4, and 5). The counterintuitive results in this thesis (Chapter 3) where an adverse effect of CAIX inhibition on doxorubicin efficacy was observed in one tumor model indicates the incomplete understanding of the mechanism of CAIX inhibitors in combination with standard treatment options. An alternative novel therapeutic target involved in multiple intracellular pathways may therefore be sAC (Chapter 7). The use of sAC inhibition in cancer is however still relatively new, since only limited but conflicting data is currently available in literature. Therefore, before sAC can be used as an anti-cancer therapeutic target its exact mechanism of action remains to be elucidated.

The last approach described in this thesis where cytotoxic drugs are targeted towards CAIX expressing cells has been described previously, although alternative approaches were used and these studies predominantly focused on renal cell carcinoma where CAIX expression becomes upregulated due to a mutation in the VHL protein preventing HIF1- α degradation. This thesis described a novel method of targeting anti-cancer drugs towards CAIX expressing cells via dual-target compounds (Chapter 6), which consist of a CAIX inhibitor moiety conjugated to an anti-cancer drug. In general,

these dual-target compounds however showed little preference for CAIX expressing cells, which minimized their practical applicability. Alternative methods to target cytotoxic anti-cancer drugs towards CAIX expressing tumors may therefore be more potent and require further investigation.

ROAD TO MARKET

Even though several aspects of tumoral CAIX expression may be promising for future marketing, additional preclinical and clinical experiments remain essential. Firstly, the prognostic value of CAIX requires quantification of its expression levels via either immunohistochemistry or non-invasive imaging, e.g. PET. Immunohistochemical evaluation of CAIX expression requires the development of a specific antibody to detect CAIX, which can potentially be marketed once its specificity is sufficiently proven. As an example, the M75 antibody is currently marketed by Bayer. However, many different CAIX-specific antibodies are already available from many different suppliers, thereby increasing the competition. The development of a fast and easy to use kit to evaluate CAIX expression might therefore be more promising, which will provide a standardized method for CAIX detection and quantification, which is currently unavailable. Evaluation of CAIX expression levels with non-invasive PET imaging may therefore be more promising. Future research should therefore focus on developing a specific CAIX tracer that can be implemented in clinical practice. This tracer can potentially be marketed once CAIX expression is found to be of clinical importance such as when CAIX is identified as a diagnostic marker to detect early malignant and/or invasive tumor lesions. In addition, such a tracer can also be potentially marketed when CAIX expression levels are proven to be predictive for treatment outcome. These expression levels can then be used to stratify patients for specific therapies that have proven to be effective, e.g. specific drug delivery approaches to CAIX expressing tumor cells. Prior to marketing however the cost-effectiveness and added benefit of this CAIX specific imaging as compared to standard clinical care needs to be evaluated, since PET imaging is currently not cost-effective enough for implementation in clinical practice.

Secondly, CAIX inhibitors will be relatively easy to market once they prove to be effective in preclinical and clinical experiments. The CAIX inhibitors described in this thesis however will not be pursued further as they were either ineffective as single agents, or were unable to increase the efficacy of standard treatment modalities (Chapter 3, 4, 5, and 6). A wide variety of alternative CAIX inhibitors are however still being developed and one of these, i.e. SLC-0111, has recently completed a phase I clinical trial. When the results of this clinical trial show that SLC-0111 is safe to administer to patients, its efficacy will remain to be evaluated in phase II/III clinical trials. These future clinical trials should also investigate the influence of SLC-0111 on the efficacy of standard treatment modalities as CAIX inhibitors may also cause adverse effects on chemotherapy efficacy

(Chapter 3). Alternative options, such as targeting CAIX expressing tumors with cytotoxic drugs however continue to be potentially clinically relevant and should therefore also be pursued further. An alternative approach than dual-targeting drugs (Chapter 6) however remains to be developed, which requires both preclinical and clinical validation before eventual marketing.

In general, targeting or imaging CAIX in tumors may be clinically relevant, improve health care, and provide gain for society. Several approaches have been described in this thesis, but the most promising approaches to utilize CAIX are most likely via imaging for diagnostic and predictive purposes, or via targeted drug delivery of cytotoxic compounds. In addition, the identification of alternative therapeutic targets in cancer remains essential, but it requires further preclinical and clinical research in order to assess the influence on health care and to estimate a gain for society.