

Exploiting tumor hypoxia for cancer treatment

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Cancer

This thesis focuses on new treatment modalities against cancer. Millions of people suffer from cancer, and cancer incidence keeps, unfortunately, rising. Cancer has a huge impact on a patient’s life since treatment is often very demanding for a patient with many hospital visits and (severe) side-effects caused by the treatment(s). Not only the patient him-/herself is affected by the disease as close relatives and friends share the emotional suffering with the patient, and often devote their time to care for the patient. Thus, cancer has a huge overall impact on society with many people suffering from its consequences. Additionally, an economic impact is apparent, in that not only treatments costs are very high, but people (patients as well as their caregivers) also retreat from the workforce because of cancer. This evidences a need for more effective and better tolerable treatment options in the battle against this heinous disease.

Anticancer treatments in general

Research on new anticancer treatments is nowadays mainly focused on targeted treatments that, compared to the conventional treatments, have the potential to cause fewer side effects, exhibit more localized treatment delivery, achieve higher tumoral concentration of anticancer therapeutics and decrease resistance of the cancer cells towards the treatment. Additionally, combination therapies are extensively being explored. In these therapies different pathways are simultaneously targeted, which can enhance efficacy in an additive or even synergistic manner compared to a monotherapy approach.

Tumor hypoxia is associated with poor prognosis, and is a known therapeutic problem, in that hypoxic tumor cells are more resistant to the conventional anticancer treatments. In this thesis, two strategies have been explored to exploit tumor hypoxia for cancer treatment, by targeting the hypoxia responsive enzyme carbonic anhydrase IX (CA IX), or by

using the hypoxia-activated prodrug (HAP) CP-506, which is to be combined with other anticancer therapies. Should these (combination) treatment strategies ultimately prove successful and applicable in humans, they can, together with any other effective anticancer treatment, aid in reducing the afore-mentioned negative impact of cancer on society.

Patient stratification

Not all cancer patients will benefit from the treatment options explored in this thesis. CA IX inhibitors only work in CA IX expressing tumors. Likewise, HAPs only work in tumors that have sufficiently low oxygen levels for activation of the HAP. However, since the majority of solid tumors does contain hypoxic areas and does express CA IX (in these areas), the potential impact of these treatments is substantial. Proper patient stratification remains, however, needed. This stratification ensures that patients do not receive unnecessary treatment, but will receive the treatment best suited for them. This reduces treatment costs, unnecessary suffering of cancer patients, and increases their chance of cure.

The CA IX positron emission tomography (PET) imaging tracer described in Chapter 3 of this thesis could aid in the stratification of cancer patients since it can be used to detect CA IX expressing tumors, and can thus identify patients who would likely benefit from a CA IX targeting treatment. This technique has many clinical benefits over e.g. tumor biopsies as it is noninvasive, repeatable, and gives an image of CA IX distribution representing the whole tumor. The idea of CA IX PET imaging is not novel, with a number of CA IX-specific imaging tracers being used for preclinical CA IX imaging. However, none of these imaging tracers is currently being used in clinical practice. Before the tracer investigated in this thesis can be used in clinical practice, it will first have to be validated in clinical trials. In a similar manner, hypoxia imaging tracers such as the hypoxia PET tracer ^{18}F -HX4 can be used for the detection and stratification of patients likely to benefit from CP-506, or any other HAP, treatment. As CA IX is considered to be a surrogate hypoxia marker, the CA IX PET imaging tracer described in this thesis could also be used for this purpose. First, however, this tracer would need to be validated in this context. Compared to e.g. ^{18}F -HX4, the radioactive particle of this tracer has a shorter half-life, reducing radiation burden to relatives as it has completely decayed within a few hours after imaging. It is also relatively cheaper, and thus reduces treatment costs, as it is easier to synthesize and no cyclotron is needed.

These imaging techniques can not only be used to stratify patients, they can also possibly be used during and after treatment, to assess the effect of the treatment. In this manner

a patient can timely receive additional and/or alternative treatment when the previous treatment proves ineffective. This further increases their chance of cure with fewer side effects.

Dual-target drugs

Dual-target drugs are conjugates of two individual therapeutic agents, each with its own mechanism of action. These agents can also specifically target cancer-associated pathways or proteins, e.g. CA IX. This way, dual-target drugs have the potential to increase tumor specificity of anticancer drugs, increase drug concentrations in the tumor only, and potentially decrease normal tissue toxicity. The dual-target CA IX inhibitors described in Chapter 4 of thesis, however, did not demonstrate effectiveness against cancer cells. Further (pre)clinical development of these compounds has not been continued. However, the relevance of these results should not be underestimated, as they can provide more insights into the underlying principles of dual-target drugs. Our results show that conjugating two molecules does not necessarily result in a compound with the desired characteristics of the parental compounds, and that this conjugation might actually decrease efficacy and/or affinity of the parental compounds. This shows that the underlying mechanisms are complex and require further investigation. Future dual-target compounds thus require extensive characterization: it should be studied whether the conjugation does not interfere with the effects of the compounds. Also, it is needed to investigate whether the active compounds reach their intended target(s). Others have shown that the dual-target approach targeting CA IX can be successful, at least in preclinical *in vivo* studies. CA IX thus remains a good target, and the dual-target drug approach remains viable and promising for further exploration. Further studies will need to prove the clinical relevance of this type of compounds as anticancer treatment.

CA IX inhibitors

The concept of inhibiting CA IX as anticancer treatment is not novel: many CA IX inhibitors have been and are still being investigated preclinically. Only a single small-molecule CA IX inhibitor, SLC-0111, has so far made it into clinical trials. Results of a phase 1 study are eagerly awaited. Should this trial prove that SLC-0111 is safe to use, further trials are needed to assess safety and efficacy of this compound. Should SLC-0111 prove safe to use as well as effective, more CA IX inhibitors may proceed into clinical trials. However, should these trials present negative results, we might have to re-think the use of CA IX inhibitors as anticancer treatments. Many potential compensatory mechanisms can be triggered in

the case of CA IX inhibition, thus it is possible that this inhibition alone is insufficient for a clinically relevant therapeutic outcome. Instead, combining CA IX inhibitors with other treatment modalities might be more effective. A second trial with SLC-0111 has recently been announced online, to determine MTD and collect preliminary data on the therapeutic efficacy of the compound in combination with the chemotherapeutic agent gemcitabine. Results of this trial will provide more insight into the clinical relevance of such combination therapies. Should such combination therapies prove successful, then the CA IX inhibitors described in Chapter 5 of this thesis could possibly be useful in such therapies, as they had very high affinity for CA IX. Promising results with these inhibitors were obtained in *in vitro* assays, however, they will first need to be tested in *in vivo* animal models, before proceeding into clinical trials. Should they prove successful, however, they can contribute to an effective anticancer treatment.

CP-506

The concept of using HAPs as anticancer treatment is not novel, with many HAPs continuously being developed and (pre)clinically investigated. One HAP, nimorazole, has made its way into clinical practice in Denmark, proving the potential of clinical relevance for this type of compounds. As such, one could argue the novelty of and need for another HAP. Nimorazole is a hypoxic cell radiosensitizer and is thus intended to be used in combination with radiotherapy. CP-506, the HAP described in Chapters 7 and 8 of this thesis, is a hypoxia-specific cytotoxin with a bystander effect. It thus has the potential to not only synergize with or increase the efficacy of radiotherapy, but also other treatment modalities including chemotherapy and immunotherapy. Its predecessor, PR-104, was a successful HAP in preclinical studies, and rapidly proceeded into clinical trials. Toxicity issues, however, hampered the use of PR-104 in solid tumors. The components of the molecule likely to be responsible for this toxicity were altered, resulting in the HAP CP-506. This HAP is thus specifically designed to be an improvement over its predecessor. As other HAPs, CP-506 is mainly intended to be used in combination therapies. The results in Chapters 7 and 8 of this thesis show CP-506 to be a promising candidate for further preclinical evaluation and clinical efficacy validation of combination approaches with radiotherapy and/or immunotherapy. A phase 1 clinical trial is being planned and expected to start in early 2019. This trial will assess the safety of CP-506 treatment in humans for the first time. Afterwards, phase 2 and 3 trials are needed to further validate CP-506 as an effective and safe anticancer treatment, as a monotherapy and in combination therapies. These trials should be set up as we propose in Chapter 6 of this thesis, i.e with proper patient stratification.

This is of importance for the potential success of these promising drugs, as the failure of HAPs in clinical trials so far can (at least partly) be attributed to an improper design of these trials. Proper experimental set-up ensures a reliable outcome on the efficacy of the HAP and improves the chance that in the future more patients will benefit from this promising treatment option. Successful results could lead to CP-506 being on the market in a couple of years. This would provide clinicians and patients with a powerful tool in the battle against cancer.