Overcoming the Barriers of Brain Cancer Treatment: Targeted and Fully NIR Absorbing Photodynamic Therapy Agents with Extremely Low Molecular Weights and Controlled Lipophilicity

Reporting

Project Information

INFRADYNAMICS

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Periodic Reporting for period 3 - INFRADYNAMICS (Overcoming the Barriers of Brain Cancer Treatment: Targeted and Fully NIR Absorbing Photodynamic Therapy Agents with Extremely Low Molecular Weights and Controlled Lipophilicity)

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Summary of the context and overall objectives of the project

Every other day we hear more good news about an advancement towards treating cancer, the truth however is quite a different story when it comes to brain cancers. The state of the art clinically used agent temozolomide increases patient survival only by several months in average. One key obstacle for many drugs is the Blood-Brain Barrier, which significantly restricts the size and lipophilicity of molecules that can be delivered into the brain. In Infradynamics(InDy) we aim to develop scientific foundations towards making an early, targeted, and light-based treatment possible for brain cancer. In the light induced treatment modality, namely photodynamic therapy(PDT), a drug called a photosensitizer(PS) is administered and a specific wavelength of light is applied to a region of interest. When PSs are exposed to this light, they produce reactive forms of oxygen(ROS) that kills nearby cells. PDT has already been demonstrated as an effective treatment modality for a group of cancers and has attained attention as due to promising properties such as no long-term side effects, short treatment times, precise light targeting, non-invasive character and being cost-effective. The PS drug for successful PDT action is required to be: 1)non-toxic, 2)water-soluble, 3)efficient ROS generator, 4) effectively targeted to tumor cells and, 5) Near infrared (NIR) light activatable due to higher tissue penetration. Additionally, low molecular weight and controlled lipophilicity is also required for effective penetration through BBB. Structurally, NIR absorption and low molecular weights are quite contradictory. In InDy advanced fluorophores based on a key insight are being pursued whereby we aim to create drugs that have strong absorption in NIR region (>700 nm) and that have a low Mw with synthetic flexibility to control lipophilicity. The elegant approach is to combine two separate “single atom” modifications that were shown to red-shift absorption maxima significantly in several fluorophore systems. Our next key step is to decorate the fluorophores with heavy atoms to attain PSs, which is essential for ROS generation. The final step will be modification towards targeting glioblastoma. Although PDT has an intrinsic selectivity by delivering light directly to tumors, realization of PS drugs that gets activated by a tumor metabolite or over-expressed enzyme is the key to realize true selectivity. In InDy we aimed to target 3 different enzymes that has been demonstrated to be up-regulated in glioblastomas.

Work performed from the beginning of the project to the end of the period covered by the report and main results achieved so far

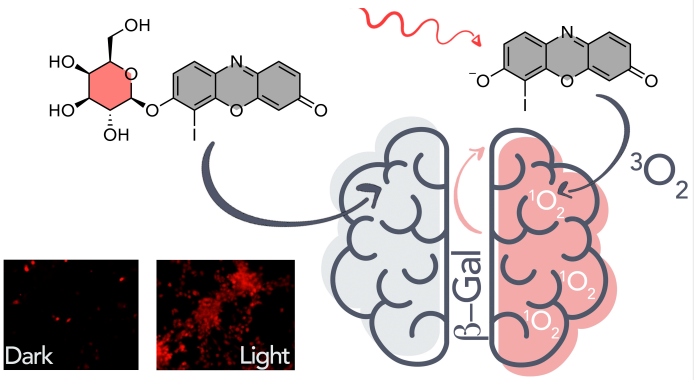
Our design principle in InDy was based on implementing two structural modifications on a common fluorophore which results in NIR absorbing materials with low MWs. Then, modification of these fluorophores with heavy atoms such as bromine or iodine which allows fluorophores. We realized however, even though fluorophores with one of the modifications were known, none of these were modified into PSs. Hence, in the first part of the project we synthesized two PSs based on these fluorophores to make sure these cores can be utilized as PDT agents (RS1 and SFI). R1 not only marks the first example of a resorufin based PS but also marks the first ever example of a monoamine oxidase (MAO) activatable therapeutic agent (ACS Med. Chem. Lett. 2020, 11, 2491, cover article).

On the other side, SFI was shown to be highly effective on colon and breast cancer cells upon light irradiation and proved to be a theranostic core thanks to its emissive nature (ACS Med. Chem. Lett. 2021, 12, 752).
Our first main target based on our design strategy in InDy was F1, which was successfully synthesized using a novel synthetic approach. We were pleased to see the material showed NIR absorption, however, photophysical characterizations revealed limited fluorescence for F1 . Next, synthetically challenging, elusive fluorophore F2 was recently attained. The absorption band is quite wide extending all the way to 700 nm which results in significant overlapping with the therapeutic window. More importantly F2 showed strong emission showing that the fluorophore can be modified into a PS. A new selenium containing PS was also realized (PS3) and photophysical studies showed high ROS generation efficiency (73%) and strong NIR absorption with promising initial in-vitro studies. As InDy evolved, we realized several additional cores with our design principle could be realized and we have made significant progress very exciting preliminary results. We also progressed for the design and synthesis of masking groups, which will render our PSs inactive until they reach tumor sites. Additionally, our detailed analyses showed that glioblastoma cells have significantly increased B-galactosidase (B-gal) activity, hence we modified of our PS, RS1, with the corresponding masking unit. The resulting PS became the first ever example of a B-gal responsive PS for selective treatment and imaging of glioblastoma cells (ACS Appl. Bio Mater., 022, 5, 9, 4284−4293).

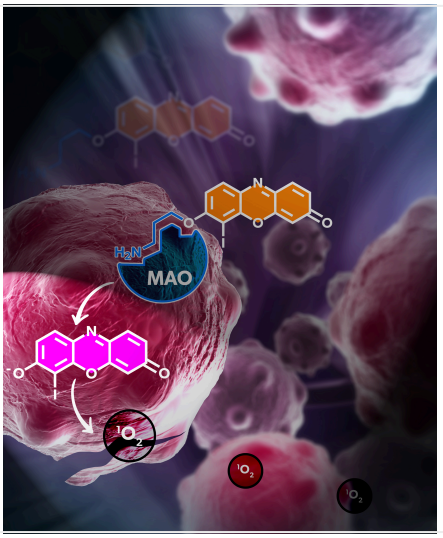
Progress beyond the state of the art and expected potential impact (including the socio-economic impact and the wider societal implications of the project so far)

1) We developed the first ever example of a B-gal responsive phototheranostic agent (PTA) for selective treatment and imaging of glioblastoma cells. PTA was tested in cell culture studies and selective photocytotoxicity was detected in glioblastoma with a negligible dark toxicity. These results demonstrated, for the first time in literature, that high B-gal level in gliomas can be utilized as an effective targeting strategy for development of next generation PDT agents for glioblastoma treatment. (Figure 1)
2)We realized the first ever example of a resorufin-based PDT agent as well as the first anti-cancer drug that can be activated by MAO (an upregulated enzyme in gliomas, and neuroblastomas) enzyme selectively in cancer cells. This important enzyme has not been used in the scope of PDT or in any drug design. Besides being first anti-cancer drug that can be activatable with a MAO enzyme, our agent also showed highly promising properties as a PS such as high singlet oxygen generation yield in aqueous solutions, red-shifted absorption signal and negligible dark toxicity. Our PS was also shown to selectively treat neuroblastoma cells via in-vitro studies. (Figure 2)
3)We developed the first ever example of a silicon fluorescein-based photosensitizer (SFI), which is also highly emissive to yield a theranostic agent. SFI is an easily accessible compound that shows highly promising properties as therapeutic and imaging agent such as water solubility, high ROS quantum yield in aqueous solutions (45%), red-shifted absorption/emission signals and negligible dark toxicity. SF-I is shown to induce cytotoxic singlet oxygen generation and consequent effective cell death in two different cancer cells with limited chemotherapy options and also utilized for imaging. (Figure 3).

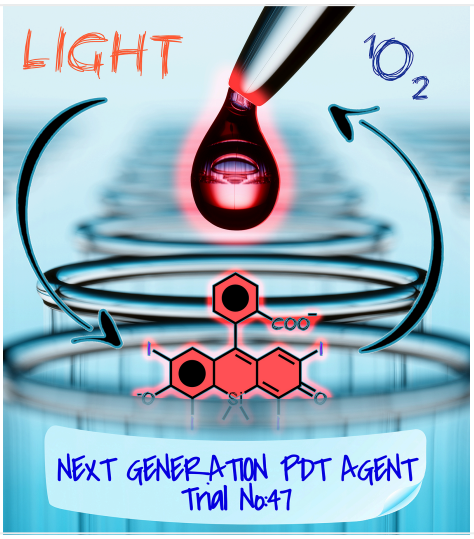
The main breakthrough of the InDy is yet to come: successful demonstration of targeted, activatable photodynamic action in in-vivo studies for effective brain cancer treatment. Towards this aim number of PSs designs have been / are being developed with great promise. Synthetic organic chemistry is full of surprises and even though we overcame several challenges up to so far, new ones will be waiting for us. With immense amount of experience gained in this novel PS platform however, we are confident that remaining final designs will be realized in the near future which will be followed by in-vitro and in-vivo studies.



Demonstration of high B-galactosidase activity in glioblastoma to be utilized for PDT action



Demonstration of iodinated resorufin to be an effective PDT agent



Demonstration of brominated SiMe2 substituted fluoresceins as effective PDT agents

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