Development of New Drugs for Brain Cancer

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Brain Cancer – a significant challenge

The number of people surviving cancer in the UK has doubled over the last 40 years as a result of scientific research, with 1-in-2 patients now living for 10 years post-diagnosis. However, nearly 10 million people globally will be diagnosed with cancer this year.

Brain cancer is amongst the poorest for survival, at 14% survival 10 years after-diagnosis. Glioblastoma Multiforme (GBM), which is commonly known as glioma, is the most aggressive form of brain tumour. The average survival after diagnosis is 12 months and even with maximum available treatment, survival is only extended to 14 months.

Why such a poor prognosis for patients? Firstly, glioma is hard to diagnose – it causes no symptoms until it has reached an enormous size. Secondly, there is only one drug currently available to treat this cancer, Temozolomide, which does not work for all patients.

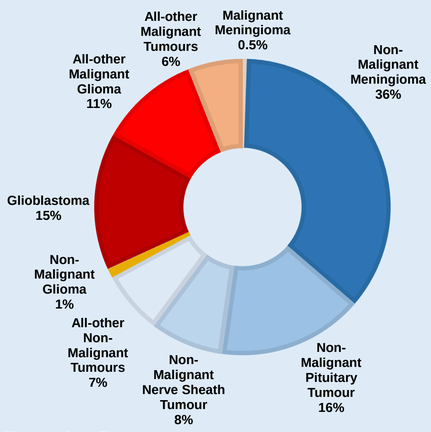

Figure 1 – The main sub-types of brain cancer by percentage occurrence. Chart showing data collected in a CBTRUS Statistical Report, examining the different types of brain cancer. Malignant cancers have been coloured red/orange and non-malignant cancers have been coloured blue

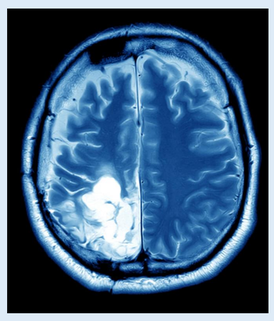

Figure 2 – MRI scan of a patient with glioblastoma, which can be clearly seen as the dense-white area – demonstrating the size and invasiveness of the tumour

The Drug Discovery Process

One of the key challenges is the length of the drug discovery process. Most drugs are designed to act against specific biological targets. For diseases, like glioma, with a complex profile of genetic mutations, a targeted approach is not suitable.

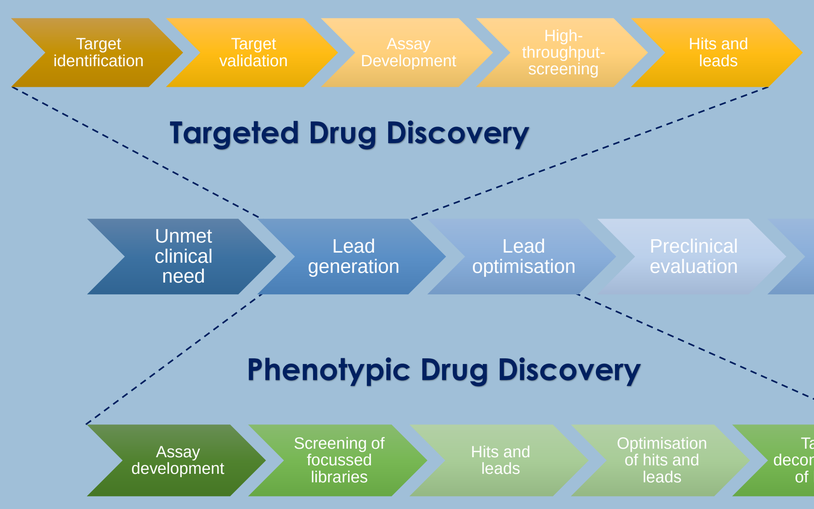

Figure 3 – Flow chart comparing the two principal types of drug discovery – targeted and phenotypic. The key differences lie in the way in which the lead molecules are generated.

Phenotypic discovery is where compounds are designed based on the ability to yield a desired biological effect, such as reduction in cancer cell growth. Phenotype-based approaches are far more appropriate for complex diseases like glioma.

What do we want to do?

The central aim of my research is to find a more reliable drug for the treatment of glioma - to help patients, improve their life-expectancies and quality. To do this we will use known anti-cancer molecules to inform the design of new molecules that will be developed using a phenotypic discovery approach.

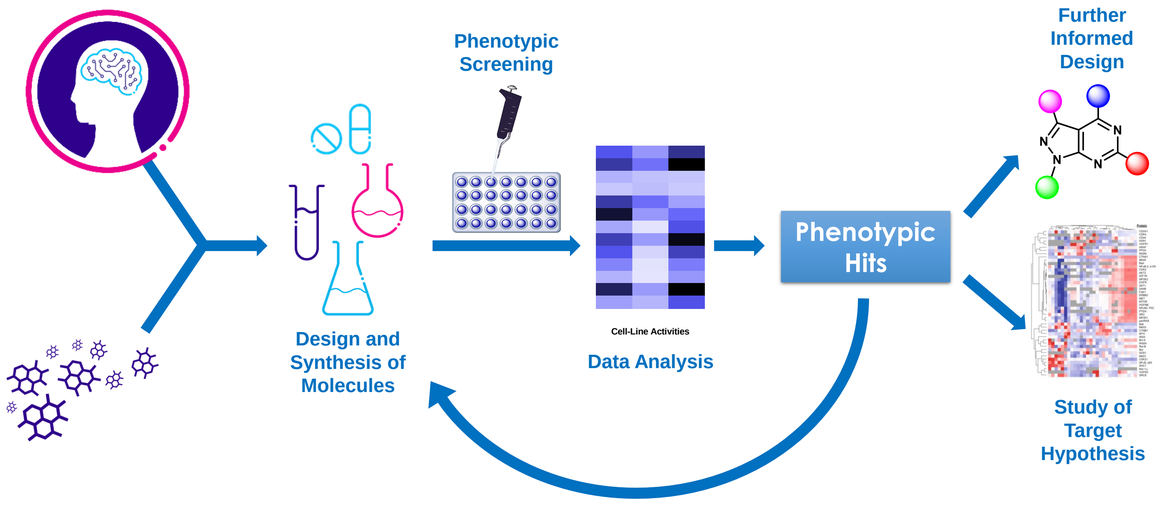

Figure 4 – Scheme showing the general workflow of my research and its key aims: to design and make a library of candidate drug compounds, to screen them in phenotypic cell-assays (observing the effect of the candidates on cells grown in the lab), to use the data to optimise compounds through rounds of design and screening and finally to use target deconvolution (where we determine the biological target of a compound) to study how a lead compound works, and whether it could be an effective treatment for patients.

Compound Design

Starting from some existing anticancer compounds, some designed in our lab, a range of new chemical compounds that could act as potential new drugs have been designed. By testing these in cancer cell-lines, which are samples of cancer tissue grown in the lab, we have been determining whether the compounds are effective at reducing growth of, or even killing, cancer cells. By looking at emerging patterns in the results, further new compounds were designed, allowing us to improve the efficacy of the compounds.

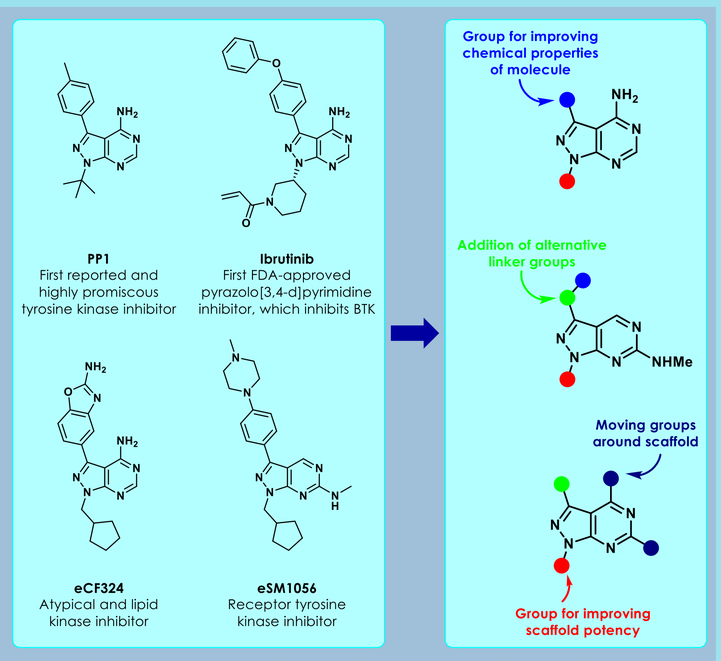

Figure 5 – Scheme showing how existing anti-cancer kinase inhibitors have been used as a basis for the design of new molecules that could be used to treat brain cancer. Alterations to the molecules aimed to improve potency against glioma cell-lines, whilst improving the physicochemical properties of the compounds. Please note, we cannot disclose the specific structures of the new compounds designed due to intellectual property reasons.

What have we achieved?

To date over 250 new compounds have been designed, synthesised and tested against brain cancer cells. Several promising compounds as a result of eight rounds of optimisation have been identified.

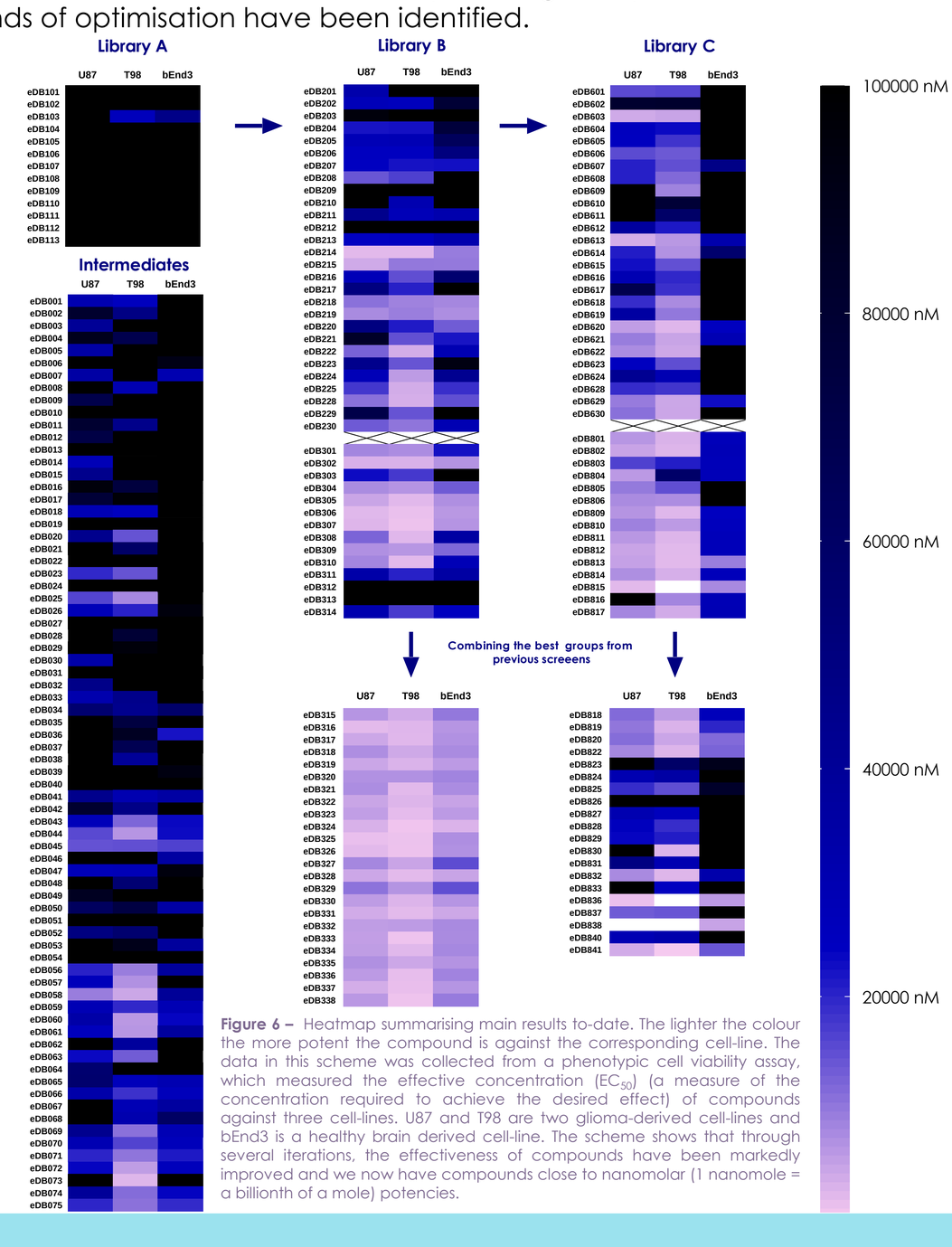

Figure 6 – Heatmap summarising main results to-date. The lighter the colour the more potent the compound is against the corresponding cell-line. The data in this scheme was collected from a phenotypic cell viability assay, which measured the effective concentration (EC_{50}) (a measure of the concentration required to achieve the desired effect) of compounds against three cell-lines. U87 and T98 are two glioma-derived cell-lines and bEnd3 is a healthy brain derived cell-line. The scheme shows that through several iterations, the effectiveness of compounds have been markedly improved and we now have compounds close to nanomolar (1 nanomole = a billionth of a mole) potencies.

What are the next steps?

As a result of research thus far, we are a small step forward to finding a new treatment for glioma. Further tests will be carried out on the lead compounds which will answer several key questions: How do the compounds work? What do the compounds interact with or target? How do the compounds behave against other cancers? Are the compounds toxic? Hopefully, by answering some of these questions we can accelerate the drug discovery process towards a potential treatment for patients suffering from brain cancer.

Acknowledgements

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