Designing new drugs for brain cancer

Dan Baillache
CRUK Edinburgh Centre, University of Edinburgh

What is the problem?

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 10 years after diagnosis. However, nearly 10 million people will be diagnosed with cancer this year.

Brain cancer is amongst the worst for survival, at 14% survival 10 years after-diagnosis. Glioblastoma Multiforme (GBM), which is commonly known as glioma, is the most common and most aggressive form of brain tumour (see Figure 1). 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 for this cancer, Temozolomide, which doesn't work for all patients.

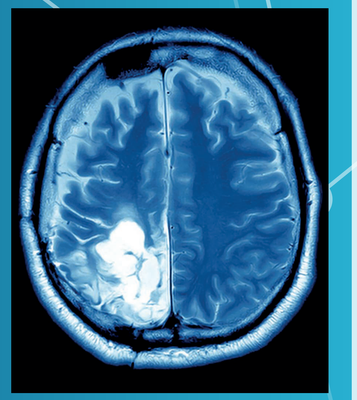

Figure 1 MRI (magnetic resonance imaging) brain scan of a patient with glioma. The light area clearly shows the size of the tumour within the brain tissue. Credit for image: akesak from iStock, https://www.istockphoto.com/gb/photo/imaging-of-the-brain-on-mri-scan-gm587797158-100904277.

What am I interested in?

I want to find a new, more reliable drug for the treatment of glioma, to help patients, improve their life-expectancies and their quality of life. However, the drug development process is a long and expensive one (see Figure 2).

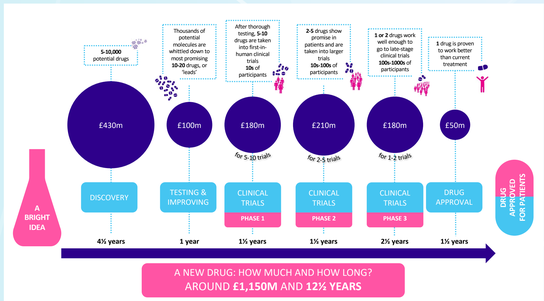

Figure 2 From Lab to Patient Flowchart showing how we get from lab-based research to a medicine on the market. On average a new drug takes around 12.5 years and costs over £1billion to develop. Furthermore, for every drug that makes it to market, over 10,000 will fail along the way - improving this 'rate of attrition' is a key challenge facing drug discovery in the future.

What did I do?

Following a phenotype-driven drug development process (see Figure 3) and starting from some existing compounds, designed in our lab, I designed a range of new chemical compounds that could act as potential new drugs (see Figure 4). By testing these in cancer cell-lines, which are samples of cancer tissue grown in a controlled environment in the lab, I have been determining whether the compounds are effective at reducing growth of, or even killing, the cancer cells. By looking at the patterns that emerged in the results, we designed further new compounds, allowing us to improve the efficacy of the compounds.

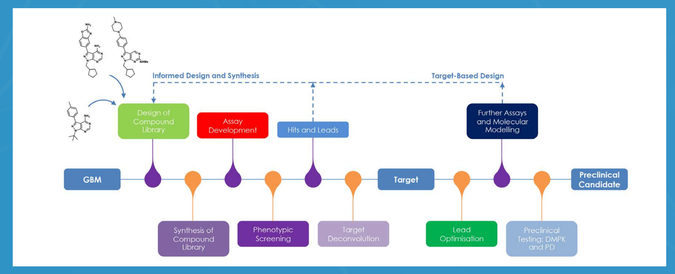

Figure 3 Scheme showing the general workflow of my research and its key aims: to design and make a library of candidate drug compounds, to screen them in phenotypic cell-assays (observing the effect of the candidates on cells grown in the lab), to use the data to optimise compounds through rounds of 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.

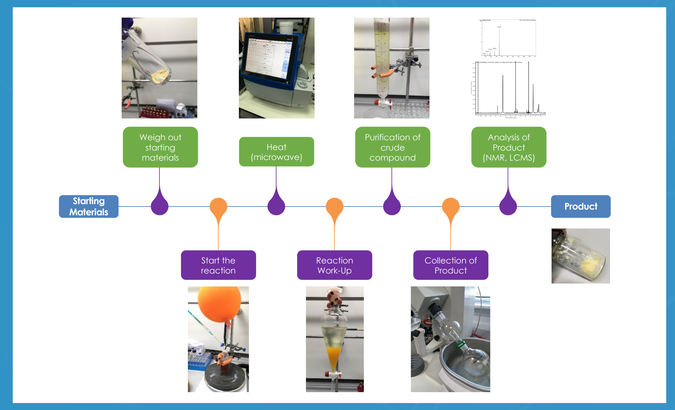

Figure 4 Scheme showing what medicinal chemistry looks like, day-to-day in the lab. For every compound that is designed, we have to work out a way of making the compound. Once we have a procedure, we use an array of techniques to take our starting materials and convert them into products. Reactions don't always work, so sometimes we have to try several different methods to find one that works!

What did I find?

To date I have designed and made over 120 new compounds and tested them against cancer cells in the lab. I have found several promising compounds as a result of four rounds of optimisation. (see Figure 5).

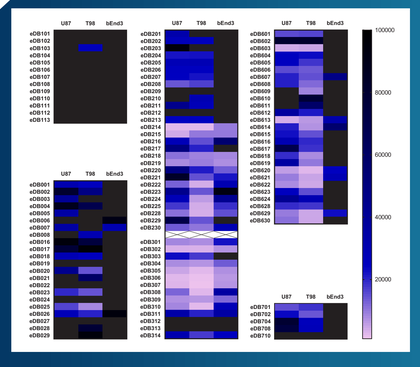

Figure 5 Heatmap summarising my results to date. Each compound tested is represented by a different eDB number. The lighter the colour the more potent the compound is against the corresponding cell-line. The data in this scheme was collected from a phenotypic cell viability assay, where we measured the effective concentration (EC50) (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 does this mean?

As a result of my work 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?
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 for patients.

Who am I?

I am a 3rd year Medicinal Chemistry PhD student at The University of Edinburgh, originally from Kent. Before moving to Scotland, I studied Chemistry for my undergraduate integrated Masters degree at The University of Bath. As part of my degree, I undertook an industrial placement year at GlaxoSmithKline PLC. When I finish my PhD, I would like to return to a career in the pharmaceutical industry. Outside of the lab, I am a keen rower and spend most of my time training.

Dan started his PhD project entitled *"Rapid development of kinase inhibitors that cross the blood brain barrier and target brain malignancies"* in 2017 and while principally based at the University of Edinburgh, supervised by Professor Asier Unciti-Broceta, he is also working closely with Merck & Co Ltd, Boston (USA).