LITTLE HERO REPORT

FUTURE LEADER FUNDING—£30,000

THE BRAIN TUMOUR CHARITY
A CURE CAN'T WAIT

Understanding the origins of Medulloblastomas

Medulloblastoma is the most common high-grade brain tumour occurring in children. Medulloblastomas are divided into the following sub-groups based on different clinical and biological characteristics: WNT, SHH, Group 3 and Group 4. Group 3 and 4 medulloblastomas account for approximately 60% of all diagnoses and are often associated with poor outcomes. The poor outcomes can be attributed to a lack of accurate preclinical models, which are crucial to test new treatments before clinical trials. Thus, it is important to conduct further research to characterise Group 3 and 4 medulloblastomas to create accurate preclinical models.

To create effective preclinical tumour models, it is imperative to know the cells from which the tumours originate. While it is known which cells WNT and SHH medulloblastomas arise from, the cellular origins of Groups 3 and 4 remain unknown. The aim of this research project, led by Dr Laure Bihannic, is to create and develop models of medulloblastoma that better mimic human tumours, and to use them to test new drug treatments. She has begun her work into the origins of Groups 3 and 4 medulloblastoma by looking at the cells present when the normal cerebellum—an area of the brain that controls coordination and balance — develops. Medulloblastomas are commonly found in this region of the brain.

Using laboratory models Laure will isolate and analyse individual cells, and then group them according to their characteristics. She will then analyse tumour samples from (ethically consented) patients and compare them to her laboratory models. Her hypothesis is that if the cells in her developmental models are similar to the tumour cells then that could be where the tumour started.

The next step in her research will be to cause medulloblastoma-like changes, aka mutations, in her developmental models. The aim is to replicate the genetic profile of children's tumours and add further evidence that she has developed an accurate model.

Lastly for this project, Laure will use the models to test drugs that specifically target the mutations she identified earlier in the work.

Details of the project

Scientific title: Dissecting the origins of medulloblastoma subgroups

Lead Researcher:
Dr Laure Bihannic

Location:
St Jude Children's Hospital, USA

Project cost:
£180,000

Duration:
3 Years

Start date:
September 2018

End date:
August 2021

'I am incredibly grateful to everyone who is involved in the charity and all their hard work. Without all their efforts, we could never do what we do. We couldn't do the science and projects like ours so thank you very much and keep up the great work'

Dr Laure Bihannic.

Lay Progress Report Year 2

During the second year of The Brain Tumour Charity Future Leaders fellowship, we have made significant progress into understanding the cellular origins of medulloblastoma (MB) subgroups. These advances are summarized according to the Aims of the project below.

Aim 1: To identify the candidate cellular origins of MB subgroups.

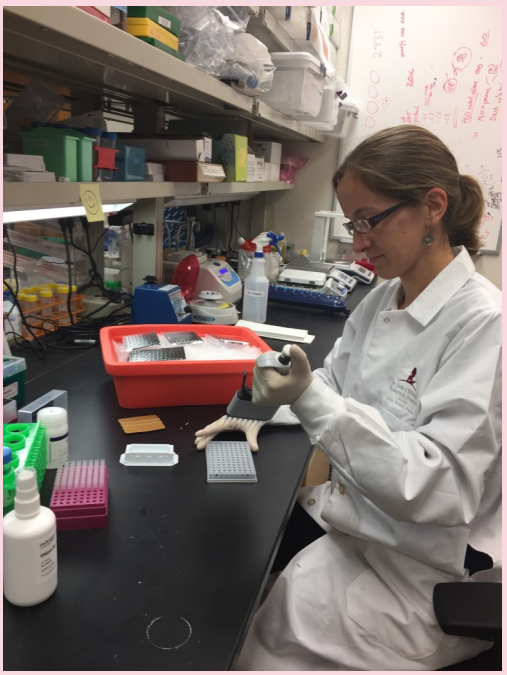
During the first year of the fellowship, by comparing the profiles of patient medulloblastoma samples and murine cerebellar cells, we identified of two populations as being candidate cells of origin of Group 4 MB, namely glutamatergic cerebellar nuclei (GluCN) and unipolar brush cells (UBCs). These findings were published in the journal Nature. The analysis with human cerebellar datasets is in progress. To gain a better understanding of these candidate cells, we isolated them from the mouse brain and further characterized them. The additional analyses performed on the prioritized cells led to the conclusion that UBCs and GluCN are strong candidate cells of origin of Group 4 medulloblastoma.

Aim 2: Functional validation of MB subgroup origins.

Preclinical models of Group 4 MB are still lacking, despite being the largest subgroup of the disease and accounting for nearly one out of every two children and adolescents diagnosed with MB. The goal of Aim 1 described above is to determine the normal cerebellar cell populations most highly similar with human MB counterparts according to subgroup. These efforts, although necessary, will be insufficient to definitively prove cellular origin without direct functional evidence. The studies outlined in Aim 2 will directly manipulate Group 4 candidate populations, GluCN and UBCs, by overexpressing genes that have been implicated in Group 4 MB formation. We are currently developing the approaches to reach the goal of developing accurate preclinical models that are subgroup specific.

Key Findings and their Impact :

We have characterized the candidate cells of origin for Group 4 MB. The identification and characterization of Group 4 cellular origin will allow a better understanding of Group 4 tumour biology and will facilitate the generation of accurate Group 4 preclinical models. These Group 4 models will be essential to evaluate targeted therapies that are requisite to improving outcomes and reducing side effects for affected patients.



Publications

Dr Laure Bihannic is co-first author of an article published in 'Nature', titled 'Resolving medulloblastoma cellular architecture by single-cell genomics'.

"Results from this study are pivotal, as they advance our understanding of the cellular composition of medulloblastoma subgroups. Being able to determine the origins of medulloblastoma subgroups will help us create better pre-clinical models for this tumour type, especially for the poorly understood Group 4 medulloblastoma. These models will help improve therapeutic testing to bring new treatments to the clinic."

A full copy of this article can be found at:

https://www.nature.com/articles/s41586-019-1434-6

THANK YOU!

TO LITTLE HERO AND ALL YOUR SUPPORTERS.