Preface

Special Edition: The NCLs/Batten Disease

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The neuronal ceroid lipofuscinoses (NCLs; also referred to as Batten disease) are a group of devastating and lethal neurodegenerative lysosomal storage diseases that usually affect children. There are currently 13 known forms of the disease, all caused by mutations in a different particular gene. While the NCLs are individually rare conditions, together they form the most common neurodegenerative disorder in children. However, until relatively recently there was no licensed therapy available for any of the NCLs. Although the genes involved have been characterised for each form of the disease, we still do not know the cellular function of many of the proteins. This highlights the continued need to better understand the underlying mechanisms that lead to this lethal condition and use this information to develop new and effective therapies.

The NCL research community is spread across the globe and has made significant advances in our understanding of the disease, the generation of tools to investigate them and now potential therapies. Much of this progress has been facilitated by the tireless patient and family organisations that not only raise funds for research but also work with clinicians to promote awareness of the diseases and educate the medical profession on diagnosis and best care practises. Other examples of research funding are the large co-ordinated grants that aim to bring together the community to tackle the most pressing challenges and questions. A recent example of this was the EU Horizon 2020 project, BATCure.

The 16th International Conference on Neuronal Ceroid Lipofuscinoses (NCL 2018) was hosted in London and welcomed the community to discuss progress made, strategies on work for the future and also celebrate landmark successes. One notable success was the clinical efficacy of Brineura, an enzyme replacement therapy for CLN2 diseases that is administered directly into the brain and is still the only licensed drug for any form of NCL. National organisations such as the Batten Disease Family Association and Batten Disease Support and Research Association (and others) have also convened meetings. While the topics covered in these meetings are vast, this Special Issues aims to capture some of the themes and provide the reader with a broad understanding of research taking place and the state-of-the-art of therapeutic modalities being investigated.

Invited reviews have been contributed by experts who have been working in the NCL arena for some time or are relative newcomers to the field. The combination of these cohorts of scientists, clinicians, professionals and experts from patient organisations means that NCL research is a hive of activity and will continue to be so for the foreseeable future. A future perspective on the directions that this research will take has been provided by Cooper and Mole who have been key opinion leaders in the NCL field for decades.

The development of various models of NCLs have had a huge impact on our understanding of the underlying disease mechanisms. Furthermore, they provide invaluable pre-clinical tools for the testing of new potential therapies. Progress in developing new models of NCLs using new technologies will be critically important in furthering our knowledge and also more accurately evaluating therapeutic efficacy of therapies. Minnis et al provide an update on the current cellular models that are available to the NCL research community ranging from simple yeast and amoeba to patient derived cells. They also cover the emergence of patient derived induced pluripotent stem cells that have been differentiated into neural cells [1]. Huber et al address the current more complex multi-cellular models of NCLs from social amoeba to larger animals that have been instrumental in pre-clinical studies facilitating therapies to clinical trials [2].

Nelvagal et al provide an update on the pathomechanisms behind the NCLs. This includes the importance of the endo-lysosomal pathway which is defective in the NCLs and the far-reaching implications this has on cellular function. There is also a reminder that while particular neuronal populations are lost in the brain, glial cells play a key role in the progressive neurodegeneration [3]. Rietdorf et al review the data pointing towards co-morbidities outside of the brain, such as heart abnormalities [4]. This raises the question as to whether therapies targeted to the brain are enough to provide life-long treatment?

Omics technologies have proven to be a powerful tool in NCL research. Butz et al review what has been learnt from new sequencing technologies and genomic studies applied to the various forms of NCLs to gain more knowledge of the molecular mechanisms [5]. Kline et al discuss how Omics applied to various forms of NCLs has led to a better understanding of which biological pathways have been affected. It is also an important technology in the search for biomarkers that can be used to measure disease progression, or monitor the efficacy of therapies [6].

Although the NCLs are a group of rare diseases, they have provided a fertile environment for testing of novel therapies. This has led to ground- breaking treatments such as the aforementioned Brineura enzyme replacement therapy for CLN2 disease. Kauss et al describe how the latest advancements in high-throughput and high-content screening will aid in identifying new or repurposed drugs for NCLs [7]. Liu et al provide a review of the current state-of-the art gene therapy approaches being developed or currently in clinical trials [8].

Finally, this Special Issue has contributions from those working directly with NCL patients and their families. This includes a review from Elmerskog et al on the challenges and recommendations around education and social support for children with Juvenile NCL [9]. Band et al also discuss the NCLs from the patient organisation perspective with their views on hurdles that they face, research and interactions with the pharmaceutical industry [10].

It is encouraging that there is clearly significant progress being made in our understanding of the NCLs and the development of treatments. However, there is still much to be learnt and there is an overwhelming need to develop life-saving and life changing therapies. We look forward to meeting as a community of scientists, clinicians, professionals, patient organisations, patients and families at the 17th International Conference on Neuronal Ceroid Lipofuscinosis that will take place in St Louis, USA.

1. Minnis, C.J., et al., *Cellular models of Batten disease.* Biochim Biophys Acta Mol Basis Dis, 2019: p. 165559.
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3. Nelvagal, H.R., et al., *Pathomechanisms in the neuronal ceroid lipofuscinoses.* Biochim Biophys Acta Mol Basis Dis, 2019: p. 165570.
4. Rietdorf, K., et al., *Cardiac pathology in neuronal ceroid lipofuscinoses (NCL): More than a mere co-morbidity.* Biochim Biophys Acta Mol Basis Dis, 2019: p. 165643.
5. Butz, E.S., et al., *Moving towards a new era of genomics in the neuronal ceroid lipofuscinoses.* Biochim Biophys Acta Mol Basis Dis, 2019: p. 165571.
6. Kline, R.A., et al., *Applying modern Omic technologies to the Neuronal Ceroid Lipofuscinoses.* Biochim Biophys Acta Mol Basis Dis, 2019: p. 165498.
7. Kauss, V., M. Dambrova, and D.L. Medina, *Pharmacological approaches to tackle NCLs.* Biochim Biophys Acta Mol Basis Dis, 2019: p. 165553.

8.   Liu, W., et al., *Experimental gene therapies for the NCLs.* Biochim Biophys Acta Mol Basis Dis, 2020: p. 165772.
9.   Elmerskog, B., et al., *16- Overview of advances in educational and social supports for young persons with NCL disorders.* Biochim Biophys Acta Mol Basis Dis, 2019: p. 165480.
10.   Band, H., F. Stehr, and N. Murphy, *Contribution of patient organisations to the NCLs.* Biochim Biophys Acta Mol Basis Dis, 2020: p. 165773.