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Rare Diseases Congress 2019: New therapies in genetic skeletal diseases achieved through drug repurposing - Michael Darren Briggs - Newcastle University

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Genetic skeletal diseases (GSDs) are a particularly diverse and sophisticated group of diseases that primarily affect the event and homeostasis of the skeleton. There are quite 450 unique and well-characterised phenotypes that home in severity from relatively mild to severe and lethal forms and although individually rare, as a gaggle of related orphan diseases, GSDs have an overall prevalence of at least 1 per 4,000 children, which represents a large unmet medical need. Our studies have focussed on a group of clinically-related GSDs that present with disproportionate short stature and early onset OA and result from dominant-negative mutations in a range of cartilage structural proteins including cartilage oligomer matrix protein (COMP), matrilin-3, aggrecan and types II, IX and X collagens. We have unequivocally established that endoplasmic reticulum (ER) stress; Opportunities now exist to accelerate drug development for the treatment of rare diseases. BLA refers to the submission process that contains specific information on the manufacturing processes, chemistry, pharmacology, clinical pharmacology, and therefore the medical effects of a biological product. If the information provided meets FDA requirements, The organization has also provided funds through small grant programs to help develop drugs/treatments for rare diseases, which can help the collection of pilot data in order to apply for larger financial support through the NIH or other mechanisms the application is approved and a license is issued, allowing the company to market the new product. The number of NMEs and BLAs approved by the Centre of Drug Evaluation and Research Disease foundations and research centres worldwide specialise in better understanding rare disorders. Here, the state-of-the-art drug discovery strategies for little molecules and biological approaches for orphan diseases are reviewed. FDA-approved new drugs have been for the treatment of rare diseases. In turn, commercial activity in this sector has gained momentum drug repurposing as an approach to quickly move programs to clinical trials is evaluated. Consideration is given to the category of biologics which include gene therapy, recombinant proteins, and autologous transplants. Advances in rare disease diagnostics and pharmacogenomics have allowed better characterizations of rare diseases, especially those that are monogenic. Progression of many rare diseases is poorly understood due to limited natural history studies. Inadequate numbers of patients recruited for clinical trials lead to outcomes lacking statistical significance Approximately 7,000 rare diseases have been identified and many have a known ethology a rare disease are usually genetic diseases induced in chondrocytes as a result of accumulated misfiled mutant proteins, is the primary cause of growth plate dysplasia and reduced bone growth in a broad group of GSDs. Moreover, including animal models and induced pluripotent stem cells (iPSCs) derived from patients are surveyed. Finally, the role of biomarkers in drug discovery and development, as well as clinical trials, cost of treatment per patient may be high due to the limited number of patients suffering from each individual rare disease is elucidated. we have recently demonstrated that reducing ER-stress, through the administration of a repurposed anti-epileptic drug carbamazepine (cbz), using ‘rare diseases’ and ‘orphan diseases’ as keywords, showed that publications related to rare diseases or orphan diseases have significantly increased over the past two decades in both cell and mouse models, restores cell homeostasis and bone growth in metaphysical chondrodysplasia, type Schmidt (MCDS) resulting from collagen X mutations.

Recent Publications

1. Bell P A, Dennis E P, Hartley C L, Jackson R M, Porter A, Boot-Hanford R P, Pergo K A and Briggs M D (2019) Mesencephalon astrocyte-derived neurotropic factor is an important factor in chondrocyte ER homeostasis. Cell Stress Chaperones. 24(1):159-173.

2. Mullan L A, Mularczyk E J, Kung L H, Forehand M, Wragg J M, Goodacre R, Bateman J F, Swanton E, Briggs M D and Boot-Handford R P (2017) Increased intracellular proteolysis reduces disease severity in an ER stress associated dwarfism. J Clin Invest. 127(10):3861-3865.

3. Gibson B G and Briggs M D (2016) the aggrecanopathies; an evolving phenotypic spectrum of human genetic skeletal diseases. Orphanet J Rare Dis. 11(1):86.

4. Briggs M D, Bell P A and Pirog K A (2014) The utility of mouse models to supply information regarding the pathomolecular mechanisms in human genetic skeletal diseases: The emerging role of endoplasmic reticulum stress (Review). Int J Mol Med. 35(6):1483-92.

5. Cameron T L, Gresshoff I L, Bell K M, Pirg K A, Sampurno L, Hartley C L, Sanford E M, Wilson R, Ermann J, Boot-Handford R P, Glimcher L H, Briggs M D and Bateman J F (2015) Cartilage-specific ablation of XBP1 signalling in mouse leads to a chondrodysplasia characterized by reduced chondrocyte proliferation and delayed cartilage maturation and mineralization Osteoarthritis Cartilage. 23(4):661-70.

This work is partly presented at 9th World Congress on Rare Diseases and Orphan Drugs June on 17-18, 2019 held at Berlin, Germany