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Orphan Drugs 2020: Network pharmacology based repurposed drugs combination for orphan diseases treatment - Daniel Cohen - Pharnext

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Abstract:
Charcot-Marie-Tooth type 1a is an orphan genetic progressive dys/demyelinating peripheral neuropathy affecting 125000 persons across Europe and US Disease, although clinically heterogeneous, impairs and very often badly disables lifetime of patients who might be bounded to wheelchair. It is primarily due to Schwann cells PMP22 protein over-expression from gene duplication. PXT 3003 , a combination of dose of three drugs including Baclofen, sorbitol and naltrexone, each drug has already approved for other indications, which was designed from network pharmacology based on screening. Preclinical experiments showed ability to lower of PMP 22 expression, to remyelinate axons and to improve histological, electrophysiological and clinical endpoints in the CMT1A PMP22 transgenic rat model over-expressing PMP22 protein. An exploratory double blind placebo controlled multicenter phase 2 was conducted on 80 mild to moderate adult patients over one year testing 3 different doses of the combination at a given ratio against Placebo. Anticipated safety was confirmed. 11 endpoints were analyzed, 2 widely used clinical composite Scores like CMTNS (impairment) and ONLS (disability) and 9 electrical and clinical quantitative measures. The most significant response was obtained with the clinical scores and a few relevant electrical measures with a transparent global dose effect. Milder patients responded better. Under the very best dose, which was still a 1/10 of usual dose of those drugs, disease state was stabilized in half the patients when, beyond stabilization, it was improved in the other half of patients. These encouraging results led us to style a pivotal phase 3 to start out end of 2015 on 300 mild to moderate adult patients across US and Europe, with ONLS as a primary clinical efficacy endpoint. Highly encouraging preliminary data obtained at the Max Planck Institute in post-natal CMT1A young RAT has also paved the way towards a pediatric trial hoping to prevent symptoms when treating young children early enough. Network pharmacology based strategies are often systematically applied to any rare or common disorders.

Methods:

Co-cultures of sensory neurons and Schwann cells

Fifteen days heterozygous rats were killed by cervical dislocation and embryos were removed from the uterus. Rat Dorsal Root Ganglia (DRG) cultures were obtained as previously described and performed at Neuronexperts laboratories (Marseille, France). The cultures were maintained in standard Neurobasal medium for 7 days to allow Schwann cells to populate sensory neurites. On day 7, the cultures were incubated with standard neuronal medium containing 50 µg/mL ascorbic acid (in order to initiate basal lamina formation and myelination) and drugs until 19 days. Our analyses of myelination were performed after 10–11 days of incubation. Three separate and independent cultures of DRG (from Transgenic (TG) embryos male rats) were performed with 6 replicates per condition.

Sciatic nerve crush:

Experiments were performed at Neurofit facilities. Sample sizes used for analyses were determined based on previous experience on assay variability. 4–5 week-old CD-1 male mice were given anaesthesia using isoflurane (2.5–3% in air). The right thigh was shaved and the sciatic nerve was exposed at mid-thigh level (5 mm proximal to the bifurcation of the sciatic nerve) and crushed for 10 s twice with a micro forceps (Holtex) with a rotation of 90° between each crush. For sham operated animals, sciatic nerves were exposed but not crushed. Finally, the skin incision was secured or joined with wound clips. After forty two days of crushing, the tibial nerve was removed from 6 mice per group to perform morphometric analysis.

Results:

As a first step of our discovery we performed a systematic analysis of available data to define a group of signalling pathways important for peripheral nerve structure and function affected in CMT1A disease. Among them, modular pathways known to affect myelin gene expression such as cAMP-dependent mechanisms, neurosteroid signalling and the Akt/Erk pathway were of particular interest. We hypothesised that these modules are integrated as a unified system that is influenced by G protein coupled receptors (GPCRs) leading to the differential regulation of genes for peripheral myelin proteins. Since PMP22 is not only a structural component of myelin, but may have signalling functions in Schwann cells, its transcriptional control could be different from “classical” myelin genes such as MPZ. The topology of these putative regulatory networks permitted us to suggest that drugs acting on different GPCRs could cause a more potent and robust influence when combined. Thus, we've focused on the drugs ready to modify relevant branches of GPCR signalling. This class of compounds is functionally pleiotropic, acting on multiple pathways and is well represented in approved pharmacopeia. This fact permitted us to apply additional safety criteria for their selection. We also preferred drugs that could be important for other aspects of peripheral nerve physiology that are affected in CMT1A, particularly drugs potentially promoting neuronal protection. Eventually, three drugs – (RS)-baclofen, naltrexone and D-sorbitol – were chosen for testing within the relevant cellular and animal models of CMT1A.

Conclusion:

In conclusion, the novel combination of three well-known and approved drugs (baclofen, naltrexone and sorbitol), identified by our Systems Biology approach, is able to improve myelination in the ex vivo myelination model of CMT1A, while single drugs displayed a lower efficacy. The combination is also able to down-regulate the expression of Pmp22 in cultured Schwannoma cells more efficiently than single drugs. The tests performed in vivo to assess the efficacy of the combination in the nerve crush mouse model demonstrate the acute neuro-

This work is partly presented at Annual Congress on Rare Diseases & Orphan Drugs on October 26-27, 2016 at Chicago, USA

regenerative and promyelinating potential of PXT3003 with the functional test demonstrating superiority of the combined action. Moreover, PXT3003 combination improves relevant parameters in the CMT1A rat model (muscular performances, heat sensitivity, histology and electrophysiology). No toxic effect of PXT 3003 was detected in animal studies.

Rational polytherapy which is based on a combinational repositioning of existing non-toxic drugs which acts in pleiotropic pathways may represent as an important novel approach for rapid development of drug in a variety of disorders. Future work will show if a similar approach could be useful in the treatment of other neglected orphan diseases where therapies are urgently needed.

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