MSMilan2023
9th Joint ECTRIMS-ACTRIMS Meeting
11–13 October 2023 | Milan, Italy

Abstract Number: 1998/P299

CN045 promotes OPC differentiation and oligodendrocyte maturation

Yan Yang * [1],Jihye Kim [1],Satish Medicetty [2],Lars Knusten [3],Richard Hamlyn [4],Bruce Trapp [1],

[1] Cleveland Clinic, Neurosciences , Cleveland, United States; [2] Cashel Neural Inc, Cleveland, United States; [3] Discovery Pharma Consulting LLC, West Chester, United States; [4] RH Pharma Consulting Ltd, Cambridge, United Kingdom

Introduction:

Remyelination failure is considered among the main causes of the irreversible neurological disability reported in MS. Remyelination is promoted by generation of new oligodendrocytes (OLs) from oligodendrocyte progenitor cells (OPCs), which are present in MS lesions but fail to differentiate and remyelinate.

Objectives/Aims:

To understand the mechanisms of action of a novel orally bioavailable, safe, effective and patentable small molecules to enhance remyelination.

Methods:

Primary mouse (plp-EGFP) and human OPCs (iPSC derived) were used to test efficacy of a small molecule, CN045, in promoting OPC differentiation. EC50 and percentage of plp-EGFP+ or MBP+ OLs were compared to known positive controls (T3, Clemastine and/or Benztropine) and DMSO. To understand possible biological mechanisms underlying effect of CN045, plp-EGFP+ OPCs treated with CN045 were subjected to global transcript profiling. Several CN045 synthetic analogues were also examined.

Results:

CN045 treatment led to significantly increase in plp-EGFP+ or MBP+ OLs in mouse and human compared to T3, Clemastine and Benztropine. Comparisons of CN045 treatment over DMSO showed 128, 104 and 123 genes were upregulated (>4 fold) on day 1, 2 and 3 of treatment. Longitudinal analysis of gene changes during Days 1-3 revealed 18 genes increased and 23 genes decreased following CN045 treatment. Increased genes belonged to the 'cholesterol' synthesis pathway which possibly was increased due to CN045 to facilitate differentiation of OPCs. In addition, novel CN045 analogs with better pharmacokinetics were also generated and tested in *in vitro* OPC differentiation assays. The majority (80%) of the novel analogs of CN045 retained OPC differentiation potential with several compounds showed greater potential on OL maturation than CN045.

Conclusion:

We describe CN045 as a potent small molecule that enhances OPC differentiation and remyelination in vivo. We identified novel and patentable analogs of CN045 that retain OPC differentiation with greater potency than CN045 and could be used for therapeutic strategies to enhance remyelination

Disclosures:

Dr. Yan Yang received compensation from Cashel and Cleveland Clinic. Dr. BD Trapp receives grant support from NINDS/NIH-R35NS09730, Sanofi-Genzyme, Fast Forward and The State of Ohio, speaking fees from Sanofi-Genzyme, advisory board fees from Disarm Therapeutcs, Therini Bio and Sanofi-Genzyme. He is founder and Chief Scientific Officer of Cashel Neural and member of the scientific advisory board of the NMSS. Dr. Jihye Kim is an employee at Cleveland Clinic, received compensation from Cleveland Clinic. Dr. S. Medicetty is a co-

founder of Cashel Neural, Inc., and he received compensation from Cashel and Cleveland Clinic. Dr. L. Knutsen received compensation from Cashel Neural Inc. He also works with NMD Pharma and served on the Advisory Board of Charcot-Marie-Tooth Association Dr. R. Hamlyn received compensation from Cashel Neural Inc.