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From translational research to a new molecule for the treatment of multiple sclerosis

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Applying high throughput gene expression microarrays, we identified that suppression of RNA polymerase 1 (POL1) pathway is associated with benign course of multiple sclerosis (MS). This finding supported the rationale for direct targeting of POL1 transcription machinery as an innovative strategy to suppress MS. Benign multiple sclerosis (BMS) occurs in about 15% of patients with relapsing-remitting MS (RRMS) that over time do not develop significant neurological disability. Aim of this study is to evaluate the biological mechanisms associated with and analyzed by Partek and pathway reconstruction performed by Ingenuity software the most informative genes. BMS signature was enriched by genes related to POL1 transcription that result in activation of the apoptotic cell death machinery. Verification of POL1 pathway key genes *RRN3, POLR1D,* and *LRPPRC* was confirmed by qRT-PCR, and RRN3 silencing resulted in significant increase in the apoptosis level of peripheral blood mononuclear cells sub-populations in RRMS patients. To target POL1 transcription machinery as a new strategy for suppression of MS disease activity, we developed and synthetized an oral POL1 inhibiting compound RAM-589.555, that selectively suppressed ribosomal biogenesis of activated immunocompetent cells. RAM-589.555 demonstrated high permeability, specificity to POL1 pathway, ability to induce apoptosis and to inhibit proliferation and viability of activated lymphocytes both *in vitro* and *in vivo*. Moreover, oral administration of RAM-589.555 blocked ribosomal RNA transcription and significantly suppressed and ameliorated experimental autoimmune encephalomyelitis the animal model of MS. Our findings demonstrate the application of translational research to target a new molecule for the treatment of MS.

Biography

Anat Achiron is a full Professor of Neurology at Tel-Aviv University, Sackler School of Medicine and Director of the Multiple Sclerosis Center at Sheba Medical Center, Israel. Her research interests are within the fields of Gene Expression and Neuro-immunology in relation to multiple sclerosis. She has extensively studied biological markers in the very early stages of the disease and is involved in studies evaluating disease related outcome variables and prediction of disease activity and treatment response. She has published over 200 publications in the scientific literature and received numerous grants and scientific awards.

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