The Highly Potent and Selective Third Generation RXR Nuclear Receptor Agonist Compound IRX4204 Has Potential for Prevention and Treatment of Normal Aging-Related Neurodegeneration

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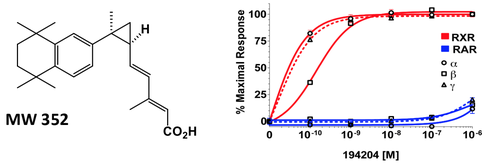
Normal aging-related neurodegeneration has been reported to be causally related to chronic low-grade inflammation in the brain, so called neuro-inflammaging (1). Neuro-inflammaging is related to overactivity of brain microglia, which produce the pro-inflammatory cytokine interleukin-6 (IL-6), and other pro-inflammatory factors. Imbalance of too few immunosuppressive T-regulatory cells (Treg) relative to Th17 cells also may contribute to the inflammaging process (2). Chronic neuro-inflammaging is implicated in long term slow loss of myelinated nerve fibers, eventually resulting in 45% fewer myelinated nerve fibers in humans at age 80 compared to age 20, and similar observed losses of myelinated nerve fibers in aging non-human primates (3,4). Disruption of functional neuro-electrical connections between neurons results in neuronal dysfunction and ultimately to death of neurons. Cumulatively these neurodegenerative processes produce loss of memory and cognitive functions, motor disability, and other functional disabilities in patients with normal brain aging, as well as in diverse types of age-related neurodegenerative conditions including Parkinson's disease (PD), and Alzheimer's disease (AD).

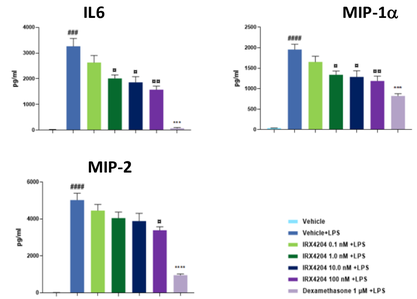
It is generally accepted within the neurodegenerative diseases research community that neuro-inflammaging establishes an at-risk environment within the brain, that may increase vulnerability for development of PD, AD, and other age-related neurodegenerative diseases, which have their own distinct pathologies overlying normal aging-related neurodegeneration. Optimal treatment of these conditions may be best accomplished by combination use of agents that also address normal aging-related neurodegeneration. An ideal candidate treatment for normal aging related neurodegeneration would decrease microglial and T-cell neuro-inflammation; protect and repair myelinated nerve fibers by promoting oligodendrocytes; and protect and restore neuronal functions, interconnections, and viability. We demonstrate here that IRX4204 has all these pharmacologic activities.

IRX4204 (4,5) is a third generation, highly selective, brain penetrant, orally available, Phase II clinical development stage RXR nuclear receptor agonist compound. It was discovered by Vidyasagar Vuligonda at Allergan Pharmaceuticals and initially developed as an insulin-sensitizing treatment for type 2 diabetes. It subsequently has been developed for treatment of cancers , neurodegenerative and autoimmune diseases. IRX4204 is 100-fold more potent at RXR agonism than bexarotene, a predecessor second generation RXR agonist compound that has shown beneficial activity in clinical trials in patients with multiple sclerosis or AD, demonstrating durable brain remyelination, and decrease of brain beta amyloid, respectively. IRX4204 also is far more selective for RXRs than either bexarotene, or 9-cis retinoic acid (the first generation RXR agonist). IRX4204 is devoid of RAR agonism at concentrations even three log 10 greater than peak RXR activating concentration. Off target activation of RAR causes clinical adverse effects with the less RXR selective compounds bexarotene and 9-cis RA, effects which are absent or decreased with IRX4204 clinical administration.

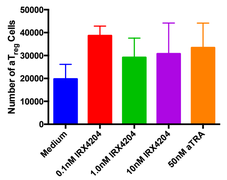
IRX4204 Is a Potent and Highly Selective RXR Homodimer Agonist with no RAR Activity at nM Concentrations



IRX4204 inhibits LPS-induced Rat Cortical Microglial Production of IL-6 and Pro-inflammatory Chemokines

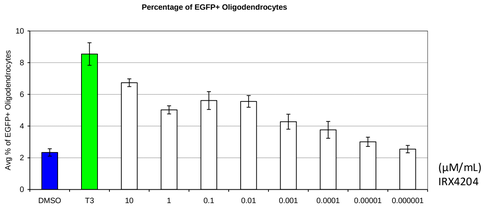


IRX4204 Promotes Human Treg Differentiation and Proliferation *In Vitro*

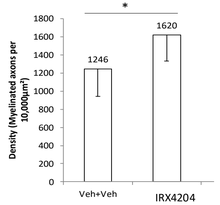


PBMCs were isolated from whole blood, then magnetically separated to enrich a ~95% pure CD4+CD45RA+ naïve T cell fraction. Cells were stimulated as indicated and analyzed via flow cytometry after 5 days in culture. The CD3+CD4+ cells were gated and analyzed for the frequency of CD127loCD25+ cells. These cells were then analyzed for FoxP3, CD39, and CD152.

IRX4204 Promotes Differentiation of Oligodendrocyte Precursor Cells into Myelin Producing PLP+ Oligodendrocytes



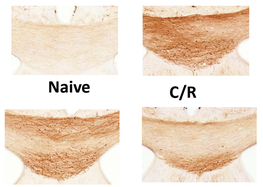
IRX4204 Promotes Remyelination in a Murine Model of Cuprizone-induced Chronic Demyelination



Mice were treated with Cuprizone + Rapamycin for 12 weeks, then IRX4204, 10 mg/kg/d PO, for 6 weeks. IRX4204 treatment resulted in a 30% statistically significant increase in myelinated axons relative to vehicle (p<0.05).

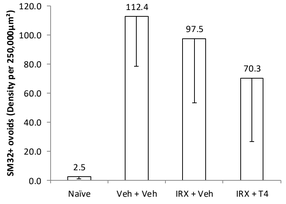
IRX4204 + Thyroid Hormone Have Combination Axonal Protective Effects in a Murine Model of Cuprizone-induced Axonal Transection

SMI-32+ Ovoids are Transected Axons – Represetative Images of Corpus Callosum



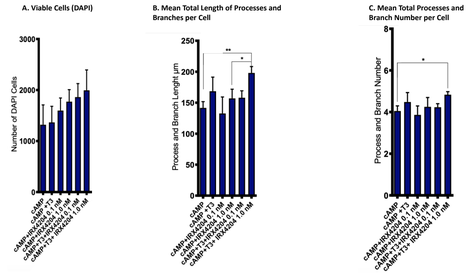
Mice were fed cuprizone diet plus rapamycin injections (C/R) for 6 weeks to induce demyelination; and concurrently were treated with either Vehicle or IRX4204 (10mg/kg, PO), or IRX4204+T4 (10mg/kg, PO, and 20ng/g, SQ) daily

SMI-32 Quantification of Transected Axons

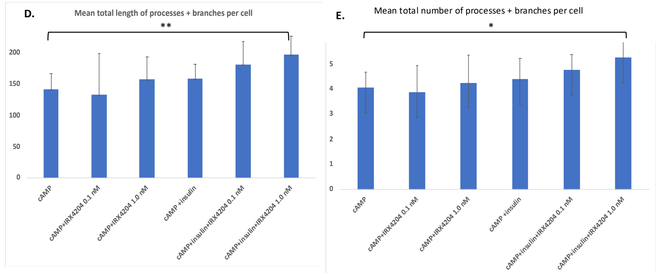


There was a significant reduction in corpus callosal axonal transection as shown by the number of SMI-32 positive ovoids in the IRX4204+T4 treatment group when compared to vehicle.

IRX4204 + T3 or Insulin Have Direct Combination Effects on Rat Cortical Neuron Survival and Neurite Outgrowth *in Vitro*



Data from 48 -hour cultures of rat cortical neurons, supplemented with cyclic adenosine monophosphate (cAMP) as a metabolic energy source. DAPI is a stain that identifies viable cells. Panel A shows that IRX4204 alone, and in combination with thyroid hormone, increased mean survival of treated cortical neurons. Panels B, CD, and E show data from an automated imaging and quantitation system for assessing outgrowth of neurites. The combination of IRX4204 plus thyroid hormone or insulin statistically significantly increased the length of neurites relative to cAMP alone (**p<.01); and IRX4204 alone (*p<.05); and increased the total number of neurites per cell relative to cAMP alone (*p<.05).



Conclusions

These findings support the potential for IRX4204 protecting against or reversing microglial or T-cell-mediated neuro-inflammaging-induced chronic loss of myelinated nerve fibers and neuronal damage in normal brain aging. Thus, IRX4204 has potential to be an effective treatment to prevent, stabilize, or even reverse clinical manifestations of normal aging-related neurodegeneration, as well as potentially being effective for treatment of other neuroinflammatory and demyelinating neurodegenerative diseases.

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COI Disclosures

Martin Sanders and Vidyasagar Vuligonda are directors, officers, shareholders, and patent inventors for Io Therapeutics, Inc., which owns issued patents for use of IRX4204 for treatment of aging-related neurodegeneration.

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