The RXR Nuclear Receptor Agonist Compound IRX4204 is a Potential New Treatment for Amyotrophic Lateral Sclerosis

Martin E. Sanders, M.D., Vidyasagar Vuligonda, Ph.D.
Io Therapeutics, Inc., Spring, TX

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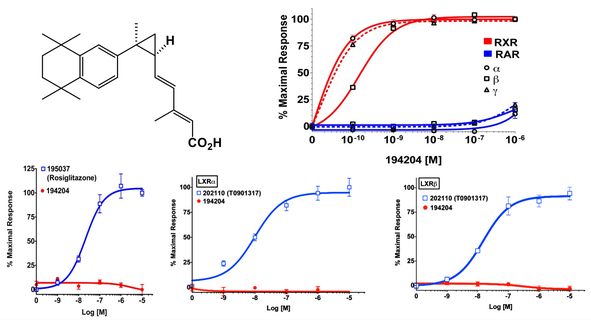
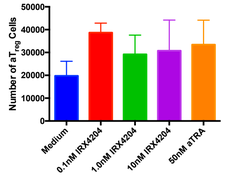
Introduction

Imbalance of Treg cells and Th17 cells and related autoimmunity is documented in ALS patients and is currently being targeted for treatment in promising studies of infusion of ex-vivo expanded autologous T-reg cells.[1] ALS also has microglial inflammation and demyelination as components of its pathophysiology. IRX4204 is a phase II clinical stage, orally available, brain penetrant, highly potent and highly selective RXR nuclear receptor agonist compound. IRX4204 promotes differentiation of human Treg cells and inhibits differentiation of human Th17 cells. It inhibits IL-17 A and F production by human Th17 cells. It is 100% effective in inhibiting autoimmunity in adoptive transfer of MBP sensitized Th17 cells in a mouse model of neuroinflammation. IRX4204 inhibits production of IL-6 and the proinflammatory chemokines MIP-1 alpha and MIP-2 and by LPS-stimulated rat cortical microglia, or mouse macrophages. It also inhibits LPS-stimulated mouse macrophage production of nitric oxide.[2] IRX4204 promotes differentiation of myelin-producing oligodendrocyte precursor cells, and is myelin protective and reparative *in vivo* in cuprizone-induced murine models of axonal protection and demyelination-remyelination. It is effective on functional and histopathologic outcomes in rodent models of PD and MS, in which it has neuroprotective activities.[3,4] IRX4204 has been administered for up to 20 months in phase I/II clinical trials under US INDs to 100 patients with cancers or Parkinson's disease, and was found to be safe, well tolerated. brain penetrant, and pharmacologically active *in vivo*.

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

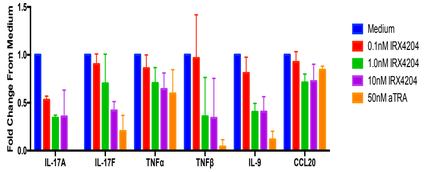


IRX4204 Promotes Human Treg Differentiation and Proliferation In Vitro



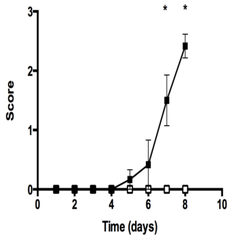
PBMCs were isolated from whole blood, then magnetically separated to enrich a ~95% pure CD4+CD45RA+ naïve T cell fraction. Cells were stimulated as indicated and analyzed via flow cytometry after 5 days in culture. The CD3+CD4+ cells were gated and analyzed for the frequency of CD127loCD25+ cells. These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

IRX4204 inhibits Th17-associated Cytokine Secretion by Human T-cells Cultured in Th17 Skewing Conditions



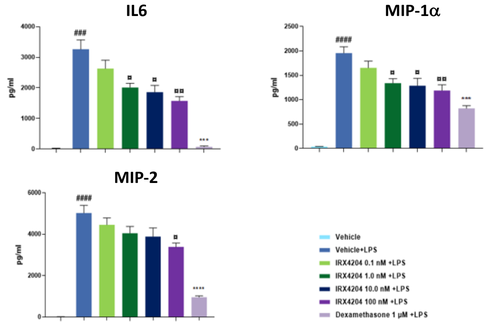
Normal Human PBMCs were isolated from whole blood, then magnetically separated to enrich a ~95% pure CD4+CD45RA+ naïve T cell fraction. Cells were cultured under Th17 skewing conditions for 5 days and stimulated anti-CD3/CD28 beads, and supernatants collected following 5 days in culture.

IRX4204 100% Prevented Th17-Mediated Autoimmune Disease *In Vivo* Mediated by Adoptively Transferred Antigen-sensitized Purified Th17 cells in a Mouse Model of Autoimmune Neuroinflammation

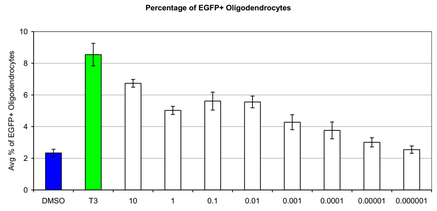


Mice were sensitized with Myelin Oligodendrocyte Glycoprotein. Purified Th17 cells were transferred to other mice that developed autoimmune encephalomyelitis. Disease activity was scored using a standard assessment of limb motor functions. IRX4204 100% and statistically significantly inhibited in vivo transmission of autoimmunity by Th17 cells

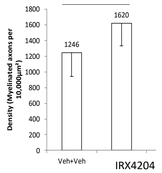
IRX4204 inhibits LPS-induced Rat Cortical Microglial Production of IL-6 and Pro-inflammatory Chemokines



IRX4204 Promotes Differentiation of Oligodendrocyte Precursor Cells into Myelin Producing Oligodendrocytes



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



IRX4204 treatment resulted in a 30% statistically significant increase in myelinated axons relative to vehicle (p<0.05).

IRX4204: Clinical Development Status

- 100 patients have been treated with IRX4204, including 85 with various cancers and 15 with early Parkinson's disease.
- IRX4204 was well-tolerated for up to 20 months of continuous oral treatment.
- PK in humans is consistent with once daily oral dosing.
- Common side effects include dose related reversible suppression of thyroid stimulating hormone, with resultant treatable hypothyroidism; mild to moderate reversible increased triglycerides; and mild to moderate reversible leukopenia.
- Oral dosing with 5 mg/day appears to be safe and potentially effective for PD.

IRX4204 is a phase II clinical stage compound for neurodegenerative diseases. An open-label Phase I/II safety and clinical activity clinical trial in early Parkinson's disease patients has been completed.

Mean Changes from Baseline to Week 2 in Total Motor Score, UPDRS, and TSH Indicate CNS Penetration in Humans and Support Potential for Clinical Efficacy of IRX4204 in PD

Dose	Total Motor Change*^	Total UPDRS Change*^	Changes in TSH
20 mg/day	-14.5%	-6.6%	-98.8%
10 mg/day	-11.7%	-13.6%	-36.6%
5 mg/day	-31.4%	-18.7%	-28.9%

*Reduction in UPDRS and Total Motor scores represent clinical improvement

^Mean changes, n=5 per group

TSH Reduction is a class effect of RXR agonists, caused by inhibition of hypothalamic TRF synthesis, and is a biomarker of brain penetrance of IRX4204 in PD patients in this study.

GMP clinical supplies of IRX4204 and matching placebo capsules have been manufactured in sufficient quantities to conduct clinical trials in multiple diseases. Phase II placebo-controlled clinical trials In Parkinson's disease and psoriasis are in preparation for expected initiation in Q3-4, 2024.

Conclusions

Based on its anti-neuroinflammatory effects, immunomodulatory effects on Treg and Th17 cells, anti-inflammatory effects on microglia cells, promotion of oligodendrocyte differentiation, myelin protective/reparative effects, neuroprotective effects in non-ALS models of neurodegeneration, demonstration of brain penetrance in humans, and safety of dosing in 100 humans for up to 20 months, IRX4204 warrants clinical testing in ALS patients.

Contact

Martin E. Sanders M.D.
Io Therapeutics, Inc.
msanders@io-therapeutics.com

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References

1. Thonhoff, JR, *et al.,* Expanded autologous regulatory T-lymphocyte infusions in ALS: A phase I, first-in-human study; Neurol, Neuroimmunol, Neuroinflamm, 2018.
2. Liby, K, *et al.,* A new rexinoid, NRX194204, prevents carcinogenesis in both the lung and mammary gland; Clin Cancer Res, 2007.
3. Wang, J, *et al.,* Selective brain penetrable Nurr1 transactivator for treating Parkinson's disease; Oncotarget, 2016.
4. Chandraratna, R. *et al.,* Treatment with retinoid X receptor agonist IRX4204 ameliorates experimental autoimmune encephalomyelitis; Am J Transl Res, 2016.

COI Disclosures

Martin Sanders and Vidyasagar Vuligonda are directors, officers, shareholders, and patent inventors of Io Therapeutics, Inc.