IRX4204

A Clinical Stage Potent and Selective RXR Agonist Compound for Treatment of Psoriasis and other Autoimmune Skin Diseases

Business Development Presentation

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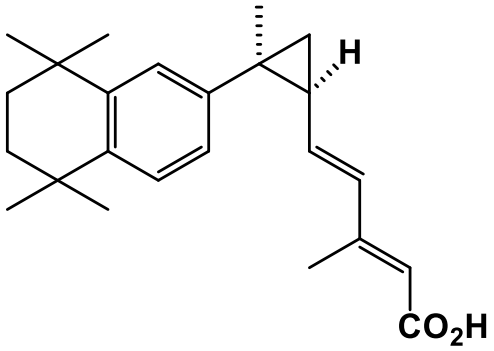
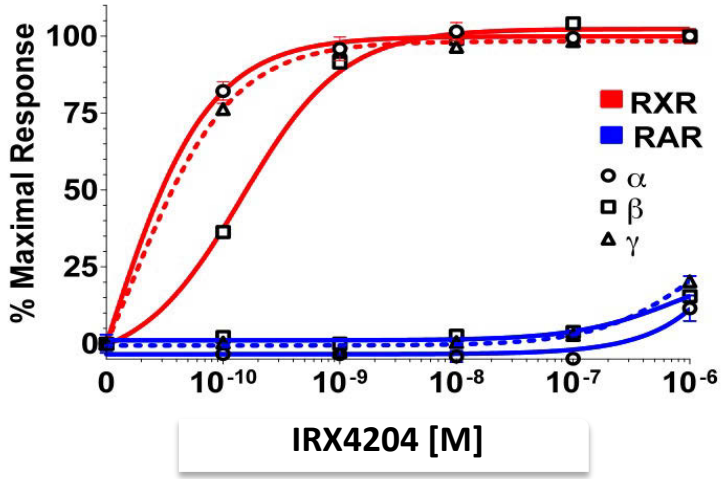
What We Are Seeking

Io Therapeutics is seeking a corporate partnership with an established biopharmaceutical company for world-wide development and commercialization of a highly potent and selective RXR nuclear receptor agonist compound IRX4204, for treatment of psoriasis and other autoimmune skin diseases.

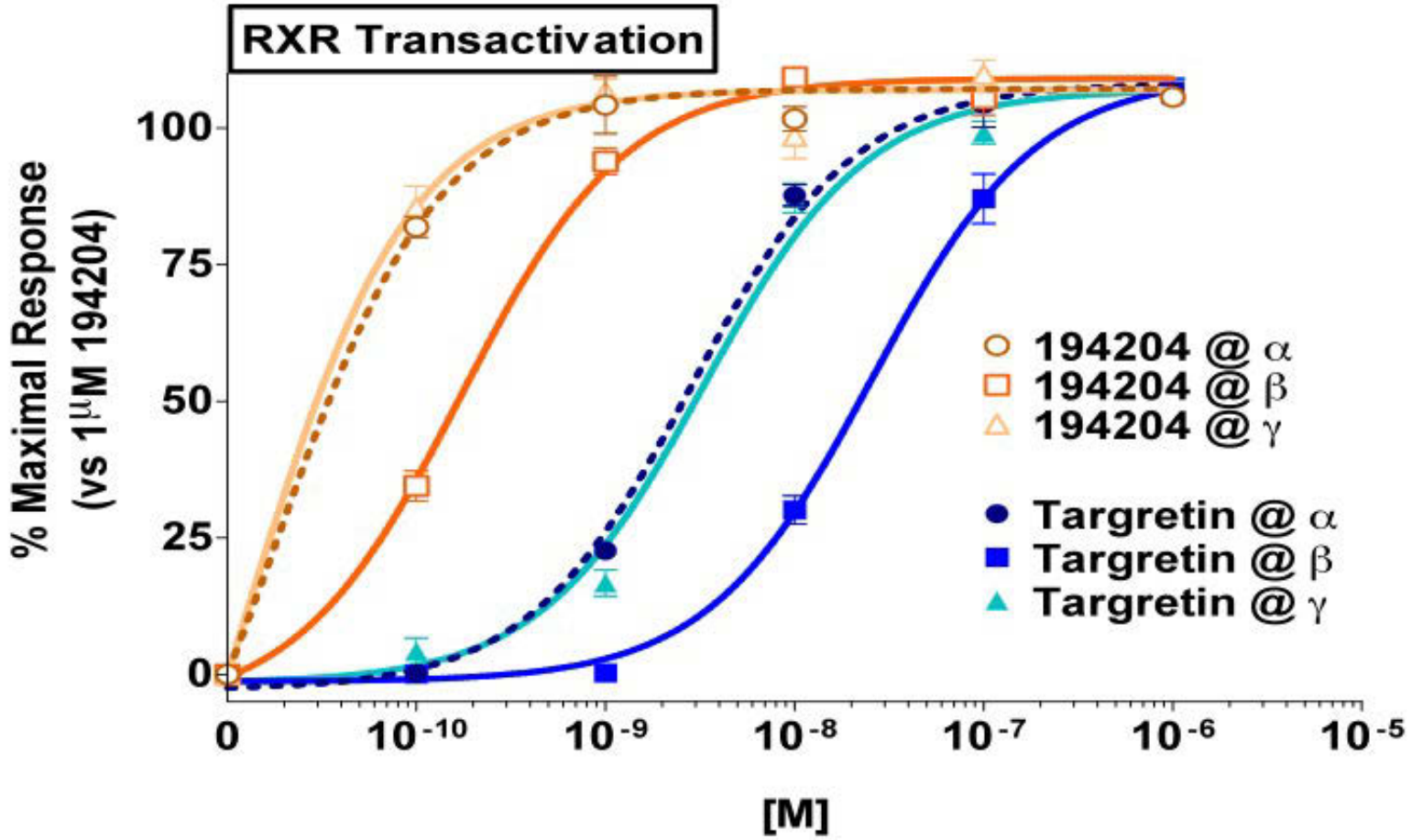
IRX4204 Activates RXR but Not RAR Nuclear Receptors at Nanomolar Concentrations



IRX4204 – A Potent RXR Homodimer Agonist with no RAR Activity at nM Concentrations



IRX4204 is Greater Than 100-Fold More Potent than Targretin (bexarotene) in Transactivation of RXR Homodimers

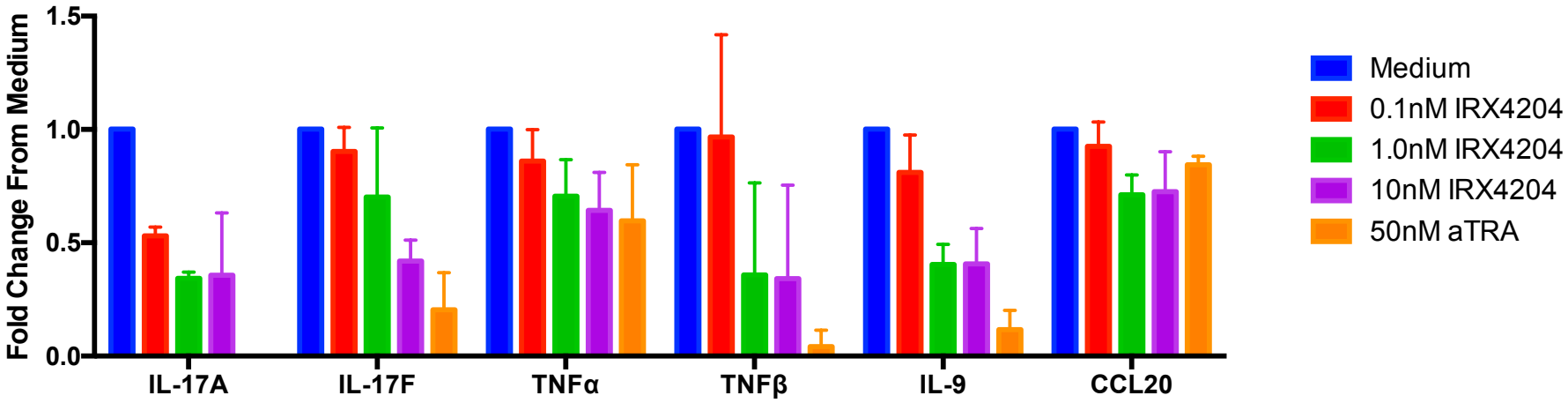


Bexarotene is a 100x less potent and far less selective RXR agonist than IRX4204. It is the only FDA approved RXR agonist. It has off target activation of RAR. It is approved only for treatment of CTCL. It has been effective orally and topically in clinical trials in psoriasis.

IRX4204 for Psoriasis and Other Autoimmune Skin Diseases

- **Imbalance of Tregs and Th17 cells and overproduction of IL-17 and TNF are documented pathologic features of psoriasis and other autoimmune diseases.**
- **IL-17 and TNF are clinically proven targets for treatment of diverse autoimmune diseases.**
- **Inhibitors of IL-17 and TNF are FDA approved for treatment of psoriasis.**
- **IRX4204 promotes human and murine Treg differentiation and inhibits human and murine Th17 differentiation.**
- **IRX4204 is a potent RXR agonist inhibitor of IL-17 and TNF production by human T-cells**
- **IRX4204 can be formulated for topical, oral, or parenteral use.**

IRX4204 inhibits Th17-associated cytokine secretion by human T-cells cultured in Th17 skewing conditions

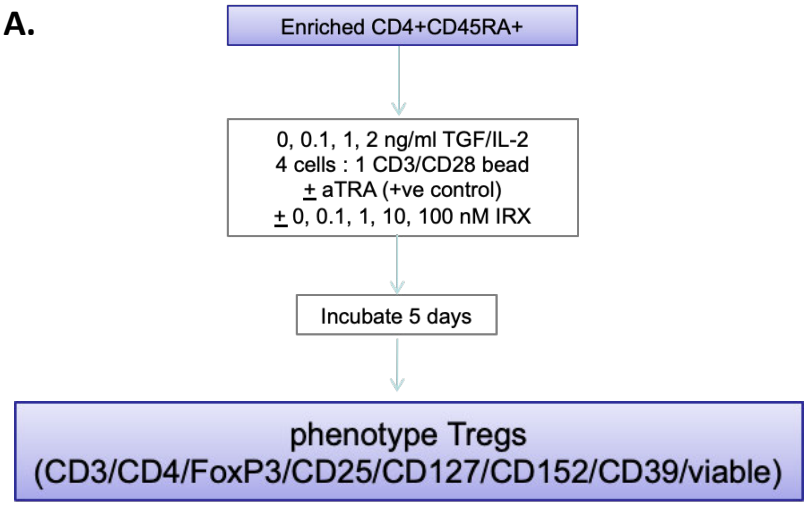


Normal Human PBMCs were isolated from whole blood, then magnetically separated to enrich a ~95% pure CD4+CD45RA+ naïve T cell fraction. Cells were cultured under Th17 skewing conditions for 5 days and stimulated anti-CD3/CD28 beads. and supernatants collected following 5 days in culture.

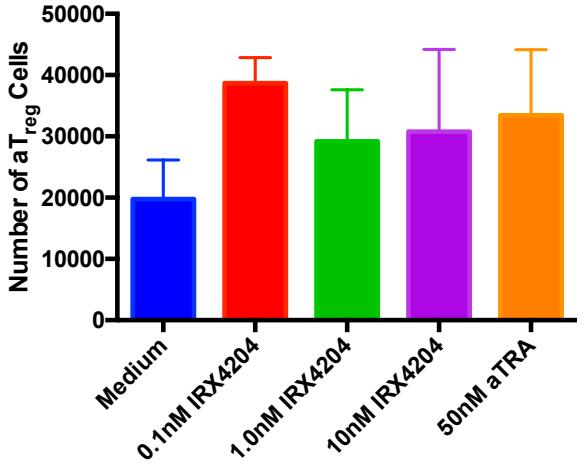
Therapeutic agents which are bioactivity neutralizing for IL-17 and TNF-α are effective in randomized controlled clinical trials, and are FDA approved for treatment of rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, and uveitis; validating IL-17 and TNF-α as therapeutic targets for diverse autoimmune diseases. The preclinical data shown above, using human T-cells in vitro, provides strong support for clinical utility of IRX4204 for treatment of these same IL-17 and TNF-α mediated diseases.

IRX4204 Promotes Human Treg Differentiation and Proliferation In Vitro

A.

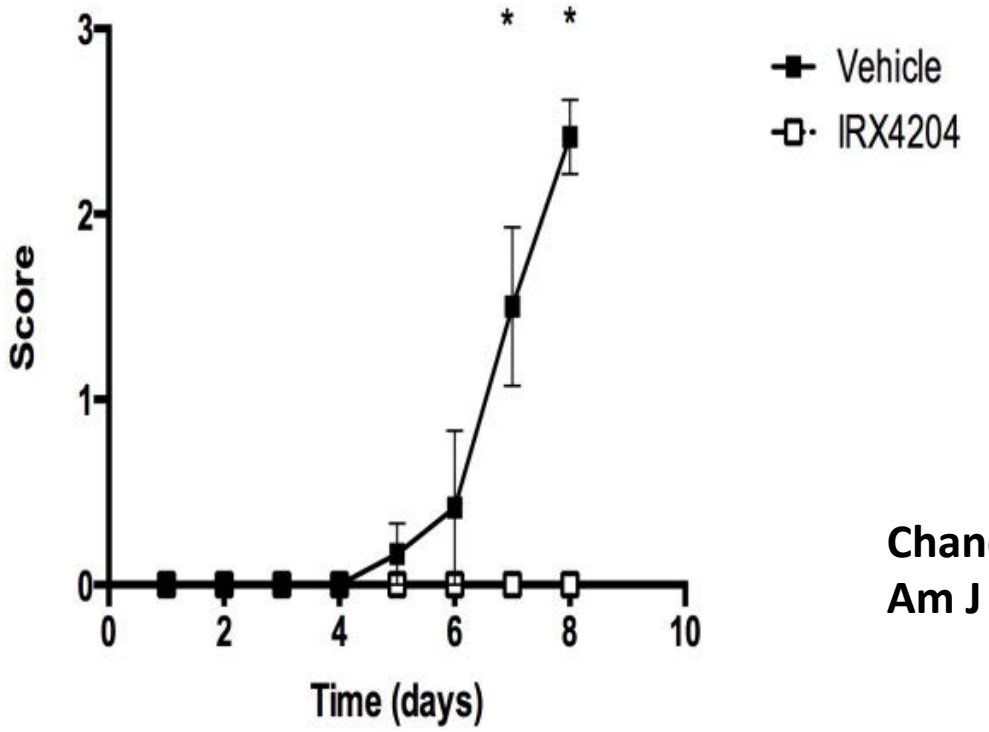


B.



IRX4204 increases Treg conversion and proliferation of naïve CD4+ T cells in Treg skewing conditions. **A.** Methods: 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. Flow cytometry gating strategy: Non-aggregate, then live, then singlet cells were gated. The CD3+CD4+ cells were gated and analyzed for the frequency of CD127loCD25+ cells. These cells were then analyzed for FoxP3, CD39, and CD152. **B.** Results: Absolute number of Treg cells from cells cultured in skewing conditions with 1ng/ml TGFβ. IRX4204 increased the number of Treg cells. The mean and SD of three normal healthy individuals are shown.

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



Chandraratna, et al.
Am J Transl Res, 2016

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 statistically significantly inhibited in vivo transmission of autoimmunity by Th17 cells.

IRX4204: Clinical Development Status

- 100 patients have been treated with oral 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 per day oral dosing.
- Common oral side effects include RXR agonist side effects known from clinical use of bexarotene, i.e., dose related reversible suppression of TSH with resultant reversible treatable hypothyroidism; mild to moderate reversible increased triglycerides; and mild to moderate reversible leukopenia.
- Open label uncontrolled phase I and II clinical trials in cancers and Parkinson's disease support clinical safety, efficacy, and dose range.
- Topical formulations of IRX4204 are under development.

IRX4204 Intellectual Property for Autoimmune Diseases

- **Io Therapeutics Owns Issued US Patents for Psoriasis and other Autoimmune Diseases:**
  Psoriasis, eczema, hidradenitis, lupus, scleroderma, and other autoimmune skin diseases;
  Autoimmune inflammatory arthritides (PSA, RA, AS, Juvenile Arthritis);
  Autoimmune gastrointestinal diseases (Crohn's, Ulcerative Colitis, Celiac Disease);
  Asthma and other allergic diseases.

- **Io Therapeutics Owns Issued International Patents for Autoimmune Diseases:**
  Io Therapeutics owns issued patents for treatment of psoriasis; as well as for many of the above listed autoimmune indications in Europe, Japan, South Korea, Hong Kong, Singapore, Australia, New Zealand, Canada, Mexico, Israel, and South Africa.

- **Io Therapeutics Owns Patents for Proprietary Methods of Synthesis and Formulations:**
  IRX4204 has 2 chiral centers and one pharmacologically desirable active stereoisomer. The company owns patents for proprietary methods for synthesis of IRX4204 of high chiral purity, and compositions of matter for intermediate compounds, issued in the US, China, Australia, Israel and pending in other countries. The company owns pending patents for salts and polymorphs of IRX4204 with increased solubility, suitable for making topical formulations for skin and other organs.