IMU-935, an Orally Available RORγt Inverse Agonist in Phase 1 Clinical Trial for Psoriasis, Inhibits Th17-Dependent Autoimmunity without Inducing Thymocyte Aberrations

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IMU-935 Overview

Introduction

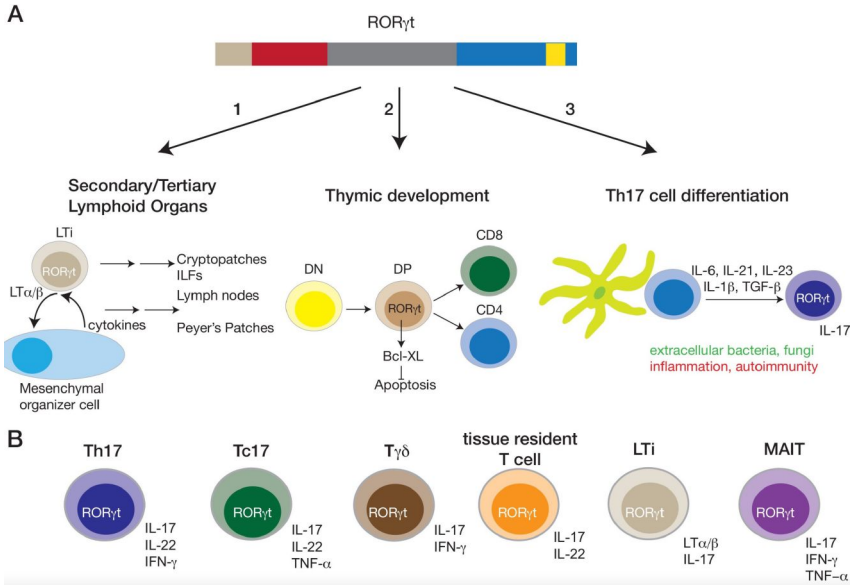
Mode of Action – *In vitro*

Mode of Action – *In vivo*

Conclusions

The Nuclear Receptor RORgamma

- Retinoic acid receptor-related orphan receptor (ROR) gamma (RORγ) is encoded by the *RORC* gene
- It consists of two isoforms
  - RORγ1: full length 518 aa
  - RORγt (RORγ2): lacks the first 21 aa. It is mainly expressed by T cells, but also in some other immune cells and is involved in IL-17 expression



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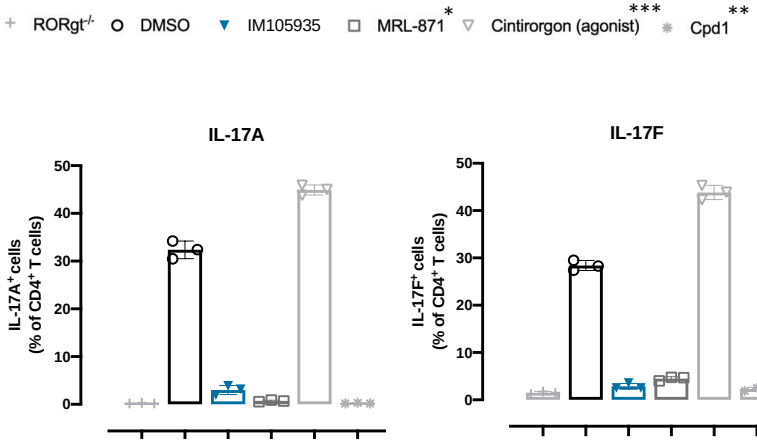
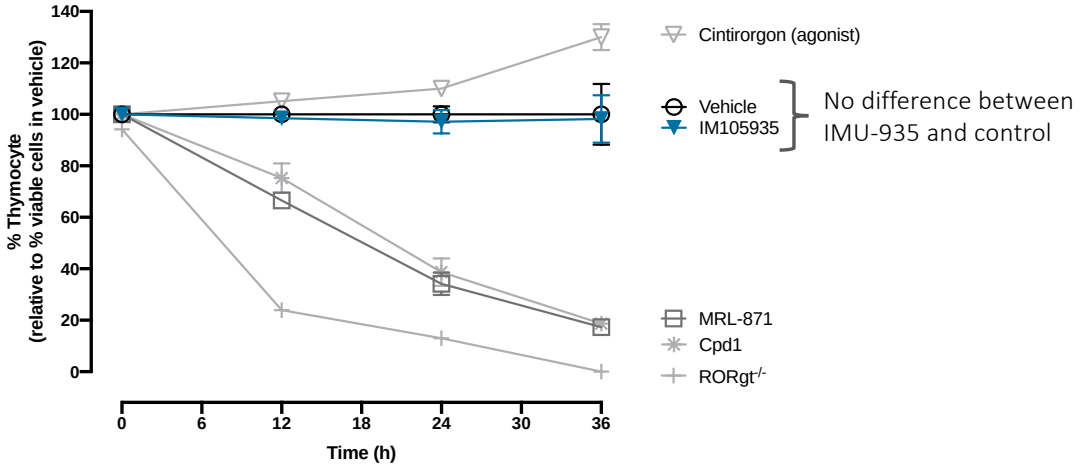
IMU-935 Potently Inhibits T_H17 Cell Differentiation but Does Not Induce Thymocyte Apoptosis

In Contrast to IMU-935, Comparator Compounds Have a Negative Impact on Thymocyte Viability and Therefore Bear the Risk of Lymphoma.



Impact on Th17 differentiation at 500 nM



Impact on thymocyte viability at 1000 nM

Sun, Zuoming. City of Hope, 2021, unpublished,

*Guo et al., 2016, Cell Reports (MRL-871), **Guntermann et al., 2017, JCI Insight (Cpd1), Mahalingam et al., 2019, ***Clin Cancer Res. (Cintirorgon)

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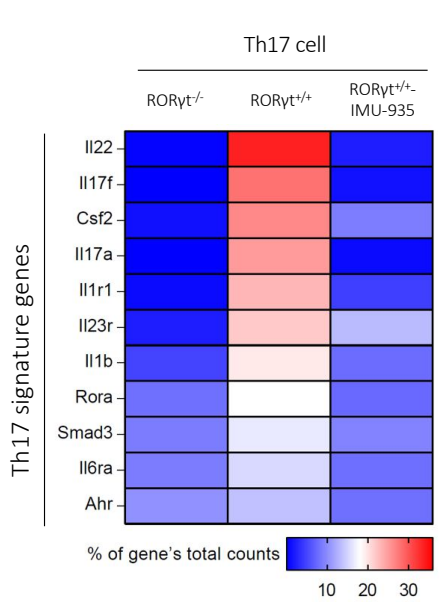
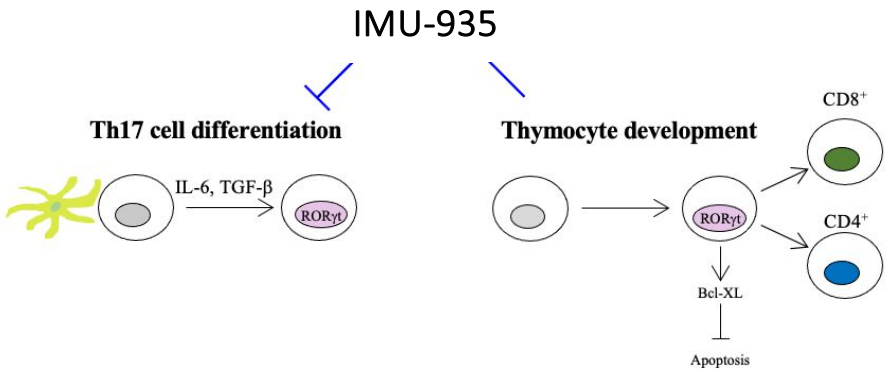
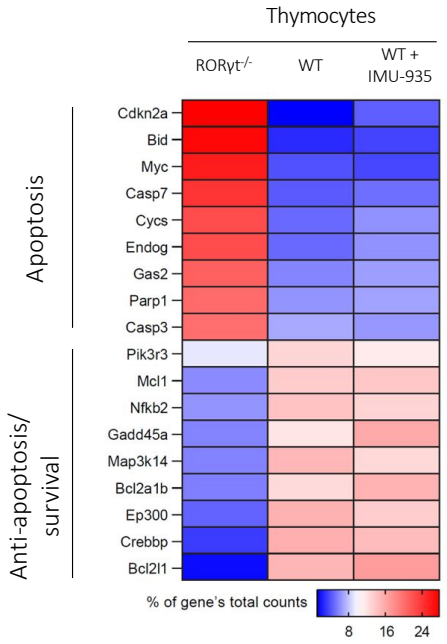
IMU-935 Blocks Th17 Differentiation But Allows Normal Thymocyte Maturation: Gene Expression Profiles







Similar gene expression pattern for Th17 signature genes in **RORγt knockout and wild type cells treated with IMU-935**

Different gene expression pattern for apoptosis and anti-apoptosis/survival signature genes in **RORγ knockout** and **IMU-935 treatment**, but similar for WT

Zuoming Sun, City of Hope, 2021

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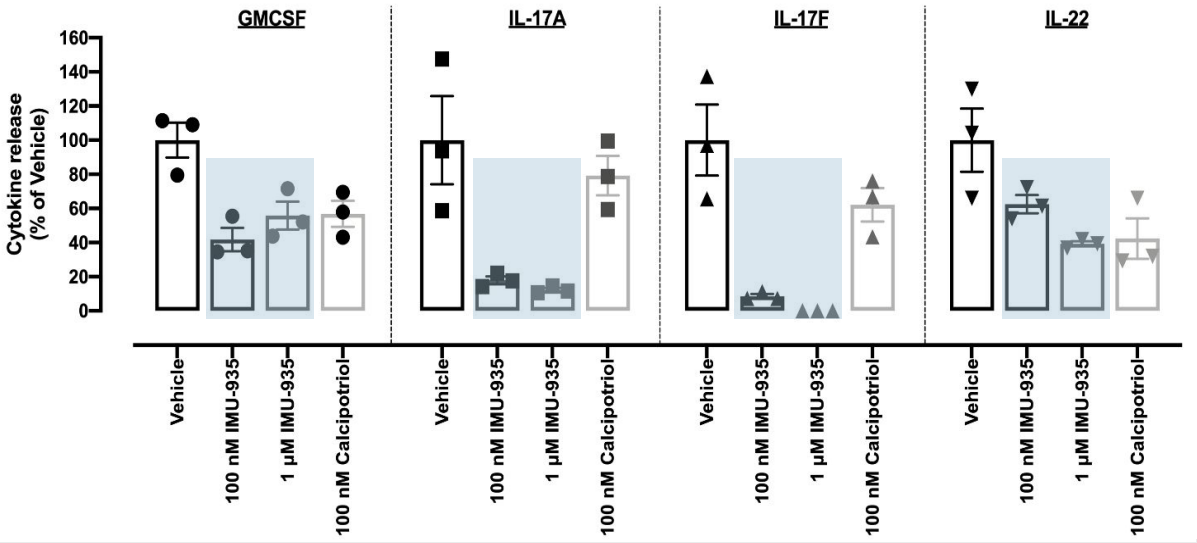
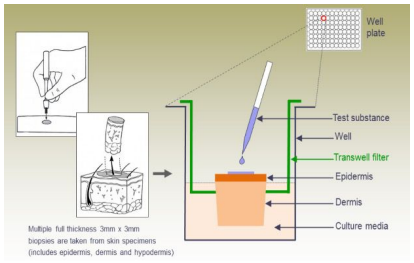
IMU-935 Potently Inhibited Cytokine Release in *Ex Vivo* Stimulated Human Skin Punches

Cytokine Inhibition in Inflamed Human Skin Model





IMU-935 is active with **< 100 nM** on
GM-CSF
IL-17A
IL-17F

Method:

Skin punches from a human healthy volunteer were *ex vivo* pretreated with IMU-935 for 24 hours and then challenged with a pro-inflammatory cytokine cocktail for another 24 hours.

Result:

IMU-935 demonstrated a strong inhibition of GM-CSF, IL-17A, IL-17F and IL-22.

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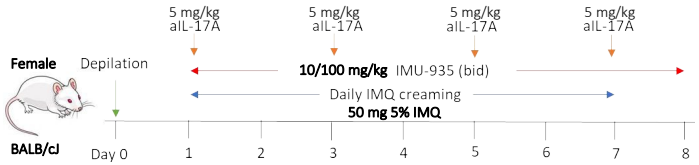
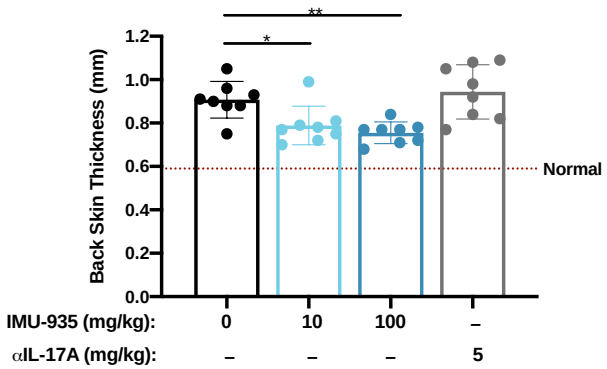
IMU-935 Demonstrated Activity in an Imiquimod Induced Psoriasis Model

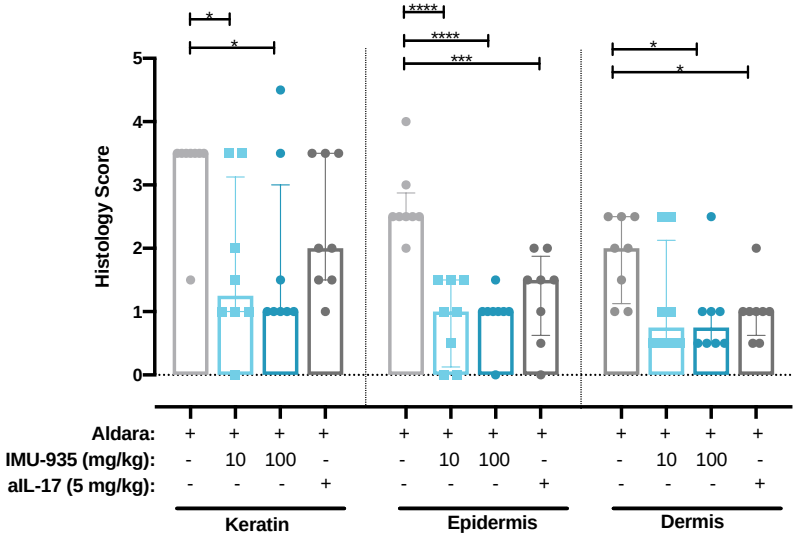
- **IMU-935 benchmarked** with an **IL-17A antibody** (InVivoMab, Clone: 17F3) demonstrating superiority of IMU-935 on skin thickness at day 8
- Interestingly, the antibody lost activity from day 6 on
- IMU-935 reduced the histological pathology scores in all skin layers



Back Skin Thickness d8



Histological Scoring Back Skin d8



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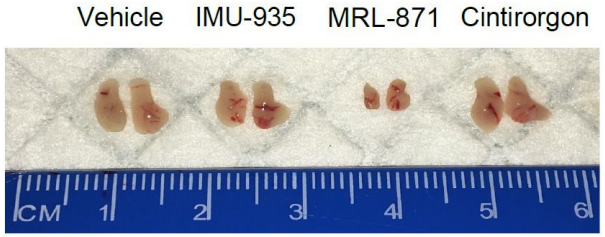
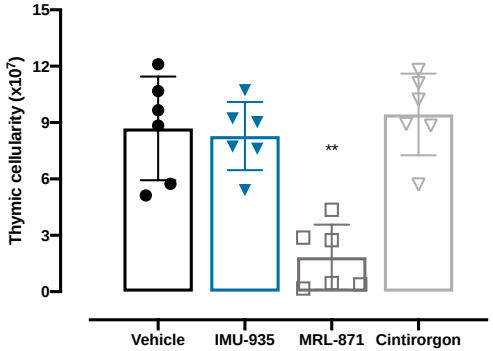
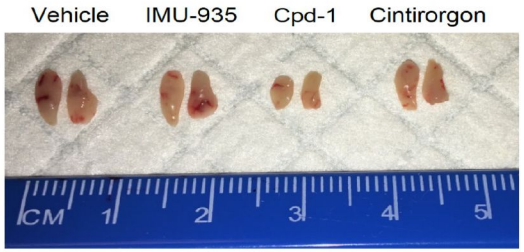
IMU-935 Allows Normal Thymocyte Maturation *In Vivo*

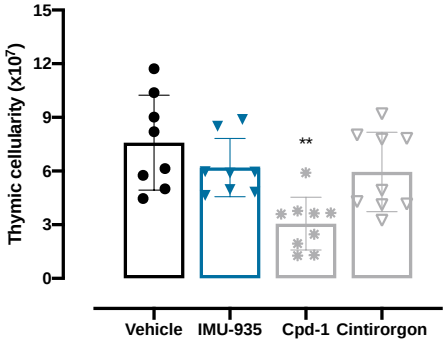
- Acute model: Treatment with IMU-935 (100 mg/kg), MRL-871 (100 mg/kg) and Cintirorgon (30 mg/kg) for 3 days (BID)





- Chronic model: Treatment with IMU-935 (100 mg/kg), Cpd1 (40 mg/kg), or Cintirorgon (30 mg/kg) for 4 weeks (BID)





In contrast to MRL-871 and Cpd1, **IMU-935 does not impact thymus size, thymocyte cell numbers or thymocyte maturation** in an acute and chronic mouse model.

Guo et al., 2016, Cell Reports (MRL-871), Guntermann et al., 2017, JCI Insight (Cpd1), Mahalingam et al., 2019, Clin Cancer Res. (Cintirorgon)
Sun, Zuoming. City of Hope, 2021, unpublished

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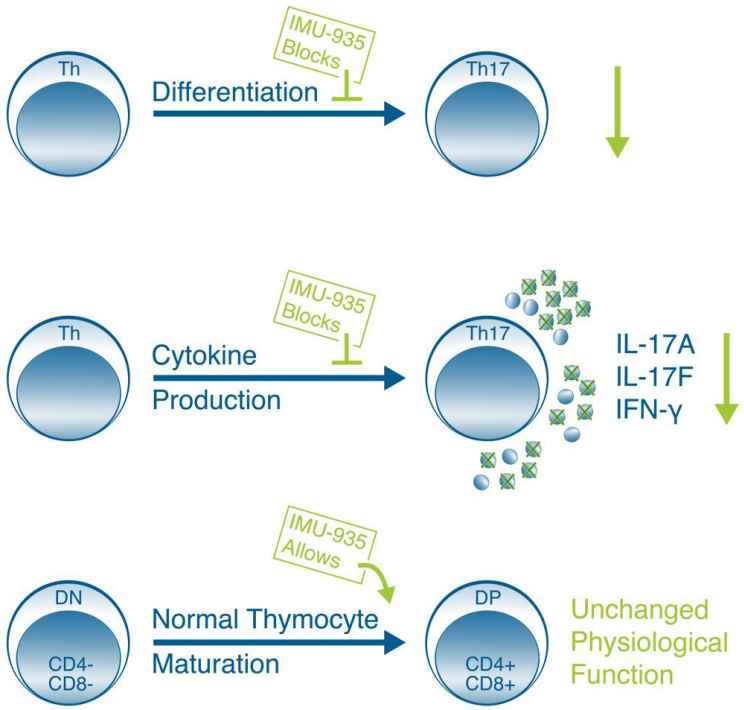
IMU-935 Selectively Inhibits Th17 Differentiation and IL-17 Secretion



- The differentiation towards Th17 cells is inhibited by IMU-935
- The production of IL-17A and IL-17F is inhibited by IMU-935
- The physiological maturation of T cells within the thymus is not affected by IMU-935

Th: T helper; IL: interleukin; IFN: interferon; DN: double-negative; DP: double-positive; CD: cluster of differentiation

Thank You!

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