IMU-935, a Potent RORγt Inverse Agonist, Effectively Inhibits T Helper 17 Cells but Maintains Normal Thymocyte Development

Evelyn Peelen, Ph.D. | Immunic Therapeutics | NASDAQ: IMUX

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Forward-looking statements included in this presentation are based on information available to Immunic as of the date of this presentation. Immunic does not undertake any obligation to update such forward-looking statements except as required by applicable law.

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Immunic Therapeutics

Company Introduction

Our Mission

We are developing a pipeline of next-generation selective oral therapies focused on offering patients with chronic inflammatory and autoimmune diseases new and clinically meaningful treatment options.

Multiple Clinical Data Readouts Expected Throughout 2022

Program	Target	Preclinical	Phase 1	Phase 2	Phase 3	Key Milestones
Vidofludimus Calcium (IMU-838)	DHODH	Relapsing Multiple Sclerosis (RMS) – ENSURE Trials				▪ RMS interim analysis planned after approx. half of the events occurred ▪ PMS interim analysis planned after half of the patients completed 24 weeks of treatment
		Progressive Multiple Sclerosis (PMS) – CALLIPER Trial				
		Primary Sclerosing Cholangitis (PSC)				
IMU-935	IL-17 / RORγt	Psoriasis				▪ H2/2022: initial psoriasis data expected
		Castration-Resistant Prostate Cancer (CRPC)				▪ Q3/2022: initial CRPC safety data expected
IMU-856	Intestinal Barrier Function	Celiac Disease				▪ Q3/2022: SAD/MAD safety data expected

■ Completed or ongoing ■ In preparation or planned

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IMU-935 Overview

Introduction

Mode of Action – *In Vitro*

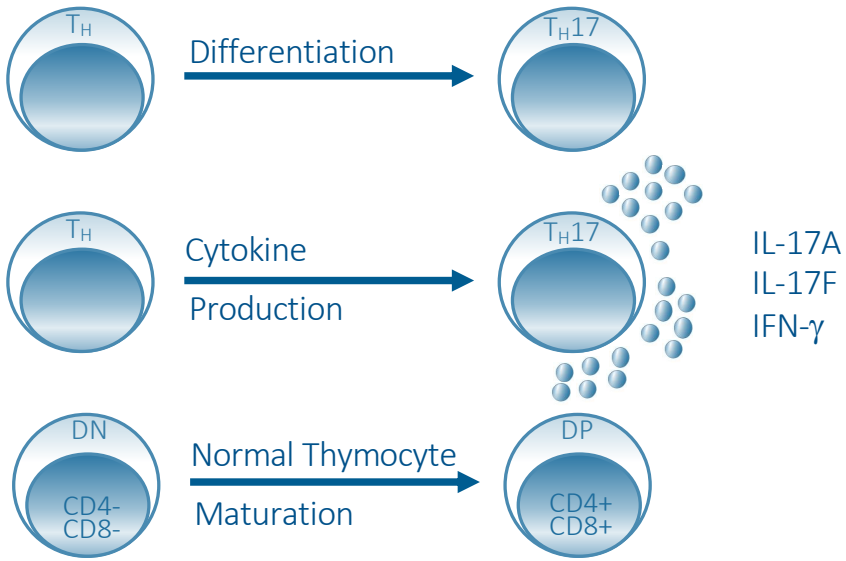
Mode of Action – *In Vivo*

Phase 1

Conclusions

The Nuclear Retinoic Acid Receptor-Related Orphan Receptor (ROR) Gamma (RORγ)

- RORγ is encoded by the gene *RORC* and 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



- RORγt important in the differentiation towards T_H17 cells
- RORγt transcription factor for IL-17A and IL-17F
- RORγt important for physiological maturation of T cells within the thymus

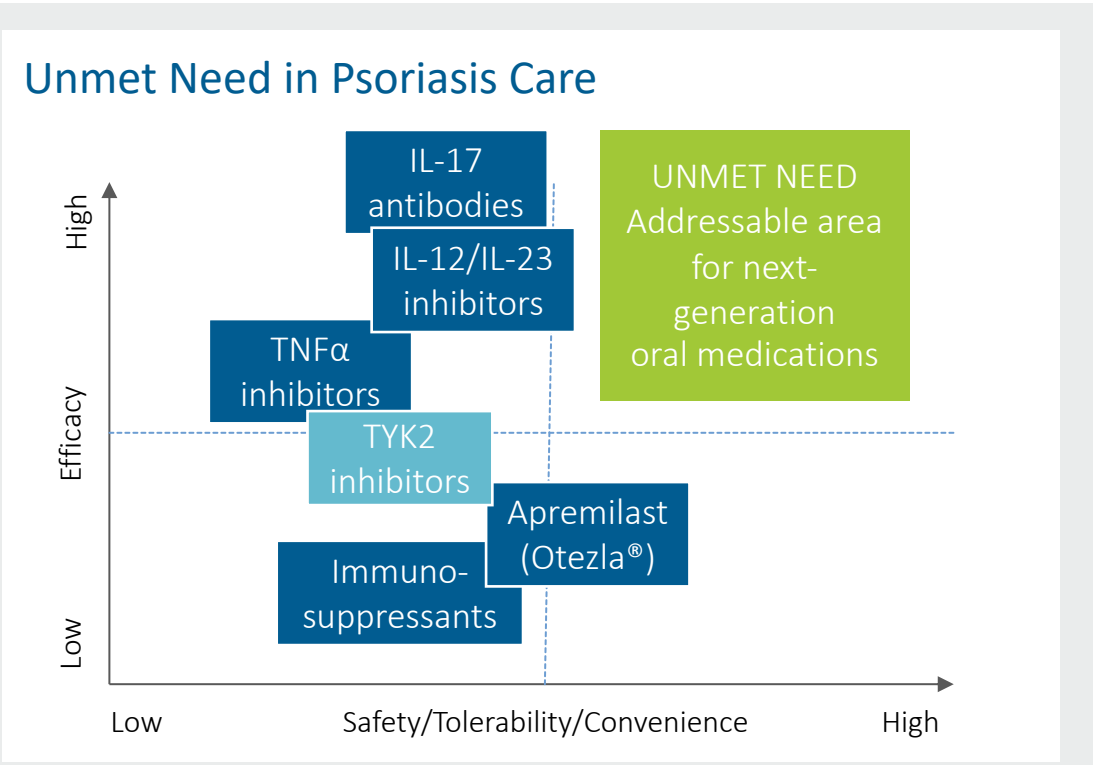
Th: T helper; IL: interleukin; IFN: interferon; DN: double-negative; DP: double-positive; CD: cluster of differentiation

Clear Need for Potent and Specific Inhibition of IL-17 in Multiple Autoimmune Diseases

IL-17 is Significant in Many Autoimmune Diseases

- Imbalance between regulatory T cells (T_{regs}) and T helper 17 (T_H17) cells contributes to autoimmune diseases, with Th17 cells secreting pro-inflammatory cytokines such as IL-17[1]
- RORγt is a master regulator of T_H17 cell development and expression of IL-17[2]

Goal: Develop a Potent, Specific, and Orally Available IL-17 Inhibitor



[1] Fasching, Patrizia, et al. Molecules 2017 22.1: 134 [2] Bassolas-Molina, Helena et.al., Front. Immunol., 22 October 2018 [
Th: T helper; IL: interleukin; TNF: tumor necrosis factor; TYK2: Tyrosine kinase 2; RORγ: retinoic acid receptor-related orphan nuclear receptor gamma

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IMU-935 Overview

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Mode of Action – *In Vitro*

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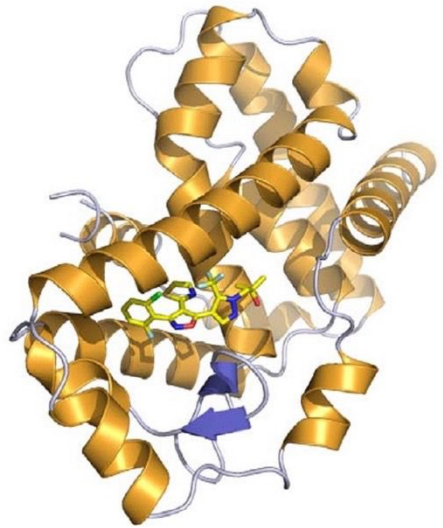
IMU-935 Inhibits Cytokines Associated With Autoimmune Diseases With an IC_{50} of 3-5 nM in Stimulated Human Lymphocytes

	IC_{50} (µM)
IL-17A	0.005
IL-17F	0.004
IFNγ	0.003
IL-1a and b	no inhibition
IL-4,5,6,8	no inhibition
RORγ (MST)	0.024
RORγ (cellular, reporter assay)	0.020
Th17 differentiation (murine)[1]	0.135

Read-out: effect on cytokine production after 48 hours in PBMC



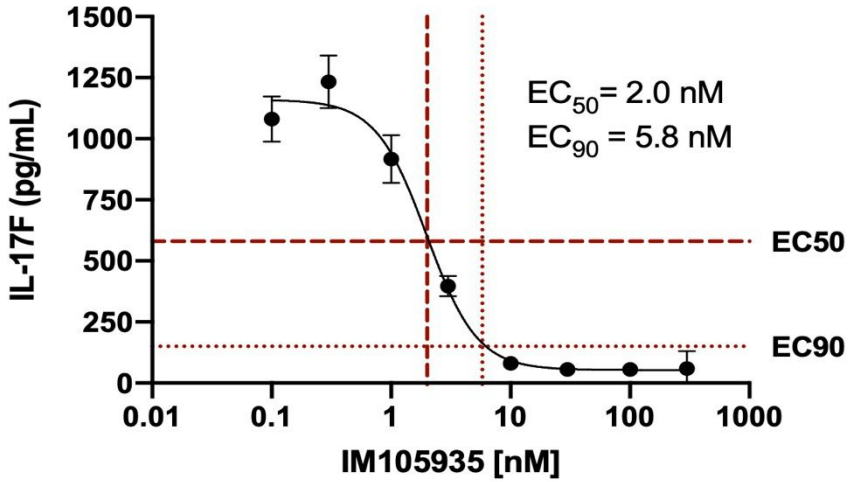
Co-crystal structure (Resolution 2.6 A) of a closely related derivative compound binds to hydroxycholesterol binding site of RORγ

PBMC: Peripheral Blood Mononuclear Cells; Th: T helper; IL: interleukin; IFN: interferon; MST: microscale thermophoresis
[1] Zuoming Sun, City of Hope, 2019

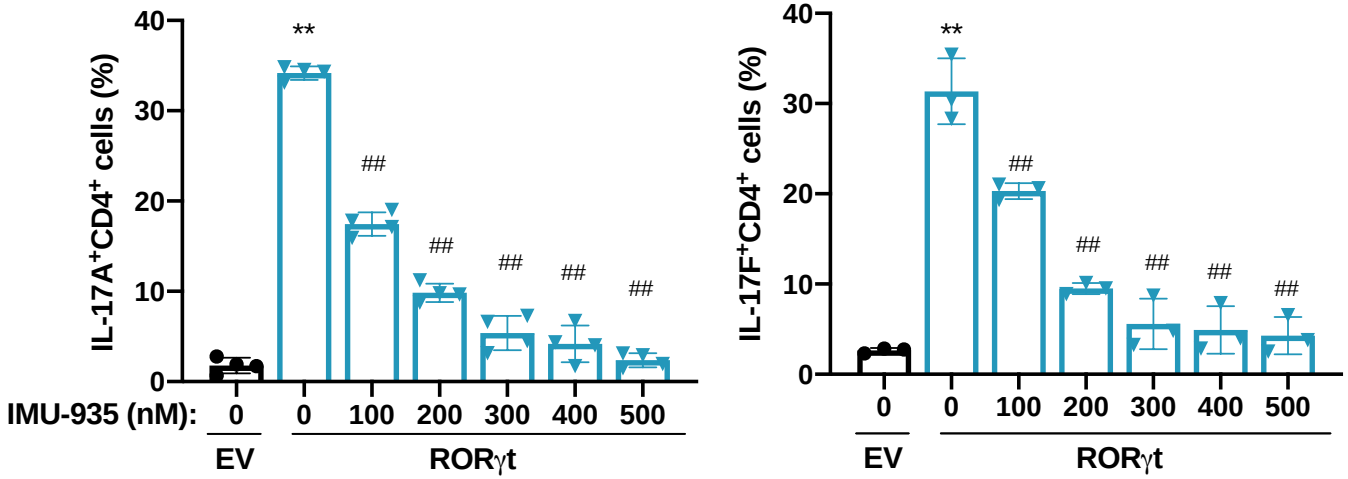
IMU-935 Potently Inhibits Human and Murine IL-17 and T_H17 Cells

- Strong inhibition of human IL-17A (EC_{50}: 5 nM) and IL-17F (EC_{50}: 4 nM) secretion and murine T_H17 cell differentiation (EC_{50}: 135 nM)

IL-17F Secretion
Human Primary PBMCs

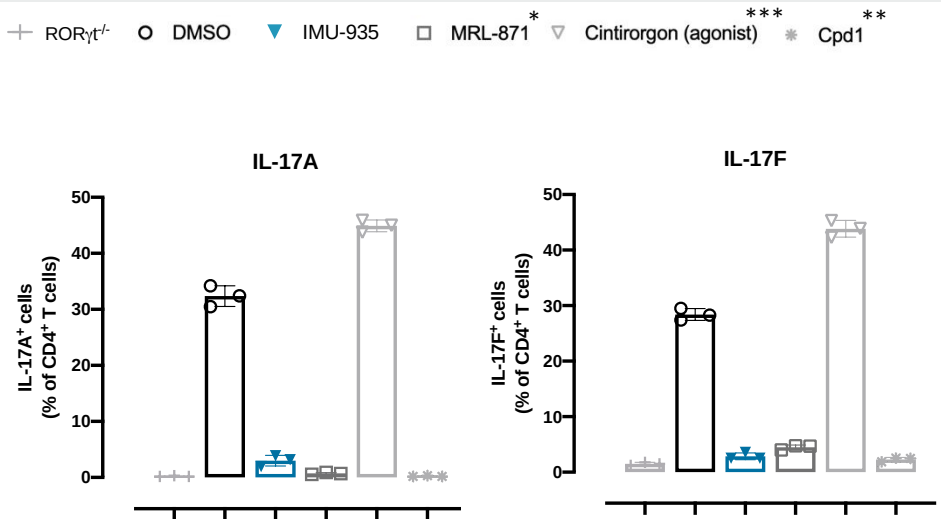


Intracellular IL-17A and IL-17F
in murine $CD4^+$ T cells

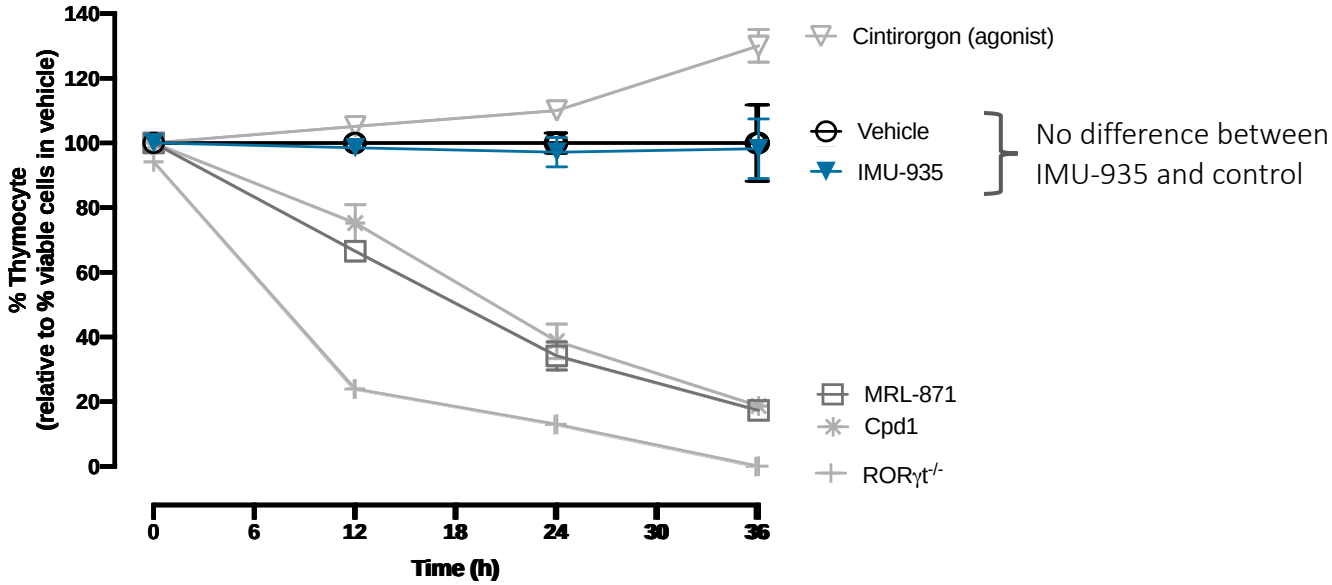


IMU-935 Potently Inhibits T_H17 Cell Differentiation but Does Not Induce Thymocyte Apoptosis

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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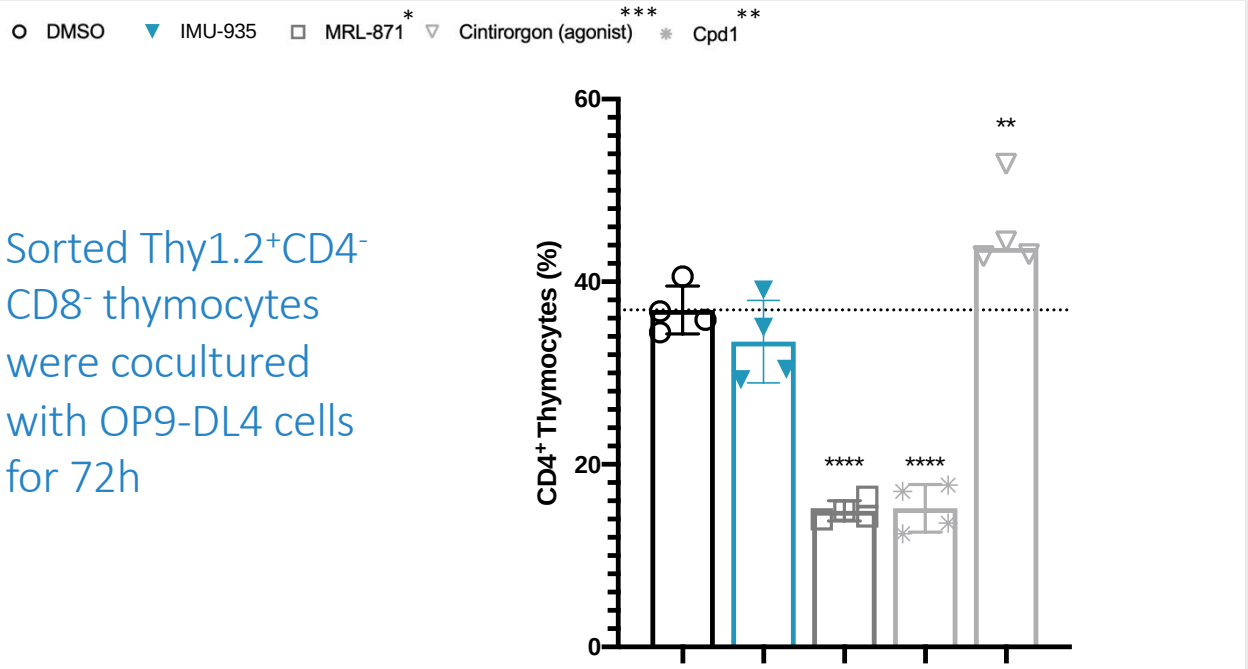
IMU-935 Does Not Impair Thymocyte Maturation *In Vitro*

In contrast to IMU-935, comparator compounds have also a negative impact on thymocyte maturation and therefore bear the risk of lymphoma.

Sorted Thy1.2^{+}CD4^{-} CD8^{-} thymocytes were cocultured with OP9-DL4 cells for 72h



Impact on thymocyte maturation at 1000 nM

Compared to the reference compounds, IMU-935 does not:

- ✓ Reduce thymocyte survival
- ✓ Affect thymocyte maturation

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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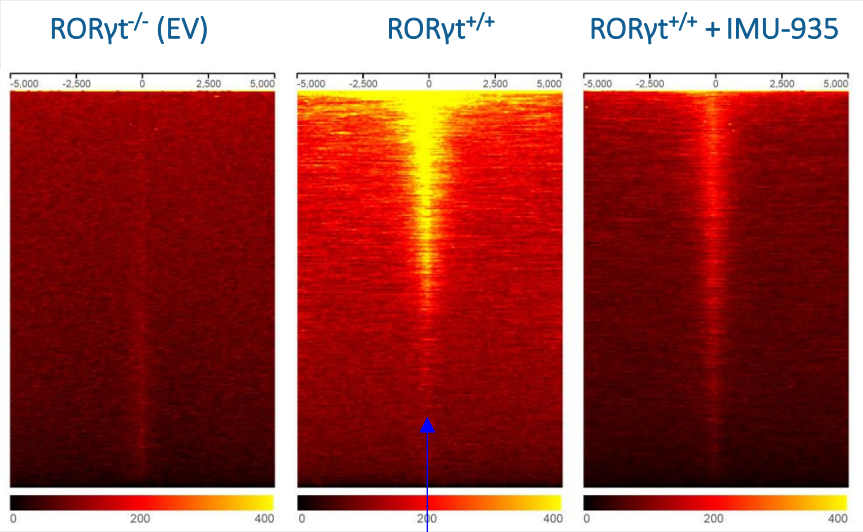
IMU-935 Attenuates RORγt Genome-Wide DNA-Binding in T_H17 Cells – No DNA binding in RORγt$^{-/-}$ or RORγt$^{+/+}$ with IMU-935

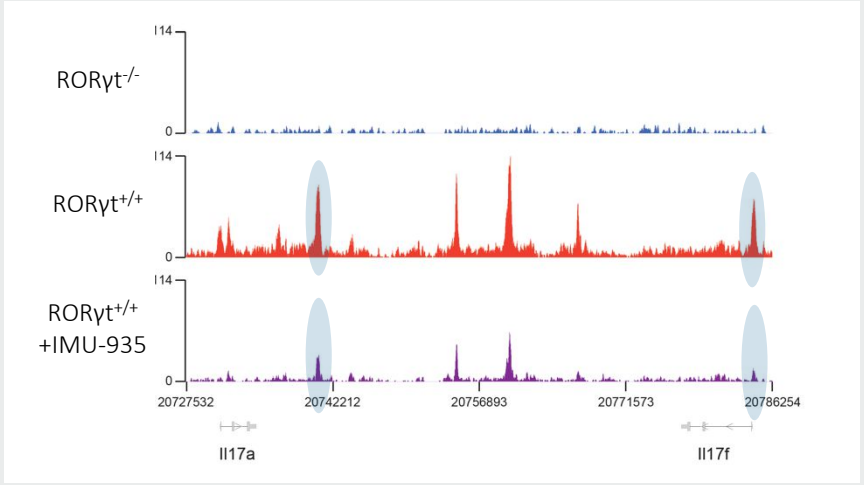


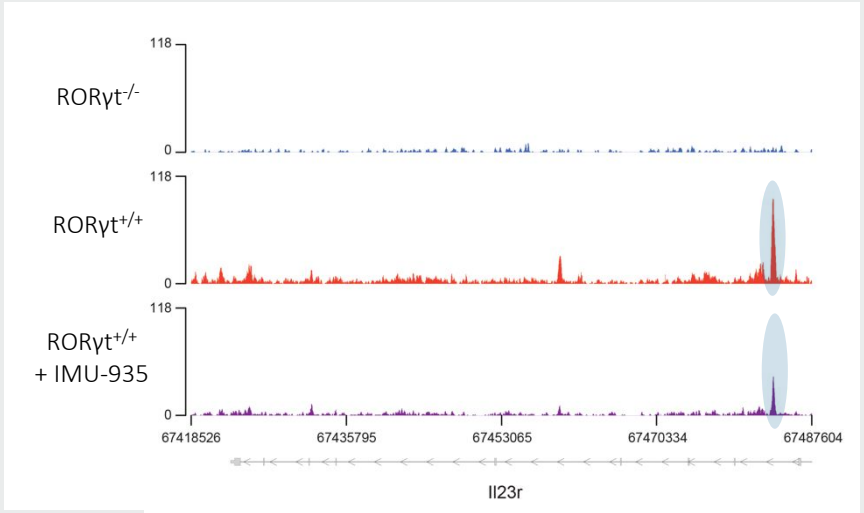
TSS plot: a common visualization method to obtain a global evaluation of enrichment around the transcription start site (TSS)

RORγt protein binds to ~3000 gene loci in murine cells under T_H17 differentiation conditions

Negative control: In RORγt knockout cells no binding to DNA loci can be detected in murine cells under T_H17 differentiation conditions

RORγt protein binds to a lower number and to a lesser extent to DNA loci in murine cells under Th17 differentiation conditions





Sun, Zuoming. City of Hope, 2021, unpublished

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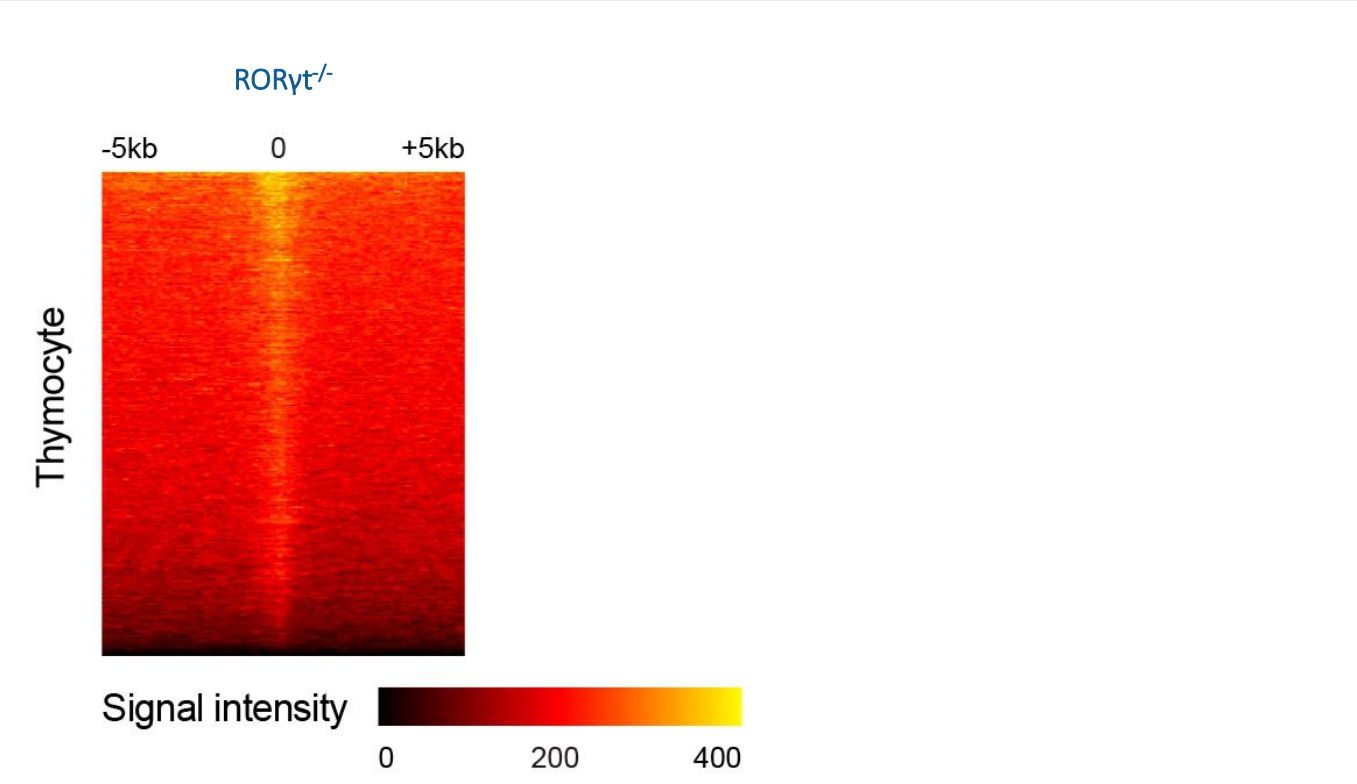
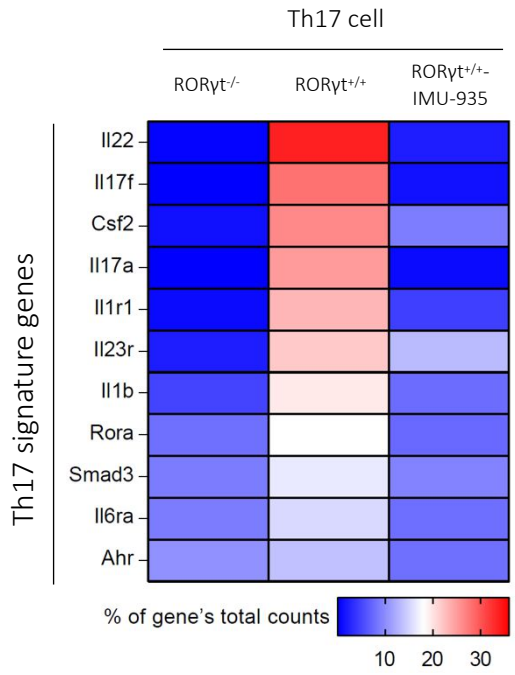
IMU-935 Does Not Affect RORγt Target Genes Critical for Thymocyte Function – DNA Binding in WT with and without IMU-935

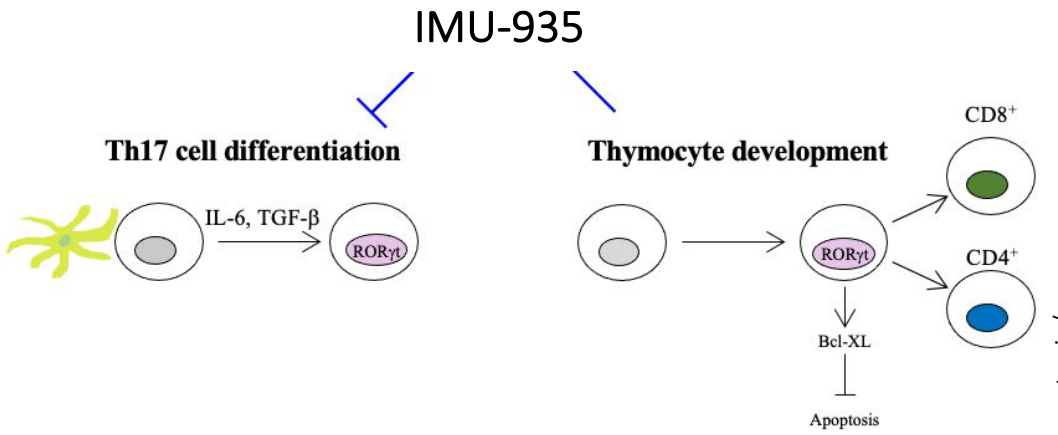


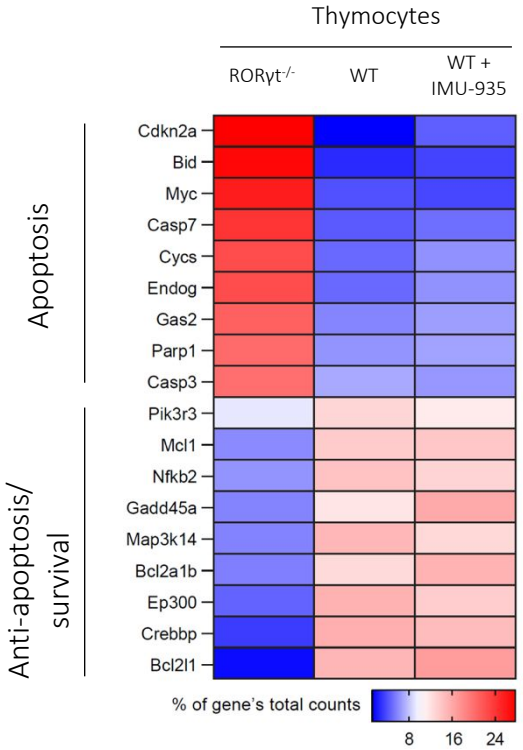
- RORγt protein binds to many gene loci in murine thymocytes
- RORγt protein binds to a similar number and to a similar extent to DNA loci in murine thymocytes in the presence of IMU-935

Sun, Zuoming. City of Hope, 2021, unpublished

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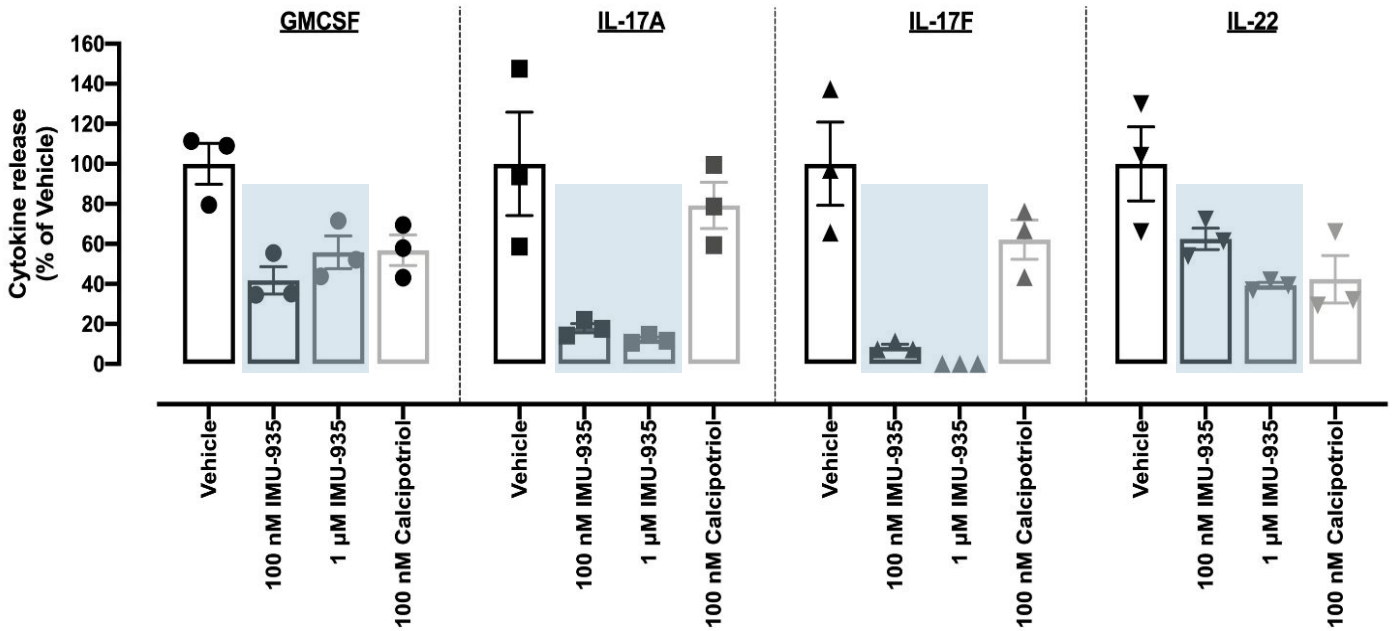
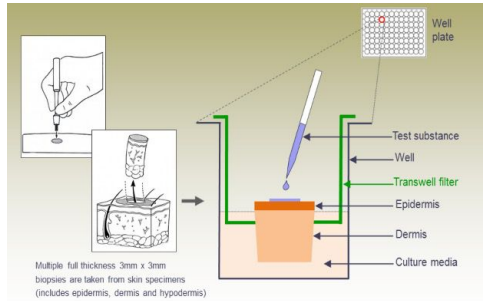
IMU-935 Potently Inhibited Cytokine Release in *Ex Vivo* Stimulated Human Skin Punches

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 Overview

Introduction

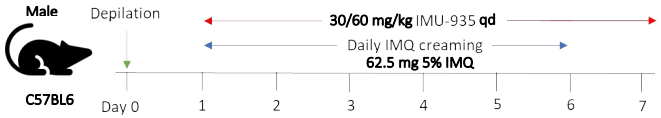
Mode of Action – *In Vitro*

Mode of Action – *In Vivo*

Phase 1

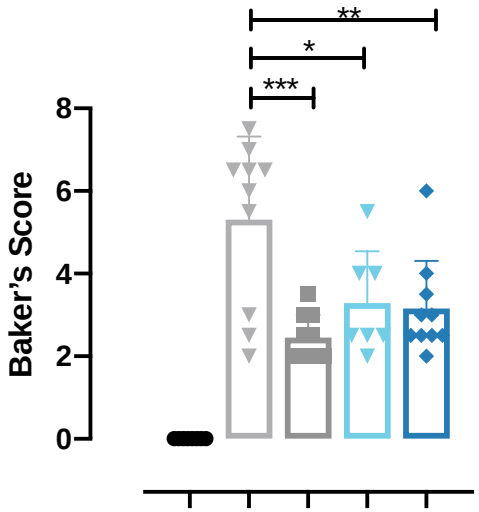
Conclusions

IMU-935 Showed Histological Improvement and Reduction in IL-17F Expression in Skin an Imiquimod Induced Mouse Model

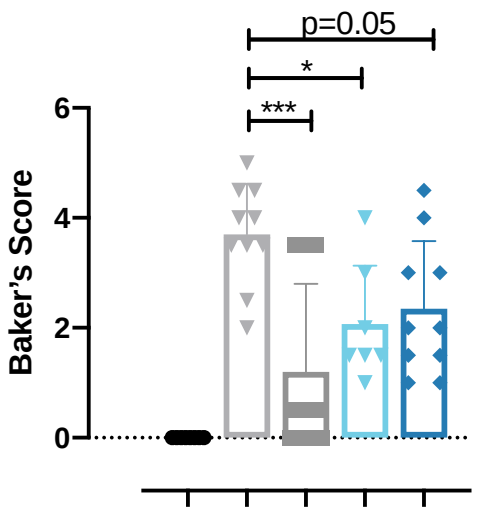


- Reduction of histological score on ear and skin
- Systemic exposure leads to dose dependent inhibition of IL-17F mRNA expression *in vivo* in the skin
- IMU-935 was more potent in IL- 17F suppression than the corticosteroid control Clobetasol

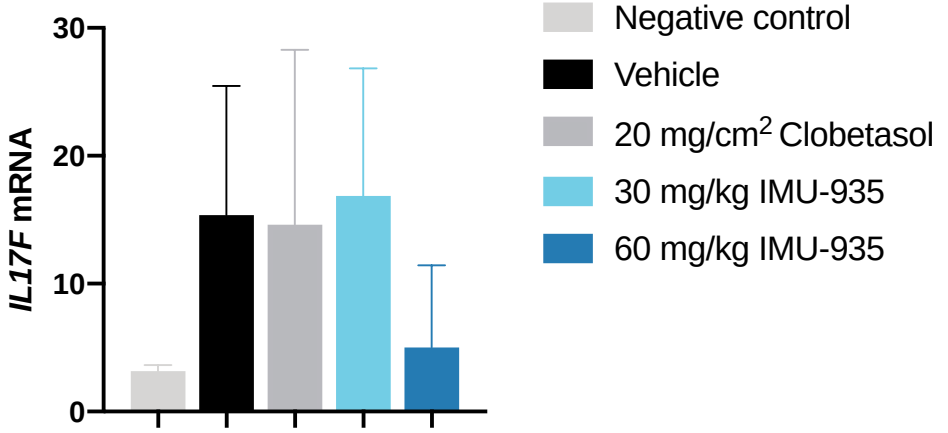
Skin Histology Score



Ear Histology Score



Skin IL-17F mRNA Expression



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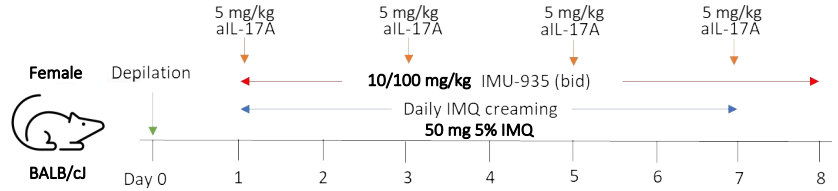
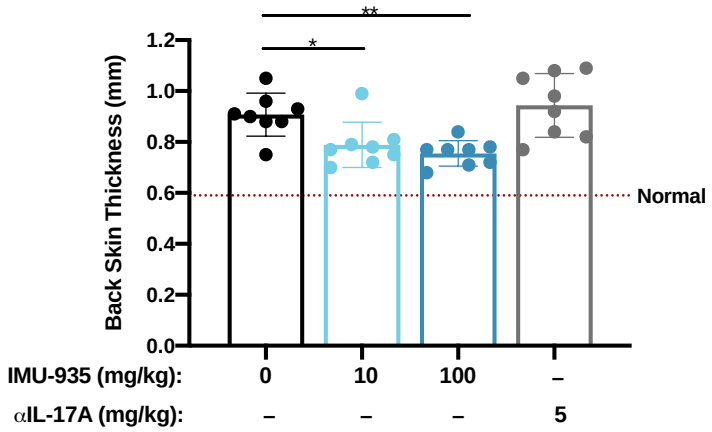
IMU-935 Demonstrated Activity in an Imiquimod Induced Psoriasis Model

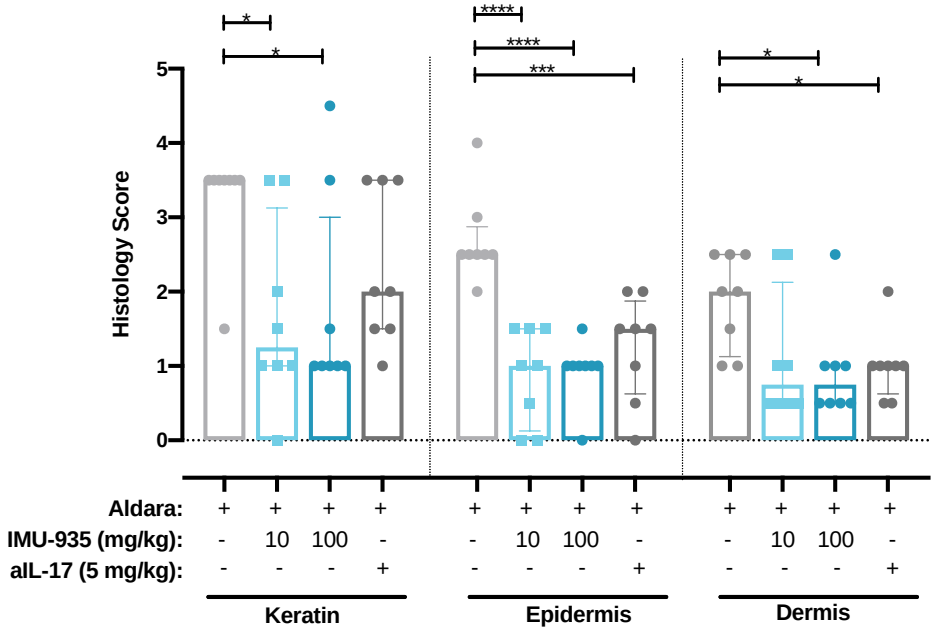
- **IMU-935 benchmarked** with an **IL-17A antibody** (InVivoMab, Clone: 17F3), demonstrating superiority of IMU-935 on skin thickness at day 8
- Interestingly, the antibody lost activity from day 6 on
- IMU-935 reduced the histological pathology scores in all skin layers



Back Skin Thickness d8



Histological Scoring Back Skin d8



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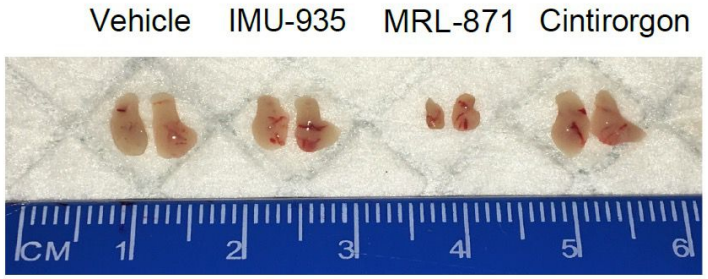
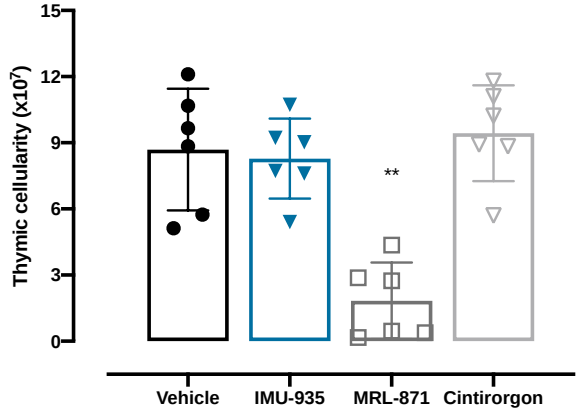
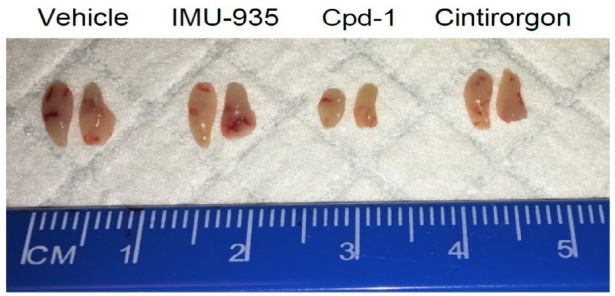
IMU-935 Allows Normal Thymocyte Maturation *In Vivo*

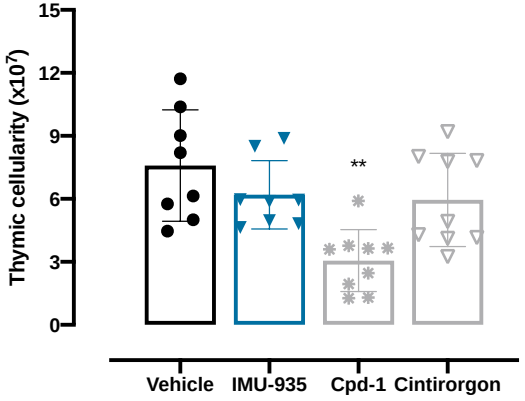
- Acute model: Treatment with IMU-935 (100 mg/kg), MRL-871 (100 mg/kg), or Cintirorgon (30 mg/kg) for 3 days (BID)





- 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 Overview

Introduction

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Mode of Action – *In Vivo*

Phase 1

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Phase 1 Clinical Trial: Trial Design and Current Status

PART A ✓

Evaluation of
single ascending doses (SAD)

—

Healthy human subjects randomized to receive single dose of IMU-935 or placebo

- Dose escalation completed: 100, 200, 300 and 400 mg of IMU-935
- Final PK analysis ongoing
- 79 subjects enrolled
- IMU-935 was well-tolerated and showed dose-linear PK

PART B ✓

Evaluation of
multiple ascending doses (MAD)

—

Healthy human subjects randomized to receive 14-day treatment of IMU-935 or placebo

- Dose escalation completed: 150 mg QD and 150 mg BID of IMU-935
- Final PK analysis ongoing
- 15 subjects enrolled
- IMU-935 was well-tolerated and steady-state was achieved after 3-6 days of dosing

PART C

Evaluation of
moderate-to-severe psoriasis patients receiving 28-day treatment of
IMU-935 or placebo

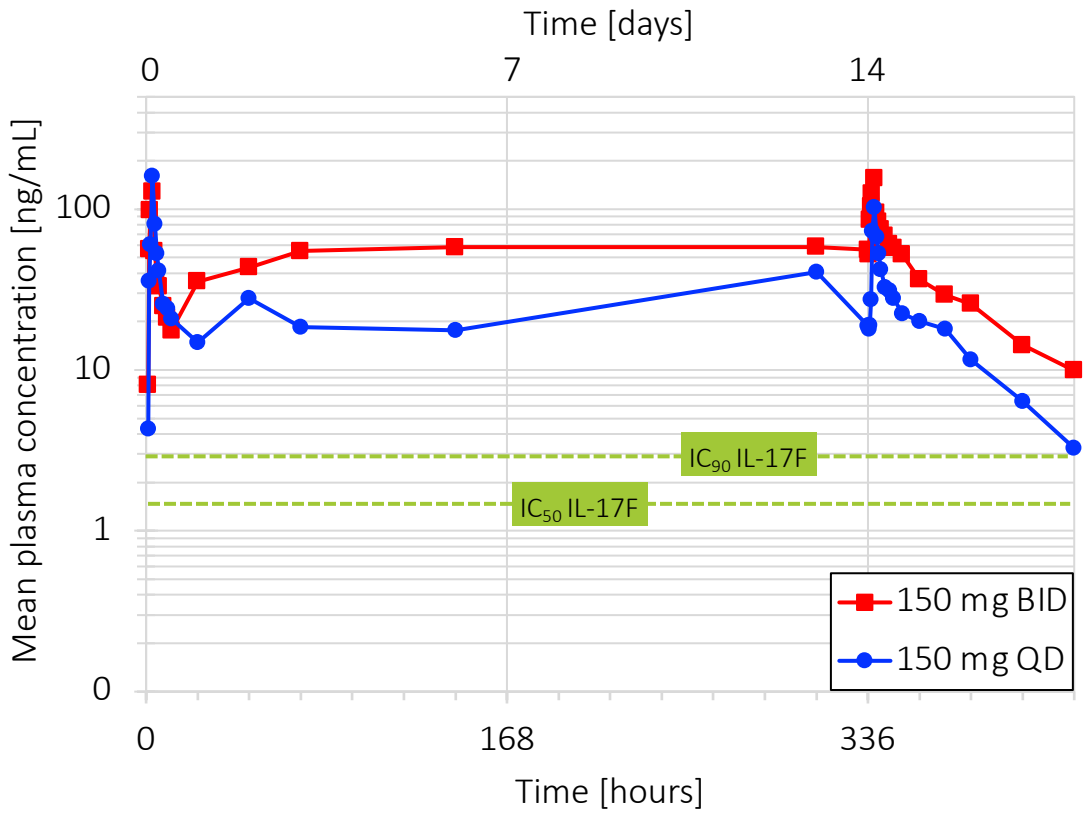
- 150 mg QD and 150 mg BID of IMU-935
- Approximately 40 patients planned to be enrolled
- Initial results expected to be available in H2/2022

PK: pharmacokinetic; QD: quaque die = once-daily; BID: bis in die = two times daily

Phase 1 Clinical Trial: Pharmacokinetic Results

Part B: Summary of QD and BID Dosing Regimen for IMU-935

IMU-935 concentration time profiles (log-linear scale)



Favorable PK Properties for IMU-935 at Steady-State Observed

Pharmacokinetic parameters in steady-state (mean)	150 mg QD	150 mg BID
$C_{max, ss}$ (ng/mL)	124	206
$C_{min, ss}$ (ng/mL)	15.7	48.5
$T_{max, ss}$ (hr)	2.8	2.4
$t_{1/2, ss}$ (hr)	29.0	38.0
AUC_{last} (hr*ng/mL)	1540	3040

Non-compartmental analysis

- Fast achievement of steady-state within first week and stable steady-state trough levels over 14-day treatment period.
- Accumulation factors of 1.29 (150 mg QD) and 2.21 (150 mg BID) allowing predictable trough levels.

Interim data, PK analysis ongoing
QD: quaque die = once-daily; BID: bis in die = two times daily; PK: pharmacokinetic; ss: steady-state; C_{max}: maximum plasma drug concentration; T_{max}: time to reach maximum plasma concentration; hr: hours; $t_{1/2}$: half-life; AUC_{last}: area under the concentration-time curve from dosing to last measurement
Accumulation factors were calculated as the relationship of $AUC_{0\text{-}tau}$ of Day 14/Day 1 (after first dosing).

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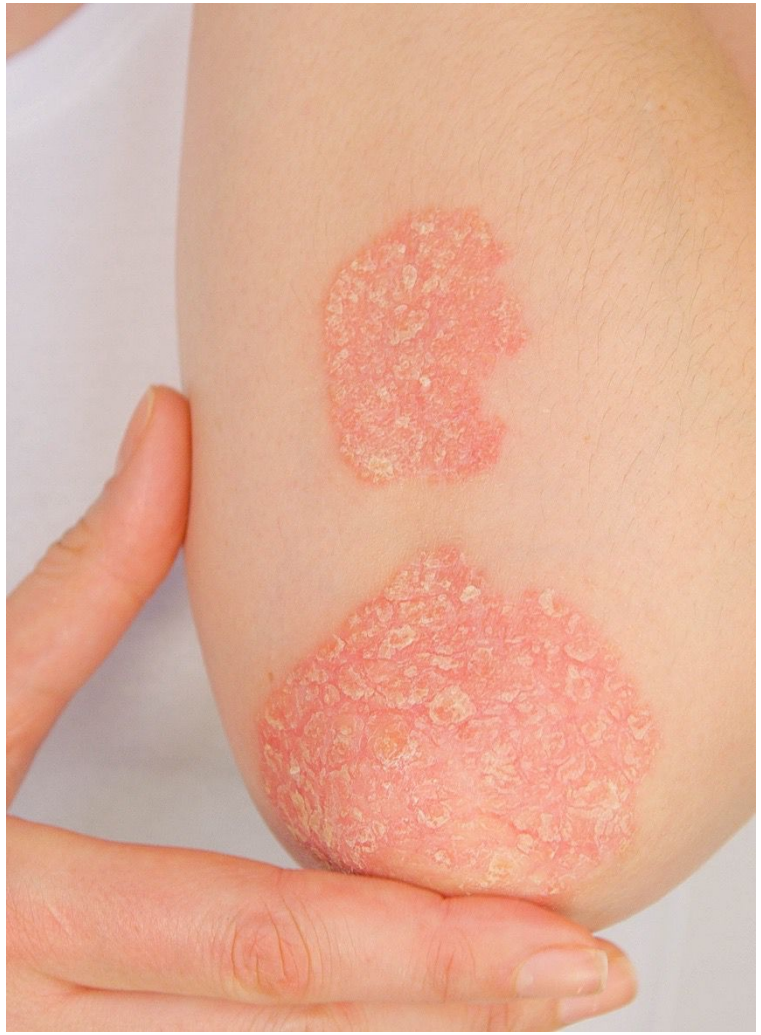
Phase 1 Clinical Trial: Summary of Safety and Tolerability Findings
Part B

Daily Dosing of IMU-935 in Healthy Human Subjects Over 14 Days Was Found to Have a Favorable Safety and Tolerability Profile

- No serious adverse events
- No dose-dependency in adverse events
- No maximum tolerated dose reached
- No trends for post-dose changes in any laboratory parameter
- No adverse events regarding any laboratory parameter
- No medically relevant changes in vital signs or 12-lead electrocardiograms as compared to placebo

IMU-935 Phase 1 Clinical Trial

Part C in Moderate-to-Severe Psoriasis Patients



Detecting Therapeutic Activity of IMU-935 in Moderate-to-Severe Psoriasis Patients

- Double-blind, placebo-controlled dose escalation study to evaluate safety, tolerability, pharmacodynamics and exploratory efficacy of IMU-935 in patients with moderate-to-severe psoriasis
- Psoriasis patients receive **28 days** of daily treatment in two cohorts:
  - First cohort of up to 16 patients receive a low dose of IMU-935 (150 mg QD) or placebo at a ratio of 3:1
    - Low dose cohort ongoing in Australia and New Zealand
  - Second cohort of up to 24 patients receive a high dose of IMU-935 (150 mg BID) or placebo at a ratio of 3:1
    - **Received regulatory approval** to proceed with the trial in Europe
- Initial results from part C are expected to be available **in H2/2022**

QD: quaque die = once-daily; BID: bis in die = two times daily

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IMU-935 Overview

Introduction

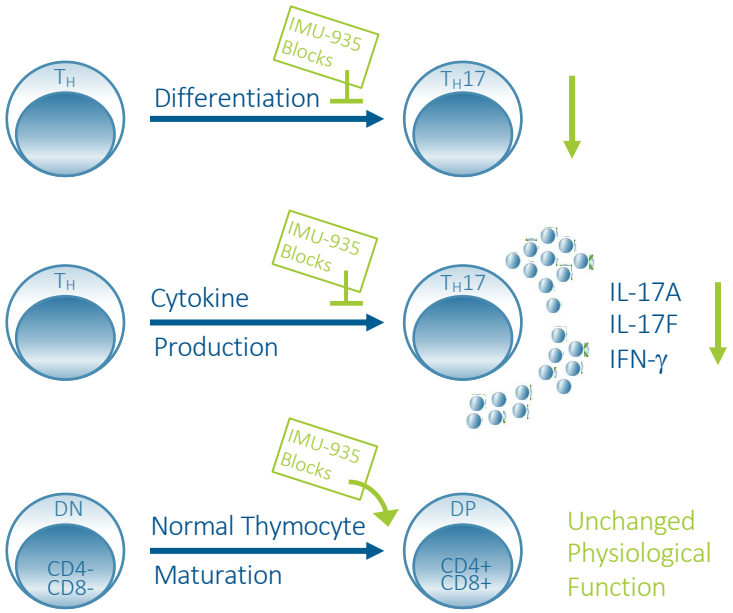
Mode of Action – *In Vitro*

Mode of Action – *In Vivo*

Phase 1

Conclusions

IMU-935 Selectively Inhibits T_H17 Differentiation and IL-17 Secretion



- The differentiation towards T_H17 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

- IMU-935 showed a good safety and tolerability profile in single and multiple ascending doses in healthy human subjects and is currently in a Phase 1C trial in psoriasis patients

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

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Thank You!

Evelyn Peelen, Ph.D.

Senior Manager Translational Pharmacology

Phone: +49 89 2080 477 27

Email: evelyn.peelen@imux.com

Web: www.imux.com

Immunic, Inc.
1200 Avenue of the Americas
New York City, NY 10036
USA

Immunic AG
Gräfelfing (Munich)
Germany

Immunic Research GmbH
Weinberg Campus
Halle (Saale)
Germany

Collaborators at City of Hope

Prof. Zuoming Sun
Dr. Hongmin Wu

Immunic Australia Pty. Ltd.
Melbourne
Australia