Immunic Therapeutics

IMU-935: Preclinical and Clinical Development Update

NASDAQ: IMUX | July 12, 2021

Cautionary Note Regarding Forward-Looking Statements

This presentation contains “forward-looking statements” that involve substantial risks and uncertainties for purposes of the safe harbor within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. These include statements regarding management’s intentions, plans, beliefs, expectations or forecasts for the future, and, therefore, you are cautioned not to place undue reliance on them. No forward-looking statement can be guaranteed, and actual results may differ materially from those projected. Immunic undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise, except to the extent required by law. We use words such as “anticipates,” “believes,” “plans,” “expects,” “projects,” “future,” “intends,” “may,” “will,” “should,” “could,” “estimates,” “predicts,” “potential,” “continue,” “guidance,” and similar expressions to identify these forward-looking statements that are intended to be covered by the safe-harbor provisions of the Private Securities Litigation Reform Act of 1995.

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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.

IMU-935: Preclinical and Clinical Development Update

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Development Pipeline

Program	Indication	Target	Preclinical	Phase 1	Phase 2	Phase 3
IMU-838	Relapsing-Remitting Multiple Sclerosis	DHODH	■	■	■	■
	Progressive Multiple Sclerosis	DHODH	■	■	■	
	Ulcerative Colitis	DHODH	■	■	■	
	Crohn's Disease	DHODH	■	■		
	Primary Sclerosing Cholangitis	DHODH	■	■	■	
IMU-935	Psoriasis	RORγt	■	■		
	Castration-Resistant Prostate Cancer	RORγt	■	■		
	Guillain-Barré Syndrome	RORγt	■	■		
IMU-856	Gastrointestinal Diseases	Intestinal Barrier Function	■	■		

■ Completed or ongoing ■ In preparation or planned

Immunic THERAPEUTICS

01

IMU-935

Introduction and Oral IL-17 Landscape

Autoimmune Diseases and IMU-935

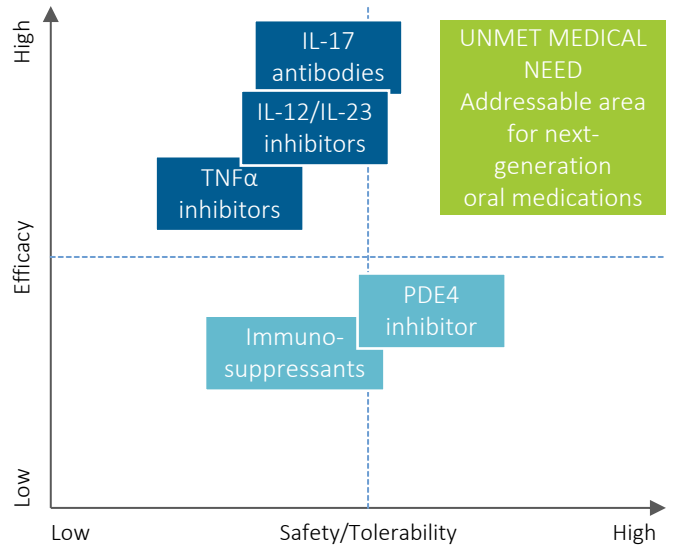
IL-17 in Autoimmune Diseases

- Autoimmune diseases affect millions of patients worldwide[1]
- Th17/IL-17/RORγt axis plays an important role in auto immunity-related diseases[2]
- Antibodies targeting this axis corroborate IL-17's role in autoimmune diseases, but are more complex, costly and less patient friendly than oral drugs[2]

Goal

- Develop an orally available and potent IL-17 inhibitor for the safe and efficacious treatment of autoimmune diseases
- Small molecule inhibitor of the pathologic functions of RORγt in autoimmune diseases without affecting physiological functions of RORγt

Unmet Need in Psoriasis Care



Strong Medical Need for Oral IL-17 Pathway Inhibitors such as IMU-935

[1] Rose, Noel R. American journal of epidemiology 2016; 183.5: 403-406 [2] Fasching, Patrizia, et al. Molecules 2017 22.1: 134
Th: T helper; IL: interleukin; TNF: tumor necrosis factor; PDE4: phosphodiesterase type 4; RORγ: retinoic acid receptor-related orphan nuclear receptor gamma

Current Landscape of Oral IL-17 Inhibitors[1]

Product	Developer	Mode of Action	Administration	Indications	Development Stage
BI730357	Boehringer Ingelheim	RORγt inverse agonist	Oral	Plaque psoriasis and psoriatic arthritis	Phase 2
Cedirogant	AbbVie	RORγt inverse agonist	Oral	Plaque psoriasis	Phase 2
AUR-101	Aurigene	RORγt inverse agonist	Oral	Psoriasis	Phase 2
IMU-935	**Immunic**	**RORγt inverse agonist**	**Oral**	**Psoriasis, Castration-Resistant Prostate Cancer, Guillain-Barré Syndrome**	**Phase 1b**
SAR-441169	Sanofi Genzyme	RORγt inverse agonist	Oral	Not disclosed	Phase 1
JTE-761	Japan Tobacco	RORγt inverse agonist	Oral	Not disclosed	Phase 1

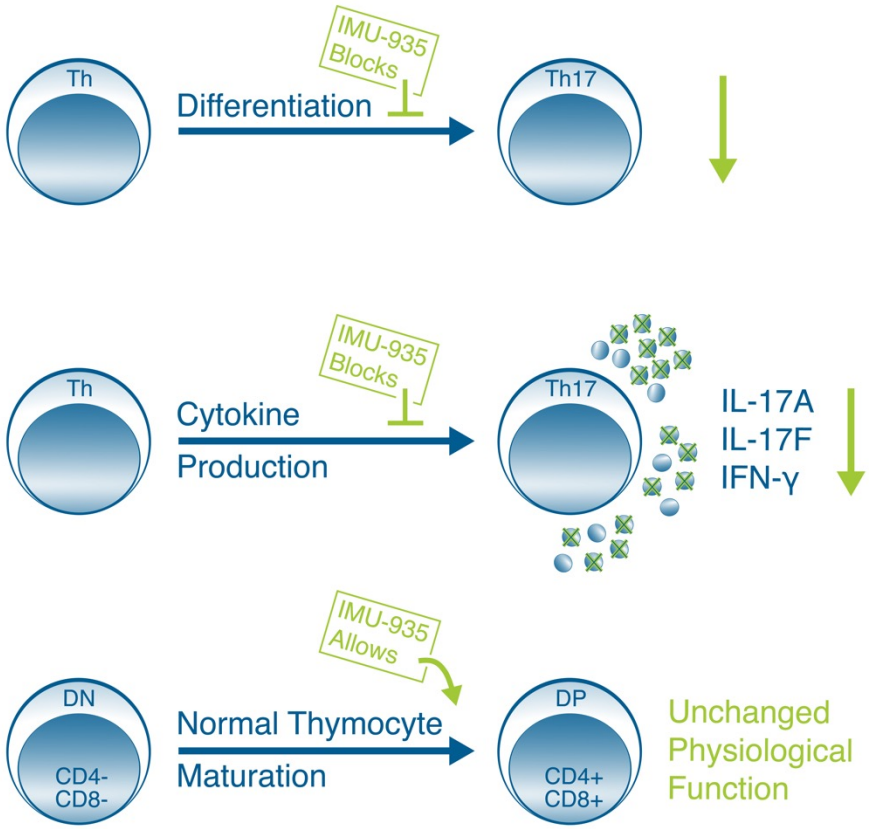
[1] Gege, C. (2021). Expert Opinion on Drug Discovery

02

IMU-935

Background Target RORγt

Main Functions of RORγt



- 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

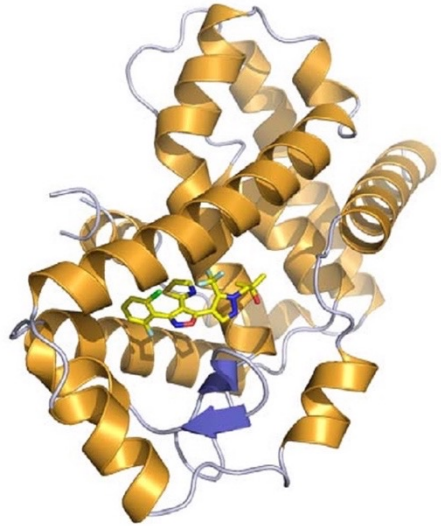
IMU-935 Has Been Observed to be Potent in Human Cells

Effect of IMU-935 in Stimulated Human PBMC at Nanomolar Concentrations

Inhibition of RORγ (20 nM) and DHODH (240 nM) leads to synergistic inhibition of cytokines associated with autoimmune diseases with 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
DHODH	0.240
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

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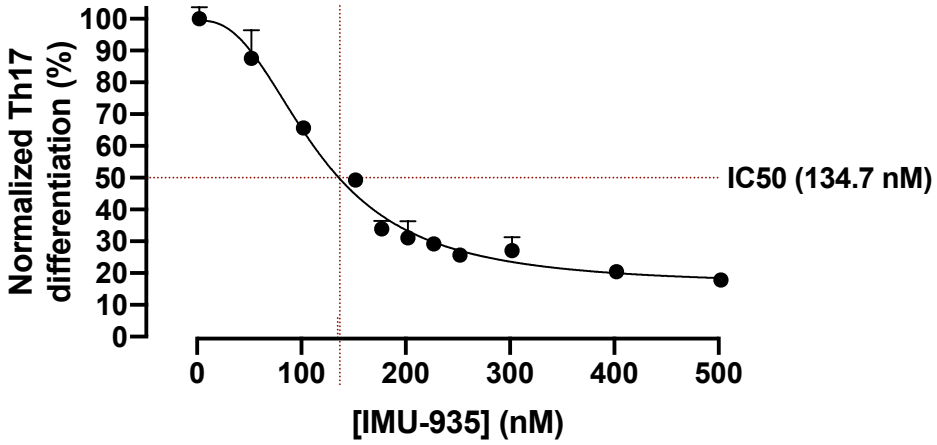
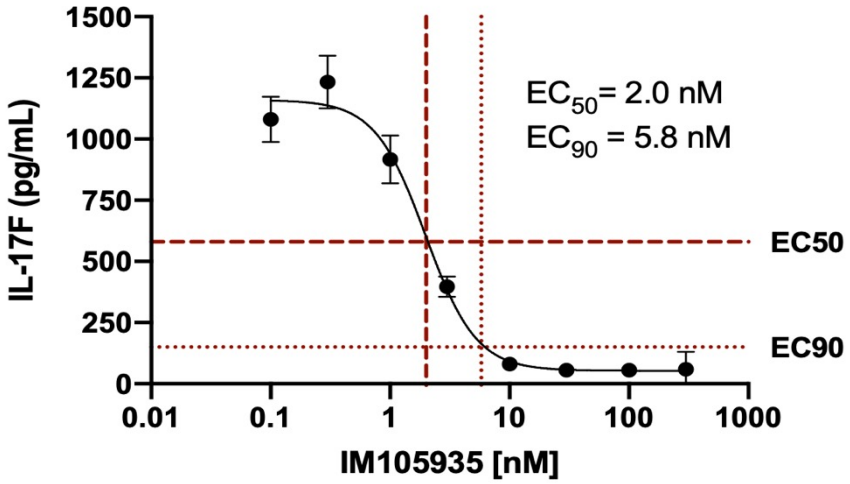
Inhibition of Th17 Differentiation and IL-17 Production

Th17 Differentiation – Murine Primary Thymocytes



The IC_{50} for Th17 differentiation of murine cells was 135 nM

IL-17F Expression – Human Primary PBMCs

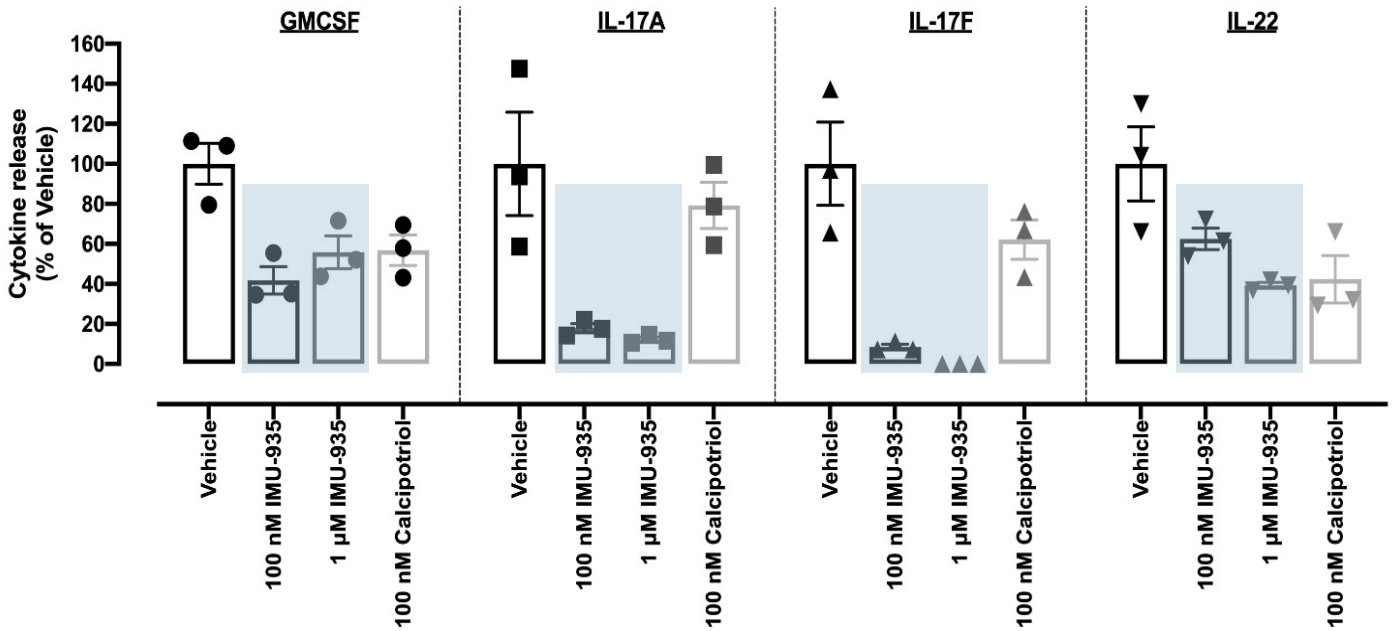


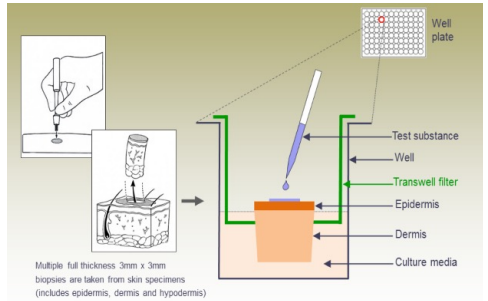
The EC_{50} for IL-17F production from stimulated human PBMCs is 2-4 nM

Zuoming Sun, City of Hope, 2020
PBMC: Peripheral Blood Mononuclear Cells; Th: T helper; IL: interleukin

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 human healthy volunteers 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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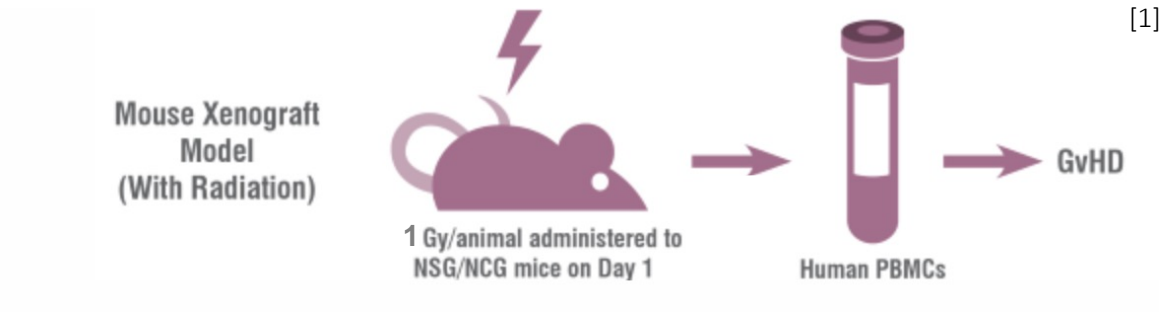
Human Graft-Versus-Host Disease and GvHD Mouse Model

Human Graft-Versus-Host Disease

- Graft-versus-host disease (GvHD) is an **immune condition** that occurs after transplant procedures when immune cells from the donor (graft cells) attack the recipient patient host's tissues
- The **disease is a side effect** that is common after an allogeneic bone marrow transplant (stem cell transplant)

Hu-PBMC-NSG™ for GvHD Studies

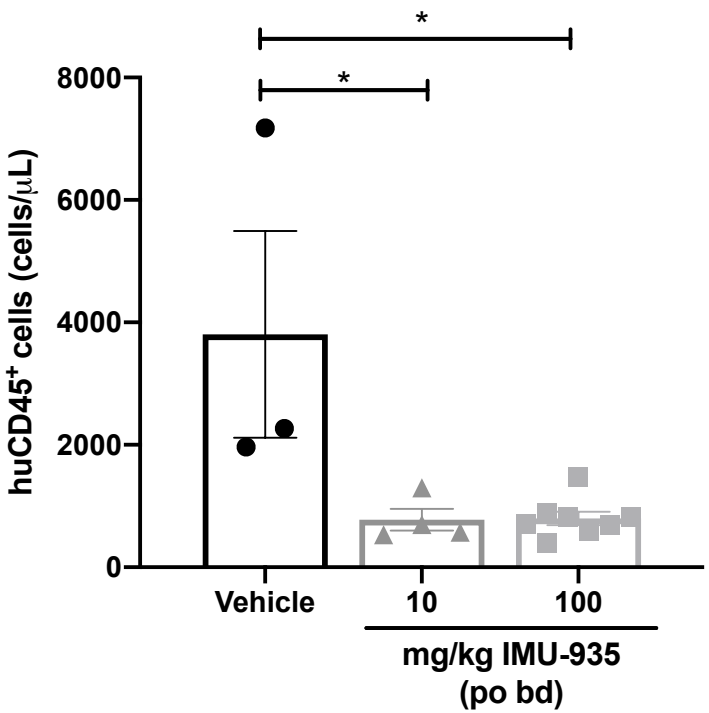


[1]

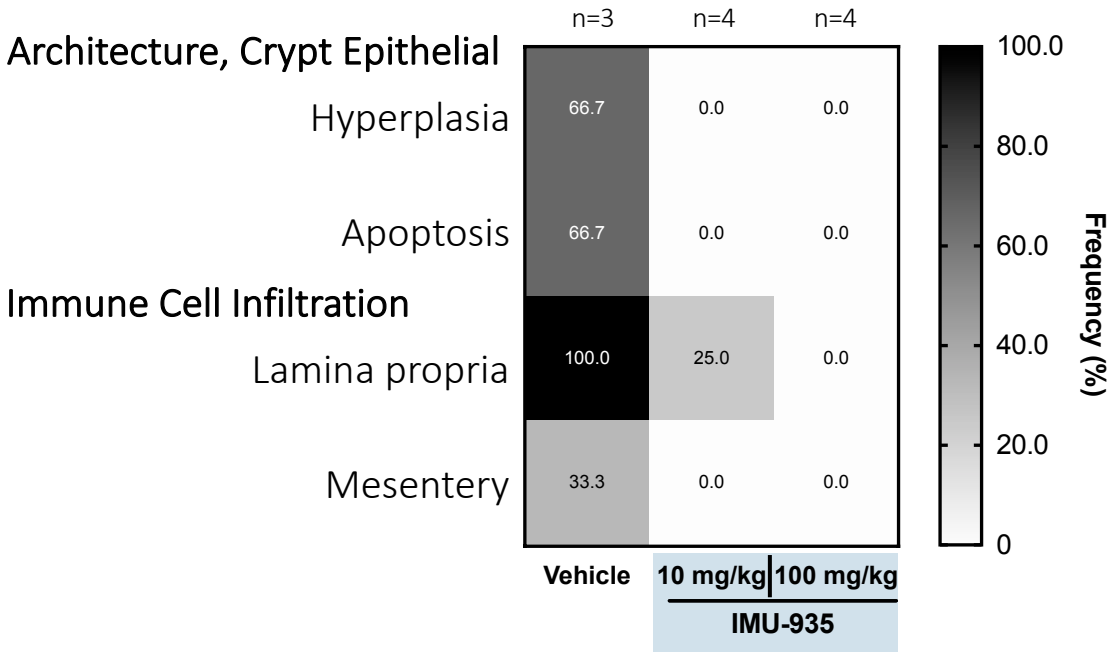
[1] Charles River Website, available at: https://www.criver.com/products-services/discovery-services/pharmacology-studies/oncology-immuno-oncology-studies/oncology-models/graft-vs-host-disease-models?region=3696

Activity of IMU-935 on GvHD is Due to a Reduction of Circulating Human T Lymphocytes

IMU-935 reduced circulating human CD45 cells (CD4⁺ and CD8⁺ T cells)



IMU-935 reduced microscopic pathology findings in the colon, typical for GvHD

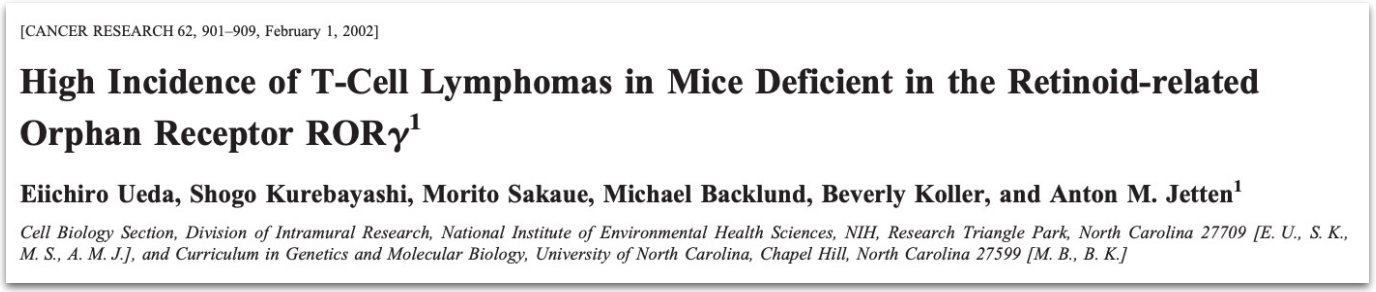


IMU-935 reduced circulating human T cells and reduced severity of the disease

GvHD: Graft-versus-Host-Disease; CD: cluster of differentiation

Challenge: RORγt Inhibition and Risk For T Cell Lymphomas

- In several publications, knock-out of RORγt was shown to correlate with a potential risk of T cell lymphomas
- Guntermann et al.[1] have shown that some small molecule inhibitors developed by Novartis and GSK show thymic aberrations
- Due to safety findings seen in animal studies by several pharma companies, some of the development projects were stopped or switched to alternative chemotypes

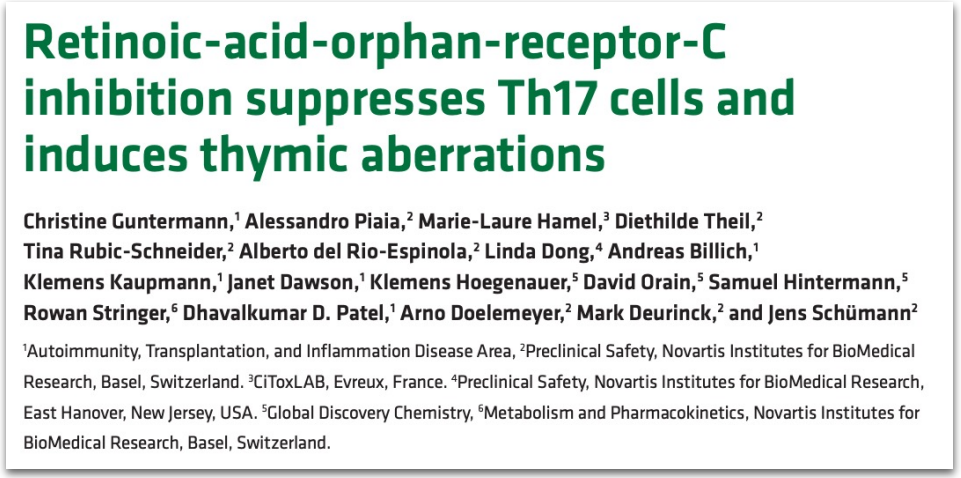


[CANCER RESEARCH 62, 901–909, February 1, 2002]

High Incidence of T-Cell Lymphomas in Mice Deficient in the Retinoid-related Orphan Receptor RORγ[1]

Eiichiro Ueda, Shogo Kurebayashi, Morito Sakaue, Michael Backlund, Beverly Koller, and Anton M. Jetten[1]

Cell Biology Section, Division of Intramural Research, National Institute of Environmental Health Sciences, NIH, Research Triangle Park, North Carolina 27709 [E. U., S. K., M. S., A. M. J.], and Curriculum in Genetics and Molecular Biology, University of North Carolina, Chapel Hill, North Carolina 27599 [M. B., B. K.]



Retinoic-acid-orphan-receptor-C inhibition suppresses Th17 cells and induces thymic aberrations

Christine Guntermann,[1] Alessandro Piaia,[2] Marie-Laure Hamel,[3] Diethilde Theil,[2] Tina Rubic-Schneider,[2] Alberto del Rio-Espinola,[2] Linda Dong,[4] Andreas Billich,[1] Klemens Kaupmann,[1] Janet Dawson,[1] Klemens Hoegenauer,[5] David Orain,[5] Samuel Hintermann,[5] Rowan Stringer,[6] Dhavalkumar D. Patel,[1] Arno Doelemeyer,[2] Mark Deurinck,[2] and Jens Schümann[2]

[1]Autoimmunity, Transplantation, and Inflammation Disease Area, [2]Preclinical Safety, Novartis Institutes for BioMedical Research, Basel, Switzerland. [3]CiToxLAB, Evreux, France. [4]Preclinical Safety, Novartis Institutes for BioMedical Research, East Hanover, New Jersey, USA. [5]Global Discovery Chemistry, [6]Metabolism and Pharmacokinetics, Novartis Institutes for BioMedical Research, Basel, Switzerland.

[1] Guntermann et al. JCI Insight. 2017;2(5):e91127

In Contrast to Full Knock-Out, RORγt Functions Can be Uncoupled[1]

Mutation Studies Show Variable Contribution of Protein Sequences to Different Phenotypes

Exchange of leucine 93 to alanine leads to **loss of Th17 differentiation capacity but maintains thymocyte maturation physiological function**

Nat Immunol. 2017 October ; 18(10): 1128–1138. doi:10.1038/ni.3832.

Two amino acid mutation disrupts RORγt function in Th17 differentiation but not thymocyte development

Zhiheng He[1,#], **Jian Ma**[1,#], **Ruiqing Wang**[1,2], **Jing Zhang**[1,2], **Zhaofeng Huang**[3], **Fei Wang**[1], **Subha Sen**[1], **Ellen V. Rothenberg**[4], and **Zuoming Sun**[1,*]

[1]Division of Molecular Immunology, Beckman Research Institute of City of Hope, Duarte, CA, United States

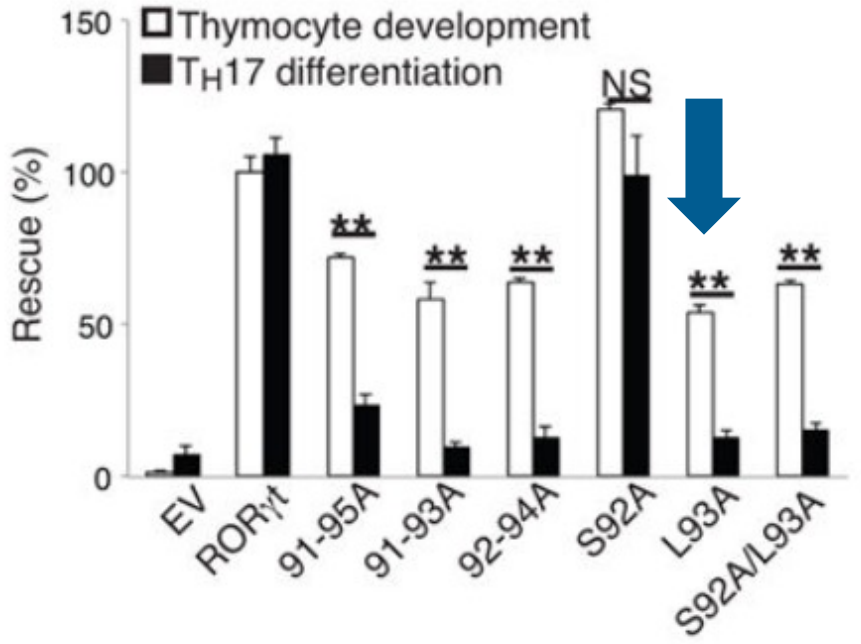
[2]Irell & Manella Graduate School of Biological Sciences, City of Hope, Duarte, CA, United States

[3]Zhongshan School of Medicine, Sun Yat-sen University, Guangzhou, Guangdong, P.R. China

[4]Division of Biology & Biological Engineering, California Institute of Technology, Pasadena, California, USA

L93A Mutation in RORC Leads to Selective TH17 Inhibition

ALA scan of Hinge region and DBD c-terminal region resulted in L93A exchange relevant for selectivity



[1] He et al. Nat. Immunol. 2017, 18, 1128-1138

Immunic THERAPEUTICS

03

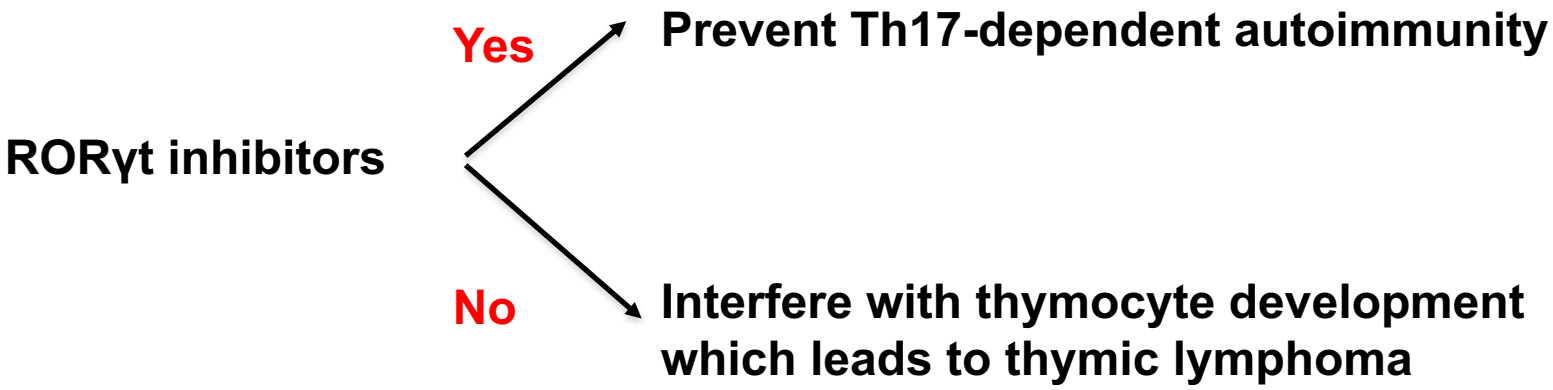
Inhibition of RORγt-Dependent Th17 But Not Thymocyte Function by IMU-935

Zuoming Sun, Ph.D.

Professor, Department of Molecular Imaging & Therapy

City of Hope,
Duarte, CA, USA

Potential Issue With RORγt Inhibitors: Lymphoma



Is it possible to have a RORγt inhibitor specifically targeting Th17 but not thymocytes?

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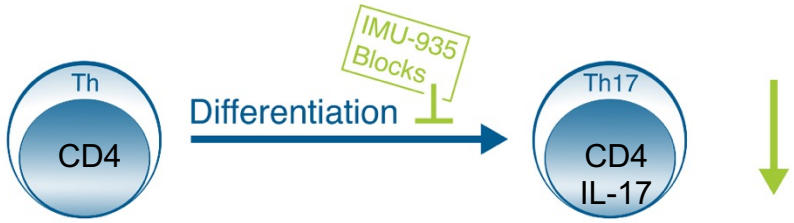
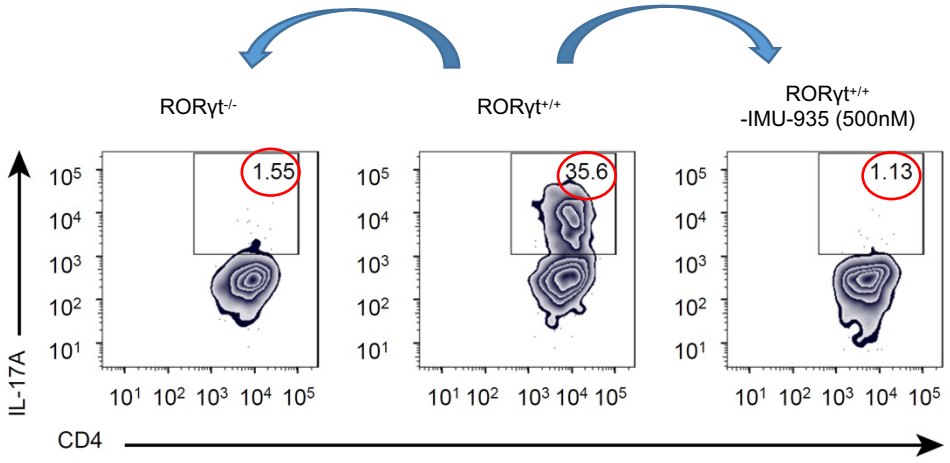
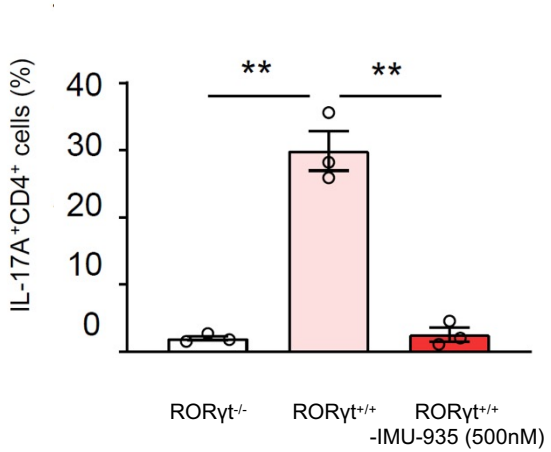
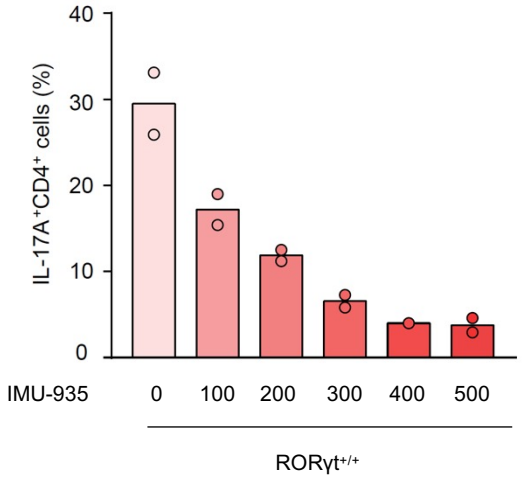
IMU-935 Inhibits Th17 Differentiation in a Dose Dependent Manner



In vitro Th17 differentiation







Th17 cells are positive for the surface marker CD4 and express/produce IL-17A, IL-17F and other cytokines

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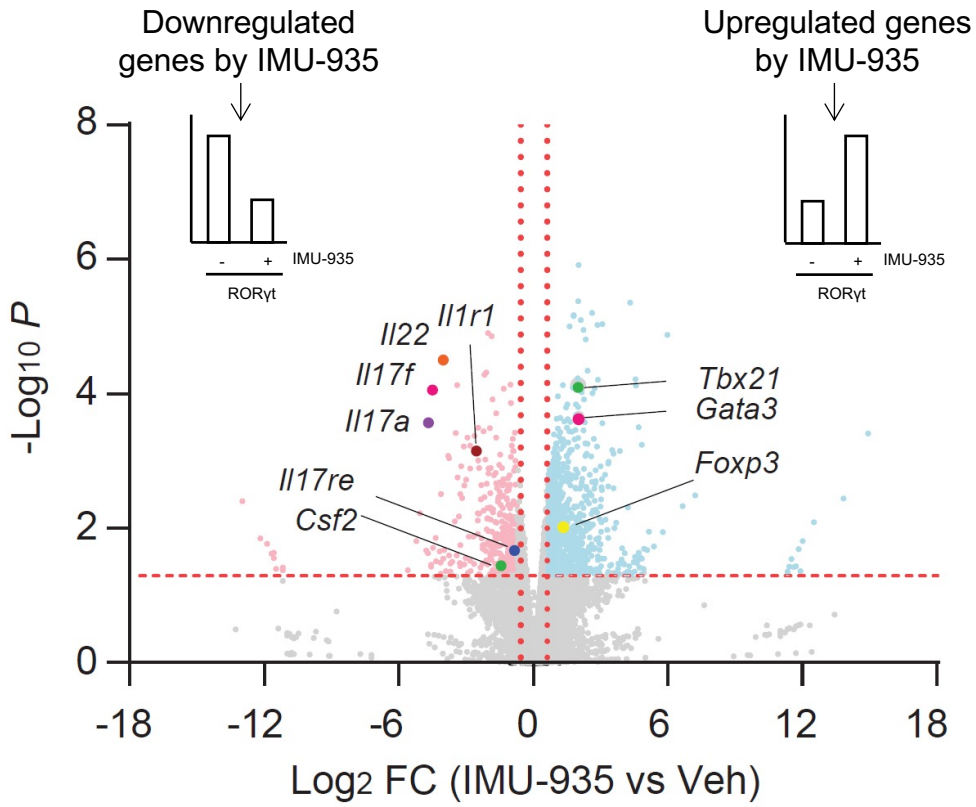
IMU-935 Modulates RORγ-Related Gene Expression Under Th17 Differentiation Conditions



Volcano plot showing DEGs by IMU-935

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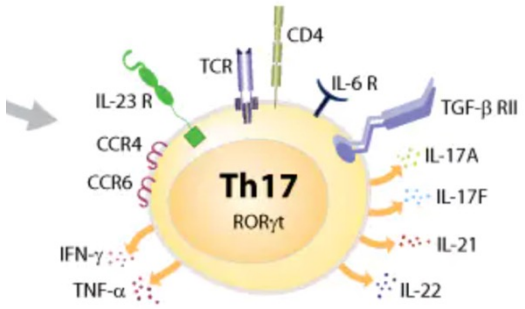
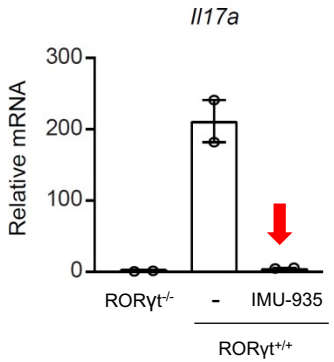
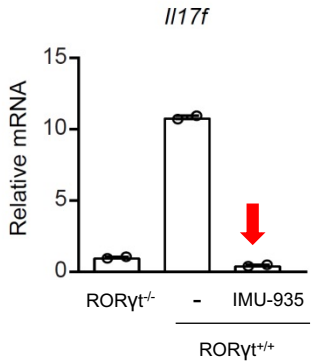
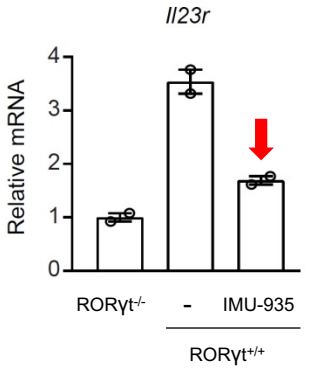
Repression of Typical Th17 Genes by IMU-935

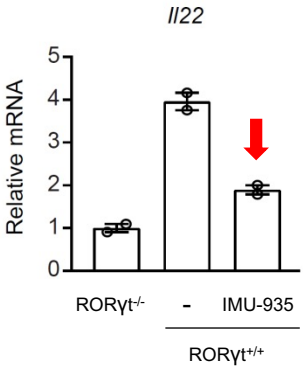
- Murine primary thymocytes, Th17 differentiation condition, 500 nM IMU-935 (CPD#1)











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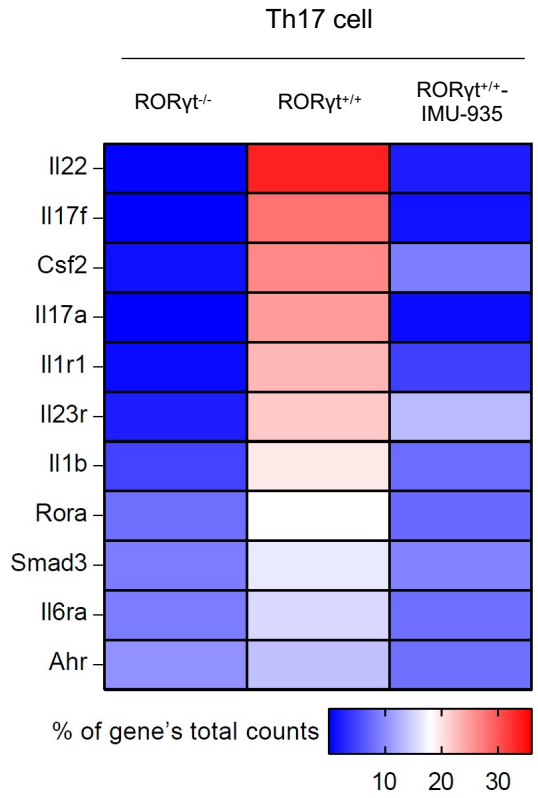
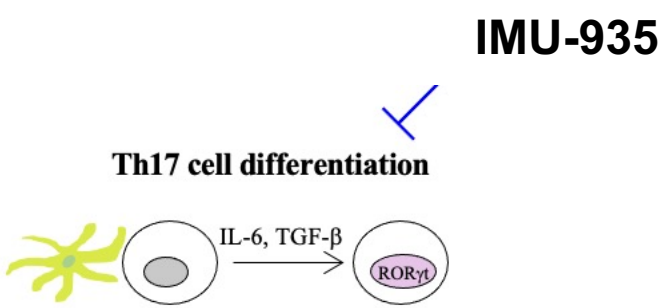
IMU-935 Blocks Th17 Differentiation and Modifies Gene Expression Profiles

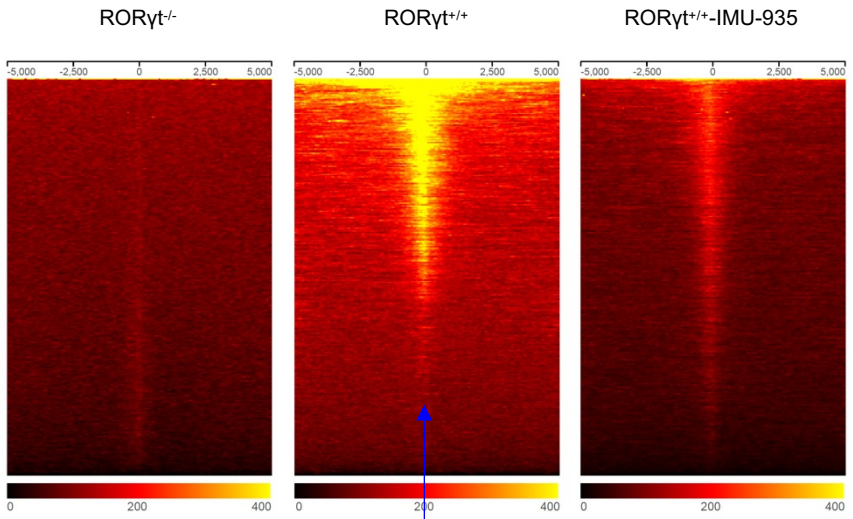




Similar gene expression pattern for Th17 signature genes in RORγt knockout and wild type cells treated with IMU-935

IMU-935 Attenuates RORγt Genome-Wide DNA-Binding in Th17 Cells

TSS plot

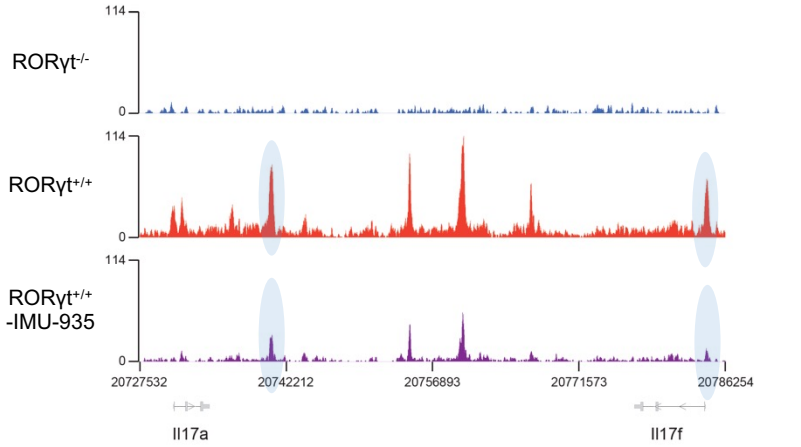


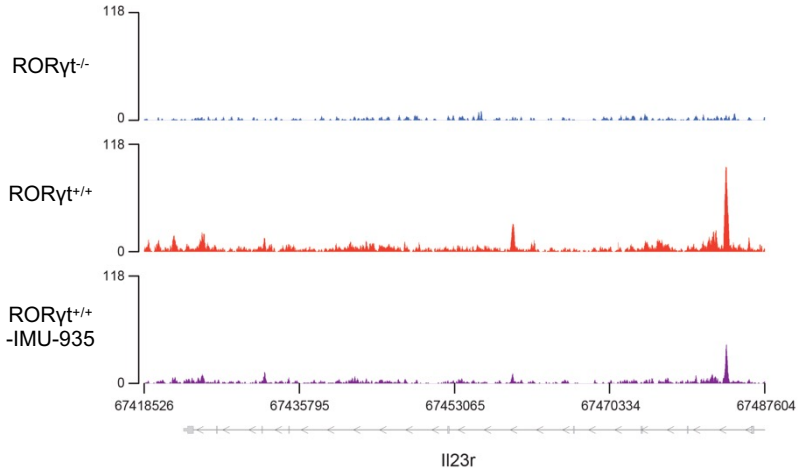
TSS plot: a common visualization method to obtain a global evaluation of enrichment around the transcription start site (TSS)

RORγt protein binds to ~3000 gene loci in murine cells under Th17 differentiation conditions

Negative control: In RORγt knockout cells no binding to DNA
loci can be detected in murine cells under Th17 differentiation conditions

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





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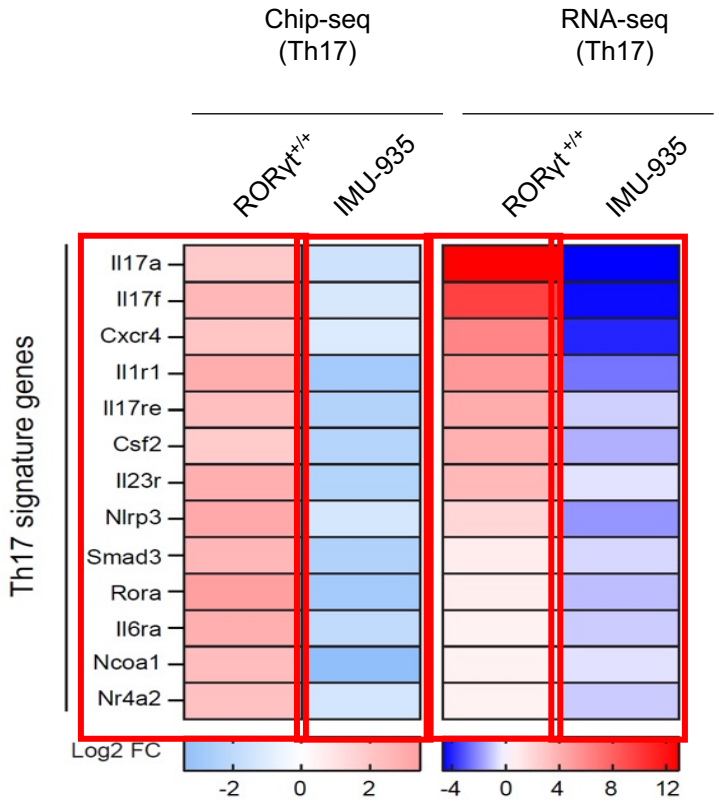
IMU-935 Attenuates RORγt DNA-Binding and Inhibits Expression of Genes Critical for Th17 Cells



IMU-935 leads to reduced binding of RORγt to DNA loci relevant for Th17 differentiation

This decreased binding leads to strongly reduced mRNA expression of the according genes

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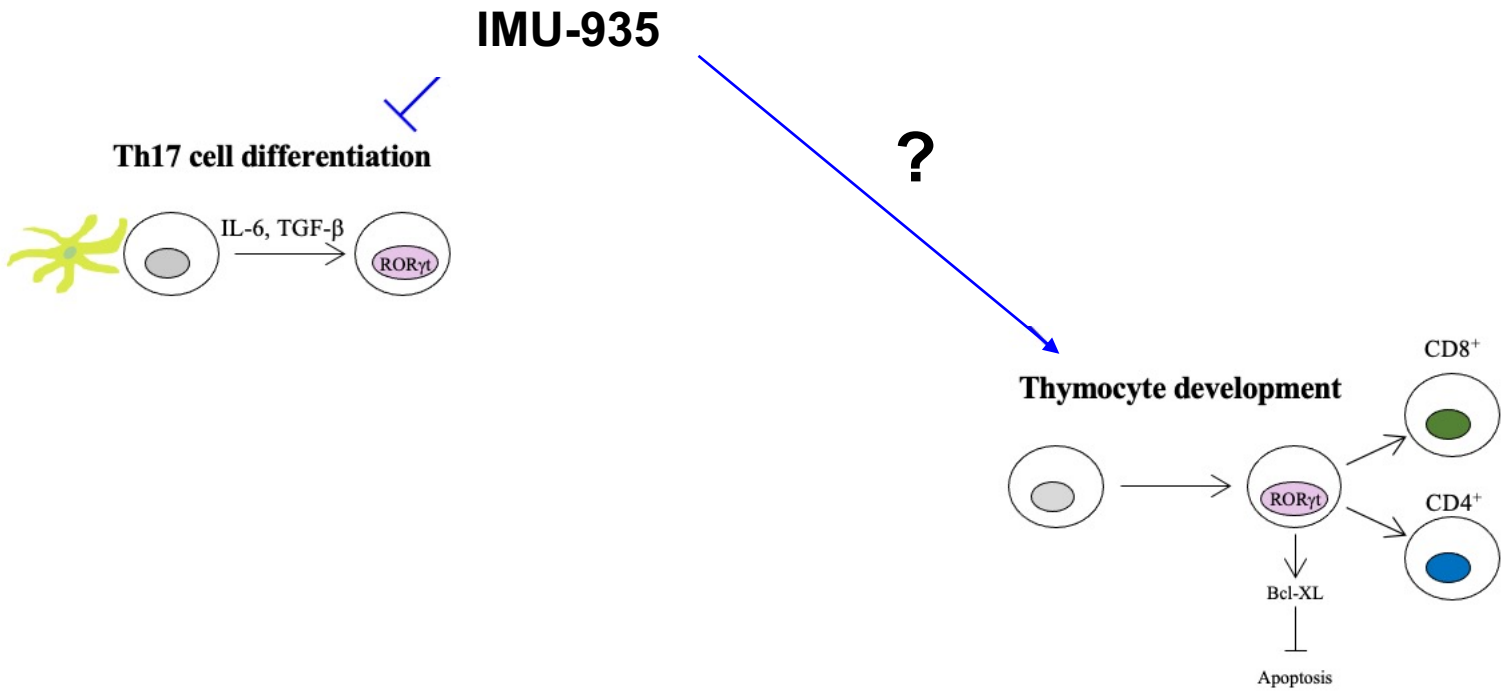
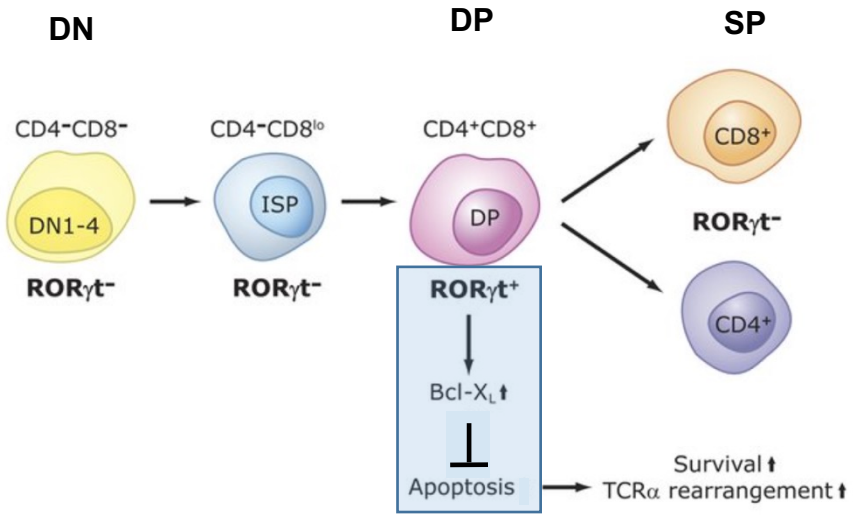
IMU-935 Blocks Th17 Differentiation – What Happens With Thymocytes?

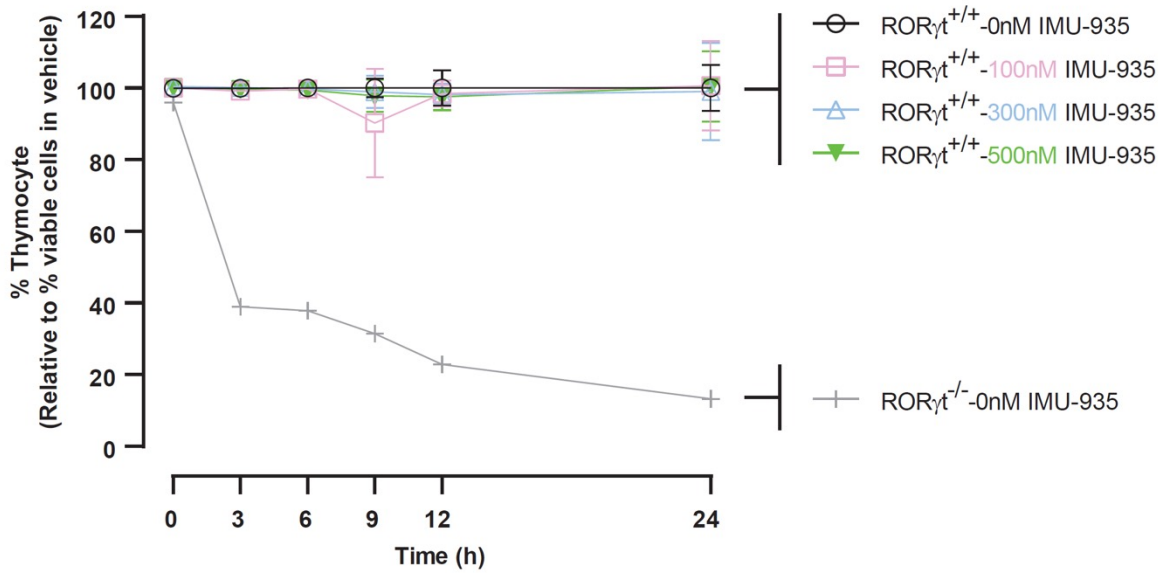


IMU-935 Does Not Impact Survival Signals During Thymocyte Maturation

- RORγt provides a **survival** signal during thymocyte maturation by upregulating the anti-apoptotic gene Bcl-XL



- Deletion of RORγt by knockout reduces the **survival/viability** of thymocytes, whereas blocking RORγt by IMU-935 does not



Nuclear receptor signaling 2009, doi: 10.1621/nrs.07003

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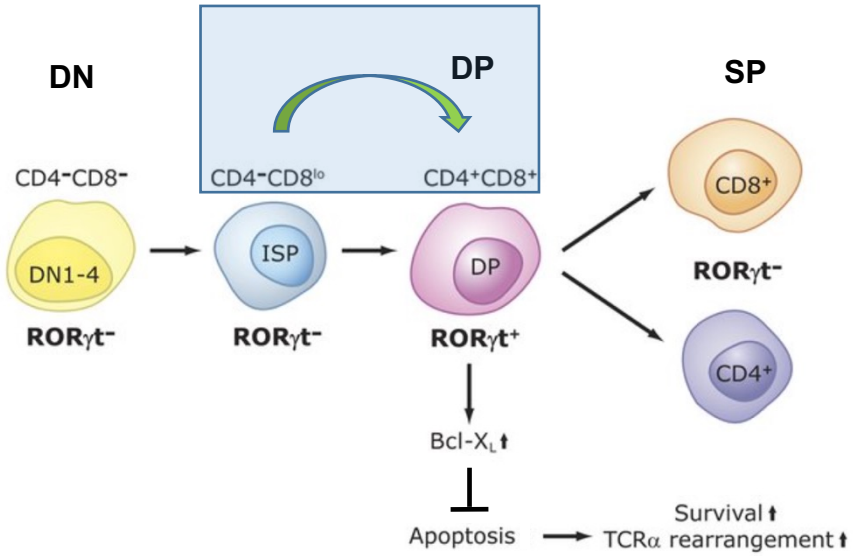
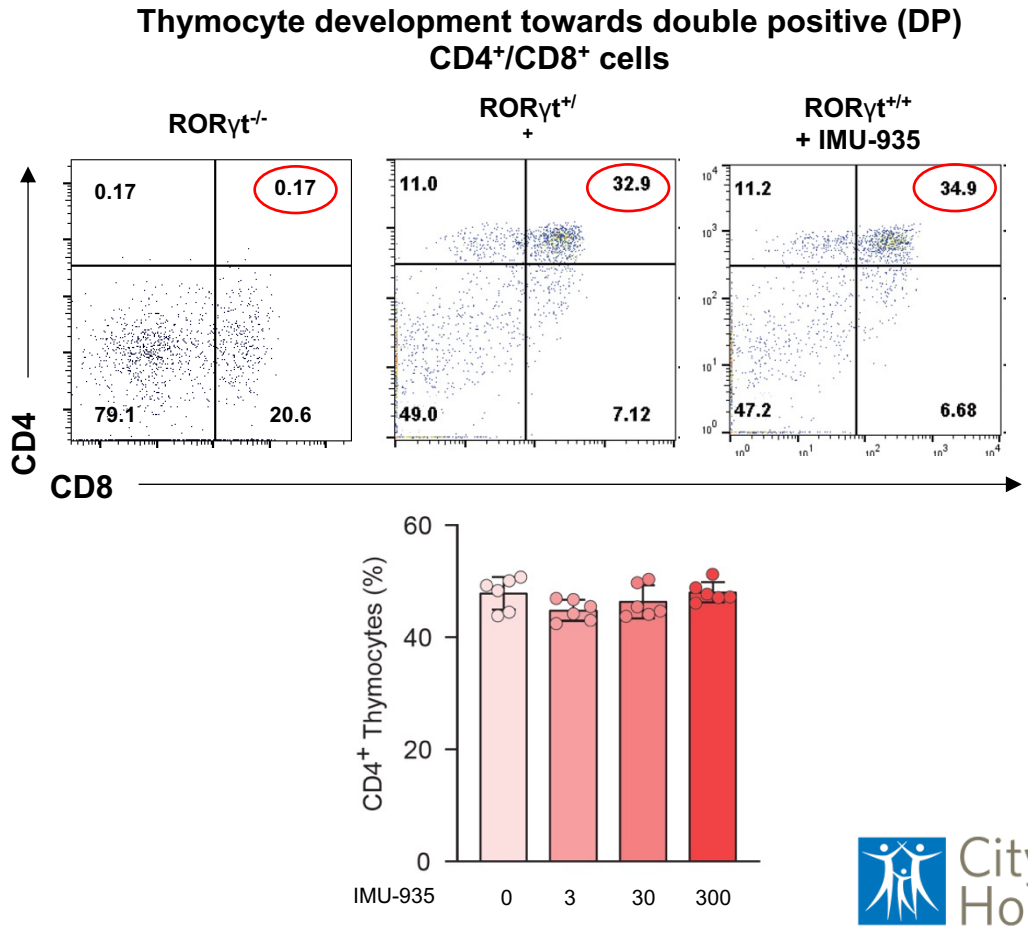
IMU-935 Does Not Impact Production of CD4⁺/CD8⁺ Cells During Thymocyte Maturation

- RORγt promotes the differentiation of ISP into DP cells



- Deletion of RORγt by knockout reduces the number of DP cells, whereas blocking RORγt by IMU-935 does not



Nuclear receptor signaling 2009, doi: 10.1621/nrs.07003

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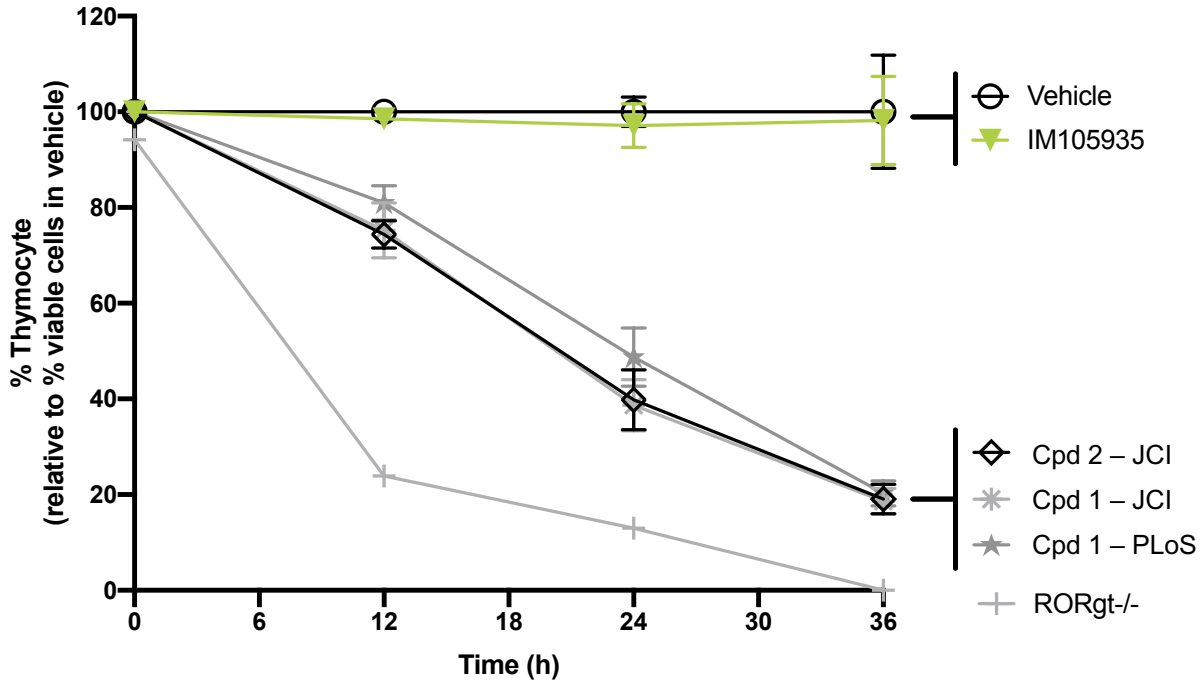
IMU-935 Does Not Induce Thymocyte Apoptosis

- In contrast to IMU-935, comparator compounds have a negative impact on thymocyte viability and therefore bear the T cell malfunction and risk of lymphoma.



Compound Name	Measured Activity	Literature Reference
Cpd 2 - JCI	Gal4: EC_{50} = 6.0 nM	Reported to induce progressive thymic alterations. JCI Insight. 2017;2(5):e91127.
Cpd 1 - JCI	Gal4: EC_{50} = 7.9 nM	Reported to induce progressive thymic alterations. JCI Insight. 2017;2(5):e91127.
Cpd 1 - PLoS	Gal4: EC_{50} = 46 nM	Reported to induce thymic aberrations. PLoS One 2017 Nov 20;12(11):e0188391.

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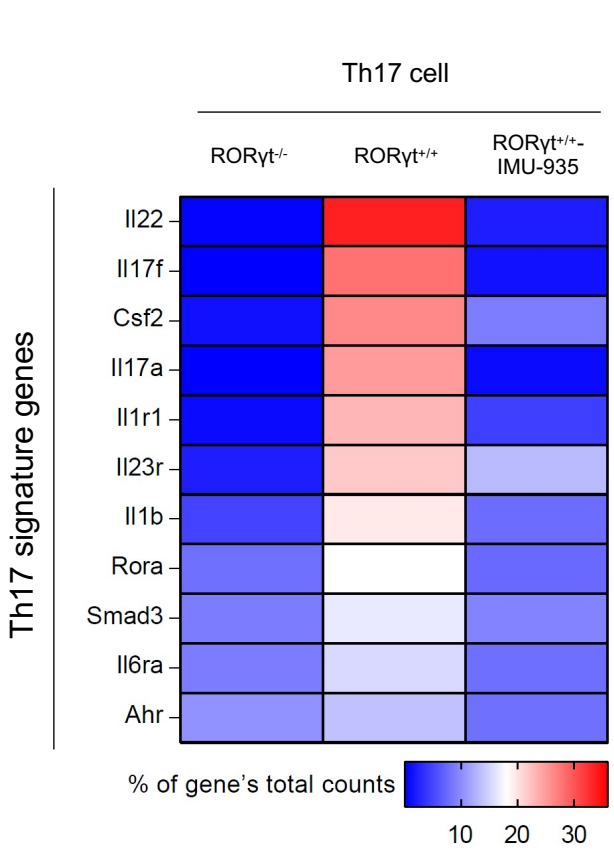
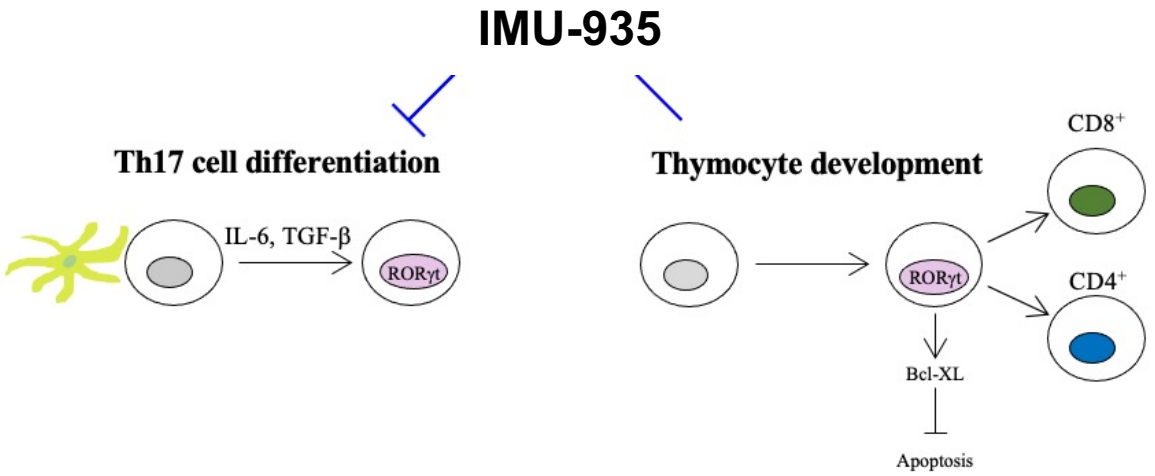
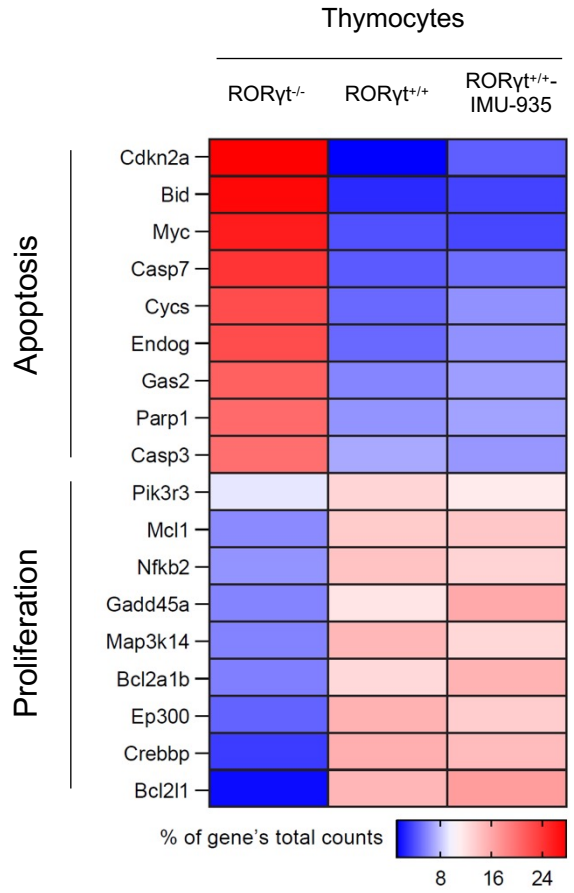
IMU-935 Blocks Th17 Differentiation But Allows Normal Thymocyte Maturation: Gene Expression Profiles







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 proliferation signature genes in **RORγ knockout** and **IMU-935 treatment**, but similar for RORγ$^{+/+}$

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Summary

RORγt has two critical functions:

- **Th17 cells**
  - Generation of Th17 cells that mediate autoimmune diseases
- **Thymocytes**
  - Thymocyte development by regulating survival and proliferation

Challenge:

- Deletion of RORγt gene or RORγt inhibitors may increase the potential risk of lymphoma

Differential effects of IMU-935 on Th17 cells and thymocytes:

- **IMU-935 inhibits the generation of Th17 cells**
  - IMU-935 inhibits Th17 differentiation
  - IMU-935 inhibits Th17 signature genes
  - IMU-935 inhibits pathways critical for generating Th17 cells
- **IMU-935 does not affect thymocyte development**
  - IMU-935 does not affect thymocyte development
  - IMU-935 does not induce thymocyte apoptosis
  - IMU-935 does not affect expression of the genes critical for thymocyte function

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04

IMU-935

Q&A RORγt

05

IMU-935

Clinical Development Status

Phase 1 Clinical Trial of IMU-935: Design and Status

PART A

Evaluation of single ascending doses (SAD)

—

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

- Dose escalation completed (still blinded)
- IMU-935 was well-tolerated and showed dose-linear PK
- Food effect cohort ongoing

PART B

Evaluation of multiple ascending doses (MAD)

—

Healthy volunteers randomized to receive 14-day treatment of either IMU-935 or placebo

- Currently ongoing
- First multiple dose cohort completed (data evaluation ongoing, still blinded)

PART C

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

- Expected to start in Q3/2021
- Initial human data expected to be available in Q2/2022

PK: pharmacokinetics

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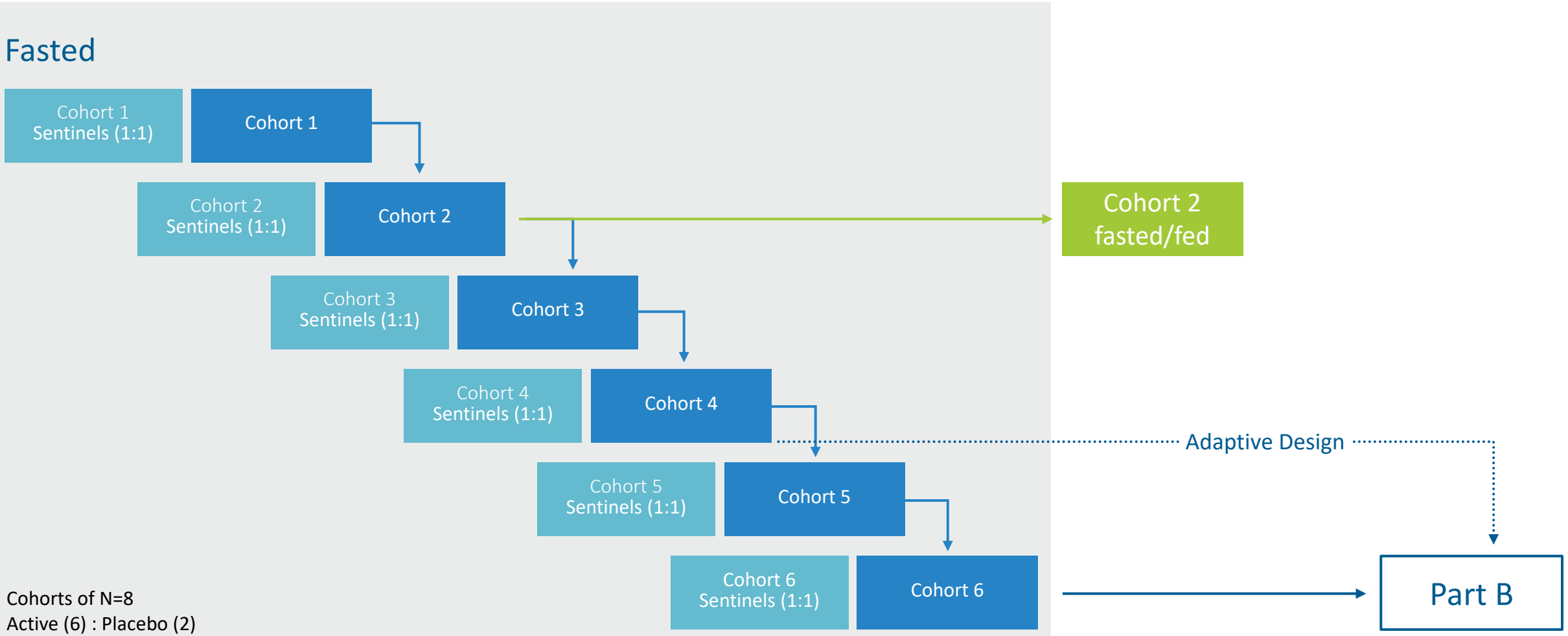
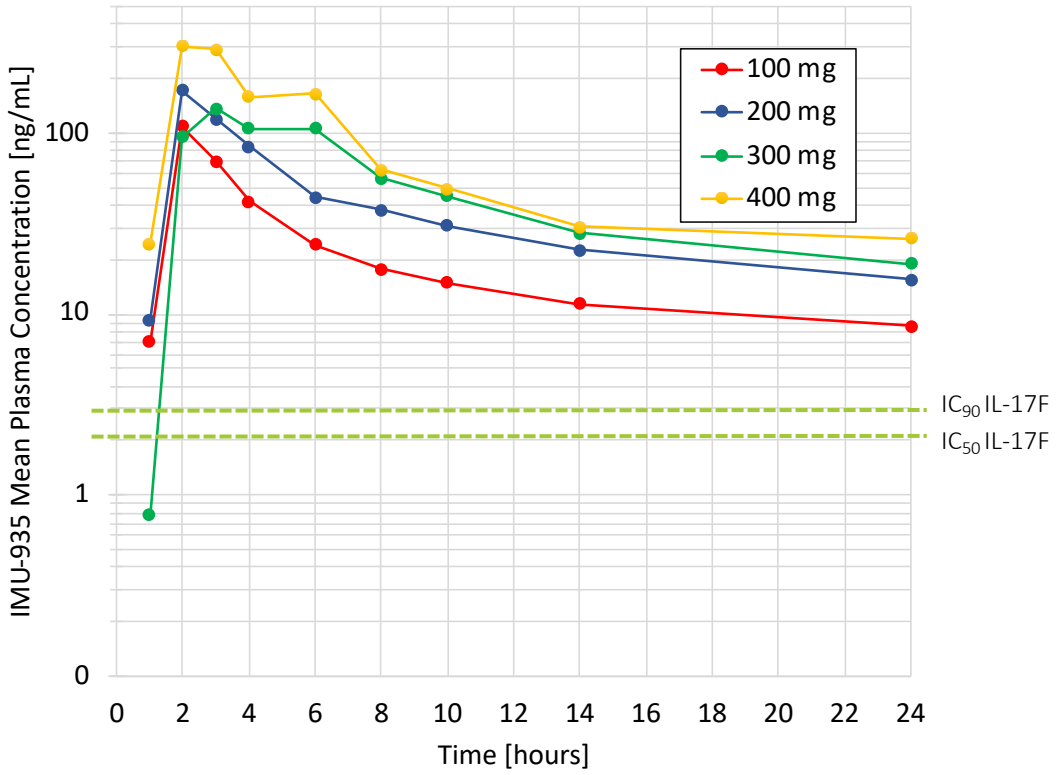
Adaptive Transition from Part A (SAD) to Part B (MAD)



Phase 1 Clinical Trial: Interim SAD Pharmacokinetic Results

New Formulation With Dose-Linear AUC



Plasma half-life new formulation: 17-26 h

T_{max}: 2.2-3.8 h

Average Pharmacokinetic Variables

Dose	C_{max} ng/mL	T_{max} (hours)	AUC_{inf} (h* ng/mL)
100 mg (3N)	119	2.20	755
200 mg (4N)	195	2.83	1440
300 mg (5N)	182	3.83	1710
400 mg (6N)	479	2.83	2940

Preliminary data

AUC: area under the curve; h: hours; C_{max}: maximum (peak) plasma drug concentration; T_{max}: time to reach maximum (peak) plasma concentration; AUC_{inf}: area under the concentration-time curve to infinity

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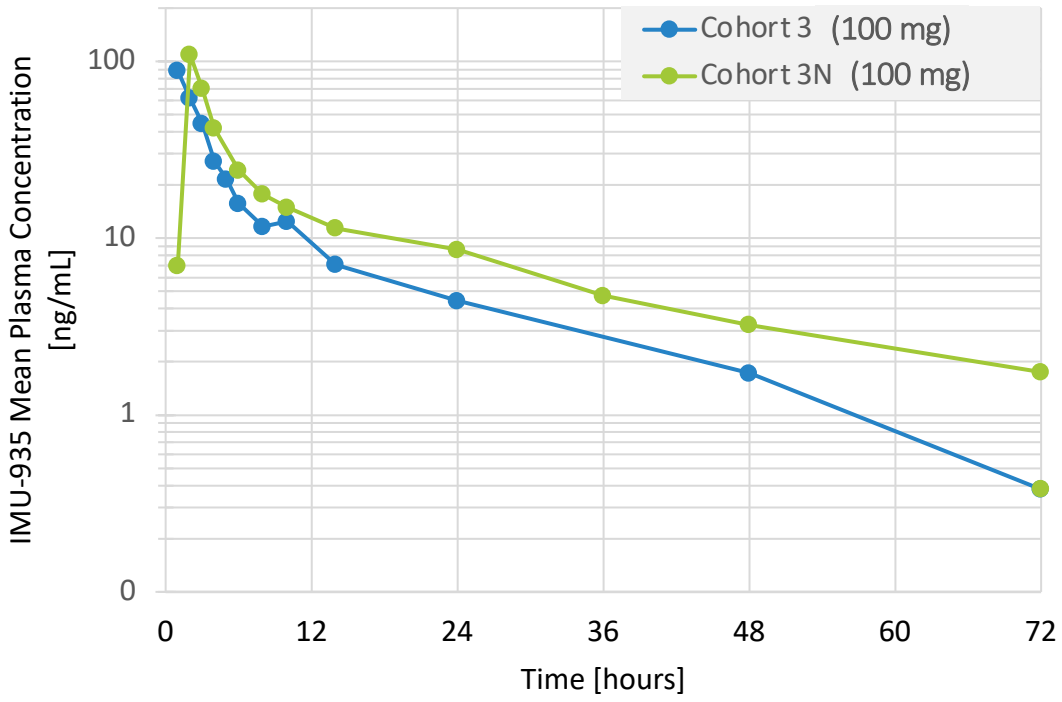
Phase 1 Clinical Trial: Interim SAD Pharmacokinetic Results

Comparison of Lipid-Based and New Formulation

IMU-935 Concentration Time Profiles (Log-Linear Scale)



Comparable Pharmacokinetics of Two Different IMU-935 Oral Formulations

Pharmacokinetic Parameters (Mean)	Cohort 3 (N=6) 100 mg Lipid-Based Formulation	Cohort 3N (N=6) 100 mg New Formulation
C_{max} (ng/mL)	95.7	119
T_{max} (hr)	1.33	2.2
$t_{1/2}$ (hr)	16.88	26.05
$AUC_{0\text{-}inf}$ (hr*ng/mL)	515	755

Non-compartmental analysis of plasma kinetics

Successful switch from lipid-based pilot formulation to new powder in a capsule formulation with improved properties

Preliminary data

C_{max}: maximum (peak) plasma drug concentration; T_{max}: time to reach maximum (peak) plasma concentration; hr: hours; $t_{1/2}$: half-life; $AUC_{0\text{-}inf}$: area under the concentration-time curve from zero to infinity

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Phase 1 Clinical Trial: Interim Blinded SAD Safety Results

Blinded Safety Data Does Not Indicate Safety Signals

	Number (%) of Subjects With TEAEs [Number of TEAEs Reported]				
	IMU-935 100 mg 3N (N=7)	IMU-935 200 mg 4N (N=8)	IMU-935 300 mg 5N (N=8)	IMU-935 400 mg 6N (N=8)	Total (N=31)
TEAEs	7 (100%) [11]	6 (75%) [21]	4 (50%) [14]	7 (88%) [13]	24 (77%) [59]
Study Drug Related TEAEs	1 (14%) [2]	3 (38%) [7]	1 (13%) [1]	4 (50%) [5]	9 (29%) [15]
Moderate or Severe TEAEs	-	2 (25%)* [2]	-	-	2 (6%) [2]
Study Drug Related, Moderate or Severe TEAEs	-	1 (13%)** [1]	-	-	1 (3%) [1]
Subjects with SAEs	-	-	-	-	0 (0%)

Benign Safety Profile

- No dose-dependency in adverse events
- No systematic findings in electrocardiogram or vital signs
- No systematic changes in laboratory parameters
- No maximum tolerated dose reached

Blinded data, i.e., the current TEAEs cannot be assigned yet to the IMU-935 or placebo treatment arms; subjects were randomized 3:1; * Moderate events of headache (related) and frozen shoulder/shoulder pain (unrelated) ; ** Moderate event of headache
TEAE: treatment-emergent adverse event; SAE: serious adverse event

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Phase 1 Clinical Trial: Interim Blinded SAD Safety Results

Related Adverse Events by Incidence

MedDRA Preferred Term	Number (%) of Subjects With Related TEAEs Occurring in ≥ 2 Subjects [Number of TEAEs Reported]				
	IMU-935 100 mg 3N (N=7)	IMU-935 200 mg 4N (N=8)	IMU-935 300 mg 5N (N=8)	IMU-935 400 mg 6N (N=8)	Total Subjects (N=31)
Constipation		1 (13%) [1]		2 (25%) [2]	3 (10%) [3]
Headache		1 (13%) [1]	1 (13%) [1]		2 (6%) [2]
Abdominal Distension		2 (25%) [2]			2 (6%) [2]

Blinded data; subjects were randomized 3:1
TEAE: treatment-emergent adverse event

Phase 1 Clinical Trial: Part C in Psoriasis Patients

Study Design

- 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 will receive 28 days of daily treatment (QD or BID)
- Up to 52 psoriasis patients will be enrolled in 2 cohorts:
  - A cohort of 16 patients will receive a low dose of IMU-935 or placebo (at a ratio of 3:1)
  - A cohort of 36 patients will receive a high dose of IMU-935 or placebo (at a ratio of 3:1)
- Expected to start in Q3/2021

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

Phase 1 Clinical Trial: Part C in Psoriasis Patients

Eligibility Criteria

- Age 18 to 65 years (inclusive)
- Diagnosis of chronic plaque-type psoriasis for at least 6 months:
  - PASI score ≥ 10, or PASI score < 10 and DLQI score >10, plus
  - Psoriasis BSA involvement ≥ 10%, plus
  - PGA score ≥ 3
- Failed to fully respond to or is intolerant and/or has a contraindication to at least one topical therapy for psoriasis

Key Objectives/Endpoints

Primary:

- Safety and tolerability

Secondary:

- Trough plasma concentrations of IMU-935
- Effects on skin symptoms (PASI, DLQI, BSA, PGA, itch rating scale)

Exploratory:

- Pharmacodynamic markers (skin biopsies, cytokines)

PASI: Psoriasis Area and Severity Index; DLQI: Dermatology Quality of Life Index; BSA: body surface area; PGA: Physician Global Assessment

06

IMU-935

Preclinical Anti-Cancer Activity

Prostate Cancer

Introduction & Definitions

- Metastatic prostate cancer has spread to the bone, distant lymph nodes or other parts of the body.
- Evidence of disease progression while being treated with androgen deprivation therapy (ADT) and having castrate levels of serum testosterone (<50 ng/dL) is considered **castration-resistant prostate cancer (CRPC)**.
- The standard staging system for newly diagnosed prostate cancer is that of the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC).

CLASSIFICATION	DEFINITION
TUMOR	
Tx	Tumor cannot be evaluated (due to lack of information)
T0	No evidence of a primary tumor
T1*	Tumor was not detected during a digital rectal exam (DRE) and cannot be seen on imaging studies (tumor may be discoverd during surgery for a reason other cancer)*
T2 T2a T2b T2c	Tumor can be detected during a DRE but is present in the prostate only Tumor is in half or less than one side (lobe) of the prostate Tumor is in more than half of one prostate lobe, but has not yet invaded the other lobe Tumor is in both prostate lobes
T3 T3a T3b	Tumor extends outside of the prostate Tumor extends outside the prostate on one or both sides Tumor has spread to the seminal vesicles (the glands on each side of the bladder)
T4	Tumor has spread to tissues near the prostate other than the seminal vesicles, such as the bladder or wall of the plevis
Nearby (regional) lymph nodes (N)	
Nx	Nearby lymph nodes are not evaluated
N0	No cancer cells are found in nearby lymph nodes
N1	Cancer cells are found in nearby lymph nodes
Distant Metastasis (M)	
M0 M1 M1a M1b M1c	Cancer has not spread beyond the prostate Cancer has spread beyond the prostate Cancer has spread to distant lymph nodes Cancer has spread to bone Cancer has spread to another organ or site, with or without bone disease

The American Joint Committee on Cancer (AJCC) TNM Staging

Standard of Care in Metastatic Castration-Resistant Prostate Cancer (mCRPC)

ESMO Guidelines

- Abiraterone or enzalutamide is recommended for asymptomatic/ mildly symptomatic men with chemotherapy-naive mCRPC
- Docetaxel is recommended for men with mCRPC
- In the post-docetaxel setting, abiraterone, enzalutamide and cabazitaxel are recommended options
- ^{223}Ra is recommended for men with bone-predominant, symptomatic mCRPC
- The use of a second AR inhibitor (abiraterone after enzalutamide or vice versa) is not recommended
- When androgen receptor splice variant 7 (AR-V7) is detected in circulating tumor cells, **patients are less likely to respond to abiraterone and enzalutamide than AR-V7-negative patients**

Table 1. Stage-matched therapeutic strategies

Localised disease	Low risk	Active surveillance Brachytherapy RP Radical RT
	Intermediate risk	RP Radical RT ± neoadjuvant ADT Brachytherapy Active surveillance
	High risk	Long-term ADT + radical RT ± neoadjuvant docetaxel RP + pelvic lymphadenectomy
Locally advanced disease		Neoadjuvant ADT + radical RT + adjuvant ADT ± neoadjuvant docetaxel RP + pelvic lymphadenectomy
M0 CRPC	High risk	ADT + apalutamide ADT + darolutamide ADT + enzalutamide
Metastatic disease	Hormone-naive	ADT + abiraterone ADT + docetaxel ADT + enzalutamide ADT + apalutamide RT for low volume ADT alone for frail patients who cannot tolerate the above treatments Bone health agent
	Castration-resistant (first line)	Abiraterone Docetaxel Enzalutamide ^{223}Ra for patients unfit for above treatments (and bone-only metastases)
	Second line or post-docetaxel	Abiraterone Cabazitaxel Enzalutamide ^{223}Ra

^{223}Ra, radium-223; ADT, androgen deprivation therapy; M0 CRPC, non-metastatic castration-resistant prostate cancer; RP, radical prostatectomy; RT, radiotherapy.

Parker C, Castro E, Fizazi K, et al. Ann Oncol. 2020;31(9):1119-1134
AR: androgen receptor; ^{223}Ra: radium-223

Resistance Formation as a Key Challenge in CRPC

Published in final edited form as:
Nat Med. 2016 May ; 22(5): 488–496. doi:10.1038/nm.4070.

ROR-γ drives androgen receptor expression and represents a therapeutic target in castration-resistant prostate cancer

Junjian Wang[1], **June X. Zou**[1], **Xiaoqian Xue**[2], **Demin Cai**[1], **Yan Zhang**[2], **Zhijian Duan**[1], **Qiuping Xiang**[2], **Joy C. Yang**[3], **Maggie C. Louie**[4], **Alexander D. Borowsky**[5], **Allen C. Gao**[3,8], **Christopher P. Evans**[3,8], **Kit S. Lam**[1,8], **Jianzhen Xu**[6], **Hsing-Jien Kung**[1,8], **Ronald M. Evans**[7], **Yong Xu**[2], and **Hong-Wu Chen**[1,8]

In patients, prostate cancer usually can be controlled for multiple years

However, mutations can arise which make prostate cancer cell clones insensitive to hormone signaling inhibition

- So called V7 mutations are frequently leading to resistance towards hormone therapy

Targeting ARV7 expression may be a good strategy to overcome resistance in CRPC

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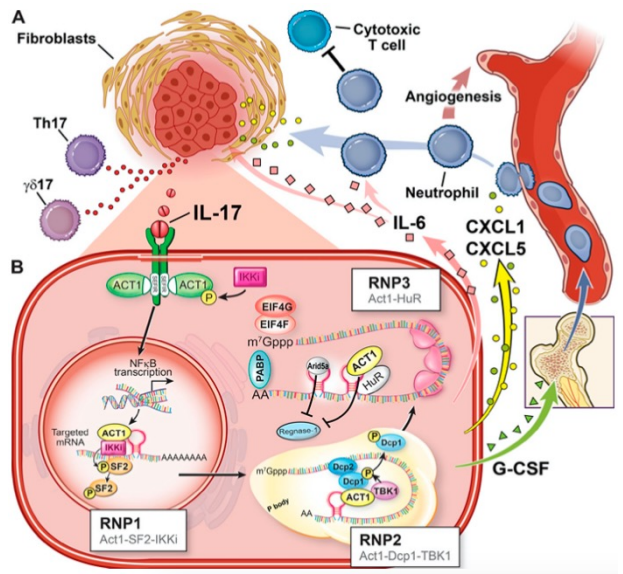
IMU-935 As Treatment Option in Castration-Resistant Prostate Cancer – Synergistic Effects by Targeting RORγ and RORγt

Inhibition of RORγ

- The androgen-receptor mutant variant AR-V7 lacks the ligand-binding domain, which is the target of enzalutamide and abiraterone, but remains constitutively active as a transcription factor.
- IMU-935 represses the mutated androgen receptor AR-V7 expression – and subsequent target genes.

Inhibition of IL-17 by RORγt Regulation

- IL-17 contributes to the formation, growth and metastasis of cancers.
  - Induces mitogenic signaling



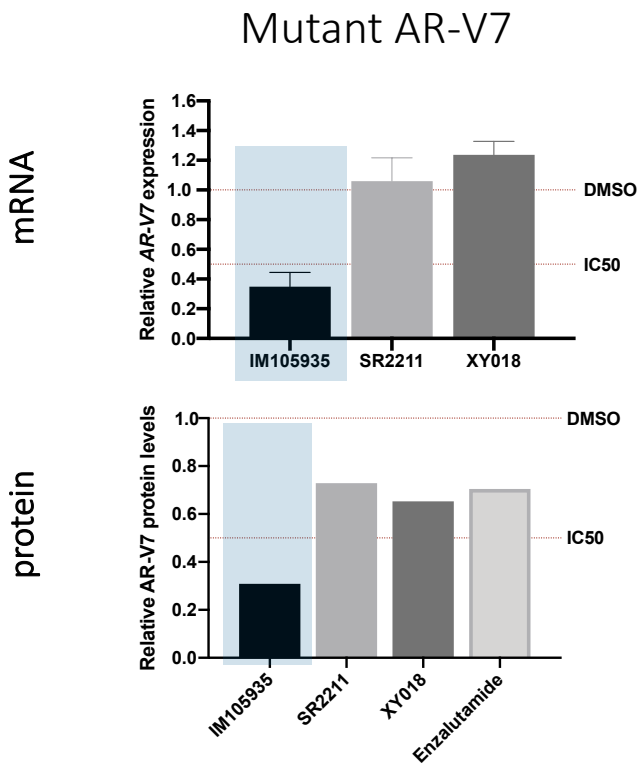
Differentiation of MDSCs

- IL-17 mediates the induction, recruitment and expansion of MDSCs.
- Next to IL-17 suppression via RORγt inhibition, IMU-935 also targets DHODH. Targeting this enzyme is an additional route to stop these tumor supportive cells.
- Supportive data regarding cell differentiation has been observed in AML cell lines using closely related molecules.

MDSC: myeloid-derived suppressor cells; AML: acute myeloid leukemia; Th: T helper; IL: interleukin
Illustration: Zhao, J., Chen, X., Herjan, T., Li, X.; J Exp Med 6 January 2020; 217 (1): e20190297

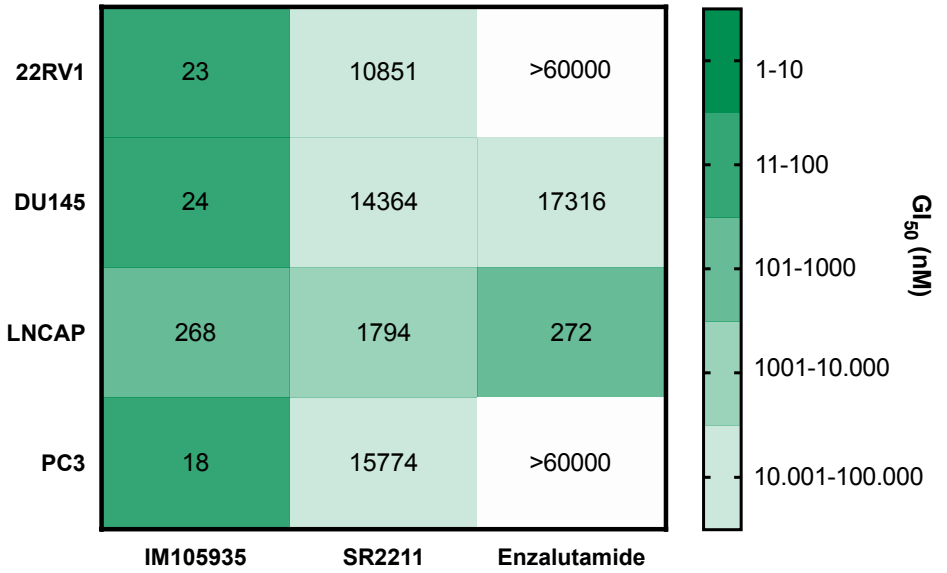
IMU-935 Demonstrated RORγ-Dependent Effects in CRPC Cells

IMU-935 Has Been Shown to Repress Expression of Mutated AR



IMU-935 Potently Inhibited Proliferation of Different Prostate Cell Lines

72h, 2d culture, read out protein staining/number of cells



AR-FL: full length/wildtype; AR-V7: variant 7/mutated form; mRNA experiment: 1µM, 48h; protein expression: 6µM, 48h; SR2211 and XY018 are RORγ inverse agonists

07

IMU-935

Planned Phase 1 Study in Castration-Resistant Prostate Cancer (CRPC)

Johann Sebastian de Bono, M.D., Ph.D.

The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust

"IMU-935 possesses a unique mechanism of action which may prove transformative in its ability to effectively treat a range of underserved diseases. Preclinical studies have shown that IMU-935 potently suppresses the expression of IL-17, indicating that it may also inhibit tumorigenesis, and suppresses the expression of AR-V7 in prostate cancer cell lines, thus potentially inhibiting tumor growth in CRPC patients. I am looking forward to collaborating with Immunic on this important phase 1 clinical trial in metastatic CRPC."

Phase 1 Clinical Trial of IMU-935 in CRPC

Study Design

- Open-label dose escalation trial to evaluate safety, tolerability, anti-tumor activity, and pharmacokinetics of IMU-935 in patients with progressive, metastatic castration-resistant prostate cancer
- Dose escalation follows a Bayesian optimal interval (BOIN) design
- An expansion cohort can be added at a therapeutically active dose level
- Main treatment will be single agent IMU-935 for 3 cycles of 28 days each
- Patients who benefit can receive extended treatment
- At each dose level:
  - A safety analysis will be performed to consider start of next dose cohort
  - An interim activity analysis will be performed upon completion of 3 months treatment
  - A main cohort analysis will be performed when the last patient in treatment reaches the 6 months follow-up visit

Principal Investigator

Johann Sebastian de Bono, M.D., Ph.D.

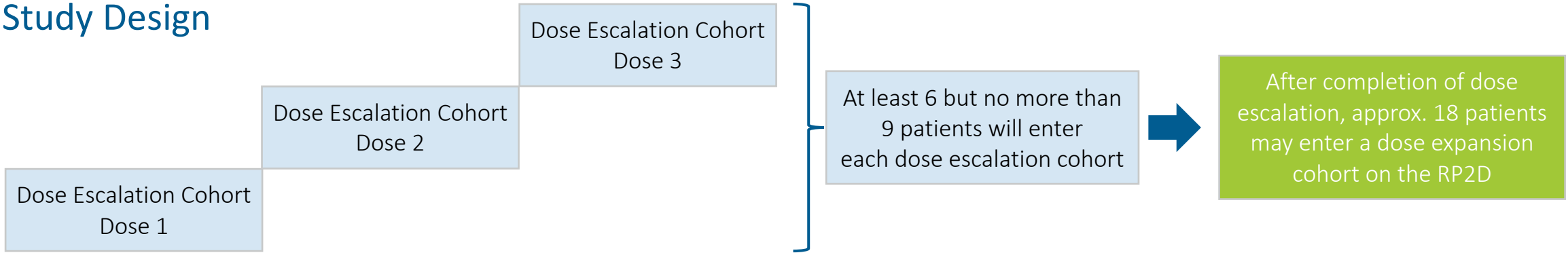
Regius Professor of Cancer Research and Professor in Experimental Cancer Medicine

The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust

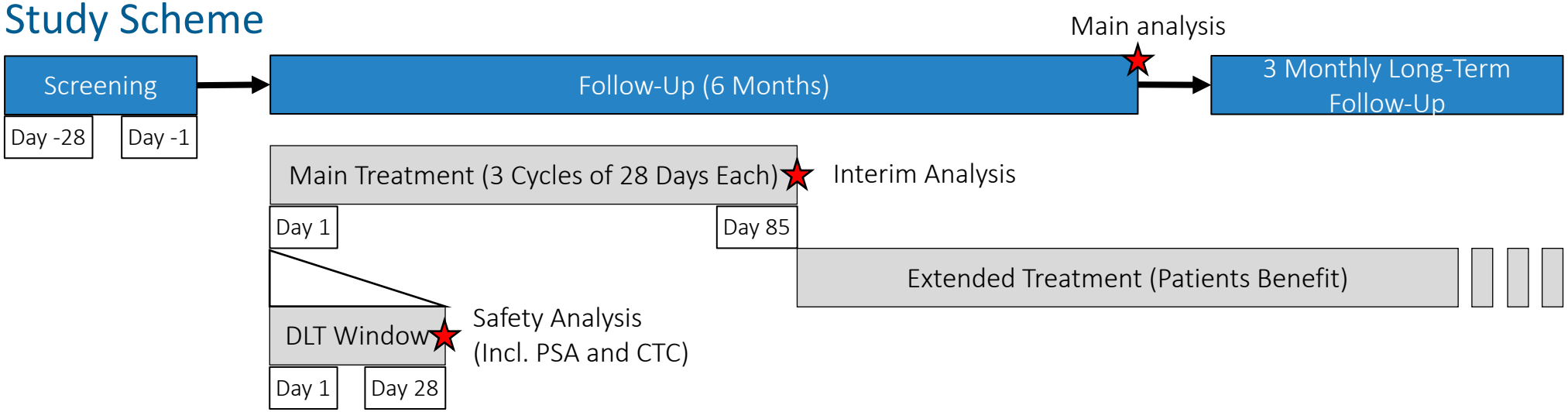
London, United Kingdom

Phase 1 Clinical Trial of IMU-935 in CRPC

Study Design



Study Scheme



RP2D: recommended phase 2 dose; DLT: dose-limiting toxicity; PSA: prostate-specific antigen; CTC: circulating tumor cells

Phase 1 Clinical Trial of IMU-935 in CRPC

Eligibility Criteria

- Age ≥ 18 years
- Histologically or cytologically confirmed adenocarcinoma of the prostate
- Progressive disease according to PCWG3 criteria
- Castration-resistant disease
- Metastatic disease

Key Objectives/Endpoints

Primary:

- Dose-limiting toxicity
- Recommended phase 2 dose (RP2D)

Secondary:

- PSA, CTC & radiographic response

Exploratory:

- Disease progression & survival
- Biomarkers (biopsies, ctDNA, cytokines, etc.)
- Population pharmacokinetics (popPK)

PSA: prostate-specific antigen; CTC: circulating tumor cell; ctDNA: circulating tumor DNA, PCWG3: Prostate Cancer Working Group 3

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08

IMU-935

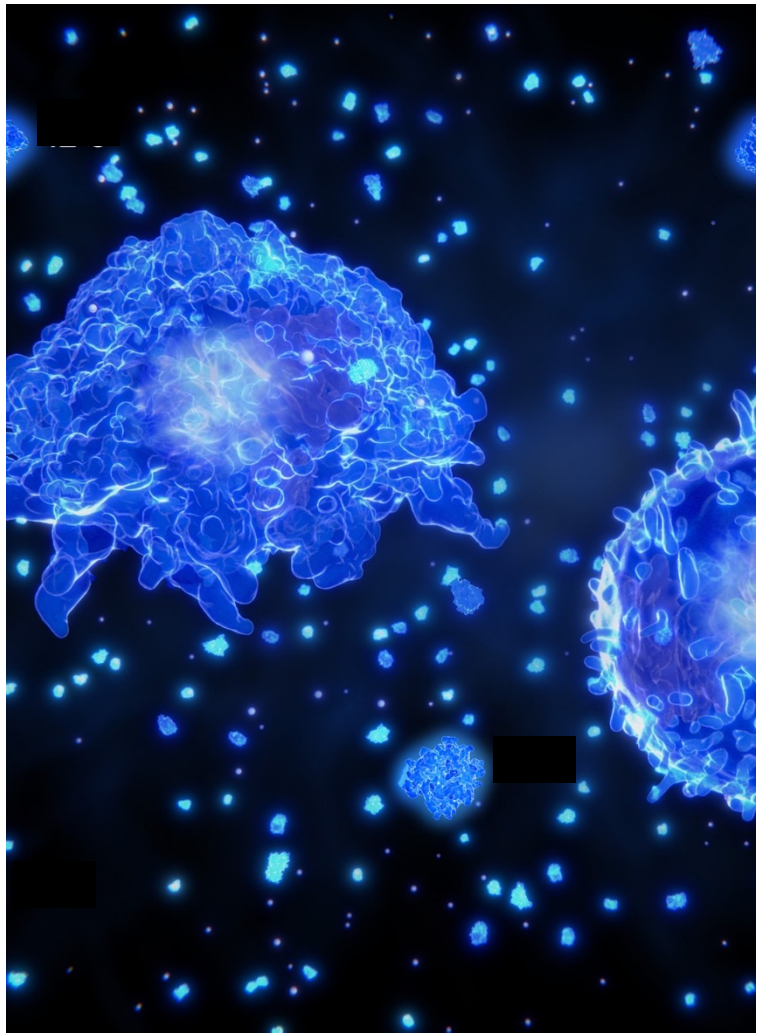
Q&A CRPC

09

IMU-935

Summary

IMU-935: An Emerging Oral IL-17 Inhibitor



- IMU-935 has been observed to be a **potent RORγt inhibitor** with an IC_{50} on IL-17A and IL-17F inhibition of ≤ 5 nM
- IMU-935 demonstrated a selective effect of inhibition of Th17 differentiation while **maintaining physiological function of thymocyte maturation**
- IMU-935 is currently tested in a phase 1 clinical trial, which is planned to be expanded to patients with **moderate-to-severe psoriasis in Q3/2021**
- In the first single ascending dose part of the phase 1 trial, IMU-935 demonstrated **suitable pharmacokinetic properties**
- A clinical phase 1 trial in patients with **mCRPC is expected to start in Q4/2021**, with Johann de Bono, M.D., Ph.D., as Principal Investigator
- **Initial human data from psoriasis patients expected to be available in Q2/2022**

Thank You!

Jessica Breu

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