

# Company Overview Presentation

Making Fresh Tracks in Medicine®

August 2023

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# ▶ Forward-Looking Statements

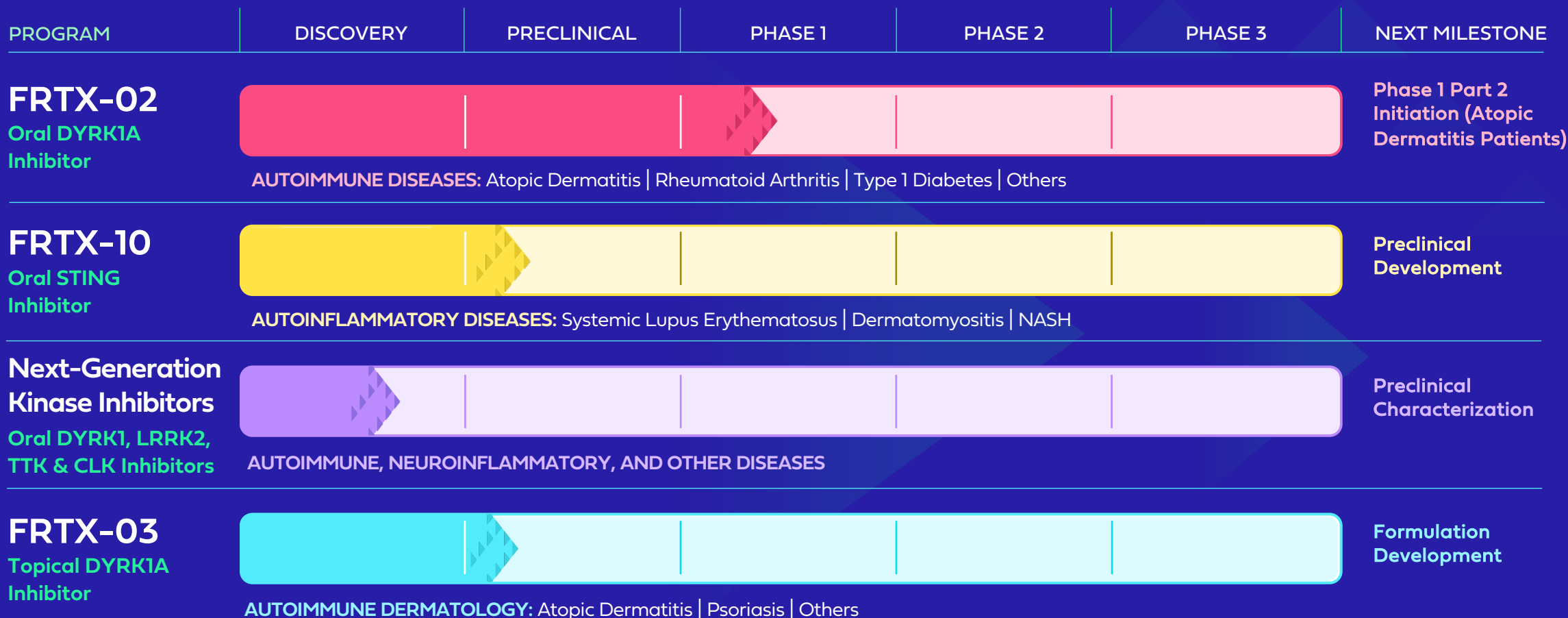
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- ▶ Further information on the factors and risks that could cause actual results to differ from any forward-looking statements are contained in FRTX's filings with the United States Securities and Exchange Commission, which are available at <https://www.sec.gov> (or at <https://www.frtx.com>). The forward-looking statements represent the estimates of FRTX as of the date hereof only. FRTX specifically disclaims any duty or obligation to update forward-looking statements.

# Fresh Tracks Therapeutics, Inc.

Clinical-stage pharmaceutical company developing innovative and groundbreaking prescription therapeutics for the treatment of autoimmune, inflammatory and other debilitating diseases

 <b>Potential First-in-Class DYRK1A Inhibitor</b>	 <b>Potential First-in-Class STING Inhibitor</b>	 <b>Cutting-Edge Kinase Inhibitors</b>	 <b>Experienced Leadership Team</b>
<ul style="list-style-type: none"><li>▶ <b>Reported positive SAD/MAD topline results from FRTX-02 Phase 1 study in March 2023</b></li><li>▶ <b>FRTX-02 is the first oral DYRK1A inhibitor tested in the clinic for autoimmune diseases</b></li><li>▶ <b>Broad therapeutic potential for debilitating autoimmune and inflammatory diseases</b></li></ul>	<ul style="list-style-type: none"><li>▶ <b>FRTX-10 preclinical development underway</b></li><li>▶ <b>Demonstrated strong proof-of-mechanism &amp; promising profile in initial preclinical studies</b></li><li>▶ <b>Potential to treat a wide array of autoinflammatory disorders and rare interferonopathies</b></li></ul>	<ul style="list-style-type: none"><li>▶ <b>Extensive library of small molecule next-generation kinase inhibitors targeting DYRK1, LRRK2, TTK, and CLK</b></li><li>▶ <b>Opportunity to explore various autoimmune, inflammatory, neurodegenerative, and oncology diseases</b></li></ul>	<ul style="list-style-type: none"><li>▶ <b>Experienced leadership team with proven track record developing and launching several novel products that achieved first-in-class and/or iconic status</b></li><li>▶ <b>Developed sofipironium bromide (first topical NCE for hyperhidrosis) from preclinical through Phase 3; Asset sold in May '22 &amp; future payments sold in July '23</b></li></ul>

# Pipeline of NCEs with First-in-Class Potential



# Executing Strategy with an Experienced Leadership Team

Our executives have developed and/or supported launches for several novel products achieving first-in-class and/or iconic status

	<p>CO-FOUNDER &amp; CHIEF EXECUTIVE OFFICER</p> <p><b>Andy Sklawer</b></p> <p> BrickellBio  Verid<sup>®</sup></p> <p> CONCORDIA PHARMACEUTICALS</p>		<p>CHIEF R&amp;D &amp; CHIEF OPERATING OFFICER</p> <p><b>Deepak Chadha</b></p> <p> BrickellBio  KYTHERA<sup>®</sup> <small>biopharmaceuticals</small></p> <p> INAMED AESTHETICS  Allergan</p>
	<p>CHIEF FINANCIAL OFFICER</p> <p><b>Albert Marchio II</b></p> <p> BrickellBio  EDGE Therapeutics, Inc.</p> <p> CYTOMX  THREE FIELDS CAPITAL</p>		<p>GENERAL COUNSEL &amp; CCO</p> <p><b>David McAvoy</b></p> <p> BrickellBio  Lilly</p> <p> ENDOCYTE  NOVARTIS</p>







# FRTX-02

Shifting the Balance Through DYRK1A Inhibition

# Potential First-in-Class Oral DYRK1A Inhibitor

FRTX-02 is a potent, highly selective, and orally bioavailable potential first-in-class DYRK1A inhibitor with strong preclinical validation and broad potential to treat debilitating autoimmune and inflammatory diseases

 Novel Autoimmunity Target	 Strong Preclinical Validation	 Significant Market Opportunity	 Phase 1 Trial Ongoing
<ul style="list-style-type: none"><li>▶ <b>Dual mechanism potentially restoring immune homeostasis</b> through enhanced regulatory T-cell differentiation and concomitant inhibition of pro-inflammatory pathways</li><li>▶ <b>Emerging field</b> with recent significant investor &amp; pharma interest</li></ul>	<ul style="list-style-type: none"><li>▶ <b>Proof-of-mechanism established</b> by thorough characterization</li><li>▶ <b>Preclinical proof-of-concept in 10+ animal models</b> of autoimmune disorders</li><li>▶ <b>Promising efficacy profile</b> vs. established therapies</li></ul>	<ul style="list-style-type: none"><li>▶ <b>Robust potential</b> across multiple different autoimmune diseases</li><li>▶ Oral &amp; topical formulations under development</li><li>▶ <b>Strong IP position (CoM)</b> in U.S. &amp; other key countries through 2038+</li></ul>	<ul style="list-style-type: none"><li>▶ <b>Reported positive SAD/MAD topline results</b> from FRTX-02 Phase 1 study in March 2023</li><li>▶ <b>Results support advancement of FRTX-02</b> as potential first-in-class treatment for autoimmune diseases</li><li>▶ FRTX-02 is first oral DYRK1A inhibitor tested in the clinic for autoimmune diseases</li></ul>

DYRK1A = Dual-specificity tyrosine phosphorylation regulated kinase 1A; CoM= composition of matter

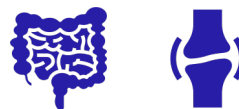
# Broad Autoimmune & Inflammatory Disease Potential

DYRK1A inhibitors offer broad potential to treat autoimmune, inflammatory, and other debilitating diseases



## AUTOIMMUNE DERMATOLOGY

Atopic Dermatitis<sup>1</sup>  
Hidradenitis Suppurativa<sup>2</sup>  
Psoriasis<sup>1</sup>



## AUTOIMMUNE AND INFLAMMATORY

Rheumatoid Arthritis<sup>3</sup>  
Type 1 Diabetes<sup>4</sup>  
Inflammatory Bowel Disease<sup>5</sup>  
Systemic Lupus Erythematosus<sup>6</sup>  
Osteoarthritis<sup>7,8</sup>



## NEUROINFLAMMATORY

Alzheimer's Disease & Others  
Tauopathies<sup>9,10,11</sup>  
Down's Syndrome<sup>12</sup>

**BROAD OPPORTUNITY  
FOR FRTX-02**

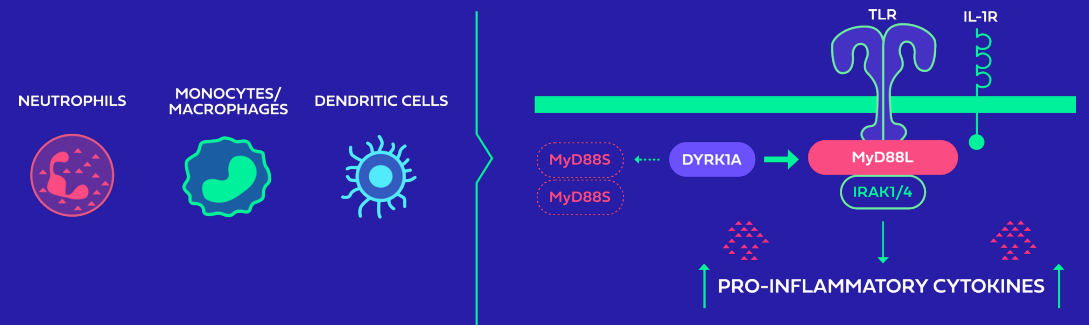
**NEXT-GENERATION KINASE  
INHIBITORS**

1. Internal data; 2. Agut-Busquet E et al., 7th European Hidradenitis Suppurativa Foundation (EHSF) Congress.(2018); 3. Guo, X. et al. Tissue Cell (2018); 4. Liu, Y. A. et al. J. Med. Chem. (2020); 5. Seo, D. H. et al. J. Crohn's Colitis (2020); 6. Li Y. et al. Blood (2021); 7. Deshmukh, V. et al. Osteoarthr. Cartil. (2019); 8. Y, Y. et al. Osteoarthr. Cartil. (2021); 9. Melchior, B. et al. Aging Cell (2019); 10. Janel, N. et al. Transl. Psychiatry 2014 48 (2014); 11. Lee, H. ju et al. Free Radic. Biol. Med. (2020). 12. Neumann, F. et al. Sci. Reports 2018 81 (2018)

## IMPAIRED T-CELL HOMEOSTASIS<sup>1,2</sup>

- 
- The diagram illustrates the imbalance between pro-inflammatory and anti-inflammatory cytokines in Treg cell dysfunction. On the left, a seesaw is tilted upwards on the right side, indicating a shift towards pro-inflammatory cytokines. The right side of the seesaw is labeled "PRO-INFLAMMATORY CYTOKINES" with a green upward arrow. Above the seesaw, a cluster of red triangles represents these cytokines, with green arrows pointing towards the Treg cells. On the right, three Treg cells are shown: "FUNCTIONAL T<sub>REG</sub> CELLS" (blue), "IMPAIRED T<sub>REG</sub> CELLS" (light blue), and "T<sub>H</sub>ELPER CELLS" (red). The transition from functional to impaired Treg cells is associated with the presence of pro-inflammatory cytokines.

- ▶ MyD88L induces inflammatory signalling cascade
- ▶ Chronic inflammation due to lack of anti-inflammatory MyD88S

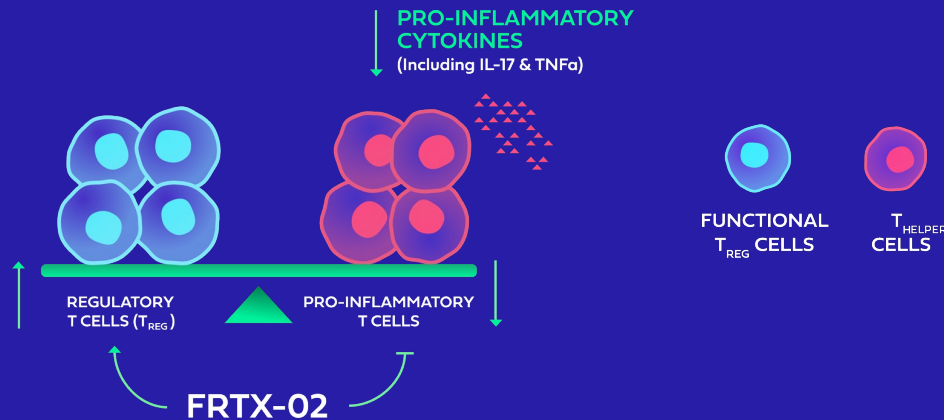


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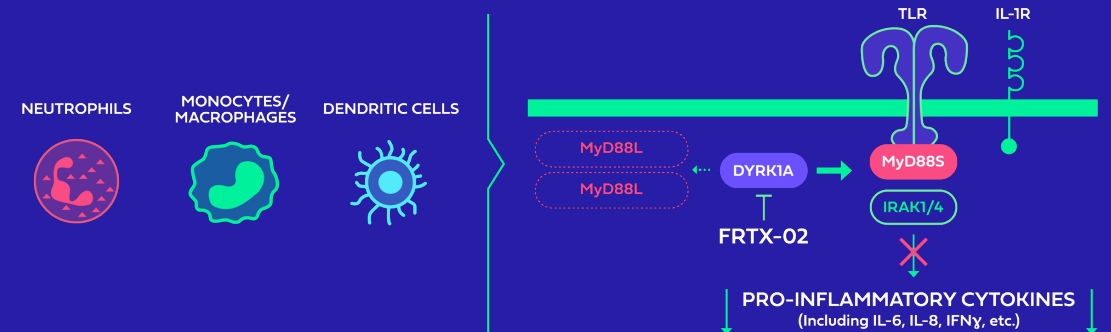
# Dual Mode of Action

FRTX-02 has a dual mode of action targeting both adaptive and innate immune responses, resulting in the restoration of T-cell homeostasis and inhibition of MyD88/IRAK4 signaling

## RESTORES T-CELL HOMEOSTASIS



## REGULATES TLR/IL-1R SIGNALING

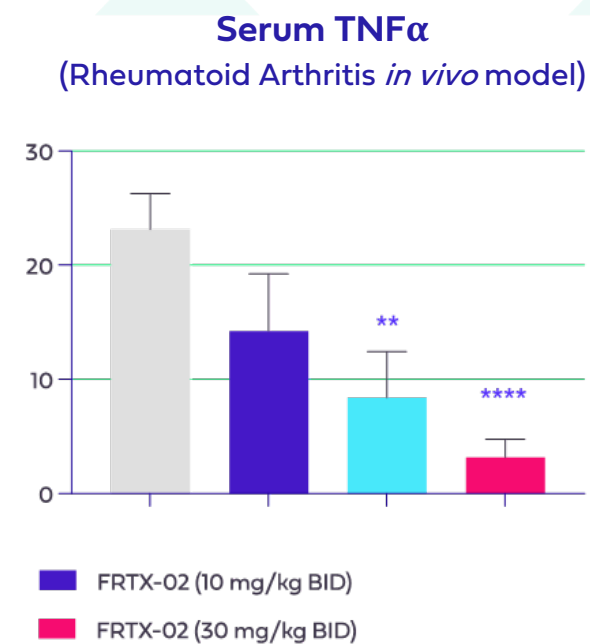
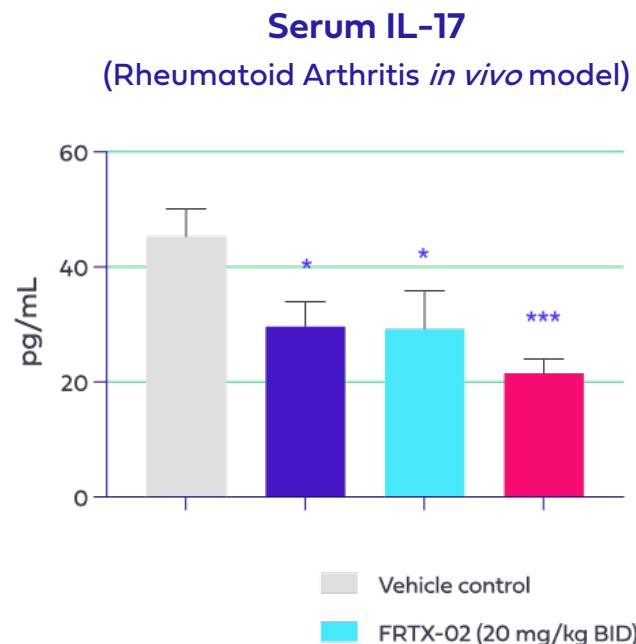
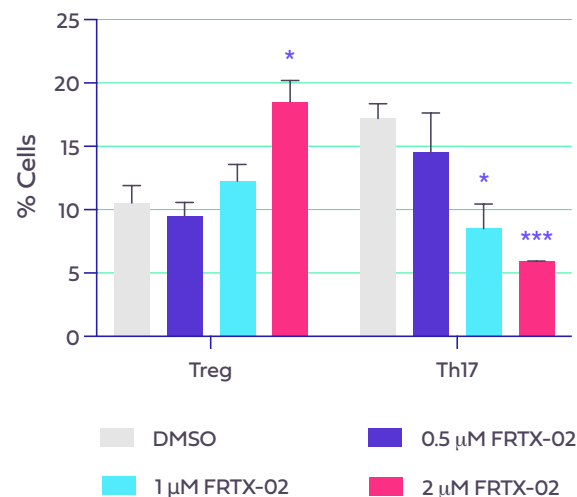


1. Noack, M. & Miossec, P. Autoimmun. Rev. (2014). 2. Lee, G. R. et al. Int. J. Mol. Sci. (2018). 3. Schaub, A. & Glasmacher, E. Int. Immunol. (2017). 4. Migliorini, P. et al. Autoimmun. Rev. (2020).

# Restoring T-Cell Homeostasis

FRTX-02 shifts the T-cell balance, yielding significant decrease in pro-inflammatory cytokines

FRTX-02 increases T<sub>reg</sub> cells & concomitantly decreases pro-inflammatory T<sub>h</sub>17 cells

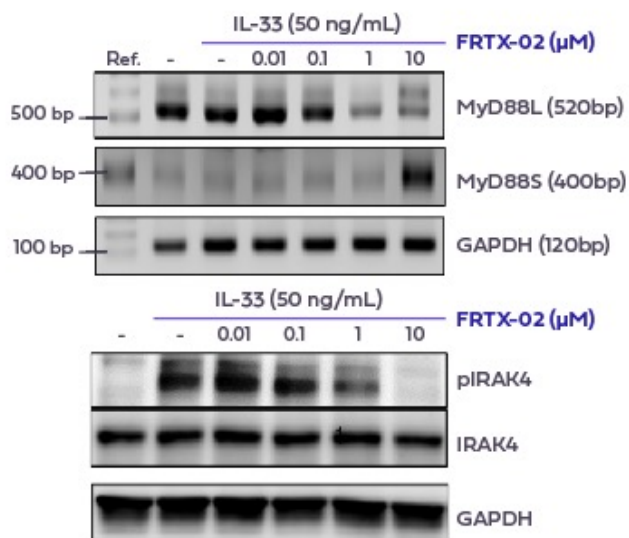


\*p<0.05, \*\*p<0.01, \*\*\* p<0.001, \*\*\*\* p<0.0001 vs. DMSO or vehicle control  
Khor, B. et al. Elife (2015); Kim, S. et al. J. Transl. Autoimmun. (2023); Talk by Prof. Bernard Khor, Benaroya Research Institute – [link](#)

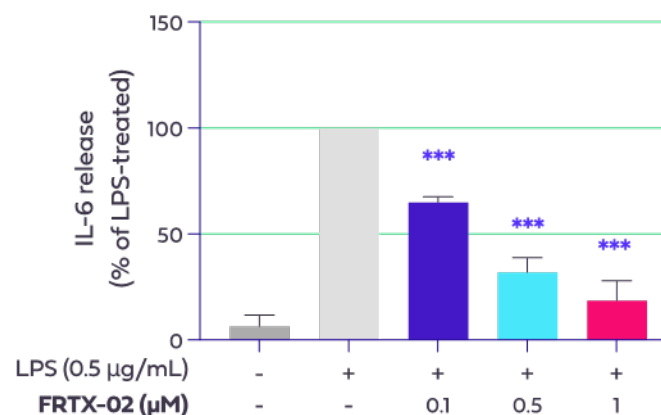
# Innate Immune Response

FRTX-02 induces alternative splicing of MyD88, thereby blocking the IRAK4 pathway and yielding greater inhibition compared to a clinical-stage IRAK4 inhibitor

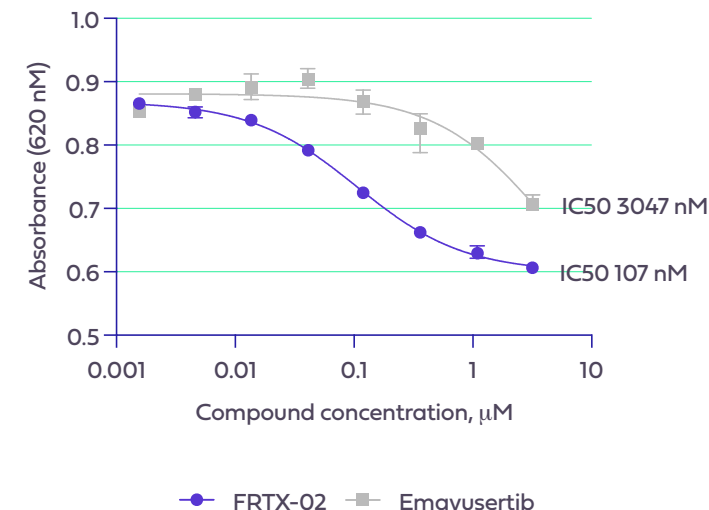
FRTX-02 favors MyD88S, resulting in reduced IRAK4 phosphorylation



Significant decrease in IL-6 release



FRTX-02 shows 30-fold higher TLR signalling inhibition vs. IRAK4 inhibitor

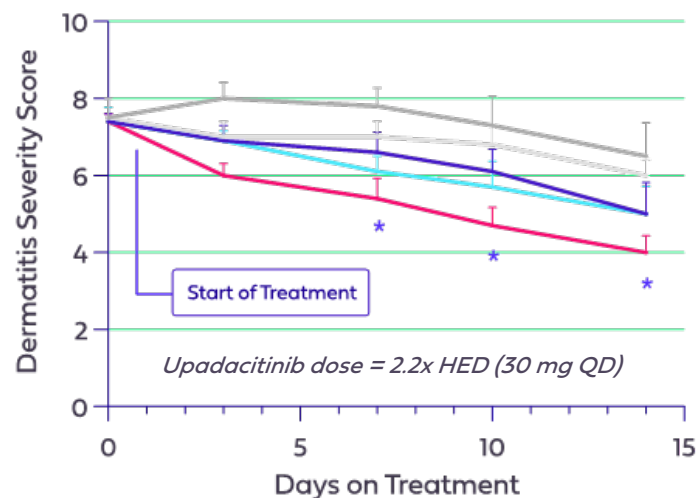


\*\*\* p < 0.001 vs. control; Kim, S. et al. J. Transl. Autoimmun. (2023).

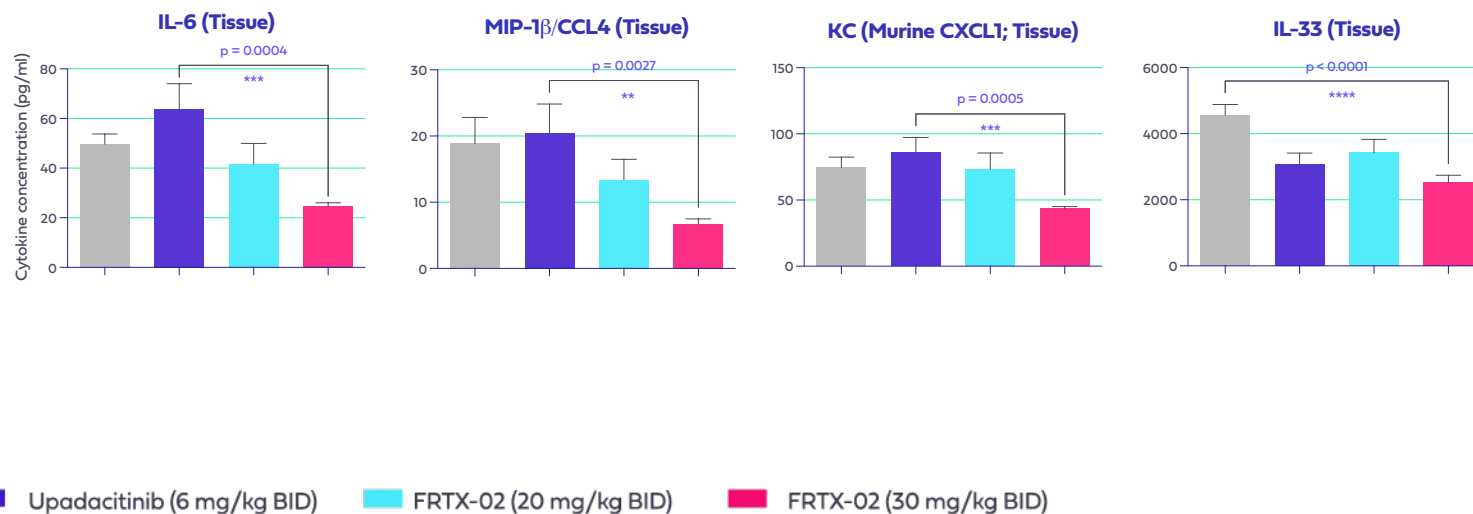
# Preclinical Efficacy in Atopic Dermatitis

FRTX-02 results in strong reduction of atopic dermatitis disease severity and pro-inflammatory cytokines in the skin, with a promising profile as compared to established therapies

Oral treatment of atopic dermatitis shows competitive effect vs. Upadacitinib (Rinvoq®)



Oral treatment resulted in significant reduction of cytokines & chemokines in the skin

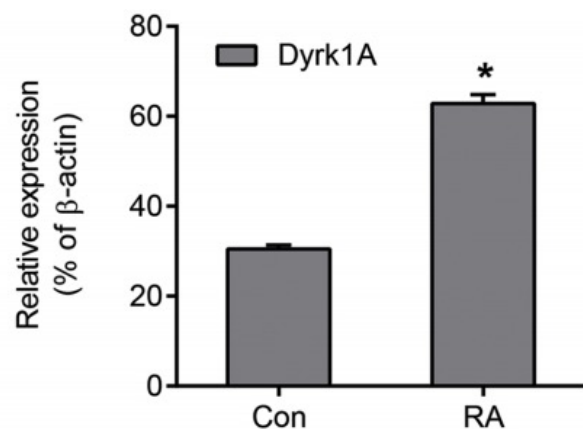


Kim, S. et al. J. Transl. Autoimmun. (2023). Atopic Dermatitis Model: TC/Nga mice, 3-week induction with house dust mite cream prior to treatment initiation (Treatment start: Day 1) Disease only and vehicle group N=4; treatment groups N=7 per group; Left: \*p<0.05 (Dunnett's test) vs. vehicle control; Right: \*\*p<0.01, \*\*\*p<0.001, \*\*\*\*p<0.0001 (unpaired, two-tailed t-test) Dermatitis Severity Score based on composite score of erythema, scarring, edema, erosion; skin tissue samples taken on Day 14 (last day of treatment) from the back of each animal

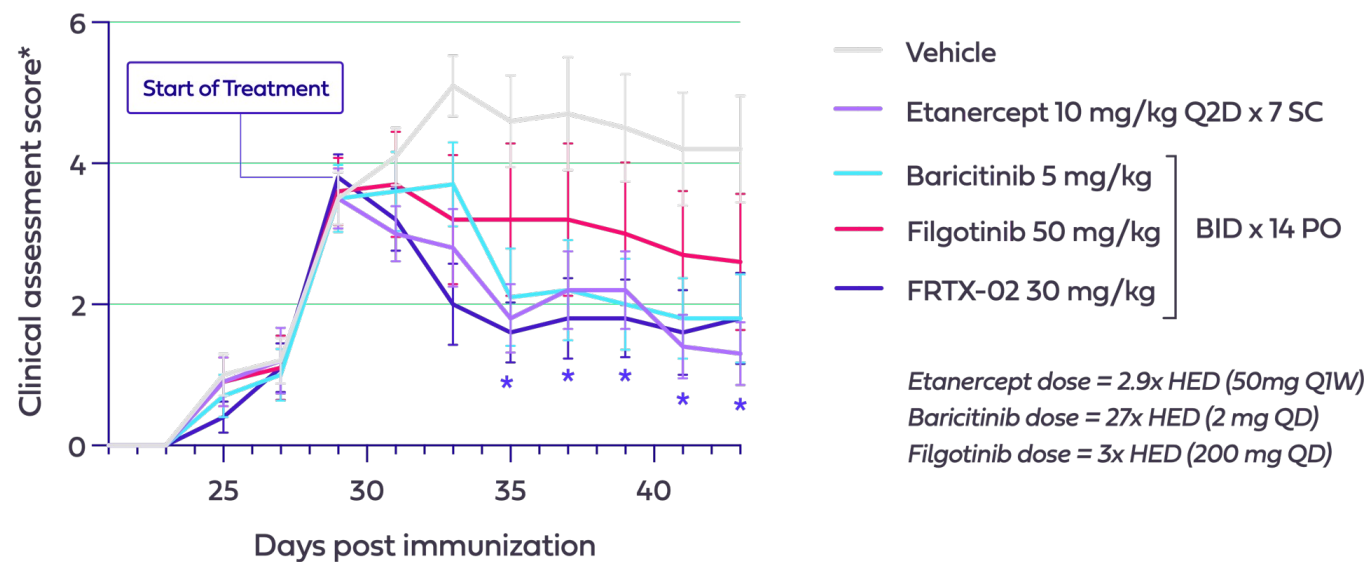
# Preclinical Efficacy in Rheumatoid Arthritis

FRTX-02 has successfully demonstrated competitive efficacy to JAK or TNF $\alpha$  inhibition in a rheumatoid arthritis model, where DYRK1A is upregulated

**DYRK1A is upregulated in synovial tissue of rheumatoid arthritis patients<sup>1</sup>**



**Oral treatment in a rheumatoid arthritis model shows competitive profile to JAK inhibitor and a biologic<sup>2</sup>**

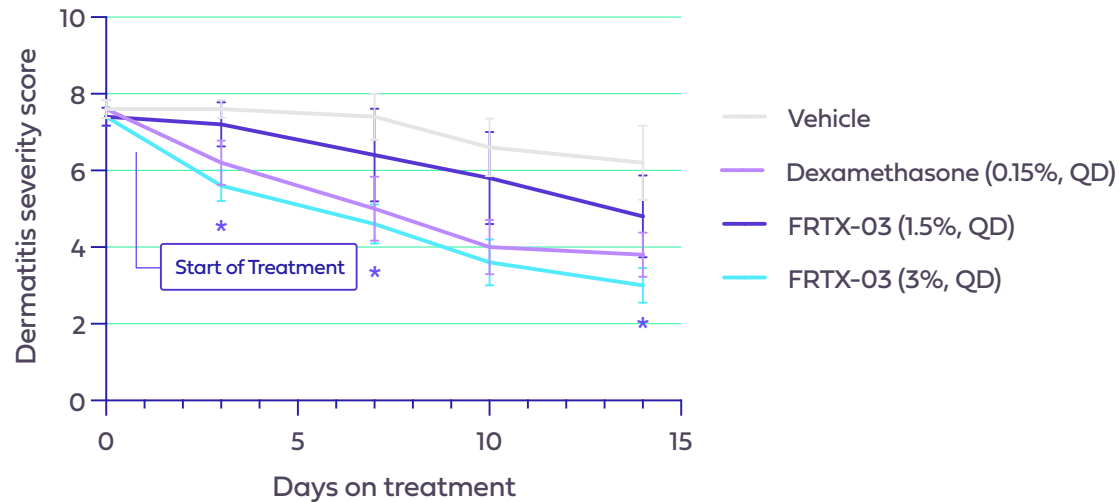


1. Guo, X. et al. Tissue Cell (2018), RA = rheumatoid arthritis, Con = healthy controls; N=9 per group., 2. Internal data: Collagen-induced arthritis (CIA) mouse model; Clinical score combines severity of lesions, Mankin scores, necrosis and synovial inflammation and hyperplasia (N=10 per group); \*p<0.05 (Dunnett's test) vs. vehicle, PO = peroral, SC = subcutaneous Based on Evaluate Pharma: Baricitinib (Olumiant®; Eli Lilly) WW Sales Forecast in RA (2026): US\$924M; Filgotinib (Jyseleca®; Galapagos) WW Sales Forecast in RA (2026): US\$ 356Mn

# Preclinical Efficacy in Atopic Dermatitis & Psoriasis

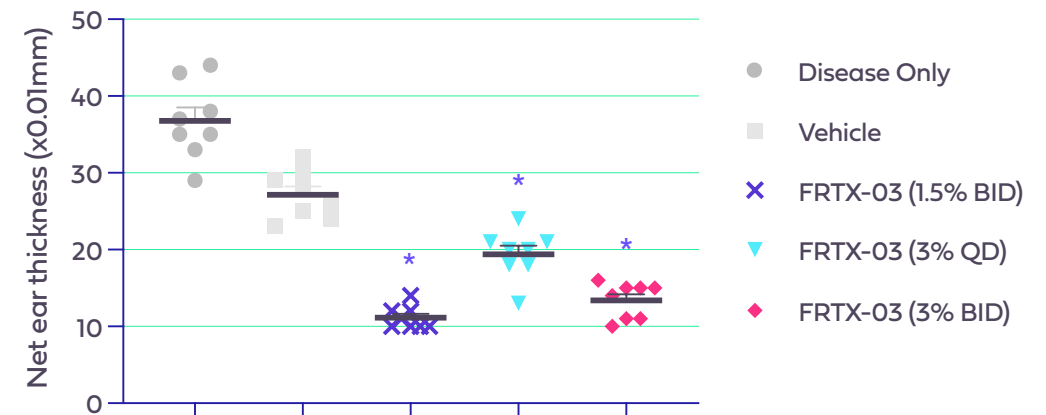
FRTX-03 results in rapid and strong reduction of disease severity of established atopic dermatitis, which was confirmed in a model of IMQ-induced psoriasis

Once-daily, topical treatment of atopic dermatitis results in rapid, significant decrease of disease burden<sup>1</sup>



Significantly reduced ear thickness was also observed in an IMQ-induced psoriasis<sup>2</sup>

After 9 days of treatment



1. Kim, S. et al. J. Transl. Autoimmun. (2023). TC/Nga mice; 3-week induction with house dust mite cream prior to treatment initiation (Treatment start: Day 1); N=5 per group; \*p<0.05 (Dunnett's test) vs. vehicle # Long-acting, potent steroids such as dexamethasone are broadly immunosuppressive and long-term include skin thinning, telangiectasias, folliculitis, and contact dermatitis, 2. Internal data: BALB/c mice; Disease induction with topical 5% Imiquimod (IMQ) cream on the right ear of animals applied once daily from day 1 to day 9; Treatment start on Day 1 for 9 consecutive days; net ear thickness was defined as the Δ of thickness of the disease-induced right ear vs. healthy left ear control; N=8 per group; \*p<0.05 (Dunnett's test) vs. vehicle

# Nonclinical and CMC Overview

Completed nonclinical studies & CMC activities for FRTX-02 support a 4-week first-in-human trial

## OVERVIEW OF COMPLETED NON-CLINICAL STUDIES

### Toxicology

- ▶ Mouse 7-day dose range finding (DRF) study
- ▶ Dog 7-day DRF study
- ▶ Mouse 4-week repeat dose
- ▶ Dog 4-week repeat dose
- ▶ Mouse 13-week repeat dose

### ADME

- ▶ Plasma & metabolic stability, PPB, Met. ID
- ▶ Predicted human metabolism (liver & kidney)
- ▶ CYP & transporter inhibition, CYP induction
- ▶ Metabolite identification

### Safety Pharmacology

- ▶ Irwin test (mouse)
- ▶ Respiratory (dog)
- ▶ Cardiovascular telemetry (dog)
- ▶ Human ventricular trabeculae/SA node
- ▶ Ion channel assay

### Genotoxicity

- ▶ Ames test
- ▶ In vitro micronucleus test
- ▶ In vivo micronucleus test

### Reproductive & Development

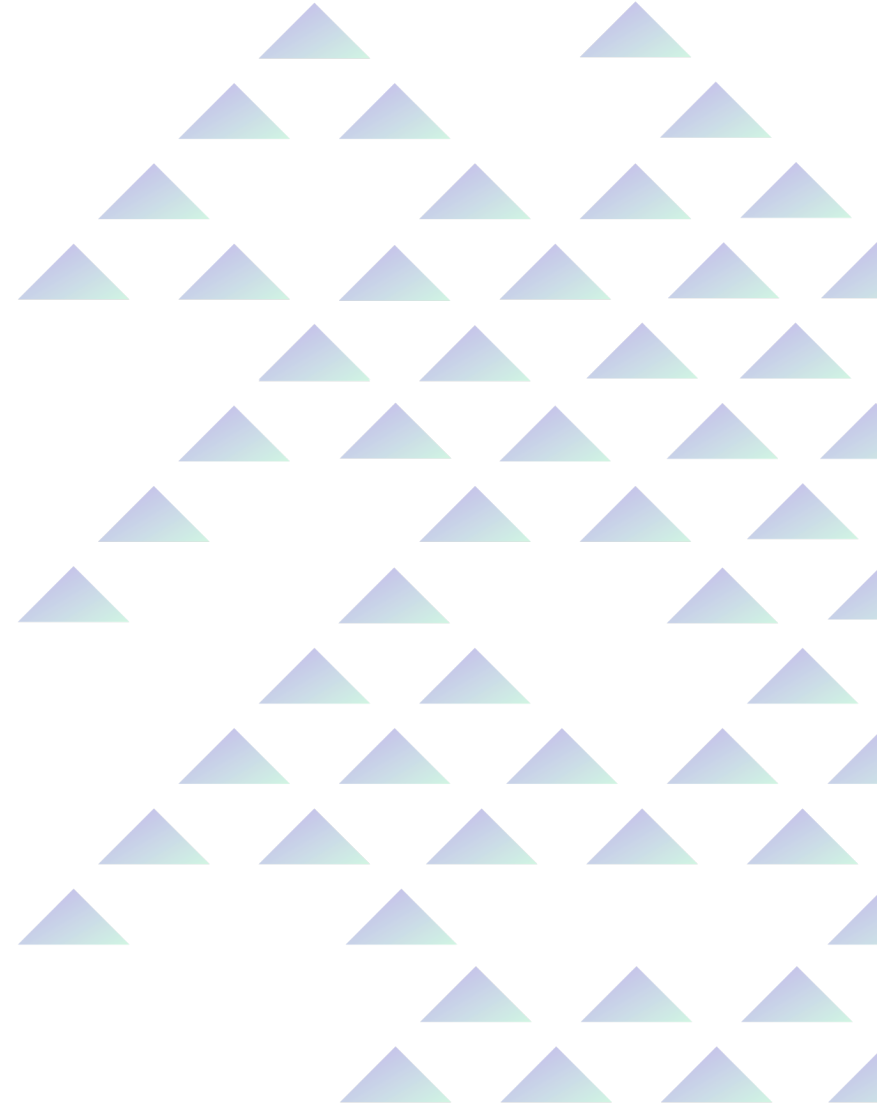
- ▶ Seg 1 (rat; customized)

## OVERVIEW OF CMC

- ▶ **GMP process development:** completed drug substance and product scale-up
- ▶ **Formulation:** oral immediate release hard capsule (multiple capsule strengths)
- ▶ **Stability:** studies of up to 36 & 24 months completed for drug substance and product
- ▶ **Phase 1 clinical trial materials:** manufacturing completed, stability testing ongoing

# FRTX-02

## Phase 1 SAD/MAD Topline Results



# Key Highlights from Part 1 (SAD/MAD)

Topline results from Part 1 (SAD/MAD) of the Phase 1 study support the continued development of FRTX-02 as a potential first-in-class, once-daily oral treatment for atopic dermatitis and/or other autoimmune diseases

- ▶ FRTX-02 was generally safe and well tolerated within the potential therapeutic dose range
- ▶ Plasma concentrations within the potential therapeutic dose range were consistent with efficacious exposure levels established in nonclinical disease models
- ▶ Pharmacokinetic (PK) data support once-daily oral dosing with FRTX-02 and steady state concentrations were attained before Day 14
- ▶ Reduction in disease-relevant cytokines was observed in exploratory *ex-vivo* lipopolysaccharide (LPS)-stimulated whole blood pharmacodynamic (PD) assays

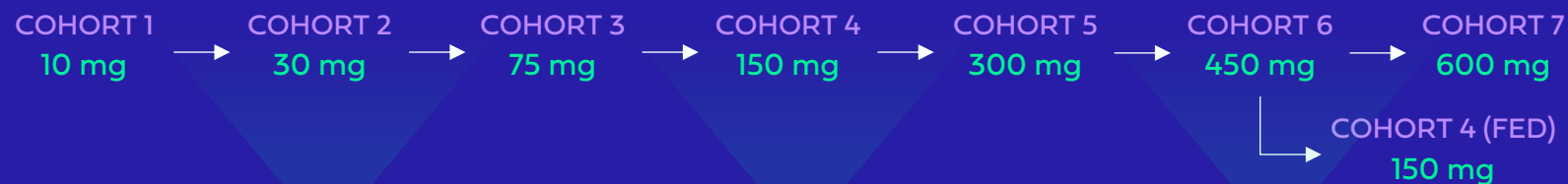
# Phase 1 Clinical Study Design Overview

FRTX-02-101 is a two-part, randomized, double-blinded, placebo-controlled study evaluating the safety, tolerability, PK and PD of oral FRTX-02 in healthy adult subjects (Part 1) and atopic dermatitis patients (Part 2)

## PART 1: SINGLE ASCENDING DOSE (SAD) PHASE

56 healthy subjects (8 per cohort) randomized 6:2 to once daily doses of FRTX-02 or placebo

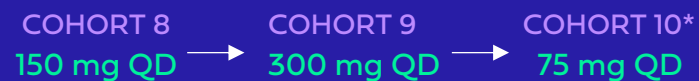
Endpoints: safety, tolerability, PK



## PART 1: MULTIPLE ASCENDING DOSE (MAD) PHASE

33 healthy subjects (11 per cohort) randomized 9:2 to either 14 once-daily doses of FRTX-02 or placebo

Endpoints: safety, tolerability, PK, exploratory PD



\*75 mg QD dose was selected for Cohort 10 based on 150 mg QD (Cohort 8) PK exposures exceeding FRTX-02 concentrations at the mouse efficacious dose (30 mg/kg BID) and safety findings from 300 mg QD (Cohort 9).

## PART 2: ATOPIC DERMATITIS

30-40 patients receiving 28 once-daily doses of FRTX-02 or placebo

Endpoints: safety, tolerability, PK, PD, exploratory efficacy

# SAD: Blinded Safety Summary

FRTX-02 was generally safe and well tolerated in all seven SAD cohorts (10 mg - 600 mg)

- ▶ No Serious Adverse Events (SAEs) and no discontinuations due to Treatment-Emergent Adverse Events (TEAEs)
- ▶ No dose-dependent trend in frequency or severity of TEAEs was observed
- ▶ All but one TEAE were mild (single count of moderate back pain unlikely related to treatment in 450 mg cohort)
- ▶ Most TEAEs were not related or unlikely related to study treatment
- ▶ No ECG or lab findings of clinical relevance

## POSSIBLY RELATED TREATMENT-EMERGENT AEs\* (>1 SUBJECT)

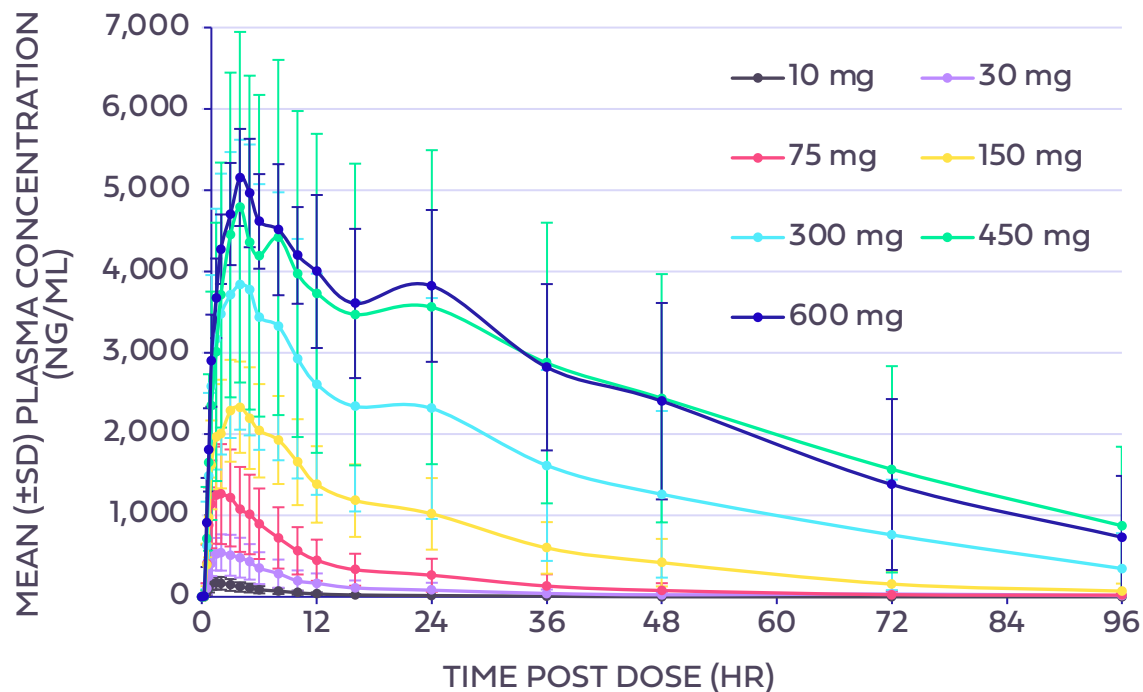
AE TERM	# SUBJECTS	SEVERITY	COHORT
HEADACHE	5	Mild (x5)	75 mg, 150 mg (FAST & FED), 600 mg
NAUSEA	2	Mild (x2)	75 mg, 600 mg

\* Per investigator assessment.

# SAD: FRTX-02 PK Summary

FRTX-02 was well absorbed for all SAD doses and reached peak plasma concentrations between 2 to 4.5 hours post dose

**FRTX-02 MEAN PLASMA CONCENTRATIONS OVER TIME**



**SAD PK PARAMETERS\***

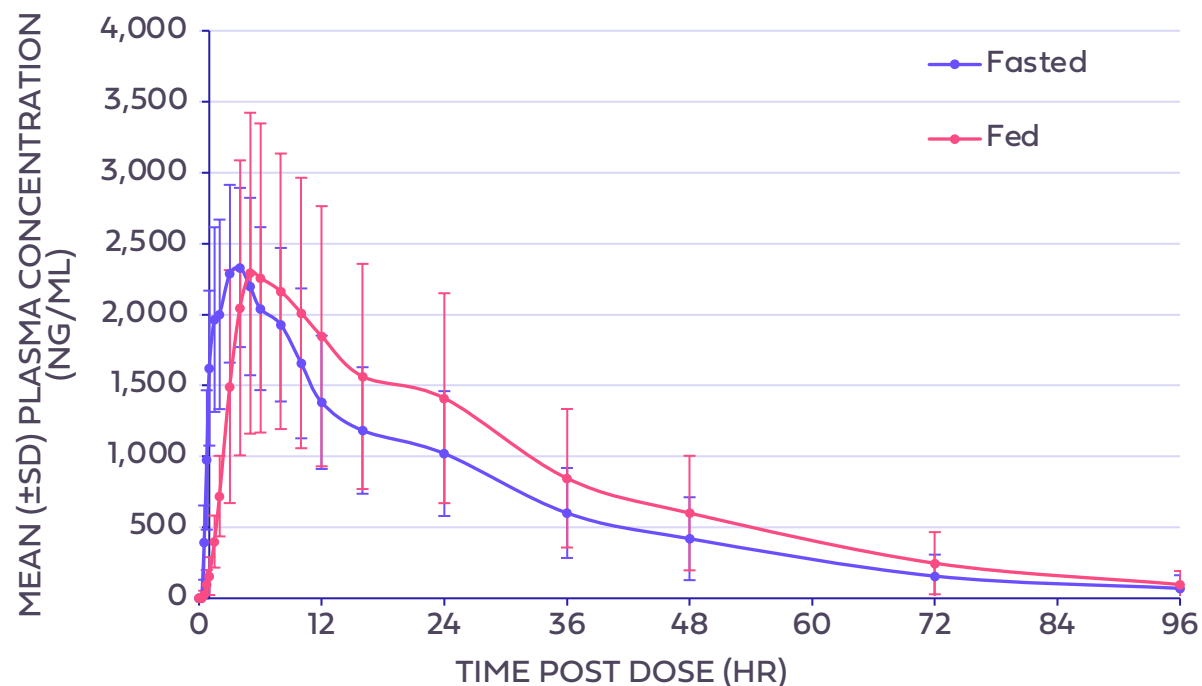
PK PARAMETER	10 MG (N=6)	30 MG (N=6)	75 MG (N=6)	150 MG (N=6)	300 MG (N=6)	450 MG (N=6)	600 MG (N=6)
$C_{MAX}$ (NG/ML)	156.54 (44.1)	530.98 (40.9)	928.27 (47.6)	2145.52 (48.1)	3052.29 (46.0)	4089.87 (43.7)	5137.33 (11.7)
$AUC_{0-24}$ (H*NG/ML)	1176.69 (49.3)	4618.56 (55.7)	9895.73 (51.2)	35194.37 (47.7)	45059.69 (50.8)	65041.61 (50.0)	93518.36 (18.2)
$T_{MAX}$ (HR)	1.82 (34.7)	2.62 (53.7)	2.50 (25.7)	6.26 (31.9)	3.80 (31.6)	3.81 (50.0)	4.31 (11.9)
$T_{1/2}$ (HR)	6.98 (33.6)	10.11 (55.2)	15.00 (65.0)	15.56 (33.7)	16.79 (47.9)	30.18 (49.9)	21.99 (52.6)

\*Geometric Mean (%CV) reported for all parameters.

# SAD: Minimal FRTX-02 Food Effect

Minimal effect of food was observed on PK of a single 150 mg oral dose of FRTX-02

150 MG FRTX-02 MEAN PLASMA CONCENTRATIONS OVER TIME



SAD PK PARAMETERS\*

PK PARAMETER	150 MG FAST (N=6)	150 MG FED (N=6)
$C_{MAX}$ (NG/ML)	2145.52 (48.1)	2316.81 (25.5)
$AUC_{0-24}$ (H*NG/ML)	35194.37 (47.7)	33867.79 (30.8)
$T_{MAX}$ (HR)	6.26 (31.9)	3.36 (30.0)
$T_{1/2}$ (HR)	15.56 (33.7)	14.96 (39.0)

\*Geometric Mean (%CV) reported for all parameters.

# MAD: Blinded Safety Summary

FRTX-02 was safe and generally well tolerated at 75 mg and 150 mg over 14 days of oral QD dosing

- ▶ No SAEs
- ▶ Majority of TEAEs were mild (single count of moderate headache possibly related to treatment in 300 mg cohort)
- ▶ No dose-dependent trend in TEAE frequency or severity observed
- ▶ No lab findings of clinical relevance
- ▶ QTc prolongation observed in two subjects in 300 mg cohort
  - ▶ Both subjects were asymptomatic, their QTc intervals returned to baseline levels and remained in the normal range after dosing cessation, and all study assessments were completed
  - ▶ Exposures where QTc prolongation was observed are 2 to 4-fold above exposures within the potential therapeutic dose range (75 mg – 150 mg)

## POSSIBLY RELATED TREATMENT-EMERGENT AEs\* (>1 SUBJECT)

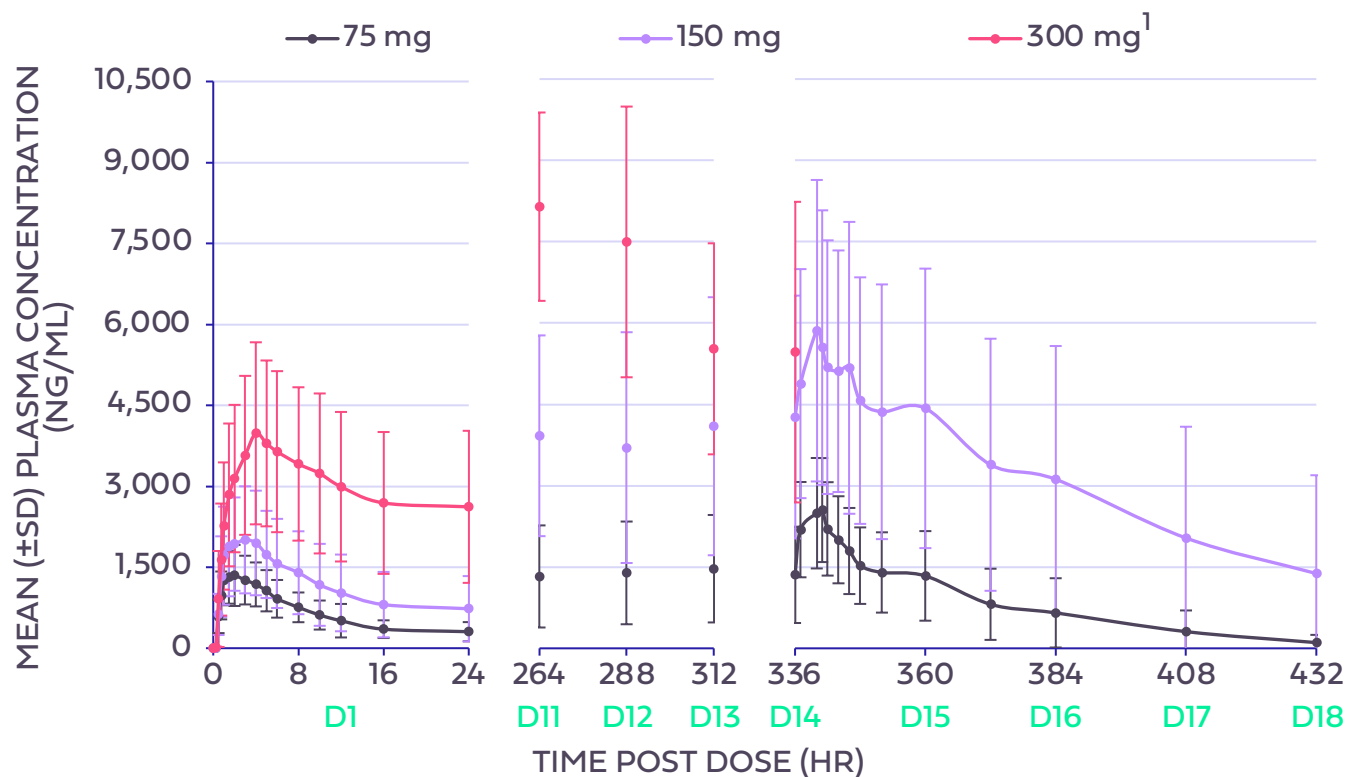
AE TERM	# SUBJECTS	SEVERITY	COHORT
CONSTIPATION	3	Mild (x3)	75 mg, 150 mg, 300 mg
HEADACHE	3	Mild (x2)	75 mg, 300 mg
		Moderate (x1)	300 mg
NAUSEA	2	Mild (x2)	75 mg, 300 mg
ECG QT PROLONGED	2	Mild (x2)	300 mg

\* Per investigator assessment.

# MAD: FRTX-02 PK Summary

MAD PK data support once-daily dosing with FRTX-02 and steady state was attained before Day 14

## FRTX-02 MEAN PLASMA CONCENTRATIONS OVER TIME



## MAD (DAY 14) PK PARAMETERS\*

PK PARAMETER	75 MG QD (N=9)	150 MG QD (N=9)
$C_{MAX}$ (NG/ML)	2450.68 (37.3)	5417.64 (46.6)
$AUC_{0-24}$ (H*NG/ML)	37898.58 (46.2)	102394.70 (50.3)
$T_{MAX}$ (HR)	2.68 (49.4)	3.25 (32.8)
$T_{1/2}$ (HR)	15.97 (37.6)	28.26 (82.46)
$C_{TROUGH}$ (NG/ML)	1355.53 (888.22)	4266.56 (2239.21)
DAY 14/1 RATIO $C_{MAX}$	1.85	2.85
DAY 14/1 RATIO $AUC$	2.80	4.20

\*Geometric Mean (%CV) reported for all parameters, except for  $C_{trough}$  where Mean (±SD) concentration is reported.

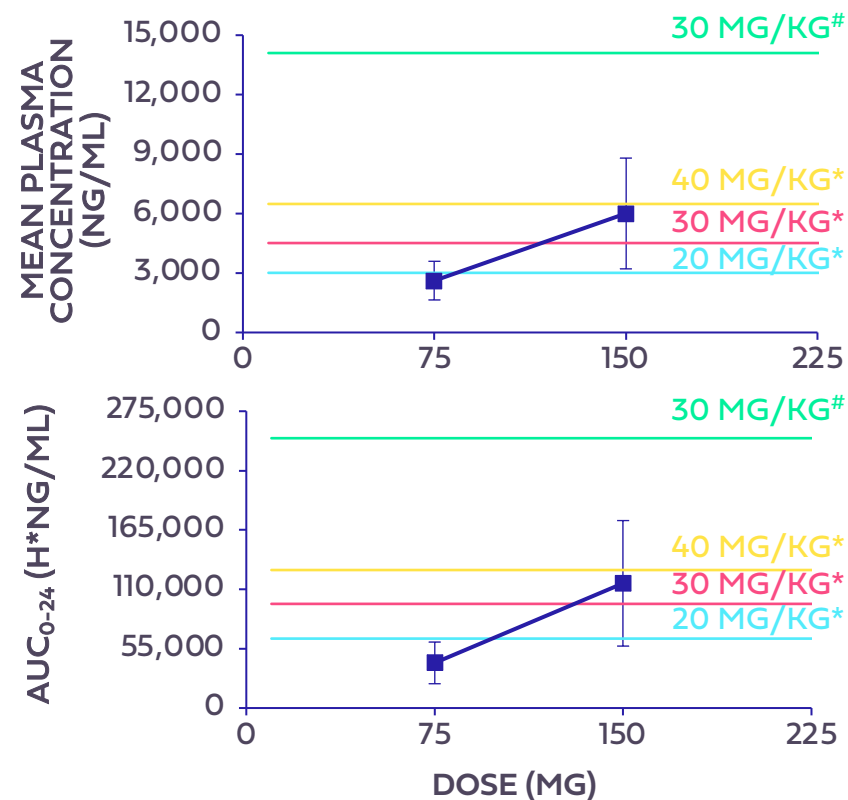
[1] 1 subject received 8, 1 subject received 9, and the remaining 7 subjects received 10 daily doses of FRTX-02; Dosing was halted (as per pre-defined protocol stopping rules) due to QTc prolongation observed in two subjects

# MAD: Therapeutic Dose Summary

Plasma concentrations within the potential FRTX-02 therapeutic dose range (75 mg and 150 mg) were consistent with efficacious exposure levels established in nonclinical disease models

- ▶ After once-daily dosing with 150 mg FRTX-02 over 14 days:
  - ▶  $C_{max}$  and  $AUC_{0-24}$  concentrations are above estimated exposures at mouse efficacious dose of 30 mg/kg BID
- ▶ After once-daily dosing with 75 mg FRTX-02 over 14 days:
  - ▶  $C_{max}$  and  $AUC_{0-24}$  concentrations are consistent with estimated exposures at mouse dose of 20 mg/kg BID
- ▶ If mouse PD effects translate to a human autoimmune patient population (next clinical study), the FRTX-02 therapeutic dose range is expected to be between 75 mg and 150 mg

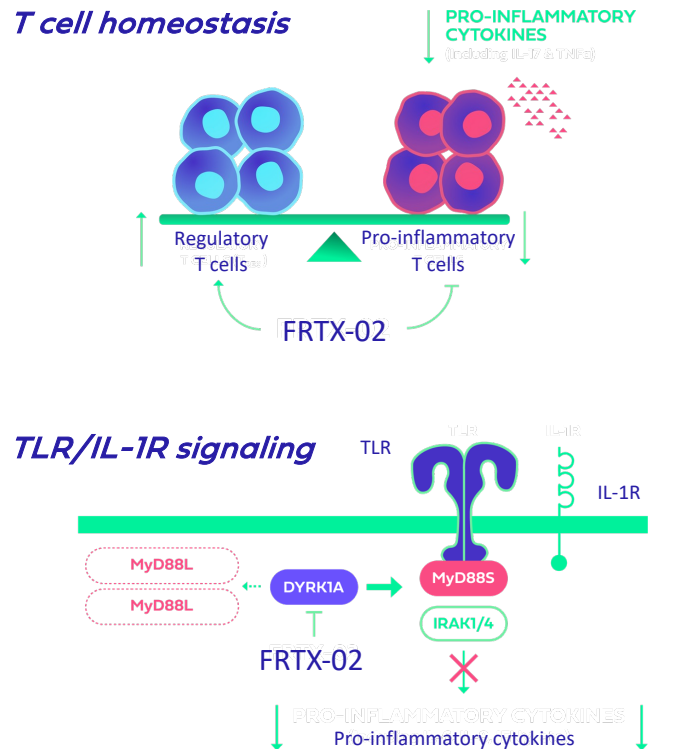
FRTX-02  $C_{MAX}$  &  $AUC_{0-24}$  (DAY 14)



\*Mouse BID Day 28 Estimates; #Dog BID Day 28 Estimates.

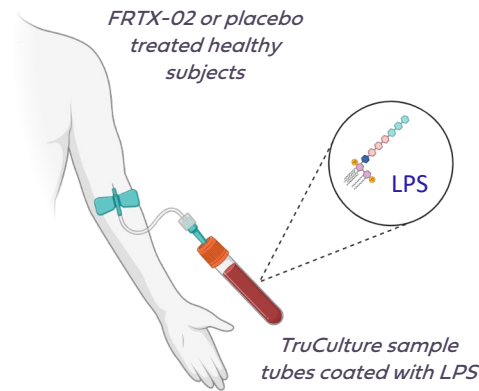
# MAD: PD Biomarker Sampling Methodology

## Dual Mode of Action



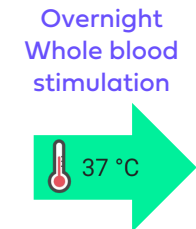
## PD biomarker assay in stimulated PBMCs from healthy subjects

### PBMC COLLECTION & STIMULATION



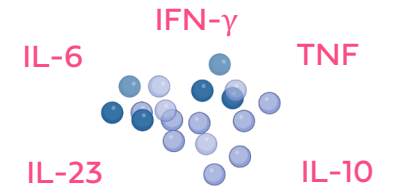
Patient blood was drawn into TruCulture® tubes coated with LPS to stimulate cytokine release

### SAMPLE PROCESSING



Plasma was separated from blood cells within the TruCulture® tube

### CYTOKINE MEASUREMENTS



Cytokines in supernatant were measured by a multiplex assay

# MAD: FRTX-02 PD Summary

Reduction in disease-relevant cytokines was observed in exploratory *ex-vivo* LPS-stimulated whole blood pharmacodynamic assays





- ▶ Exploratory PD activity was measured by impact on cytokine secretion following *ex vivo* LPS stimulation of peripheral blood mononuclear cells (PBMCs) derived from the MAD cohorts
- ▶ Cytokines were selected for assessment based on those observed to be reduced by FRTX-02 in various nonclinical disease models
- ▶ FRTX-02 demonstrated a reduction in disease-relevant proinflammatory cytokines, suggesting initial support for the FRTX-02 mechanism of action
- ▶ Mean percent cytokine reduction from baseline after 14 days of once-daily 75 mg or 150 mg FRTX-02 treatment versus placebo were in the range of approximately 66% to 20% for IFN $\gamma$ , IL-23, IL-10, IL-6, and TNF $\alpha$
- ▶ Maximum individual subject cytokine reductions from baseline were shown to be >90% for IFN $\gamma$ , >50% for IL-23, IL-10 and TNF $\alpha$ , and approximately 40% for IL-6

# FRTX-10

A First-in-Class Approach to Treating Inflammation

# Potential First-in-Class Oral STING Inhibitor

FRTX-10 is a novel, potent, and orally bioavailable covalent STING inhibitor with demonstrated proof-of-mechanism and broad potential to treat autoinflammatory and rare monogenic diseases

 Strong Scientific Rationale & Interest	 Lead FRTX-10 with Proof-of-Mechanism	 Broad Therapeutic Opportunity	 Exclusive Global Rights & Compound Library
<ul style="list-style-type: none"><li>▶ Overactivation of cGAS-STING is well documented as a key pathway in inflammatory conditions</li><li>▶ Several large pharma companies have invested in this target, given its broad potential</li></ul>	<ul style="list-style-type: none"><li>▶ Highly selective, novel, orally available STING inhibitor with low nanomolar potency</li><li>▶ Preclinical <i>in vitro</i> and <i>in vivo</i> PoM established demonstrating dose-dependent cytokine reduction</li><li>▶ Initial <i>in vitro</i> and <i>in vivo</i> DMPK and TK studies completed and additional studies ongoing</li></ul>	<ul style="list-style-type: none"><li>▶ Potential to address high unmet need diseases, ranging from broad autoinflammatory diseases to rare genetic interferonopathies</li><li>▶ Strong biomarker hypothesis may allow for targeted clinical development approach</li></ul>	<ul style="list-style-type: none"><li>▶ Acquired exclusive global rights for all uses from Carna Bio in February 2022</li><li>▶ Compound library of 300+ small molecule NCEs provides potential for strong IP protection, with CoM patents filed in 2021</li></ul>

STING = Stimulator of Interferon Genes; PoM = proof of mechanism; CoM = composition of matter

# Broad Potential in Inflammatory Diseases

STING inhibitors have the potential to treat inflammatory diseases ranging from broad autoimmune and aging-related conditions to rare genetic interferonopathies



## RARE GENETIC DISORDERS

Aicardi–Goutières syndrome (AGS)<sup>1,2</sup>  
STING-associated vasculopathy with  
onset in infancy (SAVI)<sup>1,2</sup>



## AUTOIMMUNE/INFLAMMATORY WITH BIOMARKER HYPOTHESIS\*

Systemic Lupus Erythematosus<sup>3,5</sup>  
Rheumatoid Arthritis<sup>4</sup>



## OTHER INFLAMMATORY

Age-related macular degeneration<sup>6</sup>  
Non-alcoholic steatohepatitis (NASH)<sup>7</sup>

## TARGETED THERAPY

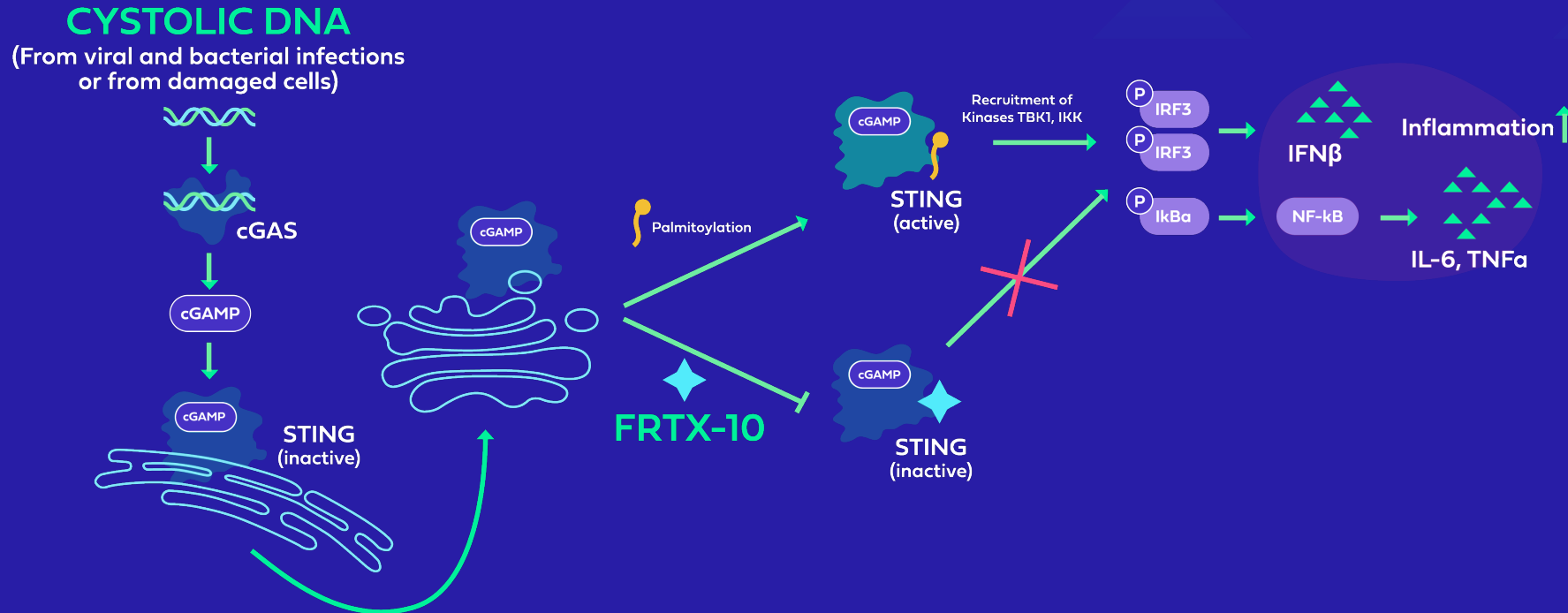
## NOVEL THERAPEUTIC APPROACH

\*Elevated cGAS expression was found in notable clinical subpopulations of SLE and RA<sup>3,4,5</sup>

1. d'Angelo, D. M., Di Filippo, P., Breda, L. & Chiarelli, F. *Front. Pediatr.* (2021). 2. Crow, Y. J. & Manel, N. *Nat. Rev. Immunol.* 2015 157(2015). 3. Crow, M. K., Olferiev, M. & Kirou, K. A. *Annu. Rev. Pathol. Mech. Dis.* (2019). 4. Wang, J. *et al. Int. Immunopharmacol.* (2019). 5. An, J. *et al. Arthritis Rheumatol. (Hoboken, N.J.)* (2017). 6. Kerur, N. *et al. Nat. Med.* 2017 241(2017). 7. Yu, Y. *et al. J. Clin. Invest.* (2019).

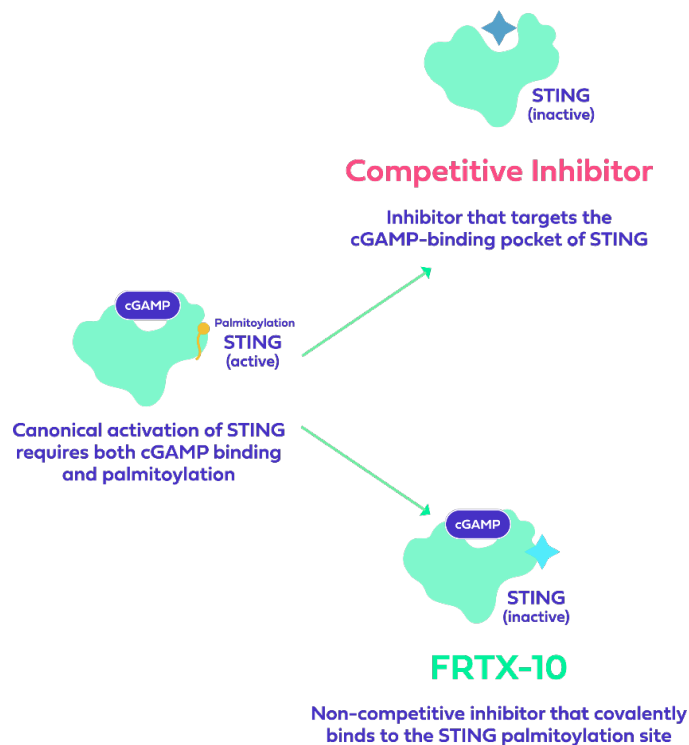
# Mechanism of Action

FRTX-10 covalently inhibits STING activation, resulting in reduction of proinflammatory cytokines such as IL-6 and Interferon (IFN)- $\beta$



# Competitive Advantage Against Other STING Inhibitors

FRTX-10 inhibits STING palmitoylation, which may present a more effective way to treat inflammation caused by aberrant STING signaling



	COMPETITIVE INHIBITOR	FRTX-10
MECHANISM	Dependent on endogenous cGAMP levels	Independent of cGAMP levels
STING VARIANTS	Potency on inhibition could vary between variants	Inhibits all four major variants of human STING
STING MUTANTS	Always active regardless of cGAMP binding	Inhibits pathologic STING mutants

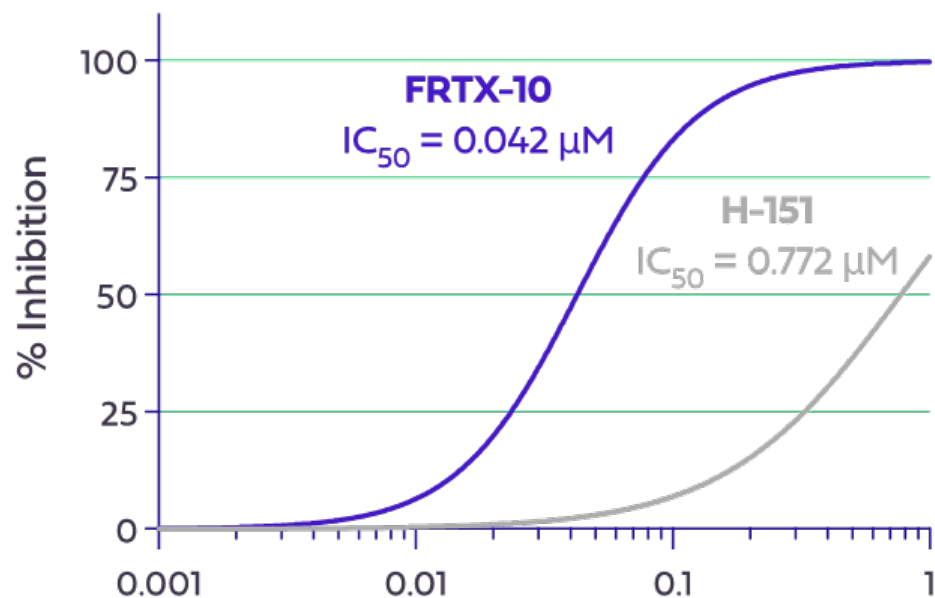
1. Mukai, K. et al. Nat. Commun. (2016). 2. Yi, G. et al. PLoS One (2013). 3. Decout, A., Katz, J. D., Venkatraman, S. & Ablasser, A. Nat. Rev. Immunol. (2021).

# Compound Overview

FRTX-10 is a highly selective STING inhibitor that exhibits potent inhibition of human and murine STING compared to other covalent inhibitors

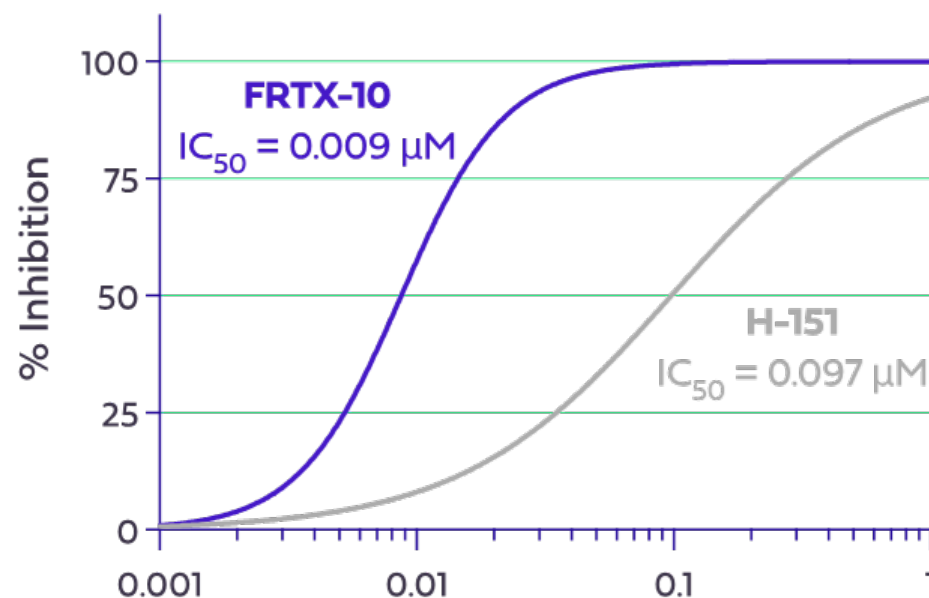
## hSTING

in HEK293 cells



## mSTING

in B16 cells

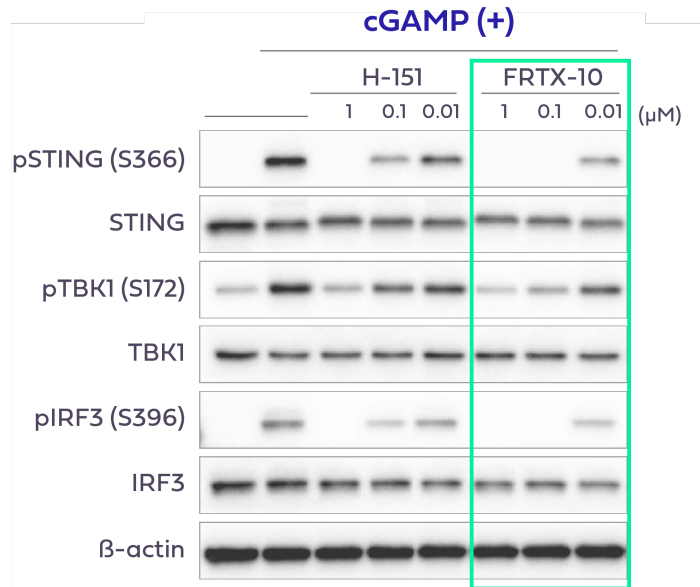


H-151 = Covalent STING inhibitor also targeting palmitoylation site; Haag, S. et al (2018) Nature, 559(7713),269-273).

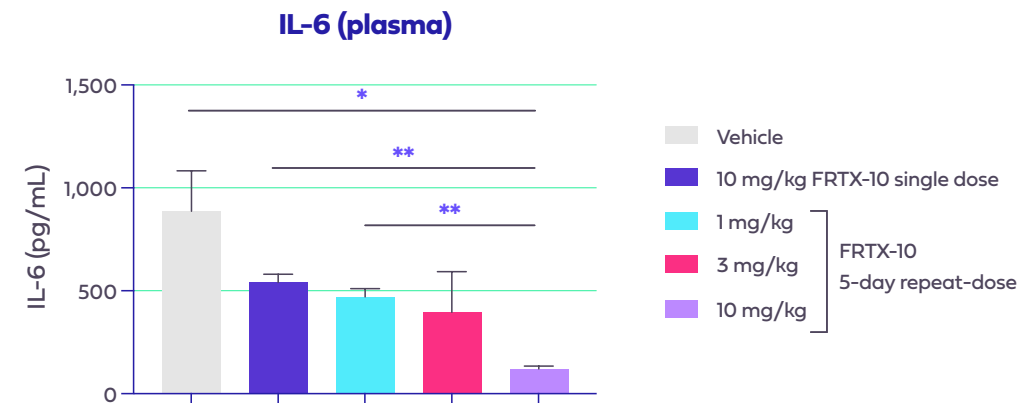
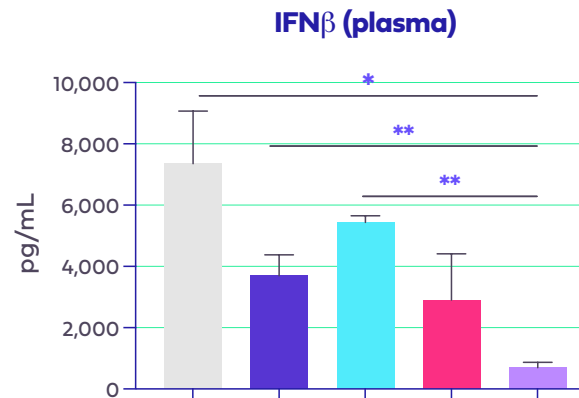
# Preclinical Proof-of-Mechanism

FRTX-10 demonstrated proof-of-mechanism on relevant pathways *in vitro*, resulting in significant reduction of key cytokines IL-6 and IFN $\beta$  after single and multiple dose oral treatment *in vivo*

FRTX-10 inhibits the phosphorylation of key proteins in the STING pathway<sup>1</sup>



Once-daily oral FRTX-10 treatment resulted in significant reduction of cytokines in a CMA-stimulated mouse model<sup>2</sup>



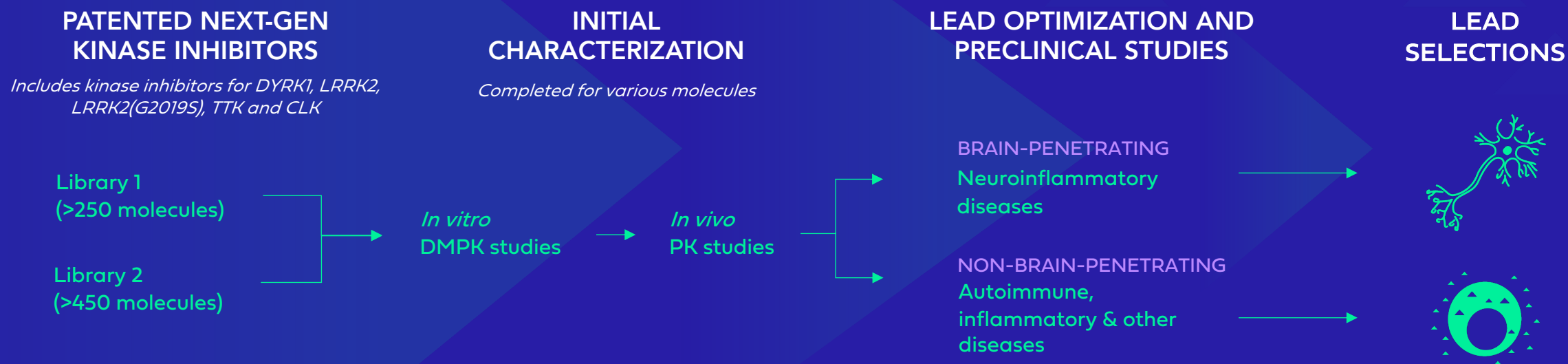
1. H-151 = Covalent STING inhibitor also target palmitoylation site; Haag, S. et al (2018) Nature, 559(7713),269-273. 2. C57BL/6N mice treated with FRTX-10 QD, single or repeated (5 days). Mice were stimulated with 224 mg/kg CMA i.p. and blood samples were taken 2 hours after CMA stimulation. Serum levels of IL-6 and IFN $\beta$  were measured by ELISA. \*p<0.05 \*\*p<0.01 (unpaired, Welch's two-tailed t-test)

# Next-Generation Kinase Inhibitors

## Platform Overview

# Platform of Next-Generation Kinase Inhibitors

Our platform of next-generation kinase inhibitors include small molecules that inhibit DYRK1, LRRK2, TTK and CLK with various potency and selectivity profiles



Internal Data

# Thank You!

Making Fresh Tracks in Medicine®

[ir@frtx.com](mailto:ir@frtx.com)

August 2023

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