ARIA PHARMACEUTICALS

System Lupus Erythematosus (SLE)

May 2022

SOUND SCIENCE

ARIA IDENTIFIES THE THERAPEUTICS MOST LIKELY TO SUCCEED

Success Rates	Industry	ARIA PHARMACEUTICALS
in vivo	1-2%	**30%**[1]
Phase II	30%	**80%**[2]

Cumulative likelihood of success *in vivo* through Phase 2

50x Higher

1 – Significantly disease-modifying hits in preclinical animal models identified by Symphony; N=18 diseases, on average 10 molecules per disease
2 – Retrospective efficacy success rate of clinical trials of molecules identified by Symphony; N=18 diseases, 283 PH2 CTs

ARIA'S STRATEGIC ADVANTAGE IN SLE

MAXIMIZED LIKELIHOOD OF CLINICAL SAFETY – HUMAN SAFETY AT PHASE I

ESTABLISHED TOLERABILITY

Multiple CCR2 inhibitors have safely completed Phase I

MAXIMIZED LIKELIHOOD OF CLINICAL EFFICACY – HUMAN EFFICACY AT PHASE II

HIGH CLINICAL PREDICTABILITY IN SLE

Symphony predicted 100% of SOCs & Phase III successes and 87.5% of Phase II successes in SLE

SYSTEMIC LUPUS ERYTHEMATOSUS (LUPUS)

MARKET

5 MILLION cases worldwide

ORGAN DAMAGE, PAIN & INFLAMMATION

COMPLEX TREATMENT WITH MULTIPLE DRUG CLASSES – e.g. hydroxychloroquine & corticosteroids

$1B

2024 Market ($/Year)[1]

SPEED AND SUCCESS

9 MOLECULES ADVANCED from hit prediction to *in vivo*

12 WEEKS from program start to *in vivo* results

LEAD MOLECULE TXR-711 IN VIVO HIGHLIGHTS:

NOVEL MOA in lupus

Significantly **IMPROVED** kidney function
Significant **DECREASE** in inflammation

COMPARABLE EFFICACY to cyclophosphamide

Severe flare treatment with **BETTER TOXICITY** profile

GOOD TOLERABILITY – clinically investigated mechanism

4 Source: (1) Pharmaceutical Intelligence Services, GlobalData LLC.

HIGH UNMET MEDICAL NEED FOR SLE

5 MILLION CASES WORLDWIDE

400K US cases

9 OUT OF 10 adults living with lupus are women

AFFLICTS PATIENTS OF CHILD-BEARING AGE 15-44yrs

HETEROGENEOUS & COMPLEX DISEASE

ORGAN INVOLVEMENT – affects kidney, CNS, skin, CV
PAIN AND INFLAMMATION mild to severe

SIGNIFICANT SYMPTOMS such as pain, extreme fatigue, hair loss, cognitive issues, and physical impairments

KIDNEY DAMAGE occurs in 60% of SLE patients

STANDARD OF CARE

HYDROXYCHLOROQUINE – well tolerated, but not efficacious

CORTICOSTEROIDS – strong efficacy with associated toxicity

SOCs DO NOT CURE disease, only manage flare ups

HETEROGENEOUS DISEASE WITH COMPLEX TREATMENT ALGORITHM

- Current complex treatment algorithm attempts specialized well-tolerated treatments first
- Efficacy failures lead to use of poorly-tolerated drugs across clinical presentations
- A broadly safe & effective treatment would become “drug of choice”, collapsing the current treatment algorithm

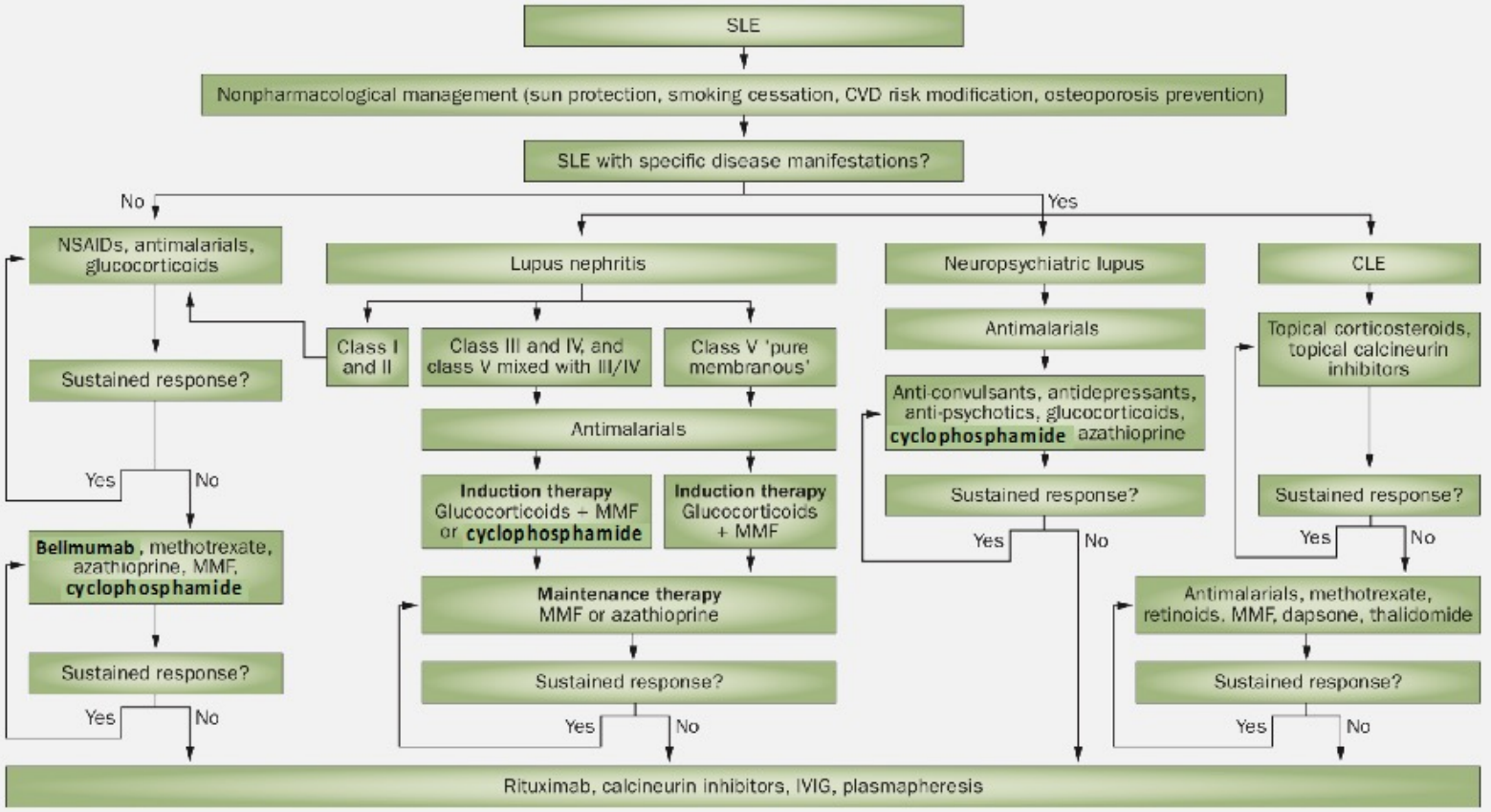

Figure 1 | Algorithm for the treatment of SLE. Abbreviations: CLE, cutaneous lupus erythematosus; CVD, cardiovascular disease; IVIG, intravenous immunoglobulin; MMF, mycophenolate mofetil; SLE, systemic lupus erythematosus.

Xiong et al 2013 *Nature Reviews Rheumatology*

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INVESTIGATIONAL DRUGS

SELECTED AGENTS – RECENTLY COMPLETED OR IN ACTIVE SLE CLINICAL TRIALS

Agent	Developer	Target(s)	Completed Phase	Primary Endpoint	Current Status	Response
Anifrolumab	AstraZeneca	IFNGR1	III	BICLA response	Approved	TULIP 1 - failed EP (8/31/2018) TULIP 2 - met EP (8/29/2019)
Baricitinib	Incyte - Eli Lily	JAK1/2	III	Reduced arthritis or rash SLEDAI*-2K	Phase III terminated	insufficient evidence to support a positive benefit: risk ratio
Obinutuzumab	Roche	CD20	II	Complete renal response	Phase III recruiting	Failed CRR at 52 weeks Successful CRR at 76 and 104 weeks [41% vs 23% (placebo) at 104 weeks]
Evobrutinib	Merck	BTK	II	SRI-4, SRI-6	Failed endpoints (2020)	SRI-4: 48.2-55.7% vs 45.6% (placebo) SRI-6: 43.6-50.0% vs 39.3% (placebo)
Vobarilizumab	Ablynx	IL6R	II	mBICLA response	Failed endpoint (2019)	43.8% vs 46.8% (placebo)
Cenerimod	Idorsia	S1PR1	I	mSLEDAI response (in Ph II)	Phase II ongoing	N/A

SRI: SLE Responder Index | BILAG: British Isles Lupus Assessment Group | BICLA: BILAG-based Combined Lupus Assessment| SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index-2000

DISCOVERY PROCESS IDENTIFIES TXR-711 & TXR-712 IN 12 WEEKS

AI-Driven Discovery

Diverse Data, Methods:

- 25 data sources
- 65 methods
- 2M+ molecule chemistry library

50K Molecules

AI-Assisted Review

Novelty and Safety:

- Novel MOA
- Safety profile
- ADME properties

3K Molecules

Hit Diligence

PhD-led Deep Dive:

- MOA relevance
- MOA safety
- IP development path

80 Molecules

Preclinical

Optimal Disease Models:

- Test diverse MOAs
- CRO availability
- Rapid *in vivo* efficacy

9 Molecules

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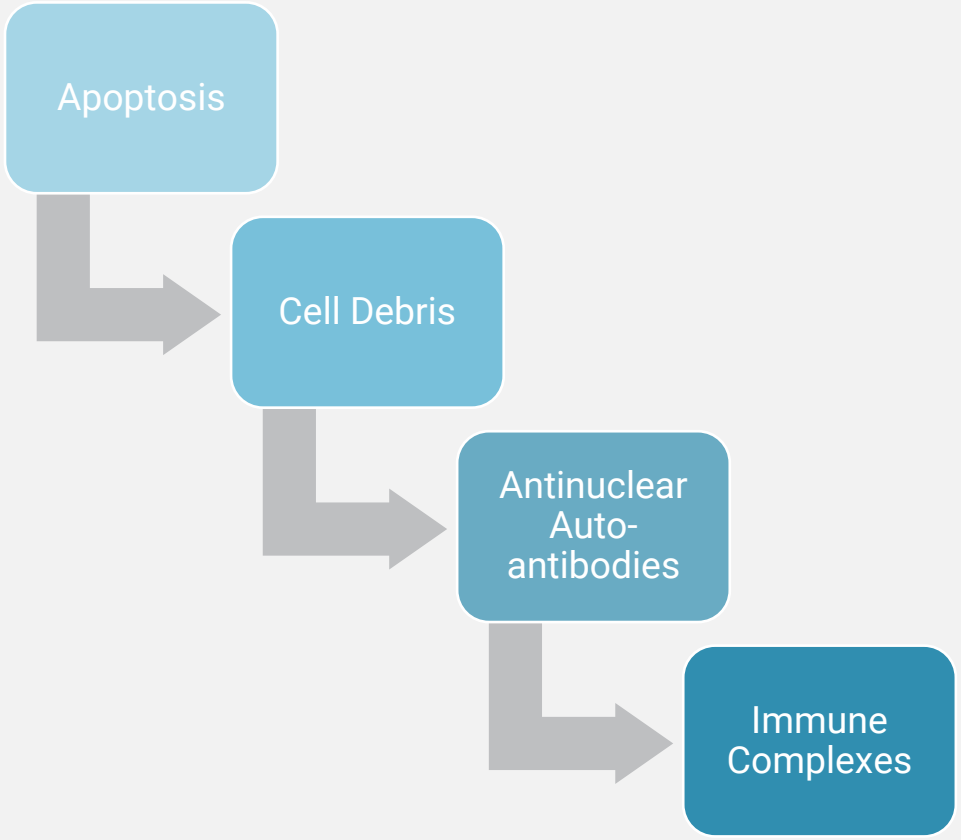
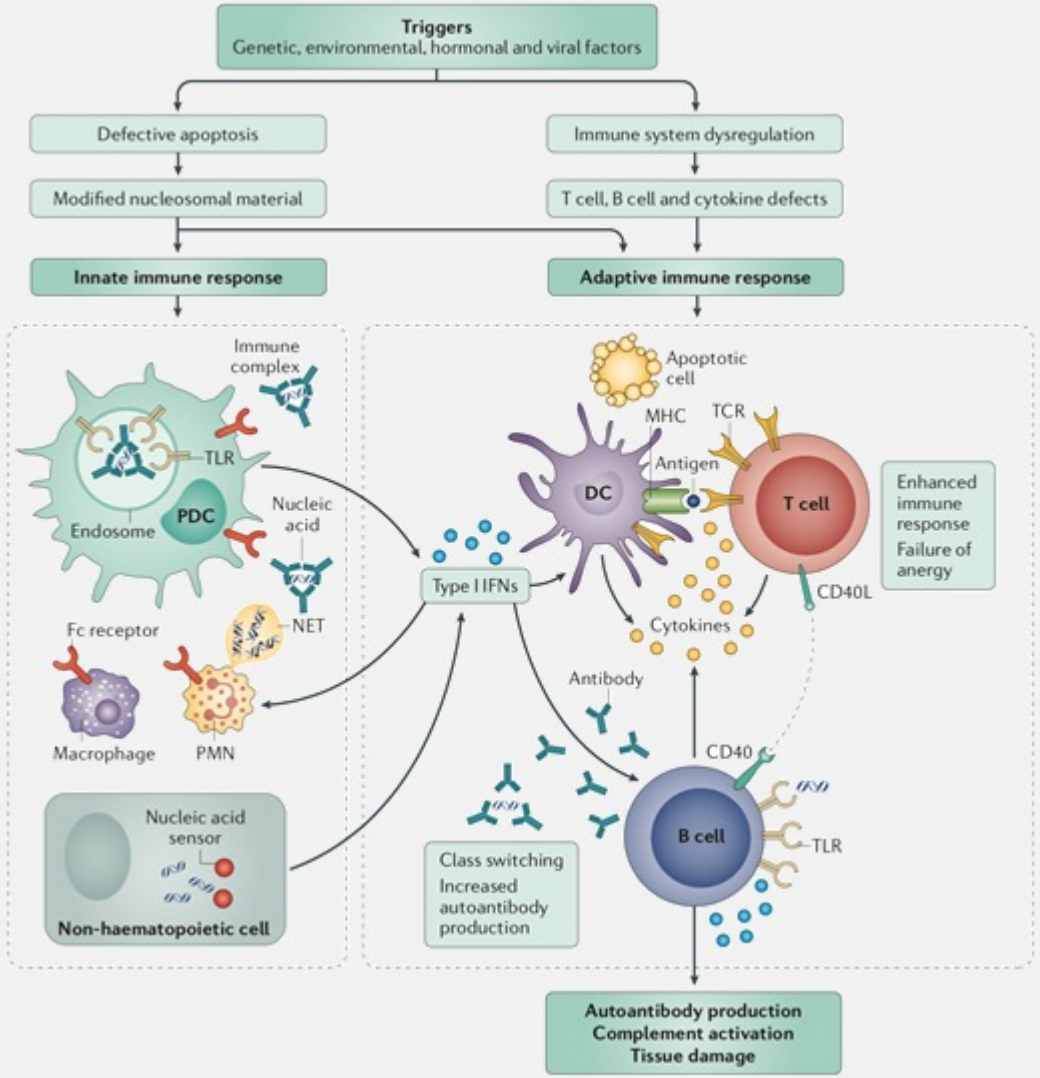
BIOLOGY OF SLE

DYSFUNCTIONAL IMMUNE RESPONSE TO APOPTOSIS THAT DRIVES INFLAMMATION





IFN: Interferon | PDC: plasmacytoid dendritic cells | DC: Dendritic cell | PMN: polymorphonuclear leukocytes | MHC: Major Histocompatibility Complex| TCR:T Cell Receptor | TLR: Toll-Like Receptor

Kaul et al 2016 *Nature Reviews Disease Primers*

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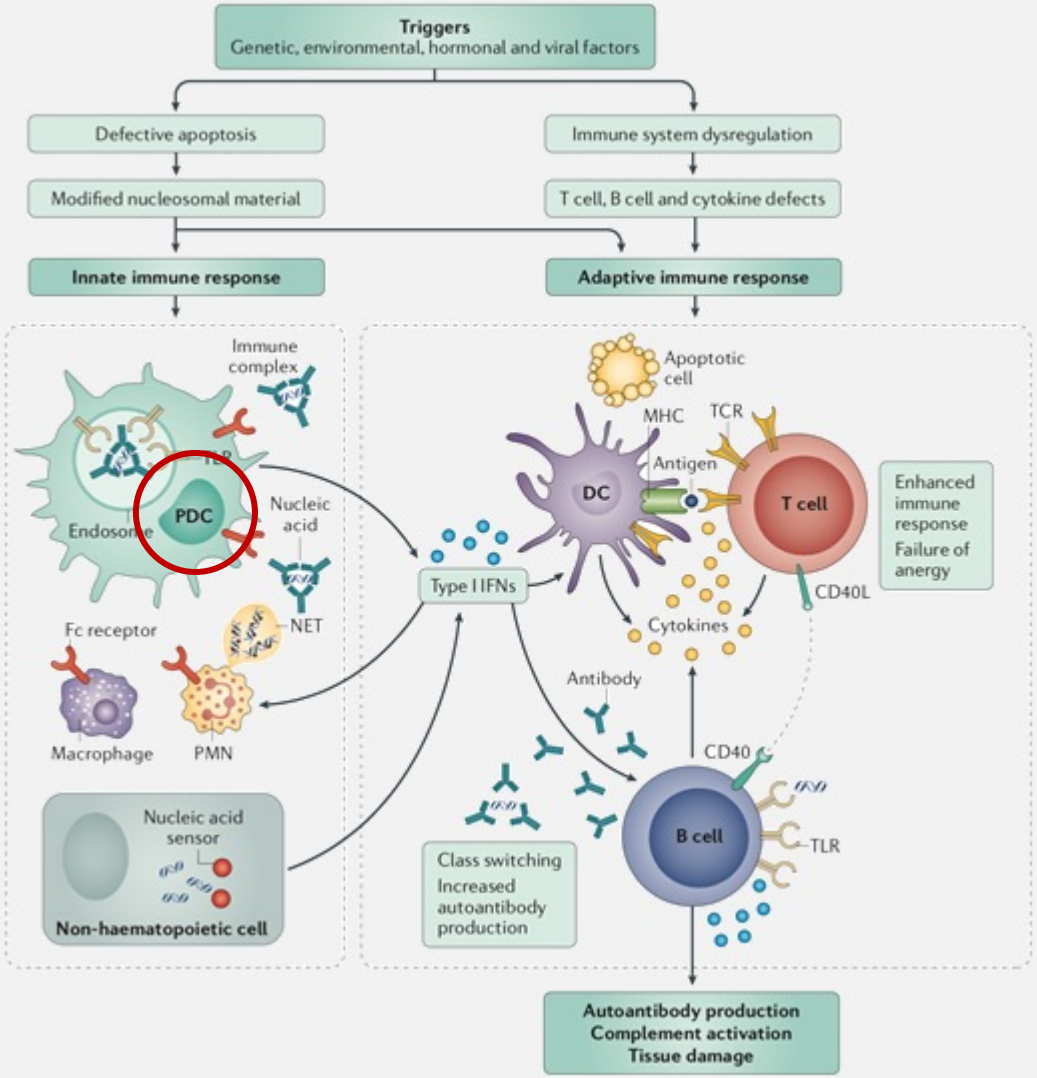
TXR-711 BACKGROUND

PLASMACYTOID DENDRITIC CELLS PLAY A PREDOMINANT ROLE IN SLE

- pDC depletion has been reported to improve preclinical outcomes in SLE models[1]
  - Including kidney inflammation
- pDCs overexpress chemokine receptor 2 (CCR2) in lupus patients
  - pDC homeostasis, is thought to be regulated by CCR2, and that CCL2, the canonical CCR2 ligand, does not play a major role[2]



Adapted from Kaul et al 2016 *Nature Reviews Disease Primers*

1. Huang, *et al.*, 2015, *Front Immunol*
2. Cedile, *et al.*, 2017, *Immunol Lett*

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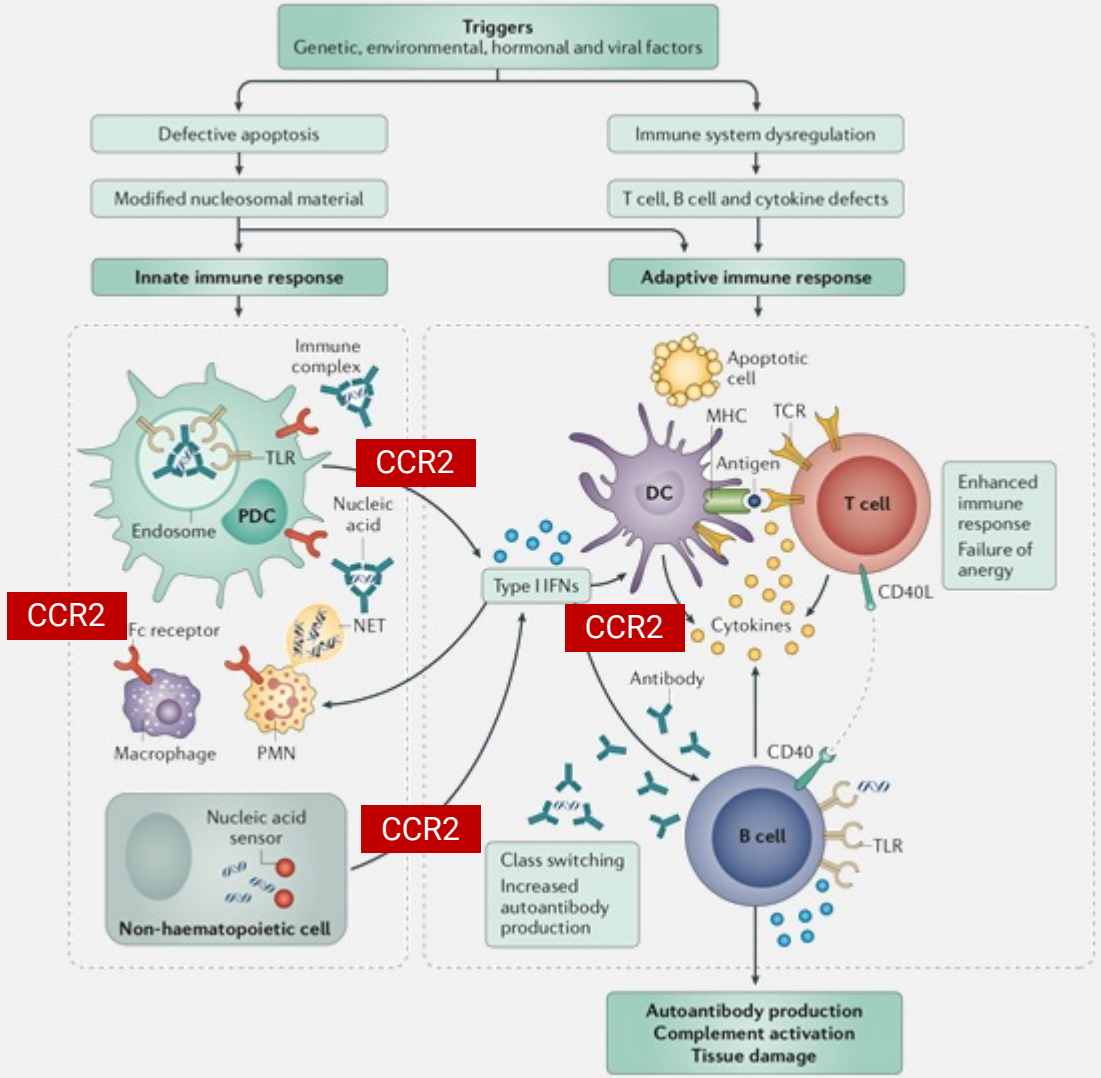
TXR-711 IS A CCR2 ANTAGONIST

- TXR-711 MOA can exert SLE efficacy by suppressing inflammation through multiple pathways & processes

- CCR2 inhibition:
  - Inhibits monocyte chemotaxis
  - Inhibits macrophage differentiation, infiltration
  - Inhibits STAT3, NF-kB, MAPK, and AKT signaling
  - Inhibits cytokine expression, oxidative stress, ER stress, inflammation

- CCR2 is highly expressed in macrophages & dendritic cells that recognize apoptotic debris



Adapted from Kaul et al 2016 *Nature Reviews Disease Primers*

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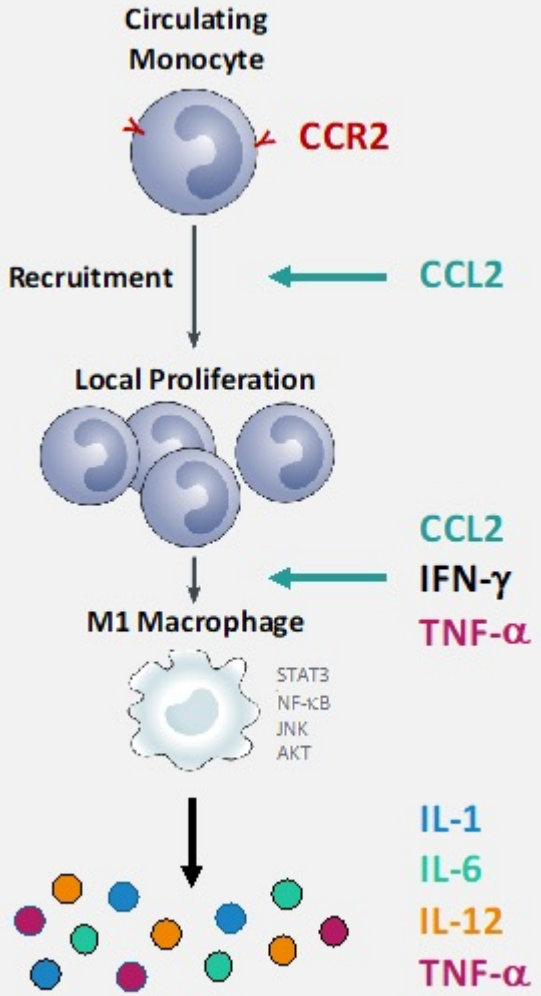
CCR2 INHIBITION REDUCES PHAGOCYTE ACTIVITY & CYTOKINE EXPRESSION

- CCR2 recruits monocytes & promotes their differentiation to IL-1, 6, 12 & TNF-α secreting M1 macrophages
- CCR2 and CCL2 are highly expressed in SLE patients, especially lupus nephritis
- TXR-711 is an equipotent inhibitor of the main CCR2 ligands, CCL2 (MCP-1), CCL7 (MCP-3), and CCL8 (MCP-2)



Adapted from Tang, P.M. *et al.* 2019, *Nat Rev Nephrol*

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CCR2 INHIBITION HAS UNIQUE ROLE IN SLE

- CCR2 inhibition has failed clinical investigation; e.g.: Atherosclerosis[1], multiple sclerosis (MS)[2], & rheumatoid arthritis (RA)[3]
  - Failures have been hypothesized to be due to redundancies in the chemokine system and/or because of the dose dependent increase in CCL2 expression that has been observed during CCR2 inhibition
- To address increases in CCL2 levels following CCR2 inhibition, our medicinal chemistry efforts aim to optimize the affinity and drug-target residence time of our CCR2 inhibitor
  - Long-residence antagonism of CCR2 has been shown to effectively inhibit the development of atherosclerosis in a mouse model[4]
- SLE chemokine pathology differs from the diseases clinically investigated with CCR2 inhibitors, particularly in the importance of pDCs
  - RA patients have very low numbers of pDCs, and their role (if any) is not well defined in RA[5,6]
  - pDCs are associated with atherosclerosis, where pDCs demonstrate dysfunctional phenotypes[7], and MS, where several clinically used treatments (e.g., IFN-β, Natalizumab, & glatiramer acetate) modulate pDC abundance and activation[8,9,10]. In both diseases CCR2 inhibition has shown initial efficacy

1. NCT02388971
2. NCT01199640
3. Vergunst, *et al.*, 2008, *Arth & Rheum*
4. Ilze Bot, *et al.*, 2017, *Sci rep*
5. Takakubo, *et al.*, 2008, *J Rheum*
6. Kavousanaki, *et al.*, 2009, *Arth & Rheum*
7. Stasiolek, *et al.*, 2006, *Brian*
8. Schwab, *et al.*, 2010, *J Immunol*
9. Kivisakk, *et al.*, 2014, *PLOS ONE*
10. Hussien, *et al.*, 2001, *J Neuroimmunol*

CCR2 INHIBITION CAN REDUCE INFLAMMATION AND IMPROVE RENAL FUNCTION

SLE-ASSOCIATED CHANGES

- IFN response triggers T/B cell adaptive immune response
  - T cell activation stimulates B cell antibody production
- Macrophage activation, polarization and recruitment
- Type I IFNs lead to activation of innate immune response through interaction w/JAK/STAT pathway
- Innate immune activation triggers IFN response and plasmacytoid dendritic cells (pDCs) activation
- Apoptotic cell debris
- Perpetual inflammation and organ damage

CCR2 INHIBITION EFFECTS

- Inhibition of IFN/STAT, NF-kB signaling result in decreased antibody production
- Inhibits cytokine expression, ox. & ER stress, inflammation
- Inhibits macrophage differentiation, infiltration, & activation
- Decreases monocyte recruitment and differentiation of IL-1, 6, 12, & TNF-α secreting macrophages
- pDC depletion
- Decrease of inflammation by dampening both innate and adaptive immune response

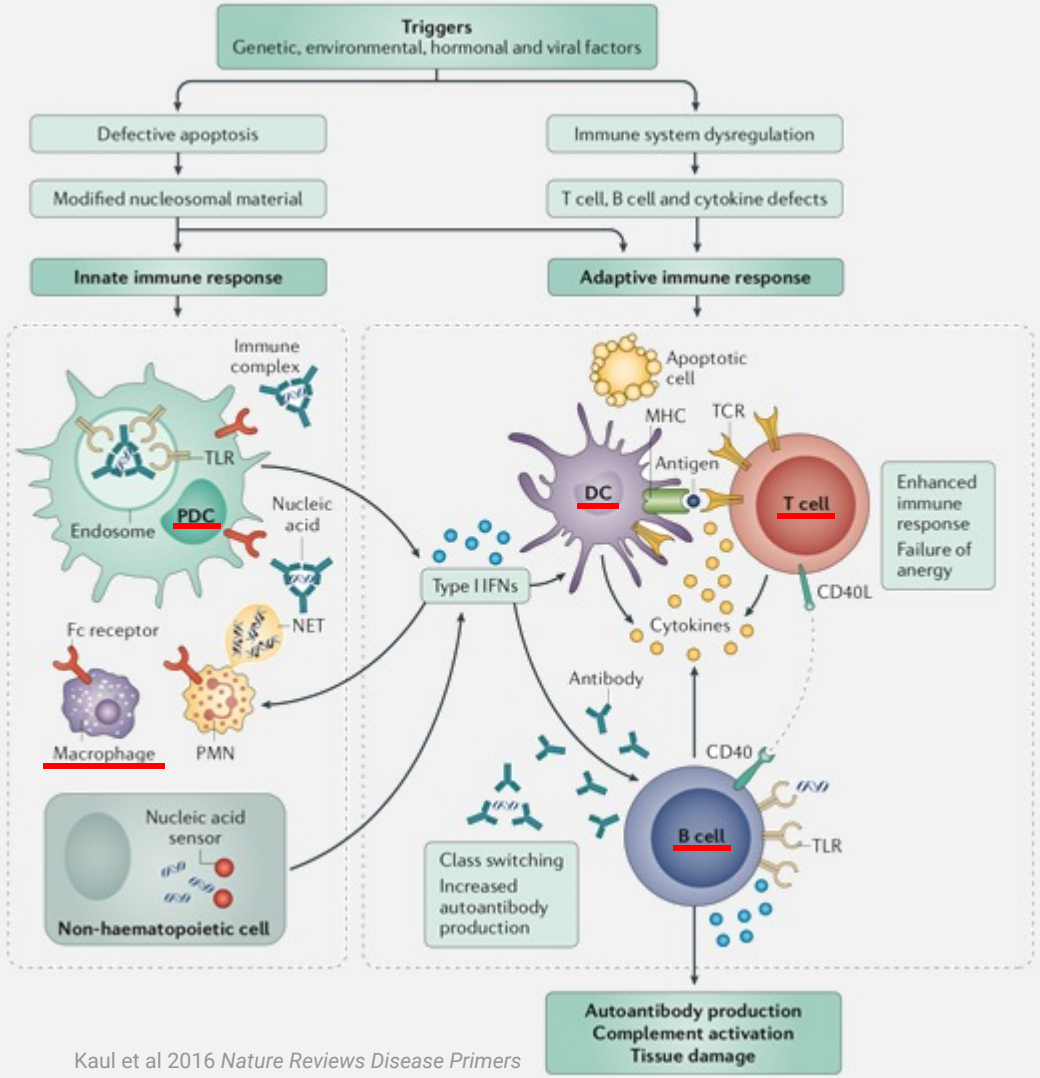
- CCR2 inhibition can block or reverse phenotypic changes associated with SLE while maintaining excellent tolerability

TXR-712 BACKGROUND

AUTOPHAGY REGULATES AUTOIMMUNE RESPONSES INCLUDING IN SLE

- Several autophagy-related genes, including LRRK2, have been genetically associated with SLE[1,2,3]
- In plasmacytoid DCs (pDCs), autophagy is required for IFN-α production[4]
- In macrophage autophagy regulates cell function and participates in pathogenesis in lupus nephritis[5]
- In dendritic cells (DCs), autophagy is required for antigen presentation[6]
- In T cells, autophagy plays a critical role in development and proliferation[7]
- In B cells, autophagy can mediate autoimmunity and inflammation[8]

IFN: Interferon | PDC: plasmacytoid dendritic cells | DC: Dendritic cell | PMN: polymorphonuclear leukocytes | MHC: Major Histocompatibility Complex| TCR:T Cell Receptor | TLR: Toll-Like Receptor



Kaul et al 2016 *Nature Reviews Disease Primers*

1. Zhang, *et al*., 2017, Oncotarget
2. Zhou, *et al*., 2010, Ann Rheum Dis
3. Ciccacci, *et al*., 2014, PLoS One
4. Weindel, *et al*., 2017, J Iummonl
5. Wang & Law, 2015, Int J Mol Sci
6. Lee, *et al*., 2009, J Immuni
7. Yin, *et al*., 2018, Front Immunol
8. Weindel, *et al*., 2015, Autophagy

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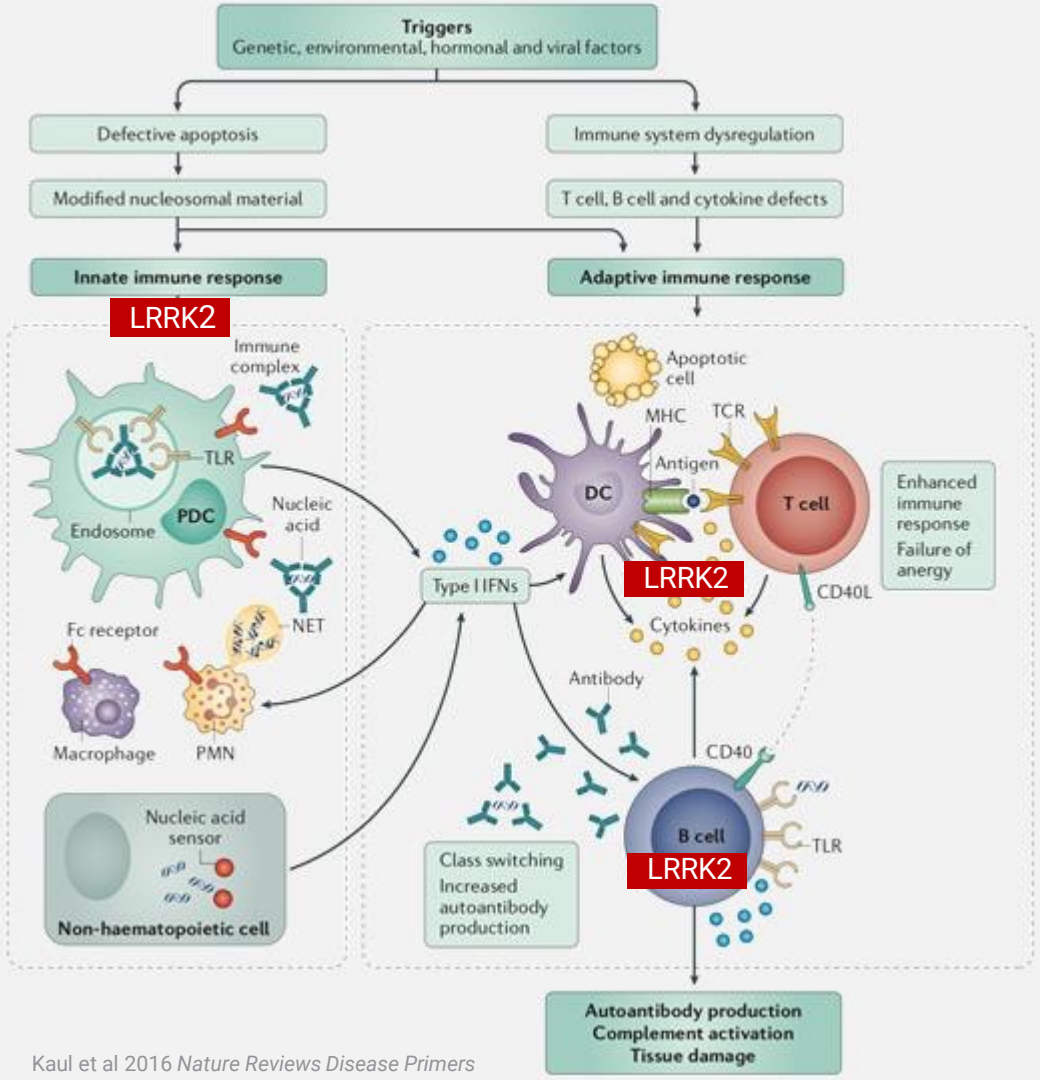
TXR-712 IS A LEUCINE-RICH REPEAT KINASE-2 (LRRK2) INHIBITOR

- TXR-712 MOA can exert SLE efficacy by suppressing inflammation through multiple pathways & processes

- LRRK2 inhibition:
  - Induces phagocyte autophagy which is involved throughout innate & adaptive immunity [1,2]
  - Inhibits pro-inflammatory signaling, e.g., NF-kB, STAT3[3]
  - Inhibits cytokine expression, oxidative stress, inflammation[3]

- LRKK2 negatively regulates autophagy
  - Autophagy induction decreases p62 expression and NF-kB activity [3]



Kaul et al 2016 *Nature Reviews Disease Primers*

1. Clarke et. al., 2015 Ann Rheum Dis.
2. Dzamko, et. Al., 2012, Biochem Soc. Trans
3. Takagawa et al 2018 *Science Translational Medicine*

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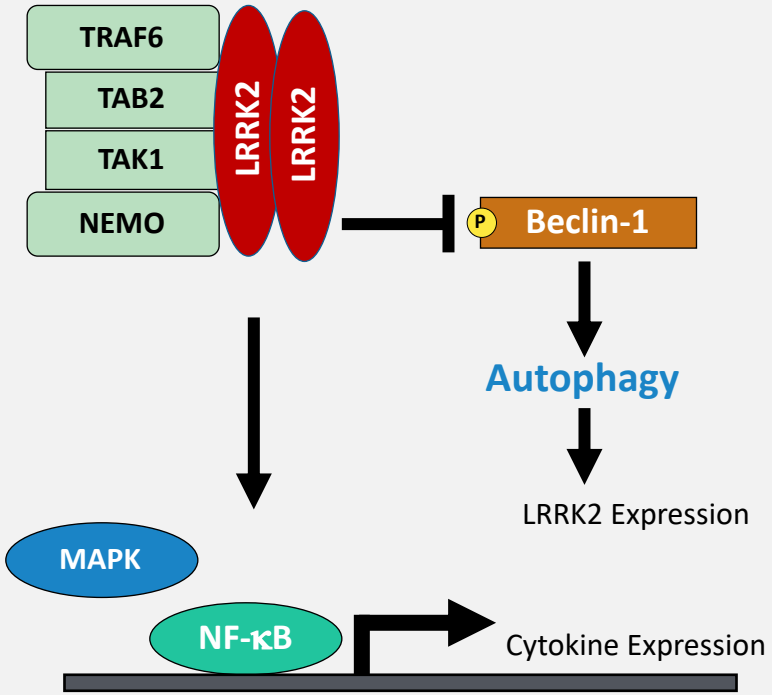
LRKK2 IS INVOLVED IN DIVERSE INFLAMMATION & IMMUNE FUNCTIONS

- LRKK2 inhibition suppresses NF-kB signaling, cytokine expression, and inflammation[1]
- LRRK2 expression in B cells isolated from SLE patients correlates with disease progression[2]
- LRRK2 mRNA and protein is up-regulated following activation of the IFN-γ receptor[3]
  - IFN-γ is a major effector of SLE



Clarke et. al., 2015 Ann Rheum Dis.

1. Takagawa et al 2018 *Sci Trans Med*
2. Zhang, *et al*., 2019, *J Trans Med*
3. Gardet, *et al*., 2010, *J Immunol*

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LRRK2 INHIBITOR DEVELOPMENT

- Selectivity in LRRK2 inhibitor design has been challenging because of the multi-domain complexity and size of LRRK2
- Efforts to date have focused on neurological disease, e.g., Parkinson's Disease, which adds the challenge of attaining CNS penetration, high plasma protein binding and efflux
- Recent drug discovery efforts have resulted in several promising selective, brain penetrant LRRK2 inhibitor chemotypes
    - Two compounds DLN201 and DLN151 have entered Phase 1b clinical trials. DNL201 was well tolerated without serious adverse events at drug concentration level with > 90% inhibition of peripheral LRRK2 activity[1]
- Medicinal chemistry efforts would focus on maximal selectivity while avoiding CNS penetration

1. Williamson, *et.al.*, 2018, *Med Chem Rev*

LRRK2 INHIBITION CAN REDUCE INFLAMMATION AND IMPROVE RENAL FUNCTION

SLE-ASSOCIATED CHANGES

- Autophagy involved across innate and adaptive immunity
- Upregulated autophagy observed in both B cells and macrophages in SLE patients
- NF-kB signaling, cytokine expression, & inflammation is upregulated
- IFN-γ receptor leads to activation of innate immune response through interaction w/JAK/STAT pathway
- Perpetual inflammation and organ damage

LRRK2 INHIBITION EFFECTS

- Induces phagocyte autophagy
- Inhibits macrophage differentiation, infiltration, & activation, and autophagy in B cells/macrophages
- Inhibits cytokine expression, NK-kB, & inflammation
- Decreases monocyte recruitment and differentiation of IL-1, 6, 12, & TNF-α secreting macrophages
- Decrease of inflammation by dampening both innate and adaptive immune response

- LRRK2 inhibition can block or reverse phenotypic changes associated with SLE while maintaining excellent tolerability

SLE: DISEASE & PRECLINICAL MOUSE MODELS

- A hallmark feature of human SLE is the presence of antinuclear antibody (ANAs), anti-double stranded DNA (anti-dsDNA) antibodies and anti-RNA or RNA associated antibodies
- Clinical manifestations include glomerulonephritis (GN), arthritis, heart disease, cutaneous lesions and neurological symptoms. Each patient presents with a unique phenotype, mouse models can recapitulate limited features of the disease but not all in one preclinical model.
- Given the high degree of clinical heterogeneity in SLE patients, preclinical mouse models summarized below have been very valuable to investigate the etiology of SLE as well as to identify and validate therapeutic targets:
    - Spontaneous: MRL/lpr, NZB/W, BXSB
    - Induced: Pristane induced
    - Accelerated: IFNα accelerated

ASSESSMENT OF HUMAN CLINICAL PRESENTATION IN PRECLINICAL MOUSE MODELS

HUMAN CLINICAL PRESENTATION	MRL/LPR MODEL	NZB/W MODEL	IFN-a ACCELERATED/ INDUCED MODEL
Autoantibody production	X	X	
Cutaneous effects	X		
Neurological effects	X		
Immune dysregulation	X	X	X
Kidney disease	X	X	X
Arthritis	X	X	
IFN signature		X	X
Cardiac effects		X	
Endothelial effects		X	

IN VIVO STUDY DESIGN

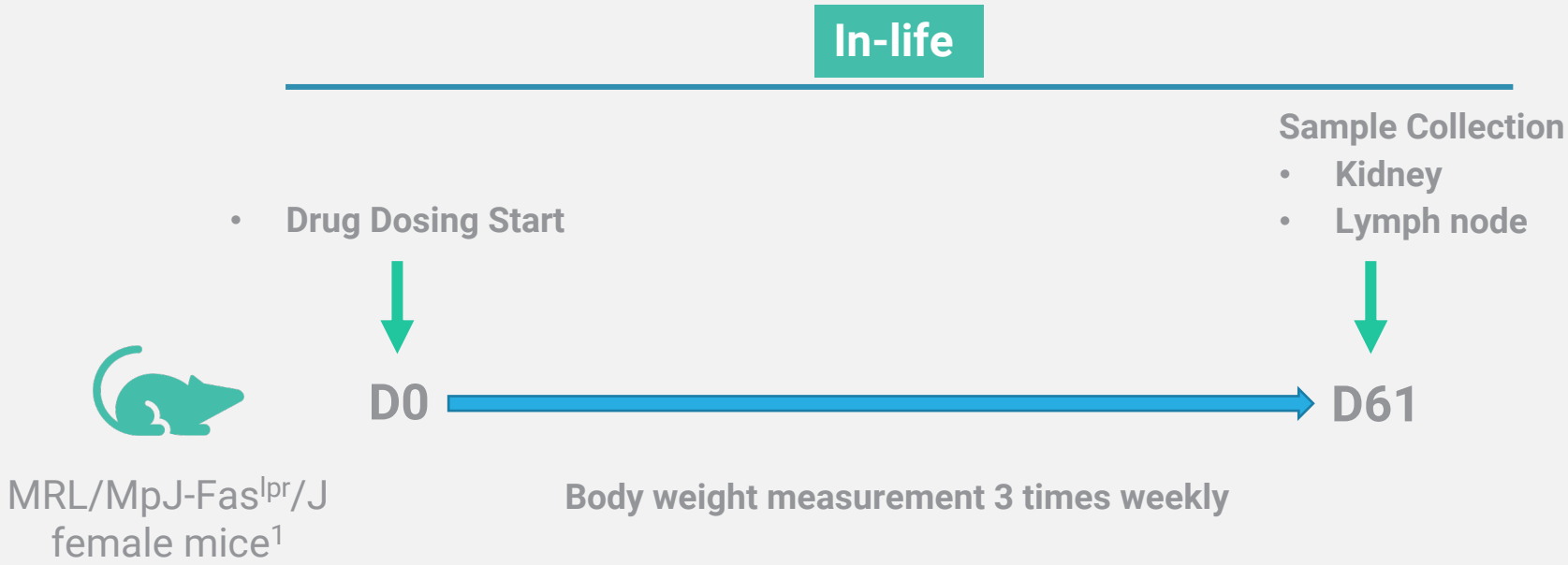
MRL/LPR MOUSE MODEL

- Lymph node weight
- Kidney weight, function
- Kidney histology

REFERENCE THERAPY

- Cyclophosphamide: flare treatment – high efficacy, but toxicity limits clinical utility

INITIAL *IN VIVO* STUDY DESIGN



Efficacy Measures

- Lymph node weight
- Kidney weight
- Kidney histology
- Kidney function: Proteinuria and blood urea nitrogen

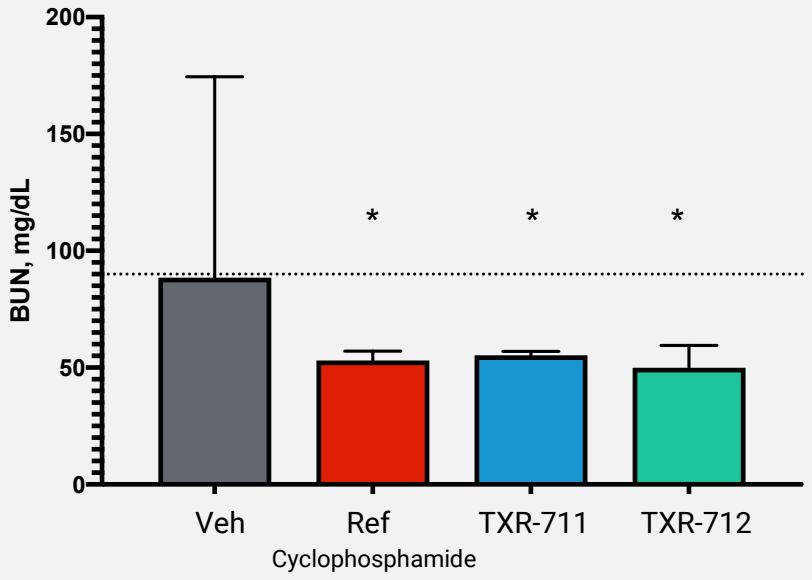
- MRL model represents human SLE better than other models
- Multiple efficacy measures assessing health of lymph nodes and kidneys
- Two candidates identified; TXR-711 MOA selected for development, TXR-712 MOA as backup
- Additional models available for further candidate investigation; e.g., NZB/W mouse model

1. Celhar & Fairhurst. 2017. *Rheumatology*

COMPARABLE KIDNEY FUNCTION EFFICACY VS CYCLOPHOSPHAMIDE

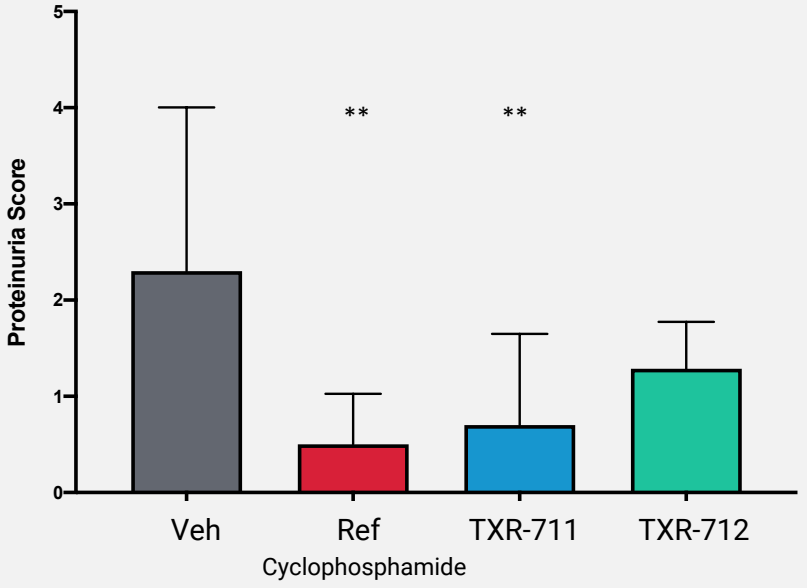
- TXR-711 significantly improves multiple renal function readouts
- Comparable to cyclophosphamide

Blood Urea Nitrogen



*. p<0.05
** p<0.01
N=10 per Group

Proteinuria



SCORE	mg/dL
0	None
1	1-29
2	30-99
3	100-299
4	300-1999
5	≥2000

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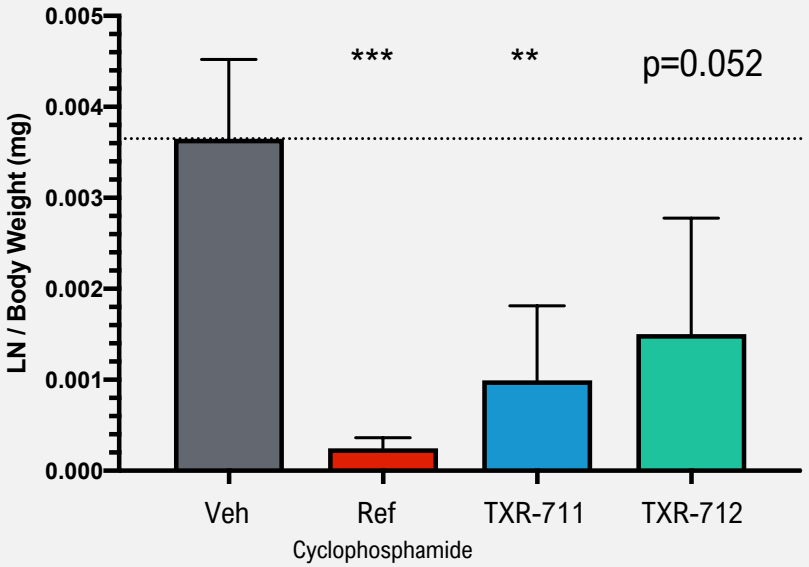
SIGNIFICANT LYMPH NODE AND KIDNEY WEIGHT IMPROVEMENTS

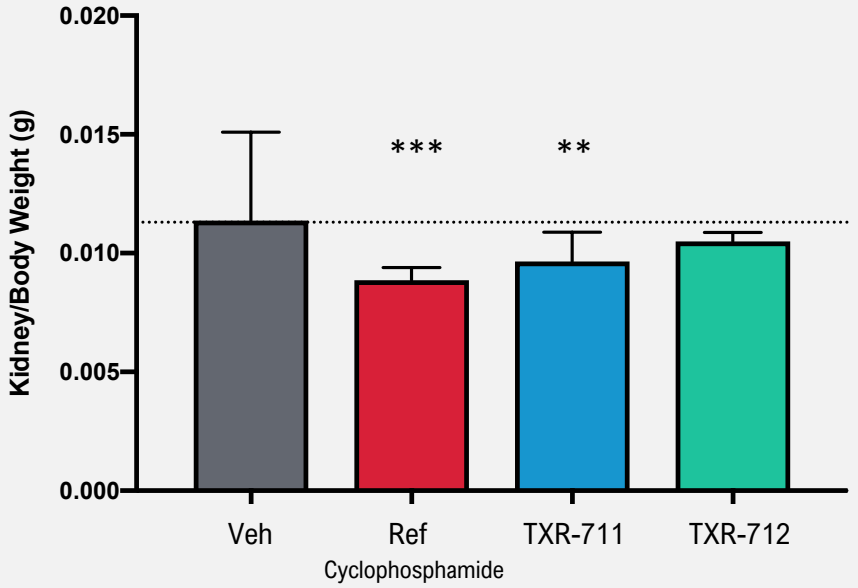
- TXR-711 significantly decreased inguinal lymph node & kidney weight normalized to body weight
- Overall body weight was stable

Inguinal Lymph Node Weight



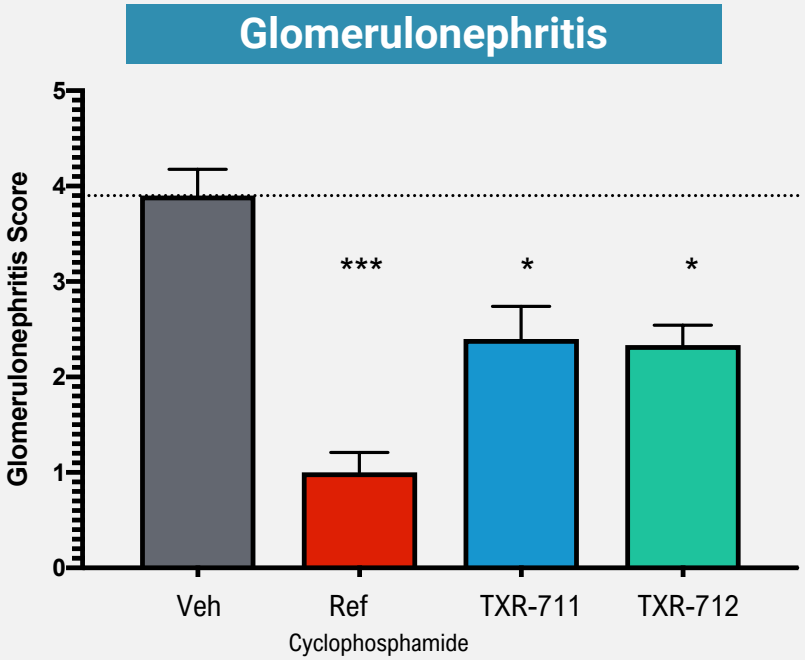
* p<0.05
** p<0.01
*** p<0.001
N=10 per Group

Kidney Weight



SIGNIFICANT KIDNEY INFLAMMATION DECREASES

- Glomerulonephritis and tubule basophilia – renal Inflammation measures
- TXR-711 significantly improves renal inflammation measures



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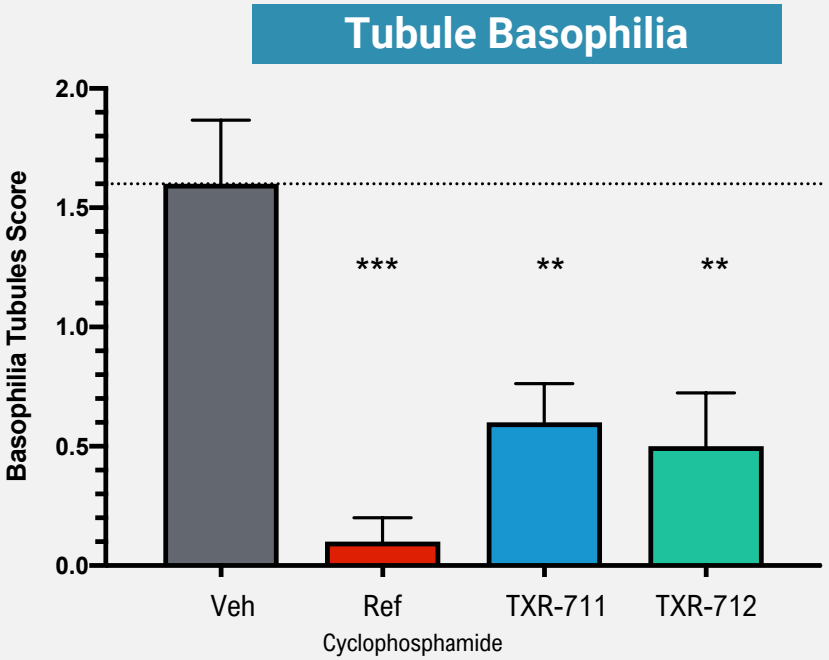
N=10 per Group



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TXR-711 SELECTED AS LEAD, TXR-712 AS BACKUP

- In the preclinical MRL/lpr mouse model, TXR-711 showed significant improvement in multiple readouts demonstrating better efficacy than TXR-712
- TXR-711 has been in clinical trials, has drug-like properties, and extensive SAR data
- Extensive SAR/SPR data learnings from several other CCR2 antagonists for optimization
- Various crystal structures for CCR2 and co-crystal with CCR2 ligands available for structure-based drug design. Well-defined pharmacophore for ligand-based, Core-hopping and SBDD.

COMPARISON OF CYCLOPHOSPHAMIDE AND TXR-711 IN MLR/LPR MODEL

EFFICACY MEASURE	CYCLOPHOSPHAMIDE	TXR-711	COMMENTS
Lymphadenopathy	Comparable decrease	Comparable decrease	
Kidney weight	Comparable decrease	Comparable decrease	
Kidney function	Significant improvement in BUN and proteinuria levels	Significant improvement in BUN and proteinuria levels	• Data comparable/equivalent to cyclophosphamide
Kidney inflammation	High dose of cyclophosphamide shows higher decrease vs. TXR-711, but at doses known to be adverse in humans for long term dosing [Significant decrease in glomerulonephritis and tubule basophilia]	Significant decrease (tubule basophilia and glomerulonephritis	• Similar to cyclophosphamide, but not identical reduction in inflammation results. One cannot expect to see identical results with 2 discrete mechanisms and tested at different doses • TXR-711 dose not optimized for highest exposure and complete target engagement (PD) • CYC, is a chemotherapeutic, immunosuppressant with remarkable immunodepletive properties.

TXR-711, CCR2 ANTAGONIST: ROLE OF CHEMOKINES & pDCs IN MRL/LPR MOUSE MODEL

- MRL/lpr model is well characterized with respect to chemokines and recapitulates the role of chemokines like CCL2 in lupus[1]
    - Chemokine receptor CCR2 deficiency reduces renal disease and prolongs survival in MRL/lpr Mice[1]
    - Involvement of CCR2 in general development of autoimmunity and in the renal involvement
- Plasmacytoid dendritic cells (pDCs), which are prominent type I interferon (IFN-I)-producing immune cells overexpress CCR2 in lupus patients[2]
- pDC depletion in MRL/lpr mouse has shown reduced antibodies, splenomegaly, decrease in GN and prolonged survival compared with pDC-intact mice[3]

1. Luckow et al, J. Am. Soc. Nephrol, 2005, 3592
2. Cedile, *et al.*, 2017, *Immunol Lett*
3. *Cao et al, Frontiers in Immunology, 2015*

INITIAL TXR-711 SUMMARY

TXR-711 DEMONSTRATES POSITIVE INITIAL EFFICACY WITH A NEW MECHANISM

GOOD TOLERABILITY – clinically investigated mechanism

KIDNEY FUNCTION – significantly improved blood urea nitrogen and proteinuria

DECREASED INFLAMMATION – significantly improved several renal inflammation measures

TXR-711 SUPPORTED BY LUPUS KOLs

Mary Crow
Director Mary Kirkland Center for Lupus Research & Professor Weill Cornell Medical College

Vibeke Strand
Adjunct Clinical Professor, Stanford School of Medicine

STRENGTHS

- "The improvements in renal histology scores for 711 and 712 are encouraging."

  – Mary Crow

- "The data is convincing… It makes sense to consider these as potential therapies."

  - Vibeke Strand

GUIDANCE

- "PD data showing drug modulation of its target would be valuable."

  –Mary Crow

- "Further testing of efficacy and PK/PD analysis should be done next."

  - Vibeke Strand

LEAD IDENTIFICATION REVEALS TXRJB2-131 AS A FRONTRUNNER CANDIDATE

- Overall profile of TXRJB2-131 improved over TXR-711
- Two provisional patent application filed in Dec 2021, covering TXRJB2-131 & other novel chemical entities

Screening Parameters		Criteria	TXR-711	TXRJB2-131
Patentability		Secured IP space	Lit. tool compound	Yes
In-vitro biology	Chemiluminescence_IC_{50} µM	< 0.1 µM	0.002	0.007
	Ca-Flux in THP1_IC_{50} µM	< 0.1 µM	0.004	0.012
	FACS binding MCP-1_IC_{50} µM (Alexa)	< 0.1 µM	0.004 /(JBL-THP1); 0.019 (WB published)	0.011
	Chemotaxis assay_THP1 _IC_{50} µM	≤ 0.5 µM	0.008/(JBL-THP1); 0.0039 (published)	0.022
In-vitro ADME	Aq. Solubility (PBS, pH 7.4) µM	>10 µM	200	193
	Caco2_A-B (x10^{-6} cm/s), ER	A-B_P_{app} > 5, ER < 2	5.15, 9.79	39.8, 0.98
	% remain@ 30 min_MLM, RLM, HLM	> 50% @ 30 min	87, - , 79	81, 94, 48
	% remain@ 120 min_Hepatocyte_ m, r, h	> 50% @ 30 min	Not done	65.8, 83.6, 52.4
	% remain@ 120 min_Plasma_m, r, h	> 70% remaining at 2 h	Not done	100, 97, 88
	% remain@ 120 min_Blood_m, r, h	> 70% remaining at 2 h	Not done	99, 100, 93
	CYP_3A4, 2D6, 2C9, 2C19_ % inhibition @10 µM	< 50% inh @10 µM	19.7, 17, 6.22, 15.2	27.8, 22.6, 6.22, 25.8
	%PPB (m, h)	< 99% bound	Not done	82, 88.1

Screening Parameters			Criteria	TXR-711	TXRJB2-131
In vivo PK	Mouse IV (1 mpk)	$t_{1/2}$ (h), C_{max} (ng/mL), AUC_{0-t} (ng·h/mL)	Sufficient oral exposure for efficacy and target engagement (compared to TXR-711)	1.37, 142, 157.7	1.43, 401, 522
		CL (mL/min/kg), V_d (L/kg)		94.4, 11.2	31.8, 3.88
	Mouse_PO (10 mpk)	$t_{1/2}$ (h), C_{max} (ng/mL), AUC_{0-t} (ng·h/mL)		1.1, 922, 1751	10.6, 2530, 4013
		%F	>40	100	77
	Rat_IV (1 mpk)	$t_{1/2}$ (h), C_{max} (ng/mL), AUC_{0-t} (ng·h/mL)	Sufficient oral exposure	1.29, 188, 202	1.79, 88.5, 207
		CL (mL/min/kg), V_d (L/kg)		82.9, 8.4	77.7, 12
	Rat_PO (10 mpk)	$t_{1/2}$ (h), C_{max} (ng/mL), AUC_{0-t} (ng·h/mL)		2.8, 623, 1785	2.92, 678, 2444
		%F	>40	88.6	100
	Dog_IV (1 mpk)	$t_{1/2}$ (h), C_{max} (ng/mL), AUC_{0-t} (ng·h/mL)	Sufficient oral exposure		0.49, 1721, 672
		CL (mL/min/kg), V_d (L/kg)			25.2, 1.07
	Dog_PO PK(suspension) (5 mpk)	$t_{1/2}$ (h), C_{max} (ng/mL), AUC_{0-t} (ng·h/mL)			5.29, 2729, 3450
		%F	>40		100
	Dog_PO (solution) (5 mpk)	$t_{1/2}$ (h), C_{max} (ng/mL), AUC_{0-t} (ng·h/mL)			14.1, 3350, 5547
		%F			100
	MRL Lpr Mouse Model		Demonstrate efficacy	Efficacious	Efficacy better than TXR-711
	hERG_IC_{50} µM		>10	>10	5.2
	Safety screen44 panel		Clean	Hits sodium channel, site 2 (67% inh @ 10 uM)	Hits hERG channel (70% inh @ 10 uM
	Chemokine panel		Selective	>1000-fold	>2000-fold
	Micro AMES		Non-mutagenic (negative)	ND	Negative

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TXRJB2-131 ADVANCED LEAD SUMMARY

***IN VITRO* BIOLOGY** –Single to double digit nM, activity comparable to reference compound in primary, secondary, & functional assays

***IN VITRO* ADME** – Excellent permeability with no potential for Pgp efflux. Acceptable liver microsomes and hepatocyte stability. Low potential for drug-drug interactions (CYPs)

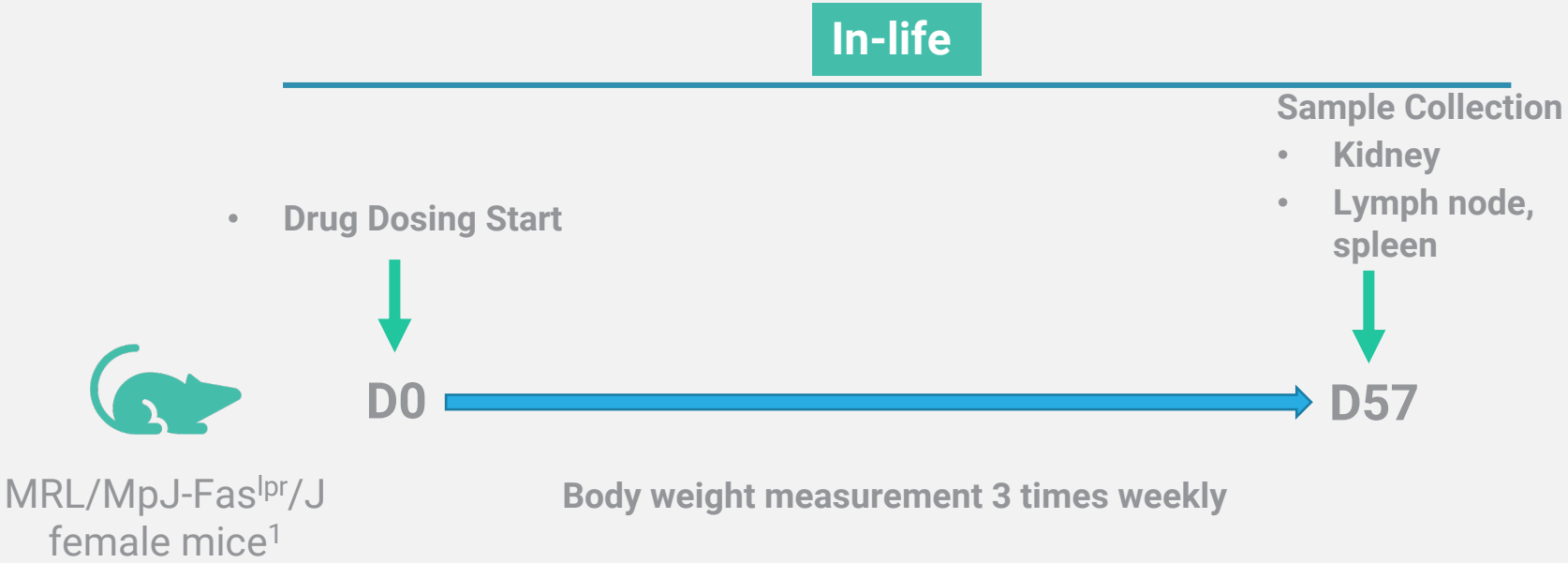
***IN VIVO* PK**– High oral bioavailability & reasonable half-life in mice, rat, & dog. Dose-dependent increase in oral exposure in mice.

***IN VIVO* EFFICACY** – TXRJB2-131 significantly reduced glomerulonephritis, decreases in inguinal lymph node and spleen weight, and improvement in skin lesions scoring

IP – Two provisional patent application filed in Dec 2021, covering TXRJB2-131 & other novel chemical entities

ONGOING & PLANNED– Compounds identified with significantly reduced hERG, PK optimization, ongoing. Conduct CV safety in dog. Cross species native assays for cytokine modulations and other SLE related biomarkers.

SECOND *IN VIVO* STUDY DESIGN



Efficacy Measures

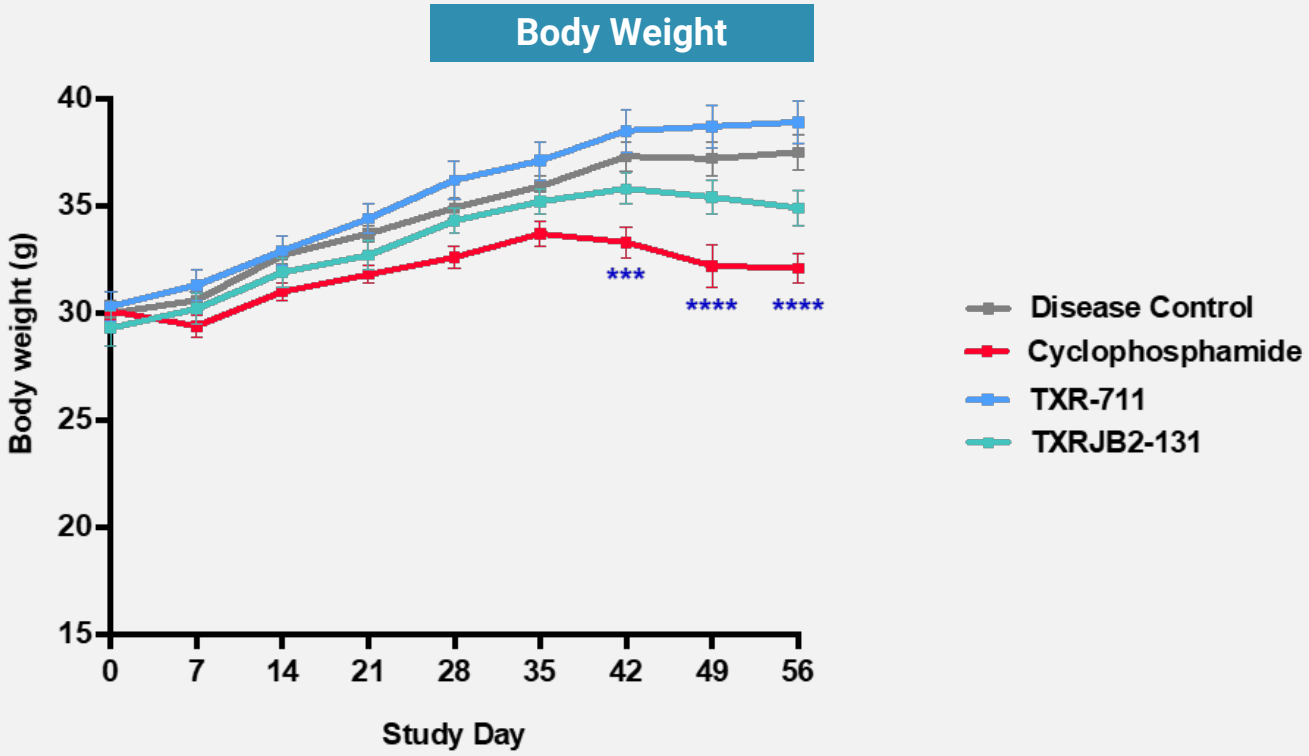
- Lymphadenopathy
- Skin lesions
- Inguinal lymph nodes/spleen/combined kidney weight
- Serum creatinine
- Blood urea nitrogen
- Neutrophil gelatinase-associated lipocalin
- Serum dsDNA-autoantibody
- Kidney histology

- MRL model represents human SLE better than other models
- Multiple efficacy measures assessing health of lymph nodes and kidneys
- Cyclophosphamide, TXR-711, and TXRJB2-131

1. Celhar & Fairhurst. 2017. *Rheumatology*

EXCELLENT TOLERABILITY FOR TXR-711 & TXRJB2-131

- TXR-711 and TXRJB2-131 did not exhibit significant body weight changes



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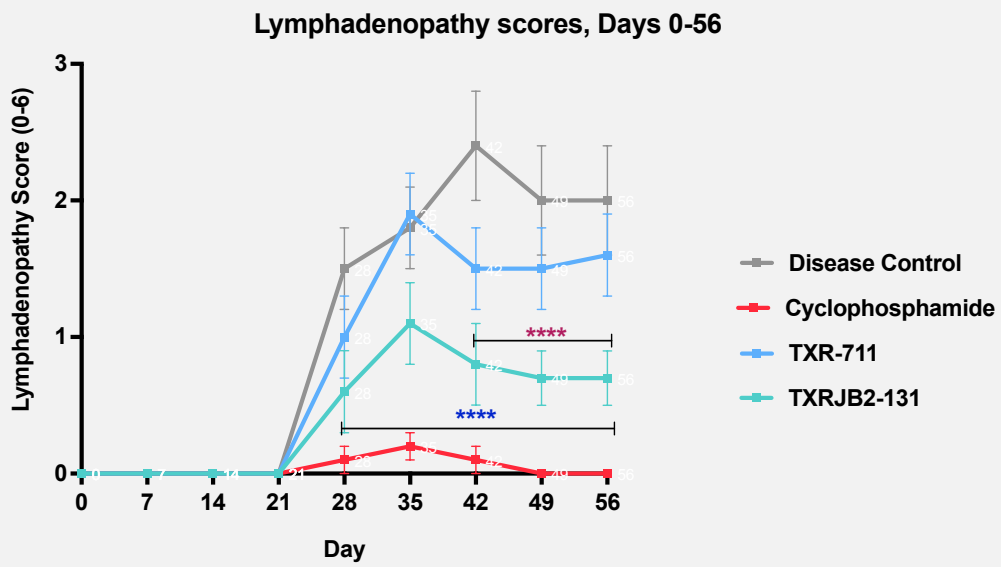
SIGNIFICANT LYMPHADENOPATHY SCORE DECREASES

- TXRJB2-131 significantly improves lymphadenopathy scores



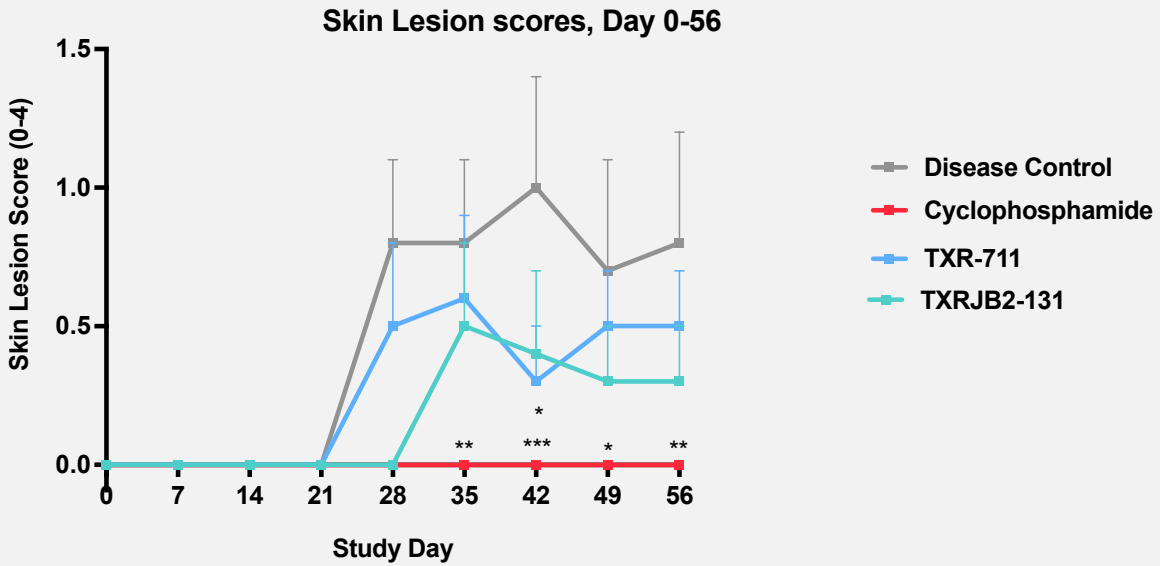
SCORE	Description
0	None
1	<1cm, 1 site
2	<1cm, 2 sites
3	<1cm, 3 sites
4	>1cm, 1 site; <1cm, 2 sites
5	>1cm, 2 sites; <1cm, 1 site
6	>1cm, 3 sites

Study Day	Disease control vs.		
	Cyclophosphamide	TXR-711	TXRJB2-131
28	<0.0001	NS	0.0055
35	<0.0001	NS	0.0055
42	<0.0001	NS	0.0415
49	<0.0001	0.0055	<0.0001
56	<0.0001	NS	<0.0001

Data shown as Mean ± SEM.
p<0.0001 for Disease control vs. Normal control on Day 0-56,
****p<0.0001 for Cyclophosphamide vs. Disease control on Day 28-56,
*p<0.05 for TXR-711 vs. Disease control on Day 42,
****p<0.0001 for TXRJB2-131 vs. Disease control on Day 42, 49 & 56.
Two Way ANOVA with Bonferroni's Multiple Comparison Test.

SKIN LESION SCORE DECREASES

- TXRJB2-131 & TXR-711 improves scoring of skin lesions by 63% & 38% respectively



SCORE	Description
0	None
1	1 or 2 lesions 2-4mm long
2	Total area <0.5cm^2
3	Total area 0.5-1.0 cm^2
4	Total area >1.0 cm^2

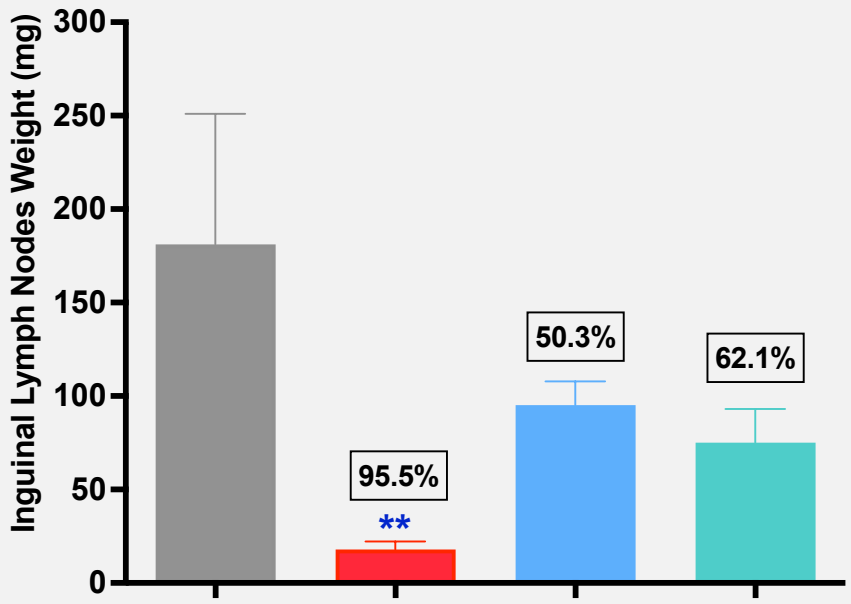
	Disease control vs.		
Study Day	Cyclophosphamide	TXR-711	TXRJB2-131
28	0.0065	NS	0.0065
35	0.0065	NS	NS
42	0.0004	0.0207	0.0575
49	0.0207	NS	NS
56	0.0065	NS	NS

Data shown as Mean ± SEM.
# p<0.05, ### p<0.001 for Disease control vs. Normal control on Day 28, 35, 42 & 56,
*p<0.05, for Cyclophosphamide vs. Disease control on Day 28, 35, & 56.
***p<0.001 for Cyclophosphamide on Day 42
*p<0.05 for TXRJB2-131 vs. Disease control on Day 28.
Two Way ANOVA with Bonferroni's Multiple Comparison Test.

LYMPH NODE & SPLEEN WEIGHT IMPROVEMENTS

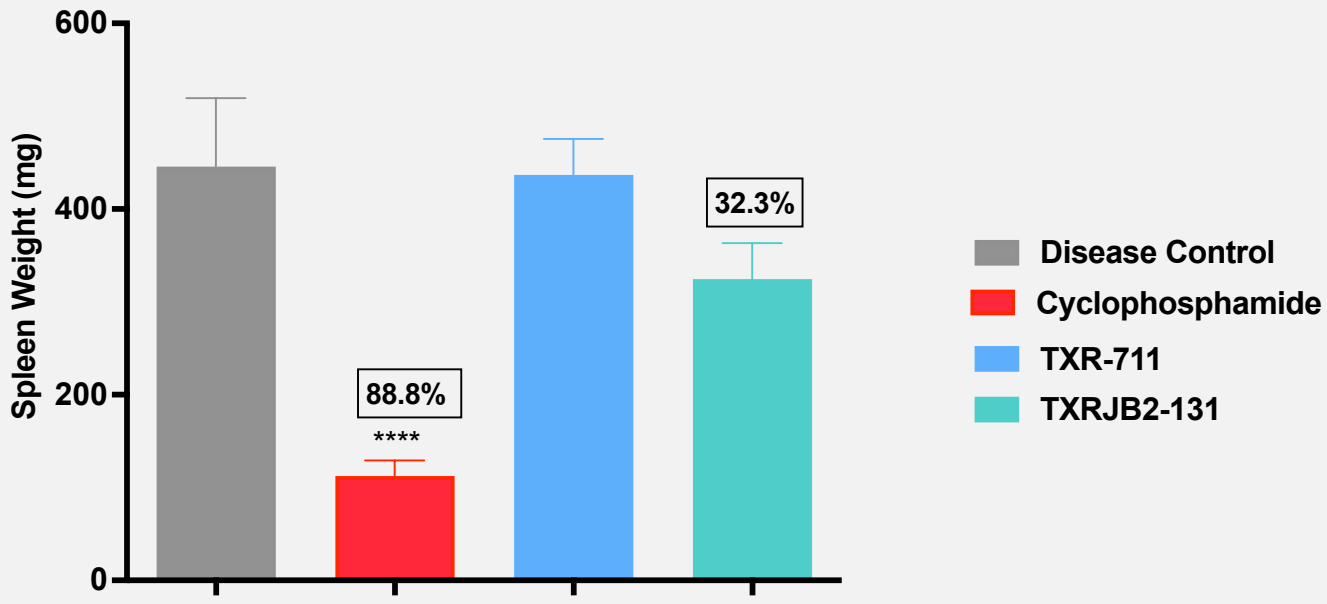
- TXRJB2-131 decreases inguinal lymph node & spleen weight

Inguinal Lymph Node Weight



Data shown as Mean ± SEM.
p<0.01 for Disease control vs. Normal control on Day 57,
**p<0.01 for Cyclophosphamide vs. Disease control on Day 57.
One Way ANOVA with Dunnett's Multiple Comparison Test.

Spleen Weight



Data shown as Mean ± SEM.
p<0.001 for Disease control vs. Normal control on Day 57,
***p<0.001 for Cyclophosphamide vs. Disease control on Day 57.
One Way ANOVA with Dunnett's Multiple Comparison Test.

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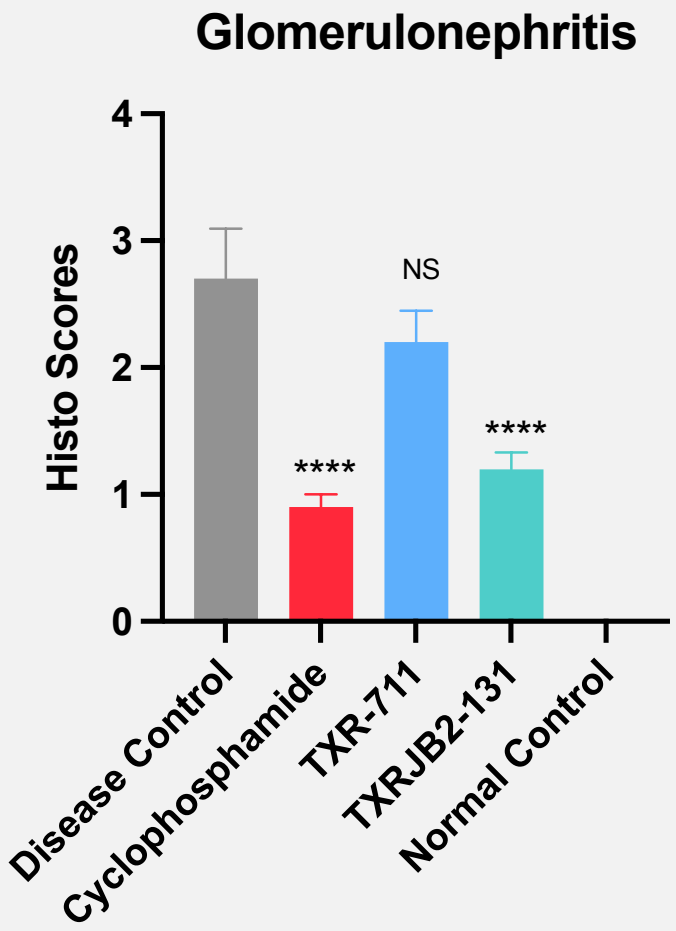
KIDNEY HISTOLOGY: SIGNIFICANT REDUCTION IN GLOMERULONEPHRITIS

- TXRJB2-131 shows significant reduction in glomerulonephritis in kidney histology



P value	Summary
< 0.0001	****
0.0001 to 0.001	***
0.001 to 0.01	**
0.01 to 0.05	*
≥ 0.05	ns

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TXRJB2-131 *IN VIVO* SUMMARY

TXRJB2-131 DEMONSTRATES POSITIVE EFFICACY AND OUTPERFORMS TXR-711

GOOD TOLERABILITY – no significant body weight changes and a clinically investigated mechanism

***IN VIVO* EFFICACY**– significantly improved lymphadenopathy scores, improved skin lesion scores, decreases in spleen and lymph node weight and, significant reduction in glomerulonephritis

PLANNED – Conduct dose response efficacy study in MRL/lpr with biomarkers.

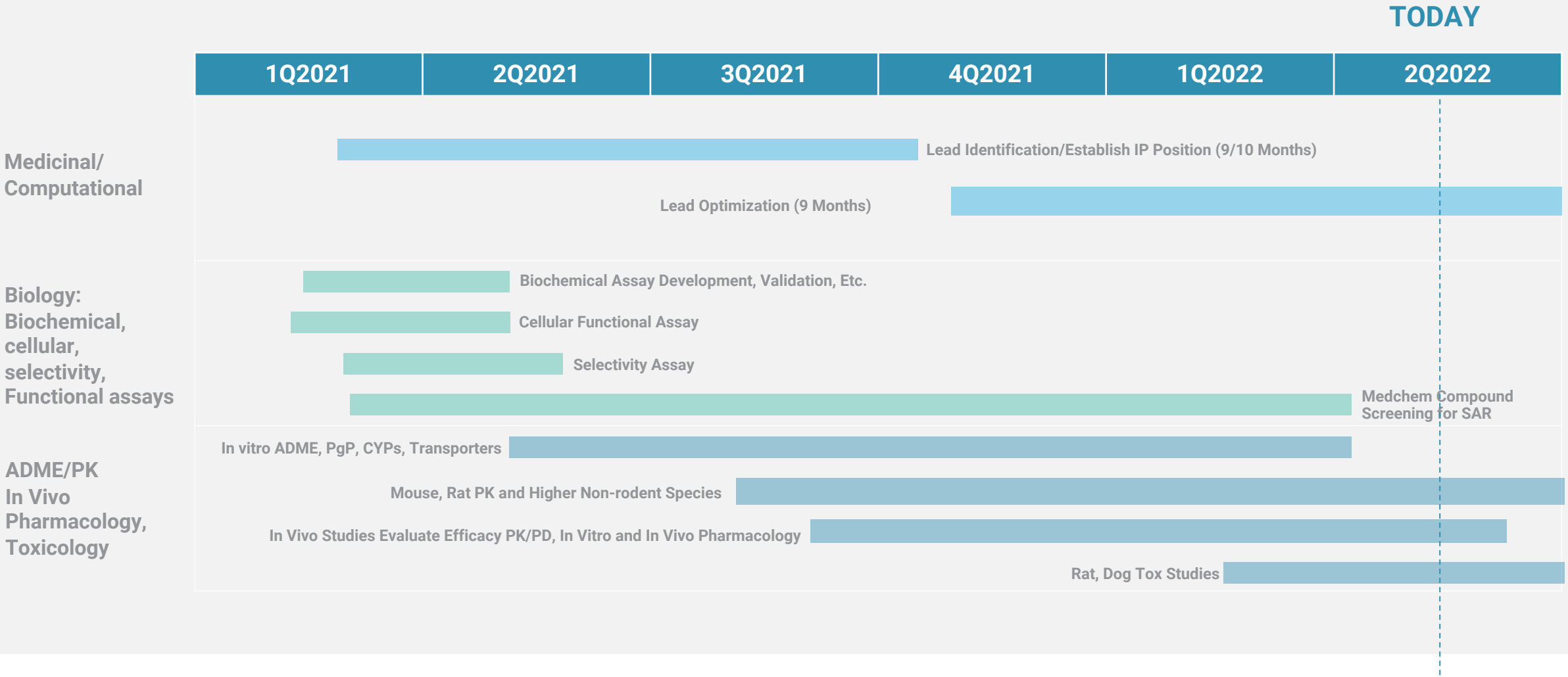
FURTHER EFFICACY MEASURES TO BE TESTED

EFFICACY MEASURE	TXRJB2-131
PK/PD	• Expected to demonstrate modulation of CCR2 target
IFN signature	• To be tested with NZB/W model and/or Accelerated/Induced model • CCR2 inhibition expected to suppress IFNα signature via IFN/STAT, NF-kB signaling and cytokine pathways
Cardiac effects	• To be tested with NZ/BW model • Expected to show protective effect of the heart. pDCs overexpress chemokine receptor 2 (CCR2) in lupus patients. pDCs are associated with atherosclerosis and initial efficacy has been shown by CCR2 inhibition
Endothelial Dysfunction	• To be tested with NZ/BW model • Expected to show decrease in endothelial dysfunction due to inhibition of cytokine expression, oxidative stress, ER stress, inflammation via CCR2 inhibition

Morel *et al.*, 2017, *Curr Opin Rheumatol. 2017*

LEAD DISCOVERY THROUGH IND CANDIDATE

DEVELOPMENT PLAN



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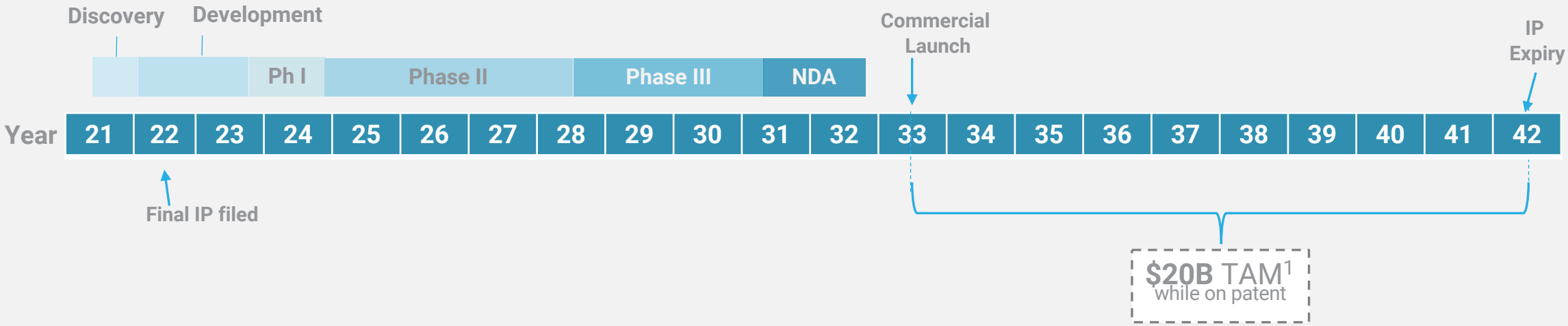
UPCOMING DEVELOPMENT PLANS

- Name development candidate upon close of financing, expected Q4-2022
  - In meantime will continue to optimize as we await resources
- Post close of financing, Kick off IND-enabling activities
  - Initiate CMC scale up, etc., within 1 quarter
  - Initiate toxicology studies within 2-3 quarters
  - Initiate regulatory activity within 2-3 quarters
- IND filing expected roughly EOY 2023 to beginning of 2024
- Initiation of Phase I one quarter after IND filing

DEVELOPMENT COSTS AND MARKET OPPORTUNITY



	Discovery	Development	Phase I	Phase II	Phase III	NDA
Approx. Cost ($110MM total)	($200K)[2]	(~$6M)[3]	(~$7M)[4]	($25M)[4]	($70M)[4]	(~$2M)[4]
Exemplar Deals	N/A[5]	Roivant – HanAll Biopharma[6,7] (2017) Single asset: • $30M upfront • $470M milestones • double digit royalties	Abbvie – Alpine Immune Sciences[7] (2020) Single asset: • $60M upfront option • $800M to exercise option with milestones • double digit royalties	Cephalon – Immupharma (2008) Single asset: • $15M option • $30M to exercise option • $470M milestones • double digit royalties	N/A[8]	N/A[8]

1. Source: Global Data 7 major markets
2. Incurred cost
3. Contracted costs
4. Estimated costs
5. This program is in development
6. Ex-Asia
7. SLE + other immunology indications
8. No relevant exemplar deals

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SUMMARY

- SLE is a $1B/yr market with high unmet need for efficacious and tolerable treatments
  - NSAIDs used for symptom management – not disease modifying. Cytotoxic immunosuppressives used for flare treatment, but not tolerable for long-term use
- TXR-711 & TXRJB2-131 (novel new chemical entity) are CCR2 antagonists
  - CCR2 inhibition can block or reverse phenotypic changes associated with SLE while maintaining excellent tolerability
  - MOA well tolerated in clinical studies in multiple indications
  - Repeatedly demonstrated efficacy in gold-standard nonclinical mouse model of SLE that compares favorably to a poorly tolerated treatment used for severe symptoms flares
    - Significant decreases in inflammation and fibrosis
- Two provisional patent applications filed in Dec. 2021, covering TXRJB2-131 & other NCEs
- Backup molecule TXR-712 is an LRRK2 inhibitor

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SoftBank Ventures ANDREESSEN HOROWITZ OS Fund Stanford StartX Med MIT STARTUP EXCHANGE

APPENDIX A

(PRECLINCAL MODELS)

IMMUNOLOGICAL CHARACTERISTICS OF PRECLINICAL MOUSE MODELS

IMMUNOLOGICAL CHARACTERISTICS	MRL/LPR MODEL	NZB/W MODEL	IFN-a ACCELERATED/ INDUCED MODEL
Lymphoproliferation	X		
Splenomegaly	X	X	
Extremely enlarged lymph nodes	X		
GN	X	X	Rapid onset without increased leucocyte infiltration
ANAs	High	Moderate	
Anti-sdDNA antibodies	High	High	
Anti-snRNP antibodies	X		
Anti-RNP antibodies			X
Anti-sm			X
Expansion of of $CD4^{-}CD8^{-}CD3^{+}$ Tcells	X		
Tcell dependent			X
IFN Signature	None	Weak	Strong
Persistence of long-lived plasma cells		X	
Accelerated disease			Rapid-onset

1. Celhar *et al.*, 2017 *Rheumatology; 56:i88-i99*
2. Morel *et al.*, 2017, *Curr Opin Rheumatol. 2017,*

PERFORMANCE OF OTHER SLE THERAPIES IN MOUSE MODELS

- CSs in NZB/W and MRL/lpr mice preserved glomerular structure and function. Additionally, CS inhibited the expression of many NF-kB-inducible genes in the glomeruli of MRL/lpr mice, such as adhesion molecules, chemokines and their receptors.
- Mycophenolate (MMF) in NZB/W mice reduced proteinuria, albuminuria, blood urea nitrogen, decreased autoantibody production and prolonged survival. In MRL/lpr mice MMF reduced albuminuria and GN but did not diminish antibody formation. MMF also effectively abrogated LN development in the IFNa-accelerated model and decrease of antibody-secreting cells in spleen.
- Antimalarial agent hydrochloroquine (HCQ) was assessed for the treatment of lupus-associated endothelial dysfunction in NZB/W mice. Longterm treatment with HCQ resulted in reduced hypertension, reduced endothelial dysfunction and less damage of the heart and kidneys. HCQ was evaluated to treat lupus-related skin lesion in MRL/lpr mice and showed significant efficacy.
- Cyclophosphamide (CYC) in NZB/W mouse model decreased autoantibody production and repressed the progression of LN without reversing the existing abnormalities. Protection from GN was achieved with long-term high dose CYC and correlated with decrease ant-DNA antibody levels. The efficacy of CYC has been reported in MRL/lpr model; prolonged survival, decreased arthritis, nephritis, reduced adenopathy and splenomegaly and reduced antibody levels.

USE AND TOXICITY OF OTHER SLE THERAPIES

- Corticosteroids (CSs) and antimalarial drug HCQ approved for SLE based on clinical experience and eminence-based intuition, not clinical trials
- Several off-label agents introduced, predominantly cyclophosphamide, methotrexate and MMF
- Despite being the pillars of SLE treatment, their mechanisms of action are not completely understood
    - NZB/W and MRL/lpr models have been extensively used to study these mechanisms and evaluate side effects, dosing regimen and response to treatment, especially the ability to delay or prevent renal disease
- Long-term CYC therapy is more efficient; however, it is associated with more side effects. Prolonged administration of CYC, especially high doses, increases the incidence of neoplasms in NZB/W mice. Long-term CYC (>1 year) in humans is also carcinogenic, causing most frequently bladder cancer, secondary acute leukemia and skin cancer
- CS therapy is associated with, weight gain, hypertension, atherosclerosis, diabetes, skin atrophy, acne vulgaris and increased risk of infection
- CSs (in combination with HCQ, CYC, MTX, MMF) is the preferred induction therapy for almost all clinical presentation of lupus.
- Mouse models of lupus will continue to be indispensable tools to study disease pathogenesis, to identify genetic susceptibility loci and targets for drug developments, and for preclinical testing of novel therapeutics