ARIA PHARMACEUTICALS

Chronic Kidney Disease (CKD)

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 CKD

MAXIMIZED LIKELIHOOD OF CLINICAL SAFETY – HUMAN SAFETY AT PHASE I

ESTABLISHED TOLERABILITY

Multiple CASP1 inhibitors have safely completed Phase I

MAXIMIZED LIKELIHOOD OF CLINICAL EFFICACY – HUMAN EFFICACY AT PHASE II

HIGH CLINICAL PREDICTABILITY IN CKD

Symphony predicted 70% of SOCs & Phase III successes and 63.6% of Phase II successes in CKD

CHRONIC KIDNEY DISEASE (CKD)

MARKET

700 MILLION cases worldwide

35% - 5-year survival rate

DIABETIC NEPHROPATHY THERAPIES - standard of care: does not stop disease progression

$13B

2024 Market ($/Year)[1]

SPEED AND SUCCESS

10 MOLECULES ADVANCED from hit prediction to *in vivo*

12 WEEKS from program start to *in vivo* results

LEAD MOLECULE TXR-1210 IN VIVO HIGHLIGHTS:

NOVEL MOA in CKD

Significant **DECREASE** of kidney fibrosis and inflammation, comparable to TGF-β mAb

Minimal body weight changes – **GOOD TOLERABILITY**

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

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HIGH UNMET MEDICAL NEED FOR CKD

700 MILLION CASES WORLDWIDE

37 MILLION US cases (470k on hemodialysis)
10 COUNTRIES with >10M cases

INCREASED PREVALENCE in women (15.6% vs. 13.5%)

INCREASED INCIDENCE & MORTALITY with age (>60% prevalence at age 80)

35% 5-YEAR SURVIVAL RATE

NEPHRON LOSS progressive and irreversible
REGENERATIVE CAPACITY LOSS

METABOLIC OXIDATIVE STRESS
MICROVASCULAR DAMAGE

FIBROSIS & INFLAMMATION

STANDARD OF CARE

DIABETIC NEPHROPATHY THERAPIES – Renin-Angiotensin blockers, Pentoxifylline, Canagliflozin

DOES NOT STOP disease progression or transition from acute kidney injury (AKI) to CKD

STANDARDS OF CARE

Target	Agents	Disease	Comments
Vitamin D Receptor	Paricalcitol	sHPT in CKD patients	Delays and treats hyperparathyroidism secondary to CKD
Renin-Angiotensin System	Angiotensin II receptor blockers and ACE inhibitors	DKD	Delays CKD progression; impact on kidney fibroblasts not yet assessed in placebo-controlled trials
SGLT2	Canagliflozin, Dapagliflozin	DKD, CKD	Delays CKD progression; impact on kidney fibroblasts not yet assessed in placebo-controlled trials
Vasopressin receptor 2	Tolvaptan	ADPKD	Delays CKD progression; impact on kidney fibroblasts not yet assessed in placebo-controlled trials
Phosphodiesterase	Pentoxifylline	DKD	Delays CKD progression in open-label clinical trials; impact on kidney fibroblasts not yet assessed in placebo-controlled trials
Endothelin	Atrasentan	DKD	Delays CKD progression; impact on kidney fibroblasts not yet assessed in placebo-controlled trials

ADPKD: autosomal dominant polycystic kidney disease; CKD: chronic kidney disease; DKD: diabetic kidney disease; SGLT2: sodium-glucose transporter 2 (SLC5A2)
Ruiz-Ortega 2018 *Nature Reviews Nephrology*

INVESTIGATIONAL DRUGS

SELECTED AGENTS – RECENTLY APPROVE & IN ACTIVE PHASE II/III CKD CLINICAL TRIALS

Agent	Developer	Target(s)	Primary Endpoint	Current Status	Response
Finerenone	Bayer AG	MCR	Time to 40% decrease eGFR or Death	Approved	eGFR decreases of 40% or death occurred in 21.1% of patients on placebo and 17.8% of patients on finerenone (p=0.0014)
Empagliflozin	Boehringer Ingelheim	SLC5A2, SLC5A1	Time to 40% decrease eGFR, ESRD, Renal, CV Death	Phase III	33% reduced risk for dialysis, transplantation or renal death
RTA 402	Reata	NRF2, NFkB	Time to 30% decreased eGFR	Phase III	Significantly smaller decline in renal function compared to placebo.
Semaglutide	Novo Nordisk	GLP1R	Time to 50% decrease eGFR, ESRD, Renal, CV Death	Phase III	Significantly smaller decline in renal function compared to placebo.
Verinurad	AstraZeneca	URAT1	UACR Ratio	Phase II	N/A

ESRD End-Stage Renal Disease; CV Cardiovascular; eGFR: Estimated Glomerular Filtration Rate; UACR: Urinary Albumin to Urinary Creatine
Khumbani 2021 *American College of* Cardiology

DISCOVERY PROCESS IDENTIFIES TXR-1210 IN 12 WEEKS

AI-Driven Discovery

Diverse Data, Methods:

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

50K Molecules

AI-Assisted Review

Novelty and Safety:

- Novel MOA
- Safety profile
- ADME properties

90 Molecules

Hit Diligence

PhD-led Deep Dive:

- MOA relevance
- MOA safety
- IP development path

25 Molecules

Preclinical

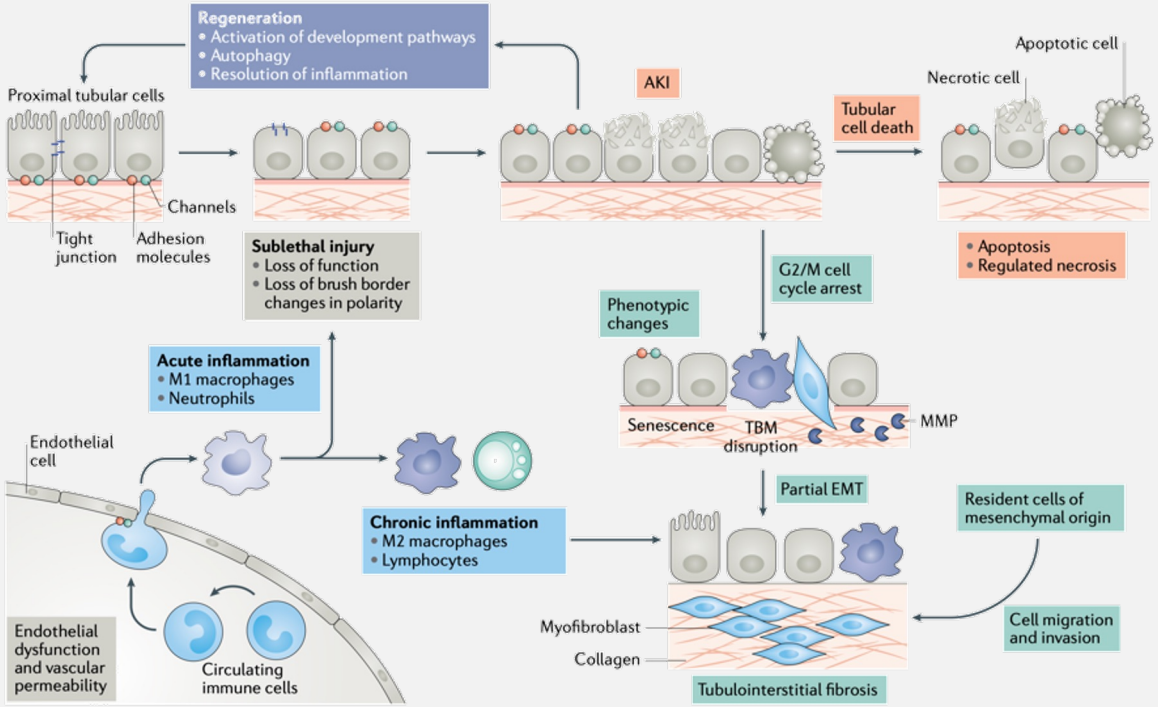
Optimal Disease Models:

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

10 Molecules

WHAT IS CKD: CHRONIC KIDNEY DISEASE?

- **Renal fibrosis and loss of function from nephron injury and death**
  - High mitochondrial content in kidney tubular epithelium - vulnerable to injury
  - Kidney injury activates developmental pathways associated with disease progression
  - Injury inducers include hypoxia, toxic compounds, proteinuria, metabolic disorders (diabetes, NAFLD), and cell senescence
  - Therapies to stop or improve renal fibrosis by affecting renal myofibroblast phenotype needed



 Ruiz-Ortega et al 2020 *Nature Reviews Nephrology*

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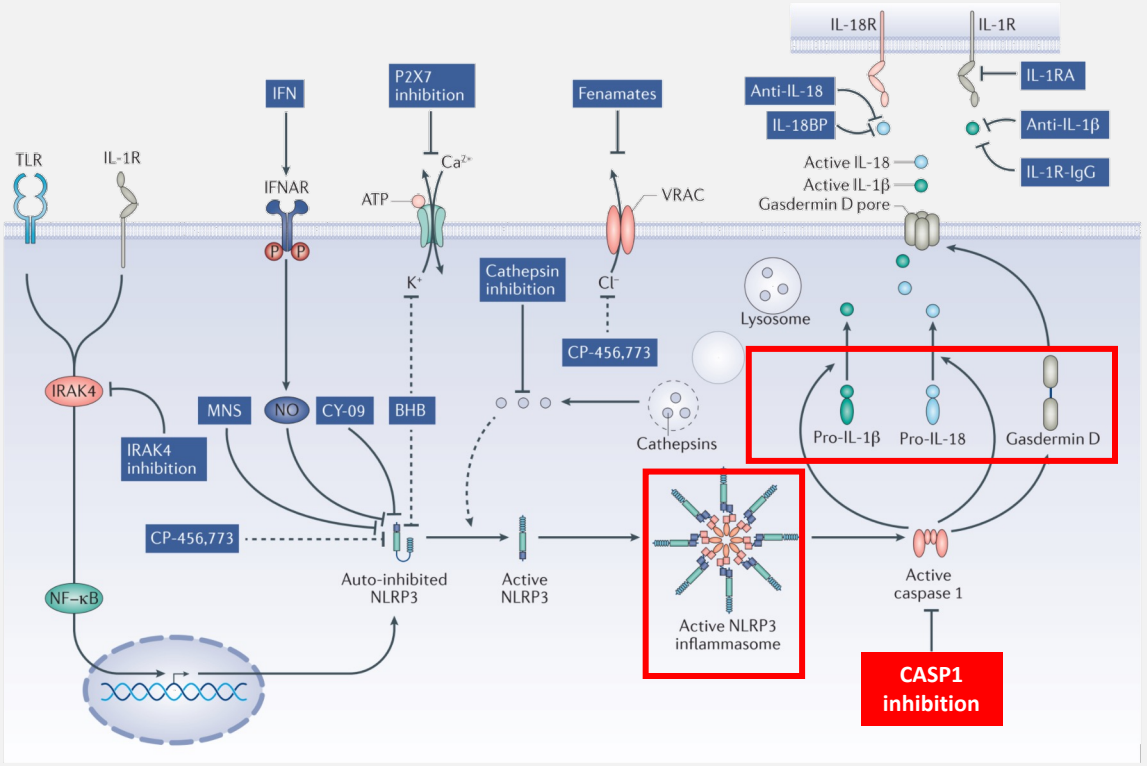
TXR-1210 IS A CASPASE-1 INHIBITOR

- Caspase-1 activity is required for NLRP3 inflammasome-mediated activation of IL-1β, IL-18, and Gasdermin D
- IL-1β, IL-18, and NLRP3 inflammasome activity regulate pyroptosis and promote fibrosis
- NLRP3 activity associated with inflammation and fibrosis following unilateral ureteral obstruction (UUO)



 Mangan et al 2018 *Nature Reviews Drug Discovery*

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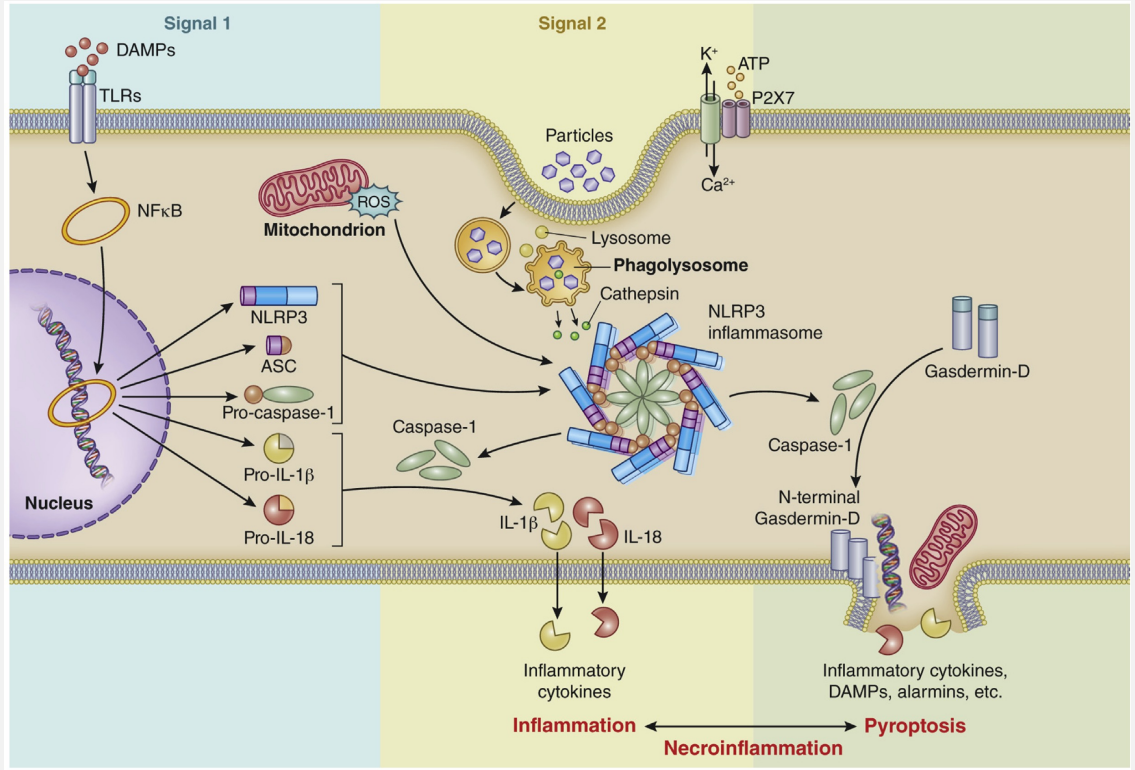
TXR-1210 MOA IS ASSOCIATED WITH RENAL INFLAMMATION AND FIBROSIS

Caspase-1 plays vital role in pyroptotic cell death and release of proinflammatory cytokines

- NLRP3 activation, a response to cellular stress associated with CKD, requires caspase-1 activity
  - Triggers include K^+ efflux, ROS, proteinuria, and metabolic cell stress
- Caspase-1 activity generates IL-1β, IL-18
  - Proteolytic cleavage releases active forms
- IL-1β and IL-18 cause inflammation and fibrosis
  - Immune cell differentiation and localization
  - TGF-β expression, activity and SMAD4 signaling
- NLRP3 inflammasome and caspase-1 activity regulates pyroptosis and additional inflammatory cell processes



 Mulay SR 2019 *Kidney International*

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CASPASE-1 SPECIFICITY PREFERABLE OVER PAN-CASPASE

- Pan-caspase inhibitors have been investigated in fibrotic liver diseases[1]
  - Poor PK properties of most pan-caspase inhibitors (peptides or peptidomimetics) limits interpretation of outcomes
- Pan-caspase inhibitors broadly suppress apoptosis, but may trigger caspase-independent forms of cell death and/or pyroptosis (affected by caspase-1activity), leading to a more prominent inflammatory response[2,3]
- Inflammasome-caspase-1 signaling has been extensively associated with fibrotic kidney diseases via both genetic and pharmacologic interventions[4]
- Non-peptide caspase-1 inhibitors have demonstrated initial efficacy in diverse indications
  - Pralnacasan showed efficacy in RA and was tolerable, but was discontinued after long-term animal exposure led to liver toxicity; no human toxicity was reported in clinical study[5,6]
  - Belnacasan, was well tolerated during investigation in psoriasis and epilepsy[7]
  - Specific caspase-1 inhibitors are theorized to minimize adverse events[1]

[1] Kudelova J 2015 *Journal of Phsiology & Pharmacology*
[2] Wu J 2019 *Aging and Disease*
[3] Swanson KV 2019 *Nature Reviews Immunology*
[4] Zhang H 2020 *Frontiers in Cell and Developmental Biology*
[5] MacKenzie SH 2010 *Current Opinion Drug Discovery Dev.*
[6] Linton S 2005 *Current Topics in Medicinal Chemistry*
[7] *NCT01048255 & NCT01501388*

CASPASE-1 INHIBITION CAN PROMOTE RENAL CELL SURVIVAL AND FUNCTION

CKD-ASSOCIATED CHANGES

- Myofibroblast activation, proliferation
- Increased mROS and oxidative stress
- Pro-fibrotic (TGFβ1) gene expression
- Pro-inflammatory (IL-1β) gene expression
- Pyroptosis
- Inflammation
- Fibrosis

CASPASE-1 INHIBITION EFFECTS

- Inhibition of IL-1β, IL-18 activation
- Suppression of mitochondrial dysfunction
- Inhibition of inflammation
- Inhibition of pyroptosis
- Inhibition of TGF-β1, SMAD signaling
- Inhibition of fibrosis
- IL-1β, IL-18 expression possible biomarkers

- Caspase-1 inhibition can block or reverse phenotypic changes associated with CKD while maintaining an excellent tolerability profile

IN VIVO STUDY DESIGN

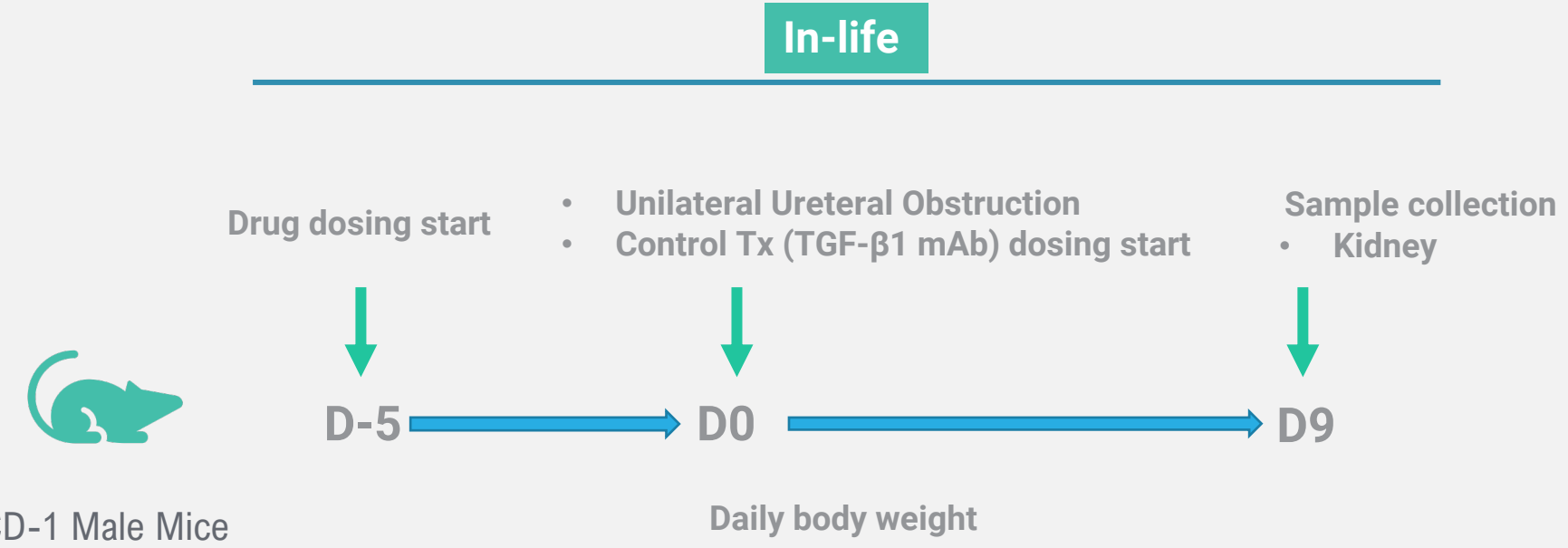
UNILATERAL URETERAL OBSTRUCTION

- H & E staining
- α-SMA staining
- Collagen staining (PSR)
- Hydroxyproline

REFERENCE THERAPY

- TGF-β1 mAB as positive control: TGF-β1 is a key mediator of signal transduction associated with fibrosis and inflammation

IN VIVO STUDY DESIGN



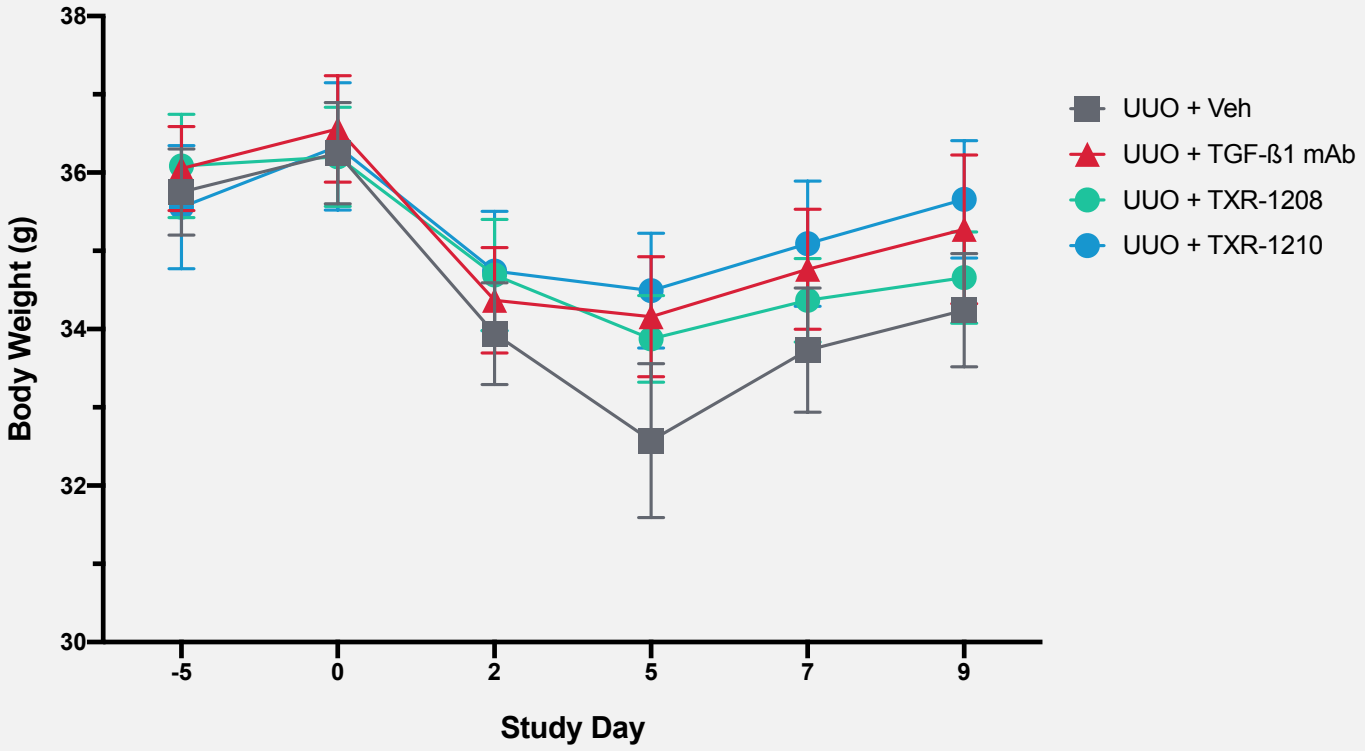
Efficacy Measures

- H & E staining
- α-SMA staining
- Collagen staining (PSR)
- Hydroxyproline

- Renal injury and fibrosis caused by obstruction of urine flow
- Benchmark POC model for initial drug candidate efficacy evaluation
- Two candidates identified; TXR-1210 selected for development, TXR-1208 as backup

EXCELLENT OVERALL TOLERABILITY OF PREDICTION HITS

- TXR-1210 weight profile comparable to TGF-β1



N=10 mice per group

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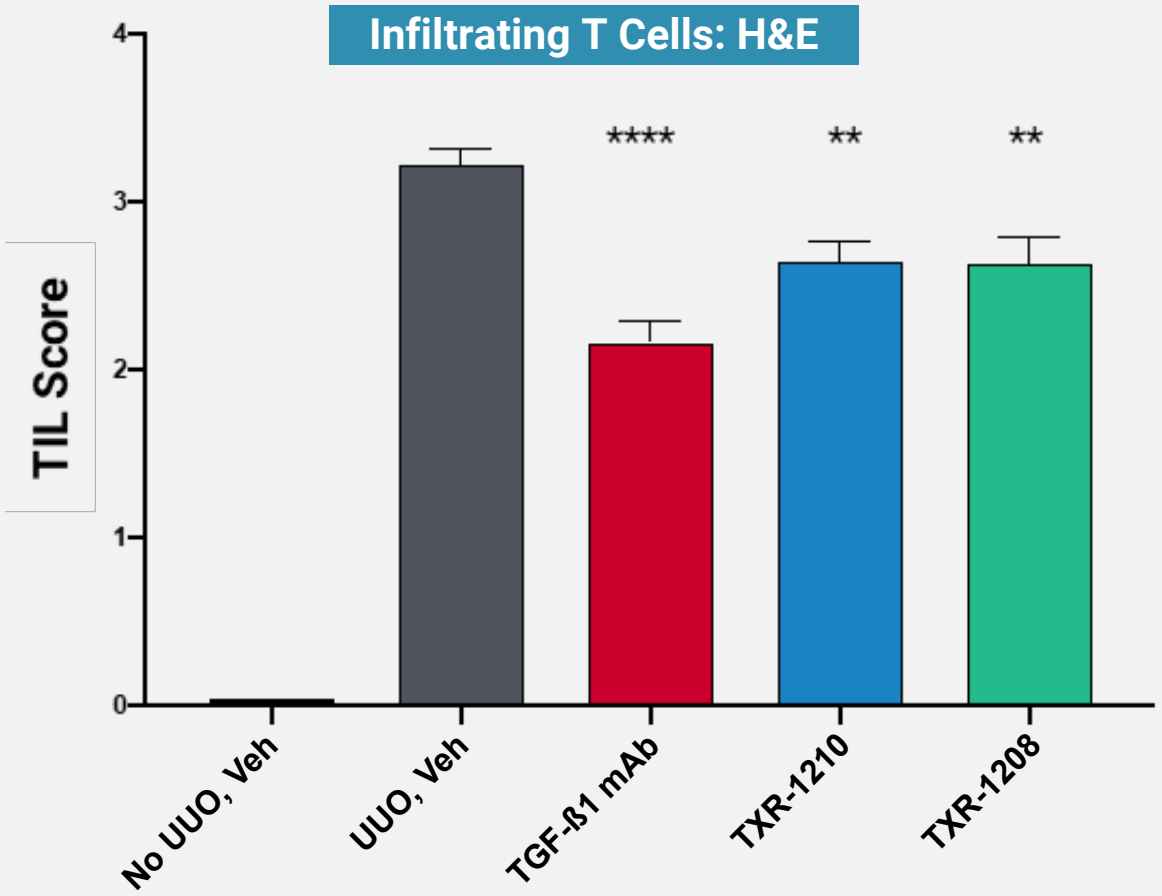
SIGNIFICANTLY DECREASED KIDNEY INFLAMMATION FOLLOWING UUO

- TXR-1210 significantly reduces infiltrating T cells in kidney tissue

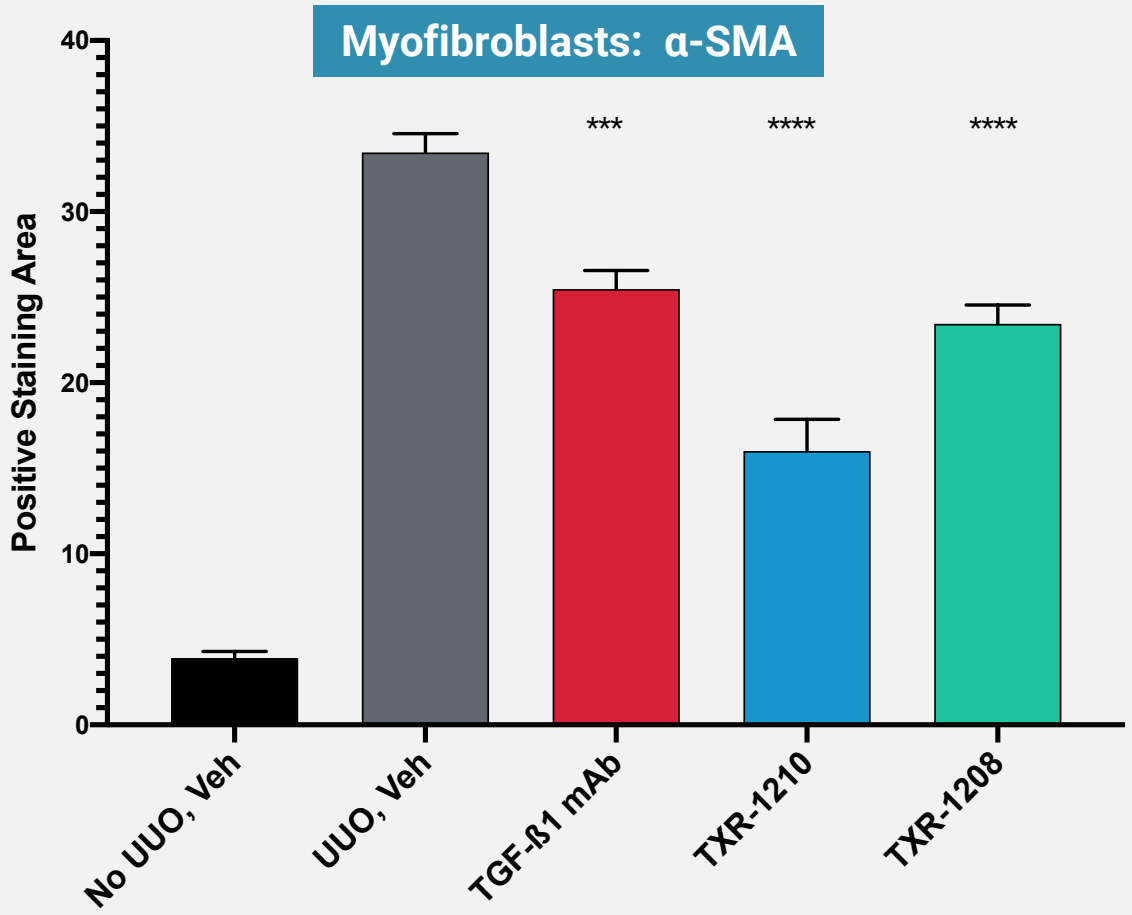


N=10 mice per group

ARIA PHARMACEUTICALS

SIGNIFICANTLY DECREASED KIDNEY FIBROSIS FOLLOWING UUO

- TXR-1210 significantly reduces myofibroblasts in kidney tissue



N=10 mice per group

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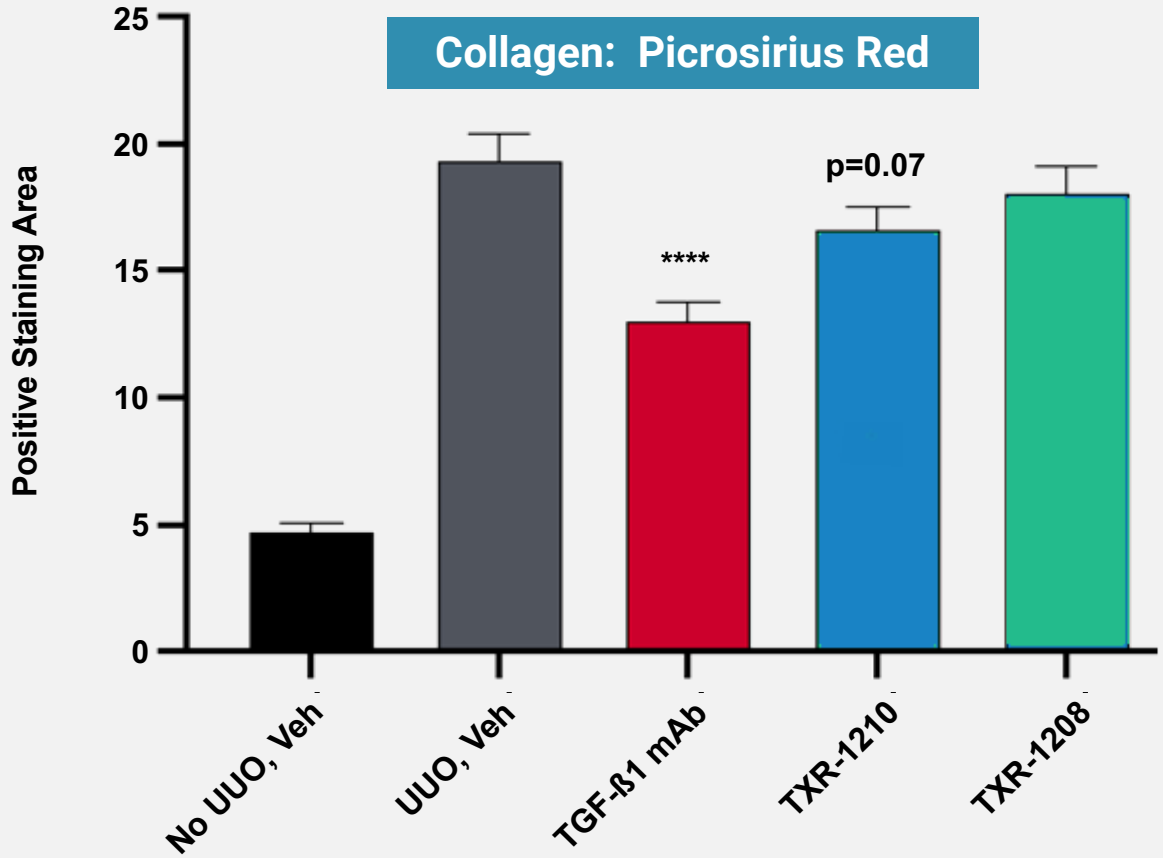
DECREASED COLLAGEN FOLLOWING UUO

- TXR-1210 reduces collagen staining in kidney tissue
- Consistent with α-SMA results, but may have measured later than optimal, dampening results



N=10 mice per group

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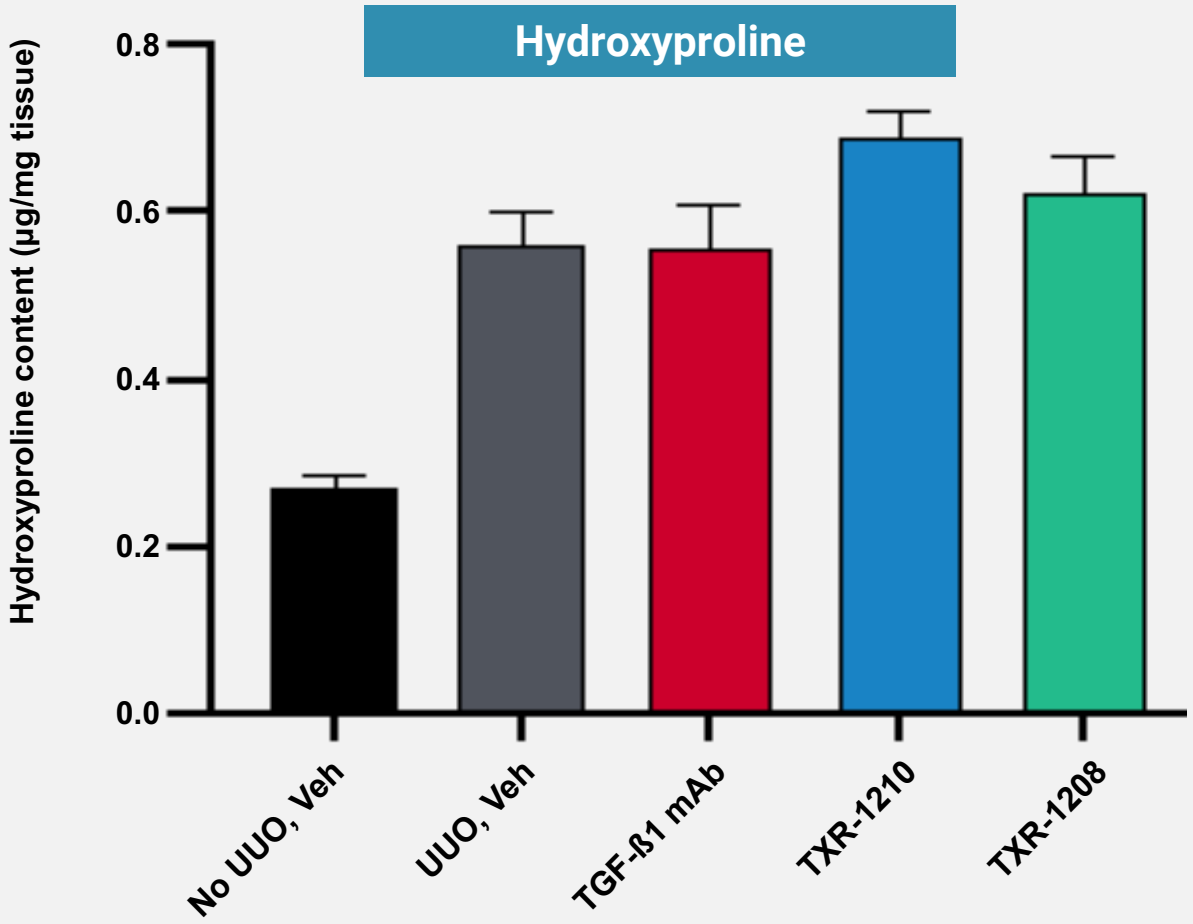
NO CHANGE IN HYDROXYPROLINE LEVELS FOLLOWING UUO

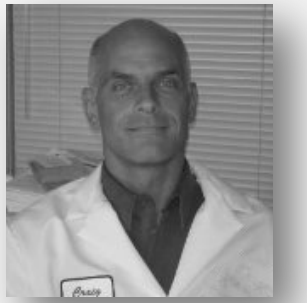
- For a more precise readout, the next study will normalize to total protein levels



N=10 mice per group

TXR-1210 SUPPORTED BY CKD KOLs

Michael J. Ross,
Chief, Division of Nephrology Albert Einstein College of Medicine



Craig F. Plato
CEO, Plato BioPharma

STRENGTHS

- Strongest aspect is some lead compounds have effect on T cell infiltration AND markers of fibrosis.

  – Michael J. Ross

- TXR-1210 looks promising

  – Craig F. Plato

CHALLENGES

- important to confirm in animal studies with proteinuria

  – Michael J. Ross

- Mouse adenine model suggested as next model

  – Craig F. Plato

TXR-1210 SUMMARY

TXR-1210 DEMONSTRATES POSITIVE INITIAL EFFICACY WITH A NEW MECHANISM

	**GOOD TOLERABILITY** – clinically investigated mechanism
	**DECREASED FIBROSIS** – significantly decreased α-SMA staining
	**DECREASED INFLAMMATION** – significantly decreased T cell infiltration
	**ONGOING** – Second UUO mouse efficacy model study completed. Waiting on kidney histology and other biomarker measures

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LEAD IDENTIFICATION REVEALS TXRJB1-071 & TXRJB1-073 FOR OPTIMIZATION

- Two class of inhibitors identified
  - TXRJB1-071 (Class 1 inhibitor): Excellent potency and selectivity. Good exposure and oral bioavailability in mouse and rat and demonstrated in vivo target engagement
  - TXRJB1-073 (Class 2 inhibitor): Good potency & selectivity and exposure in mouse & rat. Shows high efflux, SAR developed to improve efflux

Screening Parameters		Criteria	TXR-1210	TXRJB1-071	TXRJB1-073
Patentability		Secured IP space	Lit. compound	Yes	Yes
In-vitro biology	Primary Assay_IL-1β Release IC_{50} μM	< 1.00	0.575	0.21	1.3
	Secondary Assay_Caspase-1 IC_{50} μM (Active-drug)	< 0.10	0.027	0.085	ND
	Functional Assay_% inhibition of Pyroptosis IC_{50} μM		~40	>100	3.49
	*Selectivity (Caspase family)	> 50 fold	2, 3, 6, 7, 11, 14	2, 3, 4, 5, 6, 7, 8, 10, 11, 14	2, 3, 4, 6, 7, 10, 11, 14
In-vitro ADME	Aq. Solubility (PBS, pH 7.4) μM	>10 μM	136	118	3.7
	Caco2_A-B ($x10^{-6}$ cm/s), ER	A-B_> 5, ER < 2	5.09, 9.04	20.9/1.72	0.84, 20.15
	% remain@ 30 min_MLM/RLM/HLM	> 50% @ 30 min	44, 55, -, 77	66, 67, 72, 74	8, 29, 23, 47
	Plasma_M, R, H	% remain @ 2 h	<1, <1, 100	3, <1, 56	2, <1, 81
	Blood stability _M, H	% remain @ 2 h	<1, < 1, 97.8	**3, <1, 56**	2, <1, 81
	CYP inhibition_3A4, 2D6, 2C9, 2C19	< 50% inh @10 μM	41, 16, 25, 25	39, NI, 15, 39	74, 25, 14, 47
	%PPB (m, h)	< 99% bound	ND, ND, 98.8	ND, ND, 75.5	ND, ND, TBD

*Caspase-1 selectivity against other proteases ≥50X
NA: Not applicable; NI: No Inhibition

LEAD IDENTIFICATION REVEALS TXRJB1-071 & TXRJB1-073 FOR OPTIMIZATION

- TXRJB1-071 (Class 1 inhibitor): Good exposure and oral bioavailability in mouse and rat and demonstrated in vivo target engagement
- TXRJB1-073 (Class 2 inhibitor): Reasonable exposure in mouse & rat. Shows high efflux, SAR developed to improve efflux

Screening Parameters			Criteria	TXR-1210	TXRJB1-071	TXRJB1-073**
In vivo PK	Mouse_IV (1 mpk)	$t_{1/2}$ (h), C_{max} (ng/mL), AUC_{0-t} (ng·h/mL)	$t_{1/2}$ > 4 h	1.94, 34.9, 30.5	0.65, 38.5, 22.5	1.56, 2116, 954
		CL (mL/min/kg), V_{ss} (L/kg)	Cl-< 20% of hepatic blood flow	432, 61.3	550, 34.2	17.4, 0.59
	Mouse_PO (10 mpk)	$t_{1/2}$ (h), t_{max} (h), C_{max} (ng/mL), AUC_{0-t} (ng·h/mL)	$t_{1/2}$ > 4 h	1.3, 1.0, 211, 845	3.36, 1.0, 292, 677	1.89, 0.5, 1042, 1062
		%F	>40%	>100%	>100%	11.1%
	Mouse_IP (10 mpk)	$t_{1/2}$ (h), t_{max} (h), C_{max} (ng/mL), AUC_{0-t} (ng·h/mL)		4.6, 0.5, 272, 774	4.2, 1, 65, 161	5.32, 0.5, 3191, 6266
		%F		>100%	72%	66%
	Rat_IV (1 mpk)	$t_{1/2}$ (h), C_{max} (ng/mL), AUC_{0-t} (ng·h/mL)		0.23, 9.62, 3.54	0.14, 1219, 229	0.19, 1435, 216
		CL (mL/min/kg), V_d (L/kg)		4675, 79.3	75, 0.7	77.3, 0.73
	Rat_PO (10 mpk)	$t_{1/2}$ (h), t_{max} (h), C_{max} (ng/mL), AUC_{0-t} (ng·h/mL)		1.48, 0.25, 80.8, 119	(0.75, 0.25, 859, 612)*	2.11, 0.25, 86.3, 64.1
		%F		>100%	28%	3.3%
Target engagement (PK/PD),			Demonstrate	Completed (✓)	Completed (✓)	Completed (✓)
In-vivo UUO efficacy Model				Study completed, analysis ongoing	Planned	Planned

*TXRJB1-071 Rat PO PK data is for active-drug release
**TXRJB1-073 PK data is for active-drug release

TXRJB1-071 and TXRJB1-073 LEAD IDENTIFICATION SUMMARY

***IN VITRO* BIOLOGY** – Primary and functional assays in place. Identified compounds with better potency than reference

***IN VITRO* ADME** – Better permeability & lower efflux compounds identified. Good stability in liver microsome across mouse, rat, & human

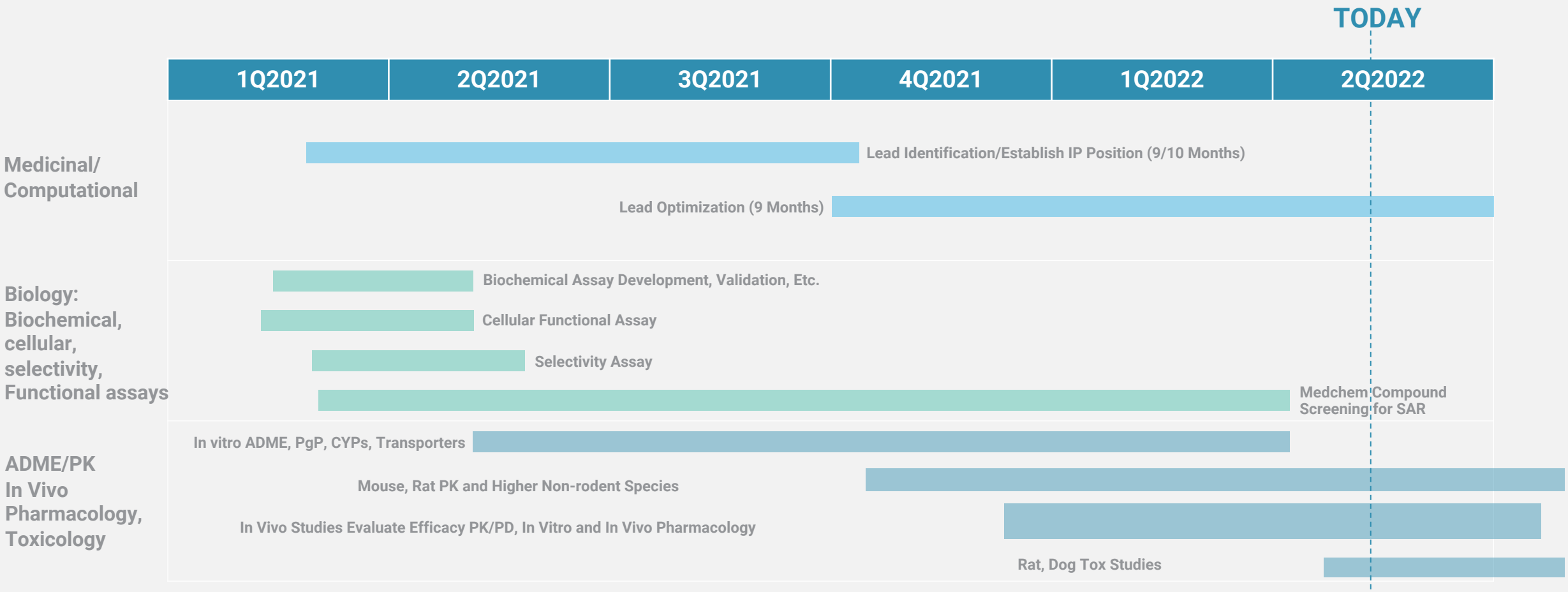
***IN VIVO* PK**– Several compounds taken into mouse & rat PK; showed better or equivalent PK properties to TXR-1210

IP – Two provisional patent applications filed – May 2022

NEXT STEPS – Continue optimization for potency and desired PK properties. Complete histology & biomarker analysis of second UUO efficacy study. Planned UUO study with front runner after scale up. PK profiling in dog. safety panel and hERG profiling

LEAD DISCOVERY THROUGH IND CANDIDATE

DEVELOPMENT PLAN



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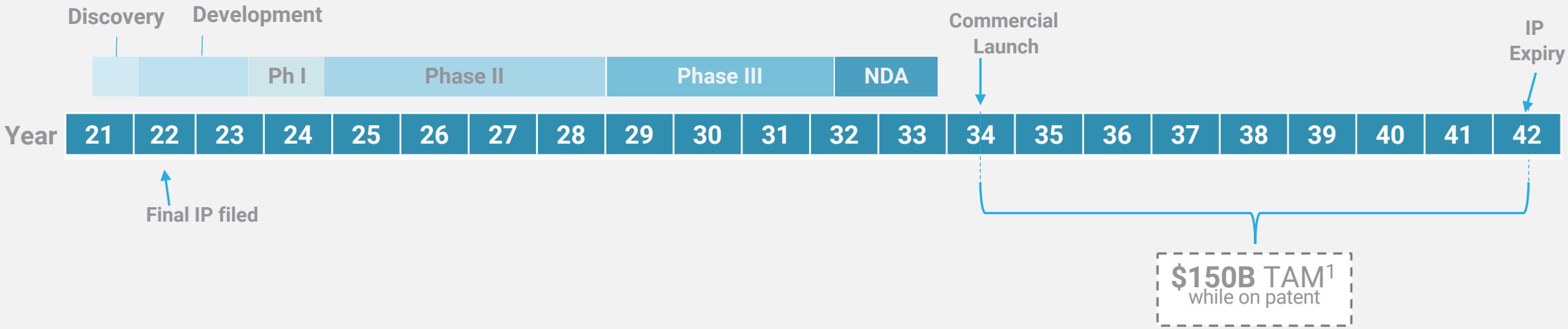
UPCOMING DEVELOPMENT PLANS

- 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 ($160M total)	**($100K)[2]**	**(~$6M)[3]**	**(~$5M)[4]**	**($30M)[4]**	**($120M)[4]**	**(~$2M)[4]**
Exemplar Deals	N/A[5]	Novo Nordisk – Epigen (2018) Single asset: • $200M across upfront and milestones • unspecified royalties	Anteris Bio – vTv Therapeutics (2020) Single asset: • $2M upfront • $150M milestones • double digit royalties	Abbott[6] & Kirin[7] – Reata (2010) Single asset: • $725M across upfront and milestones • double digit royalties	N/A[8]	N/A[8]

1. Source: Coherent Market Insights report
2. Incurred cost
3. Contracted costs
4. Estimated costs
5. This program is in development
6. Worldwide rights, Ex-US, Ex-Asia
7. Asia rights
8. No relevant exemplar deals

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SUMMARY

- CKD is a $13B/yr market with only one recently approved drug and off-label therapeutic approaches
- TXR-1210 is a caspase-1 inhibitor
  - Can block or reverse phenotypic changes associated with CKD while maintaining an excellent tolerability profile
  - MOA well tolerated in clinical studies in multiple indications
    - Selectivity key issue
  - Positive results in industry-standard preclinical mouse model of CKD
    - Significant decreases in inflammation and fibrosis
- Two provisional patent applications filed in May 2022

www.ariapharmaceuticals.com

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