Rev Therapeutics

Cardiac surgery without the risk of acute kidney injury

Series A investment opportunity to advance RRx-002, a small molecule inhibitor developed to treat cardiac surgery-associated acute kidney injury

March 2024

experienced team with extensive development and clinical experience

Business Development, Finance, Operations	Clinical and Reg. Affairs	Nonclinical Development and Toxicology	CMC

David Webb, Ph.D.
Chairman

Former VP of Research, Celgene
Synbal, Agragene, Syrrx, Cadus, OSI Pharma, Syntex, Roche
LinkedIn

Derek R. Brunelle
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Former Executive Director, J.P. Morgan
Managing Director, Silicon Valley Bank
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CMO

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SVP Development

Former VP of Development, Celgene Schering Plough, Merck
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VP Nonclinical Development*

Former VP Nonclinical Development, Kinnate Biopharma, Snr. Director, Preclinical Safety, Xeris, Novartis
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Yoshi Satoh, Ph.D.
VP Chemistry

Former medicinal chemist, 5 clinical compounds at Novartis and Celgene
LinkedIn

Co-developed FDA-approved products include: Erlotinib (Tarceva®), Alogliptin (Nesina®), Apremilast (Otezla®), Temozolomiode (Temodal®), Anti-thymocyte Globulin (Thymoglobulin®), Mycophenolate mofetil (CellCept®), Cyclosporine (SangCYA®), Celsior® (510k device), Cysteamine bitartrate (PROCYSBI®), Pomalidomide (Pomalyst®), Ezetimibe (Zetia®), Rifaximin (Xifaxan ®), Cabozantinib (Cabometyx®), Cobimetinib (Cotellic®), Tafenoquine, Asciminib (Scemblix®), Tecovirimat, Gvoke

* Consultant

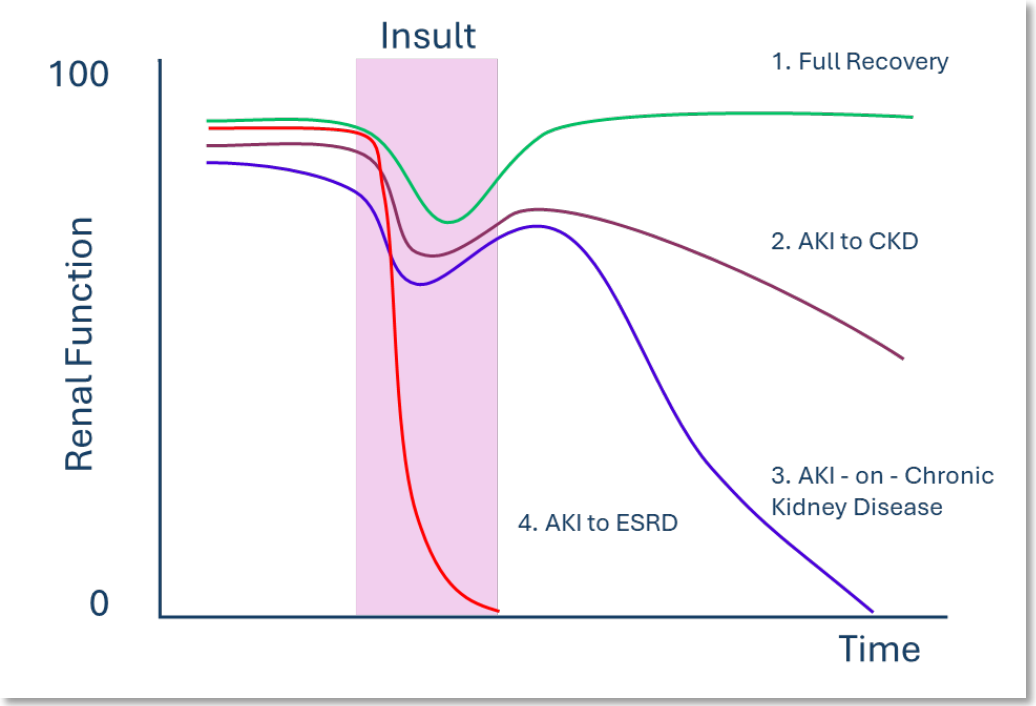
opportunity summary

Large $1B - $2B market	We are currently developing RRx-002, a patent protected [1] prodrug of RRx-003[2] to prophylactically treat cardiac surgery-associated acute kidney injury (CSA – AKI), a large unmet medical need
De-risked asset	RRx-003 was tested in multiple clinical studies and was shown to be well tolerated in both a Ph. 1 healthy volunteer study and a Ph. 2 study treating patients with IPF
Compelling preclinical data	Preclinical *in-vivo* animal data using RRx-002 corroborated the renal protective capabilities of RRx-003 shown in prior kidney ischemia / reperfusion injury *in-vivo animal* studies
Experienced team	Capital efficient virtual business model supported by team members with decades of drug development and renal disease experience; team members co-developed 17 approved drugs and collaborated on 100+ IND filings

[1] Provisional patent filed
[2] Internal name of compound developed by pharma that is no longer in clinical development

the problem

Cardiac surgery-associated acute kidney injury (CSA-AKI) is a common complication of coronary artery bypass graft (CABG) surgery which can progress to chronic kidney disease and end stage renal disease



270,000+

Est. # of CABG procedures performed annually in U.S.

10% -30%

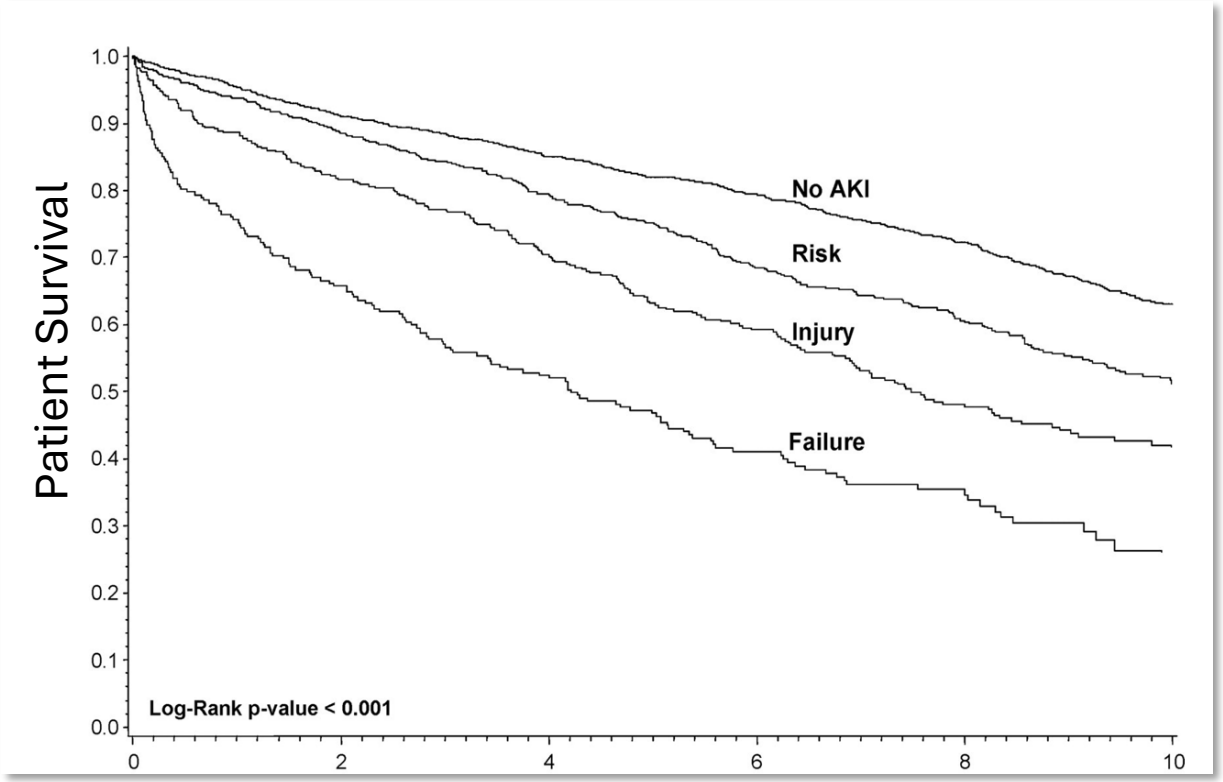
Incidence rate of CSA-AKI per CABG procedure

2% - 5%

Patients diagnosed with AKI that require renal replacement therapy

the impact on lives and healthcare system costs

CSA-AKI is associated with poorer outcomes for patients as well as increased costs for healthcare payors



Increased Mortality

Post CABG survival rates are significantly impacted by severity of AKI diagnosis

2x Cost

Index hospitalization costs for those with AKI ($77.1k vs. $38.8k)

$1.0B

Est. total incremental hospitalization costs associated with incidence of AKI

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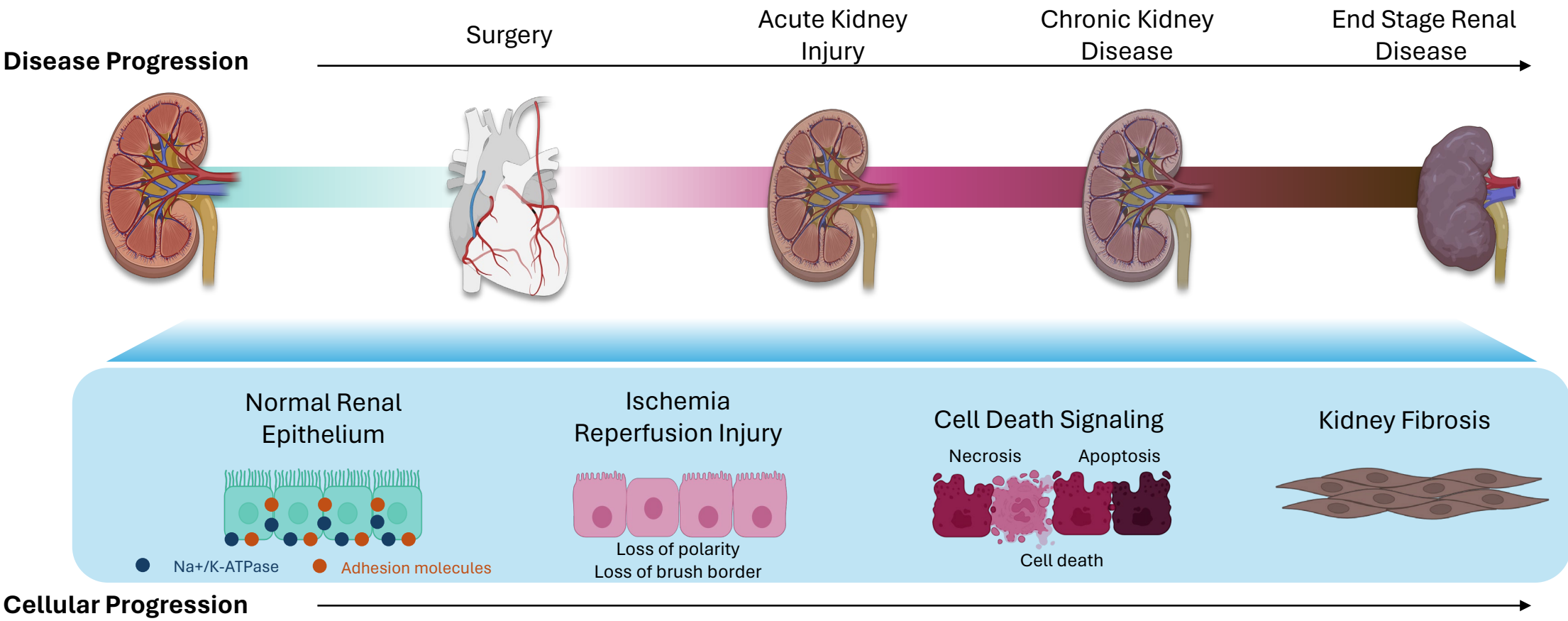
the underlying cause of the problem

Ischemia and reperfusion injury progresses to renal proximal tubular epithelial (RPTE) cell death, kidney dysfunction, and fibrosis



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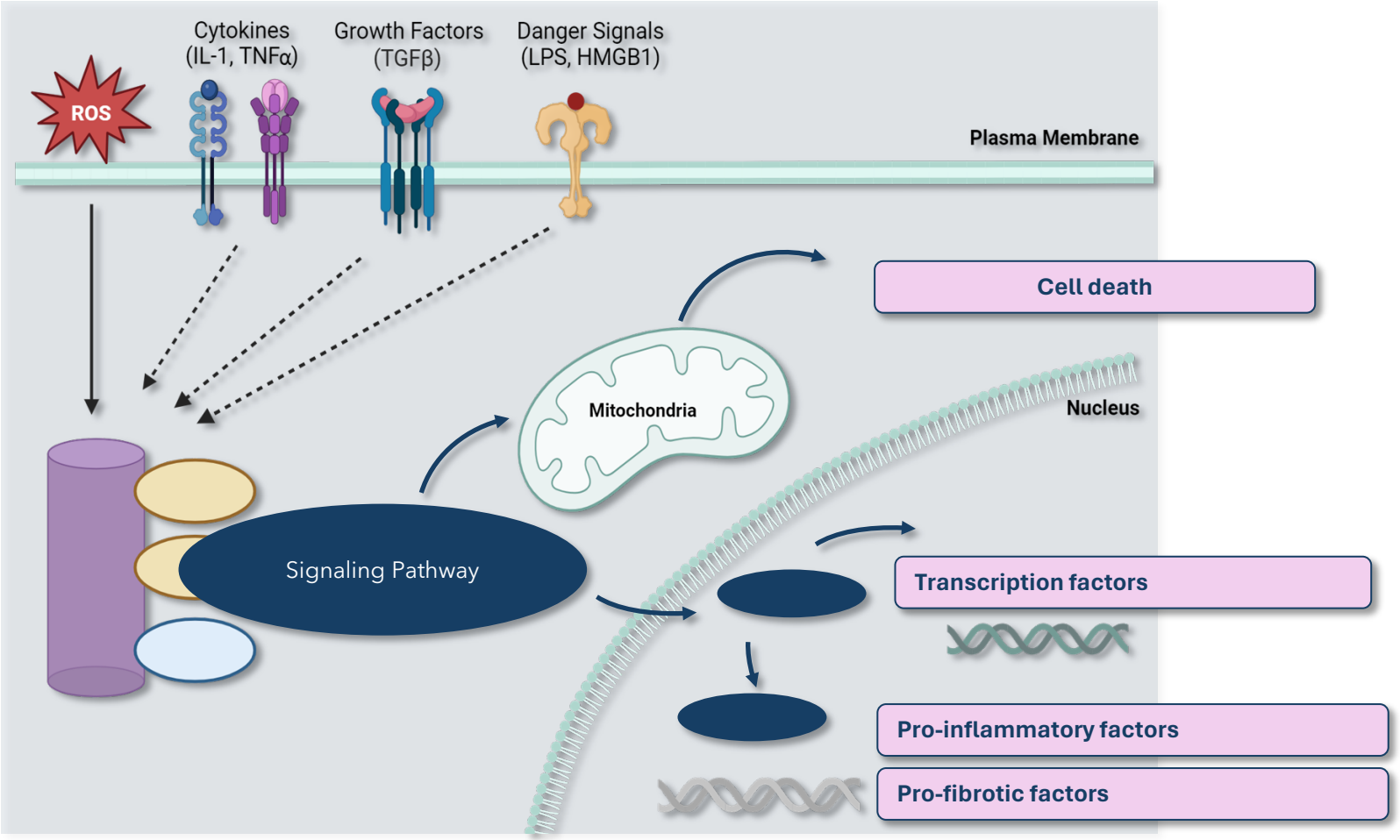
RRx-002 Program

enzymatic pathway associated with cell death, damage, and fibrosis

Target is an enzymatic pathway that is activated in response to various cellular stresses and plays an important role in cell death and inflammation

Activation of this enzymatic pathway is a common feature in human kidney injury

Inhibition can impact inflammation, cell death, and fibrosis



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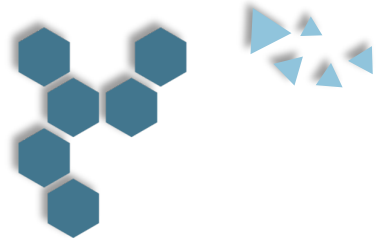
RRx-002 –a novel prodrug compound with unique properties

Parent Compound	Prodrug Compound	*In-vivo* Compound
Chemical Modification →		*Enzymatic Cleavage*
RRx-003	RRx-002	RRx-003
		
Active moiety		*Active moiety*
✓ Efficacy in multiple animal models	✓ Water soluble | allows IV admin	✓ Efficacy in animal models
✓ Shown to be safe in humans	✓ Rapidly cleaves to RRx-003	✓ Anticipated to be safe in humans
✓ Selective for primary target	✓ Prodrug moiety has no activity	
✗ Insoluble, orally available	✓ Prodrug group used in approved drugs	

RRx-002 is rapidly cleaved to the active species (RRx-003) by isoforms of alkaline phosphatase which are widely distributed throughout mammalian tissues

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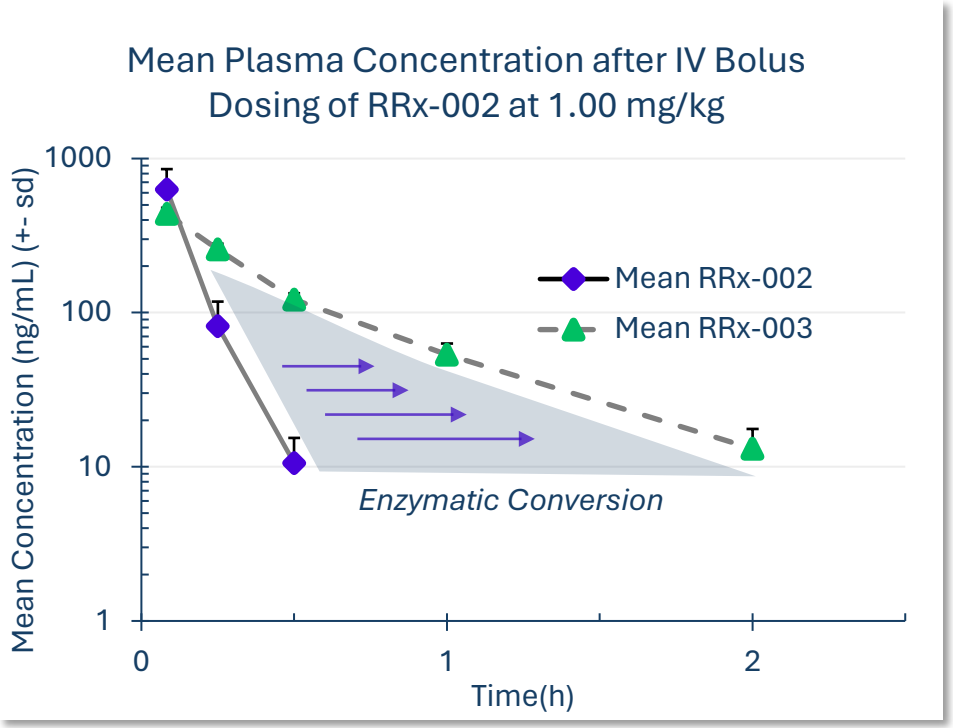
rapid enzymatic cleavage

RRx-002 shows superior pharmaceutical properties and is rapidly cleaved to RRx-003 *in-vivo*



Solubility Comparison

Compound	Solubility in PBS* at pH 7.4
RRx-002	45.6 mg/ml
RRx-003	0.060 mg/ml

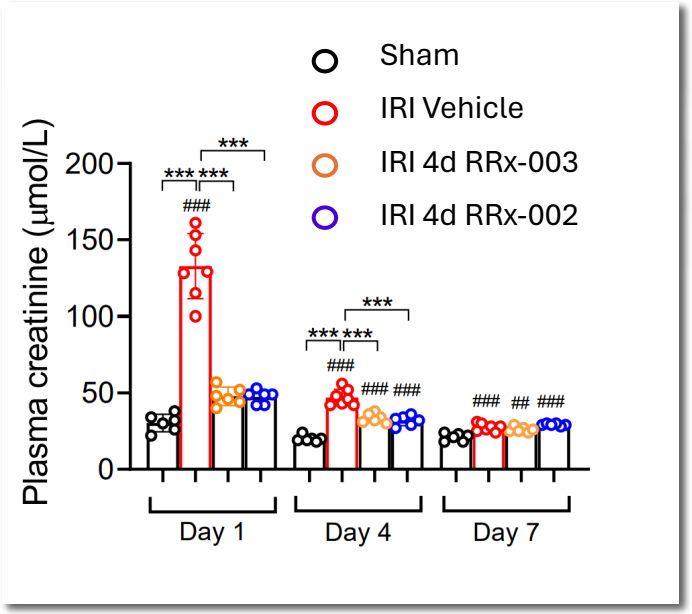
why we are excited about RRx-002

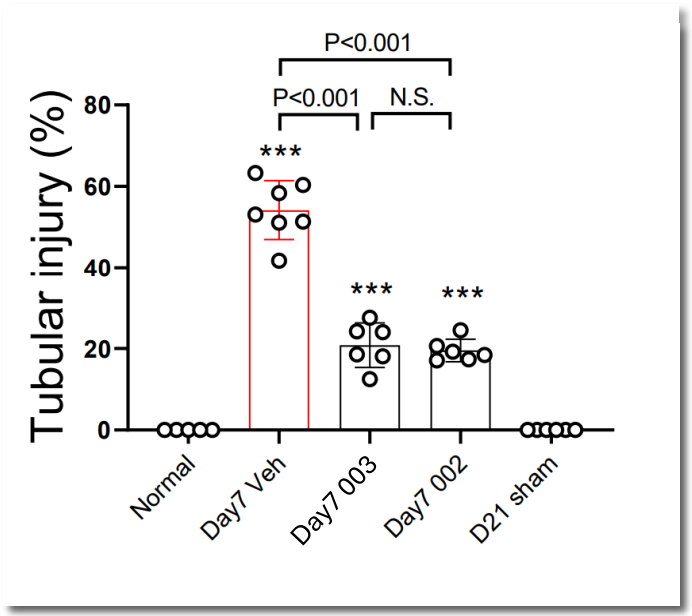
In *in-vivo* animal studies, RRx-002 showed a significant ability to protect against renal failure, renal inflammation, and renal fibrosis

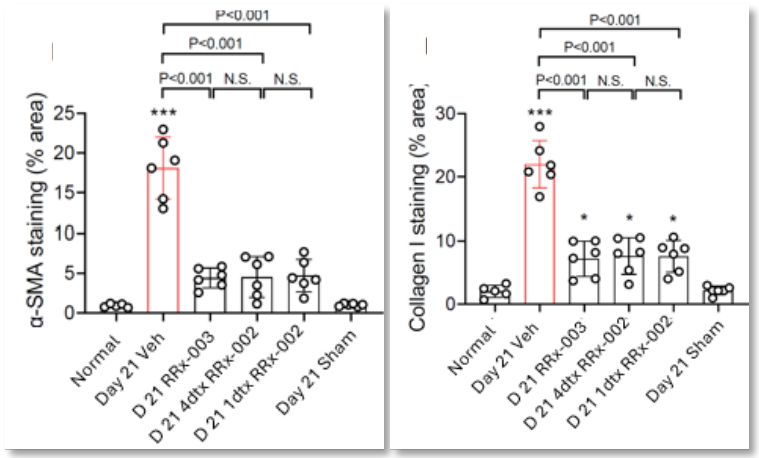
88% Reduction in plasma creatinine

65% Reduction in tubular damage

79% Reduction in fibrosis markers







α-SMA

Collagen 1

progress to date and intended use of proceeds

Key Milestones Completed with Initial Capital

- Synthesized RRx-003 and RRx-002
- PK and PD studies comparing RRx-002 and RRx-003
- Preclinical animal (rat) *in-vivo* pharmacodynamic studies with RRx-002 in warm ischemia model
- Filed provisional patent on RRx-002

- Completed Pre-IND meeting

Use of Funds

- Series A
  - T1 – IND enabling studies
    - Process CMC, drug formulation and drug product dev.
    - Complete in-vitro and in-vivo tox.
  - T 2 - SAD / MAD Ph. 1

- Series B
  - Ph. 2 (dependent on additional Series B financing)

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Appendix

competitive landscape

known agents currently in development

Sponsor	Stage	Agent	Modality	MoA	NCT	Primary Endpoint
Novartis	Ph. 2	TIN816	Recombinant human CD39 enzyme	ATP Modulator	NCT05524051	Ratio of highest serum creatine value within 5 days post-dose vs. baseline
Astra Zeneca	Ph. 3	Ultomiris™	mAb	C5 inhibitor	NCT05746559	No. of participants experiencing major adverse kidney events (MAKE) at 90 days post CPB surgery
Renibus Therapeutics	Ph. 3	RBT-1	Combo of stannic protoporphyrin & iron sucrose	Preconditioning agent	NCT06021457	Composite of death, incidence of AKI requiring RRT, ICU days, and 30-day cardiopulmonary
Mission Therapeutics	Ph. 2	MTX652	Small mol.	Inhibition of USP30	Not available	12/14/2023 press release - “assessing standard markers of renal function and renal injury over time”
AM Pharma	Ph. 2	Ilofotase alfa	Recombinant alkaline phosphatase (recAP)	Dephosphorylating and detoxifying DAMPs and PAMPS	Not available	01/16/2024 press release – “ratio between pre-and post-surgery creatine levels”
Guard Therapeutics	Ph. 2b	RMC-035	Recombinant protein (mimic of alpha-1 microglobulin)	Reductase activity, binding of free radicals and heme, and binding, protection of mitochondria	Not available	01/30/2024 R&D Day – “Change from baseline in eGFR based on serum creatine at Day 90”

select scientific papers

Title	DOI
Vives M, Hernandez A, Parramon F, Estanyol N, Pardina B, Muñoz A, Alvarez P, Hernandez C. Acute kidney injury after cardiac surgery: prevalence, impact and management challenges. Int J Nephrol Renovasc Dis. 2019 Jul 2;12:153-166.	10.2147/IJNRD.S167477
Chertow GM, Levy EM, Hammermeister KE, Grover F, Daley J. Independent association between acute renal failure and mortality following cardiac surgery. Am J Med. 1998 Apr;104(4):343-8.	10.1016/s0002-9343(98)00058-8
Bonventre, J.V. and Yang, L., 2011 Cellular pathophysiology of ischemic acute kidney injury. *J Clin Invest*. 2011;121(11):4210-4221.	10.1172/JCI45161
Alshaikh HN, Katz NM, Gani F, Nagarajan N, Canner JK, Kacker S, Najjar PA, Higgins RS, Schneider EB. Financial Impact of Acute Kidney Injury After Cardiac Operations in the United States. Ann Thorac Surg. 2018 Feb;105(2):469-475.	10.1016/j.athoracsur.2017.10.053
Schurle A, Koyner JL. CSA-AKI: Incidence, Epidemiology, Clinical Outcomes, and Economic Impact. J Clin Med. 2021 Dec 8;10(24):5746.	10.3390/jcm10245746
Casanova, A.G.; Sancho-Martínez, S.M.; Vicente-Vicente, L.; Ruiz Bueno, P.; Jorge-Monjas, P.; Tamayo, E.; Morales, A.I.; López-Hernández, F.J. Diagnosis of Cardiac Surgery-Associated Acute Kidney Injury: State of the Art and Perspectives. *J. Clin. Med.* 2022, *11*, 4576.	10.3390/jcm11154576
Jornada, D.H.; Dos Santos Fernandes, G.F.; Chiba, D.E.; De Melo, T.R.F.; Dos Santos, J.L.; Chung, M.C. The Prodrug Approach: A Successful Tool for Improving Drug Solubility. *Molecules* 2016, *21*, 42.	10.3390/molecules21010042
Leaf DE, Waikar SS. End Points for Clinical Trials in Acute Kidney Injury. Am J Kidney Dis. 2017 Jan;69(1):108-116.	10.1053/j.ajkd.2016.05.033

contact information

Thank you!

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