



ZyVersa Corporate Presentation

Q3-2022



*Restoring Health, Transforming Lives
Through Innovation*

Restoring Health, Transforming Lives Through Innovation



Corporate Overview

ZyVersa Is a Clinical Stage, Specialty Biopharma Company Focused on Renal and Inflammatory Diseases With High Unmet Needs



Renal Lead: Phase 2a-ready VAR 200, Cholesterol Efflux Mediator (2HP β CD)

- ▶ Lead indication: Focal segmental glomerulosclerosis (FSGS), an orphan kidney disease
- ▶ Potential for multiple renal indications

Anti-inflammatory Lead: IC 100, Inflammasome ASC inhibitor

- ▶ Potential for multiple inflammatory indications

- ▶ Led by a team of industry veterans from top pharmaceutical companies
- ▶ Experience encompasses over 15 therapeutic areas

>\$75B

Total
addressable
markets

ZyVersa Investor Highlights

2 Proprietary Product Platforms	<ul style="list-style-type: none"> • Anti-inflammatory and renal platforms each offer a “pipeline in a product” • Multiple potential indications in both categories target over \$75B TAM
Renal VAR 200 Cholesterol Efflux Mediator	<ul style="list-style-type: none"> • Differentiated MOA: Mediates removal of excess intracellular lipids that contribute to kidney damage and dysfunction • Renal orphan focused • Safety profile enabling FDA clearance for Phase 2 • Next catalysts: Initiate IIT study in renal patients for human proof-of-concept
Anti-inflammatory IC 100 Inflammasome Inhibitor	<ul style="list-style-type: none"> • mAb designed and engineered by leading inflammasome and monoclonal antibody experts • Differentiated MOA: ASC inhibition attenuates initiation and perpetuation of inflammation • Preclinical pharmacology supports IND indications in MS and ARDS • Initial preclinical safety established; small scale manufacturing completed • Opportunity for indication expansion: Parkinson’s disease, atherosclerosis, early Alzheimer’s disease diabetic nephropathy, atrial fibrillation, systemic lupus, lupus nephritis, heart failure, certain cancers • Next catalysts: GLP tox study for IND and cGMP manufacturing
Inflammasome Opportunity	<ul style="list-style-type: none"> • Positioned in rapidly emerging inflammasome space; mAb providing a highly differentiated MOA • Highly attractive to biopharma and investors; over \$4B in M&A activity for preclinical/phase 1 programs over last 18 months in this sector (acquisitions by Roche, Novartis and BMS)⁽¹⁾
Proven Leadership Team and SAB	<ul style="list-style-type: none"> • CEO co-founded & led multiple biopharma companies & has successful track record in licensing, M&A, raising capital, and taking companies public • Current management team built from successful leaders from CEO's prior companies <ul style="list-style-type: none"> - Prior experience at Roche, Amgen, Novartis, Abbott, Genentech and J&J - Led development of numerous top biologics through approval • SAB members are renowned leaders in inflammasome and renal research <ul style="list-style-type: none"> - Drs. Barbosa and Baker are Former global Heads of Immunology Research at J&J

1. Pitchbook as of 12/2/20

Highly Experienced Leadership Team



Stephen C. Glover

- ▶ Co-Founder, Chief Executive Officer, and Chairman
- ▶ Over 38 years in biopharmaceuticals and life sciences
- ▶ Previous roles at Coherus Biosciences, Insmed, Amgen, and Roche
- ▶ Serves on the Boards of PDS Biotechnology and Asclepius Lifesciences



Pablo A. Guzman, MD, FACC

- ▶ Chief Medical Officer and Chairman, Renal Scientific Advisory Board
- ▶ Over 40 years in medicine
- ▶ Previous roles at American College of Cardiology, Johns Hopkins University, and Holy Cross Hospital
- ▶ Serves on the Board of Holy Cross Hospital



Peter Wolfe

- ▶ Senior Vice President, Finance and Administration
- ▶ Over 20 years in biopharmaceuticals and life sciences
- ▶ Previous roles at KOS and Noven Pharmaceuticals



Nick A. LaBella, MS, RPH

- ▶ Chief Scientific Officer, Senior VP Research and Development
- ▶ Over 34 years in biopharmaceuticals and life sciences
- ▶ Previous roles at Insmed, Cardiokine, Watson Laboratories, and Sandoz



Karen Cashmere

- ▶ Chief Commercial Officer
- ▶ Over 30 years in biopharmaceuticals and life sciences
- ▶ Previous roles at Abbott (now AbbVie), EMD Serono, Noven/Novartis Joint Venture, Amgen, and Auxilium



Melda Uzbil O'Connell

- ▶ Senior Vice President, Corporate Development
- ▶ Over 17 years in academic technology commercialization, business development and fund raising
- ▶ Previous roles at Pfizer, Duke and State of Michigan

Deep pharmaceutical experience and successful track record

>35 NDA/BLA Filings, >55 New Product Launches, >15 rare disease indications, >40 Licensing Deals & Acquisitions
>\$10B+ of Licensing and M&A experience, Over \$250M of Private Capital Raised

Top Tiered Renal Scientific Advisory Board, Known for Leadership in Glomerular Research and Advocacy



Sharon G. Adler, MD

- ▶ Professor of Medicine, David Geffen School of Medicine, UCLA
- ▶ Chief, Division of Nephrology and Hypertension, Harbor-UCLA Medical Center
- ▶ Program Director, Nephrology Fellowship Training Program, Harbor-UCLA Medical Center



Daniel C. Cattran, MD, F.R.C.P. (C)

- ▶ Professor of Medicine, University of Toronto
- ▶ Chair of the Toronto Glomerulonephritis Registry



Alessia Fornoni MD, PhD

- ▶ Professor of Medicine and Chief, Katz Family Division of Nephrology and Hypertension, University of Miami Miller School of Medicine



Pablo A. Guzman, MD, FACC

- ▶ Chairman, Scientific Advisory Board
- ▶ Chief Medical Officer, ZyVersa Therapeutics



Debbie S. Gipson, MD, MS

- ▶ Professor, Department of Pediatrics, University of Michigan
- ▶ Director, Kidney Research Network Coordinating Center



Marlene Haffner, MD, MPH

- ▶ Principal & Founder, Orphan Solutions & Haffner Associates
- ▶ Former Director of Orphan Products Development, FDA

Renowned Anti-inflammatory Scientific Advisory Board, Recognized As Pioneers/Leaders in Inflammasome Inhibitor Space



Miguel S. Barbosa, PhD

- ▶ Former Global Head and Vice President of Immunology Research and External Innovation at Janssen Research & Development, Pharmaceutical Companies of Johnson & Johnson



Daniel G. Baker, MD

- ▶ Former Vice President, Immunology Research and Development, Janssen Pharmaceutical Companies of Johnson & Johnson



Doug H. Farrar

- ▶ CEO, Flatirons Biotech, Inc
- ▶ Former Cofounder and Chief Technical Officer, Coherus Biosciences
- ▶ Former SVP biologic manufacturing at Amgen and Insmad



Alan Herman, PhD

- ▶ Chairman Emeritus, former Chief Scientific Officer, Coherus Biosciences
- ▶ Formerly: Genentech, Amgen, Merck, Coherus Biosciences



William F. Bennett, PhD

- ▶ Principal, Bioscope Associates
- ▶ Formerly: Genentech, Sensus Corporation, Cor Therapeutics



Robert W. Keane, PhD: Inventor of Inflammasome Platform

- ▶ Professor Physiology & Biophysics, Neurological Surgery & Microbiology, and Immunology, UM
- ▶ The Miami Project to Cure Paralysis, UM



Juan Pablo de Rivero Vaccari, PhD: Inventor of Inflammasome Platform

- ▶ Research Assistant Professor, Department of Neurological Surgery, UM
- ▶ The Miami Project to Cure Paralysis, UM
- ▶ Distinguished Faculty Member of The Center for Cognitive Neuroscience and Aging, UM



W. Dalton Dietrich, III, PhD: Inventor of Inflammasome Platform

- ▶ Kinetic Concepts Distinguished Chair in Neurosurgery & Scientific Director, The Miami Project to Cure Paralysis, UM
- ▶ Senior Associate Dean, Discovery Science & Co-director, Institute for Neural Engineering, UM
- ▶ Professor, Neurological Surgery, Neurology, Biomedical Engineering & and Cell Biology, UM



Helen Bramlet, PhD: Inventor of Inflammasome Platform

- ▶ Professor, Department of Neurological Surgery, UM
- ▶ The Miami Project to Cure Paralysis, UM

Two Proprietary Product Platforms, Each With “Pipeline Within a Product” Potential

ZyVersa’s two proprietary platforms target unmet medical needs with unique MOAs; offer multiple opportunities for expansion beyond initial targeted indications

Product	Development	Pre-clinical	Phase 1	Phase 2	Phase 3	NDA/BLA Submission
Renal/Cholesterol Efflux Mediator						
VAR 200-01: FSGS*	→					
VAR 200-02 : Alport Syndrome*	→					
VAR 200-03: Diabetic Kidney Disease	→					
Inflammasome/ASC Inhibitor						
IC 100-01: Acute Respiratory Distress Syndrome*	→					
IC 100-02: Multiple Sclerosis	→					
IC 100-03: Parkinson's Disease	→					
IC 100-04: Pancreatic Cancer*	→					
IC 100-05: IgA Nephropathy*	→					
IC 100-06: Huntington's Disease*	→					

* Orphan diseases

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Chronic Kidney Disease Market

Despite High Unmet Needs for Effective Drugs for Chronic Renal Diseases, Drug Development Innovation Did Not Emerge Until the Last Decade

Key Drivers of Renal Drug Development Innovations

- ▶ **FDA Acceptance of Surrogate Endpoints for Approval (Changes in Proteinuria and eGFR)**
 - Shortened time and costs of drug development
 - Improved likelihood of success versus long-term outcome studies
- ▶ **Improved Understanding of the Pathogenesis of Various Renal Diseases**
 - Facilitated identification of drug targets
- ▶ **Health and Human Services' Advancing Kidney Health in America Initiative**
 - **Reduce risk of kidney failure**
 - Advance public health surveillance capabilities/research to improve identification of populations at risk and those in early stages of kidney disease
 - Encourage adoption of evidence-based interventions to delay/stop progression to kidney failure
 - **Improve access to and quality of person-centered treatment options**
 - Improve care coordination and patient education for patients/caregivers, enabling more person-centric transitions to safe and effective treatments for kidney failure
 - Introduce new value-based kidney disease payment models that align health care provider incentives with patient preferences and improve quality of life
 - Catalyze development of innovative therapies with funding from government, philanthropic and private entities, and coordinate regulatory and payment policies to incentivize innovative product development
 - **Increase Access to Kidney Transplants**
 - Increase utilization of organs from deceased donors by increasing organ recovery and reducing the organ discard rate
 - Increase number of living donors by removing donation disincentives and ensuring appropriate financial support

CKD Drug Market Large and Growing

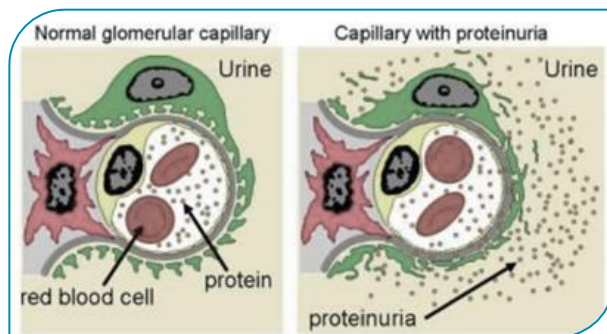
- ▶ CKD: 11 – 13% of the global population (15% of US population¹)
 - Driven by diabetes, hypertension, with heart disease, with obesity, and aging as risk factors
- ▶ No disease-modifying drugs; CKD management focused on delaying disease progression with combination of drugs
 - ACE inhibitors or ARBs to address glomerular hypertension
 - Steroids and/or calcineurin inhibitors to address inflammation
- ▶ Staggering health economic impact: cumulative costs to treat early-stage CKD greater than to treat end-stage (e.g. US Medicare spent \$81B on early stage and \$49B on end-stage CKD in 2018)²
- ▶ Global drug market size: \$14.5B in 2020, projected to grow to \$23.4B by 2030 (CAGR of 5.0% from 2021 to 2030)³

1. Chronic Kidney Disease in the United States, 2019. CDC; 2. USRDS 2020 Annual Report; 3. Nephrology Drugs Market. Allied Market Research, December 2021

Glomerular Diseases Are the 3rd leading Cause of Chronic Kidney Disease

Glomerular Disease

- ▶ Injury to the kidneys' filtration system, glomerular podocytes, causes protein to leak into the urine (proteinuria), and as it progresses nephrotic syndrome is common
- ▶ Nephrotic syndrome
 - Proteinuria (> 3.5g/day)
 - Hypoalbuminemia (<3.5g/dL)
 - Edema
- ▶ Nephrotic syndrome leads to end-stage renal disease, requiring dialysis and kidney transplant



Primary Causes of Glomerular Disease

- ▶ Focal Segmental Glomerulosclerosis (FSGS)
- ▶ Minimal-Change Nephropathy
- ▶ Membranous Nephropathy
- ▶ Hereditary Nephropathies (i.e. Alport Syndrome)

Secondary Causes of Glomerular Disease

- ▶ Diabetes Mellitus
- ▶ Lupus Erythematosus
- ▶ Amyloidosis and Paraproteinemias
- ▶ Viral Infections (i.e. Hepatitis B & C, HIV)

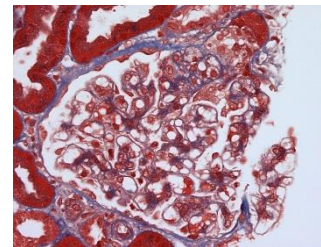
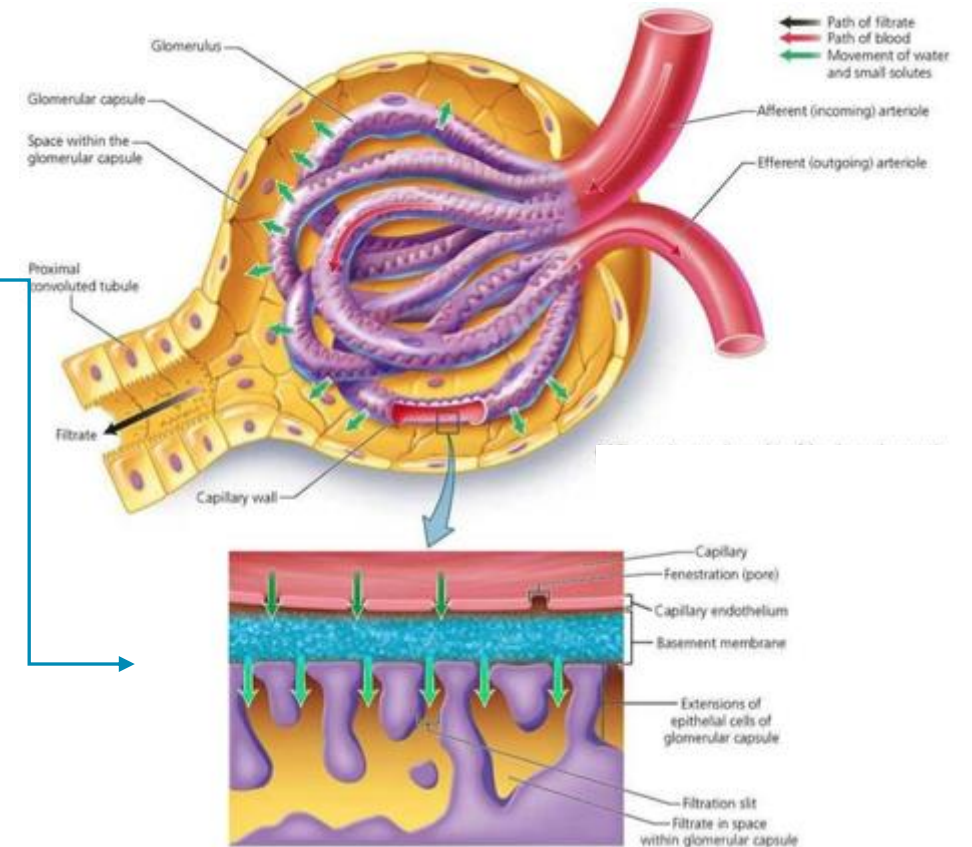
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Role of Lipids in Renal Disease

Excess Cholesterol in Podocytes Contributes to the Pathology of Glomerular Diseases

- ▶ The kidneys' filtration system, the nephron, includes a network of small capillaries known as the glomerulus
- ▶ Podocytes, which have long projections called foot processes, wrap around the capillaries; the space between them is known as a slit diaphragm (a lipid raft-like structure) serving as a selective barrier to prevent loss of protein in the urine (proteinuria)
- ▶ Maintenance of podocyte intracellular cholesterol at appropriate levels is critical to support the structural integrity and function of the podocytes and slit diaphragm; excess levels can compromise structural integrity



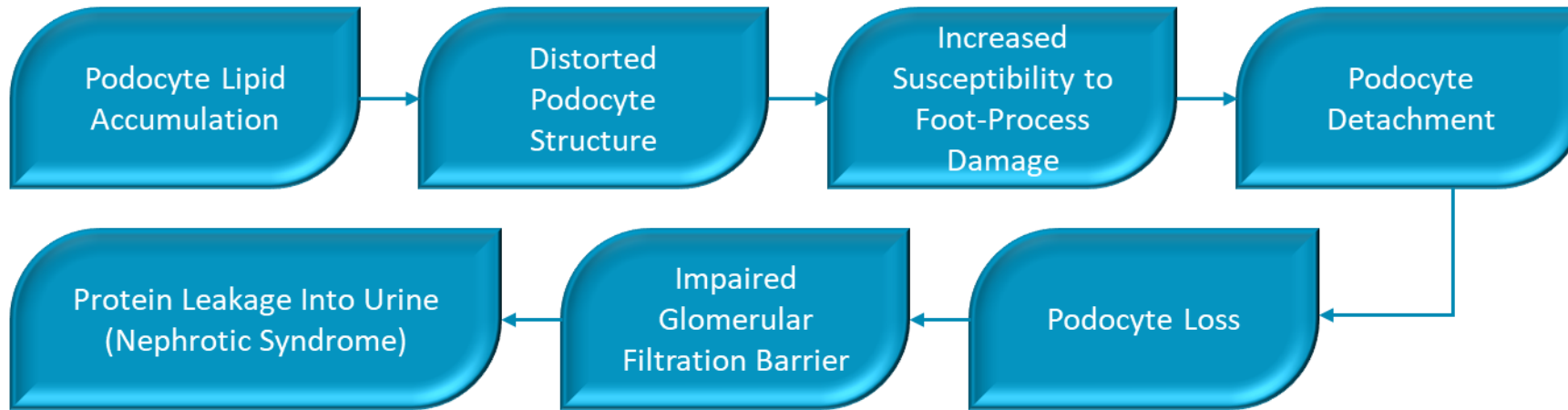
FSGS Patient's Podocyte Histology (Neptune)

Image from: <http://schoolbag.info/biology/humans/22.html>

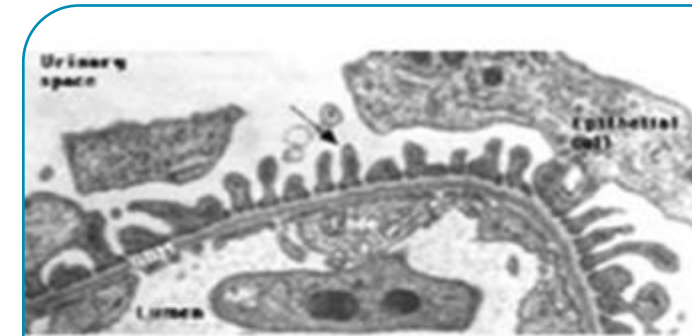
FSGS, Alport Syndrome, and Other Glomerular Diseases Are Associated With Excess Podocyte Cholesterol Resulting From Decreased Cholesterol Efflux

1. Fornoni A, Merscher S, Kopp JB. Lipid biology of the podocyte—new perspectives offer new opportunities. Nature reviews Nephrology. 2014;10(7):379-388

Accumulation of Glomerular Lipids Contributes to Structural Damage, Proteinuria, and Progression of Kidney Disease



Normal: Intact podocytes foot process



Abnormal: Flattened podocytes

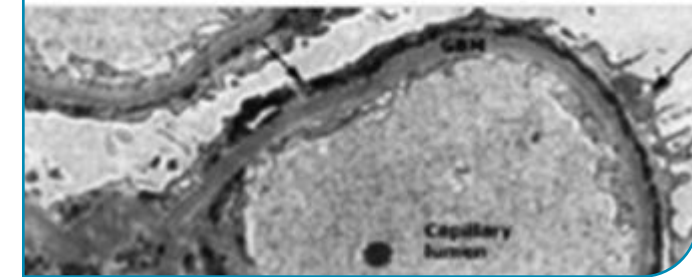


Image Adapted From D'Agati et al: *N Engl J Med* 2011; 365:2398-2411

1. Ducasa GM, Mitrofanova A, Mallela SK, et al. ATP-binding cassette A1 deficiency causes cardiolipin-driven mitochondrial dysfunction in podocytes. *J Clin Invest.* 2019;129(8):3387–3400

Current Treatment Algorithm For Nephrotic Syndrome Addresses Hypertension and Inflammation, But Not Lipids

- ▶ **Intracellular podocyte lipid accumulation from reduced cholesterol efflux** causes podocyte injury and flattened foot processes leading to proteinuria
 - No current treatments address podocyte lipid accumulation
- ▶ **Arteriole vasoconstriction** increases arteriole pressure leading to reduced blood flow and decreased glomerular filtration rate (GFR)
 - Treated with ACE inhibitors and ARBs to dilate the arterioles
- ▶ **Glomerular inflammation** results in distorted, more porous endothelial cells and contracted mesangial cells leading to proteinuria and decreased GFR
 - Treated with steroids and calcineurin inhibitors (CIs) to reduce or eliminate the inflammation

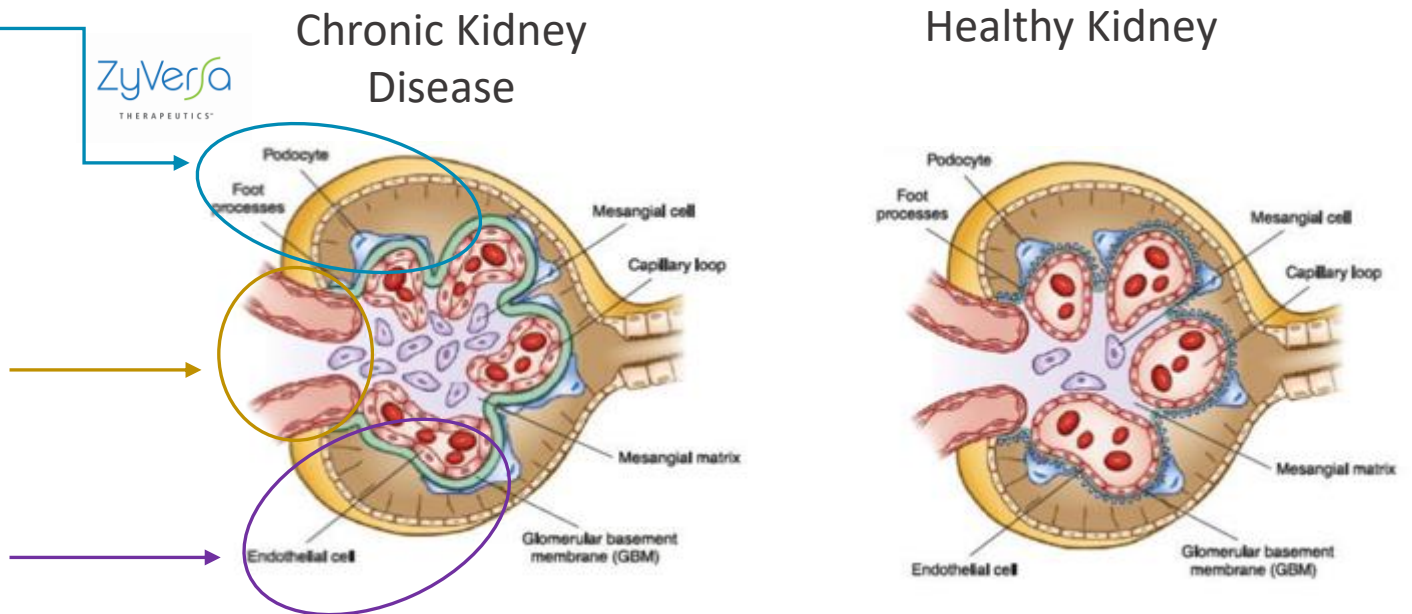


Image Adapted From Radica et al: Clin J Am Soc Nephrol 12: 2032–2045, 2017

No Drugs Target Glomerular Lipids

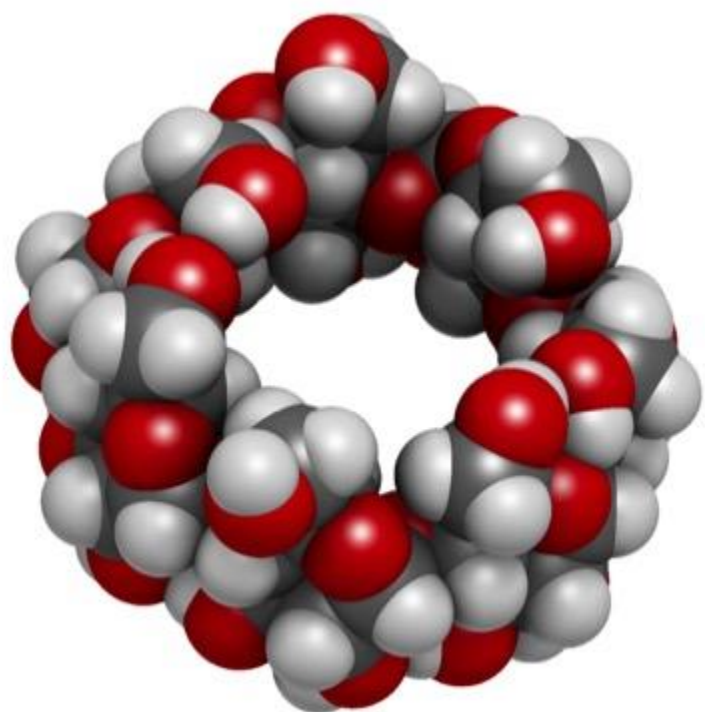
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VAR 200: Renal Program

Cholesterol Efflux Mediator
2-Hydroxypropyl-Beta-Cyclodextrin (2HP β CD)

VAR 200, 2-Hydroxypropyl-Beta-Cyclodextrin (2HP β CD) Mediates Removal of Excess Cholesterol from Podocytes



Space filling model of β -Cyclodextrin

Comprised of 7 Sugar Molecules Bound Together in a 3-D Ring

- ▶ 2HP β CD has a hydrophobic core that entraps and passively removes intracellular cholesterol from the kidney
- ▶ 2HP β CD is believed to mediate active cholesterol removal through upregulation of cholesterol efflux transporters ABCA1 and ABCG1
- ▶ Cholesterol removal restores renal structure and function

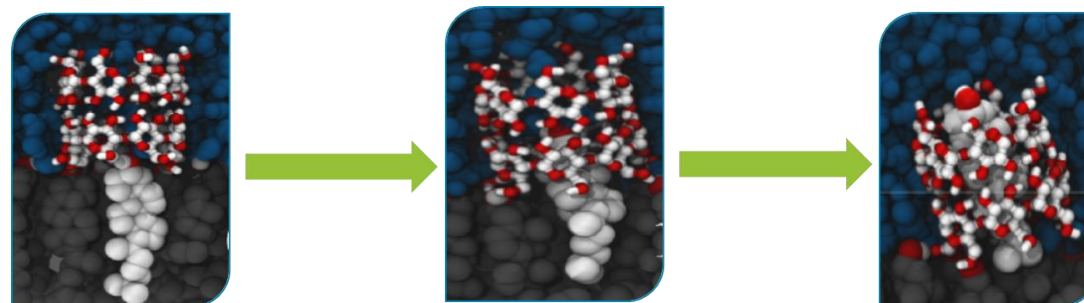


Image of β CD Adapted From Lopez et al: LoS Comput Biol 7(3): e1002020.
doi:10.1371/journal.pcbi.1002020

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VAR 200

Preclinical Proof-of-Concept

Strong Pre-clinical Support for VAR 200, With POC in 3 Different Animal Models of Kidney Disease

Diabetic Kidney Disease Model

4,000 mg/kg 3x weekly

Compared to controls, VAR 200:

- ▶ Significantly reduced cholesterol levels in kidney cells
- ▶ Protected against kidney cell damage
- ▶ Reduced urinary protein starting 8 weeks
- ▶ Significantly reduced body weight and improved metabolic control (reduced blood sugar and serum insulin)

FSGS Models

40 mg/kg/day¹; 4,000 mg/kg 3x weekly²

Compared to controls, VAR 200:

- ▶ Significantly reduced kidney cortex cholesterol
- ▶ Protected against kidney cell damage
- ▶ Reduced urinary protein (proteinuria) beginning at 8 weeks, with significant difference at 10 weeks

Reduction in proteinuria reproducible in two different models across three studies

1. Adriamycin induced; 2. Nfatc1^{nuc}

Alport Syndrome Model

4,000 mg/kg 3x weekly

Compared to controls, VAR 200:

- ▶ Significantly reduced cholesterol levels in kidney cells
- ▶ Significantly reduced kidney cell fibrosis and protected against damage
- ▶ Significantly reduced urinary and serum proteins starting at 3 weeks
- ▶ Normalized serum lipid profile

SMARTDOSE Gen II: Promising Device for VAR 200 SubQ Expansion



Patient-centric Wearable Injector

- ▶ User-focused engineering, with enhanced ergonomics
- ▶ Easy to use, intuitive design
- ▶ Visual, tactile and audible feedback to boost user confidence
- ▶ Wireless Bluetooth connectivity for user engagement
- ▶ User-loaded self-administration
- ▶ Streamlined workflow
- ▶ Ability to deliver high volume (10 mL) and high viscosity drug products
- ▶ Address a variety of delivery times through adaptable, pre-programmable technology

West Pharmaceutical Services Inc.

VAR 200 Positioning and Value Proposition

First and only disease-modifying renal drug addressing pathogenic glomerular lipid accumulation to stop progression of glomerular injury, reduce proteinuria, and delay disease progression

Value Proposition

- ▶ Induces and maintains partial or complete remission of proteinuria in patients with nephrotic syndrome
- ▶ Reduces the rate of renal disease progression, delaying or avoiding need for dialysis or renal transplant
 - Strong health/economic outcome
- ▶ Safety profile supported by decades of use as excipient and active drug in Niemann Pick Type C
- ▶ Convenient, subcutaneous delivery via patient-centric wearable device with wireless Bluetooth connectivity
 - Readily incorporated into combination therapy treatment algorithm without increasing the pill burden
- ▶ Strong IP protection
 - 7 years orphan drug exclusivity in US, 10 years in EU
 - Exclusive worldwide license to IP related to 2HP β CD for treatment of kidney diseases
 - Expanded IP portfolio with subcutaneous formulations/devices

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Anti-inflammatory Market

Immune-related Inflammatory Disorders Affect Hundreds of Millions of People Worldwide, 50 Million in U.S., With an Increasing Prevalence¹

IID Overview²⁻⁵

- ▶ Characterized by excessive or chronic activation of the immune system, resulting from aberrant changes in innate and adaptive immunity; cytokine dysregulation is pivotal to the pathophysiology
- ▶ Chronic inflammation triggers and contributes to complex diseases, such as certain cancers, atherosclerosis, stroke, ischemic heart disease, and even psychiatric disorders (major depressive disorder, schizophrenia and post-traumatic stress disorder)

Autoimmune/Autoinflammatory Diseases

- ▶ Result from development of immune reactivity towards native antigens
- ▶ Classified as inflammation against self
- ▶ Can cause multi-organ involvement, but the primary end-organ target typically drives the clinical presentation and disease definition

IID Comprises > 100 conditions¹, including type 1 diabetes, Crohn's disease, rheumatoid arthritis, and multiple sclerosis

1. Luby R, Sennett C, Hanaway P, et al, eds. Autoimmunity: A Functional Medicine Guide. Institute for Functional Medicine; 2019. 2. El-Gabalawy, H., Guenther, Lyn C., and Bernstein, Charles, N. (2010). Epidemiology of Immune-Mediated Inflammatory Diseases: Incidence, Prevalence, Natural History, and Comorbidities. The Journal of Rheumatology Supplement. May 2010, 85 -10; 3. Shaw PJ, McDermott MF, Kanneganti TD. Inflammasomes and autoimmunity. Trends Mol Med. 2010;17(2):57-64.; 4. Arakelyan A, Nersisyan L, Poghosyan D, et al. Autoimmunity and autoinflammation: A systems view on signaling pathway dysregulation profiles. PLoS One. 2017;12(11); 5. Kuek A, Hazleman BL, Ostör AJ. Immune-mediated inflammatory diseases (IMIDs) and biologic therapy: a medical revolution. Postgrad Med J. 2007;83(978):251-60;

Immune Therapies Have Significantly Evolved Over the Last 30 Years

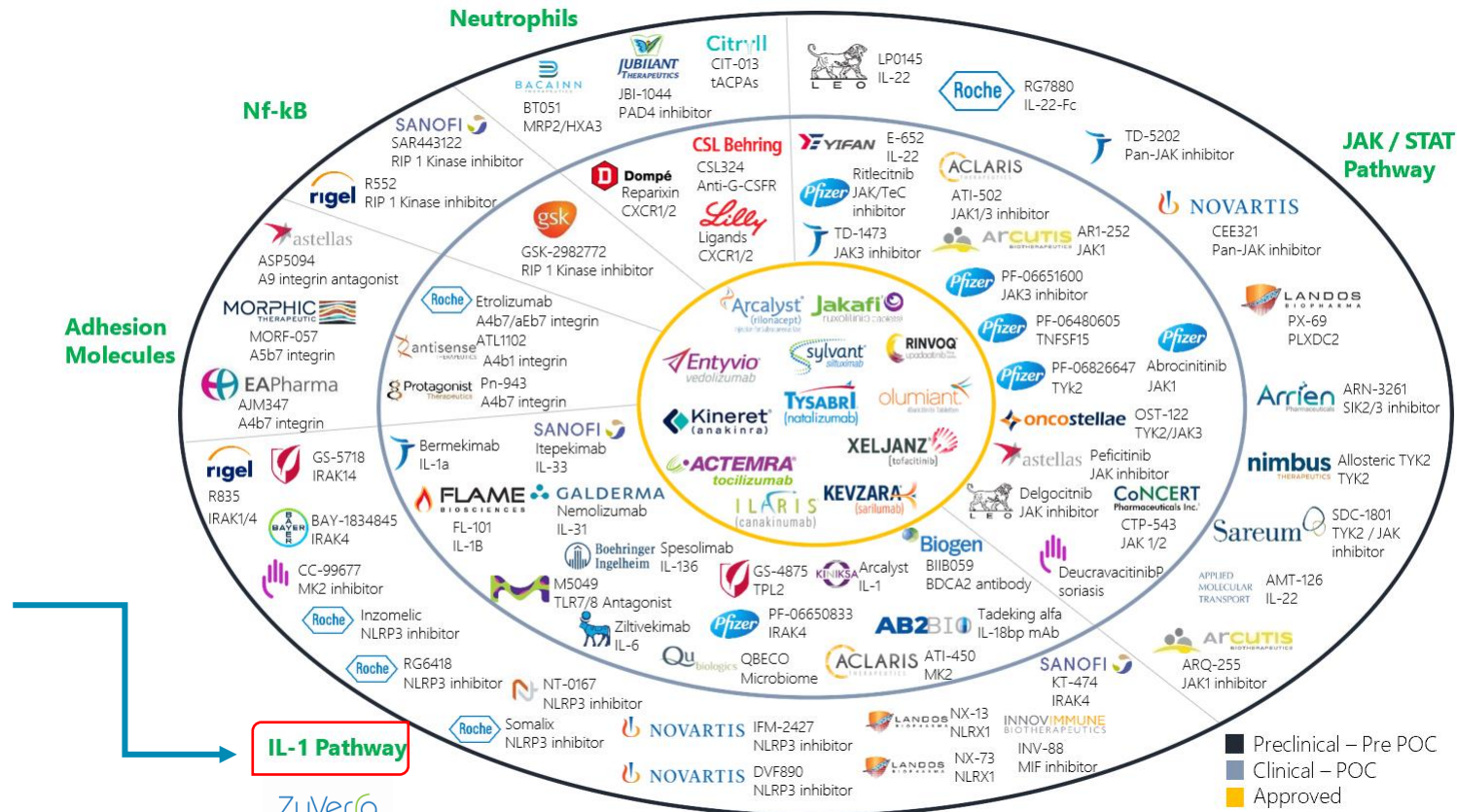
Immune Response Mechanisms Have Become Better Delineated

Inflammasome Inhibitors Targeting IL-1 & IL-18 Cytokine Pathways Are Latest Generation

► Increased insight into B and T cell development, activation, and proliferation, cytokine and chemokine signaling, and complement activation has led to

- More targeted therapeutics
- Improved safety and efficacy
- Opened opportunities for intervention in a broad range of diseases, both common and rare

► Inflammasome inhibitors target the innate immune system, blocking activation of IL-1 β & IL-18, which promote immune responses and programmed cell death (pyroptosis) leading to exacerbation of inflammation

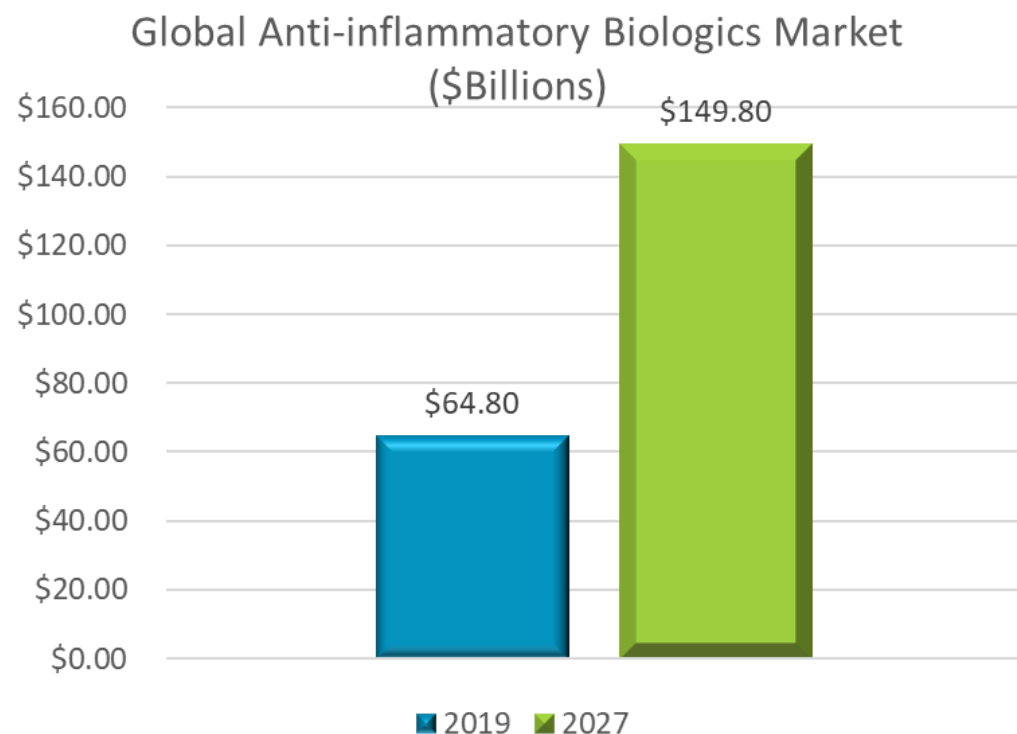


IL-1 Pathway

ZyVerfa
 THERAPEUTICS
 IC 100
 ASC Inhibitor

Source: Torreya

Anti-inflammatory Drug Market Is Large and Growing



Growth Drivers

- ▶ Rising prevalence of inflammatory diseases
- ▶ Strong drug pipeline
- ▶ Unmet need for novel anti-inflammatory drugs with improved, more predictable efficacy, and fewer side effects

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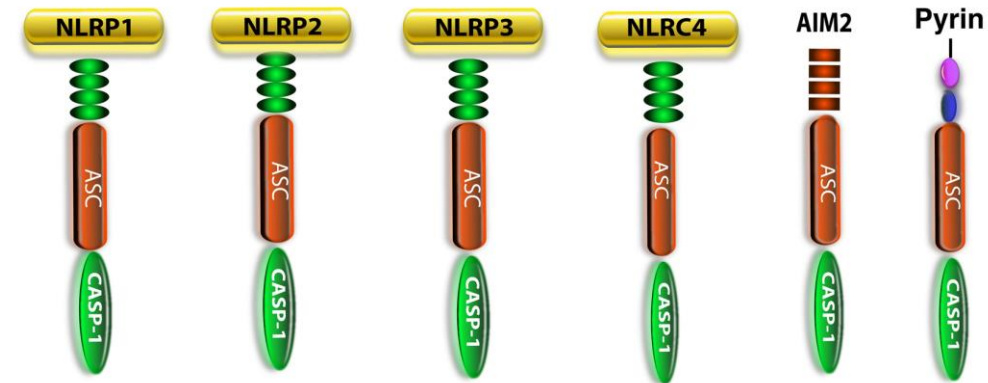


Inflammasomes

Inflammasomes Are the Central Signaling Hubs of the Innate Inflammatory Response

- ▶ Multiple inflammasomes are involved in innate immunity
- ▶ Inflammasomes are molecular complexes comprised of:
 - Sensor molecules including NLRP1, NLRP2, NLRP3, NLRC4, AIM2, and Pysin (NLRP3 best known)
 - Adaptor protein ASC
 - Pro-caspase 1
- ▶ Each of the sensor molecules respond to different pathogens or danger signals
- ▶ ASC, which recruits pro-caspase 1 into the inflammasome, is involved with formation of 12 or more sensor molecules and their associated inflammasomes
- ▶ Caspase-1 activates the cytokine IL-1 β to trigger an immune response
- ▶ Inflammasomes are named by their associated sensor molecule

Common Inflammasomes*



- NLRs (NOD-like receptor protein): Sense pathogens or endogenous sterile dangerous signals to activate the inflammasome
- AIM2 (Absent in melanoma 2): Senses bacterial and viral DNA to activate the inflammasome
- Pysin: Senses bacterial toxins that modify RhoA GTPase to activate the inflammasome
- ASC (Apoptosis associated speck-like protein containing a caspase activating recruitment domain): Mediates the interaction between the NLR sensor and pro-caspase 1 in the inflammasome complex
- Caspase 1: Activates the cytokine IL-1 β to trigger inflammation

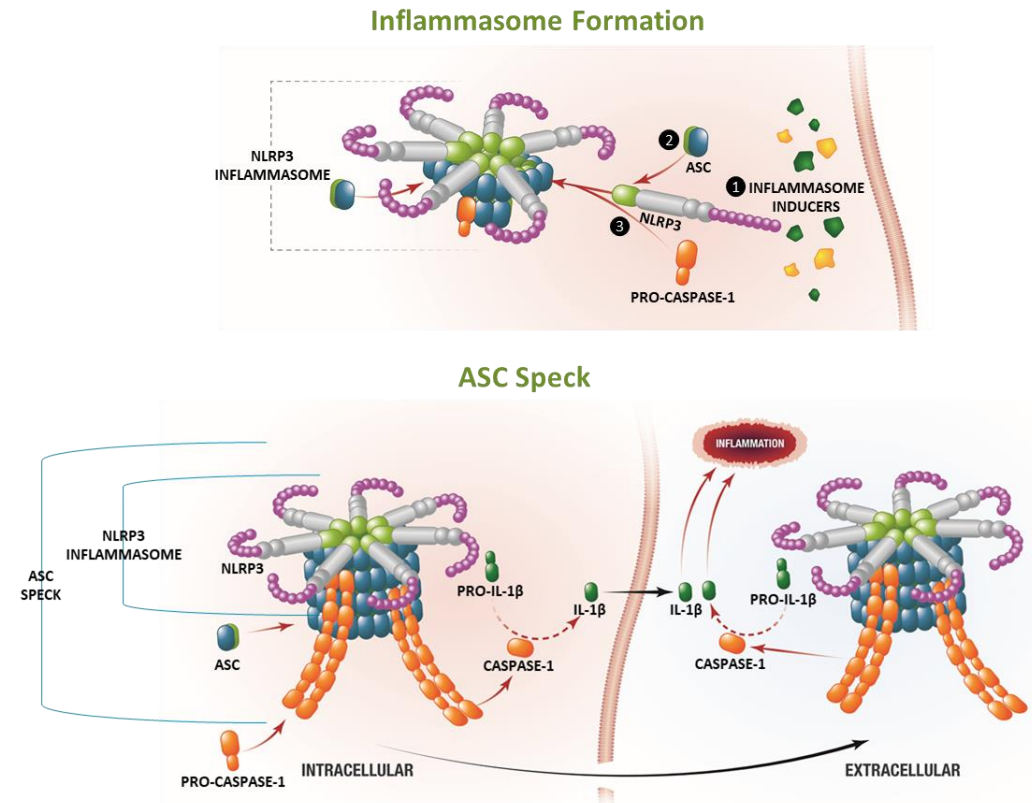
*ASC also serves as an adaptor protein in the formation of the following inflammasomes: NLRP6, NLRP7, NLRC5, NAIP2, NAIP5, NAIP6

1. Guo H, Callaway JB, Ting JP. Inflammasomes: mechanism of action, role in disease, and therapeutics. Nat Med. 2015;21(7):677-87; 2. Agrawal I, Jha S. Comprehensive review of ASC structure and function in immune homeostasis and disease. Mol Biol Rep. 2020 Apr;47(4):3077-3096

ASC Plays a Critical Role in Inflammasome Activation

Inflammasomes and the Innate Inflammatory Response

- ▶ In response to pathogens or cellular damage triggers, an intracellular sensor molecule (e.g. NLRP3) recruits ASC, which recruits pro-caspase-1 to form the NLRP3 inflammasome
- ▶ The NLRP3 inflammasome is the organizing center that recruits additional ASC and polymerizes in a prion-like structure to form a large filamentous signaling platform, known as an ASC Speck
- ▶ ASC Specks provide a scaffold for optimal pro-caspase-1 recruitment, and trigger its conversion to active caspase 1, which converts pro-IL-1 β to active IL-1 β , triggering the inflammatory process
- ▶ Activated caspase-1 drives cleavage of Gasdermin D, which triggers pyroptosis, releasing active cytokines and ASC specks into the extracellular space, with continued activation of pro-IL-1 β heightening and perpetuating the inflammatory response in neighboring cells and tissues



1. Guo H, Callaway JB, Ting JP. Inflammasomes: mechanism of action, role in disease, and therapeutics. Nat Med. 2015;21(7):677-87; 2. Franklin BS, Bossaller L, De Nardo D, et al. The adaptor ASC has extracellular and 'prionoid' activities that propagate inflammation. Nat Immunol. 2014;15(8):727-37; 3. Shaw PJ, McDermott MF, Kanneganti TD. Inflammasomes and autoimmunity. Trends Mol Med. 2010;17(2):57-64

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ASC as a Target for Treatment of Inflammatory Diseases

ASC Oligomerization Into Specks Is Critical for Inflammasome Activation, Initiation, and Perpetuation of the Innate Immune Response

- ▶ ASC oligomerization generates a multitude of caspase-1 activation sites, serving as a signal amplification mechanism for inflammasomes to generate enhanced levels of mature IL-1 β to initiate the inflammatory response¹
- ▶ ASC specks released from inflammasome-activated cells accumulate in inflamed tissues where they continue to mature cytokines to perpetuate inflammation, or they are internalized by surrounding cells to further nucleate ASC specks in their cytosol²
- ▶ Phagocytosis of ASC specks induces lysosomal damage and IL-1 β production in macrophages²
- ▶ ASC induces ASC-dependent mechanisms in otherwise ASC-deficient microglia³

ASC Inhibition Is Expected to Provide Effective Control of Inflammation

1. Dick MS, Sborgi L, Rühl S, et al. ASC filament formation serves as a signal amplification mechanism for inflammasomes. *Nat Commun.* 2016; 7: 11929; 2. Franklin BS, Latz E, Schmidt FI. The intra- and extracellular functions of ASC specks. *Immunological Reviews.* 2018;281:74–87; 3. Friker LL, Scheiblich H, Hochheiser IV, et al. B-amyloid clustering around ASC fibrils boots its toxicity in microglia. *Cell Reports.* 2020; 30(11):303743-3754

ASC is a Component of at Least 12 Types of Inflammasomes; Numerous Inflammatory Disorders Associated with Activation of Multiple Types of Inflammasomes

Inflammasomes and Disease

Dysregulated inflammasome activation is involved in a myriad of diseases and conditions:

- ▶ **Autoimmune Diseases:** Multiple sclerosis, systemic lupus erythematosus, lupus nephritis, rheumatoid arthritis and colitis
- ▶ **Metabolic Diseases:** Diabetes, atherosclerosis, non-alcoholic fatty liver disease and gout
- ▶ **Neurodegenerative Diseases:** Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis
- ▶ **Secondary Injury:** Spinal cord injury, traumatic brain injury and stroke
- ▶ **Cancer:** Lung cancer and melanoma

Disease/Condition	Inflammasomes Implicated	References
Multiple Sclerosis	AIM2, NLRP1, NLRP2, NLRP3, NLRC4	Huang 2004; Soulika 2009; Maver 2017; Freeman 2017; Noroozi 2017; Soares JL 2019
Lupus Nephritis	AIM2, NLRP3	Choubey and Panchanathan 2017; Cytokine 2019; Fu 2019
Diabetic Nephropathy	AIM2, NLRP3	Anders and Muruvue 2011; Hutton 2016
CNS Injury	AIM2, NLRP1, NLRP2, NLRP3	de Rivero Vaccari 2008, 2009, 2012; Abulafia 2009; Liu 2013; Bartolotti 2018
Alzheimer's Disease	AIM2, NLRP1, NLRP3	Ahmed 2017; Venegas 2017; White 2017; Wu 2017; Lang 2018
Rheumatoid Arthritis	AIM2, NLRP1, NLRP3, NLRP6	Goh 2017; Grandemange 2017; Li 2018; Addobbatti 2018; Lin and Luo 2016; Sode 2015; Wang 2014
Inflammatory Bowel Disease	AIM2, NLRP1, NLRP3, NLRP6, NLRC4	Vanhove 2015; Ratsimandresy 2017; Lazaridis 2017; Kanneganti 2017; Normand 2011; Levy 2015; Seregin 2017; Tye 2018; Williams 2018; Opipari and Franchi, 2015

ASC Inhibition Expected to Effectively Control Inflammation In Diverse Indications

Restoring Health, Transforming Lives Through Innovation



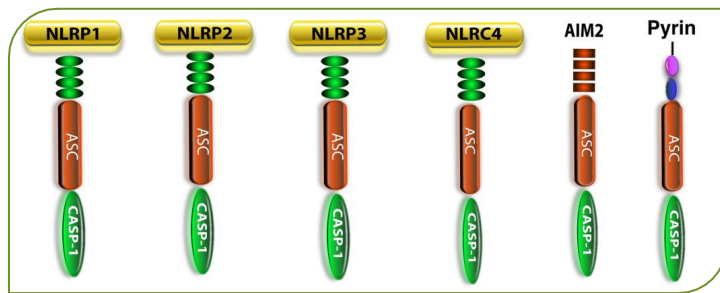
IC 100 Inflammasome ASC Inhibitor Program

mAb Targeting ASC

IC 100 Uniquely Targets Multiple Inflammasome Sensors

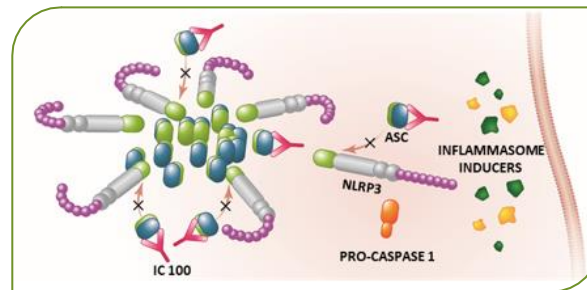
Designed To Maximize Control of Inflammation
Across a Broad Range of Conditions Without Immunosuppression

Inhibits 12 or More Types of Inflammasomes
To Control Inflammation Regardless of Its Triggers

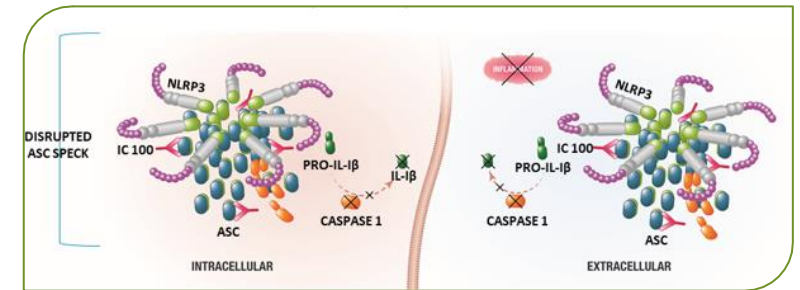


*Numerous conditions associated with activation of more than one type of inflammasome

Inhibits Inflammasome Formation
To Block Initiation Of The Inflammatory Cascade



Disrupts ASC Speck Structure & Function
To Block Perpetuation of Inflammation
For Enhanced Control



NLRP3 Inhibitors Target Just 1 Type of Inflammasome,
and Only Block Initiation of the Inflammatory Cascade

IC 100, Novel Inflammasome Inhibitor Targeting Inflammatory Diseases (>\$64B Market)

Humanized IgG4 Monoclonal Antibody Inhibiting Inflammasome ASC

- ▶ **IND Enabling Pharmacology:** Primary pharmacology studies support MS and ARDS; Mechanistic proof of concept studies support SCI and TBI.
- ▶ **Opportunity for Indication Expansion:** Targeting ASC offers potential indication expansion across multiple therapeutic areas, including renal diseases (e.g. diabetic nephropathy), atherosclerosis, neurological conditions (e.g. Alzheimer's and Parkinson's disease), and certain cancers.
- ▶ **Excellent Preclinical Safety Profile:** Rodent and NHP.
- ▶ **Excellent Tissue Penetration:** Broad, prolonged tissue distribution.
- ▶ **Differentiated MOA:** Competitive pipeline products target the NLRP3 sensor molecule. IC 100 attenuates initiation and perpetuation of the innate inflammatory response by targeting ASC in multiple inflammasomes. Offers the ability to attenuate the inflammatory response caused by activation of multiple sensor pathways.
- ▶ **Strong IP Protection:** 5 issued patents and 39 applications related to therapeutics and biomarker diagnostics. Composition of Matter issued and valid at least until Dec 28, 2037.

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IC 100 MOA

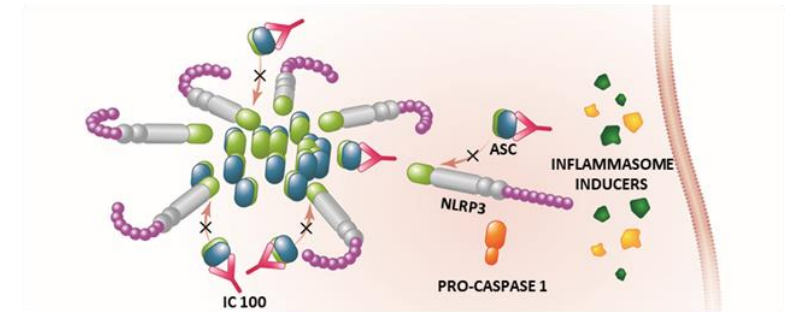
mAb Targeting ASC

IC 100 Attenuates Intracellular Initiation of the Inflammatory Response & Extracellular Perpetuation of Inflammation Without Broad Suppression of the Immune System

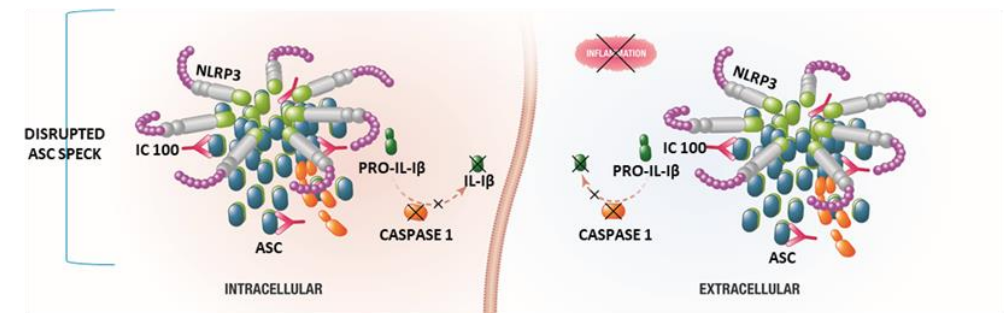
Mechanism of Action

- ▶ IC 100 inhibits intracellular ASC, blocking inflammasome formation and initiation of the inflammatory response
- ▶ IC 100 inhibits ASC in intra- and extracellular ASC Specks, disrupting their structure and function, preventing perpetuation of the massive inflammatory response associated with disease
- ▶ By targeting ASC, IC 100's MOA independent of the triggers and sensors involved
- ▶ IC 100 can inhibit 12 or more types of inflammasomes

IC 100 Blocks Inflammasome Formation



IC 100 Disrupts ASC Speck Structure and Function



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IC 100 Preclinical Proof-of-Concept

Primary Pharmacology Data Demonstrate IC 100 Has Potential As a Treatment for Multiple Sclerosis and Acute Respiratory Distress Syndrome

Multiple Sclerosis (MS)

- ▶ IC 100 was administered IP to EAE-induced mice at 10, 30, or 45 mg/kg on day 8 before appearance of clinical symptoms, followed by treatment every 4 days for 32 days
 - IC 100 at 30 mg/kg resulted in a lower number of activated myeloid cells, activated microglia, and MCHII antigen presenting cells in the spinal cord, associated with improved clinical outcomes when compared to PBS controls

Acute Respiratory Distress Syndrome (ARDS)

- ▶ Acute lung injury was induced by delivering extracellular vesicles (EV) from mice with traumatic brain injury into naïve mice, followed by IV administration of IC 100 at 5 mg/kg 1 hour after EV delivery; animals were sacrificed 24 later
 - IC 100 inhibited inflammasome activation and improved histopathological outcomes in lung tissue when compared to PBS controls

IC 100/ASC Inhibition Decreases Inflammasome Activation in Two Different Models of Traumatic Brain Injury (TBI)

Fluid Percussion Injury Model (FPI)

- ▶ Following TBI, expression of inflammasome signaling molecules, including ASC, are increased and inflammasomes are activated in cerebral cortex neurons, triggering an inflammatory response
 - Anti-ASC tool antibody was administered ICV at 15 mcg in an FPI rat model of TBI immediately after injury
 - ASC neutralization reduced inflammasome activation and decreased brain contusion volume associated with inflammation when compared with IgG control

Penetrating Ballistic-Like Brain Injury Model (PBBI)

- ▶ Following TBI, expression of inflammasome signaling molecules, including ASC, are increased, and inflammasomes are activated in microglia triggering an inflammatory response and pyroptosis
 - IC 100, an inflammasome inhibitor, was administered IV at 5 mg/kg in a PBBI rat model four hours after injury
 - IC 100 decreased inflammasome activation and pyroptosis when compared with vehicle control

1. de Rivero Vaccari JP, Lotocki G, Alonso OF et al. Therapeutic neutralization of the NLRP1 inflammasome reduces the innate immune response and improves histopathology after traumatic brain injury. *J Cereb Blood Flow Metab.* 2009 Jul;29(7):1251-61; 2. Lee SW, Gajavelli S, Spurlock MS, et al. Microglial Inflammasome Activation in Penetrating Ballistic-Like Brain Injury. *J Neurotrauma.* 2018 Jul 15;35(14):1681-1693; 3. Lee SW, de Rivero Vaccari JP, Truettner JS, et al. The role of microglial inflammasome activation in pyroptotic cell death following penetrating traumatic brain injury. *J Neuroinflammation.* 2019 Feb 8;16(1):27

IC 100/ASC Inhibition Decreases Inflammasome Activation in Spinal Cord Injury and Inflammaging (Age-related Inflammation)

Spinal Cord Injury (SCI)

- ▶ Following SCI, expression of NLRP1 inflammasome signaling molecules, including ASC, are increased and NLRP1 inflammasome is activated in spinal cord neurons, triggering an inflammatory response
 - Anti-ASC tool antibody was administered at 50 mcg in a rat model of contusive cervical spinal cord injury 20 minutes after injury
 - ASC inhibition decreased inflammasome activation, reduced spinal lesions, and improved behavioral outcomes

Inflammaging (Age-related Inflammation)

- ▶ Inflammasome signaling proteins, NLRP1, ASC, caspase-1, and IL-1 β are significantly increased in the cortex of aged mice
 - IC 100 was administered IP at 10 mg/kg in aged mice
 - IC 100 significantly reduced ASC Specks, IL-1 β , and inflammasome protein expression (NLRP1, ASC, and caspase-1)

1. de Rivero Vaccari JP, Lotocki G, Marcillo AE, Dietrich WD, Keane RW. A molecular platform in neurons regulates inflammation after spinal cord injury. J Neurosci. 2008 Mar 26;28(13):3404-14;

IC 100 Preclinical Results

Proof of Concept

- MS has potential as a lead indication (POC established in EAE model of MS)
- ARDS has potential as a secondary indication (POC established in ALI model of ARDS)
- Mechanistic POC established in animal models of spinal cord injury and traumatic brain injury

Safety

- MS animal study demonstrates attenuation of inflammation without immunosuppression
- Epigenetic screening demonstrated lower immunogenicity than many biologics
- Initial toxicology studies in rodents and NHP showed no significant safety issues, with a NOEL of 300mg/kg

Characterization

- Long projected half-life: 24 days*
- Strong binding affinity across human/non-human primate, mouse, and rat ($KD < 1$ nM), with fast association rates and low dissociation rates
- In vivo bioluminescence imaging showed that IC 100 has broad tissue distribution, crosses the blood brain barrier, and readily penetrates brain and spinal cord
- In naïve mice, liver, lung, kidney, heart, ovary and thyroid tissues were major sites of IC 100 penetration
- Confocal microscopy of fluorescently-labeled IC 100 revealed IC 100 is rapidly taken up by CNS cells and by a variety of immune cell populations
- Cell-free inflammasome assays and whole human blood inflammasome assays demonstrated that IC 100 acts intracellularly and extracellularly
- IC 100 inhibited intracellular inflammasome activation evidenced by reduction of caspase-1 processing, and it inhibited ASC oligomerization resulting in decreased release of IL-1 β

* Consistent with IgG4 half-life of 21 – 24 days¹; Based on single dose half-life study in mice (half-life 8 – 14 days)

IC 100, a Promising Treatment Option for Inflammatory Diseases

- ▶ **Inflammasomes:** Responsible for initiation and perpetuation of inflammation in response to pathogens or cellular damage triggers
 - Inflammasome adaptor ASC and its oligomerization into ASC specks important for inflammasome activation, initiation and perpetuation of the inflammatory response
 - Adaptor ASC associated with at least 6 types of inflammasomes, each responding to different triggers
- ▶ **Inflammasome Dysregulation:** Leads to chronic inflammation underlying numerous inflammatory diseases
 - Many inflammatory diseases linked to more than one type of inflammasome
- ▶ **IC 100: Novel ASC inhibitor for treatment of inflammatory diseases**
 - Humanized monoclonal IgG4 antibody that binds to a specific region of adaptor ASC
 - By targeting ASC, inhibits 12 or more types of inflammasomes; MOA independent of triggers and sensors involved
 - Inhibits inflammasome formation intracellularly, blocking initiation of the inflammatory response
 - Inhibits ASC in ASC specks, intra-and extracellularly, disrupting speck structure and function preventing perpetuation of the inflammatory response
- ▶ **IC 100 POC: Strong pharmacologic signals in a broad range of inflammatory conditions**
 - Primary POC: Multiple sclerosis, Acute Respiratory Distress Syndrome
 - MOA POC: Spinal cord injury, traumatic brain injury, and aging
- ▶ **IC 100 Safety:**
 - Attenuates the Immune System, Without Broad Immune Suppression
 - Lower immunogenicity (9%) than many biologics - less potential for acquired drug resistance and drug discontinuation due to side effects
 - No drug-related AEs or histopathology changes at weekly doses up to 300 mg/kg for 21 days in non-GLP tox studies (mice & NHP)



Thank You