ZyVersa Therapeutics Corporate Presentation

Q2-2019

ZyVersa THERAPEUTICS℠

Restoring Health, Transforming Lives Through Innovation

Cautionary Statement Regarding Forward-Looking Statements

- Certain statements contained in this presentation regarding matters that are not historical facts, are forward-looking statements within the meaning of Section 21E of the Securities Exchange Act of 1934, as amended, and the Private Securities Litigation Reform Act of 1995, known as the PSLRA. These include statements regarding management's intentions, plans, beliefs, expectations or forecasts for the future, and, therefore, you are cautioned not to place undue reliance on them. No forward-looking statement can be guaranteed, and actual results may differ materially from those projected. ZyVersa Therapeutics Inc. ("ZyVersa") undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise, except to the extent required by law. ZyVersa uses words such as "anticipates," "believes," "plans," "expects," "projects," "future," "intends," "may," "will," "should," "could," "estimates," "predicts," "potential," "continue," "guidance," and similar expressions to identify these forward-looking statements that are intended to be covered by the safe-harbor provisions of the PSLRA. Such forward-looking statements are based on ZyVersa's expectations and involve risks and uncertainties; consequently, actual results may differ materially from those expressed or implied in the statements due to a number of factors, including ZyVersa's plans to develop and commercialize its product candidates, the timing of initiation of ZyVersa's planned clinical trials; the timing of the availability of data from ZyVersa's clinical trials; the timing of any planned investigational new drug application or new drug application; ZyVersa's plans to research, develop and commercialize its current and future product candidates; the clinical utility, potential benefits and market acceptance of ZyVersa's product candidates; ZyVersa's commercialization, marketing and manufacturing capabilities and strategy; ZyVersa's ability to protect its intellectual property position; and ZyVersa's estimates regarding future revenue, expenses, capital requirements and need for additional financing.

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- This presentation does not constitute an offer to sell, or the solicitation of an offer to buy, any securities.

ZyVersa THERAPEUTICS™

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

Renal Lead: Phase 2a-ready VAR 200, 2HPβCD

- Indication: Focal segmental glomerulosclerosis (FSGS), an orphan kidney disease

Anti-inflammatory Lead: IC 100, Inflammasome inhibitor targeting ASC Component of Inflammasomes (i.e. NLRP3)

- Potential early indications
  - **Renal**: Diabetic nephropathy, lupus nephritis
  - **Non-renal Inflammatory Diseases**: Multiple Sclerosis, NASH

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

~$60.0B

Total addressable markets

ZyVersa THERAPEUTICS

ZyVersa Highlights: Late Stage P2a-ready Orphan Renal Asset and Attractive, Novel Inflammasome Inhibitor

Late Stage P2a-ready VAR 200
Targeting High Value Orphan Kidney Disease, FSGS ($2B+ Market)

Attractive Novel Inflammasome Inhibitor (IC 100)
Targeting $60B+ Inflammatory Diseases

Lead Program: VAR 200, 2HPβCD For FSGS

- **Differentiated MOA**: Targets underlying pathology (disease modifying) by eliminating intracellular lipids that result in kidney damage and dysfunction; competitive pipeline targets hypertension and inflammation
  - Supports multiple kidney indications, including Alport Syndrome and other forms of chronic kidney disease
- **Significant Proof of Concept:** Pre-clinical data in 3 different animal models of kidney disease (FSGS, Alport Syndrome, Diabetic Kidney Disease)
- **Derisked Opportunity:** FDA concurrence to move directly to Phase 2a, bypassing Phase 1, based on strong pre-clinical program and human POC in NPC
- **Strong IP Protection:** 7 years orphan drug exclusivity in U.S., 10 years in EU; exclusive worldwide license to IP related to 2HPβCD for treatment of kidney disease
- **Multiple Life Cycle Opportunities Via Drug Delivery Mechanisms**

Lead Immunity Compound: IC 100, ASC Inflammasome Inhibitor with Potential for Multiple Products & Indications

- **Differentiated MOA**: Inhibits innate inflammatory response by targeting the ASC component of multiple inflammasomes, inhibiting both the intracellular and extracellular inflammatory response cascade; competitive pipeline products inhibit the sensor molecule component (i.e. NLRP3) of sensor-specific inflammasomes, act intracellularly only, and target fewer inflammatory conditions
- **Significant Proof of Concept:** Pre-clinical support for multiple indications (MS, RA, Acute Lung Injury, Spinal Cord Injury, Traumatic Brain Injury, Stroke)
- **Potential for Companion Diagnostic**
- **Strong IP Protection:** 13 patents related to therapeutics and biomarker diagnostics, granted or pending
- **Opportunity for Indication Expansion:** Targeting ASC offers potential indication expansion across multiple therapeutic areas, including certain cancers; lipid disorders such as atherosclerosis; and neurological conditions, such as MS and Alzheimer's disease

ZyVersa THERAPEUTICS™

Highly Experienced Leadership Team

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

Name	Title	Years of Industry Experience	Prior Experience
Stephen C. Glover	Co-Founder, CEO, and President	30+	Coherus, Andrx, Roche, AMGEN, Insmed
Nick A. LaBella, MS, RPH	Chief Scientific Officer	30+	Insmed, Sandoz A Novartis Division, Cardiokine, Watson Pharmaceuticals
Pablo A. Guzman, MD, FACC	Chief Medical Officer	30+	American College of Cardiology, Johns Hopkins Medicine, Holy Cross Hospital
Karen A. Cashmere	Chief Commercial Officer	25+	Abbott, Andrx, serono, Auxilium, noven
Melda Uzbil	SVP, Corporate Development	12	Duke University, Pfizer
Peter Wolfe	SVP of Finance and Administration	17	KOS Pioneering Medicines for a Better Life, noven

Strong Board of Directors with Proven Track Record Raising Capital and Increasing Corporate Value

Stephen Glover

Co-Founder, Chief Executive Officer, and President

- Has over 32 years of experience in biopharmaceuticals and life sciences.
- Previous senior executive roles at Coherus Biosciences, Insmed, Andrx, Amgen and Roche.
- Serves on the Boards of PDS Biotechnology, INCON, and Asclepius Lifesciences.

Robert Finizio

Co-Founder, Chief Executive Officer, and Director of Therapeutics MD

- Has over 20 years of healthcare experience.
- Previous senior executive roles at CareFusion, Omnicell and Endoscopy Specialist.

Aaron Greenblatt

Chief Executive Officer, G&W Laboratories, Inc.

- Previously served as Chief Commercial Officer and Executive Vice President at G&W Laboratories.
- As the fourth generation CEO from the Greenblatt family, continues to focus on instilling the core values into the company culture.

Eric Richman

Former President & CEO of PharmAthene; Chairman of LabConnect

- More than 25 years of experience as a life science executive.
- As a founding member of MedImmune, was responsible for commercialization of rare disease and oncology products.
- Former Venture Partner at Brace Pharma Capital; serves on the Boards of ADMA Biologics and NovelStem International.

Jules A. Müsing

Chairman of the Board

- Retired senior executive with more than 36 years experience in the pharmaceutical and biotechnology industries on a global basis.
- Previous executive roles at Johnson & Johnson, Janssen Pharmaceuticals, Ortho Biotech and Ares Serono.

Anthony Giovinazzo

Former President and CEO of Sunovion CNS Development Canada

Executive Chairman of Sublimity Therapeutics.

- Has in excess of 38 years of professional experience.
- Serves on the Board of Promis Neurosciences.

Andrew (DW) Kim

Founder and CEO, Riverstone Investment Co., Ltd.

Chairman of INCON and NDFOS.

- Has in excess of 15 years of professional experience.
- Former Co-founder & CIO at Liberty Investment Co., Ltd..

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

W. DALTON DIETRICH, III, PH.D.

- Scientific Director, The Miami Project, Kinetic Concepts Distinguished Chair in Neurosurgery, Senior Dean for Discovery Science, UM
- Professor, Neurological Surgery, Neurology and Cell Biology

HELEN BRAMLET, PH.D.

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

ROBERT W. KEANE, PH.D.

- Professor, Departments of Physiology & Biophysics, UM
- The Miami Project to Cure Paralysis

MIGUEL S. BARBOSA, PH.D.

- Former Global Head and Vice President of Immunology Research and External Innovation at Janssen Research & Development

DOUG H. FARRAR

- CEO, Flatirons Biotech, Inc
- Former Cofounder and Chief Technical Officer, Coherus Biosciences

JUAN PABLO DE RIVERO VACCARI, PH.D

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

WILLIAM F. BENNETT, PH.D.

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

Alan Herman, PH.D.

- Chairman Emeritus, former Chief Scientific Officer at Coherus BioSciences
- Formerly: Genentech, Amgen, Merck, Coherus

DANIEL G. BAKER, MD

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

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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

Alessia Fornoni M.D., Ph.D.

- Chief, Division of Nephrology & Hypertension
- Director, Peggy & Harold Katz Family Drug Discovery Center, University of Miami Miller School of Medicine

Pablo A. Guzman, MD, FACC

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

Jonathan J. Hogan, MD

- Clinical Director, Penn Glomerular Disease Center
- Assistant Professor of Medicine, Hospital of the University of Pennsylvania

Gerald B. Appel, MD

- Co-Director, Clinical Nephrology, New York-Presbyterian Hospital/Columbia University Medical Center
- Professor of Clinical Medicine and Director of the Glomerular Kidney Disease Center, Columbia University College of Physicians and Surgeons

Debbie S. Gipson, MD, MS

- Professor, Department of Pediatrics and Communicable Diseases, University of Michigan
- Associate Director, UM Clinical Research Management workgroup of the Michigan Institute for Clinical and Health Research

Marlene Haffner, MD, MPH

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

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ZyVersa Pipeline Focuses on Orphan/non-Orphan Renal and Inflammatory Diseases with High Unmet Medical Needs

Product	Development	Pre-clinical	Phase 1	Phase 2	Phase 3	NDA/BLA Submission
Renal Diseases						
VAR 200: 2HPβCD for FSGS*						
VAR 300: 2HPβCD for Alport Syndrome*						
IC 200: ASC Inhibitor for Lupus Nephritis*						
IC 300: ASC Inhibitor for Diabetic Kidney Disease						
Non-renal Inflammatory Diseases						
IC 100: ASC Inhibitor for Multiple Sclerosis						
IC 400: ASC Inhibitor for NASH						

* Orphan renal diseases

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IC 100 Inflammasome Inhibitor

Immune-related Inflammatory Disorders (IID) Affect 5 – 7% of Population in Western Societies, With an Increasing Prevalence[1]

IID Overview[2,3,4]

- 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 also triggers and contributes to other 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
- Comprise > 80 conditions, including type 1 diabetes, Crohn's disease, rheumatoid arthritis, and multiple sclerosis

1. 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 2-10; 2. Shaw PJ, McDermott MF, Kanneganti TD. Inflammasomes and autoimmunity. Trends Mol Med. 2010;17(2):57-64.; 3. Arakelyan A, Nersisyan L, Poghosyan D, et al. Autoimmunity and autoinflammation: A systems view on signaling pathway dysregulation profiles. PLoS One. 2017;12(11); 4. 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.

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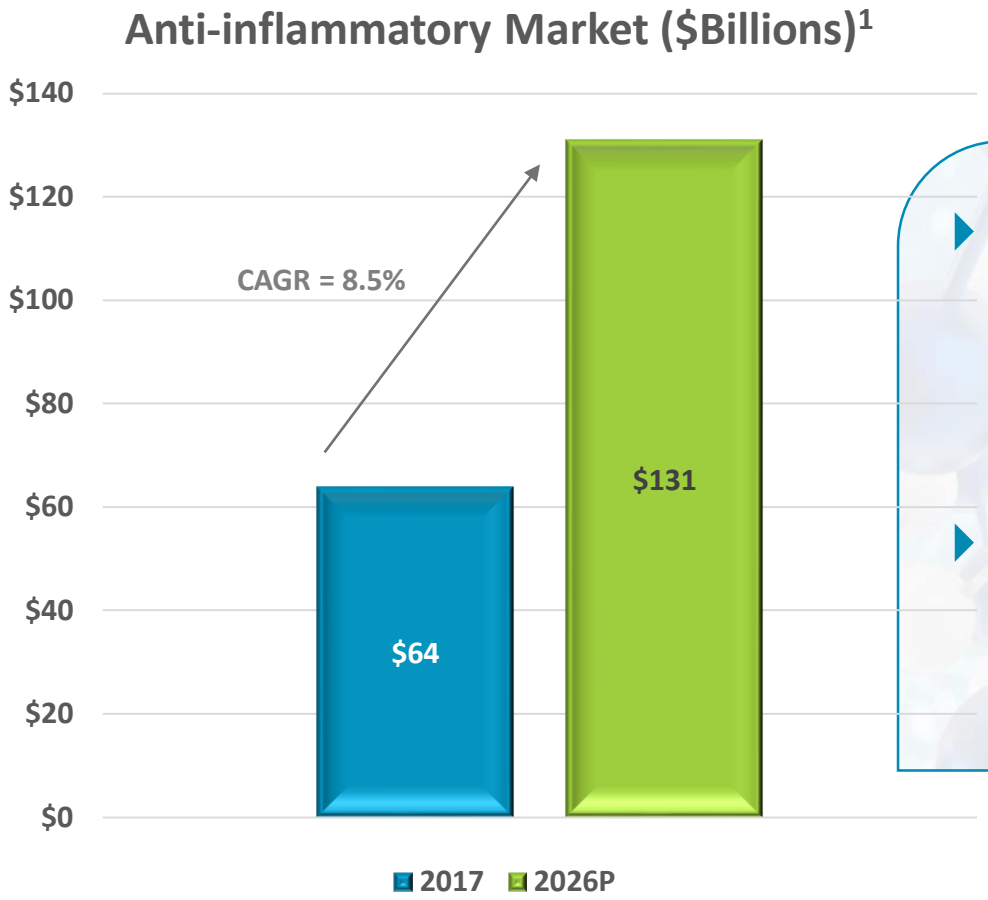
Anti-inflammatory Drug Market Is Large and Growing, With Strong Biopharma Interest

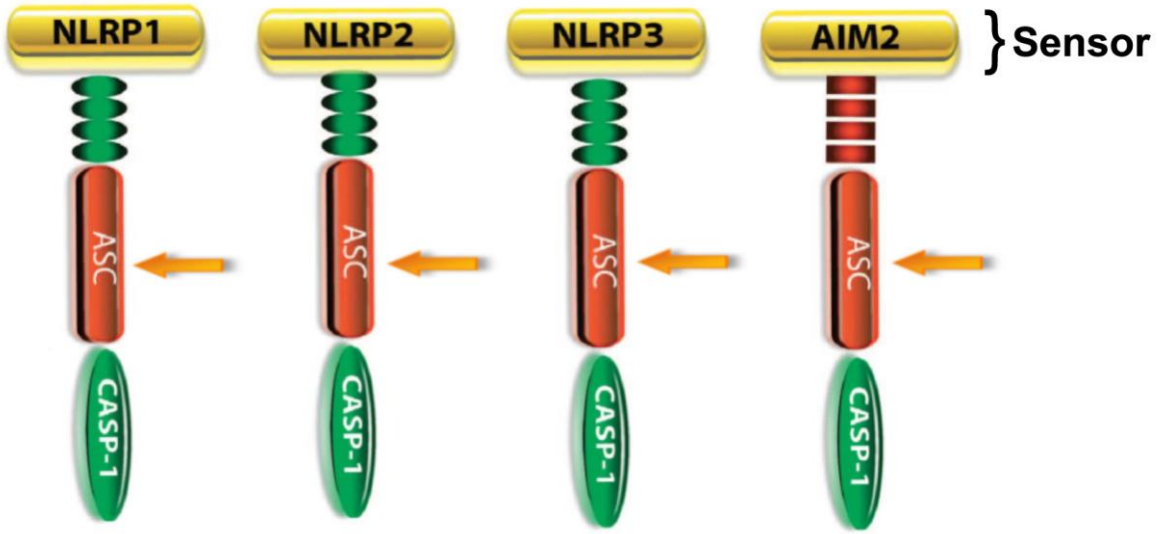


- Anti-inflammatory growth drivers: Rising prevalence of inflammatory diseases and strong drug pipeline
  - Key pharma companies: Eli Lily, Pfizer, BMS, AstraZeneca, Hoffmann-La Roche, AbbVie, Genentech, GlaxoSmithKline, Amgen, Johnson & Johnson, and Novartis[2]
- Unmet need for novel anti-inflammatory drugs, with improved, more predictable efficacy, and fewer side effects

1. Credence Research, Inc. Anti-inflammatory Therapeutics Market - Growth, Future Prospects and Competitive Analysis, 2018-2026; 2. Absolute Reports. Global Anti-Inflammatory Therapeutics Market Research 2018, size, Revenue, Growth Factors, key drivers, opportunities with global forecast 2023

Inflammasomes Are the Central Signaling Hubs of the Inflammatory Response

- Multiple inflammasomes are involved in innate immunity
- Inflammasomes are molecular complexes comprised of:
  - Sensor molecules including NLRP1, NLRP2, NLRP3, and AIM2 (NLRP3 best known)
  - Adaptor protein ASC
  - Pro-caspase 1
- Each of the sensor molecules respond to different stimuli
- ASC is associated with multiple sensor molecules, and is common to many inflammasomes



1. NLRs (NOD-like receptor protein): Senses pathogen or other triggers to activate the inflammasome
2. 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

Guo H, Callaway JB, Ting JP. Inflammasomes: mechanism of action, role in disease, and therapeutics. Nat Med. 2015;21(7):677-87

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Inflammasomes Are Linked to Immune-related Inflammatory Disorders

Inflammasomes and Disease

- **Autoinflammatory disorders** strongly linked with NLR inflammasome mutations, which increase release of IL-1β, causing cryopyrin-associated periodic syndromes (CAPS)
- **Polygenic inflammatory disorders (i.e. gout and pseudogout)** attributed to inflammation from free fatty acids and monosodium urate crystals driven by NLRP3 inflammasomes
- **Auto-immune diseases** have increasing evidence of inflammasome involvement
  - **MS**: ASC inhibitors demonstrate significant improvement in clinical scores, lower number of activated myeloid cells in the spinal cord and spleen, and lower number of microglial cells in the spinal cord in MS mouse model
  - **NASH**: In steatohepatitis mouse models, NLRP3 inhibitors dampen liver inflammation and fibrosis
  - **RA:** Patients with excessive NLRP3 activation develop joint pain and arthritis
  - SLE: Leukocytes demonstrate increased AIM2 expression; IL-1 blockade demonstrated a therapeutic benefit
  - **Lupus Nephritis:** Patient renal biopsies demonstrate increased levels of caspase 1 and NLRP3; NLRP3, caspase 1, and IL-18 inhibition limit renal injury in mouse models
  - **Diabetic Nephropathy:** Intrarenal inflammasome activation demonstrated in type 1 and type 2 diabetic mouse models; human observational studies suggest IL-1β and IL-18 may contribute to diabetic nephropathy

Inflammasomes Implicated in Disease

Inflammasome	Disease/Injury
NLRP1	Spinal Cord Injury (SCI) Traumatic Brain Injury (TBI) Stroke
NLRP3	Alzheimer's Disease (AD) Multiple Sclerosis (MS) Encephalomyelitis Diabetes Chronic Obesity Rheumatoid Arthritis Myocardial Dysfunction Colitis Gout Chronic Infantile Neurological Cutaneous and Articular syndrome (CINCA) Muckle-Wells syndrome (MWS) Familial cold-induced autoinflammatory syndrome (FCAS) Familial cold urticaria (FCU)
NLRP6	Colitis
NLRP12	Colitis Asthma Allergy Contact Hypersensitivity
AIM2	Systemic Lupus Erythematosus

Shaw PJ, McDermott MF, Kanneganti TD. Inflammasomes and autoimmunity. Trends Mol Med. 2010;17(2):57-64.

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Inflammasomes Activate the Innate Immune Response

Inflammasomes and the Innate Inflammatory Response

- In response to pathogens or other immune triggers, an intracellular sensor molecule (i.e. 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 pro-caspase-1 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 conversion of pro-caspase 1 to active caspase 1, which converts pro-IL-1β to active IL-1β, which triggers the inflammation process
- ASC Specks are released outside the cell to create a signaling platform that induces a massive extracellular inflammatory response

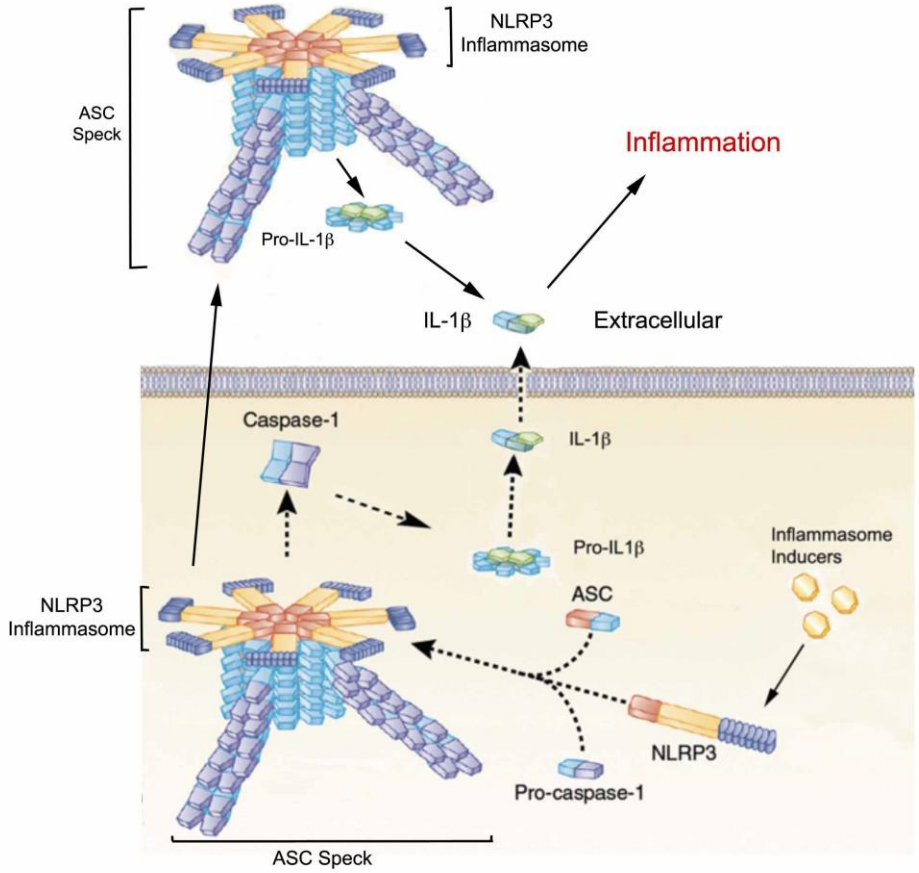


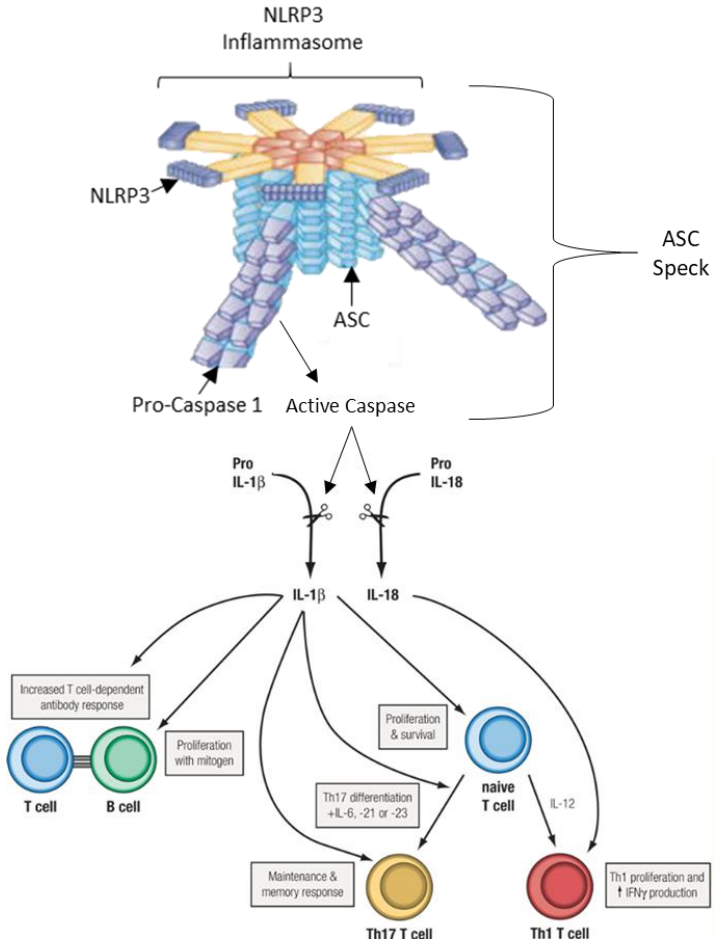
Image Adapted From Guo et al. Nat Med. 2015;21(7):677-87

Guo H, Callaway JB, Ting JP. Inflammasomes: mechanism of action, role in disease, and therapeutics. Nat Med. 2015;21(7):677-87; 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; Shaw PJ, McDermott MF, Kanneganti TD. Inflammasomes and autoimmunity. Trends Mol Med. 2010;17(2):57-64.

Inflammasome Activation of Cytokines Impact the Adaptive Immune Response

Inflammasomes and the Adaptive Inflammatory Response

- Through activation of cytokines, inflammasomes have a role in adaptive immunity by amplifying T and B cell responses
- IL-1β can act on lymphocytes in several ways including upregulating IL-2 receptor expression, prolonging survival of T cells, enhancing antibody production by B cells, and increasing B cell proliferation
- IL-1β and IL-18 play a critical role in driving the differentiation and amplification of Th17 and Th1 cells, respectively



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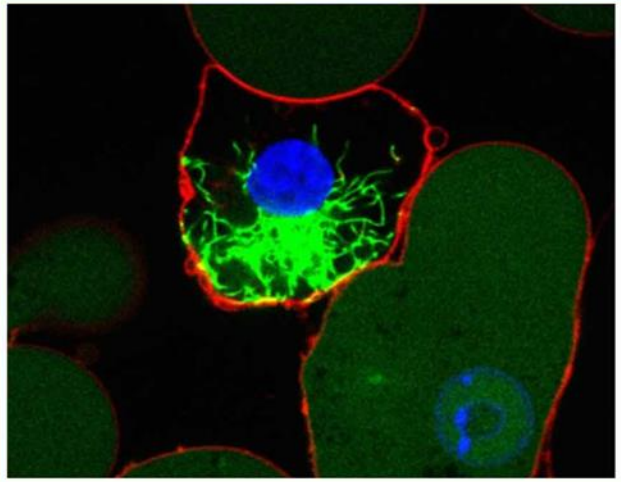
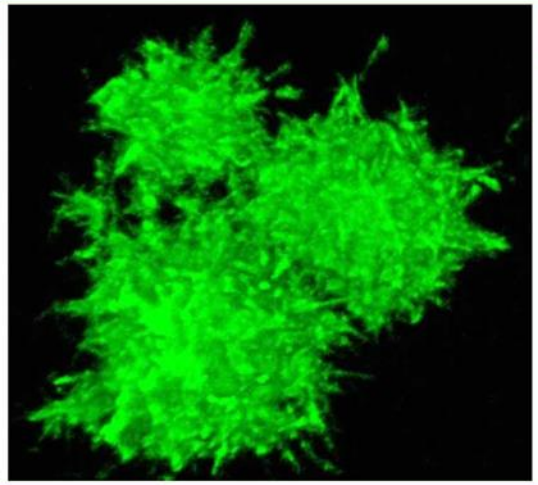
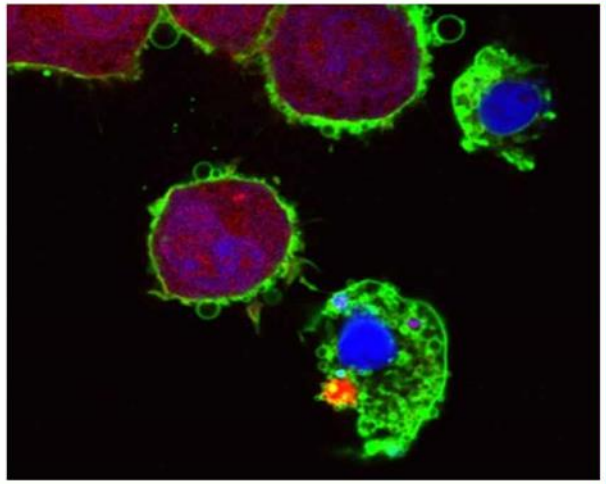
Histological Depiction of Activated ASC Aggregation and Release From Cells



Mouse macrophages showing nuclei (blue), plasma membrane (red), and ASC (green). The center cell's inflammasome has been activated, and ASC is aggregating.



3D Reconstruction of 3 ASC Specks



An ASC speck (red) is being released from a cell (bottom). In the cells that appear red, the inflammasomes have not been activated and ASC is spread out through the cytosol. Nuclei are blue and plasma membrane is green.

The Scientist, 2014

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IC 100: A Novel Inflammasome Inhibitor (Targets ASC)

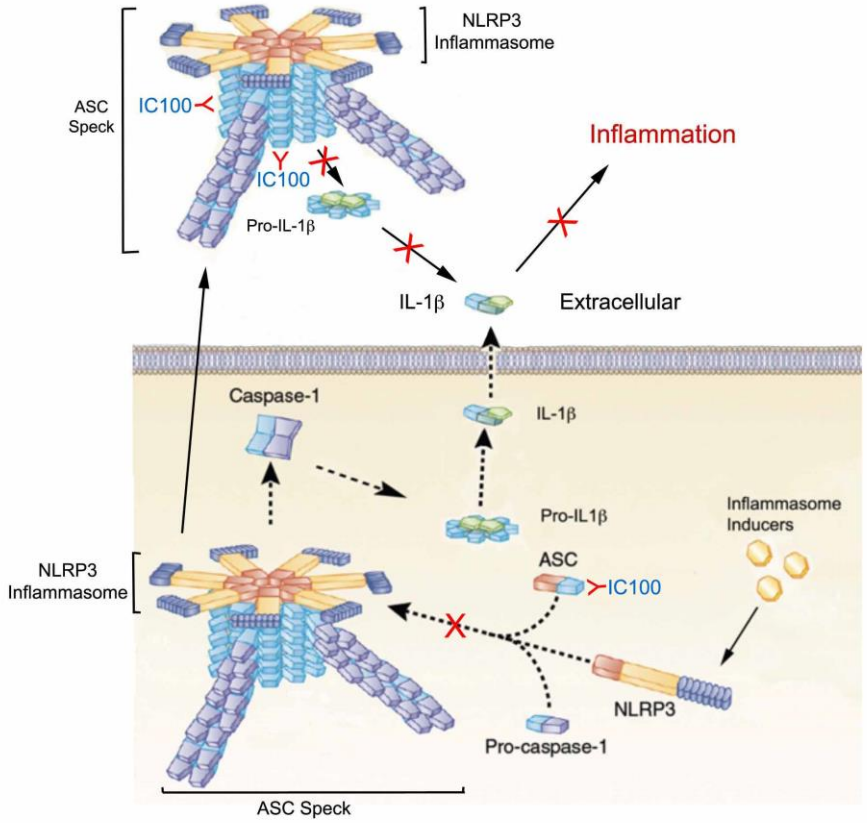
Inhibits Intracellular Initiation of Inflammatory Cascade & Extracellular Perpetuation of Inflammation

IC 100

- A MAb targeting the adaptor protein ASC component of Inflammasomes

Mechanism of Action

- IC 100 inhibits intracellular ASC, which prevents oligomerization and ASC Speck formation, inhibiting the inflammatory cascade
- Outside the cell, IC 100 binds to the ASC component of the ASC Speck, thereby inhibiting perpetuation of the massive inflammatory response



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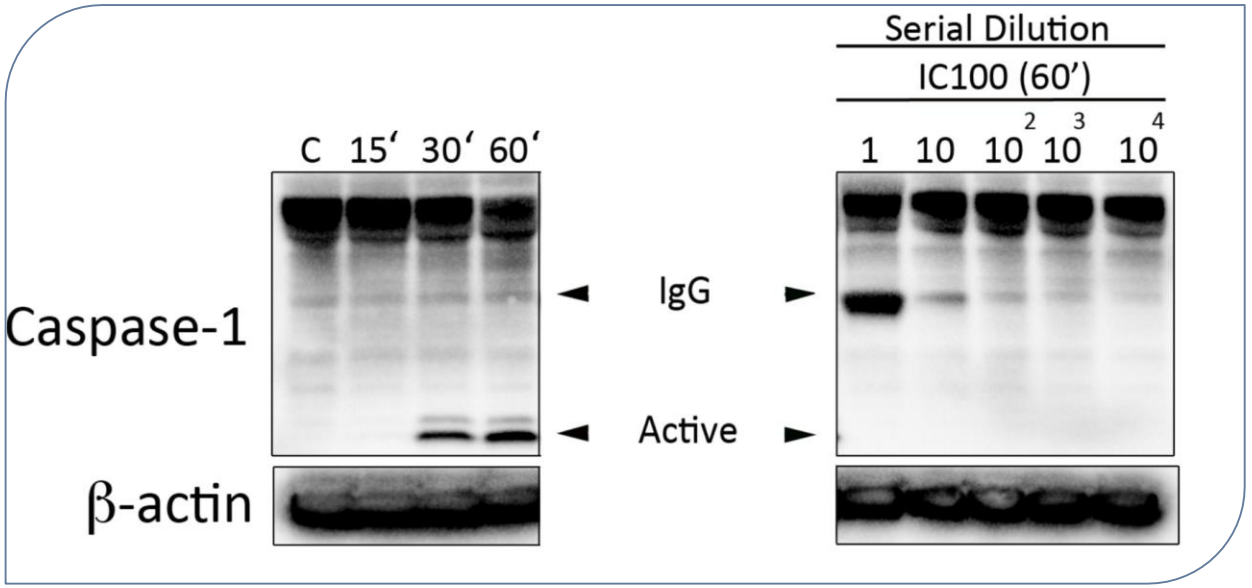
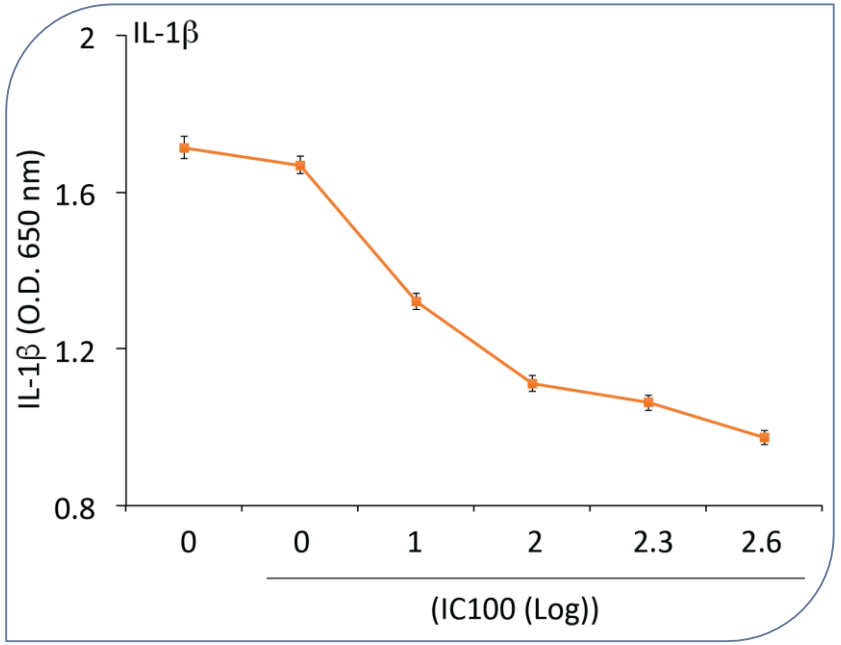
IC 100 Inhibits Caspase-1 and IL-β Activation in Vitro

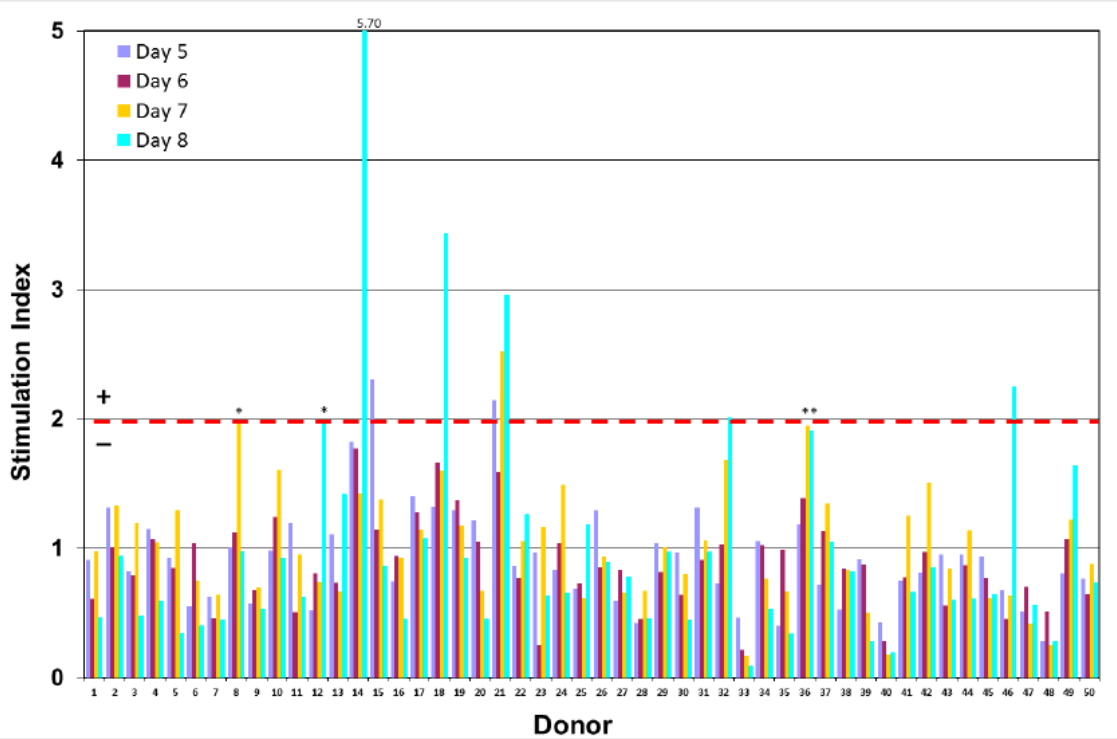




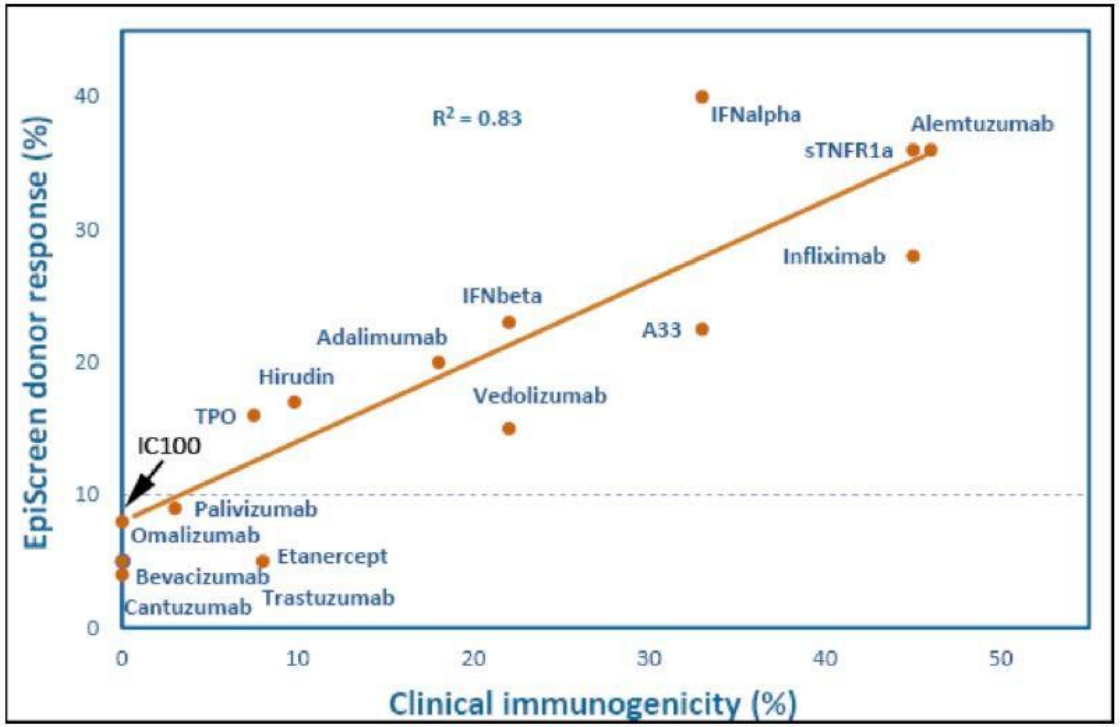
N= 6 to 12 samples per group (THP1 cells)
Dunn's multiple Comparison *p<0.05 compared to ATP

IC 100 Has Low Immunogenicity (9%)

Healthy donor T-cell proliferation response



IC 100 Immunogenicity (9%) Lower Than Many Mabs Based on Epi-Screening



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IC 100
Scientific Support

Preclinical Data Demonstrate IC 100 Has Potential As a Treatment for Spinal Cord Injury, Traumatic Brain Injury, and Stroke

Spinal Cord Injury (SCI)

- IC 100 was administered IV at 3mg/kg two hours after spinal cord injury in mice
  - IC-100 inhibited caspase-1 activation in the spinal cord 24 hours after injury, which was not demonstrated with the saline control
- Anti-ASC tool antibody was administered at 50 mcg in a rat model of contusive cervical spinal cord injury 20 min after injury
  - Improved histopathological and behavioral outcomes were demonstrated, consistent with decreased inflammasome activation

Traumatic Brain Injury (TBI)

- Anti-ASC tool antibody was administered ICV at 15 mcg in a rat model of traumatic brain injury immediately after injury
  - Improved histopathological outcomes were demonstrated with anti-ASC tool antibody compared to IgG control
  - Results were consistent with decreased inflammasome activation

Stroke

- Anti-NLRP1 tool antibody was administered into the right lateral ventricle at 5 mcg in a stroke mouse model immediately after stroke
  - Decreased inflammasome activation was demonstrated with anti-NLRP1 tool antibody compared to control

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Preclinical Data Demonstrate IC 100 Has Potential As a Treatment for Acute Lung Injury, Rheumatoid Arthritis, and Multiple Sclerosis

Acute Lung Injury (ALI)

- 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 compared to PBS, anti-hTNF controls

Rheumatoid Arthritis (RA)

- Mice with collagen-antibody-induced arthritis received IP administration of IC 100 at 3 mg/kg on days 8, 11, 14, 17, and 20
  - There were no significant changes in clinical score or paw volume in mice receiving IC 100 when compared to control mice without induced arthritis

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 3 days for 32 days
  - IC 100 at 30 mg/kg resulted in a lower number of activated myeloid cells in the spinal cord and spleen, a lower number of microglial cells in the spinal cord, and improved clinical outcomes consistent with these changes, when compared to PBS controls

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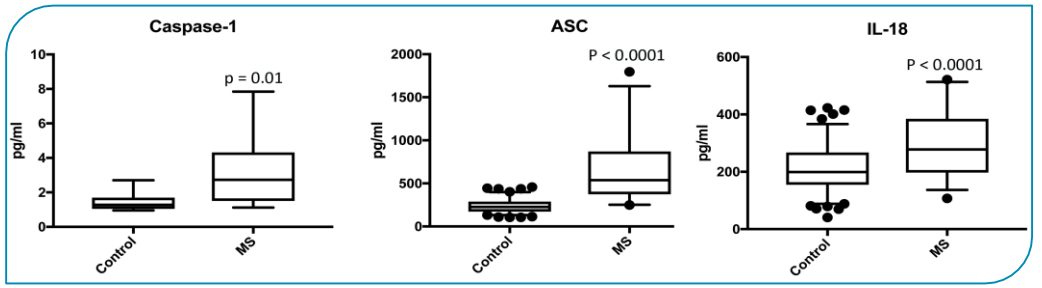
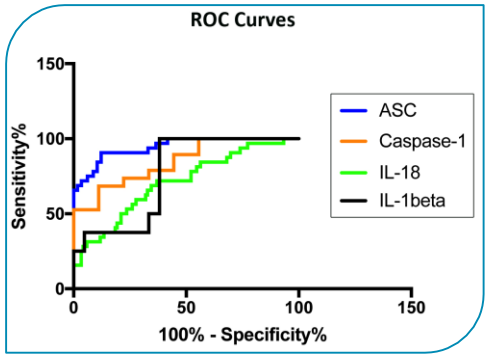
ASC As Biomarker

ASC Has Potential as a Serum Biomarker

Disease/Condition	ASC (pg/ml)
Multiple Sclerosis	> 352.4
Depression	> 273.7
Stroke	> 404.8
TBI	> 275
Mild Cognitive Impairment (MCI)	> 264.9
Healthy	< 195.3



BIOMARKER	Cut-off point (pg/ml)	Sensitivity	Specificity	AUC	95% CI	p-value
Caspase-1	>1.302	89%	56%	0.848	0.703-0.9929	0.0034
ASC	>352.4	84%	90%	0.9448	0.9032-0.9864	<0.0001



Two-tailed t-test. **Caspase-1:** *N* = 9 control and 19 MS; **ASC**: *N* = 115 control and 32 MS

Keane RW, Dietrich DW, de Rivero Vaccari JP. Inflammasome Proteins as Biomarkers of Multiple Sclerosis. Frontiers in Neurology. Multiple Sclerosis and Neuroimmunology. 2018 Mar 19;9:135.

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IC 100 Value Proposition

By Targeting ASC, IC 100 Has Potential for Broad Indications, More Effective Reduction of Inflammation, and an Excellent Safety Profile

IC-100 Novel Approach	IC-100 Value Proposition
▸ Targets innate immunity - Most anti-inflammatory drugs target adaptive immunity	▸ Targets early stages of inflammation ▸ Has low immunogenicity, with less potential for acquired drug resistance ▸ Potentially safer (leaves other immune pathways intact to respond when needed)
▸ Targets both intracellular and extracellular inflammasome-mediated responses - Other drugs in development work intracellularly only (i.e. NodThera and IFM pipeline)	▸ More effective reduction of inflammation
▸ Uniquely targets adapter ASC, which is associated with at least 5 sensor molecules and associated inflammasomes - Other inflammasome inhibitors in development each target only 1 sensor molecule (i.e NodThera and IFM Pipeline)	▸ Ability to target a broader group of inflammatory conditions
▸ ASC is a potential serum biomarker for various inflammatory diseases	▸ Enables targeting patients most suitable for IC 100, and monitoring drug effectiveness

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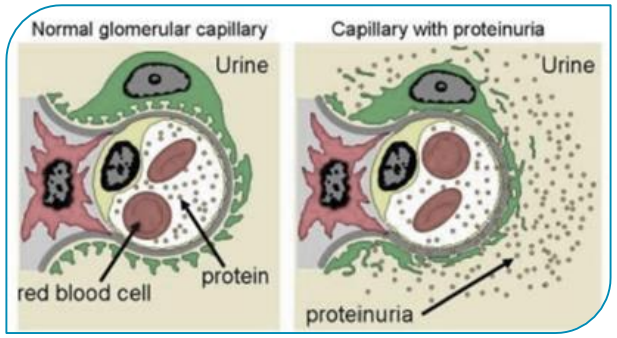
2HPβCD for FSGS (VAR 200) and Alport Syndrome (VAR 300)

Glomerular Diseases Are the 3rd leading Cause of Chronic Kidney Disease, Which Affects 15% of the Adult Population

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

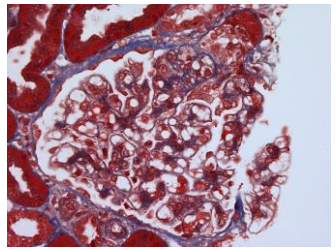
- Diabetes Mellitus
- Lupus Erythematosus
- Amyloidosis and Paraproteinemias
- Viral Infections (i.e. Hepatitis B & C, HIV)

National Kidney Foundation; NIH National Institute of Diabetes and Digestive and Kidney Diseases; Nephcure; Cohen EP: Nephrotic Syndrome. e-medicine, updated December 21,2015

Excess Cholesterol in Podocytes Contributes to the Pathology of Glomerular Diseases

- The kidneys' filtering system is comprised of a capsule (glomerular or Bowman's capsule) containing a tuft of small blood vessels 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, Alport Syndrome, and Other Glomerular Diseases Are Associated With Excess Podocyte Cholesterol Resulting From Decreased Cholesterol Efflux



FSGS Patient's Podocyte Histology (Neptune)

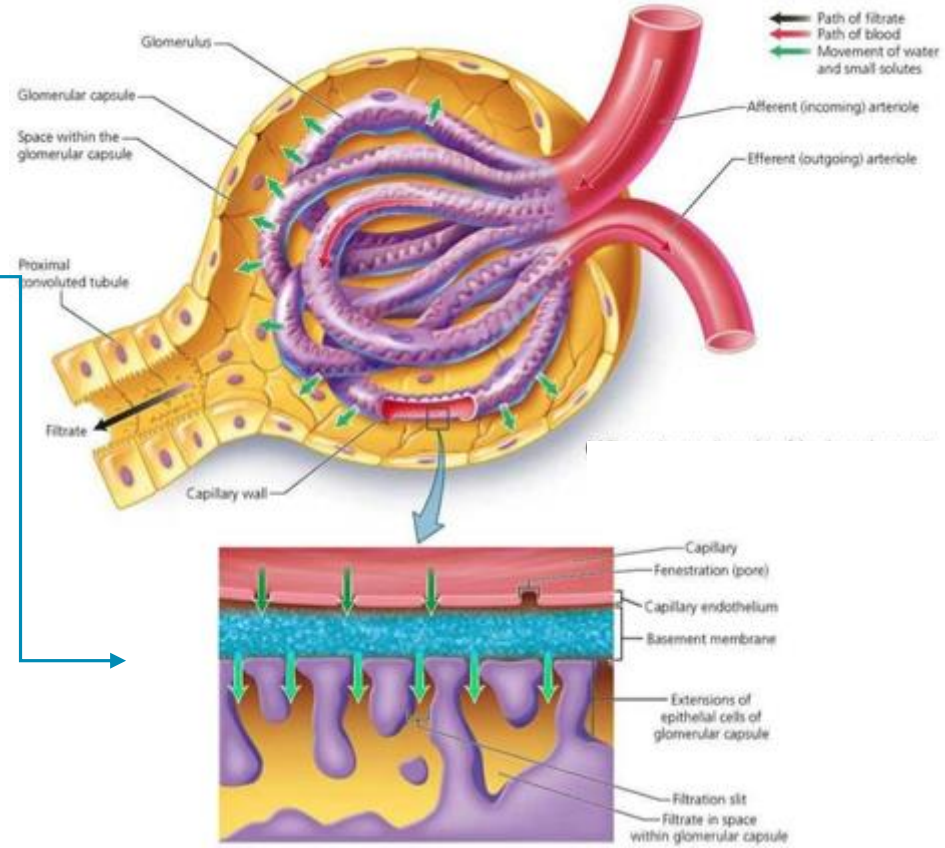


Image from: http://schoolbag.info/biology/humans/22.html

Fornoni A, Merscher S, Kopp JB. Lipid biology of the podocyte—new perspectives offer new opportunities. Nature reviews Nephrology. 2014;10(7):379-388. doi:10.1038/nrneph.2014.87.at

Focal Segmental Glomerulosclerosis (FSGS)

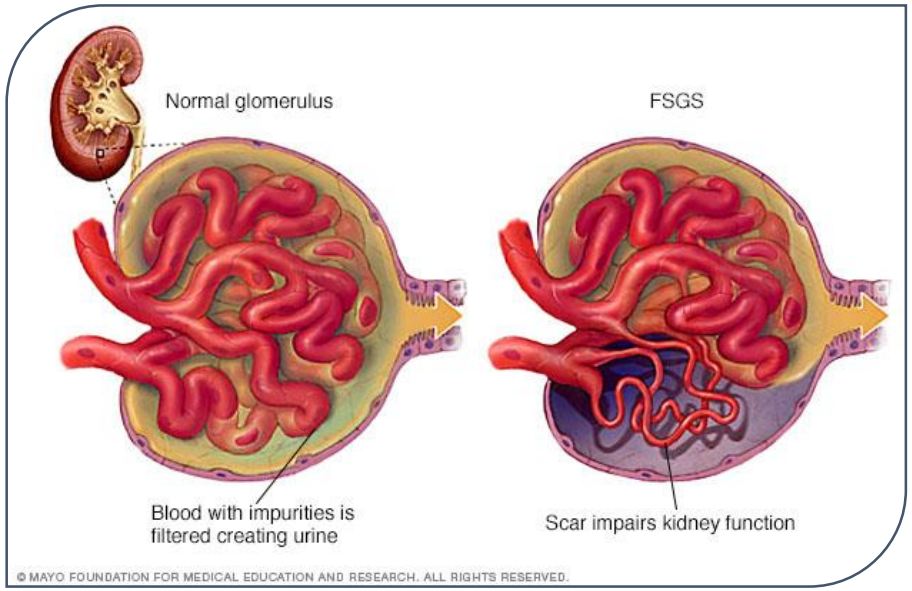
Most common primary glomerular disease in adults, affecting up to 80,000

- FSGS Causes symptomatic proteinuria (nephrotic syndrome), with or without renal insufficiency
- It is focal (affects only some glomerulus) and segmental (affects only part of glomerulus)
- Primary disease (80% of patients) is idiopathic, no etiology can be identified
- Secondary disease is associated with illicit drug use, HIV or other viral infections, inflammation, toxins, or intra-renal hemodynamic alterations

Current standard of care:

- ACE inhibitors, ARB's, dietary modification, control of blood pressure, statins, and steroids (in nephrotic patients)

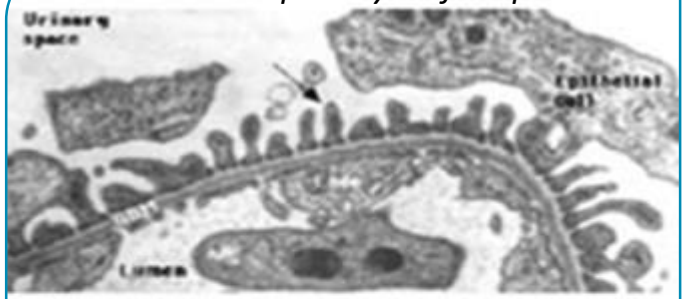
Currently no FDA-approved therapies that are specific for FSGS



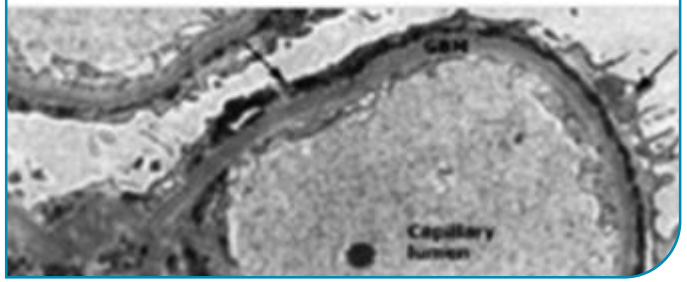
Nephcure; Cohen EP: Nephrotic Syndrome. e-medicine, updated December 21,2015 ; BMJ Best Practice, Focal Segmental Glomerulosclerosis, updated November 13, 2017

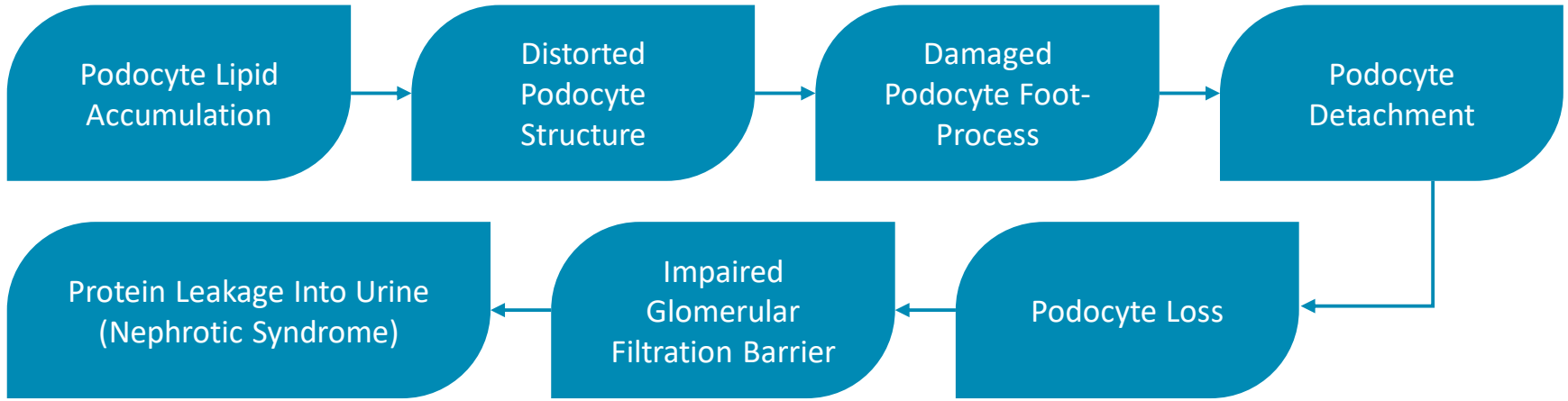
In FSGS, Excess Podocyte Cholesterol Causes Structural Damage to the Kidney's Filtration Barrier, Resulting in Proteinuria and Nephrotic Syndrome

Normal: *Intact podocytes foot process*



Abnormal: *Flattened podocytes*





Pedigo CE et al. Local TNF causes NFATc1-dependent cholesterol mediated podocyte injury. *J Clin Invest* 2016; Sep 1;126(9):3336-3350. doi: 10.1172/JCI85939; D'Agati VD, Kaskel FJ, Falk RJ. Focal Segmental Glomerulosclerosis. *N Engl J Med* 2011; 365:2398-2411

FSGS Prognosis Is Poor, Leading to End Stage Renal Disease in 35%

FSGS returns in **30-40% of patients** after a kidney transplant

Nephcure; Cohen EP: Nephrotic Syndrome. e-medicine, updated December 21,2015; Neptune; Pedigo CE et al. Local TNF causes NFATc1-dependent cholesterol mediated podocyte injury. J Clin Invest 2016; Sep 1;126(9):3336-3350. doi: 10.1172/JCI85939; D'Agati VD, Kaskel FJ, Falk RJ. Focal Segmental Glomerulosclerosis. N Engl J Med 2011; 365:2398-2411

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Alport Syndrome (AS)

Progressive, inherited form of kidney disease that is often associated with neural hearing loss and ocular abnormalities, affecting up to 60,000

- Pathophysiology: mutations in genes encoding members of the type IV collagen family, that ultimately cause lipid accumulation and scarring of the basement membranes of the glomerulus, the inner ear (cochlea), and the eye
- Disease hallmark: blood in the urine (hematuria) early in life, with progressive decline in kidney function ultimately resulting in kidney failure
- Bilateral hearing loss from abnormalities of the inner ear occurs in late childhood or early adolescence, generally before the onset of kidney failure
- Patients may have misshapen lenses in the eyes (anterior lenticonus) and abnormal retina coloration, which seldom lead to vision loss

Current standard of care:

- Angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs) for patients with proteinuria

Currently no FDA-approved therapies that are specific for AS

Kashtan CE.. Clinical manifestations, diagnosis and treatment of hereditary nephritis (Alport syndrome). UpToDate.com, pulled 8/26/16.
Saxena R. Alport Syndrome. emedicine.Medscape.com, pulled 8/26/16.

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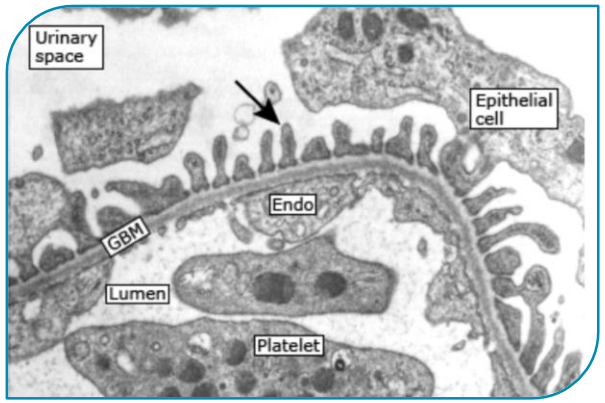
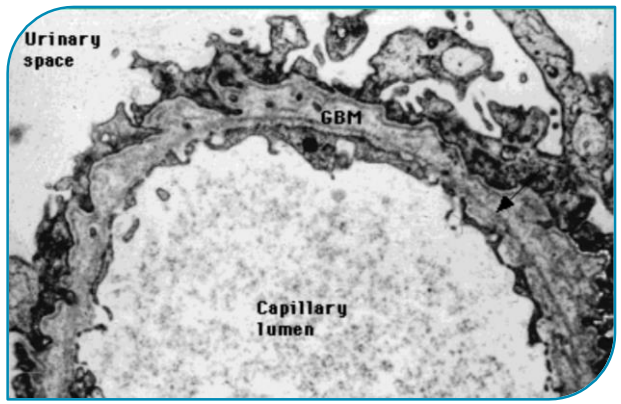
In Alport Syndrome, Lipid Accumulation Contributes to Podocyte Injury and Loss

Normal Podocyte



Podocyte From Patient With AS



Uniform Thinning of Glomerular Basement Membrane (GBM) & Hematuria → Focal Increase in GBM Cellularity → Lipid-laden Foam Cells in the Interstitial Infiltrate & Glomerulosclerosis → Thickening, Fraying, & Laminations of the GBM & Damaged Podocyte Foot-Processes → Podocyte Detachment → Podocyte Loss → Impaired Glomerular Filtration Barrier → Protein Leakage Into Urine (Nephrotic Syndrome)

Kashtan CE. Genetics, pathogenesis, and pathology of hereditary nephritis (Alport syndrome). UpToDate.com, pulled 8/26/16; Wickman L, Hodgin JB, Wang SQ, Afshinnia F, Kershaw D, Wiggin RC. Podocyte Depletion in Thin GBM and Alport Syndrome. PLoS One 2016; 11(5): e0155255

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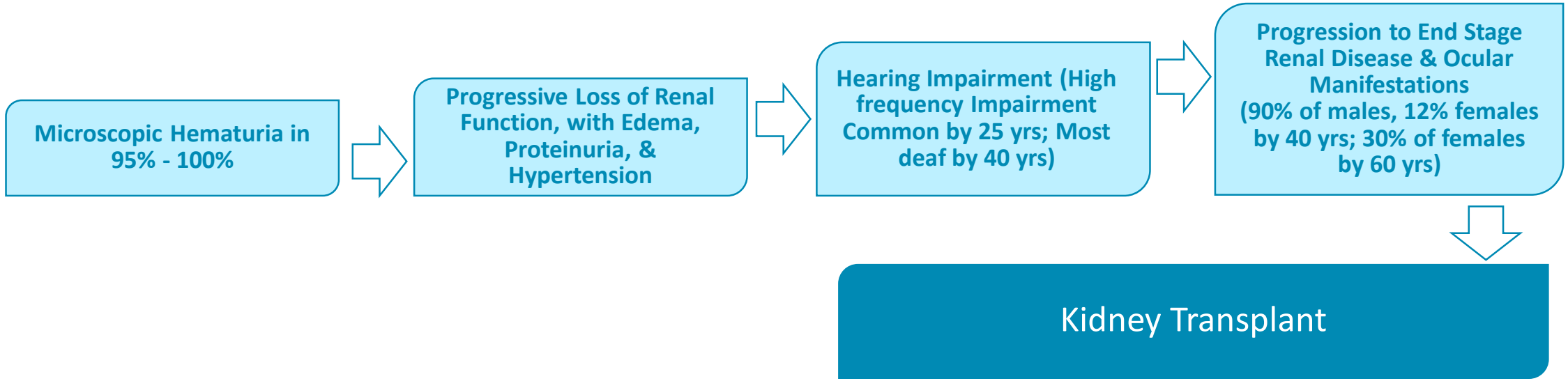
AS Prognosis Is Poor*



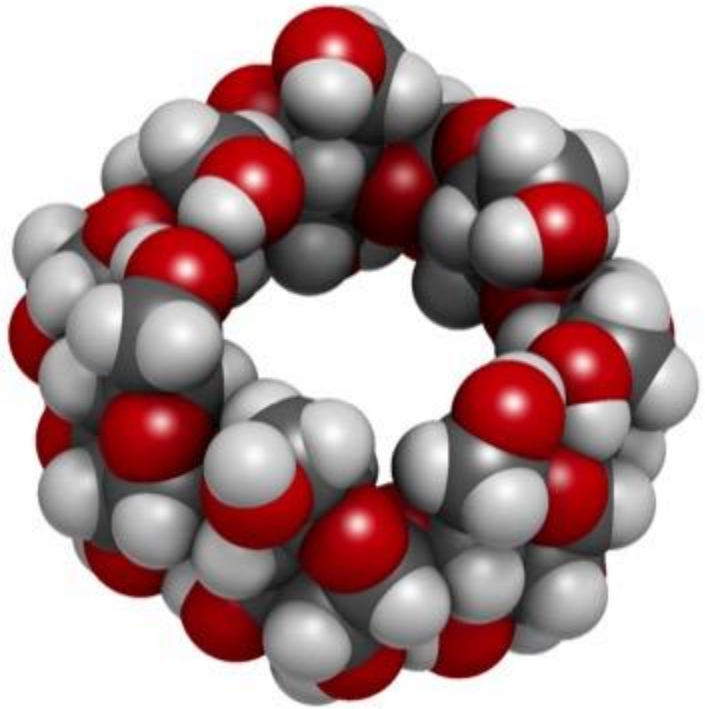
Kidney transplant preferred over dialysis
Good outcomes in 97%.

*Based on clinical manifestations of patients with X-linked disease (85%); prognosis of those with ARAS (10-15%) & ADAS (<5%) is similar, but progression is slower in ADAS

Kashtan CE. Clinical manifestations, diagnosis and treatment of hereditary nephritis (Alport syndrome), UpToDate.com, updated December 17, 2015; Saxena R. Alport syndrome, emedicine.medscape.com, updated July 21,2015

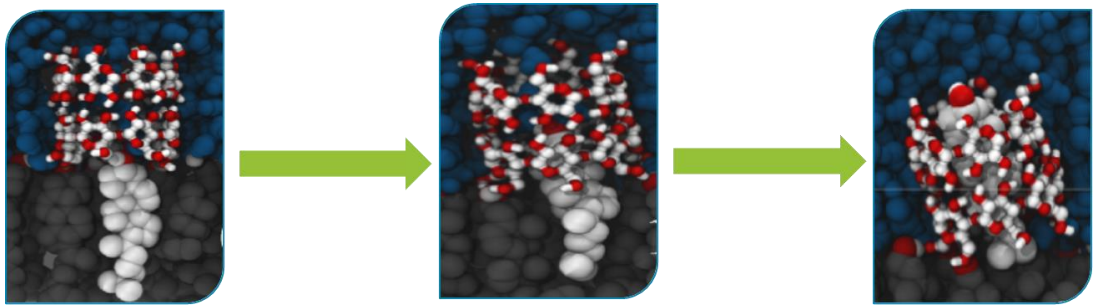
ZyVersa THERAPEUTICS

ZyVersa's Lead Candidate, 2-Hydroxypropyl-Beta-Cyclodextrin (2HPβCD) Promotes Cholesterol Removal from Podocytes, Slowing Progression of Podocyte Injury and Renal Disease



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

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



Although novel as an active drug for use in kidney disease, 2HPβCD has been used extensively in humans for over 20 years as a drug excipient to improve drug delivery, and as a food additive for which it is classified as GRAS (generally recognized as safe)

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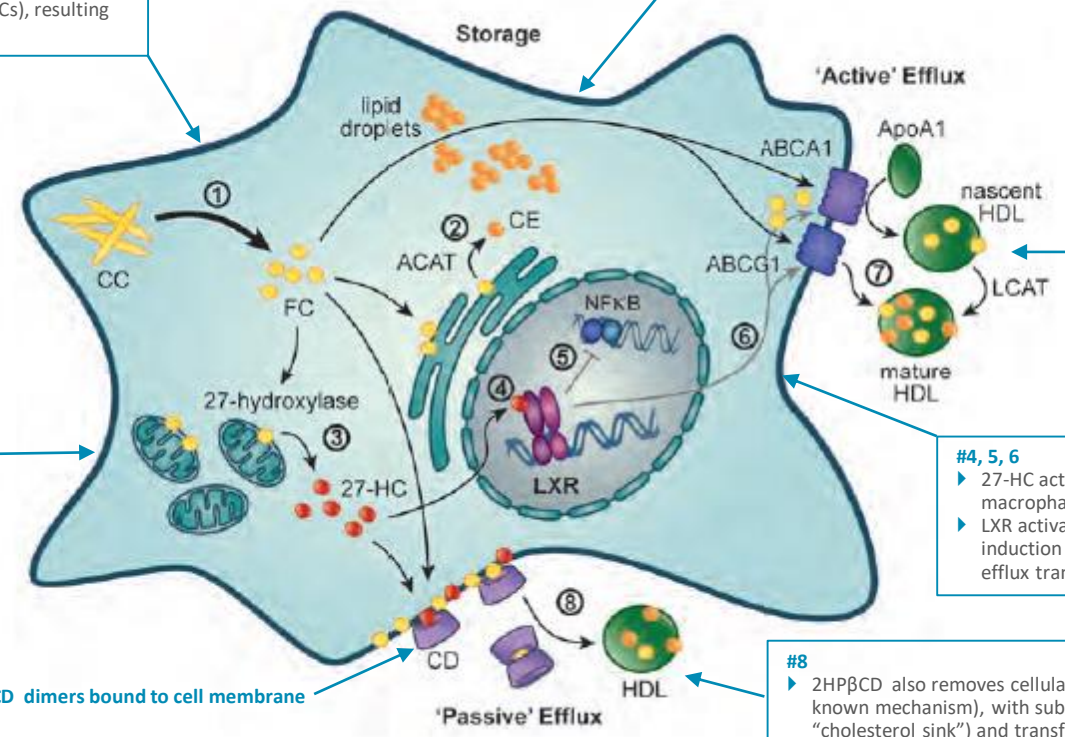
2HPβCD Proposed Mechanism of Action
Based on Atherosclerosis Model[1,2]

#1
- Once bound to the cell membrane, 2HPβCD promotes the dissolution of intracellular cholesterol crystals (CCs), resulting in an increased cellular free cholesterol (FC) pool

#2
- 2HPβCD increases the turnover of intracellular cholesterol pools, leading to increased intracellular cholesterol storage, cholesterol metabolism, and "active" and "passive" cholesterol efflux
- Liberated free cholesterol is esterified by ACAT in the endoplasmic reticulum (ER) resulting in nontoxic storage of cholesterol esters (CE) in cytoplasmic lipid droplets



#3
- Free cholesterol is metabolized into oxysterols (e.g. 27-HC by mitochondrial 27-hydroxylase) by mitochondrial 27-hydroxylase

#7
- ABCA1 transfers cellular free cholesterol to lipid-poor ApoA1 particles generating nascent HDL particles
- Esterification of free cholesterol in HDL particles by LCAT generates mature HDL particles, which accept cellular free cholesterol from ABCG1

#4, 5, 6
- 27-HC activates LXR-transcription factors resulting in transcriptional reprogramming of the macrophages
- LXR activation mediates the repression of NF-κB-mediated inflammatory responses and induction of cellular cholesterol efflux pathways, including the upregulation of cholesterol efflux transporters ABCA1 and ABCG1

#8
- 2HPβCD also removes cellular free cholesterol and oxysterols from the cell membrane (best known mechanism), with subsequent formation of 2:1 inclusion complexes (2HPβCD as "cholesterol sink") and transfers them to cholesterol acceptors, such as HDL (2HPβCD as "cholesterol shuttle")

Image from Alena Grebe PhD Dissertation

1. Alena Grebe PhD Dissertation: Targeting cholesterol crystals in atherosclerosis with cholesterol solubilizing 2-hydroxypropyl-β-cyclodextrin, University of Bonn, Germany, March 2016; 2. Zimmer S, et al. Cyclodextrin promotes atherosclerosis regression via macrophage reprogramming. Sci Transl Med. 2016 Apr 6;8(333):333ra50.

Molecular Mechanism of Cyclodextrin Mediated Cholesterol Extraction From Cell Membranes[1]

B
- CD dimers bind to the membrane surface assuming either a tilted or untilted configuration

A
- Association of CDs in aqueous solution leads to the formation of dimers

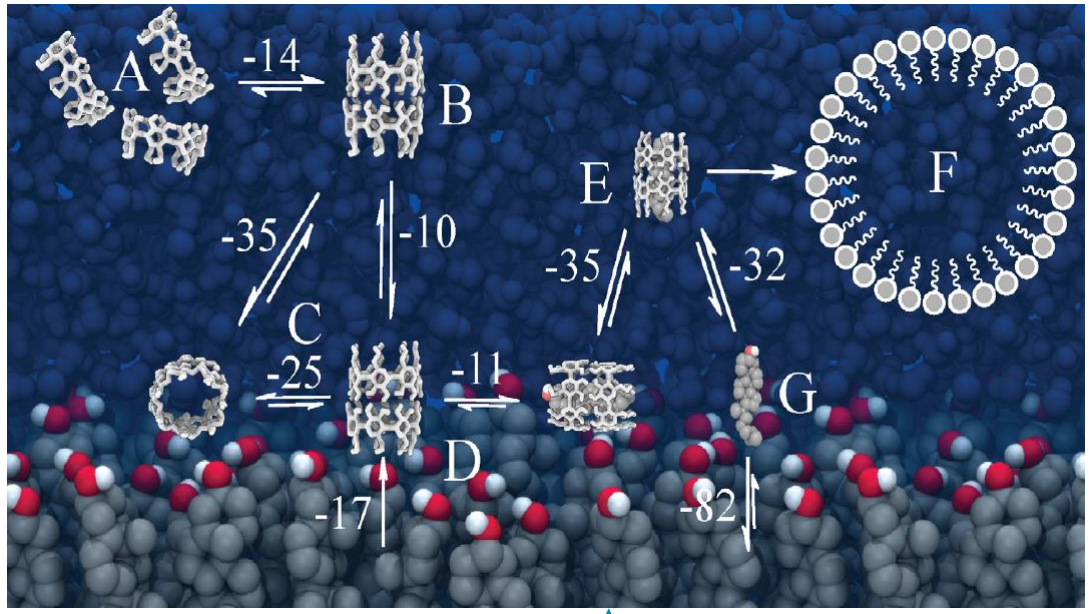


Image from Lopez et al

C
- The tilted configuration (middle) is suitable to extract cholesterol, allowing the formation of a membrane-bound complex

F, G
- Direct release of cholesterol from the membrane (G) is energetically much more costly (-82) than CD-facilitated release (-17)
- Energy values are in kJ mol^{-1}

D, E
- Release of the complex from the surface brings cholesterol in solution, facilitating its transfer to other membranes

1. Lopez CA, et al. Molecular Mechanism of Cyclodextrin Mediated Cholesterol Extraction. PLoS Comput Biol 7(3): e1002020. doi:10.1371/journal.pcbi.1002020

ZyVersa THERAPEUTICS℠

2HPβCD
Scientific Support

Strong Pre-clinical Support for 2HPβCD, With POC in 3 Different Animal Models of Kidney Disease

Enables clinical development to progress directly to Phase 2a in FSGS patients

FSGS Model
(40 mg/kg daily)

Compared to controls, 2HPβCD:

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

The effect of 2HPβCD on proteinuria was reproducible in two studies with a total of three 2HPβCD treatment arms

Alport Syndrome Model
(4,000 mg/kg 3 times weekly)

Compared to controls, 2HPβCD:

- 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

Diabetic Kidney Disease Model
(4,000 mg/kg 3 times weekly)

Compared to controls, 2HPβCD:

- 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)

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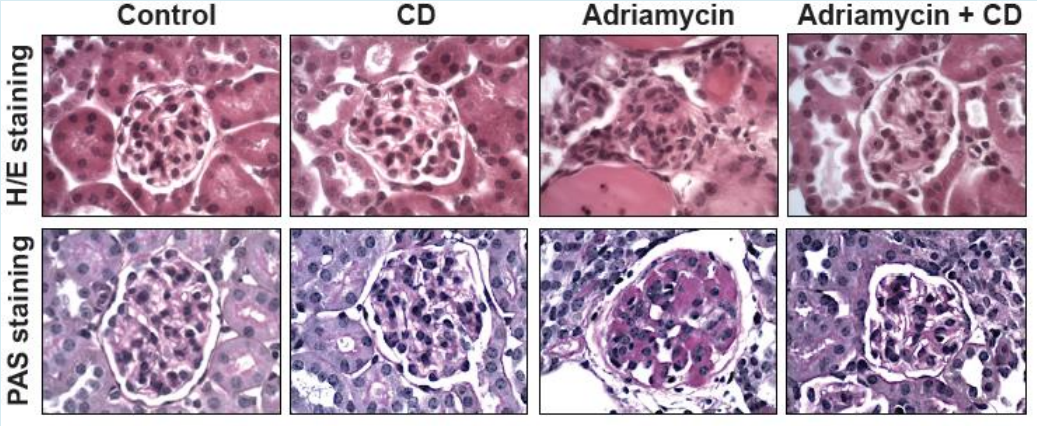
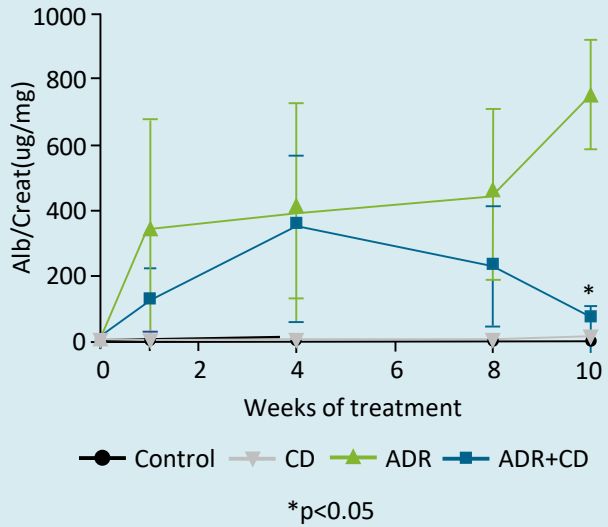
2HPβCD Protected Podocytes, Attenuating Glomerular Cell Damage in an Adriamycin FSGS Mouse Model





- 2HPβCD attenuated the increase in Alb/Cr induced by Adriamycin, separating from the untreated group after week 4, with significant reduction in albuminuria at 10 weeks
- 2HPβCD (40 mg/kg/day) prevented the significant increase in mesangial expansion demonstrated in ADR treated mice

Mitrofanova A, Wahl P, Morales X, Correa M, Pedigo C, Ducasa GM, Bruke GW, Merscher S, Kretzler M,Martini S, Fornoni A. Cyclodextrin Protects Podocytes in Focal Segmental Glomerulosclerosis (FSGS). Presented at the Kern Lipid Conference August 3 – 5, 2015, Vail Colorado

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2HPβCD Value Proposition

2-Hydroxypropyl-Beta-Cyclodextrin Has Potential to Delay Progression of FSGS and Alport Syndrome, Improve Quality of Life, and Reduce Heath Economic Burden

Provide a first-in-class Disease Modifying Treatment with potential to:

- Induce remission of proteinuria (reduce urinary protein)
- Delay progression to end stage renal disease (time to dialysis or transplant)
- Improve quality of life
- Reduce health economic burden associated with kidney disease

ZyVersa Therapeutics Corporate Presentation

Q2-2019

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Restoring Health, Transforming Lives Through Innovation