March 29, 2022

2022 Research & Development Day

ADX-629: A First-in-Class, Oral RASP Modulator for the Treatment of Systemic Disease

Nasdaq: ALDX

March 29, 2022

Todd C. Brady, M.D., Ph.D., Chief Executive Officer

Welcome and Opening Remarks

Nasdaq: ALDX

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Agenda

TIME (ET)	TOPIC	PRESENTER
10:00 – 10:15 a.m.	RASP Overview	Todd C. Brady, M.D., Ph.D. *Chief Executive Officer*, Aldeyra Therapeutics
10:15 – 10:45 a.m.	RASP and Inflammation	Geoffrey M. Thiele, Ph.D. *Umbach Professor*, Internal Medicine, University of Nebraska Medical Center
10:45 – 11:15 a.m.	ADX-629 in *In vivo* and *In vitro* inflammatory models	Michael J. Duryee, MS *Instructor,* Internal Medicine, University of Nebraska Medical Center
11:15 – 11:30 a.m.	Questions	
11:30 – 11:40 a.m.	Break	
11:40 – 11:50 a.m.	Preclinical Activity of ADX-629	Adam Brockman, Ph.D. *Director of Translational Science,* Aldeyra Therapeutics
11:50 – 12:20 p.m.	Proof-of-Concept Top-Line Data	Todd C. Brady, M.D., Ph.D.
12:20 – 12:35 p.m.	New Molecules, New Indications	Adam Brockman, Ph.D.
12:35 – 12:55 p.m.	Questions	
12:55 – 1:00 p.m.	Concluding Remarks	Todd C. Brady, M.D., Ph.D.

ALDEYRA'S MISSION is to discover and develop innovative medicines that improve the lives of patients who suffer from immune-mediated diseases.

OUR APPROACH is to create therapies that modulate immunological systems, instead of directly inhibiting or activating single protein targets, with the goal of optimizing multiple pathways at once while minimizing toxicity.

Aldeyra is a Well-Capitalized Biotechnology Company with a Broad Immunology Pipeline and Near-Term Catalysts

PRODUCT CANDIDATES	DISEASE TARGETS	DEVELOPMENT STAGE	NEXT EXPECTED MILESTONE
RASP PLATFORM FOR OCULAR AND SYSTEMIC IMMUNE-MEDIATED DISEASES			
Reproxalap (ophthalmic solution)	Dry Eye Disease	Phase 3	Mid-2022: Final Pivotal Trial Results
	Allergic Conjunctivitis	Phase 3	2023: Final Pivotal Trial Results
ADX-629 (oral administration)	Ethanol Toxicity, Chronic Cough, Sjögren-Larsson Syndrome, Minimal Change Disease	Phase 2a	2022 and 2023: Trial Completion
RASP-Modulator Discovery Platform	Multiple Immune-Mediated Retinal and Systemic Indications	Preclinical	2023: IND Submission
VITREOUS METHOTREXATE PLATFORM FOR RARE RETINAL INFLAMMATORY DISEASES			
ADX-2191 (intravitreal injection)	Primary Vitreoretinal Lymphoma (U.S. FDA Orphan Drug Designation)	Pre-NDA	H2 2022: Regulatory Update
	Proliferative Vitreoretinopathy (U.S. FDA Orphan Drug and Fast Track Designation)	Phase 3	H2 2022: Part 1 GUARD Trial Results
	Retinitis Pigmentosa (U.S. FDA Orphan Drug Designation)	Phase 2	H2 2022: Trial Results

As of 12/31/2021, cash and cash equivalents were $229.8M, which is expected to be sufficient to fund operations through the end of 2023, based on projected operating expenses.[†]

[†]Company guidance as of March 17, 2022. **IND** = Investigational New Drug. **NDA** = New Drug Application.

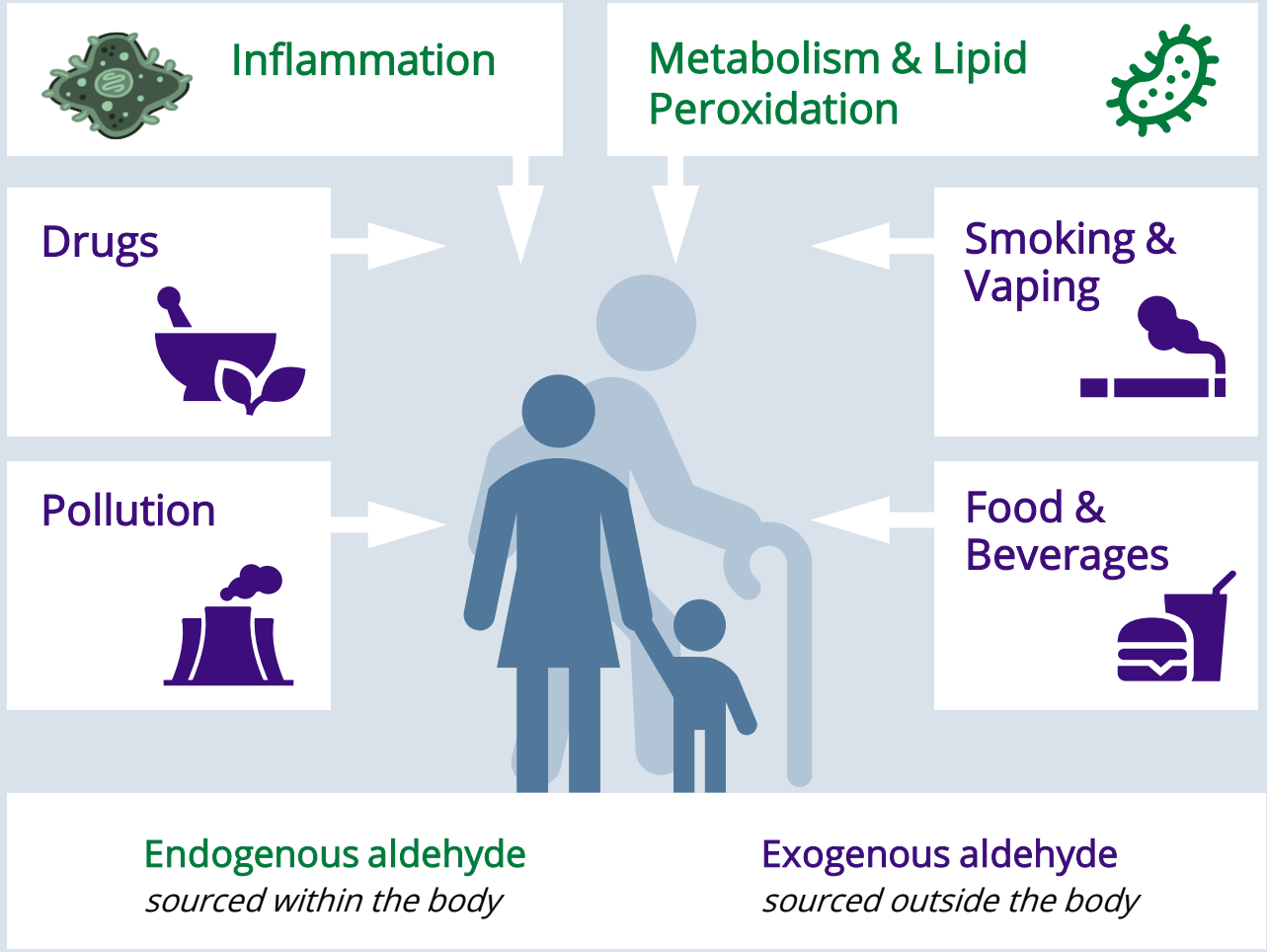
Reactive Aldehyde Species (RASP)

RASP are formed by a variety of metabolic processes, including:

- glucose metabolism,
- alcohol oxidation,
- lipid peroxidation, and
- polyamine metabolism.

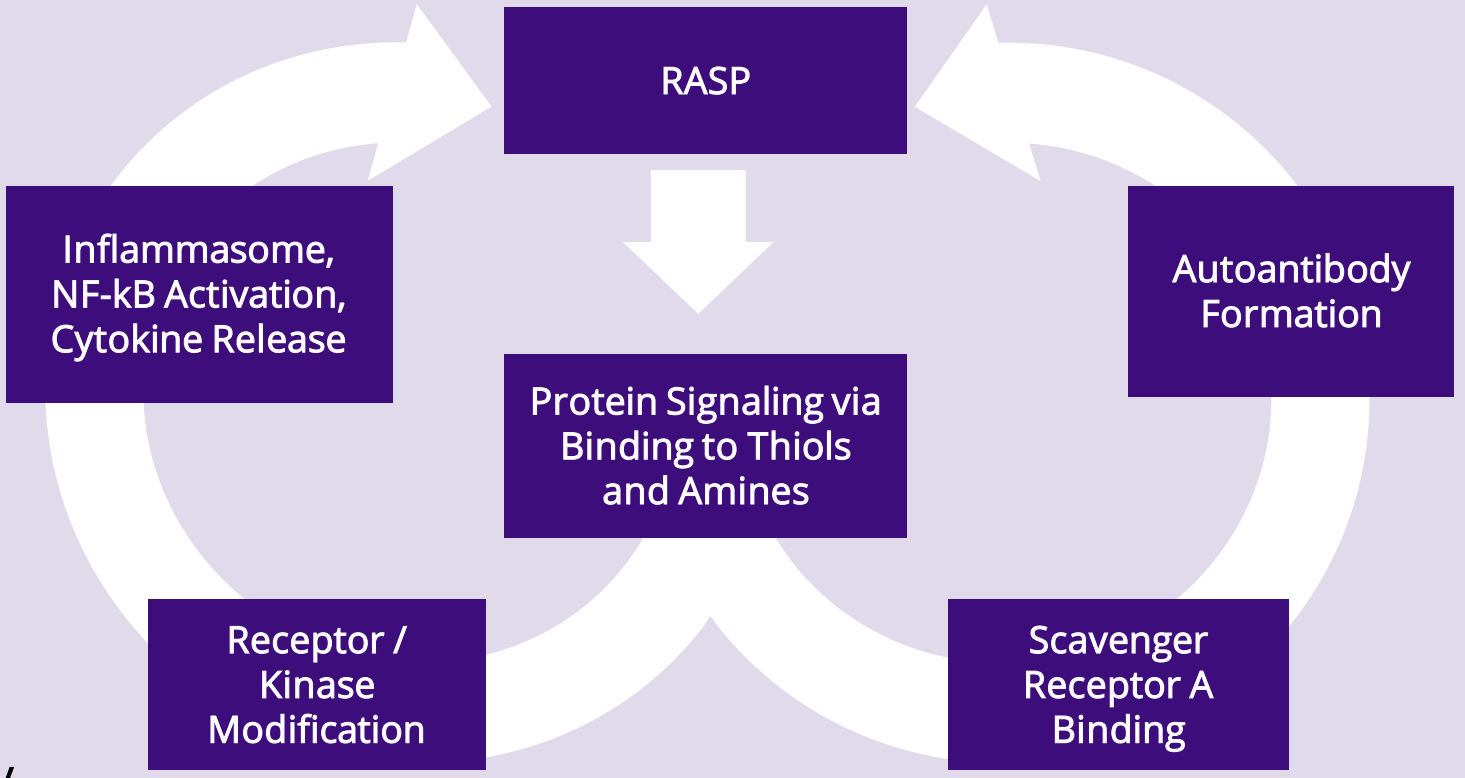
RASP are eliminated by chemical and enzymatic means:

- biomolecular adduction (thiol and amine covalent binding) and
- aldehyde dehydrogenases and reductases.



RASP Induce Inflammation via Multiple Mechanisms

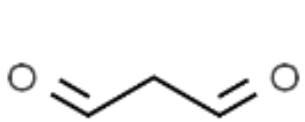
- Aldehydes **covalently bind** thiol (Michael addition) and amine (Schiff base) residues on proteins.
- Direct protein binding leads to **conformational and functional** changes in proteins, which in turn initiate a pro-inflammatory signaling cascade.
- Aldehyde-protein adducts are ligands for **Scavenger Receptor A**, subsequently leading to autoantibody formation against the adducted protein.



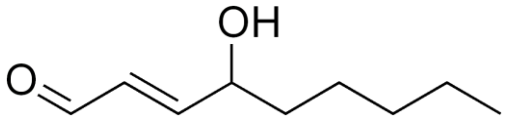
RASP Signaling is Mediated by Covalently Binding Proteins

Lipid-derived aldehydes such as **malondialdehyde** (MDA), **hydroxynonenal** (HNE), and acrolein are the most studied regarding inflammatory signaling

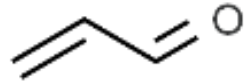
Cysteine thiols are the most sensitive to aldehyde adduction, followed by the amines of **lysine and histidine**.



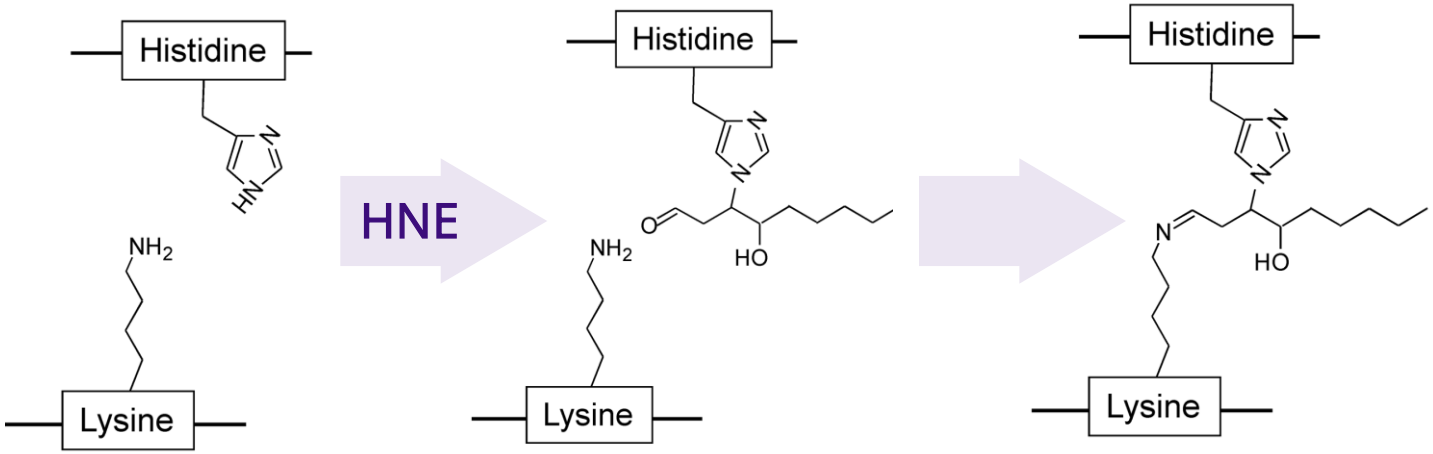
MDA



HNE



Acrolein

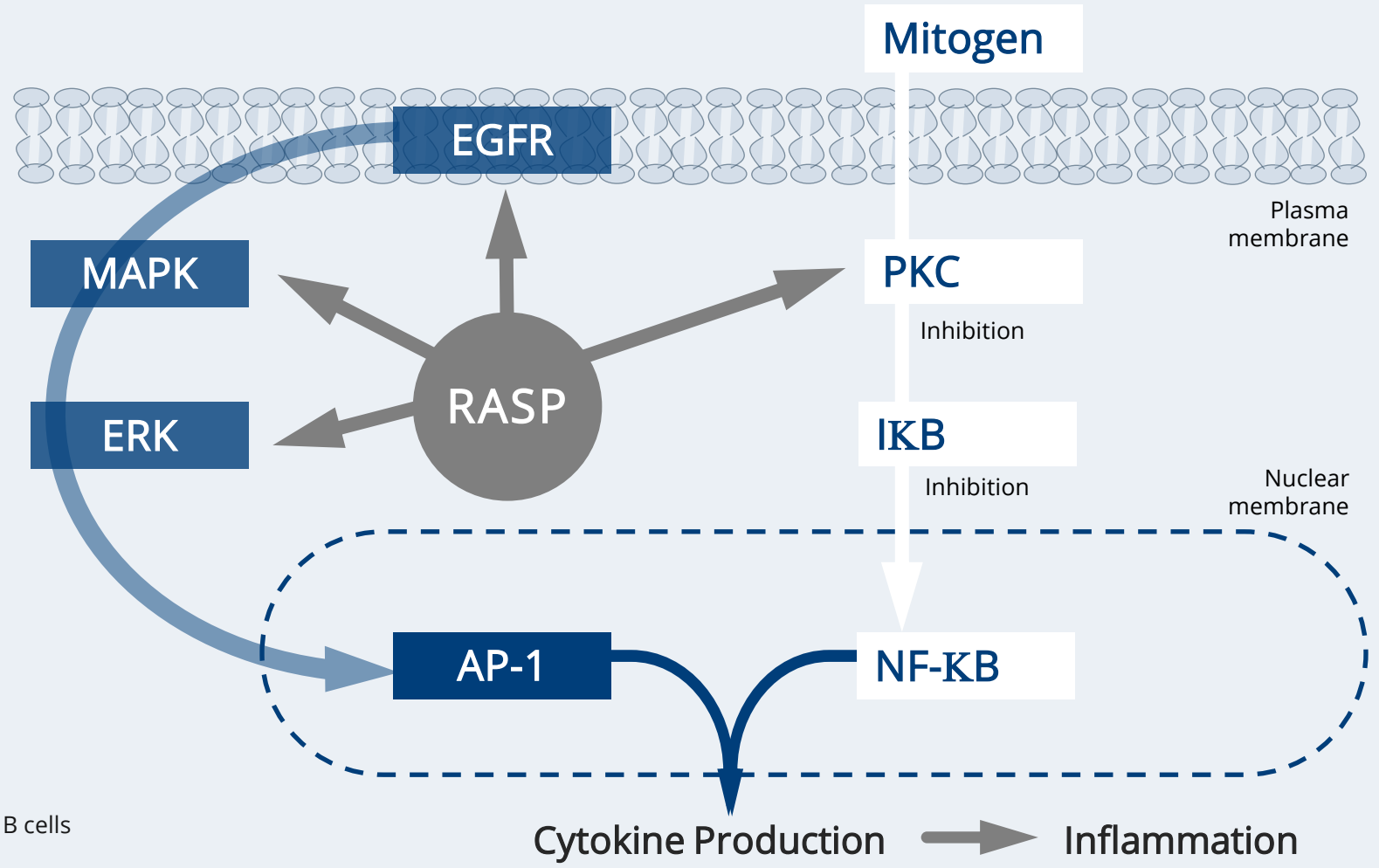


Michael adduct

Schiff base crosslink

The Pro-Inflammatory RASP Signaling Cascade is Well Characterized

RASP signaling occurs via adduction to kinases and receptors. Both pathways communicate cell surface signals to the nucleus, leading to the expression of transcription factors including AP-1 and NF-ΚB.



IΚB – IκB kinase
AP-1 – activator protein 1
PKC – protein kinase C
MAPK – mitogen-activated protein kinase
EGFR – epidermal growth factor receptor
ERK – extracellular signal-regulated kinase
NF-ΚB – nuclear factor of kappa-light-chain-enhancer of activated B cells

RASP Signaling is Fundamentally Different from Receptor Signaling

RASP activity represents a novel pro-inflammatory signal transduction paradigm, **distinct from ligand/receptor interactions**.

MECHANISM	BOND	OUTPUT	MEMORY
RASP	**Covalent**	**Analog** Pluripotent and contingent on adduct levels	**Solid-State** Outcome dependent on prior adduct levels
Ligand/ Receptor	**Ionic, Hydrogen**	**Digital** Unipotent and contingent on binding or no binding	**Flash** Outcome independent of prior binding state

RASP modulation is one of the few examples of pharmacologic therapies that do not directly target proteins and do not effect digital outcomes.

Source: Higdon A, Diers AR, Oh JY, Landar A, Darley-Usmar VM. Cell signalling by reactive lipid species: new concepts and molecular mechanisms. Biochem J. 2012 Mar 15;442(3):453-64.

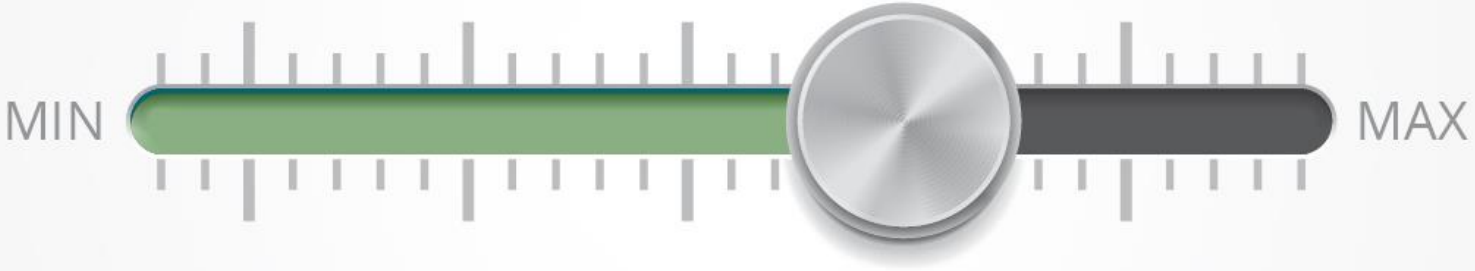
Aldeyra is Developing Technology Designed to Modulate Biological *Systems*…Not Single Targets

TRADITIONAL PHARMACOLOGY IS LIMITED TO TWO OUTCOMES

Most immunological drugs shut down **specific molecules**, obstructing the immune system and leading to toxicity.

Aldeyra is Developing Technology Designed to Modulate Biological *Systems*…Not Single Targets

SYSTEMS-BASED PHARMACOLOGY ALLOWS FOR INFINITE CONTROL



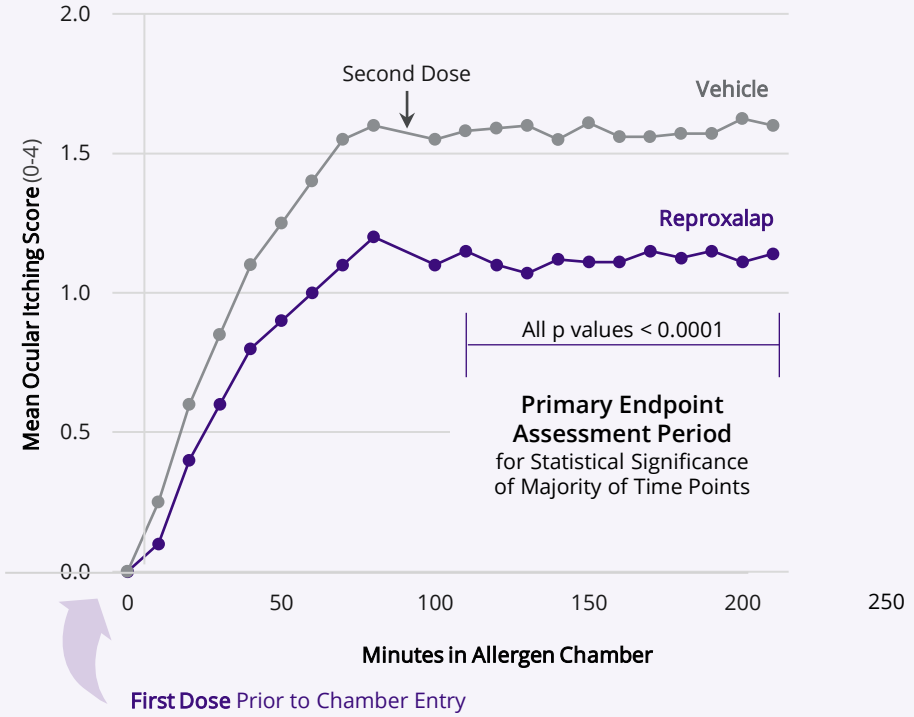
In contrast, **modulation of the immune system** maintains immune function, but allows for lower levels of inflammation.

Aldeyra is One Pivotal Trial Away from NDA Submission of Reproxalap for Allergic Conjunctivitis†

The Phase 3 INVIGORATE Allergen Chamber Trial

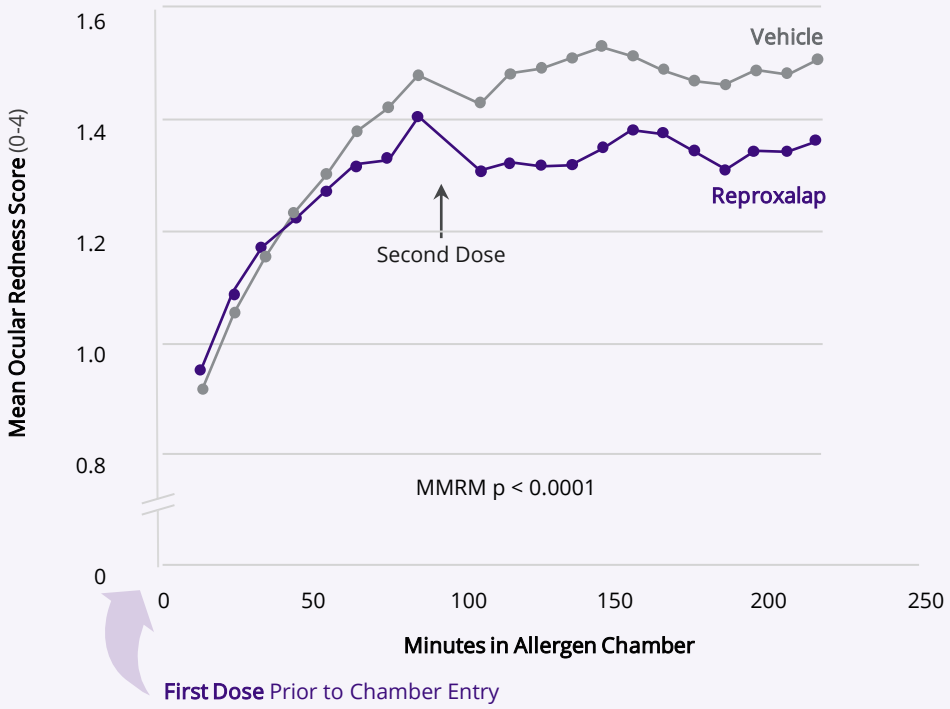
Primary Endpoint

Reduction in Ocular Itching Over Pre-Specified Time Frame



Key Secondary Endpoint

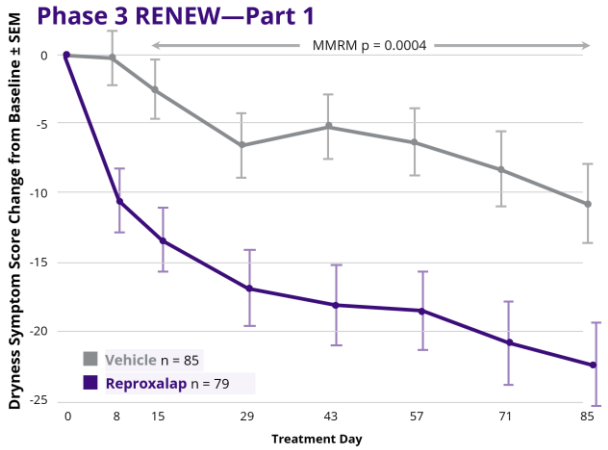
Reduction in Ocular Redness Over the Entire Chamber

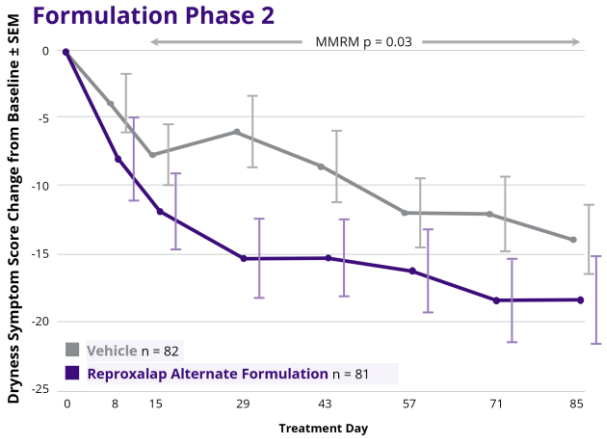


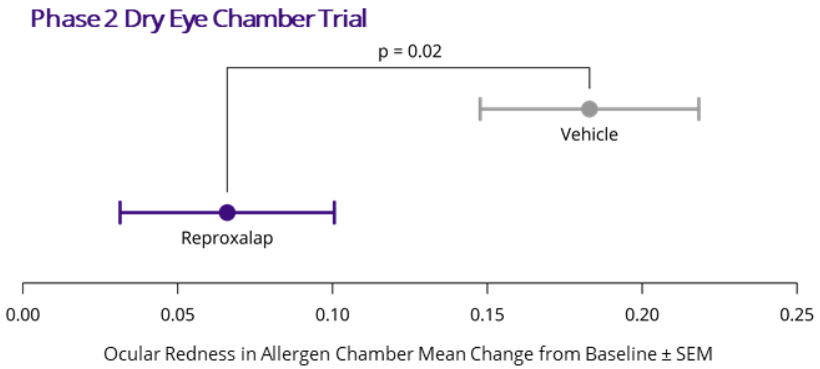
†NDA submission requirements depend, in part, on clinical results and regulatory feedback. **Source**: INVIGORATE clinical trial results. Topical ocular reproxalap has been studied in more than 1,500 patients with no observed safety concerns; mild and transient instillation site discomfort is the most commonly reported adverse event in clinical trials. **MMRM** = mixed model repeated measures.

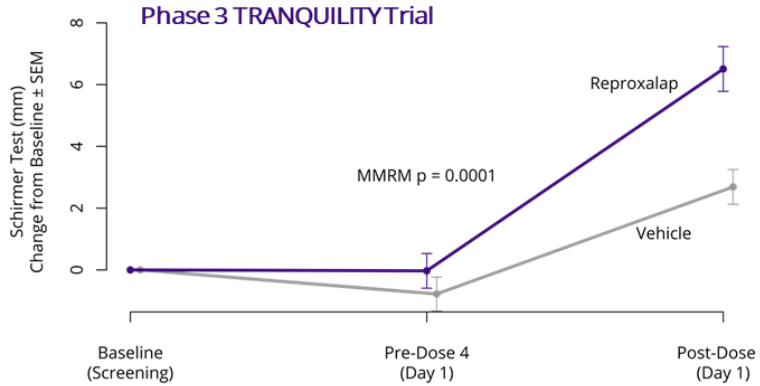
Aldeyra is One Pivotal Clinical Trial Away from NDA Submission of Reproxalap for Dry Eye Disease†

To satisfy efficacy requirements for dry eye disease, the FDA requires two positive trials with the same symptom and two positive trials with the same sign.‡









Symptoms

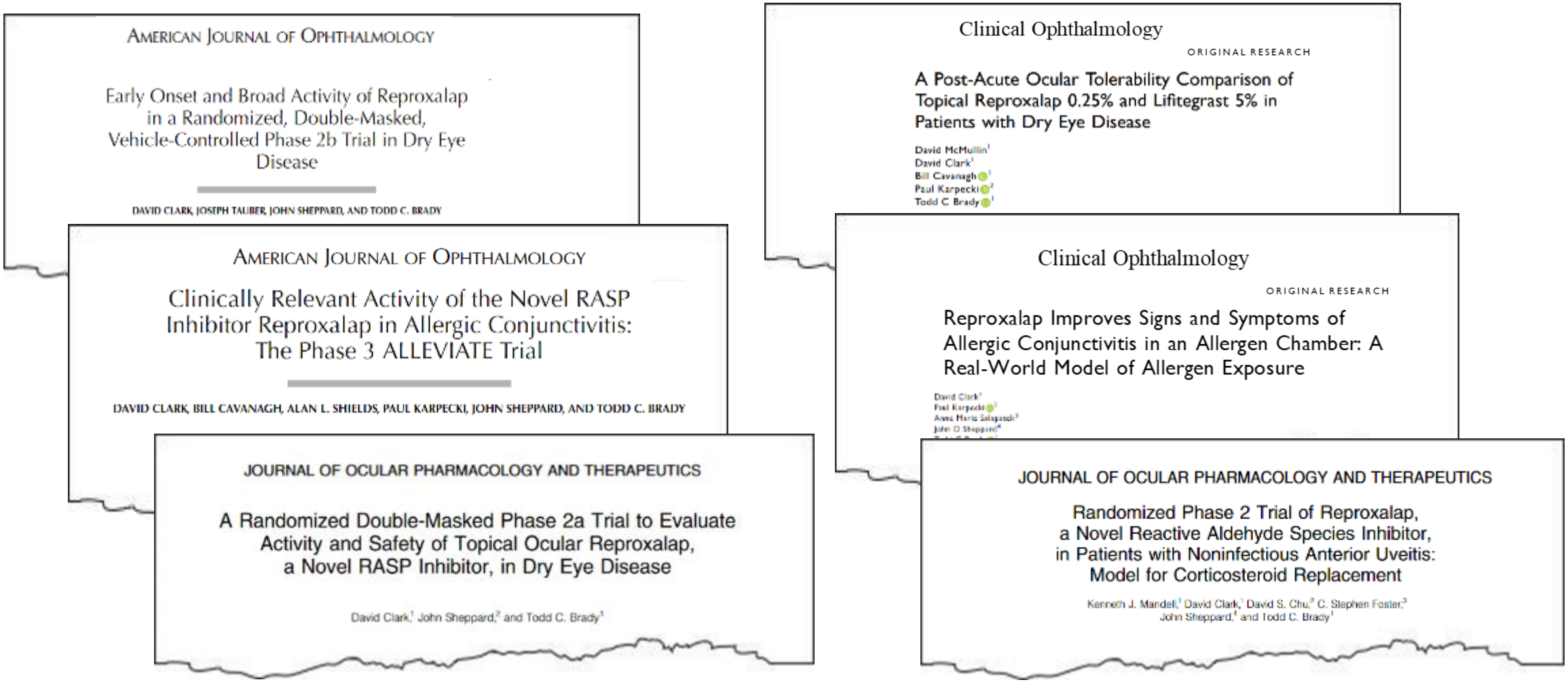
Aldeyra intends to submit two previously completed 12-week adequate and well-controlled **symptom trials** that pre-specified patient-reported ocular dryness score as a primary endpoint or a co-primary endpoint.

Signs

Aldeyra has shown statistically significant results in **ocular redness** in the Phase 2* dry eye chamber trial and in **Schirmer test** in the Phase 3 TRANQUILITY Trial#. Both ocular redness and Schirmer test are FDA-sanctioned, objective signs of dry eye.

†NDA submission requirements depend, in part, on clinical results and regulatory feedback. ‡Draft U.S. Food and Drug Administration (FDA) guidance. *Adequate and well-controlled Phase 2 or Phase 3 clinical trials can be submitted as pivotal. #Schirmer test was a secondary endpoint in the TRANQUILITY Trial. **Sources**: Clinical trial results on file. **MMRM** = mixed model repeated measures. **SEM** = standard error of the mean. Topical ocular reproxalap is an investigational drug candidate that has been studied in more than 1,500 patients with no observed safety concerns; mild and transient instillation site discomfort is the most commonly reported adverse event in clinical trials.

The Activity of Lead RASP Modulator Reproxalap is Supported by Marquee Peer-Reviewed Publications



Topical ocular reproxalap is an investigational drug candidate that has been studied in over more than 1,500 patients with no observed safety concerns; mild and transient instillation site discomfort is the most commonly reported adverse event in clinical trials.

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Reactive Aldehyde Species and Inflammation: Evidence for Malondialdehyde and Acetaldehyde as Pro-Inflammatory Mediators

Geoffrey M. Thiele, Ph.D.
Umbach Professor of Rheumatology
Department of Internal Medicine
Division of Rheumatology and Immunology

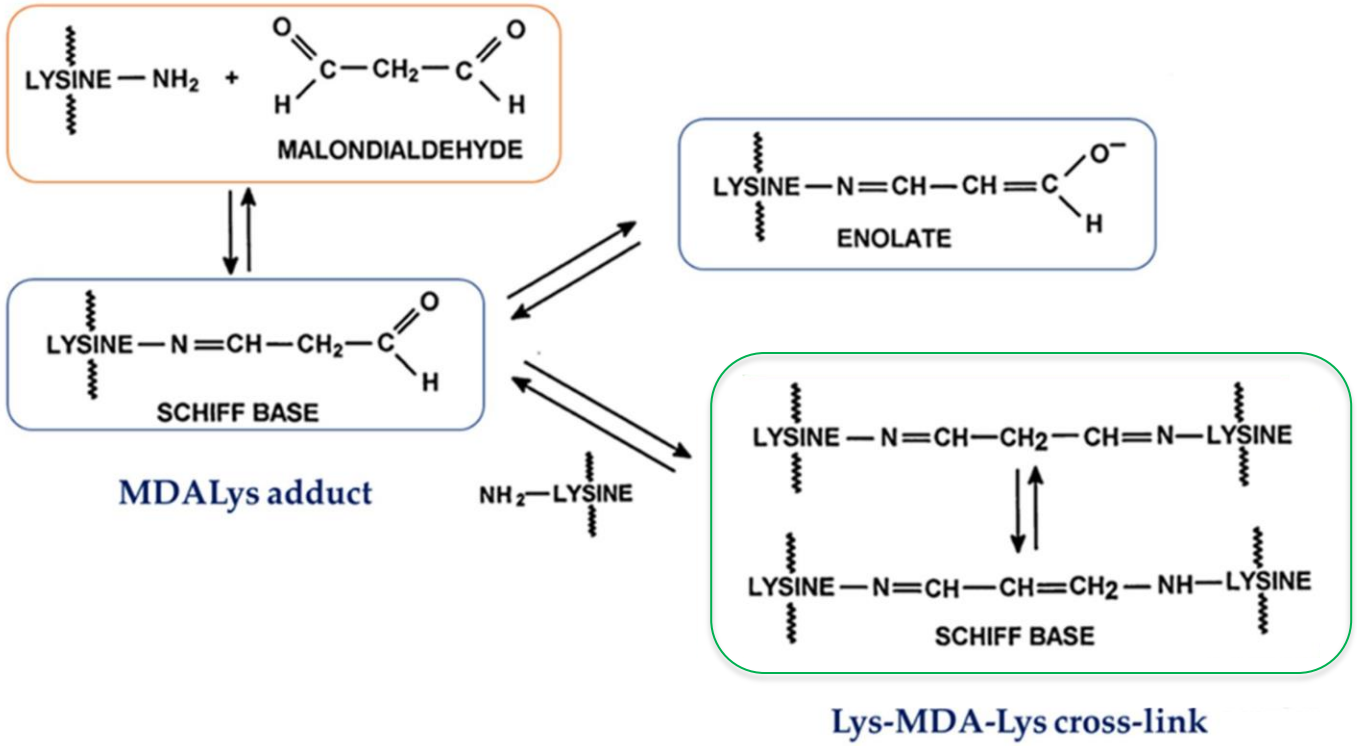
Disclosures

- **Funding from various sources:**
  - **NIH**
  - **DOD**
  - **VA Merit Review**
  - **Rheumatology Research Foundation**
  - **Bristol Myers Squibb; Investigator Initiated**
  - **Aldeyra Therapeutics; Investigator Initiated Studies**
- **Sanofi/Regeneron; Speaker for unbranded information; IL-6 and its inhibitors**

Malondialdehyde

- **Where does it come from?**
    - Generated from the peroxidation of lipids in the membranes of cells.
    - Breakdown of malondialdehyde can generate acetaldehyde.
- **Toxic effects of malondialdehyde.**
    - Causes stress to cells.
    - Reacts with proteins to inactivate function.
    - Forms adducts that generate immune responses.
    - Reacts with DNA causing mutagenesis.
    - Increases inflammation.

Formation of the Malondialdehyde Adduct

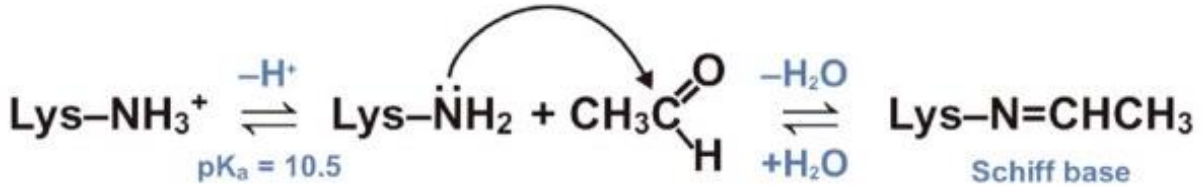


Acetaldehyde

- **Where does it come from?**
    - Metabolite of ethanol breakdown.
    - Found in cigarette and cannabis smoke.
    - Found in the manufacture of plastics.
- **Toxic effects of acetaldehyde**
    - Causes flushing syndrome in individuals that lack the aldehyde dehydrogenase gene. (can't metabolize acetaldehyde).
    - Forms adducts on proteins.
        - Impairs protein functions.
        - Damages enzymes.
        - Damages DNA (promoting mutagenesis).
    - Increases inflammation and fibrogenesis.
    - Increases stress by damaging cells.
    - Promotes fatty liver.
    - Contributes to hangovers.

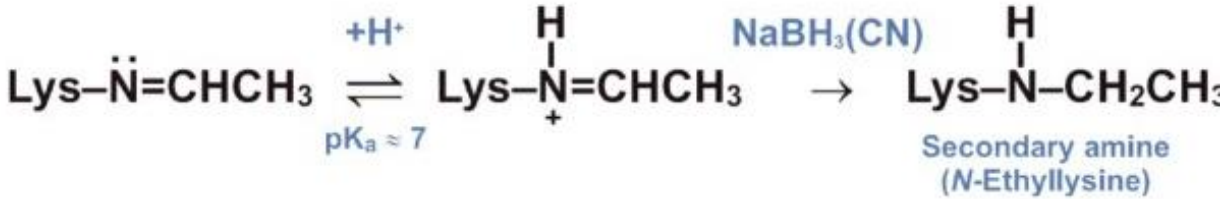
Formation of the Acetaldehyde Adduct

Non-Reduced adduct



Reduced adduct

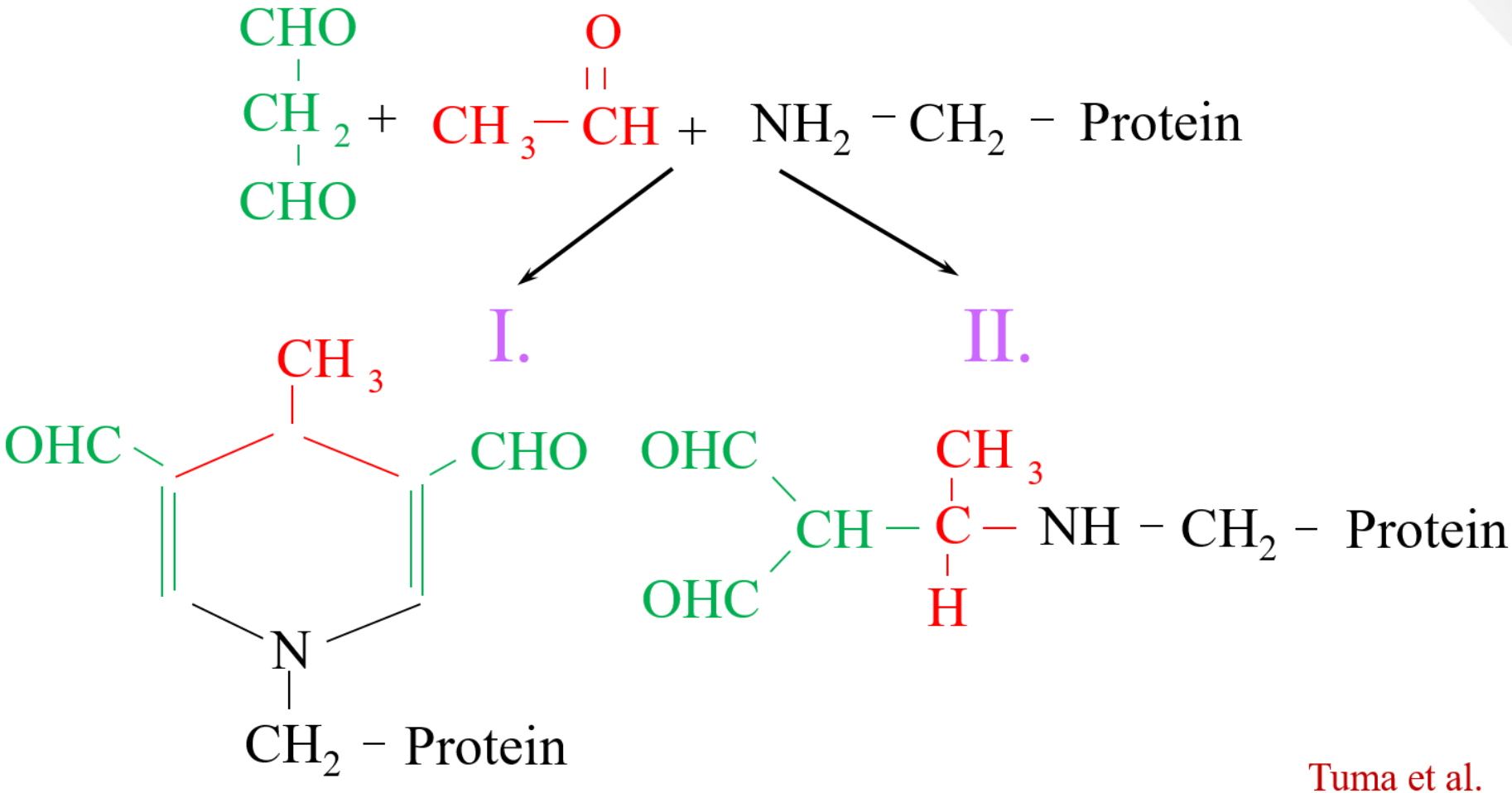
- **N-ethyl lysine (NEL)**



Malondialdehyde-Acetaldehyde (MAA)

- **Where does it come from?**
  - Generated from a reaction between malondialdehyde, acetaldehyde and protein(s).
  - MAA is found in any tissue that is undergoing stress and inflammation.
  - Only a small amount of acetaldehyde is needed to promote the formation of the MAA adduct.
  - Once formed this adduct is extremely stable and impossible to breakdown into individual components.
- **Toxic effects of MAA**
  - Causes additional stress to cells.
  - Inactivates protein function.
  - Forms adducts that generate immune responses.
  - Increases inflammation.

Formation of the MAA Adduct



Tuma et al.
Hepatology

Why Do We Care?

- Breakdown of both acetaldehyde and malondialdehyde occur normally in the body with minimal side effects daily.
- However, too much of something is always bad for business.
- When concentrations of these aldehydes increases, cells die or become functionally challenged.
    - Increase in aldehyde levels is the precursor to several diseases.
    - They can bind proteins, forming **adducts**, which can be recognized by the immune system as foreign (even though they are normal proteins in your body)
        - Autoimmune disease could be initiated.

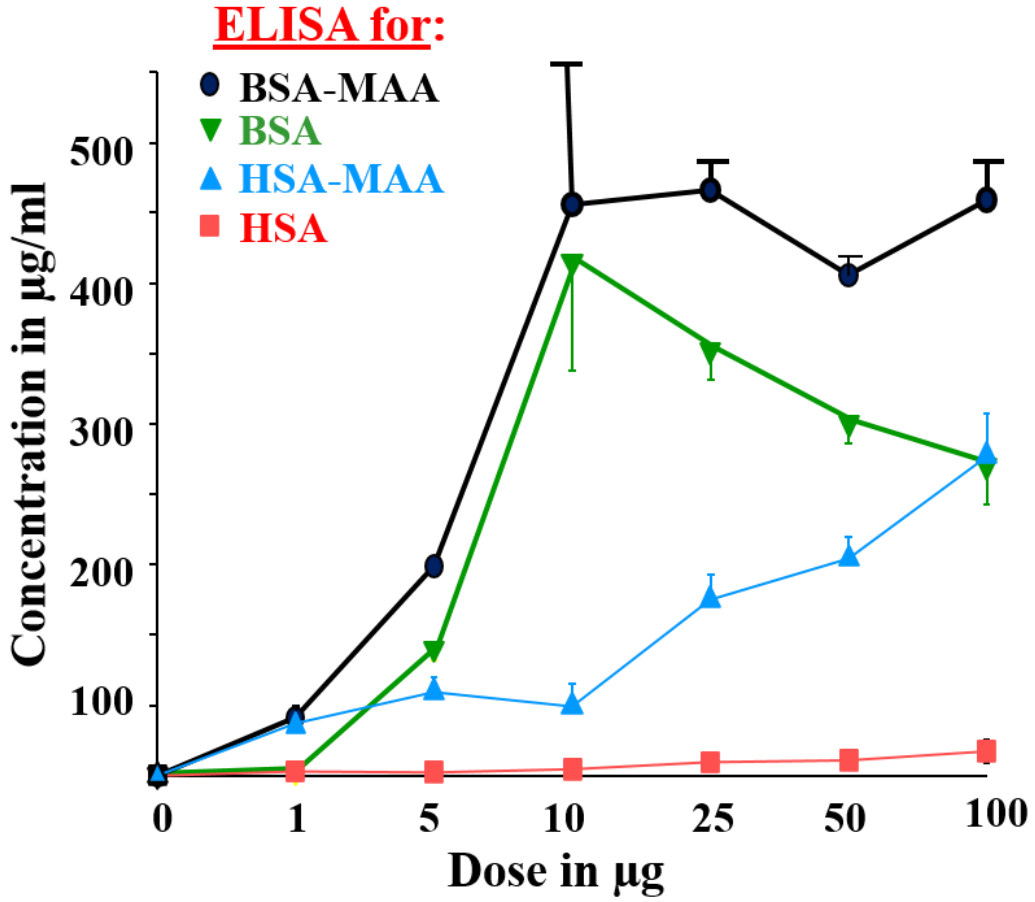
Protein Modifications (ADDUCTS)

- **In biology, normal proteins in the body can become altered by certain chemicals changing their biological function.**
- **WE TERM THESE ADDUCTS**
- **Properties of adducts**
    - Covalent and generally enzymatic modification of proteins following protein biosynthesis
    - Occur on the amino acid side chains or at the protein's C- or N- termini
    - Consequences of non-enzymatic modification
    - Most sites where this occurs need a functional group that serves as a nucleophile

Immune Response to MAA Modified Bovine Serum Albumin

- Original intent was to determine if we could produce an immune response in mice
  - So, immunized mice with MAA-modified bovine serum albumin
    - Freund's complete adjuvant at week 1
    - Freund's incomplete adjuvant at weeks 3 and 5
  - This was the intent but an error occurred
    - We immunized mice intraperitoneally with different concentrations of BSA or BSA-MAA once a week for 5 weeks, but no adjuvant
  - By ELISA, we evaluated the antibody to:
    - BSA, BSA-MAA: The immunizing antigens
    - HSA, and HSA-MAA: Response to MAA

Immune Response to MAA Modified Bovine Serum Albumin (No Adjuvant)



Antibody response of mice immunized for 5 weeks with 0, 1, 5, 10, 25, 50 and 100 µg of bovine serum albumin (BSA)-MAA. Antiserum was tested by ELISA for antibody activity to BSA, BSA-MAA, Human serum albumin (HSA), and HSA-MAA. Results are expressed as the means ± SE of the concentration in µg/ml from 5 mice/group.

Model of MAA-Induced Autoimmune Hepatitis (MIAH)

- **The data above demonstrated that the modification of foreign proteins could induce immune responses to that foreign protein in the absence of adjuvant**
- **Therefore, we hypothesized that the modification of mouse liver cytosols with MAA will result in the development of an autoimmune response to the cytosolic (self) proteins, and would mimic the parameters observed in alcoholic liver disease.**
- **This model has been termed the MAA-Induced Autoimmune Hepatitis (MIAH) model**

Conclusions

- **Using self proteins modified with MAA, and no adjuvants we were able to:**
  - **Break immune tolerance to the self protein**
  - **Produce antibody and T cell responses to self proteins and MAA**
  - **Develop a low-grade autoimmune liver disease as evidenced by:**
    - **AST/ALT levels**
    - **Inflammatory infiltrates**
- **MAA may be involved in the development and/or progression of alcoholic liver disease**

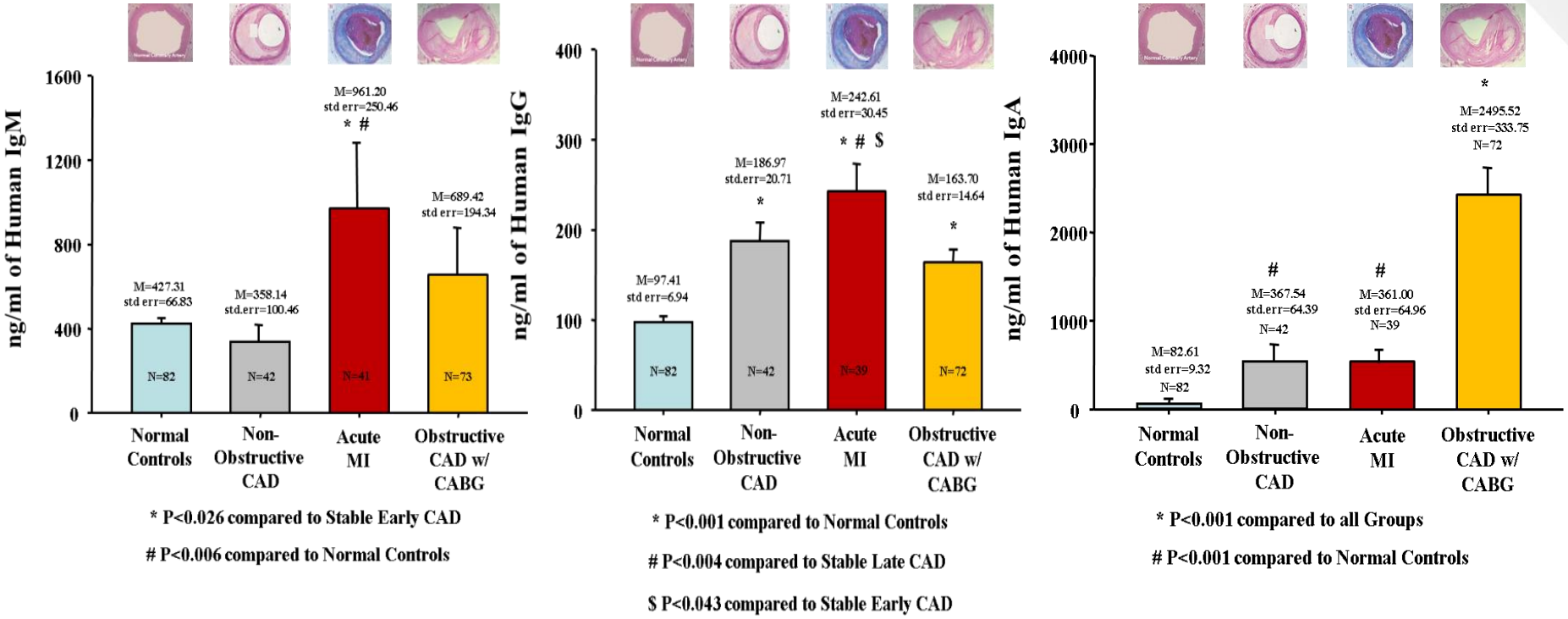
Biological Relevance of Aldehyde Adducts

- Cardiovascular Disease
- Inflammatory Bowel Disease (IBD)
- Smoking related diseases
- Rheumatoid arthritis
- Alcoholic liver disease

MAA and Cardiovascular Disease

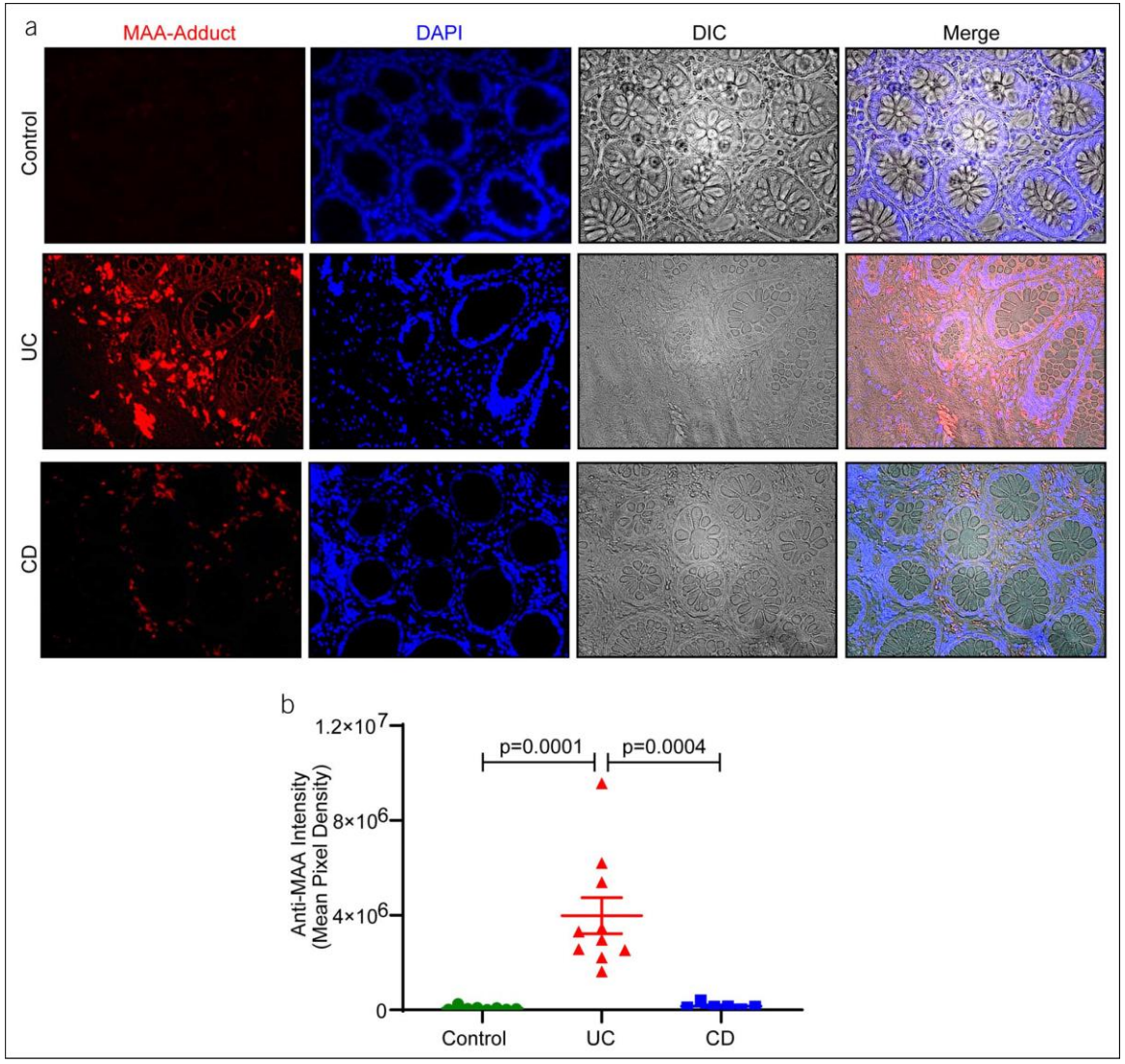
Confocal Microscopy of MAA in atheroma. Left Panel = Mouse IgG isotype control; Right Panel = Mouse anti-MAA staining with Cy3 reporter (80X).

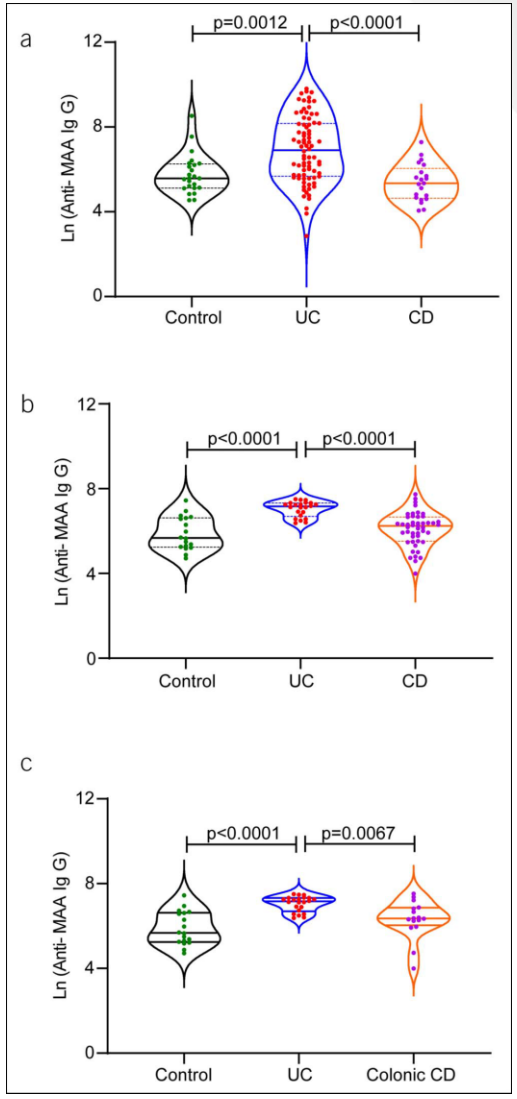
MAA and Cardiovascular Disease



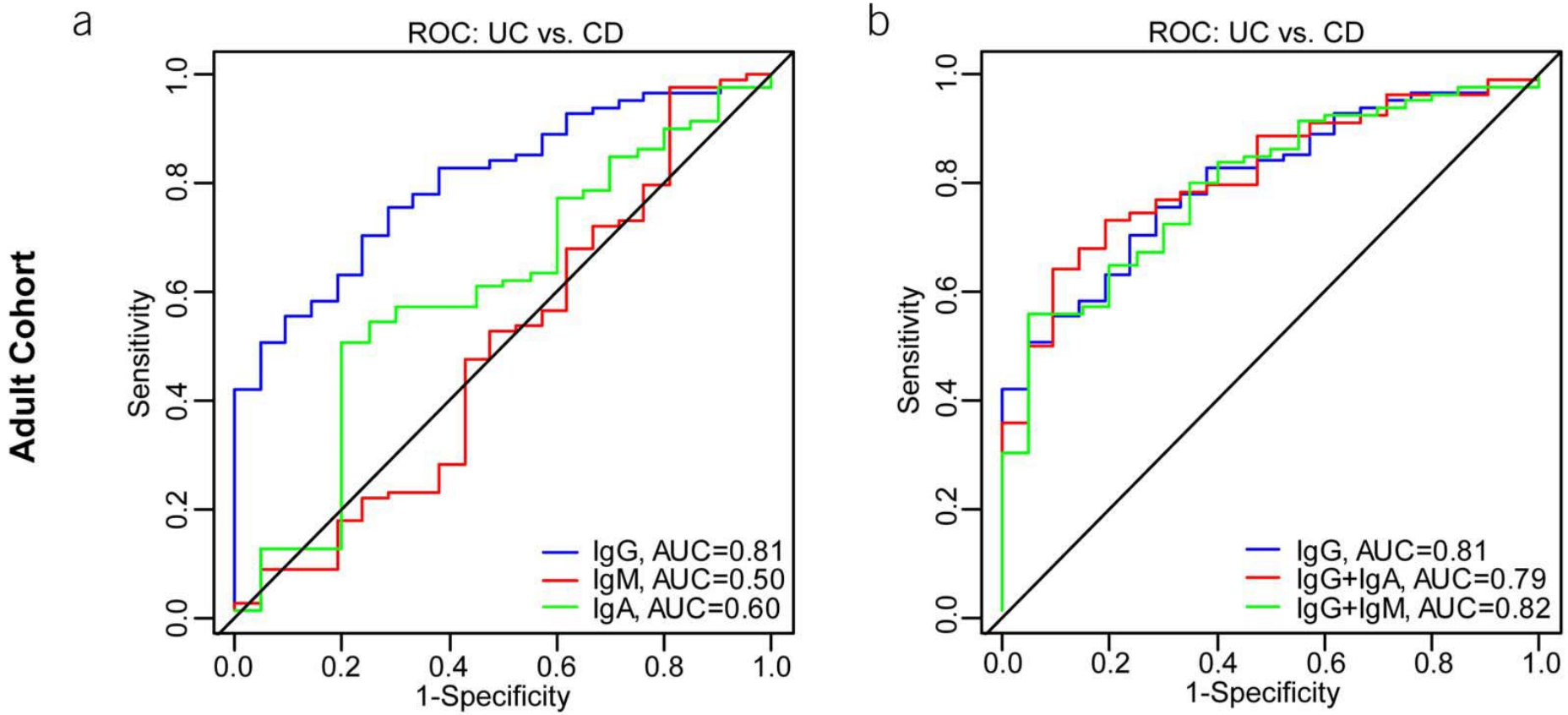
Serum Concentrations of IgG, IgM, and IgA Antibody to MAA in Normal Controls as Compared to Individuals with Known Coronary Artery Disease (CAD)

MAA and IBD


a
MAA-Adduct
DAPI
DIC
Merge
Control
UC
CD
b
Anti-MAA Intensity (Mean Pixel Density)
1.2×10^7
8×10^6
4×10^6
0
p=0.0001
p=0.0004
Control
UC
CD


a
Ln (Anti- MAA Ig G)
p=0.0012
p<0.0001
Control
UC
CD
b
Ln (Anti- MAA Ig G)
p<0.0001
p<0.0001
Control
UC
CD
c
Ln (Anti- MAA Ig G)
p<0.0001
p=0.0067
Control
UC
Colonic CD

MAA and IBD


Adult Cohort
a
ROC: UC vs. CD
Sensitivity
1-Specificity
0.0
0.2
0.4
0.6
0.8
1.0
IgG, AUC=0.81
IgM, AUC=0.50
IgA, AUC=0.60
b
ROC: UC vs. CD
Sensitivity
1-Specificity
IgG, AUC=0.81
IgG+IgA, AUC=0.79
IgG+IgM, AUC=0.82

MAA and Rheumatoid Arthritis

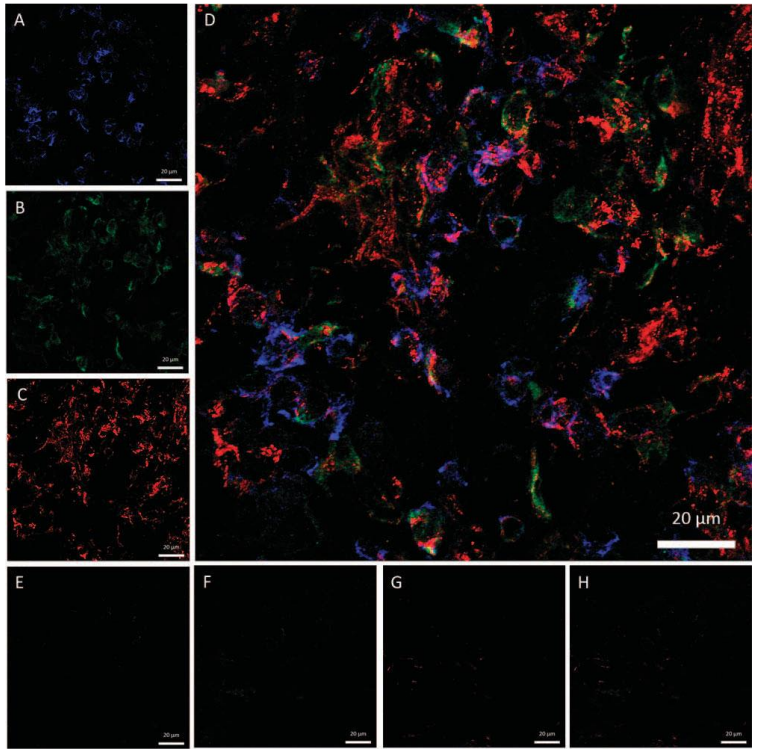


Figure 1. Confocal colocalization images of malondialdehydeacetaldehyde (MAA) and citrullinated proteins in synovial joint tissue from patients with rheumatoid arthritis (RA) and patients with osteoarthritis (OA). Frozen joint sections from 3 RA patients and 3 OA patients were stained for the presence of MAA, citrullinated proteins, and CD45 using an IgG polyclonal rabbit anti-MAA antibody,IgM monoclonal mouse anticitrulline antibody, and IgG2b anti-rat CD45

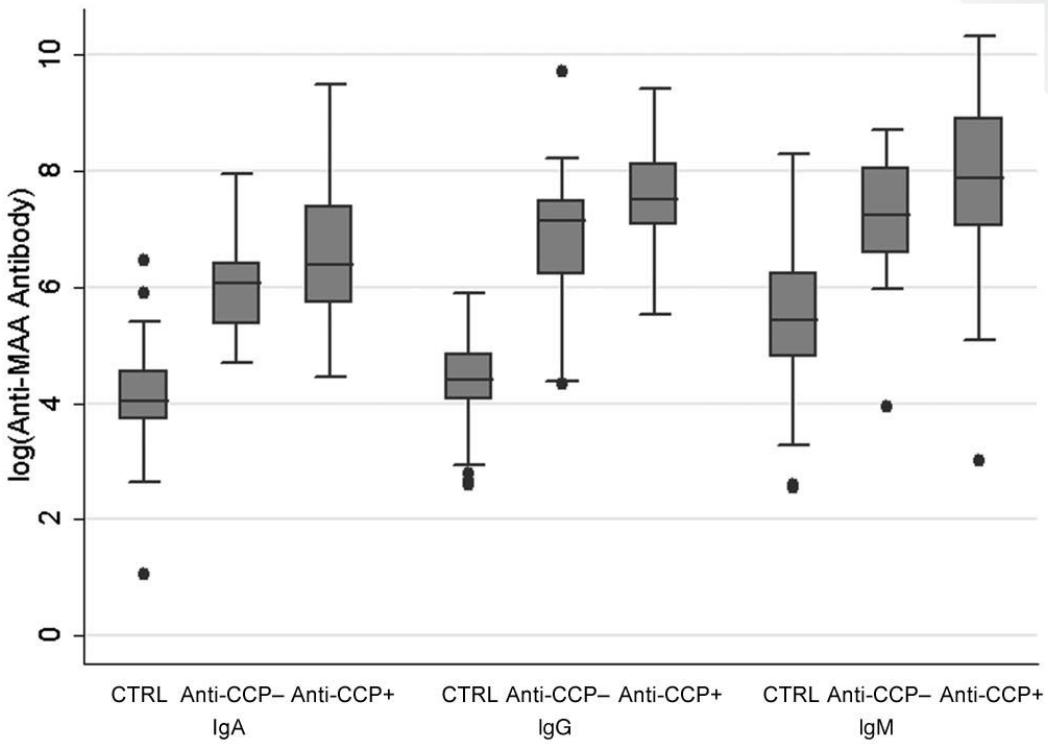
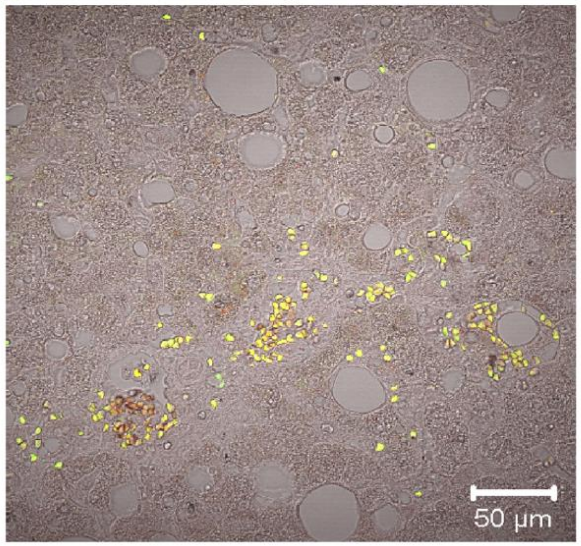
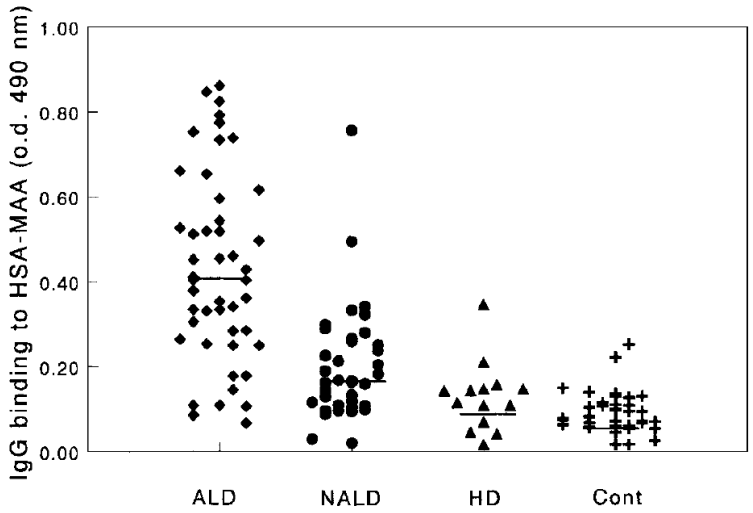


Figure 2. Differences in anti–malondialdehyde-acetaldehyde (anti-MAA) antibody isotype concentrations between rheumatoid arthritis (RA) patients and healthy controls. Controls (n 80) were matched to RA patients (n 80) based on age, sex, race, and smoking status, with RA patients stratified as anti–cyclic citrullinated peptide (anti-CCP) positive or negative. Data are shown as box plots. Each box represents the 25th to 75th percentiles. Lines inside the boxes represent the median. Lines outside the boxes represent the 10th and 90th percentiles. Symbols represent outliers.

MAA and Alcoholic Liver Disease

- **MAA adducted proteins act as antigens and antibody responses are formed in the body to both the MAA and the carrier proteins modified.**
  - **Both have been discovered in alcoholic liver diseased patients.**





- **MAA adducted proteins bind scavenger receptors on cells and can be internalized.**
- **MAA adducted proteins generate T-cell proliferative responses.**
- **MAA adducted proteins cause cells to release pro-inflammatory cytokines that aid in inflammation.**

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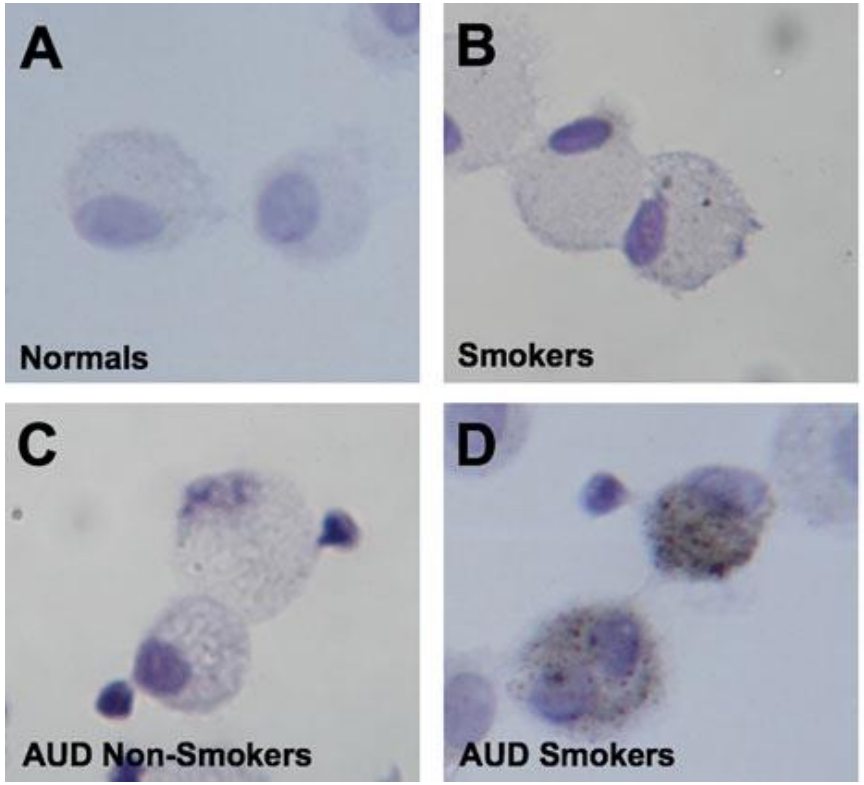
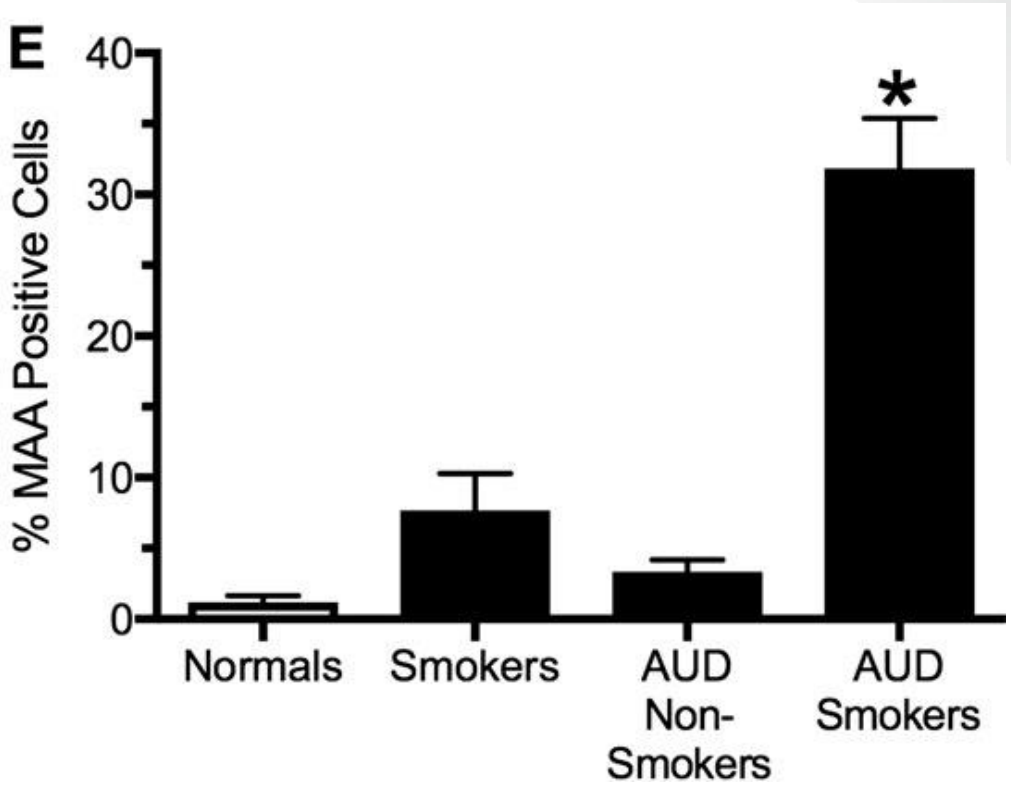
MAA in Alcohol and Smoking Disease





Immunohistochemical staining for malondialdehyde–acetaldehyde (MAA)-adducted protein. Bronchoalveolar lavage cells (mostly macrophages) from non-alcohol use disorders (AUD)/noncigarette smokers (AUD/Smoker; panel A), AUD subjects who did not smoke cigarettes (AUD/Smoker; panel B), cigarette smokers without AUDs (AUD/+Smoker; panel C), and AUD subjects who smoked cigarettes (+AUD/+Smoker; panel D) stained for MAA-adducted protein. Cells stained positive for MAA adduct were counted under microscope and calculated as % of MAA-positive cells in the total number of cells counted for each group (E). Values are presented as the mean SEM and analyzed by 1-way ANOVA with Tukey's post hoc multiple comparisons. Subject numbers were as follows: normal nonsmokers (22), smokers (22), AUD nonsmokers (20), and AUD smokers (45). *$p \leq 0.05$ versus other groups.

The Reactive Aldehyde Species (RASP) Platform

- We have tried anti-inflammatory, anti-fibrotic and anti-oxidant agents to abrogate the effects of MDA, AA and MAA in different Diseases.
    - Never with any real luck.
- Aldeyra Therapeutics has a platform that has been proven to irreversibly bind RASP and eliminate them from the system.
    - Basically what we call an “aldehyde sink.” ADX-629 is the model compound
    - Binds free acetaldehyde (AA) and malondialdehyde (MDA)
    - Appears to also bind Malondialdehyde-Acetaldehyde (MAA)
- Does this work????????

Agenda

TIME (ET)	TOPIC	PRESENTER
10:00 – 10:15 a.m.	RASP Overview	Todd C. Brady, M.D., Ph.D. *Chief Executive Officer*, Aldeyra Therapeutics
10:15 – 10:45 a.m.	RASP and Inflammation	Geoffrey M. Thiele, Ph.D. *Umbach Professor*, Internal Medicine, University of Nebraska Medical Center
10:45 – 11:15 a.m.	ADX-629 in *In vivo* and *In vitro* inflammatory models	Michael J. Duryee, MS *Instructor,* Internal Medicine, University of Nebraska Medical Center
11:15 – 11:30 a.m.	Questions	
11:30 – 11:40 a.m.	Break	
11:40 – 11:50 a.m.	Preclinical Activity of ADX-629	Adam Brockman, Ph.D. *Director of Translational Science,* Aldeyra Therapeutics
11:50 – 12:20 p.m.	Proof-of-Concept Top-Line Data	Todd C. Brady, M.D., Ph.D.
12:20 – 12:35 p.m.	New Molecules, New Indications	Adam Brockman, Ph.D.
12:35 – 12:55 p.m.	Questions	
12:55 – 1:00 p.m.	Concluding Remarks	Todd C. Brady, M.D., Ph.D.

Evaluation of ADX-629 in *In vitro* and *In vivo* inflammatory models

Michael J. Duryee, MS.
Department of Internal Medicine
Division of Rheumatology and Immunology

University of Nebraska Medical Center

Models to Test Hepatic Inflammation

- **Cell lines**

  Immortalized cells taken from the livers of animals or humans and grown in culture.

- **Primary cells**

  Cells removed from the livers of animals or humans and grown in culture.

- **Animals**

  Feeding ethanol and looking at outputs.

- **Humans**

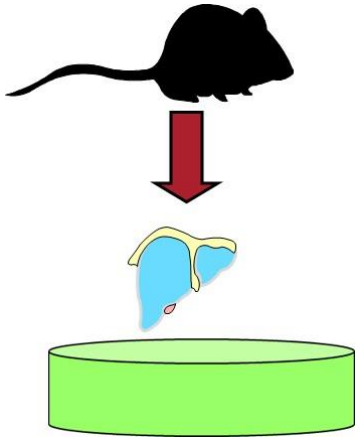
  Determining severity of liver disease from ethanol and drawing conclusions.

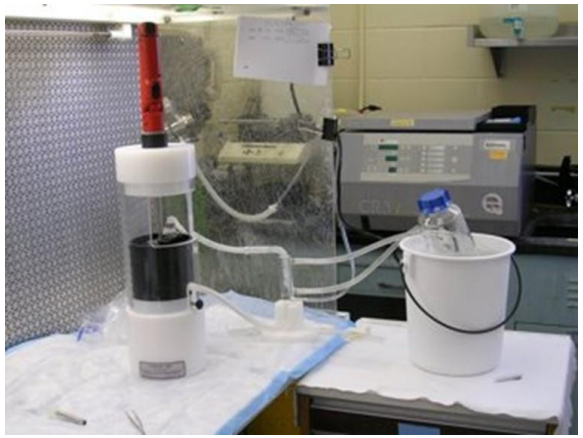
Wouldn’t it be great if there was a model that could eliminate the caveats we have with these systems.

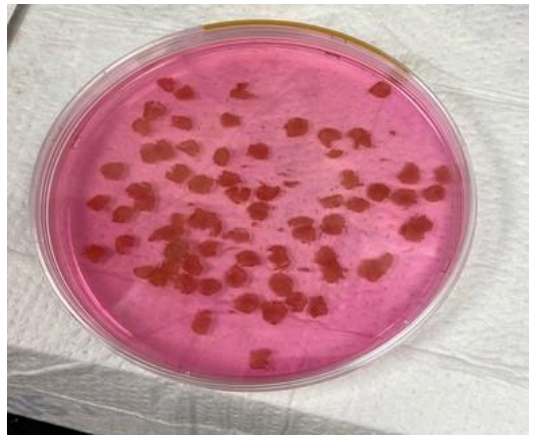
Background on Precision Cut Liver Slices

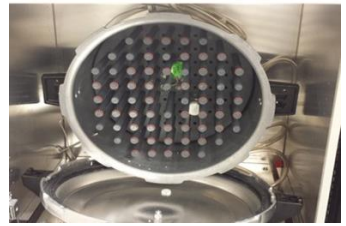
- ***in vivo*** **studies were expensive and cumbersome**
- ***in vitro*** **studies were difficult as:**
  - **Isolated hepatocytes are no longer hepatocytes after about 8 hours of culture. No albumin, ADH**
  - **Hepatocyte cell lines (even transfected) do not behave like hepatocytes *in vivo***
  - **Artificially add metabolites to initiate responses as the ethanol is not metabolized**
- **Model in the literature using Precision Cut Liver Slices**
  - **Maintains cellular integrity for 96 hours**
  - **Maintains cellular function**
  - **Metabolizes ethanol**
  - ***ex vivo/in vitro*** **model**

Precision Cut Liver Slices (PCLS)





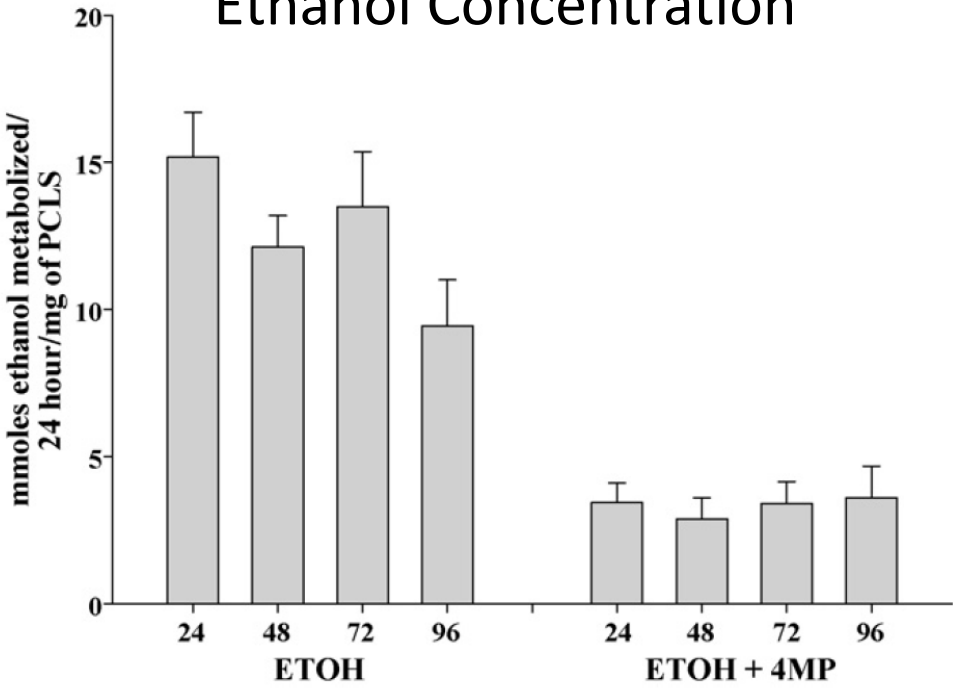




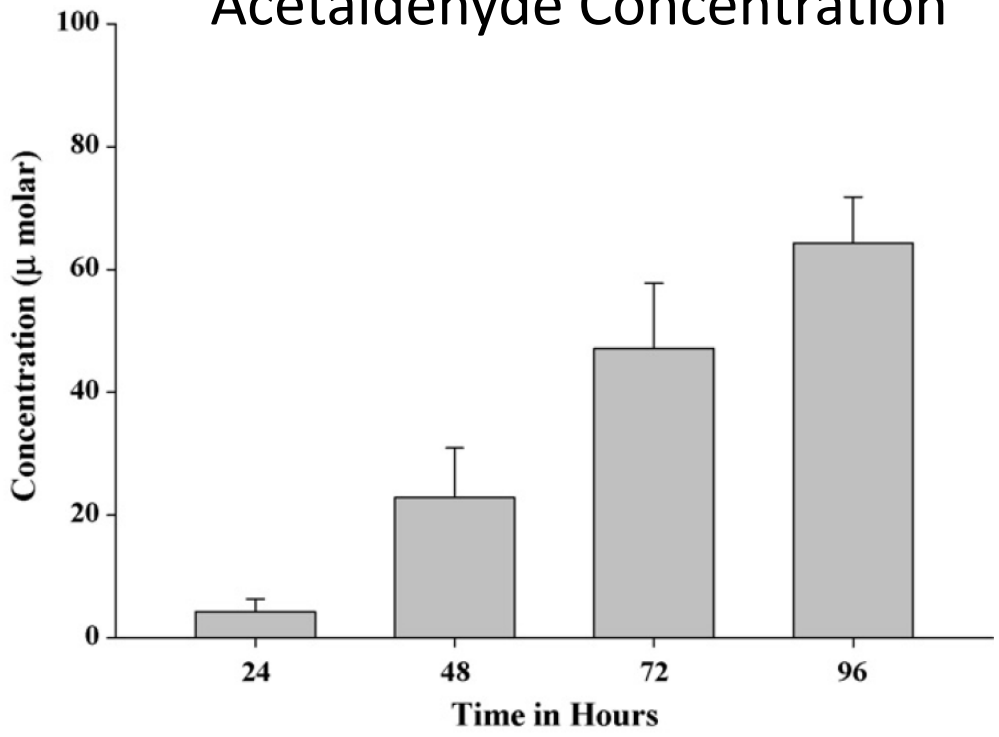
- **Livers are removed and placed on a V7 preservation buffer.**
- **Cylindrical tissue cores (8 mm) are cut using a hand-held coring tool**
- **Cores are then loaded into the Vitron tissue slicer and cut to a 250-µm thickness**
- **Slices are placed in Williams E medium containing D-glucose and gentamicin (WEGG) under 95% O2-5% CO2 (carbogen) at 37 degrees Celsius for 30 min.**
- **Slices are floated onto a titanium screen containing rollers from Vitron. These rollers are inserted into sterile 20-ml glass vials containing 1.7 ml of serum-free WEGG medium or WEGG medium containing 25 mM ethanol.**

Ethanol Metabolism by PCLSs

Ethanol Concentration



Acetaldehyde Concentration



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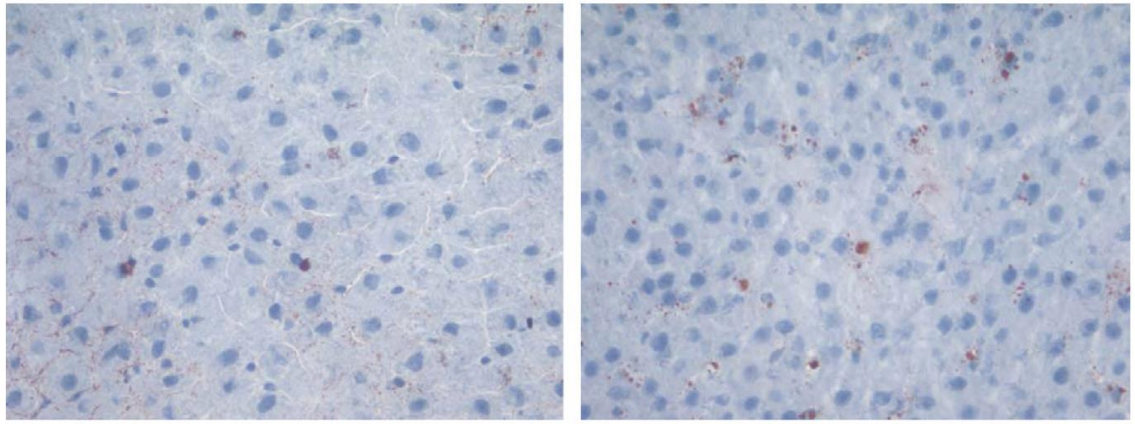
Fats Accumulate in PCLSs



(A) Time 0 Slice

(B) Control Slice 48 hour

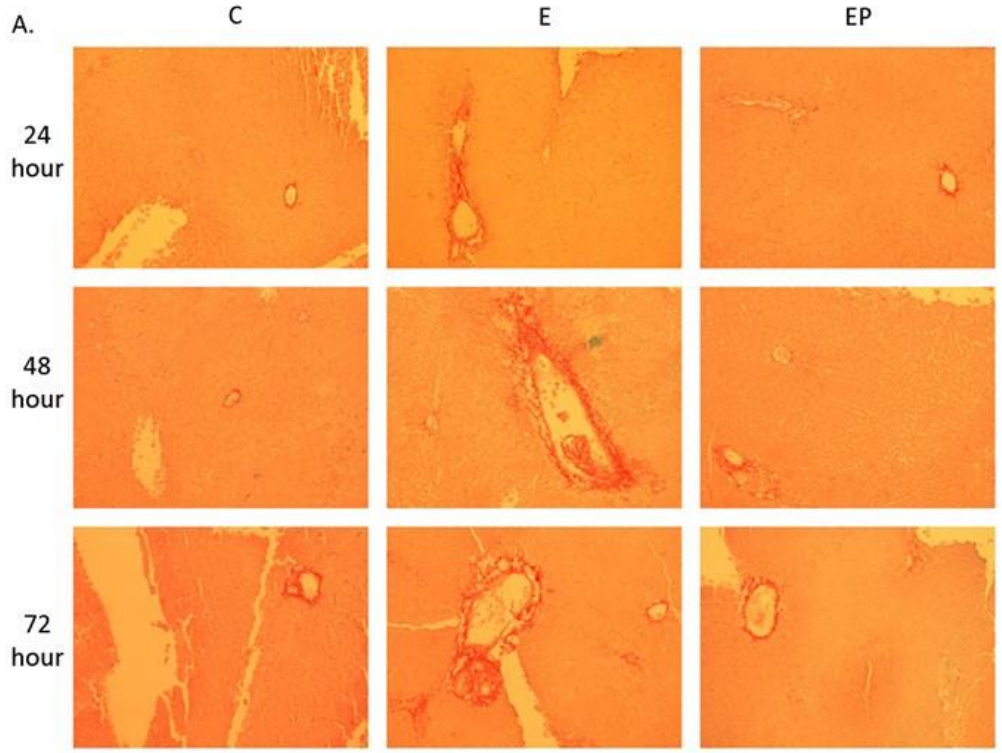
(C) Ethanol Slice 48 hour

(D) Ethanol + 4MP Slice 48 hour

Klassen et.al Biochemical Pharmacology

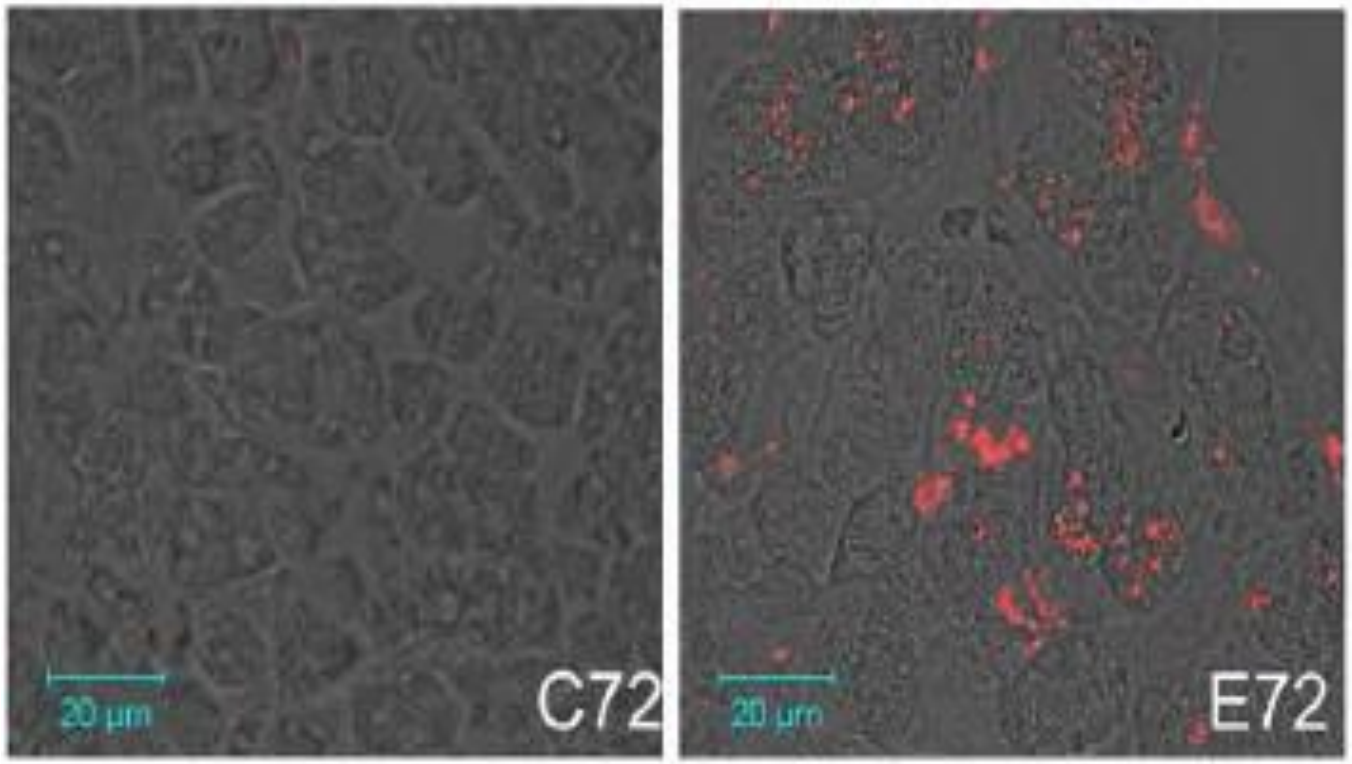
Fibrosis is Induced in PCLSs

Sirius Red Stain



Schaffert et.al AJP Gastointest Liver Physiol

Presence of MAA in PCLSs Exposed to EtOH



Duryee et.al AJP-Gastro Liver Physiol

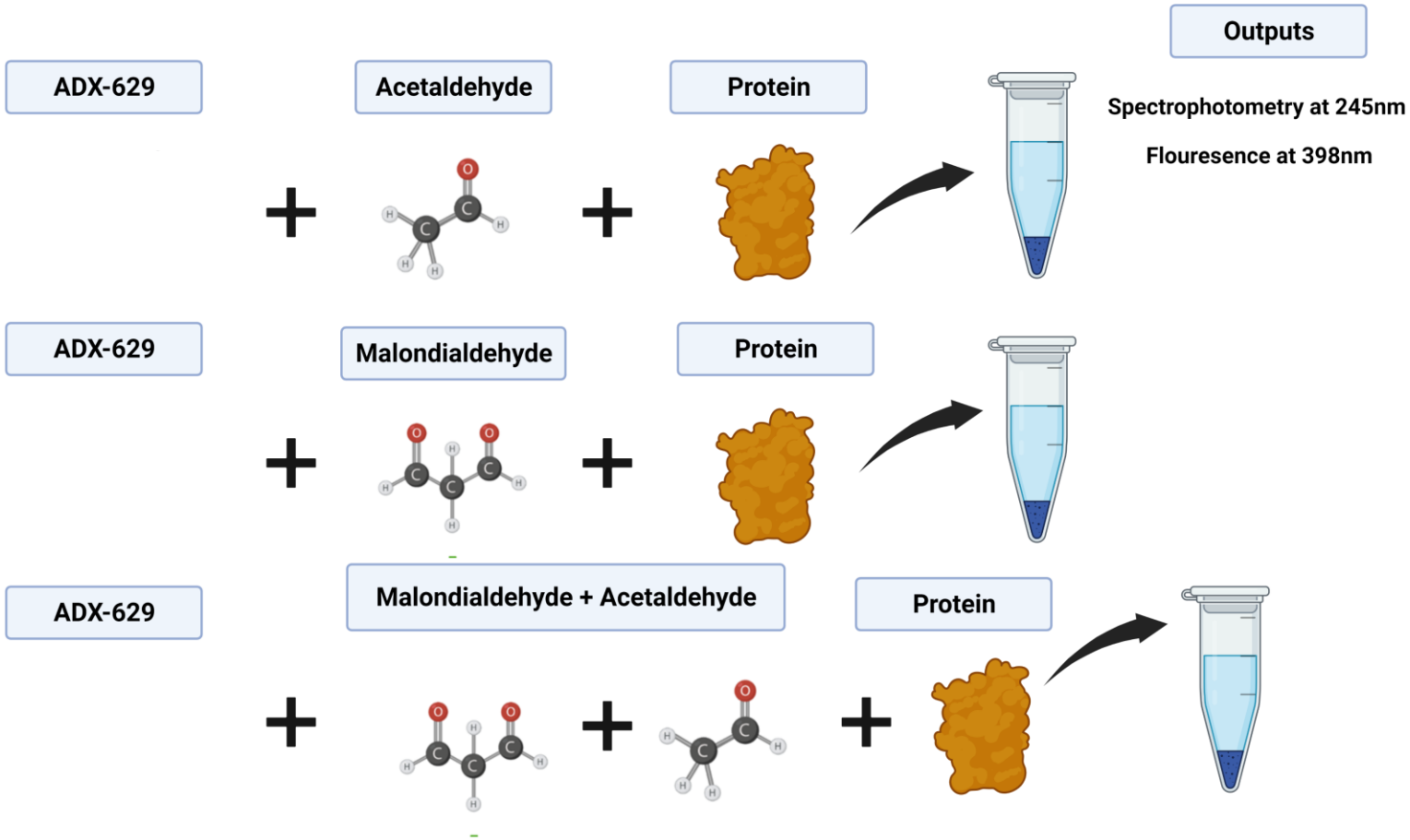
Liver Slices as a Model for RASP-Mediated Inflammation

- PCLSs are an excellent model for:
  - Evaluating the development of alcoholic fatty liver
    - The media used has no serum, fats or other factors
    - The effects are purely due to the alcohol
  - Assessing the development of alcoholic fibrosis
    - Again, nothing is added to the culture system
- The only adduct we found using antibodies was MAA
- PCLSs give the same results at 3 days in culture with EtOH as feeding the animals the Lieber-DeCarli for 5 weeks and making "fresh" PCLSs (Data not shown).
- Excellent for cutting down on the length of time for feeding and the number of rats/mice
- But, could they be used for evaluating ADX-629 scavenging of aldehydes

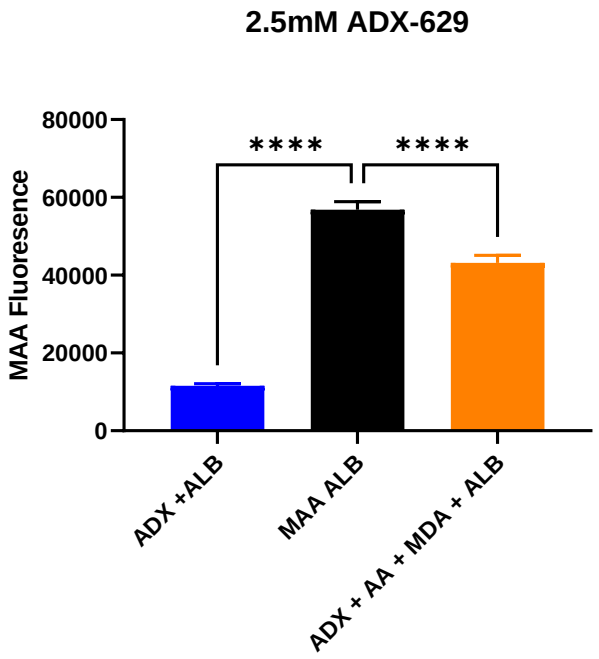
Evaluation of ADX-629

- ***In Vitro*** **experiments to determine if ADX-629 sequesters acetaldehyde, malondialdehyde or the combination of both from binding proteins.**
- **Precision cut liver slices incubated with ethanol to determine ADX-629's role in alcohol metabolism.**
    - **Mice**
    - **Human**
- ***In vivo*** **experiments feeding mice ethanol, treating with ADX-629 and looking at its ability to block the effects of aldehydes.**

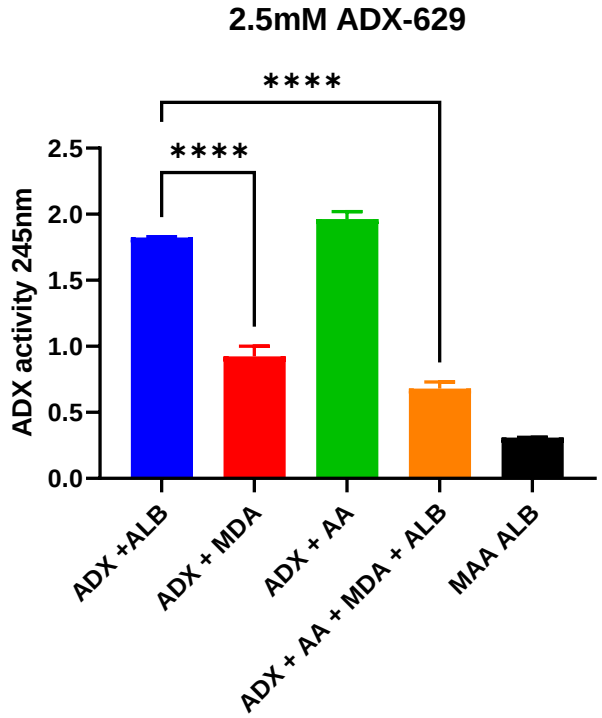
ADX-629 *In vitro* binding of RASP in a protein milieu



in vitro Inhibition of MAA Formation



ADX-629 inhibits MAA formation.

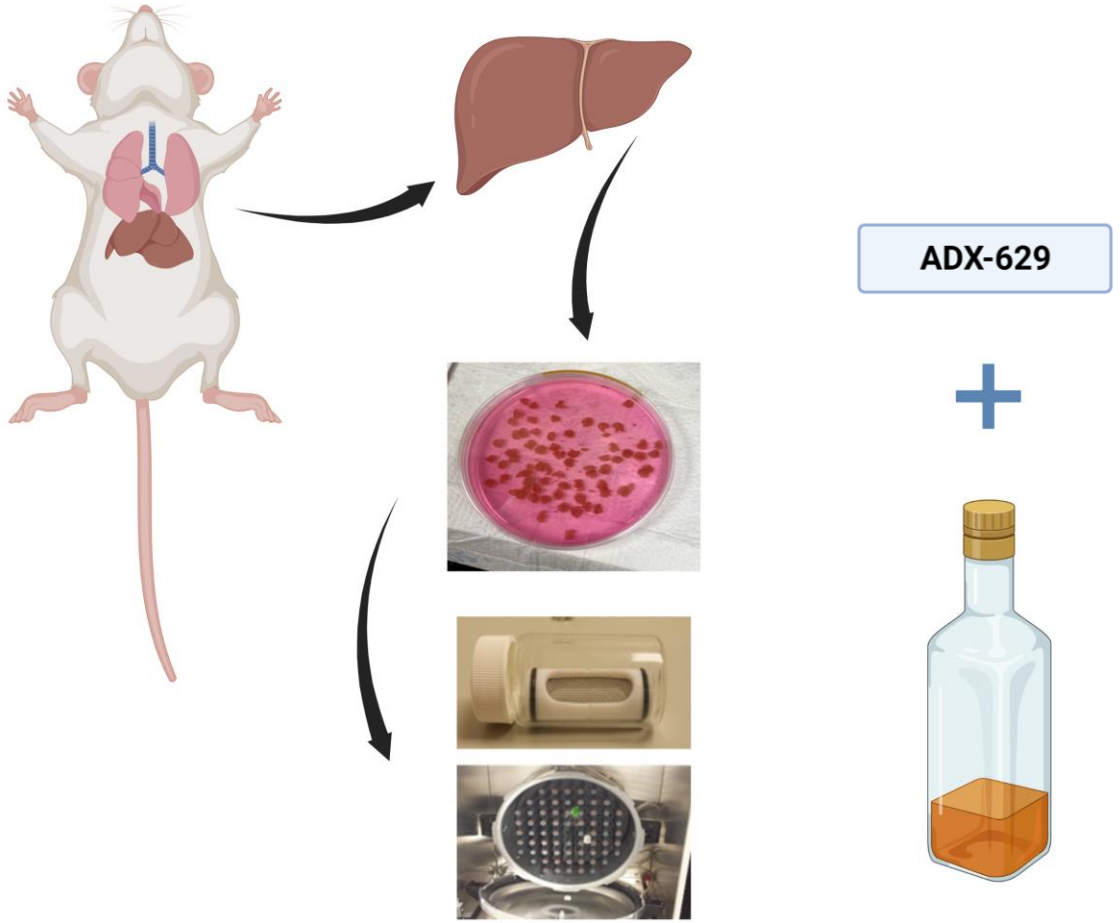


ADX-629 levels can be measured at 245nm and decrease with MDA and the components of MAA.

ADX-629 *In vitro* Study Conclusions

- **Prevents the formation of MAA on proteins as determined by Fluorescence at 398nm.**
- **Sequesters malondialdehyde preventing adduct formation as determined by analysis at 245nm.**
- **Potentially forms an adduct that renders acetaldehyde inactive from binding to proteins.**

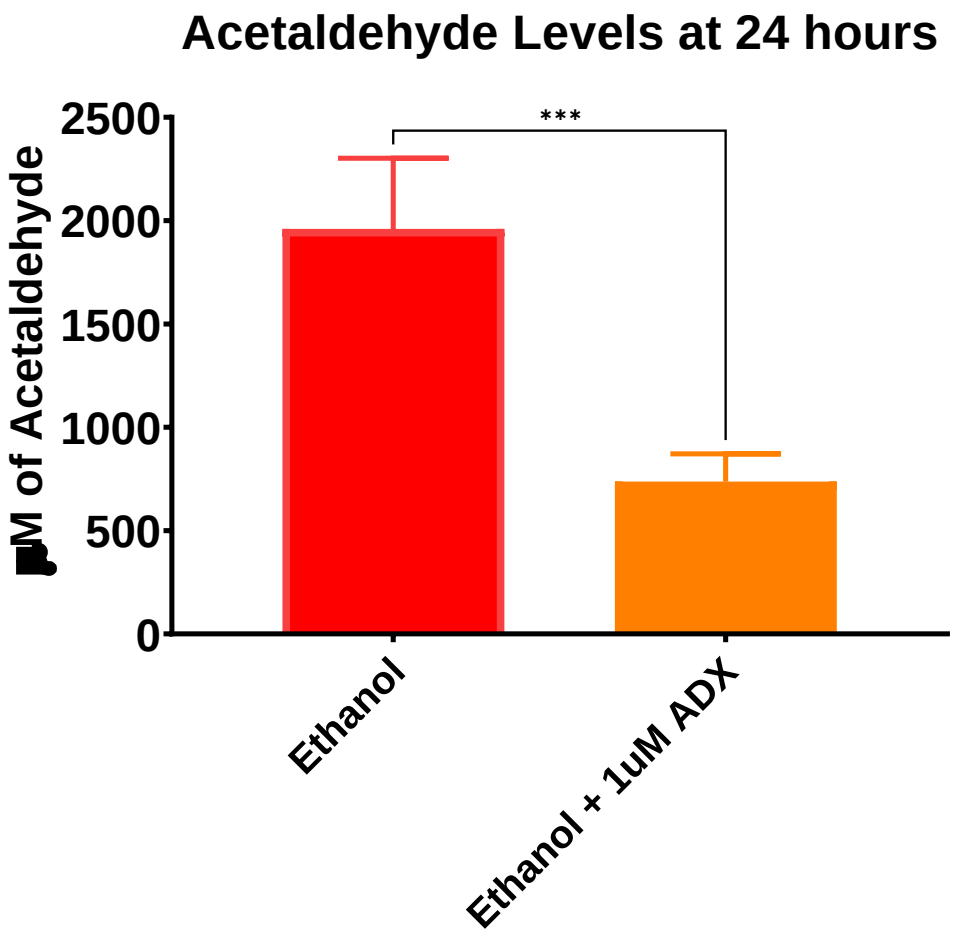
ADX-629 Treatment in Precision Cut Mouse Liver Slices

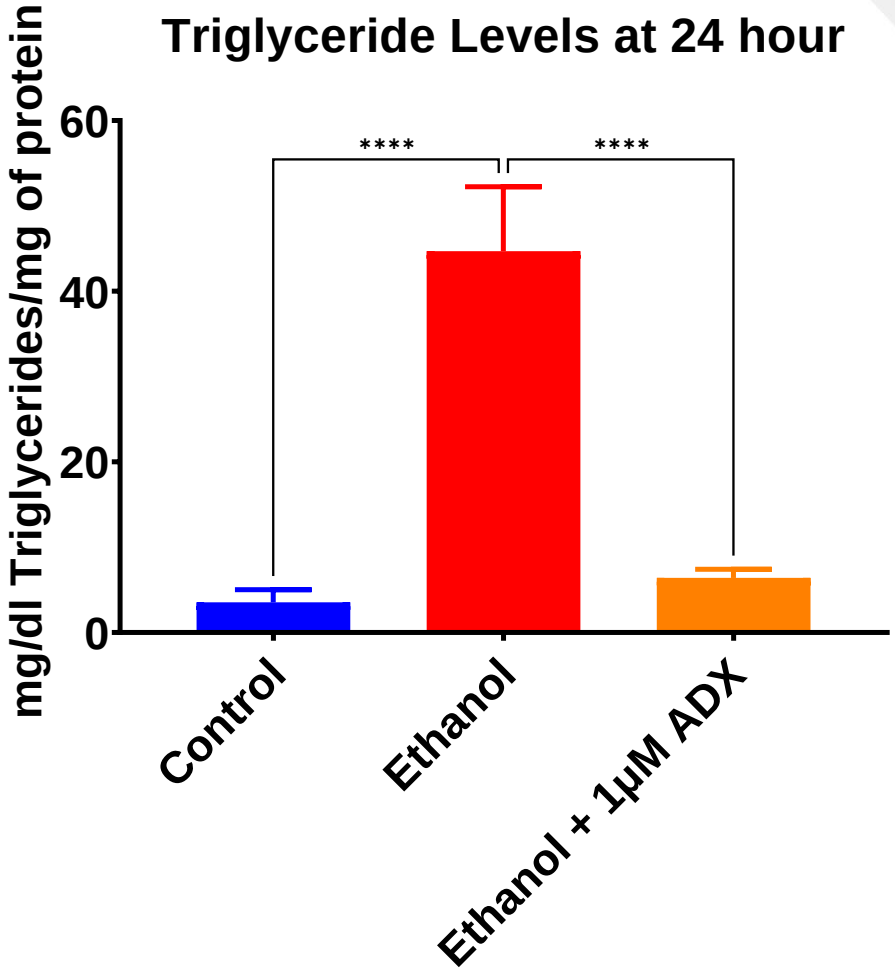


Testing for

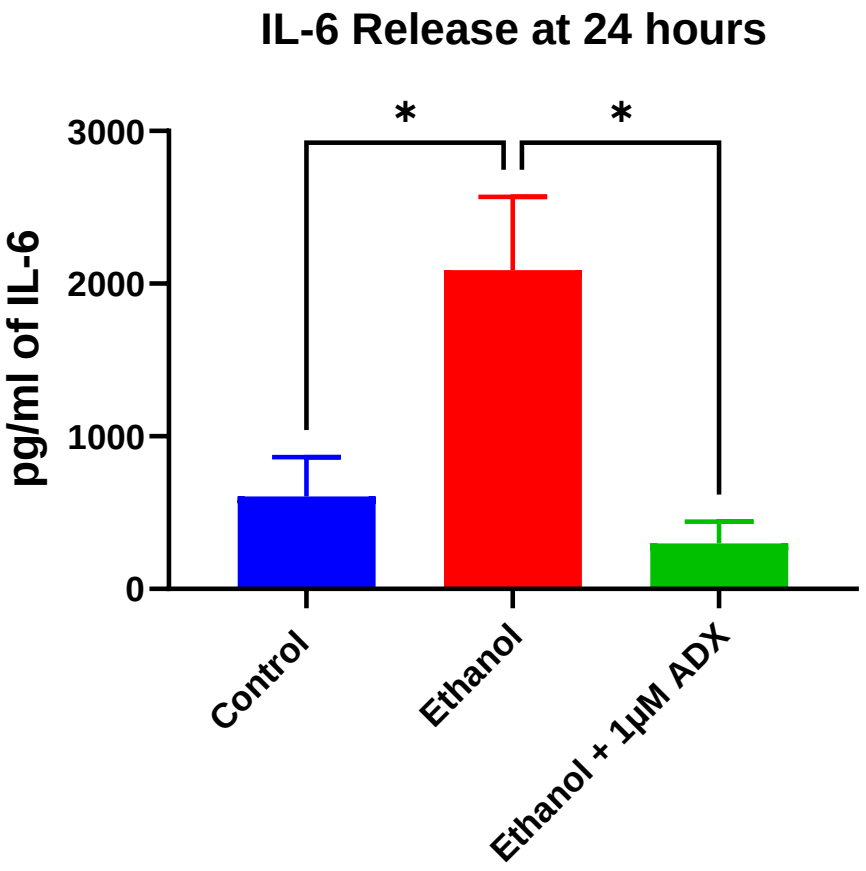
1. Acetaldehyde levels
2. Triglycerides
3. Inflammation
4. Toxicity

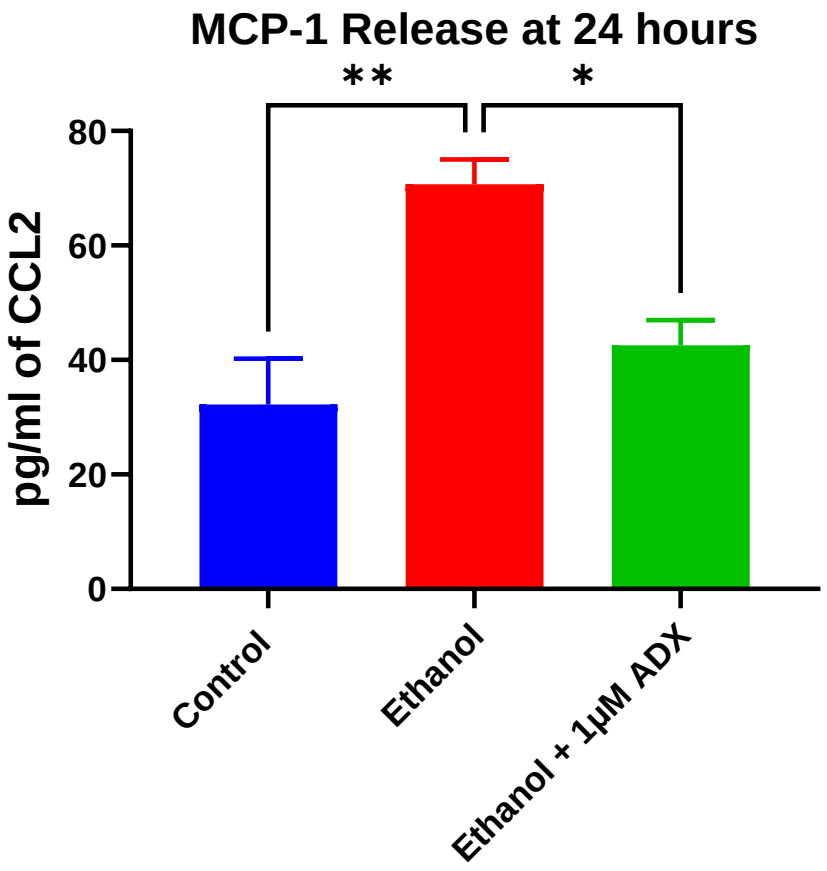
ADX-629 Reduces Acetaldehyde and Triglyceride Levels



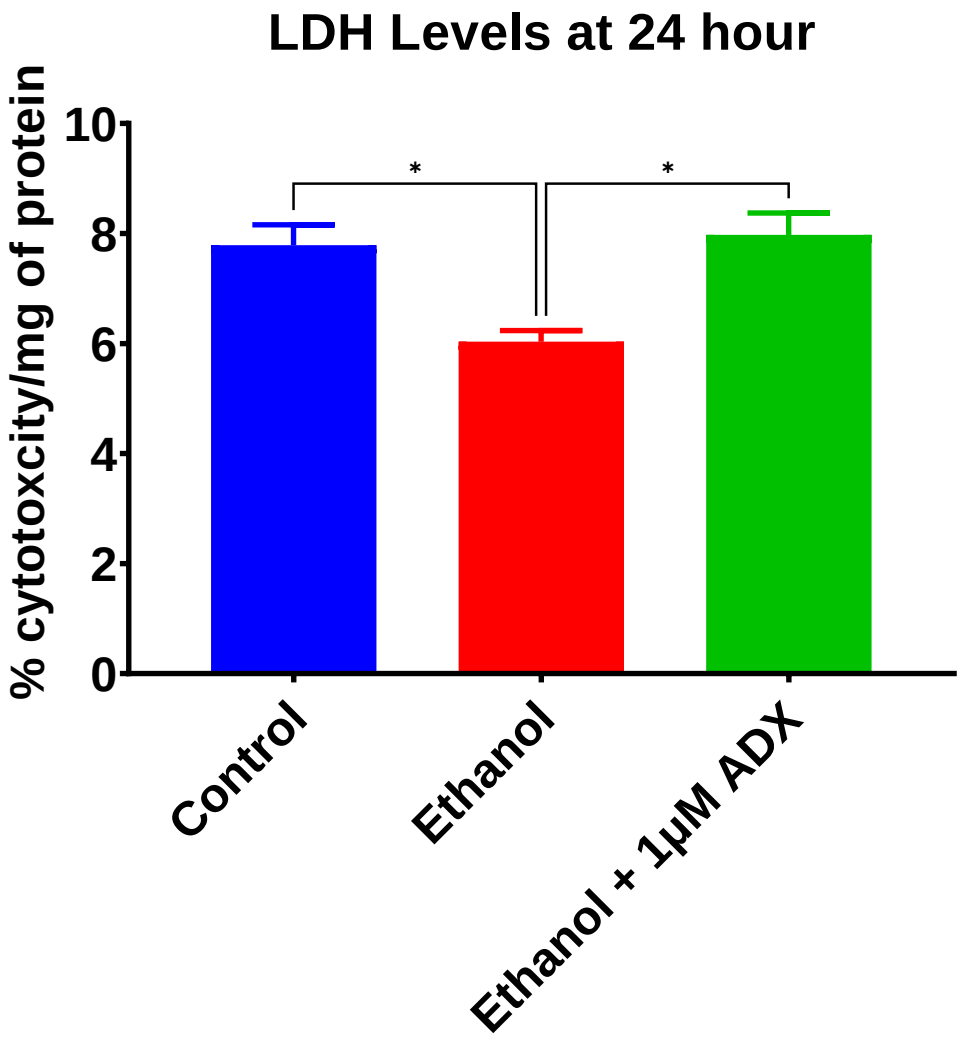


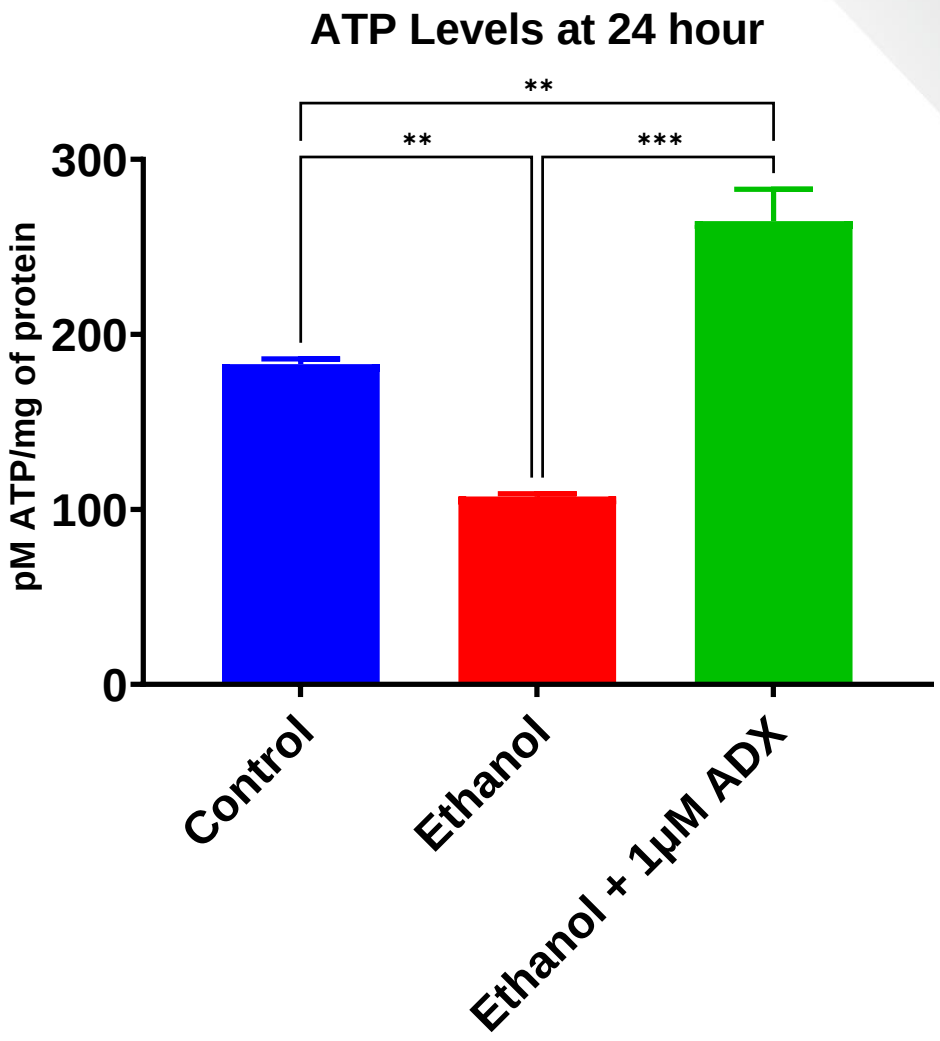
ADX-629 Stops Inflammation Induced in PCLS





ADX-629 is not Toxic in the PCLS System



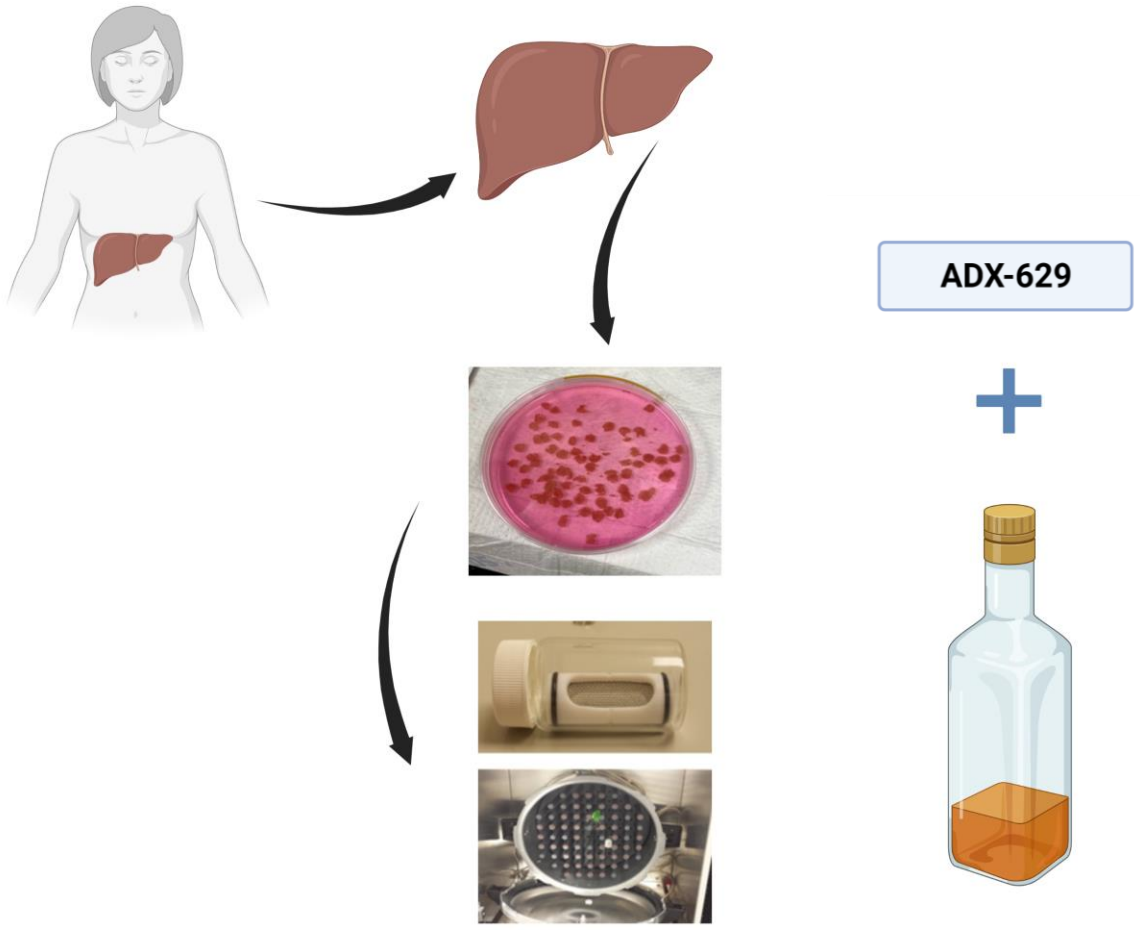


ADX-629 Treatment in Precision Cut Mouse Liver Slices: Conclusions

- **ADX-629 demonstrated great anti-inflammatory potential**
  - **Decreased acetaldehyde levels generated by ethanol metabolism**
  - **Reduced triglyceride levels**
  - **Lowered inflammatory cytokines**

- **No toxic effects were observed**

ADX-629 Treatment in Precision Cut Human Liver Slices

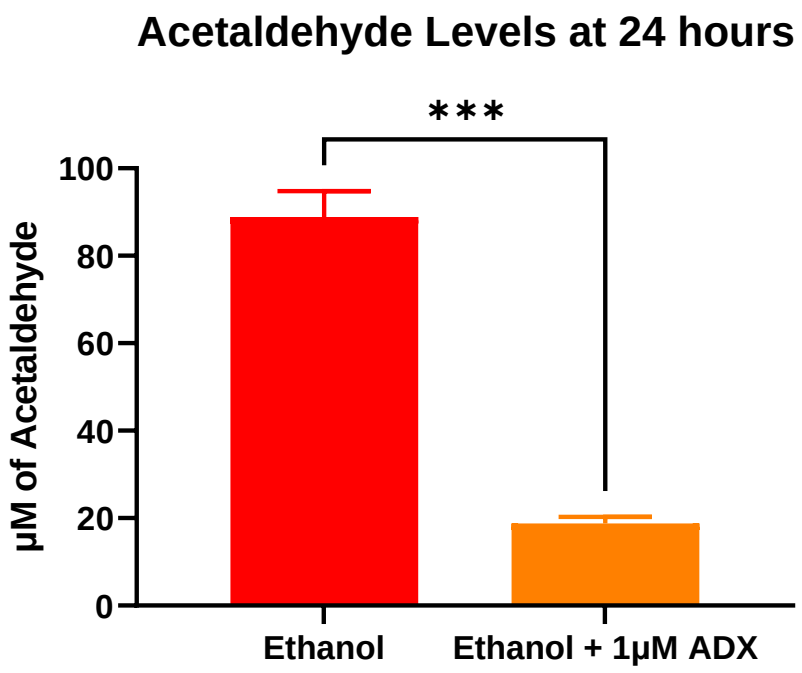


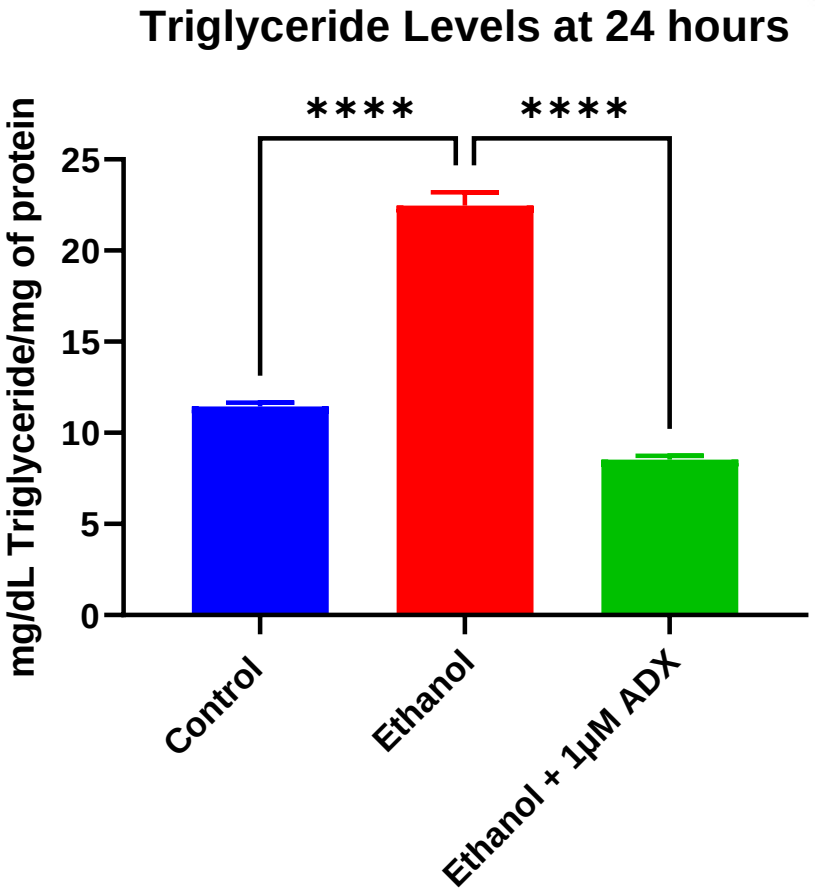
A human female liver was donated for research through the Nebraska organ recovery system. The liver was too fatty to be transplanted.

Testing for

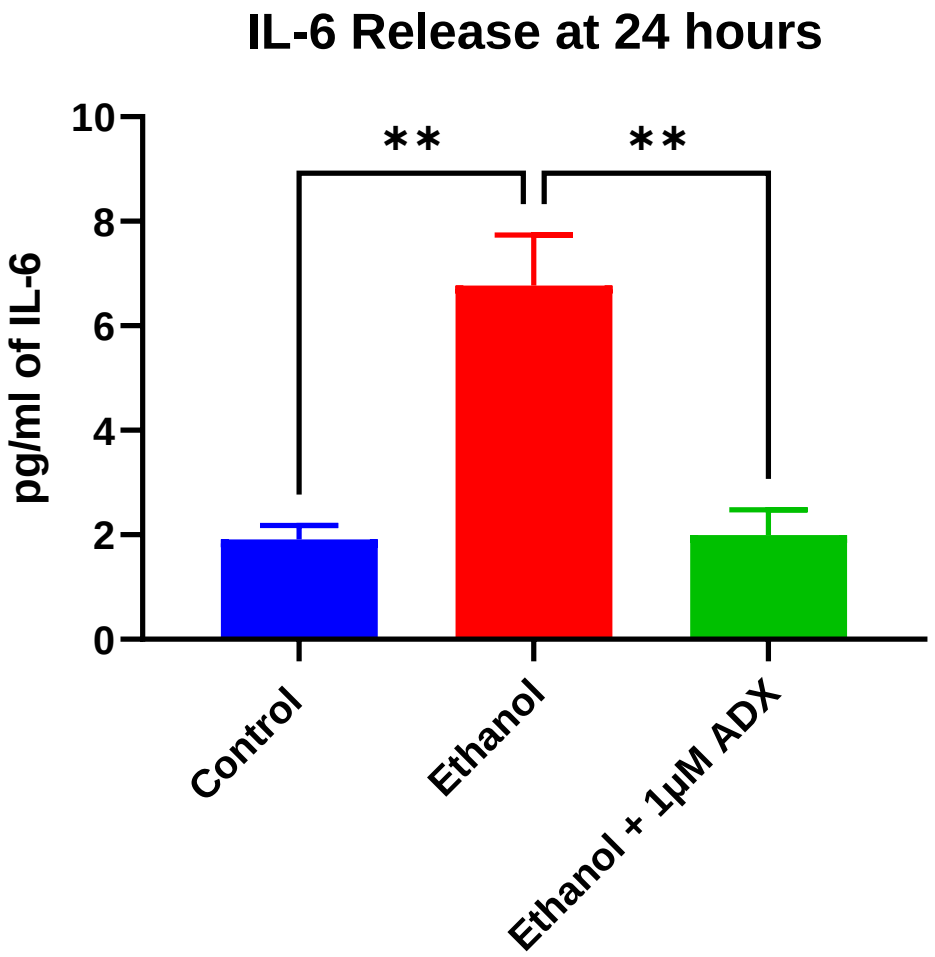
1. Acetaldehyde levels
2. Triglycerides
3. Inflammation
4. Toxicity

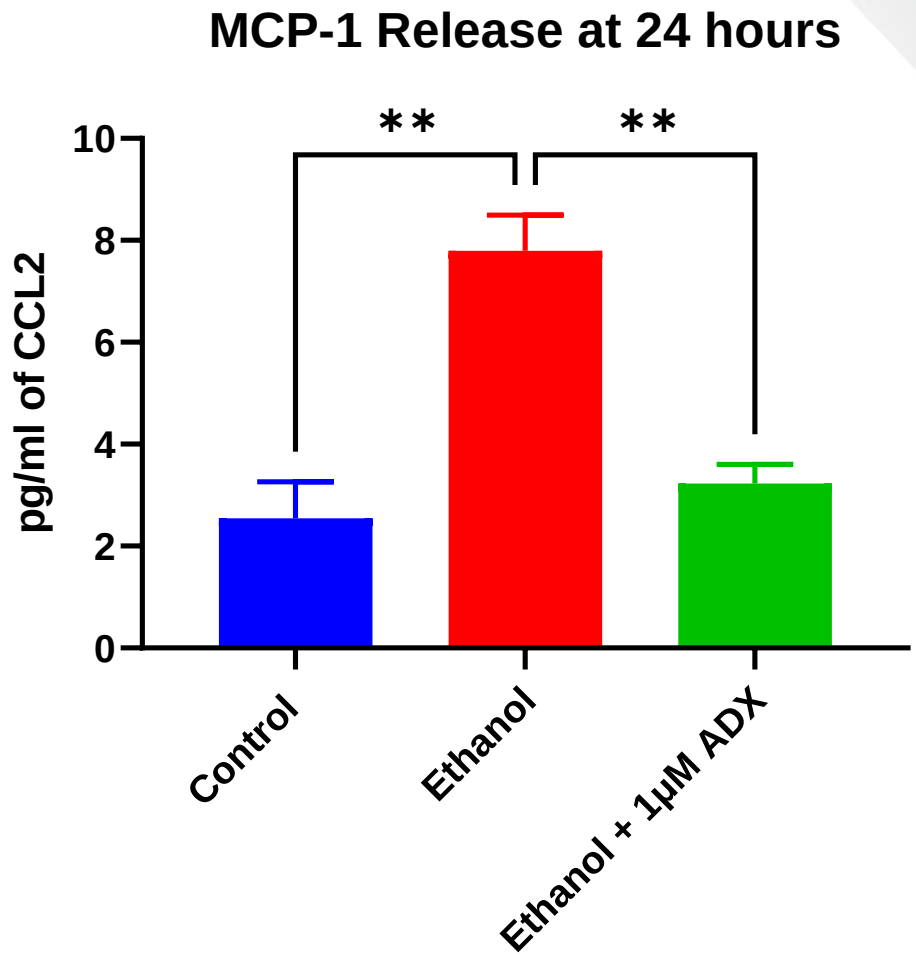
ADX-629 Reduces Acetaldehyde and Triglyceride Levels



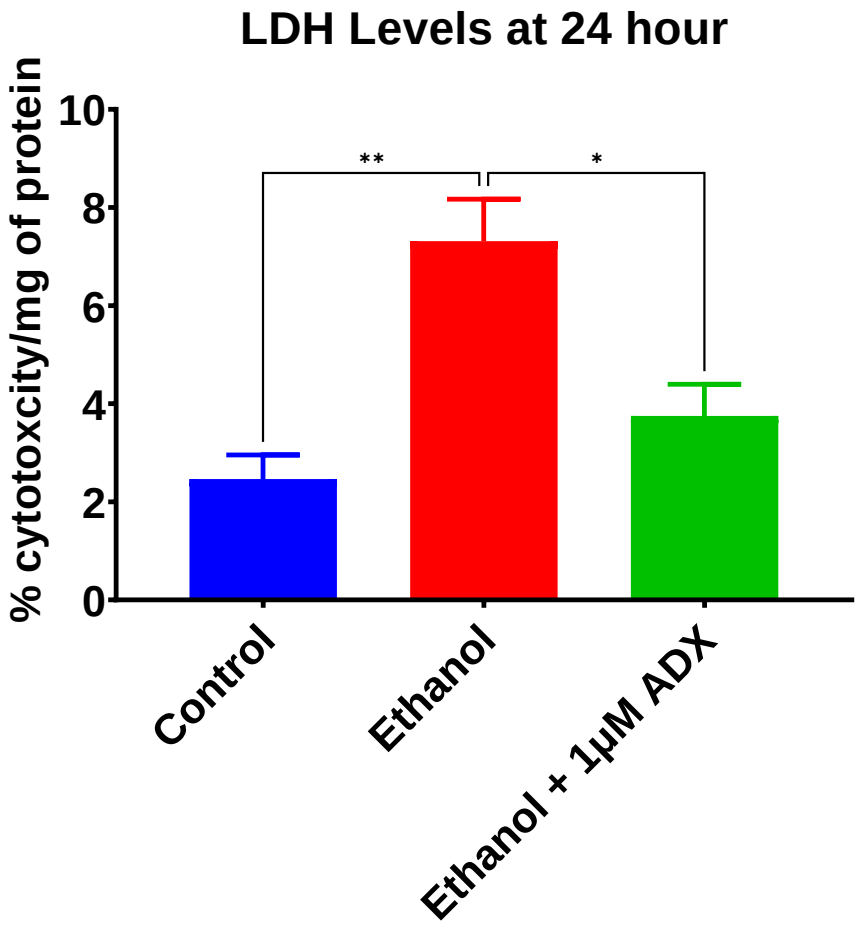


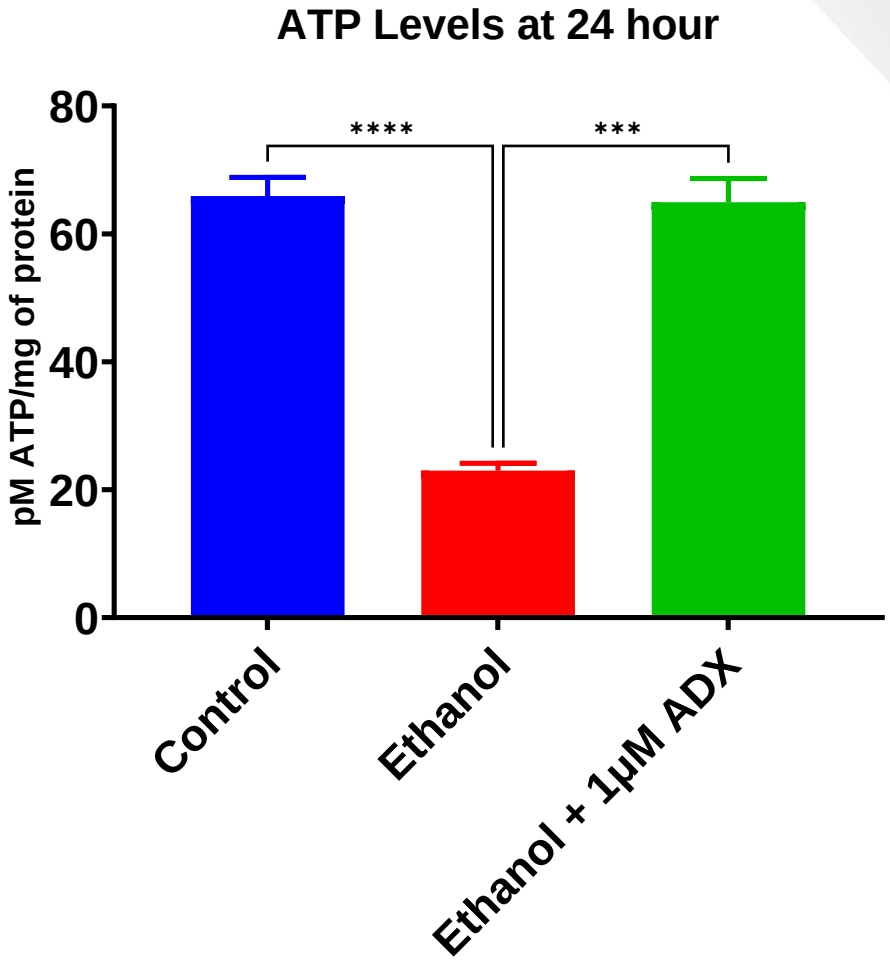
ADX-629 Stops Inflammation Induced by PCLS





ADX-629 is not Toxic in the PCLS system



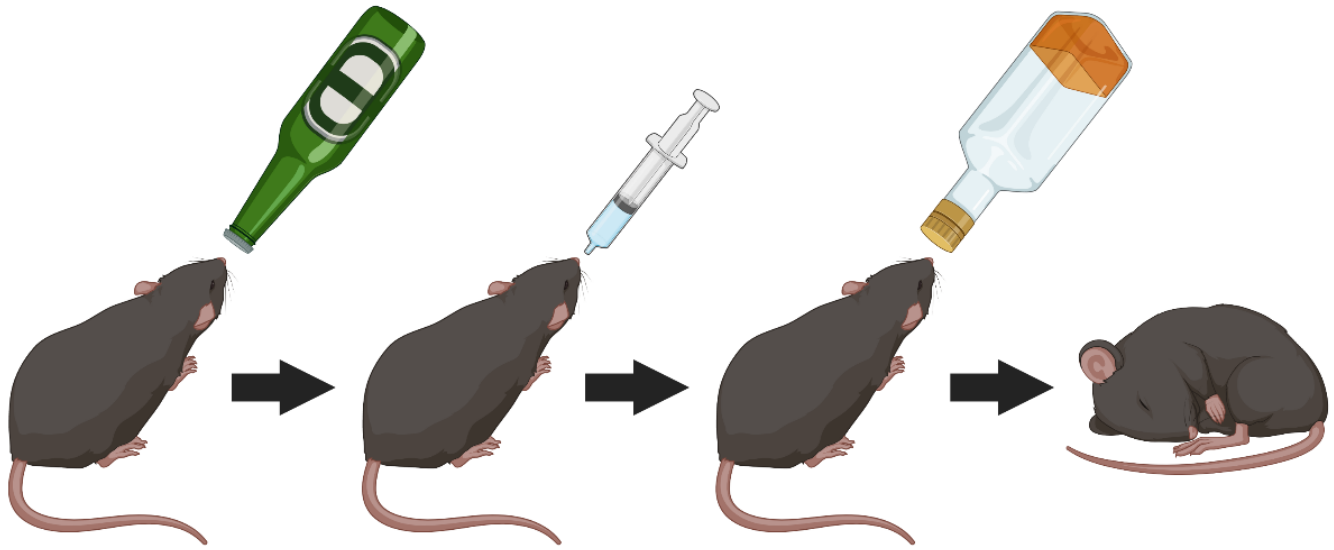


ADX-629 Treatment in Precision Cut Human Liver Slices Conclusions

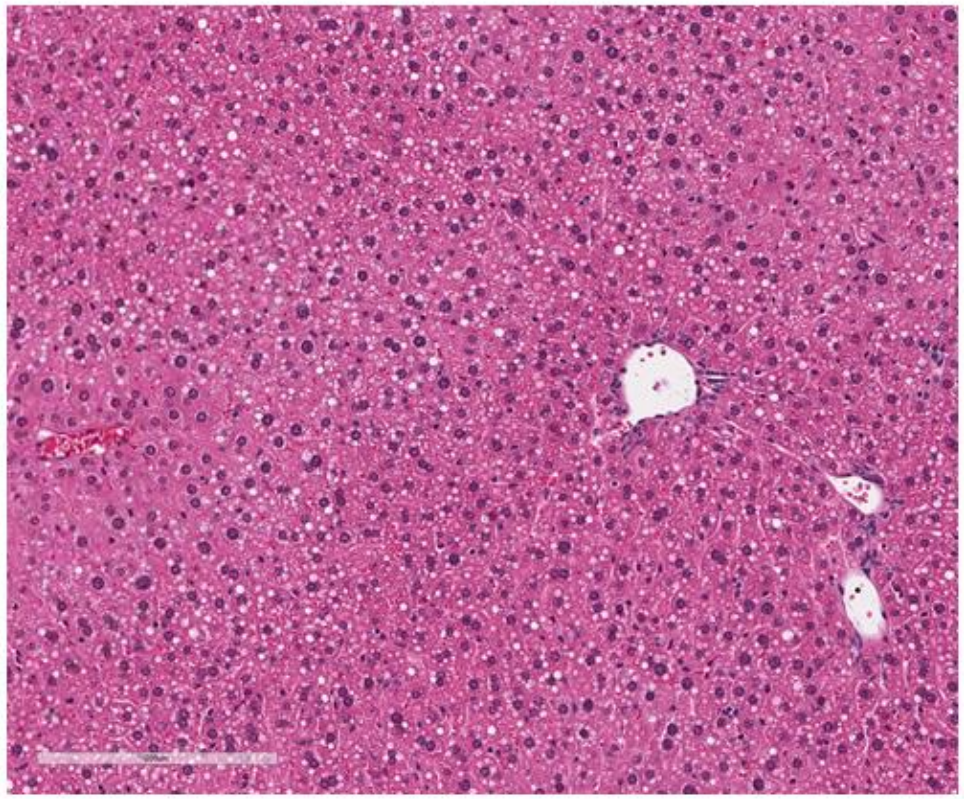
- **Statistically significant decreases observed with ADX-629 treatment with respect to:**
  - **Acetaldehyde**
  - **Triglycerides**
  - **Inflammatory cytokines**

- **No toxic effects were observed**

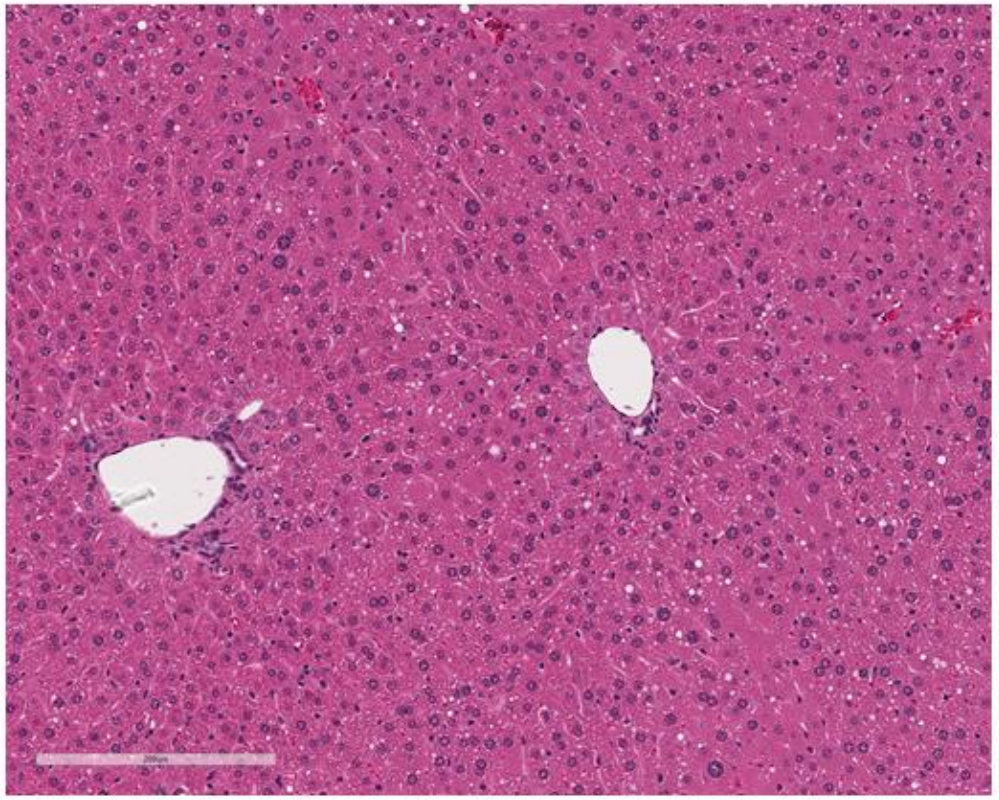
ADX-629 Treatment in an Animal Model of Alcoholic Liver Disease (ALD)



H&E Images of Livers Following Treatment

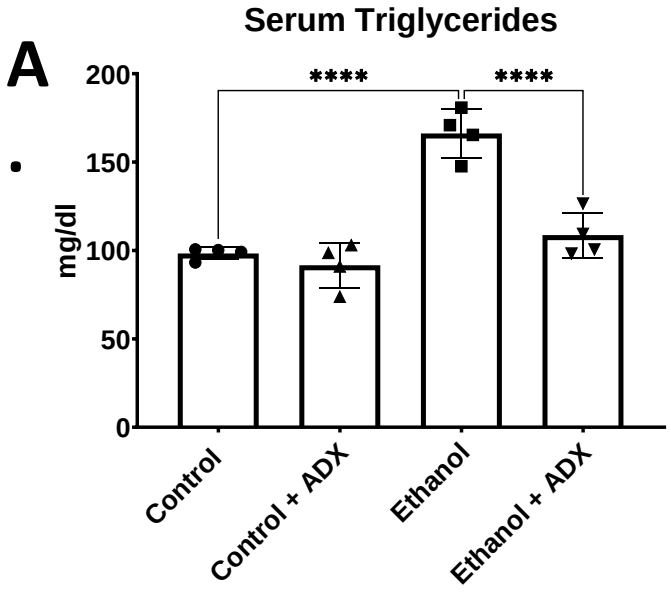


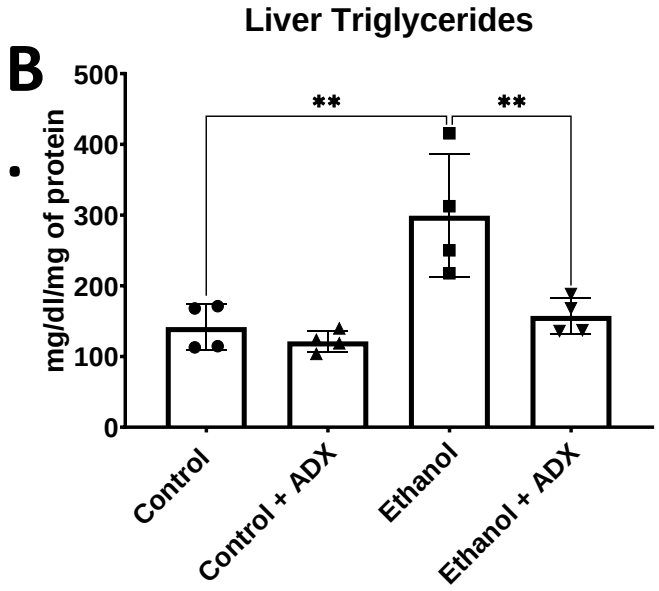
Ethanol Liver

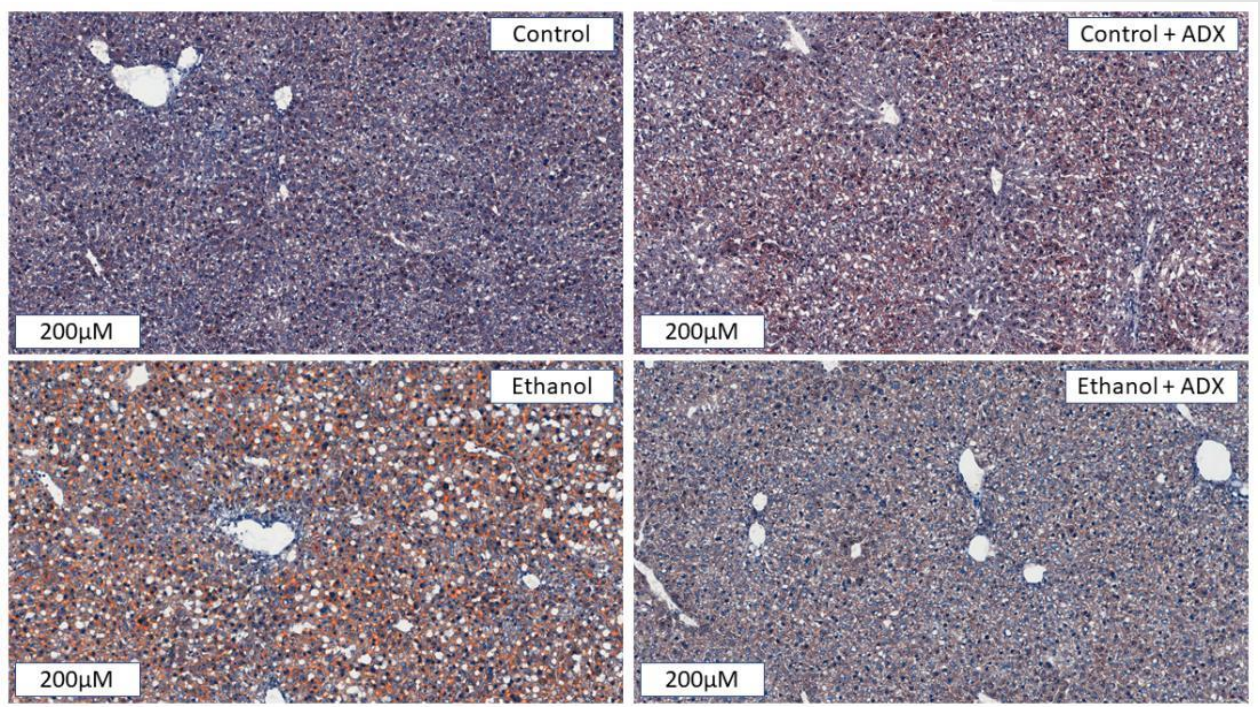


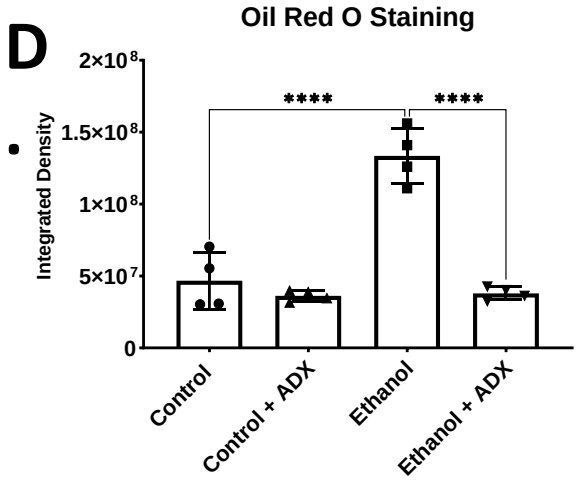
Ethanol Liver Treated with ADX-629

ADX-629 Treatment Reduces Fats in the Liver

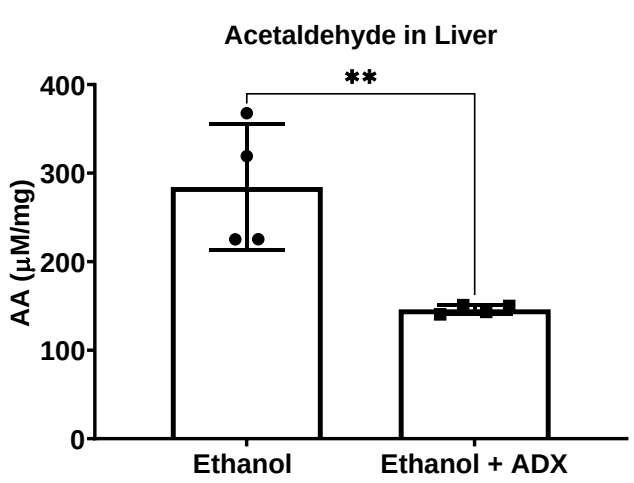


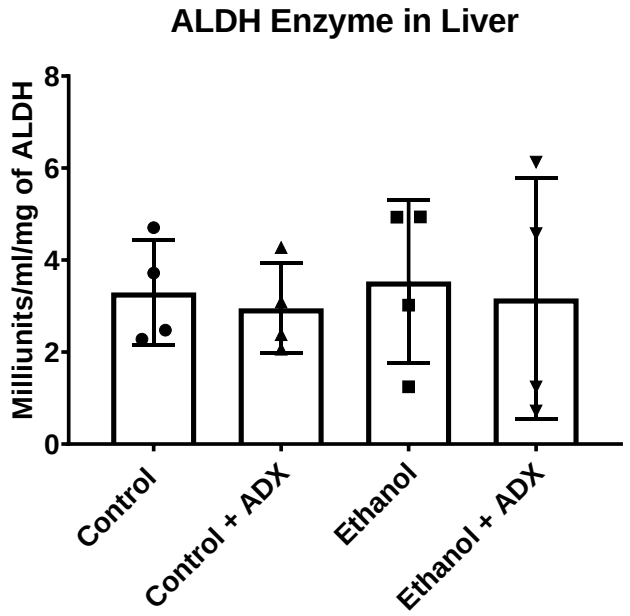




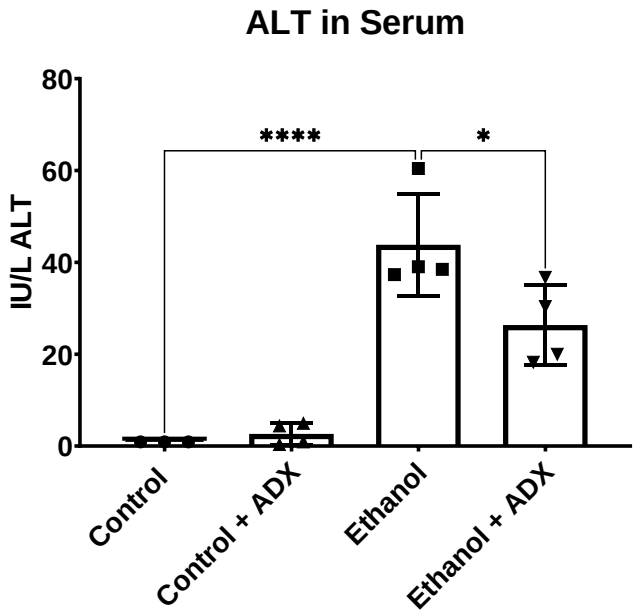


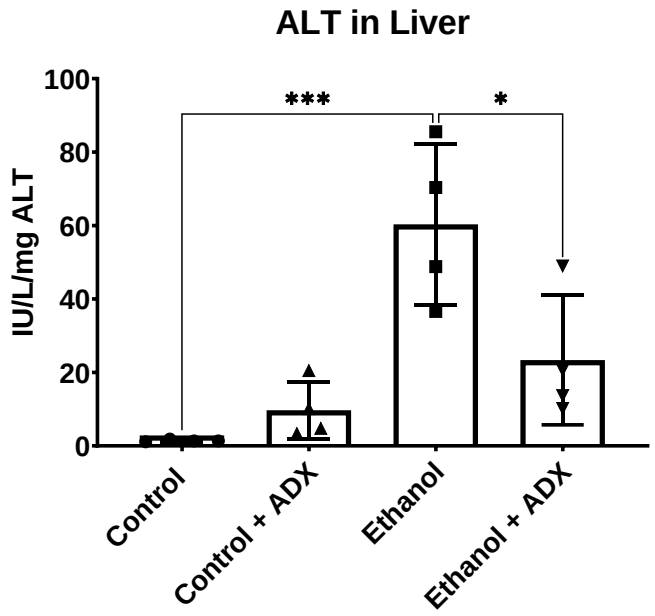
ADX-629 Treatment Reduces Acetaldehyde Concentrations in the Liver



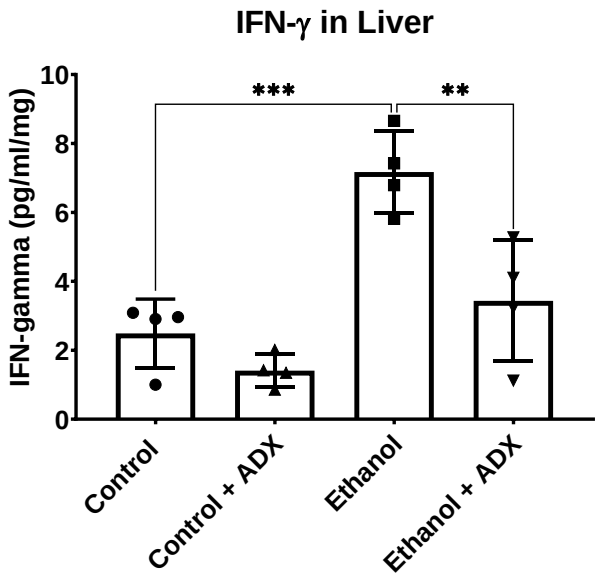


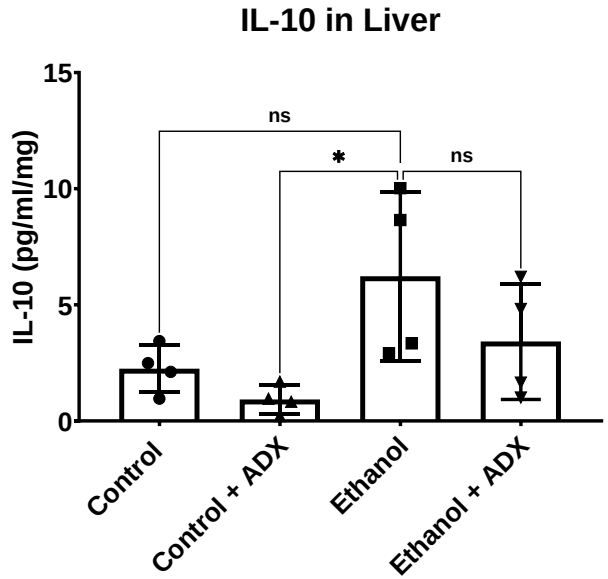
ADX-629 Treatment is Safe

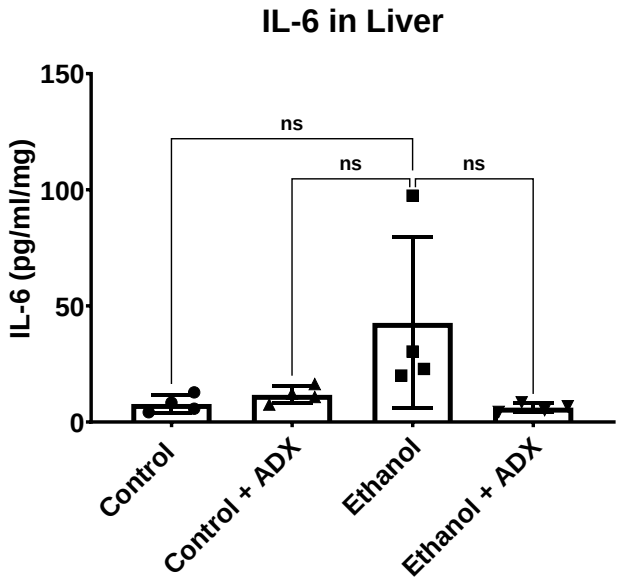


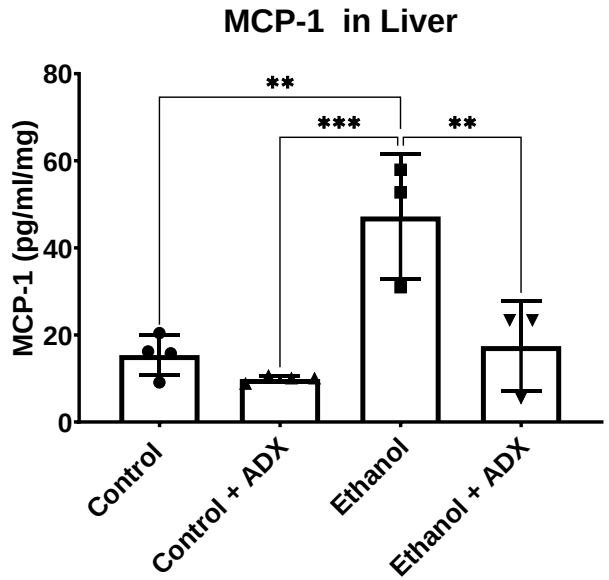


ADX-629 Treatment is Anti-Inflammatory









ADX-629 Treatment in an Animal Model Alcoholic Liver Disease Conclusions

- Fatty liver was restored to normal
- Acetaldehyde was significantly decreased
- Treatment showed no signs of toxicity
- Inflammation was decreased in response to treatment

Final Conclusions

The utility of ADX-629 to prevent the formation of RASP-protein adducts (including MAA adducts) *in vivo* and hence affect the inflammatory cascade is a very exciting proposition.

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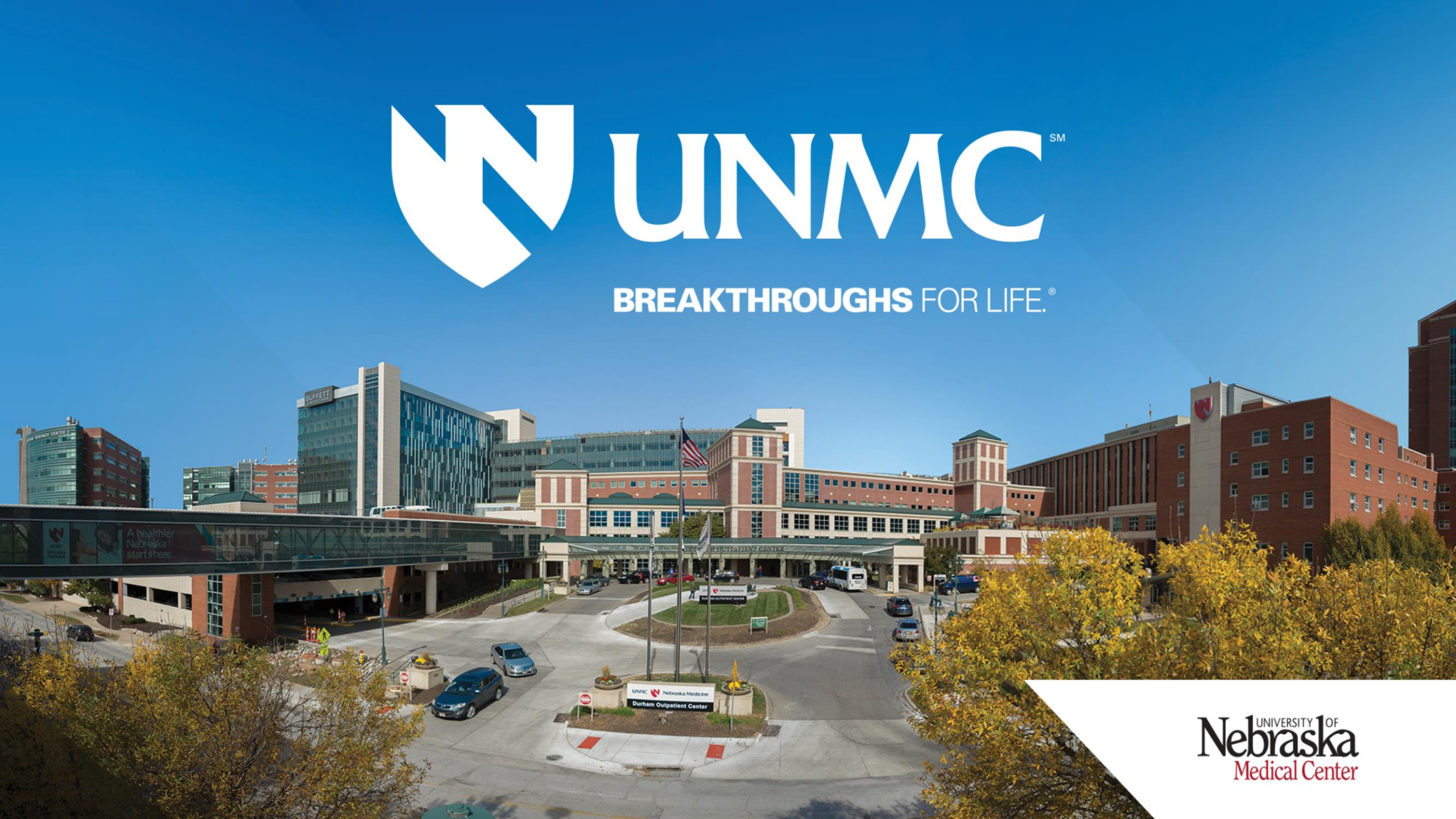
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University of Nebraska Medical Center

Agenda

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10:00 – 10:15 a.m.	RASP Overview	Todd C. Brady, M.D., Ph.D. *Chief Executive Officer*, Aldeyra Therapeutics
10:15 – 10:45 a.m.	RASP and Inflammation	Geoffrey M. Thiele, Ph.D. *Umbach Professor*, Internal Medicine, University of Nebraska Medical Center
10:45 – 11:15 a.m.	ADX-629 in *In vivo* and *In vitro* inflammatory models	Michael J. Duryee, MS *Instructor,* Internal Medicine, University of Nebraska Medical Center
11:15 – 11:30 a.m.	Questions	
11:30 – 11:40 a.m.	Break	
11:40 – 11:50 a.m.	Preclinical Activity of ADX-629	Adam Brockman, Ph.D. *Director of Translational Science,* Aldeyra Therapeutics
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12:20 – 12:35 p.m.	New Molecules, New Indications	Adam Brockman, Ph.D.
12:35 – 12:55 p.m.	Questions	
12:55 – 1:00 p.m.	Concluding Remarks	Todd C. Brady, M.D., Ph.D.

March 29, 2022

Questions

Nasdaq: ALDX

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March 29, 2022

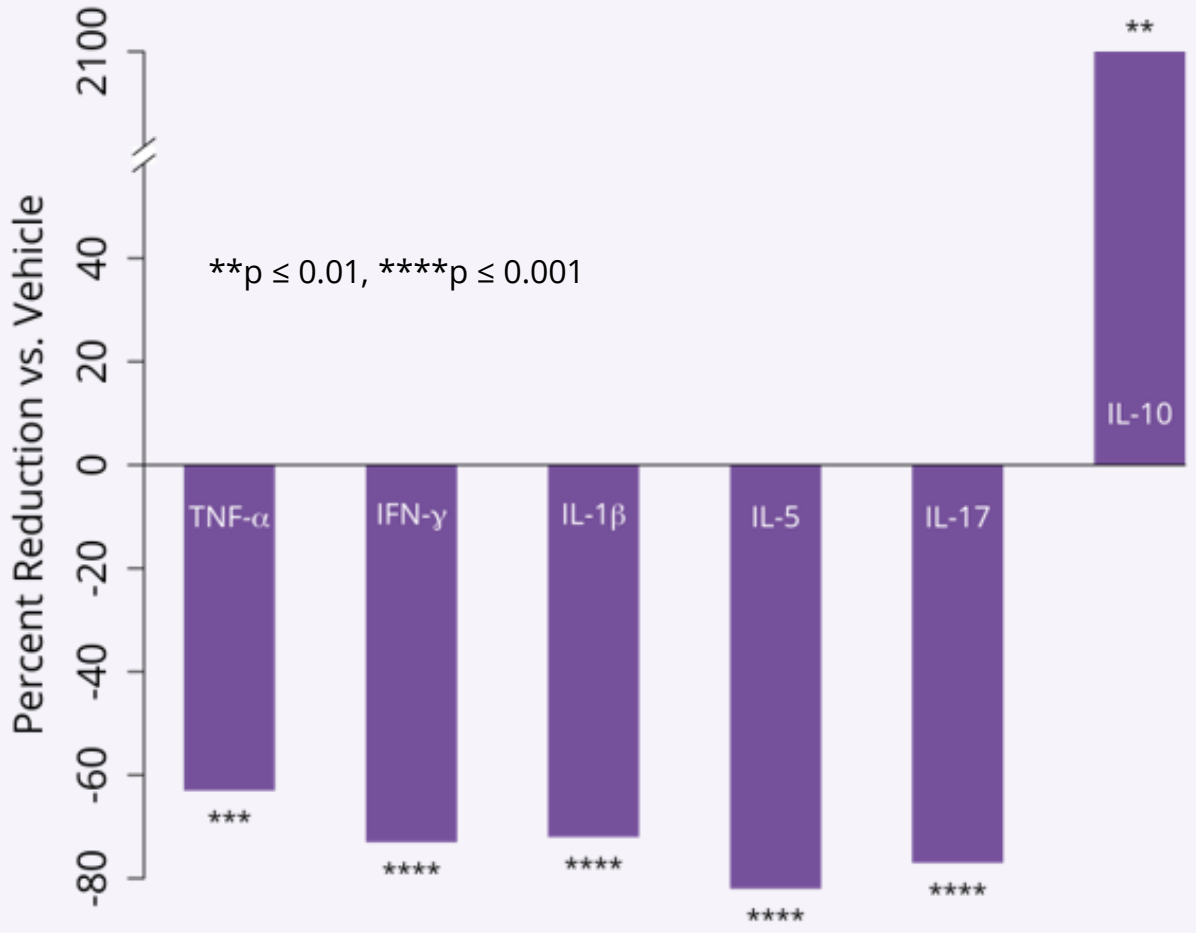
Adam Brockman, Ph.D., DABT, Director of Translational Science

Preclinical Activity of ADX-629 in Models of Inflammation

Nasdaq: ALDX

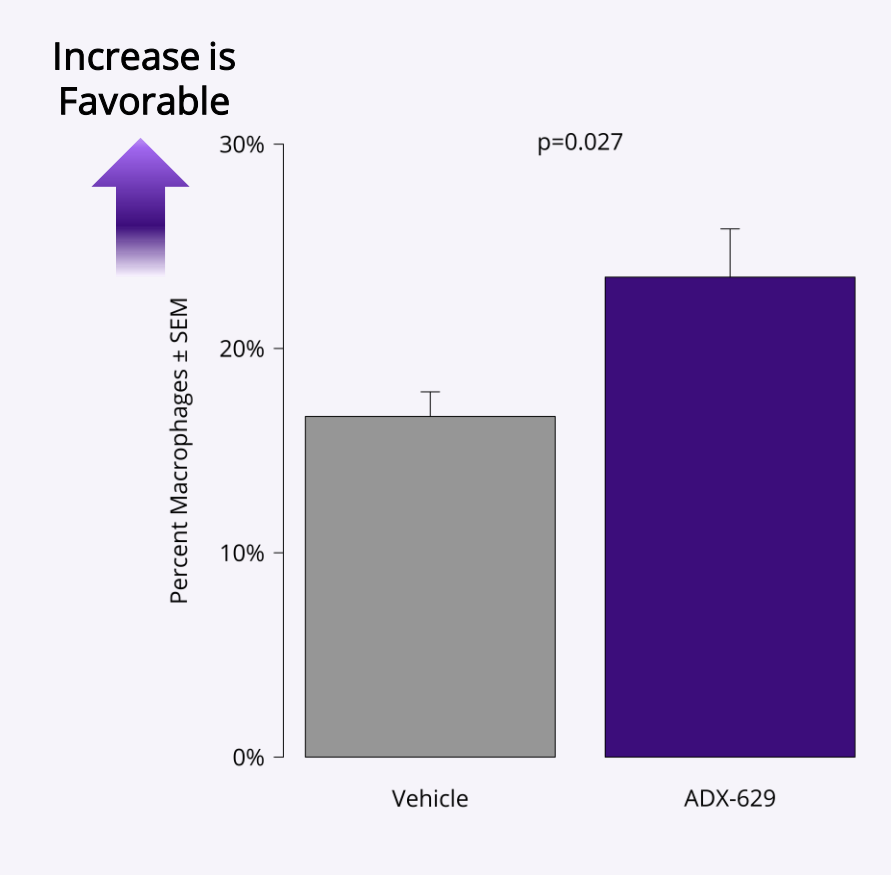
In a Murine Model of Cytokine Storm, ADX-629 Broadly Reduced Inflammatory Cytokines and Increased IL-10

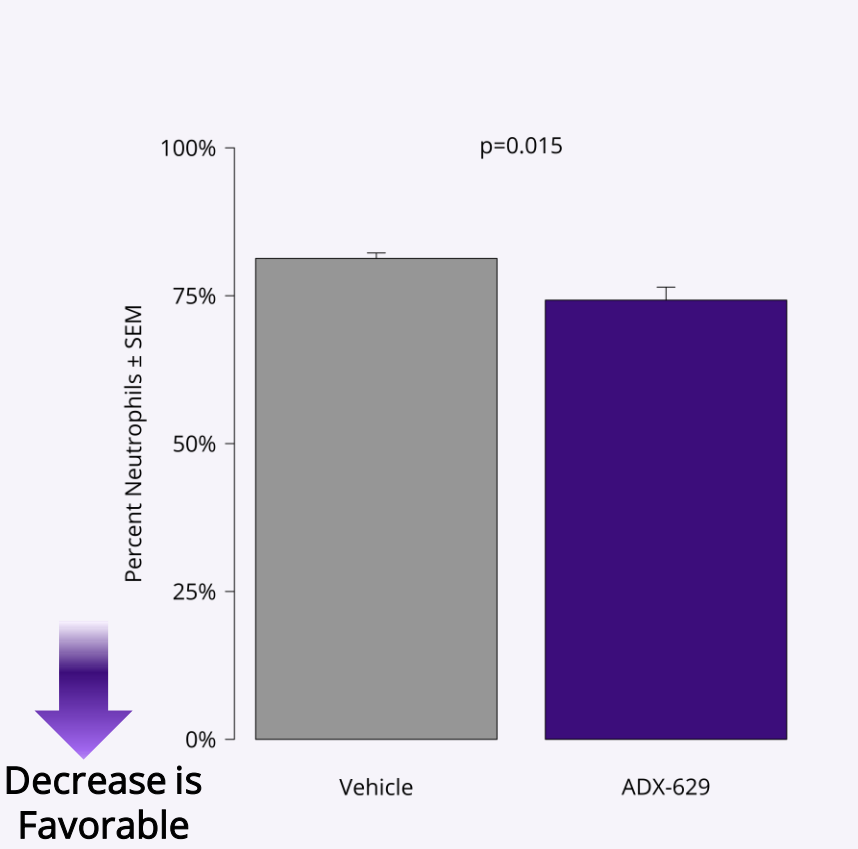
- Endotoxin model of cytokine storm
- ADX-629 100mg/kg administered intraperitoneally 15 minutes prior to endotoxin
- TH1, TH2, TH17 down-regulation in addition to up-regulation of the key anti-inflammatory cytokine, IL-10



ADX-629 Treatment Reduced Cellular Infiltrate in a Murine Model of Acute Respiratory Distress Syndrome (ARDS)

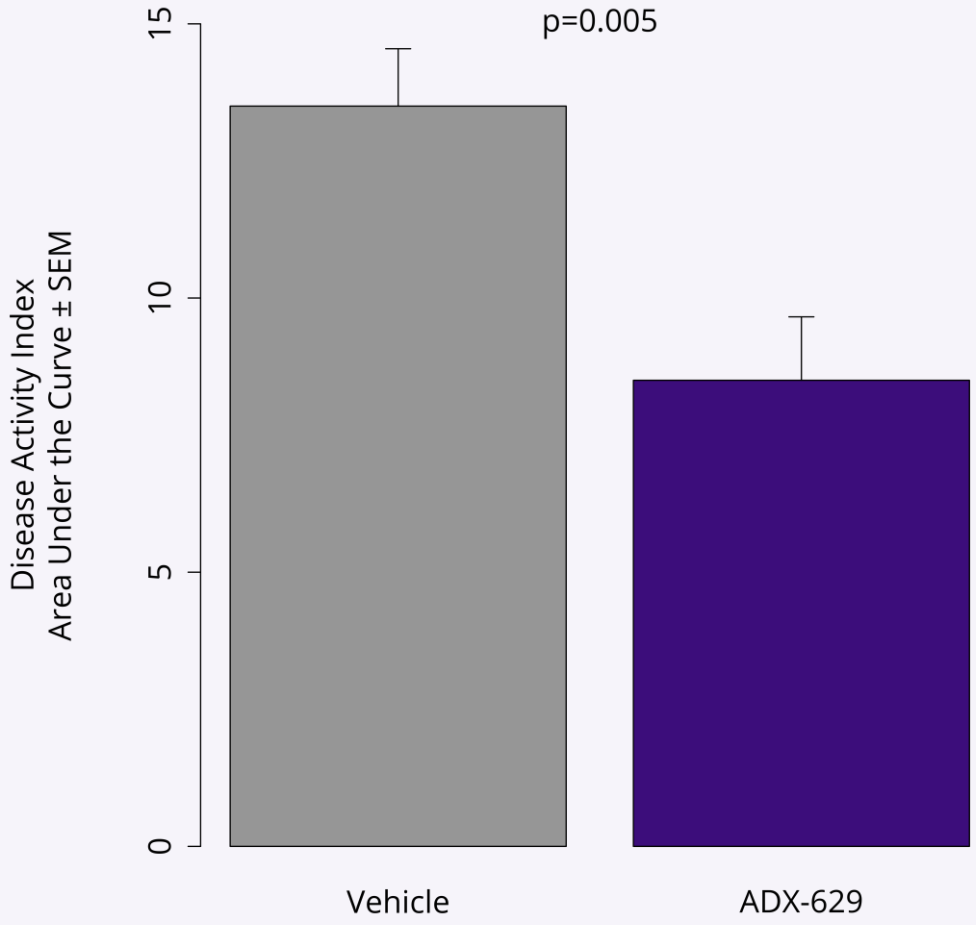
- Endotoxin model of ARDS
- ADX-629 120mg/kg administered orally two hours prior to endotoxin
- Increased percentages of macrophages and decreased neutrophils in bronchoalveolar lavage fluid





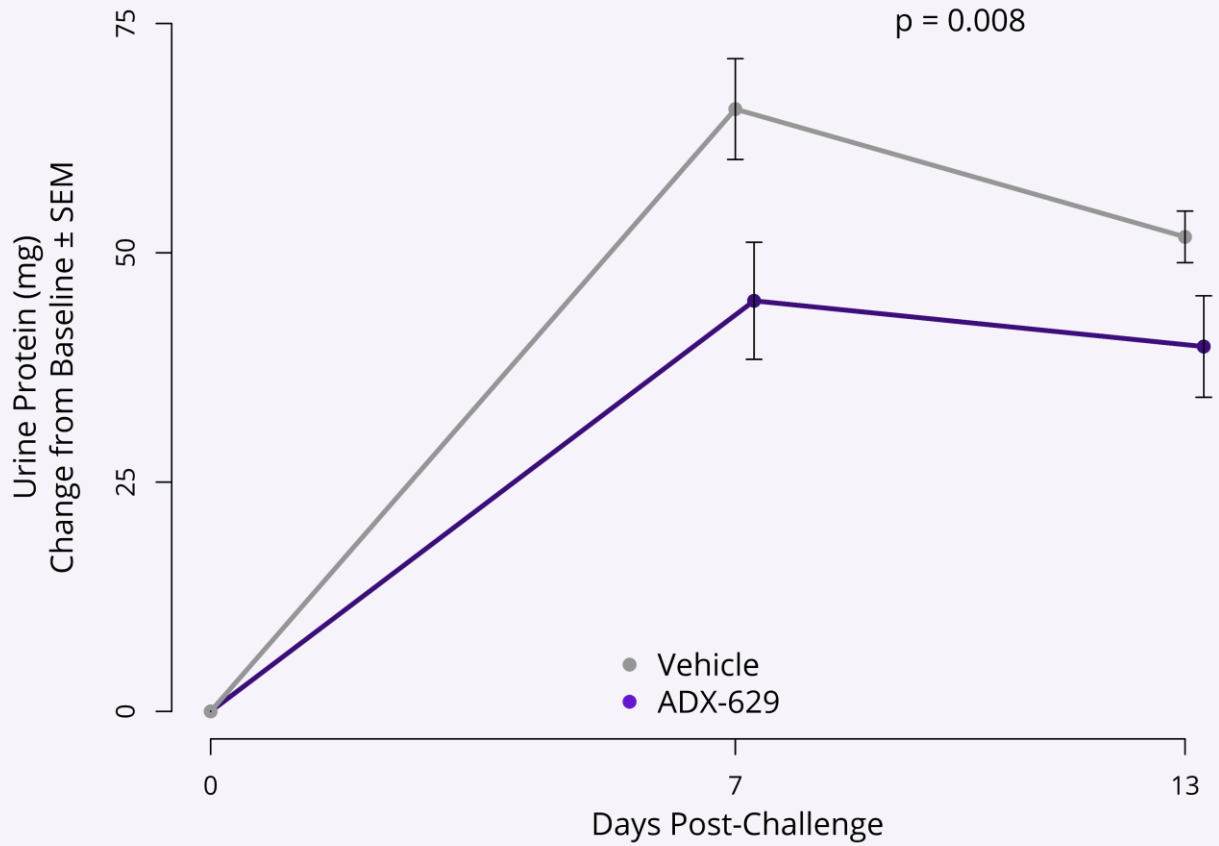
ADX-629 Reduced Disease Activity Index Score in Murine Model of Ulcerative Colitis

- Dextran sulfate sodium model of ulcerative colitis
- ADX-629 100mg/kg administered intra-peritoneally daily for 6 days
- Statistical reduction in disease activity index



In a Rat Model of Nephritis, ADX-629 Reduced Proteinuria

- Puromycin aminonucleoside (PAN) model of nephritis
- ADX-629 250mg/kg administered orally twice daily for 13 days
- Statistical reduction in proteinuria at 7 and 13 days



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March 29, 2022

Todd C. Brady, M.D., Ph.D., Chief Executive Officer

ADX-629 Proof-of-Concept Top-Line Clinical Trial Data

Nasdaq: ALDX

ADX-629, a RASP Modulator for Oral Administration, Is a First-in-Class Pharmacologic Approach and Highlights the Future of Aldeyra

ADX-629 is an investigational first-in-class, orally available covalent modulator of pro-inflammatory RASP, and potentially represents a new paradigm in the understanding and treatment of systemic immune-mediated disease.

A comprehensive systemic disease initiative was implemented to assess the activity of ADX-629 in three types of severe inflammation: autoimmune disease; allergic inflammation, and infectious disease.

RASP-MODULATION IN SYSTEMIC DISEASES

Phase 2 Proof-of-Concept, Indication-Selecting Clinical Trials in Three Types of Severe Inflammation

1 Phase 2 clinical trial in COVID-19

Infectious Disease

2 Phase 2 allergen-challenge clinical trial in atopic asthma

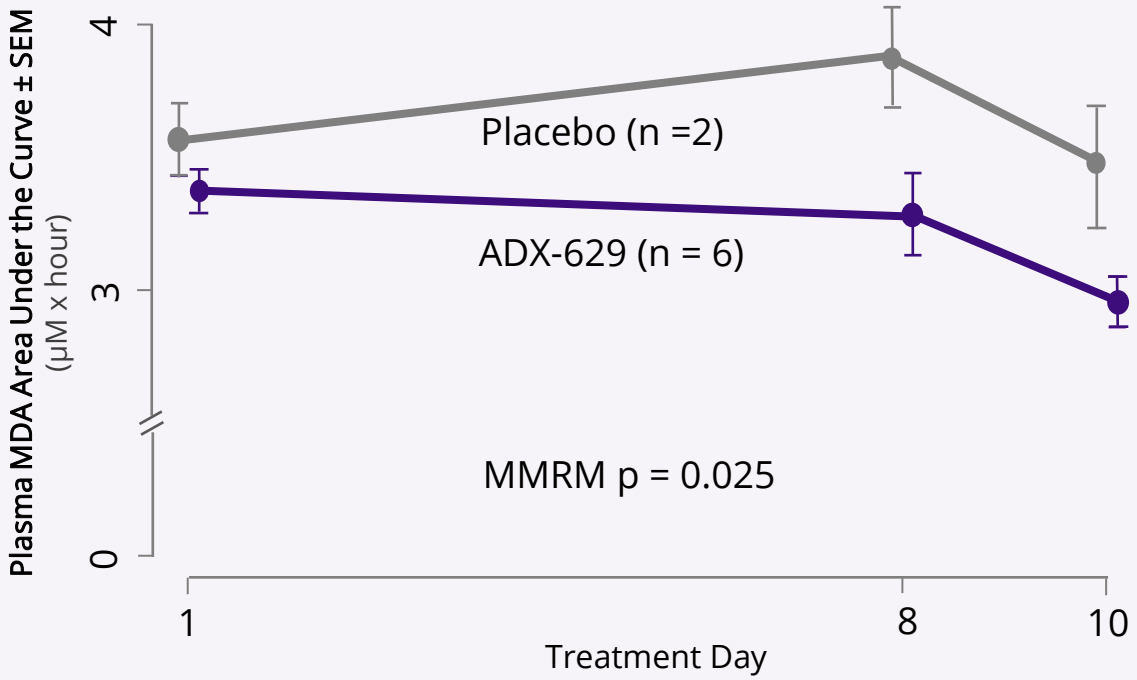
Allergic Inflammation

3 Phase 2 clinical trial in psoriasis

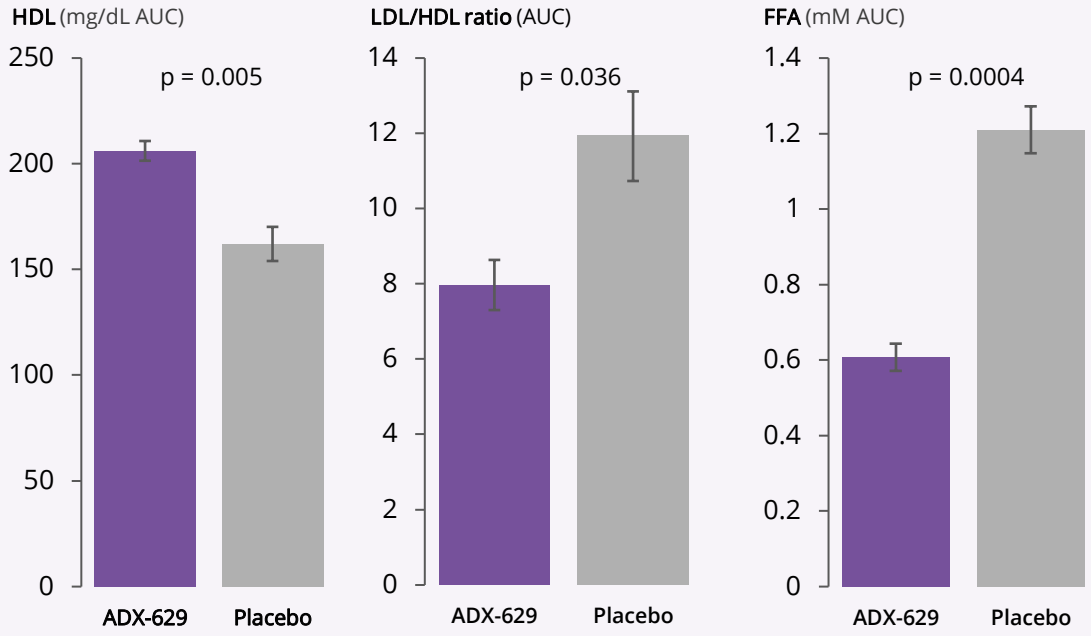
Autoimmune Disease

ADX-629 Reduced RASP vs. Placebo in Phase 1 Clinical Trial, Demonstrating Target Engagement, and Improved Lipid Profiles

RASP LEVELS OVER 10 DAYS OF DOSING

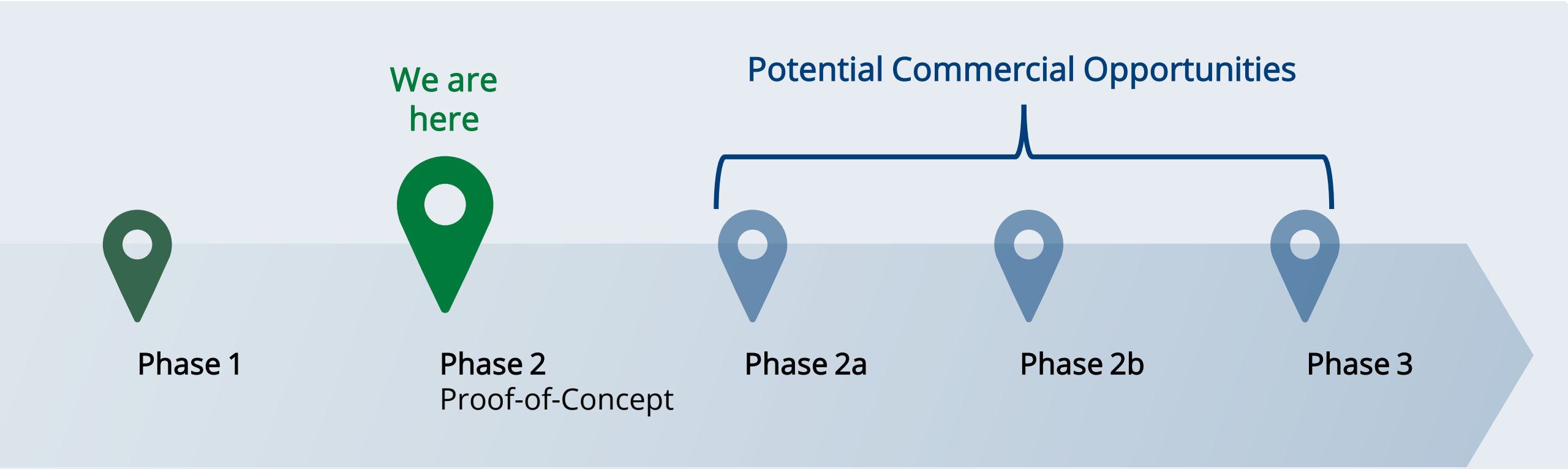


PLASMA LIPID PROFILE AFTER FATTY MEAL



Source: ADX-629 Phase 1 clinical trial results. **MDA** = malondialdehyde. **SEM** = standard error of the mean. **MMRM** = mixed model repeated measures. **HDL** = high-density lipoprotein. **LDL** = low-density lipoprotein. **FFA** = free fatty acids.

Proof-of-Concept Trials Are Designed to Select Indications for Subsequent Clinical Trials



A Phase 2 Proof-of-Concept Safety, Tolerability, and Activity Trial of ADX-629 in Patients with Mild to Moderate COVID-19

DESIGN	Multi-center, randomized, double-masked, parallel-group, placebo-controlled
DOSING	300mg ADX-629 or placebo twice-daily for 28 days 2:1 randomization
PATIENTS	11 (4 placebo, 7 ADX-629) Mild to moderate COVID-19, not on supplemental oxygen
ENDPOINTS	Clinical: Supplemental oxygen use, hospitalization, mechanical ventilation, intensive care unit admission, death, National Institute of Allergy and Infectious Diseases (NIAID) score Pharmacodynamic: Plasma cytokine, RASP levels

Baseline Characteristics Were Similar Across Treatment Groups

	PLACEBO (n=4)	ADX-629 (n=7)
COVID-19 Status	Mild (25%), Moderate (75%)	Mild (29%), Moderate (71%)
Mean Age (years)	55	49
BMI	31	29
Gender	Male (50%), Female (50%)	Male (57%), Female (43%)
Immunological History	0	2 (29%)
Respiratory History	0	2 (29%)

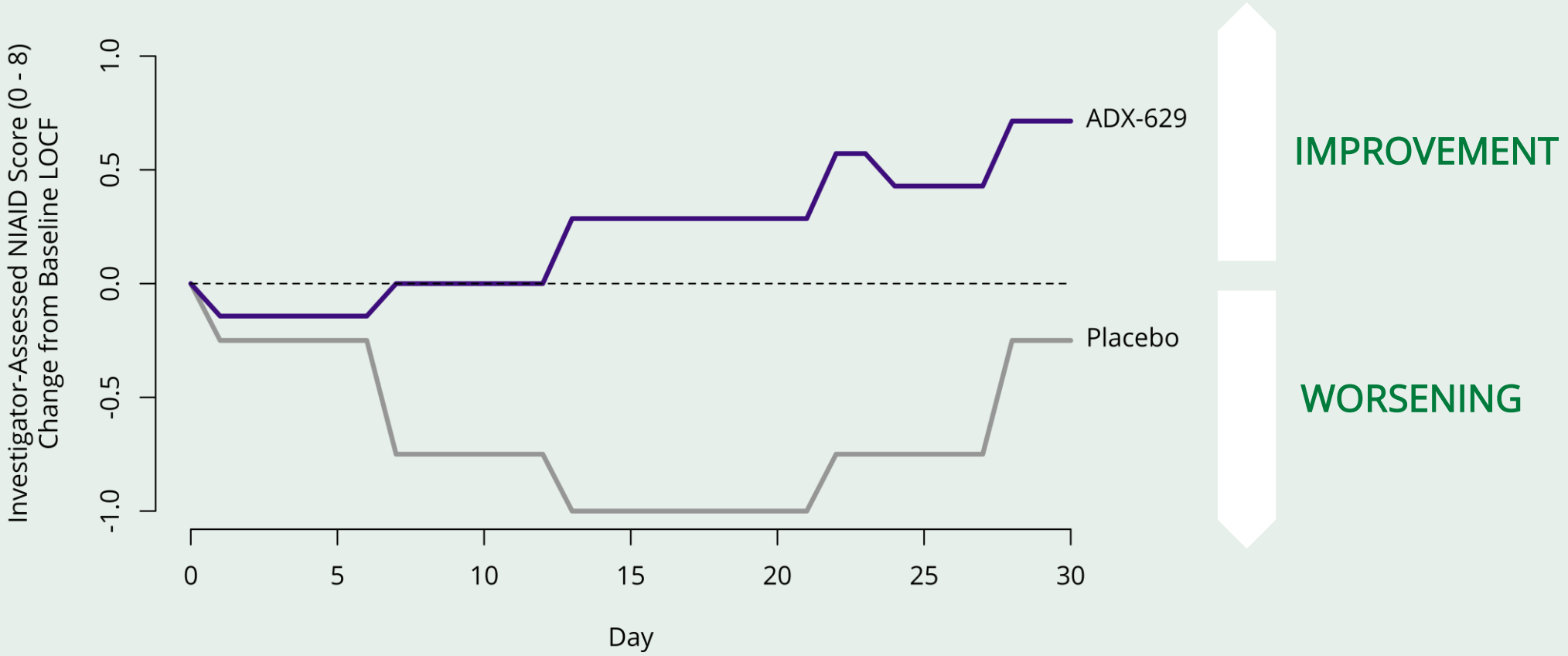
Compliance, Exposure, and Top-Line Clinical Results Were Similar Across Treatment Groups

	PLACEBO (n=4)	ADX-629 (n=7)
Compliance	98%	95%
Mean Exposure (days)	23	28
Treatment Discontinuations	1 (25%)	0
Supplemental Oxygen	1 (25%)	0
Hospitalization	1 (25%)	0
Mechanical Ventilation	0	0
ICU Admission	0	0
Death	0	0

The National Institute of Allergy and Infectious Diseases (NIAID) Score is a Leading Indicator of COVID-19 Outcomes

NIAID SCORE	DESCRIPTION
8	Not hospitalized, no limitation on activities
7	Not hospitalized, limitation on activities and/or requiring home oxygen
6	Hospitalized, not requiring supplemental oxygen or ongoing medical care
5	Hospitalized, not requiring supplemental oxygen, requiring ongoing medical care
4	Hospitalized, requiring supplemental oxygen
3	Hospitalized, on noninvasive ventilation or high-flow oxygen devices
2	Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation
1	Death

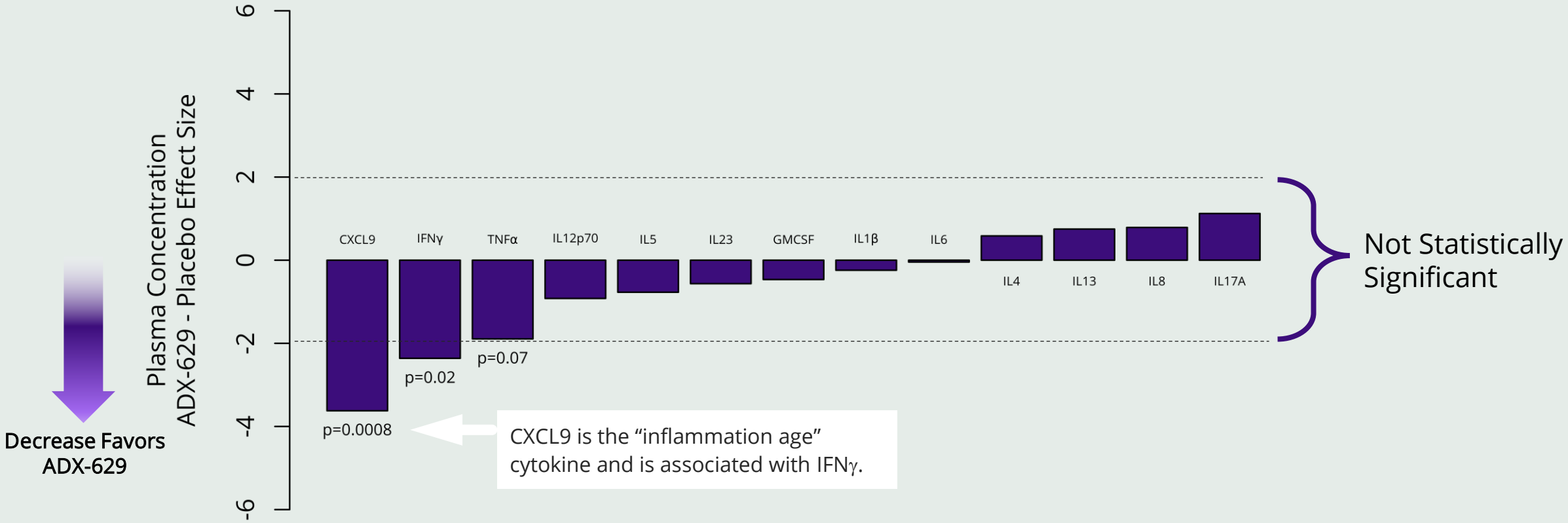
NIAID Score Was Consistently Higher in the ADX-629 Treatment Group Than in the Placebo Treatment Group



Adverse Events Favored the ADX-629 Treatment Group

	PLACEBO (n=4)	ADX-629 (n=7)
Serious Adverse Events	1 (25%; hypoxia)	0
Severe	1 (25%; hypoxia)	0
Moderate	2 (50%; elevated ALT, AST)	1 (14%; pelvic pain)
Mild	0	2 (29%; flatulence, itching)
Caused Discontinuation	1 (25%)	0

Pro-Inflammatory Cytokines Were Reduced



Effect size = ADX-629 minus placebo, divided by standard deviation of contrast. Data derived from mixed model for repeated measures analysis of change from baseline over all post-baseline assessments. Sayed N et al. An inflammatory aging clock (iAge) based on deep learning tracks multimorbidity, immunosenescence, frailty and cardiovascular aging. Nat Aging. 2021 Jul;1:598-615.

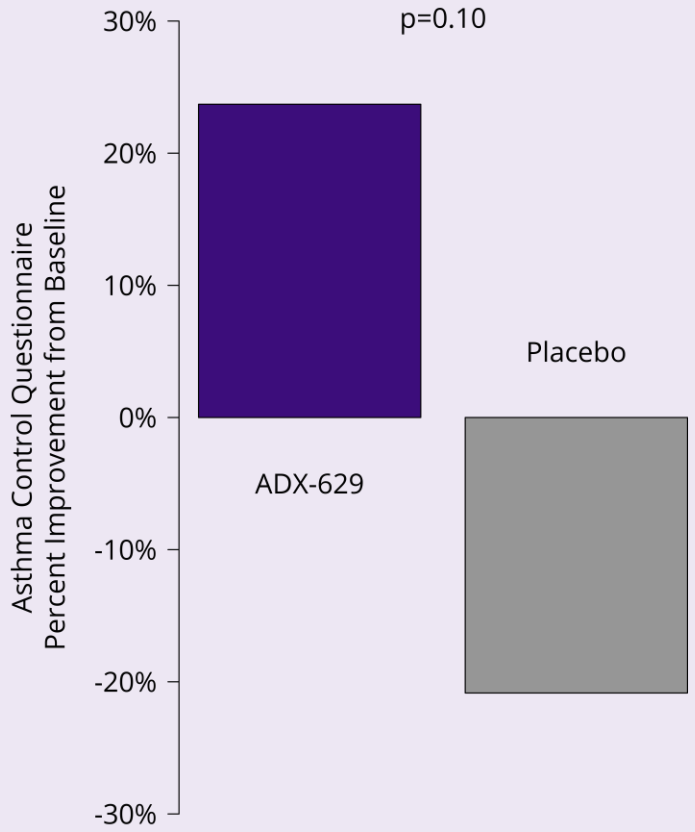
A Phase 2 Proof-of-Concept Safety, Tolerability, and Activity Trial of ADX-629 in Patients with Mild Asthma

DESIGN	Single-center, crossover, allergen challenge
DOSING	300mg ADX-629 or placebo twice-daily for 7 days
PATIENTS	8
ENDPOINTS	Clinical: Asthma Control Questionnaire, sputum cell counts, forced expiratory volume (FEV) following allergen and methacholine challenge Pharmacodynamic: Plasma cytokine, RASP levels

The Asthma Control Questionnaire is a Combination of Symptom and FEV Assessments

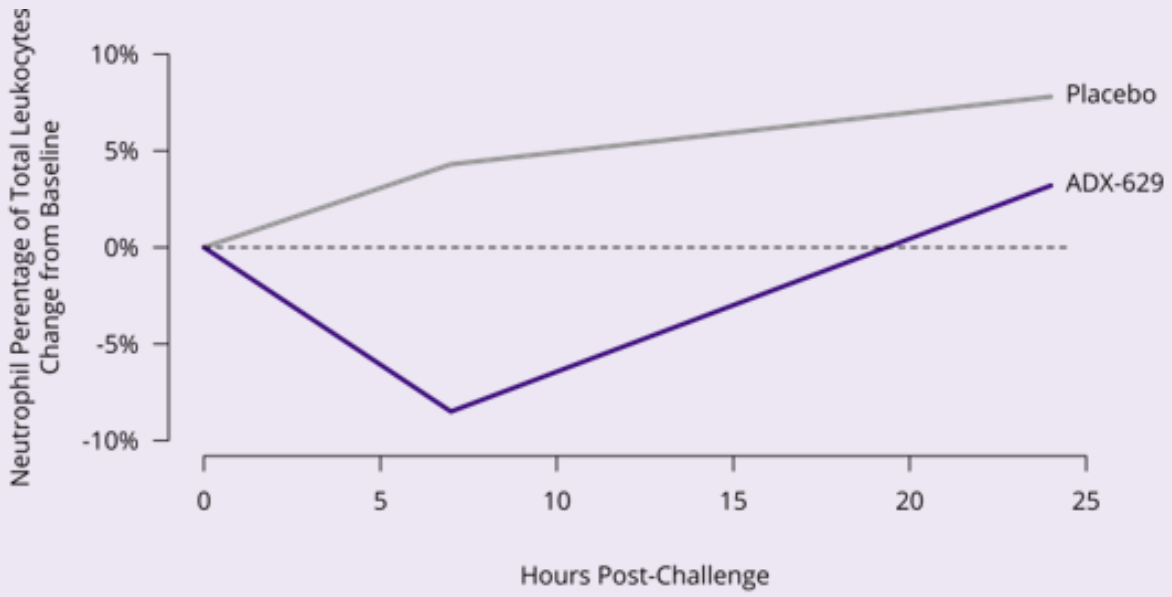
QUESTION	RANGE
Sleeping	0=Normal, 6=Unable to sleep
Morning Symptoms	0=None, 6=Very severe
Activity Limitation	0=None, 6=Totally limited
Shortness of Breath	0=None, 6=Very severe
Wheezing	0=None, 6=Constant
Bronchodilator Use	0=None, 6=More than 15 inhalations per day
Forced Expiratory Volume	0=More than 95% predicted, 6=Less than 50% predicted

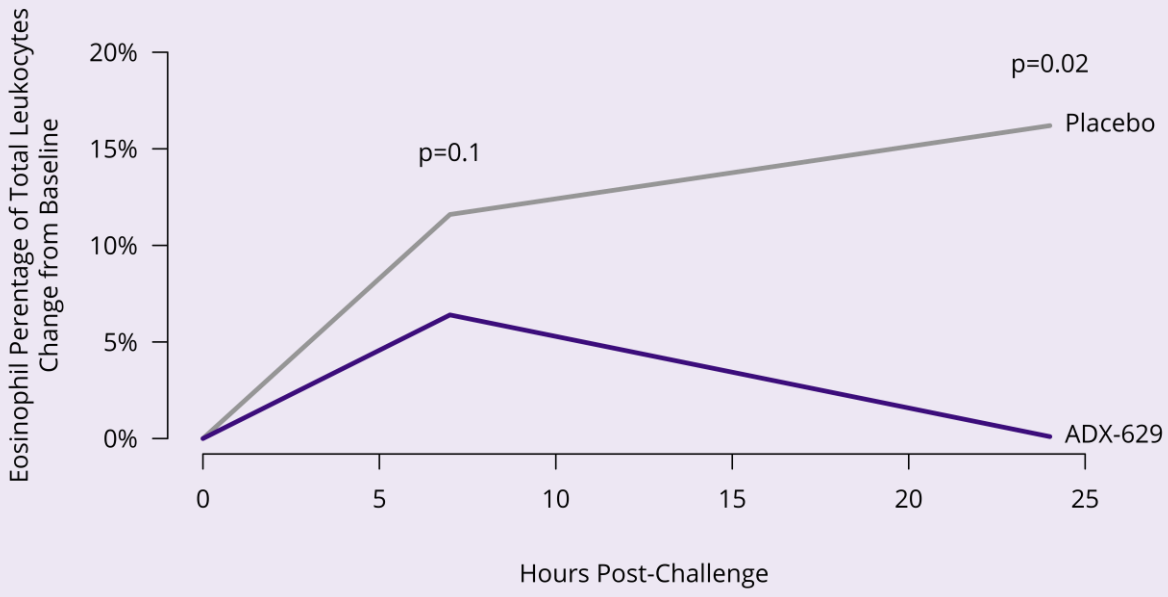
Symptom Improvement Favored ADX-629 Over Placebo



P value is derived from mixed model for repeated measures analysis of treatment group comparison.

Reductions in Eosinophil and Neutrophil Sputum Cell Counts Supported Drug Activity



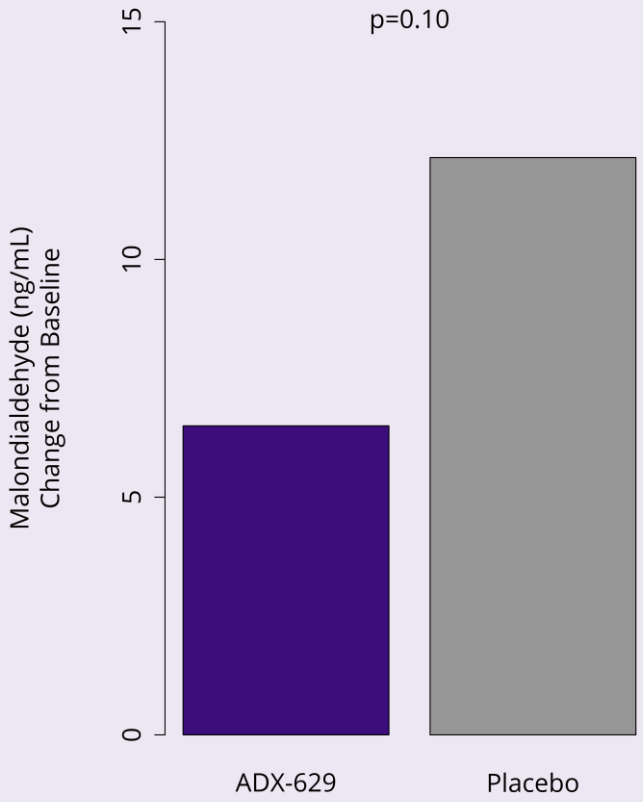


P values are derived from mixed model for repeated measures analysis of placebo group comparison to 0 (no change).

No Safety Concerns Were Evident from Adverse Events

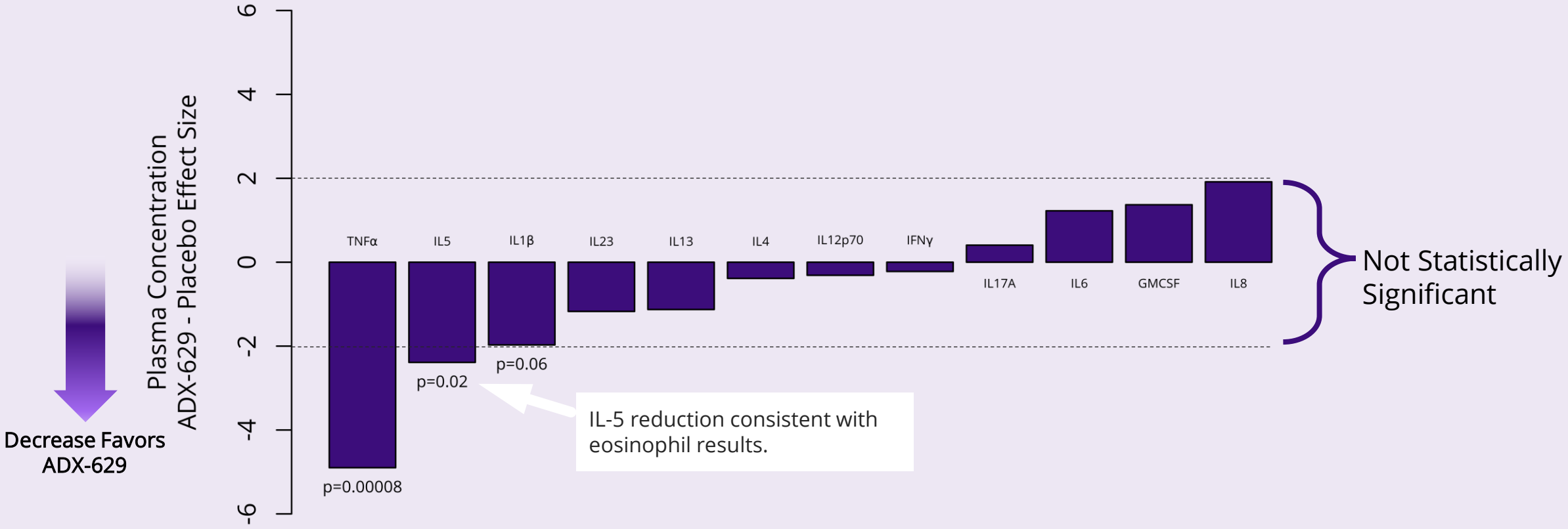
	PLACEBO (n=8)	ADX-629 (n=8)
Serious Adverse Events	0	0
Severe	0	0
Moderate	0	1 (13%; appetite, cough, dyspnea)
Mild	1 (13%; congestion, pruritis)	0
Caused Discontinuation	0	1 (13%)

Reduction in Plasma Malondialdehyde Levels Correlated with Clinical Response



P value is derived from mixed model for repeated measures analysis of change from baseline over all post-baseline assessments.

Pro-Inflammatory Cytokines Were Reduced

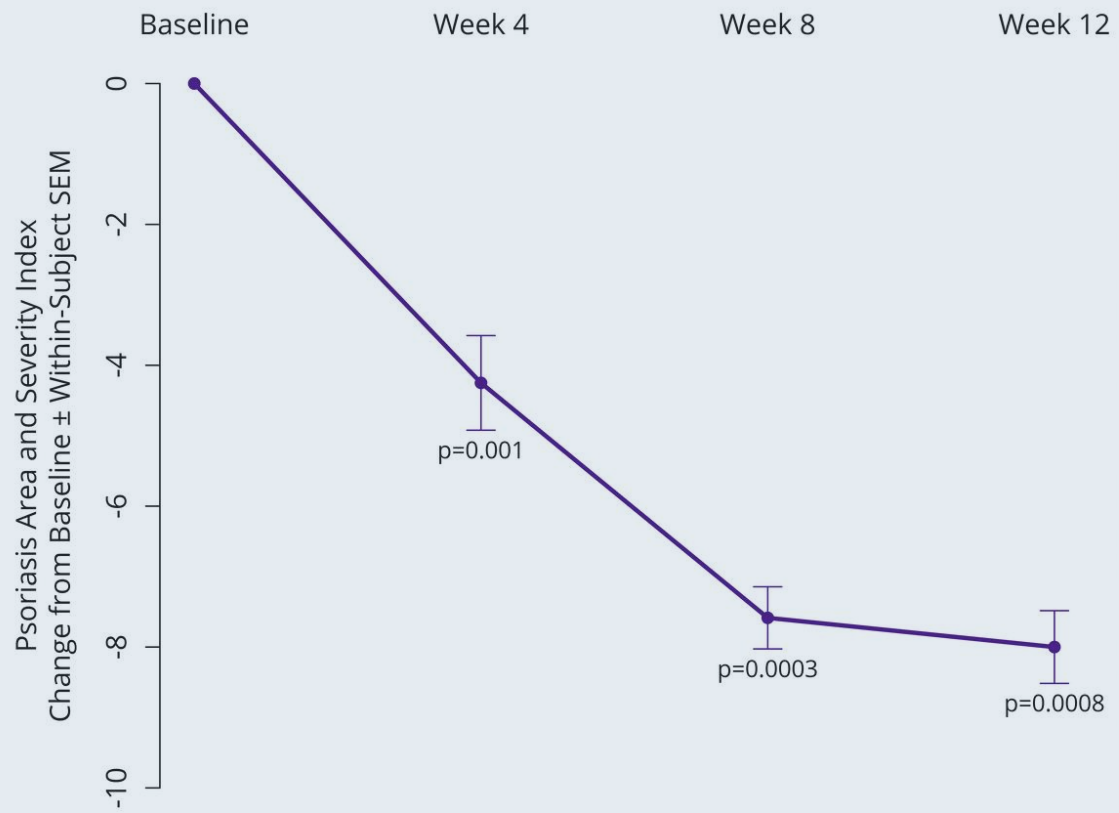


Effect size = ADX-629 minus placebo, divided by standard deviation of contrast. Data derived from mixed model for repeated measures analysis of change from baseline over all post-baseline assessments.

A Phase 2 Proof-of-Concept Safety, Tolerability, and Activity Trial of ADX-629 in Patients with Mild to Moderate Psoriasis

DESIGN	Multi-center, single-arm
DOSING	250mg ADX-629 twice-daily for 90 days
PATIENTS	10
ENDPOINTS	Clinical: Psoriasis Area and Severity Index (PASI), Investigator Global Assessment (IGA) Pharmacodynamic: Plasma cytokine, RASP levels

Psoriasis Area and Severity Index Statistically Decreased Over Time



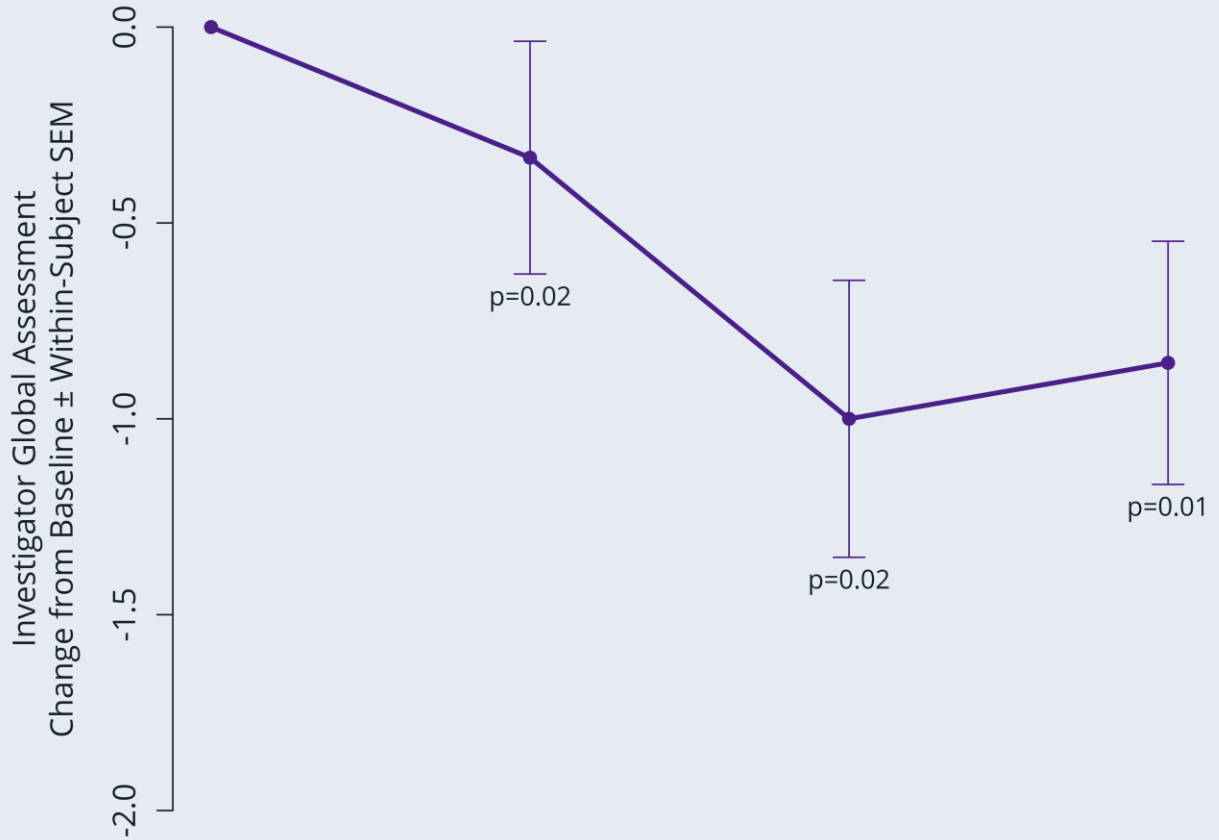
SEM = standard error of the mean. P values derived from mixed model for repeated measures analysis of comparison to 0 (no change).

PASI 50% and 75% Responders Significantly Increased Over Time

WEEK OF TREATMENT	PASI-50	PASI-75
4	29% (p=0.047)	0
8	57% (p=0.001)	0
12	38% (p=0.014)	25% (p=0.051)

PASI = psoriasis area and severity index. PASI-50 and PASI-75 responders are defined as patients with PASI scores that improved (decreased) from baseline by at least 50% and 75%, respectively. P values derived from one-sided Clopper-Pearson Exact Tests.

Investigator Global Assessment Supported PASI Results

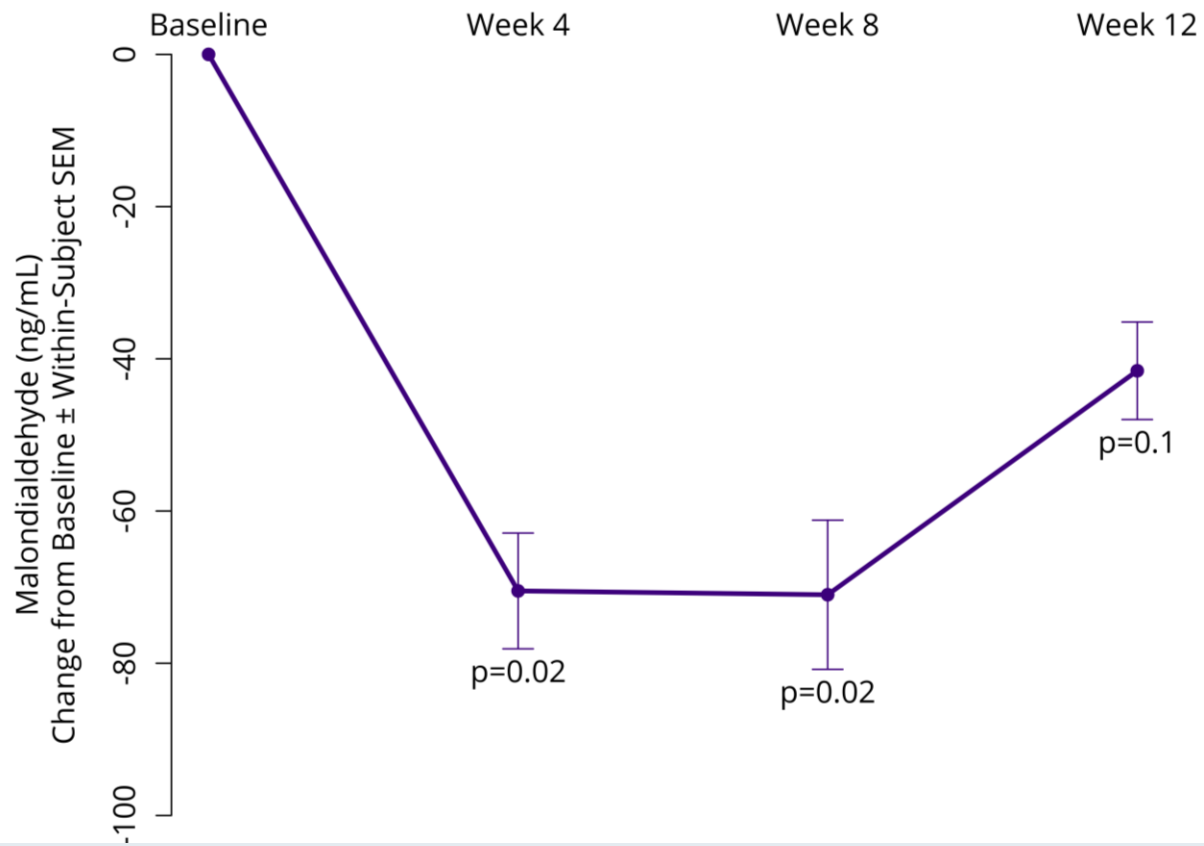


SEM = standard error of the mean. P values derived from mixed model for repeated measures analysis of comparison to 0 (no change).

No Safety Concerns Were Evident from Adverse Events

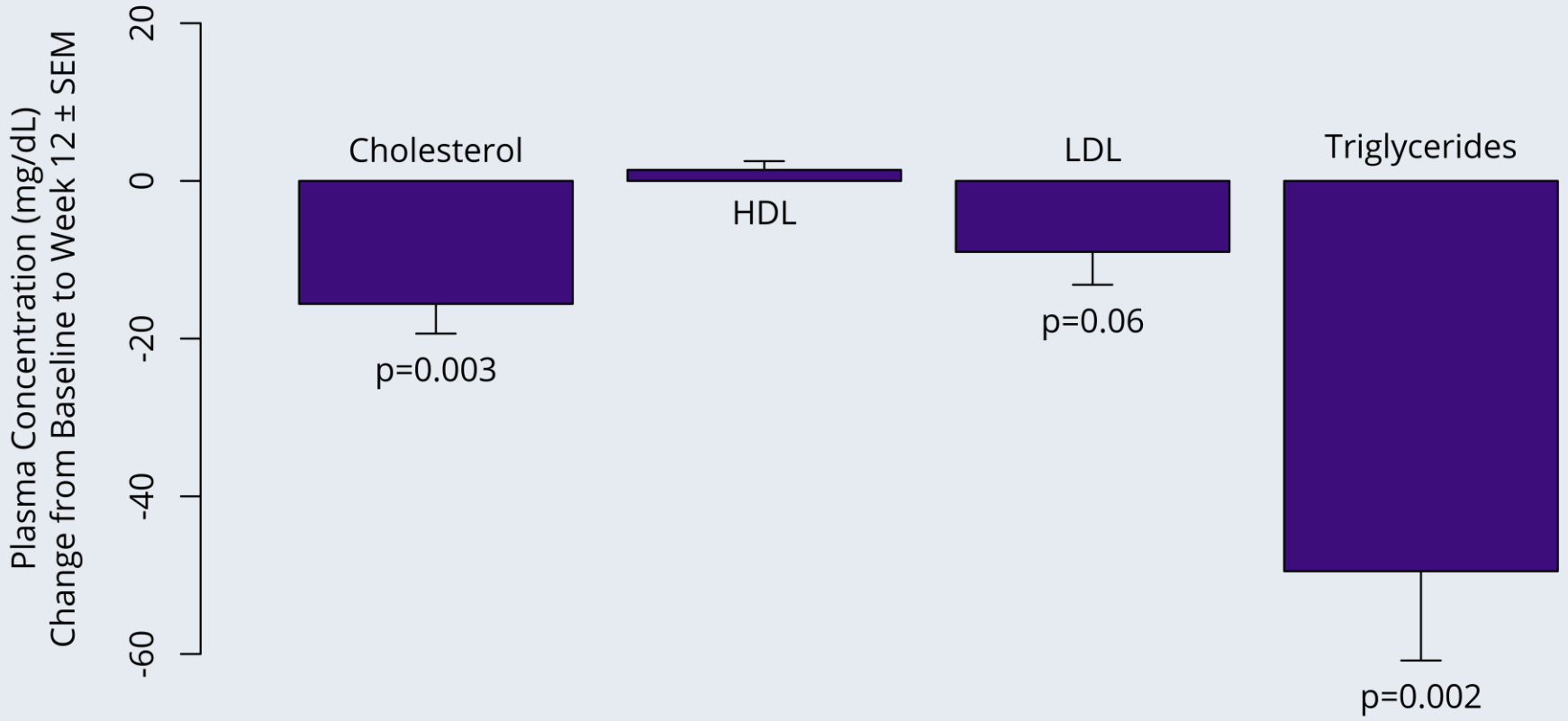
ADVERSE EVENT	NUMBER (%; adverse event)
Serious Adverse Events	0
Severe	0
Moderate	1 (10%; psoriasis)
Mild	2 (20%; diarrhea, sprain)
Caused Discontinuation	1 (10%)

Reduction in Plasma Malondialdehyde Levels Correlated with Clinical Response



SEM = standard error of the mean. P values derived from mixed model for repeated measures analysis of comparison to 0 (no change).

Beneficial Changes Observed in Lipid Profiles Consistent with Preclinical and Phase 1 Results

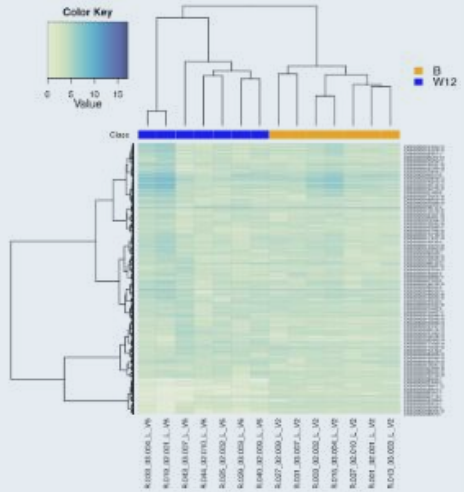


SEM = standard error of the mean. **HDL** = high-density lipoprotein. **LDL** = low-density lipoprotein. P values are derived from one-way t test comparison to 0 (no change).

Lesional Tissue Analysis Suggested Normalization of Gene Expression

The DermTech Smart Sticker™ Workflow

Hierarchical Clustering



	Lesional vs non-lesional		Lesional		Non-Lesional
	BL vs BNL (n=7)	w12L vs w12NL (n=7)	BL vs w4L (n=7)	BL vs w12L (n=7)	BNL vs w12NL (n=7)
DEGs (FC>2 and p<0.05)	2469	578	556	3157	835
Pathways (Adjusted p < 0.1)	39	0	1	180	2

DEG = differentially expressed gene. **FC** = fold change. **BL** = baseline lesional. **BNL** = baseline non-lesional. **w4L** = Week 4 lesional. **w12L** = Week 12 lesional. **w12NL** = Week 12 non-lesional.

ADX-629 Consistently Demonstrated Preliminary Safety and Activity Across Different Inflammatory Diseases

COVID-19

Asthma

Psoriasis

No safety signals observed from adverse events

Clinical activity demonstrated across a variety of types of inflammation, suggestive of the upstream activity of RASP modulation

ADX-629 and related RASP modulators to be **advanced to development indications**

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Adam Brockman, Ph.D., DABT, Director of Translational Science

New Molecules, New Indications

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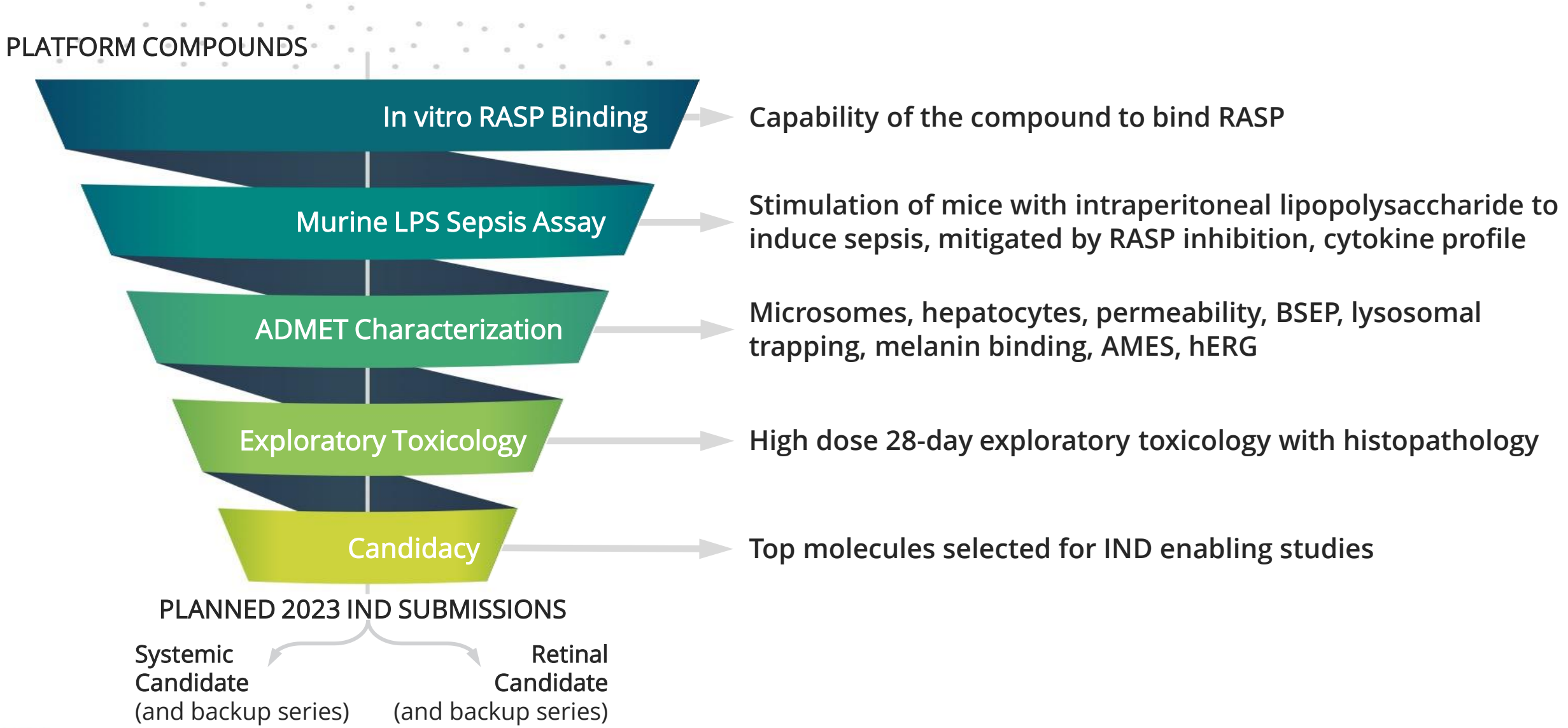
RASP Modulator Platform



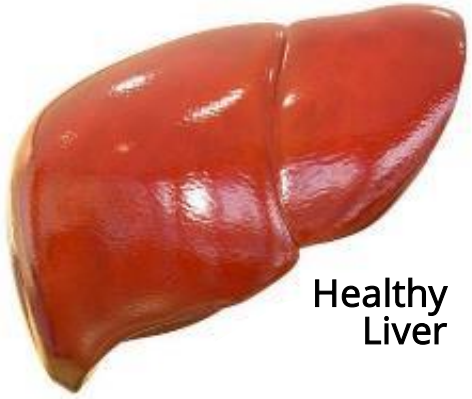
ADMET = absorption, distribution, metabolism, excretion, and toxicity. **BSEP** = Bile salt export pump. **AMES** = Ames test. **hERG** = human ether-a-go-go-related gene. **IND** =Investigational New Drug.

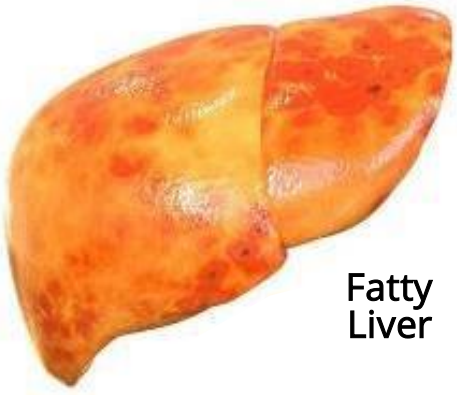
Development Indications for ADX-629 and New RASP Modulators Are Supported by Mechanistic Rationale and Clinical Results

INDICATION	RATIONALE
Ethanol Toxicity/Steatohepatitis	Acetaldehyde sequestration, clinical and preclinical evidence of lipid lowering
Chronic Cough	Evidence of RASP in sputum, symptomatic and cell results in asthma
Sjögren-Larsson Syndrome	Fatty aldehyde dehydrogenase deficiency, clinical RASP reduction
Minimal Change Disease	Corticosteroid synergy in uveitis with reproxalap†, TH1 activity in psoriasis, activity in PAN model

PAN = puromycin aminonucleoside nephrosis. †Mandell KJ, Clark D, Chu DS, Foster CS, Sheppard J, Brady TC. Randomized Phase 2 Trial of Reproxalap, a Novel Reactive Aldehyde Species Inhibitor, in Patients with Noninfectious Anterior Uveitis: Model for Corticosteroid Replacement. J Ocul Pharmacol Ther. 2020 Dec;36(10):732-739.

Ethanol Toxicity and Fatty Liver Disease Affect Millions of Patients Worldwide





Up to 10% of adults in the U.S. abuse ethanol, which when done chronically can lead to the development of liver disease.

Approximately 12 million adults in the United States have alcoholic fatty liver disease (AFLD).

The **incidence of steatohepatitis is increasing** in males and females.

Up to 50% of patients with AFLD develop **cirrhosis**.

The classic clinical syndrome of AFLD consists of **jaundice, varying degrees of hepatic failure, abdominal distress, fever, and leukocytosis**.

No approved treatments are currently available for the treatment of ethanol toxicity and AFLD, though medications (e.g., corticosteroids) may be used to reduce liver inflammation.

Sources: Company estimates; UpToDate (Ethanal intoxication in adults updated 03/19/20). . Wong et al. JAMA. 2019;321(17):1723-25. Neuman et al. Exp Mol Pathol. 2014;97(3):492-510. Singh et al. World J Gastroenterol. 2017;23:6549-6570.

Chronic Cough is A Common Disease with No Currently Approved Therapy

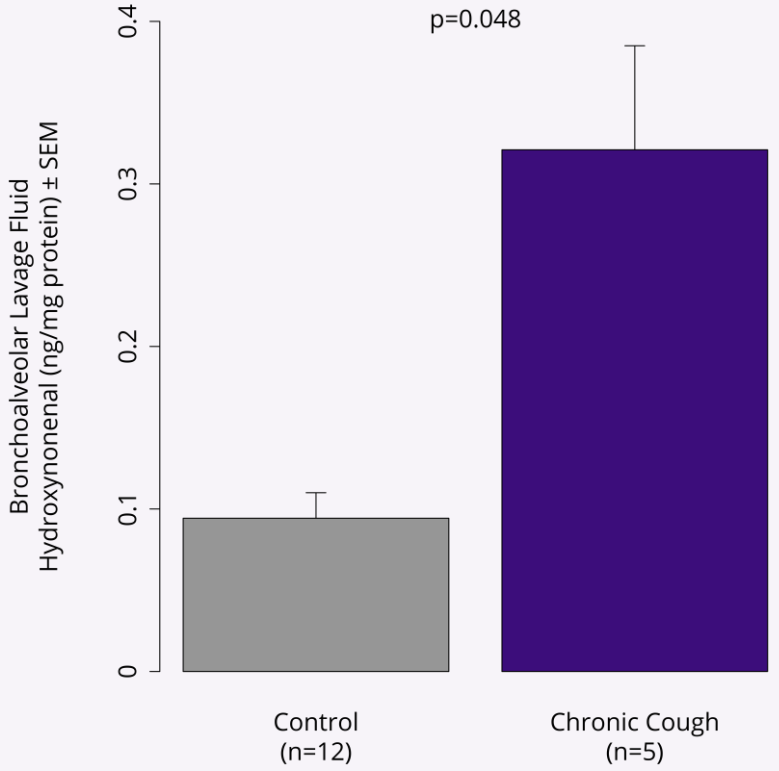
Chronic cough is defined as a cough that lasts eight weeks or longer in adults.

Affects an estimated 13M adults in the United States, and up to approximately 10% of people worldwide.

In the U.S., people with chronic cough are more frequently female (60%), have an average age of 50, and are often current smokers (30%).

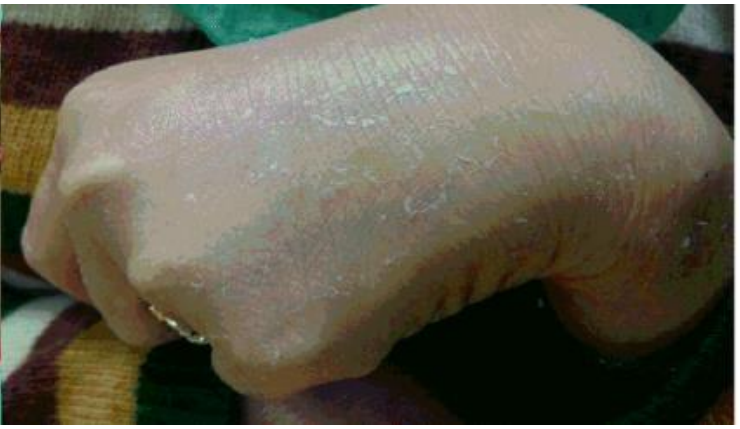
Quality of life is impaired in patients with chronic cough and has been associated with anxiety, depression, and sleep disturbance.

RASP are increased in the lungs of patients with chronic cough.



Sources: Company estimates; Meltzer et al. J Allergy Clin Immunol Pract. 2021;9:4037-4044. Arinze et al. ERJ Open Res. 2021;6:00300-2019; data on file.

Sjögren-Larsson Syndrome (SLS) Is a Rare Neurological and Dermal Condition with No Approved Therapy



Autosomal recessive neurocutaneous disorder caused error of metabolism involving fatty alcohol oxidation

The prevalence of SLS is approximately **1,300 patients in the United States.**

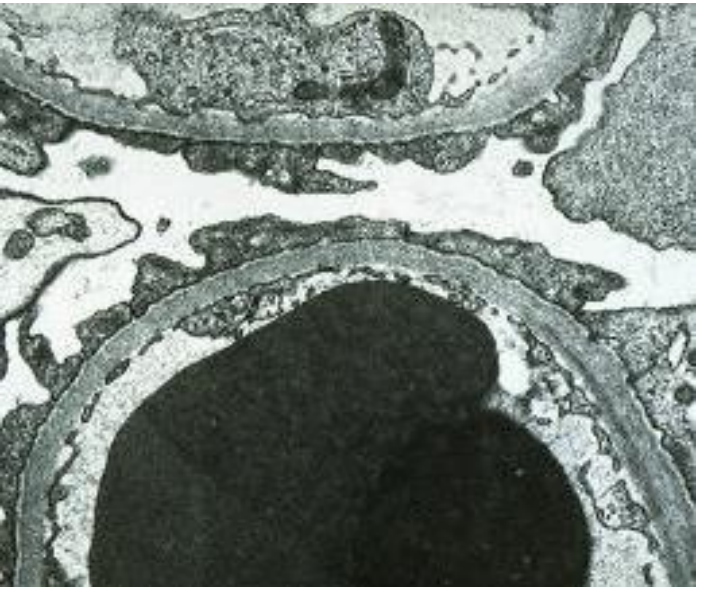
Caused by mutations in *ALDH3A2* and results in abnormal metabolism of aldehydes and alcohols.

Dermatologic features in addition to **motor, cognitive, speech, and ocular manifestations.**

Sources: UpToDate (Sjögren-Larsson syndrome updated 10/27/21). Rizzo et al. Expert Opin Orphan Drugs. 2016;4:395-406. Willemsen et al. Brain. 2001;124:1426-37.

Minimal Change Disease Is a Rare Kidney Disease with No Approved Therapy

Minimal change disease is characterized by effacement of epithelial cell foot processes.



Major cause of nephrotic syndrome in children reaching 90% of cases in children and approximately 10%-15% of adults.

The incidence in children ranges from ~1,400 to ~5,000 in the U.S. while the exact prevalence is not well understood.

Treatment involves corticosteroids and other immunosuppressant alternatives.

Relapse occurs in 40%-50% of children often during corticosteroid tapering or soon after corticosteroid discontinuation, requiring second-line therapy.

In adults, relapses are frequent, occurring in 56% to 76% of patients.

Sources: Company estimates; Vivarelli et al. Clin J Am Soc Nephrol. 2017;2:332-345. UpToDate (Minimal Change Disease updated 12/3/21).

Development Indication Phase 2a Trials Initiating in 2022 Represent Varied Trial Designs and Are Expected to Complete in 2022 and 2023†

INDICATION	PLANNED DESIGN	PLANNED ENDPOINTS	EXPECTED COMPLETION
Ethanol Toxicity	Crossover, ethanol challenge, acute dosing, ~20 subjects	Symptoms, plasma chemistry, flushing	H2 2022
Chronic Cough	Crossover, 28-day dosing, ~50 subjects	Cough frequency, symptoms	2023
Sjögren-Larsson Syndrome	Baseline-controlled, ~6 subjects	Plasma biomarkers, magnetic resonance imaging, quality of life	2023
Minimal Change Disease	Baseline-controlled, ~ 6 subjects	Relapse (corticosteroid dependency, proteinuria)	2023

†Timing depends, in part, on restrictions related to the COVID-19 pandemic, the availability of clinical research facilities and staffing, the ability to recruit patients, and regulatory feedback.

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Questions

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March 29, 2022

Todd C. Brady, M.D., Ph.D., Chief Executive Officer

Concluding Remarks

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Upcoming Planned Clinical Milestones*

Phase 3 TRANQUILITY-2 Trial of reproxalap in dry eye disease

Top-line results expected mid-2022

Part 1 of Phase 3 GUARD Trial of ADX-2191 in proliferative vitreoretinopathy

Results expected H2 2022

Phase 2 clinical trial of ADX-2191 in retinitis pigmentosa

Results expected H2 2022

Phase 2a clinical trials of ADX-629 in ethanol toxicity, chronic cough, Sjögren-Larsson Syndrome and minimal change disease

Expected completion in 2022 and 2023

*The timing of ongoing clinical trials depend, in part, on restrictions related to COVID-19, the availability of clinical research facilities and staffing, and the ability to recruit patients.

We Are Creating What We Believe Are Best-in-Class Therapeutic Platforms for Modulation of Inflammatory Disease

Unparalleled drug discovery and development engine targeting RASP, with multiple early and late-stage milestones expected over the next two years†

- Reproxalap NDA submission in dry eye disease expected mid-2022
- ADX-629 advancing to Phase 2 trials in four new indications
- New compounds for systemic and retinal disease expected in the clinic in 2023

Unique methotrexate formulation with orphan drug status in three rare retinal diseases

- ADX-2191 represents potential gold-standard treatment for proliferative vitreoretinopathy, retinitis pigmentosa, and primary vitreoretinal lymphoma.

†Timing depends, in part, on restrictions related to the COVID-19 pandemic, the availability of clinical research facilities and staffing, the ability to recruit patients, and regulatory feedback.
‡NDA submission requirements depend, in part, on clinical results and regulatory feedback. **NDA** = New Drug Application.