



Research Day 2018

Update on Research Programs

June 26, 2018

New York

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Our Mission

Developing Next-Generation Medicines to Improve the Lives of Patients with Immune-Mediated Diseases

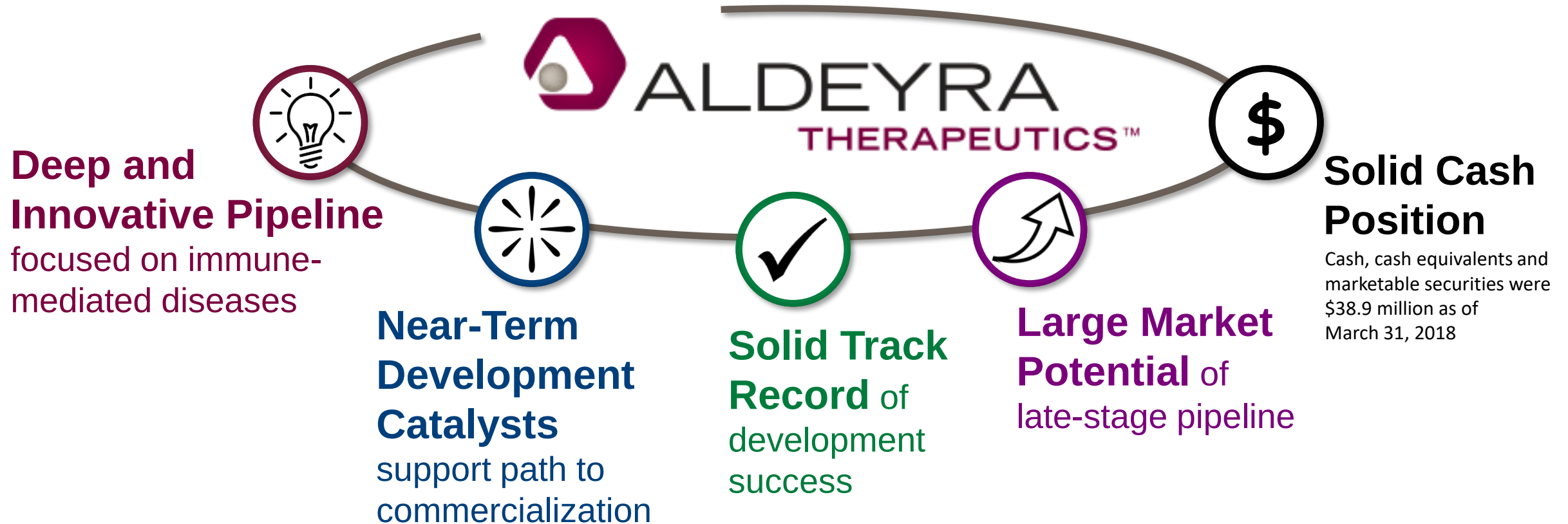


Suffer from some form of **immune-mediated disease**



Disease control elusive despite existing therapies, and thus **novel approaches are needed**

Developing Next-Generation Medicines to Improve the Lives of Patients with Immune-Mediated Diseases



Reproxalap: Lead Candidate With Significant Commercial Potential



*Ocular
Inflammation*

Dry Eye Disease

**Allergic
Conjunctivitis**

**Noninfectious
Anterior Uveitis**



*Inborn Errors
of Metabolism*

**Sjögren-Larsson
Syndrome**

Estimated
U.S. Population¹

20 million

30 million

150,000
flares per yr.

1,000³

**Reproxalap
Development Stage**

Phase 2b

Phase 3

Phase 3

Phase 3

**Potential
Competitive Advantages²**

- **Rapid onset, broader activity**
- **Non-drying, durable activity, responder superiority vs. vehicle**
- **No expected risk of glaucoma or other corticosteroid toxicities**
- **Clinically demonstrated efficacy**
- **No FDA therapy currently approved**

¹ Aldeyra estimates based on internal market research and publicly available information.

² Pending clinical data, regulatory discussions, payor negotiations, competition, potential legislative changes, and other factors, which may not be in Aldeyra's control. Preliminary assumptions are subject to change.

³ Extrapolated from a Swedish estimate and a U.S. genetic mutation analysis, it is generally assumed that there are approximately 1,000 Sjögren-Larsson Syndrome (SLS) patients in the United States and a greater number of SLS patients in Europe.

Deep and Innovative Pipeline

Approach	Compound	Indication	Preclinical	Phase 1	Phase 2	Phase 3	Next Expected Milestone
RASP Inhibitors	Reproxalap Ocular	Dry Eye Disease					Phase 2b results H2-2018
		Allergic Conjunctivitis					Phase 3 results H2-2018 / 2019
		Noninfectious Anterior Uveitis					Phase 3 results 2019
	Reproxalap Dermal	Sjögren-Larsson Syndrome					Phase 3, Part 1 results 2019
	ADX-629 Systemic	Autoimmune Disease					
	ADX-103	Retinal Disease					
	Not Disclosed	Systemic Inflammatory Disease				<i>Research Collaboration</i> 	
Hsp90 Inhibitors	ADX-1612	Lymphoproliferative Immune Disease					
		Ovarian Cancer				<i>Investigator Sponsored Trial</i>	
		Mesothelioma				<i>Investigator Sponsored Trial</i>	Phase 2 results H2-2018
	ADX-1615	Autoimmune Disease					
		Cancer					
Anti-Inflammatory	Not Disclosed	Ocular Inflammation					

2018 Progress and Near-Term Development Catalysts Support Path to Commercialization

H1 2018

- ✓ Initiated reproxalap **Phase 2b clinical trial in dry eye disease**
- ✓ Initiated reproxalap **Phase 3 clinical trial in allergic conjunctivitis**
- ✓ Entered into **research collaboration with Johnson & Johnson Innovation** in systemic inflammatory diseases
- ✓ Disclosed **in-license of a Hsp90 inhibitor**
- ✓ Clinical sites initiated for reproxalap **Phase 3, Part 1 clinical trial in Sjögren-Larsson Syndrome**

H2 2018

Anticipated Milestones*

- First patient enrolled in reproxalap Phase 3, Part 1 clinical trial in Sjögren-Larsson Syndrome **Q3 2018**
- Reproxalap dry eye disease Phase 2b clinical trial results **H2-2018**

2019

- Reproxalap allergic conjunctivitis Phase 3 results **H2-2018/early 2019**
- Reproxalap noninfectious anterior uveitis Phase 3 clinical trial results **2019**
- Reproxalap Sjögren-Larsson Syndrome Phase 3, Part 1 clinical trial results **2019**

*Contingent on funding, regulatory review, and other factors.



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Developing Next-Generation Medicines to Improve the Lives of Patients with Immune-Mediated Diseases

Targeting RASP

- ADX-629 for Systemic Immune-Mediated Diseases
- ADX-103 for Inflammatory Retinal Disease

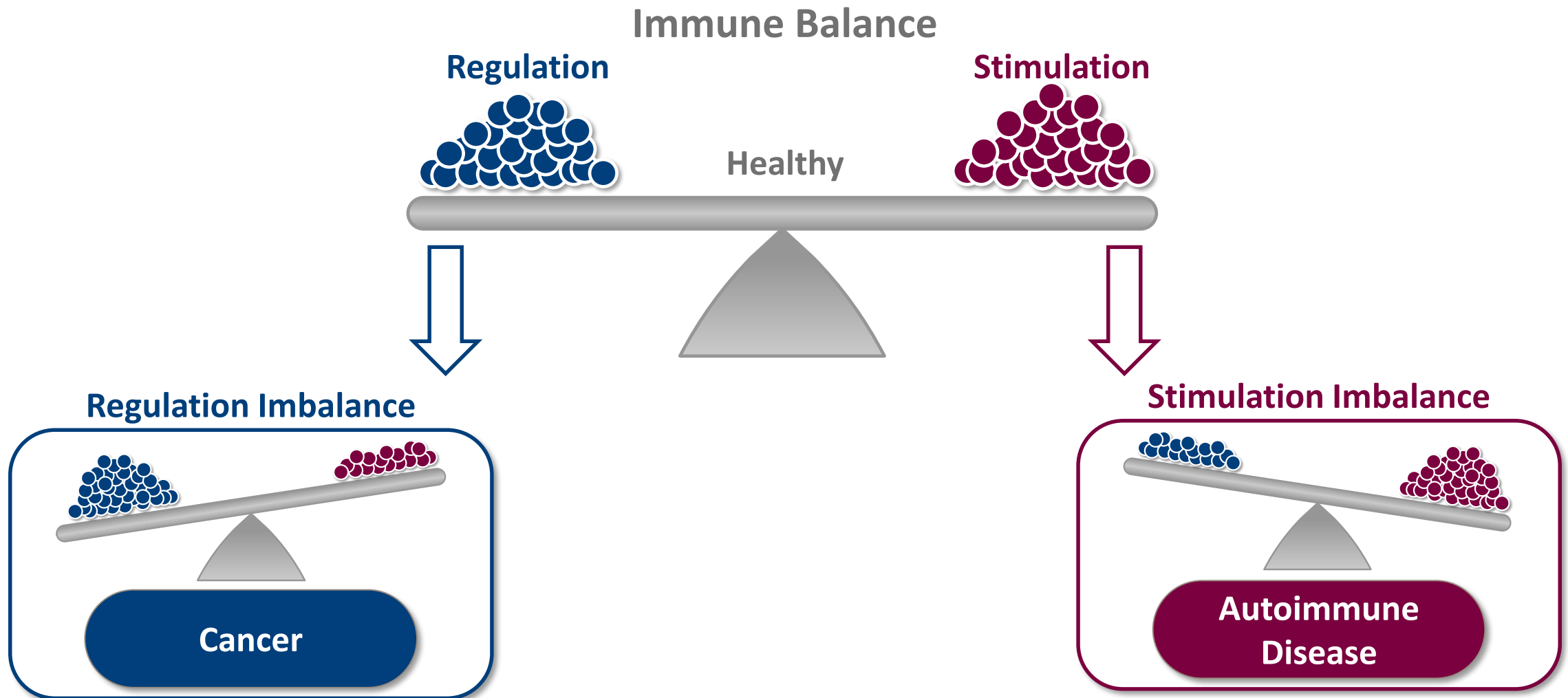
Targeting Hsp90

- ADX-1612 for Lymphoproliferative Immune Disease and Cancer
- ADX-1615 for Autoimmune Disease and Cancer

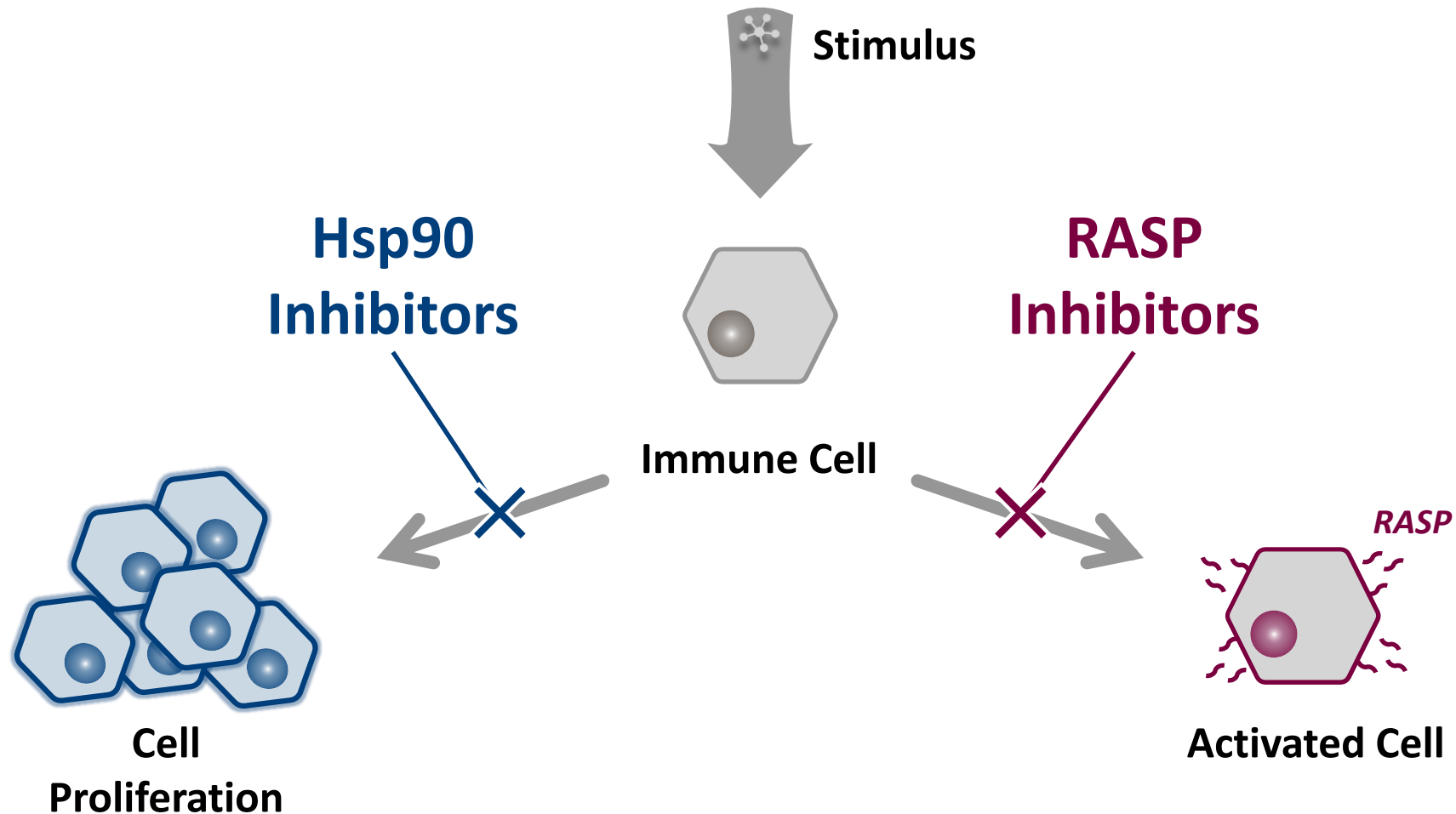
Partnership Update

- J&J Innovation

Immune System Balance is Complex



Novel Approaches to Address Immune-Mediated Disease



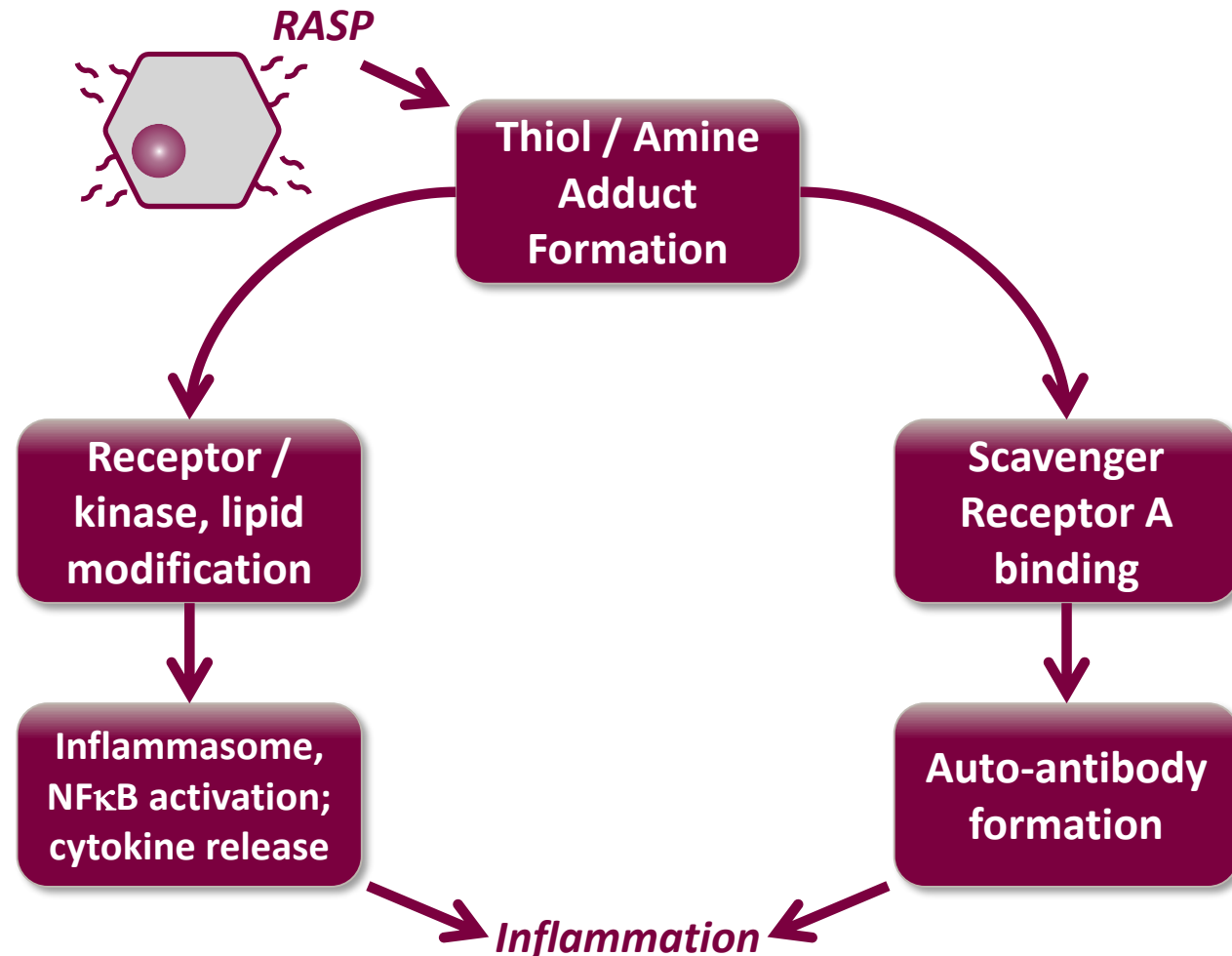


Targeting RASP for Systemic Immune-Mediated Diseases

ADX-629

Targeting RASP: Mediators of Inflammation and Activators of the Immune System

Activated Immune Cell



Scientific Literature

Cardiovasc Res. 2010 Nov 1;88(2):352-9. HNE-induced 5-LO expression is regulated by NF-κB/ERK and Sp1/p38 MAPK pathways via EGF receptor in murine macrophages.

Biofactors. 2005;24(1-4):229-36. Role of 4-hydroxy-2,3-nonenal in the pathogenesis of fibrosis.

Cell Mol Biol Lett. 2015 Dec;20(4):647-62. The advanced lipoxidation end product precursor malondialdehyde induces IL-17E expression and skews lymphocytes to the th17 subset.

J Leukoc Biol. 2012 Nov;92(5):1055-67. Proinflammatory effects of malondialdehyde in lymphocytes.

Diabetes. 2008 Apr;57(4):879-88. Proinflammatory effects of advanced lipoxidation end products in monocytes.

ADX-629: A Novel Pre-Clinical RASP Inhibitor for Treatment of Systemic Immune-Mediated Disorders

NASH (non-alcoholic steatohepatitis)



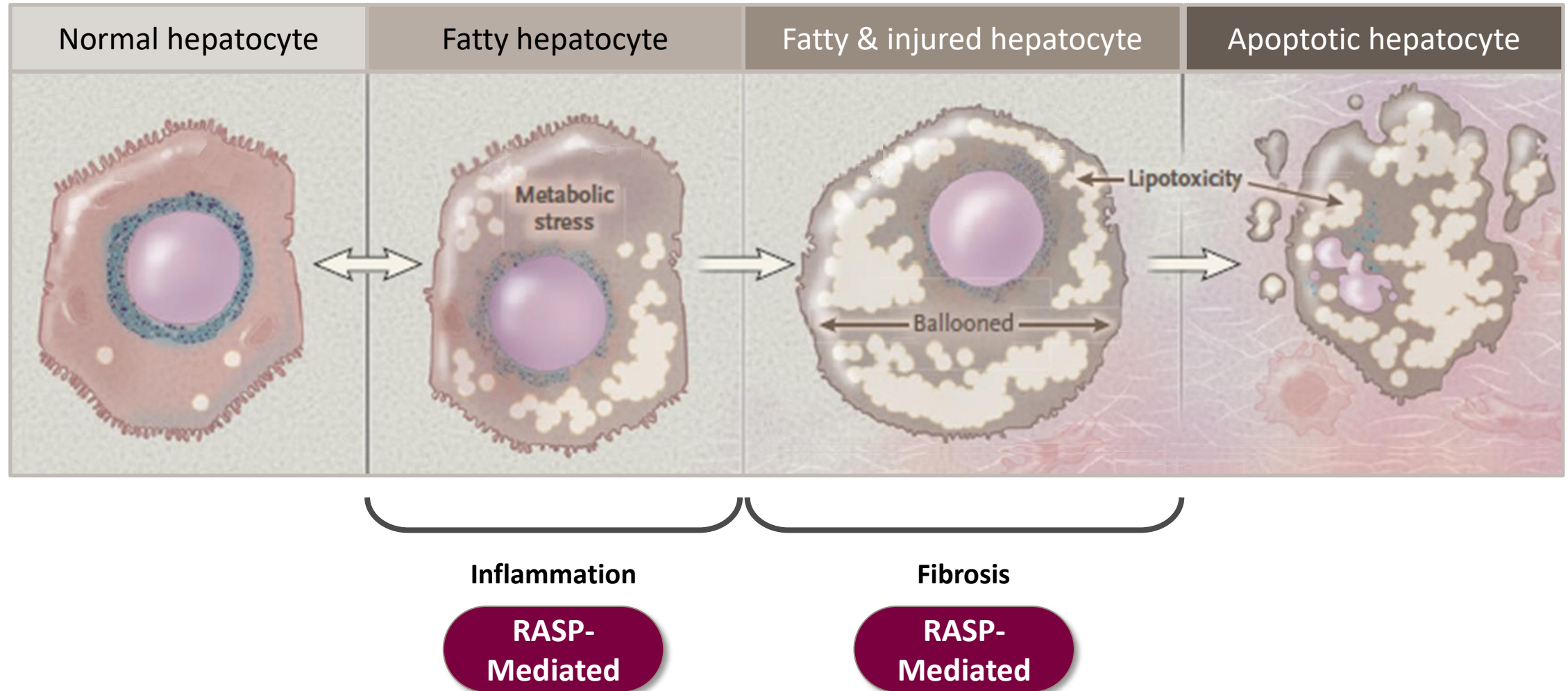
- Highly prevalent disease characterized by liver inflammation, fibrosis, cirrhosis, and hepatocellular carcinoma
- No FDA-approved therapy
- RASP end-products observed in NASH

IBD (inflammatory bowel disease)

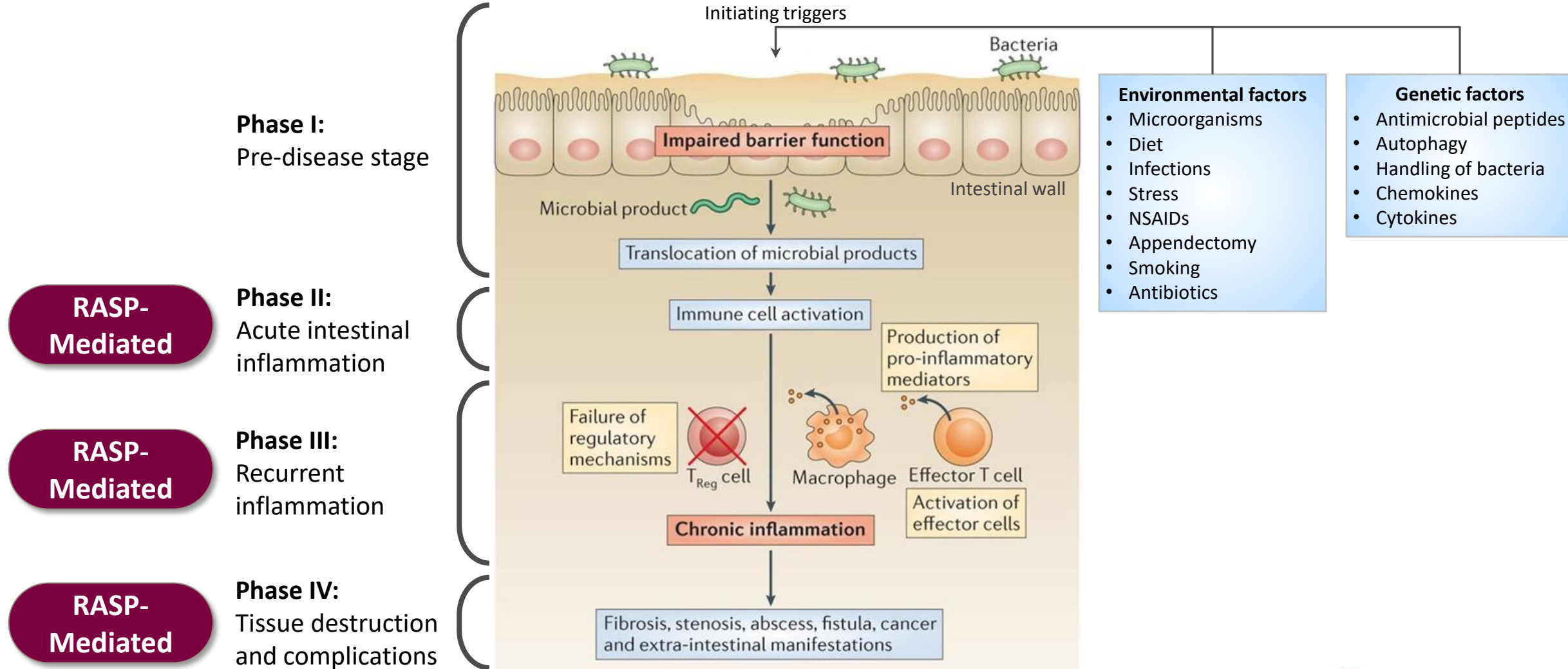


- Over one million patients in the U.S. suffer from Ulcerative Colitis and Crohn's Disease
- Chronic autoimmune disease with variable response to therapy
- RASP observed in preclinical models; decreased RASP metabolism observed in diseased human intestinal tissue

NASH Pathogenesis: Chronic Progression of Inflammation and Fibrosis



IBD Pathogenesis: Chronic Relapsing Intestinal Inflammation



ADX-629: A Pre-Clinical Novel RASP Inhibitor

ADX-629 is an analog of reproxalap

Reproxalap has **demonstrated activity in immune-mediated diseases**

Pre-Clinical Models

- ✓ Sepsis
- ✓ Inflammatory pain
- ✓ Oral mucositis
- ✓ Allergic dermatitis
- ✓ Contact dermatitis
- ✓ Acute lung injury
- ✓ Corneal fibrosis

Clinical Trials

- ✓ Dry eye disease
- ✓ Allergic conjunctivitis
- ✓ Noninfectious anterior uveitis

ADX-629 Decreased LPS-Induced Pro-inflammatory Cytokine Levels and Increased Levels of an Anti-inflammatory Cytokine in Animal Models

- ADX-629 (100 mg/kg) was administered intraperitoneally to mice
- LPS was administered intraperitoneally (1 mg/kg) 15 minutes later
- Blood was collected 2 hours after ADX-629 administration and plasma cytokines measured by ELISA

Pro-Inflammatory				Anti-Inflammatory	
Cytokine	Decrease	Cytokine	Decrease	Cytokine	Increase
RANTES	93.8%	IL-15	72.1%	IL-10	2103%
MIP-1 α	93.1%	IL-9	72.0%		
IL-12(p40)	92.4%	IL-1 β	71.5%		
G-CSF	91.1%	IFN γ	71.3%		
LIF	85.8%	IL-12(p70)	68.8%		
MIG	83.3%	IL-1 α	67.5%		
IL-5	82.3%	IL-7	65.2%		
IL-17	77.4%	LIX	62.0%		
M-CSF	75.1%	TNF α	60.3%		
GM-CSF	73.7%	IL-3	56.0%		
IL-13	73.6%	VEGF	55.2%		
IL-15	72.1%	Eotaxin	26.1 %		

p values range from < 0.05 to < 0.0001

Potential ADX-629 Development Overview

IND-Enabling Toxicology

Phase 1 Clinical Trial

Phase 2a NASH Clinical Trial

Phase 2a IBD Clinical Trial

✓ Planning to initiate clinical testing in 2019



Targeting RASP for Inflammatory Retinal Disease

ADX-103

ADX-103: A Structurally Distinct Pre-Clinical RASP Inhibitor

Potential product candidate for treatment of retinal disease

- Diabetic macular edema (DME)
- Dry age-related macular degeneration (AMD) / Stargardt's Disease
- Posterior uveitis

RASP observed in retinal disease

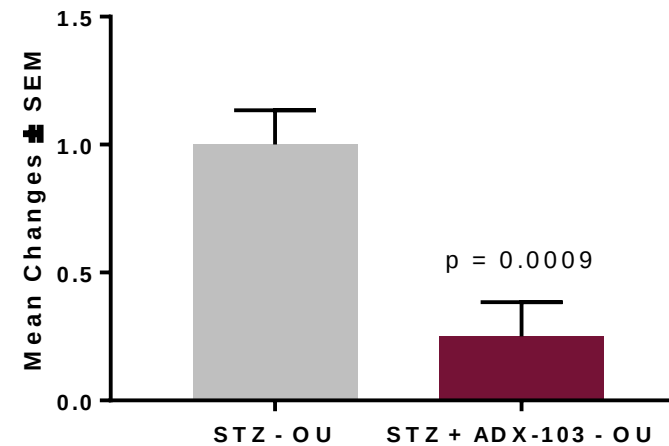
- DME: Glyoxal, methylglyoxal, allysine
- AMD/Stargardt's Disease: Retinaldehyde
- Posterior uveitis: Malondialdehyde, 4-hydroxynonenal

Efficacy in several preclinical models of ocular inflammation

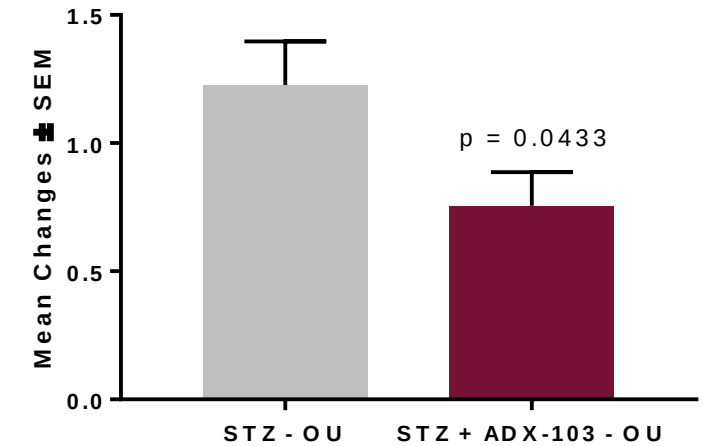
Diabetic Macular Edema: ADX-103 Blocked Diabetes-Induced Retinal Changes in Animal Models

- Male Norway rats were administered streptozotocin (STZ), 55 mg/kg IP, on Day 0 to induce diabetes
- Two single doses of ADX-103 (17.5 µg each) were administered intravitreally, after induction of diabetes (Days 42 and 57)
- Histopathology of the retina was conducted at Day 71

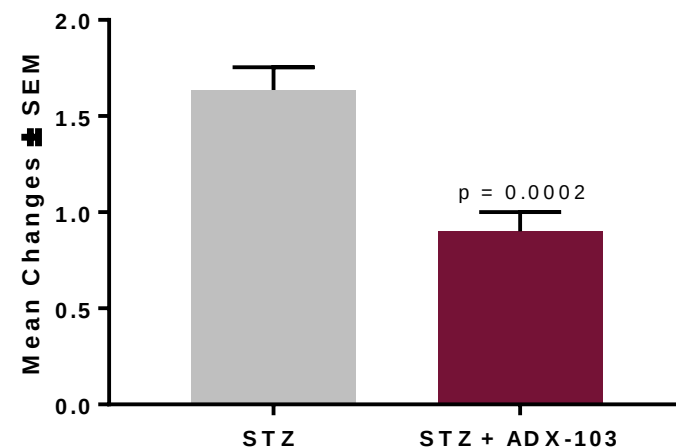
Neutrophil Infiltration at Day 71



Retinal Vascularity Changes at Day 71



Retinal Thickness Changes at Day 71



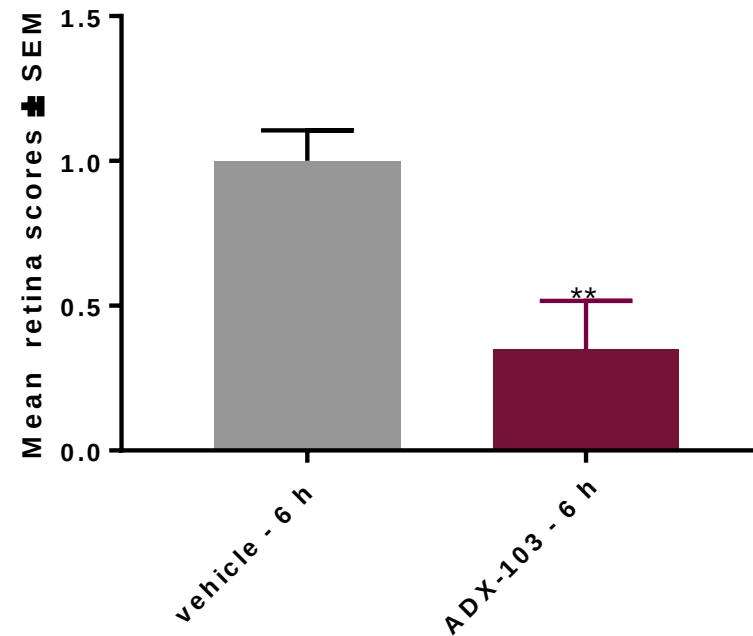
Scale:

- 1 = minimal microscopically visible changes
- 2 = mild microscopically visible changes
- 3 = moderate microscopically visible changes

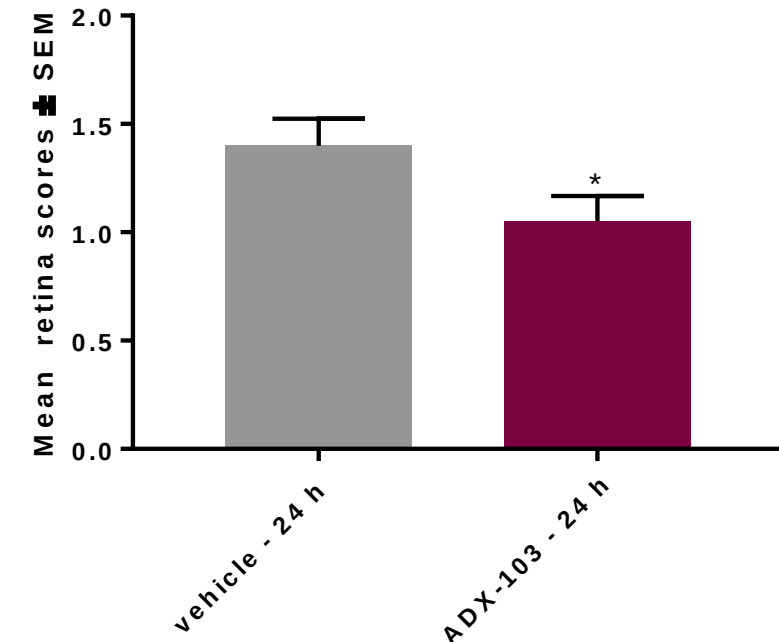
Endotoxin-Induced Uveitis: ADX-103 Decreased Ocular Inflammation in Animal Models

- Ocular inflammation in rats induced by footpad injection of a bacterial endotoxin (LPS)
 - Severe model
 - Peaks at 24 hours
- A single intravitreal dose of ADX-103 (25 µg/eye) was administered at hour 1 post-LPS administration
- Retina-choroid complex was scored for inflammatory changes at six and 24 hours

Retinal Inflammation at 6 Hrs. Post Insult



Retinal Inflammation at 24 Hrs. Post Insult



* $p < 0.05$; ** $p < 0.01$

Potential ADX-103 Retina Program Overview

IND-Enabling Toxicology

Phase 1/2 Clinical Trial

Phase 2 Clinical Trial

✓ Planning to initiate clinical testing in 2019



Targeting Hsp90 for Lymphoproliferative Immune
Disease and Cancer

ADX-1612

ADX-1612: Clinically Advanced Asset With Extensive Preclinical, Nonclinical, and Clinical Data

In-licensed for potential in immune-mediated disease

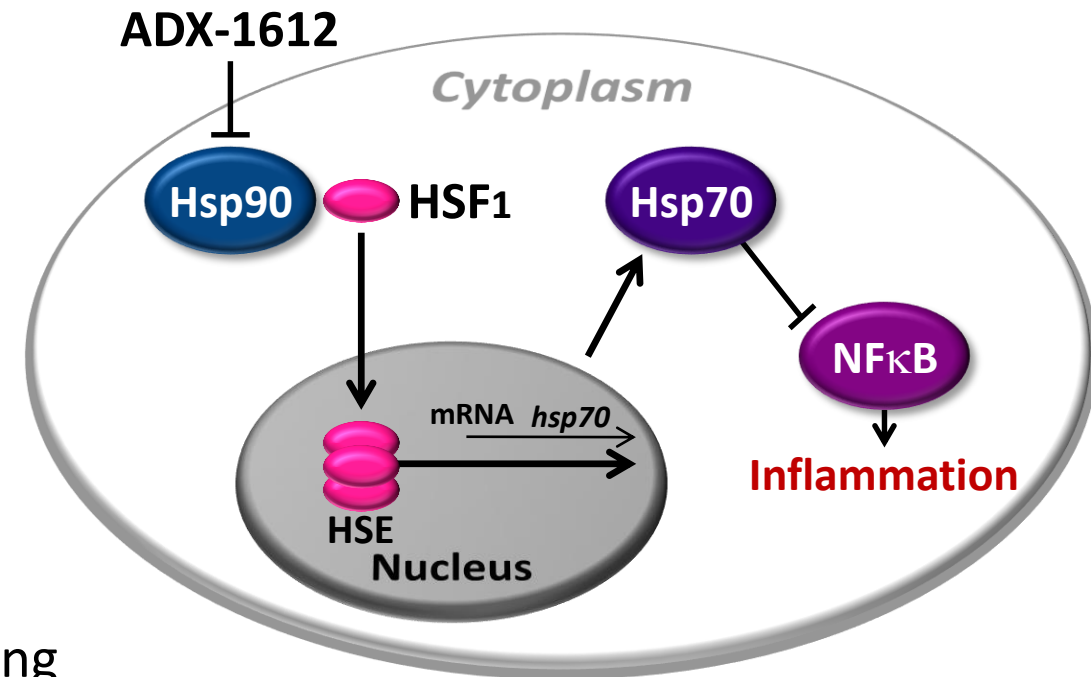
- Preclinical efficacy in immune disorders
 - Unregulated proliferation of immune cells
- Lymphoproliferative/immunoproliferative disorders
 - Hyperactive immune system
- IV formulation

ADX-1612 clinically-tested in oncology as ganetespib

- Ongoing Investigator-Sponsored Trials (ISTs) using ADX-1612 in combination with platins

ADX-1612: Expanding The Potential Repertoire for Treatment of Immune-Mediated Diseases

- ADX-1612
 - Hsp90 inhibitor
- Hsp90
 - Upregulated in stressful conditions
 - Role in antigen presentation in dendritic cells
 - Client proteins involved in signal transduction and cell cycle (e.g., cell proliferation, survival, apoptosis)
- Inhibition of Hsp90
 - Prevents proper folding of client proteins, leading to degradation and disruption of cell cycle
 - Prevents DNA repair



Adapted from Tukaj and Wegrzyn Cell Stress and Chaperones 21:213 – 218, 2016.

ADX-1612: Observed Effects on Vasculitis in a Patient With Leukemia in Phase 1 Clinical Trial

Vasculitis:

Inflammation of blood vessel walls

- Fever, headache, fatigue, weight loss, aches and pains, night sweats, rash, ulcers, numbness or weakness
- ✓ Clearing of limb rash after first ADX-1612 treatment

Pre-Treatment



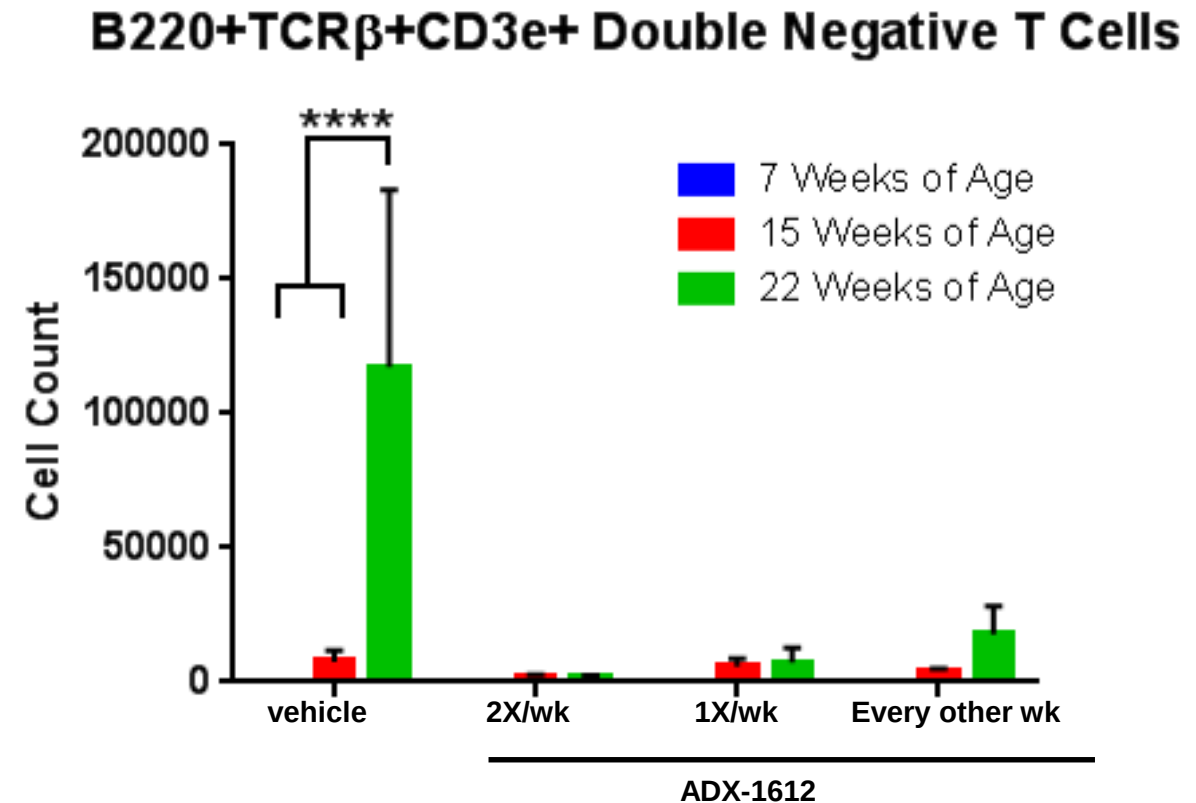
Post-Treatment



ADX-1612: Inhibition of Immune Cell Proliferation Observed in an Animal Model of Lupus

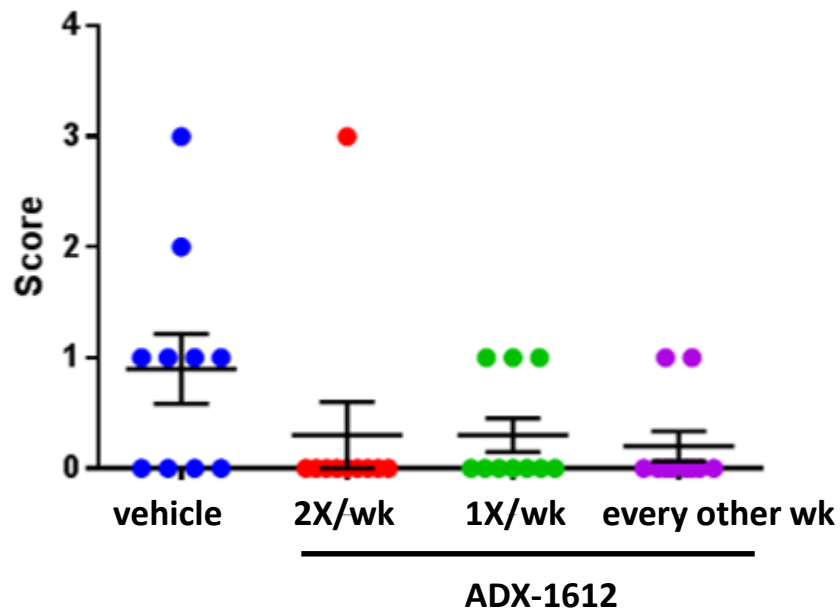
Systemic autoimmunity
(MRL/lpr mouse)

- Treatment was initiated at 7 weeks of age and continued through 22 weeks of age
- Dosing: 50 mg/kg, IV
 - twice weekly
 - once weekly
 - every other week

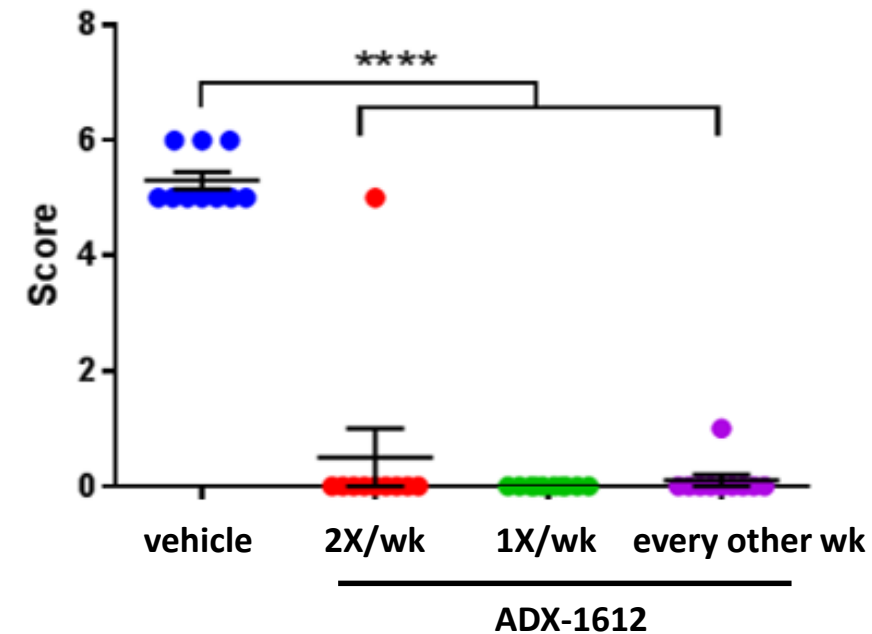


ADX-1612: Skin Lesions and Lymphadenopathy Decreased in an Animal Model of Lupus

Skin Lesion Score at 22 Weeks



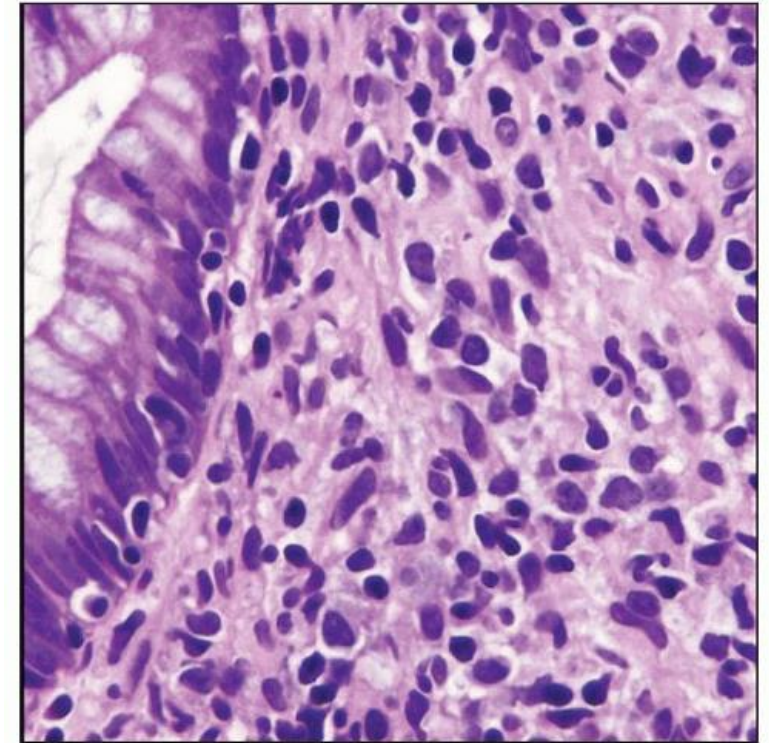
Lymphadenopathy Score at 22 Weeks



Proposed Indication:

Post-Transplant Lymphoproliferative Disorder (PTLD)

- PTLD occurs after stem cell transplant or organ transplant
 - Most serious complication of transplantation, resulting from immunosuppression
 - Uncontrolled proliferation of lymphocytes
 - Medication-induced reduction in immune surveillance
 - Imbalance between immunosuppression and immune surveillance
 - May progress to lymphoma
 - No optimal therapy
- Hsp90 overexpressed in lymphomas
- Initiation of Phase 2a clinical trial currently anticipated in 2019



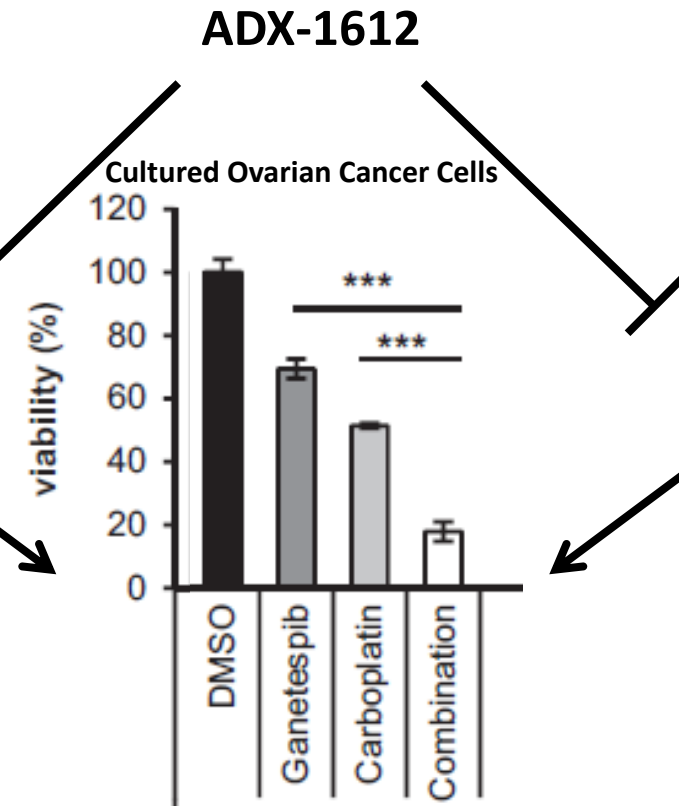
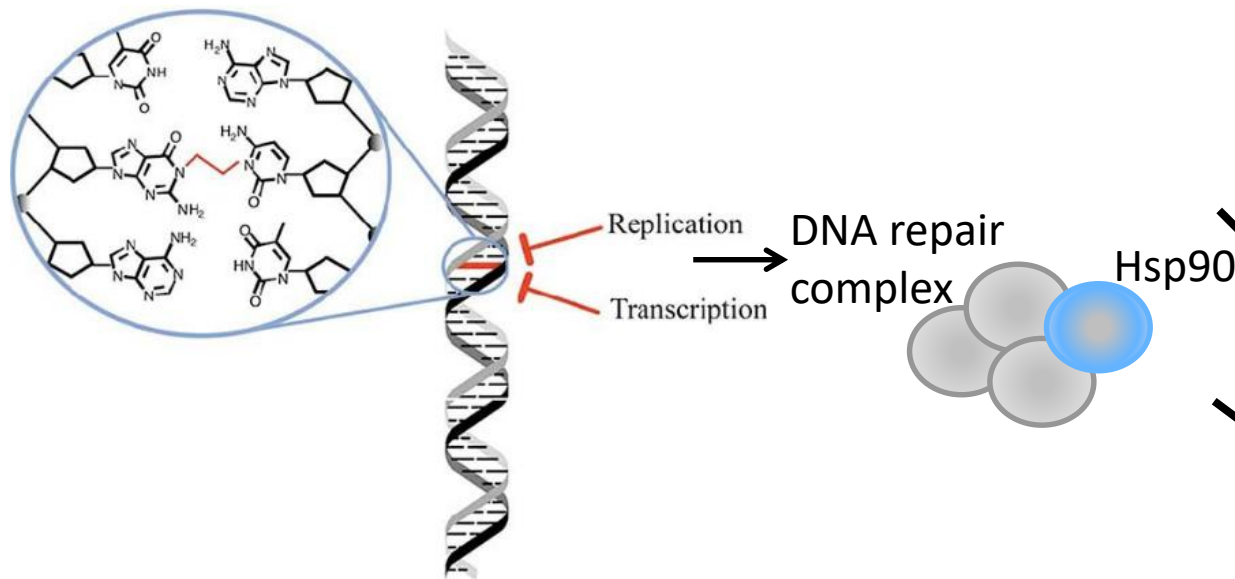
Polymorphic post-transplant lymphoproliferative disorder (PTLD) involving the rectum.
Source: Yin and Lin; Basicmedical Key

Rationale for Synergism of Hsp90 Inhibitor and Platins for The Treatment of Cancer

Platins induce
DNA damage...

...But damaged DNA
can be repaired

Inhibition of Hsp90 prevents repair and inhibits
proteins involved in tumor cell survival



Key Cancer Proteins

Wee1
Chk1
Src
Raf
MEK
PDK1
AKT
HIF-1 α
IKK
Apaf-1
STAT3
STAT5

ADX-1612: A Promising Asset for Oncology

Investigator-sponsored trials (IST) in cancer ongoing

- **Mesothelioma:**
ADX-1612 + pemextred (antimetabolite) /
platinum (DNA damage inducer) therapy
 - Expected data readout **2H 2018**
- **Ovarian cancer (EUDARIO):**
ADX-1612 + carboplatin + niraparib (PARP inhibitor)
 - Initiation currently anticipated **2H 2018**

ADX-1615: Oral Pro-Drug of ADX-1612

- Orally administered
- Oral administration may be better suited to treatment of chronic immune-mediated disorders
- May also be useful in oncology setting
- Has shown activity in mast cell tumors in dogs (monotherapy)
 - Manuscript submitted
- Next Steps
 - Manufacturing
 - IND-enabling toxicology studies
 - Clinical testing could begin as early as 2020



Partnership Update

Partnership Update

Johnson & Johnson Innovation: Collaborative research agreement

- **Focus:** RASP inhibitors (not including reproxalap)
- **Indications:** immune-mediated diseases characterized by **systemic inflammation**
- Governed by **Joint Scientific Review Committee**
- Limited option for Janssen to negotiate exclusive license to compounds developed during the collaboration





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- ✓ Clinical sites initiated for reproxalap **Phase 3, Part 1 clinical trial in Sjögren-Larsson Syndrome**

H2 2018



First patient enrolled in reproxalap Phase 3, Part 1 clinical trial in Sjögren-Larsson Syndrome **Q3 2018**



Reproxalap dry eye disease Phase 2b clinical trial results **H2-2018**

2019



Reproxalap allergic conjunctivitis Phase 3 results **H2-2018/early 2019**



Reproxalap noninfectious anterior uveitis Phase 3 clinical trial results **2019**



Reproxalap Sjögren-Larsson Syndrome Phase 3, Part 1 clinical trial results **2019**

Early-Stage Development Expected Milestones: Novel Approaches to Address Immune-Mediated Disease

H2 2018

Anticipated Milestones*



ADX-1612 mesothelioma clinical trial results
(investigator sponsored trial) **H2-2018**



ADX-1612 ovarian cancer clinical trial initiation
(investigator sponsored trial) **H2-2018**

2019



ADX-629 Phase 1 clinical trial initiation **2019**



ADX-629 NASH and/or IBD Phase 2a clinical trials initiation
following Phase 1



ADX-103 retinal disease Phase 1/2 clinical trial initiation **2019**



ADX-1612 lymphoproliferative immune disease Phase 2 clinical
trial initiation **2019**

*Contingent on pre-clinical studies, funding, regulatory review, and other factors.

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		Cancer					
Anti-Inflammatory	Not Disclosed	Ocular Inflammation					