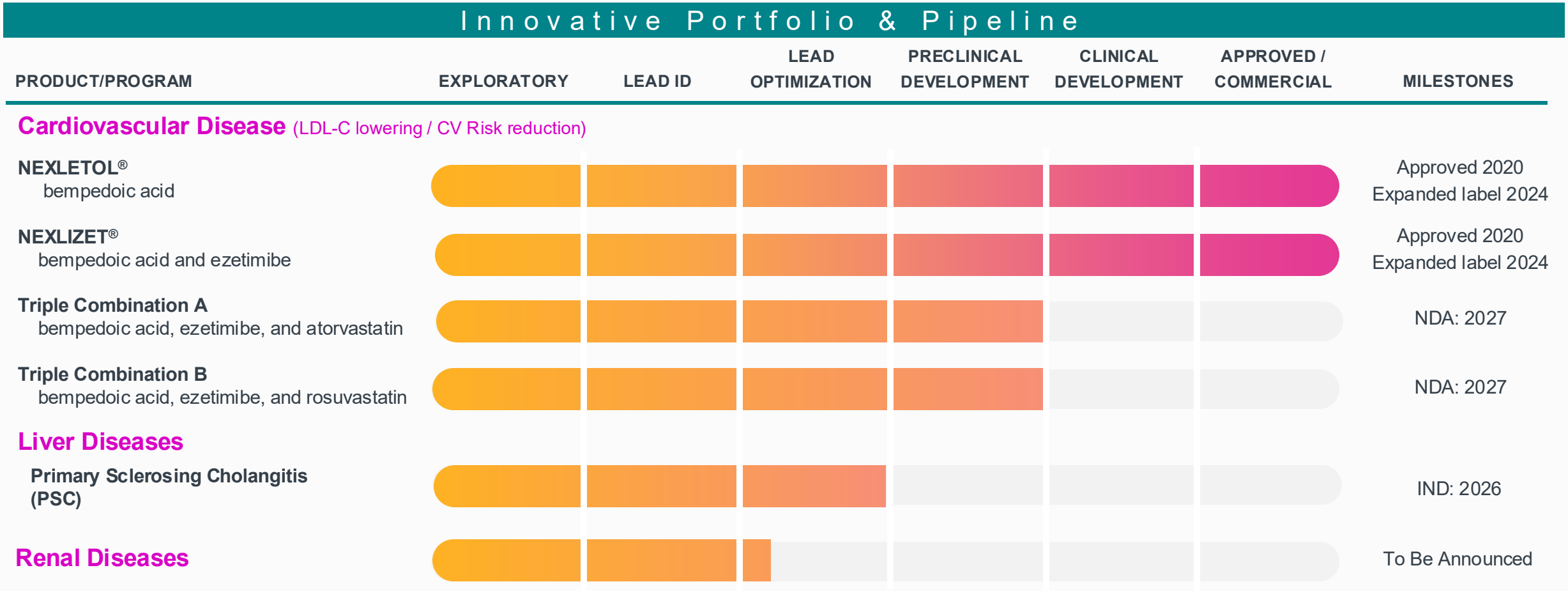
ESPERION®

Esperion's Next Generation ACLY Inhibition PSC Discovery Program

Heather Powell, PharmD
Head of Medical Affairs

Expanding Our Pipeline Through ACLY Innovation and Expertise

Innovative Portfolio & Pipeline



ACLY: ATP citrate lyase; LDL-C: low-density lipoprotein cholesterol; CV: cardiovascular; NDA: New Drug Application; IND: Investigational New Drug

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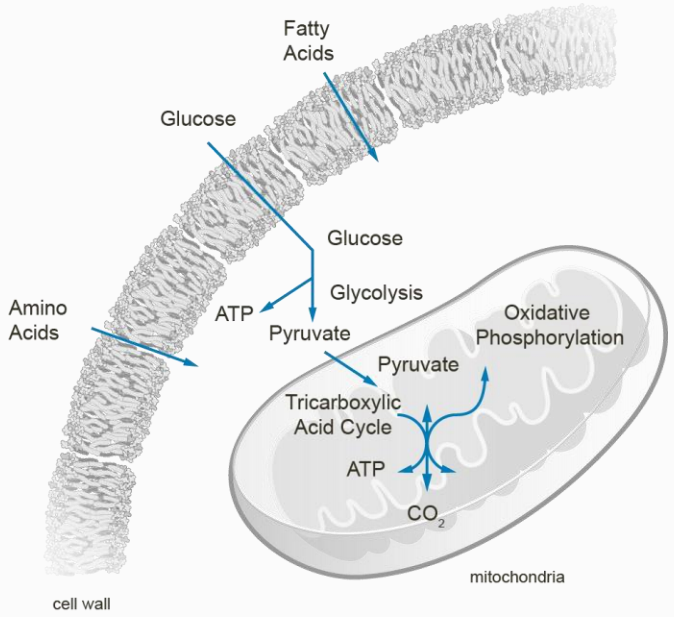
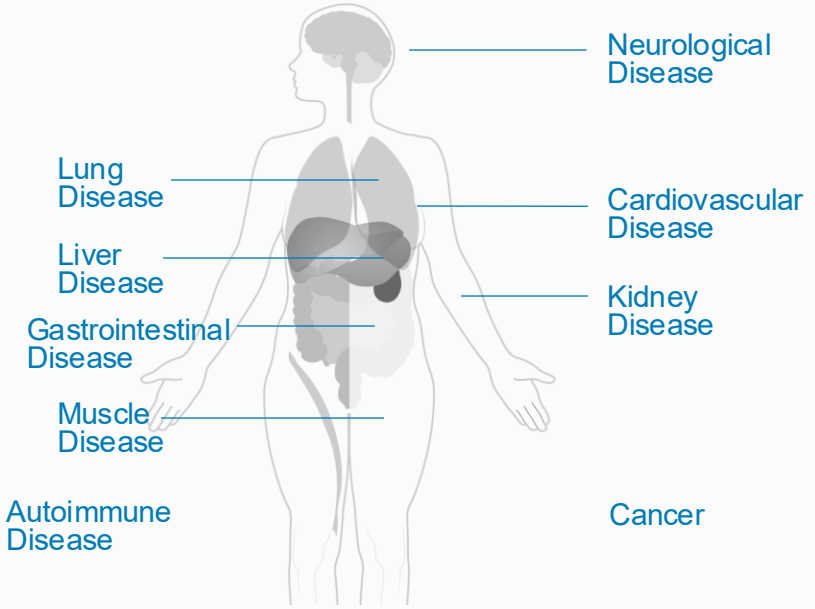
Dysregulated Cellular Energetics Drive Many Diseases[1-3]

Metabolic Energy Pathways



Dysregulation

Development of Disease



When dysregulated, there is disruption of the tricarboxylic acid (TCA) cycle leading to abnormal energy production and utilization

ATP: adenosine triphosphate

1. Ren J, et al. *J Mol Med*. 2010;88:993–1001; 2. Rocha M, et al. *Medicinal Research Reviews*. 2013;00:1–30; 3. Javadov S, et al. *Cells*. 2020;9:1177
Adapted from https://www.britannica.com/science/catabolism

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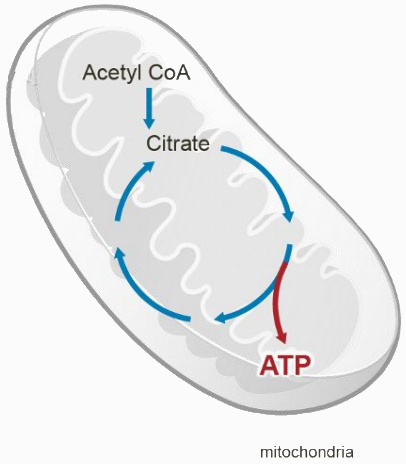
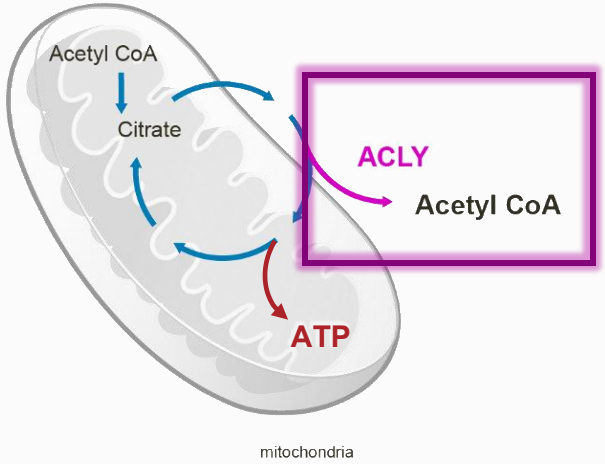
The Canonical and Non-Canonical TCA Cycles are Critical Energy Pathways in All Cells[1-3]

Canonical TCA (Krebs) Cycle



- Consumes lipids and carbohydrates to **generate ATP—energy production**
- Occurs in **mitochondria only**

Non-Canonical TCA Cycle



- Utilized by **highly proliferative cells**, cancer cells and stem cells with high energy demands
- Occurs **across mitochondria, cytoplasm, and nucleus**

ACLY: ATP citrate lyase; TCA: tricarboxylic acid; ATP: adenosine triphosphate; Acetyl CoA: acetyl coenzyme A

1. Arnold PK, et al. *Nature*. 2022;603:477–481; 2. Mateska I, Alexaki VI. *Sig Transduct Target Ther.* 2022;7:201; 3. Chen G, et al. *Biomedicine & Pharmacotherapy.* 2023;168:115741

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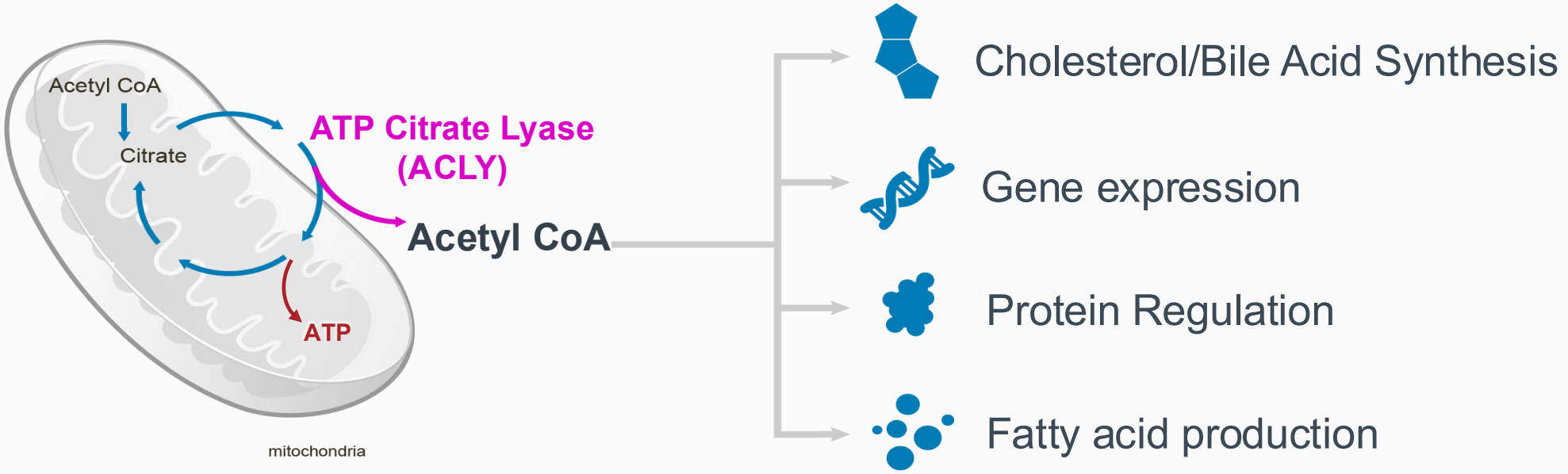
ACLY is the Key Enzyme in the Non-Canonical TCA Cycle[1,2]

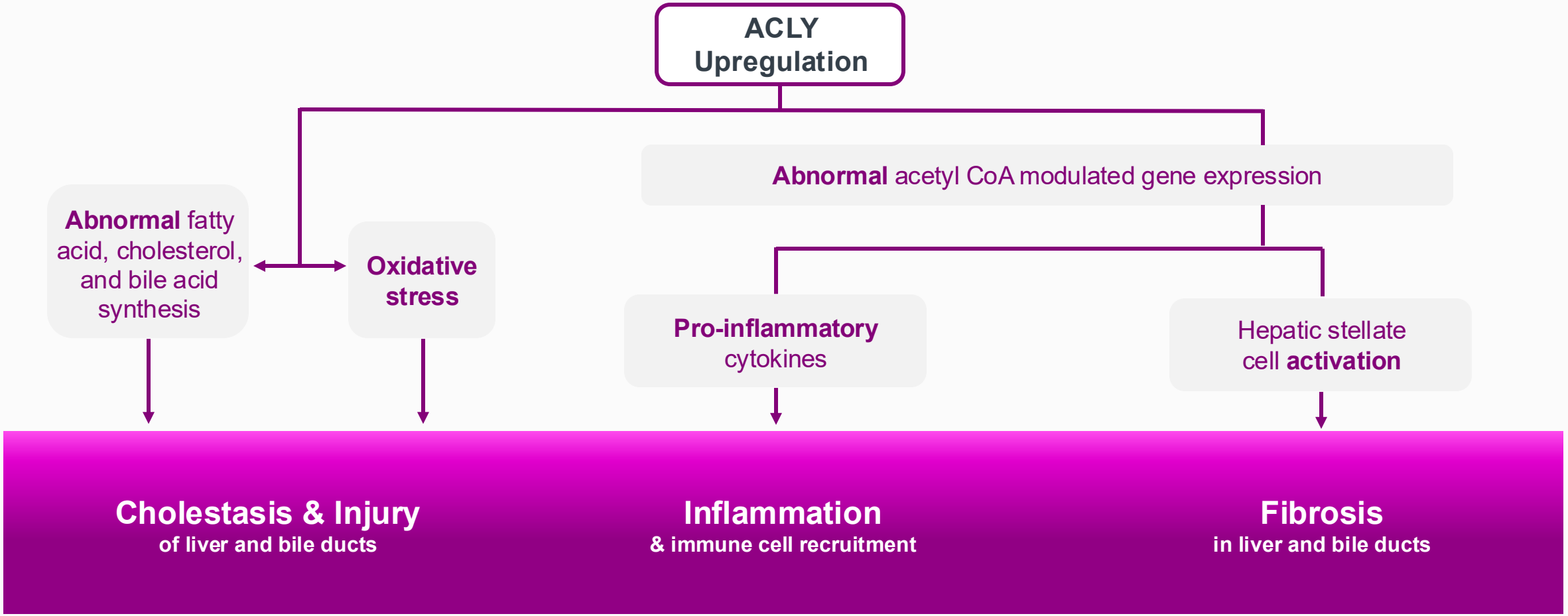
Acetyl CoA production regulated energetic and metabolic process in multiple cell types



ACLY: ATP citrate lyase; TCA: tricarboxylic acid; ATP: adenosine triphosphate; Acetyl CoA: acetyl coenzyme A

1. Mateska I, Alexaki VI. *Sig Transduct Target Ther.* 2022;7:201; 2. Chen G, et al. *Biomedicine & Pharmacotherapy*. 2023;168:115741

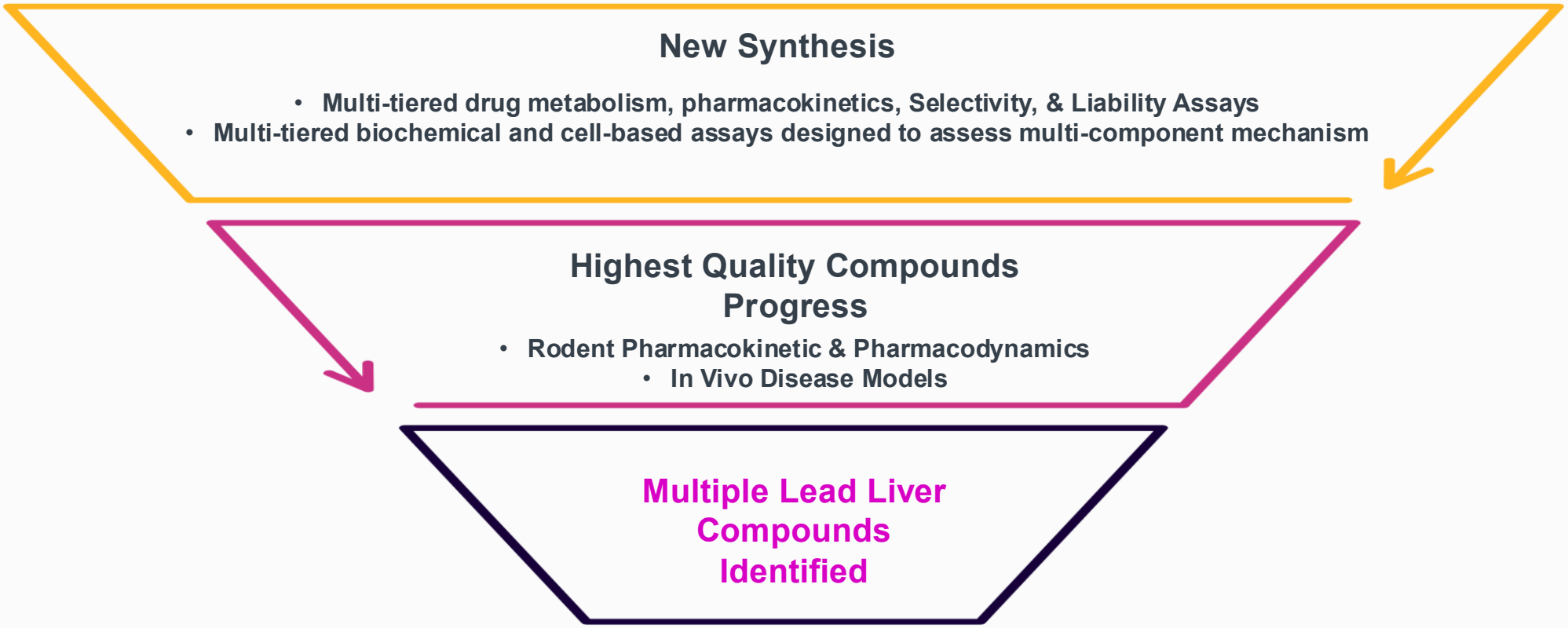
ACLY Upregulation is Directly Related to Multiple Mechanisms of PSC Progression



ACLY: ATP citrate lyase; PSC: primary sclerosing cholangitis; Acetyl CoA: acetyl coenzyme A

Identification of Lead Candidates for PSC

Utilized state of the art drug discovery technology to design highly potent and selective molecules



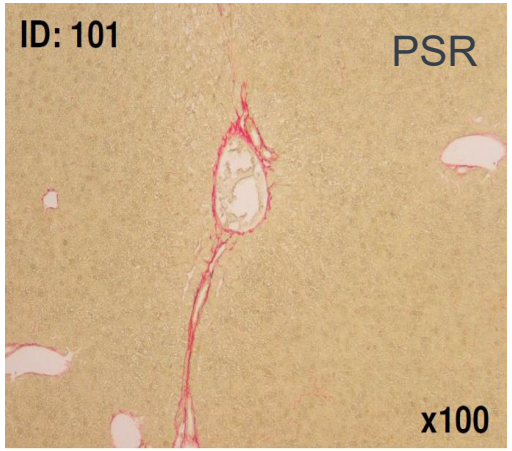
ACLY: ATP citrate lyase; SAR: structure-activity relationship; nM: nanomolar; cryo-EM: cryogenic electron microscopy

ESP-1336 Reduces Liver Inflammation and Fibrosis in a Chemical-Induced Injury Model

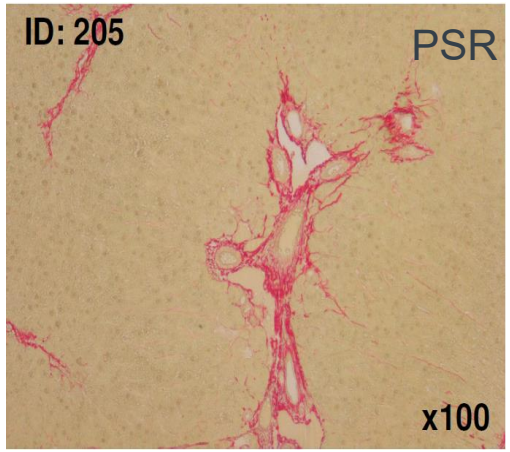
Inflammation
& immune cell recruitment

Fibrosis
in bile and liver ducts

Control (No Toxin)

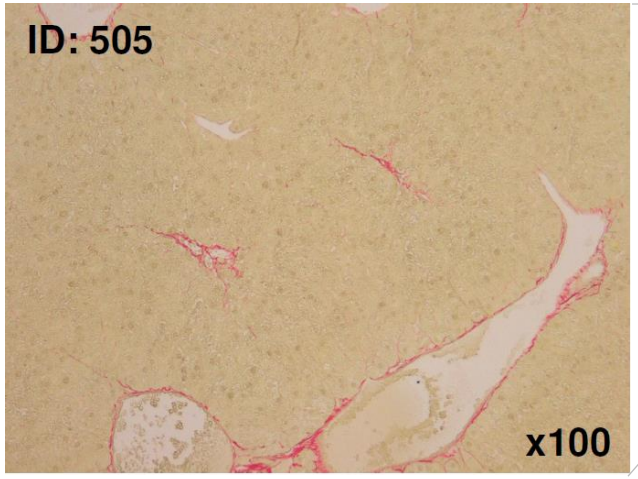


Chemical-Induced Liver Injury

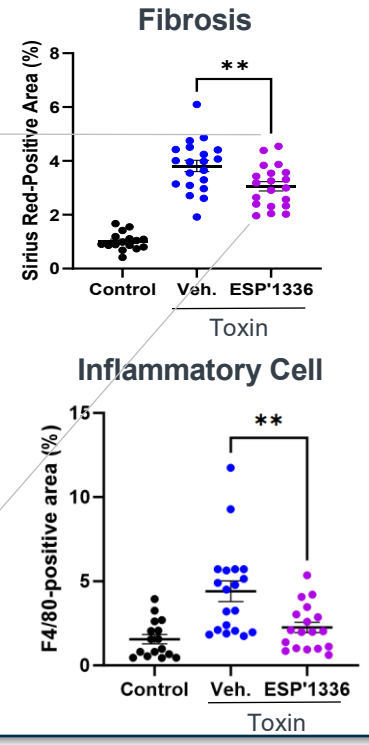


Nonspecific inflammation & fibrosis

ESP-1336 + Chemical-Induced Liver Injury



ESP-1336 reduced markers of liver inflammation and fibrosis



**One-way ANOVA vs. Vehicle p<0.01

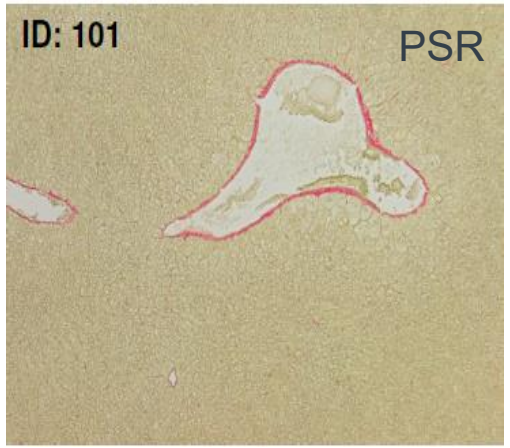
Toxin = CCl_4 (carbon tetrachloride)

ACLY Improves Liver Injury and Fibrosis in a Model of Progressive Biliary Obstruction

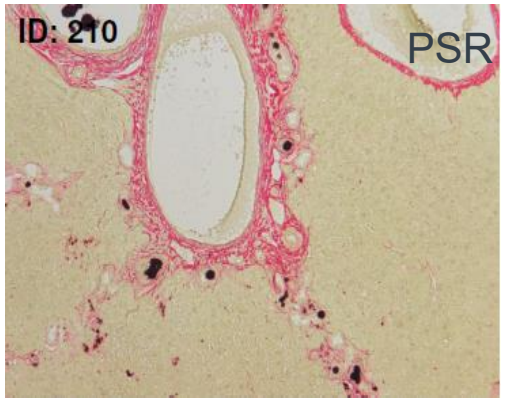
Cholestasis & Injury
of bile and liver ducts

Fibrosis
in bile and liver ducts

Control (No Toxin)

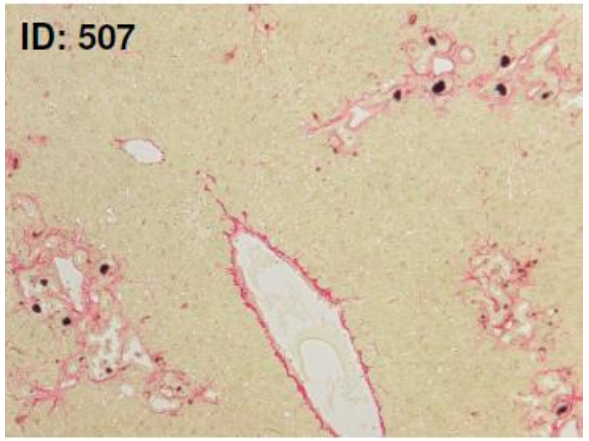


Feed-induced Progressive Biliary Obstruction

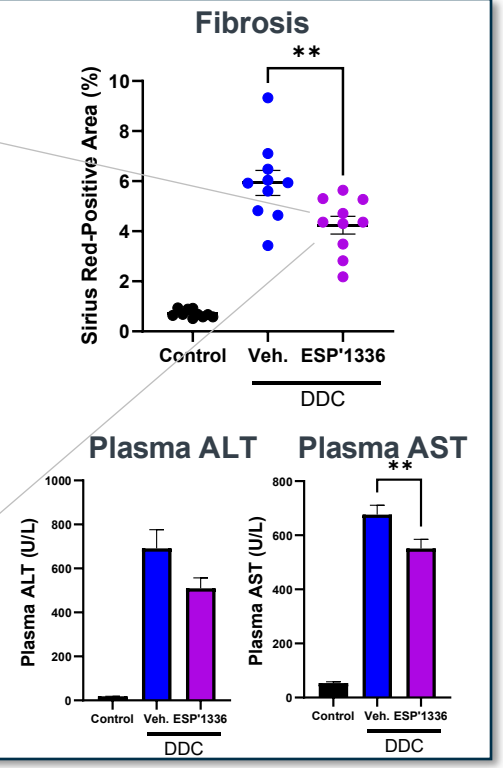


Accumulation of toxic bile acid; inflammation, necrosis immune cell recruitment & fibrosis

ESP-1336 + Feed-induced Progressive Biliary Obstruction



ESP-1336 treatment reduced elevation of liver enzymes and fibrosis



N=10; One-way ANOVA vs. Vehicle **; p<0.01

Feed induced injury through DDC (3,5-diethoxycarbonyl-1, 4-dihydrocollidine); AST: aspartate aminotransferase; ALT: alanine aminotransferase

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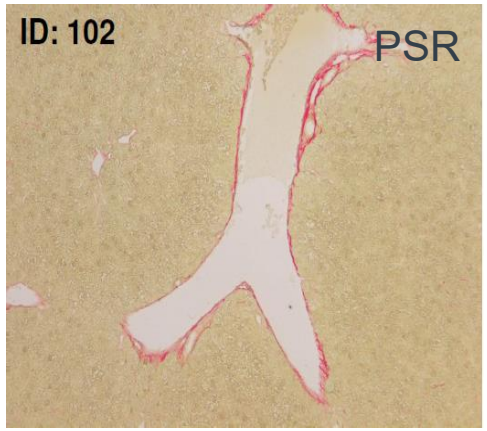
ESP-1336 Improves Liver Injury and Fibrosis in a Model of Hepatic Inflammation

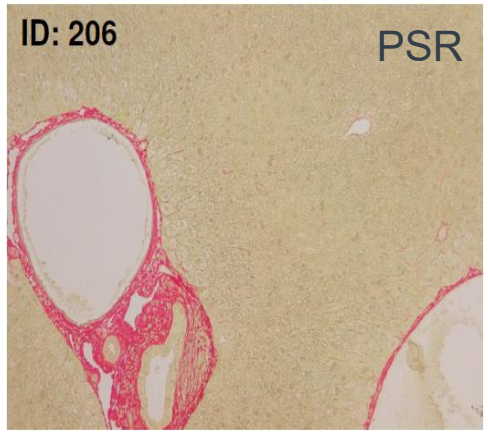
Cholestasis & Injury
of bile and liver ducts

Fibrosis
in bile and liver ducts

Control (No Toxin)

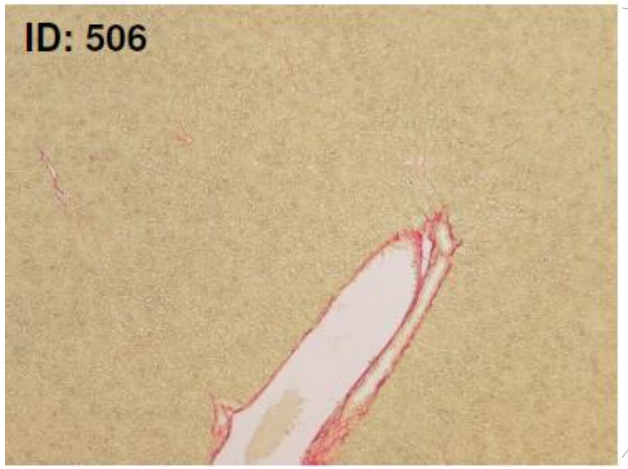


Feed-Induced Hepatic Inflammation

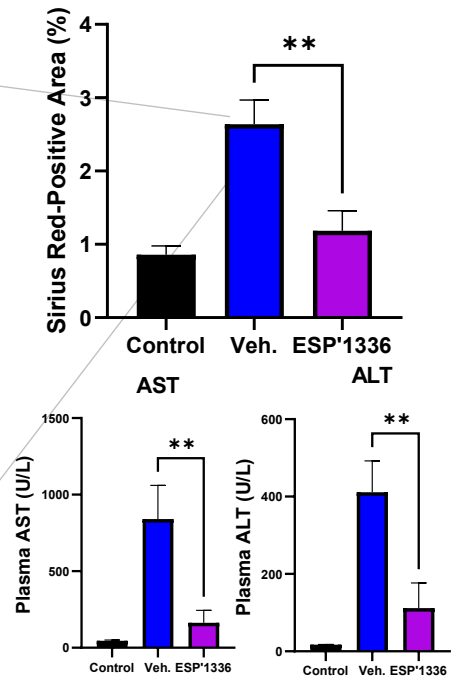


Rapid development of fibrosis

ESP-1336+Feed-Induced Hepatic Inflammation



ESP-1336 reduces fibrosis and markers of liver injury



**One-way ANOVA vs. Vehicle p<0.01

Feed-induced inflammation through ANIT(alpha-naphthylisothiocyanate); AST: aspartate aminotransferase; ALT: alanine aminotransferase

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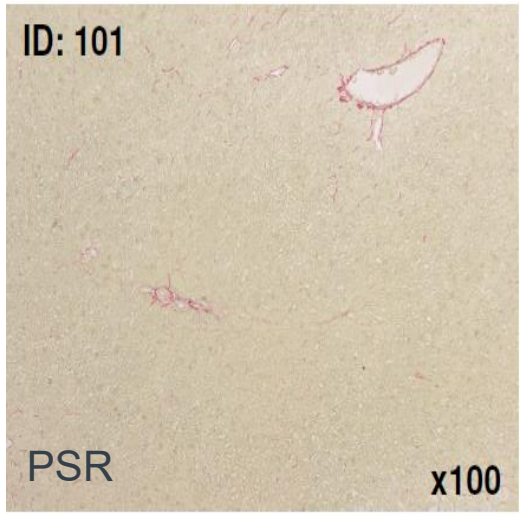
ESP-1336 Improves Liver Injury, Immune Cell Recruitment, and Fibrosis in a Severe Obstructive Model of Cholestasis

Cholestasis & Injury of bile and liver ducts

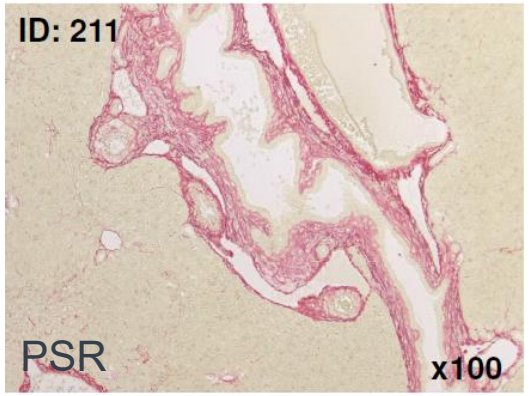
Inflammation & immune cell recruitment

Fibrosis in bile and liver ducts

Control (No Damage)

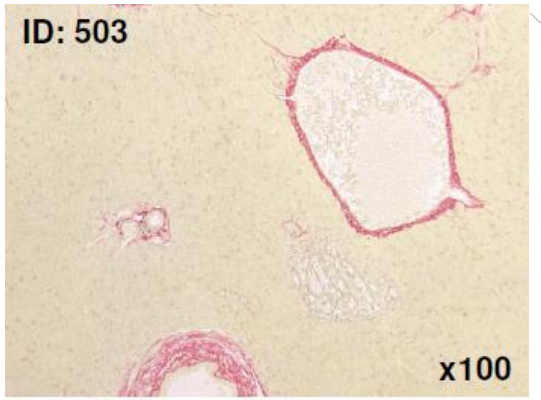


Bile duct ligation (BDL): accumulation of toxic bile acid

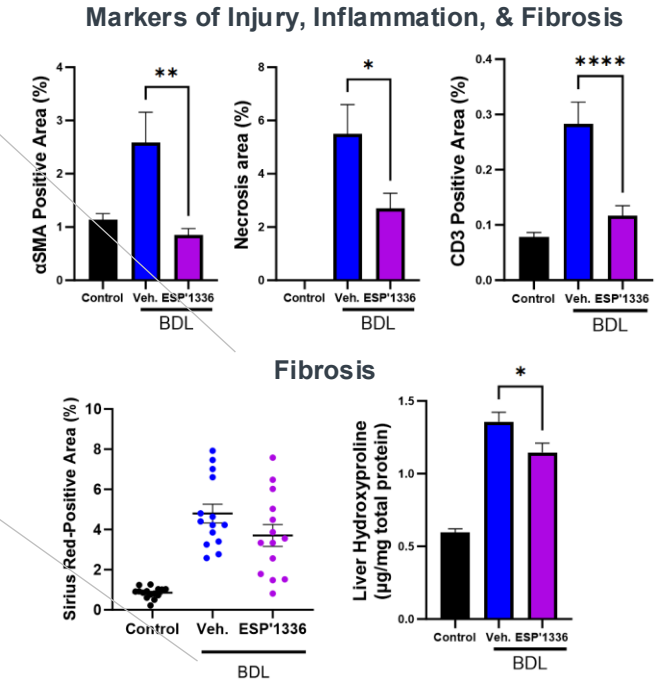


Inflammation, necrosis, immune cell recruitment & fibrosis

ESP-1336 + BDL



ESP-1336 reduces liver necrosis, T-cell infiltration, and markers of fibrosis/ myofibroblast formation



N=14-15; One-way ANOVA vs. Vehicle *; p<0.05, **; p<0.01, ****; p<0.0001

αSMA: alpha-smooth muscle actin

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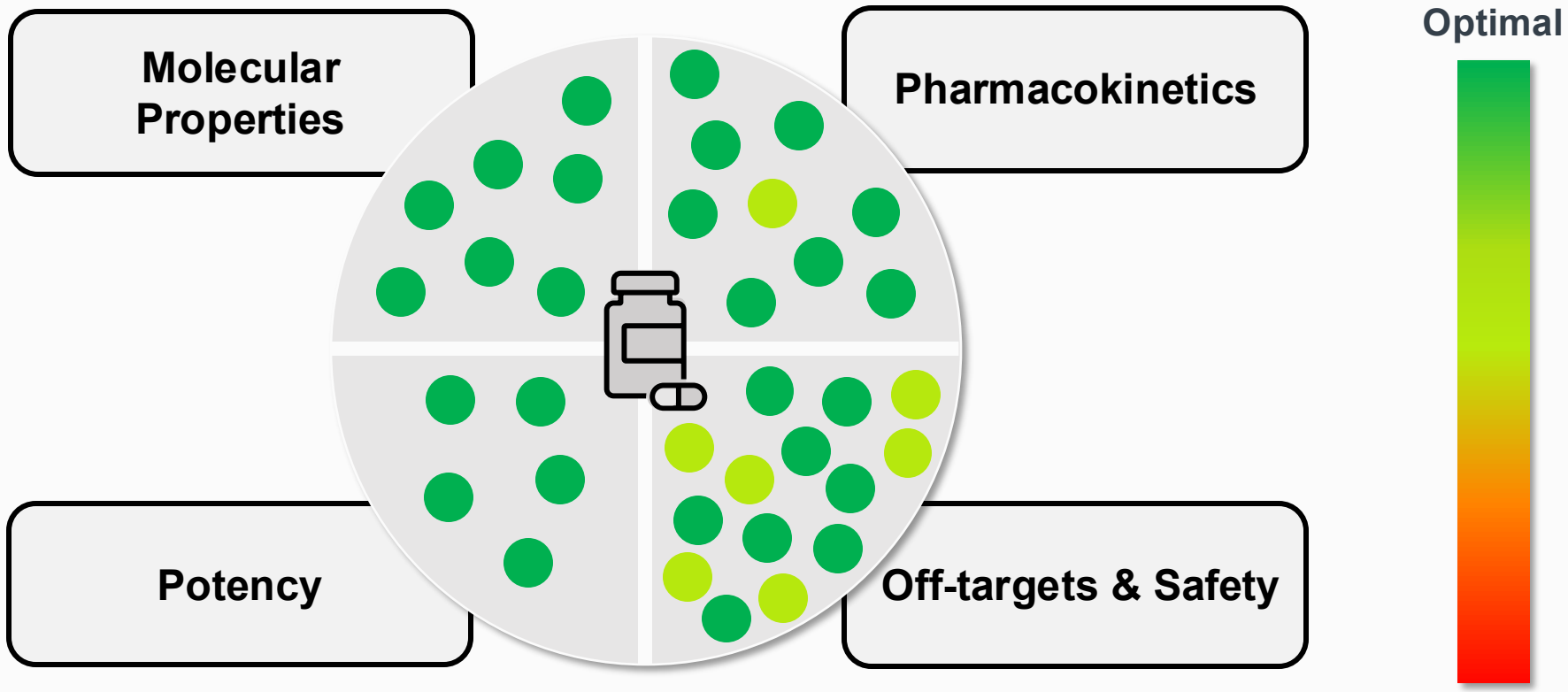
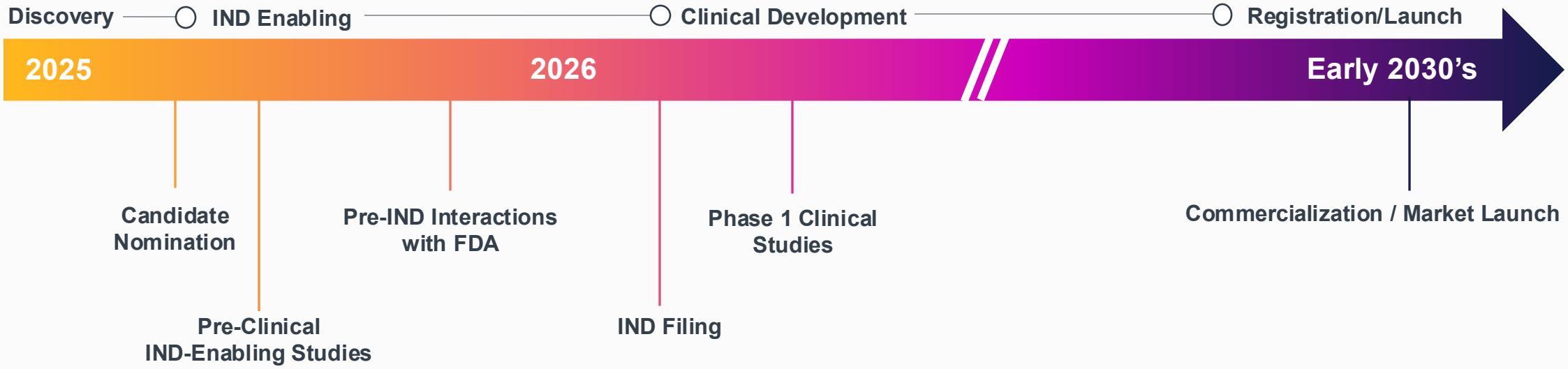
Lead Compounds are Well-Characterized with Data Supporting Daily Oral Dosing



No Anticipated Liabilities

We’re Off to a Strong Start



IND: Investigational New Drug; FDA: Food and Drug Administration

No Approved Therapy with Proven Efficacy to Cure or Halt PSC Progression

Esperion's oral next generation ACLY inhibitor has the potential to directly inhibit all 3 mechanisms of PSC disease progression

- **Cholestasis & Injury**
  of liver and bile ducts
- **Inflammation**
  & immune cell recruitment
- **Fibrosis**
  in liver and bile ducts

ACLY: ATP citrate lyase; PSC: primary sclerosing cholangitis

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