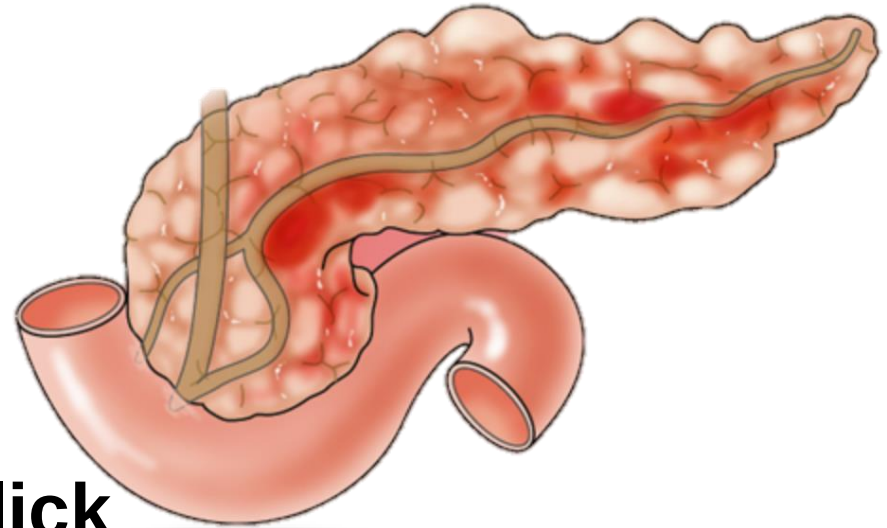


New calcium-targeting therapies for acute pancreatitis

PancreasFest: 2019



Fred Gorelick

Yale School of Medicine/VA HealthCare CT

Conflicts of Interest: Dr. Gary Desir, a collaborator, has a financial interest in Bessor Pharmaceutical, a company developing renalase as a diagnostic and therapeutic agent

Funding: NIDDK, NCI, DOD, Veterans Administration

Collaborators: Gary Desir (Yale), Larry Miller (Mayo), Markus Lerch (Greifswald)

An ideal therapy

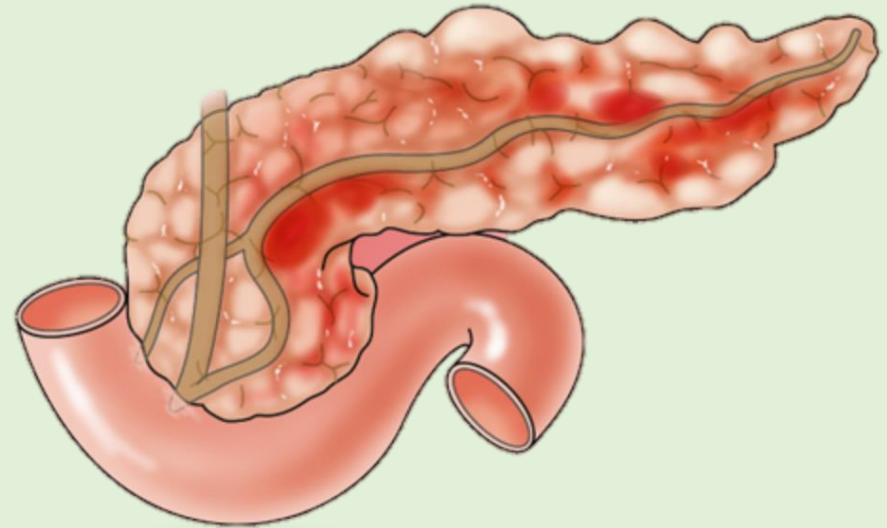
Value given prophylactically or therapeutically

High therapeutic index

Low cost

Multiple targets in acute injury

Promotes recovery



Phases and effectors

INJURY RESPONSES

Acute

- Immediate**
- Intermediate**

Stabilization

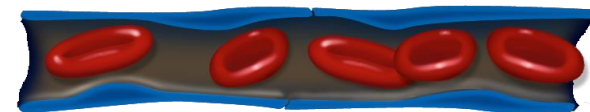
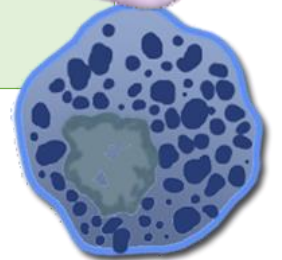
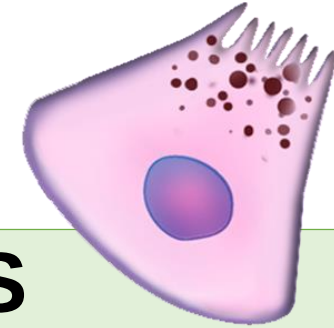
Recovery

EFFECTORS

Acinar cell

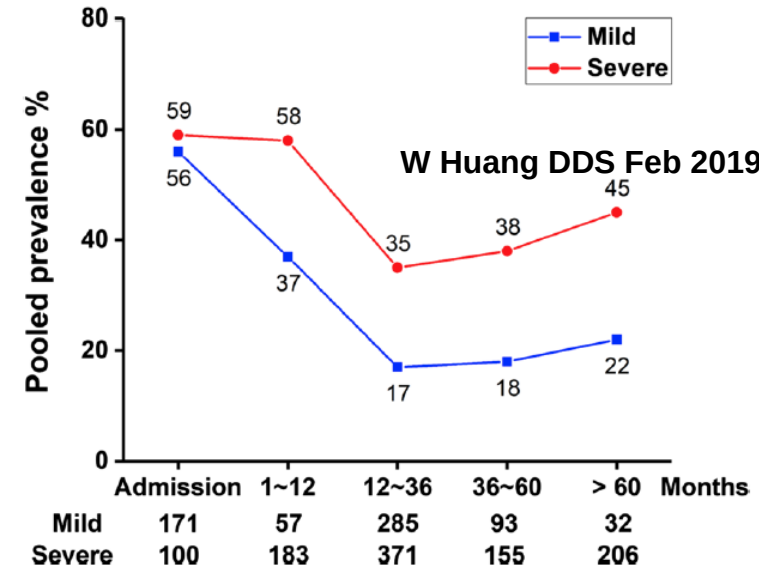
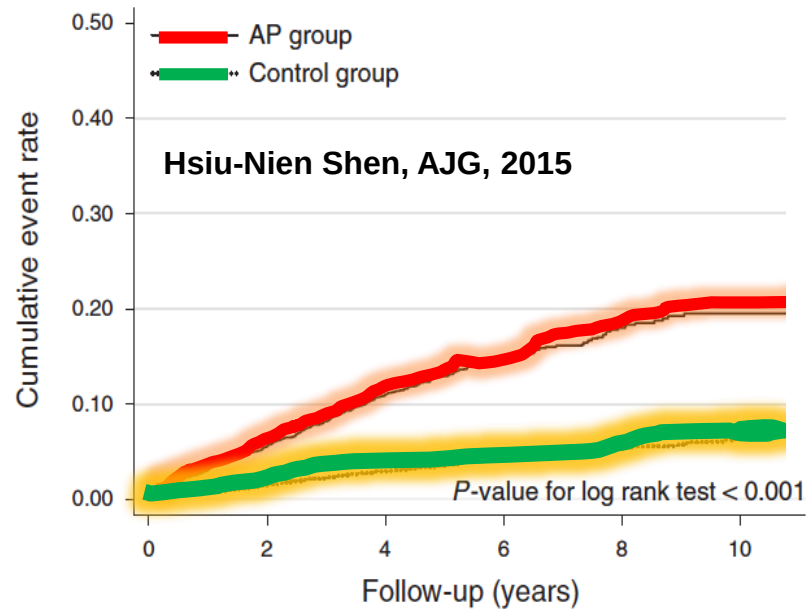
Inflammatory cells

Vascular



Acute Pancreatitis

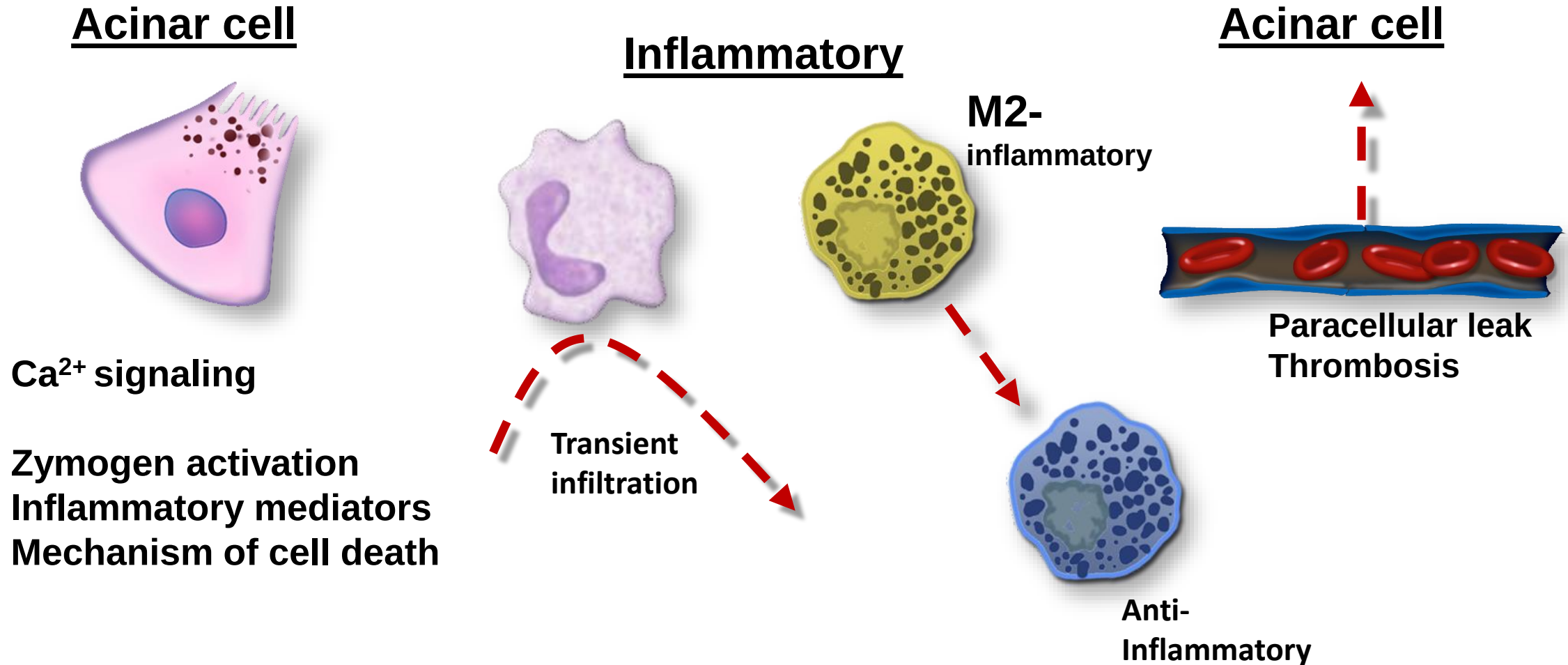
Both exocrine and endocrine insufficiency develop often



- Risk DM independent of severity
- Other studies up to 40% -population dependent (male, etoh,hyperlipidemia)
- Rate up to 80% in recurrent acute
- Risk similar for pancreatic exocrine insufficiency (PEI) but severity dependent
- Implications: need to follow AP patients long-term for diabetes and PEI

Also: Das Gut 2014; 63(5):818-31; Tu BMC Gastro 2017; R. Hollemans: Pancreatology, 2018; Petrov and Yadav, Nature Reviews, 2018; Huang DDS

Multiple cell types mediate disease



New/rational therapies

Targets: 1

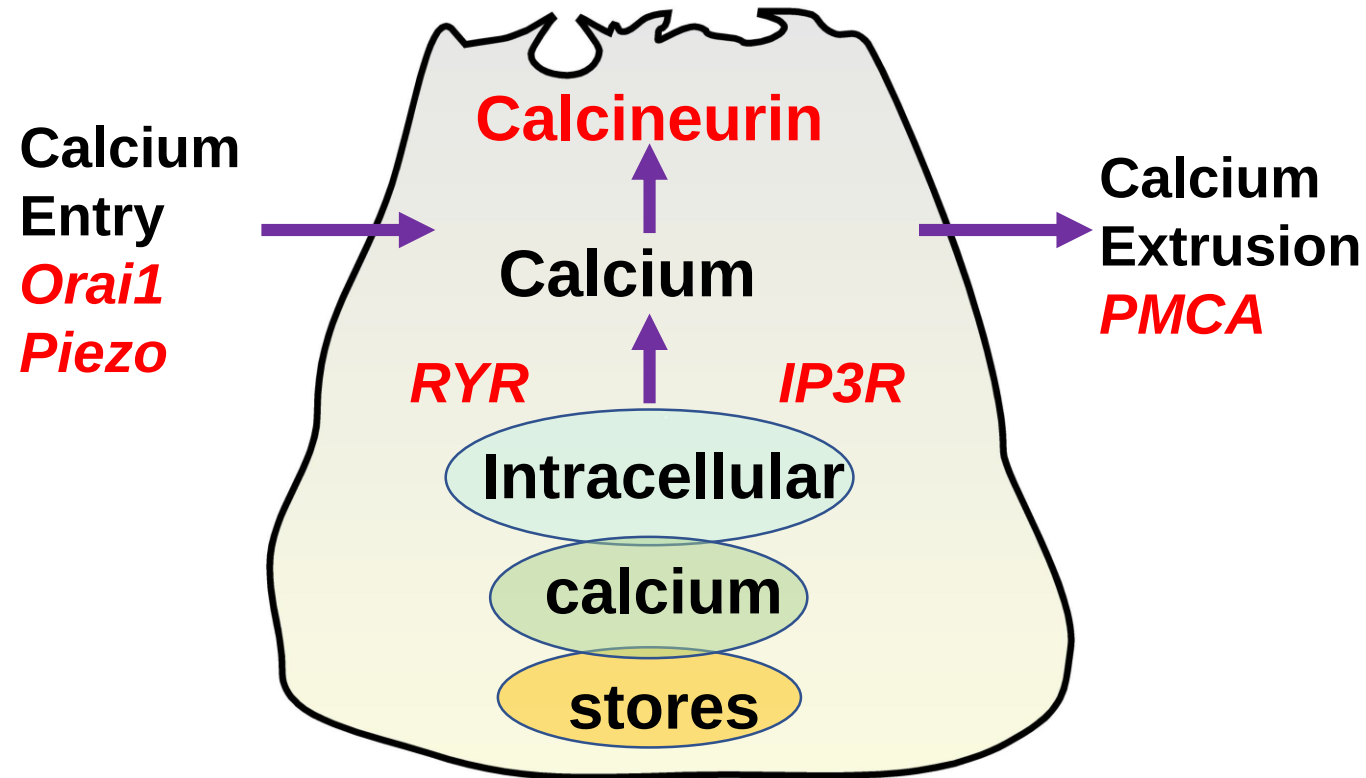
- Store-operated calcium entry
- Mitochondrial transition pore
- Autophagy stimulation
- Unfolded protein response
- Inflammasome: GPR81/lactate
- Kynurenine inhibition
- Neurogenetic inflammation (alpha-2-adrenergic receptor agonist)

Targets: 2

- COX (prostaglandin) inhibition
- TNF synthesis and activity
- Angiopoietin inhibition
- Lipase inhibition/generation of FFA from TG
- IL6 receptor inhibitor
- Thrombin inhibition
- Microbiome (FMT)

Acute Pancreatitis

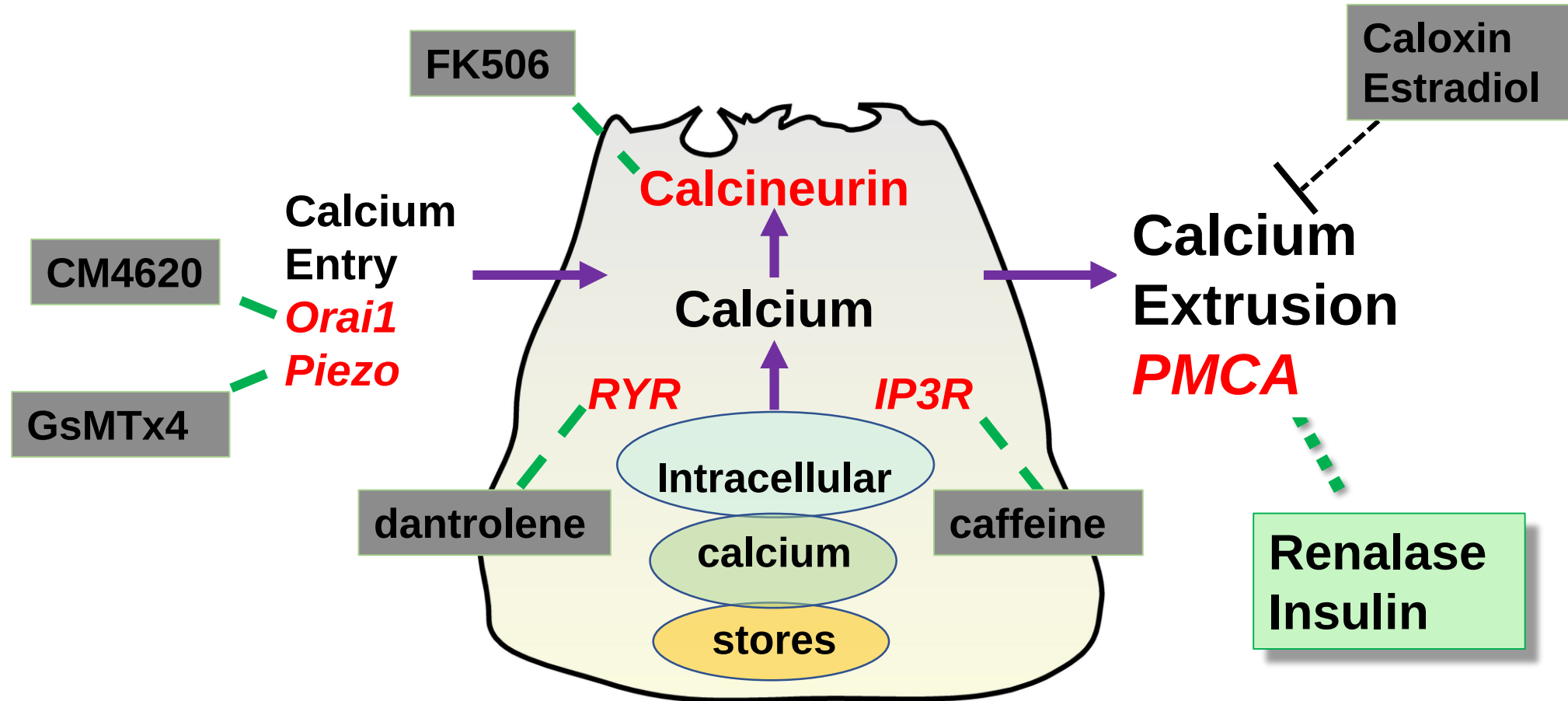
Calcium signaling: targeting for treatment



- Husain S. PNAS 2005 and AJP 2012 (dantrolene)
- Orabi Al Cell Mol Gastroenterol Hepatol 2017 (Calcineurin/NFATc)
- Gerasimenko PNAS 2013 and Wen L Gastroenterology 2015 (ORAI1)
- Mankad 2012 and Samad 2014 (JBC)
- Romac..Liddle, Nat Comm. 2018

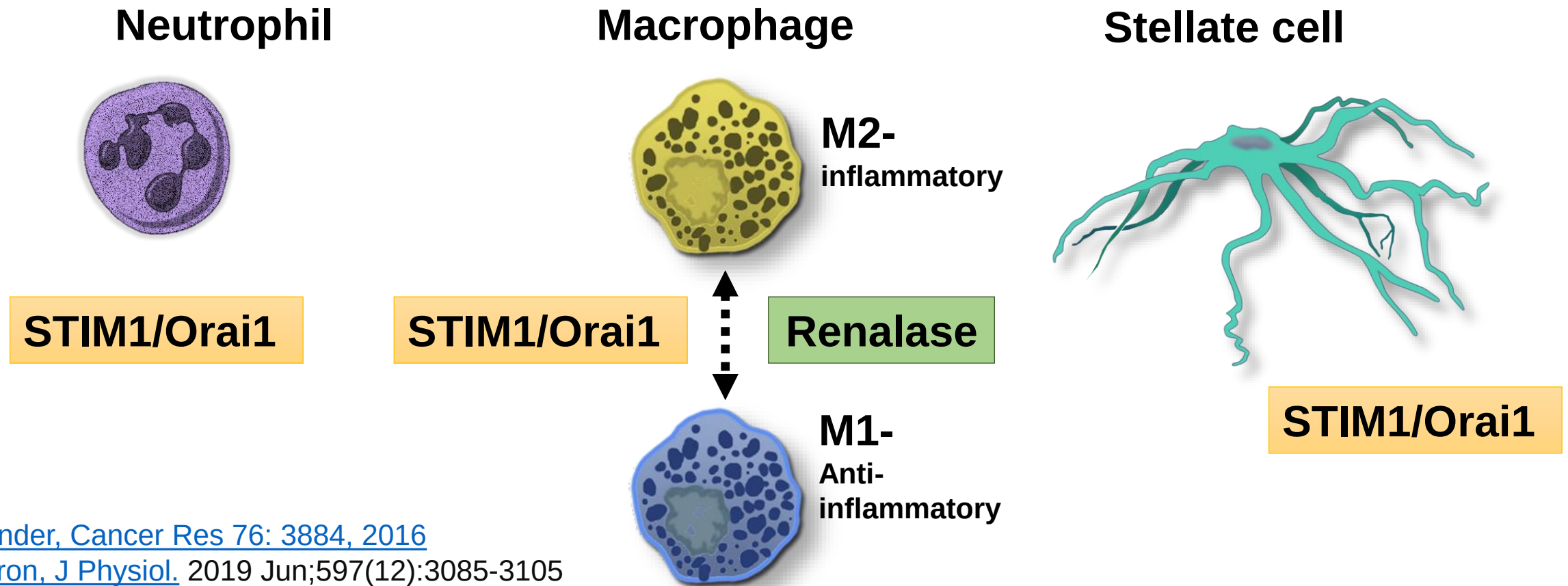
Acute Pancreatitis

Calcium signaling: targeting for treatment



Some calcium-targeting agents reduce both acinar cell and inflammatory cell pancreatitis responses

Calcium signaling drives activation of others pancreatitis responders



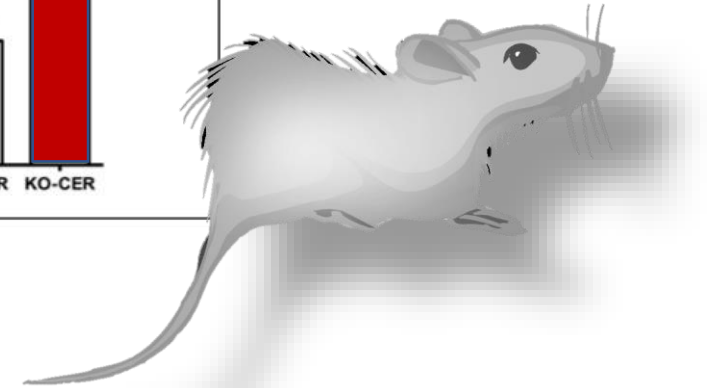
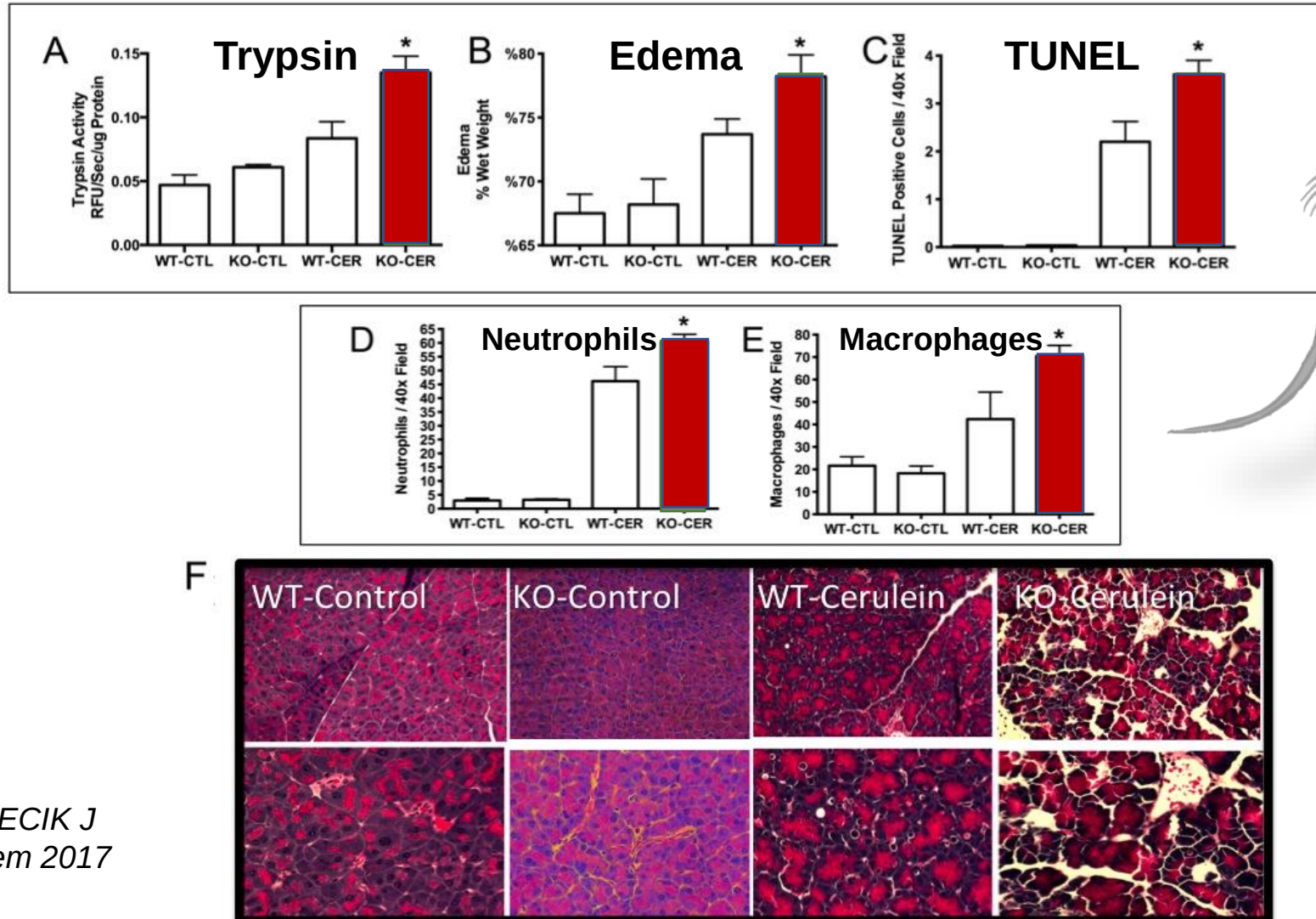
[Hollander, Cancer Res 76: 3884, 2016](#)

[Waldron, J Physiol. 2019 Jun;597\(12\):3085-3105](#)

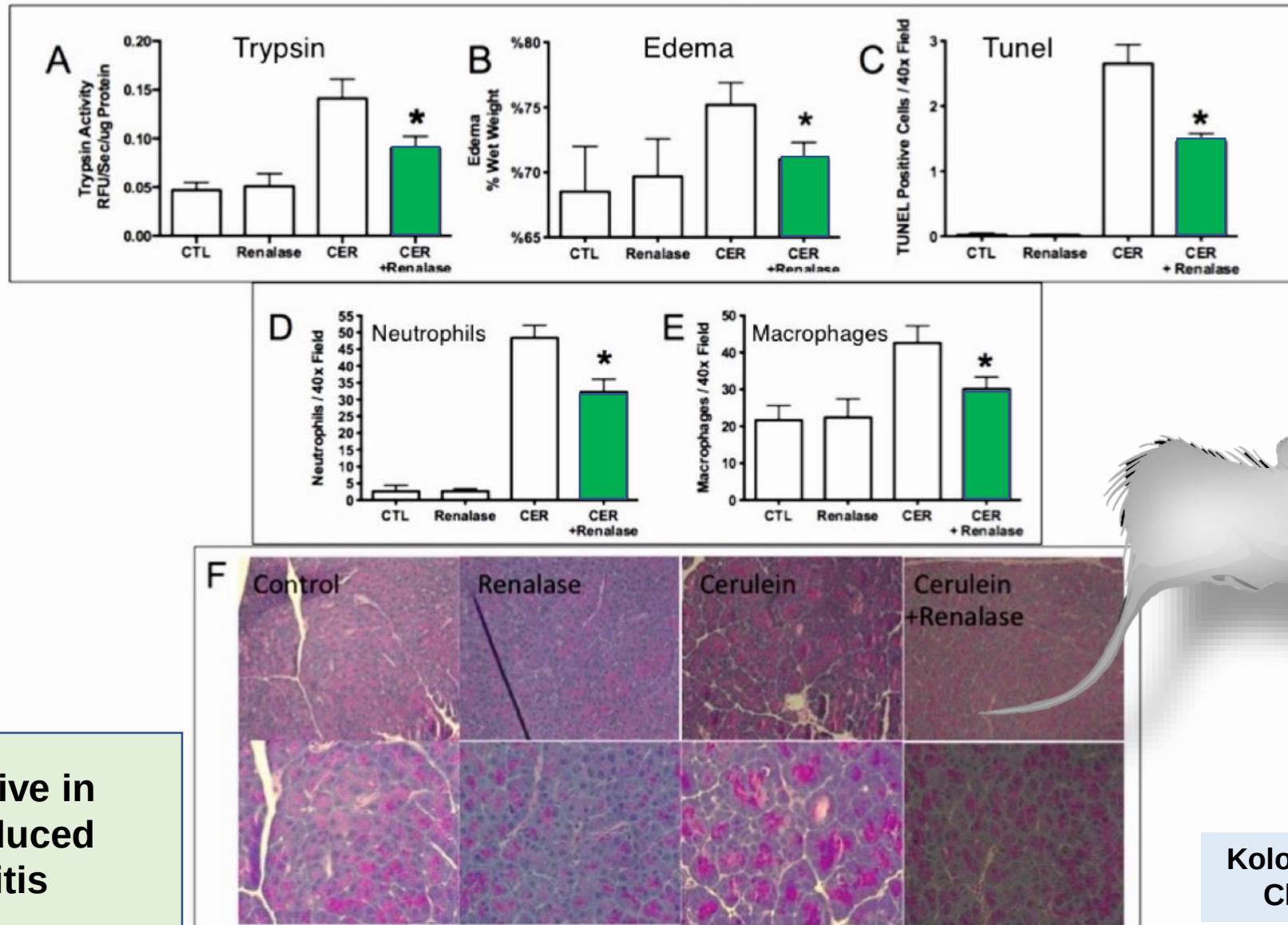
Renalase: (RNLS) a new survival factor

- 37 kD secretory protein (RNLS1; RNLS2 not secreted) made by the kidneys and other tissues
- NADH/FAD and catecholamine binding domains
- Pro-survival: activates plasma-membrane calcium ATPase 4B (PMCA4b) and calcium efflux; also activates ERK and AKT
- Pro-survival activity contained in 22 aa domain
- Pro-survival factor in pancreatic cancer and melanoma
- Reduced levels in renal failure

Renalase deficiency worsens cerulein pancreatitis



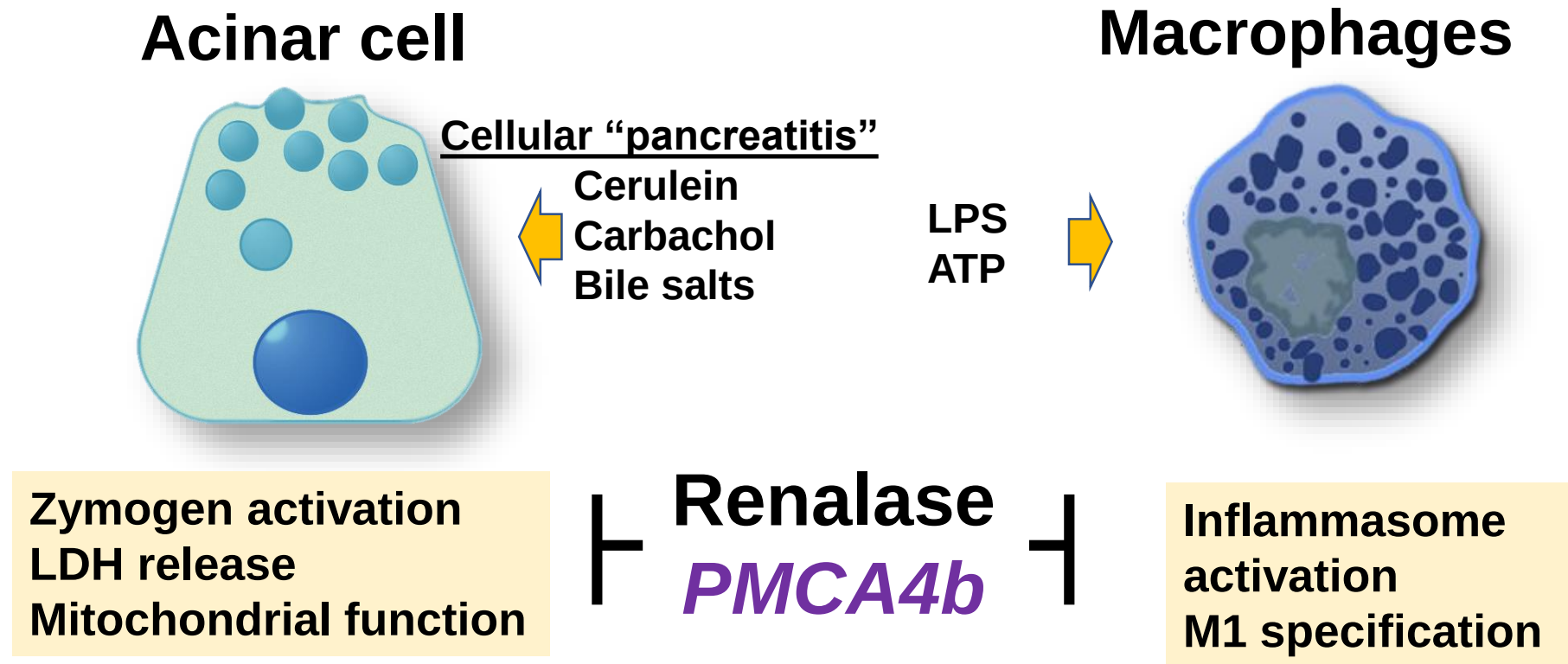
Exogenous renalase reduces cerulein AP severity when given after onset (2 hrs)*



***Also effective in
arginine-induced
pancreatitis**

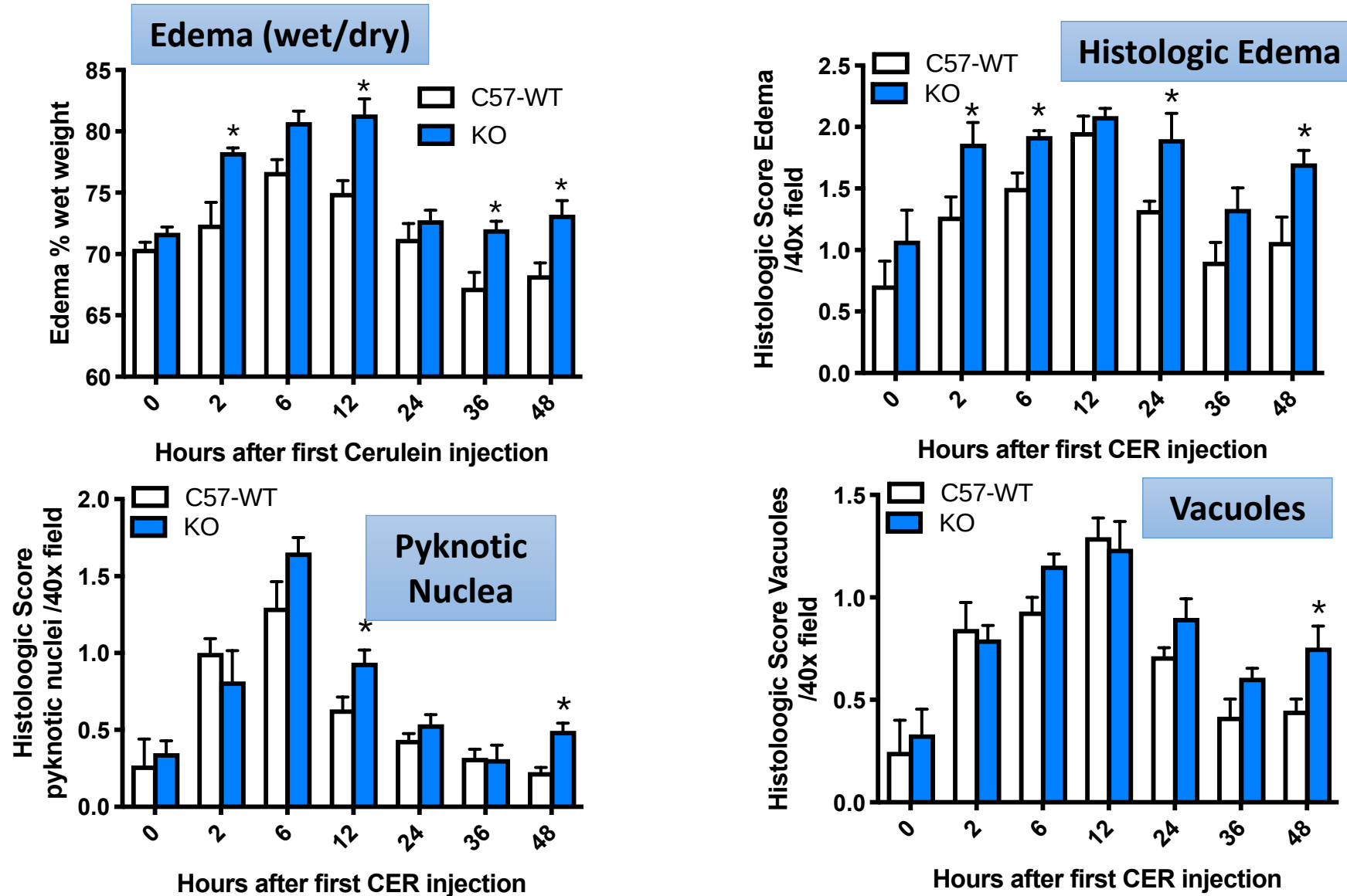
Acute Pancreatitis

Renalase reduces injury responses in acinar cells and macrophages



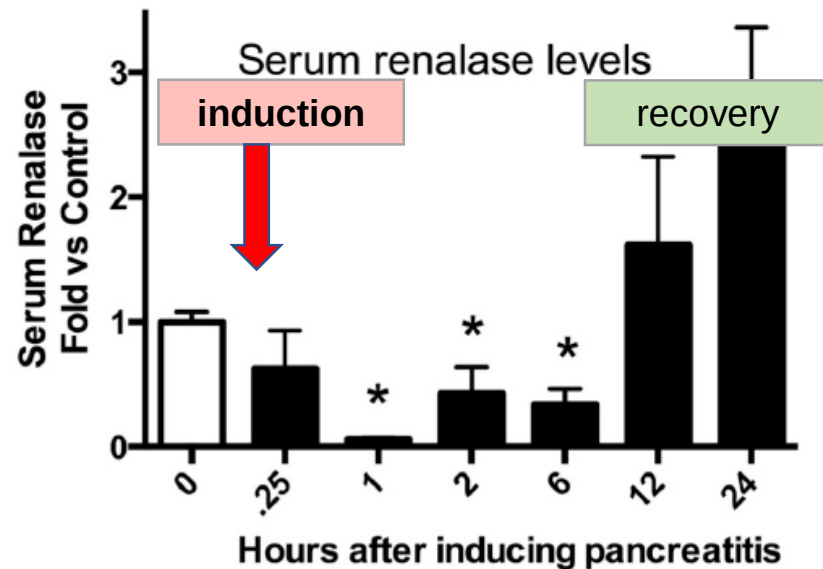
Acute Pancreatitis

RNLS-KO mice have delayed cerulein AP recovery



Serum renalase levels decrease with the onset of acute pancreatitis

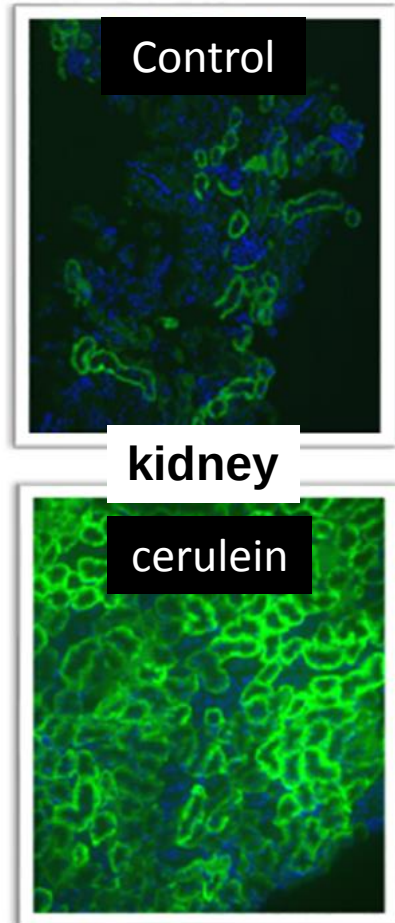
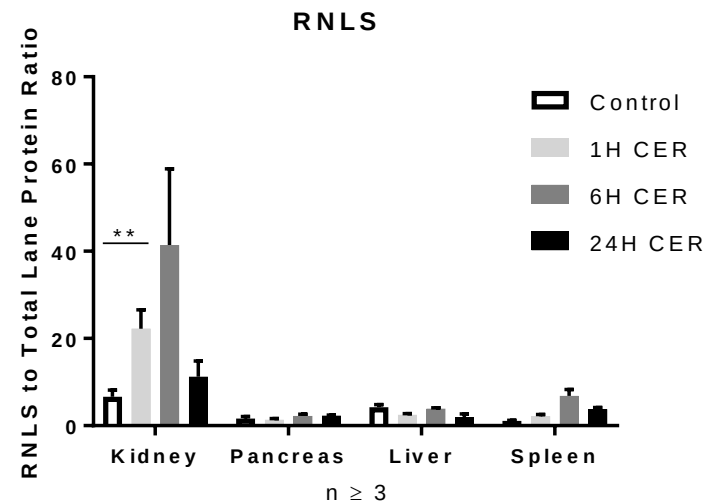
Murine



*p<0.05; n= 4-6 for each time point after induction.

Kolodecik J Biol Chem 2017

RNLS partitions to the kidney



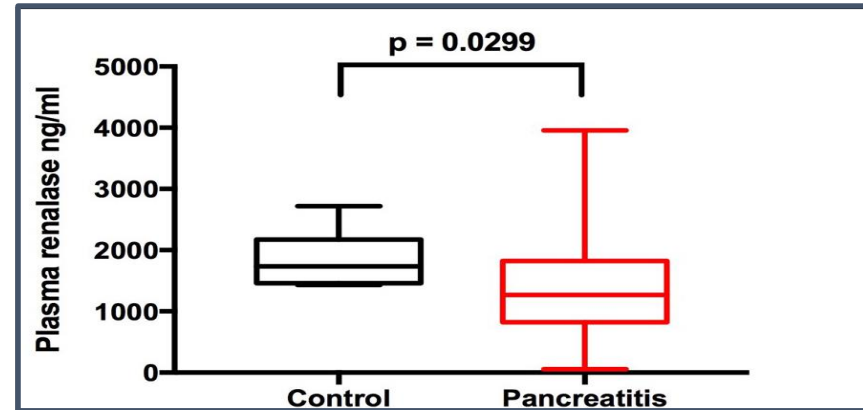
Could serum renalase levels have prognostic value in human acute pancreatitis?

**Serum
renalase levels
fall in clinical
AP and may
predict
severity**

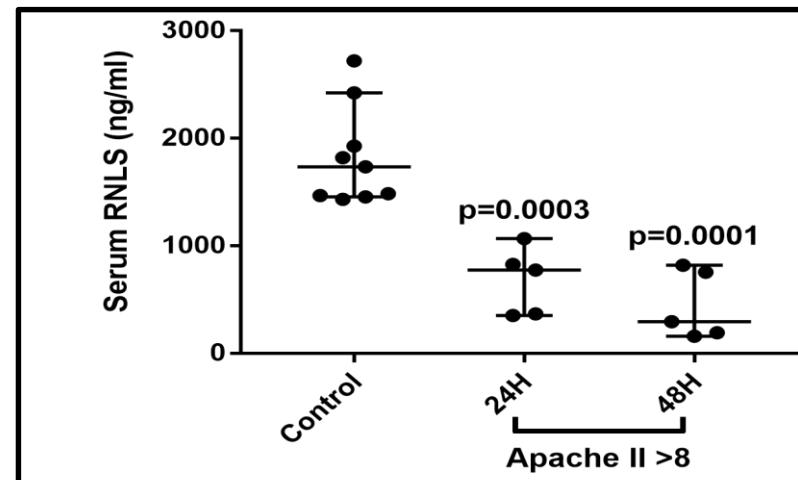
*With M Lerch
and G Desir*

Serum by ELISA

Plasma RNLS are decreased in acute pancreatitis



Plasma RNLS maybe dramatically reduced in severe AP



Summary of renalase data:

- Secretory protein with paracrine and hormonal actions
- A broadly active survival factor
 - Acute injury
 - Select cancers (**negative** effects on survival- PDAC, melanoma)*
- Requires PMCA4b; possibly other co-receptors
- Blood levels decrease in experimental AP and in humans with AP – may correspond to severity
- May modulate AP recovery
- Exogenous RNLS reduces experimental AP severity

*Hollander, Cancer Res 2016; Guo, Sci Repts 2016

New and rationale calcium targeting therapies: *Suggestions for the future*

EFFECT ON:

SAP to MOF transition

- *Pulmonary*
- *Renal*
- *Vascular*
- *Intestinal*
- **Recovery**
- **Short-term**
 - Unresolved AP
 - Infections
- **Long-term**
 - Exocrine
 - Endocrine
 - Neoplasia
 - Infections

