Mechanisms of Chronic Pancreatitis

Andrea Geisz

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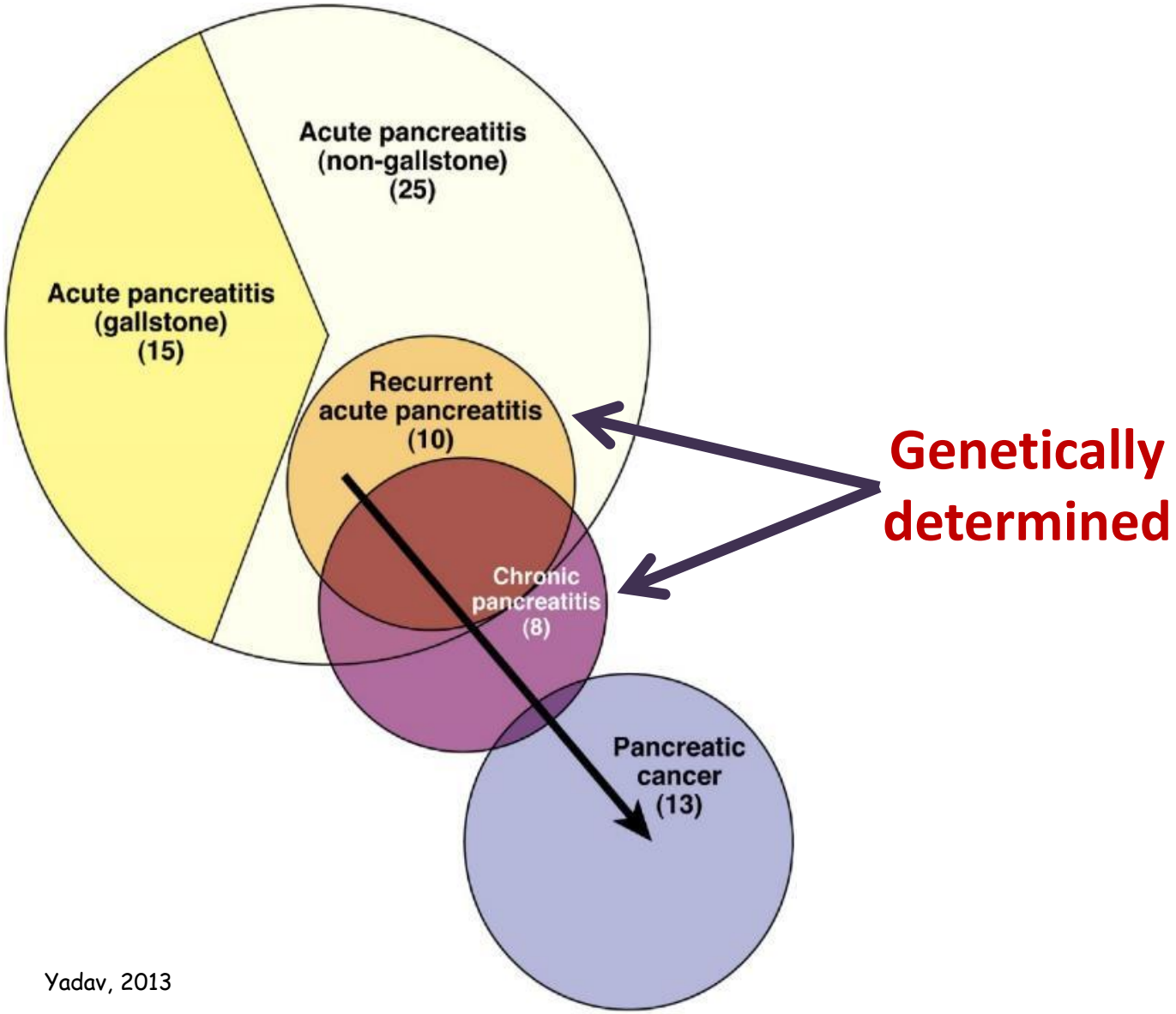
Department of Molecular and Cell Biology
July 21, 2022


Acute pancreatitis
(non-gallstone)
(25)
Acute pancreatitis
(gallstone)
(15)
Recurrent
acute pancreatitis
(10)
Chronic
pancreatitis
(8)
Pancreatic
cancer
(13)
Genetically
determined

Yadav, 2013

Pathological pathways in chronic pancreatitis

Ductal pathway

- CFTR
- CLDN2
- TRPV6

Misfolding-dependent pathway

- PRSS1
- CPA1
- CEL and CEL-HYB

Trypsin-dependent pathway

- PRSS1
- SPINK1
- CTRC
- CTRB1-CTRB2 locus inversion

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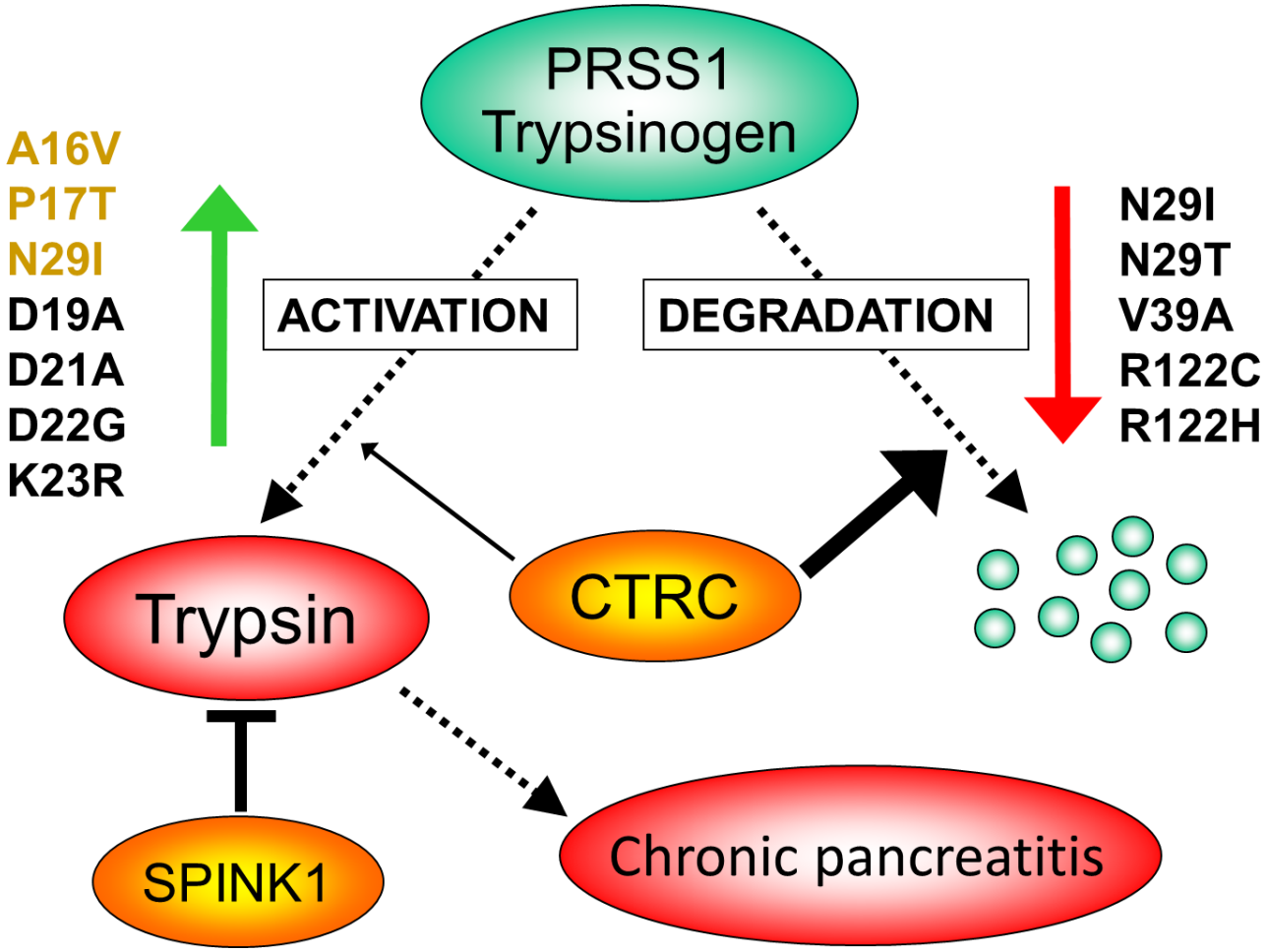
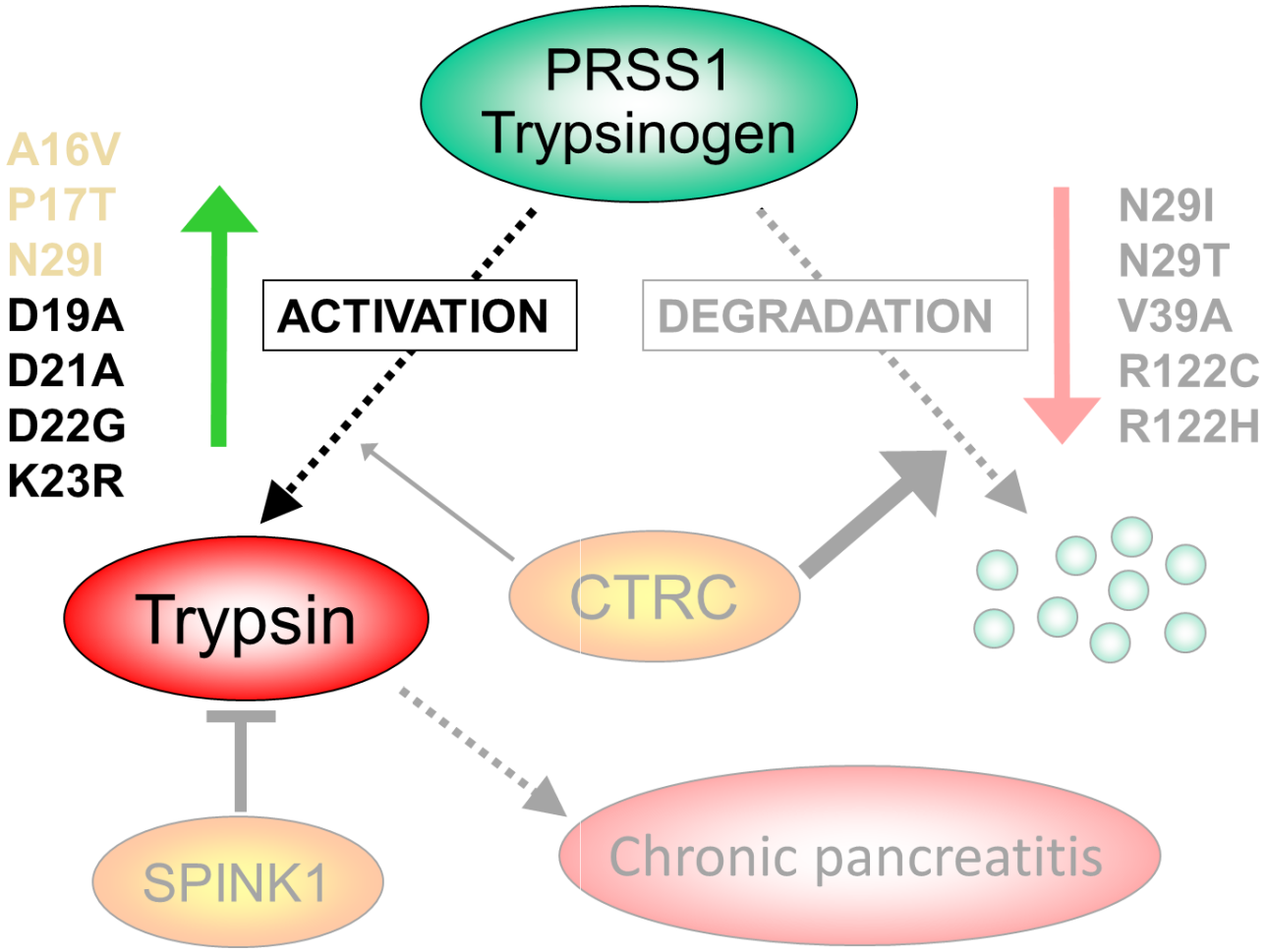
Trypsin-dependent pathway



Trypsin-dependent pathway



nature COMMUNICATIONS

ARTICLE

DOI: 10.1038/s41467-018-07347-y OPEN

A preclinical model of chronic pancreatitis driven by trypsinogen autoactivation

Andrea Geisz[1] & Miklós Sahin-Tóth[1]

Effect of D23A mutation on T7 mouse trypsinogen *in vitro*

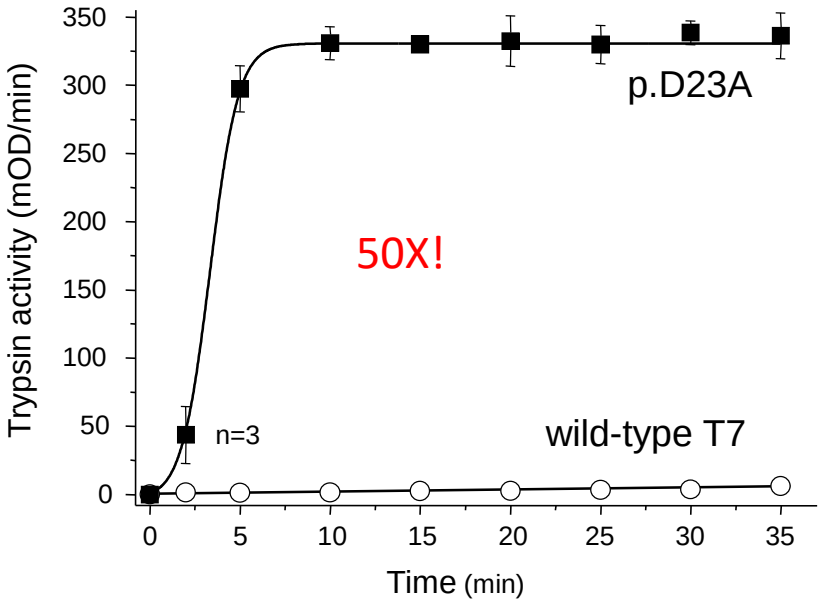
Human PRSS1

Ala^{16}-Pro^{17}-Phe^{18}-Asp^{19}-Asp^{20}-Asp^{21}-Gly^{22}-Lys^{23} – trypsin

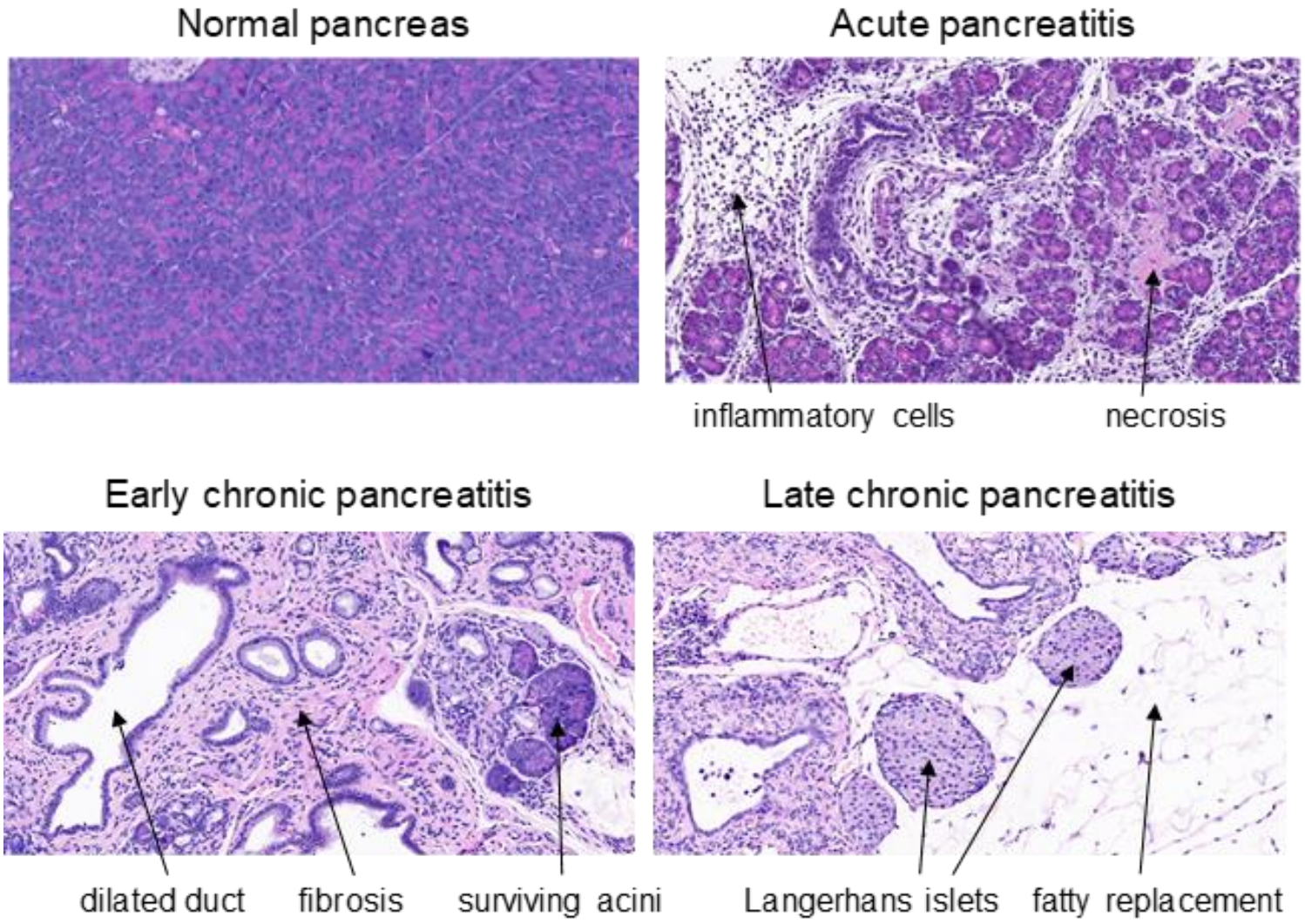
Mouse T7

Leu^{16}-Pro^{17}-Leu^{18}-Asp^{19}-Asp^{20}-Asp^{21}-Asp^{22}-Ala^{23}-Lys^{24} – trypsin

Trypsinogen autoactivation

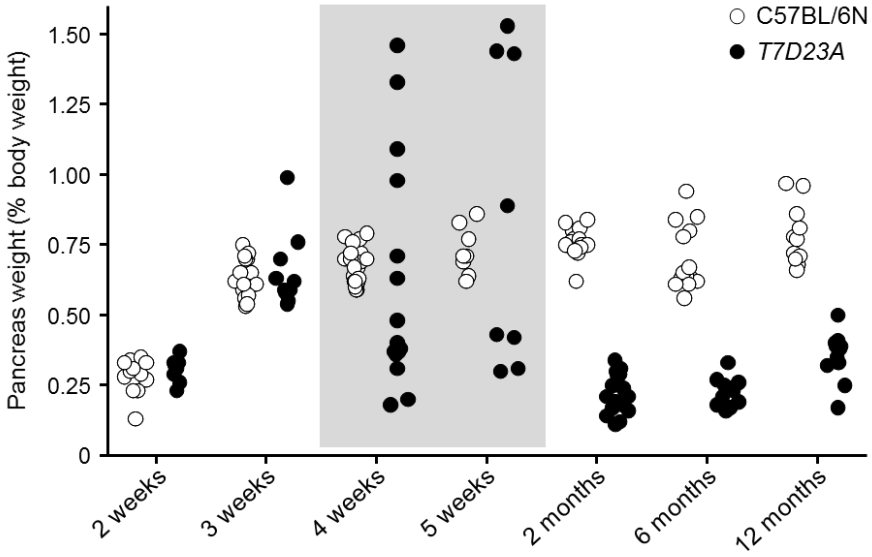


Phenotype of *T7D23A* mouse

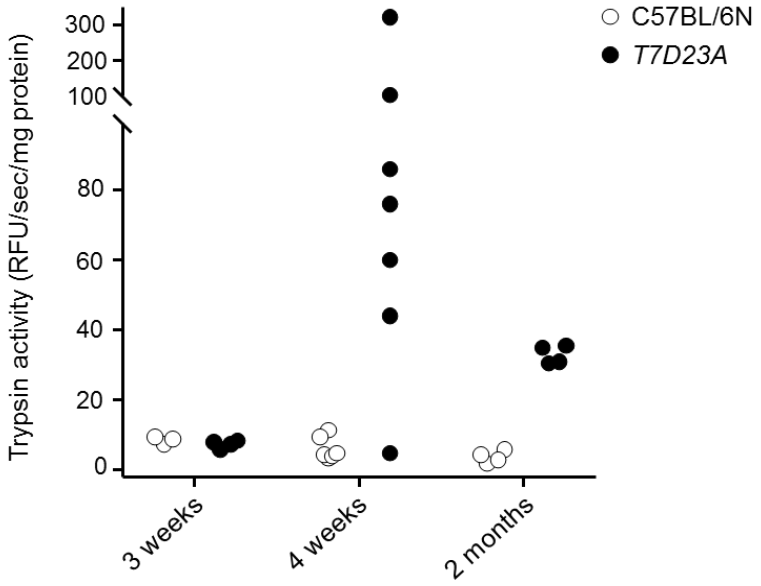


Phenotype of *T7D23A* mouse

Pancreas weight



Intrapancreatic trypsin activity



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World J Gastroenterol 2006 April 7; 12(13):1985-1990
World Journal of Gastroenterology ISSN 1007-9327

EDITORIAL

Co-localization hypothesis: A mechanism for the intrapancreatic activation of digestive enzymes during the early phases of acute pancreatitis

Gijs JD van Acker, George Perides, Michael L Steer

JCI The Journal of Clinical Investigation

Role of cathepsin B in intracellular trypsinogen activation and the onset of acute pancreatitis

Walter Halangk, … , Christoph Peters, Jan Deussing

J Clin Invest. 2000;106(6):773-781. https://doi.org/10.1172/JCI9411.

Am J Physiol Gastrointest Liver Physiol 283: G794–G800, 2002.
First published April 10, 2002; 10.1152/ajpgi.00363.2001.

Cathepsin B inhibition prevents trypsinogen activation and reduces pancreatitis severity

GIJS J. D. VAN ACKER, ASHOK K. SALUJA, LAKSHMI BHAGAT, VIJAY P. SINGH, ALBERT M. SONG, AND MICHAEL L. STEER
Department of Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts 02215

Received 15 August 2001; accepted in final form 1 April 2002

SCIENTIFIC REPORTS

OPEN

Engineering mouse cationic trypsinogen for rapid and selective activation by cathepsin B

Alexandra Demcsák[1,2], Andrea Geisz[1] & Miklós Sahin-Tóth[1,2]

Received: 8 February 2019
Accepted: 7 June 2019
Published online: 24 June 2019

enterokinase, trypsin, cathepsin B

16 17 18 19 20 21 22 23 24

Leu-Pro-Leu-Asp-Asp-Asp-Asp-Asp-Lys---trypsin **wild type T7**

~~enterokinase, trypsin~~, cathepsin B

Normal activation

Leu-Pro-Leu-Asp-Asp-Asp-Asp-**Ala**-**Gly**---trypsin **D23A,K24G**

Increased activation

Leu-Pro-Leu-Asp-Asp-Asp-**Ala**-Asp-**Gly**---trypsin **D22A,K24G**

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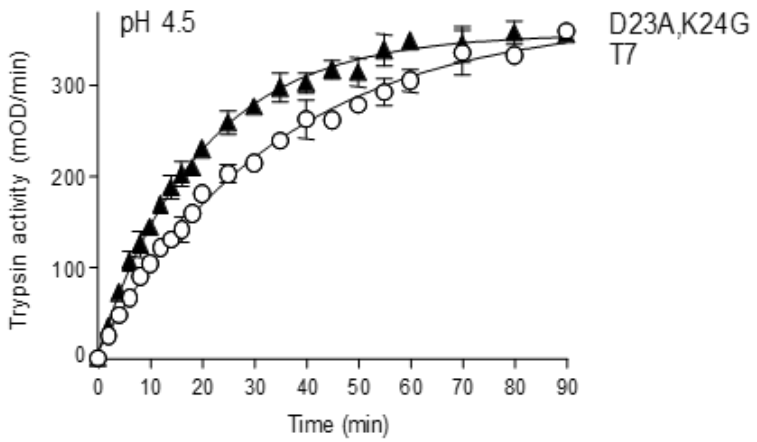
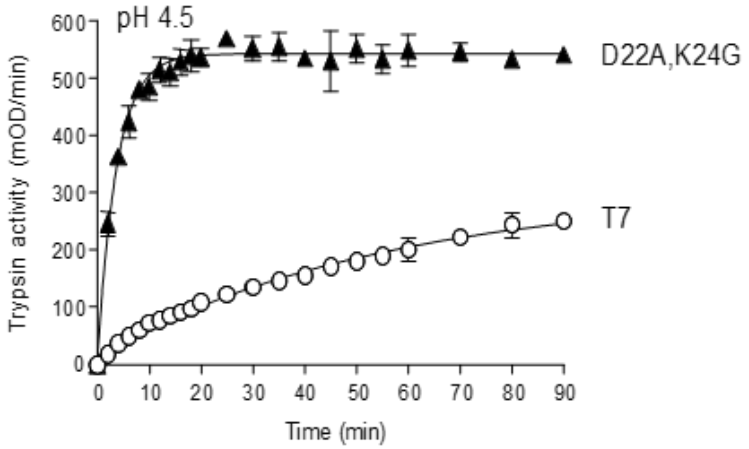
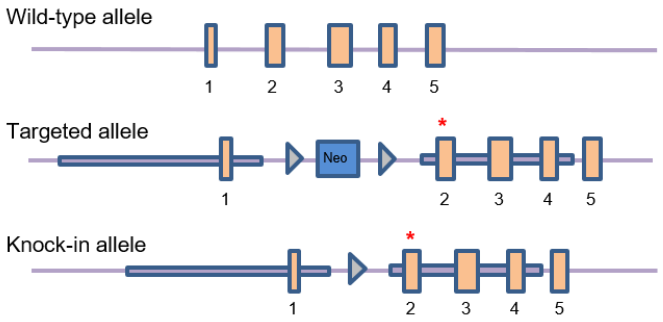
D23A,K24G

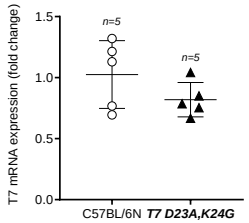


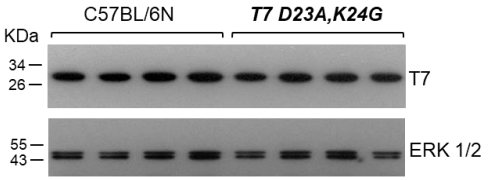
D22A,K24G

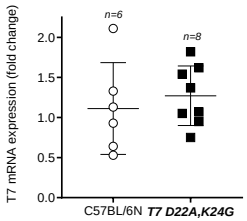


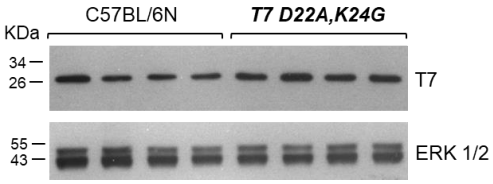
Generation of the *T7D23A,K24G* and *T7D22A,K24G* mice



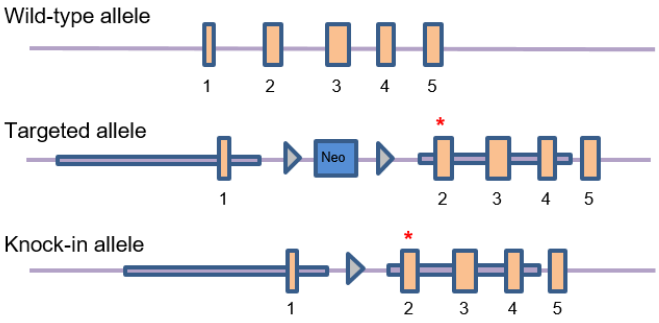


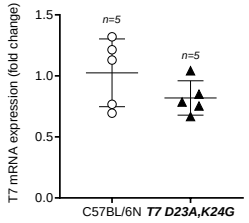


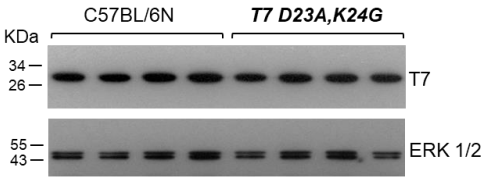


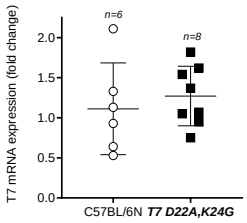


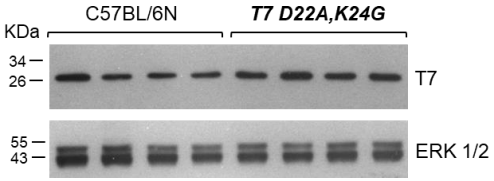
Generation of the *T7D23A,K24G* and *T7D22A,K24G* and *Ctsb-KO* mice

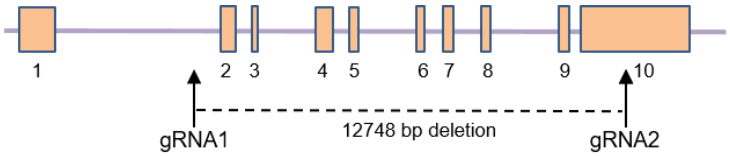


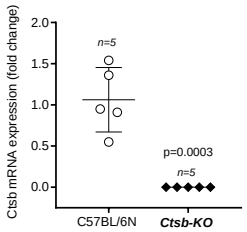


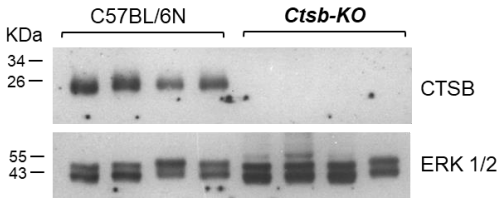






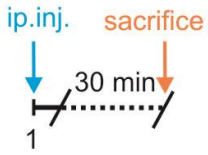




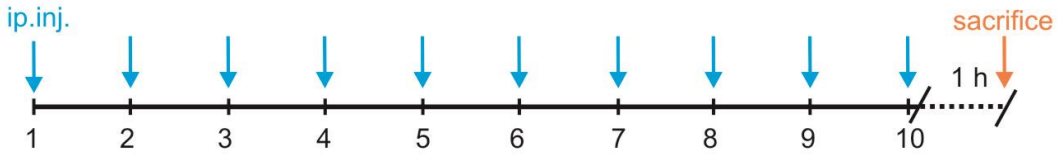


Cerulein-induced pancreatitis models

intrapancreatic trypsin activation



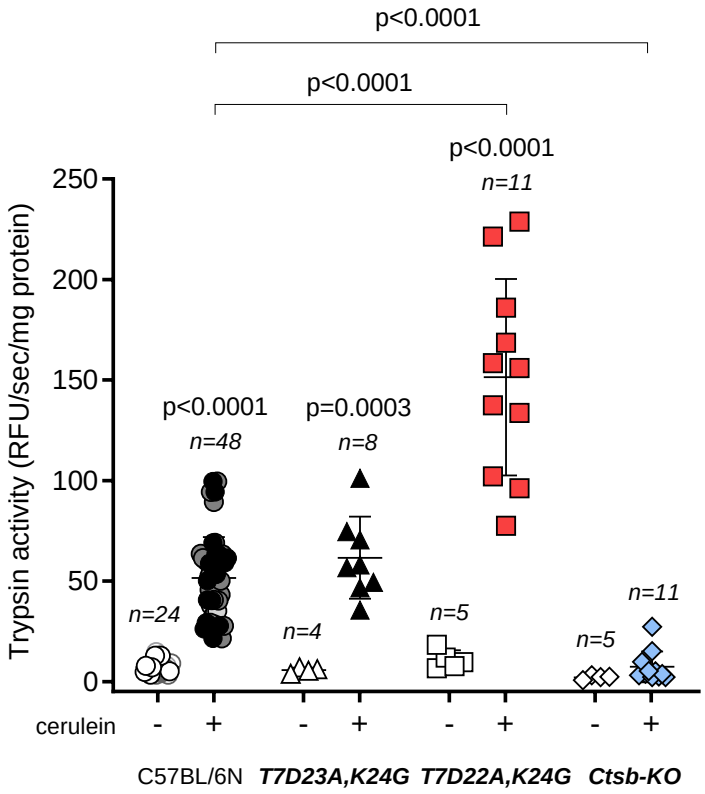
acute pancreatitis



parameters

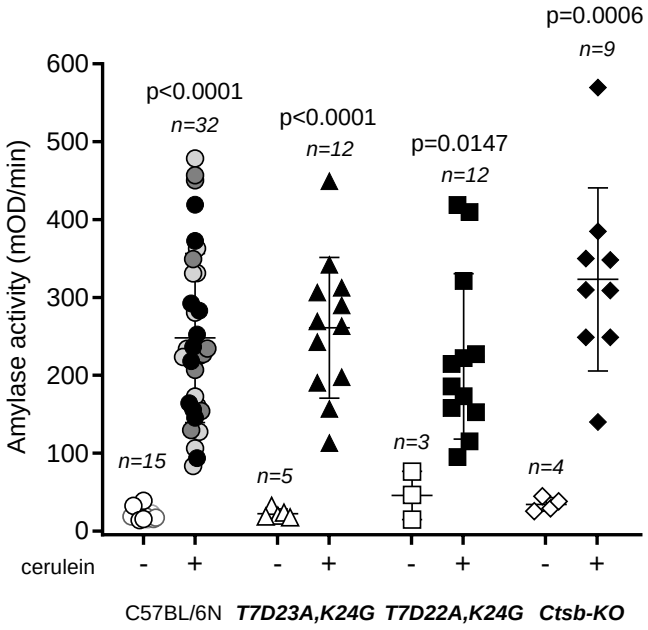
- trypsin activity
- pancreas weight
- plasma amylase
- histology

Cerulein-induced intrapancreatic trypsin activation

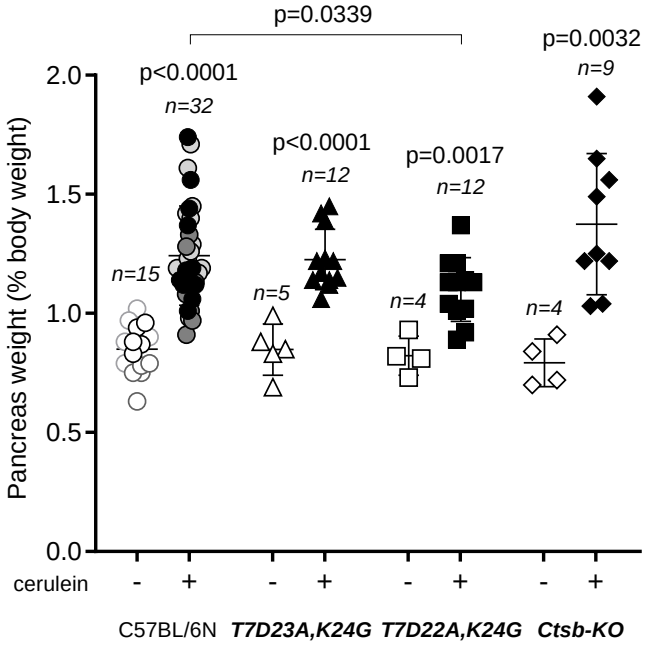


Cerulein-induced acute pancreatitis

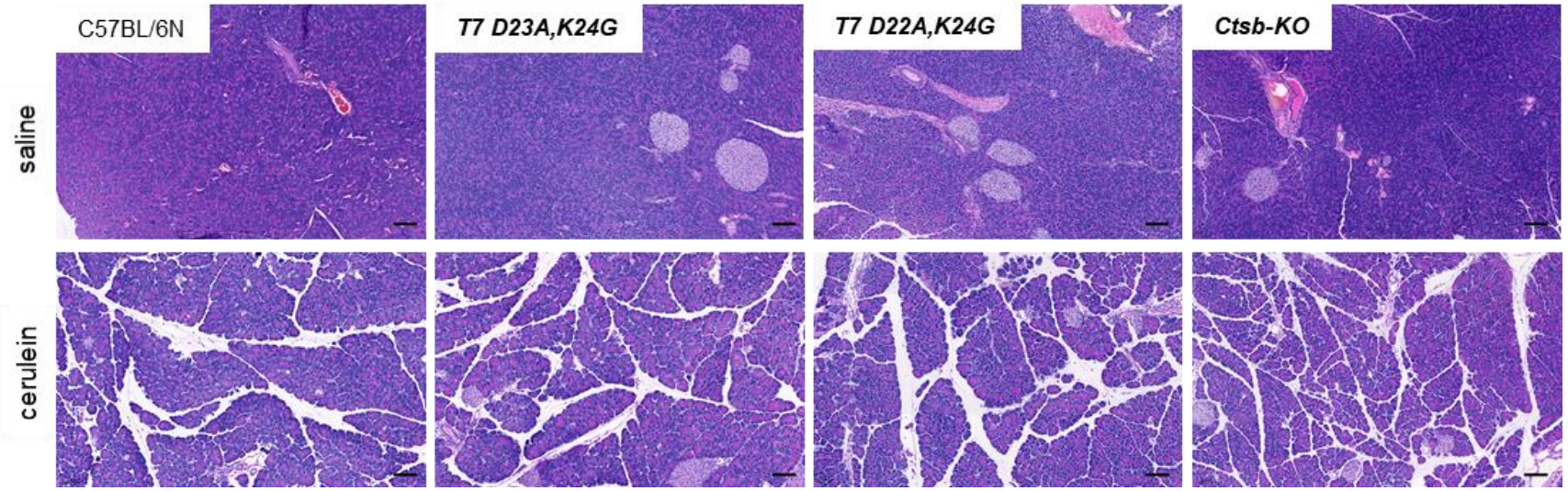
Plasma amylase

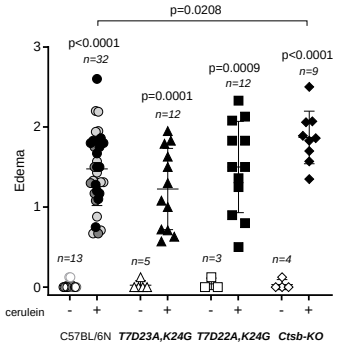


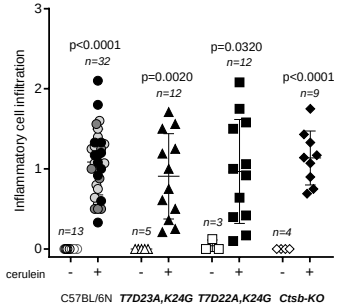
Pancreas weight

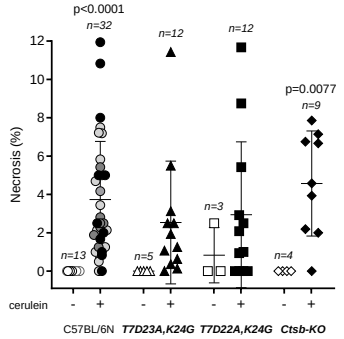


Cerulein-induced acute pancreatitis

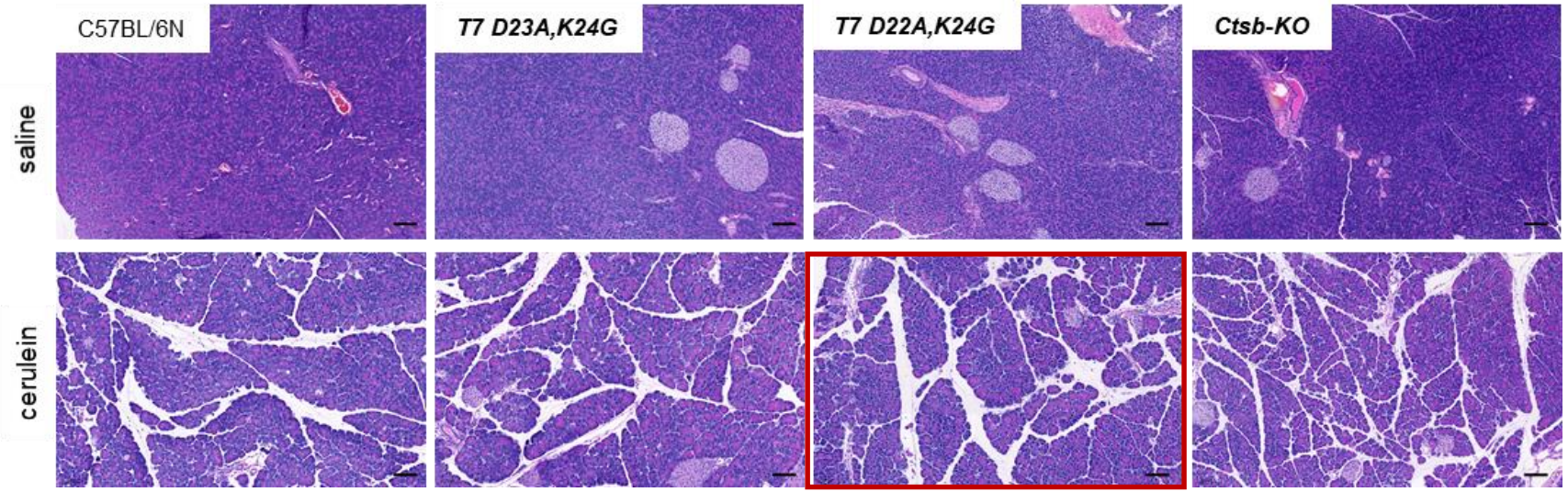


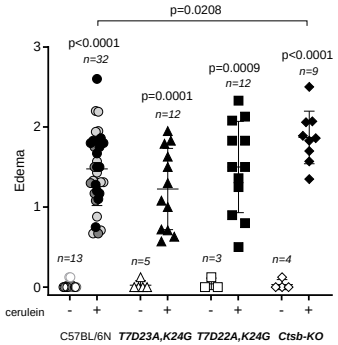


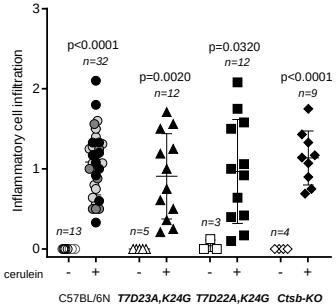


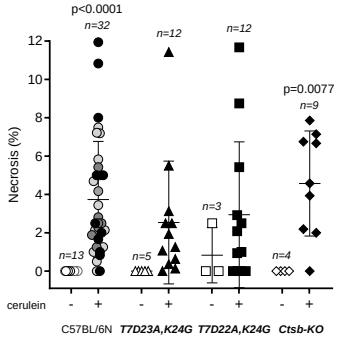


Cerulein-induced acute pancreatitis









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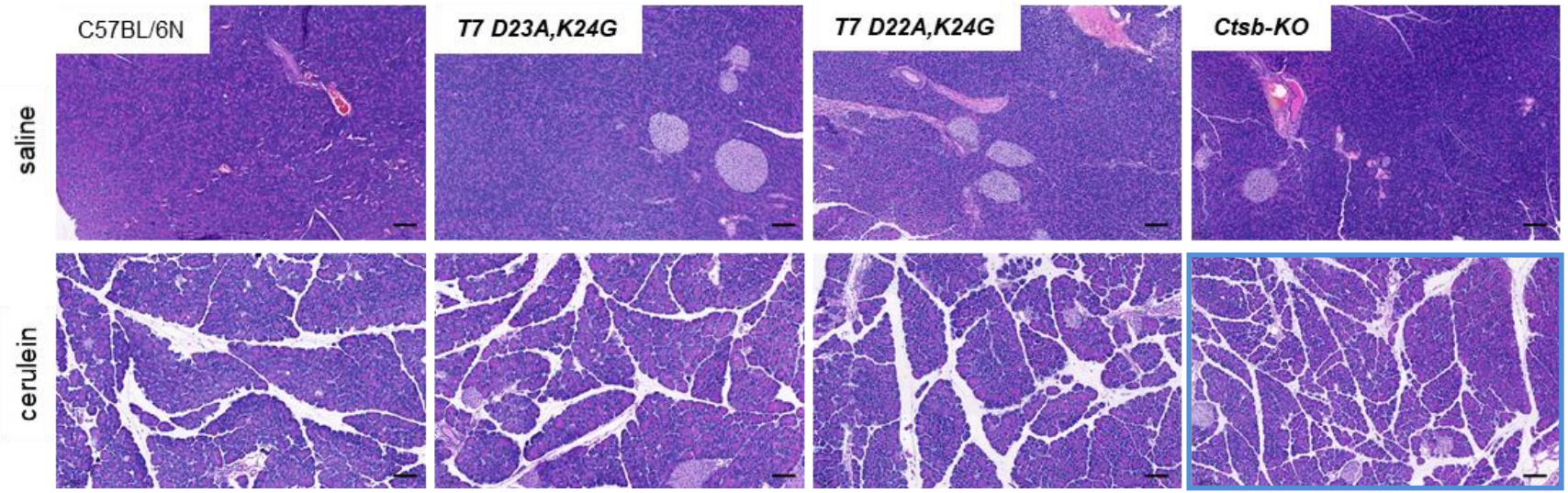
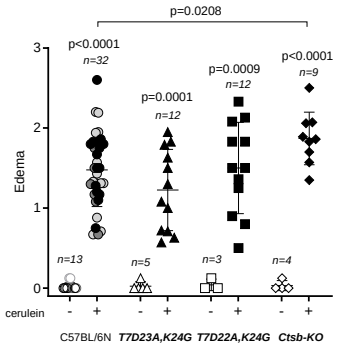
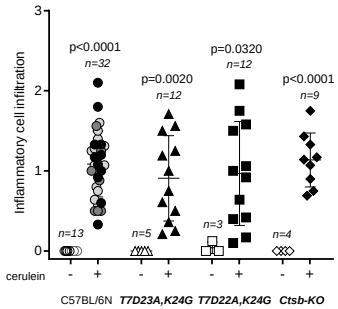
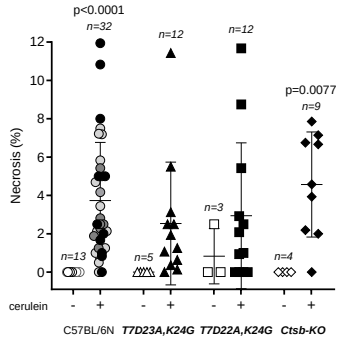
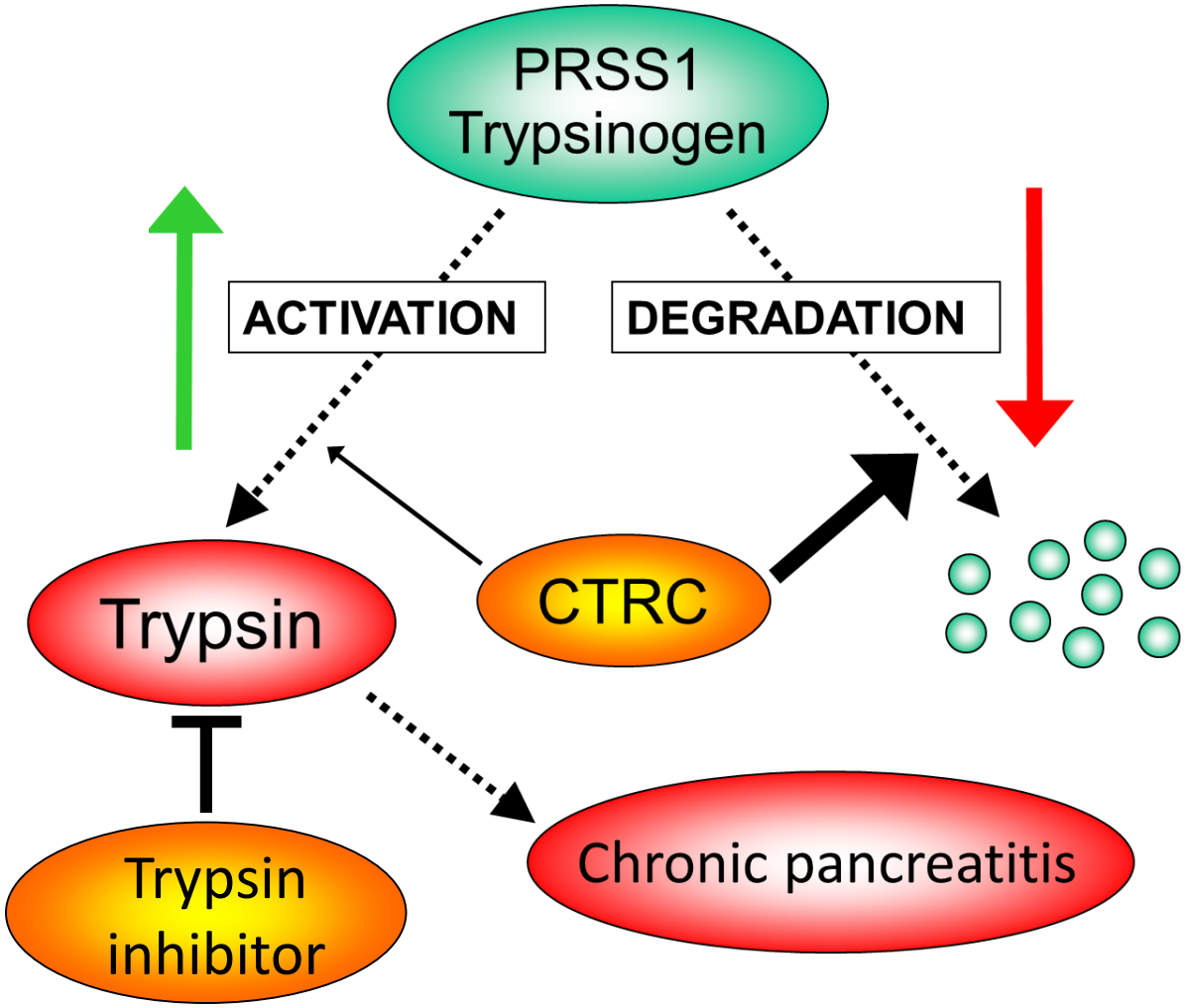








Therapeutic approaches



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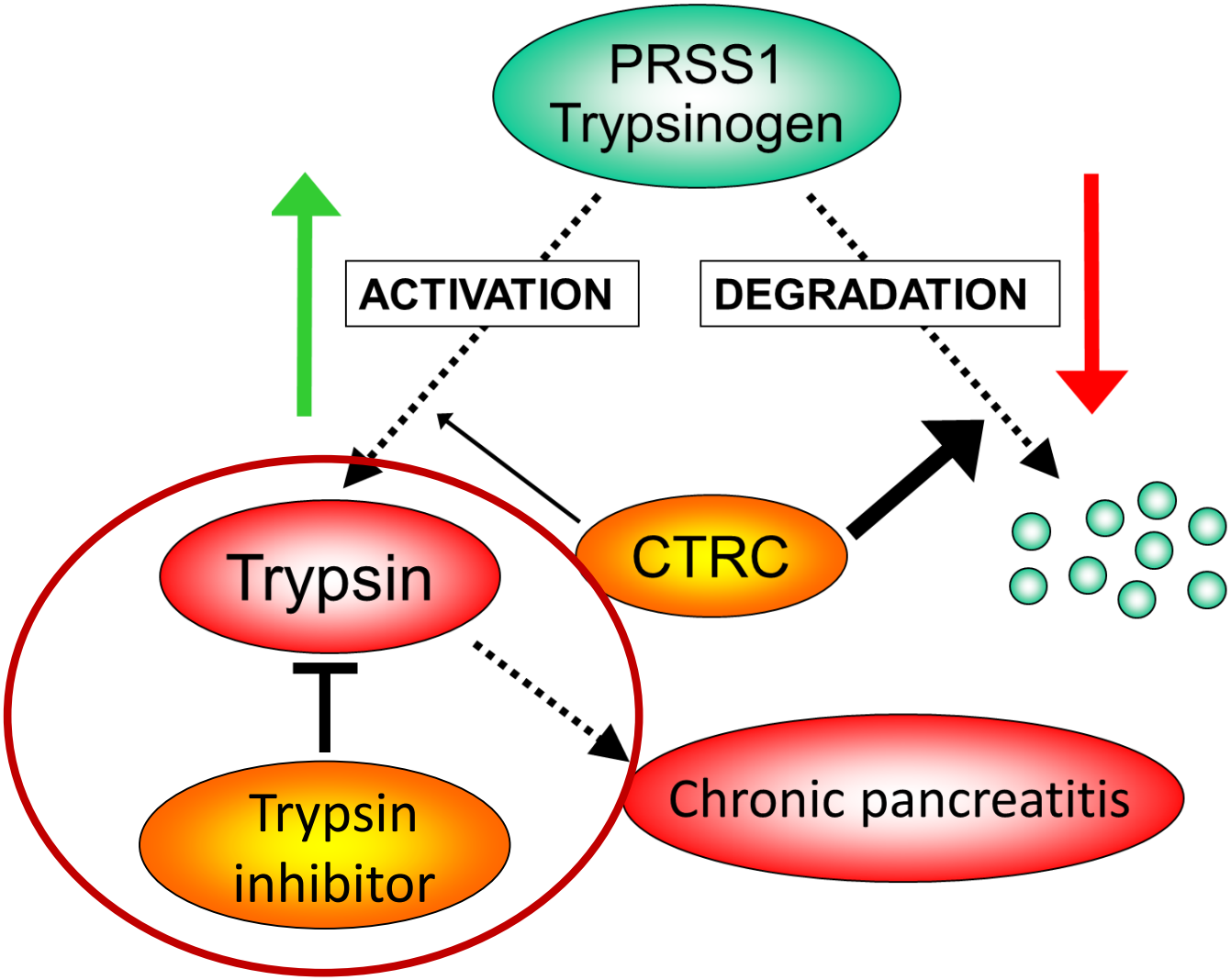

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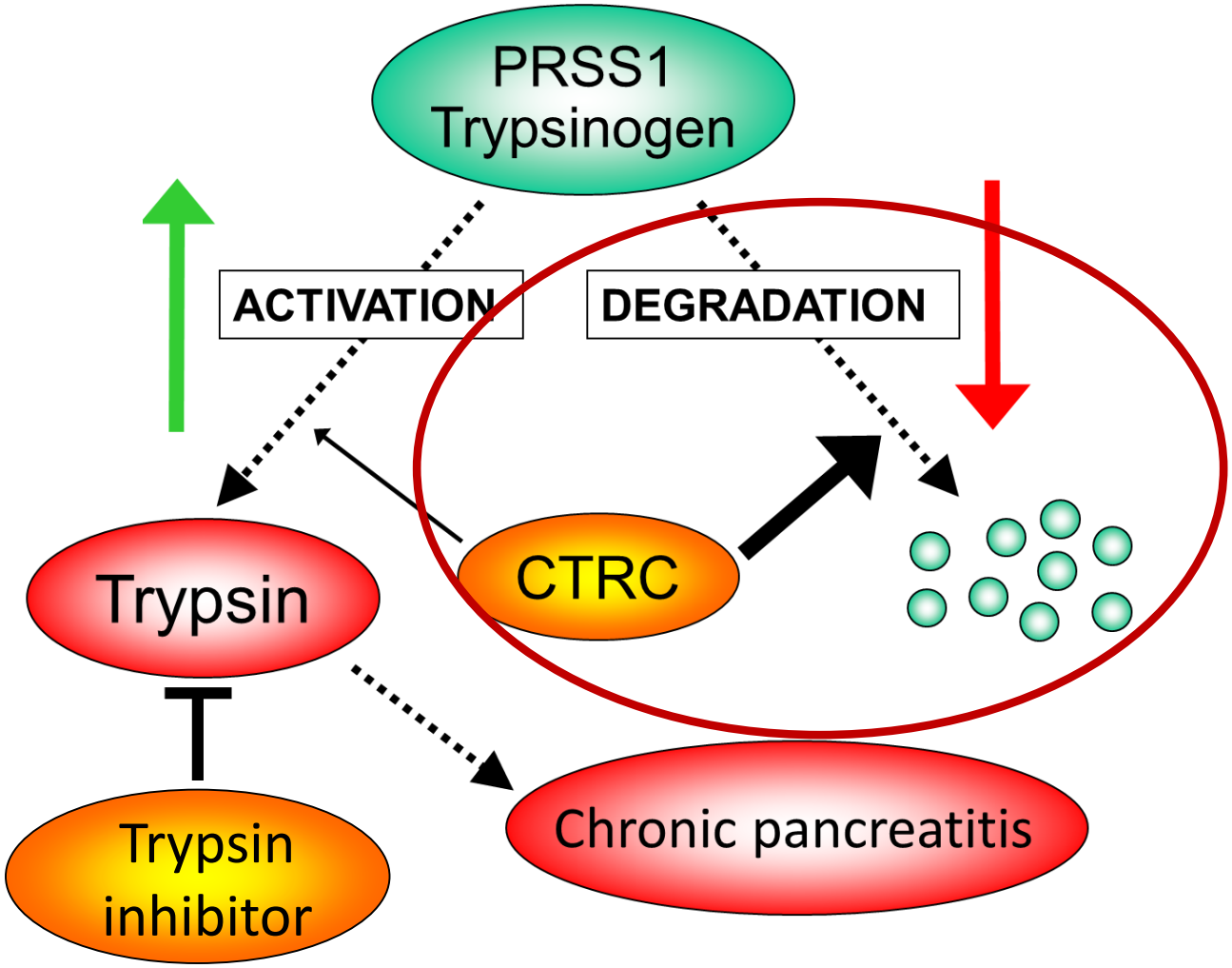

Miklos Sahin-Toth
Alexandra Demcsak

Anna Orekhova
Thanh Tran

BOSTON UNIVERSITY

Discovery Award DoD
Research Scholar Award AGA
Young Investigator in Pancreatitis Grant APA