Granulin and Its Roles in Opisthorchiasis & Cholangiocarcinoma

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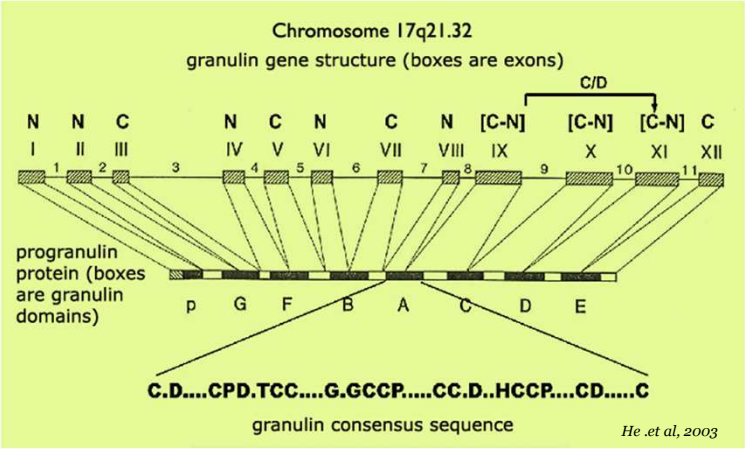
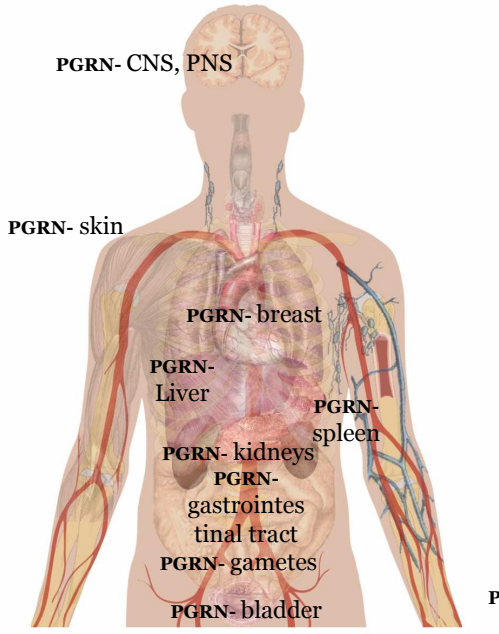
GRANULIN is…



Granulin (GRN) 6-10 kDa, Progranulin (PGRN) 60-90 kDa in mammals



Distribution

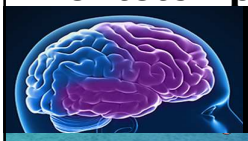
- Epithelin precursor, Granulin-Epithelial Precursor, PGRN
- Keratinocyte, white blood cells, macrophage

PGRN- wounded epithelia

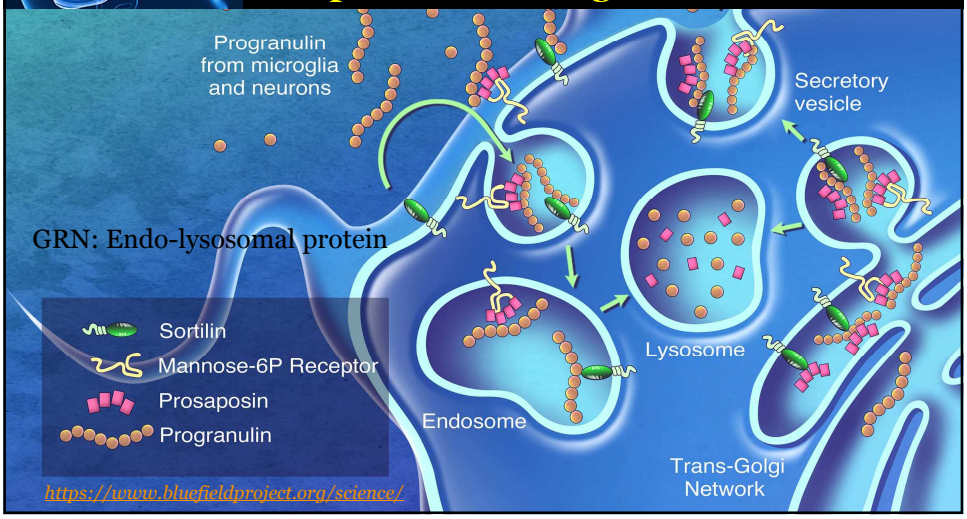
GRNs Functions

- Cell cycle control and wound healing
- Numerous mutations in human PGRN gene linked to psychiatric disorders including Alzheimer's disease and frontotemporal dementia

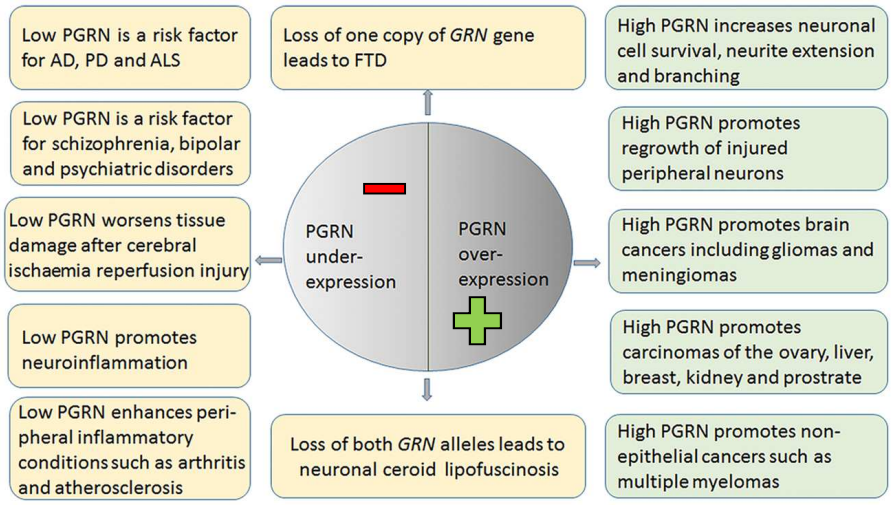
Frontotemporal dementia (FTD)



- **Memory disorders**
- **Personality changes**
- **Impaired reasoning**



Deficiency vs. Excess of PGRN associated with diseases



Bateman et al., 2018

Development

- Cell maturation
- Neurotrophic factor
- Sexual determination in embryo
- Embryonic implantation

Inflammation & wound healing

- From keratinocytes, macrophages and neutrophils
- Protection and promotion

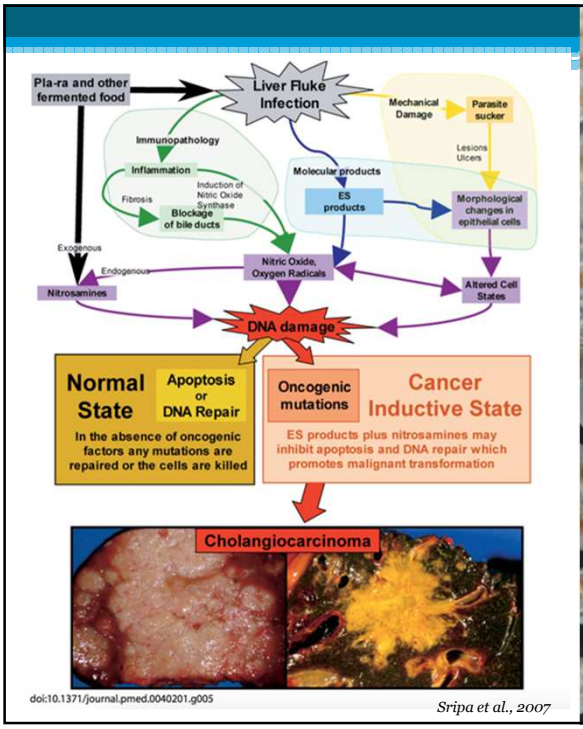
PGRN

- Mitogenesis
- Neuronal outgrowth
- Tumorigenesis

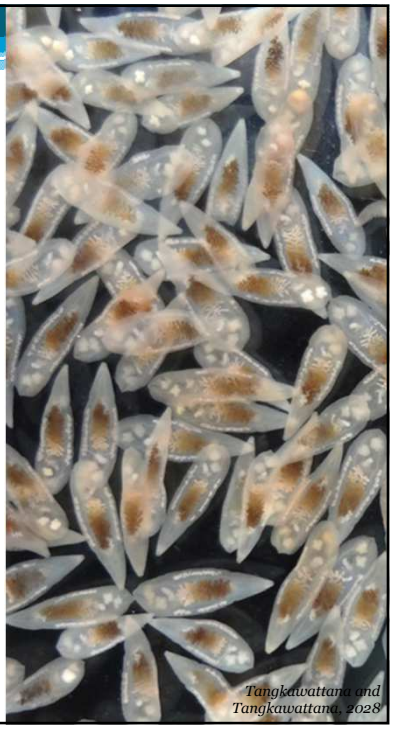
Cell proliferation

- Lysosomal function and organization

Protein homeostasis

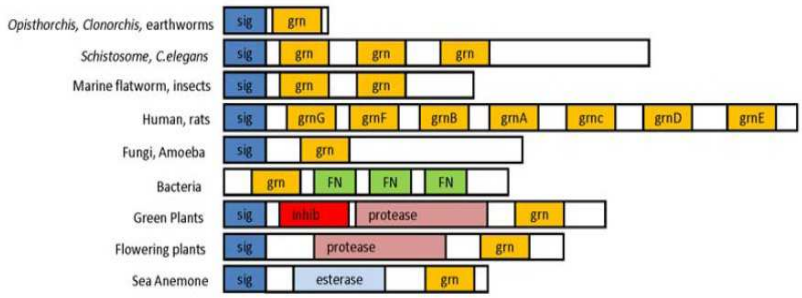


Sripa et al., 2007



Tangkawattana and Tangkawattana, 2018

PGRN in human, animals and plant species



Smout et al, 2009

- ES granulin (Ov-GRN-1, Ov-GRN-2), is transcribed in both juvenile and adult stages.
- Ov-PGRN required for endogenous regulation of cell growth, development and maintenance.
- Ov-GRN-1 and -2 orthologues were also identified in *C. sinensis*.

(Young et al., 2014)

GRN vs. *O. viverrini*

Increased cell proliferation of mouse fibroblast NIH-3T3 in vitro induced by ES product(s) from *O. viverrini* *(Thuwajit et al., 2004)*

Detection of GRN in the ES products of *O. viverrini* and its binding to mammalian biliary epithelial cells in situ *(Smout et al., 2009)*

Transcriptome study of OvES showed mixture of proteins that have been associated with cancers *(Mulvenna et al., 2009)*

* proteases, protease inhibitors, growth factors and anti-apoptotic proteins

Ov granulin causes host cells to proliferate.

The proliferative activity of fluke secreted proteins was blocked by antibodies against granulin *(Smout et al., 2009)*

O. viverrini secreted proteins accelerated wound resolution in human cholangiocytes

Recombinant Ov-GRN-1 induced angiogenesis and accelerated mouse wound healing *(Smout et al., 2015)*

Ov-GRN-1 was internalized by human cholangiocytes and induced gene and protein expression changes associated with wound healing and cancer pathways *(Smout et al., 2015)*

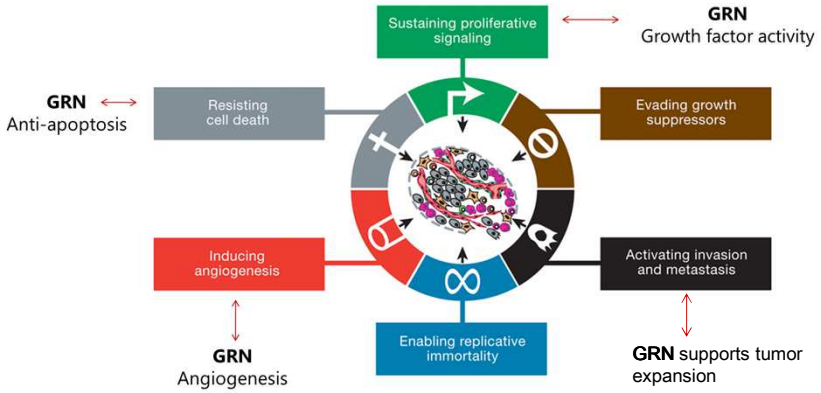
Development of a potent wound healing agent based on the liver fluke granulin structural fold

(Bensal et al., 2017)

GRN vs. Tumors

- Over-expression of PGRN is linked to tumorigenesis in liver cancers, and is associated with an aggressive and invasive tumor phenotype.
- GRN is a potent proliferative agent but has other pro-tumor qualities that are not yet well characterized.
- It may promote carcinoma progression by
  - Promoting angiogenesis
  - Insensitivity to apoptosis
  - Promotion of tumor invasion and anchorage

Granulin in Cancers



Modified from Hanahan and Weinberg, 2010

GRN & Cholangiocarcinoma

- Over-expression of PGRN is an indicator of poor prognosis for a range of cancer types, and anti-GRN antibodies have been successfully employed in mice as therapy for hepatocellularcarcinoma (HCC)

Granulin (PGRN) in CCA development

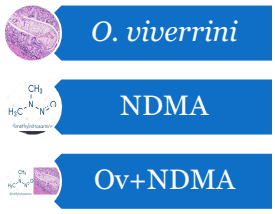
DOI:10.22034/APJCP.2018.19.9.2437
Granulin Expression in O. Viverrini-Induced Cholangiocarcinogenesis

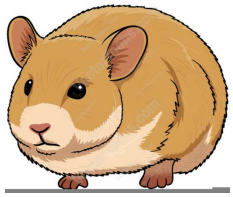
RESEARCH ARTICLE

Editorial Process: Submission:06/18/2017 Acceptance:07/30/2018

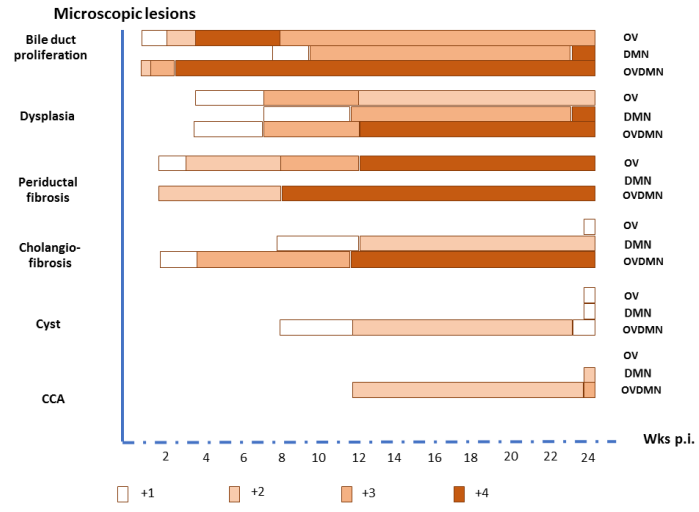
Granulin Expression in Hamsters during *Opisthorchis viverrini* Infection-Induced Cholangiocarcinogenesis

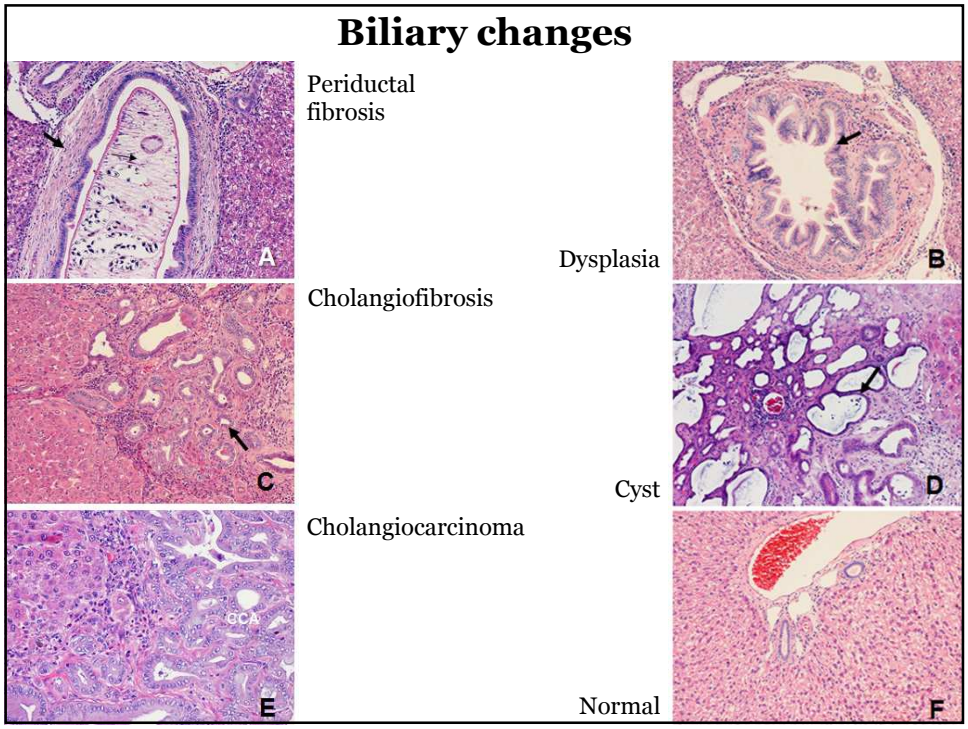
Songkiad Upontain[1,2], Piya Sereerak[2], Thewarach Laha[2,3], Banchob Sripa[2,4], Prasarn Tangkawatana[5], Paul J. Brindley[6], Sirikachorn Tangkawatana[2,7]*

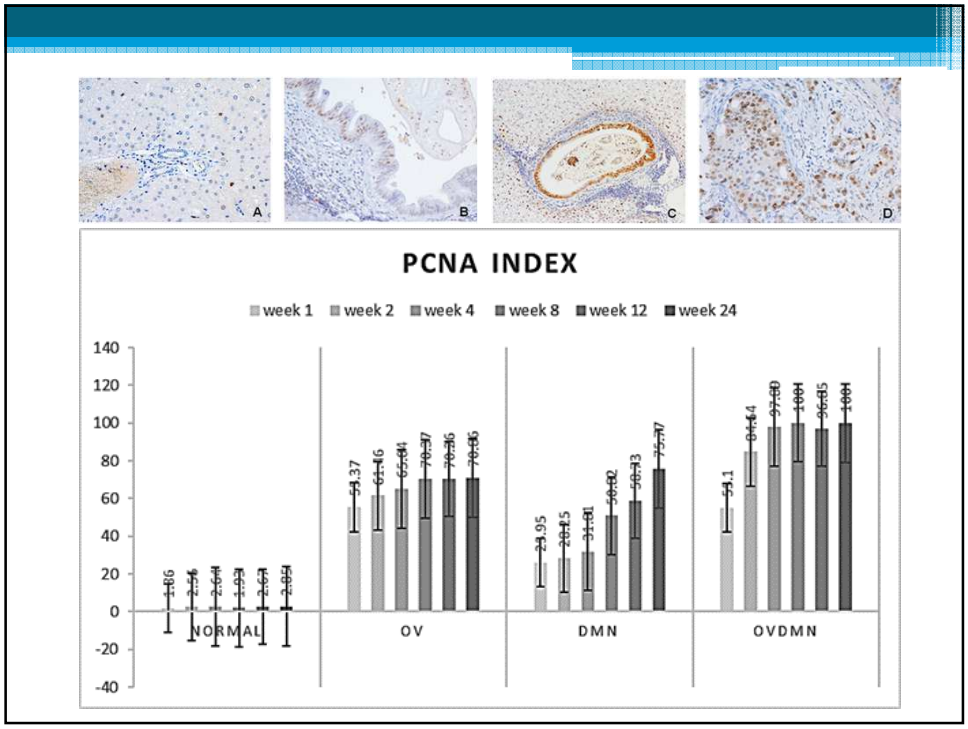




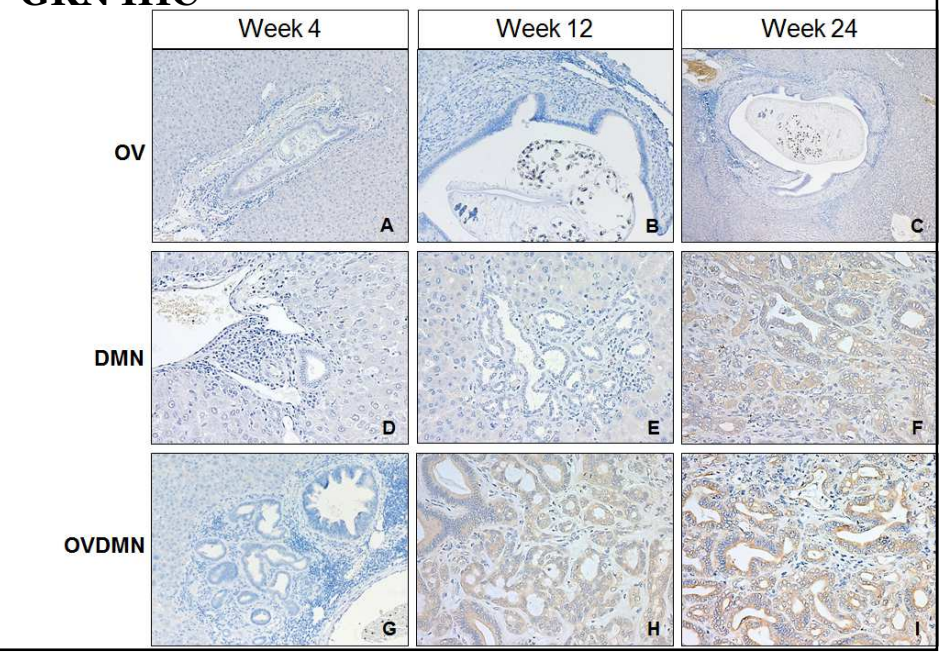
Schematic outline of biliary lesions in hamsters from 3 treatments

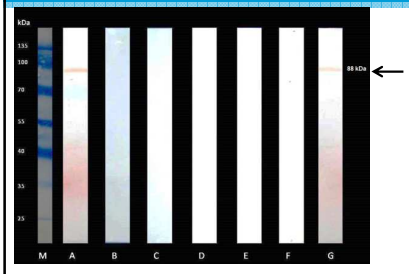


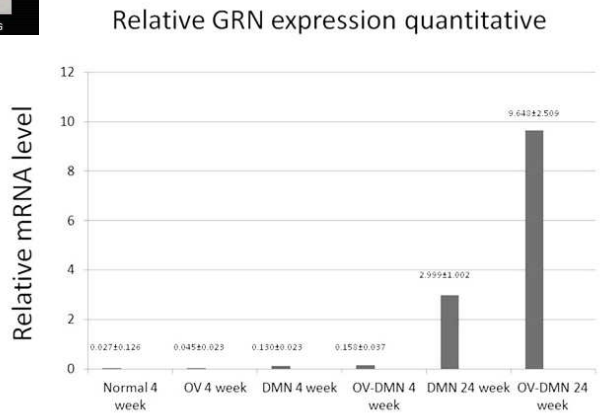

Biliary changes
Periductal fibrosis
Dysplasia
Cholangiofibrosis
Cyst
Cholangiocarcinoma
Normal
A
B
C
D
E
F
CCA


A
B
C
D
PCNA INDEX
week 1
week 2
week 4
week 8
week 12
week 24
140
120
100
80
60
40
20
0
-20
-40
NORMAL
OV
DMN
OVDMN

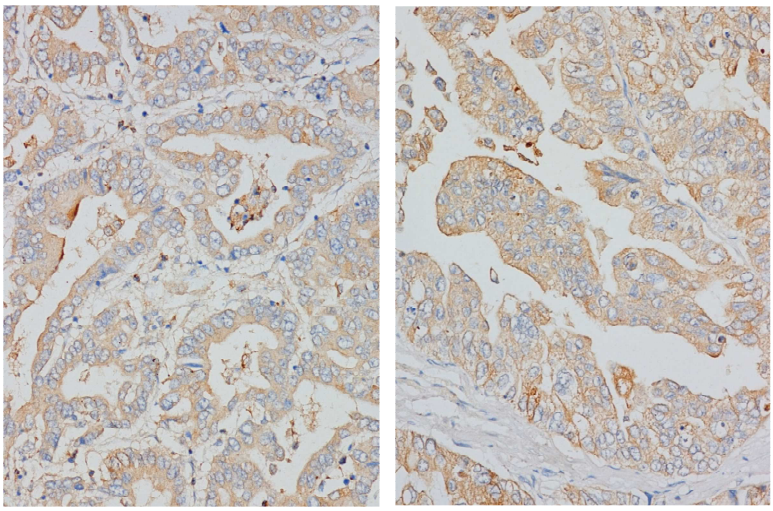
GRN IHC


Week 4
Week 12
Week 24
OV
DMN
OVDMN
A
B
C
D
E
F
G
H
I


kDa
88 kDa
M
A
B
C
D
E
F
G


Relative GRN expression quantitative
Relative mRNA level
12
10
8
6
4
2
0
0.027±0.126
0.045±0.023
0.130±0.023
0.158±0.037
2.999±1.002
9.648±2.509
Normal 4 week
OV 4 week
DMN 4 week
OV-DMN 4 week
DMN 24 week
OV-DMN 24 week

PGRN in Human CCA



Future Perspectives

- Prognostic markers for CCA?
- Targeted therapy?

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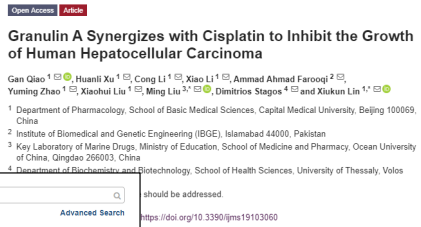
Tumor Biology and Immunology

Macrophage-Derived Granulin Drives Resistance to Immune Checkpoint Inhibition in Metastatic Pancreatic Cancer

Valeria Quaranta, Carolyn Rainer, Sebastian R. Nielsen, Meirion L. Raymant, Muhammad S. Ahmed, Dannielle D. Engle, Arthur Taylor, Trish Murray, Fiona Campbell, Daniel H. Palmer, David A. Tuveson, Ainhoa Mielgo, and Michael C. Schmid

DOI: 10.1158/0008-5472.CAN-17-3876 Published August 2018



Open Access Article

Granulin A Synergizes with Cisplatin to Inhibit the Growth of Human Hepatocellular Carcinoma

Gan Qiao [1], Huanli Xu [1], Cong Li [1], Xiao Li [1], Ammad Ahmad Farooqi [2], Yuming Zhao [1], Xiaohui Liu [1], Ming Liu [3,*], Dimitrios Stagos [4] and Xiukun Lin [1,*]

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should be addressed.

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Targeting granulin may serve as a potential therapeutic strategy to **restore CD8+ T-cell** infiltration in metastatic pancreatic ductal adenocarcinoma.

In conclusion…

- Wound healing agent

- Prognostic marker (CCA, Neurodegenerative disesaes, etc.)
- Targeted therapy

Acknowledgement

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