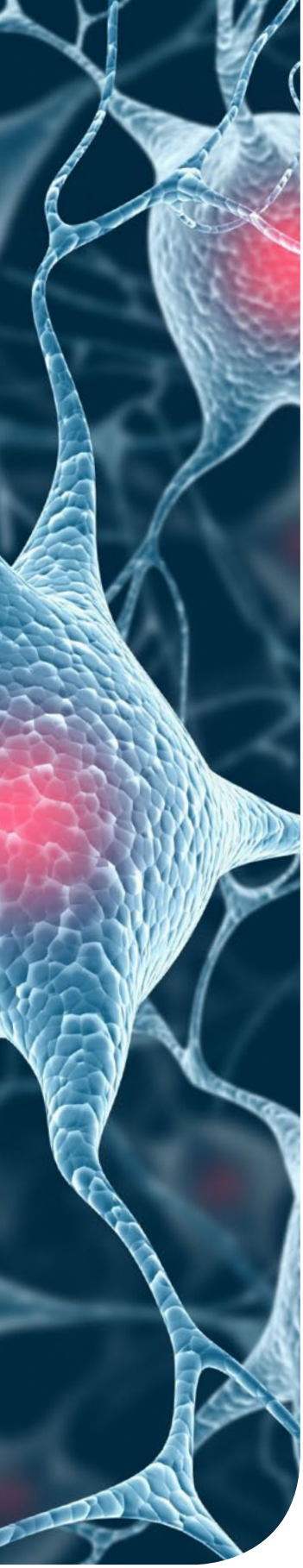

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Progranulin [PGRN]

Introduction

Progranulin [1] (PGRN; granulin (precursor); GRN [2], epithelin precursor [3]; proepithelin (PEPI) [4]; PC cell-derived growth factor (PCDGF) [5]; acrogranin [6]; paragranulin) is a 593aa cysteine-rich protein of 68.5kDa, that is typically secreted in a highly glycosylated 88kDa form. As a result of proteolytic cleavage of PGRN by extracellular proteases, a family of active 6kDa peptides (granulins (GRNs) A to G and paragranulin) are formed that each contain 10-12 highly conserved cysteine residues. The *PGRN* gene is widely expressed, particularly in epithelial and hematopoietic cells and the protein shows multifunctional biological activities.

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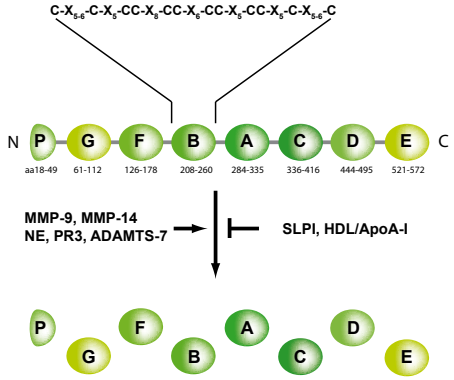

FIGURE: Structure and cleavage of PGRN. Each circle represents a granulin domain containing the consensus motif of 12 cysteine residues. PGRN can be cleaved in single granulin domains by MMP-9, MMP-14, NE, PR3 and ADAMTS-7. Both SLPI and high density lipoprotein (HDL)/apolipoprotein A-I (Apo A-I) can bind PGRN and inhibit PGRN cleavage. Adapted from L. De Muynck & P. Van Damme; J. Mol. Neurosci. **45,** 549 (2011)

PGRN – A key adipokine mediating insulin resistance and obesity & a potential biomarker for several cancer types, neuroinflammation, FTLD and Alzheimer's Disease

Contents

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Biological Effects of Progranulin [PGRN]

Mitogenic and Tumor Promoting Effects

PGRN has been reported to be highly expressed in a variety of cancer cells [7]. The correlation of high PGRN levels with tumor severity and the reduced tumor formation after PGRN knockdown [8] confer an essential role of PGRN in cellular proliferation and cancer. PGRN promotes multiple steps of the tumor progression cascade. Apart from stimulating the tumor growth, it also enhances migration, invasiveness, transformation, anchorage independence and chemoresistance of tumor cells [7, 9-13]. PGRN stimulates angiogenesis by upregulating vascular endothelial growth factor (VEGF) [13].

Cartilage Repair

PGRN stimulates cell growth in chondrocytes. The interaction between PGRN and COMP (cartilage oligomeric matrix protein) appears essential for the effect on chondrogenesis. COMP has an important function in maintaining the cartilage matrix and is degraded in osteoarthritis and rheumatoid arthritis. Binding of the PGRN A domain to COMP potentiates chondrocyte proliferation [14]. PGRN also prevents the degradation of COMP by ADAMTS-7 and ADAMTS-12 by disturbing their interaction with the EGF-like domain in COMP and by inhibiting the TNF-α induced increase in ADAMTS-7 and ADAMTS-12 expression [15].

Inflammation/Neuroinflammation Modulator

PGRN and GRNs have opposing inflammatory effects. Granulin peptides increase the expression of pro-inflammatory cytokines IL-1β, IL-8, and TNF-α, whereas PGRN is a potent inhibitor of TNF-α and promotes the upregulation of Th2 cytokines such as IL-4, IL-10 and IL-5 [2, 4, 16, 17]. A tight control of the conversion of full-length PGRN into granulin peptides appears to be pivotal. Several anti-inflammatory factors, such as SLPI and high density lipoprotein (HDL)/apolipoprotein A-I (Apo A-I), bind and protect PGRN from proteolytic processing by neutrophil or macrophage-released proteases [16, 18]. PGRN was shown to antagonize the effects of TNF-α on the TNF receptor [19]. PGRN thus serves as a negative feedback loop for TNF-α signaling. PGRN could function in the CNS neuroprotective by stimulating the production of anti-inflammatory Th2 cytokines, thereby suppressing proinflammatory responses and supporting endogenous neuroprotective neuroinflammation.

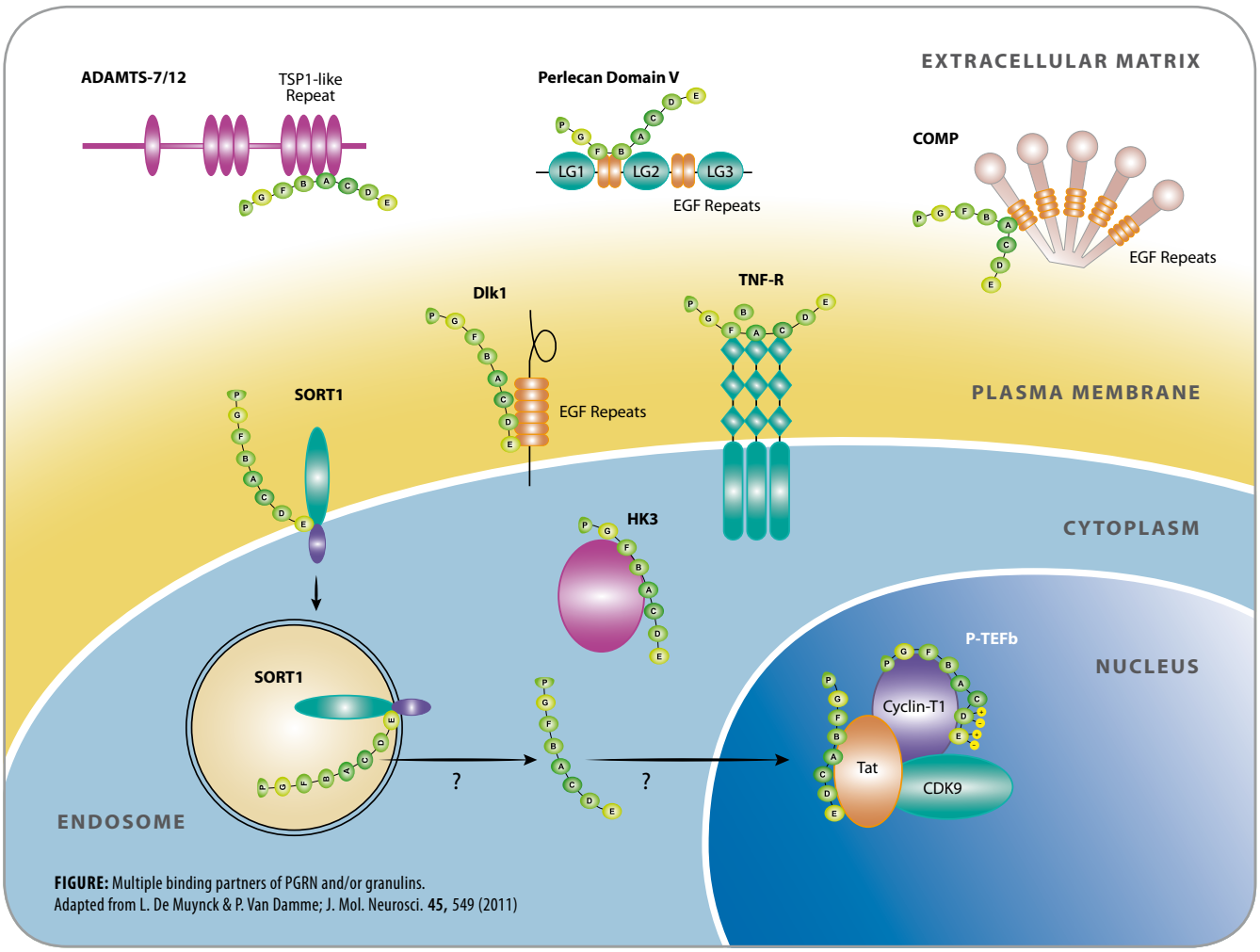

FIGURE: Multiple binding partners of PGRN and/or granulins.
Adapted from L. De Muynck & P. Van Damme; J. Mol. Neurosci. **45,** 549 (2011)

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Wound Healing

PGRN is an important modulator of wound healing [20]. Administration of exogenous PGRN to fresh wounds leads to accumulation of neutrophils, macrophages and fibroblast around a cutaneous wound and increased neovascularization of the damaged tissue. Pro-inflammatory signals such as TNF-α stimulate neutrophils and make them release their granule content, including elastase. PGRN inhibits neutrophil activation and degranulation by blocking TNF-α [4]. Direct interaction of PGRN with the TNF receptor has indeed recently been found to block the pro-inflammatory actions of TNF-α [19].

Neurodegeneration & Neuroprotection

Microglia show an increased accumulation and activation in neurodegenerative disease through both the proliferation of resident microglia and infiltration of bone-marrow derived cells into the CNS. They exhibit a dual role in neuroinflammation, being both neurotoxic (so-called M1 microglia) and neuroprotective (so-called M2 microglia) depending on the interaction with their environment and the timing of the activation. Microglia display increased PGRN expression following a variety of acute and chronic insults to the CNS, suggesting that PGRN plays a central role in the regulation of the neuroinflammatory response. It is anticipated that PGRN affects microglial proliferation, recruitment, differentiation, activation and phagocytosis [17].

PGRN appears to enhance survival and neurite outgrowth *in vitro* and *in vivo* [21]. Neurons treated with PGRN displayed enhanced phosphorylation of the serine/threonine kinase Akt and the glycogen synthase kinase-3β (GSK-3β), a substrate of Akt, with subsequent inactivation of GSK-3β [22]. Akt is a major component of pro-survival signaling pathways and regulates several functions including cell growth, apoptosis and survival among others.

FTLD [Frontotemporal Lobar Degeneration]

Mutations in PGRN have been found to be a common cause of familial FTLD [23, 24]. Since PGRN has neurotrophic properties and most mutations are predicted to result in a heterozygous loss of gene expression, PGRN deficiency is thought to cause neurodegeneration in these patients. The PGRN mutations cause reduced production and/or secretion of functional granulins and accumulation of the nuclear protein TDP-43 [25, Review]. Reduced GRN blood and CSF levels proved to be a valuable biomarker for early detection and diagnosis of GRN mutation carriers in FTLD [26-28]. Abnormal aggregation of TDP-43 was shown to be present in several neurodegenerative diseases and might be directly linked to the loss of PGRN and increased cellular stress [25, Review].

Metabolism

Elevated progranulin serum concentrations are associated with visceral obesity, elevated plasma glucose and dyslipidemia. Progranulin has been suggested as a novel marker of chronic inflammation in obesity and type-II diabetes (T2D) that closely reflects omental adipose tissue macrophage infiltration [29]. Recently, the physiological role of PGRN in hypothalamic glucose-sensing and appetite regulation has been described [30].

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Progranulin [PGRN] – A Multifaceted Biomarker

In several studies decreased or increased PGRN levels in serum, plasma and cerebrospinal fluid (CSF) were associated with diseases. PGRN levels could be used as a possible prognostic biomarker. The measurement of PGRN protein levels in plasma could be a quick and inexpensive assay.

- Breast Cancer [1]
- Epithelial Ovarian Cancer (EOV) [2]
- Hepatocellular Carcinoma (HCC) [3]
- Cholangiocarcinom (CCA) [4]
- Frontotemporal Lobar Degeneration (FTLD) [5]
- Alzheimer's Disease (AD) [6; 7]
- Visceral Obesity, Elevated Plasma Glucose, and Dyslipidemia [8]
- Nonalcoholic Fatty Liver Disease (NAFLD) [9]

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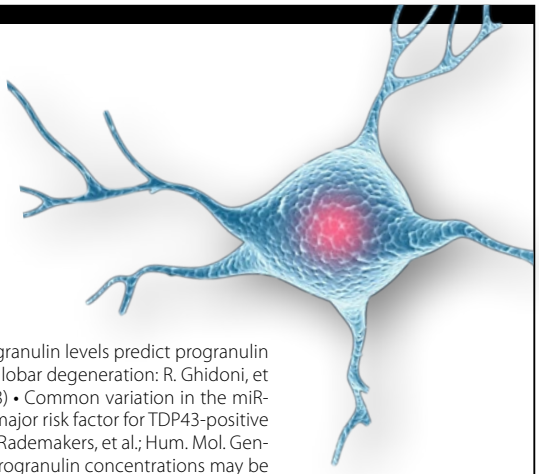

Progranulin ELISA Kits

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Progranulin (human) ELISA Kit

AG-45A-0018EK-KI01		1 x 96 wells
AG-45A-0018TP-KI01	Twin Plex	2 x 96 wells
AG-45A-0018PP-KI01	Penta Plex	5 x 96 wells

Direct measurement of human progranulin in human serum, plasma or cell culture supernatants. SENSITIVITY: 32pg/ml.

Progranulin (mouse) ELISA Kit

AG-45A-0019EK-KI01		1 x 96 wells
AG-45A-0019TP-KI01	Twin Plex	2 x 96 wells
AG-45A-0019PP-KI01	Penta Plex	5 x 96 wells

Direct measurement of mouse progranulin in mouse serum or cell culture supernatants. SENSITIVITY: 60pg/ml.

new Progranulin (rat) ELISA Kit

Coming soon – Please Inquire!

LIT (HUMAN): Low plasma progranulin levels predict progranulin mutations in frontotemporal lobar degeneration: R. Ghidoni, et al.; Neurology **71,** 1235 (2008) • Common variation in the miR-659 binding-site of GRN is a major risk factor for TDP43-positive frontotemporal dementia: R. Rademakers, et al.; Hum. Mol. Genet. **17,** 3631 (2008) • Serum progranulin concentrations may be associated with macrophage Infiltration into omental adipose tissue: B.S. Youn, et al.; Diabetes **58,** 627 (2009) • Progranulin plasma levels as potential biomarker for the identification of GRN deletion carriers. A case with atypical onset as clinical amnestic Mild Cognitive Impairment converted to Alzheimer's disease: M. Carecchio, et al.; J. Neurol. Sci. **287,** 291 (2009) • Low Serum Progranulin Predicts the Presence of Mutations: A Prospective Study: E.C. Schofield, et al.; J. Alzheimers Dis. **22,** 981 (2010) • A novel progranulin mutation causing frontotemporal lobar degeneration with heterogeneous phenotypic expression: G. Rossi, et al.; J. Alzheimers Dis. **23,** 7 (2011) • Progranulin expression in brain tissue and cerebrospinal fluid levels in multiple sclerosis: M. Vercellino, et al.; Mult. Scler. **(Epub ahead of print)** (2011) • Loss of function mutations in the progranulin gene are related to pro-inflammatory cytokine dysregulation in frontotemporal lobar degeneration patients: P. Bossù, et al.; J. Neuroinflammation **8,** 65 (2011) • Progranulin Genetic Screening in Frontotemporal Lobar Degeneration Patients From Central Italy: S. Bagnoli, et al.; Cell Mol. Neurobiol. **(Epub ahead of print)** (2011) • Optimal Plasma Progranulin Cutoff Value for Predicting Null Progranulin Mutations in Neurodegenerative Diseases: A Multicenter Italian Study: R. Ghidoni, et al.; Neurodegener. Dis. **(Epub ahead of print)** (2011) • **(MOUSE):** Progranulin enhances neural progenitor cell proliferation through glycogen synthase kinase 3β phosphorylation: T. Nedachi, et al.; Neuroscience **185,** 106 (2011)

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- Progranulin: normal function and role in neurodegeneration: J.L. Eriksen & I.R. Mackenzie; J. Neurochem. **104,** 287 (2008)
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- The molecular basis of frontotemporal dementia: M. Neumann, et al.; Expert Rev. Mol. Med. **11,** (2009)
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- Structure, function, and mechanism of progranulin; the brain and beyond: H. Toh, et al.; J. Mol. Neurosci. **45,** 538 (2011)
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- Progranulin and TDP-43: Mechanistic Links and Future Directions: S. Kumar-Singh; J. Mol. Neurosci. **45,** 561 (2011)
- Progranulin: A promising therapeutic target for rheumatoid arthritis: C.J. Liu; FEBS Lett. **585,** 3675 (2011)
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Latest Insights

PGRN – A Key Adipokine mediates Insulin Resistance and Obesity

T. Matsubara, et al. recently found that prgranulin (PGRN) is a key adipokine mediating high fat diet (HFD)-induced insulin resistance and obesity through IL-6 in adipose tissues. By differential proteome analysis of cellular models of insulin resistance, they identified PGRN as an adipokine induced by TNF-α and dexamethasone. PGRN in blood and adipose tissues was markedly increased in obese mouse models. PGRN deficiency blocked elevation of IL-6, an inflammatory cytokine, induced by HFD in blood and adipose tissues. They suggest that PGRN may be a promising therapeutic target for obesity.

LIT: PGRN is a Key Adipokine Mediating High Fat Diet-Induced Insulin Resistance and Obesity through IL-6 in Adipose Tissue: T. Matsubara, et al.; Cell Metab. **15,** 38 (2012)

Genetic Link between Amyotrophic Lateral Sclerosis and Frontotemporal Dementia in the C90RF72 Gene

Two independent reports in Neuron, by M. DeJesus-Hernandez, et al. and A.E. Renton, et al. claim that an expanded GGGGCC hexanucleotide repeat in the C9ORF72 gene on chromosome 9p21 provides a genetic link between amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). The C9ORF72 repeat expansion is the most frequent cause of inherited ALS and FTD to be identified so far and has been observed in a significant number of cases of sporadic FTD and ALS. The DNA expansion probably disrupts multiple mechanisms in motor nerve cells (motor neurons) and other nerve cells in the brain, leading to their premature failure and cell death. First insights into the molecular mechanisms underlying the development of ALS and FTD support the role of defects in RNA processing. Evidence for the generation of toxic RNA foci as a result of GGGGCC repeat expansions was provided. The GC-rich mRNA could be the cause for disease by recruiting and sequestering RNA-binding proteins into the foci, leading to aberrant splicing of RNAs. 10 additional reports have been published since October 10, 2011 addressing C9ORF72.

LIT: Expanded GGGGCC hexanucleotide repeat in noncoding region of C9ORF72 causes chromosome 9p-linked FTD and ALS: M. DeJesus-Hernandez, et al.; Neuron **72,** 245 (2011) • A hexanucleotide repeat expansion in C9ORF72 is the cause of chromosome 9p21-linked ALS-FTD: A.E. Renton, et al.; Neuron **72,** 257 (2011)

Optimal Plasma Progranulin Cutoff Value

R. Ghidoni, et al., using the AdipoGen™ Progranulin (human) ELISA Kit (AG-40A-0018) established a new plasma progranulin protein cutoff level of 61.55 ng/ml that identifies, with a specificity of 99.6% and a sensitivity of 95.8%, null mutation carriers among subjects attending to a memory clinic. Affected and unaffected PGRN null mutation carriers did not differ in terms of circulating progranulin protein. A significant disease anticipation was observed in PGRN$^+$ subjects with the lowest progranulin levels. The authors propose a new plasma progranulin protein cutoff level useful for clinical practice.

LIT: Optimal Plasma Progranulin Cutoff Value for Predicting Null Progranulin Mutations in Neurodegenerative Diseases: A Multicenter Italian Study: R. Ghidoni, et al.; Neurodegener. Dis. **(Epub ahead of print)** (2011)

Proteins

Progranulin (human) (rec.)

AG-40A-0068-C010 10 µg
AG-40A-0068-C050 50 µg

Produced in HEK293 cells. Signal peptide and mature human progranulin (aa 1-593) is fused at the C-terminus to a FLAG®-tag. **PURITY:** ≥95% (SDS-PAGE). **ENDOTOXIN CONTENT:** <0.1EU/µg protein (LAL-test).

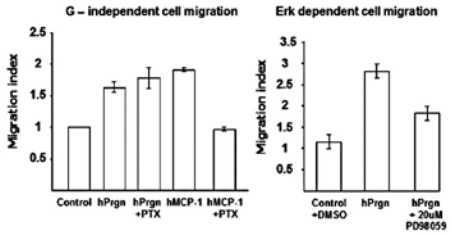


FIGURE: Transwell migration assay comparing Progranulin (human) (rec.) and human monocyte chemoattractant protein-1 (hMCP-1) using PTX-treated or PD98059-treated THP-1 cells.

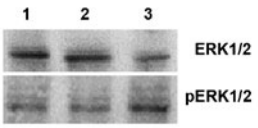
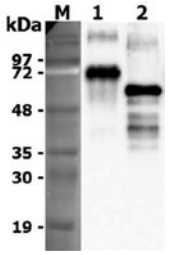


FIGURE: ERK phosphorylation induced by Progranulin (human) (rec.) in THP-1 cells. To examine the signal of phospho-p44/42 MAPK and p44/42 MAP kinase, reactions were carried out at 37°C over 0, 30, 60, mins, respectively by adding the Progranulin (human) (rec.) (100ng/ml) to the THP-1 monocyte cells, which were maintained with serum starvation for 24hrs.

FIGURE: Deglycosylation of Progranulin (human) (rec.).

METHOD: 1µg of Progranulin (human) (rec.) is denatured with 1X glycoprotein denaturing buffer at 100°C for 10 min. After the addition of NP-40 and G7 reaction buffer, two-fold dilutions of PNGase F are added and the reaction mix is incubated for 1 hour at 37°C. Separation of reaction products are visualized by immunoblotting using antibody against anti-Progranulin (human), pAb (Prod. No. AG-25A-0112).



Progranulin (mouse) (rec.)

AG-40A-0080-C010 10 µg
AG-40A-0080-C050 50 µg

Produced in HEK293 cells. Signal peptide and mature mouse progranulin (aa 1-589) is fused at the C-terminus to a FLAG®-tag. **PURITY:** ≥95% (SDS-PAGE). **ENDOTOXIN CONTENT:** <0.1EU/µg protein (LAL-test).

LIT: Progranulin enhances neural progenitor cell proliferation through glycogen synthase kinase 3β phosphorylation: T. Nedachi, et al.; Neuroscience **185,** 106 (2011)

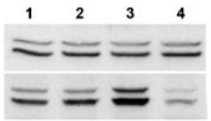


FIGURE: ERK phosphorylation induced by Progranulin (mouse) (rec.) in MCF10A cells. To examine the signal of phospho-p44/42 MAPK and p44/42 MAP kinase, reactions were carried out at 37°C over 0, 5, 10, 30, mins, respectively by adding Progranulin (mouse) (rec.) (500ng/ml) to the MCF10A human breast epithelial cells, which were maintained with serum starvation for 24hrs.

new Progranulin (rat) (rec.)

AG-40A-0194-C010 10 µg
AG-40A-0194-C050 50 µg

Produced in HEK293 cells. Signal peptide and rat progranulin (aa 1-602) are fused at the C-terminus to a FLAG®-tag. **PURITY:** ≥95% (SDS-PAGE). **ENDOTOXIN CONTENT:** <0.1EU/µg protein (LAL-test).

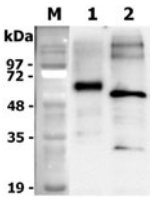


FIGURE: Deglycosylation of Progranulin (rat) (rec.). **METHOD:** 1 µg of Progranulin (rat) (rec.) is denatured with 1X glycoprotein denaturing buffer at 100°C for 10 min. After the addition of NP-40 and G7 reaction buffer, twofold dilutions of PNGase F are added and the reaction mix is incubated for 1 or 3 hours at 37°C. Separation of reaction products is visualized by immunoblotting using anti-FLAG-HRP antibody.

Granulin C

Granulin C (human) (rec.) (His)

AG-40A-0129-C010 10 µg
AG-40A-0129-C050 50 µg

Produced in *E. coli*. The mature peptide of human granulin C (aa 364-430) is fused at the C-terminus to a His-tag.

anti-Granulin C (human), pAb

AG-25A-0090-C100 100 µg

From rabbit. **IMMUNOGEN:** Recombinant human granulin C. **SPECIFICITY:** Reacts with human granulin C and human progranulin. **APPLICATION:** WB.

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Antibodies

anti-Progranulin (human), mAb (PG359-7)

AG-20A-0052-C100 100 µg

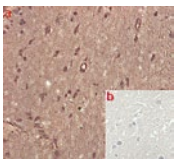
CLONE: PG359-7. **ISOTYPE:** Mouse IgG1. **IMMUNOGEN:** Recombinant human progranulin. **SPECIFICITY:** Recognizes human progranulin. Detects a band of ~90kDa by Western blot. **APPLICATION:** IHC (PS), IP, WB.

LIT: Progranulin A-mediated MET signaling is essential for liver morphogenesis in zebrafish: Y.H. Li, et al.; JBC **285,** 41001 (2010)

FIGURE: Immunohistochemical staining of human tissue using anti-Progranulin (human), mAb (PG359-7) at 1:100 dilution.

A. Immunoperoxidase staining (cytoplasmic) of formalin-fixed, paraffin-embedded human cerebellum (200x, brown colour).

B. Isotype control with IgG1 (negative control).



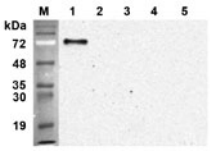
anti-Progranulin (mouse), mAb (PG319-1)

AG-20A-0077-C050 50 µg
AG-20A-0077-C100 100 µg

CLONE: PG319-1. **ISOTYPE:** Rat IgG2. **IMMUNOGEN:** Recombinant mouse progranulin. **SPECIFICITY:** Recognizes mouse progranulin. Detects a band of ~90kDa by Western blot. **APPLICATION:** WB.

FIGURE: Western blot analysis using anti-Progranulin (mouse), mAb (PG319-1) at 1:2'000 dilution.

1: Mouse Progranulin (FLAG®-tagged).
2: Human Progranulin (FLAG®-tagged).
3: Human Granulin C (FLAG®-tagged).
4: Human Granulin F (FLAG®-tagged).
5: Human DLL1 (FLAG®-tagged) (negative control).



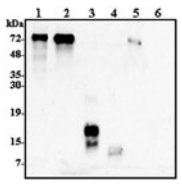
new anti-Progranulin (human), pAb

AG-25A-0112-C100 100 µg

From Guinea pig. **IMMUNOGEN:** Recombinant human progranulin. **SPECIFICITY:** Recognizes human progranulin. Detects a band of ~90kDa by Western blot. Weakly cross-reacts with mouse progranulin. Cross-reacts with human GRN-C and human GRN-F. **APPLICATION:** ELISA, WB.

FIGURE: Western blot analysis using anti-Progranulin (human), pAb at 1:2'000 dilution.

1: Human Progranulin (FLAG®-tagged) (50ng).
2: Human Progranulin (tag-free) (100ng).
3: Human Granulin C (FLAG®-tagged) (50ng).
4: Human Granulin F (FLAG®-tagged) (50ng).
5: Mouse Progranulin (FLAG®-tagged) (50ng).
6: Negative Control (FLAG®-tagged).



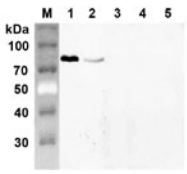
anti-Progranulin (mouse), pAb

AG-25A-0093-C100 100 µg

From rat. **IMMUNOGEN:** Recombinant mouse progranulin. **SPECIFICITY:** Recognizes mouse progranulin. Detects a band of ~90kDa by Western blot. Weakly cross-reacts with human progranulin. **APPLICATION:** WB.

FIGURE: Western blot analysis using anti-Progranulin (mouse), pAb at 1:2'000 dilution.

1: Mouse Progranulin (FLAG®-tagged).
2: Human Progranulin (FLAG®-tagged).
3: Human Granulin C (FLAG®-tagged).
4: Human Granulin F (FLAG®-tagged).
5: Human ANGPTL3 (FLAG®-tagged) (negative control).



Coming soon!

new anti-Progranulin (rat), pAb

Please Inquire!

Purified (PF) = Purified (Preservative free); FACS = Flow Cytometry; ICC = Immunocytochemistry; IP = Immunoprecipitation; IHC = Immunohistochemistry (FS = Frozen Sections, PS = Paraffin Sections); WB = Western blot; BP = Blocking Peptide

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- **Correct processed protein (at the N-terminus)**
- **Affinity purified**
- **Low endotoxin levels (<0.1EU/µg)**

new Progranulin (human) (rec.) (untagged)

AG-40A-0188-C010		10 µg
AG-40A-0188-C050		50 µg
AG-40A-0188AA-C500	BULK	500 µg

Produced in HEK293 cells. Signal peptide and human progranulin (aa 1-593) is untagged. Reflects the native sequence with no additional aa. **PURITY:** ≥95% (SDS-PAGE). **ENDOTOXIN CONTENT:** <0.1EU/µg protein (LAL-test).

LIT: Involvement of Progranulin in Hypothalamic Glucose Sensing and Feeding Regulation: H.K. Kim, et al.; Endocrinology (Epub ahead of print) (2011)

new Progranulin (mouse) (rec.) (untagged)

AG-40A-0189-C010		10 µg
AG-40A-0189-C050		50 µg
AG-40A-0189AA-C500	BULK	500 µg

Produced in HEK293 cells. Signal peptide and mouse progranulin (aa 1-589) is untagged. Reflects the native sequence with no additional aa. **PURITY:** ≥95% (SDS-PAGE). **ENDOTOXIN CONTENT:** <0.1EU/µg protein (LAL-test).

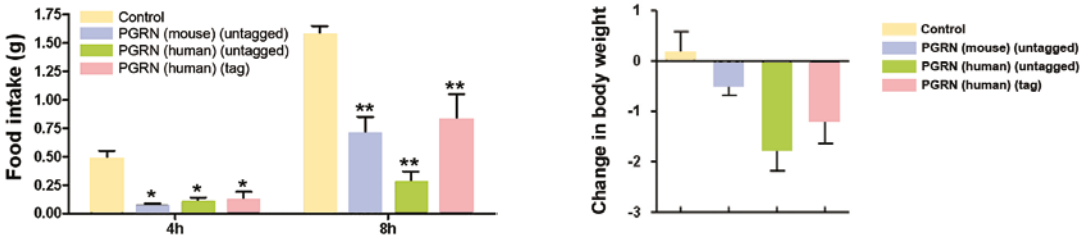

FIGURE: Regulation of food intake and body weight in mice by human and mouse untagged Progranulin.

Coming soon!

new Progranulin (rat) (rec.) (untagged)

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FEB-2012