

# Multiple therapeutic effects of progranulin on experimental acute ischaemic stroke

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Pharmacology, Pharmaron

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Brain. 2015 Jul;138(Pt 7):1932-48.

# Outline

1 Background

2 Materials and Methods

3 Results

4 Conclusion

# Outline

1 Background

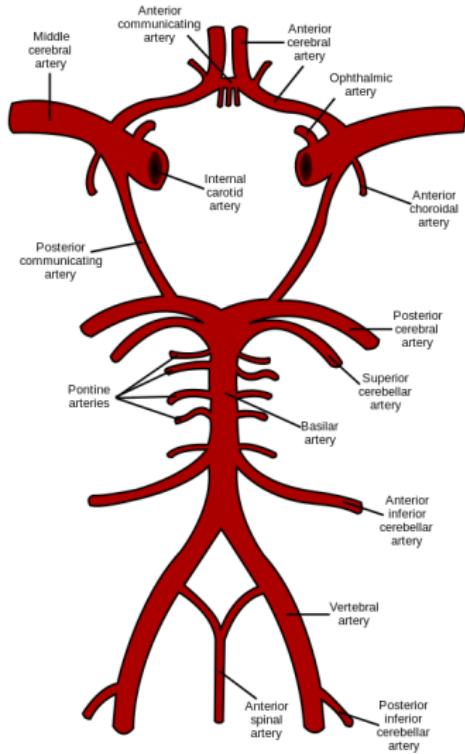
2 Materials and Methods

3 Results

4 Conclusion

# What's the stroke

- A stroke is a medical emergency in which the blood supply to any portion of the brain is interrupted or reduced.
- Alternative names:  
Cerebrovascular accident/  
disease (CVA), Cerebral  
infarction, Cerebral hemorrhage.



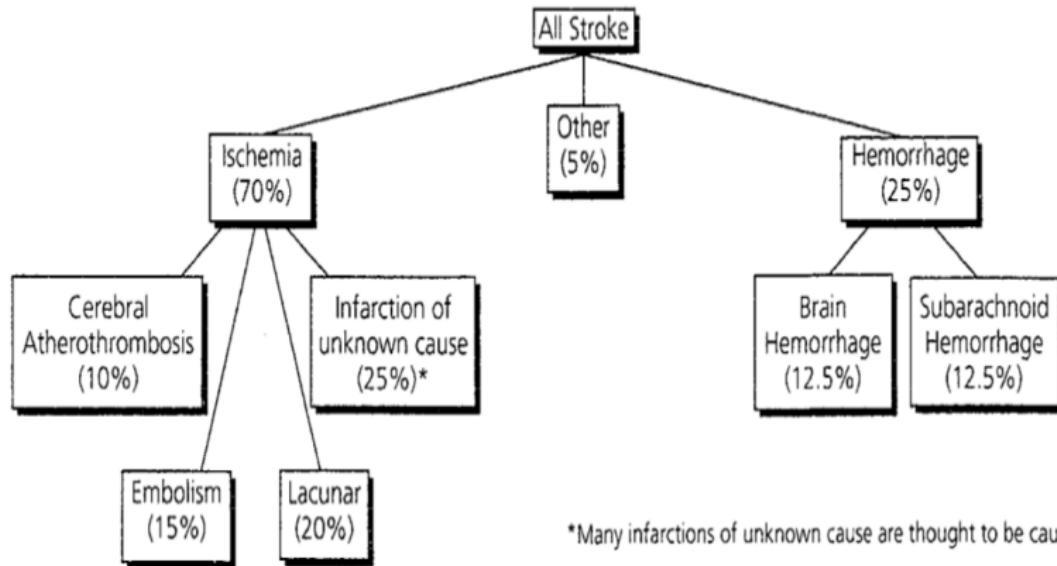
The Circle of Willis Anatomy

# What's the impact of stroke?

- Stroke is the third leading cause of death in the United States (First in China)
  - Someone suffers a stroke every 40 seconds
  - About 795,000 Americans suffer a stroke each year (2% in 2012-2013)
  - About every 4 minutes, someone dies of a stroke
- Stroke is a leading cause of serious, long-term long disability
- About 6.4 million Americans are stroke survivors
- Americans will pay about \$71.5 billion in 2012 for stroke-related related medical costs and lost productivity (¥ 40 billion in China)

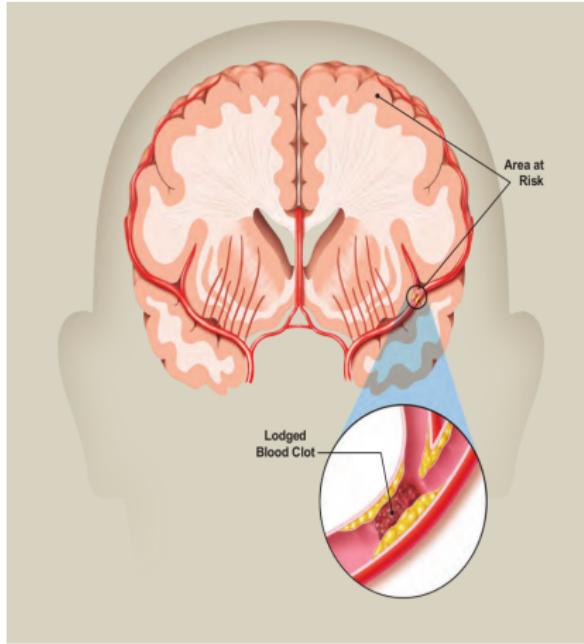
# Types of stroke

Approximate Breakdown of Types of Stroke



\*Many infarctions of unknown cause are thought to be caused by embolism.

# Types of stroke



own of T  
oke  
er  
(b)  
any infarct

## NORMAL

Blood flows easily through a clear artery.



## BLOCKAGE

An artery can become blocked by **plaque** (a fatty substance in the wall of the artery) or a **blood clot**, which reduces blood flow to the brain and causes a stroke. This picture shows **atherosclerosis**, a hardening of the arteries. Atherosclerosis is caused partly by cholesterol or plaque buildup.



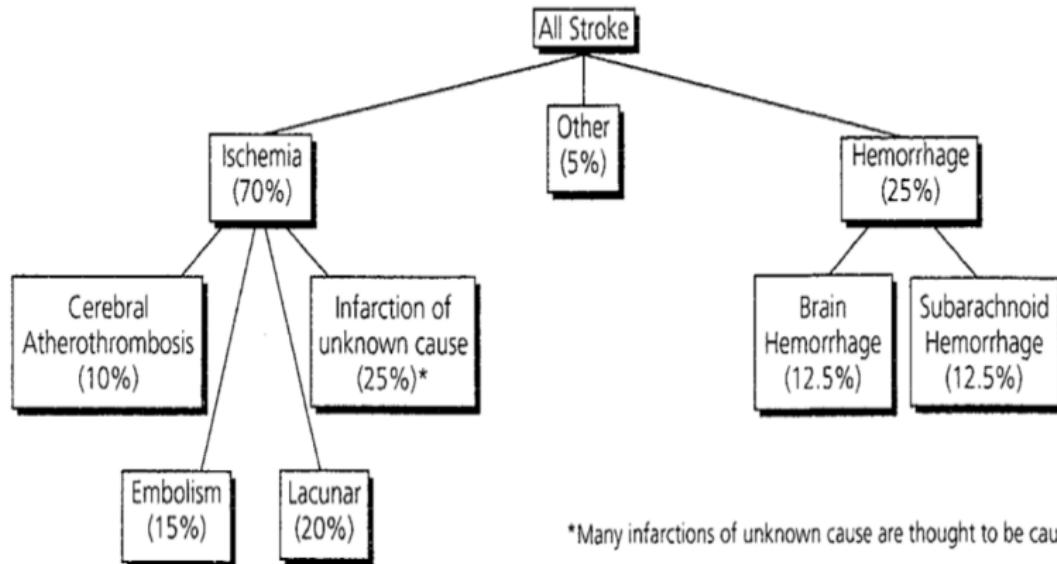
## CLOT DISSOLVES

The plaque or blood clot breaks up and blood flow is restored to the brain. This may happen during a TIA (see page 11), in which brain cells recover and there are no permanent signs of a stroke.



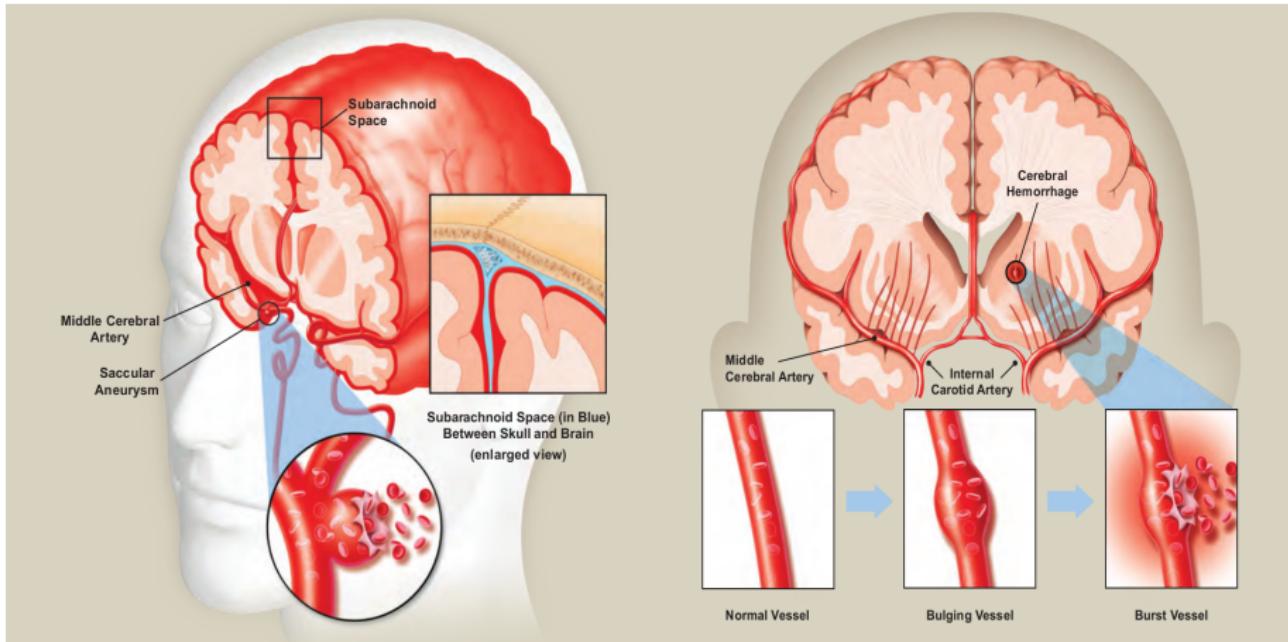
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# Types of stroke



# Stroke therapy

**Table 1. Current Approaches for Stroke Therapeutics**

Restoration of Blood Flow (Acute)

Intra-arterial and intravenous tPA

Mechanical thrombectomy

Magnetic resonance-guided focused ultrasound

Neuroprotection (Acute)

Hypothermia

PSD-95

Cell Replacement Therapies (Recovery)

Endogenous stem cells

Exogenous stem cells

Induced stem cells

Modulation of Circuits (Recovery)

Transcranial direct current stimulation

Transcranial magnetic stimulation

Optogenetic stimulation

MR-guided focus ultrasound

Stereotactic radiotherapy

Brain-Machine Interface (Recovery)

Cortical signals to induce movement

Spinal cord signals to induce movement

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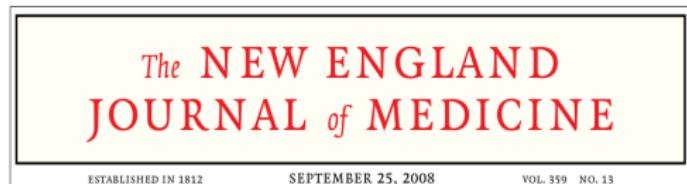
Thrombolysis with Alteplase 3 to 4.5 Hours  
after Acute Ischemic Stroke

Werner Hacke, M.D., Markku Kaste, M.D., Erich Bluhmki, Ph.D., Miroslav Brozman, M.D., Antoni Dávalos, M.D.,  
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### Thrombolysis with Alteplase 3 to 4.5 Hours after Acute Ischemic Stroke

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### 1,026 Experimental Treatments in Acute Stroke

Victoria E. O'Collins, B.Sc.,<sup>1</sup> Malcolm R. Macleod, MRCP, PhD,<sup>3</sup> Geoffrey A. Donnan, MD, FRACI,<sup>2</sup> Laura L. Horky, MD, PhD,<sup>2</sup> Bart H. van der Worp, MD, PhD,<sup>4</sup> and David W. Howells, PhD<sup>1</sup>

**Objective:** Preclinical evaluation of neuroprotectants fostered high expectations of clinical efficacy. When not matched, the question arises whether experiments are poor indicators of clinical outcome or whether the best drugs were not taken forward to clinical trial. Therefore, we endeavored to contrast experimental efficacy and scope of testing of drugs used clinically and those tested only experimentally. **Methods:** We identified neuroprotectants and reports of experimental efficacy via a systematic search. Controlled *in vivo* and *in vitro* experiments using functional or histological end points were selected for analysis. Relationships between outcome, drug mechanism, scope of testing, and clinical trial status were assessed statistically. **Results:** There was no evidence that drugs used clinically (114 drugs) were more effective experimentally than those tested only in animal models (912 drugs); for example, improvement in focal models averaged  $31.3 \pm 16.7\%$  versus  $24.4 \pm 32.9\%$ ,  $p > 0.05$ , respectively. Scope of testing using Stroke Therapy Academic Industry Roundtable (STAIR) criteria was highly variable, and no relationship was found between mechanism and efficacy. **Interpretation:** The results question whether the most efficacious drugs are being selected for stroke clinical trials. This may partially explain the slow progress in developing treatments. Greater rigor in the conduct, reporting, and analysis of animal data will improve the transition of scientific advances from bench to bedside.

Ann Neurol 2006;59:467–477

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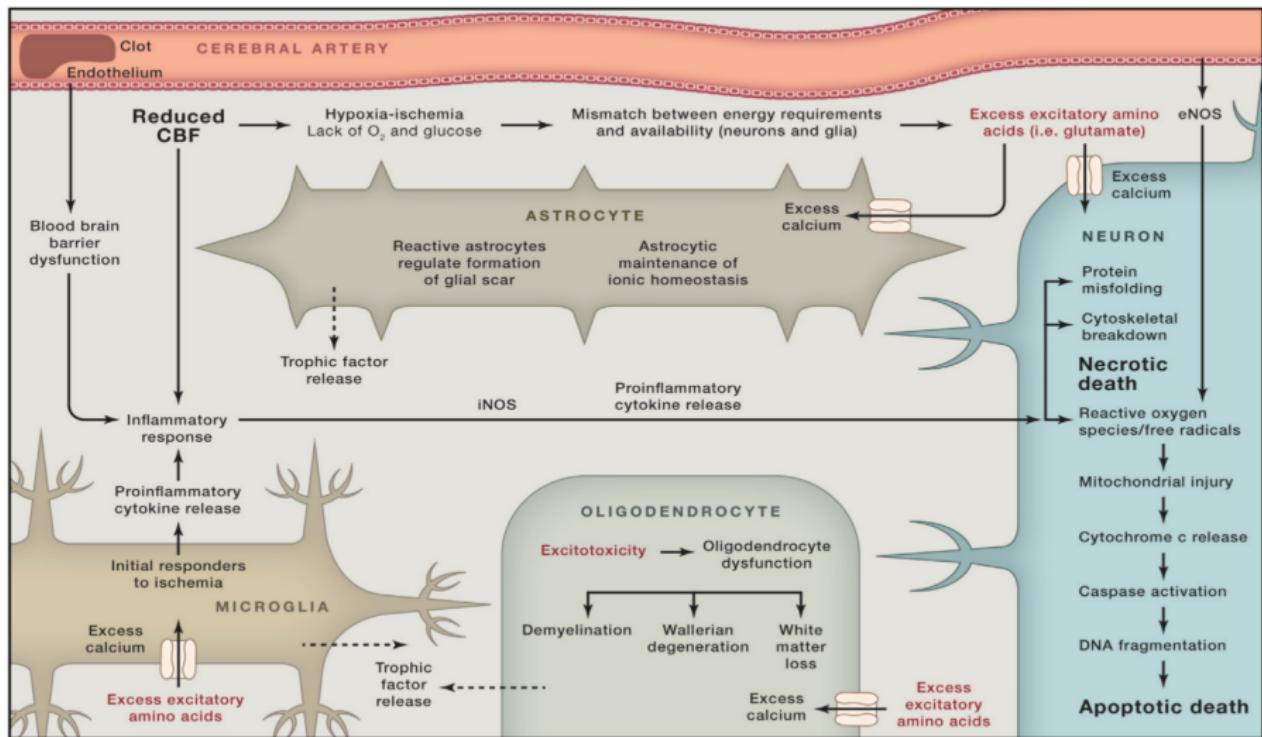
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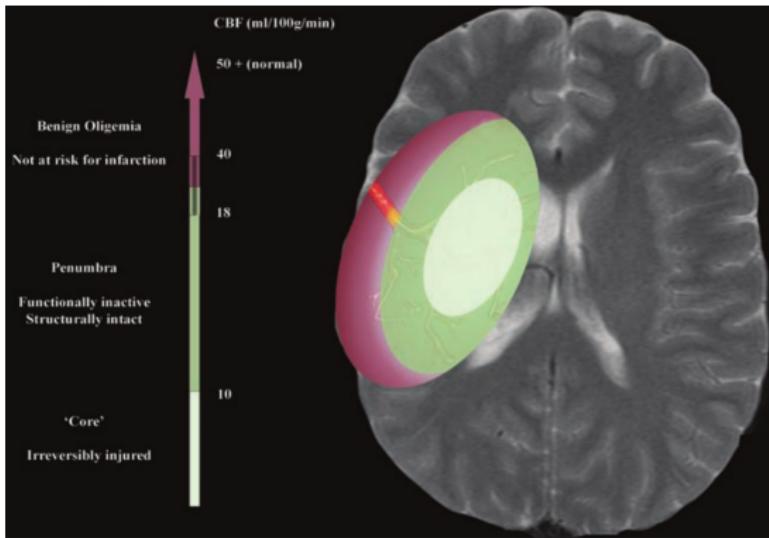
Neuroprotection and neurorepair: some treatments under investigation and their mechanisms.

Class	Treatment	Mechanism	References
Anti-excitotoxicity	Magnesium sulfate Tet-NB28® (NA-1)	Decrease of glutamate release; NMDA ion channel blocker; physiologically calcium channel blocker; hypothermia Inhibition of the formation of NMDA-receptor/PSD-95/nNOS complex	Mayer et al. (1984); Kang et al. (2011); Song et al. (2013) Aarts et al. (2002); Bräane et al. (2011)
Antioxidant	Edaravone, Ebselen	Scavenger of ROS	Lapchak & Zivin (2007); Barroso et al. (2005); Lapchak (2010a); Parrish & Sies (2013)
Haematopoietic growth factors	Uric acid NOX inhibitors G-CSF EPD	Scavenger of ROS NOX isoforms inhibition Reduction of glutamate-induced excitotoxicity; anti-inflammation; anti-apoptotic; enhancement of neurogenesis and angiogenesis	Ames et al. (1981); Yu et al. (1998); Kleineicz et al. (2010); Rademacher et al. (2013); Villa et al. (2003); Hasselblatt et al. (2006); England et al. (2009); Minnerup et al. (2009b)
Cytokine antagonists	IL-1 $\alpha$ Levostatin, Simvastatin Mincycline	Anti-inflammatory HMGB1a reductase inhibitors; pleiotropic activities	Lodwick & Ratwani (1996); Barnwell et al. (2009); Cimino et al. (2007)
Antibiotics		Anti-inflammatory; reduction of microglia activation and MMP-9; anti-oxidant; anti-apoptotic	Tikka et al. (2001); Machado et al. (2006); Schildknecht et al. (2011)
Other	Albumin	Haemodilution; microvascular response; improvement of collateral circulation and CBF; reduction of brain swelling	Belayev et al. (2001); DeFazio et al. (2012)
Non-pharmacological	Hypothermia	Reducing metabolic demand; preserving energy stores; decreasing lactate, glutamate and ROS; anti-inflammatory; prevention of apoptosis; reduction of BBB disruption and cerebral oedema	Karlier et al. (1994); Ercanlisa et al. (2003); Campos et al. (2010b); Yenay & Han (2012)
Neuro-vascular, repair	CDP-choline (Citicoline)	Cell membrane phospholipids; energy metabolism; choline precursor, SRTI	Aldabat et al. (2001); Hurtado et al. (2005); Villa et al. (2001); Hursido et al. (2013); Irving et al. (2005)
Immunotherapy	GSK249320	Monoclonal antibody against myelin-associated glycoprotein; prevention of axonal outgrowth	Zheng et al. (2010); Oki et al. (2012); Tomero et al. (2012); Obukata et al. (2014)
Regenerative medicine	Cell-based therapy	Therapy factor production; angiogenesis; immunomodulation; anti-inflammatory	Hoyle et al. (2006); Tang et al. (2006); Dinagat et al. (2009); Wei et al. (2012)
Endogenous restoration	Pre-Per-conditioning	Multiple targets, including inflammation; post-translational; epigenetic mechanisms	

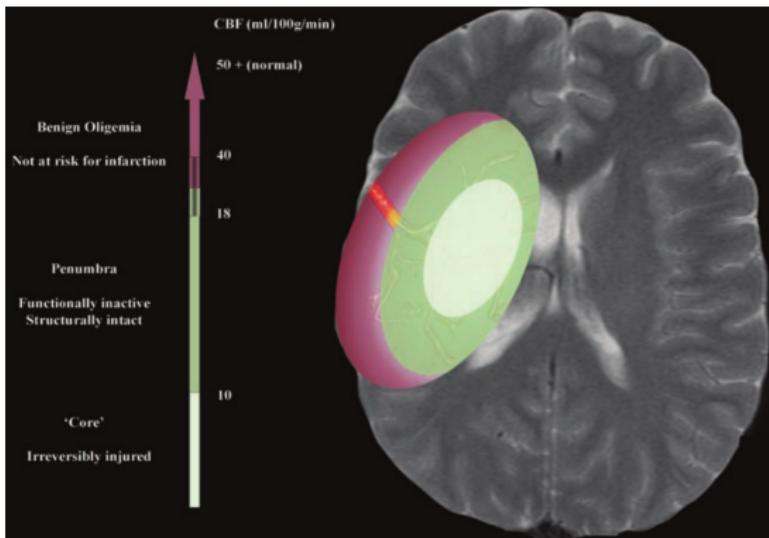
# Pathophysiology of stroke



# Stroke therapy



# Stroke therapy



## Stroke therapeutic strategy

- Broaden the therapeutic time window
  - The new thrombolytics
  - Neuroprotection agents-**progranulin**
- Therapy is recovery stage
  - Neuroprotection agents
  - Stem cell therapy
  - Chinese traditional medicine
  - Acupuncture
  - .....

# Progranulin (PGRN)

- A widely expressed secreted N-linked glycoprotein growth factor
- Two isoforms:
  - The glycosylated immature isoform (58–68 kDa)
  - The fully glycosylated mature secretory isoform (~88 kDa)
- Multiple physiology effects

# Progranulin (PGRN)

- A widely expressed glycoprotein
- Two isoforms
  - The glycosylated form (~88 kDa)
  - The full-length form (~88 kDa)
- Multiple pathologies

Consequences of reduced progranulin levels		
Affected cell types:	Cause Neurological disease	Modulate susceptibility to Metabolic disease
Neurons and microglia	 <p>Cause Neurological disease</p> <ul style="list-style-type: none"> <li>• Heterozygous deficiency causes frontotemporal dementia (FTD)</li> <li>• Homozygous deficiency causes neuronal ceroid lipofuscinosis (NCL)</li> <li>• Reduced progranulin levels might be a risk factor for Alzheimer disease</li> </ul>	 <p>Modulate susceptibility to Metabolic disease</p> <p>Adipocytes and macrophages</p> <ul style="list-style-type: none"> <li>• Homozygous deficiency protects against diet-induced obesity and insulin resistance in mice</li> <li>• Homozygous deficiency promotes atherosclerosis in genetic models</li> </ul>

# The relationship of PGRN and stroke

First, Protected vascular from cerebral ischaemia

- Recombinant PGRN could suppress cerebral oedema in focal MCAO
- PGRN knockout mice prompt post-ischaemic BBB disruption

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## Second, PGRN is involved in neuroinflammation

- PGRN was induced in activated microglia
- Microglia activation increased infarct area in ischemia
- PGRN suppress secretion of pro-inflammatory cytokines and recruitment of neutrophils

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- PGRN was induced in activated microglia
- Microglia activation increased infarct area in ischemia
- PGRN suppress secretion of pro-inflammatory cytokines and recruitment of neutrophils

## Third, PGRN exhibit protective effects on neuronal cells

- TARDBP (TDP-43) is involved in cerebral ischemia
- PGRN inhibits caspase 3 to suppress TARDBP cleavage

# Aim to study

The study were designed to clarify the effects of PGRN on regulation of blood–brain barrier function, suppression of inflammation, and neuroprotection against acute focal cerebral ischaemia.

# Outline

1 Background

2 Materials and Methods

3 Results

4 Conclusion

# Methods used in the article

Focal cerebral ischaemia model

Immunoblotting

Immunofluorescence staining and confocal microscopy

Immunohistochemistry

Measurement of the volume of the cerebral infarct and oedema

Neurological evaluations

# Methods used in the article

C6 cell culture and analysis of glycosylation

Primary cell cultures

Oxygen–glucose deprivation

Cell counting protocols

PCR and quantitative real-time PCR

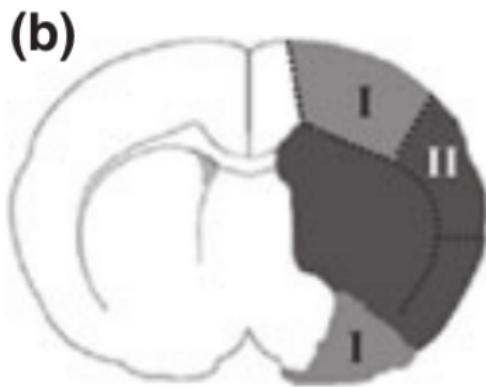
Focal embolic ischaemia model

# Markers used in the article

- MAP2-neuronal cells
- ERp57-endoplasmic reticulum
- Golgi-58k-Golgi apparatus
- LAMP1-lysosome
- CD68/ED1-microglia
- DAPI-neuclei
- vWF,CD31-endothelial cells
- GFAP-astrocytes

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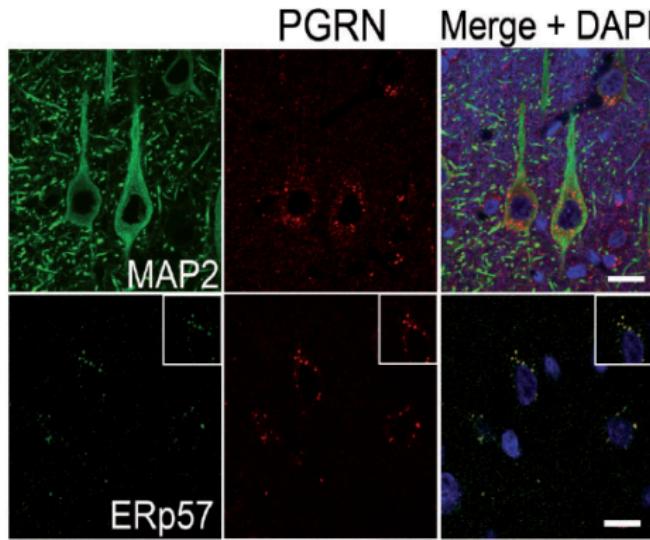
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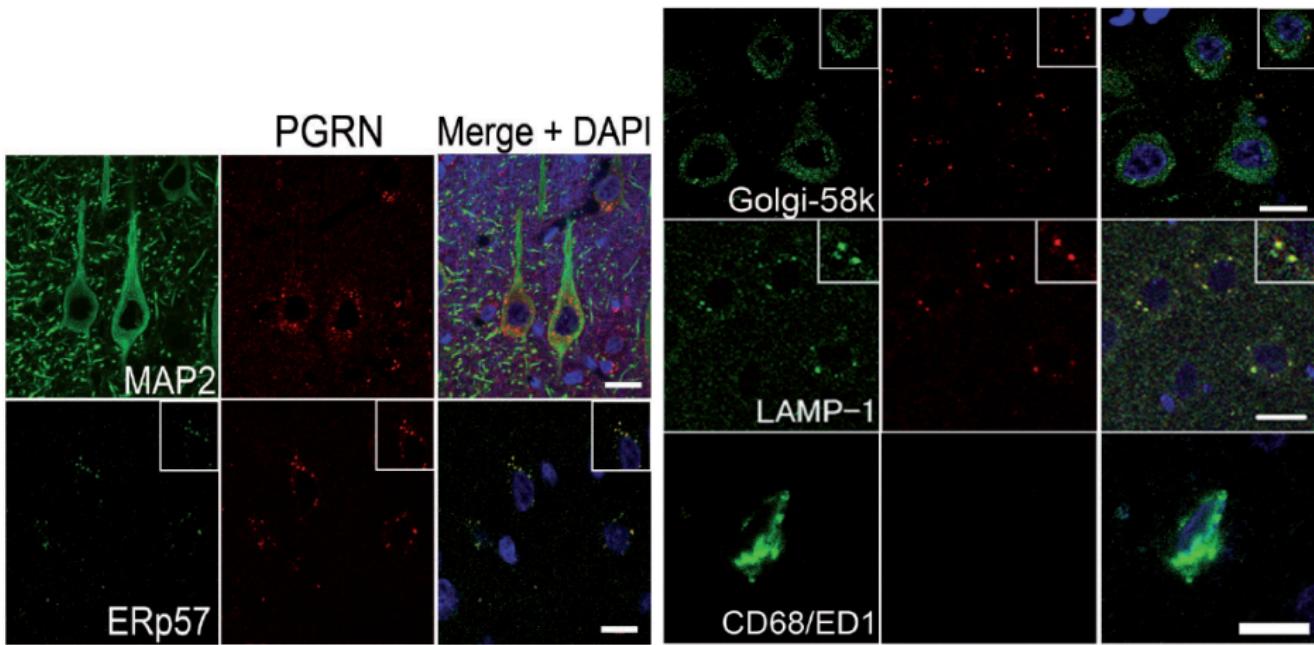
4 Conclusion

## The expression and localization of PGRN on non-ischemia cortex



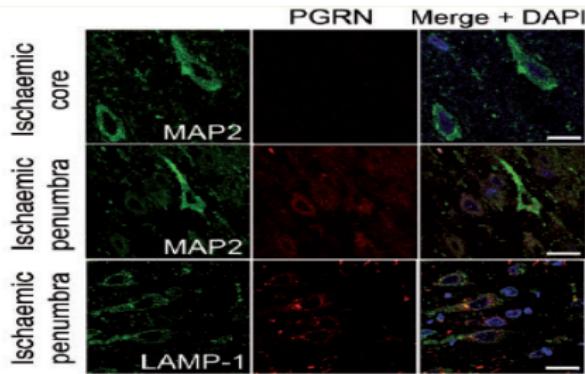
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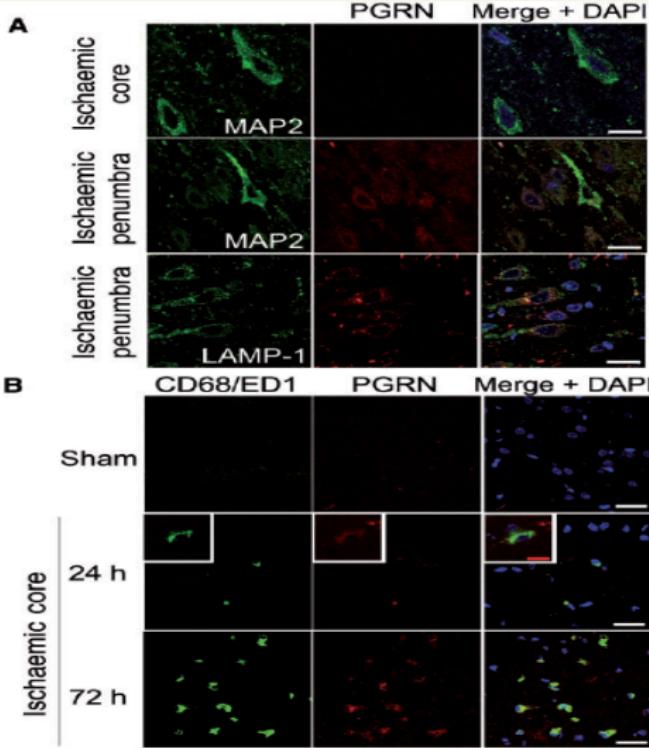
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# The expression and localization of PGRN on ischemia cortex

**A**

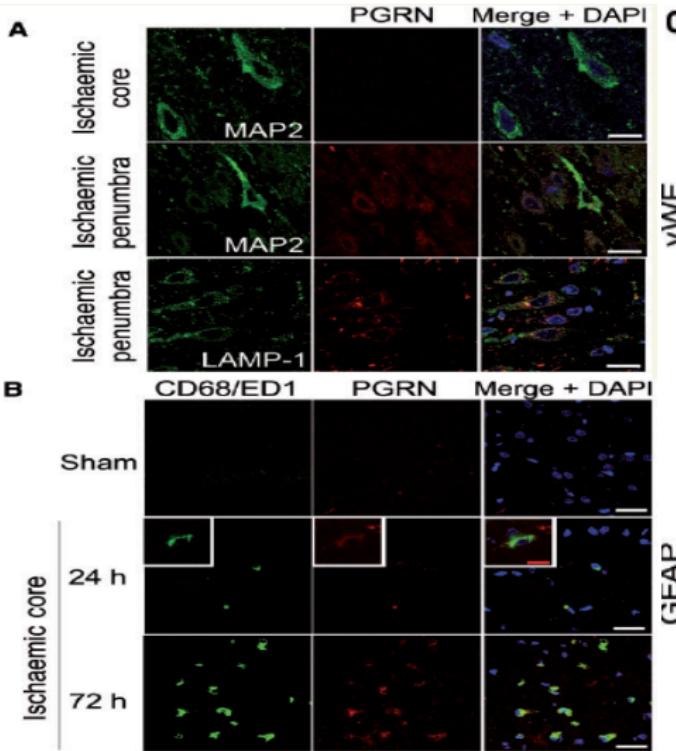
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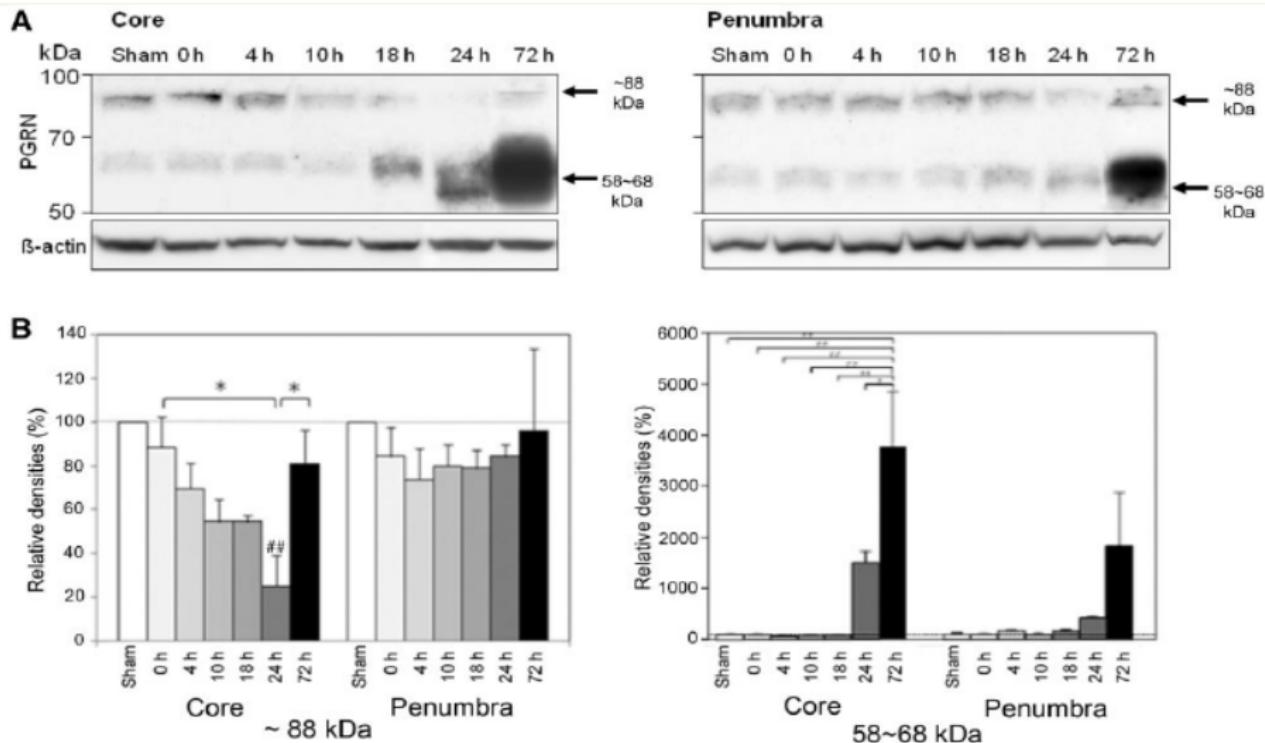
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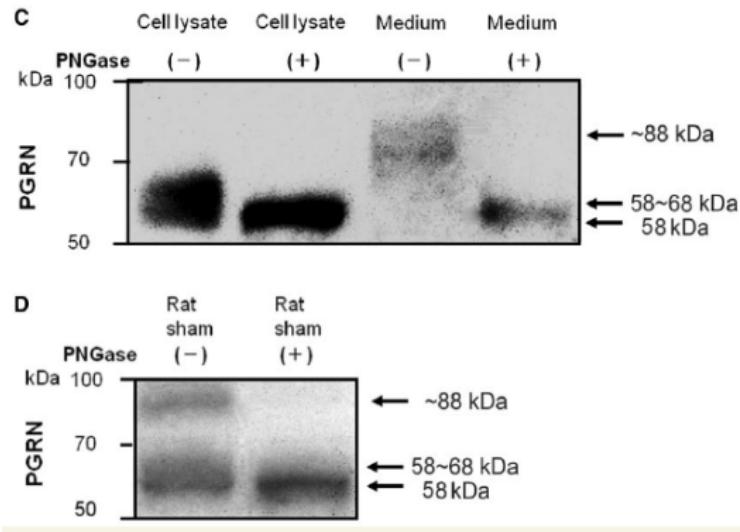


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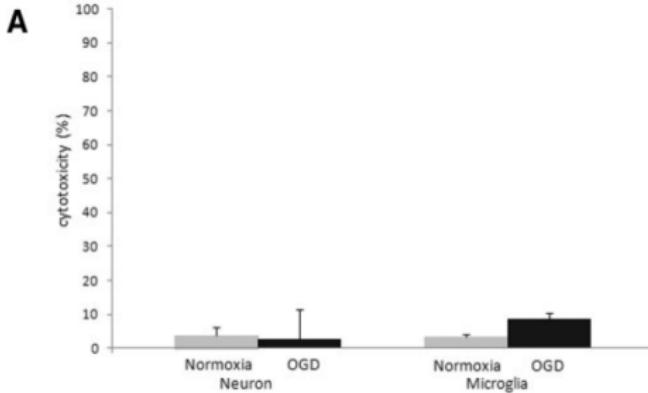
# PGRN temporal changes and its glycosylated status after ischemia



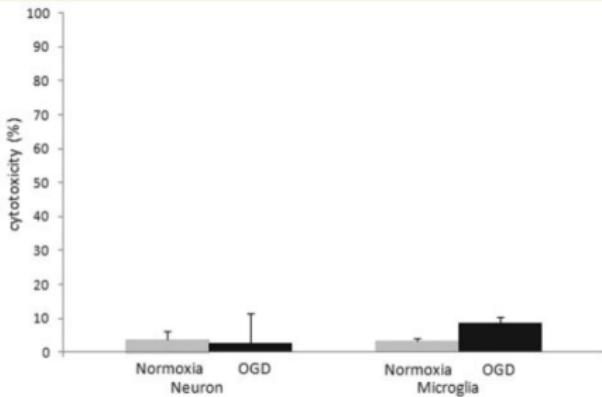
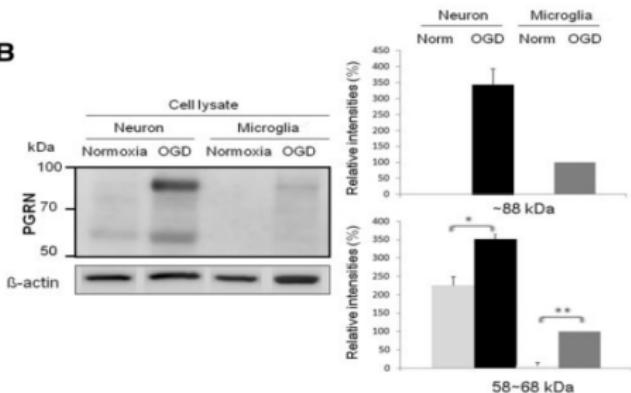
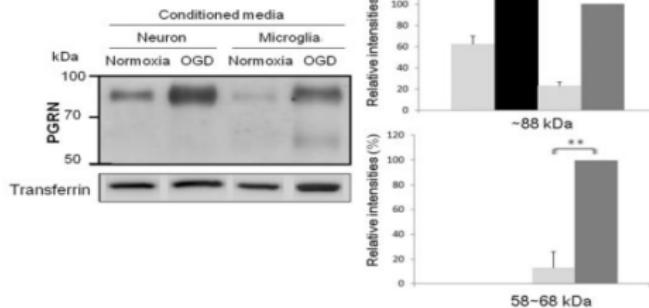
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## Production and secretion of the two isoforms of PGRN after OGD



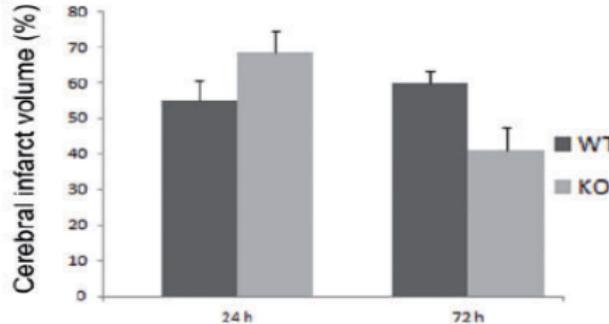
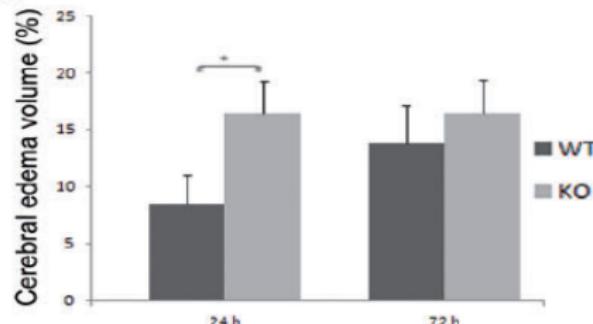
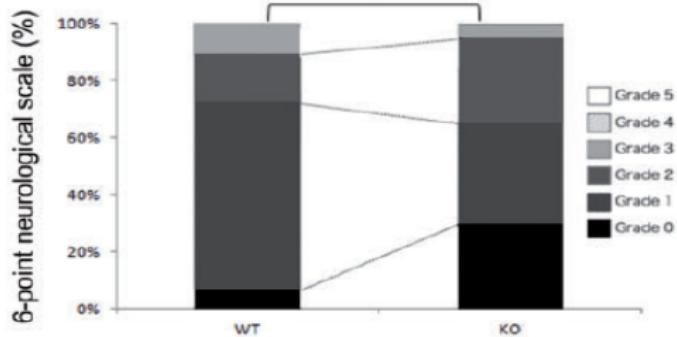
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**A****B****C**

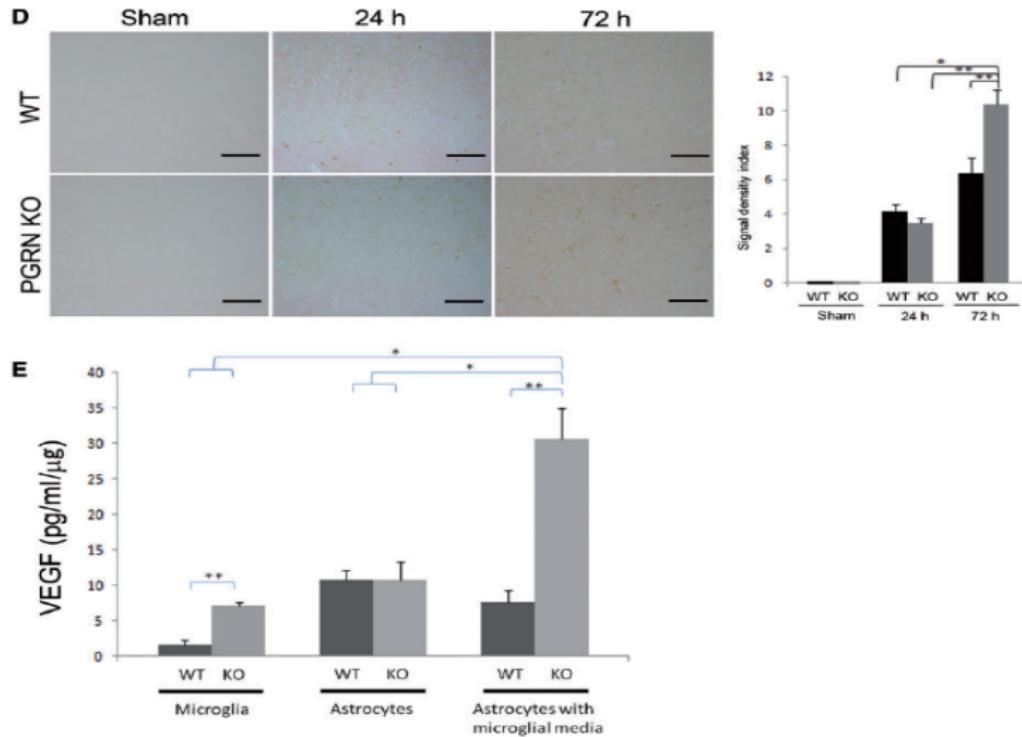
# Summary

- The author demonstrated a dynamic change in progranulin expression:
  - PGRN's expression in microglia increased in the border of ischemic core and penumbra
  - PGRN's expression in viable neurons increased within the ischemic penumbra
  - PGRN's expression in endothelial cells increased within ischemia penumbra
- ~88 kDa progranulin decreased, whereas the 58–68 kDa progranulin markedly increased at 24 h and 72 h after reperfusion
- 58-68 kDa PGRN was secreted only from the microglia after ischemia

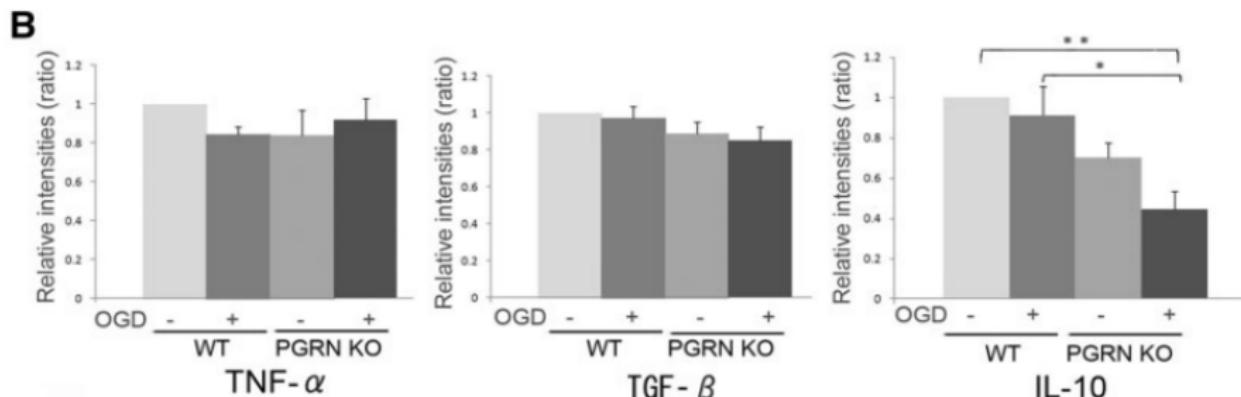
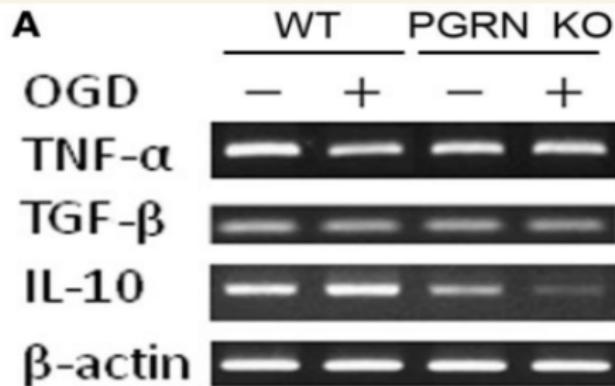
# PGRN attenuate BBB disruption after cerebral ischaemia via VEGF

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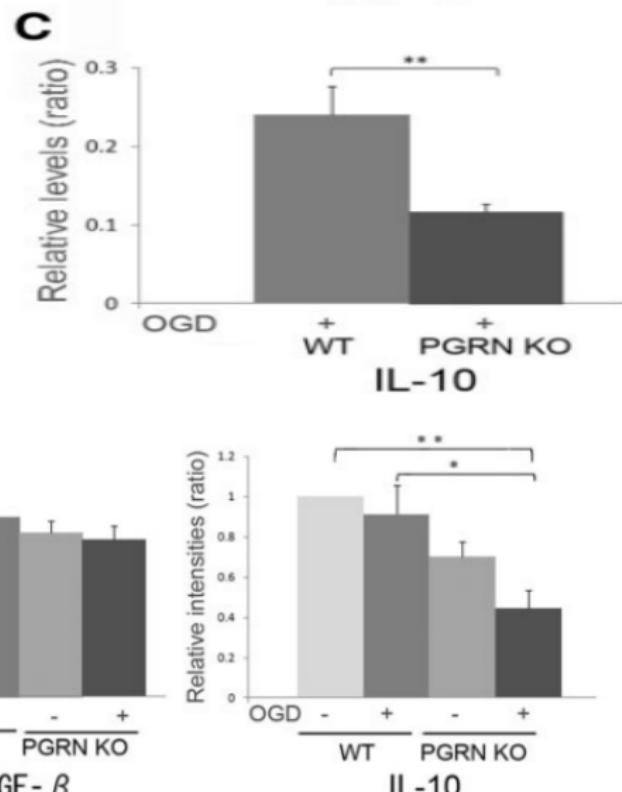
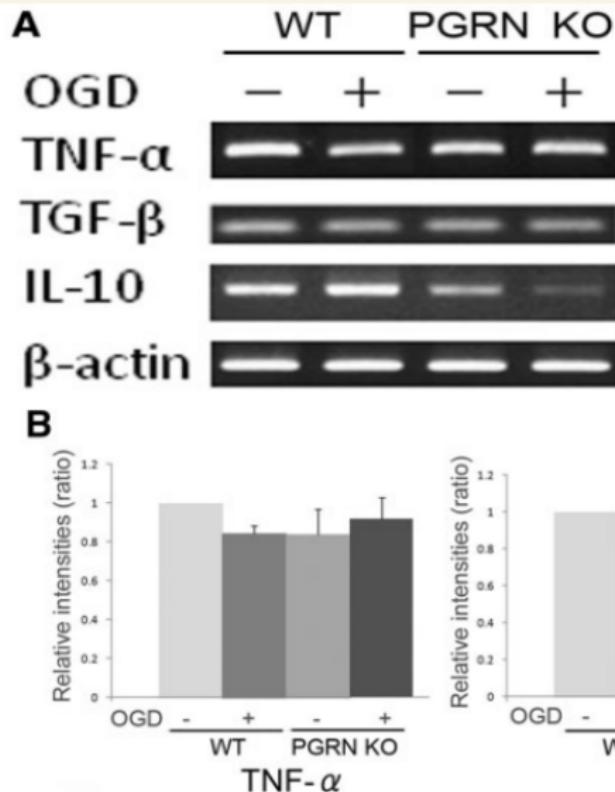
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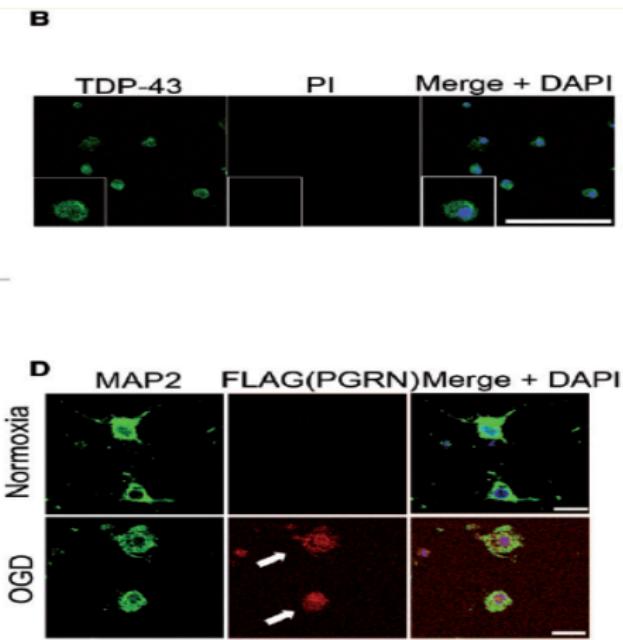
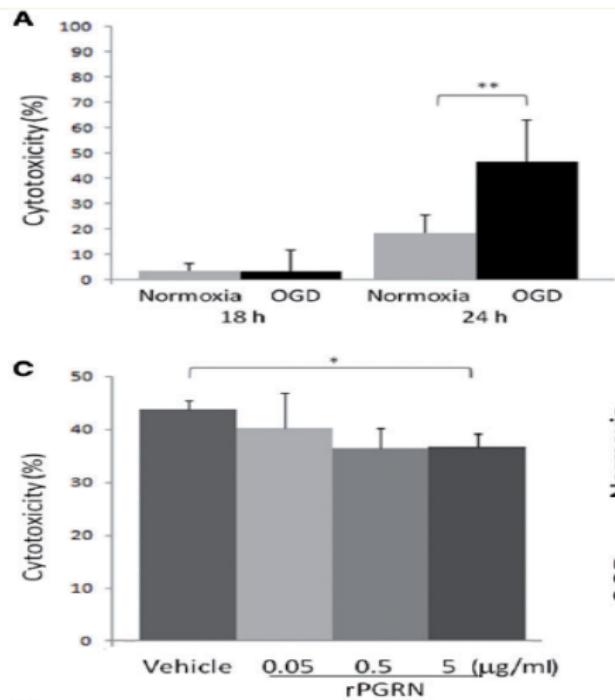
# PGRN suppress neuroinflammation after cerebral ischemia via IL-10



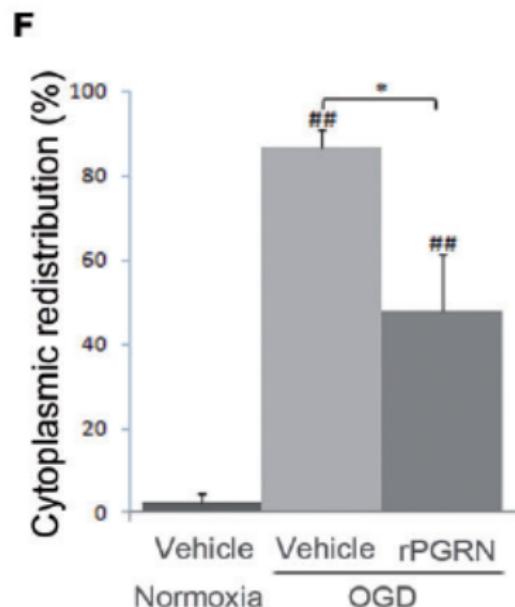
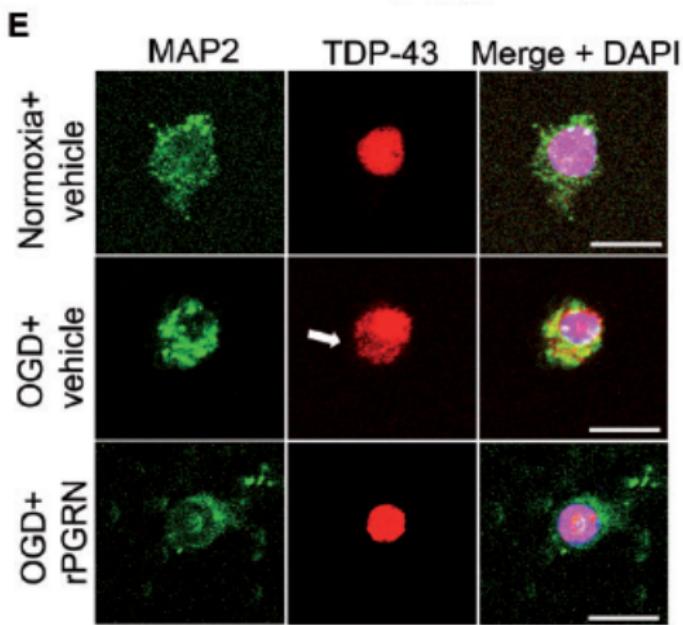
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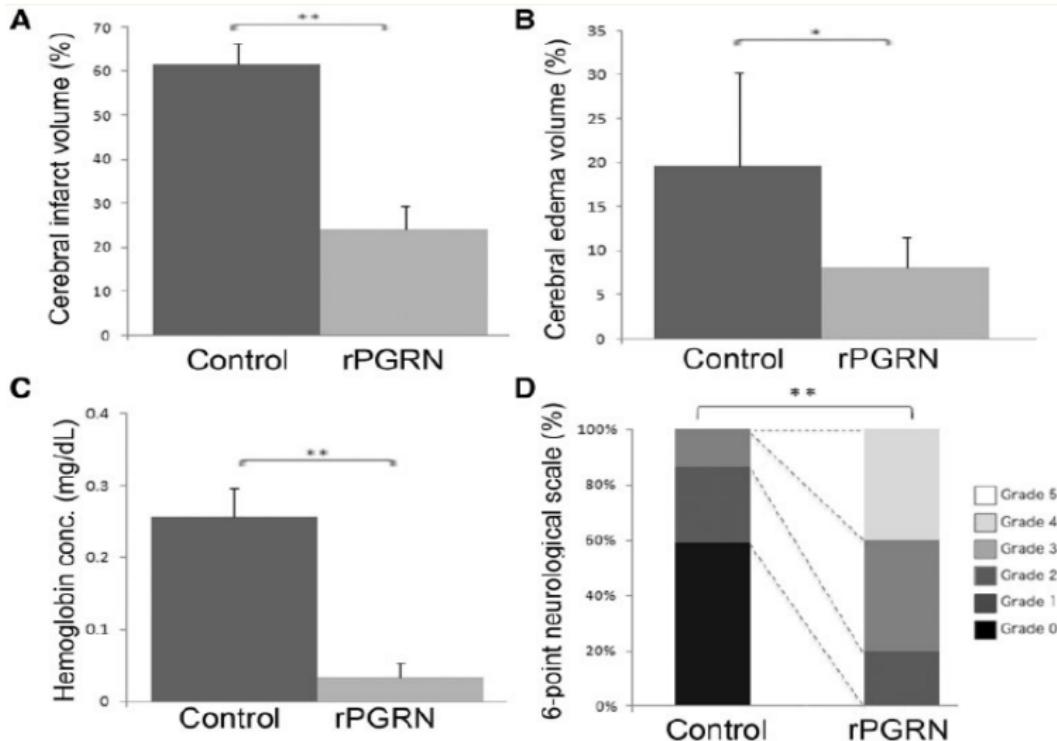
# PGRN protect neuron from cerebral ischemia in part by the inhibition of abnormal cytoplasmic redistribution of nuclear TARDBP



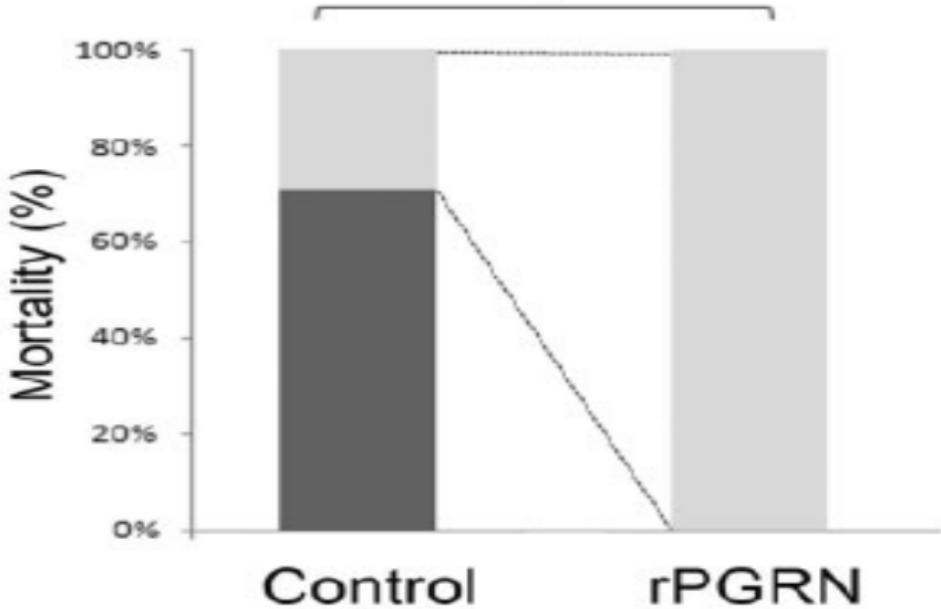
PGRN protect neuron from cerebral ischemia in part by the inhibition of abnormal cytoplasmic redistribution of nuclear TARDBP



# Therapeutic effects of PGRN with tPA for cerebral ischaemia



## Therapeutic effects of PGRN with tPA for cerebral ischaemia

**E**

# Outline

1 Background

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4 Conclusion

# Conclusion

- First, the author firstly demonstrated the dynamic changes of PGRN, and the 58-68 kDa PGRN was secreted only from the microglia after ischemia
- Second, PGRN provides vascular protection, anti-neuroinflammation, and neuroprotection related in part to VEGF, IL10 and TARDBP
- Third, the possibility that recombinant PGRN could be used as a novel neurovascular protective drug with anti-inflammatory effect after delayed tPA treatment

# References

(1) (2) (3) (4) (5) (6) (7) (8)

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7. A. D. Nguyen, T. A. Nguyen, L. H. Martens, L. L. Mitic, R. V. Farese, *Trends in Endocrinology & Metabolism* **24**, 597–606 (2013).
8. V. E. O'Collins *et al.*, *Annals of neurology* **59**, 467–477 (2006).

# Some Comments of mine

The study design is complete

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But

- The precise mechanisms of PGRN on ischemia

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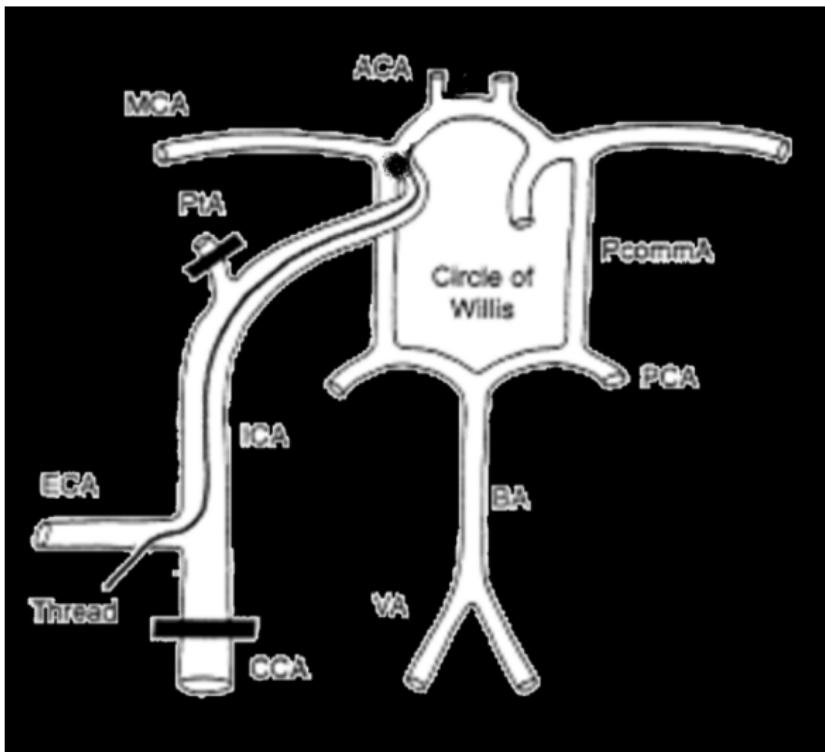
# Some Comments of mine

The study design is complete

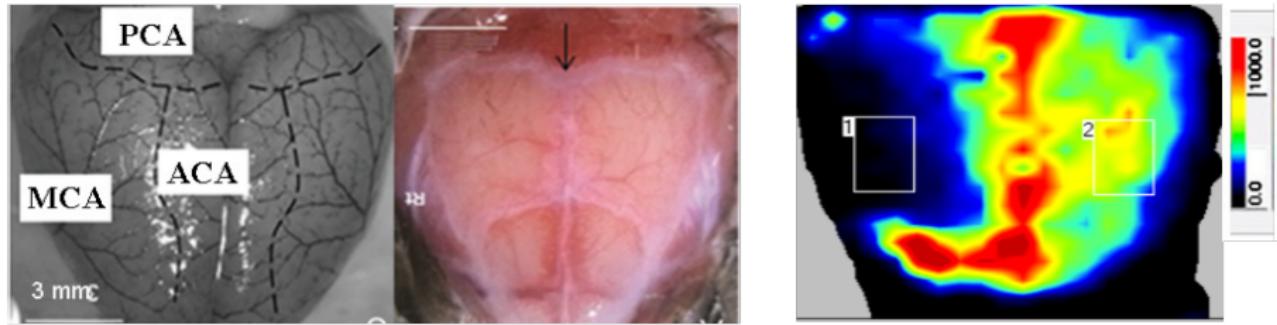
But

- The precise mechanisms of PGRN on ischemia
- Western blot results isn't beautiful
- The MCAO model validation standard

# Focal cerebral ischemia model

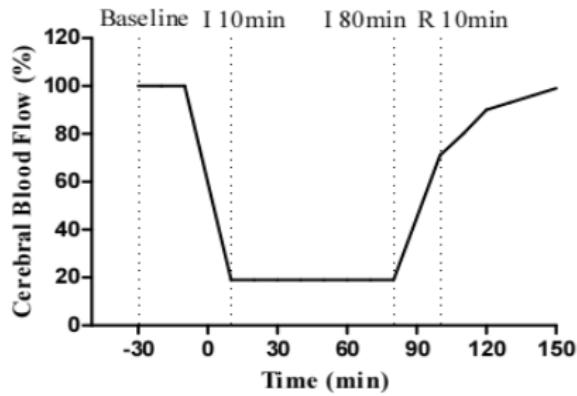


# Focal cerebral ischemia model



## Focal ischemia model validation standard

- I -30 min CBF Baseline 100%
- I 10 min CBF < 20% ,  
I 80 min CBF < 20%
- R 10 min CBF > 70%



# Methods to search and obtain the article

The screenshot shows a Firefox browser window with several tabs open. The active tab is on PubMed, displaying search results for 'SET-2 xenograft'. The results show two articles. The left sidebar contains filters for Article types, Text availability, and other search parameters. The right sidebar includes sections for 'New feature', 'Find related data', 'Search details' (with a query for 'SET-2 AND ("heterografts" OR "heterografts" OR "xenograft")'), and 'Recent Activity'.

Article Type	Title	Author(s)	Publication Date	PMID
Novel pyrrole carboxamide inhibitors of JAK2 as potential treatment of myeloproliferative disorders.	Brasca MG, Gnocchi P, Nesi M, Amboldi N, Avanzi N, Bertrand J, Bindì S, Canevari G, Casero D, Ciomei M, Colombo N, Cribioli S, Fachin G, Felder ER, Galvani A, Isacchi A, Motto I, Panzeri A, Donati D.	Bioorg Med Chem. 2015 May 15;23(10):2387-407. doi: 10.1016/j.bmcl.2015.03.059. Epub 2015 Mar 28.		25682525
Pyrrole-3-carboxamides as potent and selective JAK2 inhibitors.	Brasca MG, Nesi M, Avanzi N, Ballinari D, Bandiera T, Bertrand J, Bindì S, Canevari G, Carenzi D, Casero D, Ceriani L, Ciomei M, Cirigliano A, Colombo M, Cribioli S, Cristiani C, Della Vedova F, Fachin G, Fasolini M, Felder ER, Galvani A, Isacchi A, Mirizzi D, Motto I, Panzeri A, Pesenti E, Vianello P, Gnocchi P, Donati D.	Bioorg Med Chem. 2014 Sep 1;22(17):4998-5012. doi: 10.1016/j.bmcl.2014.06.025. Epub 2014 Jun 21.		25009002

# Methods to search and obtain the article

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<p><b>The oral HDAC inhibitor pracinostat (SB939) is efficacious ...</b><br/>
<a href=)  
 作者: V Novotny-Diermayr - 2012 - 被引用次数: 32 - 相关文章  
 2012年5月4日 - This was also more pronounced in **SET-2** cells than HEL92.1.7 cells ...  
 Treatment of mice bearing MV4-11 **xenografts** with pracinostat (25 or 50 ...

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 Immunodeficient Models **Xenograft** Data Catalog - Volume 1. Research ... 2 Fox Chase SCID® Mouse (C.B-17 SCID) ... 9 **SET2** tumor growth graph. Liver.

**Setting up a wide panel of patient-derived tumor xenografts ...**  
[www.ncbi.nlm.nih.gov/.../Literature/PubMed Central \(PMC\) -](http://www.ncbi.nlm.nih.gov/.../Literature/PubMed%20Central%20(PMC)%20-%20Marius%20Ilie%20-%202015-01-01)  
 作者: M Ilie - 2015 - 被引用次数: 11 - 相关文章  
 2014年12月3日 - **Setting up a wide panel of patient-derived tumor xenografts** of non-small cell lung cancer by improving the preanalytical steps. Marius Ilie 1,2,3 ...

# Methods to search and obtain the article

The screenshot shows the Sci-Hub homepage in a Firefox browser. The main visual is a black silhouette of a raven standing on a brick wall, holding a key in its beak. To the right of the raven, the word "SCI-HUB" is written in large red letters. Below it is a red banner with the text "...to remove all barriers in the way of science". A search bar is present below the banner, with the placeholder "enter URL, PMID / DOI or search string". To the right of the search bar is a red button with a white key icon and the word "open". In the top right corner of the page area, there is a badge with a gold medal and a ribbon, accompanied by the text "the first website in the world to provide mass & public access to research papers". The browser's address bar shows the URL "sci-hub.io". The bottom navigation bar includes links for "about", "ideas", "community", and "donate".

# Methods to search and obtain the article

The screenshot shows an open Microsoft Outlook window displaying an email message. The subject of the email is "For article 'Multiple therapeutic effects of progranulin on experimental acute ischaemic stroke' - 邮件 (HTML)". The message body contains the following text:

发件人: Xiaowei Mao  
收件人: 't-shimo@bri.niigata-u.ac.jp'  
抄送:  
主题: For article "Multiple therapeutic effects of progranulin on experimental acute ischaemic stroke"

Dear Masato Kanazawa,

I read your paper named "Multiple therapeutic effects of progranulin on experimental acute ischaemic stroke", but I couldn't get the supplementary, could you send me a copy ?

Thank you.

Xiaowei Mao

# Methods to search and obtain the article

The screenshot shows an email client interface with a redacted header. The subject line is "Re: Fwd: For article "Multiple therapeutic effects of progranulin on experimental acute ischaemic stroke" - 部件 (纯文本)". The body of the email contains the following text:

答复此邮件的时间为 2015/12/2 8:25。  
已删除该邮件多余的换行符。

发件人: Masato Kanazawa <masa@bri.niigata-u.ac.jp>  
收件人: Xiaowei Mao  
抄送: t-shimo@bri.niigata-u.ac.jp  
主题: Re: Fwd: For article "Multiple therapeutic effects of progranulin on experimental acute ischaemic stroke"

邮件 brain-2014-01642-File010.pdf (43 KB) brain-2014-01642-File011.pdf (803 KB)

Dear Dr Mao,

Thank you so much for your request of our manuscript.

I am the first author on the PGRN manuscript published in journal of Brain, entitle "Multiple therapeutic effects of progranulin on experimental acute ischaemic stroke".

Please find an attached PDF file.

We are very willing to give us some comments from you.

If you have any questions, please do not hesitate to contact us.

Yours sincerely,

Masato Kanazawa, M.D., Ph.D.

Takayoshi Shimohata, M.D., Ph.D.

=====

Masato Kanazawa M.D., Ph.D., FACP

Assistant Professor

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Brain Research Institute

Niigata University 1-757

Asahimachi-dori, Chuo-ku,

Niigata 951-8585, Japan

Tel: Japan(81)-25-227-0666

Fax: Japan(81)-25-223-6646

Cellular in Japan: 070-6566-4536

# Methods to search and obtain the article

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**作者:** Sawant SHBodhankar SL

**杂志:** Renal failure 2016 Apr; 38(3):411-23.

**Pubmed链接:** <http://pubmed.cn/26795298>

**全文链接:** Taylor & Francis

**求助者:** Jingyaping

**求助时间:** 2016-03-02 16:58

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**作者:** Tirelli UErrante DDolcetti RGioglini ASerraino DVaccher EFranceschi SBolocioli MCcarbone A

**杂志:** Journal of clinical oncology: official journal of the American Society of Clinical Oncology 2006 Jul; 24(7):4760-87



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