CCM 文件 07/2015

香港大學與中醫藥有關的中風及腦血管病研究工作

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香港大學中醫藥學院

腦卒中：中國人的頭號殺手

中風為人類致死病因的第2位。中風在中國位列第一位殺手。大多數(60-80%)遺留不同程度的後遺症，¼ - ¾的腦卒中患者可能在2-5年內復發。

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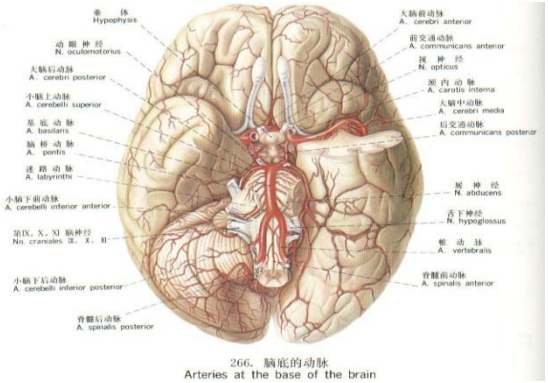
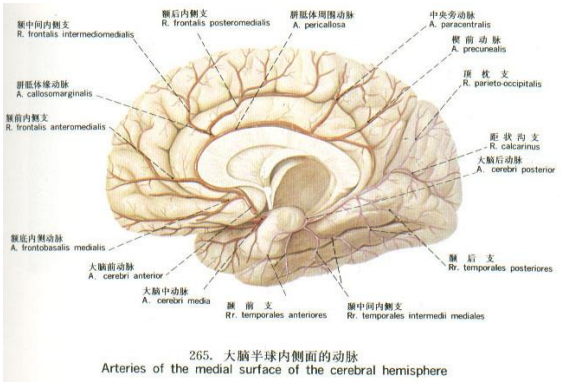
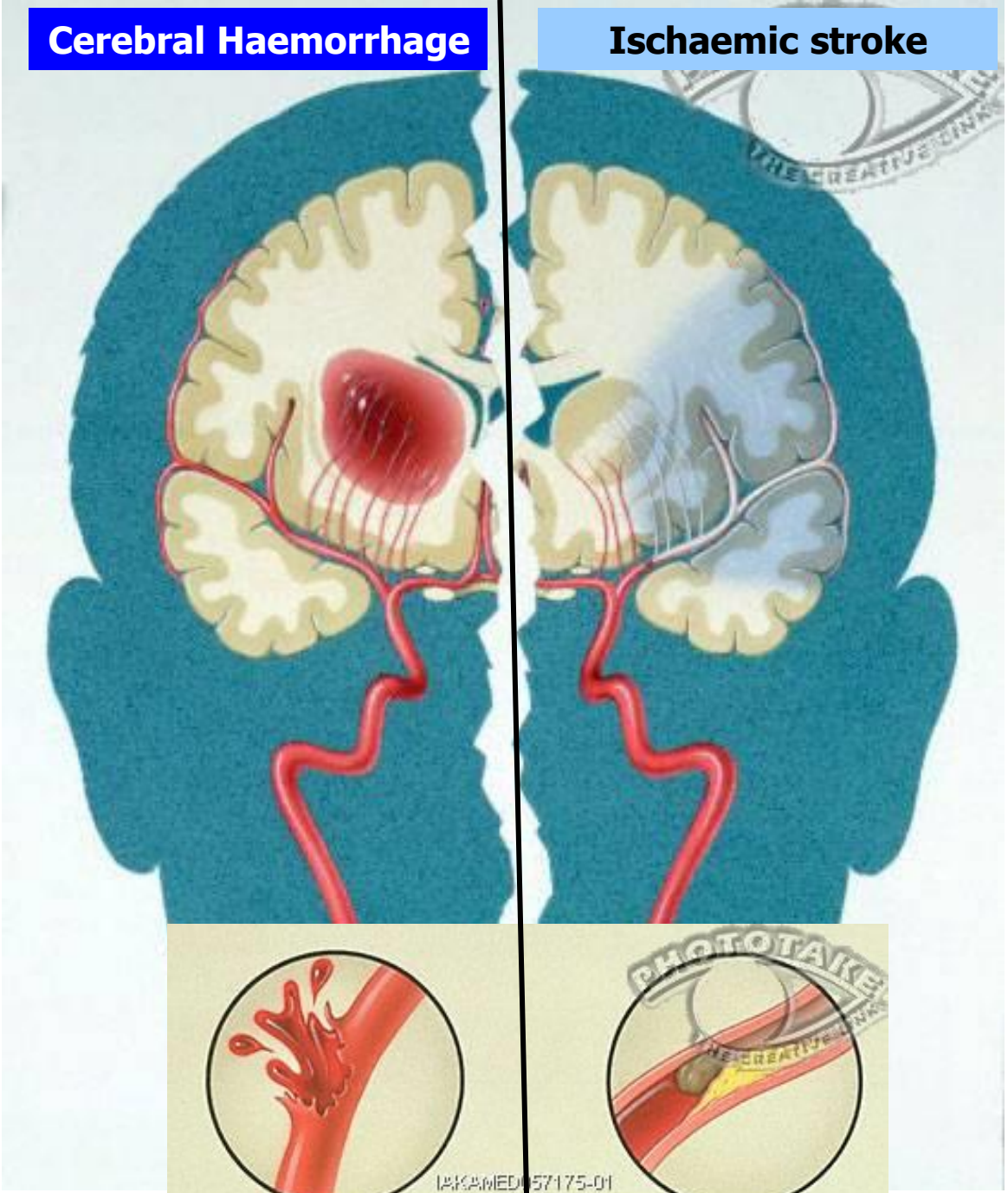


266. 脑底的动脉
Arteries at the base of the brain



265. 大脑半球内侧面的动脉
Arteries of the medial surface of the cerebral hemisphere


Cerebral Haemorrhage
Ischaemic stroke
PHOTOTAKE
IAKAMED057175-01
© JOHN KARAPELOU, OMI / Phototake
Viewed by Kui Fu Stanley Tam on 2/27/2003

脑卒中治療的困境

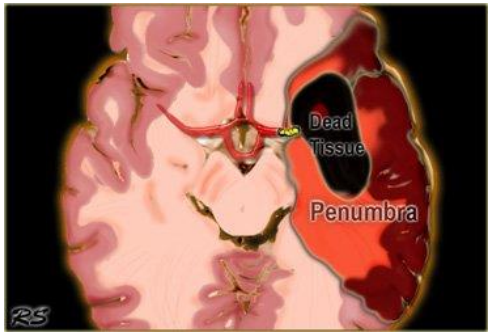
- rt-PA is only FDA approved drug, but it must be used within 4.5 hrs golden time window after ischemic stroke with the potential risk of hemorrhagic transformation.

- No effective clinical therapeutic approach is available, leaving long-term disability.

- Even surgical treatment cannot increase clinical outcome including mortality and disability in acute hemorrhagic stroke.

  A large RCT 1033 patients from 83 centers in 27 countries failed to show a benefit of surgery over conservative treatment in acute hemorrhagic stroke. (Mendelow AD, et al. Lancet. 2005;365(9457):387-397)

1996年美國FDA批准tPA治療急性缺血性腦卒中



纖溶酶原

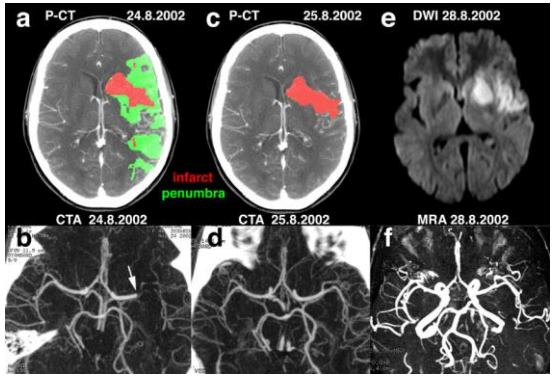
tPA

纖溶酶

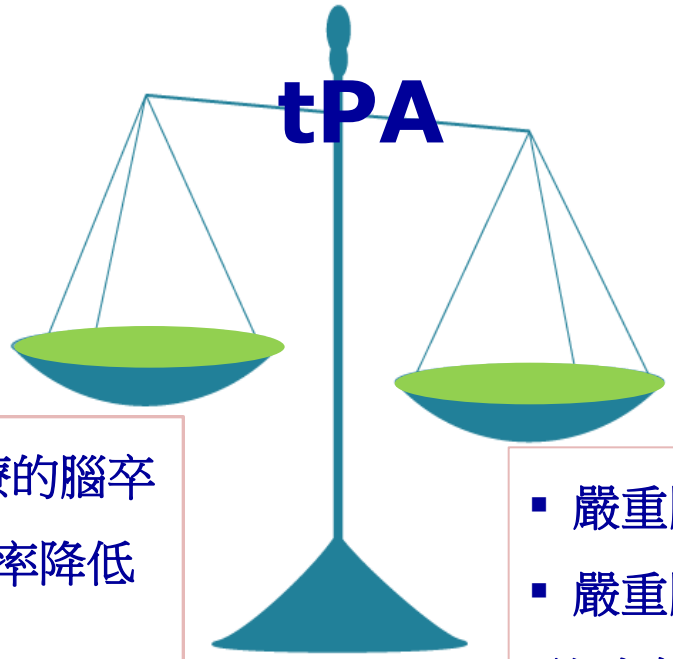
血栓

腦動脈

挽救缺血腦組織



tPA溶栓治療腦卒中:兩難選擇



- 經tPA及時治療的腦卒中病人，致殘率降低30%。

- 嚴重腦出血風險增加10倍
- 嚴重腦出血的死亡率高達61%
- 迄今無法準確預測腦出血風險

神經保護藥：可望而不可及。

- >1000個化合物在動物卒中模型上被證明治療卒中有效
- 114個化合物進入了臨床實驗
- 0個化合物有效

Neuroprotection: the end of an era?
(Lancet 2006)

手術治療對出血性中風的療效也不肯定

Early surgery versus initial conservative treatment (STICH Trial)

- 1033 primary ICH patients
- ICH onset within 72 hrs
- Favorable outcome at months
  - **Early surgery: 26%**
  - **Initial conservative: 24%**

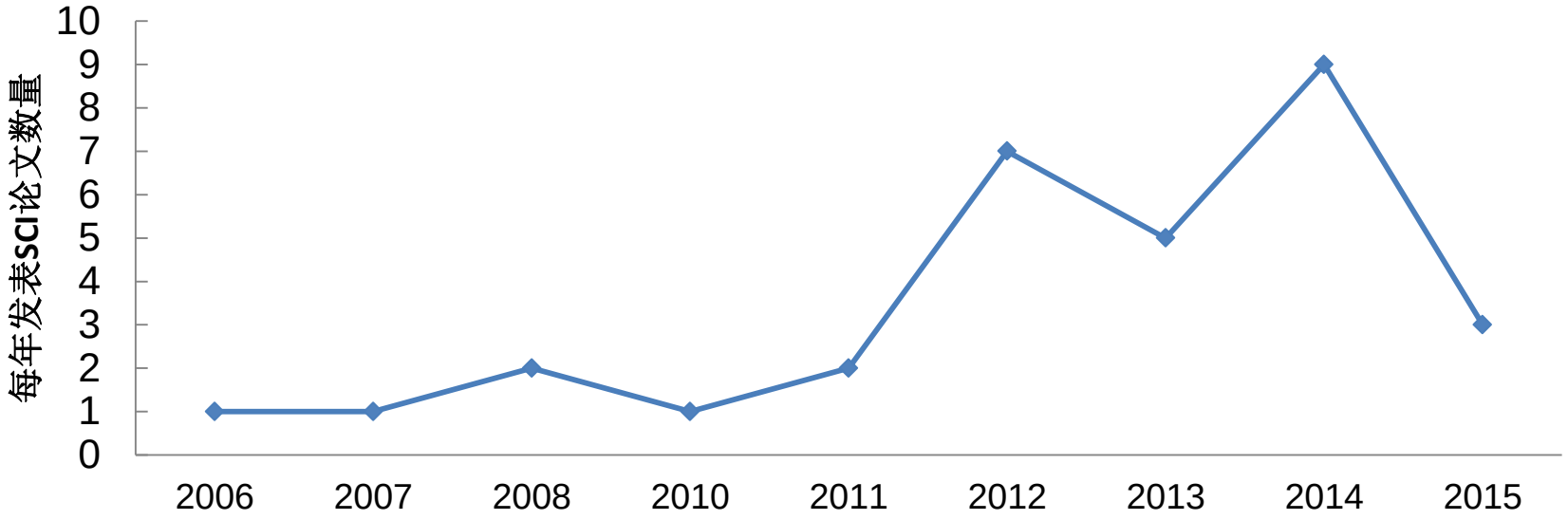
  (p=0.414)

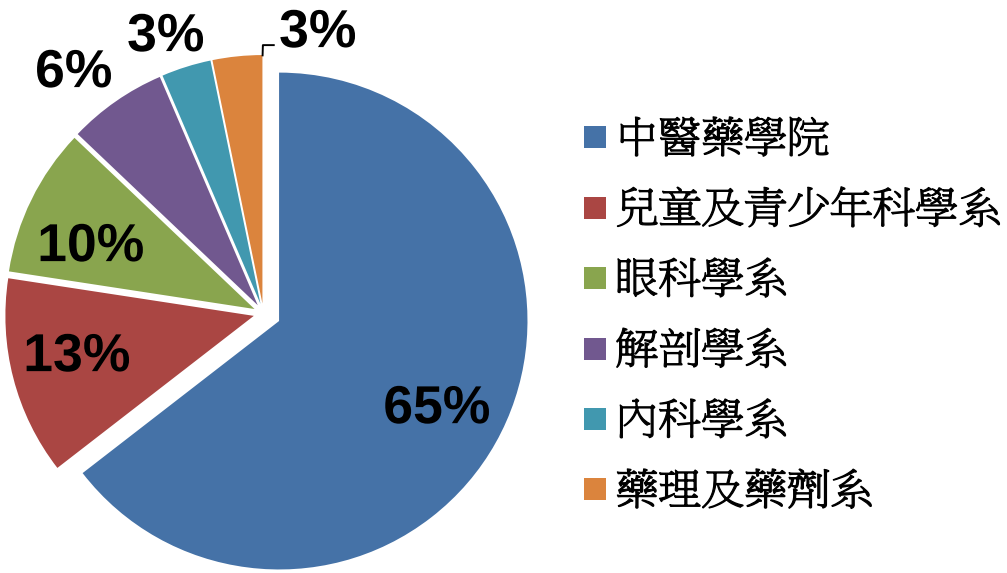
A large RCT 1033 patients from 83 centers in 27 countries failed to show a benefit of surgery over conservative treatment in acute hemorrhagic stroke. (Mendelow AD, et al. *Lancet* 2005;365(9457):387-397)

發展新的中風診斷與治療方法刻不容緩

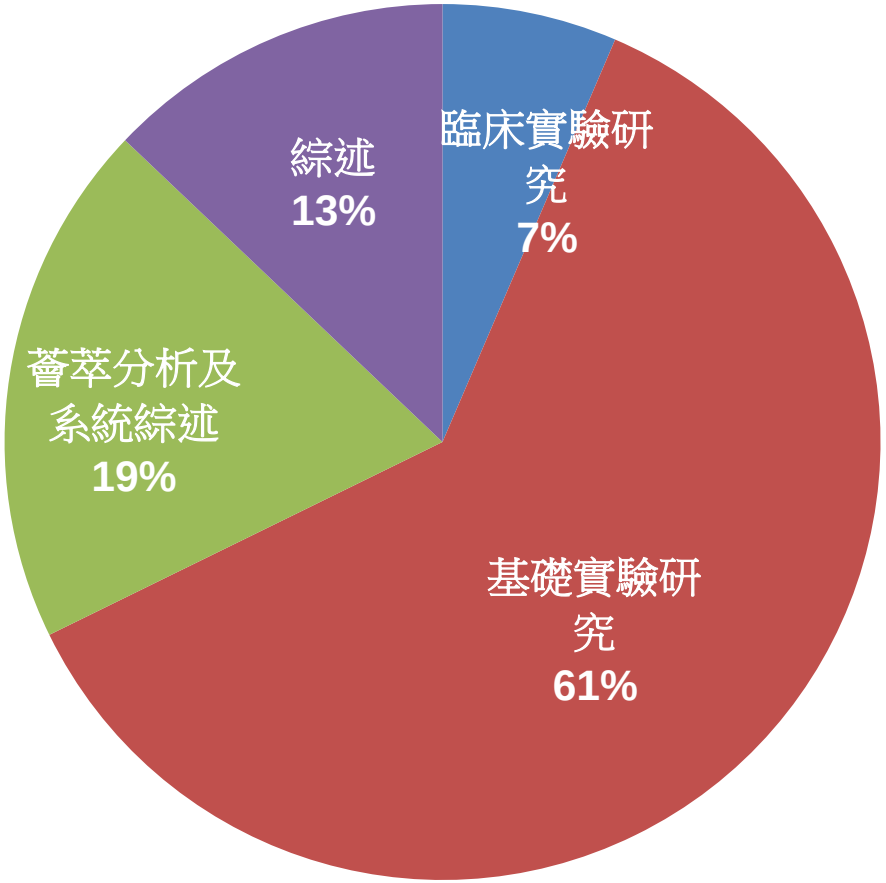
中醫藥是重要的治療方向？

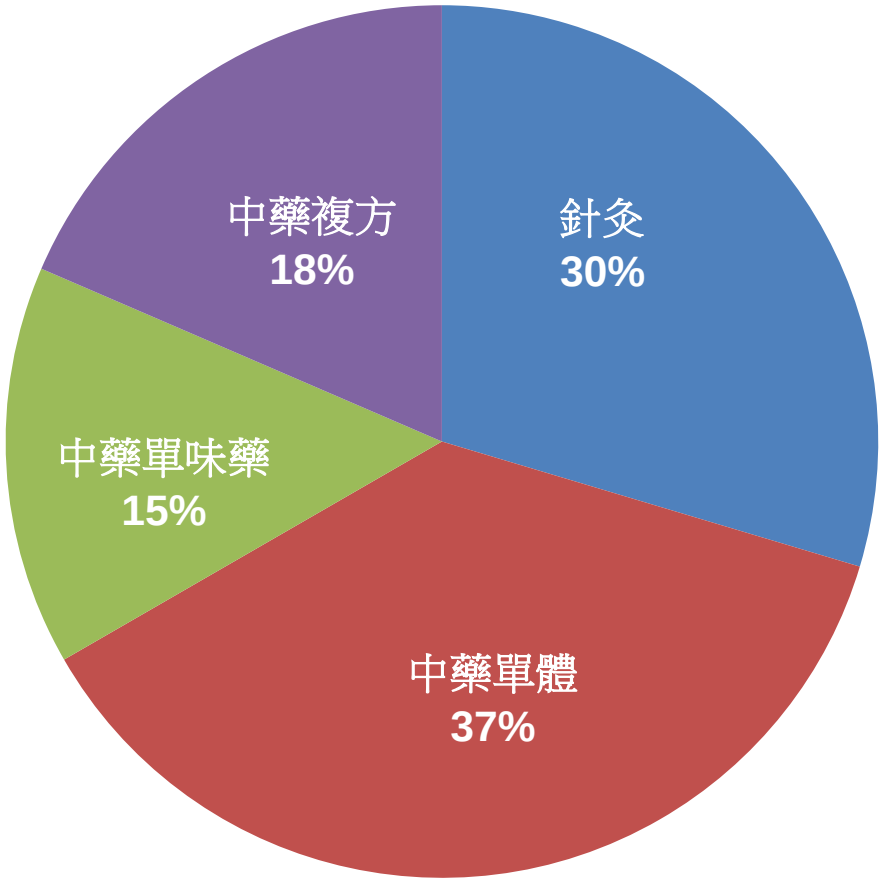
香港大學與中醫藥有關的中風相关研究的科研論文發表情況





研究類型及研究對象


臨床實驗研究
7%
基礎實驗研究
61%
薈萃分析及系統綜述
19%
綜述
13%


針灸
30%
中藥單體
37%
中藥單味藥
15%
中藥複方
18%

香港大學中醫藥學院與中醫藥有關的中風及腦血管病主要研究方向

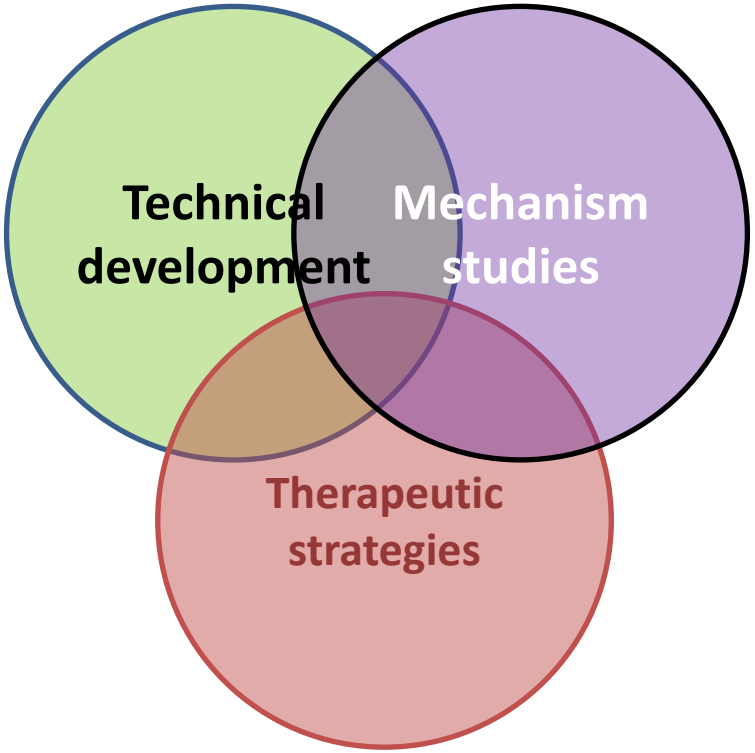
主要研究方向及課題：

1. 缺血性中風後神經毒性以及血腦屏障破壞的機制探討以及中醫藥的干預治療作用研究
2. 缺血性中風後神經再生的機制探討以及中醫藥對於中風後修復的作用研究
3. 缺血性中風後T-PA延時溶栓引起出血轉化的機制研究以及中醫藥的干預作用研究
4. 針灸（電針）對於中風後抑鬱的臨床研究
5. 傳統中藥治療中風複方以及針灸於中風相關的薈萃分析

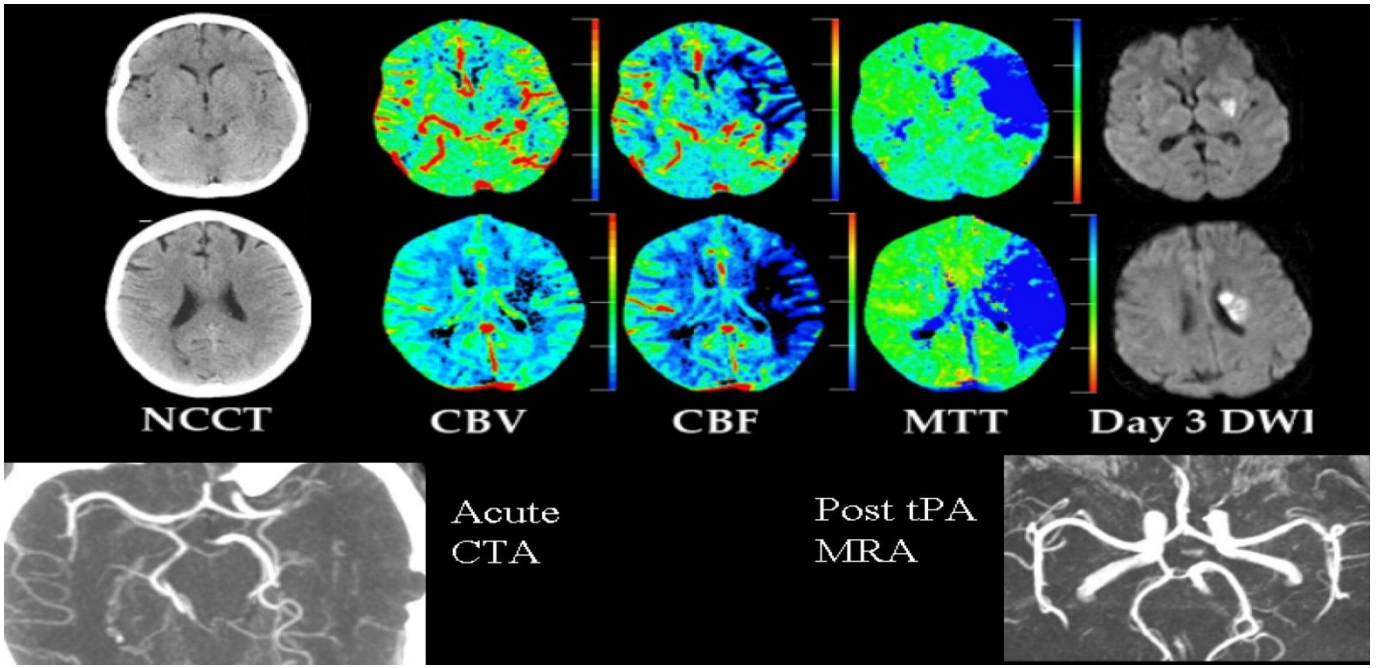
我們實驗室的工作及貢獻

- Brain Oxygen Mapping/ Novel Moleular Targets
- BBB breakdown and neurotoxicity
- Delayed T-PA treatment induced hemorrahage
- Post-stroke neurogenesis

Ischemic stroke



多種電腦成像技術為診斷與治療中風提供了有力的工具



Patient imaged with multimodal CT at 3.5 hours after stroke. M1 occlusion on CT angiography (CTA) (lower left). Small area of reduced cerebral blood volume (CBV) in lentiform nucleus and deep white matter but surrounded by much larger areas of reduced cerebral blood flow (CBF)/prolonged mean transit time (MTT) consistent with ischemic penumbra. Minimal change seen on non-contrast CT (NCCT). Patient treated with intravenous (IV) thrombolysis and had major early neurologic improvement, complete recanalisation on follow-up magnetic resonance angiography (MRA) (lower right), and only a small amount of infarction on follow-up diffusion-weighted imaging (DWI) (corresponding to pre-treatment areas of reduced CBV).

案例1：EPR脑氧成像：
發展新型直接檢測技術腦氧分佈地形圖技術

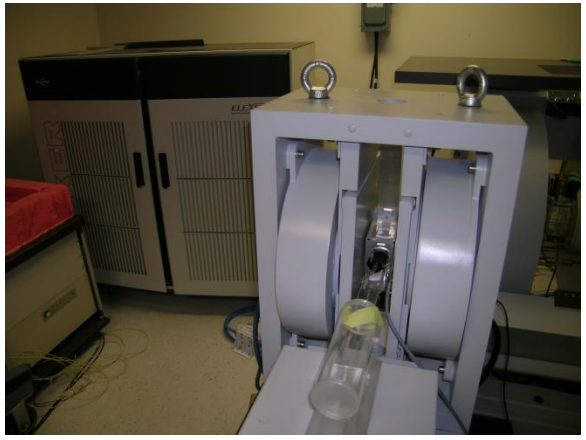
- 儀器研發
- How to increase instrumental sensitivity for *in vivo* EPR oximetry?

- 发展新型磁回声探针用于脑氧测定

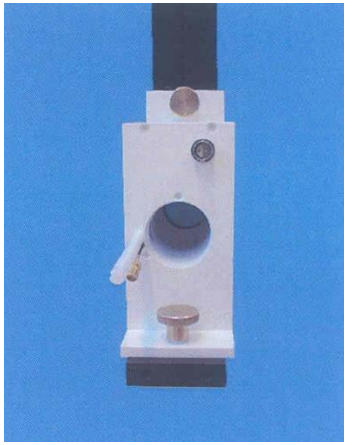
  The probes must be highly sensitivity to oxygen concentration, high permeability of blood brain barrier (BBB), low or no cytotoxicity and be able to retain in brain with relatively high concentration.

L-band EPR imaging system

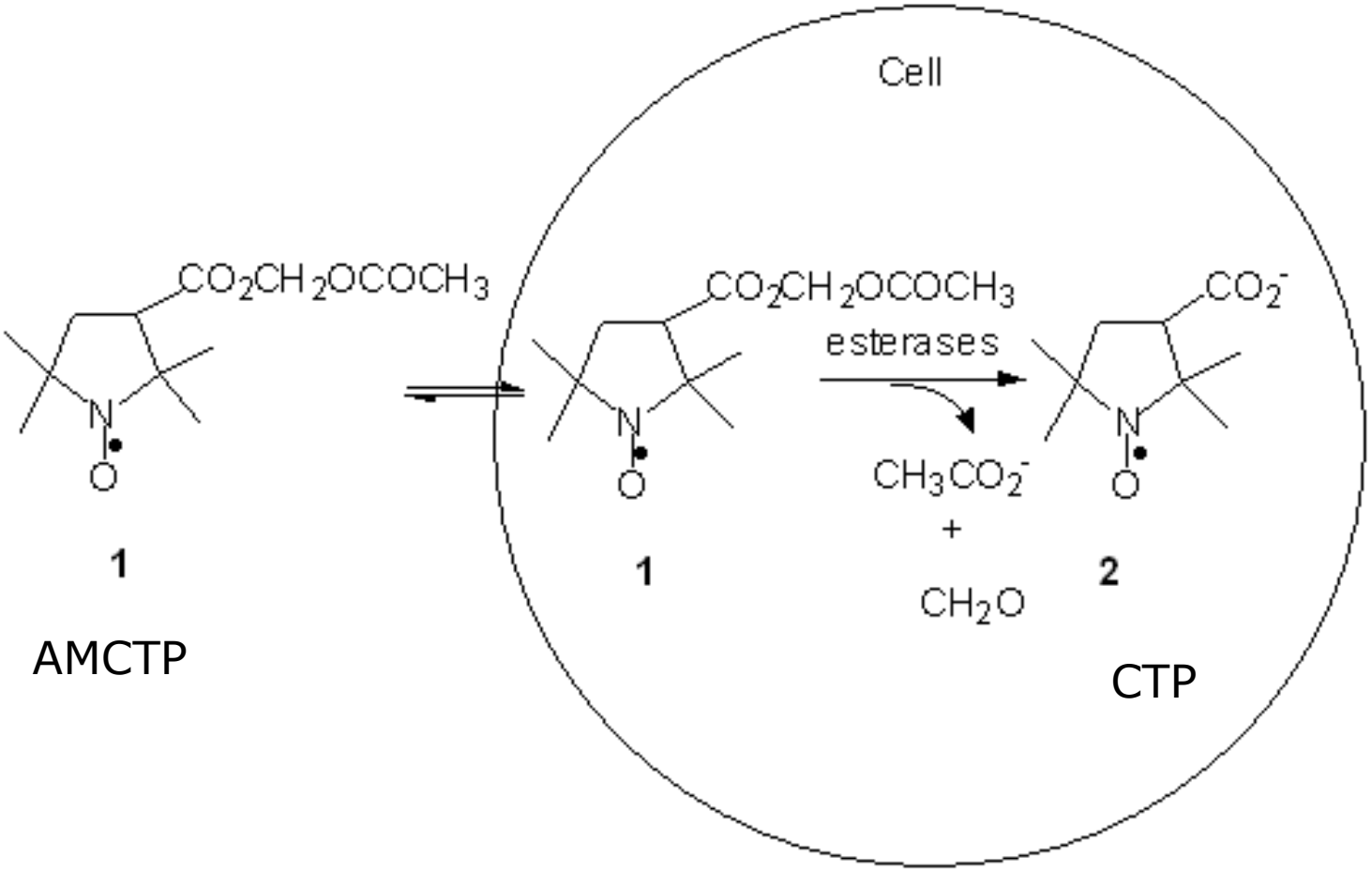
The Imaging system comprises a dedicated magnet equipped with 3D planar gradients and L-band EPR spectroscopy.



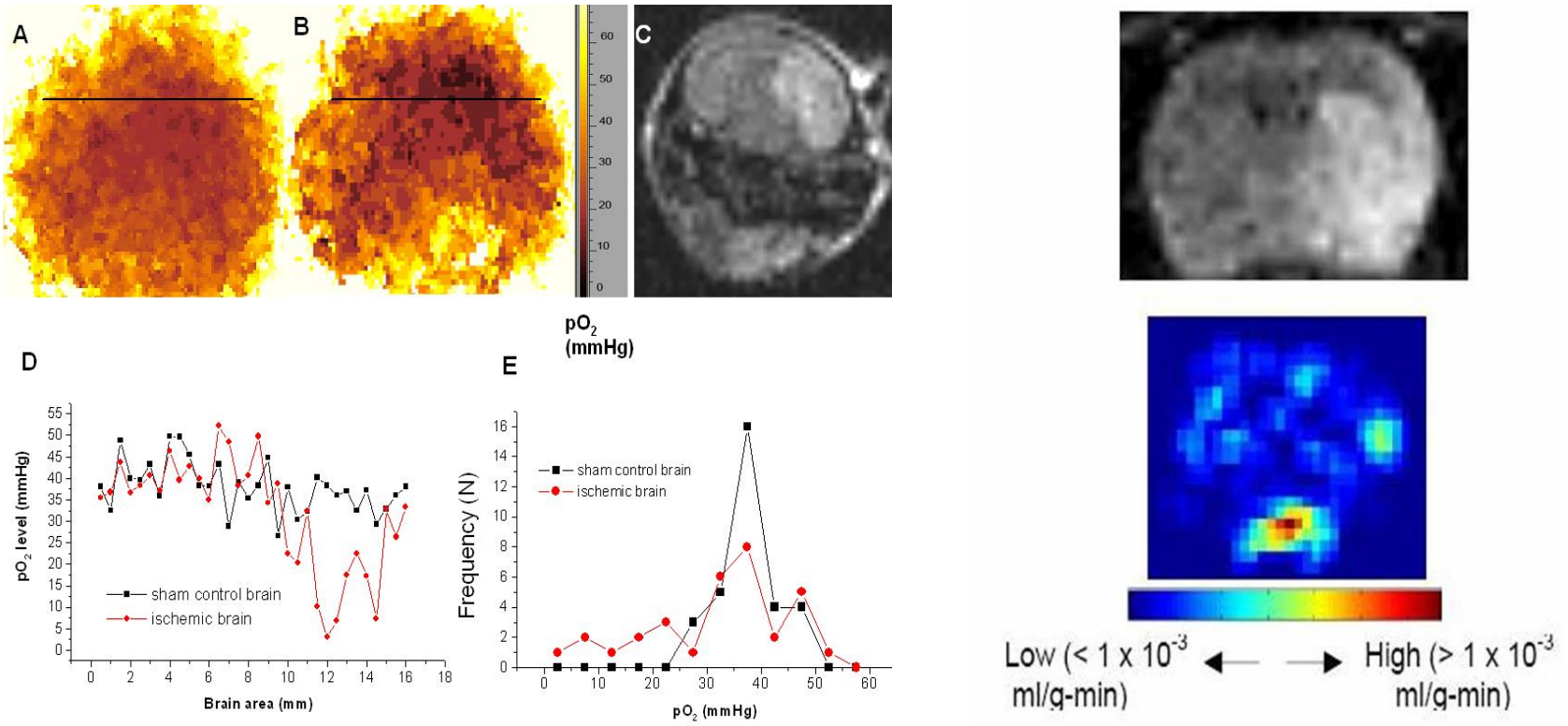
Animal probe can be mounted for horizontal or vertical access



Scheme of principle for intracellular distribution of AM ester-modifies nitroxide in brain



Development of Electron Paramagnetic Resonance Imaging Technology for Mapping Brain Oxygen Distribution and BBB permeability



EPR pO2 imaging and diffusion weight MR image show the site of the ischemic lesion (hyper intense region). The permeability coefficient color map demonstrates regions of high and low permeability with regions of high permeability corresponding to BBB breakdown

Shen JG, et al. ***Magnetic Resonance in Medicine* 55**, 1433-1440, 2006

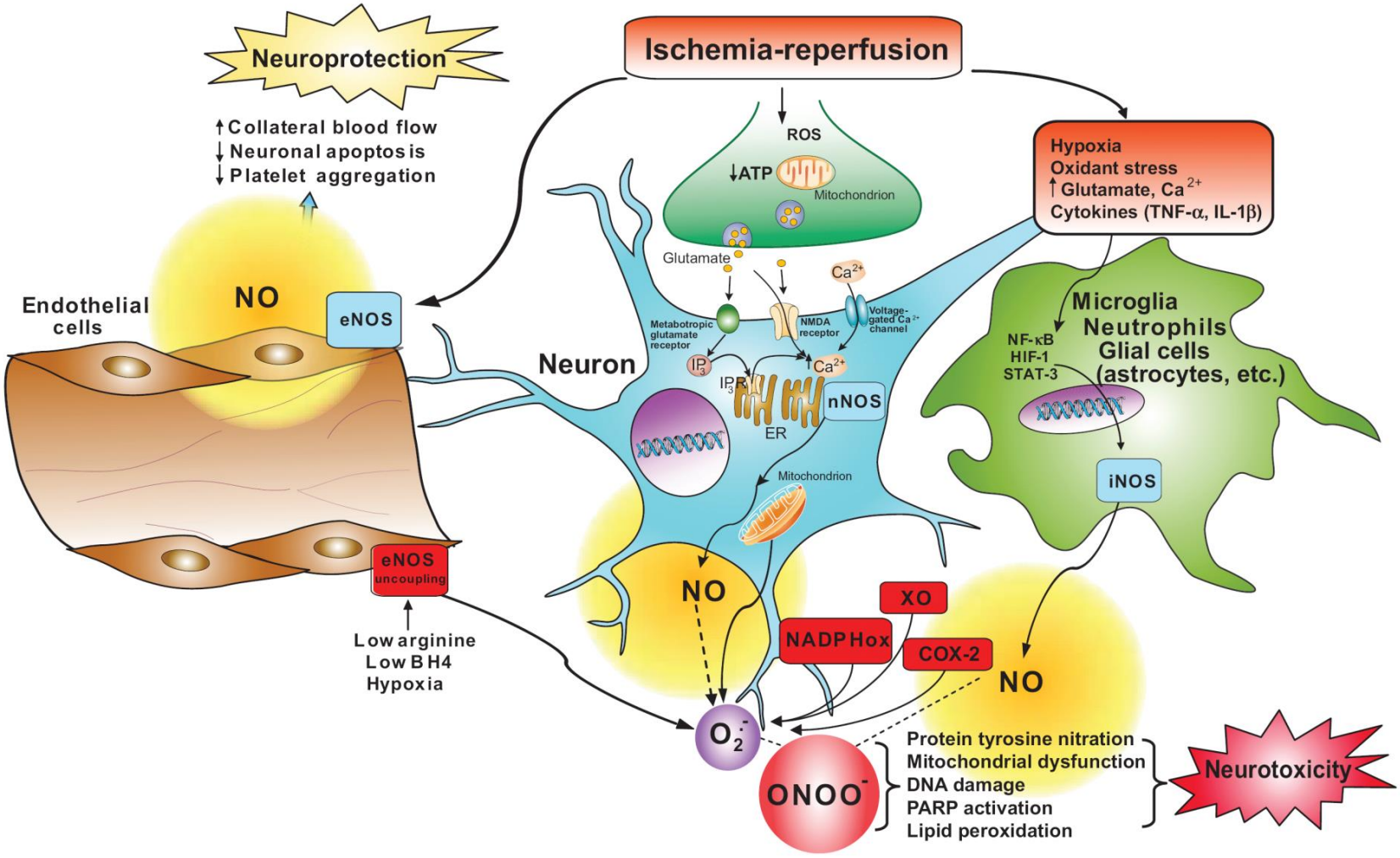
Shen JG, et al. ***Journal of Cerebral Blood Flow and Metabolism*** 29:1695-703, 2009

Miyake M, **Shen JG,** et al ***Journal of Pharmacology and Experimental Therapeutics*** 318, 1187-1193, 2006.

案例2：血管神經單元研究

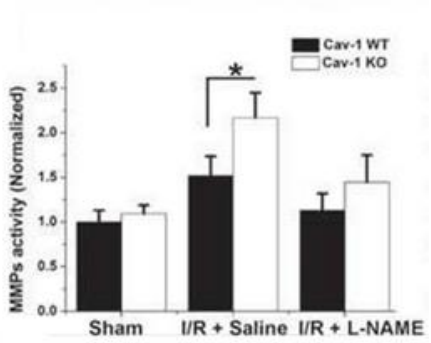
活性氮(RNS)在腦卒中血管神經單元損傷中的作用及中藥治療新靶點

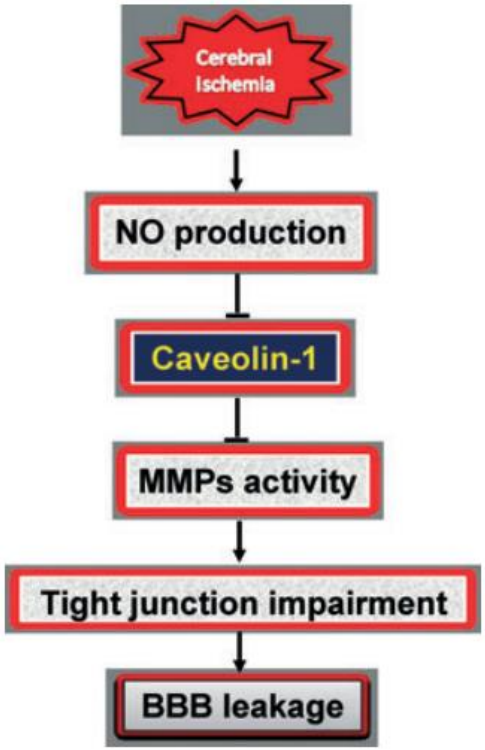
Roles of RNS in pathophysiology of stroke

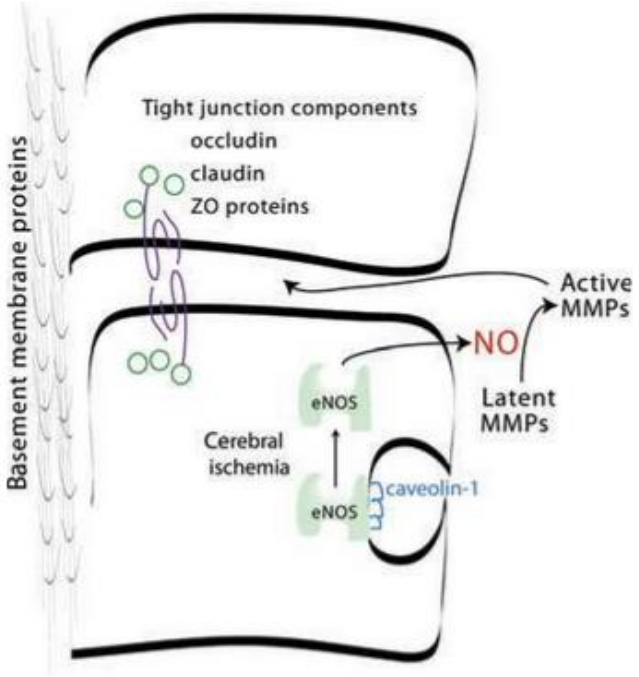


Pacher, P., Beckman, J., & Liaudet, L. ***Physiol Rev.***, 2007, 87: 315-424

中風血腦屏障破壞新機制及藥物治療新靶點







Gu Y, Zheng G, Liu K, **Shen JG*.** *Journal of Neurochemistry* 120(1):147-156, 2012
Liu WL, Hendren J, Yuan ZR, **Shen JG**, Liu KJ. *Journal of Neurochemistry* 108:811-820, 2009

发展RNS阻断剂：中风治疗的新策略

NOS inhibitors:

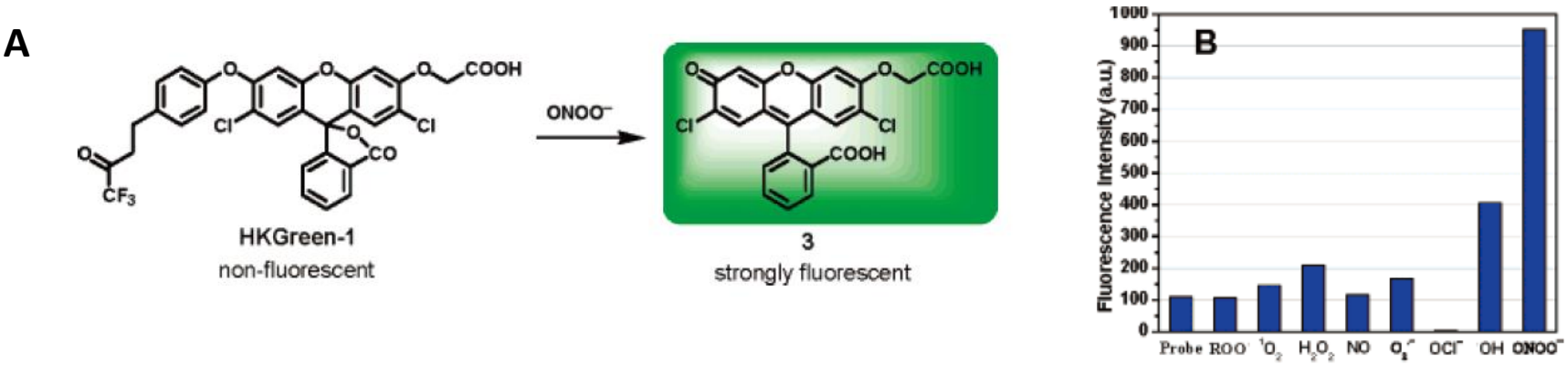
- **Non-selective NOS inhibitor:** L-NAME,
- **nNOS inhibitors**: Tirilazad; ARL 17477 ; Delta-(S-methylisothioureido)-*L*-norvaline (*L*-MIN)
- **iNOS inhibitors**: 1400W; aminoguanidine

Peroxynitrite scavengers and decomposers:

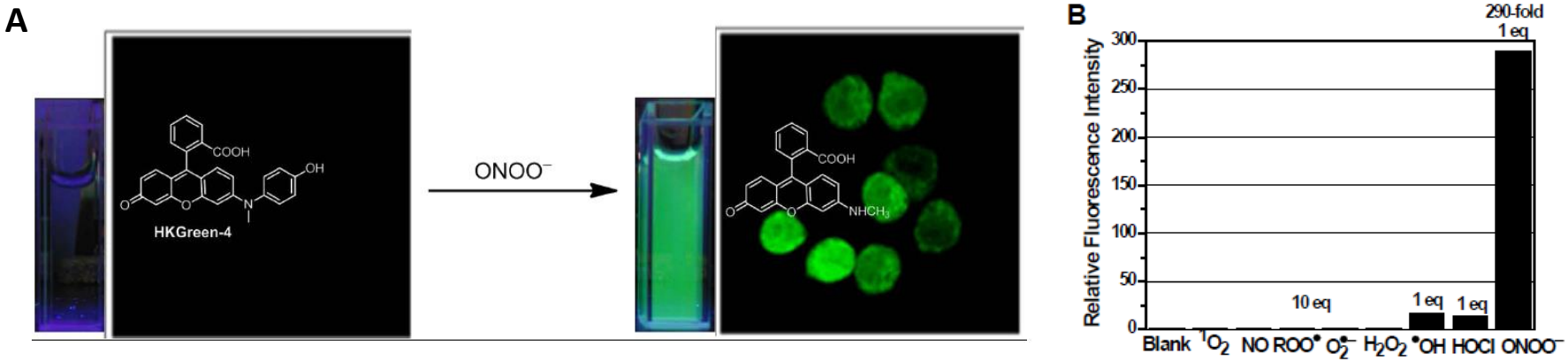
- **Peroxynitrite decomposition catalysts (PDCs):** FeTMPyP, FeTPPS
- **Peroxynitrite scavenger:** uric acid
- **Phenolic peroxynitrite scavengers**:
  Curcumin; Resveratrol; Catechin; Caffeic acid
- **Non phenolic peroxynitrite scavengers:**
  Ebselen; Edaravone; Betulinic acid; Melatonin

Chen XM, Chen HS, Xu MJ, **Shen JG***. ***Acta Pharmacologica Sinica*** 34(1):67-77; 2013

发展新型过氧亚硝基荧光探针: HKGreen-1, HKGreen-4

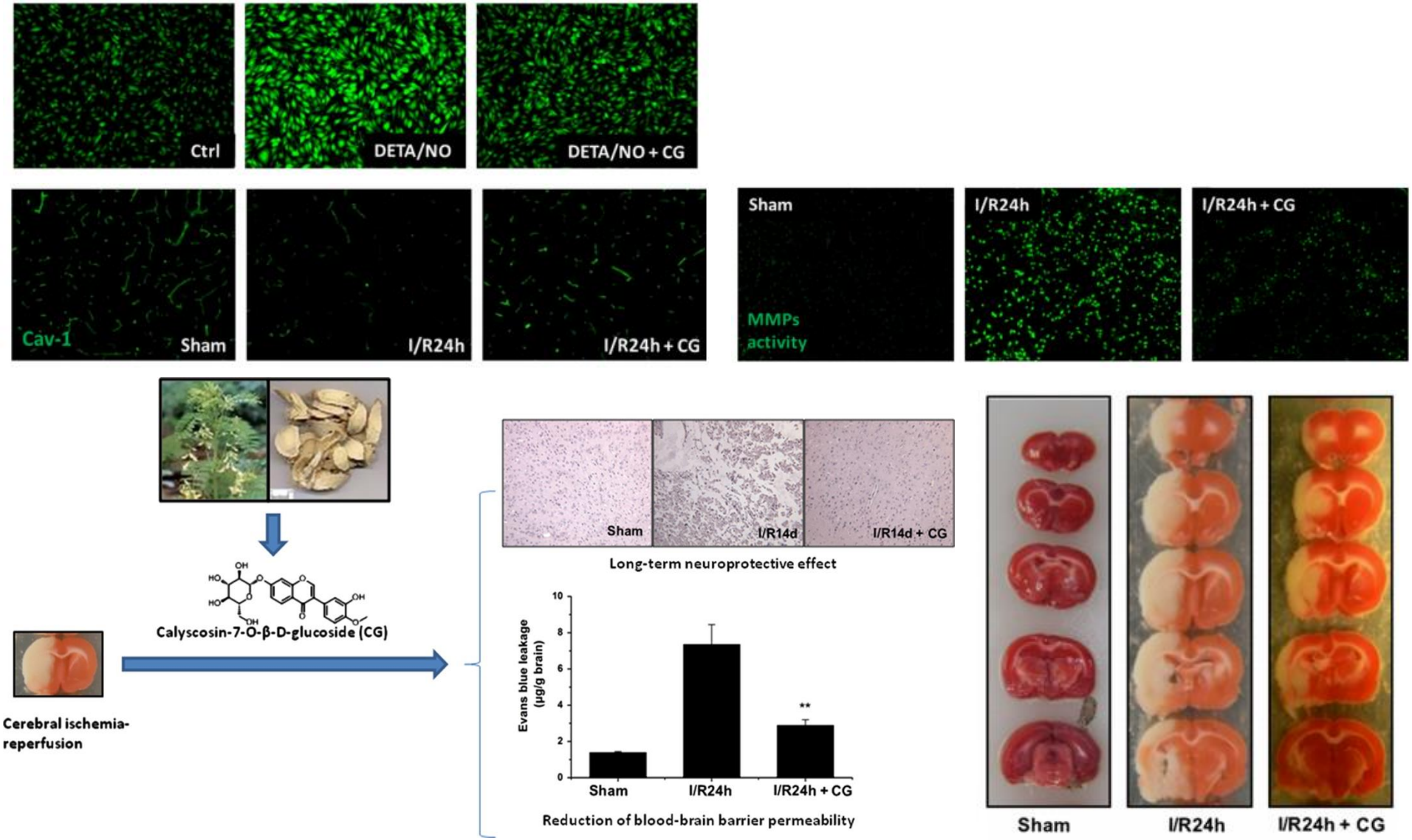


Yang D, Sun ZN, Peng T, Wang HL, **Shen JG,** Chen Y, Tam PK. ***Methods Mol Biol.*** 591:93-103,2010.
Yang D, Wang HL, Sun ZN, Chung NW, **Shen JG***. ***Journal of The American Chemical Society*** 128(18):6004-5, 2006



Peng T, Wong NK, Chen X, Chan YK, Ho DH, Sun Z, Hu JJ, **Shen J**, El-Nezami H, Yang D. ***Journal of The American Chemical Society*** 136(33):11728-34, 2014.

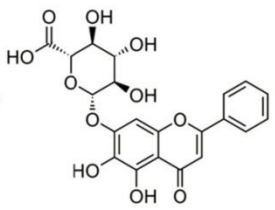
毛蕊異黃酮在腦缺血再灌注損傷中調節一氧化氮/小凹蛋白1/金屬蛋白酶通路並且保護血腦屏障完整性



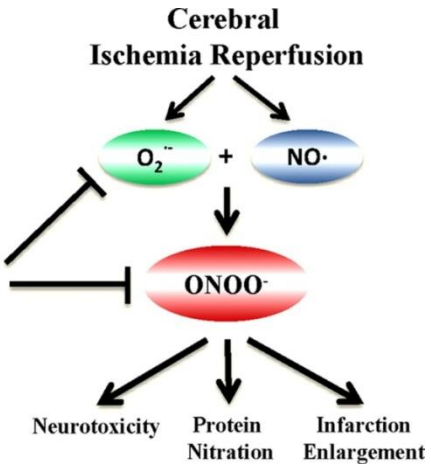
Fu SP, Gu Y, Jiang JQ, Chen X, Xu MJ, Chen XM, Shen JG*. ***Journal of Ethnopharmacology*** 155: 692-701, 2014.

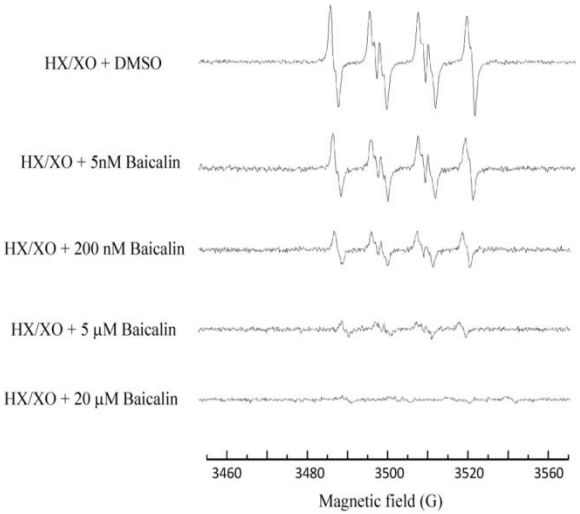
黃芩苷可以清除過氧化亞硝基並且改善腦缺血再灌注損傷中內源性亞硝基介導的神經毒性

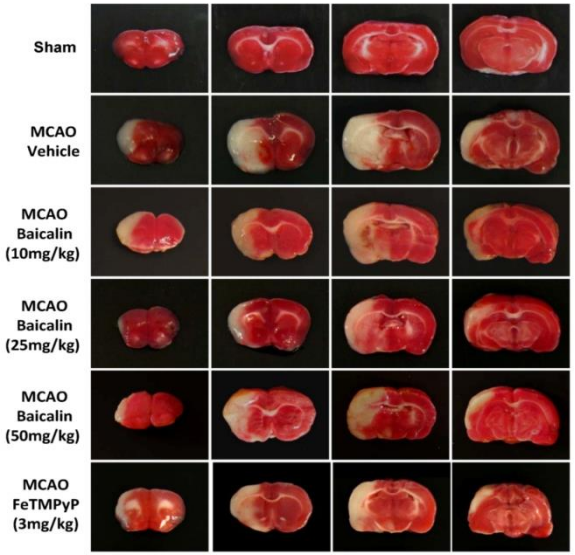
Scutellariae Baicalensis Georgi

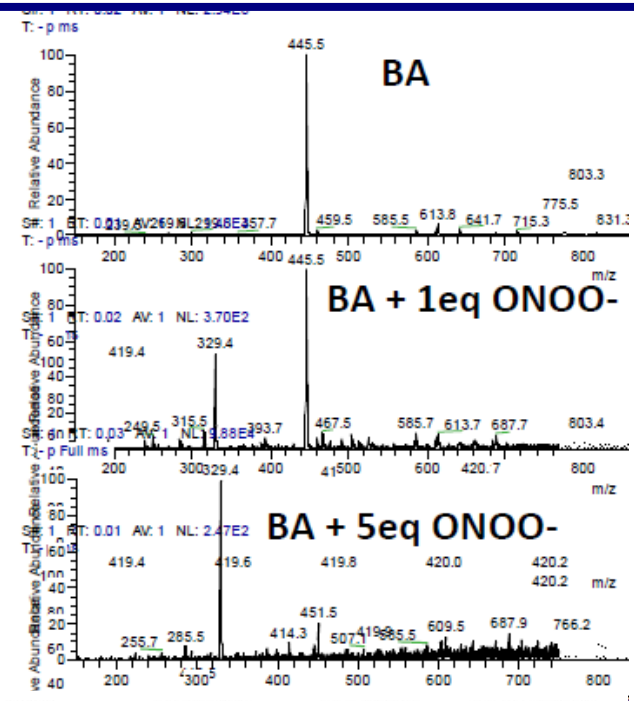


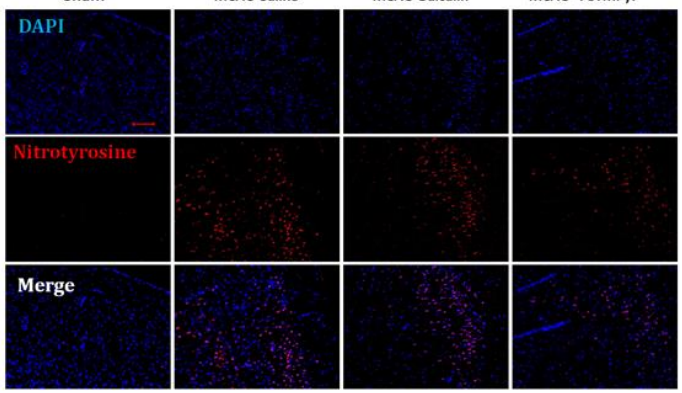
Baicalin











Xu MJ, Chen XM, Gu Y, Peng T, Yang D, Chang RC, So KF, Liu KJ, Shen JG*. ***Journal of Ethnopharmacology*** 150(1):116-24. 2013

案例3:薈萃分析補陽還五湯在缺血性中風的作用研究

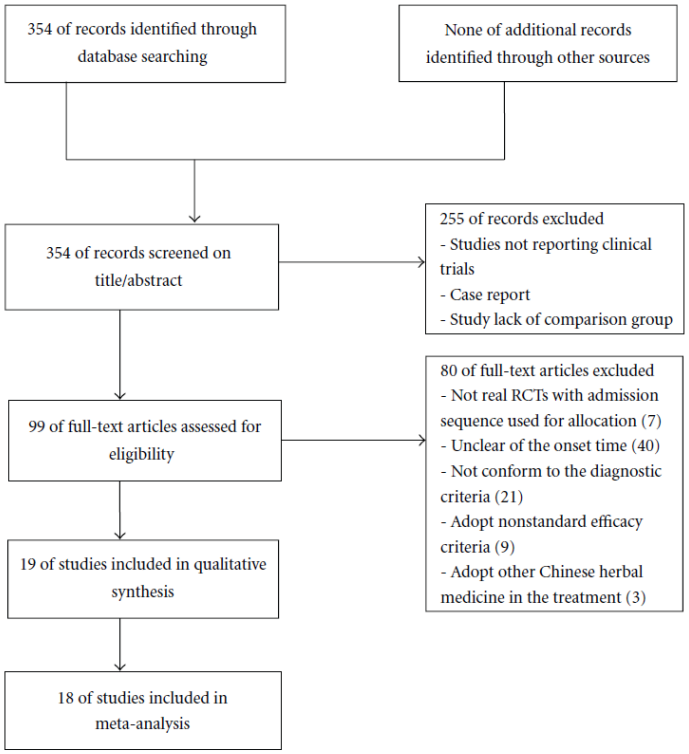


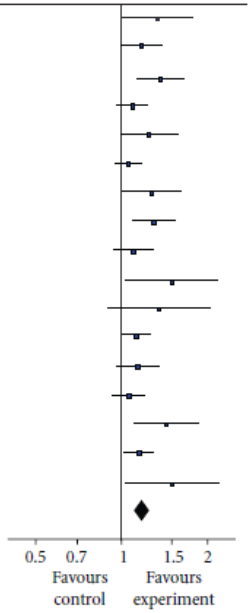
Figure 1: Flowchart of trials selection process.

Table 4: Meta-analyses of the total effective rate of BHD therapy for acute ischemic stroke.

Study or subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk ratio M-H, random, 95% CI
Chen, 2007 [32]	28	32	21	32	3.0%	1.33 [1.00, 1.77]
Cui et al., 2005 [34]	49	50	25	30	6.6%	1.18 [1.00, 1.39]
Fang et al., 2005 [27]	58	65	47	72	5.5%	1.37 [1.13, 1.65]
Guo, 2009 [25]	56	57	27	30	9.1%	1.09 [0.96, 1.24]
Jia et al., 2010 [26]	30	32	21	28	4.1%	1.25 [0.99, 1.58]
Kang, 2006 [30]	35	36	35	38	10.4%	1.06 [0.95, 1.18]
Lin, 2008 [31]	30	32	22	30	4.0%	1.28 [1.01, 1.61]
Liu, 2010 [35]	52	55	40	55	6.2%	1.30 [1.09, 1.55]
Lv, 2009 [39]	33	35	30	35	7.0%	1.10 [0.94, 1.29]
Run, 2001 [37]	21	24	14	24	1.8%	1.50 [1.04, 2.17]
Shi and Zhang, 1995 [36]	17	21	12	20	1.5%	1.35 [0.89, 2.04]
Wang and Yu, 2005 [38]	62	64	55	64	10.4%	1.13 [1.01, 1.26]
Wu and Luo, 2011 [23]	33	35	29	35	6.3%	1.14 [0.96, 1.35]
Yan and Mei, 2004 [33]	55	60	52	60	9.1%	1.06 [0.93, 1.20]
Zhang, 2004 [24]	36	40	25	40	3.4%	1.44 [1.11, 1.87]
Zhang et al., 2010 [12]	77	82	67	82	9.7%	1.15 [1.02, 1.29]
Zheng et al., 2004 [40]	24	27	13	22	1.8%	1.50 [1.04, 2.18]
Total (95% CI)		**747**		**697**	**100.0%**	**1.18 [1.12, 1.24]**
Total events	696		535			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 24.82$, $df = 16$ ($P = 0.07$); $I^2 = 36\%$

Test for overall effect: $Z = 6.02$ ($P < 0.00001$)



通過薈萃分析及系統綜述，我們發現補陽還五湯可以顯著改善中風后神經功能且是安全的選擇。但是由於臨床實驗質量和數量有限，結論還不足以臨床推薦使用。

Hao CZ, Wu F, Shen JG, Lu L, Fu DL, Liao WJ, Zheng GQ. ***Evidence-based Complementary and Alternative Medicine*** *2012, Article ID.* 630124

案例4:密集顱電針刺激結合身體針灸對於中風後抑鬱症治疗的临床研究

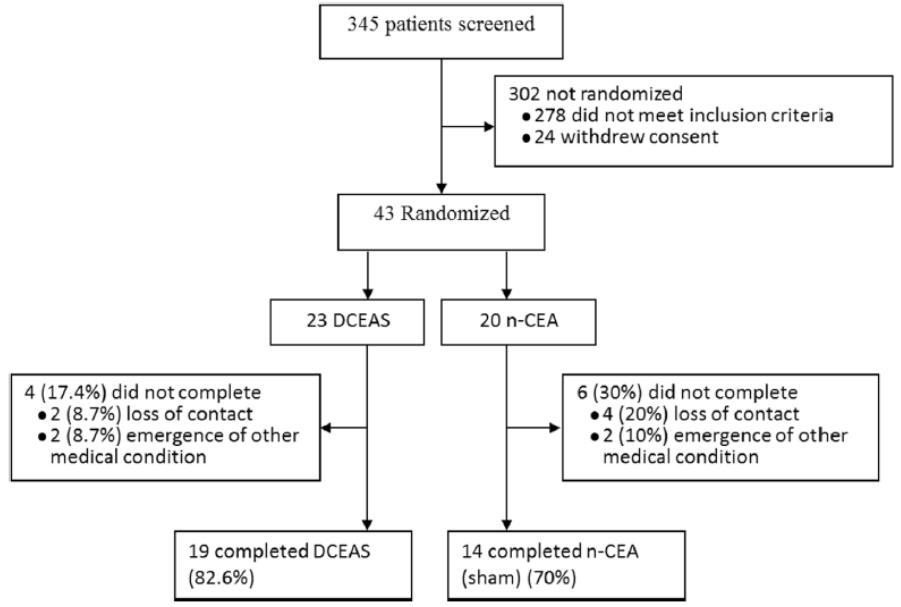


Figure 1 Enrollment flow. Of 345 patients screened, 43 eligible subjects were randomly assigned to n-CEA (sham) (n = 20) and DCEAS (n = 23) group. For n-CEA (sham), 14 subjects completed; while for DCEAS, 19 completed.

採用單盲，隨機對照臨床實驗，評價綜合使用密集顱電針刺激結合身體針灸及血清素抑制劑對於中風後抑鬱症的療效，結果顯示採用I密集顱電針刺激組比未侵入性電針假手術組顯示了對於中風後抑鬱症更好的治療作用。

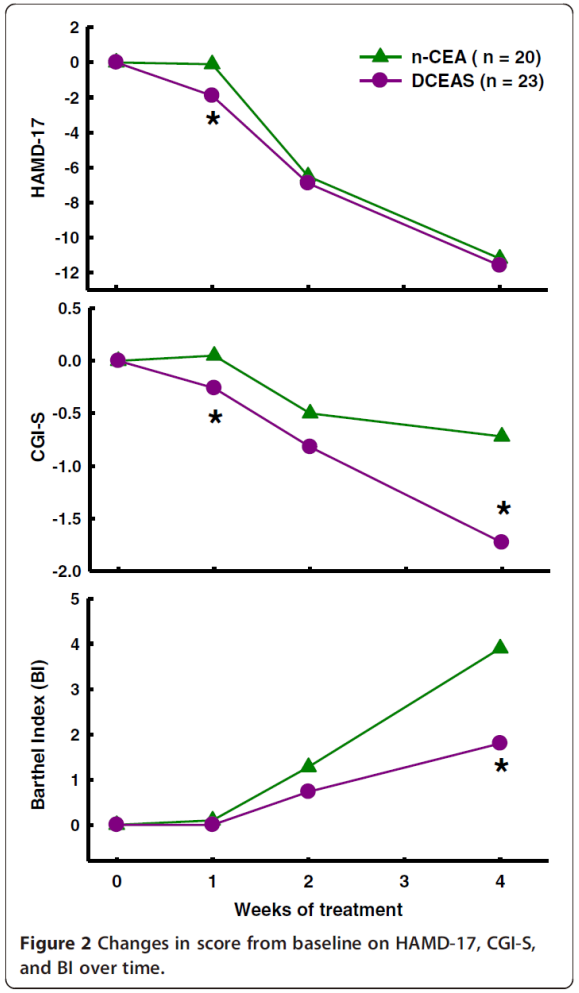


Figure 2 Changes in score from baseline on HAMD-17, CGI-S, and BI over time.

Man SC, Hung BH, Ng RM, Yu XC, Cheung H, Fung MP, Li LS, Leung KP, Leung KP,Tsang KW, Ziea E, Wong VT, Zhang ZJ. ***BMC Complement Alternative Medicine.*** 14:255, 2014.

創新科技研究發展方向

1、轉化醫學研究： 開展中藥治療中風生物靶標的研究

2、中藥產品及新藥研究： 與業界合作進行有關中藥複方及新型中藥製劑治療中風的研究。

3、中藥複方治療中風的臨床研究： 如安宮牛黃丸的臨床藥理與毒理學研究及與之相關的新產品研發

謝謝