香港腦科基金會（伊利沙伯醫院）& 香港小腦萎縮症協會（香港醫管局）

Management of Cerebellar Ataxias: From Bench to Bedside

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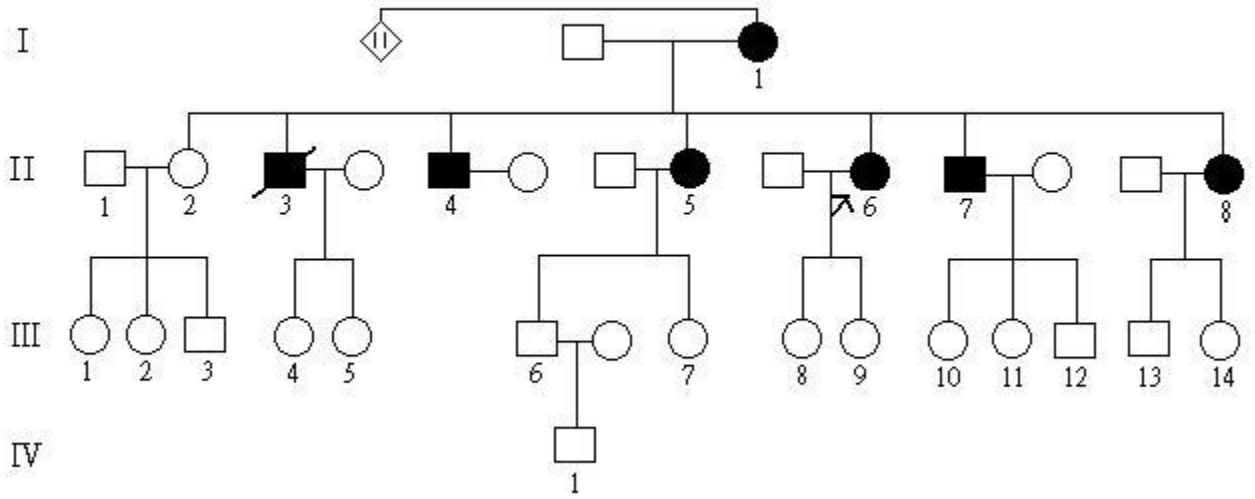
一個家族的故事



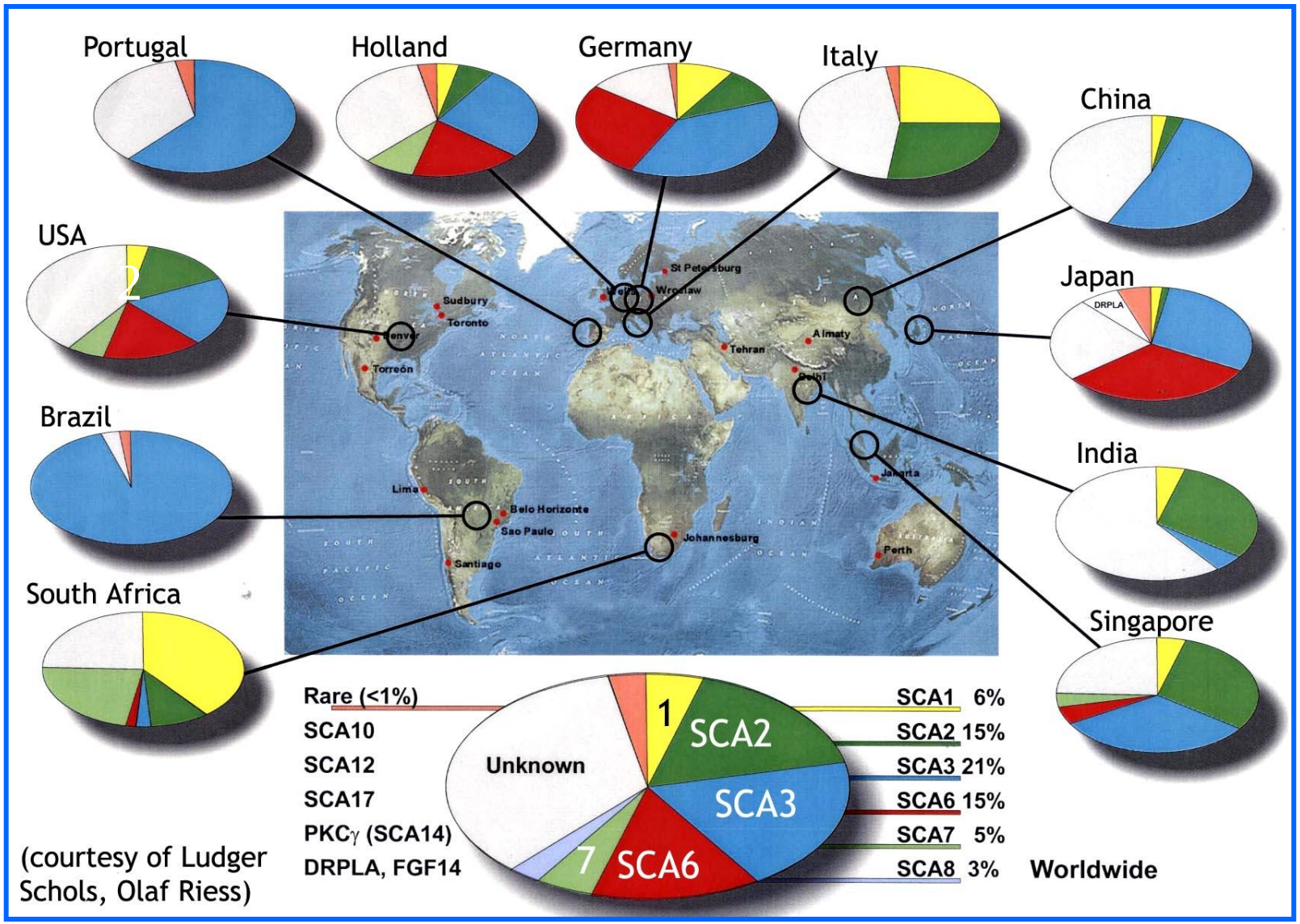
Spinocerebellar ataxias (SCAs)

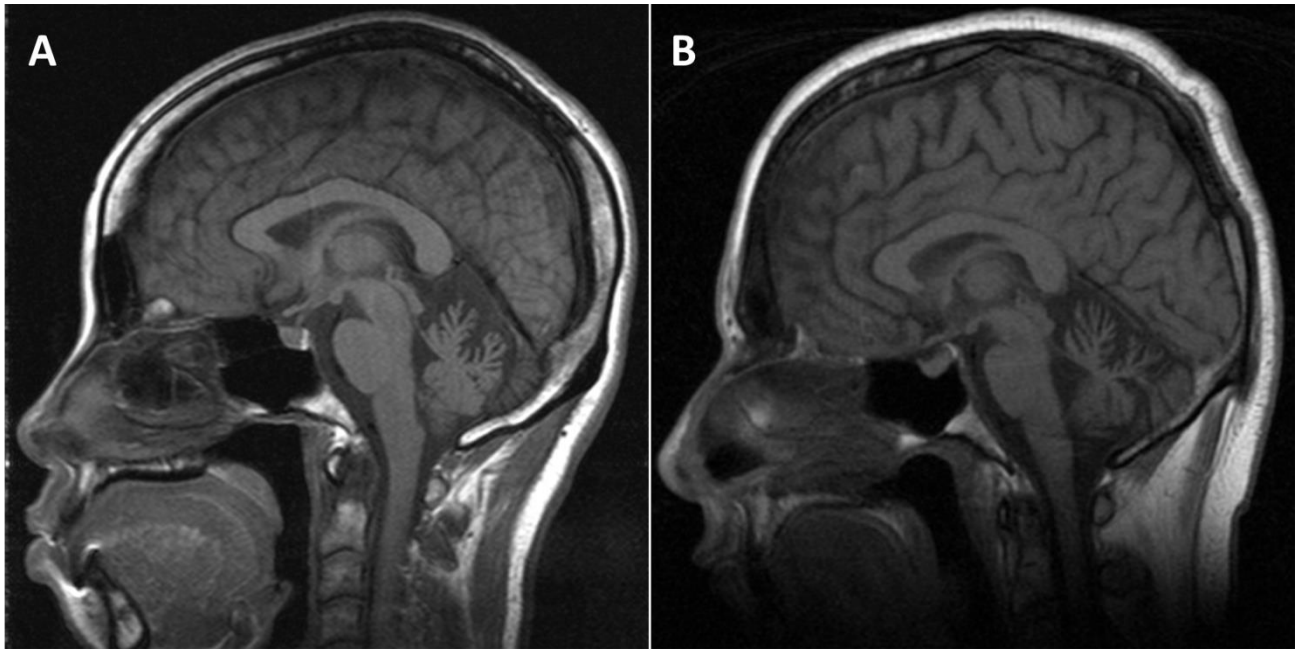
- Autosomal **dominant** neurodegenerative diseases with a prevalence of 5-10/100,000.
- Progressive loss of coordination → ataxia in gait and limb movements, dysarthria and dysphagia. Progressive and fatal evolution in 10 to 30 years.
- Onset of symptoms: during 3rd or 4th decade
- **Pathology**: Degeneration of neurons in the brainstem, the cerebellum +/- its afferent/efferent fibres.
- Forty-three loci identified so far.
- **Twenty percent** remain molecularly unassigned.
- Treatment: limited, or nil.

Ataxia	Locus	Gene	Type of Mutation	Protein or Complex	OMIM Accession No.
Coding Repeat Expansions[a]					
DRPLA	12p13.31	*ATN1*	(CAG)n	Atrophin 1	125370
SCA1	6p23	*ATXN1*	(CAG)n	Ataxin 1	164400
SCA2	12q24	*ATXN2*	(CAG)n	Ataxin 2	183090
SCA3/MJD	14q32.1	*ATXN3*	(CAG)n	Ataxin 3	109150
SCA6	19p13	*CACNA1A*	(CAG)n	Calcium channel, voltage-dependent, P/Q-type, α-1A subunit	183086
SCA7	3p14	*ATXN7*	(CAG)n	Ataxin 7	164500
SCA17	6q27	*TBP*	(CAG)n	TATA box binding protein	607136
Noncoding Repeat Expansions[b]					
SCA8	13q21.33	*ATXN8, ATXN8OS*	(CTG*CAG)n	Ataxin 8 and ATXN8 opposite strand (nonprotein coding)	608768
SCA10	22q13.31	*ATXN10*	(ATTCT)n	Ataxin 10	603516
SCA12	5q32	*PPP2R2B*	(CAG)n	Protein phosphatase 2, regulatory subunit B, β	604326
SCA31	16q21	*BEAN1*	(TGGAA)n	Brain expressed, associated with NEDD4, 1	117210
SCA36	20p13	*NOP56*	(GGCCTG)n	NOP56 ribonucleoprotein homologue (yeast)	614153
Other Types of Mutations[c]					
SCA5	11q13.2	*SPTBN2*	Point mutations	Spectrin, β, nonerythrocytic 2	600224
SCA11	15q15.2	*TTBK2*	Point mutations	Tau tubulin kinase 2	604432
SCA13	19q13.33	*KCNC3*	Point mutations	Potassium voltage-gated channel, Shaw-related subfamily, member 3	605259
SCA14	19q13.42	*PRKCG*	Point mutations	Protein kinase C, λ	605361
SCA15/16/29	3p26.1	*ITPR1*	Point mutations, large deletions	Inositol 1,4,5-trisphosphate receptor, type 1	606658, 117360
SCA18	7q31.1	*IFRD1*	Point mutations	Interferon-related developmental regulator 1	607458
SCA19/22	1p13.2	*KCND3*	Point mutations, small deletions	Potassium voltage-gated channel, Shal-related subfamily, member 3	607346
SCA20	11p11.2-q13.3	Not applicable	Genomic duplication	Region with ≥12 genes	608687
SCA23	20p13	*PDYN*	Point mutations	Prodynorphin	610245
SCA26	19p13.3	*EEF2*	Point mutations	Eukaryotic translation elongation factor 2	609306
SCA27	13q34	*FGF14*	Point mutations	Fibroblast growth factor 14	609307
SCA28	18p11.21	*AFG3L2*	Point mutations	AFG3 adenosine triphosphatase family gene 3-like 2 (*Saccharomyces cerevisiae*)	610246
SCA35	20p13	*TGM6*	Point mutations	Transglutaminase 6	613908
Unknown Mutations					
SCA4	16q22.1	?	?	?	600223
SCA21	7p21.3-p15.1	?	?	?	607454
SCA25	2p21-p13	?	?	?	608703
SCA30	4q34.3-q35.1	?	?	?	613371
SCA32	7q32-q33	?	?	?	613909
SCA34	6p12.3-q16.1	?	?	?	133190
SCA37	1p32	?	?	?	HGNC 43726

JAMA Neurology 2014;71:832

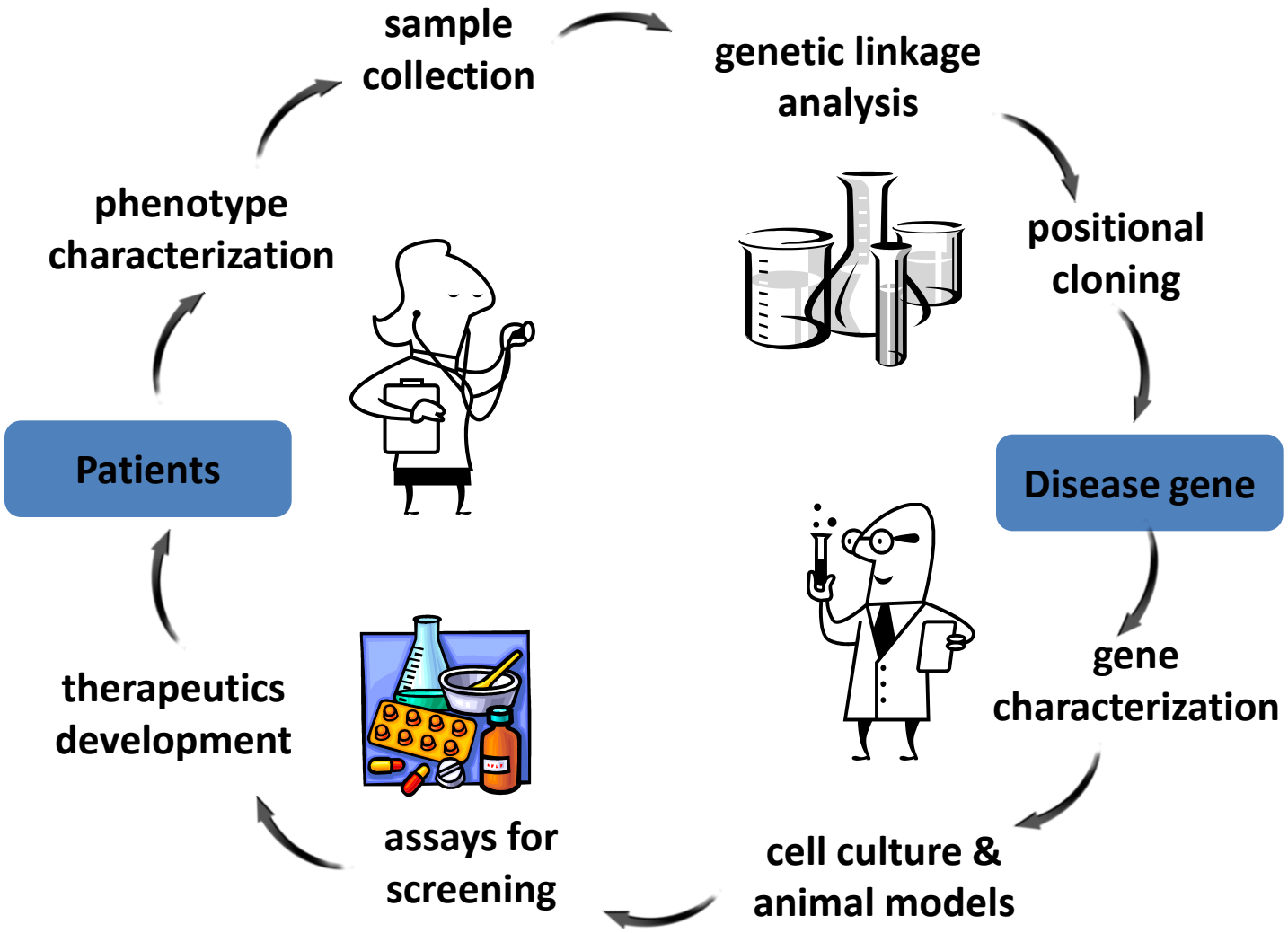
Worldwide distribution of SCAs





Current age: 47 YO
Duration of illness: 15 yrs

Current age: 36 YO
Duration of illness: 12 yrs



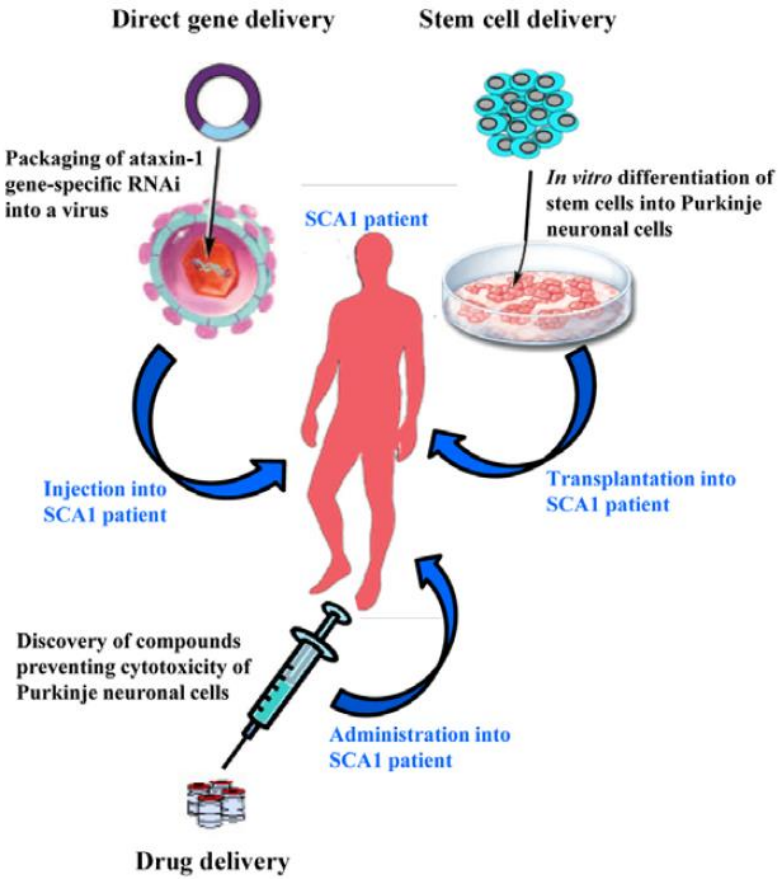
Over 2,000 disease genes have been identified in the past 20 years. Now we can use what we have learned to develop effective treatment for patients with hereditary diseases.

Unmet Medical Needs

- Therapeutics!
- Therapeutics!
- Therapeutics!

Potential Therapeutic Strategies

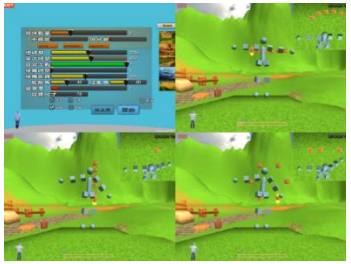
- Physical therapy
- Protein mis-folding
  - Enhancing molecular chaperone activity in neurons, i.e. HSP70
- Toxic proteolytic fragments
  - Impeding the formation of putative toxic oligomers or enhancing degradation of the mutant protein.
- Oxidative stress
  - Scavenging free radicals or boosting mitochondrial functions- trial of high doses of **coenzyme Q10** in HD.
- Gene therapy: RNAi, gene editing, ASO—etc.
- Cell therapies

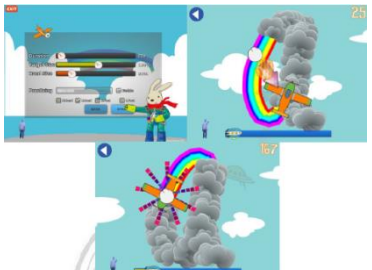


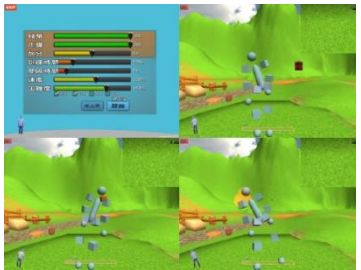
Mol Cell 2009;27:621

Exergaming vs. Conventional Training: a Randomized Controlled Trial (NCT Identifier: NCT02900508)

- Six patients with SCA3 in each group.
- Forty minutes per session, 3 sessions per week for a 4-week training period.
- Outcome mesures:
  - Primary- SARA.
  - Secondary- upper-limb function (the 9-hole peg test (NHPT) and gait performance (GaitRite)).







Small Molecule Drugs

- Expanded ataxin-2 and ataxin-3 interact with type 1 inositol 1,4,5-trisphosphate receptor (InsP3R1), an intracellular Ca^{++} release channel, and sensitize it to activation.
  - **Dantrolen**e, a calcium ion stabilizer, alleviated motor deficits and neuronal cell loss in SCA2 (J Neurosci 2009;29:9148) and SCA3 (J Neurosci 2008;28:12713) mouse models.

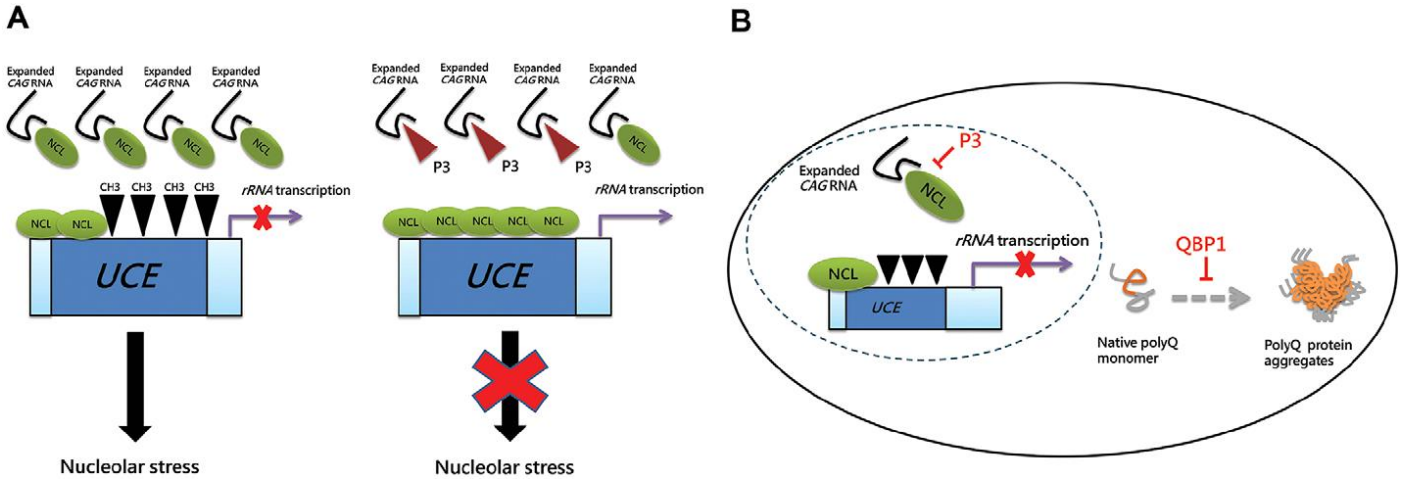
© 2016. Published by The Company of Biologists Ltd | Disease Models & Mechanisms (2016) 9, 321-334 doi:10.1242/dmm.022350

RESEARCH ARTICLE

SUBJECT COLLECTION: TRANSLATIONAL IMPACT OF *DROSOPHILA*

Assessing a peptidylic inhibitor-based therapeutic approach that simultaneously suppresses polyglutamine RNA- and protein-mediated toxicities in patient cells and *Drosophila*

Qian Zhang[1,2], Ho Tsoi[1,2], Shaohong Peng[1,2], Pan P. Li[3], Kwok-Fai Lau[2,4,5], Dobrila D. Rudnicki[3], Jacky Chi-Ki Ngo[2,4] and Ho Yin Edwin Chan[1,2,4,5,*]



Prof. H.Y. Edwin Chan (left) and Prof. C.K. Jacky Ngo
陳浩然(左)及敖志祺教授手上分別為QBP1及P3的三維模型

(A) P3 suppressed expanded-CAG-RNA-induced nucleolar stress. (B) Suppression of RNA toxicity and protein toxicity utilizing the P3-QBP1 combination treatment strategy. CH3, methyl group.

RNAi gets its due – quickly!

Americans win Nobel medicine prize

POSTED: 9:49 a.m. EDT, October 2, 2006

Andrew Fire, left, and Craig Mello pose in March after receiving an award in Germany.

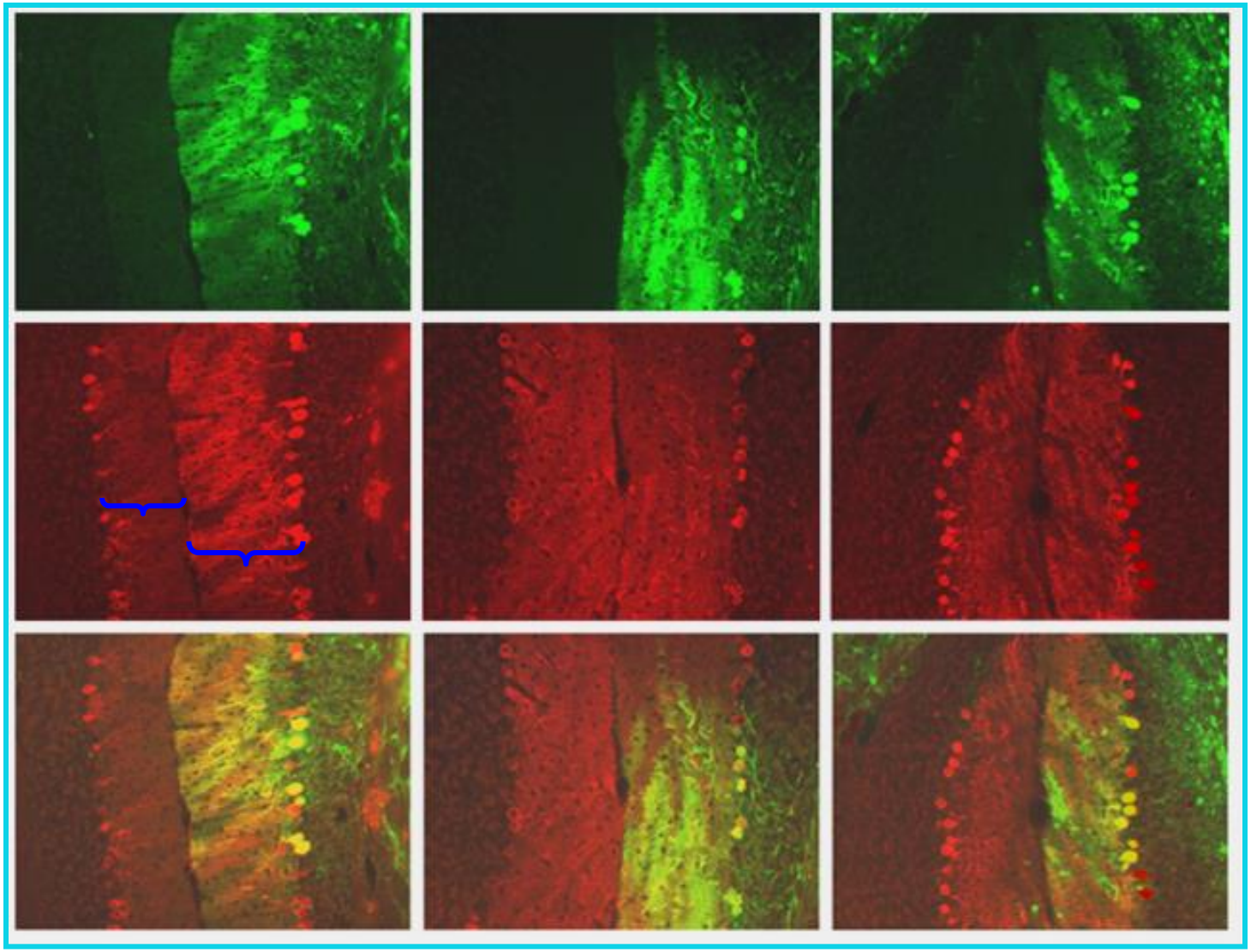
STOCKHOLM, Sweden (AP) -- Americans Andre
Prize in physiology or medicine Monday for disc
effect of specific genes, opening a new avenue

"RNA interference" is already being widely used
the function of genes and it is being studied as
AIDS and hepatitis viruses and for other conditi
cancer.

Fire, 47, of Stanford University, and Mello, of the
School in Worcester, published their seminal w

RNA interference occurs naturally in plants, ani
Institute in Stockholm, which awarded the prize
activity of genes and helps defend against viral

"This year's Nobel laureates have discovered a



Xia et al., (2004) Nat Med 10:816

Developing Allele-Specific RNAi for SCA6

Neurobiology of Disease 43 (2011) 533–542

Contents lists available at ScienceDirect

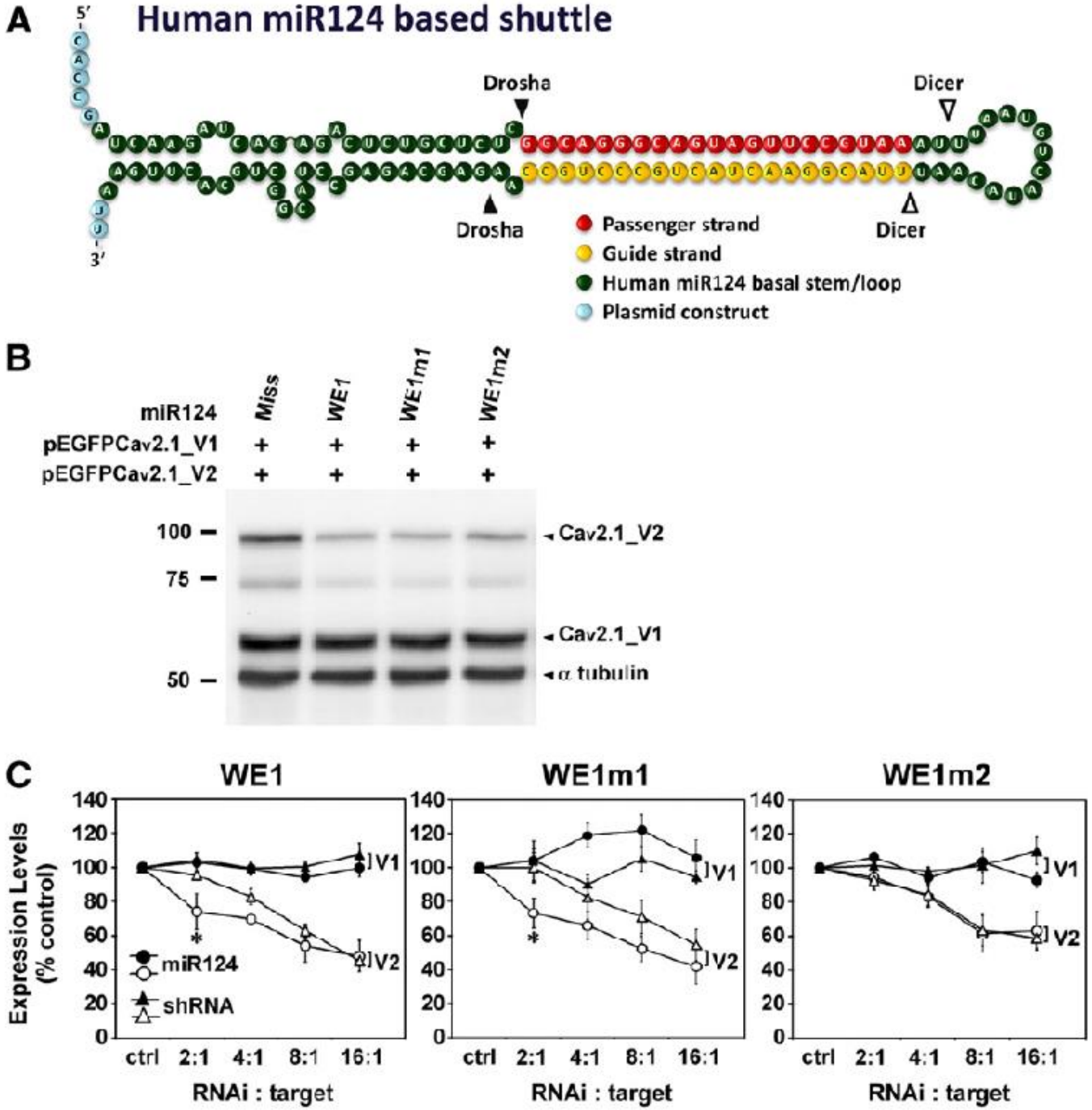
Neurobiology of Disease

journal homepage: www.elsevier.com/locate/ynbdi

Splice isoform-specific suppression of the $Ca_V2.1$ variant underlying spinocerebellar ataxia type 6

Wei-Ling Tsou [a,b], Bing-Wen Soong [c], Henry L. Paulson [b,*], Edgardo Rodríguez-Lebrón [b,**]

[a] Institute of Neuroscience, School of Life Sciences, National Yang-Ming University, Taipei, Taiwan
[b] Department of Neurology, University of Michigan, Ann Arbor, Michigan, USA
[c] Department of Neurology, National Yang-Ming University and Taipei Veterans General Hospital, Taipei, Taiwan


A
Human miR124 based shuttle
5′
3′
Drosha
Dicer
Drosha
Dicer
Passenger strand
Guide strand
Human miR124 basal stem/loop
Plasmid construct
B
miR124
pEGFPCav2.1_V1
pEGFPCav2.1_V2
Miss
WE1
WE1m1
WE1m2
100
75
50
Cav2.1_V2
Cav2.1_V1
α tubulin
C
WE1
WE1m1
WE1m2
Expression Levels (% control)
140
120
100
80
60
40
20
0
V1
V2
miR124
shRNA
ctrl
2:1
4:1
8:1
16:1
RNAi : target

Neuro-transplantation

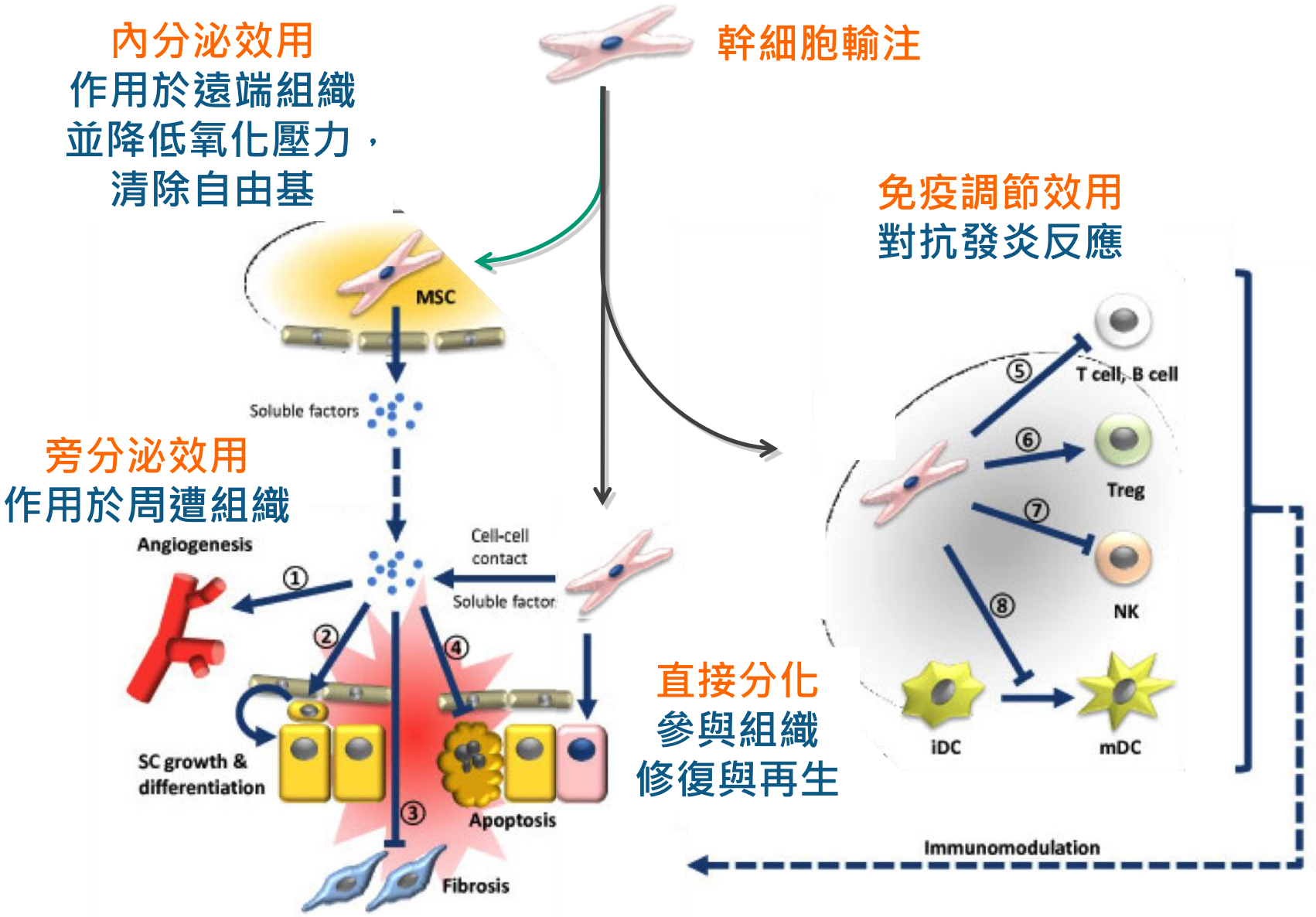
- Embryonic (fetal) neural tissue
- Embryonic (fetal)or adult neural stem cells
- Embryonic stem cells
- Adult stem cells
- **Mesenchymal stem cells** isolated from various tissues (BM, **adipose tissue**)
- Carcinoma stem cells

(Rossi & Cattaneo: Nat Rev Neurosci 2002;3:401)

A Phase I/IIa Clinical Trial: Treatment of cerebellar ataxias with adipose-derived mesenchymal stem cells.

“以異體脂肪間葉幹細胞治療小腦運動失調症”臨床試驗

間葉幹細胞作用機制



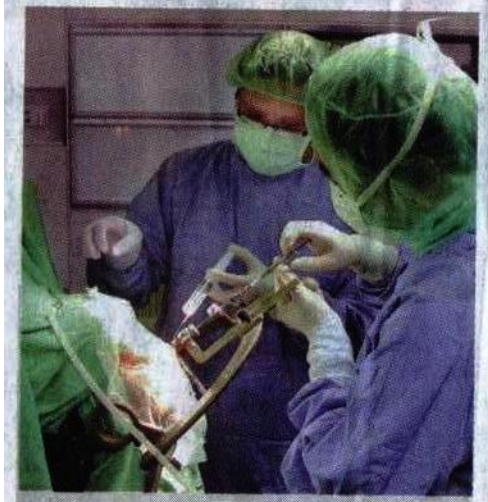
Carrion and Figueroa Stem Cell Research & Therapy 2011, 2:23

幹細胞治療是否安全而且有效?

幹細胞治中風 台灣醫療大突破

林欣儀／台中報導

台灣醫療大突破！中國醫藥大學北港附設醫院院長林欣榮，5年來針對30名中風導致偏癱的患者，透過自體幹細胞移植，百分百改善了他們的失能情況。



進行幹細胞移植的醫療團隊，將濃縮成1CC的細胞注入患者受傷的腦神經內。（林欣榮提供）

原本必須靠輪椅行動的患者，現在都能站立行走；林欣榮的研究成果也被美國知名期刊採用，最近將刊出。

7年前因中風導致右手右腳無力的黃先生，歷經治療及復健後仍倚賴輪椅進出；因右手無法使力，生活起居都得靠家人協助，在歷經1年半輪椅人生後，5年前他加入林欣榮的醫療實驗，採用自體周邊血液幹細胞移植方式做治療。

林欣榮說，這項研究是收集患者本身的周邊血液，經濃縮為1CC後，進入手術室，採最安全的局部麻醉方式；將濃縮後的幹細胞注入患者腦部神經受損處，前後時間約1小時。

經注入幹細胞後，黃先生原本無法動彈的右手，在1個月後就發現小拇指可以隨心意上下移動，讓他相當雀躍；更令人高興的是，緊接著2根指頭、3根指頭陸續能隨心所欲活動，到了半年後，他的右手已能舉起。原本要依賴輪椅的腿部也能站起並緩慢移動。現在黃先生雖右腳仍有些跛，但快步走不再困難，甚至可踏上跑步機小跑步做復健；昨天還高興的參加兒子婚禮。

林欣榮說，這起實驗目前進行到第2期，是針對偏癱的30名患者作實驗，原本採一半進行幹細胞移植配合復健的研究組，一半只做復健的控制組，結果發現研究組恢復快速，並將控制組的患者加入進行自體幹細胞移植，結果30人都有顯著進步，現都不必再靠輪椅行動。

林欣榮說，這起研究已獲美國《細胞移植雜誌》（Cell Transplantation）接受，將於近日刊出他的實驗成果；這本雜誌在細胞研究方面排行世界第四，顯示台灣在幹細胞移植方面的成果確實獲得肯定。

為幫助更多患者，林欣榮下一步決定嘗試臍帶血移植的方式，目前與永生臍帶血公庫取得合作。他說，預計實驗人數為12人，只要80歲以下、中風超過半年者都可以報名。（相關新聞刊A7）

責任副總編輯／張慧英　編輯／林佳綠

幹細胞治療是否安全而且有效?

救救我家 漸凍人籲開放人體實驗

林欣儀／台中報導

在外商公司擔任工程師的郭先生，2年前發現罹患漸凍症，人生從彩色變黑白，近半年來，病情急速惡化，只能期盼幹細胞療法人體實驗帶來生機。但相關計畫案仍卡在衛福部，郭先生昨天在家人陪同下向衛福部做出生命的吶喊，盼儘速通過該案。

中國醫藥大學北港附設醫院院長林欣榮（右）12日說，已向衛生福利部申請進行自體脂肪幹細胞治療漸凍人的臨床試驗，漸凍人郭先生（中）希望政府盡快開放。（中央社）

「救救我家！」逐漸無力的手在紙上寫出扭曲的字體，40歲的郭先生說，真的好想再抱抱親愛的女兒，坐在她的床邊為她說睡前故事；無奈身體沒辦法負荷，感覺就像被判了死刑，不知何時會執行，每天活在驚恐中。

其實，原本是「人生勝利組」的郭先生，從紐約取得碩士學位後，回台擔任外商公司的工程師，每天最愛的就是運動健身；2年前突然感覺脖子容易落枕，之後肺炎住院，經檢查才知罹患漸凍症，真的沒法相信。

半年前，郭先生的病情急速惡化，現在得靠輪椅代步！昨天，他在家人陪同下出席記者會，用口齒不清的發音懇求衛福部，儘速通過已經卡了8個月的漸凍人臨床試驗計畫。

郭太太無奈說，從半年前知道有醫生計畫利用脂肪幹細胞移植進行漸凍人治療後，就開始關注此事，原本衛福部去年底要核准，沒想到至今未通過，讓家人希望落空，漸凍人的生命消逝很快，真的沒有多少時間可以等了。

郭先生說，願意散盡千萬家財，希望可以參加這項計畫、當白老鼠，不只是為自己，也為全台灣2000多名漸凍人發聲，若有機會以幹細胞延長生命，或許有機會等到藥物研發成功的那天。

幹細胞治療是否安全而且有效?

台灣醫界觀點

幹細胞治療效果 有待檢驗

洪欣慈／台北報導

幹細胞一直被脊髓損傷者、神經疾病患者視為治癒的一線曙光，數年前前總統陳水扁孫子出生時保留下來的臍帶血，也被寄予讓其夫人吳淑珍再站起來的厚望。醫師表示，幹細胞相關研究與臨床試驗一直在進行，但要證明療效，恐還有漫漫長路要走。

台大台成幹細胞治療中心主任唐季祿表示，周邊血液幹細胞是藉由施打白血球生長激素（G-CSF），將骨髓中的幹細胞驅動至血液中，再經由血液分離機收集取得，目前主要用於治療血癌等血液疾病，抽取技術已十分純熟。

唐季祿說，過去國內外有許多研究，欲試驗周邊血液幹細胞對於帕金森氏症、中風等神經疾病的療效，但都還有爭議，原因在於中風病人經過一段時間，也會自己慢慢恢復機能，是否由幹細胞促成不得而知，國內外報告結果也不一。

他表示，幹細胞要運用於治療中風，效果最好的應是神經幹細胞，但因其需在體外培養、培養成功後再放回身體裡，需嚴格的體外培養條件，國內外對這部分的法規也較嚴格。

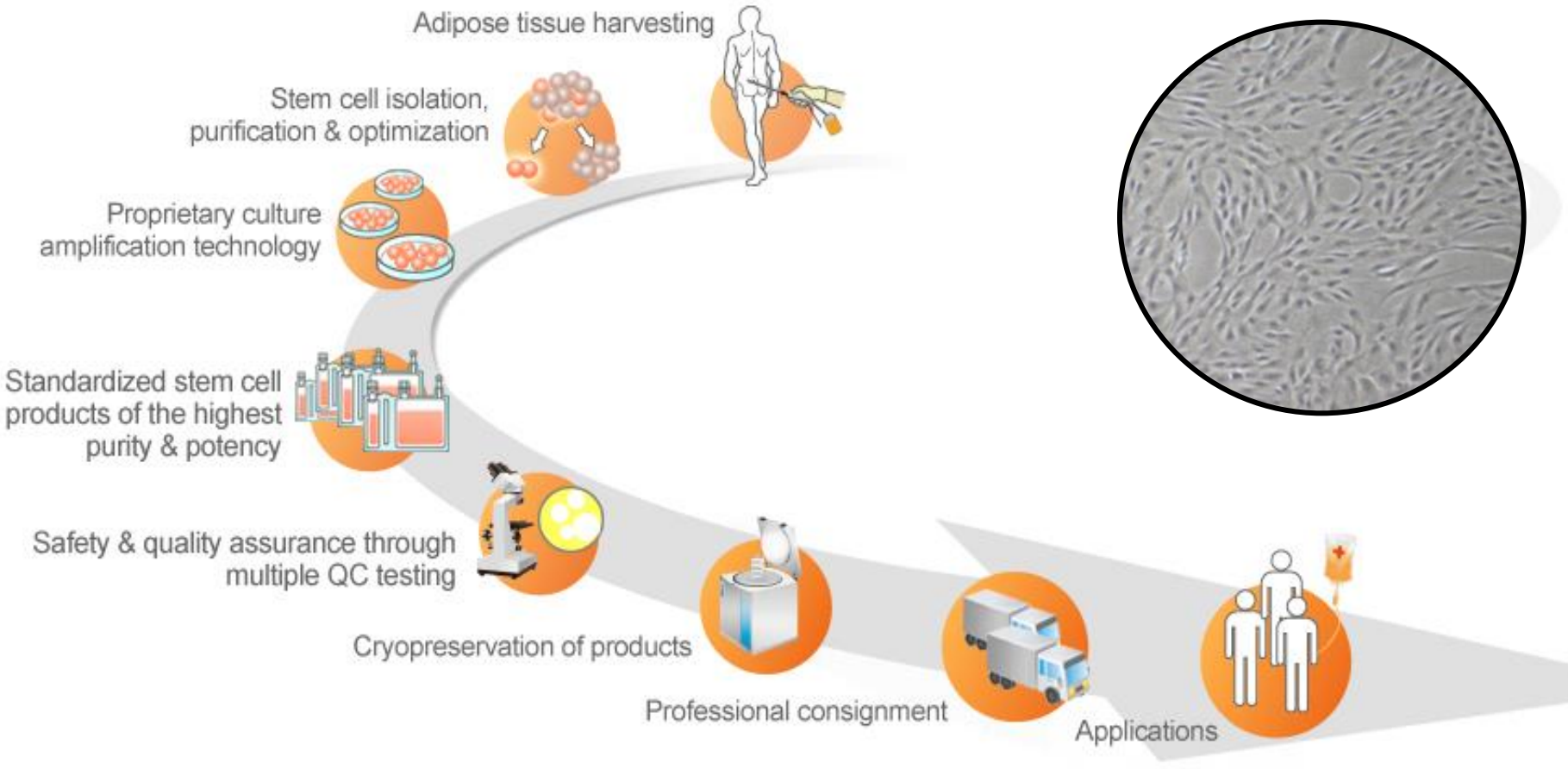
台大神經部腦中風加護病房主任鄭建興表示，很多國家都使用不同來源的幹細胞來進行腦中風試驗，但成效可能會依急性、慢性腦中風的不同，或患者病變狀況而有所差異。這次林欣榮的試驗看起來有得到一些效果，但要推廣到一般治療，恐怕還有很大一段距離。

馬偕醫院癌症中心主任謝瑞坤表示，人體免疫系統比想像中複雜，加上要操控生長因子並非易事，這也是多數幹細胞研究尚無法直接運用於臨床的原因，初步臨床結果還需更廣泛試驗，才能確認療效。

仲恩生醫科技
STEMINENT

Investigational product - Stemchymal®

(脂肪間葉幹細胞)



The Design of the Phase I Clinical Trial
（第一期臨床試驗的設計）(NCT Number: NCT01649687)

➢ Objectives:

- Primary: To ascertain the **safety** of intravenously infused allogeneic ADMSCs.
- Secondary: To evaluate the **efficacy** of intravenously infused ADMSCs for treatment of cerebellar ataxias.

➢ Sample Size:

6~8 qualified subjects (with either SCA3 or MSA-C)

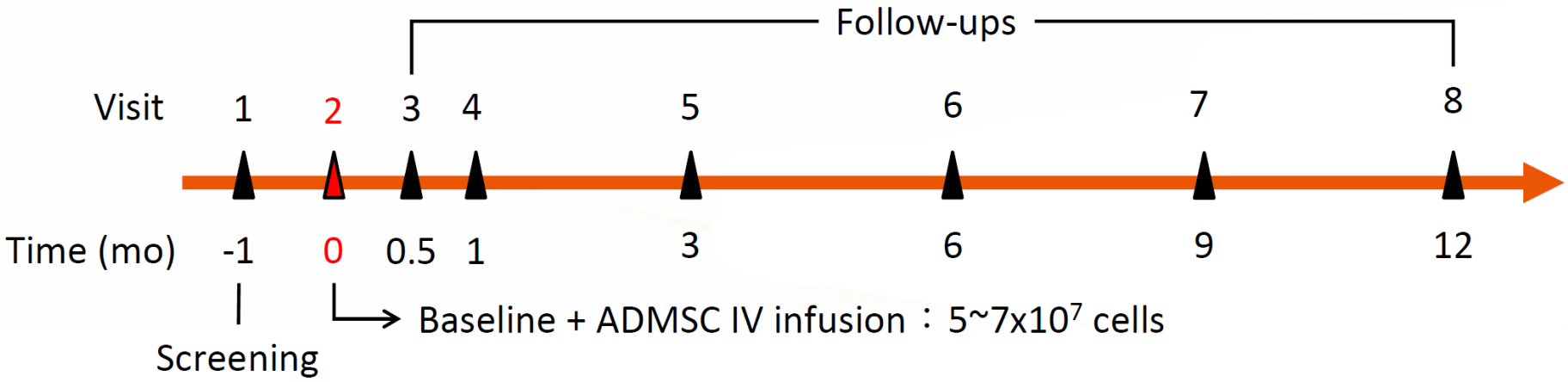
➢ Outcome Measures:

- SARA, SOT, MRS, PET

Subject Demographics

Subject	Age/ Gender	Diagnosis	CAG repeats	Age at onset (years)	Disease duration (years)	SARA at baseline
#1	66/M	SCA3	27/69	59	7	13
#2	52/F	MSA-C	14/26	50	3	13.5
#3	62/F	SCA3	28/71	55	7	13.5
#4	21/F	SCA3	27/79	16	5	12
#5	51/F	SCA3	14/74	38	13	16
#6	48/M	SCA3	26/70	43	5	12.5
#7	42/F	SCA3	14/73	31	11	13.5

Timeline


Follow-ups
Visit
1
2
3
4
5
6
7
8
Time (mo)
-1
0
0.5
1
3
6
9
12
Baseline + ADMSC IV infusion：5~7x10^7 cells
Screening

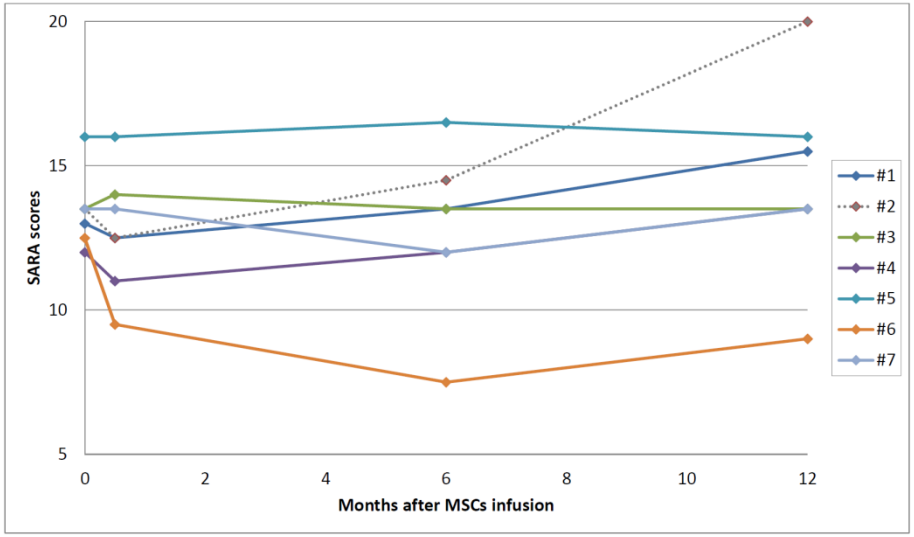
Safety - AEs

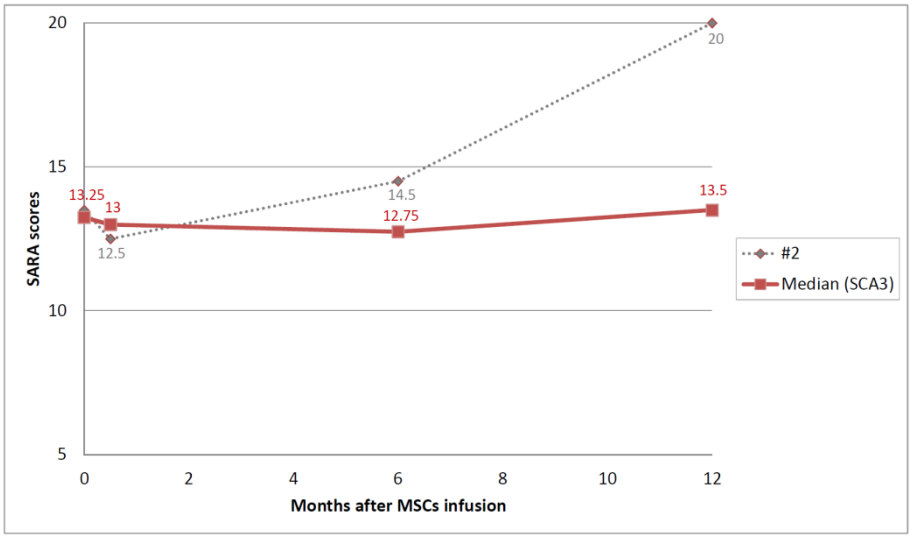
- **AEs occurred during the one-year follow-up**

Subject	SAE/ AE	Months after ADMSC infusion	Event	Outcome*
#2 (MSA-C)	SAE	1.3	Stiffness (neck & hands), dysphagia & drooling of saliva	1
	AE	8	Worsening of constipation	1
	AE	8	Worsening of rigidity	1
#3	AE	1.5	Senile cataract	1
	AE	1.5	Chronic angle-closure glaucoma	2
	AE	7	Fall injury (leg)	1
	AE	10.5	Diarrhea	1
#6	AE	1.3	Skin eruption	1
	AE	6.5	Diabetes mellitus	2
#7	AE	11	Fall injury (face)	1

* 1: resolved, 2: not resolved

Efficacy - the longitudinal changes in SARA scores





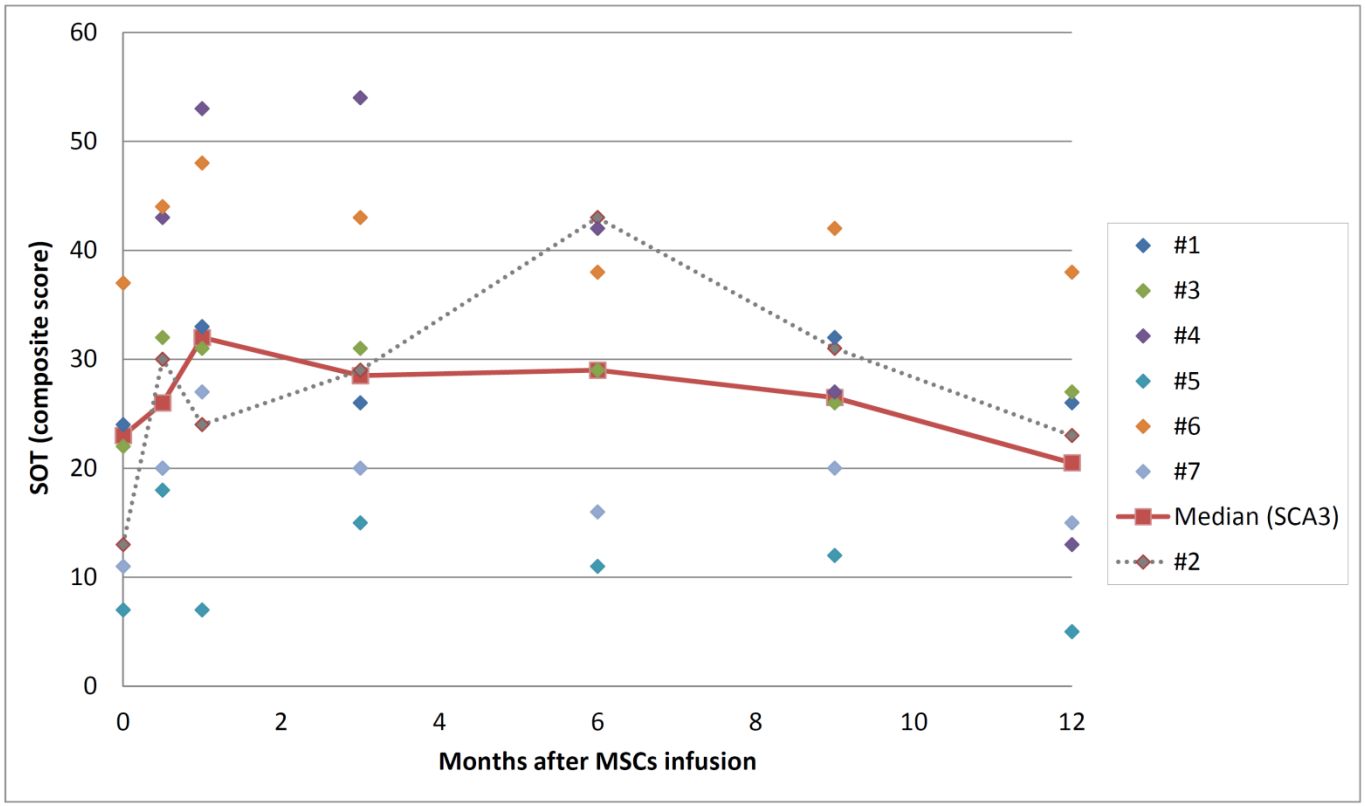
	0.5 M	6 M	12 M
Change from baseline Median (Q1, Q3)	**-0.25** (-1, 0)	**0** (-1.5, 0.5)	**0** (0, 1.5)

Natural history of disease progression - SARA (*Mov Disord. 2011 Sep;26(11):2081-7*)

TABLE 3. Disease progression[a] prospectively measured with SARA in the study populations

	SCA2	SCA3	SCA6	SCA17	MSA-C	Statistics[b]	GSS
No. of patients	11	45	9	5	45		4
Total score (points/y)	2.88 ± 2.32	3.00 ± 1.52*	2.04 ± 0.76*	4.50 ± 2.22	4.62 ± 2.28	<0.001	31.04 ± 12.10[c]

Efficacy - the longitudinal changes in SOT

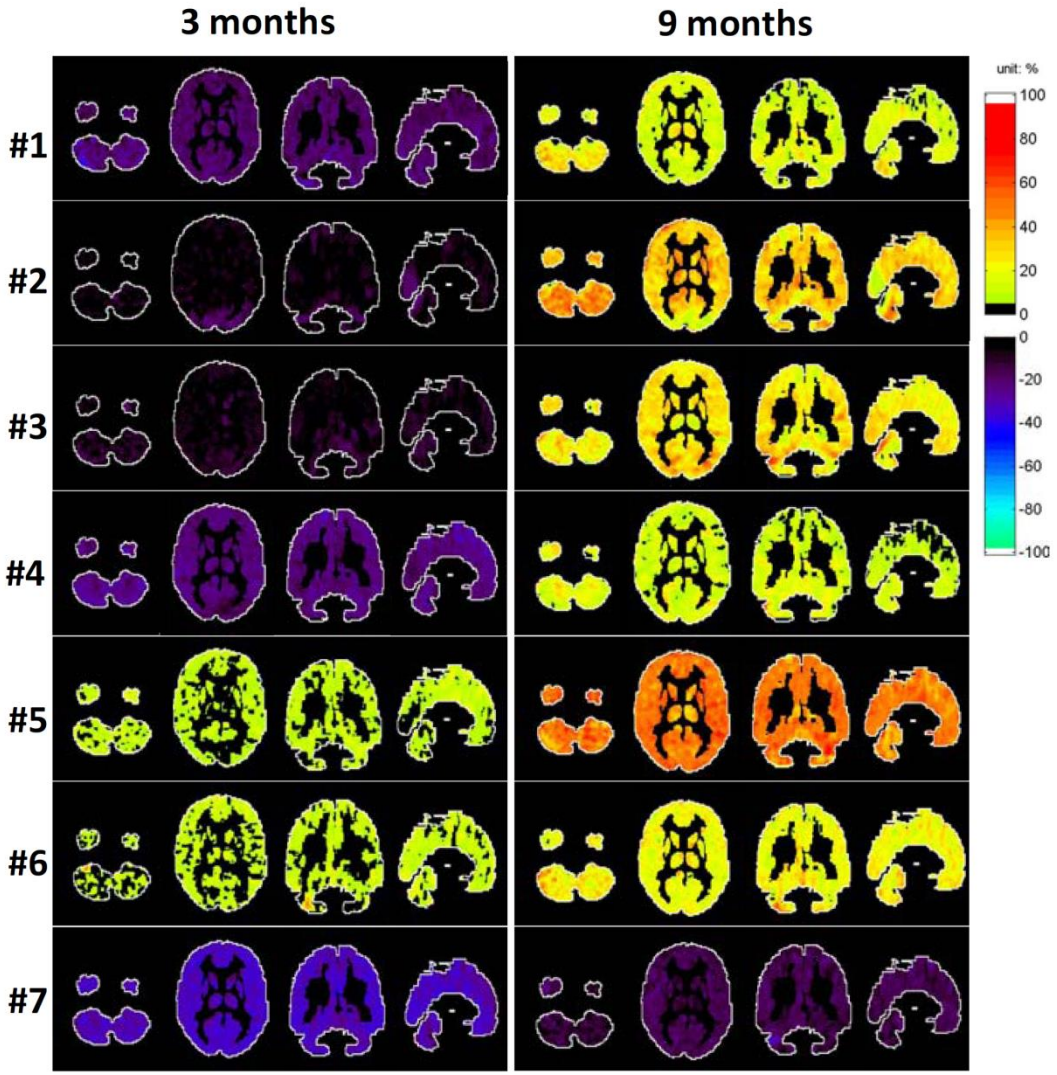


	0.5 M	1 M	3 M	6 M	9 M	12 M
Change from baseline Median (Q1, Q3)	**8** (6, 10)	**10** (9, 16)	**8.5** * (6, 9)	**5** * (4, 5)	**5** (4, 8)	**1.5** (-2, 4)

* $p < 0.05$

Efficacy - PET

- The parametric ratio images of ^{18}F-FDG PET at three and nine months after ADMSC infusion

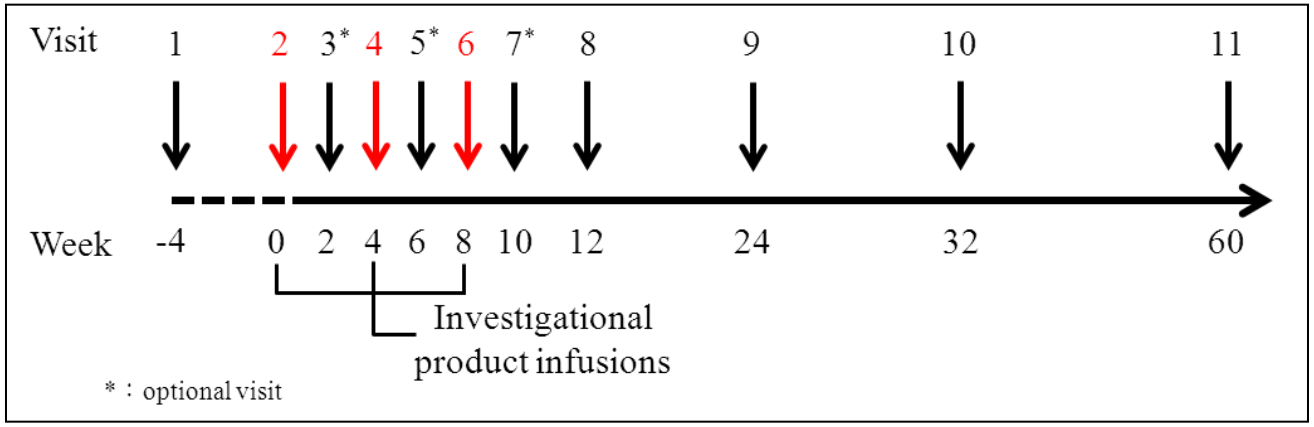


第一期臨床試驗成果之檢討

1. 人數太少！
2. 追蹤時間不夠久！
3. 缺少對照組!
4. 劑量是否足夠?
5. 評估方式不夠多元！
6. 安全性及治療效果證據力不夠強.
7. 若真有效,機制為何?

The Design of the Upcoming Phase II Clinical Trial
（第二期臨床試驗的設計）

- Stratified randomization, double-blind, placebo-controlled
- Estimated enrollment : 5~6 donors/ 60 subjects
- Investigational product :
  - Stemchymal® : 7 x 10^7 MSCs / infusion
  - Placebo : vehicle only
- Treatment regimen: 3 infusions at 4-week interval




企鵝家族
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協會介紹 | 小腦萎縮症 | 家族專區 | 最新消息 | 聯絡資訊 | 討論區
回首頁
社團法人中華小腦萎縮症病友協會
小腦萎縮症
認識疾病 GO
自我診斷 GO
產前篩檢 GO
醫藥處理 GO
運動復健 GO
醫師學者專欄 GO
論文研究 GO
相關連結 GO
新聞專區
季刊下載
企鵝家族
生命的傳承 不再是悲劇的延伸
提升人性安養照顧 是對生命的愛與尊重
最新消息
more.. GO
【琴聲傳遞關懷、樂聲分享大愛】~ 「陳瑞斌鋼琴三重奏慈善音樂會」~ 2007/4/12
熱門商品
test1
家族專區
社會福利
人性安養
相關法令
保險規劃
心情故事
常見問題

台灣的脊髓小腦運動失調症病友會
（企鵝家族）

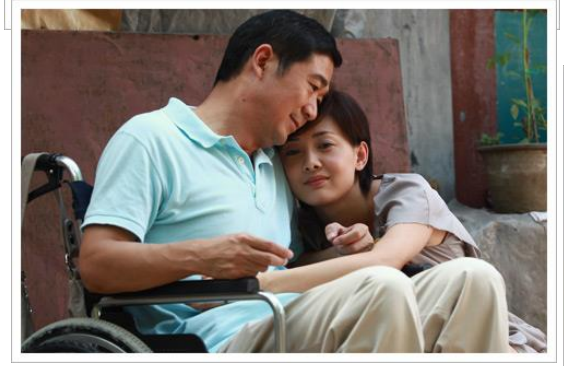
Equivalent to 香港小腦萎縮症協會, NAF, Euro-Ataxia---.

http://www.youtube.com/watch?v=atscBa9-kCE
http://www.youtube.com/watch?v=qwG68WCONOc&feature=fvwrel

http://www.youtube.com/watch?v=R6aOvsPbleQ

http://www.youtube.com/watch?v=B5otiufeg50&feature=related


养父
亲情史诗剧




我的媽媽是爸爸
6/20(一)起
週一至週四晚間八點
CH39 中天娛樂台
戲劇大腕 張國立 陪您一起感動

SRCA
2018

MAY
24-26

TAIPEI
TAIWAN

The 9th International Symposium of the
Society for Research on the Cerebellum and Ataxias

SRCA 2018

The 9th International Symposium of the Society for Research on the Cerebellum and Ataxias

MAY 24-26, 2018

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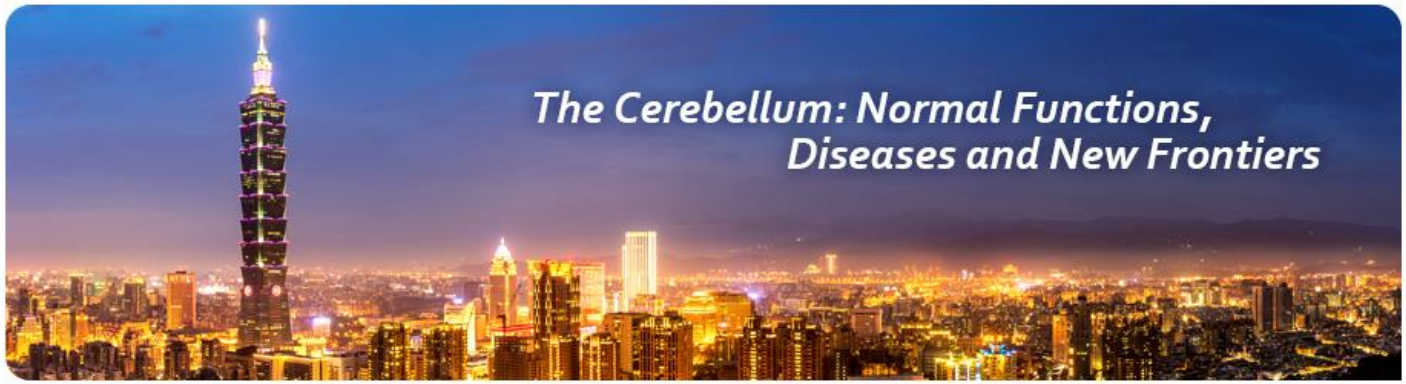
Welcome Message | Committee | General Information | Program | Abstract | Registration | Sponsors | Accommodation



On-line Registration

Online Submission

Hotel Information

News

September 16, 2017 SRCA 2018 Official Website is Launched!

Important Dates

Last Day for Cancellation of Registration with 75% Refund	October 28, 2016
Abstract Submission Opens	November 1, 2016
Registration System Opens	December 15, 2016
Deadline for Abstract Submission	January 15, 2017
Notification of Proposal & Abstract Audit Results	January 31, 2017
Deadline for Early Registration	February 28, 2017
Deadline for Pre-registration	April 15, 2017

THANK YOU ALL!

bwsoong@ym.edu.tw