School of Life Sciences
The Chinese University of Hong Kong

生命科學學院

「中大跨學科研究團隊為罕見神經系統疾病研發新藥物」記者會

"CUHK Inter-disciplinary Research Team Finds Novel Drug Candidate for Rare Neurological Diseases" Press Conference

February 23, 2016 (Tuesday)

Laboratory of Drosophila Research
CUHK
Est 2002

研究團隊 The Research Team

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香港小腦萎縮症協會 Spinocerebellar Ataxia Association

資助單位 Supporting Units

香港中文大學 The Chinse University of Hong Kong
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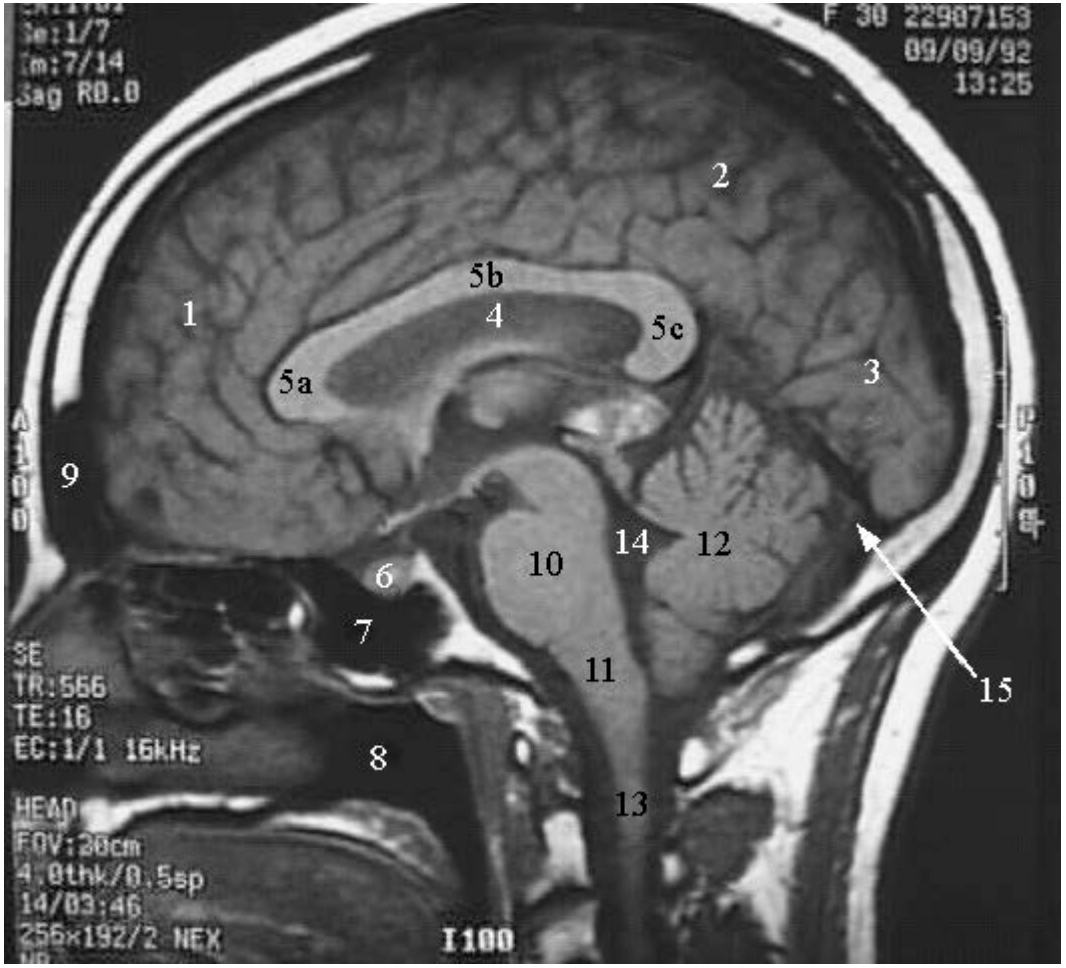
周大福慈善基金 Chow Tai Fook Charity Foundation

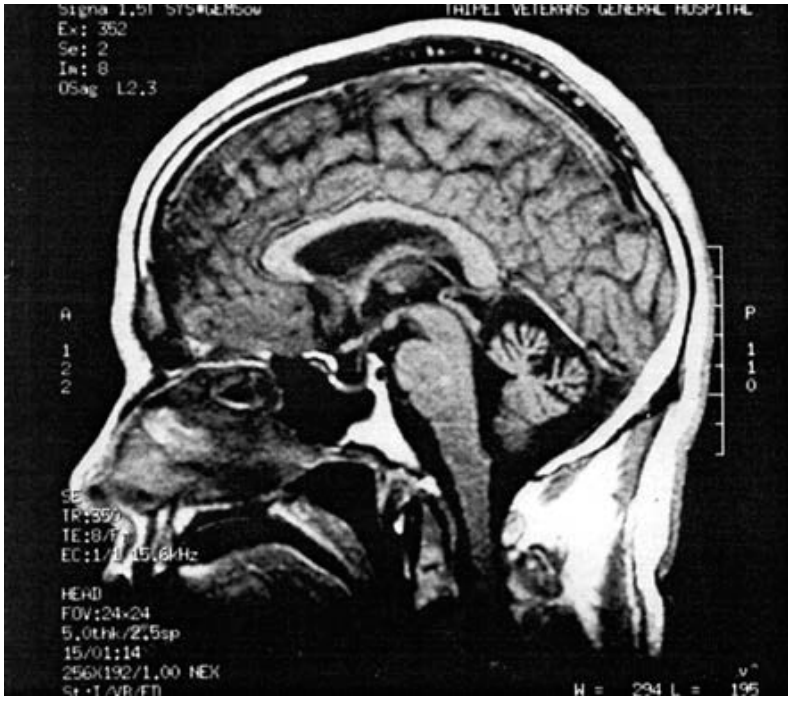
小腦與小腦萎縮症

Cerebellum and Spinocerebellar Ataxia

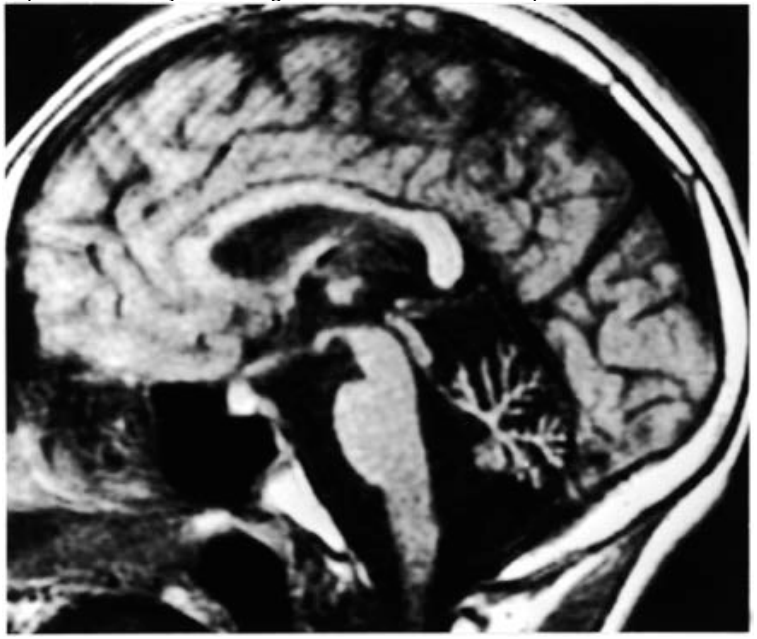


http://www.med.umich.edu/lrc/coursepages/m1/anatomy2010/html/radiology/xray/head_mri_midline.html

12. Cerebellum (小腦)



http://brain.oxfordjournals.org/content/126/6/1293/F2.expansion



http://hmg.oxfordjournals.org/content/8/11/2047.long

小腦萎縮症 Spinocerecbellar Ataxias

- 醫學名稱是脊髓小腦運動失調症 。
  Spinocerebellar Ataxias (SCAs)

- 患者的小腦、腦幹和脊髓由於基因變異，產生退化性萎縮 。
  A group of genetic disorder that causes deterioration of cerebellum

- 一般患者在成年期發病，發病年齡大部份從二十至四十歲開始 。
  Adult onset, age of onset: ~20-40 years of age

症狀 Symptoms

走路時步履不穩，肢體搖晃
靜止站立時，軀幹失去平衡，身體會前後搖晃 。

Walking gait disturbance, limb shaking
When standing still, the trunk out of balance, the body rocks back and forth.

http://dx.doi.org/10.14802/jmd.15006 / J Mov Disord 2015;8(2):67-75
pISSN 2005-940X / eISSN 2093-4939

多聚谷氨酰胺小腦萎縮症

Polyglutamine Spinocerebellar ataxias (polyQ SCAs)

SCA3是最常見的polyQ SCA類型

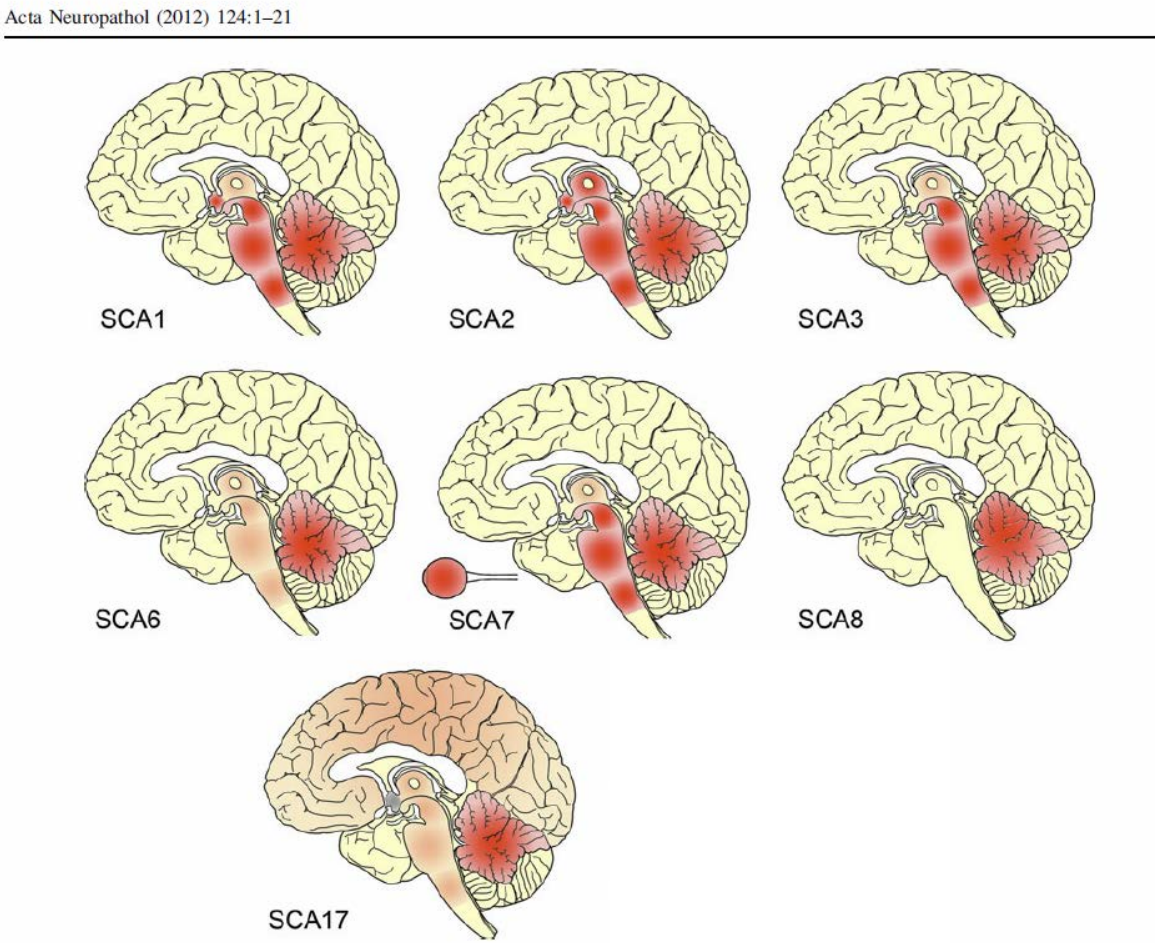
SCA3 is the most common type of polyQ SCA.

Table 1. SCA: distinguishing features and molecular genetics

Disorder	Distinguishing features	Gene/locus	Protein or types of mutation
SCA1	Pyramidal signs, peripheral neuropathy	*ATXN1*	CAG repeat, ataxin-1
SCA2	Slow saccades; less often myoclonus, areflexia	*ATXN2*	CAG repeat, ataxin-2
SCA3	Slow saccades, persistent stare, extrapyramidal signs, peripheral neuropathy	*ATXN3*	CAG repeat, ataxin-3 (MJD1)
SCA4	Sensory neuropathy	16q22.1	
SCA5	Early onset but slow progression	*SPTBN2*	Beta III spectrin
SCA6	May have very late onset, mild, may lack family history, nystagmus	*CACNA1A*	CAG repeat, alpha 1A P/Q calcium channel subunit
SCA7	Macular degeneration	*ATXN7*	CAG repeat, ataxin-7
SCA8	Mild disease	*ATXN8/ATXN8OS*	CTG*CAG repeat
SCA9	Not assigned		
SCA10	Generalized or complex partial seizures	*ATXN10*	ATTCT repeat, ataxin-10
SCA11	Mild disease	*TTBK2*	Tau tubulin kinase-2
SCA12	Tremor, dementia	*PPP2R2B*	CAG repeat in 5′ region, protein phosphatase 2A
SCA13	Mental retardation	*KCNC3*	Voltage gated potassium channel KCNC3
SCA14	Intermittent myoclonus with early onset disease	*PRKCG*	Protein kinase C gamma
SCA15/16	Slowly progressive	*ITPR1*	Inositol 1,4,5-triphosphate receptor 1
SCA17	Gait ataxia, dementia	*TBP*	CAG repeats, TATA binding protein
SCA18	Pyramidal signs, weakness, sensory axonal neuropathy	7q22-q32	
SCA19/22	Predominantly cerebellar syndrome, sometimes with cognitive impairment or myoclonus	*KCND3*	Voltage-gated potassium channel Kv4.3
SCA20	Palatal tremor and dysphonia	11q12	
SCA21	Extrapyramidal signs	7p21.3-p15.1	
SCA23	Distal sensory deficits	*PDYN*	Prodynorphin
SCA24	Recessive inheritance; redesignated as SCAR4	1p36	
SCA25	Sensory neuropathy, facial tics, gastrointestinal symptoms	2p21-p13	
SCA26	Pure cerebellar ataxia	19p13.3	
SCA27	Cognitive impairment	*FGF14*	Fibroblast growth factor 14
SCA28	Ophthalmoparesis and ptosis	*AFG3L2*	Catalytic subunit of the mitochondrial AAA protease
SCA29	Early onset, non-progressive ataxia; may be an allelic variant of SCA15	3p26	
SCA30	Slowly progressive, relatively pure ataxia	4q34.3-q35.1	
SCA31	Decreased muscle tone	*BEAN*	(TGGAA) n repeat
SCA32	Cognitive impairment, affected males with azoospermia and testicular atrophy	7q32-q33	
SCA33	Not assigned		
SCA34	Skin lesions consisting of papulosquamous erythematous ichthyosiform plaques	6p12.3-q16.2	
SCA35	Late onset, slowly progressive gait and limb ataxia	*TGM6*	Transglutaminase 6
SCA36	Late onset, truncal ataxia, dysarthria, variable motor neuron disease, and sensorineural hearing loss	*NOP56*	GGCCTG repeat
SCA37	Late onset, falls, dysarthria, clumsiness, abnormal vertical eye movements	1p32	
SCA38	Adult onset, axonal neuropathy	*ELOVL5*	
SCA40	Adult onset, brisk reflexed, spasticity	*CCDC88C*	

SCA: spinocerebellar ataxias, CAG: coronary angiography.

多聚谷氨酰胺小腦萎縮症所影響的區域
Affected brain regions in polyglutamine spinocerebellar ataxias



如何開展此項研發工作？
How this investigation was initiated?

於2012年,我們發現多聚谷氨酰胺小腦萎縮症中的毒性RNA干擾核仁功能。

In 2012, we reported that polyQ SCAs RNA interfered with nucleolus function.

傳訊及公共關係處

主頁 / 新聞稿 / 傳媒報導 / 活動 / 活動重溫 / 專家名錄 / 資源分享 / 傑出成就 / 統計資料 / 到訪中大
中大傳動

新聞稿

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二零一二年八月九日

中大科學家揭示小腦萎縮症致病通路
為現時無法治癒的神經系統疾病開拓新治療方向

香港中文大學（中大）生命科學學院陳浩然教授帶領其科研團隊揭示了導致小腦萎縮症的「核仁應激信號通路」，為這現時無法治癒的神經系統疾病開拓新的治療方向。研究結果最近刊載於全球權威科學期刊《美國國家科學學院院刊》。

我們發現具毒性的RNA分子會干擾核仁素的功能，阻止細胞核製造核糖體。

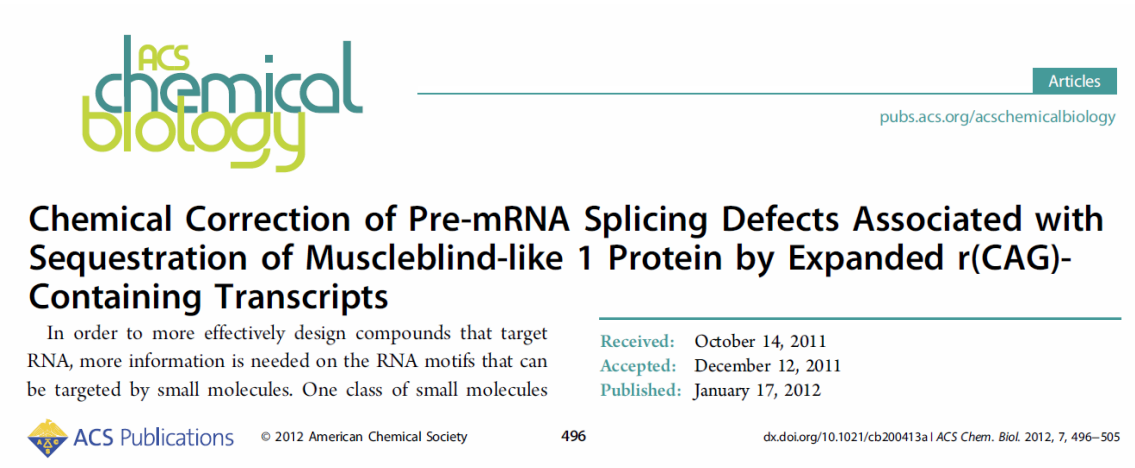
我們決心開發能有效壓制毒性RNA的抑制劑，以抑制神經細胞退化。

Toxic RNA interferes with nucleolin function in polyQ SCAs, disrupting ribosome synthesis.

We decided to develop inhibitor that can suppress the toxic effect of RNA.

於2012年，當時只有一個polyQ SCA的毒性RNA抑制劑(D6)的報導，而且這研究主要以細胞作研究模型。

In 2012, there was only one polyQ SCA RNA toxicity inhibitor (D6) reported, and this study was solely based on cell-based experimental approach.



ACS chemical biology

Articles

pubs.acs.org/acschemicalbiology

Chemical Correction of Pre-mRNA Splicing Defects Associated with Sequestration of Muscleblind-like 1 Protein by Expanded r(CAG)-Containing Transcripts

In order to more effectively design compounds that target RNA, more information is needed on the RNA motifs that can be targeted by small molecules. One class of small molecules

Received: October 14, 2011
Accepted: December 12, 2011
Published: January 17, 2012

dx.doi.org/10.1021/cb200413a | *ACS Chem. Biol.* 2012, 7, 496–505

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我邀請來自不同學科領域,包括結構生物學,多肽工程技術,材料科學及藥理學的專家,組成跨學科的研究團隊以開發能有效壓制毒性RNA的抑制劑。

I invited experts from different disciplines, including structural biologist, peptide engineer, material scientist and pharmacologist, to form a multi-disciplinary research team with the aim to develop RNA toxicity inhibitors for polyQ SCAs.

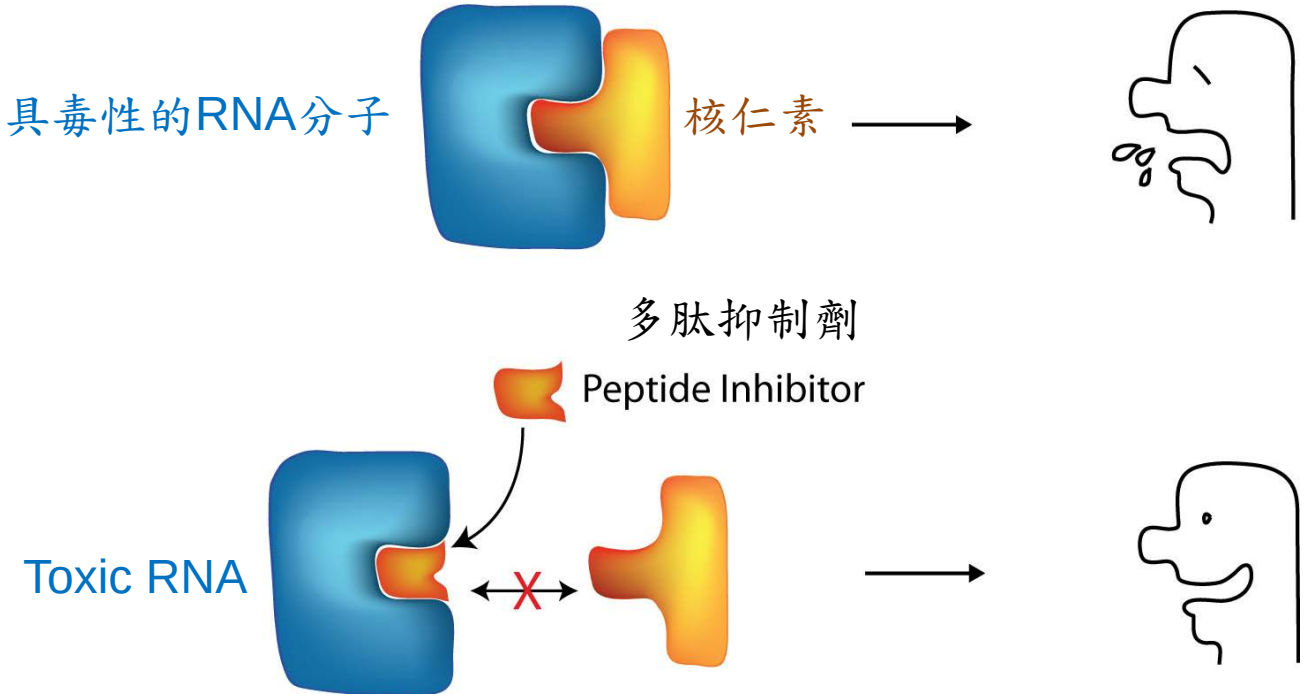
什麼是多肽抑制劑?
What is a Peptide Inhibitor?

- 多肽抑制劑由氨基酸所組成

  Peptide inhibitors are composed of amino acids

多肽抑制劑的作用機理：

Mechanism of peptide inhibitor:



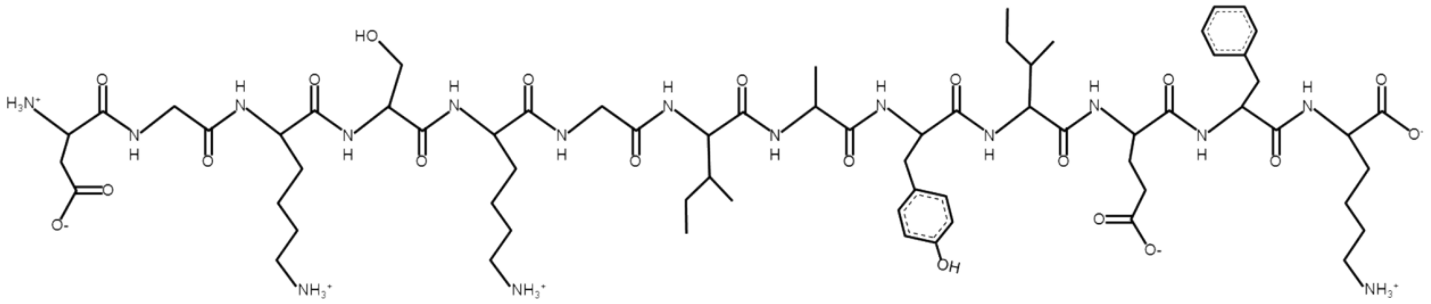
多肽抑制劑的優點 **Advantages of Peptide Inhibitors**

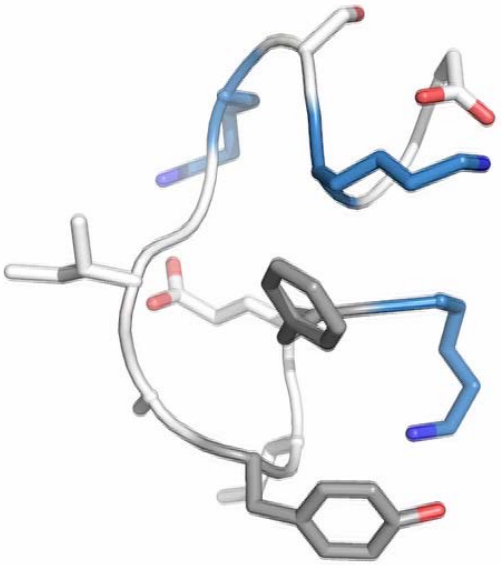
- 高活性 High activity
- 高特異性 High specificity
- 低毒性 Low toxicity
- 不會在器官內積聚 Will not accumulate in organs

減少對患者的副作用

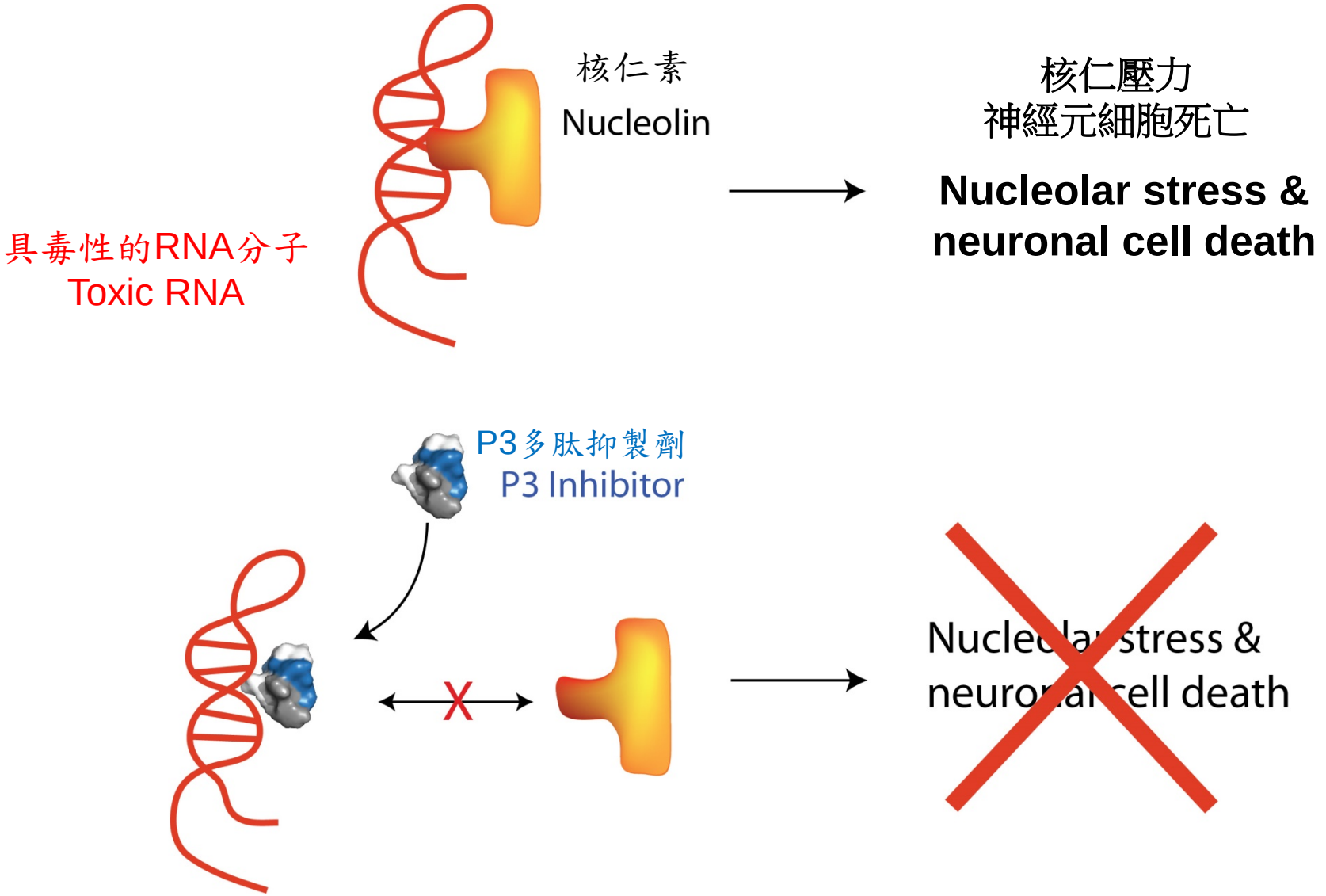
Less side-effects to patients

P3多肽抑制劑的分子結構
Molecular structure of P3 Peptidyic Inhibitor



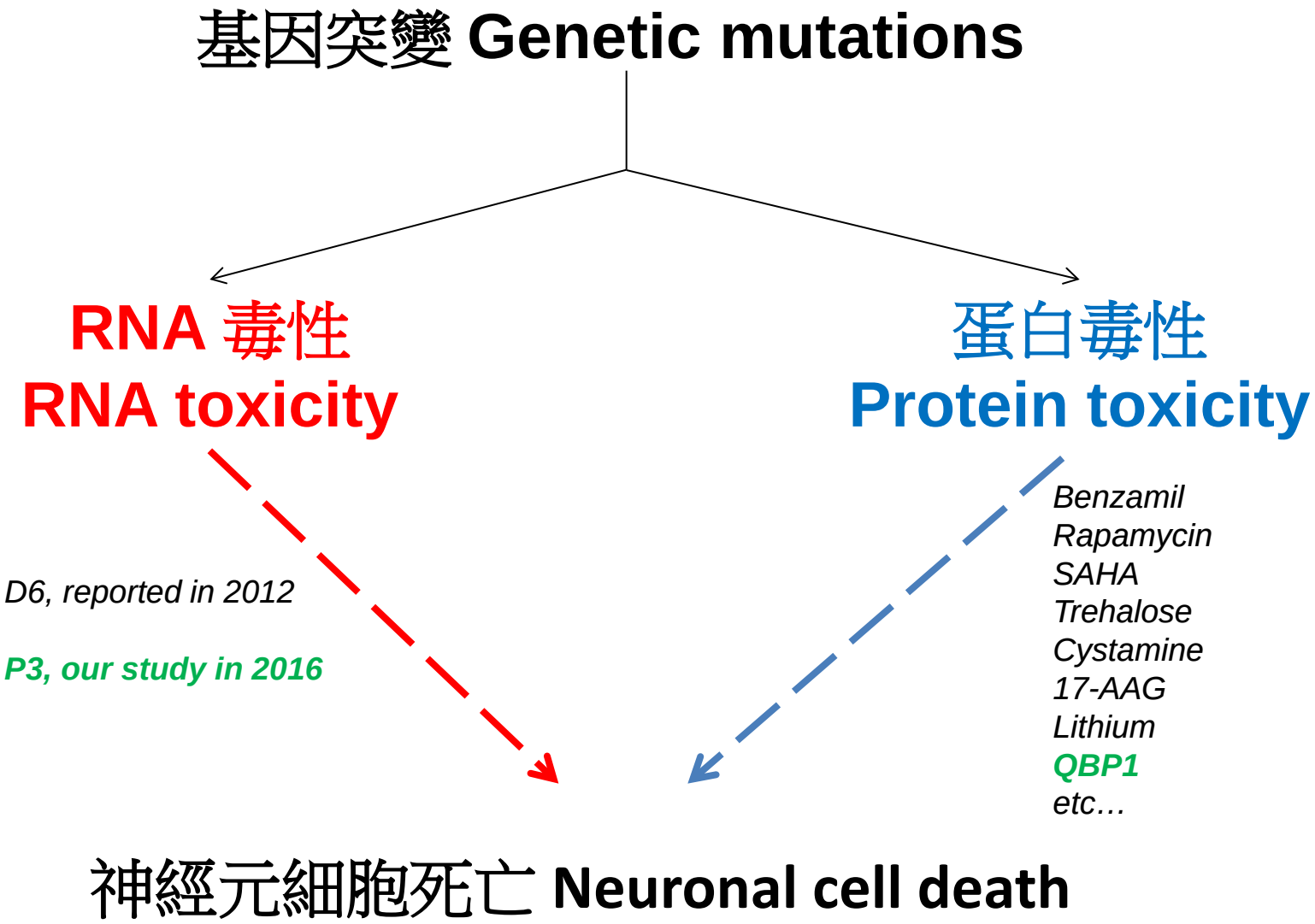


P3的作用機制
Mechanism of action of P3



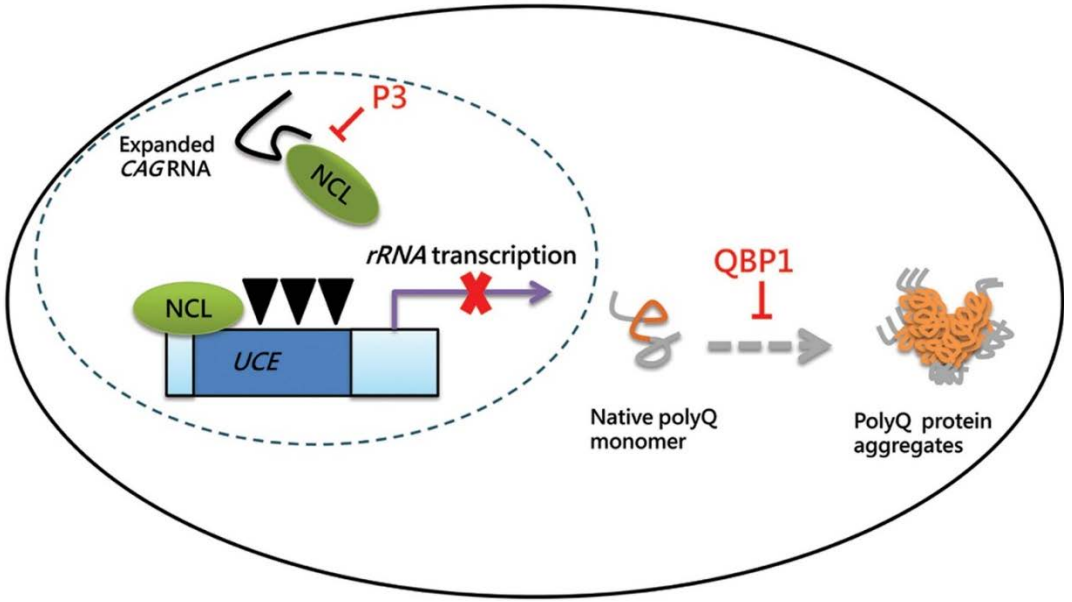
RNA和蛋白質均具有毒性

Both RNA and protein are toxic in polyQ SCAs



基於P3的研究成果，我們發展出一種針對致病RNA及蛋白質而建立的創新的P3/QBP1綜合式polyQ SCA疾病療法。

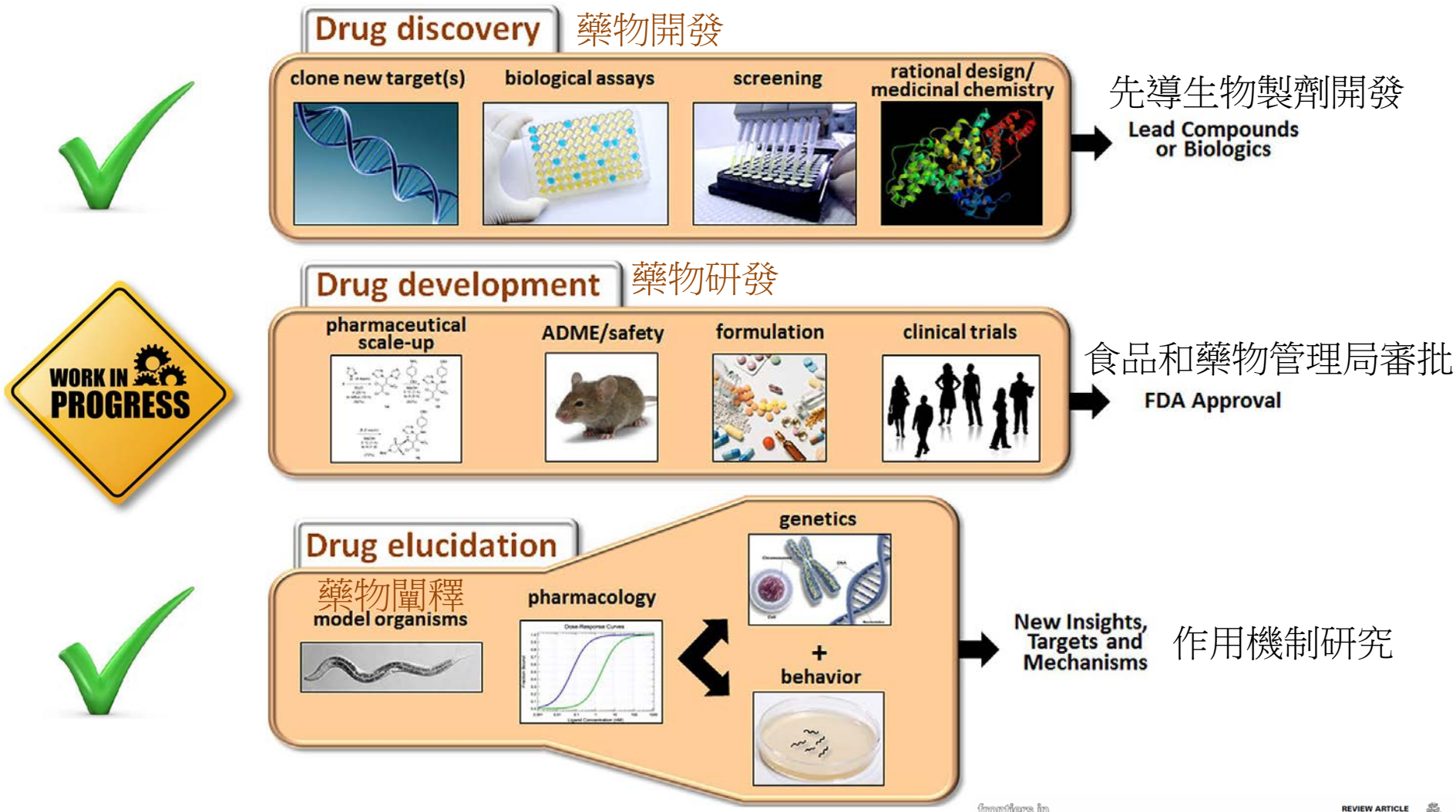
Based on the P3 technology, we further developed an innovative combinatorial treatment prototype, allowing the simultaneous targeting of both the toxic RNA and protein in polyQ SCAs.



RNA和蛋白質均具有毒性

Both RNA and protein are toxic in polyQ SCAs

Drug development progress of P3
P3多肽抑制劑研發的進展



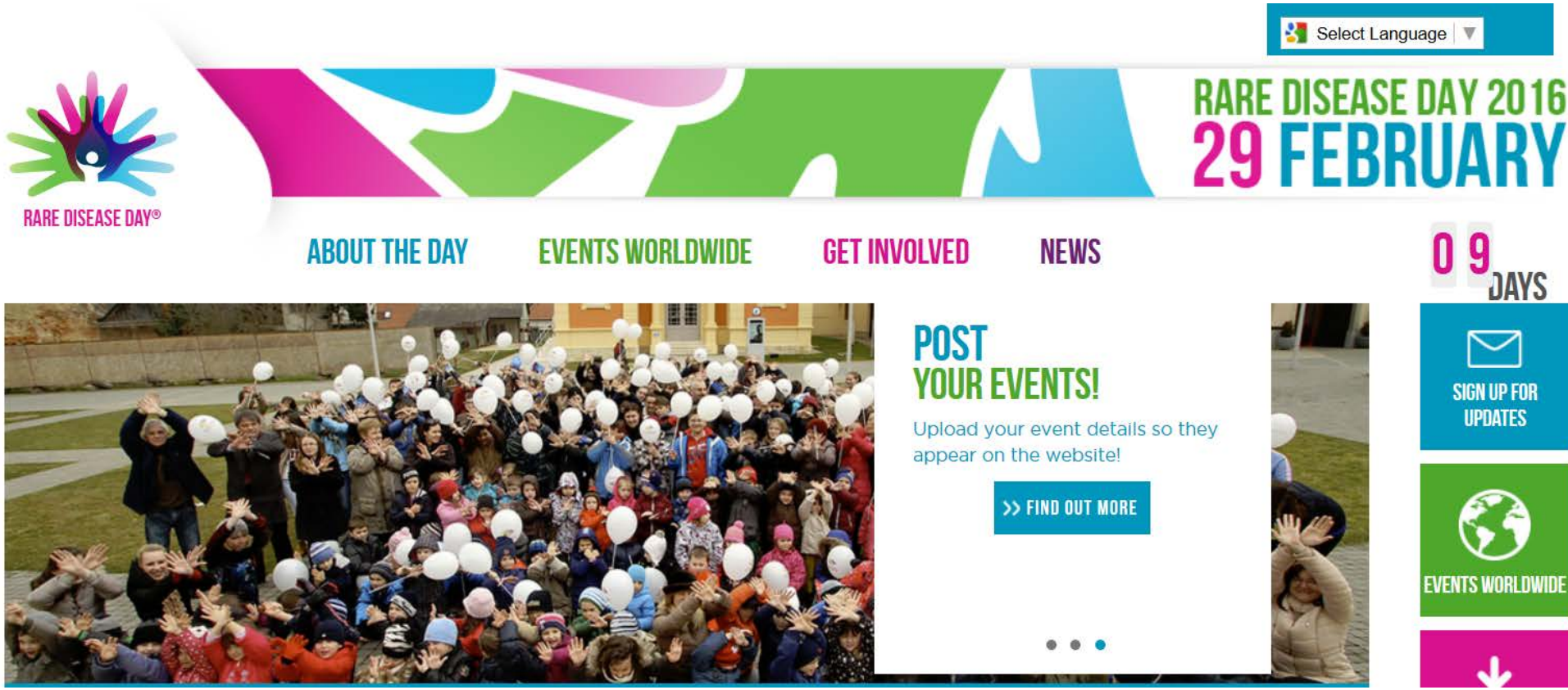
frontiers in PHARMACOLOGY
REVIEW ARTICLE

這項發明如何為病患者帶來幫助？
How this invention can benefit patients in HK and the world?

為生物醫學界及臨床醫生提供了一個嶄新的角度去開發治療的藥物
Provides a new perspective to the biomedical and clinical communities for polyQ SCA therapeutic development.

攝於香港小腦萎縮症協會周年會員大會 (source: http://hkscaa.org/main_photo_album.php?article=55#55)

2016年2月29日為「**國際罕見病日**」，目的是提高世界各地公眾對罕見疾病的關注。



Thank You

謝謝