Number 17, 2012.03.01.

臺灣大學「發育生物學與再生醫學研究中心」電子報

Research Center for Developmental Biology and Regenerative Medicine Newsletter

中心網頁：http://homepage.ntu.edu.tw/~ntucdbrm622/

中心主任：楊偉勛 教授
榮譽主任：鍾正明 院士

總編輯：謝豐舟教授
副總編輯：吳益群教授
編輯顧問：孫以瀚研究員、邱英明教授

編輯幹事： 陳敏慧教授、徐善慧教授、謝武勳副教授、
黃彥華副教授、李士傑副教授、黃敏銓副教授、
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王弘毅助理教授、劉逸軒助理教授、陳佑宗助理教授、
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鄭乃禎醫師、鄭暉騰醫師、陳沛隆醫師、顏伶汝副研究員

美編製作：劉麗芳
發行日期：**2012年 03月 01 日**

本次主題

1. 活動預告

   (1) 2012.03.02-專題演講

   台大生物化學暨分子生物學研究所/游偉絢助理教授

   (2) 2012.03.19-專題演講

   中研院分子生物研究所/簡正鼎研究員

   (3) 2012年- 台大杜鵑花節藝術祭

   2012.03.9-03.21【榮格與他的小三 vs 佛洛依德】舞台劇

   (4) 2012.3.9-3.25 -追求真實的筆尖

   (5)2012.06.27-06.30-第五屆東亞線蟲會議

   5th East Asia *C. elegans* Meeting

2. 鍾正明院士回台工作照片

3. 腦科學重大突破—清華大學發現儲存長期記憶的腦細胞

   清華大學/江安世教授

   CURRICULUM VITAE/Ann-Shyn Chiang

4. **2011.02.15-專題演講**

   Calorie restriction and aging: the role of neurons

   王培育 助理教授/政治大學神經科學研究所

活動預告:

演講人 ：游偉絢助理教授
台大生物化學暨分子生 物學研究所

主　題：

Orchestrate the nucleus matrix proteins by Matrilysin(MMP-7;PUMP-1) involved in tumorigenesis

時　間：　2012年03月02日，星期五，
12:30-1:30pm

地　點：　台大醫學院202教室

研究專長與學經歷:

http://www.mc.ntu.edu.tw/department/ibmb/chinese/teacher/YuWeiHsuan/YuWH_set.htm

活動預告:

演講人：簡正鼎研究員
中研院分子生物研究所

主　題：

Neuronal dendrites and synapses: the make and the use of them.

時　間：　2012年03月19日，星期一，
10:30-11:30Am

地　點：　台大醫學院202教室

研究方向與經歷:
http://www.imb.sinica.edu.tw/~ctchien/index_c.html

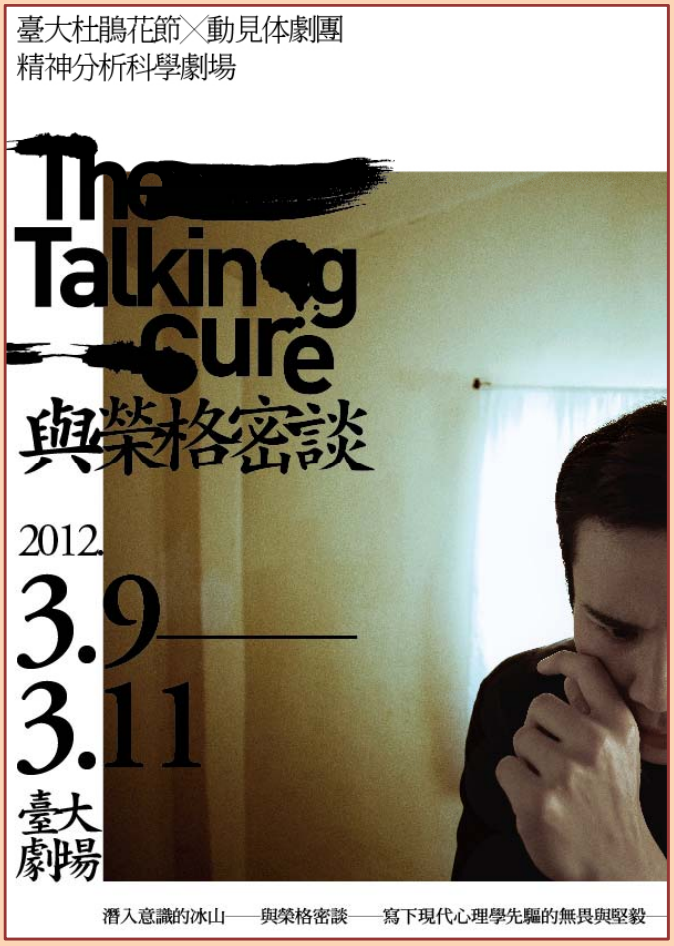
活動預告:

2012年
台大杜鵑花節藝術祭

謝豐舟 教授

在中止了兩年之後，**2012**年的台大杜鵑花節又能再次以「藝術」與「知識」結合的理念展開，令人格外振奮。在經費拮據之下，李校長仍然批准了這次預算，他的理由是因為「這個活動有延續性」。除了前兩年的舞台劇之外今年又有一項新嘗試就是科學插畫展。

【榮格與他的小三 vs 佛洛依德】舞台劇



2012年1月17日晚上7點，摸黑走過台大校園到一號館戲劇系的118排練室看“與榮格密談”（The Talking Cure）舞台劇的第四次完整排練。雖然之前台大杜鵑花節已經上過「哥本哈根」與「達爾文之後」兩齣舞台劇，但這次却是我第一次去看排練，實地體驗了一齣舞台劇準備的過程。

在中止了兩年之後，2012年的台大杜鵑花節又能再次以「藝術」與「知識」結合的理念上演舞台劇，令人格外振奮。在經費拮據之下，李校長仍然批准了這次演出的預算，他的理由是因為「這個活動有延續性」，也就是說從2008年的「哥本哈根」，2009年的「達爾文之後」兩齣戲下來，這個活動已經指出提升台大校園人文氣息的一條有效途徑，值得投入資源加以延續。今年再度演出「與榮格密談」之後，每年三月的杜鵑花節，台灣大學上演舞台劇的傳承將更為成形。相信若能再延續個二、三年或三、五年，這個活動會像行之百年的「牛津劍橋划船賽」一樣成為一個「傳統」，成為台灣大學的一部份。

活動要能長期延續，一定要有一個主體來承擔。我與戲劇系王怡美主任討論，王主任肯定地承諾，只要經費沒問題，戲劇系願意來主辦這個活動。我們也談到既然已經累積了三年的經驗，也許可以用這三次演出為題材，進行一個學術研討會來討論相關的議題，例如此種演出對校園與社會的影響，劇本如何選擇，將來如何永續經營----。

今年演出的**The Talking Cure**是以「心理分析」為經，佛洛依德與榮格的互動為緯。以現代的流行用語，本劇的劇名也許可以用「榮格與他的小三vs佛洛依德 」更貼近劇情，更為聳動。**The Talking Cure**是編劇克里斯多夫漢普頓（**Christopher Hampton**）在**2003**年改編約翰卡爾著作《最危險的療程》（**John Kerr, A Most Dangerous Method: the Story of Jung, Freud, and Sabina Spielrein**）的舞台劇作，敘述心理學巨擘榮格與其女病人莎賓娜兩人間的複雜關係。當時已婚的榮格為莎賓娜治療精神疾病，榮格在她身上常是驗證精神分析始祖佛洛伊德所提出的新療法──「談話治療」，發現受良好教育的莎賓娜有受虐傾向與性成癮的問題，在多年的治療過程中，他們的關係從醫病轉變為朋友與師徒，榮格更漸漸為她聰穎卻複雜的心靈所吸引，兩人曖昧之情最終一發不可收拾，痊癒出院，正攻讀心理學的莎賓娜於是和榮格陷入熱戀。也因為莎賓娜的研究案例，榮格才有機會正式結識佛洛伊德，但他與莎賓娜之間複雜的關係卻也間接導致師徒兩人關係決裂，分道揚鑣。

巧合的是由**The Talking Cure** 劇本改編的電影「危險療程」也正在台北上演。

「心理分析」在目前似乎是過時的東西，不過「潛意識」的存在大家都可以接受，「夢」雖然是每個人的親身體驗但這方面的進一步瞭解却仍未見。近年來，腦神經科學蓬勃發展，正是以現代腦神經科學方法來檢視心理分析所主張之「潛意識，夢，自我」的大好時機。看來，**2012**杜鵑花節演出**The Talking Cure**，也像**2008**年的「哥本哈根」以及**2009**年的「達爾文之後」一般，具有深刻的時代意義。

活動預告:

「追求眞實的筆尖」

格雷琴・凱・哈伯特(Gretchen Kai Halpert)的科學插畫展

展覽時間: **2012.3.9-3.25 10:00-17:00**
展覽地點:臺大校本部，總圖書館**1F**多功能展覽廳
系列活動:

2012.3.9 10:00 開幕茶會，臺大總圖書館 **(自由入場)**
14:30 主題演講，臺大總圖書館國際會議廳
主題：什麼是科學插畫？
"What Is Scientific Illustration? "
講者：格雷琴・凱・哈伯特
需線上報名：**http://ctld.ntu.edu.tw/fd/reg**

2012.3.14 18:30 科學插畫專題演講
醫學院基礎醫學大樓 **102**講堂 **(**自由入場**)**

●預約一場導覽：請來信**hsiehningwang@ntu.edu.tw**
或洽**(02)3366-4782**
以上活動皆為免費活動，參加並能獲得插畫紀念卡片！

●地址與交通：
臺大校本部：臺北市羅斯福路四段**1**號（捷運公館站**3**號出口）
臺大醫學院基礎醫學大樓：臺北市中正區仁愛路**1**段**1**號
（捷運臺大醫院站**2**號出口）

●活動網址：**http://arts.ntu.edu.tw/activity/view/sn/40**

活動預告:

展覽小簡：

科學家為什麼要畫畫？他們又會以如何的角度來詮釋？理性與感性能否並存，而寫實度與想像力又能不能相互結合？同時身為藝術家與科學家的格雷琴・凱・哈伯特(Gretchen Kai Halpert)正是要以她的手繪作品帶領我們進入如此的新世界。此次畫展將呈現植物、生物、醫學三個主題的科學插畫作品，藝術家並將親自帶領系列工作坊及講座。原來藝術家是多麼仰賴科學的眼光，注視著自然中的種種細節與表情，而整個世界就是她的畫室，題材唾手可得。

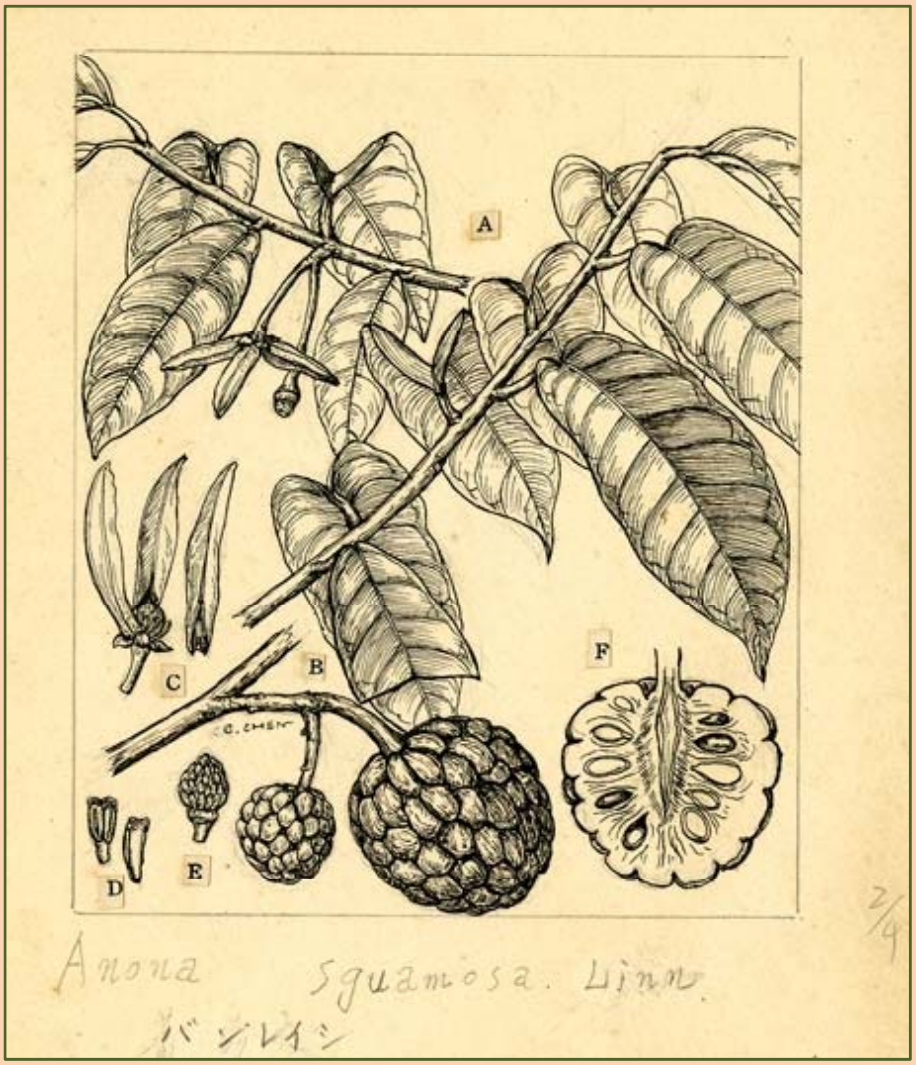
關於展覽：

大自然是科學家的畫室，透過他們精準的筆，我們重新微觀這個世界。

2012.03.09 開始，藝文中心邀請你來參加這場結合科學與藝術的展覽–「追求真實的筆尖」，欣賞格雷琴・凱・哈伯特**(Gretchen Kai Halpert)**的科學插畫。

格雷琴此次受邀**2012**杜鵑花節蒞臨臺大，展出涵蓋植物、生物及醫學三主題的手繪作品，並搭配講座與工作坊，帶領我們進入科學家的「藝」想世界！臺大雖位於臺北大都會，卻連結著豐富的自然資源。美麗校園是我們的寶藏，更是生活的場域，藝術家提醒我們那些經常忽略的景致，能透過真實細膩的記錄保留下來。好風景值得一再回味，藝術其實就發生在動手畫下的那一刻。

The natural history of British quadrupeds/ Edward Donovan
圖片來源：臺大圖書館



Anona squamosa　番荔枝/ 陳建鑄 繪　　圖片來源：臺大圖書館

藝術家簡介：

曾擔任自然科學插畫家協會（GNSI）前主席的格雷琴，學歷背景跨及科學與藝術。她於康乃迪克學院取得植物學學士學位，在紐黑文大學（新港大學）研究所攻讀生物學插畫，並於羅德島設計進修學院取得科學與科技插畫執照。她曾長年於耶魯大學與羅德島醫院擔任研究科學家，同時亦於羅德島設計進修學院、布朗大學、惠敦學院與各家機構開班教授插畫課，目前定居於紐約。這次格雷琴將帶著多件專為此展創作的作品來臺，包含為杜鵑花節而準備的「紐約野生杜鵑」。由於科學插畫在臺灣的發展仍不蓬勃，她期許能透過展覽帶給觀眾不同的啟發。

藝術家網站：www.gretchenhalpert.com

活動預告:

第五屆東亞線蟲會議

5th East Asia *C. elegans* Meeting

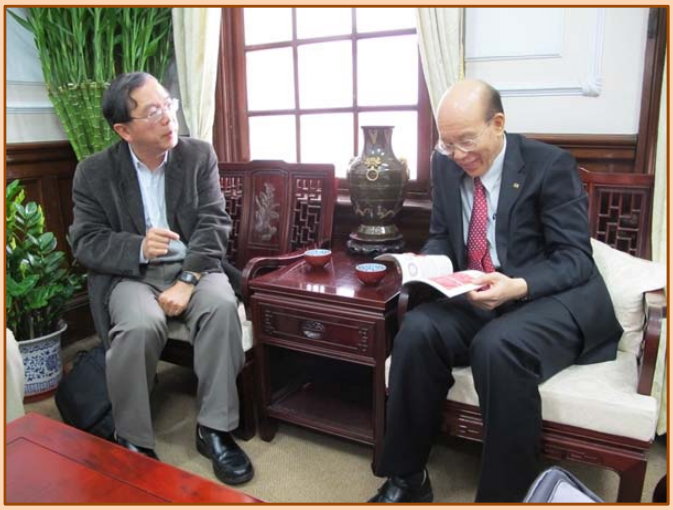
- **時間**:2012.6.27~2012.6.30
- **地點**:劍潭青年活動中心
- **報名方式**:線上報名
- **會議與報名網址**:

http://eawm2012.lifescience.ntu.edu.tw/

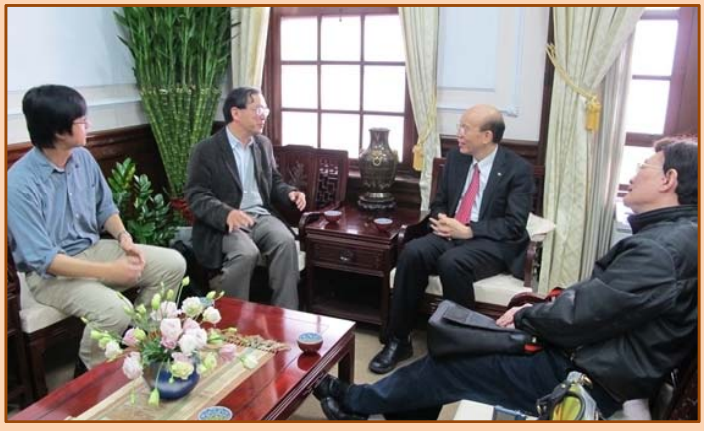
- **聯絡人**:

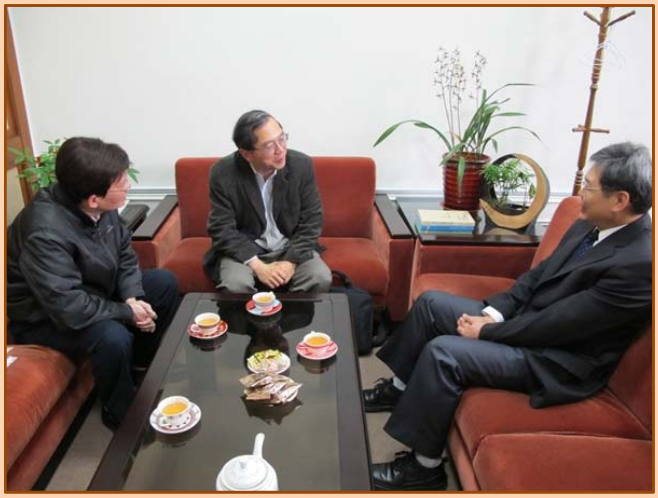
台灣大學 分子與細胞生物學研究所
吳益群老師實驗室 助理 歐惠雯
Tel:(02)3366-2483
Fax:(02)3366-5248

鍾正明院士回台工作照片:



2012年2月14日-鍾院士與校長及副校長討論研究計畫





鍾正明院士回台工作照片:

鍾院士與iEGG研究群作討論研究

狂賀!!

本中心諮詢委員

清華大學
江安世教授

榮登 Science

Visualizing Long-Term Memory Formation in Two Neurons of the *Drosophila Brain*
Chun-Chao Chen, *et al.*
Science ***335, 678 (2012)***

請見隨信附件檔案

腦科學重大突破－清華大學發現儲存長期記憶的腦細胞

February 9, 2012 Hsinchu, Taiwan

國立清華大學江安世教授所帶領的跨領域研究團隊，經過七年的努力，發現長期記憶的形成所需的新生蛋白質，僅發生於來自於腦中少數幾顆神經細胞內。

這項研究成果以長篇完整論文的方式發表在**2012**年**2**月**10**日的**Science**期刊上。

江安世教授表示，「神經科學領域的長期目標，就是瞭解學習與記憶如何在腦中留下印象？一個新的經驗最初發生在哪裡？這些新且不穩定的經驗，又是如何轉化成穩定的長期記憶呢？」。

神經科學家很早就瞭解到，人腦中一個稱為海馬迴的地方，對於各種事件的記憶儲存非常重要。 受到學習經驗的刺激時，海馬迴會提昇大腦皮質區儲存記憶的效率。 然而，人腦內包含了近千億顆神經細胞，想要從中找到哪顆細胞參與哪些工作，無異是大海撈針。

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幸運的是，果蠅許多生存基本的行為（例如學習、記憶、專注力、睡眠、探索環境等等）都與人類非常相似。 而這些行為也透過許多與人類相似的基因調控著。 然而，果蠅腦內的神經網絡卻比人腦簡單太多了。 而且，經過百年來的研究，科學家們在果蠅身上建立了完整且豐富的基因工具。 這些優點也成功地讓科學家，能夠藉利用果蠅來研究許多疾病的分子機制，例如阿茲海默症、帕金森氏症及亨丁頓跳舞症等。

過去的實驗證實，在各種動物身上都可觀察到，長期記憶的形成需要蛋白質生成。 為了確定果蠅腦內哪些地方參與了蛋白質的生成，研究團隊發展了新的基因工具，來阻斷特定神經元的蛋白質生成。 藉此，研究團隊大量且有系統的篩選果蠅腦內，哪些神經元的蛋白質合成，參與了長期記憶的形成。 令人訝異的是，居然只需要抑制腦內兩顆神經元（稱為**DAL**）的蛋白質新生成，就可以成功阻斷長期記憶的形成。 此外，即便過去一直認為蕈狀體才是學習與記憶的中心，研究團隊卻發現，阻斷蕈狀體的數千個神經元，並不會阻斷長期記憶。這也是始料未及的。

不論是果蠅腦或是人類腦，長期記憶的形成都需要重複的學習，並且在每次學習之間給予適當的休息時間。 這群台灣的科學家們，就是透過這種間隔式學習，來篩選損害長期記憶受損的突變種。 並與聖地牙哥Dart Neuroscience的Tim Tully博士合作，已經確認了許多長期記憶所需的基因。 在測試記憶形成的過程中，江安世研究團隊嘗試著尋找，這群長期記憶的基因在哪裡被活化。 他們發現許多長期記憶相關基因，都會在DAL神經元被活化。 利用基因工程技術，在DAL神經元內抑制這些基因活化的結果，讓本篇Science論文的第一作者陳俊朝證實了，這些基因在DAL神經元的活性便是長期記憶形成的基礎。

江安世研究團隊也與台灣暨南大學的傅在峰助理教授合作，共同發展出全新的基因工程技術，得以直接且即時觀察單一神經元內新生成蛋白質的合成。 研究發現， **DAL**神經元至少有兩組長期記憶相關基因**——CaMKII**與**period**的活性，只在間隔式學習之後提高了。

兩顆**DAL**神經元如何控制如此複雜的記憶呢？ 陳俊朝與他的研究夥伴發現，阻斷**DAL**神經元送出訊號給其他神經，會損害長期記憶的行為。 而且這樣的損壞只發生在阻斷記憶重新回憶之時，而非發生在阻斷學習或是記憶固化的過程。 除此之外，陳俊朝也指出，**DAL**神經元的軸突（輸出端）更與蕈狀體的樹突（輸入端）直接連接。

這些發現，暗示了一個長期記憶處理與回憶過程的簡單模式：記憶形成的時候，在蕈狀體內暫時保存的電子訊號，會刺激**DAL**神經元的電子活性，並且啟動**DAL**內的蛋白質合成。 這一連串的刺激，會改變**DAL**本身的結構與功能。而回憶的過程中，若再次接觸到當初學習的刺激，**DAL**會釋出電子訊號，加速蕈狀體內的電子活性。 因此，藉由在一個複雜網路中的少數神經元（例如**DAL**）改變活性（例如蛋白質新生成），果蠅可以根據先前的經驗（記憶）來決定並調整自己的行為。

江安世教授說，「透過找到各種 *“記憶神經元”*，我們將可以確認更多“記憶蛋白質”。藉此，將得以全盤地瞭解學習與記憶或是相關疾病的分子機制。 我們也將利用各種最新發展的基因工具，來建構更完整的果蠅記憶神經網絡圖譜。 而人腦是否也將記憶儲存在複雜網絡中的少數神經節點裡的蛋白質合成，則有待進一步的確認。」

2011年1月5日，江安世 教授於台大醫學院 演講照片

2012/01/10

CURRICULUM VITAE

Ann-Shyn Chiang (江安世)

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RESEARCH INTERESTS

We aim to understand how genes and circuits orchestrate complex behavior in *Drosophila*. Three main approaches are taken: (i) to construct a brain-wide wiring diagram at single-cell resolution; (ii) to manipulate specific nodes in the circuits to understand how the brain encodes and decodes information; and (iii) to develop innovative technologies for functional connectomics research.

REPRESENTATIVE PUBLICATIONS (*: corresponding author)

1. Lai JSY, Lo SJ, Dickson BJ and Chiang AS* (2012) An auditory circuit in the *Drosophila* brain. **Proc Natl Acad Sci USA** doi: 10.1073,
2. Chen CC, Wu JK, Lin HW, Pai TP, Fu TF, Wu CL, Tully T, Chiang AS* (2012) Visualizing long-term memory formation in two neurons of the *Drosophila* brain. **Science** doi: 10.1126, 678–685.
3. Lee PT, Lin HW, Chang YH, Fu TF, Dubnau J, Hirsh J, Lee T and Chiang AS* (2011) A serotonin-mushroom body circuit modulating the formation of anesthesia-resistant memory in *Drosophila*. **Proc Natl Acad Sci USA** doi: 10.1073, 13794–13799.
4. Wu CL, Shih MF Lai SY, Yang HT, Turner GC, Chen L, Chiang AS* (2011) Heterotypic gap junctions between two neurons in the *Drosophila* brain are critical for memory. **Curr Biol** 21, 848-854.
5. Chiang AS*, Lin CY, Chuang CC, Chang HM, Hsieh CH, Yeh CW, Shih CT, Wu JJ, Wang GT, Chen YC, Wu CC, Chen GY, Ching YT, Lee PC, Lin CY, Lin HH, Wu CC, Hsu HW, Huang YA, Chen JY, Chiang HJ, Lu CF, Ni RF, Yeh CY, Hwang JK (2011) Three-dimensional reconstruction of brainwide wiring networks in *Drosophila* at single cell resolution. **Curr Biol** 21, 1-11.
6. Lin HH, Lai JSY, Chin AL, Chen YC, Chiang AS* (2007) A map of olfactory representation in the *Drosophila* mushroom body. **Cell** 128, 1205-1217.
7. Wu CL#, Xia S#, Fu TF, Wang H, Chen YH, Leong D, Chiang AS*, Tully T* (2007) Specific requirement of NMDA receptors for long-term memory consolidation in *Drosophila* ellipsoid body. **Nat Neurosci** 10, 1578-1586.
8. Xia S, Miyashita T, Fu TF, Lin WY, Wu CL, Pyzocha L, Lin IR, Saitoe M, Tully T, Chiang AS* (2005) NMDA receptors mediate olfactory learning and memory in *Drosophila*. **Curr Biol** 15, 603-615.

Corrigendum: Optogenetics

The standfirst of the feature "Shining new light on the brain" (Curr. Biol. (2011), *21*, R831–R833) stated that optogenetic control of neurons has only been around for six years. It has now come to our attention that the fundamental concept of targeting sensitivity to light to specific neurons, so that their electrical activity could be controlled optically, was established several years before the work on which the feature focused.

Specifically, Gero Miesenböck's group, then at the Memorial Sloan-Kettering Cancer Center in New York, expressed a light-responsive combination of three proteins, namely rhodopsin, arrestin-2, and the α subunit of the corresponding G protein, in cultured neurons and showed that action potentials could be triggered by illumination (Neuron (2002), *33*, 15–22). This method is more complex than the later invention based on channelrhodopsins, as it needs two helper proteins in addition to the light-sensitive rhodopsin itself. The response is also slower, as there is a diffusion step between the sensory rhodopsin and the neuronal reaction.

In the following year, the same group replaced this system with ion channels gated by photochemically controlled ligands (Proc. Natl. Acad. Sci. USA (2003), *100*, 1352–1357), which reduces the number of proteins needed to one, speeds up the response, and generates large photocurrents. In April 2005, four months before Deisseroth's first publication on the channelrhodopsin method, Miesenböck's group (then at Yale University) published the first evidence of optogenetic control in a live animal (*Drosophila*), using this approach with caged ATP as the light-responsive ligand that activates the ion channel (Cell (2005), *121*, 141–152).

In November 2004, the groups of Richard Kramer, Dirk Trauner, and Ehud Isacoff at Berkeley applied optogenetic control to silence, rather than activate neurons, using photoisomerisation of an antagonist to a potassium channel (Nat. Neurosci. (2004), *7*, 1381–1386). In October 2006, a meeting review co-authored by Deisseroth, Miesenböck and others (J. Neurosci. (2006) *26*, 10380–10386) coins and defines the term 'optogenetics'.

Michael Gross

Q & A

Ann-Shyn Chiang

Ann-Shyn Chiang is a professor of Life Science and Director of the Brain Research Center at National Tsing Hua University in Taiwan. He is also an International Faculty member at the Kavli Institute for Brain and Mind (KIBM) at the University of California, San Diego. Chiang acquired his Ph.D. in entomology at Rutgers University from 1986–1990. In 1992, after two years of a postdoc in the same laboratory studying cockroach neuroendocrinology with Coby Schal, he returned to his home country, Taiwan. In 2001, during his sabbatical leave, he went to Cold Spring Harbor Laboratory to study Drosophila *memory with Tim Tully. Since then his research has aimed at delineating the memory circuits of the* Drosophila *brain, in the hope of increasing our understanding of how genes and circuits orchestrate complex behaviors. By 2010, Chiang and his colleagues had mapped over 16,000 single neurons, approximately 15% of the total number of neurons in the* Drosophila *brain, and established the FlyCircuit database for on-line access and data mining (work published earlier this year in this journal: Curr. Biol. 21, 1–11).*

What got you interested in biology in the first place? It was totally unexpected. As an undergraduate, biology classes were never fun for me. There were too many facts to know and too many species names to remember. Doing experiments changed my view. Even now, I still remember the excitement at the moment when I first saw a bacterium, *Bacillus thuringiensis*, completing its life cycle within the alimentary canal of a caterpillar. I was totally fascinated by the microscopic world inside the body of an insect. It was like entering an alien territory. Everything was intriguing and exciting. There was a part of me that I was not aware of until then. I began to learn all the microscopic techniques that would help me to see more.

How did you switch from working on the cockroach to working on* Drosophila*? As a graduate student, I was fascinated by the acute and insightful observations of my mentor, Coby Schal, on how male cockroaches pursue females in the forest (Science *215*, 1405–1407). Later, at Tsing Hua University, in trying to understand how the brain controls sexual behavior and reproduction, we serendipitously discovered that juvenile hormone synthesis in cockroaches is regulated by NMDA receptors. Knowing the importance of this molecule in learning and memory, I immediately realized that this would be a good chance to see if insects actually use the same molecules as humans to learn and remember. I wrote a letter to Coby asking for his advice. "Tim Tully at Cold Spring Harbor Laboratory has discovered dozens of memory genes in *Drosophila*. He will be the best person to address this question", Coby said. During my first week at Cold Spring Harbor Laboratory, Tim Tully sparked my interest with his olfactory associative learning paradigm and sealed my commitment to mapping memory circuitry.

So why study memory in fruit flies? One time, at Cold Spring Harbor Laboratory, I was looking at the expression pattern of a Gal4 line inserted in an unknown gene causing defective long-term memory, and noted that its expression pattern was quite similar to that of *mampus*, a candidate memory gene. Next day, the unknown Gal4 insertion was sequenced and identified. "This is perhaps the first time for anyone to predict a gene from anatomy; the Gal4 is inserted in the *mampus* gene", Tim told me. A few years later, together with other colleagues, we reported that flies use NMDA receptors, as well as many other gene products, for olfactory associative

learning and memory. Despite the distinct differences in gross anatomy of the brain, fruit flies and humans appear to use many similar molecules for basic demands in daily life. With the most sophisticated genetic tool box for spatiotemporal manipulation of genes and circuits available in fruit flies, I, like many other scientists in the field, believe that studying fruit flies will help us understand basic principles of how our brain functions.

Why do you want to build a wiring diagram of the fly brain? As an entomologist, I was always intrigued by various wonderful insect behaviors. When I first returned from Rutgers to Tsing Hua, almost every biologist in Taiwan was doing something related to genomics. Knowing several genome projects would be eventually completed, I wanted to do something different. In 1993, Francis Crick and Ted Jones challenged the field to construct a connectional map of the human cortex, as it was the essence of human mind. In their words, "without it there is little hope of understanding how our brains work except in the crudest way" (Nature *361*, 109–110). A major obstacle faced by all three-dimensional reconstruction methods is that nerve fibers (axons and dendrites) are extremely fine and usually project into a large space. We decided that the fruit fly brain would be the best system for constructing a connectional map, because its small size increases our chance for success while still accounting for relatively complex behaviors. Understanding how the brain networks acquire, process, store, maintain and retrieve information is perhaps one of the most important questions in biology. I believe that lessons gained from mapping fly brain networks can serve as a proof-of-concept pilot study for mapping and understanding our own brain.

What makes you think it is possible to reconstruct the fly brain circuitry? Confocal microscopy for biologists arrived in the early 90s and offers the possibility of removing the out-of-focus background fluorescence in a thick tissue. In theory, the connections between all neurons in the brain could be reconstructed from a series of confocal images, as originally proposed by Marvin Minsky, inventer of the confocal microscope. However, opacity intrinsic to most biological tissues thicker than 100 µm, or a depth of about 5–10 cells, hinders light transmission and emission. After much trial and error, we developed an aqueous tissue clearing agent, FocusClear, that makes fly brains, as well as most biological tissues, transparent (Methods *30*, 86–93). Such a transparent-brain preparation allows for crystal clear visualization of any internal structures fluorescently labeled in an intact whole mount three-dimensional configuration without sectioning. Another key technology, mosaic analysis with a repressible cell marker, also arrived in time for arbitrary labeling of single neurons with transgenic GFP (Trends Neurosci, *24*, 251–254). By then, we knew that the successful construction of a connectional map of the fly brain was only a matter of time.

***How much more time do you think it may take to finish the whole-brain wiring diagram in* Drosophila?** Thus far, we have reconstructed approximately 20,000 single neurons in the *Drosophila* brain. At the current speed of 5000 neurons a year, it will take more than 20 years to complete the fly wiring diagram. However, recent advances in multicolor Brainbow labeling of single neurons and automated three-dimensional imaging and processing make us believe that the connectional map may be completed much faster than this. Large-scale mapping projects at Janelia Farm and several other institutes will also accelerate this process. The projection would be even more optimistic if a standardized platform were available that would enable the integration of data collected from different institutes and accommodate all these neurons into a final atlas.

How did you find people to work on such an interdisciplinary project and how do you envision the impact of such interdisciplinary studies? Mapping brain networks requires expertise from several different fields, including anatomy, genetics, bioimaging, computer science, neuroinformatics, and network analysis. We were very lucky that there are local experts in all these fields. To the surprise of many visitors, our team was initially gathered through a bottom-up approach. Scientists across multiple disciplines were attracted not only by their intrinsic curiosity about the brain's functions but also by the beautiful images of brain circuits generated in my laboratory. For years, some of us were devoted to mapping brain circuits with little grant support. We now have around 20 laboratories devoted either to mapping brain circuits or to studying circuit functions. In addition to the center grant, many investigators have their own investigator-originated grants for participating in the project. It seems that the bottom-up approach works best for interdisciplinary studies.

What else is needed after the map of whole-brain wiring diagram is completed? The completion of single neuron maps in the brain is only the first step towards understanding the brain's operation. The brain not only responds to external stimuli but also controls internal bodily functions. Neuroanatomically, once the whole-brain mapping is completed, in the future we plan to extend the network to cover the whole body. Such a map is basically acting as a hypothesis-generating tool to predict synaptic connectivity, functional connectivity and effective connectivity between neurons within a circuit orchestrating specific behaviors. What is needed most is an extensive collection of genetic drivers expressed in only a few specific neurons for validation and manipulation of the predicted circuits. Also, automated behavior machines will be essential for high-throughput and large-scale screens of effective genes and proteins in targeted single neurons. Finally, an open-access resource for the integration of all levels of information on brain networks will help us greatly to understand how genes and circuits control behaviors.

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"All the News That's Fit to Print"

The New York Times

National Edition

Today, cloudy, windy, colder with flurries, high 28. Tonight, partly cloudy, windy, cold, low 20. Tomorrow, cold, windy, partly sunny, high 30. Weather map is on Page A22.

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Letters

The Puzzle Generation

To the Editor:

As an avid reader of The New York Times, I was delighted to see a special section devoted to puzzles (Dec. 7). As a professor of mathematics, I was disappointed to see not a single mention of the incredible teaching and learning tool KenKen.

Elementary educators have repeatedly lamented the difficulty of getting their students to practice arithmetic. Now a puzzle comes along that children cannot get enough of and which enables them to practice arithmetic without even realizing it. Twenty years from now, you will see KenKen puzzles in every elementary classroom in America.

HAROLD REITER
Charlotte, N.C.

ILLUSTRATIONS BY CRAIG FRAZIER

The Fabulous Fibonacci

To the Editor:

I was surprised that your section on problem solving made no mention of one of the most influential books in the history of mathematics: Fibonacci's "Liber Abaci," published in 1202 and devoted entirely to problem solving.

Chapter 12 presents a problem involving the regeneration of rabbits, from which emanates the famous Fibonacci sequence — the most ubiquitous numbers in our civilization. Perhaps even more important, the book's first sentence introduces Hindu-Arabic numerals to the European culture.

ALFRED S. POSAMENTIER
Dobbs Ferry, N.Y.

The writer is the author of the 2007 book "The Fabulous Fibonacci Numbers."

To the Editor:

Puzzle solving is a very small subset of problem solving, and the two should not be equated at all. I will not dispute that there is a particular kind

Decoding the Human Brain, With Help From a Fly

By NICHOLAS WADE

Taiwanese researchers have managed to bar code some 16,000 of the 100,000 neurons in a fruit fly's brain and to reconstruct the brain's wiring map.

In terms similar to those that define computers, the team describes the general architecture of the fly's brain as composed of 41 local processing units, 58 tracts that link the units to other parts of the brain, and six hubs.

Biologists see this atlas of the fly brain as a first step toward understanding the human brain. Six of the chemicals that transmit messages between neurons are the same in both species. And the general structure — two hemispheres with copious cross-links — is also similar.

"I think this is the beginning of a new world," said Ralph Greenspan, a neurobiologist at the University of California, San Diego. Biologists should now be able to match the fruit fly's well-studied behaviors to the brain circuits established by the new atlas, he said.

The atlas is maintained on a supercomputer in Taiwan which fly biologists around the world can query. They can also add to the atlas by uploading their own images of fruit fly neurons. "So I think this will really accelerate progress," said Josh Dubnau, a neurobiologist at the Cold Spring Harbor Laboratory on Long Island.

The Taiwan team is led by Ann-Shyn Chiang, who has been working on the project for the last decade. He has assembled a group of 40 people, who include computer programmers and engineers, working on a budget of about $1 million a year.

The basis of the atlas is a technique for visualizing the three-dimensional structure of individual neurons, including the cell's nucleus, its long axon, and the little branches, or dendrites, with which it makes contact with other neurons.

The complex structure of a neuron can be made apparent with a green fluorescent protein modeled on one used by jellyfish. The gene for the protein is inserted into the fruit fly's genome, along with another gene that represses it. Dr. Chiang developed a technique for lifting the repression on the gene in just one neuron at a time. When the gene is expressed, the green fluorescent protein reaches every part of the neuron, defining its structure in exquisite detail.

He also invented a remarkable solvent for making the Drosophila brain transparent. This is essential if the glowing green neuron is to be imaged precisely. The solvent is so effective that if a researcher fails to keep an eye on the dissected brain as it lies on a microscope slide, the brain will simply disappear when the solvent is added, Dr. Dubnau said.

Each fly's brain is a different size and shape, so Dr. Chiang's team had to define average dimensions for the female and the male brain, creating a virtual brain with standard dimensions. They then developed algorithms for recasting the 3D image of each neuron so as to bring it into register with the standard brain. This means that the 16,000 neuron images, each taken from a different fly, can all be compared.

Each neuron is then given a bar code with the coordinates of where its cell nucleus lies within the standard Drosophila brain, as well as information about which other parts of the brain the neuron connects to, and which kind of chemical transmitter it uses.

A major setback occurred partway through the project when Dr. Chiang found he could gather data five times as fast if he recorded the neuron images in a different way. "Painfully," he said in an e-mail, "we had to throw all the old data away," even though 3,000 neurons had already been imaged.

The neuron bar codes are numerical data that can be manipulated by computer. With 16,000 images in hand, Dr. Chiang's team was able to analyze the general architecture of the female fruit fly's brain. The basic element, which they call a local processing unit, is a group of neurons with connecting interneurons that do not extend beyond the group. Tracts of longer-range neurons connect the local processing units with one another.

The local processing units correspond with the known anatomical regions of the fly brain. They are the same in all flies, and handle specific tasks like taste or movement.

The fly brain turns out to be "a hybrid system of grid computing and a supercomputer," Dr. Chiang said. "It tells us how a complex brain is put together and operates. Given the growing evidence for conservation in genetic programs underlying brain development and function, the human brain is likely to consist of similar basic operation units."

The only nervous system so far explored in greater detail is that of the C. elegans roundworm, another laboratory organism. But the little worm's system has only 302 neurons and perhaps does not fully deserve to be called a brain. The fly brain, with its 100,000 neurons, may prove a better starting point for understanding the human brain, which has an estimated 100 billion neurons, each with about 1,000 synapses.

"The beauty of this paper is in the completeness of what he did; it's in the foresight it took to develop over a decade or more a whole suite of new methods to tackle a problem they saw as fundamental," Dr. Dubnau said, referring to the Chiang team's work. Dr. Chiang's report is published in the latest issue of Current Biology.

"Yesterday I almost fell out of my chair," said Olaf Sporns, who designs computer models of neural circuits at Indiana University. The matrix showing the interconnectivity of the fly brain in Dr. Chiang's article struck Dr. Sporns as amazingly similar to the matrix he had constructed recently for the human cortex.

The construction of the fly and mammalian brains seems to follow the same "small world" principle, that of high local clustering of neurons, together with long-range connections. "So there's a commonality here, and I think that has to do with the fact that these systems have to accomplish similar goals," Dr. Sporns said.

"Researchers may now be able to pinpoint how information flows through the fly brain network to accomplish certain outcomes," he said.

Dr. Chiang said he will continue to build his atlas until all 100,000 fly brain neurons have been imaged. He said he does not at present plan to map the synapses, the precise connections that one neuron makes with others.

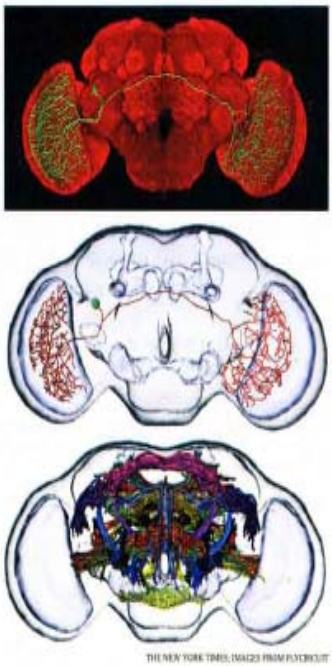
Dr. Greenspan, however, said it should be possible in principle to map synapses by splitting in two the gene for the green fluorescent protein used to delineate the neurons. The neurons could be made to export the half-proteins to their synapses, and when the two halves fused, they would glow green and let the synapse be scanned and mapped.

With a full wiring diagram of the fly brain's neurons and all their synaptic connections, researchers could test their ideas about how information flowed in the brain, and even compute the output that should follow a given input.

"It's not out of the question that if we had a complete cellular map and a good database, that we could create virtual organisms," Dr. Sporns said.

Assembling an Atlas of the Fruit Fly Brain

Taiwanese researchers have succeeded in tracing the wiring of a fruit fly's brain.



A SINGLE NEURON glows green with a fluorescent protein, revealing a branching pathway extending to lobes behind the fly's eyes. The researchers evaluated more than 16,000 neurons from male and female flies, a portion of the roughly 100,000 neurons in the fly's brain.

A SKELETON DIAGRAM shows the same neuron traced in three dimensions and mapped onto a standardized model of a female fruit fly brain. A dot marks the nucleus of the neuron, while thin lines highlight the long axon and branching dendrites.

A WIRING DIAGRAM derived from a map of thousands of neurons reveals 58 neural tracts, drawn in different colors, which communicate with distant areas of the brain. Analysis of the brain structure helped researchers locate 41 local and six larger hubs for processing information.

Source: Current Biology

THE NEW YORK TIMES; IMAGES FROM FLYCIRCUIT

Calorie restriction and aging: the role of neurons

王培育助理教授
國立政治大學神經科學研究所

隨著現今社會老年人口持續增加，了解老化成為目前研究上一個相當重要的議題，而大腦功能退化則是老化的主要現象。經研究證實，限制飲食中的卡路里攝取可有較延長個體的壽命**(Figure 1)**，並可降低及延緩老化相關的疾病如：神經退化性疾病、癌症與心血管疾病的發生。許多卡路里限制 **(calorie restriction)**影響的生理及細胞分子機轉已逐漸揭開，然而其延長壽命的機制並不十分清楚。儘管如此，卡路里限制的概念已被廣泛的運用於治療老化相關的疾病上。

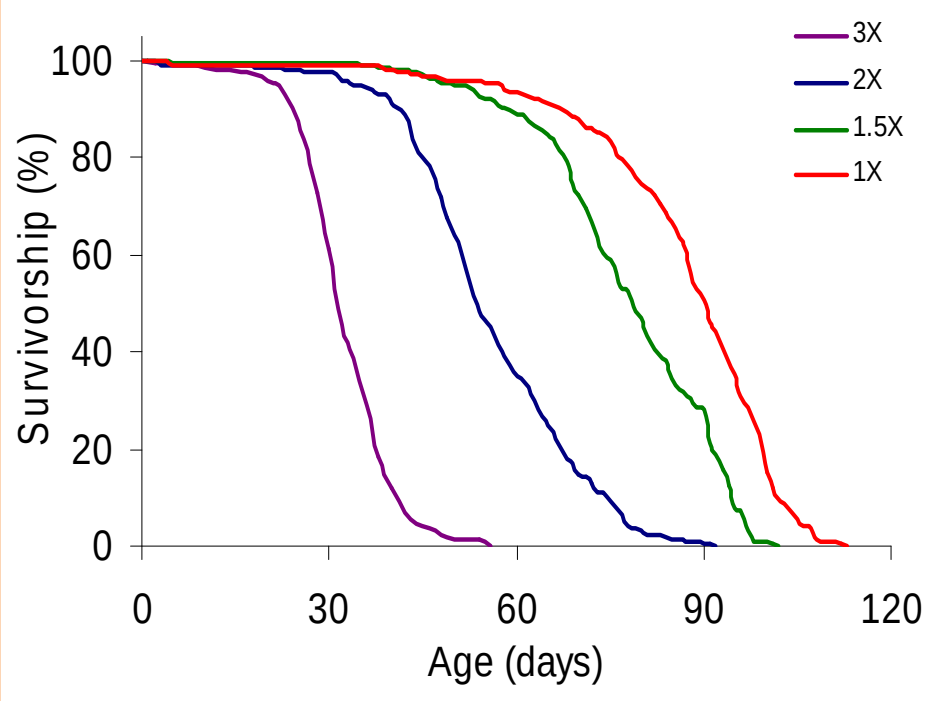


Figure 1. Calorie restriction extends lifespan in *Drosophila melanogaster*. 1X = 10% sucrose and yeast. Each lifespan analysis was performed on more than 200 flies.

目前我們的研究著重於卡路里限制對於心智功能的影響，利用小鼠於抬高式T形迷津 (***elevated T-maze)***及被動迴避試驗 (***passive avoidance test)***的行為表現，我們發現卡路里限制可以顯著增強小鼠學習與記憶的能力，而血清素相關的訊息傳遞則扮演著極為重要的角色，在往後的實驗中我們將繼續探尋卡路里限制影響學習與記憶的分子機轉。

除此之外，我們也同時研究基因對老化的影響，利用果蠅為研究模式，我們發現**I'm not dead yet (Indy)** 的基因突變可顯著延長果蠅的壽命，而**Indy**功能則與**Krebs cycle** 的中間代謝物之運送有關 (**Wang et al., 2009**)。利用微陣列分析 (***microarray analysis)***，我們進一步證實**Indy**突變延長壽命的機轉可能是透過調控動物體內養分的吸收、利用及儲存，進而影響細胞內粒線體的功能，而這些改變則造成**Indy**突變果蠅有著類似卡路里限制的生理狀態 (**Neretti et al., 2009**)。

參考文獻

Neretti, N., Wang, P.-Y., Brodsky, A. S., Nyguyen, H. H., White, K. P., Rogina, B., & Helfand, S. L. (2009). Long-lived Indy induces reduced mitochondrial reactive oxygen species production and oxidative damage. *Proceedings of the National Academy of Sciences, 106*(7), 2277-2282.

Wang, P.-Y., Neretti, N., Whitaker, R., Hosier, S., Chang, C., Lu, D., . . . Helfand, S. L. (2009). Long-lived Indy and calorie restriction interact to extend life span. *Proceedings of the National Academy of Sciences, 106*(23), 9262-9267.

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