Systems Biology Lab
系統生物學研究室

阮雪芬

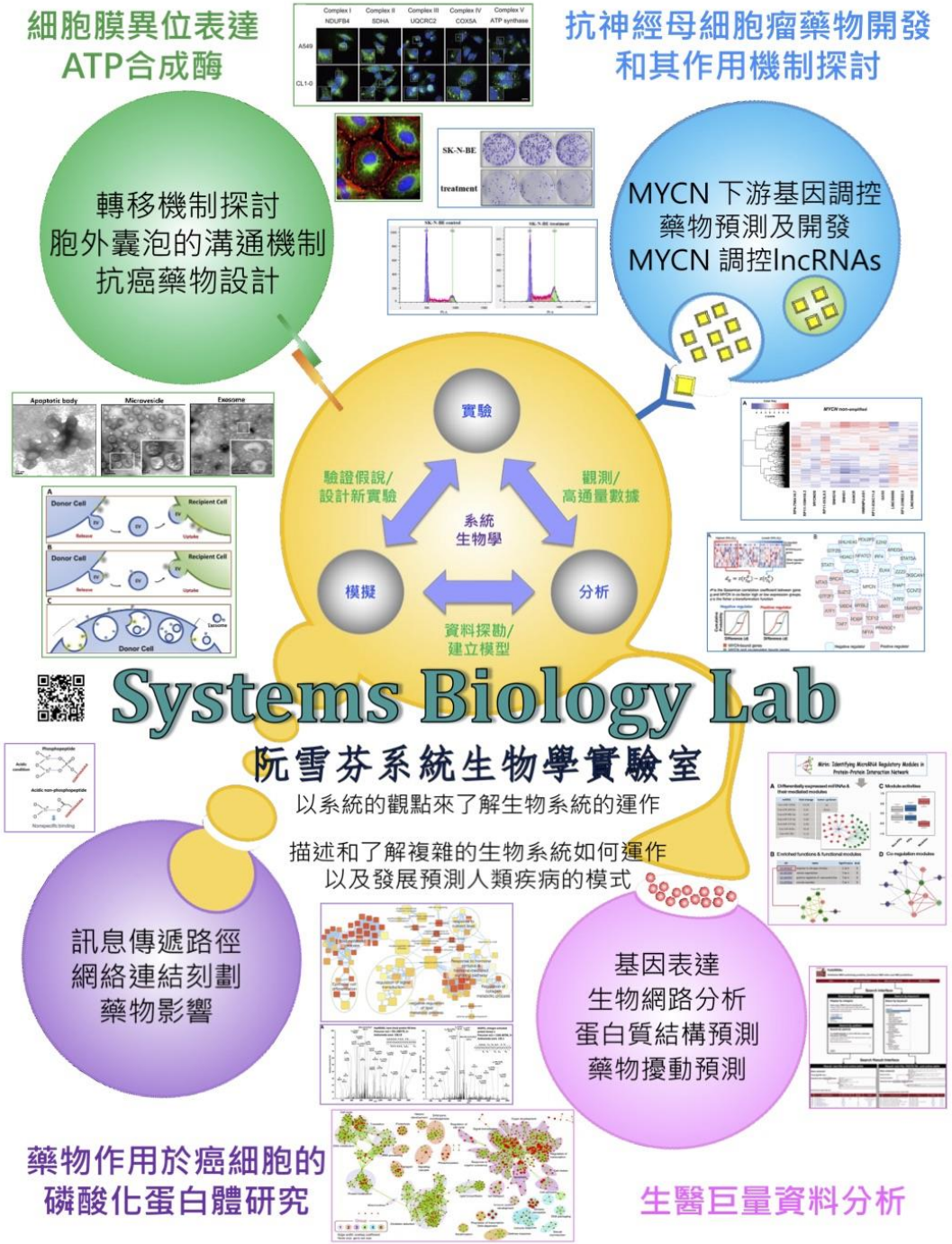
Nov. 25, 2017

Systems Biology Lab

阮雪芬系統生物學實驗室

以系統的觀點來了解生物系統的運作

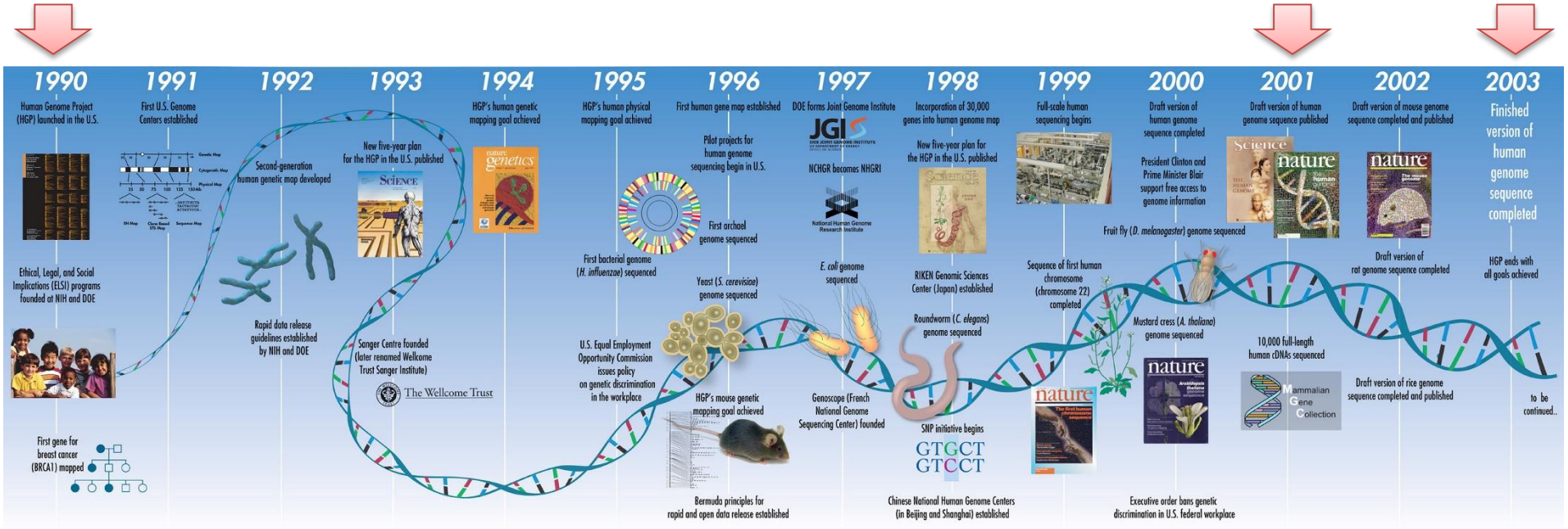
描述和了解複雜的生物系統如何運作
以及發展預測人類疾病的模式



NEUROBLASTOMA STUDY
神經母細胞瘤研究

Human Genome Project

- The Human Genome Project begins in 1990.
- The first draft of human genome was released in 2001 and finished version was launched in 2003.



https://www.mun.ca/biology/scarr/Human_Genome_Project_timeline.html

Science
125 Questions

1 July 2005

WHAT DON'T WE KNOW?

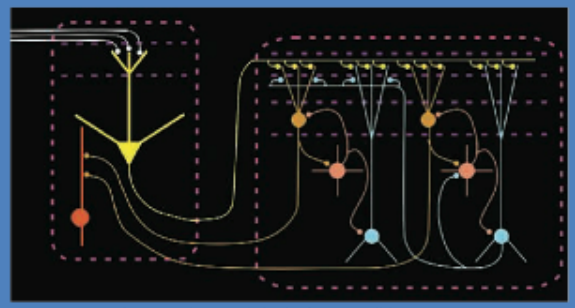
How Will Big Pictures Emerge From a Sea of Biological Data

Biology is rich in descriptive data—and getting richer all the time. Large-scale methods of probing samples, such as DNA sequencing, microarrays, and automated gene-function studies, are filling new databases to the brim. Many subfields from biomechanics to ecology have gone digital, and as a result, observations are more precise and more plentiful. A central question now confronting virtually all fields of biology is whether scientists can deduce from this torrent of molecular data how systems and whole organisms work. All this information needs to be sifted, organized, compiled, and—most importantly—connected in a way that enables researchers to make predictions based on general principles.

Enter systems biology. Loosely defined and still struggling to find its way, this newly emerging approach aims to connect the dots that have emerged from decades of molecular, cellular, organismal, and even environmental observations. Its proponents seek to make biology more quantitative by relying on mathematics, engineering, and computer science to build a more rigid framework for linking disparate findings. They argue that it is the only way the field can move forward. And they suggest that biomedicine, particularly deciphering risk factors for disease, will benefit greatly.

The field got a big boost from the completion of the human genome sequence. The product of a massive, trip-to-the-moon logistical effort, the sequence is now a hard and fast fact. The biochemistry of human inheritance has been defined and measured. And that has inspired researchers to try to make other aspects of life equally knowable.

Molecular geneticists dream of having a similarly comprehensive view of networks that control genes: For example, they would like to identify rules explaining how a single DNA sequence can express different proteins, or varying amounts of protein, in different circumstances (see p. 80). Cell biologists would like to reduce the complex communication patterns traced by molecules that regulate the health of the cell to a set of signaling rules. Developmental biologists would like a comprehensive picture of how the embryo manages to direct a handful of cells into a myriad of specialized functions in bone, blood, and skin tissue. These hard puzzles can only be solved by systems biology, proponents say.



Systems approach. Circuit diagrams help clarify nerve cell functions.

The same can be said for neuroscientists trying to work out the emergent properties—higher thought, for example—hidden in complex brain circuits. To understand ecosystem changes, including global warming, ecologists need ways to incorporate physical as well as biological data into their thinking.

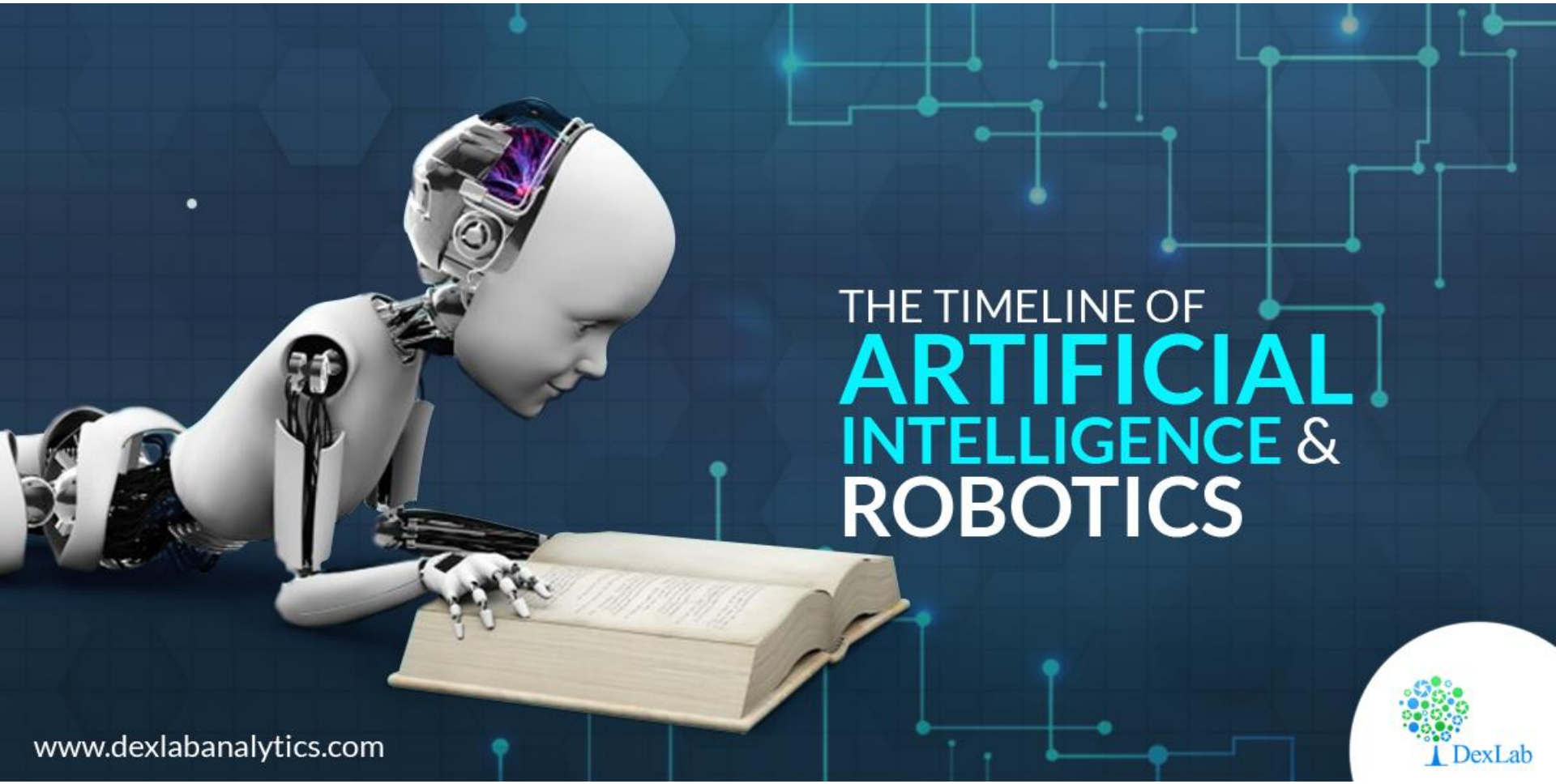
Today, systems biologists have only begun to tackle relatively simple networks. They have worked out the metabolic pathway in yeast for breaking down galactose, a carbohydrate. Others have tracked the first few hours of the embryonic development of sea urchins and other organisms with the goal of seeing how various transcription factors alter gene expression over time. Researchers are also developing rudimentary models of signaling networks in cells and simple brain circuits.

Progress is limited by the difficulty of translating biological patterns into computer models. Network computer programs themselves are relatively simple, and the methods of portraying the results in ways that researchers can understand and interpret need improving. New institutions around the world are gathering interdisciplinary teams of biologists, mathematicians, and computer specialists to help promote systems biology approaches. But it is still in its early days.

No one yet knows whether intensive interdisciplinary work and improved computational power will enable researchers to create a comprehensive, highly structured picture of how life works.

—ELIZABETH PENNISI

Artificial intelligence

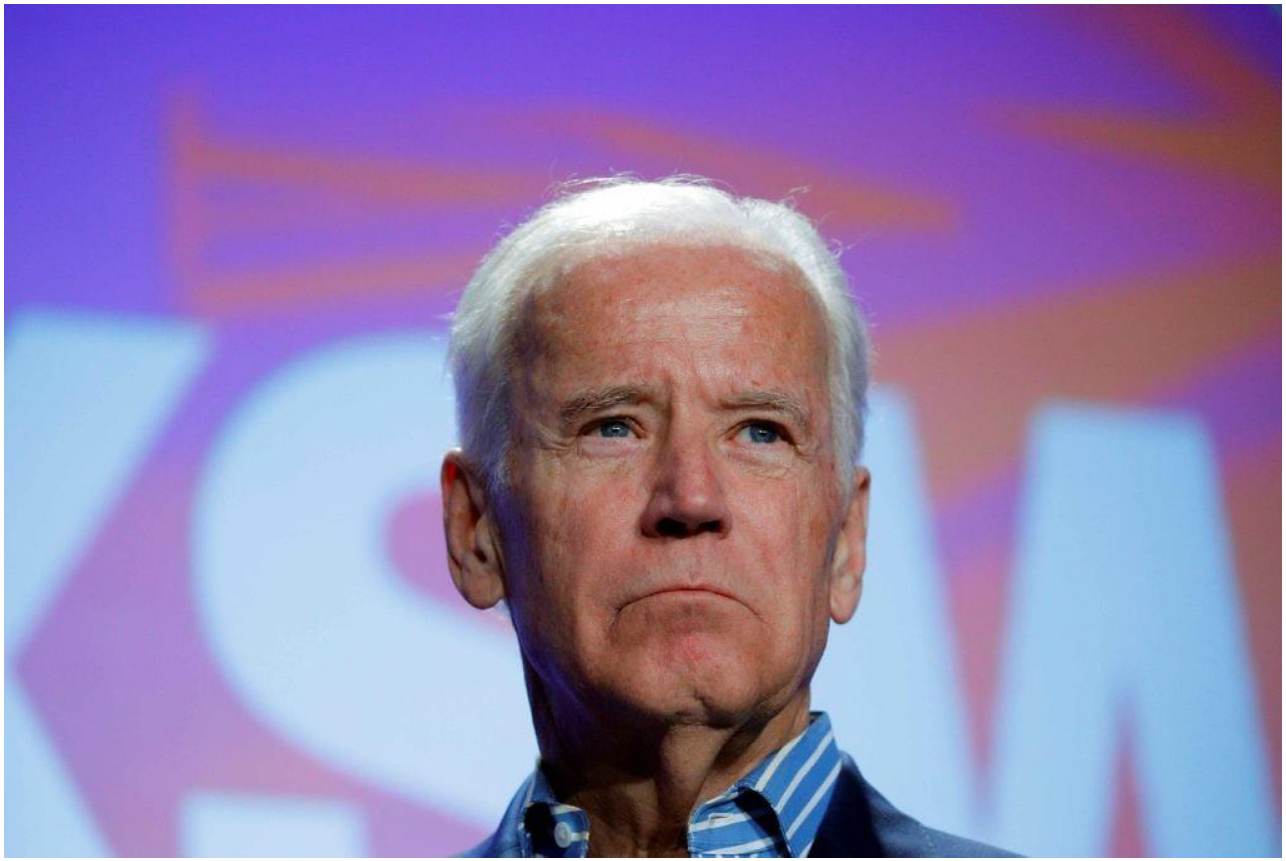


https://www.dexlabanalytics.com/wp-content/uploads/2017/07/The-Timeline-of-Artificial-Intelligence-and-Robotics.png

「今天能做到的事，我一天都不要等。」

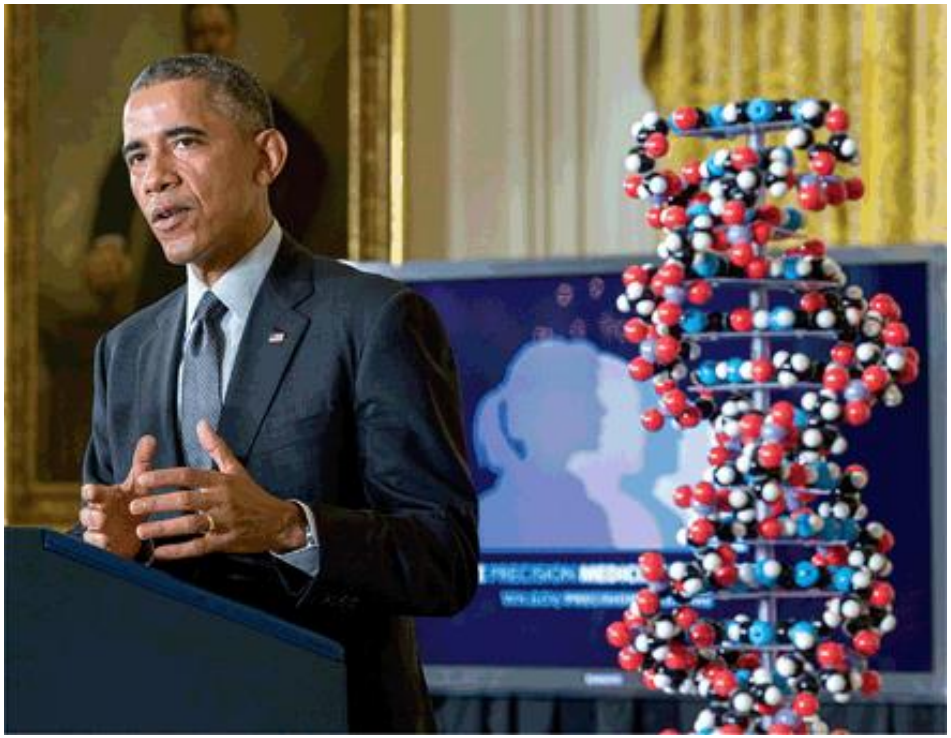
I am unwilling to postpone, for one day longer, the things we can do now.

在科技方面，拜登認為超級電腦、大規模計算和大數據是攻克癌症的關鍵。



Precision medicine

- NIH now has a plan for carrying out the study of more than a million Americans that President Obama called for in January 2015 as part of his Precision Medicine Initiative.

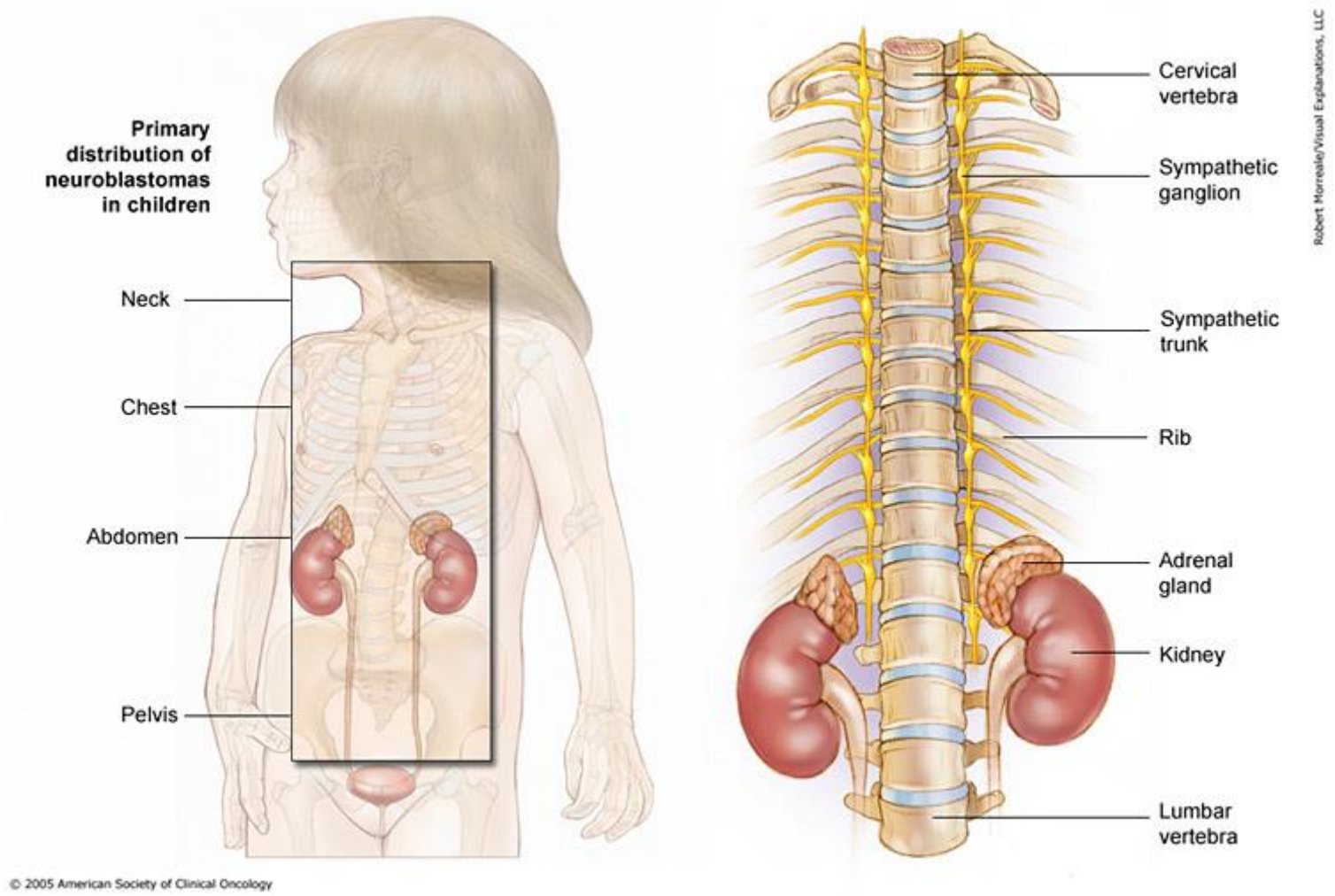


Jocelyn Kaiser. NIH opens precision medicine study to nation. *Science* 25 Sep 2015: Vol. 349, Issue 6255, pp. 1433

Personalized medicine: Time for one-person trials

Schork NJ. Nature. 2015 Apr 30;520(7549):609-11.

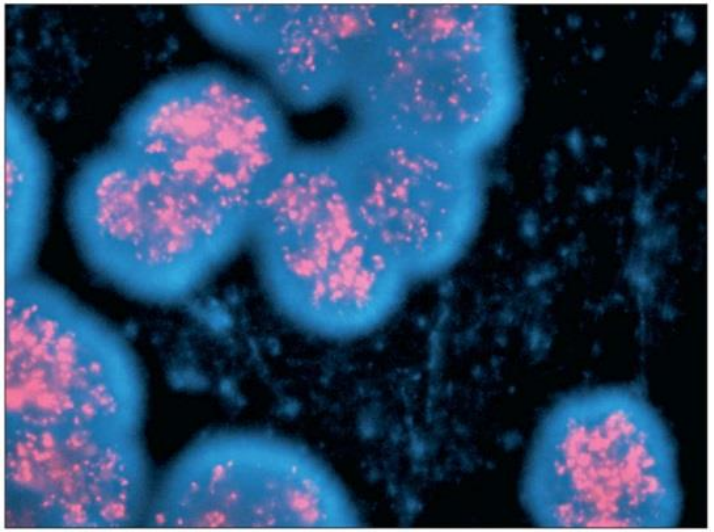
神經母細胞瘤是交感神經系統腫瘤



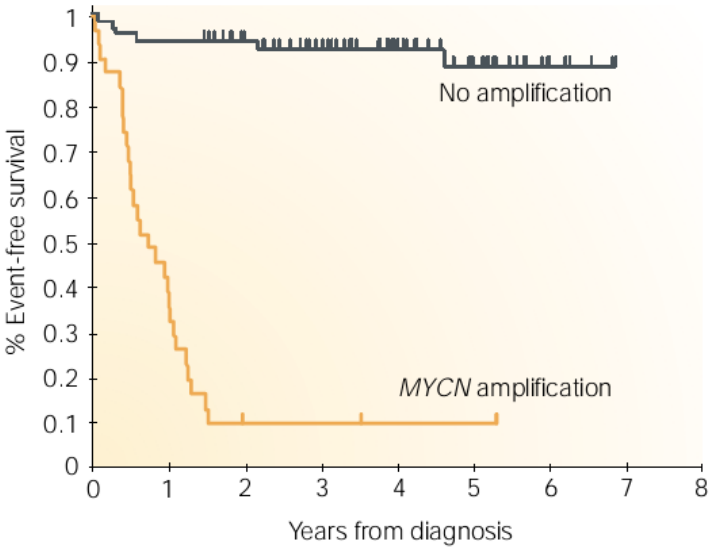
http://inrgdb.org.s103725.gridserver.com/wp-content/uploads/2014/01/neuroblastoma.jpg

Mycn status is risk factor

Mycn amplification



Mycn effect on survival

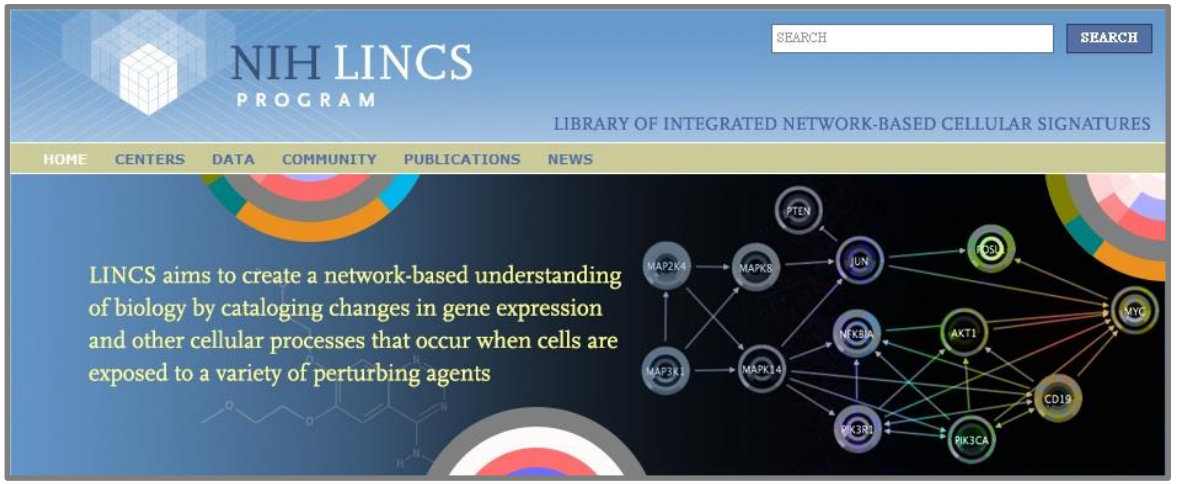


Lancet. *369*, 2007

Nat Rev Cancer. *13*, 397-411, 2013

LINCS: Library of Integrated Network-based Cellular Signatures

a catalog of perturbation responses



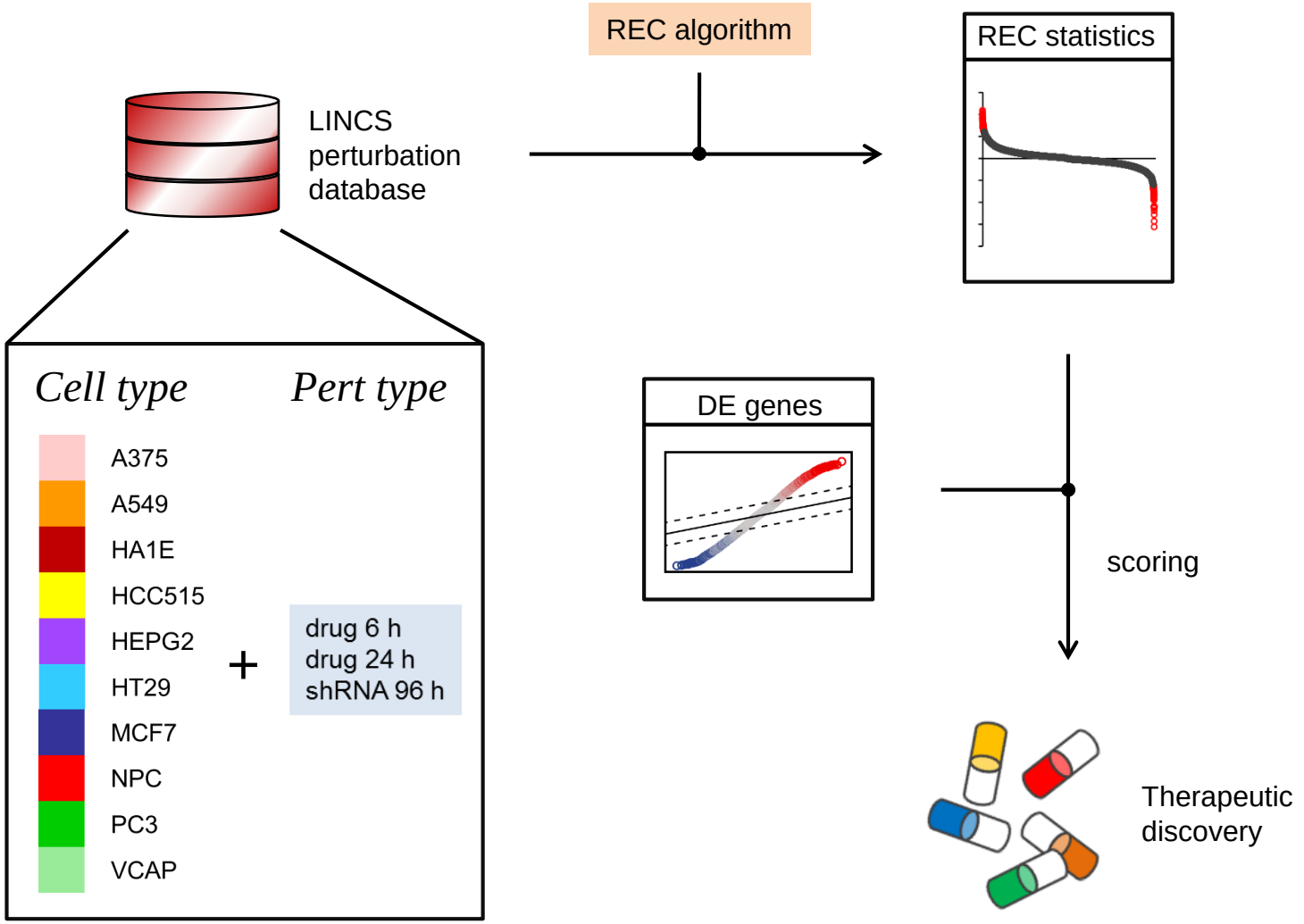
the 2rd generation of CMap

Now six centers get involved:

- **Drug Toxicity Signature Generation Center** (Icahn School of Medicine at Mount Sinai)
- **HMS LINCS Center** (Harvard Medical School)
- **LINCS Center for Transcriptomics** (Broad Institute)
- **LINCS Proteomic Characterization Center for Signaling and Epigenetics** (Broad Institute)
- **Microenvironment Perturbagen (MEP) LINCS Center** (Oregon Health and Science University)
- **NeuroLINCS Center** (University of California, Irvine)

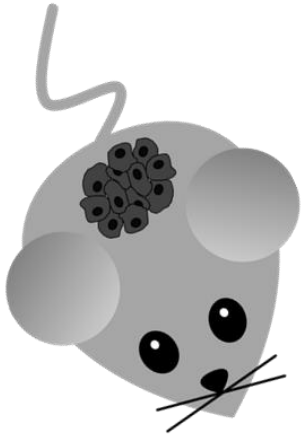
http://www.lincsproject.org/

Using bioinformatics, we discover many compounds which have potential therapeutics



Q1: Ongoing and need to be solved

- Whether these compounds can kill NB cells? In animal model? In human model?
- Combination therapy (合併治療)

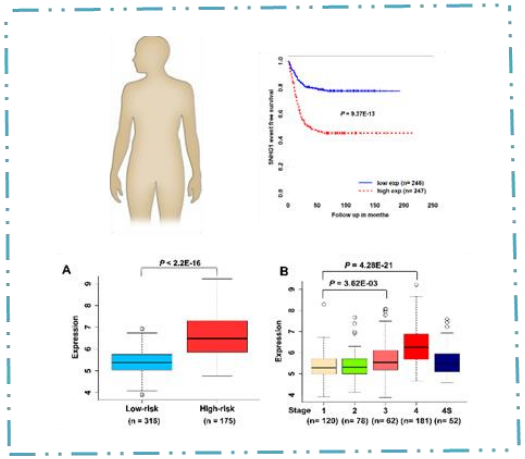


Q2: Ongoing and need to be solved

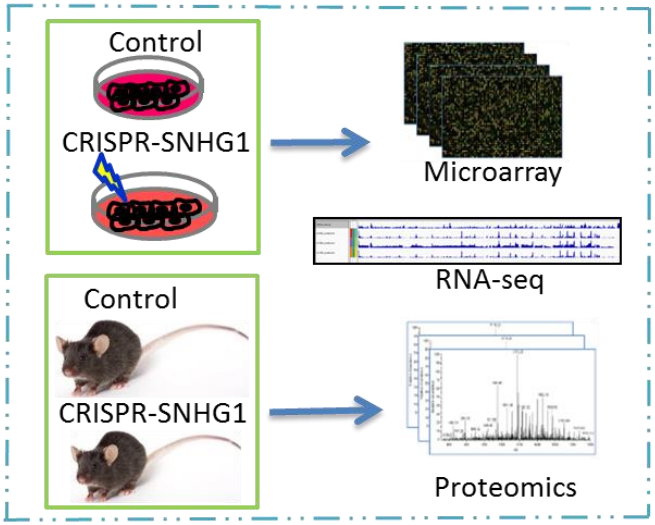
The role of lncRNA SNHG1 in NB progression?

長鏈非編碼核糖核酸: SNHG1

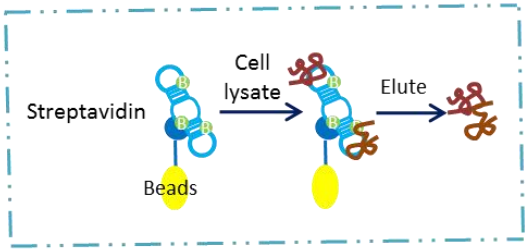
Prognostic potential of SNHG1 and its regulated molecules (Aim 1 & 7)



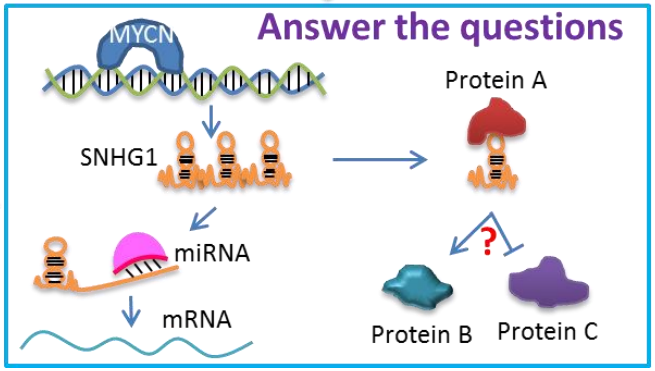
Transcriptome and proteome (Aim 2, 3 & 4)



RNA-protein pull down (Aim 5 & 6)



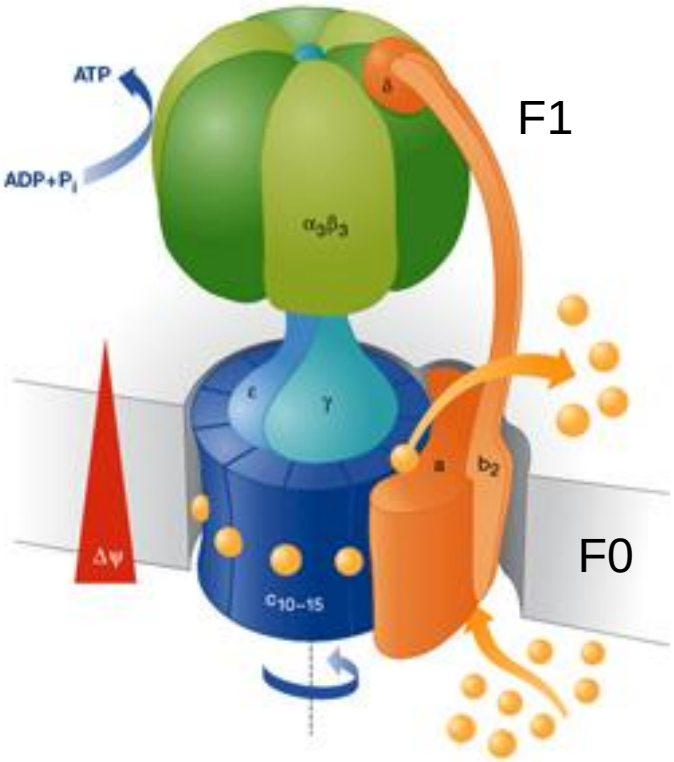
Answer the questions



STUDY ON ATP SYNTHASE
ATP 合成酶研究

- “All enzymes are beautiful, but ATP synthase is one of the most beautiful as well as one of the most unusual and important.”

- Paul Boyer

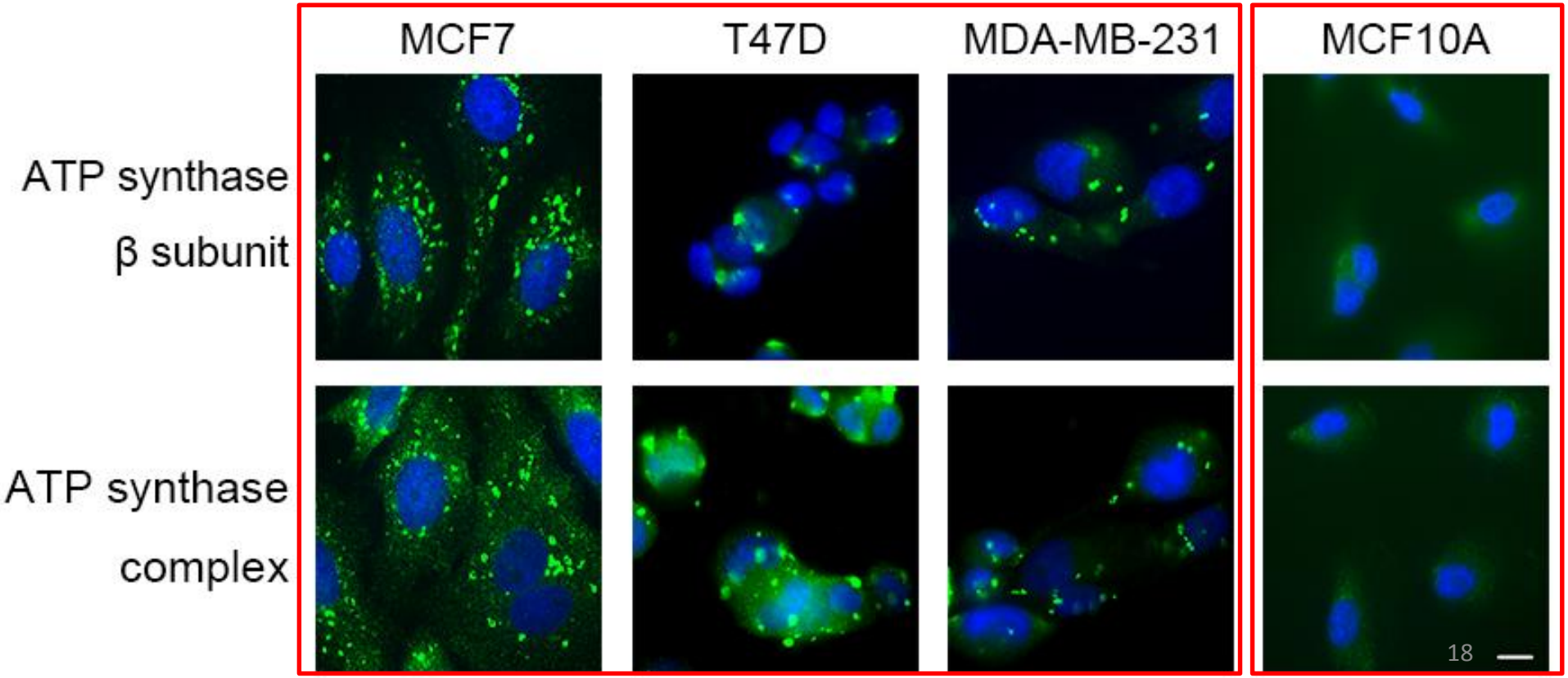


Two functional domains

- F0: integral to the membrane
- F1 ATP-ase: soluble portion

Expression of active ATP synthase on the surface of breast cancer cells

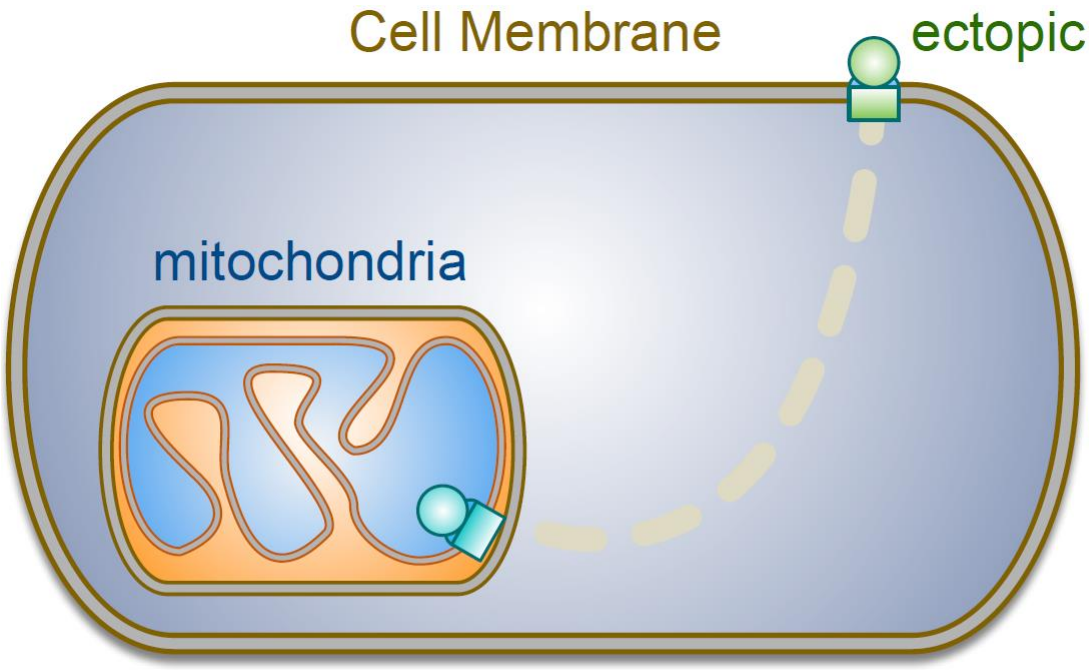
We observed punctate localization of ectopic ATP synthase on the PM of cancer cells but not on MCF10A cells.



Chang HY, et al, Juan HF. Cell Death & Disease (2014)

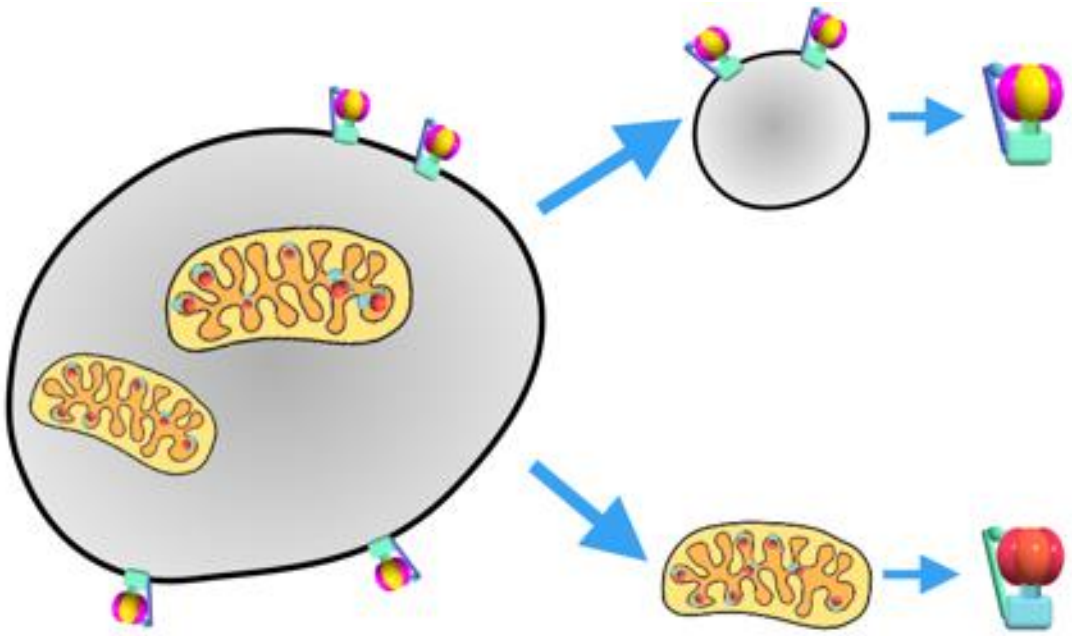
Q1: Ongoing and need to be solved

How do mitochondrial ATP synthases transport to cell membrane?

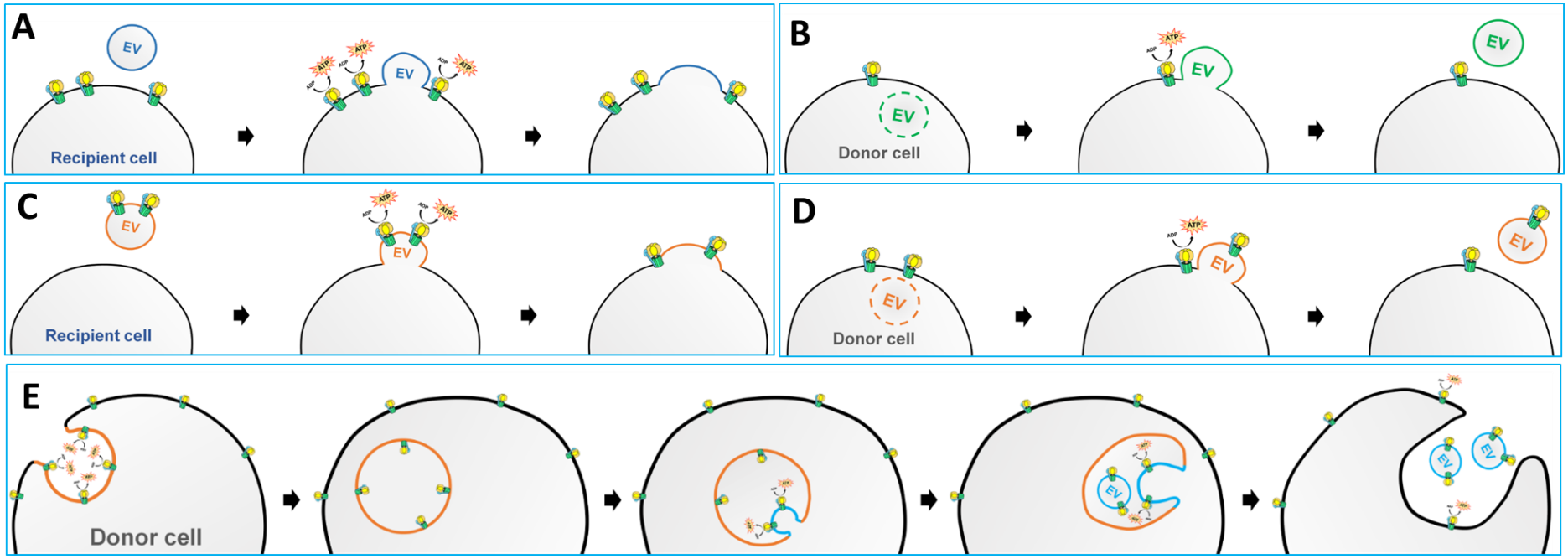


ATP synthase trafficking

Q2: whether the complex structures of ATP synthase on plasma membrane are different from mitochondria



Q3: Role of ectopic ATP synthase in cell-cell communications mediated by extracellular vesicles



Achievements in the recent five years
近五年研究成果 (2013 - now)

- SCI Journal papers: 42
- Book: 1
- Book chapter: 1
- Conference papers/abstracts: 79
  - 39 poster award or travel grant, not including NTU life Science College award

研究計畫

執行中

一. 以蛋白體學技術探討受異位表達ATP合成酶運送影響之磷酸化與乙醯化交互作用動態變化 (8/1/2016-7/31/2019, MOST)

二. 以蛋白體學探討ATP合成酶如何透過胞外囊泡進行細胞與細胞間的溝通 (8/1/2017-7/31/2020, MOST)

三. 以基因表現巨量數據尋找高危險群神經母細胞瘤之新穎組合治療策略 (1/1/2018-12/31/2021, NHRI)

四. 浸潤免疫細胞之Rab37與癌細胞之WDR4協同調控肺腫瘤微環境中逃避免疫攻擊的機制 (8/1/2017-7/31/2020, Co-PI)

申請中

整合基因體編輯和多層體學方法探討長鏈非編碼核糖核酸SNHG1在高危險性神經母細胞瘤的分子功能 (臺大醫院計畫)

系統生物學研究室成員

PI: 1位
Co-PI: 1位
博士後: 1位
博士生: 8位
碩士生: 9位
大學專題生: 3位
高中生: 1位

已擔任教職的博士畢業生及博士後

黃翠琴: 臺北醫學大學
林振慶: 陽明大學
張心儀: 日本京都大學
陳卓逸: 陽明大學
許家郎: 臺大醫院

學生申請到國外大學

美國哈佛、史丹福、康乃爾、約翰·霍普金斯、杜克、加州大學舊金山分校、加州大學聖地牙哥分校等大學
日本東京大學
歐洲歐盟學程

Welcome to join us