

How a **bio**informatician like me
could be a co-author of a
Science paper?

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A cooperation between NCKU & University of Chicago



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The piRNA targeting rules and the resistance to piRNA silencing in endogenous genes

Donglei Zhang^{1,2,*}, Shikui Tu^{3,4,*}, Michael Stubna¹, Wei-Sheng Wu⁵, Wei-Che Huang⁵, Zhiping Weng³, Heng-Chi Lee^{1,†}

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**Nature (2009), Cell (2012),
Science(2018)**

Heng-Chi Lee, PhD

Small RNAs-mediated epigenetic regulation & genome surveillance

Assistant professor, Molecular Genetics and Cell Biology

B.S., Life science, National Yang-Ming University, Taiwan 2001

Ph.D., Genetics and Development, UT Southwestern Medical School 2008



What does a bioinformatician (程式工具人) do?

- Bioinformaticians apply **information technology** to biological, medical, and health research.
- They use **computational tools** to **gather and analyze data** in fields such as population, biology, genetics, and pharmaceutical development.
- I want to be a **computational biologist**.
- Not a technician who just develops or uses computational tools for doing biological research.

My expertise

1. **Analyzing high-throughput biological data** (會用 data analysis pipeline)
(RNA-seq, ChIP-seq, Ribo-seq, Mass spectrometry data, Microarray, TCGA data)
2. **Developing bioinformatics algorithms** (會用數學及統計理論開發生物資訊演算法)
(predict **yeast cell cycle/heat shock TFs**; reconstruct **yeast transcriptional regulatory modules, pathways and networks**)
3. **Answering interesting biological questions** (A computational biologist's task)
(要有能力去問有趣的生物問題、整理大量生物量測資料、使用統計測試去做假設檢定，最終得出 **novel** 的生物知識)

RESEARCH

Open Access



Functional redundancy of transcription factors explains why most binding targets of a transcription factor are not affected when the transcription factor is knocked out

4. Constructing biological databases and web servers

(會寫程式處理生物資料及建構網站，碩士班學生即可勝任)

- 現代生物學家已經很難用腦中的生物知識直接看出高通量實驗技術所量測到的資料有何生物意義，資料的複雜度使得必須使用各種程式工具才能從中 mining 出有生物意義的資訊。
- 由於大部分生物學家不具備使用及撰寫資料處理程式的能力，所以網頁資料庫及網頁伺服器的研究領域應運而生。
- 我們這些生物資訊學家會去開發各種生物學家所需要的程式工具並將之包裝成網站，生物學家只要在網頁點選就可以執行程式得到他想看的資訊。
- 因此，網頁資料庫及網頁伺服器的研究領域已經是生物研究中非常重要且熱門的分支。

What are biological databases?

- **Biological databases** are libraries of life sciences information, collected from scientific experiments, published literature, high-throughput experiment technology, and computational analysis.
- **Databases** are important **tools** in assisting scientists to **analyze and explain a host of biological phenomena**.
- **Primary databases (苦工型)** often hold only one type of specific data which is stored in their own archive.
- They upload new data explored in experiments and update entries to ensure the quality of the data.
- **Secondary databases (創意型)** are databases, which **use other databases as their source of information**, thus they get their data by requesting other databases.
- They often already process or analyze the data matching the corresponding request to get new results.

10 biological databases from my lab

Species	Name	Journal
Yeast	YPA (Yeast Promoter Atlas) Featured Article	NAR 2011
Yeast	YTRP (Yeast Transcriptional Regulatory Pathway)	Database 2014
Yeast	YNA (Yeast Nucleosome Atlas) 廖泓鈞	BMC Genomics 2014
Fly	cis-MEP (cis-regulatory Module Epigenetic Profile Database for Drosophila Melanogaster)	BMC Systems Biology 2014
Yeast	CoopTFD (Cooperative TFs Database)	Database 2016
Yeast	YCRD (Yeast Combinatorial Regulation Database)	Plos One 2016
Human & Mouse	CSmiRTar (Condition Specific miRNA Targets) 曾大千	Plos One 2017
Yeast	YGMD (Yeast Gene Modules Database)	Database 2017
Human	p53BLD (p53 Binding Loci Database) 廖泓鈞	Submitted to Scientific Reports
Human	HRPDviewer (Human Ribosome Profiling Data Viewer) 曾大千	Submitted to Database

p53BLD (p53 Binding Loci Database)

- Demo
- <http://cosbi4.ee.ncku.edu.tw/p53BLD/>

What are biological web servers?

- **Web-based software resources** which are of value to the biological community.
- **Software programs that run on the web** and provide useful computations on DNA, RNA and protein sequences or structures; analysis of high throughput sequencing data and microarray data; metagenomic and microbiome analysis, network and pathway analysis; biological text mining; tools for synthetic biology; and innovative visualizations.
- The web servers can **provide new biological insights**.

7 biological web servers from my lab

Species	Name	Journal
Yeast	YGA (Yeast Genes Analyzer)	Gene 2012
	MissVIA (Missing Value Imputation Atlas)	BMC Systems Biology 2013
	iPhos (a toolkit to streamline the alkaline phosphatase-assisted comprehensive LC-MS phosphoproteome investigation) 廖寶琦	BMC Bioinformatics 2014
Yeast	YAGM (Yeast Associated Gene Miner)	BMC Systems Biology 2015
Yeast	PCTFPeval (Predicted Cooperative TF Pairs evaluator)	BMC Bioinformatics 2015
	MVIAeval (Missing Value Imputation Algorithm evaluator)	BMC Bioinformatics 2017
C. elegans	piScan (piRNA target site prediction tool) 芝加哥大學李亨啓教授	Submitted to NAR

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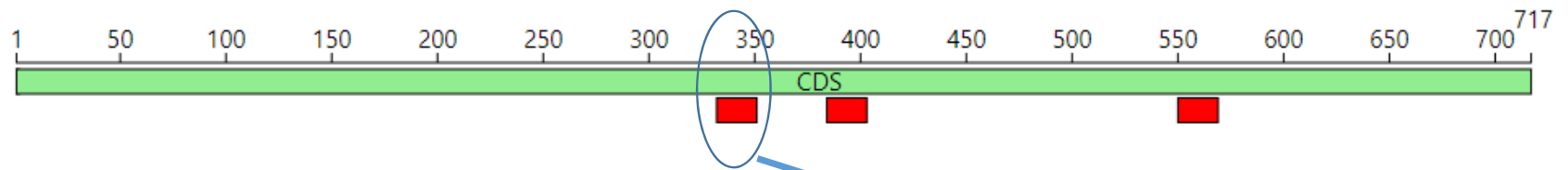
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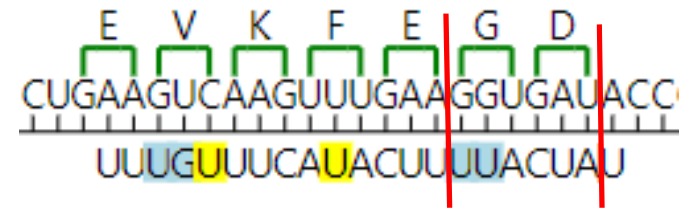
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Abstract

- Piwi-interacting RNA (**piRNA**) is the largest class of small non-coding RNA molecules expressed in animal cells.
- piRNAs **silence transposons** to safeguard genome integrity in animals.
- The broad targeting capacity of piRNAs underlies the **germline silencing of transgenes** in *C. elegans*.
- Here, we show that **piRNA targeting** in *Caenorhabditis elegans* **can tolerate a few mismatches but prefer perfect pairing at the seed region**.
- **Transgenes engineered to avoid piRNA recognition are stably expressed.**



■ non-GU mismatch
 ■ GU mismatch
 ■ mismatch at the 1st position of piRNA
 | seed region
 ┌ Codon



piRNA targeting rules

piRNA targeting in *C. elegans* prefers **perfect pairing at a piRNA seed region** but otherwise can tolerate a few mismatches.

piRNA targeting rules

Default Setting

5' input sequence 3'

3' piRNA #1 5' 3' piRNA #2 5'

seed non-seed

5' piRNA 3'

1 2 7 8 21

Number of mismatches allowed at seed region:

- number of non-GU pairs ≤
- number of GU pairs ≤

Number of mismatches allowed at non-seed region:

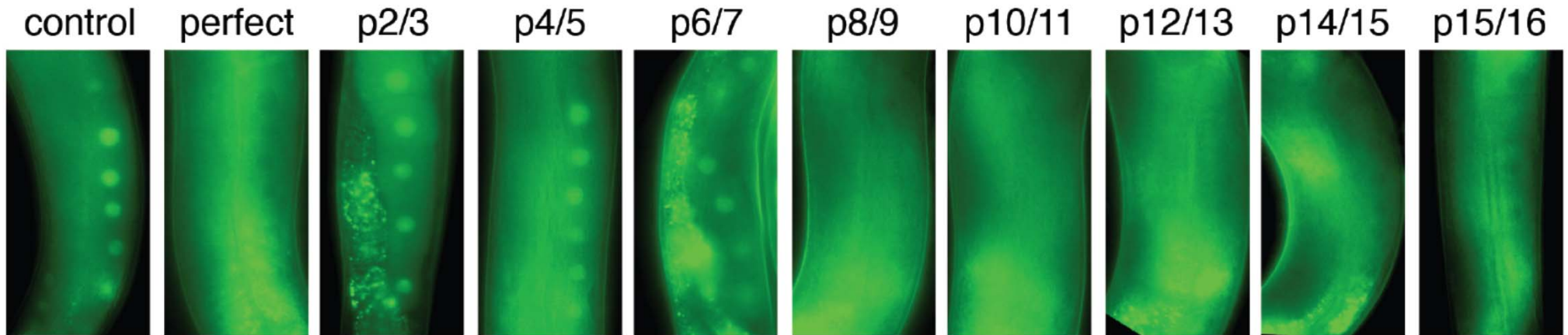
- number of non-GU pairs ≤
- number of GU pairs ≤

Total number of mismatches at seed & non-seed regions ≤

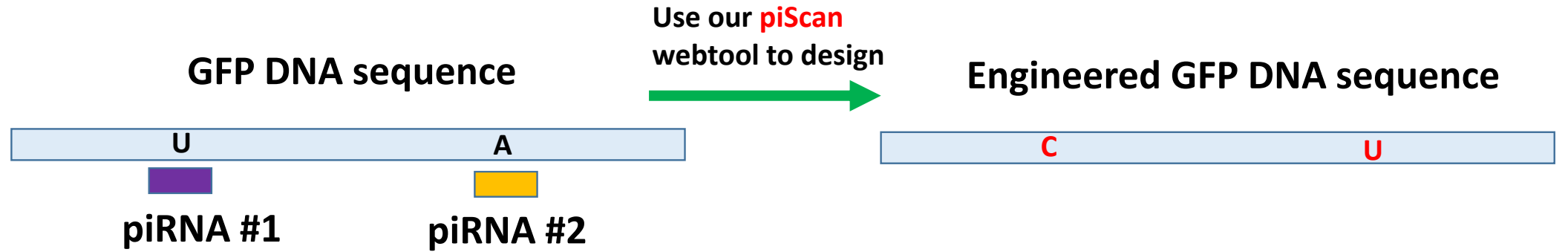
Position of mismatches in
gfp-targeting piRNA #1

GFP
expression

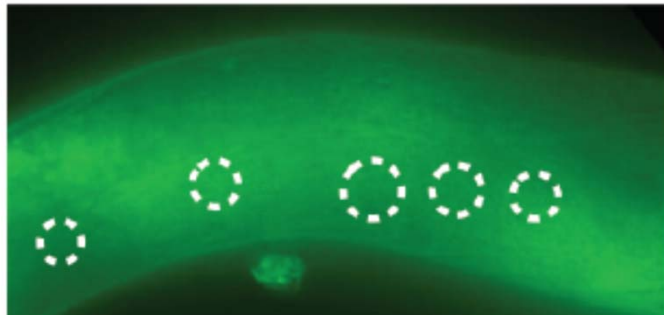
	Perfect	5'	UGUUUCAUAUGAUCUGGGUAU	3'	-
di	p2/3	5'	U <u>UC</u> UUCAUAUGAUCUGGGUAU	3'	+
	p4/5	5'	UGU <u>GG</u> CAUAUGAUCUGGGUAU	3'	+
	p6/7	5'	UGUUU <u>AC</u> AUGAUCUGGGUAU	3'	+
	p8/9	5'	UGUUUCA <u>AC</u> UGAUCUGGGUAU	3'	-
	p10/11	5'	UGUUUCAUA <u>CU</u> AUCUGGGUAU	3'	-
	p12/13	5'	UGUUUCAUAUG <u>UC</u> CUGGGUAU	3'	-
	p14/15	5'	UGUUUCAUAUGAU <u>AC</u> GGGUAU	3'	-
	p15/16	5'	UGUUUCAUAUGAUC <u>GT</u> GGUAU	3'	-



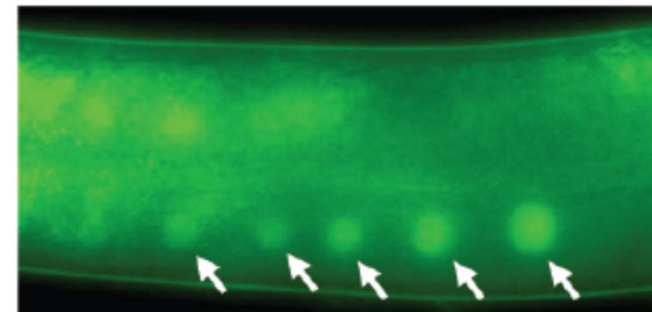
Transgenes engineered to avoid piRNA recognition are stably expressed.



GFP is silenced by piRNA targeting



Engineered GFP is expressed by escaping piRNA targeting



piScan

- Demo
- <http://cosbi4.ee.ncku.edu.tw/piScan/>

Q & A