



# 生醫期中報告 ---


## MICROARRAY



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# Outline


- Introduction
  - Principles
  - Manufacturing methods
  - Applications
  - Future developments
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# Introduction

- DNA chips: cDNA (complementary DNA) microarray, Oligonucleotide (寡核苷酸) microarray, Intergenic array
- Protein chips: protein microarray, Oligopeptide (寡肽) microarray, Mabs array
- Tissue chips




# DNA microarray

- Also called gene chip, DNA chip, biochip
  - DNA spots attached to a solid surface  
(矽晶元或是特殊玻璃片)
  - DNA spot contains picomoles of probes
  - probe (reporters): special DNA sequence
- 




# Protein chip

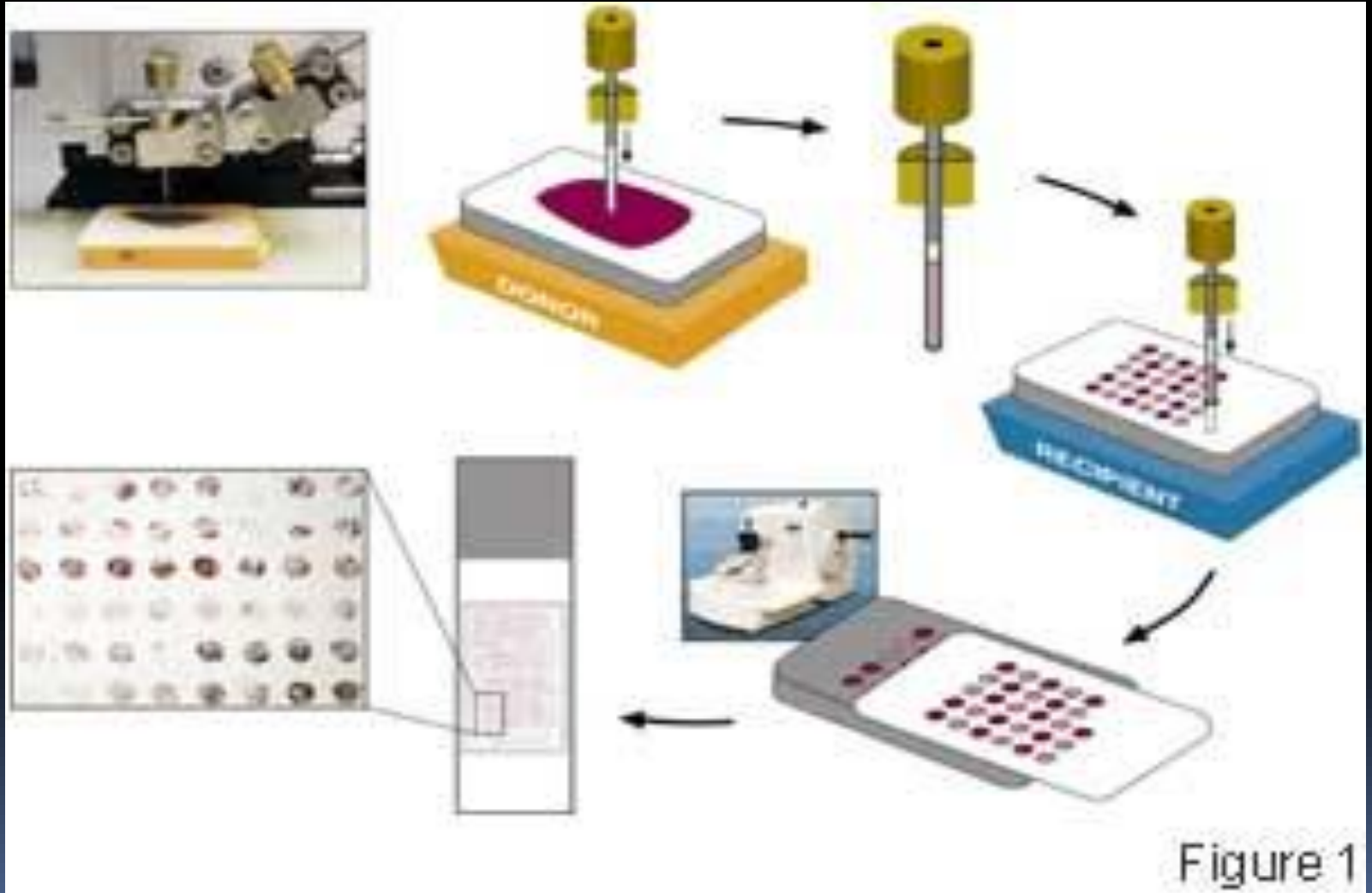
- Protein–Protein array
  - DNA-Protein array: Double-stranded DNA
  - antibody
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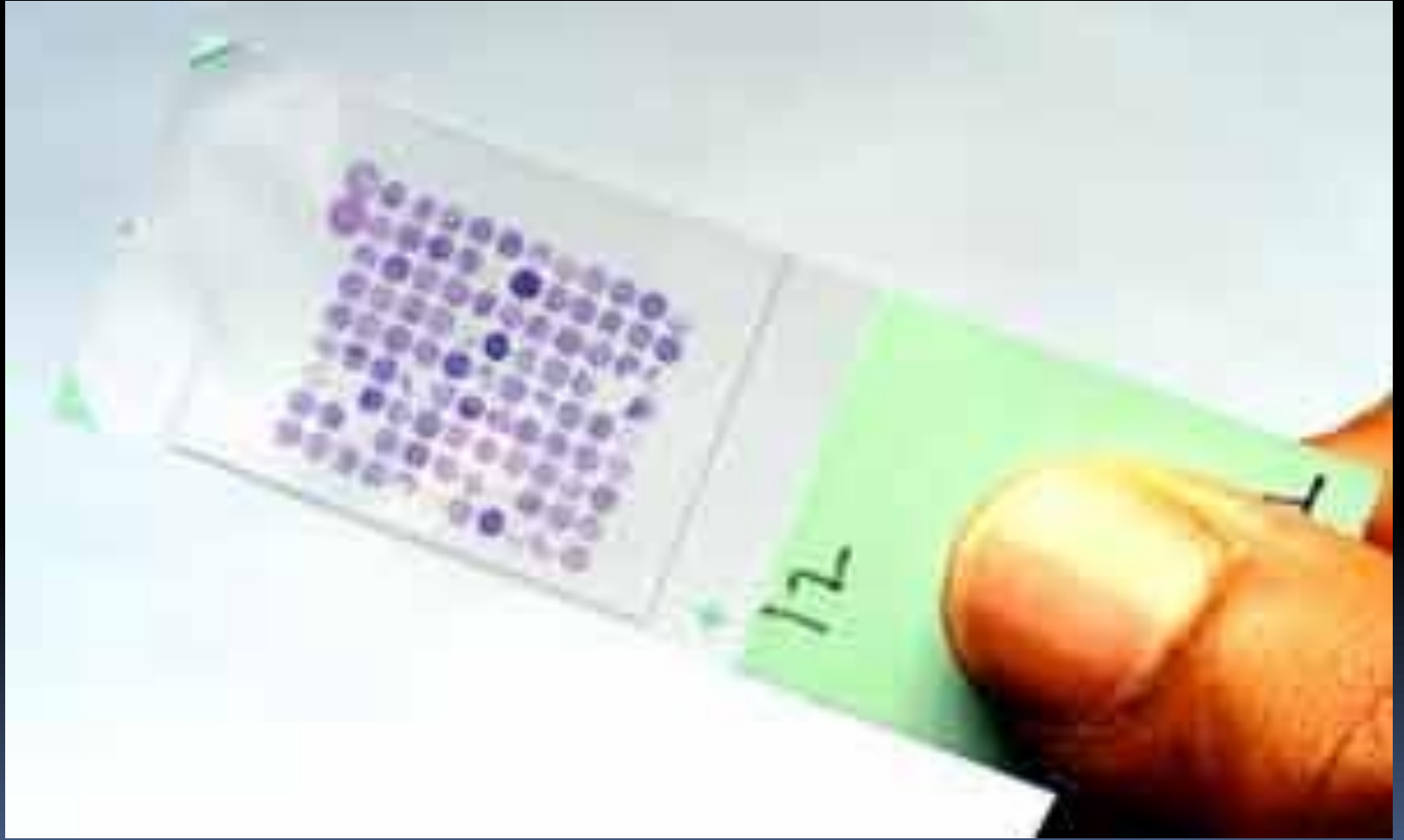


# Tissue chip

- 0.6 - 3.0 mm (diameter) cores of tissue
  - paraffin blocks or frozens
  - multiple individual tissue samples
  - 50 - 500 tissues or more per slide block
  - analyzed with a wide-variety of techniques
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# Tissue chip

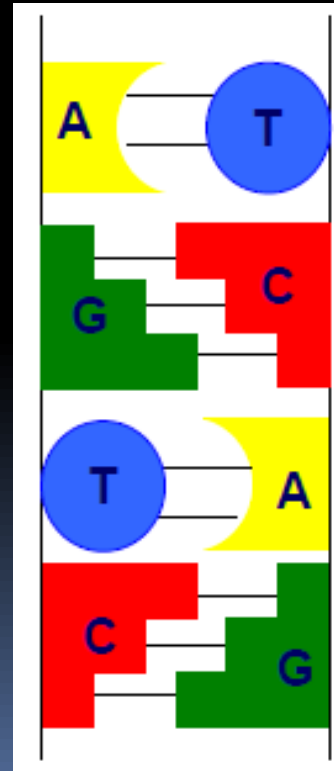






# 原理 -- hybridization

- DNA --- 由 G, A, C, T 四種核苷酸組成
- 雙股 DNA 藉著 G, C 間的三個氫鍵和 A, T 間的兩個氫鍵做結合





# Hybridization


- A single-stranded DNA molecule with a known sequence is labeled with a radioactive isotope or fluorescent dye and then used as a “probe” to detect a fragment of DNA or mRNA.

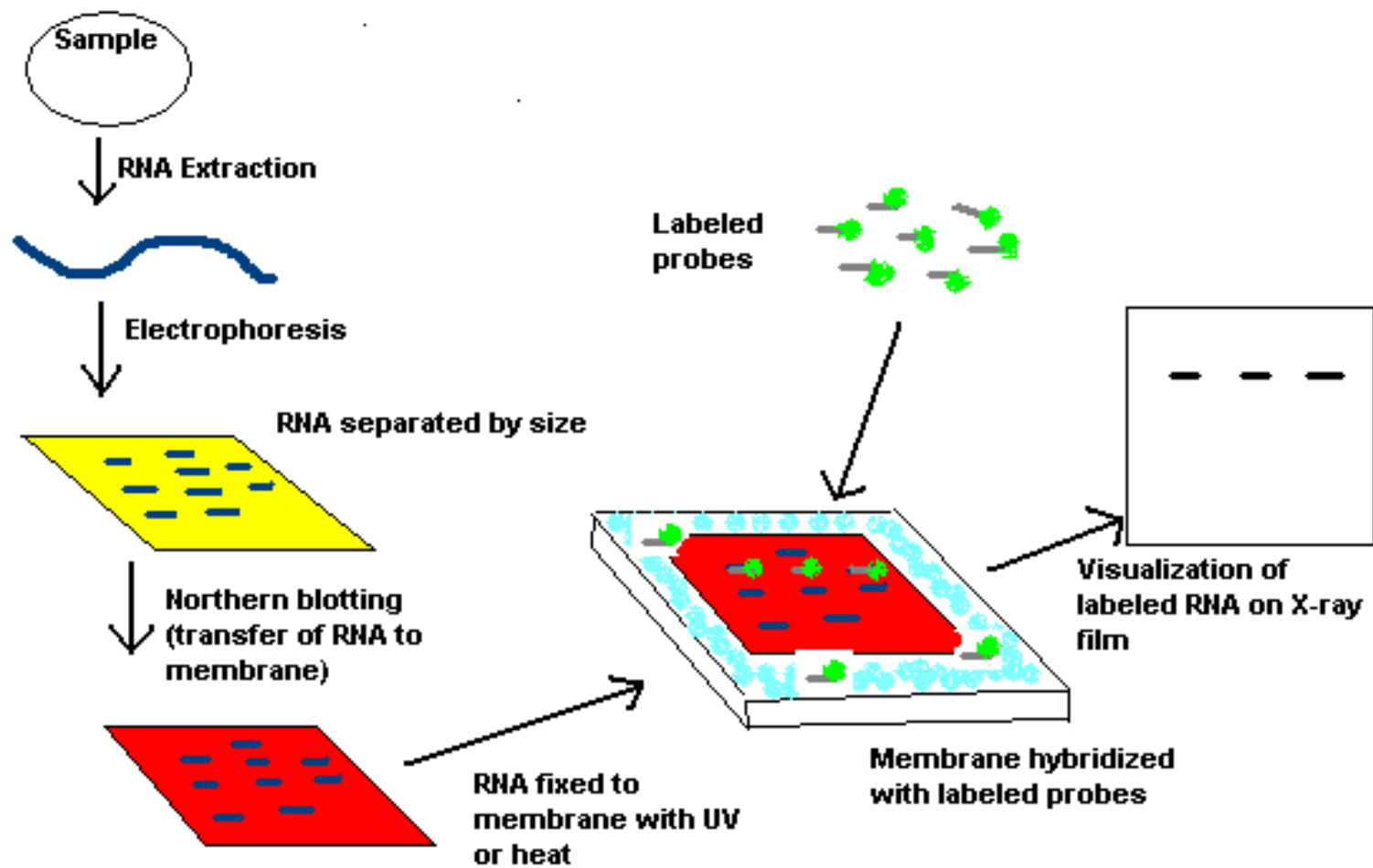
## For example ...


- If a researcher wants to know whether gene A is expressed in a particular tissue, the researcher would make a radio-labeled DNA probe by using a small piece of gene A, isolate mRNA from the tissue of interest, bind the mRNA to a solid medium (such as a nylon filter), and then hybridize the probe to the filter.





# Northern blot technique

- If gene A is expressed in the tissue, the researcher would see a radioactive signal on the filter.
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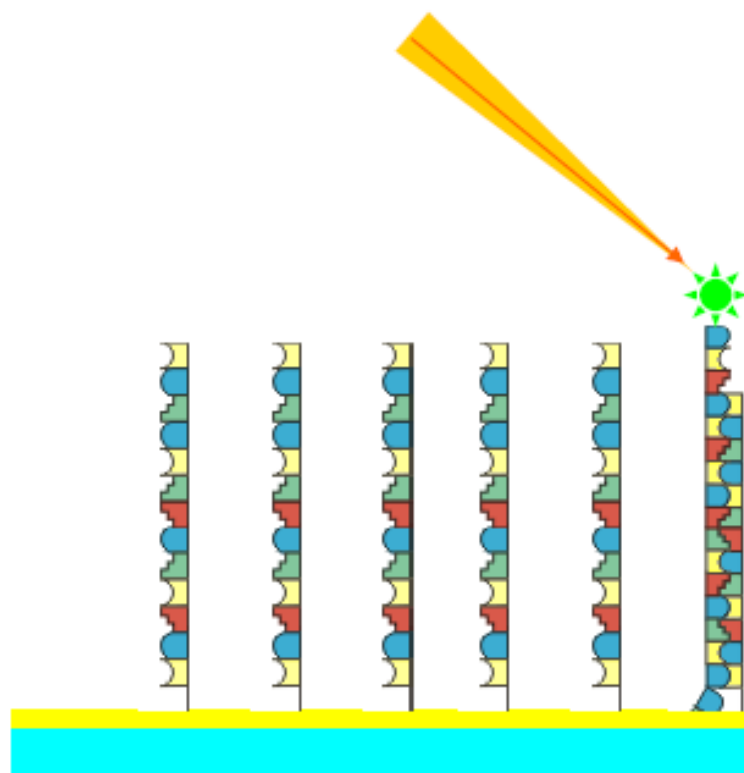


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- Imagine the power of being able to do thousands of these experiments at a time...
  - Here comes the DNA microarray !!!

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- DNA microarrays use the same DNA probe detection method but on a much larger scale.
  - Each microarray is made up of many bits of single-stranded DNA fragments arranged in a grid pattern on the glass or plastic surface.

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- When sample DNA or RNA is applied to the array, any sequences in the sample that find a match will bind to a specific spot on the array.
  - A computer then determines the amount of sample bound to each spot on the microarray.





4. 偵測方法: DNA-DNA 雜配

5. 訊號偵測

3. DNA 陣列

2. 表面塗劑

1. 載體

# Manufacturing methods

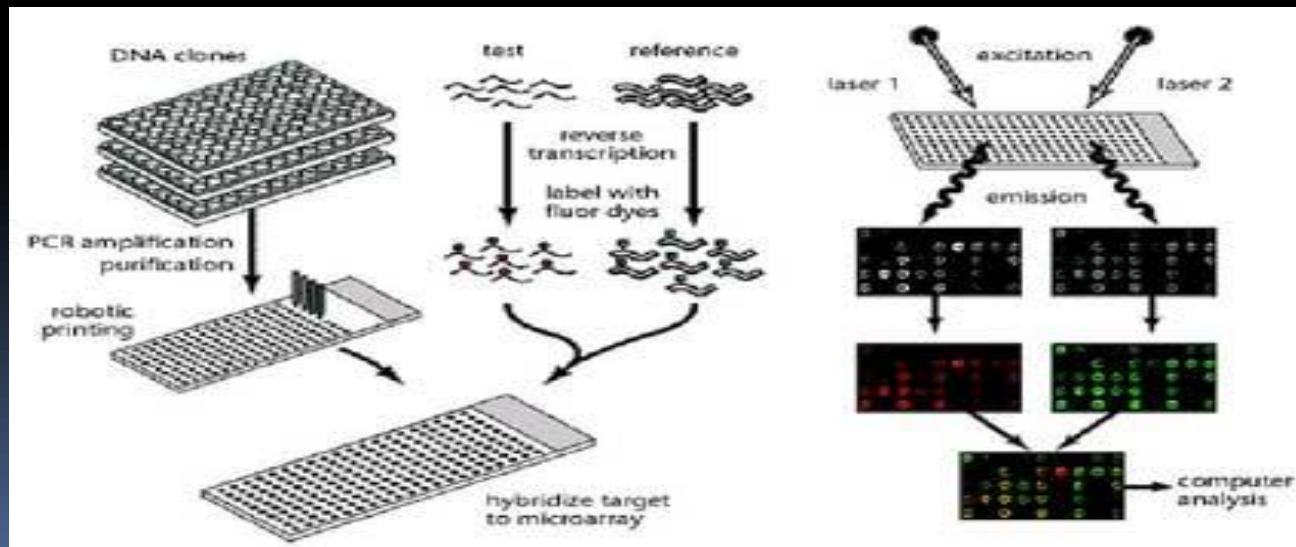
- Stanford
- 原位合成法(in situ synthesized)
- 微珠佈放法

# Stanford

- cDNA array(Complementary)
- 預先合成核酸探針放於玻片載體
- 探針長度20~70鹼基
- 優點：較長的探針長度可增加專一性。
- 缺點：晶片密度較原位合成法低，須有良好的保存設計。
- spotting & injet printing


# Spotting

- 用鋼針probe溶液直接點在附帶蛋白膜的玻璃/合成晶片上
- 成本低，probe長度不受限
- 分離probe費時，生產速度慢



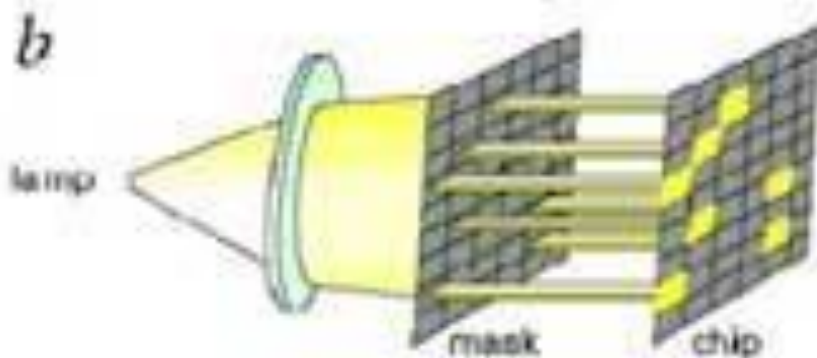
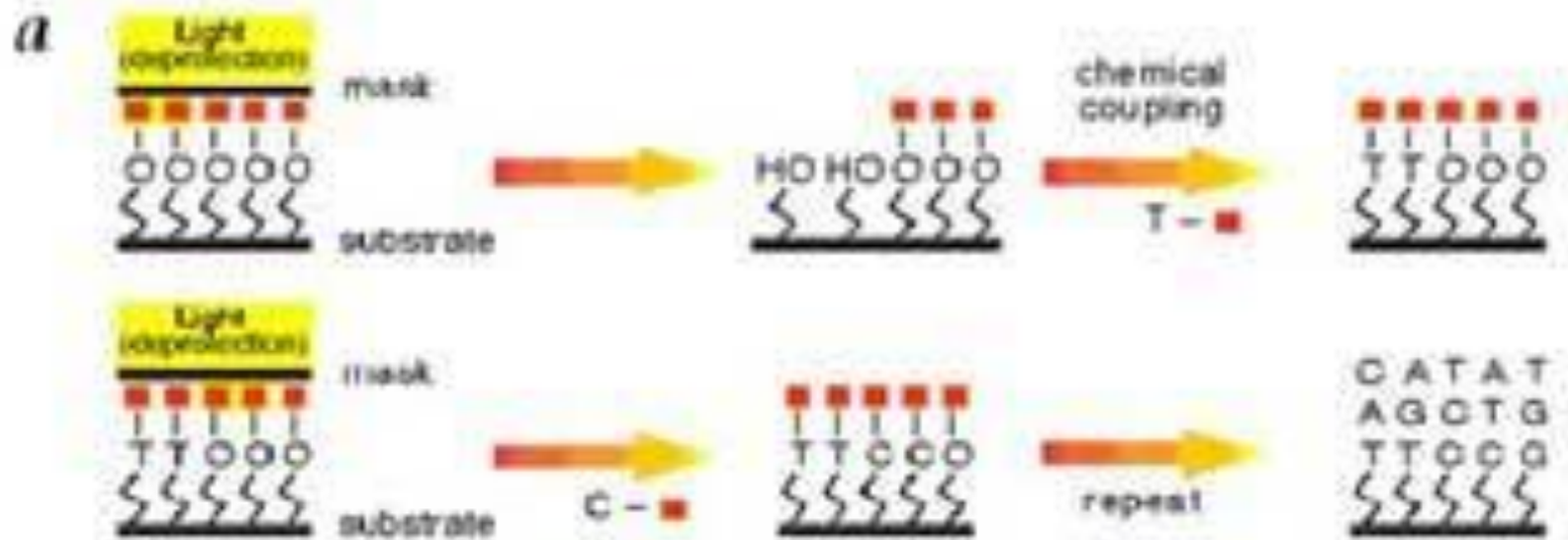


# Injet printing

- 似噴墨印表機的原理
  - 噴頭好壞影響晶片
  - 客製化設計且製作速度快
  - 昂貴
- 

# 原位合成法

- 似電子晶片製作的光刻法(Photolithography)
- 利用光罩控制反應位置
- 超高密度
- probe長度較短(25個鹼基)，須以多個probe對應一個基因降低誤判率



# 微珠佈放法

- Illumina公司
- probe 製作於微小顆粒上，再放置到載體



# 分類 --- 依據製作方式

- 在晶片上合成之寡核苷酸晶片  
(in situ synthesized oligonucleotide chips)
- 先合成之DNA晶片  
(pre-synthesized DNA chips)

# 寡核苷酸晶片

- 製作方式類似電子產業光蝕刻的方式，進行核苷酸的合成，將長度約 25 個鹼基的核苷酸合成在約指甲大小的晶片上。
- 製備完全機械化，成本高昂


# 先合成之 DNA 晶片

- 將預先合成好的 DNA 探針，通常長度為 100 ~ 5000 個鹼基，利用點陣 (spotting) 或是噴墨的方式，固定於晶片上。
- 製作成本較低，目前國內實驗室大多採用此種基因晶片。



# Application

## DNA

- monitoring gene expression
  - genomic structure, DNA sequencing
  - DNA-protein or RNA-protein interaction
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# Application

## Protein

- protein interaction
- epitope mapping
- Immobilized enzymes





# Application

## Tissue

- diseases
  - drug discovery
  - environmental testing
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# Future developments

- 基因表現的藍圖: 了解疾病和基因間的關係
- 毒理學上的分析: 檢測有機毒物對特定基因之表現
- 基因的定序: 同時且大量的做基因定序
- 法醫學上的應用: 檢定快速、準確且易攜帶，可望成為未來法醫現場辦案的利器

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- 藥物篩選: 將藥品與其接受器(receptors) 緊密結合的特性運用在晶片上
  - 蛋白質晶片: 將探針改為蛋白質，進行更深入的蛋白質生物學的研究
  - 免疫反應分析: 利用抗原抗體的結合性
- 



# Reference

- 生物晶片專題  
<http://biolaw.myweb.hinet.net/data/data12/2001070201.htm>
- 生物晶片概論  
[http://www.chichen6.tcu.edu.tw/teaching/20071015\\_SNP,%20protein%20Chips%20\(BC4\).pdf](http://www.chichen6.tcu.edu.tw/teaching/20071015_SNP,%20protein%20Chips%20(BC4).pdf)
- Tissue Microarray  
<http://www.microarraystation.com/tissue-microarray/>