認識微型ＲＮＡ(MicroRNA)在生物醫學的功用

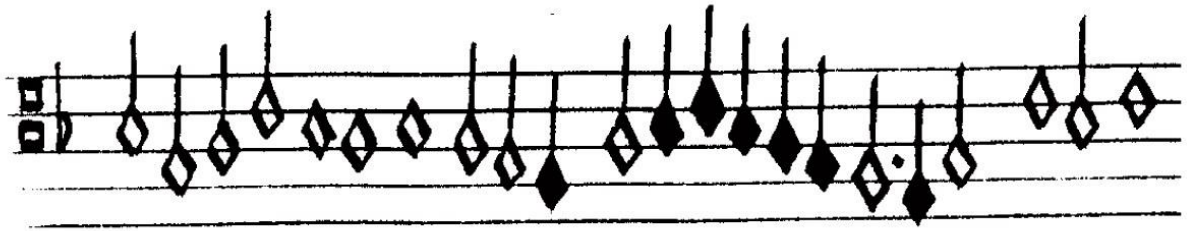
系統生物與生物資訊研究所

馬念涵

4/07/2015

排列組合的美妙
---提供不同的訊息

(A) **molecular biology is...**

(B) 

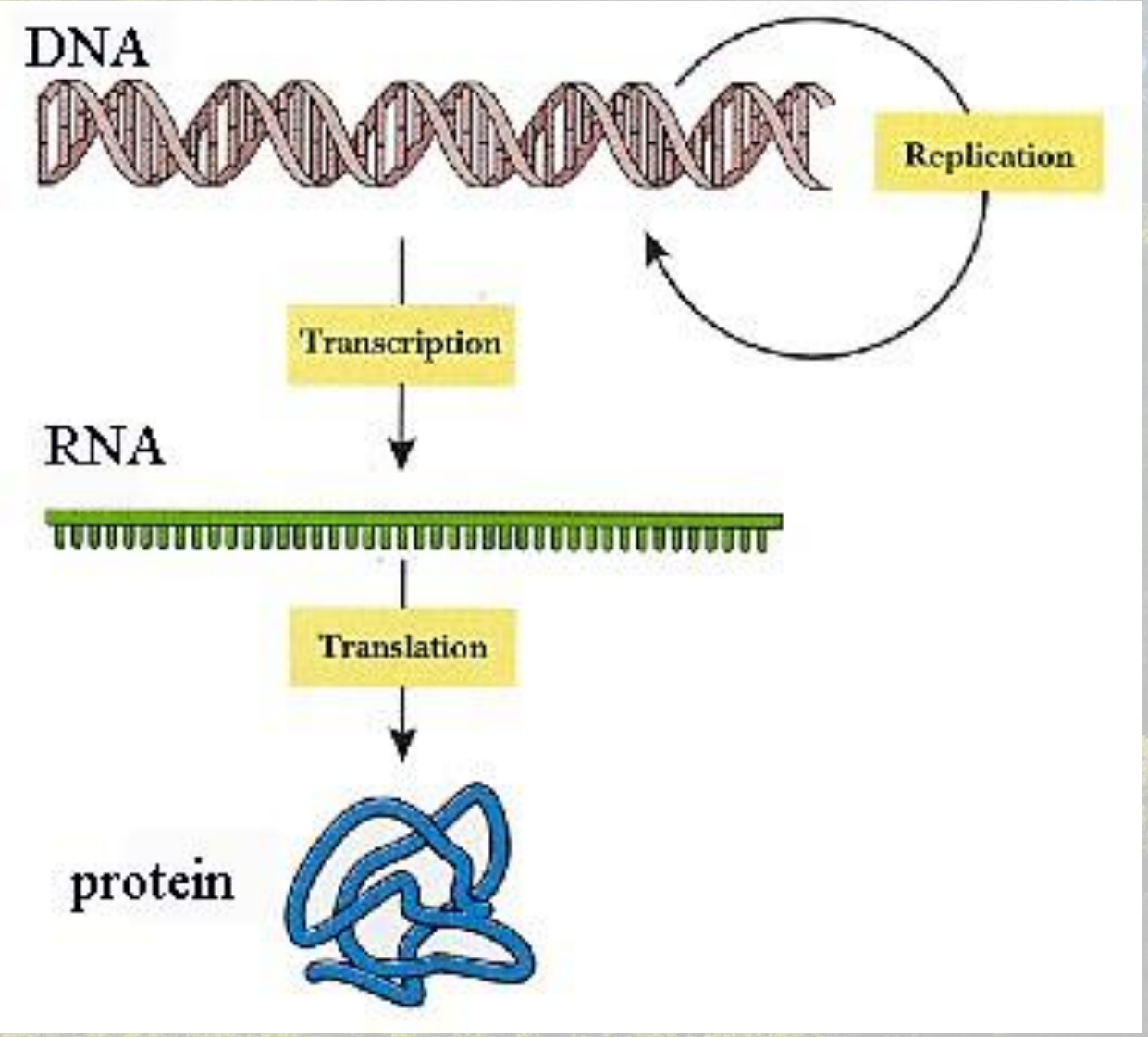
(C) •▬ •▬•• •• ▬•▬• •

(D) 乡田胞生物草乐趣无穷

(E) **TTCGAGCGACCTAACCTATAG**

Figure 5-8 Essential Cell Biology 3/e (© Garland Science 2010)

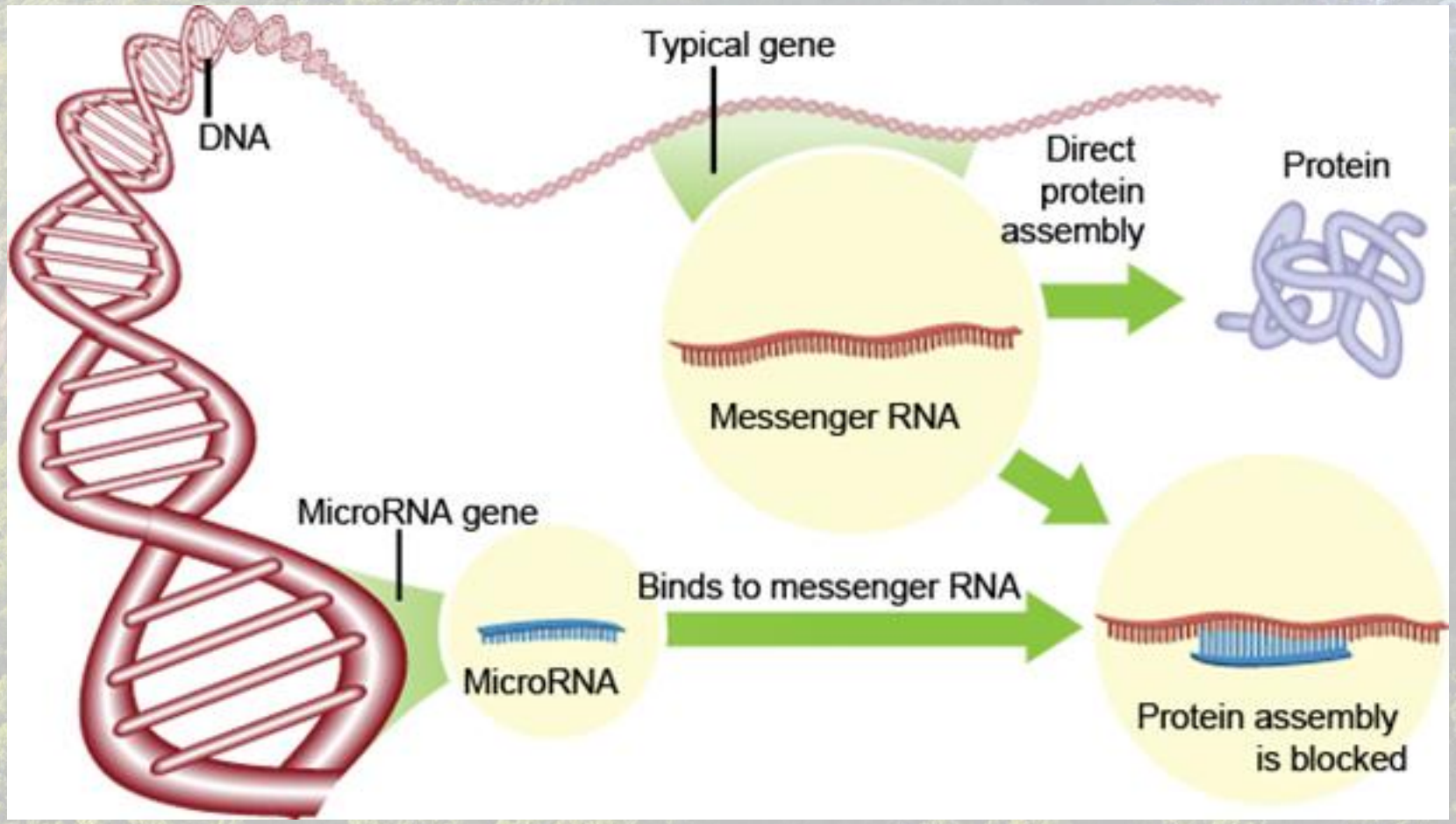
The Central Dogma



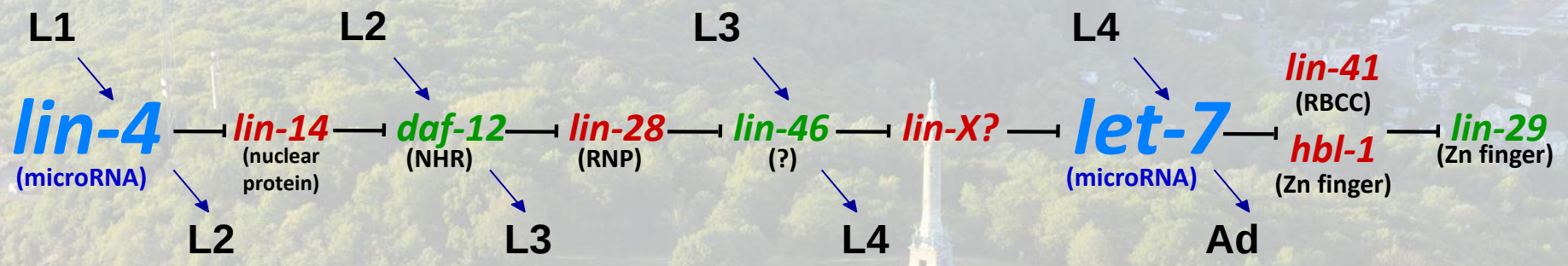
Non-coding RNAs are important regulators of gene expression

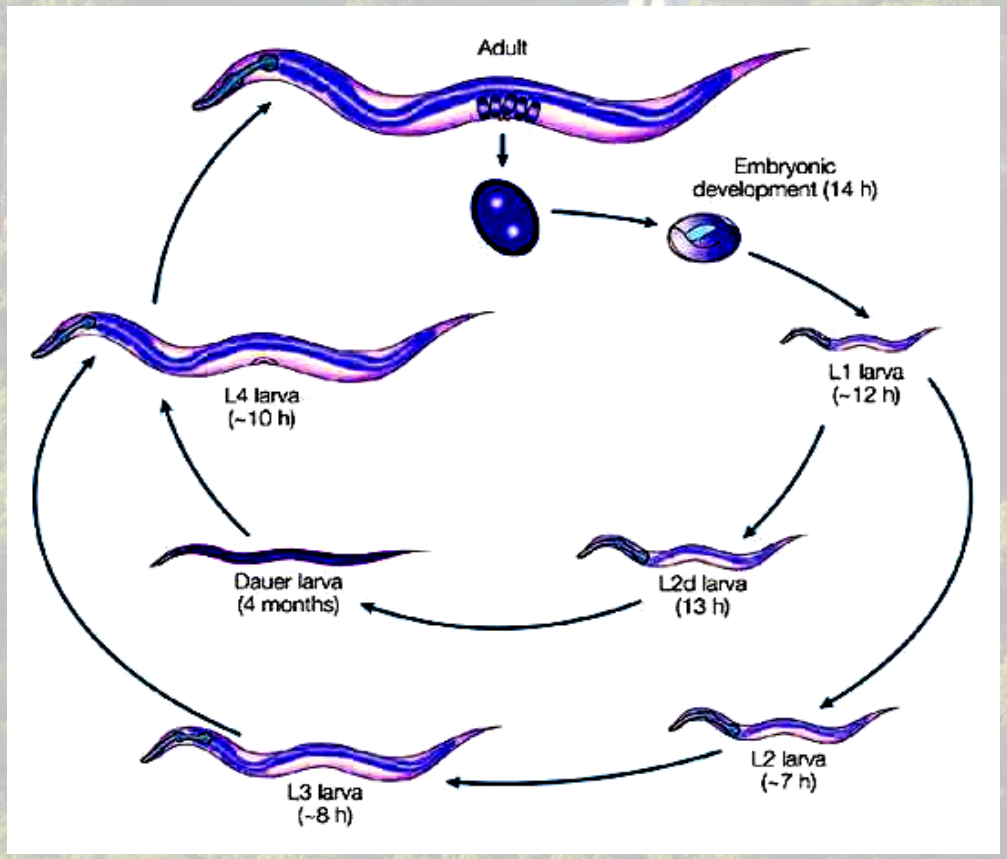
A new paradigm of gene regulation

Non-coding RNAs



MicroRNAs were discovered in *C. elegans*

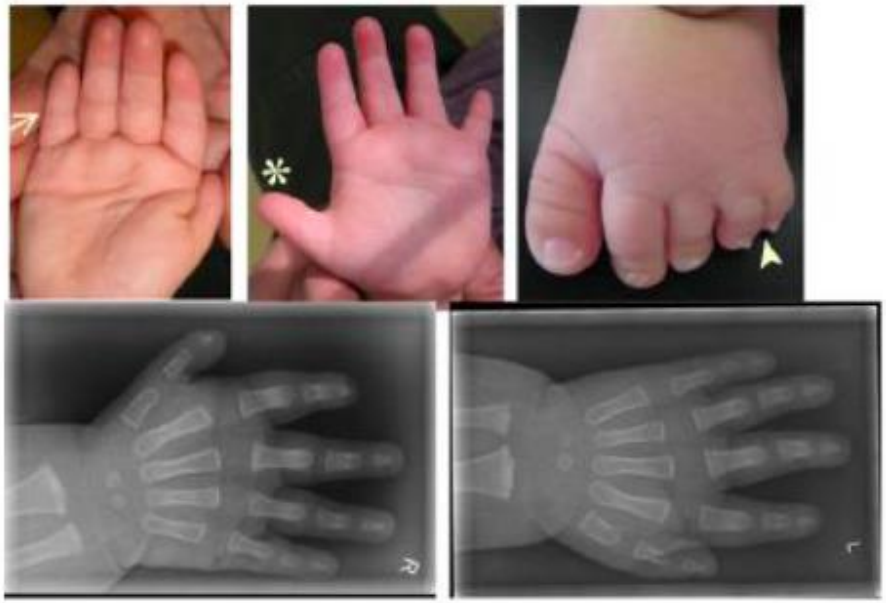


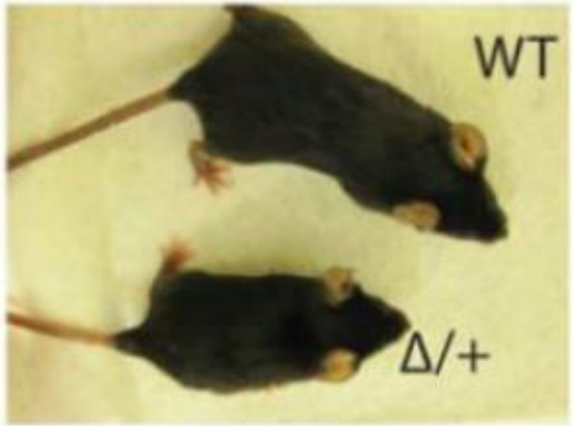


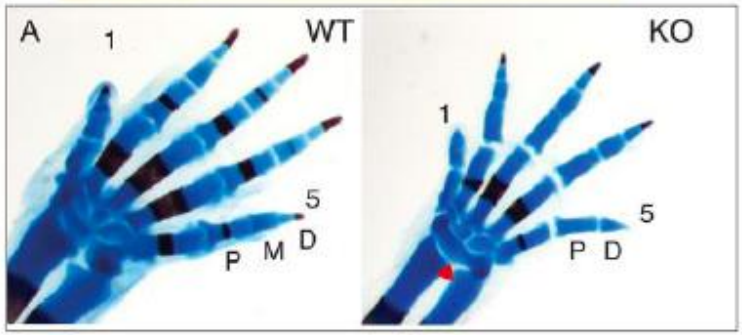
miRNA and inherted disease

miR-17-92 polycistron

Example of miRNA mutation responsible for a developmental defect in humans (de Pontual Nat Genet. 2011)







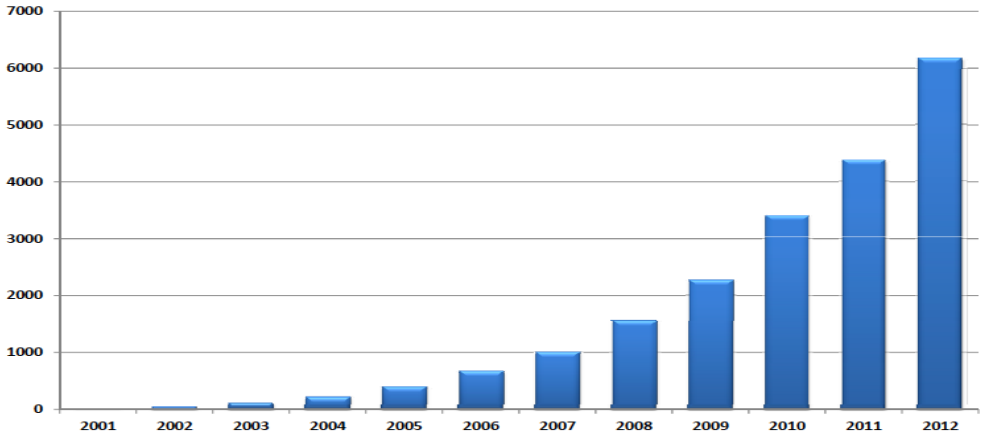
Hemizygous deletion –
Short stature and digital abnormalities

miRNA: A rapidly emerging field

Discoveries

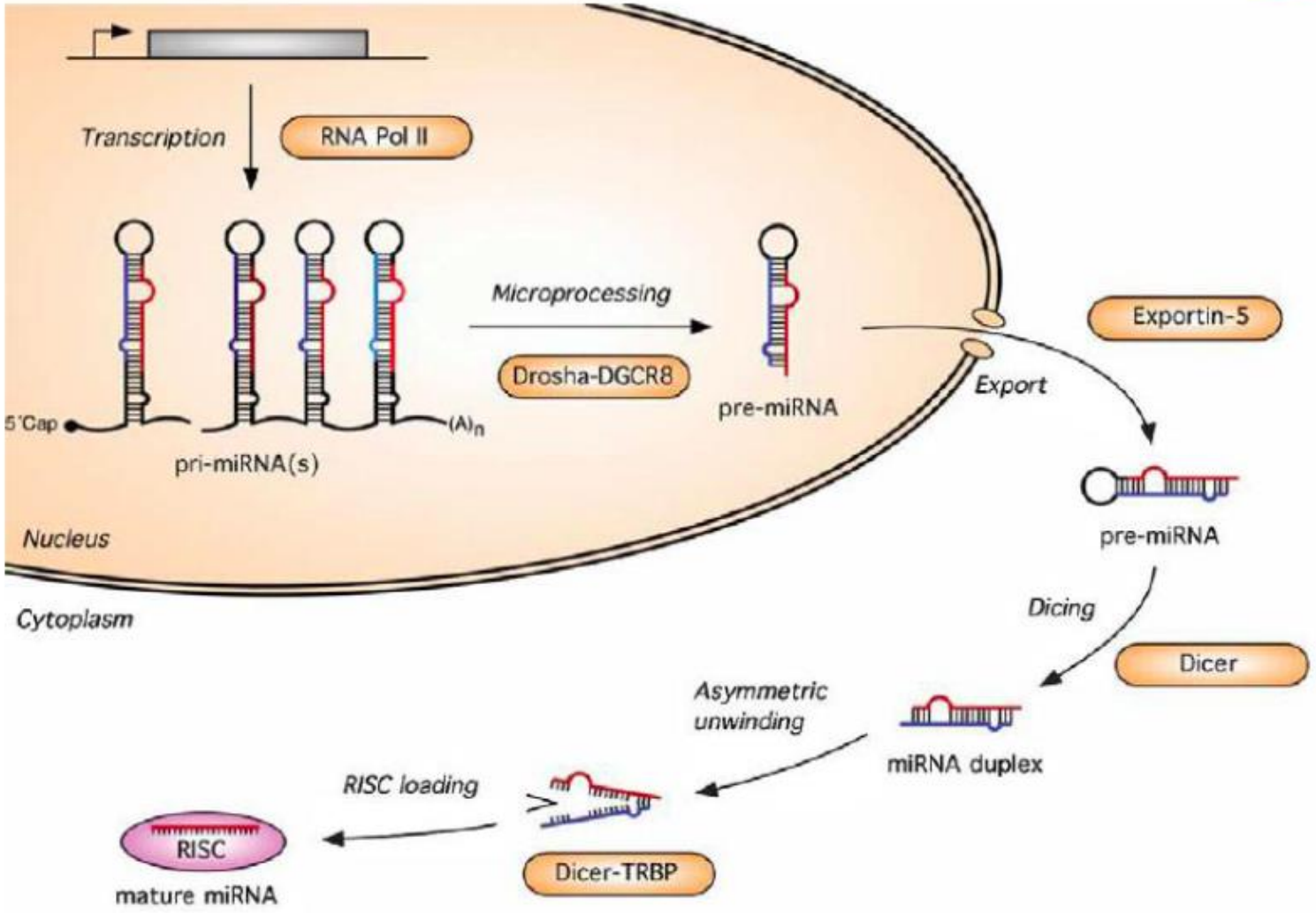
1993	1998	1999	2001	2002	2004	2005
The first miRNA, *lin-4*	dsRNA to be the trigger of RNAi	siRNAs as guide for RNAi	**miRNAs established as large class of gene regulators**	**miRNAs implicated in cancer**	First IND application for therapeutic siRNA	**miRNAs shown to act as oncogenes**

Publications in PubMed



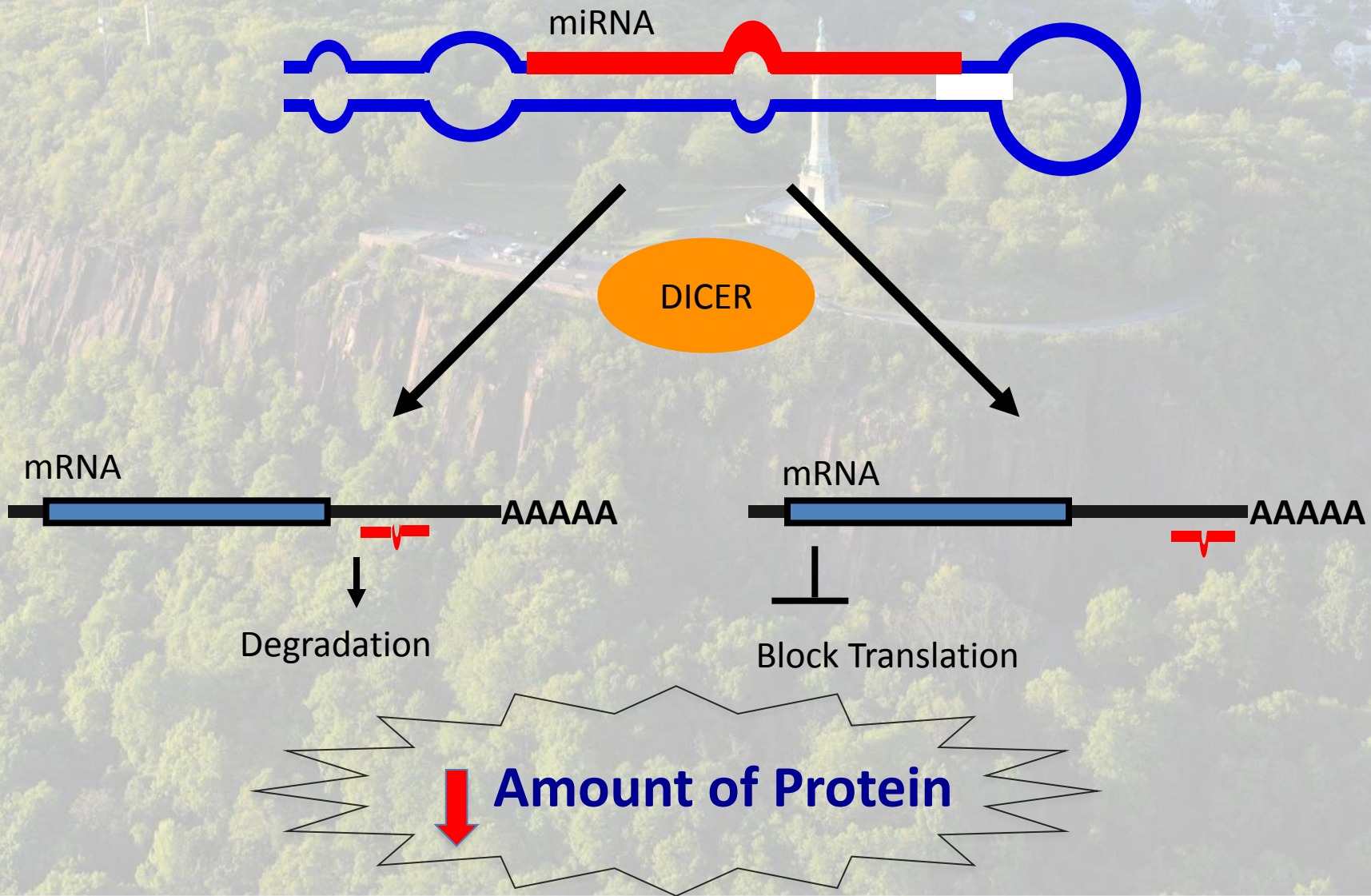
http://www.interna-technologies.com/index.php

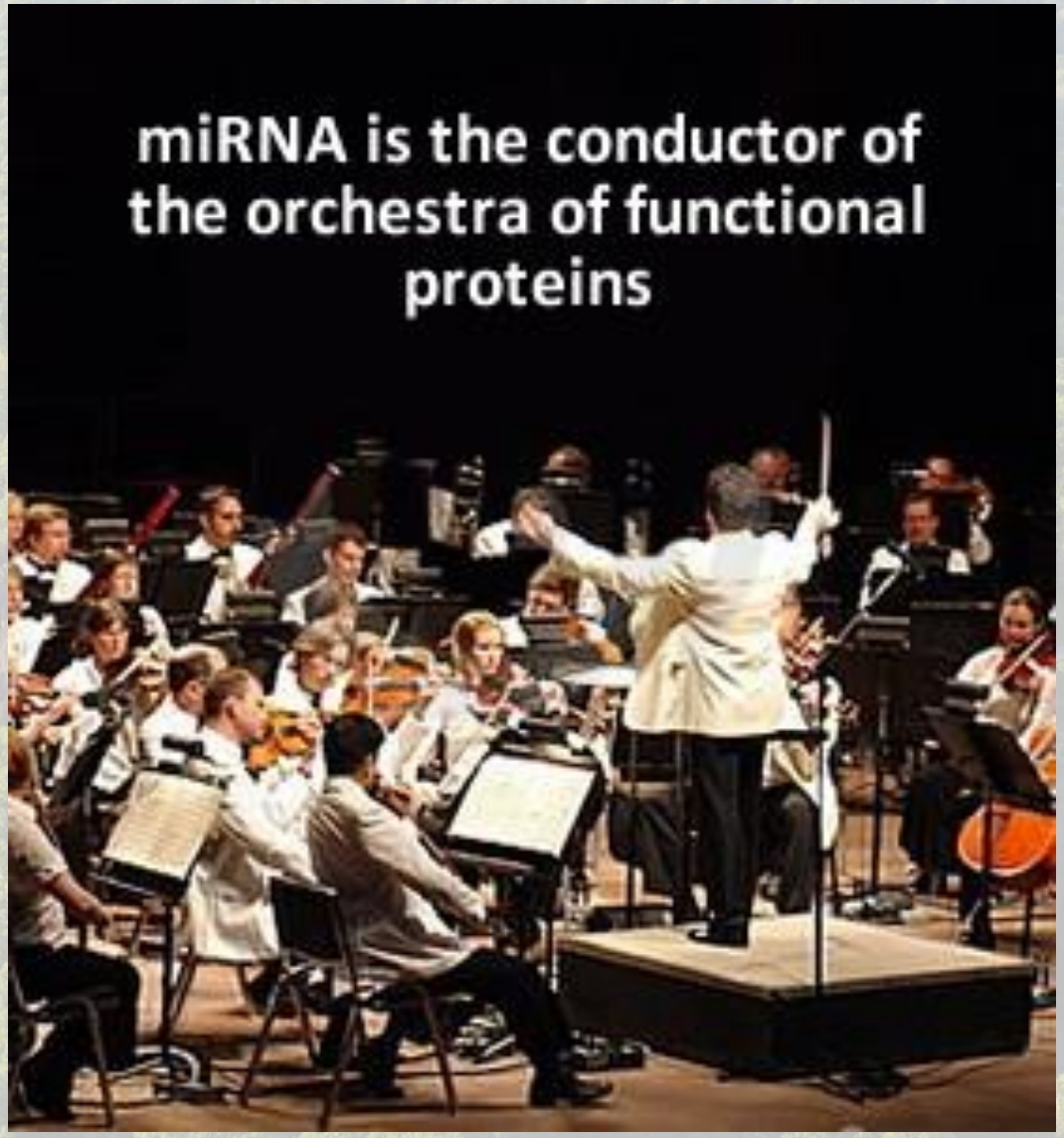
micrioRNA processing



Wienholds 2005 FEBS letters

MicroRNAs regulate gene expression using multiple mechanisms



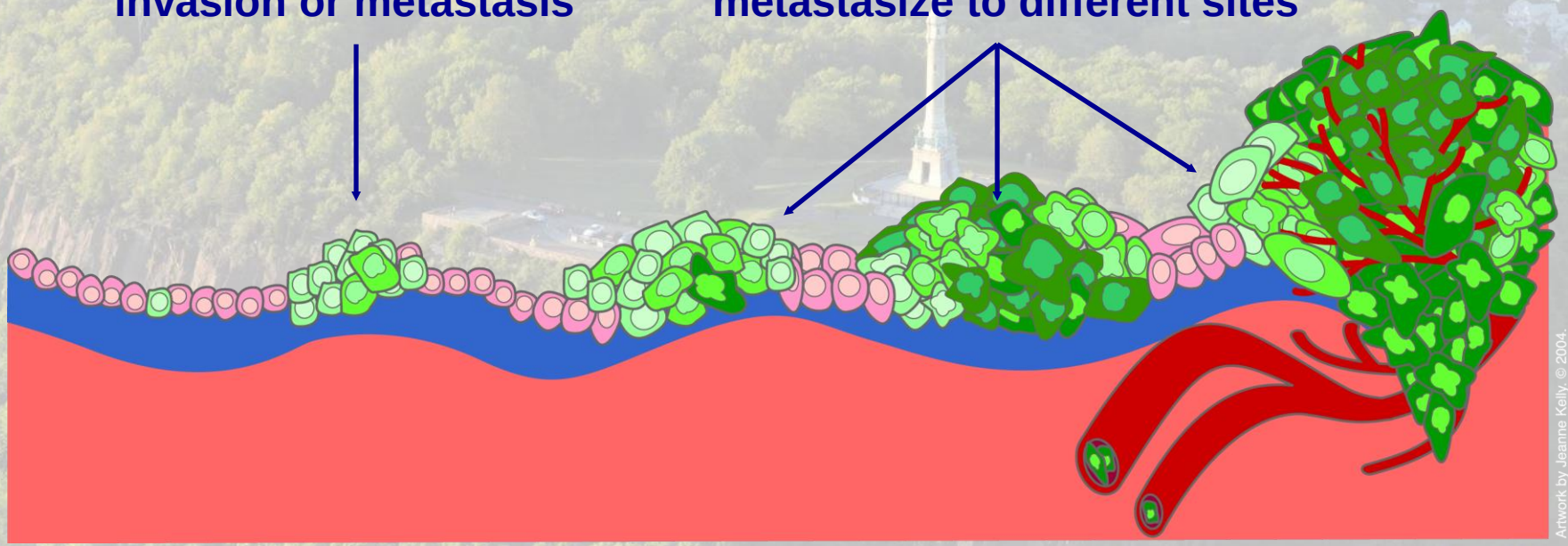


- **Affect >60% gene expression**

Cancer Tends to Involve Multiple Mutations

Benign tumor cells grow only locally and cannot spread by invasion or metastasis

Malignant cells invade neighboring tissues, enter blood vessels, and metastasize to different sites



Time

Mutation inactivates suppressor gene

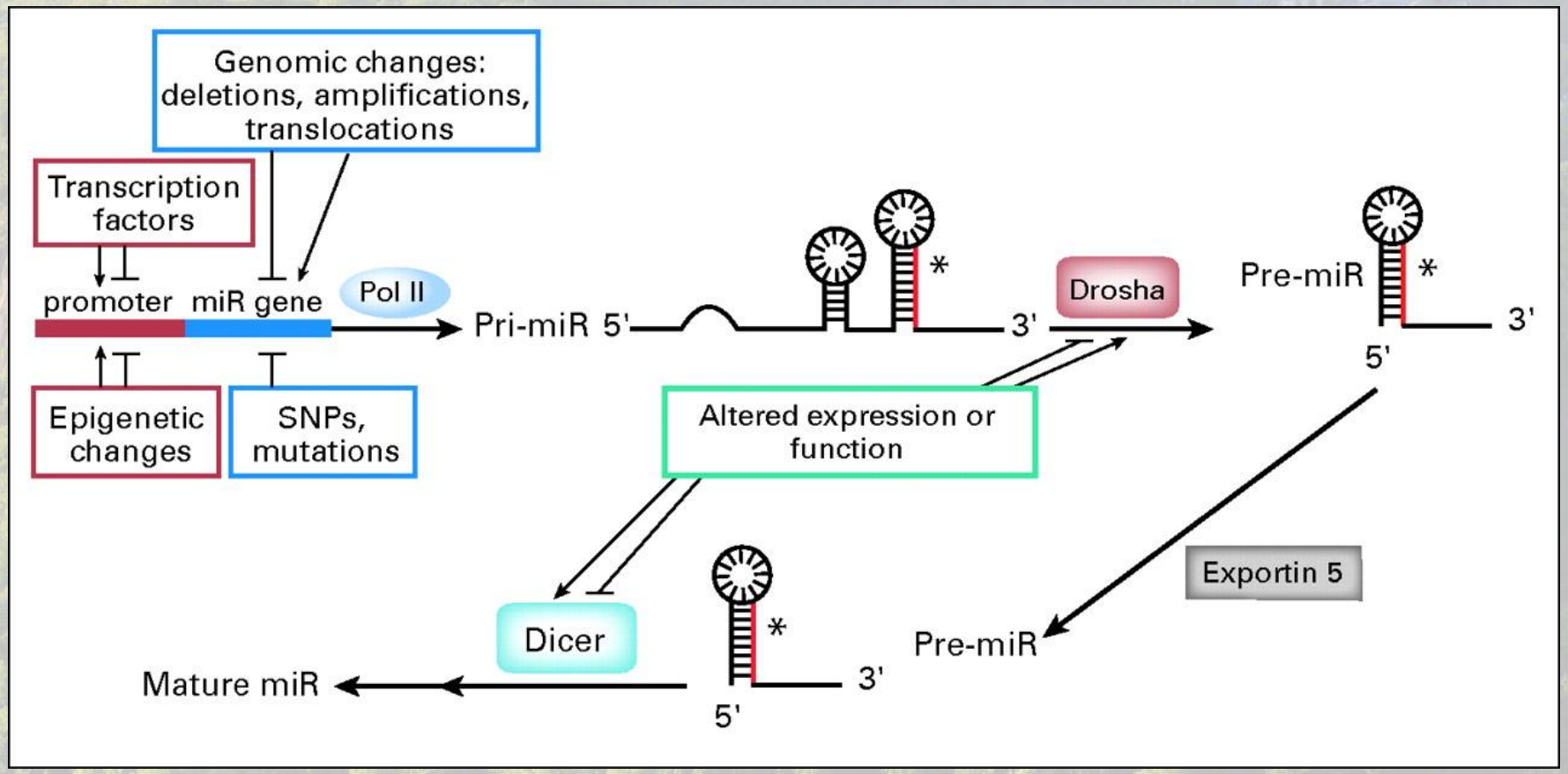
Cells proliferate

Mutations inactivate DNA repair genes

Proto-oncogenes mutate to oncogenes

More mutations, more genetic instability, metastatic disease

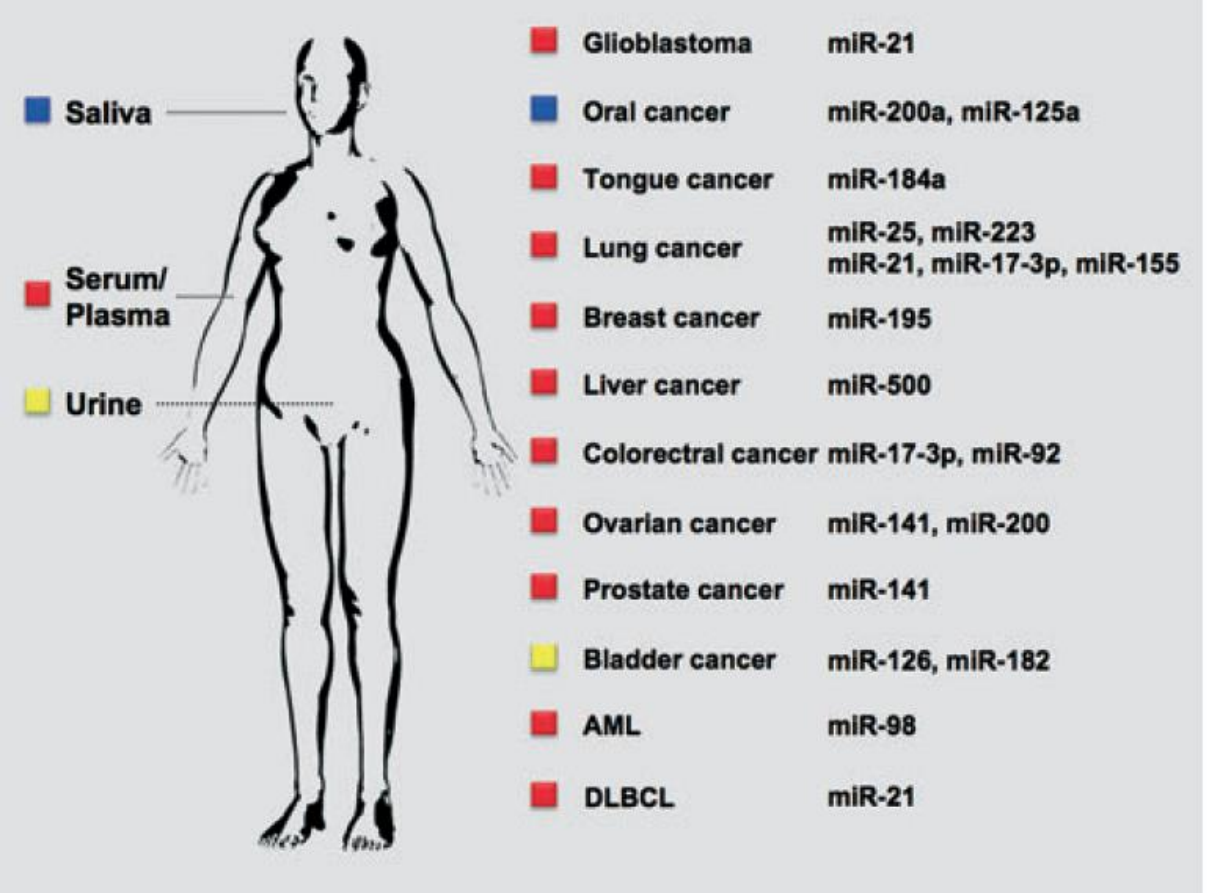
Mechanisms of microRNA mis-regulation in diseases



Iorio, M. V. et al. J Clin Oncol; 27:5848-5856 2009

➢Circulating microRNAs in the body fluid: a new potential biomarker for cancer diagnosis and prognosis

-The first paper was published in 2008



Cancer Science 2010, vol.101, p2087-2092

miRNA expression: a new potential biomarker

Clinical Chemistry 56:6
998–1006 (2010)

Molecular Diagnostics and Genetics

Robust MicroRNA Stability in Degraded RNA Preparations from Human Tissue and Cell Samples

Monika Jung,[1] Annika Schaefer,[1,2,3] Isabel Steiner,[1,2,4] Carsten Kempkensteffen,[1] Carsten Stephan,[1] Andreas Erbersdobler,[4] and Klaus Jung[1,2*]

nature

Vol 435|9 June 2005|doi:10.1038/nature03702

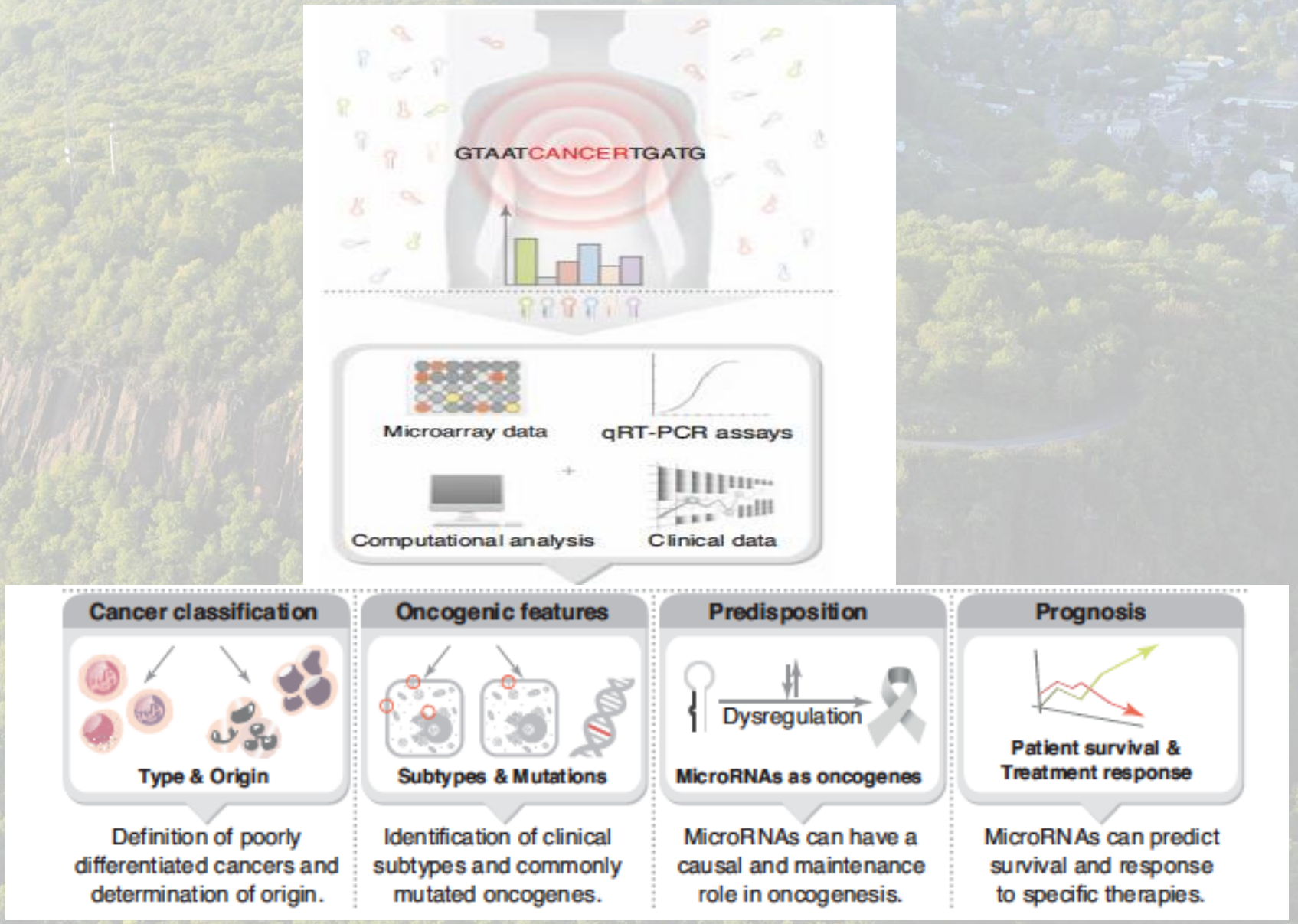
LETTERS

MicroRNA expression profiles classify human cancers

Jun Lu[1,4*], Gad Getz[1*], Eric A. Miska[2*†], Ezequiel Alvarez-Saavedra[2], Justin Lamb[1], David Peck[1], Alejandro Sweet-Cordero[3,4], Benjamin L. Ebert[1,4], Raymond H. Mak[1,4], Adolfo A. Ferrando[4], James R. Downing[5], Tyler Jacks[2,3], H. Robert Horvitz[2] & Todd R. Golub[1,4,6]

microRNA profiles are more effective in cancer classification than mRNA profiles containing over 16,000 genes

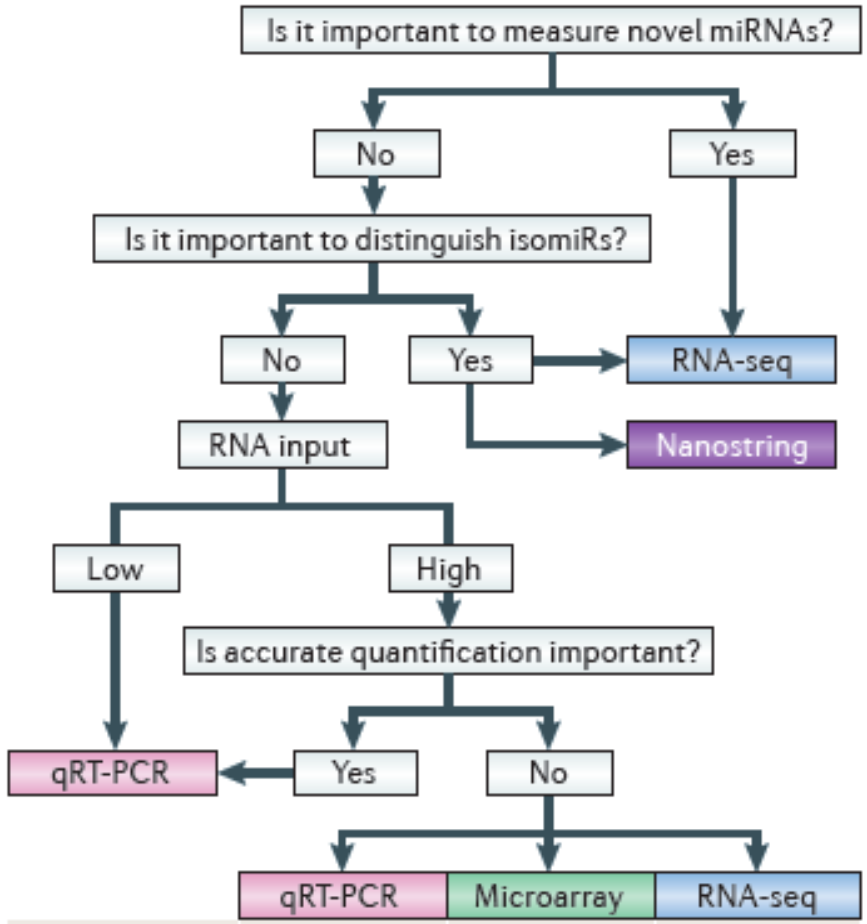
➢Circulating microRNA in the body fluid: a new potential biomarker for disease diagnosis and prognosis



Modified from TRENDS in Molecular Medicine

Systems biology comes to the rescue!

MicroRNA profiling: approaches and considerations

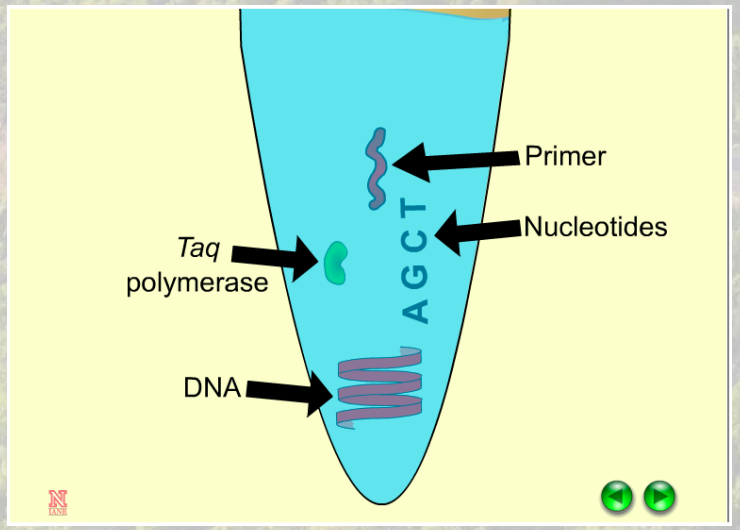


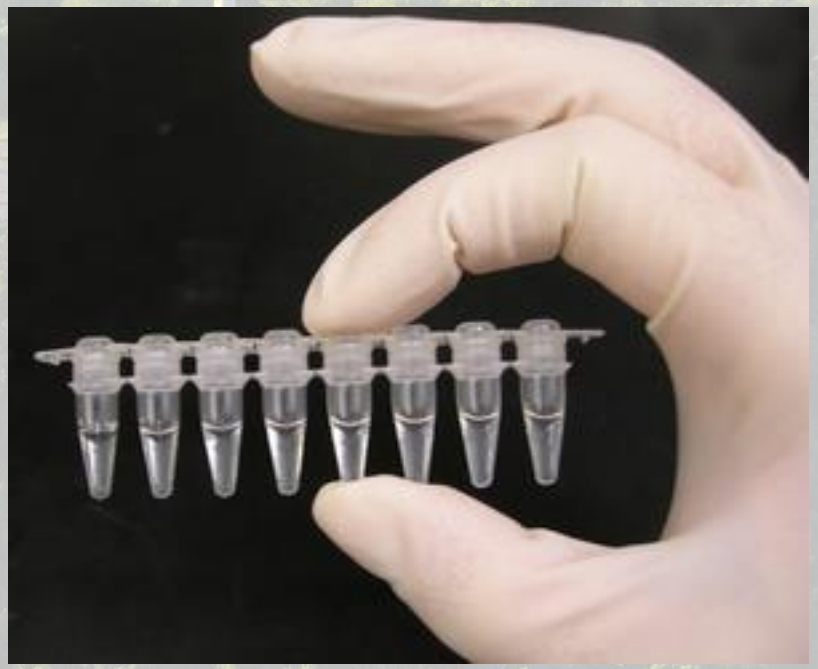
	qRT-PCR	Microarray	RNA-seq
Sensitivity	+++	+/++	++
Dynamic range	++++	+	+++
Cost	$$	$	$$$*

Nature Reviews Genetics 2012, 13,358-369

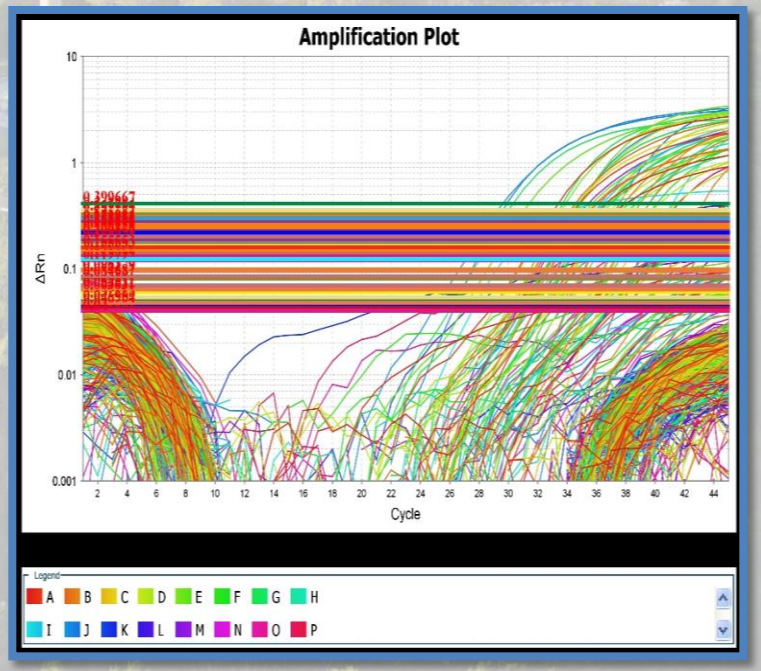
如何檢測微量的檢體?

高通量PCR聚合酶連鎖反應





MicroRNA Analysis



The TaqMan® Array Human MicroRNA Card (Containing a total of 754 human microRNAs)

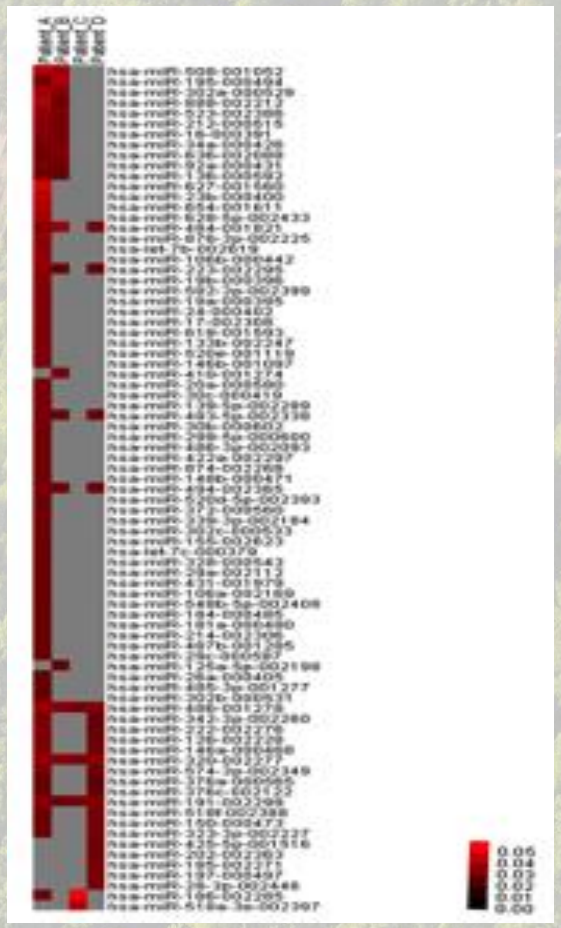
Output Data (CT Value)

microRNAs as biomarkers

Plasma microRNAs profiles

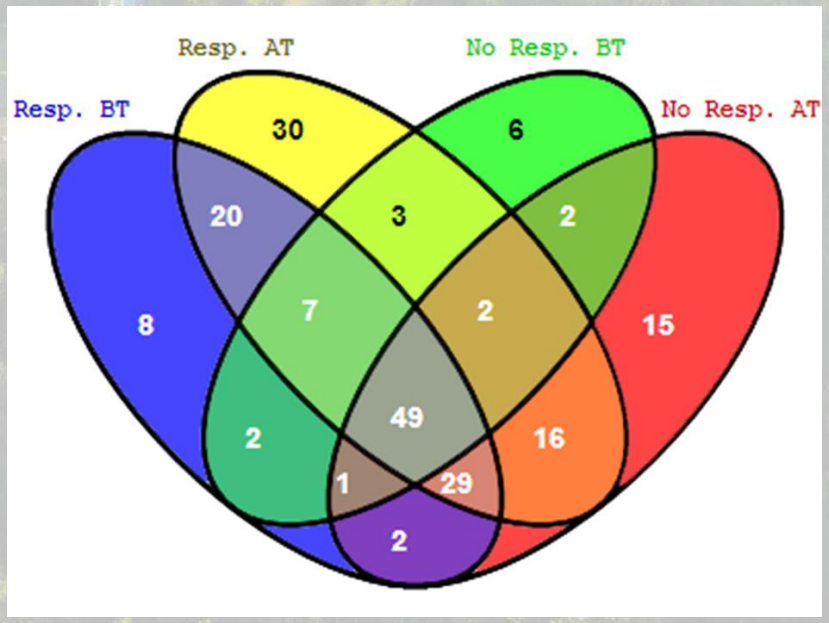
Diagnosis:

UC vs non-UC in kidney dialysis patients



Prognosis:

Radiation Therapy Response or no response



Nianhan Ma Lab

What are the advantages of microRNAs in therapy?

Cancer-signaling network

↓

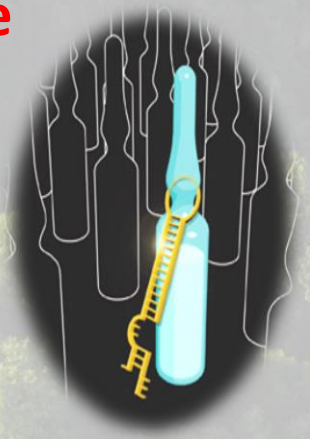
Effective therapies

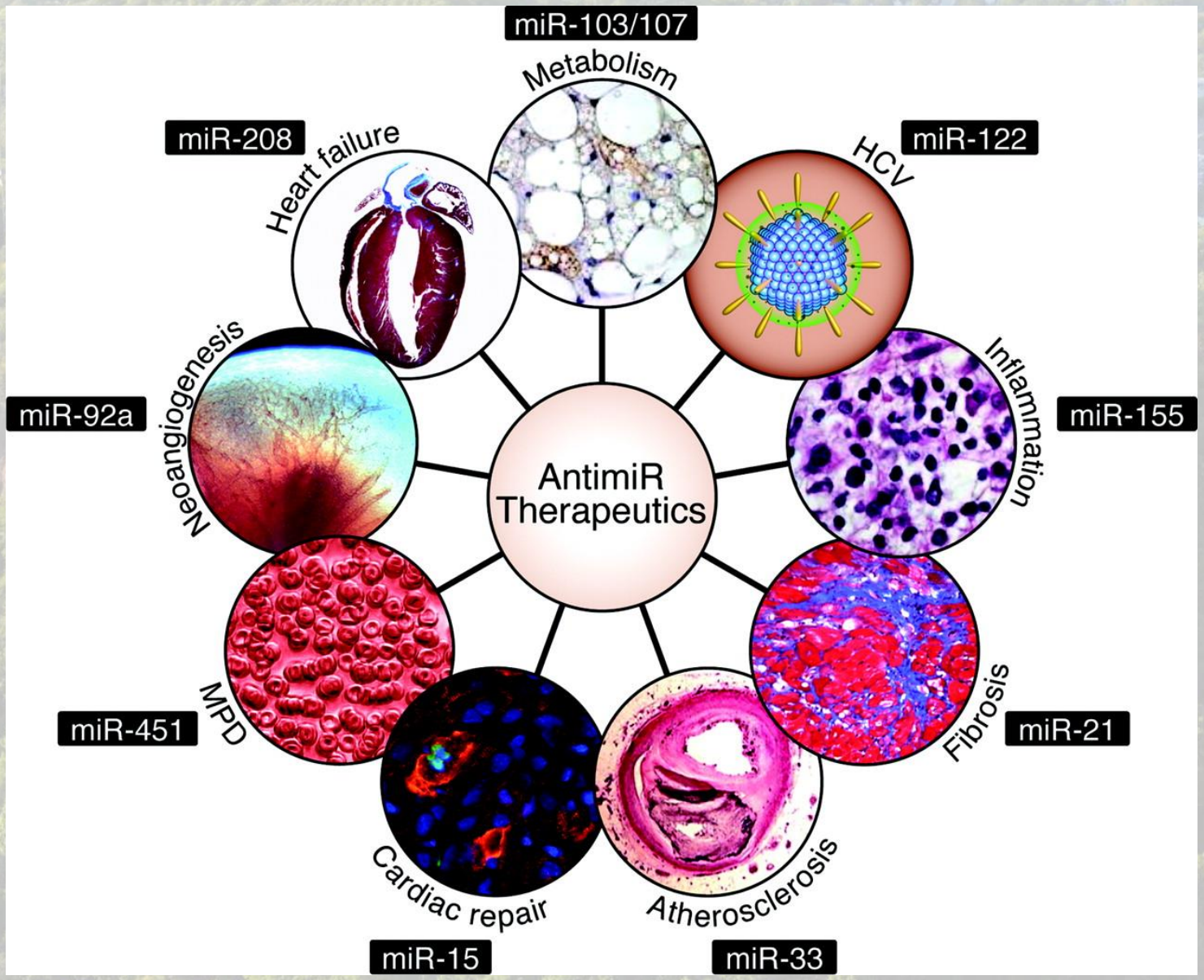
↓

Drug resistance,
Drug-induced toxicity.

⊣ microRNAs

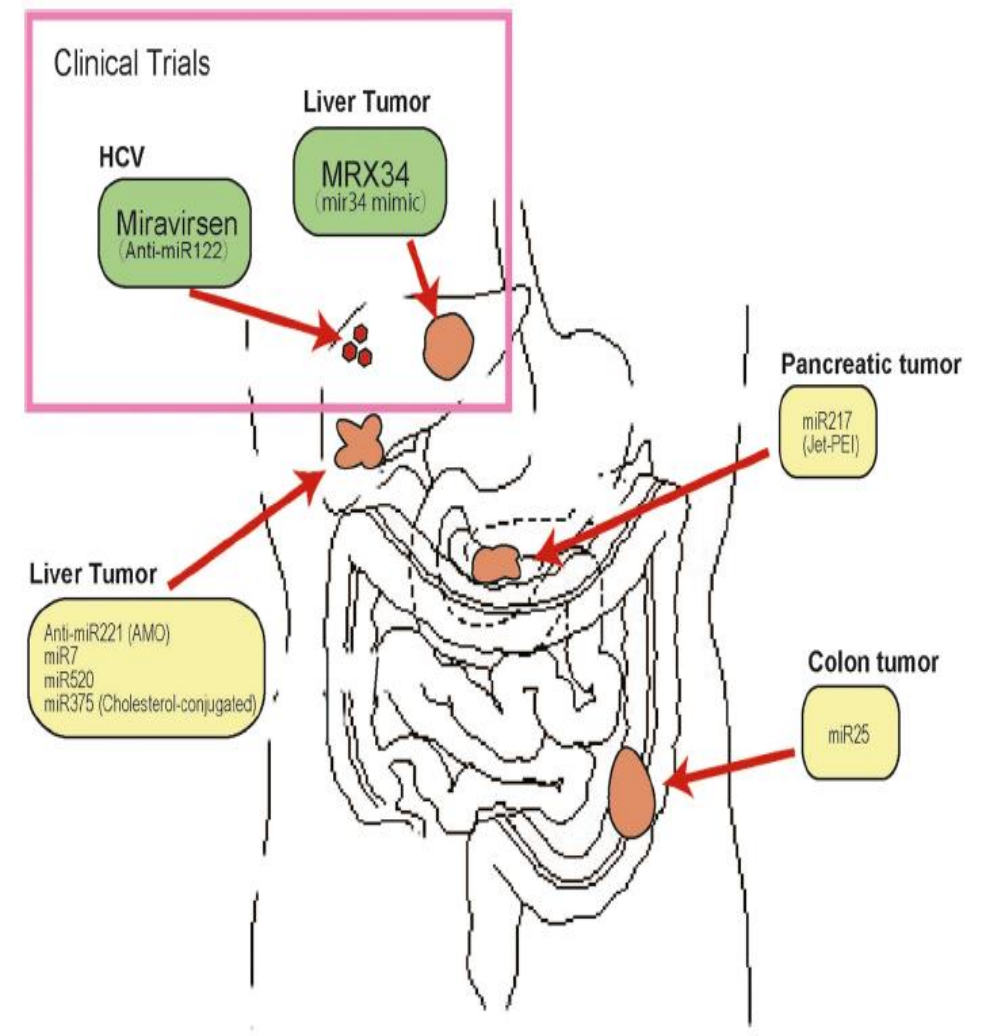
1) Regulate multiple genes
→ effective treatment
2) Endogenous
→ Less toxicity
→ Less "off-target" effect
→ reduce side effects
3) Drug resistance





Circulation Research 2012; 110:496-507

MicroRNAs Therapy in Cancer



*Molecular and Cellular Therapies 2013, **1**:5*

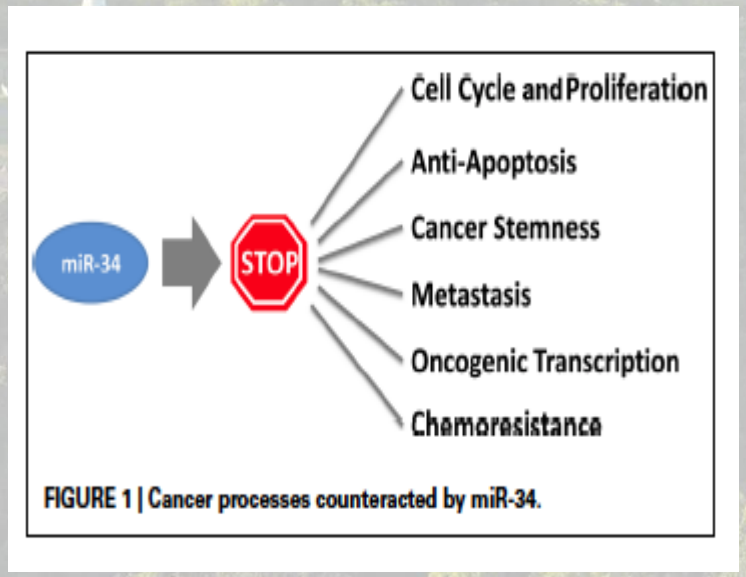


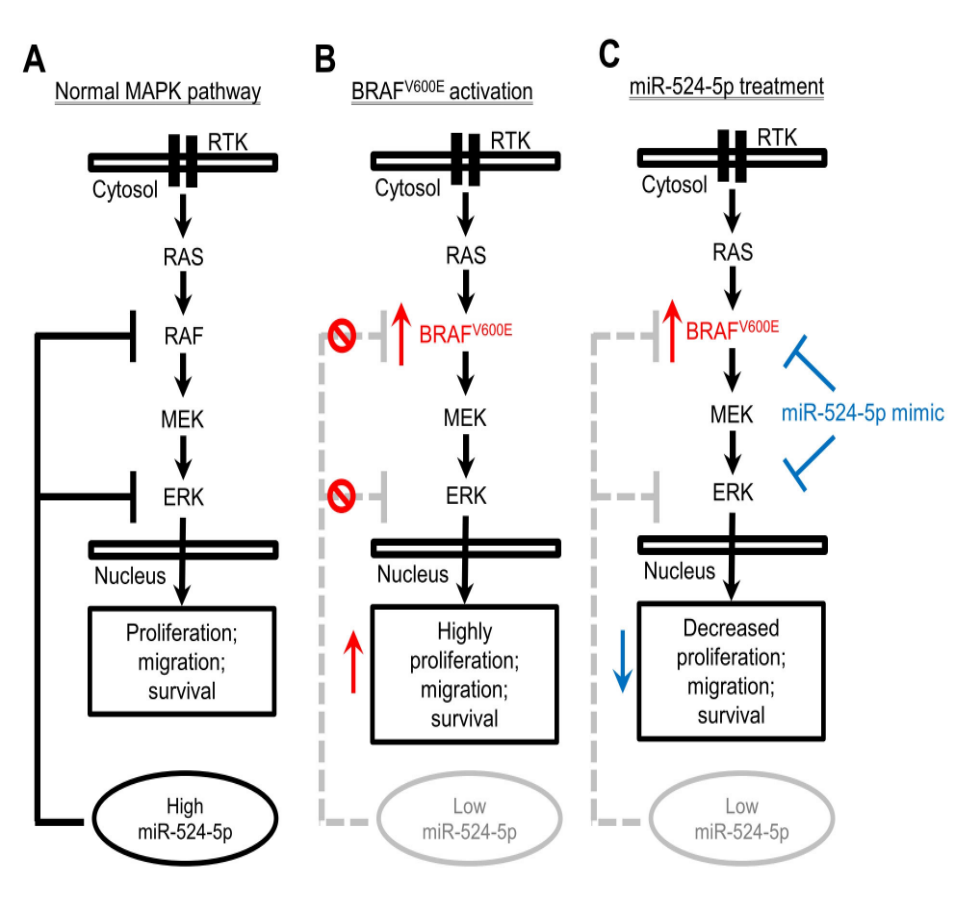
FIGURE 1 | Cancer processes counteracted by miR-34.

Frontiers in Genetics 2012,vol.3,p1-9

Develop microRNAs as the therapeutic tool

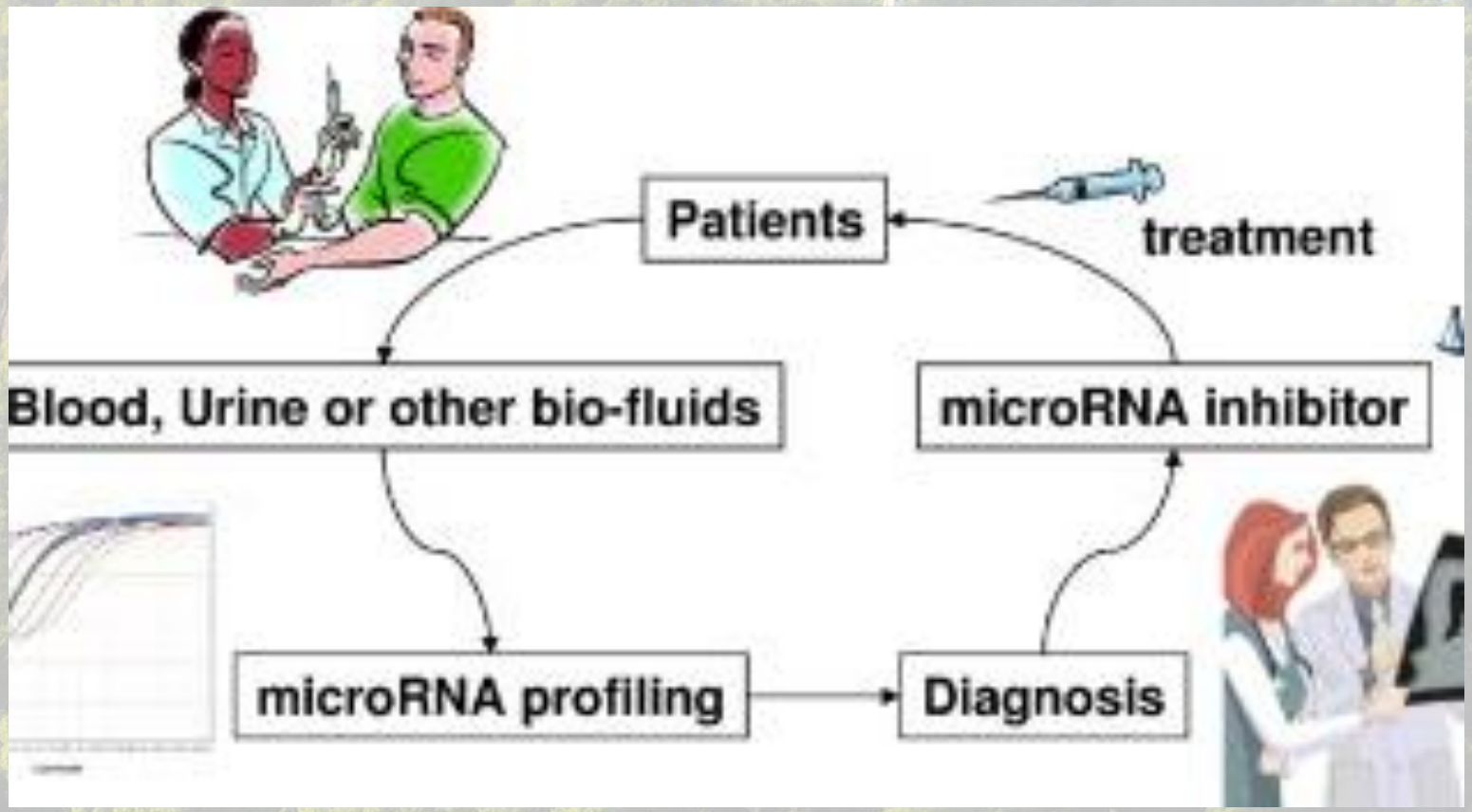
Nianhan Ma Lab

MicroRNAs function study



miR-524 as therapeutic miRNA for melanoma

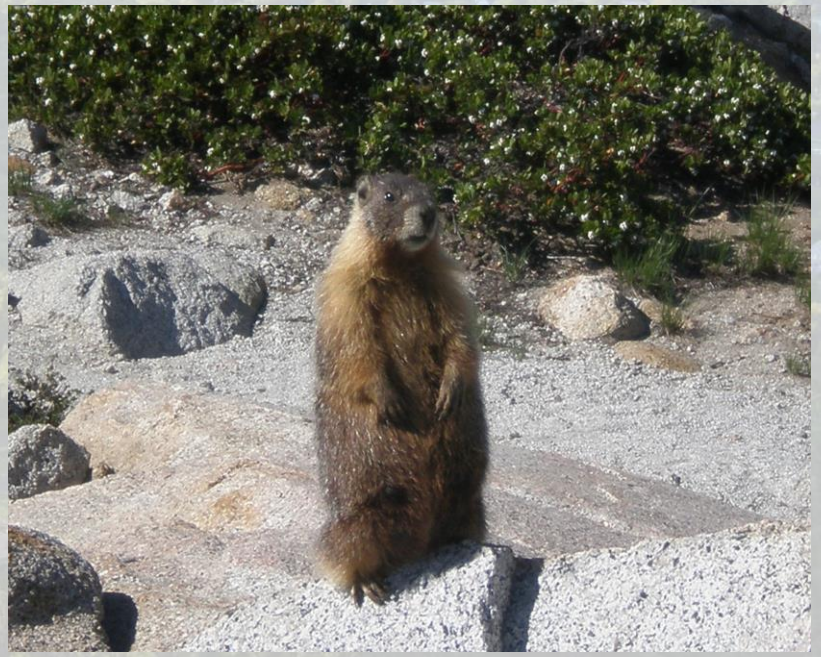
Future clinical application



Summary

- miRNAs are frequently mis-regulated and expressed at aberrant level in diseased tissue when compared to normal tissues.
- Circulating microRNAs are a new potential biomarker for disease diagnosis and prognosis
- miRNAs are natural molecules and are therefore less likely to induce side effects.

Any Questions ???



Lab intro **跨領域合作**

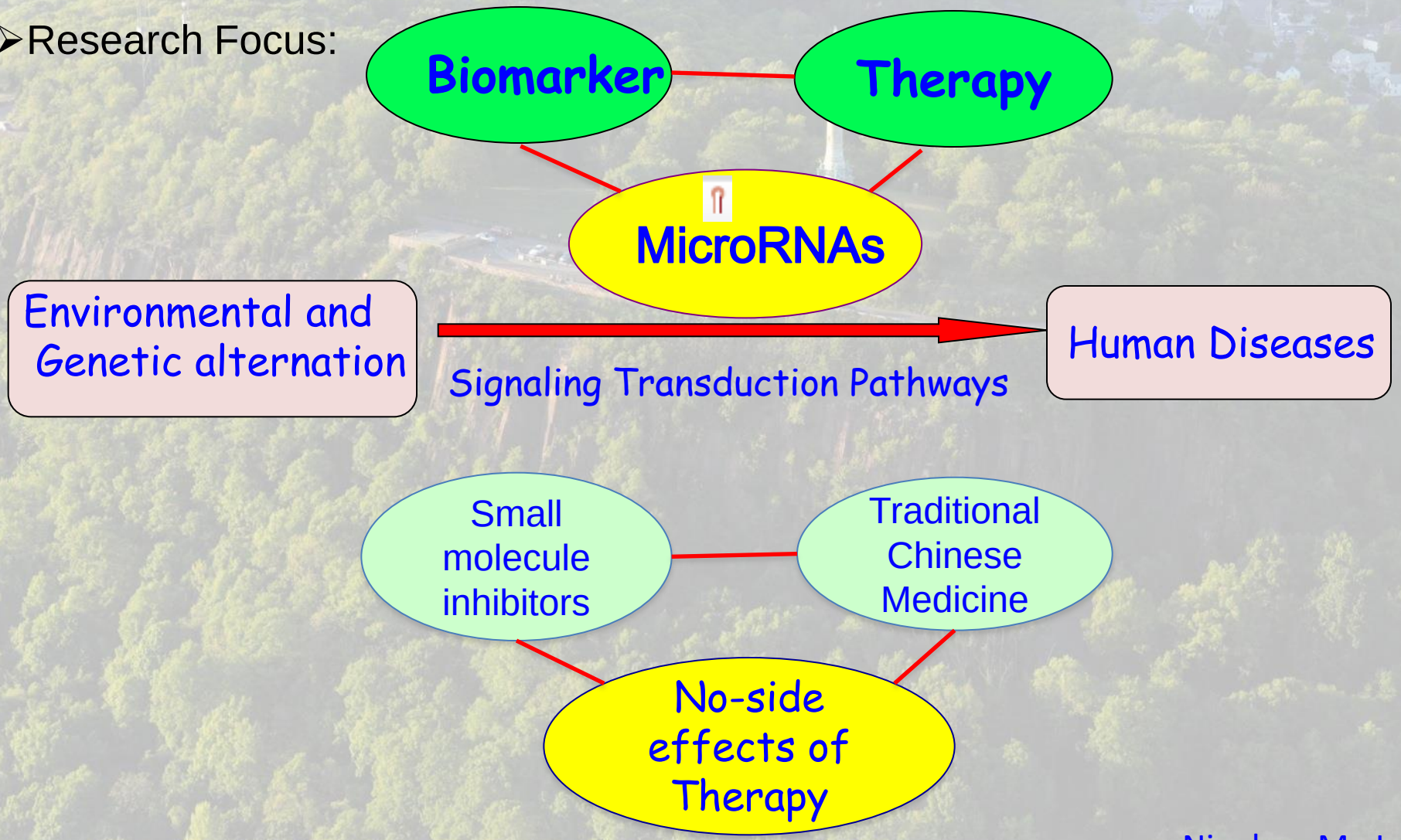
http://www.cc.ncu.edu.tw/~manhlin/Welcome.html

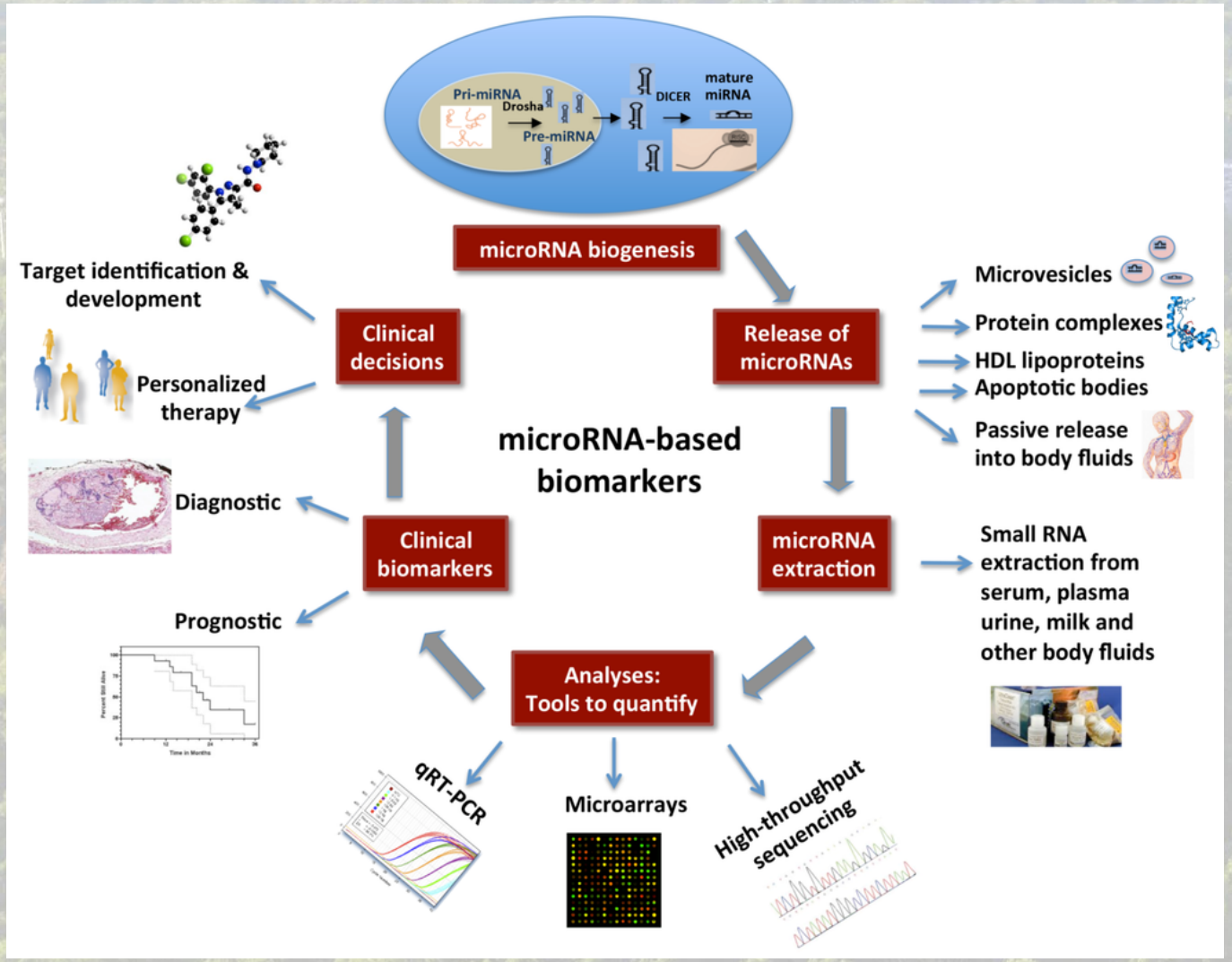
THANK YOU FOR YOUR ATTATION!!

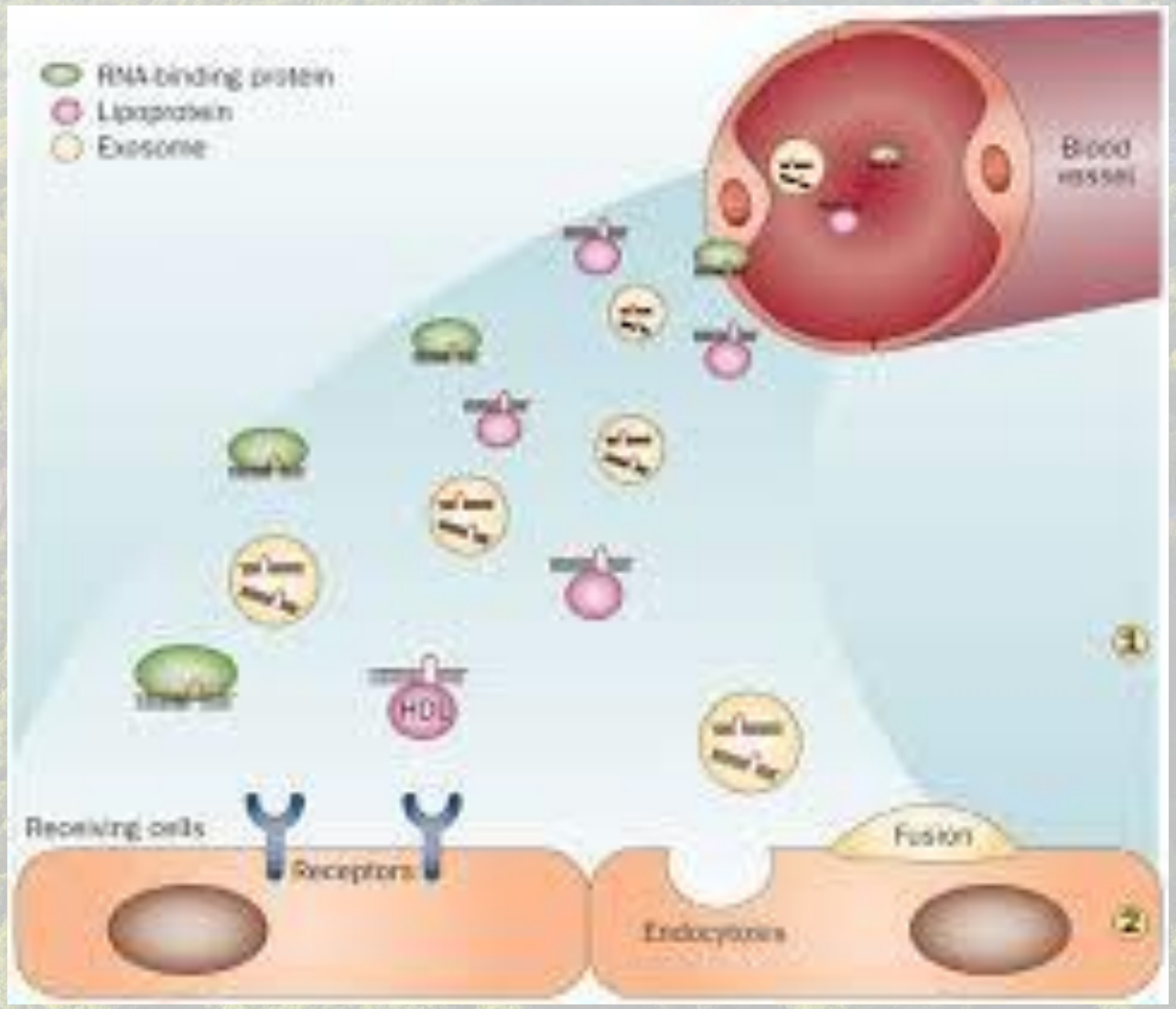
Systems Molecular Medicine Laboratory
系統分子醫學實驗室

Systems Molecular Medicine Laboratory
系統分子醫學實驗室

➢Research Focus:




Pri-miRNA
Drosha
Pre-miRNA
DICER
mature miRNA
microRNA biogenesis
Release of microRNAs
Microvesicles
Protein complexes
HDL lipoproteins
Apoptotic bodies
Passive release into body fluids
microRNA extraction
Small RNA extraction from serum, plasma urine, milk and other body fluids
microRNA-based biomarkers
Clinical biomarkers
Diagnostic
Prognostic
Clinical decisions
Target identification & development
Personalized therapy
Analyses: Tools to quantify
qRT-PCR
Microarrays
High-throughput sequencing


RNA-binding protein
Lipoprotein
Exosome
Blood vessel
HDL
Receiving cells
Receptors
Fusion
Endocytosis
1
2