

miRNA and Cancer : *miRNA as a Key Regulator in Cancer*

Sofia Mubarika
2nd Symposium Biomolecular Update in Cancer
PERABOI
Padang 18 Mei 2013

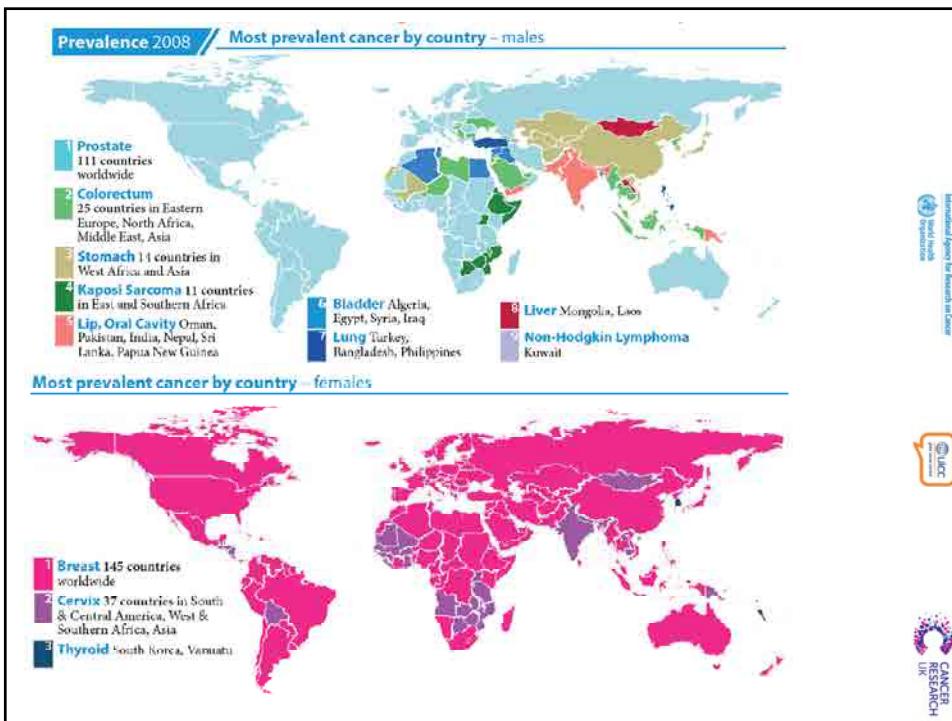
Cancer Problems in Indonesia

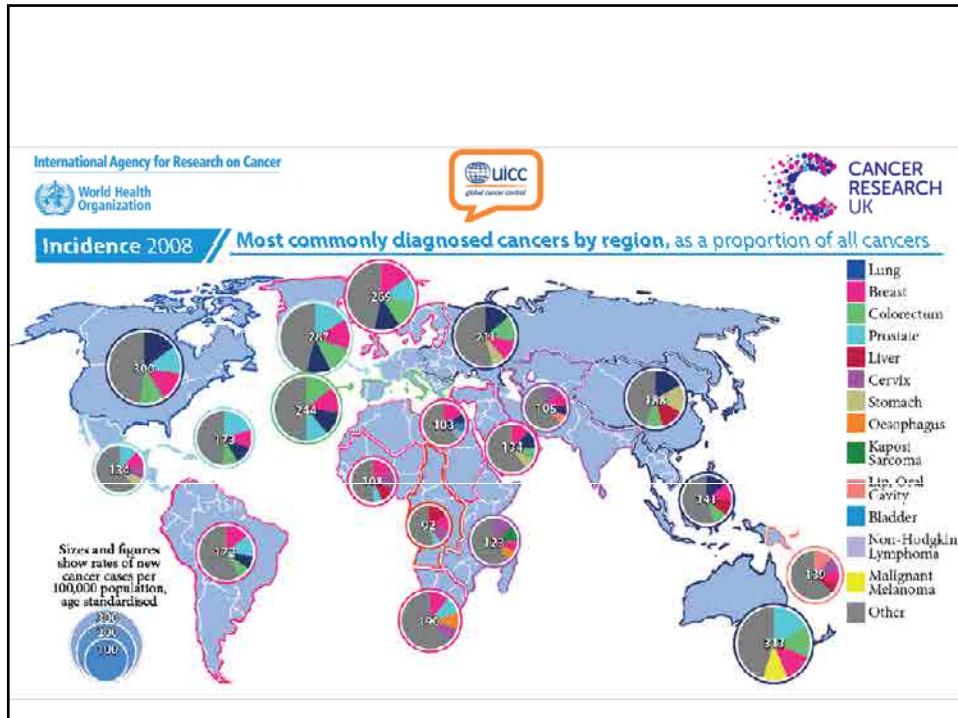
- 1. Chemoresistency / recurrency**
- 2. Cancer is Heterogenous, Limited Data on Cancer Genetic**
- 3. Biomarkers in cancer - specific Indonesia**
- 4. Proteomic era**
- 5. Individualised therapy**
- 6. Consortium /Multicenter research on cancer**

Cancer Incidence and Mortality, Estimates : 2005-2010

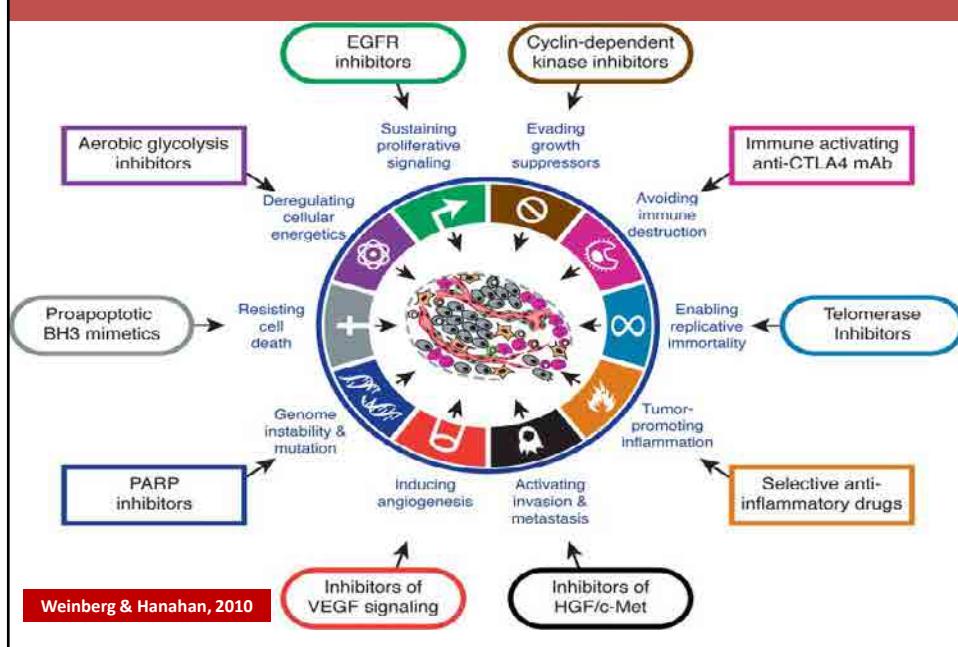
	Population (2005 estimates [total]) (2010 estimates [by age])			Years of Life Expectancy (2005-2010 estimates)	Number of New Cases of Cancer* (2008 estimates)		Number of Cancer Deaths* (2008 estimates)	
	Total (thousands)	% under 15	% over 60		% of total	% of total	% of total	% of total
Africa	587,092	40%	5%	54	715,571	6	541,779	7
Eastern Africa	210,570	44%	5%	53	221,076	2	173,676	2
Middle Africa	122,501	45%	5%	48	66,895	-	53,229	1
Northern Africa	205,814	31%	7%	58	164,350	-	125,801	2
Southern Africa	56,938	31%	7%	52	79,179	-	52,816	1
Western Africa	291,270	43%	5%	51	184,074	-	136,259	2
Asia	4,075,309	26%	10%	69	6,092,359	46	4,072,332	54
Eastern Asia	1,046,125	19%	14%	74	3,720,058	29	2,440,351	32
South-Central Asia	1,728,752	31%	7%	64	1,423,213	11	978,914	13
South-Eastern Asia	775,628	27%	9%	70	725,446	6	501,048	7
Western Asia	224,108	32%	7%	71	223,042	2	151,021	2
Europe	731,568	15%	22%	75	3,208,882	25	1,715,240	23
Central and Eastern Europe	293,488	15%	19%	69	983,408	8	626,007	8
Northern Europe	97,518	17%	23%	79	482,080	4	242,422	3
Southern Europe	152,318	15%	24%	80	713,401	6	362,773	5
Western Europe	187,848	18%	24%	80	1,029,993	8	464,038	6
Latin America and Caribbean	676,102	28%	10%	73	966,608	7	542,061	7
Caribbean	41,629	27%	12%	72	79,347	-	47,842	1
Central America	149,000	30%	9%	75	170,564	-	106,326	1
South America	394,892	27%	10%	73	650,087	5	385,881	5
Northern America	245,053	24%	18%	78	1,683,870	13	638,328	8
Oceania	34,837	24%	15%	76	135,864	1	55,072	1
More developed regions	1,229,219	17%	22%	77	5,555,281	44	2,744,840	35
Less developed regions	5,590,843	29%	9%	66	7,107,273	56	4,819,962	64
World	6,750,062	27%	11%	68	12,662,554	100	7,584,802	100

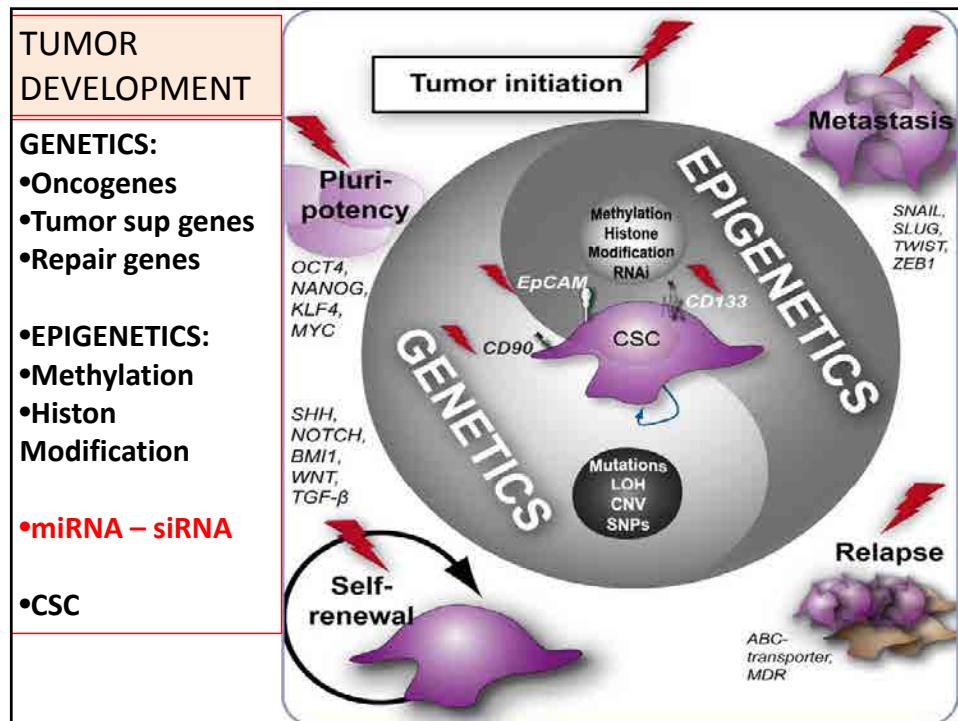
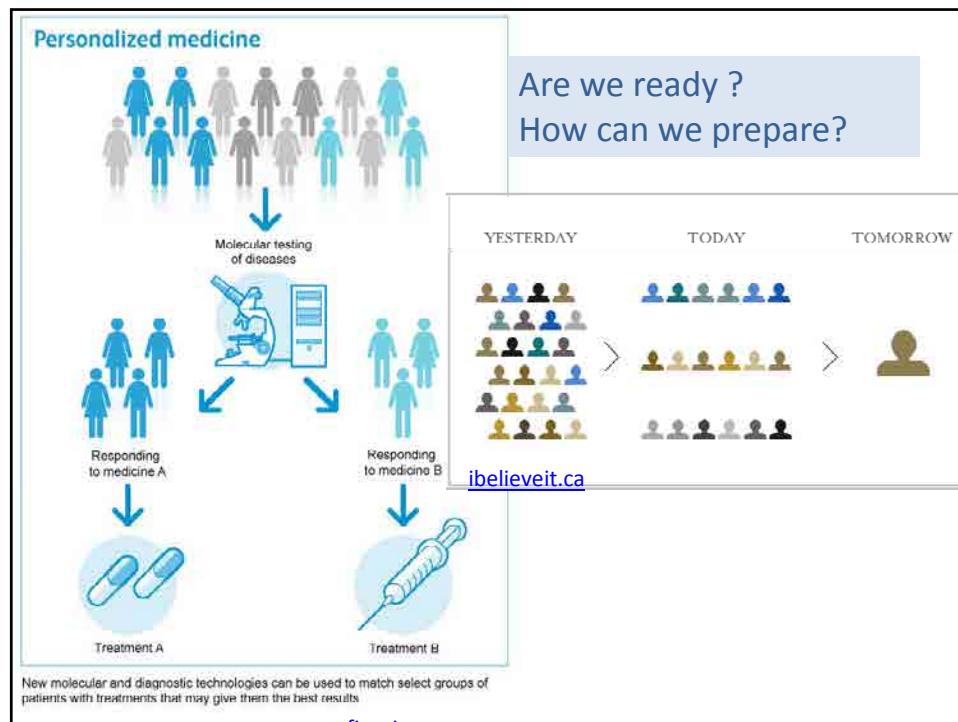
Prepared by Cancer Research UK
Original data sources:
1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C and Parkin DM. GLOBOCAN 2008 v1.2. Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10. In: IARC, Lyon; 2010.
2. UN. World Population Prospects: The 2008 Revision. In: United Nations, Department of Economic and Social Affairs, Population Division; 2009.

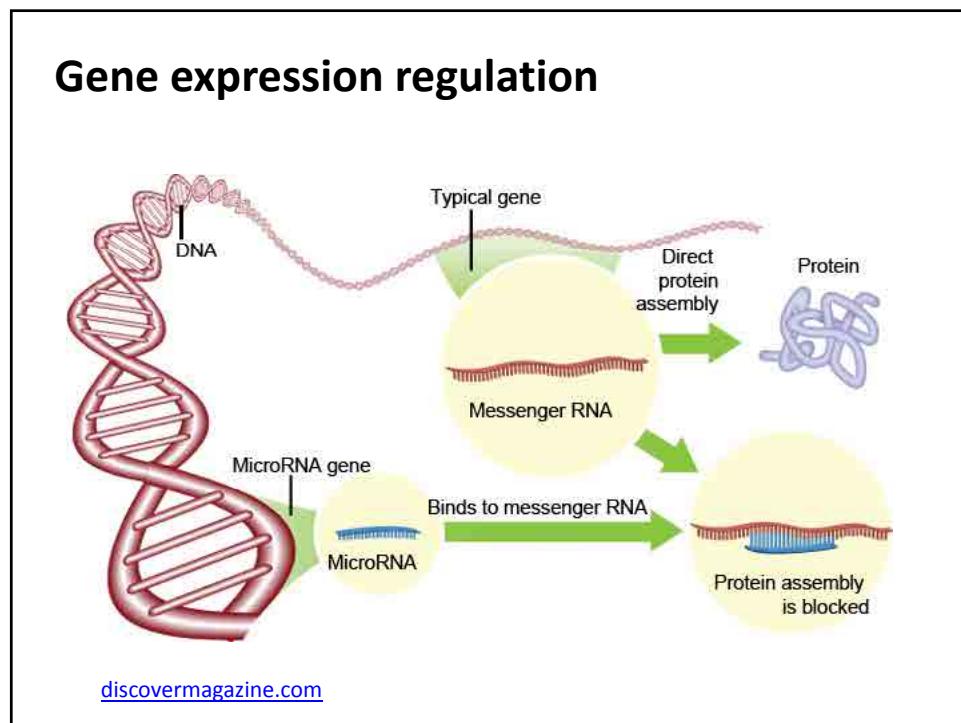
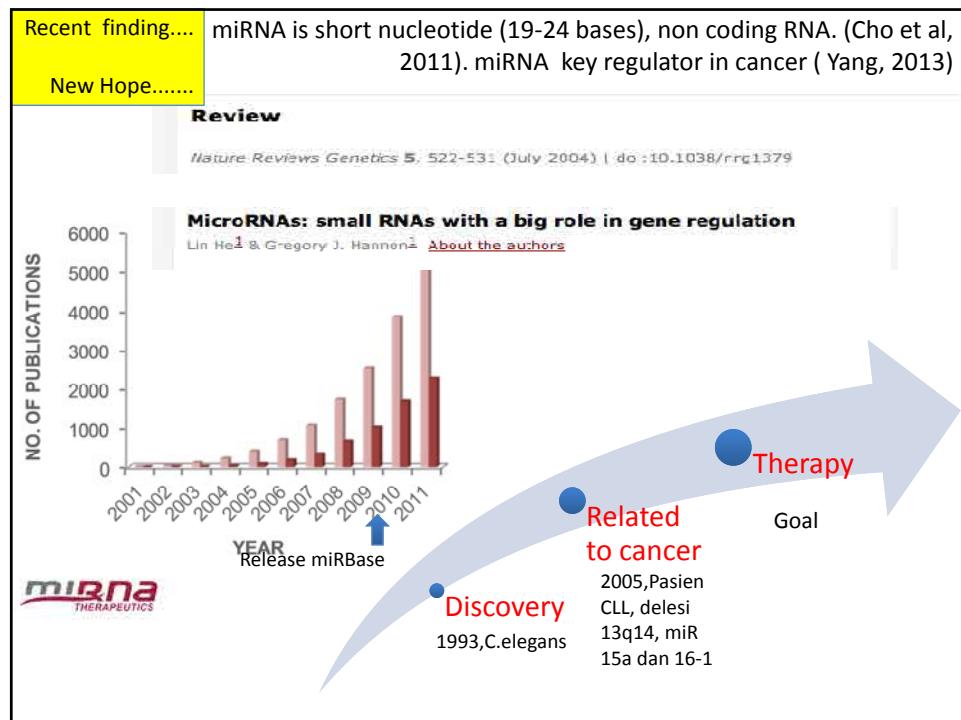


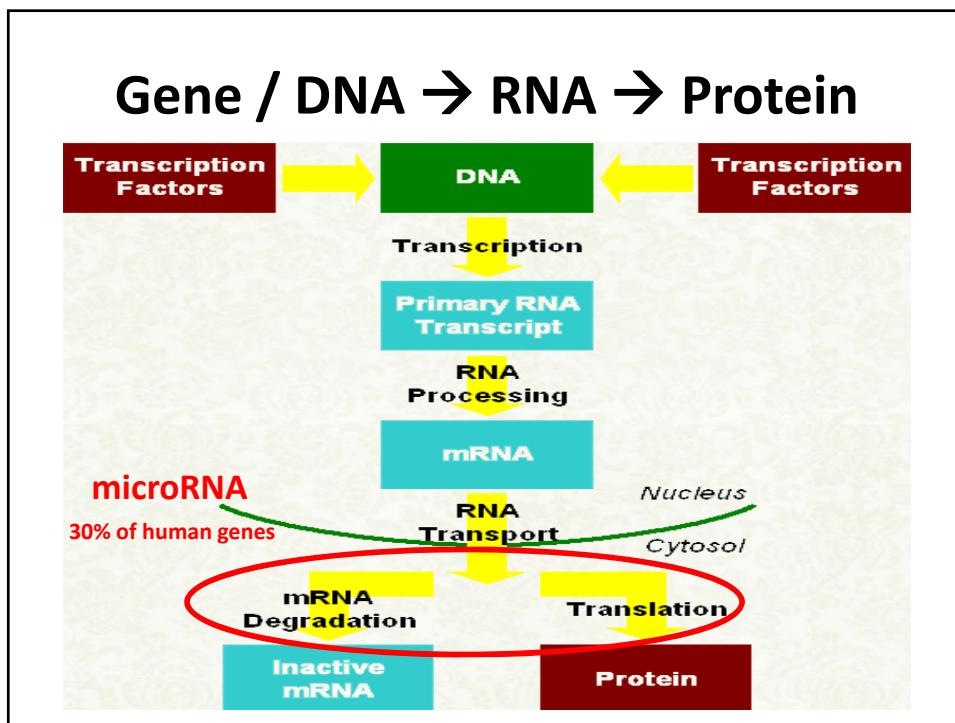
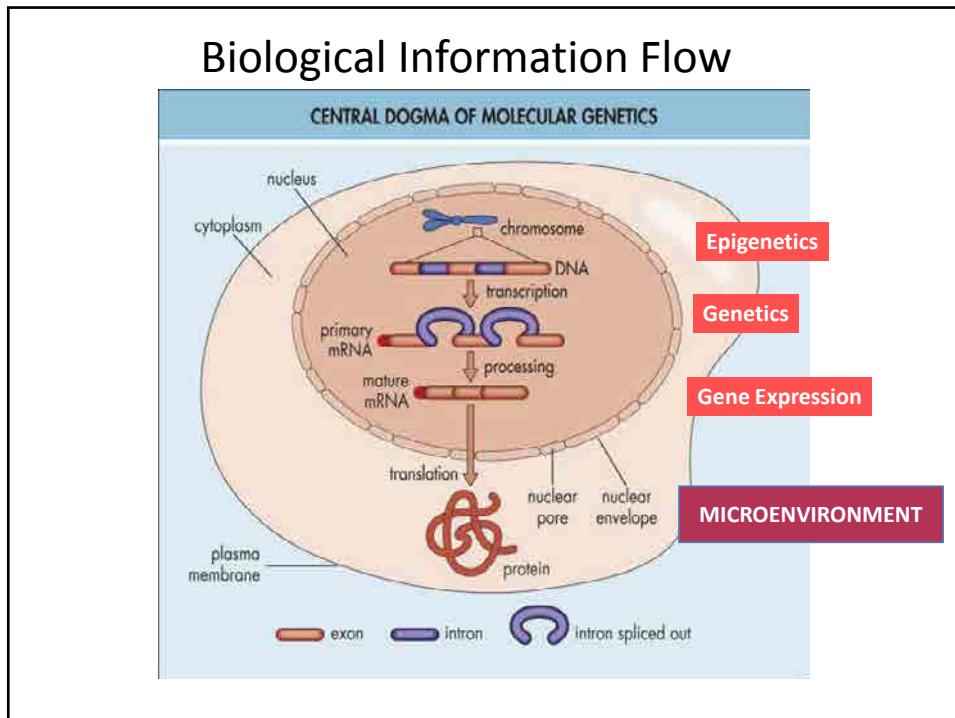


the Hallmarks of Cancer - Targetted









Gene Regulatory Mechanisms

- **Transcriptional Mechanisms**

- Type of promoters & RNA polymerase
- Control of Transcription
- Transcription Factors and TFBS

- **Translational Mechanisms**

- *Micro RNAs (miRNAs and RITS complexes)*
 - Translational control
 - mRNA degradation
 - Promoter activation
- **Silencer RNAs (siRNAs & RISC complexes) degrading mRNA**



- **Epigenetic Mechanisms**

- Chromatin remodeling
- Histone modifications (acetylation, phosphorylation, methylation ...)
- DNA methylation

Biogenesis of miRNA

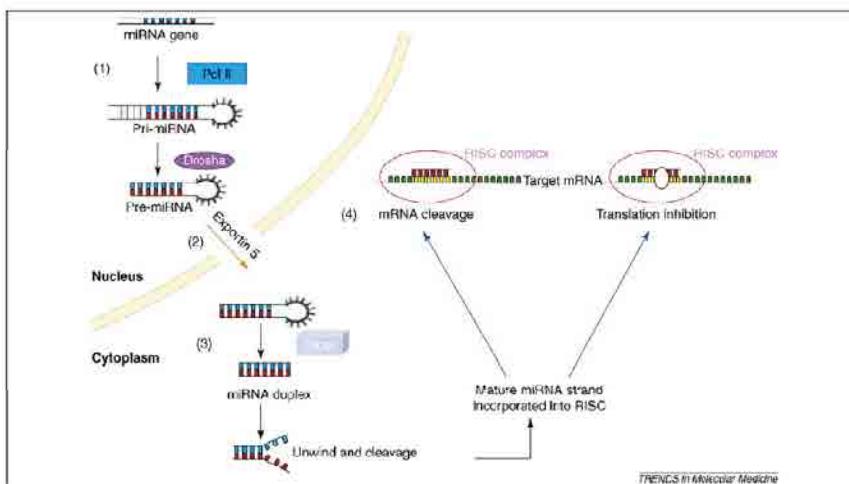


Figure 1. MicroRNA biogenesis. (1) MiRNAs are transcribed by RNA polymerase II (pol II) into long primary miRNA transcripts of variable size (pri-miRNA), which are recognized and cleaved in the nucleus by the RNase III enzyme Drosha, resulting in a hairpin precursor form called pre-miRNA. (2) This pre-miRNA is exported from the nucleus to the cytoplasm by exportin 5 and is further processed by another RNase enzyme called Dicer (3), which produces a transient 19–24 nucleotide duplex. Only one strand of the miRNA duplex (mature miRNA) is incorporated into a large protein complex called RISC (RNA induced silencing complex). (4) The mature miRNA leads RISC to cleave the mRNA or induce translational repression depending on the degree of complementary sites between the miRNA and its target.

www.sciencedirect.com

Garzon, 2006, Trends in Molecular Medicine Vol 12 No 12

Post-Transcriptional Regulation

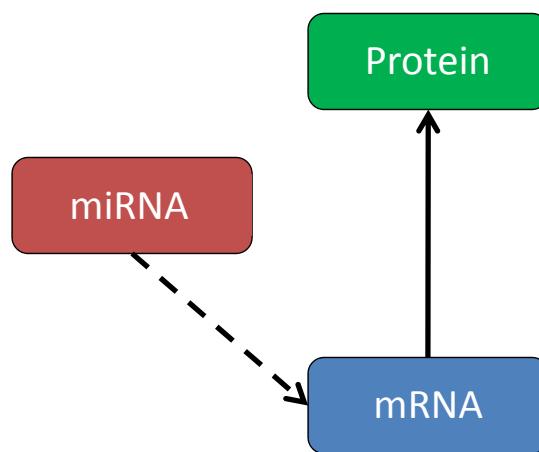
- Event
 - miRNA binds to mRNA target at 3' Untranslated Region (UTR)
 - Binding due to approximate complementation of miRNA to mRNA
- Effect
 - Target mRNA is degraded
 - Translation is blocked by the miRNA binding
 - Target protein is not produced

... no protein... no function !!

Michigan State University
Microbiology & Molecular Genetics 445

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Post-Transcriptional Regulation



miRNA genes (Chrom 1 – 22)

- miRNA in cancer :

1. Oncogenic miRNA

(Oncomirs) → induce cancer proliferation by down regulating expression of tumor suppressor genes

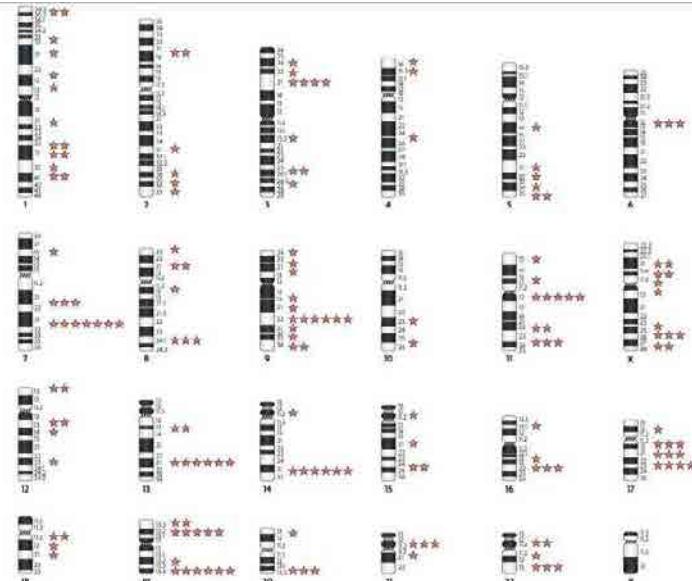
1. Tumor suppressor miRNA

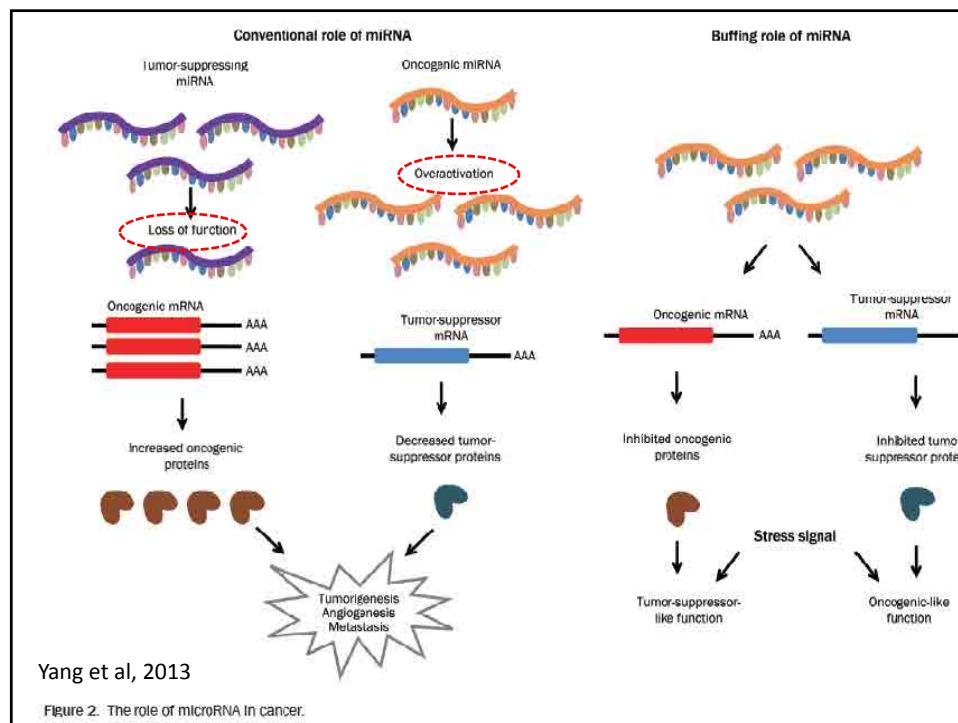
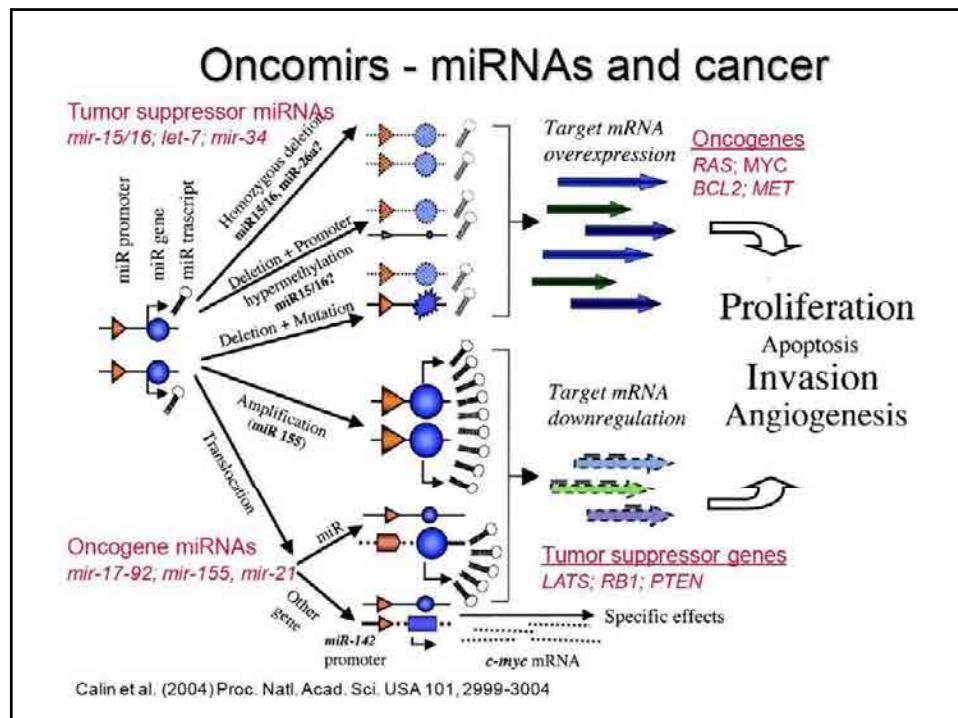
(mirsupp) inhibit cancer progression by targetting oncogenes post-transcriptionally

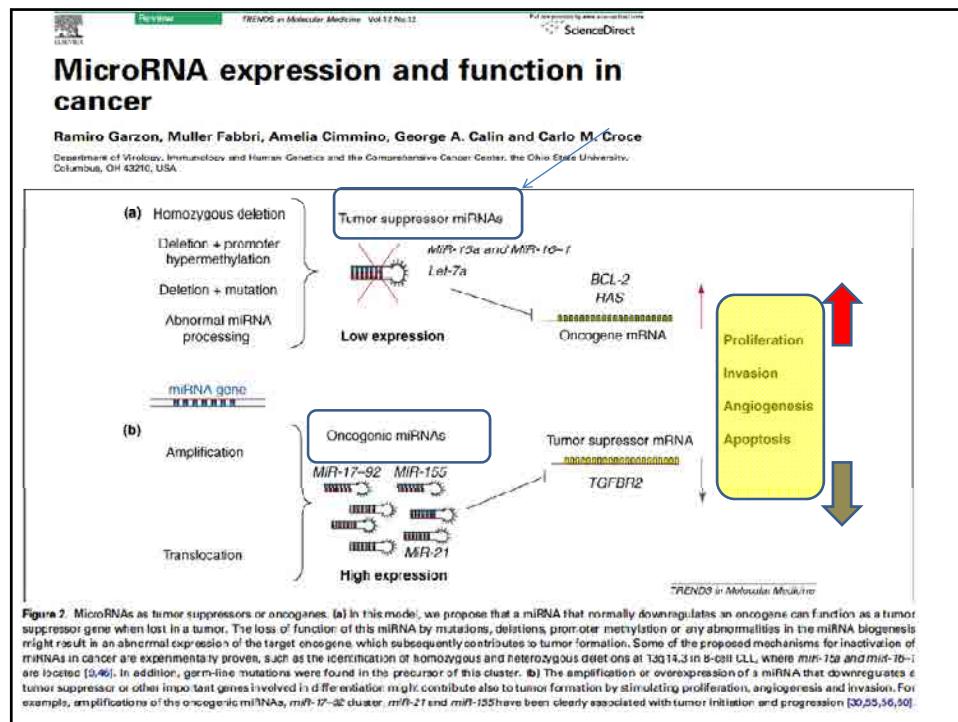
- Carcinogenesis
- Metastasis
- Angiogenesis
- Drug resistance

(Cho et al., 2009)

miRNOncogenes or Tumor Suppressor Genes (Croce A [Nat Rev Genet. 2009 Oct;10\(10\):704-14.](#))





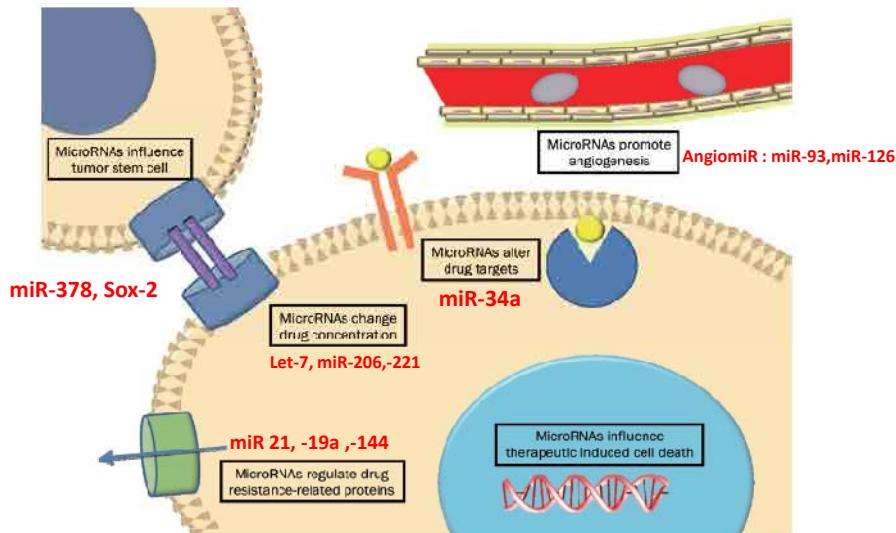


miRNA regulate Drug Resistance

- MDR : resistance to 1 drug followed by resistance to multiple :
 - MDR protein belongs to ATP Binding cassette Family) -> P-gp/MDR-1/ABCB1/CD243)
 - Transmembrane protein – protect influx drug by pumping out)
- miR-19, miR-21, miR-34a → mRNA MDR-1

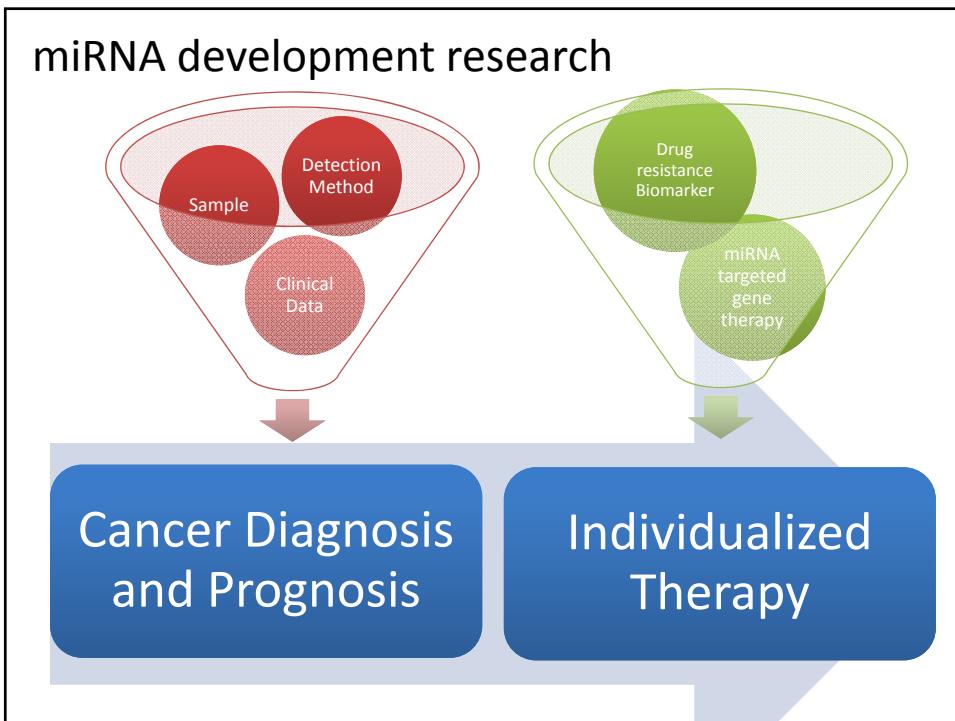
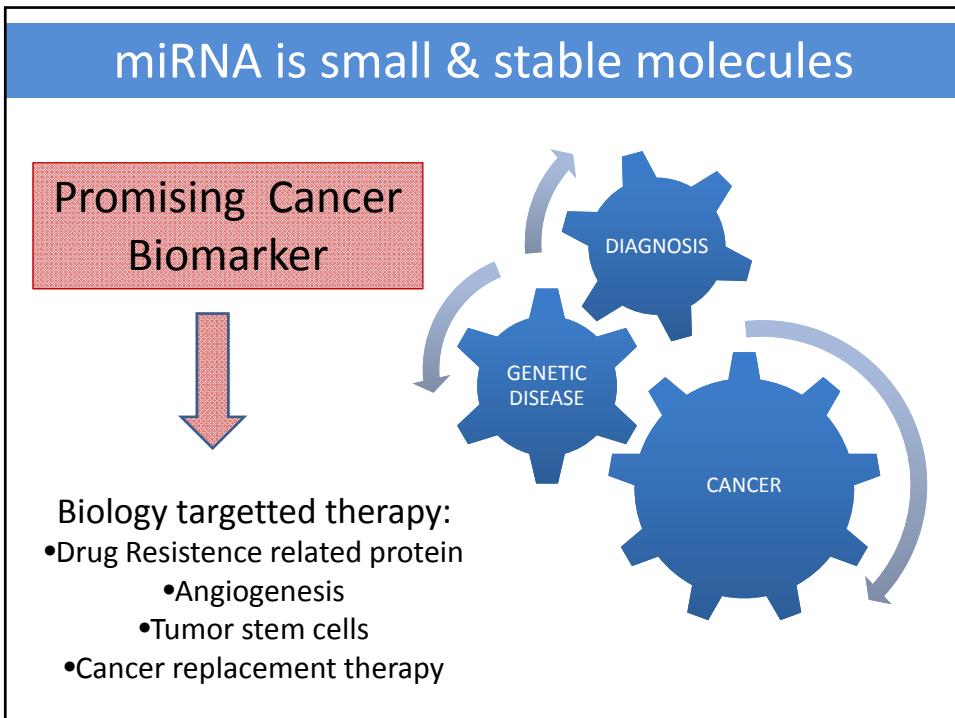
↓
- *Oligomer use to silence miRNA*
Allow drugs to be effective in cancer treatment

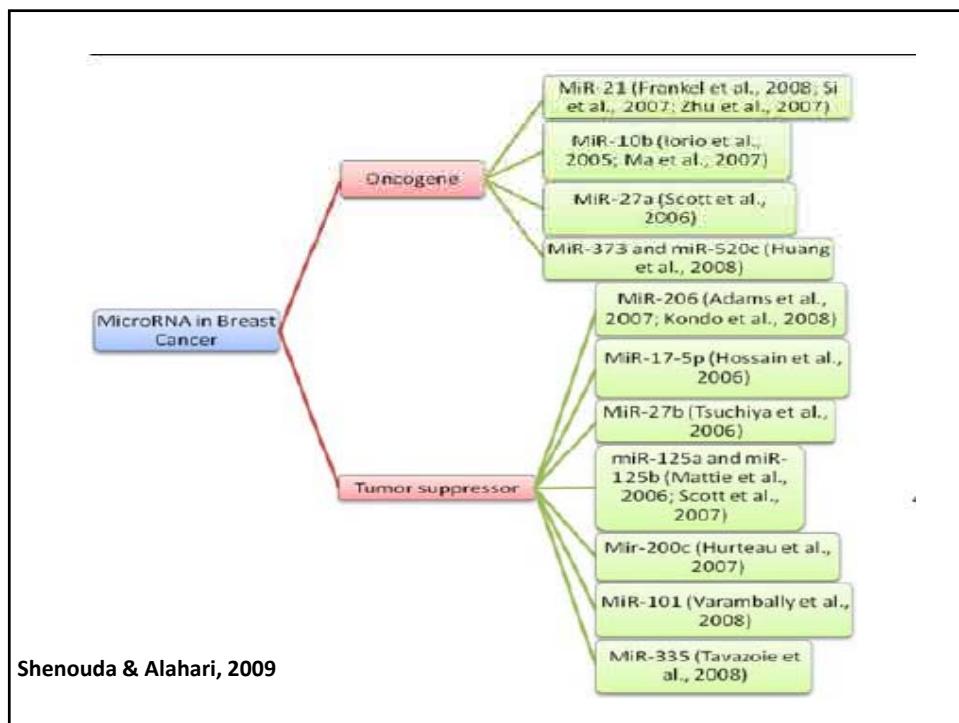
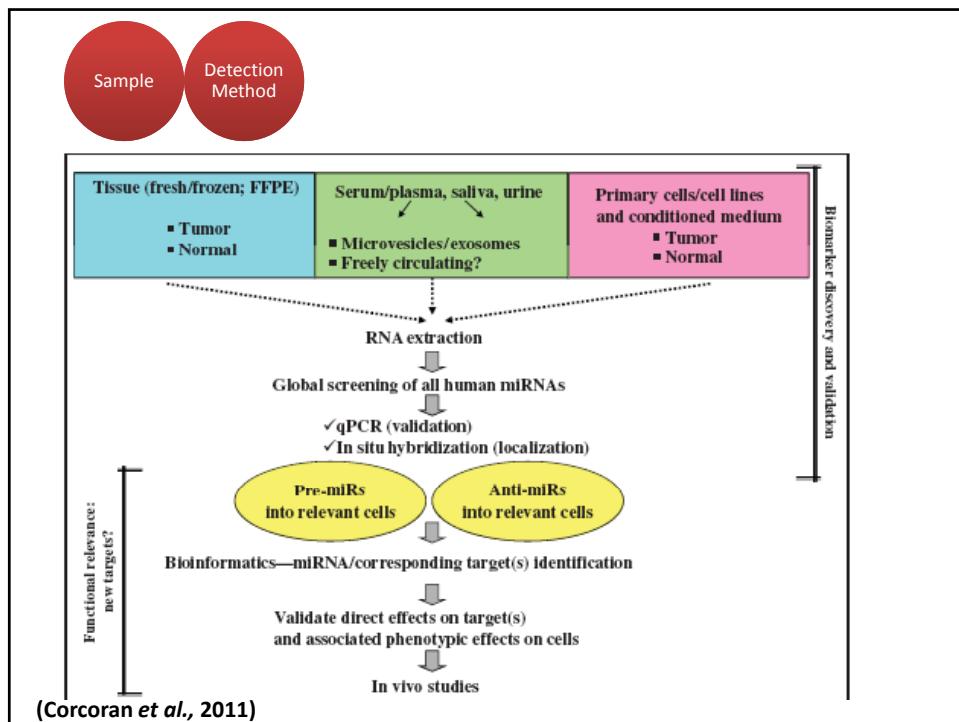
miRNA regulate drug resistance, angiogenesis, TCS – at multiple level

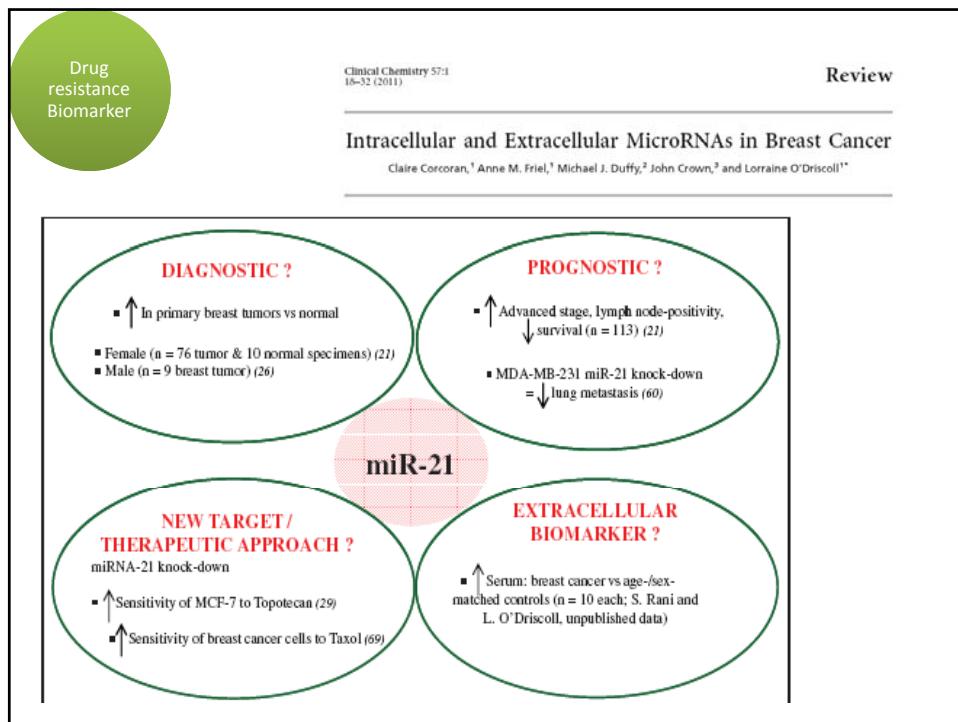


miRNA Future Treatment Applications and Industry Predictions

- FDA Issues
 - Many drugs stopped in phase-3 of development !!
- miRNA on track to appropriate applicable maturation







Differential Expression in Cancer Cells

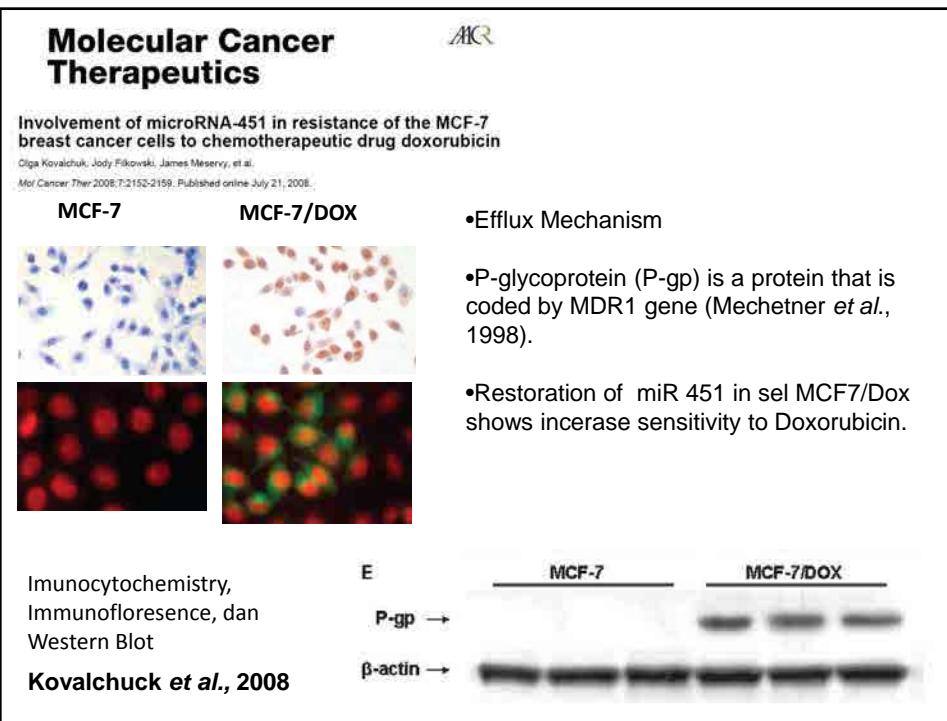
Microarray miRNA profiling allows for identification of the miRNA found in a tissue sample

Comparisons between cancerous, metastatic, drug resistant and healthy cells create miRNA libraries for further investigation

miRNA correlated with specified cancer

Cancer type	Upregulated	Downregulated
Breast cancer	miR-10b, miR-21, miR-22, miR-27a, miR-155, miR-210, miR-221, miR-222, miR-328, miR-373, miR-520c	let-7, miR-7, miR-9-1, miR-17/miR-20, miR-31, miR-125a, miR-125b, miR-146, miR-200 family, miR-205, miR-206, miR-335
CLL	miR-21, miR-155	miR-15, miR-16, miR-29b, miR-29c, miR-34a, miR-143, miR-145, miR-181b, miR-223
Lung cancer	miR-17-92 cluster, miR-21, miR-106a, miR-155	miR-1, let-7 family, miR-7, miR-15a/miR-16, miR-29 family
Lymphoma	miR-17-92 cluster, miR-155	miR-143, miR-145
Prostate cancer	miR-221, miR-222	miR-15a-miR-16-1 cluster, miR-101, miR-127, miR-449a
Glioblastoma	miR-21, miR-221, miR-222	miR-7
Hepatocellular carcinoma	miR-17-92 cluster, miR-21, miR-143, miR-224	miR-1, miR-101, miR-122a
Colorectal cancer	miR-17-92 cluster, miR-21	miR-34a, miR-34b/c, miR-127, miR-143, miR-145, miR-342
Gastric cancer	miR-21, miR-27a	miR-143, miR-145
Ovarian cancer	miR-214	miR-34b/c, miR-200 family
Melanoma	miR-221, miR-222	let-7a, miR-34a
Head and neck squamous cell carcinoma	miR-21	let-7d, miR-138, miR-205

Li et al., 2010



miRNA targeted gene therapy

Published OnlineFirst August 31, 2010; DOI: 10.1158/0008-5172.CAN-10-2010

Review

Cancer Research

The Promise of MicroRNA Replacement Therapy

Andreas G. Bader¹, David Brown², and Matthew Winkler^{1,2}

Abstract

MicroRNAs (miRNA), a class of natural RNA-interfering agents, have recently been identified as attractive targets for therapeutic intervention. The rationale for developing miRNA therapeutics is based on the premise that aberrantly expressed miRNAs play key roles in the development of human disease, and that correcting these miRNA deficiencies by either antagonizing or restoring miRNA function may provide a therapeutic benefit. Although miRNA antagonists are conceptually similar to other inhibitory therapies, restoring the function of a miRNA by miRNA replacement is a less well characterized approach. Here we discuss the specific properties of miRNA replacement and review recent examples that explored the therapeutic delivery of miRNA mimics in animal models of cancer. *Cancer Res* 70(16): 5057–5067. © 2010 American Association for Cancer Research.

Figure 1. Oncology-directed miRNA replacement therapy. Loss of a tumor suppressor miRNA leads to hyperactivation of inherently oncogenic pathways and tumorigenesis. Administration of a miRNA mimic reinstates the function of the missing tumor suppressor miRNA and suppresses oncogenic pathways and cancer cell growth.

frontiers in GENETICS

REVIEW ARTICLE Published: 02 July 2012 doi: 10.3389/fgene.2012.00120

miR-34 – a microRNA replacement therapy is headed to the clinic

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Mim Therapeutics, Inc., Austin, TX, USA

Cellular processes:

- Cell cycle
- Apoptosis/Bcl2 pathway
- Wnt signaling/Smad3
- Cell Cycle and Proliferation
- Anti-Apoptosis
- Cancer Stemness
- Metastasis
- Oncogenic Transcription
- Chemoresistance

Genes:

Gene	Title	Reference
CDK4	Cyclin-dependent kinase 4	Gao et al., 2002
CCNE2	Cyclin E2	Gao et al., 2002
CDKN1	Cyclin D1	Gao et al., 2002
CDKN6	Cyclin-dependent kinase 6	Kwon et al., 2009
BCL2	B-cell lymphoma/leukemia 2	Elizalde et al., 2007; Cole et al., 2009
3RT1	Sin3a 1, histone deacetylase 1	Conradt et al., 2009
YY1	Ying yang 1 transcription factor	Brenner et al., 2001; Tsai et al., 2008
BRCA5	Survivin	Gao et al., 2002
JAK1	Janus kinase 1	Bhattacharyya et al., 2008; Liu et al., 2010
WN11	Wingless-related MM\VV integration site inserter 1	Bhattacharyya et al., 2008; Liu et al., 2010
NOTCH1	Notch signaling 1, transcription-associated	Li et al., 2010
LETF1	Lethal enhancer blocking factor 1	Dobrev et al., 2011; Xie et al., 2011
WN12	Wingless-type MM\VV integrator site family member 2	Kim et al., 2010
CTNNB1	Beta-Catenin	Dobrev et al., 2011
L196	Lipid/diacylglycerol acyltransferase/malatate protein 6	Mah et al., 2010
MIA2	Mitochondria associated 1 family member 2	Oliver et al., 2010
TP532	Tenui usculi D2	Baldarelli et al., 2010
AKT1	Akt1, receptor tyrosine kinase	Baldarelli et al., 2010; Mekhilia et al., 2010
MYO14	Vimentin myosin-coiled-coil related oncogene 6	Gao et al., 2002; Liu et al., 2010
CDG1	Hoxbox 8/11/12/13/14/15/16	Li et al., 2010
NAV3G	Nav3.3 homolog, transcription factor	Li et al., 2010
SOX2	Sex determining region Y-box 2 transcription factor	Li et al., 2010
MET	Met proto-oncogene, transducin-like protein kinase receptor	Gao et al., 2002
MAP2K1	Mitogen activated protein kinase kinase 1 (MAPK1)	Elizalde et al., 2007
RRAS	Ras-like GTPase	Gao et al., 2002
M-H-R4	Human telomerase reverse transcriptase alpha	Gao et al., 2002
CD3D	CD7 transcription factor D	Avioli et al., 2002
MYB	V-myc myeloblastosis viral oncogene homolog	Bhattacharyya et al., 2008
MYC	V-myc myeloblastosis viral oncogene homolog	Gao et al., 2002
ACSL1	Acyl-CoA synthetase long-chain fatty acid member 1	Gu et al., 2010
LOXA	Ly6/uPAR angiogenesis A	Oliver et al., 2010
IMPDH	IMP deamidase/nucleophosmin homologous	Gao et al., 2002

FIGURE 1 | Cancer processes counteracted by miR-34.

Conclusion

1. miRNA play as a key role in cancer
 - drug resistency, metastasis, angiogenesis,
 - self renewal (TCS)
2. miRNA in physiological condition – to buffer/homeostasis
3. Cancer is heterogenous → personalised medicine is a future direction in clinical medicine
4. Therapeutic strategis focus on rebalancing miRNA network
5. miRNA profiling – promising diagnostic, prognostic

