frontiers in
GENETICS

MINI REVIEW ARTICLE
published: 28 February 2011
doi: 10.3389/fgene.2011.00007

Circulating microRNAs as minimally invasive biomarkers for cancer theragnosis and prognosis

William C. S. Cho*

Department of Clinical Oncology, Queen Elizabeth Hospital, Kowloon, Hong Kong

Edited by:
Michael Rossbach, Genome Institute of Singapore, Singapore

Reviewed by:
Haruhiko Siomi, Keio University School of Medicine, Japan
Dong Xu, University of Missouri, USA

****Correspondence:***
William C. S. Cho, Department of Clinical Oncology, Queen Elizabeth Hospital, Kowloon, Hong Kong.
e-mail: chocs@ha.org.hk

Novel cancer biomarker discovery is urgently needed for cancer theragnosis and prognosis, and among the many possible types of samples, blood is regarded to be ideal for this discovery as it can be collected easily in a minimally invasive manner. Results of the past few years have ascertained the quantification of microRNA (miRNA) as a promising approach for the detection and prognostication of cancer. Indeed, an increasing number of studies have shown that circulating cancer-associated miRNAs are readily measured in plasma or serum and they can robustly discriminate cancer patients from healthy controls, as well as distinguishing between good-prognosis and poor-prognosis patients. Furthermore, recent findings also suggest the potential of circulating miRNAs in the screening, monitoring, and treatment of cancer. This article summarizes the most significant and latest discoveries of original researches on circulating miRNAs involvement in cancer, focusing on the potential of circulating miRNAs as minimally invasive biomarkers for cancer theragnosis and prognosis.

Keywords: blood-based biomarker, cancer, circulating microRNA, minimally invasive biomarker, molecular tumor marker, oncomir, prognosis, theragnosis

INTRODUCTION

In terms of suffering and death, cancer is tragic yet partly preventable. The developments of valid biomarkers to prevent, detect, and treat this devastating disease can save millions of lives. However, the establishment of clinically validated biomarkers for cancer remains an insurmountable task despite the advances in molecular biology. An ideal tumor marker should be measured easily, reliably, and cost-effectively using a minimally invasive assay with high analytical sensitivity and specificity. Results of the last few years have ascertained the quantification of microRNA (miRNA) as a promising approach for the detection and prognostication of cancer (Cho, 2007, 2010a). Nevertheless, it remains uncertain whether circulating miRNA is tumor specific and whether systemic miRNA analysis has utility in cancer management. Indeed, miRNA is present in human blood in a remarkably stable form protected from endogenous RNase activity (Mitchell et al., 2008). An increasing number of studies have shown that circulating cancer-associated miRNAs (oncomirs) are readily measured in plasma or serum and they can robustly discriminate cancer patients from healthy controls. This article summarizes the most significant and latest findings of original researches on circulating miRNAs involvement in cancer, focusing on the potential of circulating miRNAs as minimally invasive biomarkers for cancer theragnosis and prognosis (**Table 1**).

MiRNA AND CANCER

MicroRNAs are emerging as important modulators in cellular pathways, and they appear to play a key role in tumorigenesis (Cho, 2010b). Numerous studies have documented the implications of miRNAs in nearly every carcinogenesis process, including tumor development, apoptosis, invasion, and metastasis, as well as anticancer drug resistance (Cho, 2009, 2010c).

ROLE OF CIRCULATING miRNAs IN THE MOLECULAR PATHOGENESIS AND PROGRESSION OF CANCER

Previous study has suggested that profiling of circulating miRNAs may help identify promising biomarkers of various pathologic conditions (Ji et al., 2009). In the study of chronic lymphocytic leukemia (CLL), low expression of *miR-29b*, *miR-29c*, *miR-181* family, and *miR-223* were found to be strongly associated with disease progression in CLL cases harboring 17p deletion, whereas high expression of *miR-181a* in those harboring trisomy 12 suggested more aggressive disease. These biomarkers may be clinically useful to assess the tumor behavior in CLL (Visone et al., 2009). A pilot study also evaluated the circulating miRNAs associated with tumor progression in breast cancer patients. It provided evidence that the relative concentration of *miR-155* in serum significantly discriminated primary breast cancer patients from healthy women. Within the primary breast cancer cohort, patients at advanced tumor stages had significantly higher *miR-34a* than patients at early tumor stages. In the metastatic patients, *miR-10b*, *miR-34a*, and *miR-155* correlated with the presence of overt metastases (Roth et al., 2010).

DIAGNOSTIC AND PROGNOSTIC VALUE OF CIRCULATING miRNAs FOR CANCER

The releases of miRNAs from malignant cells in body fluids are candidate diagnostics for a variety of cancers. A recent study reported that the release of miRNAs from breast cancer cells into blood, milk, and ductal fluids was selective and that the selection of released miRNAs might correlate with malignancy. In particular, the bulk of *miR-451* and *miR-1246* produced by malignant mammary epithelial cells was released into the blood, but the majority of these miRNAs produced by non-malignant mammary epithelial cells was

Table 1 | A summary of the reported circulating microRNAs.

MicroRNA	Deregulation in cancer	Theragnostic and prognostic value	Sensitivity	Specificity	AUC	*P* value	Reference
let-7a	Decrease in gastric cancer	Discriminate gastric cancer from healthy controls	–	–	–	0.002	Tsujiura et al. (2010)
let-7f	Decrease in NSCLC	Associated with overall survival in NSCLC	–	–	–	0.038	Silva et al. (2011)
miR-1	Decrease in NSCLC	Associated with overall survival in NSCLC	–	–	–	<0.001	Hu et al. (2010)
miR-10b	Increase in breast cancer	Associated with metastases in breast cancer	–	–	–	0.014	Roth et al. (2010)
miR-17	Increase in gastric cancer	Discriminate gastric cancer from healthy controls	52%	93%	0.743	0.0001	Zhou et al. (2010)
miRs-17+ 106a	Increase in gastric cancer	Discriminate gastric cancer from healthy controls	63%	80%	0.741	0.0002	Zhou et al. (2010)
miR-17-3p	Increase in CRC	Discriminate CRC from healthy controls	64%	70%	0.717	<0.0001	Ng et al. (2009)
miR-17-5p	Increase in gastric cancer	Discriminate gastric cancer from healthy controls	–	–	–	0.05	Tsujiura et al. (2010)
miR-20b	Decrease in NSCLC	Associated with advanced stages and lymph node metastases in NSCLC	–	–	–	<0.01	Silva et al. (2011)
miR-21	Increase in CLL harboring 17p deletion	Associated with overall survival in CLL	–	–	–	0.033	Rossi et al. (2010)
	Increase in gastric cancer	Discriminate gastric cancer from healthy controls	–	–	–	0.006	Tsujiura et al. (2010)
miRs-21 + 126+ 210 + 486-5p	Deregulate in NSCLC	Discriminate stage I NSCLC from healthy controls	73%	97%	–	<0.05	Shen et al. (2011)
miRs-21 + 155+ 196a + 210	Increase in pancreatic adenocarcinoma	Discriminate pancreatic adenocarcinoma from healthy controls	64%	89%	0.820	<0.05	Wang et al. (2009)
miR-29a	Increase in CRC	Discriminate CRC from healthy controls	69%	89%	0.844	<0.0001	Huang et al. (2010)
miRs-29a + 92a	Increase in CRC	Discriminate CRC from healthy controls	83%	85%	0.883	<0.0001	Huang et al. (2010)
miR-29b	Decrease in CLL harboring 17p deletion	Associated with progression in CLL	–	–	–	<0.001	Visone et al. (2009)
miR-29c	Decrease in CLL harboring 17p deletion	Associated with progression in CLL	–	–	–	0.03	Visone et al. (2009)
miR-30d	Increase in NSCLC	Associated with overall survival in NSCLC	–	–	–	<0.001	Hu et al. (2010)
miR-30e-3p	Decrease in NSCLC	Associated with short disease-free survival in NSCLC	–	–	–	0.009	Silva et al. (2011)
miR-34a	Increase in breast cancer	Discriminate advanced stages from early stages in breast cancer	–	–	–	0.01	Roth et al. (2010)
		Associated with metastases in breast cancer	–	–	–	0.003	
miR-92	Increase in CRC	Discriminate CRC from gastric cancer, IBD, and healthy controls	89%	70%	0.885	<0.0001	Ng et al. (2009)
miR-92a	Increase in CRC	Discriminate CRC from healthy controls	84%	71%	0.838	<0.0001	Huang et al. (2010)

miR-106a	Increase in gastric cancer	Discriminate gastric cancer from healthy controls	–	–	–	0.008	Tsujiura et al. (2010),
			48%	90%	0.684	0.0066	Zhou et al. (2010)
miR-106a/let-7a	Increase/decrease in gastric cancer	Discriminate gastric cancer from healthy controls	86%	80%	0.879	<0.001	Tsujiura et al. (2010)
miR-106b	Increase in gastric cancer	Discriminate gastric cancer from healthy controls	–	–	0.721	<0.001	Tsujiura et al. (2010)
miR-107	Increase in CN-AML patients aged ≥60	Target *NFIX* in CN-AML	–	–	–	–	Schwind et al. (2010)
miR-144	Decrease in CN-AML patients aged ≥60	Associated with adverse prognostic marker *FLT3*-ITD in CN-AML	–	–	–	<0.05	Whitman et al. (2010)
miR-148a	Increase in CN-AML patients aged ≥60	Target *DNMT3B* in CN-AML	–	–	–	–	Schwind et al. (2010)
miR-155	Increase in CN-AML patients aged ≥60	Associated with adverse prognostic marker *FLT3*-ITD in CN-AML	–	–	–	<0.05	Whitman et al. (2010)
	Increase in breast cancer	Discriminate primary breast cancer from healthy controls	–	–	–	0.0001	Roth et al. (2010)
		Associated with metastases in breast cancer	–	–	–	0.002	
miR-181a	Increase in CLL harboring trisomy 12	Associated with progression in CLL	–	–	–	<0.05	Visone et al. (2009)
miRs-181a, b, c, d	Decrease in CLL harboring 17p deletion	Associated with progression in CLL	–	–	–	<0.03	Visone et al. (2009)
		miR-181b associated with treatment-free survival in CLL	–	–	–	0.006	Rossi et al. (2010)
miR-195	Increase in breast cancer	Discriminate breast cancer from other cancers and from healthy controls	88%	91%	–	<0.001	Heneghan et al. (2010a)
miR-200a	Increase in pancreatic cancer	Discriminate pancreatic cancer from healthy controls	84%	88%	0.861	<0.001	Li et al. (2010)
miR-200b	Increase in pancreatic cancer	Discriminate pancreatic cancer from healthy controls	71%	97%	0.850	<0.001	Li et al. (2010)
miR-208	Increase in CN-AML patients aged ≥60	Target *ERG* in CN-AML	–	–	–	–	Schwind et al. (2010)
miR-223	Decrease in CLL harboring 17p deletion	Associated with progression in CLL	–	–	–	0.024	Visone et al. (2009)
miR-302d	Decrease in CN-AML patients aged ≥60	Associated with early developmental stages and stemness in CN-AML	–	–	–	<0.05	Schwind et al. (2010)

(Continued)

Table 1 | Continued

MicroRNA	Deregulation in cancer	Theragnostic and prognostic value	Sensitivity	Specificity	AUC	*P* value	Reference
miR-451	Increase in breast cancer	Associated with malignancy in breast cancer	–	–	–	<0.05	Pigati et al. (2010),
	Decrease in CN-AML patients aged ≥60	Associated with adverse prognostic marker *FLT3*-ITD in CN-AML	–	–	–	<0.05	Whitman et al. (2010)
miR-486	Increase in NSCLC	Associated with overall survival in NSCLC	–	–	–	<0.001	Hu et al. (2010)
miR-499	Decrease in NSCLC	Associated with overall survival in NSCLC	–	–	–	<0.001	Hu et al. (2010)
miR-1246	Increase in breast cancer	Associated with malignancy in breast cancer	–	–	–	<0.05	Pigati et al. (2010)

AUC, area under curve; CLL, chronic lymphocytic leukemia; CN-AML, cytogenetically normal acute myeloid leukemia; CRC, colorectal cancer; IBD, inflammatory bowel disease; ITD, internal tandem duplication; NSCLC, non-small cell lung cancer.

retained. Their findings suggest that the selective release of miRNA is an important consideration for the identification of circulating miRNA as molecular tumor marker (Pigati et al., 2010).

An investigation of plasma miRNAs in colorectal cancer (CRC) indicated that *miR-29a* and *miR-92a* could significantly discriminate neoplasia from healthy controls, and combined analyses using these two miRNAs revealed higher sensitivity and specificity. These data suggest that plasma *miR-29a* and *miR-92a* have strong potential as minimally invasive biomarkers for the detection of CRC (Huang et al., 2010). Another study found that plasma *miR-92* also had significant diagnostic value for CRC. This biomarker could significantly differentiate CRC from gastric cancer, inflammatory bowel disease, and normal subjects, suggesting it to be a potential minimally invasive molecular marker for CRC diagnosis (Ng et al., 2009).

In the analysis of serum miRNAs, most pancreatic cancers displayed hypomethylation and over-expression of *miR-200a* and *miR-200b*, silencing of *SIP1* by promoter methylation, and retention of E-cadherin expression. The elevated serum levels of *miR-200a* and *miR-200b* in most patients with pancreatic cancer may have diagnostic utility (Li et al., 2010). On the other hand, profiling of *miR-21*, *miR-155*, *miR-196a*, and *miR-210* showed that miRNA profiling in plasma could also differentiate pancreatic adenocarcinoma patients from healthy controls. These results show the feasibility of developing plasma miRNA profiling as a sensitive and specific blood-based biomarker assay for pancreatic cancer that has the potential of translation to the clinic with additional improvements in the future (Wang et al., 2009). Similarly, the concentrations of *miR-21*, *miR-17-5p*, *miR-106a*, and *miR-106b* were significantly higher in gastric cancer patients than healthy controls, whereas *let-7a* was lower in gastric cancer patients. The levels of aberrantly expressing miRNAs were also significantly reduced in post-operative samples than pre-operative controls. These findings suggest that detection of circulating miRNAs may provide new complementary tumor markers for gastric cancer (Tsujiura et al., 2010).

The identification of a patient who is prognostically good or poor is very important for the development of effective treatment approach (Cho, 2011a). Recent findings have revealed a great potential of circulating miRNA signatures as molecular fingerprints to predict survival of cancer patients. Genome-wide serum miRNA-expression analysis found that the levels of four miRNAs (*miR-1*, *miR-30d*, *miR-486*, and *miR-499*) were significantly associated with the overall survival of non-small cell lung cancer (NSCLC) patients. These four serum miRNA signatures may serve as an independent minimally invasive predictor for the overall survival of NSCLC (Hu et al., 2010). Moreover, the evaluation of plasma miRNAs also detected decreased levels of *let-7f*, *miR-20b*, and *miR-30e-3p* in the vesicles of NSCLC patients than healthy controls. The plasma levels of *let-7f* and *miR-30e-3p* were associated with overall survival and short disease-free survival, respectively. These results suggest that plasma vesicle-related miRNAs obtained by minimally invasive methods can serve as circulating tumor biomarkers of discriminating and prognostic values (Silva et al., 2011). On the other hand, quantitative reverse transcription-polymerase chain reaction (qRT-PCR) analysis in CLL patients with chromosome 17p deletion also found that *miR-21* expression levels were significantly higher in patients with poor overall survival, whereas lower *miR-181b*

expression levels significantly predicted treatment-free survival. A 21FK score (*miR-21* qRT-PCR, fluorescence *in situ* hybridization, Karyotype) was developed to stratify patients according to overall survival and it was found to be a useful tool for distinguishing between good-prognosis and poor-prognosis CLL patients (Rossi et al., 2010).

POTENTIAL OF CIRCULATING miRNAs IN SCREENING, MONITORING, AND TREATMENT OF CANCER

Cancer is often diagnosed at a late stage with concomitant poor prognosis. Developing minimally invasive biomarkers that can diagnose cancer, particularly at an early stage, may improve its outcome. Evaluated by qRT-PCR, a panel of four plasma miRNAs (*miR-21*, *miR-126*, *miR-210*, and *miR-486-5p*) yielded 86% sensitivity and 97% specificity in distinguishing NSCLC patients from the healthy controls. Furthermore, the panel of miRNAs produced 73% sensitivity and 97% specificity in identifying stage I NSCLC patients. These results confirm that altered expressions of the miRNAs in plasma may provide potential blood-based biomarkers for NSCLC at an early stage (Shen et al., 2011).

To determine whether circulating miRNAs were tumor specific, a panel of oncomirs in the whole blood of pre-operative cancer patients (melanoma, breast, colon, prostate, and renal cancers) were assessed. Elevated circulating *miR-195* was found to be breast cancer specific and it could significantly differentiate breast cancer from other cancers and from healthy controls (Heneghan et al., 2010a). Furthermore, the circulating levels of *miR-195* and *let-7a* decreased in breast cancer patients post-operatively to levels comparable with healthy controls (Heneghan et al., 2010b). These findings suggest that circulating miRNAs have potential use as breast cancer biomarkers for early stage disease and they may also prove to be useful in clinical management during the peri-operative period. In fact, the detection of occult cancer cells in peripheral blood has recently received a great deal of attention regarding the prediction of post-operative cancer recurrence and for novel strategies of adjuvant therapy. In the peripheral blood samples from post-operative gastric cancer patients, the levels of *miR-17* and *miR-106a* were significantly higher than those in healthy controls. These results indicate that the detection of miRNAs in peripheral blood may also be a tool for monitoring circulating tumor cells in patients with gastric cancer (Zhou et al., 2010).

In primary cytogenetically normal acute myeloid leukemia (CN-AML) patients aged 60–69 years, *FLT3*-internal tandem duplication (ITD) was found to be significantly associated with overall survival and shorter disease-free survival. It was revealed that *FLT3*-ITD-associated miRNA-expression signatures included over-expressed *miR-155*, as well as under-expressed *miR-144* and *miR-451*. These miRNA-expression signatures may provide biologic insights for novel therapeutic approaches in older CN-AML patients with molecular high risk (Whitman et al., 2010). Conversely, low *BAALC* and *ERG* expression levels were identified to be associated with better outcome in older CN-AML patients aged ≥60 years. *HOX* genes and *HOX*-gene-embedded miRNAs were up-regulated in low *BAALC* expressers, whereas low *ERG* expressers presented with up-regulation of *miR-148a* which targeted *DNMT3B*. These miRNA-expression signatures may aid in identifying new targets and novel therapeutic strategies for older patients with low *BAALC* and *ERG* expressions (Schwind et al., 2010).

CONCLUSION

MicroRNA is a cutting-edge topic in the scientific and medical fields, the identification of oncomirs as blood-based biomarkers proceeds at a fast pace (Cho, 2011b). Numerous promising developments have been elucidated using omics technologies in cancer research (Cho, 2010d). The applications of microarray, microfluidics, nanofluidics, next generation sequencing, qRT-PCR, and bioinformatics have enabled the discoveries of a number of circulating miRNAs as potential biomarkers for cancer theragnosis and prognosis. These blood-based biomarkers have a revolutionary impact on cancer research over recent years. A number of circulating miRNAs have been found to be promising molecular tumor markers for early detection or survival prediction, some were even revealed to be involved in cancer progression or metastasis. The prospect for circulating miRNAs as minimally invasive biomarkers for cancer is excellent, although there are some challenges that the researchers have to conquer before these small non-coding RNAs can be fully understood and utilized (Cho, 2011c). With the accessibility of large sample sets, the range of technologies available, and the increasing evidences that there is a signature of changes derived by cancer in blood which may contribute to theragnosis and prognosis, all suggest that circulating miRNAs, perhaps accompanying other markers, will become widely used minimally invasive biomarkers for cancer in the future.

REFERENCES

Cho, W. C. (2007). Oncomirs: the discovery and progress of miRNAs in cancers. *Mol. Cancer* 6, 60.

Cho, W. C. (2009). Role of miRNAs in lung cancer. *Expert Rev. Mol. Diagn.* 9, 773–776.

Cho, W. C. (2010a). MiRNAs: potential biomarkers for cancer diagnosis, prognosis and targets for therapy. *Int. J. Biochem. Cell Biol.* 42, 1273–1281.

Cho, W. C. (2010b). MiRNAs in cancer – from research to therapy. *Biochim. Biophys. Acta* 1805, 209–217.

Cho, W. C. (2010c). MiRNAs as therapeutic targets for lung cancer. *Expert Opin. Ther. Targets* 14, 1005–1008.

Cho, W. C. (2010d). "Omics approaches in cancer research," in *An Omics Perspective on Cancer Research*, ed. W. C. Cho (Berlin: Springer), 1–9.

Cho, W. C. (2011a). Molecular diagnostics for monitoring and predicting therapeutic effect in cancer. *Expert Rev. Mol. Diagn.* 11, 9–12.

Cho, W. C. (2011b). *MiRNAs in Cancer Translational Research*. Berlin: Springer.

Cho, W. C. (2011c). Grand challenges and opportunities in deciphering the role of non-coding RNAs in human diseases. *Front. Genet.* 2:1. doi: 10.3389/fgene.2011.00001

Heneghan, H. M., Miller, N., Kelly, R., Newell, J., and Kerin, M. J. (2010a). Systemic miRNA-195 differentiates breast cancer from other malignancies and is a potential biomarker for detecting noninvasive and early stage disease. *Oncologist* 15, 673–682.

Heneghan, H. M., Miller, N., Lowery, A. J., Sweeney, K. J., Newell, J., and Kerin, M. J. (2010b). Circulating microRNAs as novel minimally invasive biomarkers for breast cancer. *Ann. Surg.* 251, 499–505.

Hu, Z., Chen, X., Zhao, Y., Tian, T., Jin, G., Shu, Y., Chen, Y., Xu, L., Zen, K., Zhang, C., and Shen, H. (2010). Serum microRNA signatures identified in a genome-wide serum microRNA expression profiling predict survival of non-small-cell lung cancer. *J. Clin. Oncol.* 28, 1721–1726.

Huang, Z., Huang, D., Ni, S., Peng, Z., Sheng, W., and Du, X. (2010). Plasma microRNAs are promising novel biomarkers for early detection of colorectal cancer. *Int. J. Cancer* 127, 118–126.

Ji, X., Takahashi, R., Hiura, Y., Hirokawa, G., Fukushima, Y., and Iwai, N. (2009). Plasma miR-208 as a biomarker of myocardial injury. *Clin. Chem.* 55, 1944–1949.

Li, A., Omura, N., Hong, S. M., Vincent, A., Walter, K., Griffith, M., Borges, M., and Goggins, M. (2010). Pancreatic cancers epigenetically silence SIP1 and hypomethylate and overexpress miR-200a/200b in association with elevated circulating miR-200a and miR-200b levels. *Cancer Res.* 70, 5226–5237.

Mitchell, P. S., Parkin, R. K., Kroh, E. M., Fritz, B. R., Wyman, S. K., Pogosova-Agadjanyan, E. L., Peterson, A., Noteboom, J., O'Briant, K. C., Allen, A., Lin, D. W., Urban, N., Drescher, C. W., Knudsen, B. S., Stirewalt, D. L., Gentleman, R., Vessella, R. L., Nelson, P. S., Martin, D. B., and Tewari, M. (2008). Circulating microRNAs as stable blood-based markers for cancer detection. *Proc. Natl. Acad. Sci. U.S.A.* 105, 10513–10518.

Ng, E. K., Chong, W. W., Jin, H., Lam, E. K., Shin, V. Y., Yu, J., Poon, T. C., Ng, S. S., and Sung, J. J. (2009). Differential expression of microRNAs in plasma of patients with colorectal cancer: a potential marker for colorectal cancer screening. *Gut* 58, 1375–1381.

Pigati, L., Yaddanapudi, S. C., Iyengar, R., Kim, D. J., Hearn, S. A., Danforth, D., Hastings, M. L., and Duelli, D. M. (2010). Selective release of microRNA species from normal and malignant mammary epithelial cells. *PLoS ONE* 5, e13515. doi: 10.1371/journal.pone.0013515

Rossi, S., Shimizu, M., Barbarotto, E., Nicoloso, M. S., Dimitri, F., Sampath, D., Fabbri, M., Lerner, S., Barron, L. L., Rassenti, L. Z., Jiang, L., Xiao, L., Hu, J., Secchiero, P., Zauli, G., Volinia, S., Negrini, M., Wierda, W., Kipps, T. J., Plunkett, W., Coombes, K. R., Abruzzo, L. V., Keating, M. J., and Calin, G. A. (2010). MicroRNA fingerprinting of CLL patients with chromosome 17p deletion identify a miR-21 score that stratifies early survival. *Blood* 116, 945–952.

Roth, C., Rack, B., Muller, V., Janni, W., Pantel, K., and Schwarzenbach, H. (2010). Circulating microRNAs as blood-based markers for patients with primary and metastatic breast cancer. *Breast Cancer Res.* 12, R90.

Schwind, S., Marcucci, G., Maharry, K., Radmacher, M. D., Mrózek, K., Holland, K. B., Margeson, D., Becker, H., Whitman, S. P., Wu, Y. Z., Metzeler, K. H., Powell, B. L., Kolitz, J. E., Carter, T. H., Moore, J. O., Baer, M. R., Carroll, A. J., Caligiuri, M. A., Larson, R. A., and Bloomfield, C. D. (2010). BAALC and ERG expression levels are associated with outcome and distinct gene and microRNA expression profiles in older patients with de novo cytogenetically normal acute myeloid leukemia: a cancer and leukemia group B study. *Blood* 116, 5660–5669.

Shen, J., Todd, N. W., Zhang, H., Yu, L., Lingxiao, X., Mei, Y., Guarnera, M., Liao, J., Chou, A., Lu, C. L., Jiang, Z., Fang, H., Katz, R. L., and Jiang, F. (2011). Plasma microRNAs as potential biomarkers for non-small-cell lung cancer. *Lab. Invest.* doi: 10.1038/labinvest.2010.194. [Epub ahead of print].

Silva, J., García, V., Zaballos, A., Provencio, M., Lombardía, L., Almonacid, L., García, J. M., Domínguez, G., Peña, C., Diaz, R., Herrera, M., Varela, A., and Bonilla, F. (2011). Vesicle-related microRNAs in plasma of NSCLC patients and correlation with survival. *Eur. Respir. J.* doi: 10.1183/09031936.00029610. [Epub ahead of print].

Tsujiura, M., Ichikawa, D., Komatsu, S., Shiozaki, A., Takeshita, H., Kosuga, T., Konishi, H., Morimura, R., Deguchi, K., Fujiwara, H., Okamoto, K., and Otsuji, E. (2010). Circulating microRNAs in plasma of patients with gastric cancers. *Br. J. Cancer* 102, 1174–1179.

Visone, R., Rassenti, L. Z., Veronese, A., Taccioli, C., Costinean, S., Aguda, B. D., Volinia, S., Ferracin, M., Palatini, J., Balatti, V., Alder, H., Negrini, M., Kipps, T. J., and Croce, C. M. (2009). Karyotype-specific microRNA signature in chronic lymphocytic leukemia. *Blood* 114, 3872–3879.

Wang, J., Chen, J., Chang, P., LeBlanc, A., Li, D., Abbruzzesse, J. L., Frazier, M. L., Killary, A. M., and Sen, S. (2009). MicroRNAs in plasma of pancreatic ductal adenocarcinoma patients as novel blood-based biomarkers of disease. *Cancer Prev. Res. (Phila.)* 2, 807–813.

Whitman, S. P., Maharry, K., Radmacher, M. D., Becker, H., Mrózek, K., Margeson, D., Holland, K. B., Wu, Y. Z., Schwind, S., Metzeler, K. H., Wen, J., Baer, M. R., Powell, B. L., Carter, T. H., Kolitz, J. E., Wetzler, M., Moore, J. O., Stone, R. M., Carroll, A. J., Larson, R. A., Caligiuri, M. A., Marcucci, G., and Bloomfield, C. D. (2010). FLT3 internal tandem duplication associates with adverse outcome and gene- and microRNA-expression signatures in patients 60 years of age or older with primary cytogenetically normal acute myeloid leukemia: a cancer and leukemia group B study. *Blood* 116, 3622–3626.

Zhou, H., Guo, J. M., Lou, Y. R., Zhang, X. J., Zhong, F. D., Jiang, Z., Cheng, J., and Xiao, B. X. (2010). Detection of circulating tumor cells in peripheral blood from patients with gastric cancer using microRNA as a marker. *J. Mol. Med.* 88, 709–717.

Conflict of Interest Statement: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 03 January 2011; accepted: 11 February 2011; published online: 28 February 2011.

Citation: Cho WCS (2011) Circulating microRNAs as minimally invasive biomarkers for cancer theragnosis and prognosis. Front. Gene. ***2****:7. doi: 10.3389/fgene.2011.00007*

This article was submitted to Frontiers in Non-Coding RNA, a specialty of Frontiers in Genetics.