

of miRNAs as biomarkers for clinical trials in oncology. To provide a more specific example, Corcoran et al. (162) explored the use of a panel of miRNAs, as well as exosomes that contain miRNAs, for their potential to assess the clinical outcome in patients with prostate cancer.

In an example from lung adenocarcinoma, a panel of four miRNAs was found to be capable of distinguishing patients with lung adenocarcinoma from normal subjects (163). The four miRNAs were miR-21, miR-486, miR-375, and miR-200b. Please note that each of these names represents a different sequence of some 21–23 nucleotides. In detail, in patients with lung adenocarcinoma, the concentrations in sputum of miR-21, miR-200b, and miR-375 were higher than in normal subjects, while the concentration of miR-486 was lower. After investigating the panel of four biomarkers, the investigators successfully validated the panel, where this validation was conducted with 64 patients with lung adenocarcinoma.

The take-home lessons from this study are as follows. First, the study shows that a lung cancer biomarker can be provided by sputum (rather than from a lung biopsy). Secondly, the study demonstrates the utility of biomarkers with *increased expression* as well as the utility of biomarkers with *decreased expression*. And third, the study reveals that an exploratory

clinical trial and a validation clinical trial involve two separate study designs.

This concerns DNA circulating free in the bloodstream, that is, DNA that is free and not in any cells. In a study of 30 women, Dawson et al. (164) determined that circulating tumor DNA was detectable in nearly all of the women, while CTCs were detectable in 87% of the women. A goal of this study was to improve upon earlier findings that a biomarker protein (CA 15-3) had only moderate sensitivity in detecting breast cancer. Dawson et al. (165) and others (166) have used the term “liquid biopsy” to refer to the use of free DNA in the circulation, rather than tissue biopsies, for assessing tumor burden in patients. An advantage of a liquid biopsy is the ease of repeated sampling during the course of chemotherapy.

### c. Exosomes

Regarding exosomes, most types of cells, including tumor cells, secrete small vesicles. These small vesicles have been called exosomes and microvesicles. Exosomes contain proteins, as well as various types of nucleic acids, including DNA, RNA, and miRNAs. Exosomes are found in blood plasma, ascites fluid, and urine. In the context of oncology, exosomes can be used as biomarkers for

<sup>162</sup>Corcoran C, et al. miR-34a is an intracellular and exosomal predictive biomarker for response to docetaxel with clinical relevance to prostate cancer progression. *The Prostate* 2014;74:1320–34.

<sup>163</sup>Yu L, Todd NW, Xing L, et al. Early detection of lung adenocarcinoma in sputum by a panel of microRNA markers. *Int. J. Cancer* 2010;127:2870–8.

<sup>164</sup>Dawson SJ, Tsui DW, Murtaza M, et al. Analysis of circulating tumor DNA to monitor metastatic breast cancer. *New Engl. J. Med.* 2013;368:1199–209.

<sup>165</sup>Dawson SJ, Tsui DW, Murtaza M, et al. Analysis of circulating tumor DNA to monitor metastatic breast cancer. *New Engl. J. Med.* 2013;368:1199–209.

<sup>166</sup>Toss A, et al. CTC enumeration and characterization: moving towards personalized medicine. *Ann. Transl. Med.* 2014;2:108 (16 pp.).