Host: Welcome to the podcast from *Clinical Chemistry.* I am Bob Barrett. Biomarkers are used to identify the risk, presence and severity of disease, to guide diagnostic and therapeutic interventions, and to provide clues to disease mechanisms.

The search for new disease biomarkers remains a large and growing enterprise, and this is particularly true in the area of cardiovascular disease.

The November issue of *Clinical Chemistry* published a paper by researchers at the National Cardiovascular Center Research Institute in Osaka, Japan, which attempted to identify microRNAs that might accurately reflect myocardial injury in vitro.

In these studies, a systematic search identified a cardiac-specific microRNA that is detectable in circulating plasma following a myocardial injury using standard real-time RT-PCR techniques.

Dr. Gregory Tsongalis is the Director of Molecular Pathology at Dartmouth-Hitchcock Medical Center, and he is our guest in this podcast.

Tell us, Dr. Tsongalis, what exactly are microRNAs.

Dr. Gregory Tsongalis: MicroRNAs are small sequences of nucleic acids that average in size between 15 and 25 bases that we use to typically discard as artifactual or degraded nucleic acids. Now we are finding that these small molecules have very, very specific functions and regulatory roles in cellular processes.

Host: So why are they so intriguing as potential new biomarkers?

Dr. Gregory Tsongalis: I think unlike other biomarkers or new biomarkers that we are looking at now, these really have a sense of specificity that are unlike anything that's ever been looked at before. They are very, very specific for tissue and cell types. They are very specific for disease versus normal states of tissues themselves. So, I don't think we have ever seen that degree of specificity before.

The other issue with the microRNAs is that they are incredibly stable compared to routine gene expression assays that look at much larger length messenger RNA fragments. Because they are so small, they don't degrade as quickly or don't fall into the instability category. And I think finally, there is now this whole literature based on looking at these in

the circulation and being able to detect very specific microRNA molecules that are floating around that could potentially be disease specific.

Host: Where do microRNAs in the circulation come from?

Dr. Gregory Tsongalis: I think just like other biomarkers that clinical chemists used to measuring in the circulation, these can come from a number of different sources, probably the primary sources of them being leaked out of injured cells, or the cells that have become apoptotic and lost their nucleic acid content into the circulation. I think on the oncology side, that's another intriguing and a possibility for finding these in the circulation and that has to do with this whole issue of circulating tumor cells and identifying these microRNAs in a cell population that's not typically in the circulation.

Host: So, what is the significance of microRNA-208 or microRNA-490 in the heart?

Dr. Gregory Tsongalis: Well, I think with respect to a recent publication in *Clinical Chemistry*, they have shown that microRNA-490 isn't really specific for heart tissue or heart disease. It can be found or is expressed in other tissues in addition for the cardiac tissues.

So, that really isn't going to be a marker that I think would have a lot of diagnostic or prognostic characteristic.

The microRNA-208 though is one again, in a recent article in *Clinical Chemistry*, that showed very, very good sensitivity and specificity for heart disease. I think what the authors of this paper showed very, very nicely is that the expression levels of microRNA-208 actually correlates very well with troponin I level in cardiac disease patients. Then they also showed that the specificity of this marker is such that you don't see it in other benign types of diseases of the heart.

Host: So, with that in mind, could one or more microRNAs replace the more traditional types of biomarkers for cardiac disease?

Dr. Gregory Tsongalis: I think there is a really good potential for this and I think probably the biggest advantage of the microRNAs we have mentioned a couple of times already is the specificity, and I think we have the technologies to be able to detect these at very, very small amounts in the circulation or in cells and

tissues. So, I don't think the sensitivity is going to be as big of an issue as you might think, but the specificity of these markers really give them the potential to replace a lot of the existing biomarkers that we look at.

Host: In your opinion, are there other potential roles for microRNAs in the clinical selling?

Dr. Gregory Tsongalis: Oh sure! There is a number of different roles including diagnostics and prognostics, but I think probably one of the more exciting roles that we are starting to see articles on now and the literature is this whole area of therapeutic and actually targeting the microRNAs with what's been termed the antagomirs or antisense molecules that will hybridize to these microRNAs and not allow them to function in the regulatory roles that they usually function.

The broad-spectrum therapeutics once we figure out what the biological significance of some of these markers are, I think is very, very exciting.

Host: Dr. Gregory Tsongalis is the Director of Molecular Pathology at Dartmouth-Hitchcock Medical Center in New Hampshire, and he has been our guest in this podcast from *Clinical Chemistry*. I am Bob Barrett. Thanks for listening.

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