



# On the Trail of Genomic Pioneers



Meet Dr. Michael Mattie,  
Principal Scientist,  
Discovery Technologies and  
Infectious Diseases,  
Glaxo SmithKline

## 1) Would you tell us a bit about your educational background and research experience?

As a graduate student in toxicology at Duke University I studied molecular mechanisms of toxicity induced by metals and reactive oxygen species, with an emphasis on signal transduction pathways affected by exposure to such toxicants. After completing my PhD I had a desire to get into more transnational research in oncology and gain exposure to genomics technologies. I had the opportunity to do my postdoctoral training at the University of California San Francisco Comprehensive Cancer Center in the laboratory of Dr. Chris Haqq. His research interest is focused on transcriptional profiles of normal prostate and prostate tumor tissues. As a member of Dr. Haqq's lab I had the opportunity to gain experience in microarray and qRT-PCR technologies to study gene expression in prostate cancer and worked on two separate clinical trials examining the effects of dietary and/or lifestyle intervention on prostate cancer (MENS-Molecular Effects of Nutritional Supplements and GEMINAL-Gene Expression in Men undergoing Nutrition and Lifestyle intervention). I started my postdoc in 2003 and the microRNA field was in its infancy at that time. After hearing a lecture by Michael McManus, Dr. Haqq and I were inspired to investigate the role of microRNAs in prostate cancer. At the time there were not a lot of tools for doing miRNA research. A lot of labs were still using cloning techniques to identify miRNAs. Coming from a microarray lab, we went the route of creating our own custom miRNA microarrays. In collaboration with Genisphere Inc. we were able to devise a way to label and amplify miRNAs for detection on our microarray platform. In addition to our study of miRNAs in prostate cancer we have also studied miRNA expression in breast cancer in collaboration with Dr. Chris Benz at the Buck Institute for Age Research. I have been a Principal Scientist at GlaxoSmithKline for nearly four years where I am currently supporting drug discovery efforts in the infectious diseases area.

## 2) Your paper demonstrates that optimized high-throughput microRNA expression profiling offers novel biomarker identification from small

## clinical samples such as breast and prostate cancer biopsies. In your opinion what research focus areas and challenges will help getting the best out of miRNA profiling?

Larger studies and extensive clinical validation will help to identify miRNAs that have true diagnostic value. From our experience and published reports, microRNA profiles have appeared to be more useful in terms of their diagnostic value than messenger RNA profiles. The fact that miRNAs are stable in FFPE (formalin-fixed paraffin embedded) tissue samples opens up a wider array of available diagnostic specimens for such validations. Poor stability of messenger RNA in FFPE samples and the ability to amplify it has been an issue for doing such kinds of transcriptomic studies. Being able to go back to older archived tissues from patients with known clinical outcomes obviously allows you to do the kinds of studies that are needed to validate the diagnostic and predictive value of a particular profile. Recent advances in technology for detection of microRNA have pushed the ability to detect levels from even a single cell so even samples with limited material are possible to evaluate now. I think what will be of even more clinical value is validation of miRNA signatures that have either prognostic value or can aid in predicting whether a patient is likely to respond to a particular course of treatment.

## 3) To a broader audience, how do you think miRNAs will help in finding new class of cancer biomarkers?

I think there is a great potential for miRNAs as a new class of biomarkers. Several studies have demonstrated the ability of miRNA profiling to classify tumors, identify the tissue of origin, to predict progression or potential for metastasis or recurrence. As with any biomarker, use of miRNA(s) in the clinic will require a lot of further clinical validation. Companies like Rosetta Genomics have been very active in this area and have made great strides in making this a reality. In an era where there has been a push for personalized medicine and a shift in the



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pharmaceutical and biotechnology companies to focus on more targeted therapies, there will be an increasing need to have diagnostic tests that are able to accurately predict response to therapies. Recent examples in the literature suggest some miRNAs play a role in response/resistance to drugs and there have been some other reports of expression of microRNAs isolated from serum which may potentially be better biomarkers than current ones used in the clinic with controversial diagnostic value.

**4) Which study or research paper/s or work have strongly influenced your thought and research goals?**

Carlo Croce and George Calin were very early pioneers in the microRNA field and their seminal study that linked miR-15/16 to cancer really put microRNAs on the map. I have been strongly influenced and inspired by the work out of the labs and collaborators of other trailblazers in this field such as Frank Slack, Scott Hammond, David Bartel, Greg Hannon, Victor Ambrose, Gary Ruvkun, Bryan Cullen and Peter Sarnow, to name just a few. Having recently transitioned into research on infectious diseases I have been highly intrigued by recent studies implicating a role for various microRNAs in viral diseases, such as miR-122 and hepatitis C.

**5) Where do you see your research leading in future?**

The role of miRNAs in numerous biological processes has been thoroughly demonstrated by expression profiling, but there still remains a lot of work to be done in determining the functional role for many of the miRNAs that have been identified. I am very interested in the idea of miRNA modulation as a novel therapeutic strategy for several disease areas. As with RNAi therapeutics, delivery is still a major technical hurdle but I am optimistic that safe and effective delivery technologies will eventually be found.

**6) A great deal of your work focuses on the Cancer research. What would you say are the most important things that have been discovered about this over the years and what will be role of Genomics in it in the years to come?**

I think what amazes me the most is that in addition to microRNAs, several other classes of non-coding RNAs are just beginning to be discovered and understood. We used to think that a large percent of the human genome was just junk DNA, but we are now seeing that a lot of those bits are part of a much more intricate system with many levels of gene regulation than we previously thought. Recent advances in sequencing technologies have contributed to being able to identify many of these new classes of non-coding RNAs. Along with the Genomics era came a hope that a new boom in treatments for disease would come. The contribution of genomics has yet to fully realize its potential and it will take a lot of integrative approaches to make sense of the increasing amount of information we find ourselves swimming in.

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