



**Rolf Renne, Ph.D**

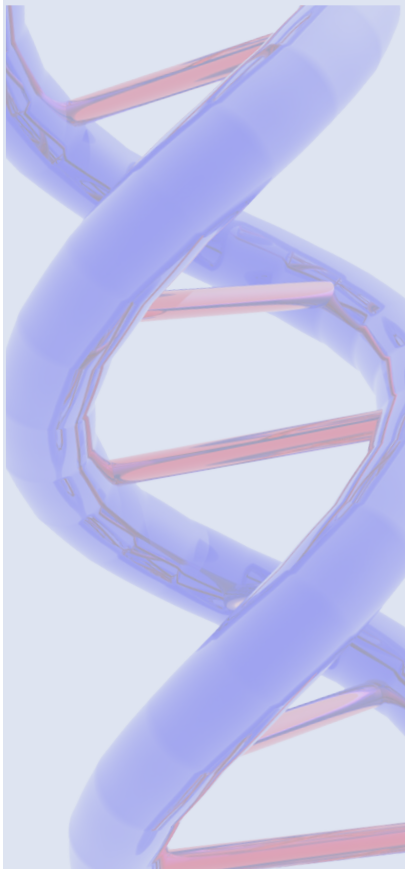
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# UF Genetics Institute Research Letters

**Rolf Renne** answers some questions about his recent paper in the **Journal of Virology**. His work dealing with **Kaposi’s Sarcoma herpesvirus** and **microRNAs** was also discussed in **Cell Host & Microbe** in January.

Kaposi’s Sarcoma-Associated Herpesvirus-Encoded MicroRNA Mimics Host miR-155 Involved in B-Cell Development

Kaposi’s sarcoma-associated herpesvirus (KSHV) encodes 17 microRNAs (miRNAs), which are expressed in both latent and lytic infection. KSHV miRNAs target cellular genes involved in angiogenesis, proliferation, and apoptosis. Skalsky et al. (p. 12836-12845) describe one KSHV miRNA, miR-K12-11, which has 100 percent seed sequence homology to human miR-155, a critical regulator of B-cell development and oncogenesis. Reporter assays and gene expression profiling show that both miRNAs regulate a common set of target genes. Hence, KSHV encodes an ortholog of miRNA-155, which may contribute to KSHV lymphomagenesis.



## Why do you think your paper is significant?



We were one of four laboratories which initially described KSHV miRNAs and earlier in 2007 described the first host target genes for these novel regulators of gene expression PLoS Pathog. 2007 May 11;3(5):e65.

However, the realization that some viral miRNAs show sequence conservation to cellular ones suggested that viral miRNAs, like other viral genes pirated from the host, represent yet another example for “molecular mimicry”. This was particular exciting since miR-155 was the first human miRNA shown to be oncogenic. Furthermore, given what we know about miR-155 function and B cell development, it is very tempting to speculate that miR-K12-11 directly contributes to KSHV-associated lymphomagenesis. However, it is important to state that while our initial observation is exciting, this question needs to be addressed in the appropriate animal models. Work into that direction is currently ongoing.



### **Would you summarize the significance of your paper in layman's terms?**



We now know that one of the reasons why viruses utilize miRNA genes is to mimic cellular miRNA genes. For example the human miRNA 155 activates B cells. In KSHV infected cells the expression of viral miRNAs does exactly the same and it is fair to say that most viruses favor activated cells for their replication. We have found several more viral miRNAs which could mimic other cellular orthologs. Hence, this mimicry represents a novel concept rather than an anomaly.



### **How did you become involved in this research, and were there any particular problems encountered along the way?**



The first virally encoded miRNA was discovered by Thomas Tuschl's lab in 2004 in Epstein-Barr Virus, another human herpesvirus associated with cancer. Since we had worked for years on tissue culture models for KSHV we had all the tools in the lab to ask whether KSHV encode miRNAs. Several months later we had isolated 12 microRNA genes and published our findings in the Journal of Virology. The project has since been a "fast and exciting ride" with only one major problem. It is very competitive. Every study is accompanied by similar studies from 2 to 3 other laboratories. However, the good thing is that so far in this field the data from all labs confirm all major findings. It also helped that we have received funding from both the State of Florida and the NIH/NCI to continue this work.



### **Where do you see your research leading in the future?**



There are two major directions. Within the basic research lab we want to have a better understanding why herpesviruses have evolutionarily conserved these miRNAs. In which steps in the viral life cycle are they advantageous? With respect to miR-155 and miR-K12-11 the next question clearly is: Does the viral miRNA mimic miR-155 function during hematopoiesis in an animal model? In that case KSHV miR-K12-11 would clearly be a candidate "oncogene". The more long-term translational or applied ramifications of this work are outlined below.



### **Are there any translational implications for your research?**



Not immediately. - However, on the long run there could be a diagnostic as well as a potential therapeutic target associated with viral microRNAs. First, during a collaboration with the NCI, we have analyzed the microRNA genes of 40 patients world wide and found that they are largely conserved. However, they were polymorphisms and ongoing studies will delineate whether these might be associated with particular disease outcomes, in other words whether they could serve as biomarkers for onset of certain disease stages.

Secondly, we have submitted a new proposal which involves investigators from the College of Dentistry, Prof. Edward Chan and the College of Liberal Arts and Science, Dr. Weihong Tan of the Department of Chemistry, with the goal to target virally expressed miRNAs for therapeutics. The question we ask is whether inhibiting of viral miRNA will have an effect on tumor cell survival.