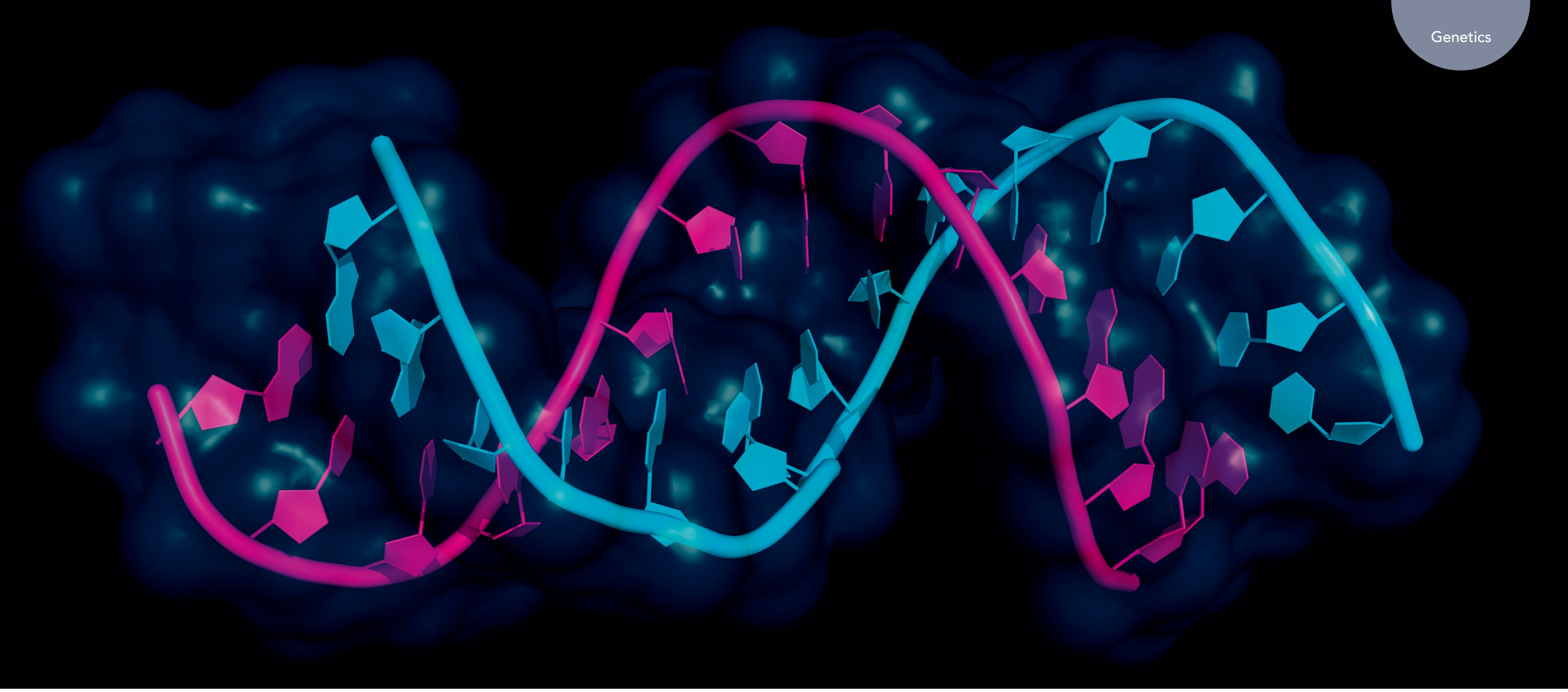


MicroRNAs as the micro managers of gene expression

Recent work indicates that more than half of human protein-coding genes are regulatory targets of MicroRNAs (miRNAs). **Dr Glen Borchert**, Assistant Professor at the University of South Alabama, is examining the roles that miRNAs play during growth and development, how miRNAs contribute to speciation, and how miRNA dysregulation can lead to oncogenesis.

The DNA in a cell's nucleus codes for all the proteins which that cell needs to function. This code is first transcribed into messenger RNA (mRNA) which can then be edited by enzymes and translated into proteins by cellular machinery. Each cell contains all the DNA of the organism, but not all of it is needed in every cell type or at every stage of development. Therefore, a range of processes exist which act to regulate which proteins a cell produces, including: how the DNA is packaged in the nucleus, which parts localise to specific regions of the nuclear envelope, or – further downstream – how mRNAs are edited and regulated.

DECIPHERING THE DNA CODE

MicroRNAs (miRNAs), are usually around 20 nucleotide bases long (the building blocks of DNA and RNA) and repress gene expression by base-pairing to mRNAs. Base-pairing occurs when the sequence of nucleotides on one strand lines up and connects to a complementary sequence on the other strand, with the resulting double strand unable to be translated and consequently repressed by the cell. These are not the only 'rogue' RNAs which do this, but they are unusual in that they only require very short complementary sequences to do so.

Of note, Dr Borchert's early work definitively demonstrated that miRNAs are often produced by the enzyme Pol III effectively dispelling the then widely accepted paradigm that microRNAs were exclusively generated by the enzyme RNA Polymerase II (Pol II).

MICRO MOLECULES BRING BIG CHALLENGES

Since making his first major discovery, Dr Borchert has now set up a research lab to look further into these unusual molecules and investigate how they carry out their function of refined gene control within the cell. However, there are a number of difficulties in identifying the targets of these tiny tricksters: some regulate edited RNAs which no longer possess the exact sequence specified in the genome which coded it; some have been formed from larger non-coding sections of RNA and therefore may well regulate other non-

Life arose from small molecule interactions, and … life and all cellular activity are still primarily coordinated by small, noncoding RNAs

coding sections themselves; yet others come from transposable elements, so-called 'jumping genes', so likely pair with similar elements in other sequences.

Undaunted by this task, Dr Borchert's lab is currently running four principal, separate but related projects to develop their understanding of these particularly difficult scenarios. The first project aims to ascertain the molecular origins of specific miRNAs to facilitate target prediction. This is particularly important for identifying miRNAs whose origins lie within the transposable elements mentioned.

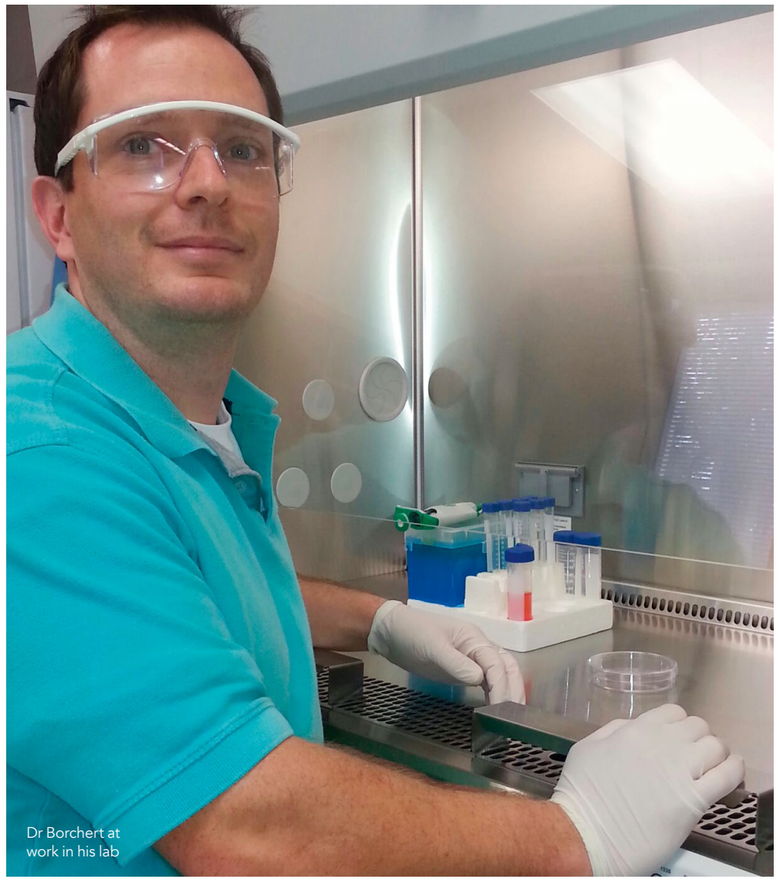
JUMPING INTO THE GENOME

Student researchers in the Borchert lab actively search both previously characterised and novel genomes to identify these elements and compare them to known miRNAs. Once a miRNA's progenitor sequence is known, the team use a unique computational strategy to limit target searches to transcripts containing that transposable element, narrowing down the field of potential targets and increasing their success rate.

To date, the team have identified more than a thousand such origins for miRNAs – a third of those which have been characterised. They have published extensively on the work, showing novel and surprising insights into the formation of these molecules from pre-existing genetic elements. One such situation is thought to occur when two of these transposable elements are inserted at the same location in the genome. When this section is later transcribed, they can fold onto themselves to create a 'hairpin'. Hairpin structures are implicated in a wide range of RNA interactions, directing RNA folding, altering structural stability for messenger RNA, providing recognition sites for RNA binding proteins, and serving as a substrate for enzymatic reactions. Clearly the generation of these structures in miRNA, from adjacent transposable elements in the genome, has the potential to affect many translation processes.

SEARCHING THROUGH THE SEQUENCES

A second project aims to identify novel miRNA sequences by using the latest technology to sequence genomes. Alongside this, the researchers trawl



Dr Borchert at work in his lab

Dr Borchert recognises that this is a fast moving and developing field, but with his extensive background he is ideally placed to drive the research forward

publicly available datasets to identify sequences which code for structural elements and miRNAs, utilising cutting-edge computing techniques to assist them in the laborious search.

A similar project's goal is to describe miRNA molecules from a range of eukaryotic (predominantly plants and animals) and prokaryotic (bacterial) organisms, adding to the wealth of knowledge on how diverse species have developed using these simple factors.

Dr Borchert says he believes that life arose from small molecule interactions, and stresses the importance of greater understanding when he says that "life and all cellular activity are still primarily coordinated by small, noncoding RNAs."

The fourth project draws a link between these processes and the potential benefits to medicine through developing a better understanding of the basis of miRNA interactions. Using the libraries of small RNA molecules associated with

Q&A

Why do you believe that miRNAs are so important in coordinating cellular activity?

MicroRNAs represent a major level of regulatory complexity in that a single microRNA can coordinate the actions of dozens of distinct genes – turning them on or off in unison.

What are the implications of your discovery that miRNAs have their own polymerase?

Knowing which polymerase generates a microRNA allows you to understand what elements are responsible/necessary for its production.

What are the potential medical benefits of harnessing miRNA biology?

MicroRNA dysregulation has now repeatedly been found to be the causal event driving the genesis of many forms of cancer as well as other types of disease. Correcting the levels of these microRNAs – what initially drives the onset of malignancy, – represents an extremely attractive therapeutic strategy.

Why are we only now beginning to understand the full potential of these molecules?

We overlooked microRNAs for decades due to their small size (~20 nucleotides). While thousands of microRNA discoveries have been made since their discovery in humans early last decade, the even smaller number of nucleotides necessary for their interaction with mRNAs (~7 nucleotides) continues to confound our efforts to definitively identify the pertinent regulatory targets of microRNAs.

How do you see this field developing in the near future?

Excitingly, a host of similar new noncoding RNA molecules (sno-derived RNAs, tRNA fragments, lncRNAs, sRNAs, etc…) are just now beginning to be discovered and although these are quite distinct in terms of origin and structure, they appear to function similarly to microRNAs in terms of genetic regulation and suggest the world of noncoding RNA regulations is significantly more complex than currently appreciated.

The world of noncoding RNA regulations is significantly more complex than currently appreciated

oncologies (cancer), the group hopes to identify how these molecules and their dysregulation may be implicated in the initiation and progression of these diseases.

WHEN MANAGEMENT GOES WRONG

This is where what might appear as a wholly academic study of small molecule biology becomes much more pertinent. miRNAs have been associated with a range of developmental disorders and other diseases, from hearing and sight loss to heart and kidney disease. The crucial role miRNAs play in the regulation of stem cell progenitors differentiating into adipocytes (fat cells), means that they have even been seen as a factor in obesity. In fact, there are such a range of diseases that they are affiliated with, that a public register has been developed to document the known relationships between miRNA dysregulation and human disease.

Dr Borchert recognises that this is a fast moving and developing field, but with his extensive background in identifying not just thousands of miRNAs, but also the mechanisms and molecules which produce them, he is ideally placed to drive the research forward. Passionate about his research and the development of skills in his student researchers, he is also preparing the next generation of scientists who may go on to make the great discoveries of the future.

Detail

RESEARCH OBJECTIVES

Dr Borchert specialises in microRNAs and other related forms of noncoding RNAs, transposable elements and genomics. His research explores the regulation of gene expression by miRNAs and, in particular, their role during growth and development, how miRNAs contribute to speciation, and how their misregulation can lead to oncogenesis.

FUNDING

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- National Institutes of Health (NIH)

COLLABORATORS

- Yaguang Xi (LSU Health Science Center)
- Oliver McDonald (Vanderbilt University)
- Hank Bass (Florida State University)
- Mark Gillespie (USA COM)

BIO

Dr Glen Borchert received a BS in Biology from the University of Tennessee, PhD in Genetics at the University of Iowa and held postdocs at Illinois State and UC Berkeley. He was named a NSF CAREER Investigator in 2014 for his work on microRNAs at the University of South Alabama.

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