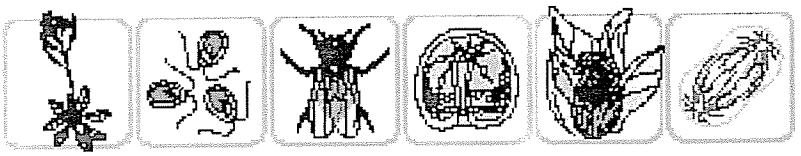


Developmental, Cell
and Molecular Biology Group
Department of Biology

LSRC Building, Research Drive • Box 91000
Duke University • Durham, NC 27708-1000

David R McClay
Professor
(919)613-8188
Fax: (919)613-8177
e-mail: dmcclay@duke.edu

4 November 2005

Dear Committee,

I am very pleased to recommend Cynthia Bradham for a position in your department. Cyndi has been a postdoc in my lab for five years. She came into the lab with no background in developmental biology but with an extensive research background in biochemistry. Her interests in development grew from a fascination over how cells become differentially specified in a short period early in development and then eventually build an embryo. Cyndi arrived with mastery of molecular biology, and biochemistry, and had to learn many of the technologies associated with developmental biology, as well as gain an understanding of the field itself. She has done that and has done it well. She built an impressive series of probes and now entertains a number of questions about how an embryo uses its axial information for patterning. These will serve her well as she pursues her career.

The current focus of the lab is on transcription factors and signal transduction to ask how cells prepare themselves for morphogenesis. In a collaboration with Eric Davidson we identified more than 75 transcription factors and at least 12 signal transduction events that program cells, specify axes, establish primitive boundaries, and prepare cells for the motile events of gastrulation. The completion of the sea urchin genome provided an additional 500 transcription factors to our database, and both laboratories established which of these are expressed during development, and when. Gene regulatory networks were constructed. Cyndi has been a major contributor to that effort and has built tools to ask how the oral-aboral axis (equivalent roughly to the dorsal-ventral axis in other deuterostomes) is established, and works. Her first big paper is in Press on that subject, and Cyndi has at least three additional papers nearing completion, including two that will be exceptional. These are on top of a large group of publications from her earlier work and several earlier papers from the lab.

Cyndi discovered that p38 kinase activation is the earliest known asymmetric molecular event in oral-aboral specification. For 30 min, at 5- 6 hr into development p38 MAPK signals in the oral half of the embryo and not in the aboral half. That asymmetry activates Nodal, and Nodal then is expressed throughout the oral compartment to activate the oral gene regulatory network. Using the database, high throughput screens and other approaches Cyndi now has a number of genes downstream of Nodal that set up the oral-aboral axis. The goal of this project is first to build the gene regulatory networks governing the oral and aboral compartments, and eventually to understand how growth factors and patterning information, activated by these networks, are provided to the skeletogenic cells with high spatial precision.

In a project nearing completion, Cyndi shows that chordin is expressed in the oral territory, downstream of p38 MAPK and Nodal, and necessary to counter BMP signal in the oral half embryo. The important effect of that inhibition is a necessary activity for specification of neurogenesis. In the absence of chordin, no neural development proceeds.

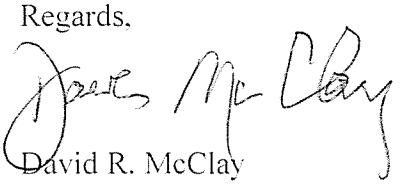
In yet another project she shows that growth of the skeleton is downstream of a transcription factor called orthopedia which is expressed by three cells on either side of the embryo. Those three ectoderm cells provide signaling to the mesoderm beneath and cause the skeleton to grow in their direction. Otp is downstream of the Nodal signaling system, but the expression in only three cells requires additional territorial refinement. Cyndi has the tools to decipher how the three cells are chose, and she also has several insights on how the three cells might signal to the skeletogenic cells to permit them to build the skeleton. This is an exciting set of studies because it provides insight into how an embryo uses one set of cells to provide patterning information used by other cells.

For her research Cyndi identified a number of upstream components of the signaling system in the ectoderm and used by the mesenchyme cells as they build the skeleton with the correct spatial coordinates. She employed bioinformatics, microarray screens, multiple secondary screens and a wide variety of molecular tools both with high throughput, and with a focus on the function of individual molecules. Cyndi is well trained and provides a major intellectual source for graduate students and postdocs along our corridor.

Cyndi Bradham is intelligent, driven to succeed, and fearless in taking up challenges well outside her original training. When she entered my laboratory she was already 37 and I asked her why she was taking such a huge risk with a new field and a new system, especially in the sea urchin, which hardly has the central attention of developmental biology. She indicated that its simplicity and potential as a model for studies in development appealed to her, and now with the sea urchin genome sequenced and with a number of experimental tools, the early network analysis of sea urchin specification offers one of the richest resources for understanding how embryos work. Cyndi Bradham is an important young mind in that field

I recommend her with great enthusiasm. Forty-four students have trained with me so far and 42 of those scholars are in the academy and active in research and teaching (#43 is with Zeiss and #44 is a patent attorney). Many of those students enjoy excellent research careers in Research 1 Universities (Harvard, Stanford, Brown, Utah, Duke, Minnesota, Carnegie-Mellon, Wisconsin, Chicago, Texas, UCSF, Princeton, etc). By way of comparison with that excellent group of former students who have been successful, Cyndi Bradham compares very favorably. She is smart, knowledgeable about the field, aggressive in pursuing questions, fearless in addressing issues, and she has a good perception of where science is going. She writes well so I have no concerns about her abilities in writing grants or in continuing her high level of productivity. She has many good scientific problems she plans to take with her. She is an excellent teacher with experience. And she will make a wonderful colleague. I recommend her with the highest enthusiasm.

Regards,



David R. McClay
Arthur S. Pearse Professor of Biology
Professor of Neurobiology
Professor of Marine Science