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THE NONSENSE SUPPRESSOR

Newsletter of the Department of Biology
College of Arts & Science
University Of Rochester
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Newest Biology Faculty Researcher Explores Chromatin Domains and Boundaries

The Biology Department welcomes its newest faculty member, Assistant Professor Xin Bi. Xin and his group moved to Rochester from the Department of Biochemistry at University of Nebraska-Lincoln in July. The Bi group (research technician Joseph Sandmeier; two graduate students, Qun Yu and Yanfei Zou; and a postdoctoral fellow, Hengping Xu) has settled in their newly designed lab space in Hutchison 304. The team continues their NIH-funded research on heterochromatin domains and boundary elements in the yeast model system.

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Eukaryotes organize their DNA into highly folded chromatin with distinct functional domains. Genes are usually repressed in heterochromatin, whereas euchromatin allows gene expression. However heterochromatin regions can have euchromatin as their nearest neighbors. This raises questions about their molecular composition and the mechanisms by which distinct chromatin domains are organized and maintained. In a series of studies of the silenced chromatin loci in the yeast *Saccharomyces cerevisiae*, Xin and colleagues have been identifying DNA sequences that block the spread of silent chromatin. Their evidence suggests that multiple mechanisms may be involved, including specific DNA structures (http://www.rochester.edu/College/BIO/faculty/Bi.html).

The path that led Xin to Rochester, New York began in Jinan, a town in Shangdong Province, China. Like all future scientists, Xin loved to read about science (from leaf structure to bridge constructions, from fly's eye to telescope). His early reading materials also included ancient classical Chinese novels. After graduating from the University of Science and Technology of China, Xin arrived at the Johns Hopkins University via the prestigious CUSBEA program that placed top Chinese students in scientific labs in the USA. A rotation in Leroy Liu's lab in the Department of Biological Chemistry changed his plan

to study immunology; instead Xin stayed on to study RecA-independent recombination in *E. coli* for his Ph.D. thesis. He then moved to Princeton University to work with Jim Broach in the Department of Molecular Biology; his postdoctoral research supported by a fellowship from the American Cancer Society. It was there that Xin started to study his long-time interest—chromatin topology and silencing, which has been his group's focus in Nebraska and now in Rochester.

From the first month since their arrival Xin and his team have been interactive participants at the yeast group meetings as well as the Chromatin Journal Club. Xin wishes though that he had more time to build his daughter, Joyce, a swingset. Xin, his wife Ya-Hui and kindergartener, Joyce reside in Pittsford.

Ongoing Biology Research Follows Diverse Paths

Adam Mason, Postdoctoral Fellow, Goldfarb lab

First let me say a little about my background and personal life. I was raised in Buffalo, NY, in the town of Grand Island (the little island you go over on the way to Toronto or Niagara Falls). I graduated from SUNY Geneseo in 1995 with a B.S. in Biology and I started graduate school at the University of Rochester in 1996. In the year between undergraduate and graduate school I spent a really fun year living in Denver, Colorado. I currently live in Chili with my wife Rebecca, our daughter Molly and my dog Gabriella. As if that wasn't enough, we are expecting a second baby in April. I spend most of my free time being with my family, playing volleyball, doing work at my church, or getting frustrated with the Buffalo Bills and Sabres.

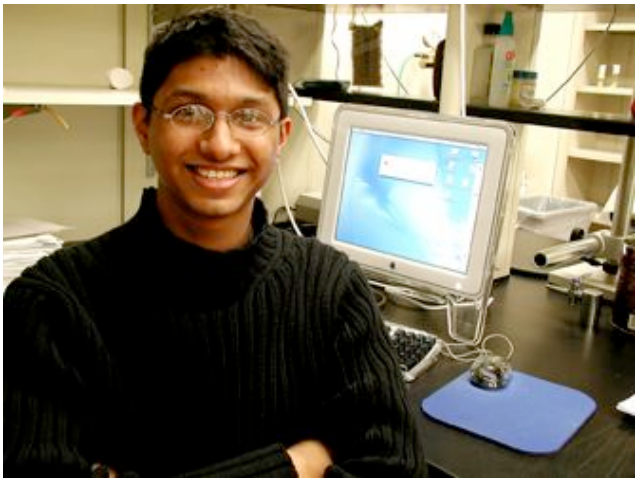
I worked with Dave Goldfarb and Robert Fleming on my thesis project studying functional specificity within the importin β gene family. Importin βs are cytoplasmic receptors for classical nuclear localization sequence-containing nuclear proteins. Using *Drosophila melanogaster* as a model system we were able to demonstrate that different importin β paralogs are required for distinct developmental processes *in vivo*. In addition, using transgene rescue assays we discovered that the conventional *Drosophila* importin βs served both redundant and paralog specific cellular functions. This was the first direct *in vivo* evidence that different importin β paralogs serve distinct functions.

After the completion of my degree in June of 2003 I decided to stay in Dave's lab to study programmed cell death in the budding yeast *S. cerevisiae*. Programmed cell death (PCD) is a process first described in metazoan animals by which cells destroy themselves in a genetically regulated manner. This process is essential for development and maintenance of homeostasis in multicellular organisms. Many diseases are caused by defects in the PCD machinery. Surprisingly, the process of PCD is conserved in single celled organisms like yeast. PCD in yeast can be induced by inducing oxidative stress or by expression of human pro-apoptotic proteins. Dave's lab has recently begun studying the role of regulating nuclear transport in PCD. My co-worker Nataliya Shulga has observed an increase in the permeability of the nuclear pore complex upon induction of PCD that is dependent on the yeast metacaspase Mca1. In addition, an undergraduate, Satyen Undavia, and I have discovered that many yeast nucleoporins are degraded after induction of PCD. We found that nucleoporin degradation is independent of Mca1 activity, but is dependent on the yeast vacuolar aspartic protease Pep4. Pep4 is a homolog of the human lysosomal protease, cathepsin D. It has recently been demonstrated that cathepsin D was released from the lysosome in staurosporine-treated human fibroblasts. Cytoplasmic cathepsin D catalyzed the caspase-independent release of Apoptosis Inducing Factor and cytochrome c from mitochondria. We are currently testing the hypothesis that cathepsin-mediated PCD is an ancient cell death pathway that is conserved between humans and yeast.

Naina Phadnis, Graduate Student, Sia lab

I joined the Biology Department in September, 2001, after graduating with a Masters in Microbiology from Pune, India. One year down the road I chose to work with Dr. Elaine Sia to study mitochondrial genome maintenance in the budding yeast *Saccharomyces cerevisiae*. When I first joined the lab, I thought of mitochondria as those typical kidney bean shaped organelles which are the "power houses" of the cell. Today, after a year of working on mitochondrial genome maintenance, I know that these organelles are dynamic structures which change form and shape and do much more than just produce ATP. My project aims at understanding mitochondrial genome replication by analyzing the protein interactions of the mitochondrial polymerase. Even though mitochondrial genome replication has been studied for the past thirty years, our knowledge of the mechanism of replication and segregation of mitochondrial DNA has many missing pieces. Mitochondrial DNA is thought to replicate using a transcription dependent mechanism where the RNA polymerase provides the primer for elongation of the DNA chain. Interestingly however, certain strains of yeast which have undergone large deletions in their mitochondrial genome can maintain their "" genomes without the presence of the RNA polymerase. What then initiates genome replication in these strains? In addition many other factors involved in the replication process are yet to be identified. I am making use of bacterial and yeast two hybrid screens, tandem affinity purification and synthetic lethal screens in order to find the mitochondrial replication complex proteins. Dr. Sia has developed mitochondrial reporter constructs which can measure the rate of frame shift mutations and rate of homologous recombination in the mitochondrial genome. Using these powerful genetic tools, members of the laboratory plan to study the factors that affect the rate of recombination and mutation in the mitochondrial genome. Many diseases and aging related disorders are thought to occur due to mutations on the mitochondrial genome and this study would provide good information on the forces causing these diseases. Shona Mookerji, a fourth year graduate student in our laboratory is studying the role of the mitochondrial mismatch repair gene *MSH1*. Leah Jablonski joined our laboratory this year and is studying the mitochondrial genome maintenance gene *MGM101*. Altogether the three of us are taking a three gene approach to put together the puzzle of mitochondrial genome replication, repair, segregation and maintenance.

Nitin Phadnis, Graduate Student, Orr/Fry labs



Despite my interest in evolutionary biology for several years, I did not have an opportunity to study it as a formal science. Reading books by popular scientists and having discussions with professors was my only access to the field. When I joined the UR Biology department, I knew I was at the right place to develop my evolutionary interests.

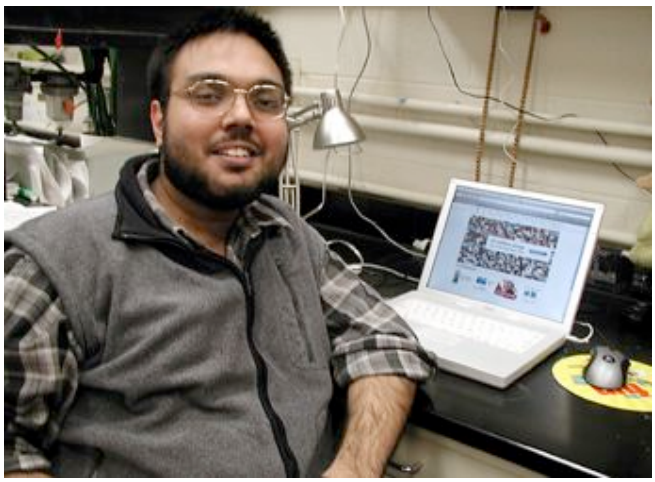
I studied microbiology for my undergraduate degree and after two years of grad school at the Indian Institute of Science I joined UR in August, 2002. I am now co-advised by Drs. Allen Orr and James Fry. Not surprisingly, the topics of my graduate research lie in the region of overlap of the expertise of the two laboratories, i.e., the genetics of speciation and the genetics of phenotypic evolution (adaptation).

It has been only a few months since I started my graduate research *per se* but I am already working on several projects. During my Orr lab rotation, I started working on experimental evolution using the RNA bacteriophage MS-2. Since I came from a microbiology background, a microbial evolution project seemed a wise choice. Andrea Betancourt (a senior graduate student in the Orr lab) had cultured replicate populations of MS-2 in a cold environment (30°C) for about 100 generations. Using whole genome sequencing, she studied the mutations that spread through the populations during the process of 'cold adaptation'. Her evolved populations now provided ideal material to study 'reverse evolution'. I took her evolved populations and put them back at their original temperature (37°C) for 100 generations. I performed whole genome sequencing at regular intervals and kept track of the ongoing genetic changes. In light of recent theory by Dr. Orr on the genetics of adaptation, I asked the following questions: 1) How often do I see reversion mutations/mutations at the same site? 2) How often do I see convergent evolution? 3) What is the fitness distribution of each mutation that has spread in the populations? I will have the answers soon, but it already looks as though site reversions occur at almost 50% of all evolved sites.

I have also begun working on the fine mapping of hybrid sterility factors between *Drosophila pseudoobscura pseudoobscura* and its sister-subspecies *D. pseudoobscura bogotana*. What makes this case interesting is that hybrid sterility between these subspecies appears to be associated with hybrid meiotic drive. The role of meiotic drive in speciation has been controversial and has attracted a great deal of attention lately: Does the sweep of meiotic drive genes through species ultimately cause the sterility of species hybrids? The key goal of my work is to determine if hybrid sterility and hybrid meiotic drive in this system—which represents *the* classic example of two young taxa in the process of speciation—are caused by the same genes. To determine this, I will take advantage of the many molecular tools that have become available with the recent sequencing of the entire *D. pseudoobscura* genome. I am also interested in the role of chromosomal rearrangements in speciation and will hopefully have something going on it soon.

Apart from these projects, I am on the look out for other interesting avenues for long-term research. The *Drosophila* model system is new to me, and I am learning to harness its awesome genetic tools! I also hope to gain some experience in theoretical studies and in molecular population genetics. I am fortunate to have Andrea Betancourt, J.P Masly and Yuseob Kim as my colleagues, each one of them being generous with guidance in their areas of expertise. And of course, for the kind of things that I want to learn, what could be better than working with Dr. Orr and Dr. Fry?

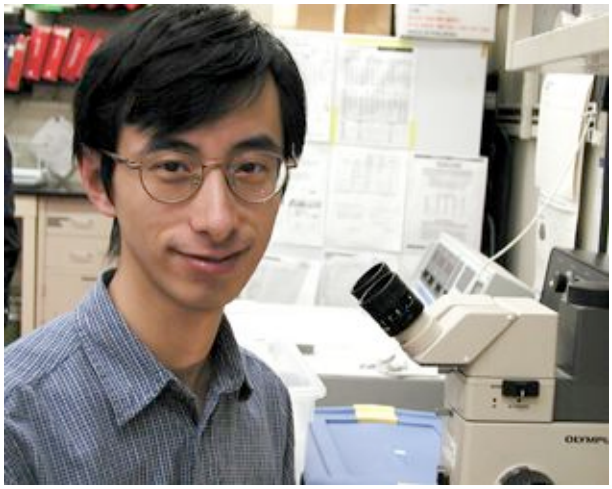
Adi Sethi, Graduate Student, Angerer lab



The sea urchin embryo is an intensely studied developmental system. Several key features of this system have attracted developmental biologists for decades. Some of these features are: (1) an optically transparent embryo greatly facilitating light microscopy and studies of key developmental events such as morphogenesis; (2) availability of large numbers of eggs and thereby embryos at a single shedding allowing for relatively easy biochemical and molecular analyses; (3) completion of embryonic development from a single celled zygote to a free swimming , feeding pluteus larva in three days; and (4) conservation of basic molecular pathways implicated in the development of higher organisms. Furthermore, the fully formed pluteus larva has all three germ layers and only five major tissue types, and virtually every cell of the embryo has been lineage mapped at high resolution. This makes the system tractable to experimental manipulations and yet simple enough in the range of its tissue types to allow for clear correlations of gene expression and function.

The sea urchin inherently remains a non genetic system however, since the pluteus larva undergoes a relatively long period of metamorphosis to form a juvenile larva and later on an adult. This precludes powerful forward genetic analyses possible with more classical genetic systems such as the fruit fly *Drosophila melanogaster* and the nematode *C. elegans*. By necessity then, most experimental methods are molecular and take a reverse genetic approach. Over three years ago, our lab pioneered the use of morpholino-based antisensing as a gene knockdown approach in this system, a technique which has since gone on to become a powerful standard for the field. Morpholinos are synthetic nucleotide (Continued on p. 16)

Che-Chia Tsao, Graduate Student, Gorovsky Lab

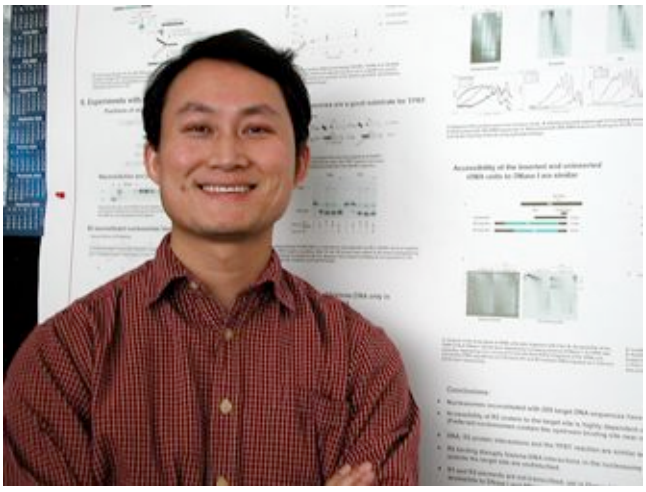


In a lab where the exciting explorations on the nucleus and nuclear events occupy the center of the universe, studying cellular appendages seems peripheral to the core. However, as a ciliated protozoan, *Tetrahymena thermophila*, the Gorovsky Lab's favorite organism, is also an excellent model to elucidate microtubule (MT) diversity and functions. *Tetrahymena* has 17 different MT systems, and, especially interesting to me, it has many, many cilia. Having cilia is not trivial since cilia/flagella ubiquitously exist from protozoa to human but are absent in higher plants and fungi. Defects in cilia can affect human health; abnormal cilia can lead to respiratory and reproductive problems and cause kidney disease and retinal degeneration. Cilia even determine the sidedness of the vertebrate body. Still, most of our current knowledge about this highly conserved organelle relies on the studies of protozoa.

To begin my project on cilia assembly, I did a subtractive screening to isolate genes which were highly induced during cilia regeneration. In starved *Tetrahymena*, we can deciliate the cells and allow them to rapidly regenerate cilia in a synchronized manner. The screening identified motor and cytoskeleton proteins, as well as intraflagellar transport (IFT) components. IFT is a common mobility required for cilia/flagella assembly and maintenance in diverse organisms. The IFT cargos, moving back and forth with motor proteins along the long axis of the cilia, are composed of 16 polypeptides. Two IFT homologs were obtained from our screening, and I cloned and knocked out one of them. The *IFT172* knockout cells cannot assemble functional cilia and therefore lose the ability to swim, ingest food particles and finish cytokinesis. Epitope-tagged Ift172 proteins localize in the cilia and closely associate with basal bodies, the MT organization centers for the cilia. These results are consistent with the putative role of IFT. Rescue experiments using different deletion constructs showed that both the N- and C-terminal regions of Ift172p are indispensable to make cilia. It is likely that the two regions separately interact with different factors which are important for the IFT function and cilia assembly. Alternatively, Ift172p needs both regions to form an interface to bind other proteins. Overexpression of various truncated forms of Ift172p and immuno-biochemical analysis of tagged proteins may provide more details.

Recently the draft sequence of *Tetrahymena* macronucleus genome has become accessible to the research community. Without having to spend months on fishing and cloning genes, now I can expand the studies to other conserved but less characterized IFT and ciliary proteins. By looking closely into what is going on within these small hairy monsters, maybe we can know a little bit more about our own kind someday. Bearing that in mind, I guess nothing is too marginal to be pursued in depth—even though it does not sit at the center of the world.

Junqiang Ye, Graduate Student, Eickbush lab



It is well known that transposable elements are abundant in eukaryotes and consequently have the potential to be disruptive to the genome. The Eickbush lab studies model retrotransposable elements R1 and R2 within the 28S ribosomal RNA gene (rDNA) in insects. R1 and R2 mobilize themselves by a simple mechanism called target-primed reverse transcription (TPRT), the mechanism of making cDNA directly from a nick in the chromosome generated by the element-encoded endonuclease. There are hundreds of copies of rDNA units in insects and one might imagine that all these copies could eventually be inserted by R1 and R2 elements. However the insertion of R1 and R2

disrupts the rDNA and makes the inserted unit non-functional. That could obviously be very harmful to the host cell. The persistence of these elements for millions of years implies that they must be highly regulated. My research focuses on the influence of chromatin structure on the expression of R2 elements. Specifically, I want to know whether the R2 protein is still capable of conducting the TPRT reaction when its target site lies in chromatin structure, and what is the influence of chromatin structure on the transcription of these elements.

For the first question, I conducted biochemical studies of the R2 TPRT reaction with *in vitro* reconstituted nucleosomes. Different nucleosome core particles were reconstituted by mixing the R2 target DNA with purified histones in a manner that the R2 recognition site was placed in different positions in the nucleosome. Each reconstituted nucleosome was tested with R2 protein for target site binding, cleavage and TPRT. The experiments showed that the R2 protein reacts with reconstituted nucleosomes in a position dependent manner. R2 is most reactive to nucleosomes when its upstream binding site is close to one edge of the nucleosome. Moving the target site to the middle or the other end of the nucleosome greatly inhibits the R2 activity. Most intriguingly, once the protein gains access to the DNA of the nucleosome, the R2 protein is completely capable of conducting the TPRT reaction. Footprint studies indicate that the binding of the R2 protein to its target DNA inside the nucleosome is similar to its binding to free DNA, yet the structure of the other DNA regions of the nucleosome remains unchanged.

The second part of my research is to determine what effects R2 insertion has on the chromatin structure of rRNA genes and their transcription. It has been shown that inserted rDNA units accumulate transcripts at least two orders of magnitude lower than uninserted rDNA units. This can potentially be explained by different chromatin structures of the inserted and uninserted rDNA units, transcriptional regulation at the promoter, or the instability of the inserted transcripts. My recent nuclear run-on experiments demonstrate that R1 and R2 elements are co-transcribed with rRNA at a fairly high level. This suggests that these elements are transcribed but RNA is rapidly degraded. Consistent with the run-on data, nucleases (DNase I and Micrococcal nuclease) accessibility assays showed no difference between uninserted and inserted rDNA units. Now I am conducting more sensitive psoralen cross-linking experiments to determine whether there are two different types of chromatin structures of rDNA in *Drosophila melanogaster*.

The expression of R1 and R2 elements is a complex process involving chromatin structure, rRNA transcription and processing and possibly more. We expect to have a better understanding about this in the near future.

I don't understand. She doesn't make sense.
Berend-Jan Velthuis, Graduate Student, Werren Lab

"Men," she said, "they're all the same. They think of only one thing." Plain and utter nonsense, of course! In fact, males, with all their colorful features, personal qualities and other characteristics, are all slightly different from each other. Which may well be exactly why it is so hard to find just the right one.

Looking back, a life-long fascination for females must have been the ultimate cause that brought me to the Werren lab. My interest germinated at an early age. But it was not until I was an undergraduate that I became truly fascinated by how females perceive and interact with their surroundings; how they do value what's right under their nose, but also tend to shop around for "more" or "better." And how, almost intuitively, they always seem to know exactly what's right for them and promptly act on it when given the opportunity.

I am of course talking about *Nasonia*, a genus of tiny parasitic wasps that for decades has captured the hearts of many good men. King, Hamilton, van den Assem, Charnov and Werren all shared my fascination

for how females adopt their (oviposition) behavior so as to maximize returns from their investments. Like many haplo-diploids, you must know, *Nasonia* females are able to manipulate the sex of their offspring and they use this feat to exert considerable local parental control (Nunney and Luck, 1985) over the sex life of their offspring! Yes, mom knows best! In fact, the life history of *Nasonia* is such that many aspects of female behavior have immediate and direct effects on lifetime fitness. Coincidentally, this is also relevant for those

(Continued on p. 7)

Department Retreat Highlighted by Science, Socialization and Relaxation

The 2003 Biology Department retreat was held at The Thendara Inn and Restaurant on Canandaigua Lake. The day began at 9:00 a.m. with coffee, tea and muffins. The science presentations were grouped into four sessions lasting an hour each—two in the morning and two in the afternoon with David Hinkle moderating in the morning and Tip Benyajati in the afternoon. Lunch/Relaxation/Social Events from 12:00 to 2:30 provided time to walk and play outside and enjoy the beautiful day on the lakeside.

Session I speakers were: **Rita Miller, "**Some things that we don't know about spindle positioning in yeast;" **Elaine Sia, "**Maintenance of mitochondrial DNA in yeast;" **Rulang Jiang, "**Toward understanding the molecular basis of craniofacial birth defects using animal models."

Session II speakers were: **Xin Bi, "**Chromosomes domains of gene expression and their boundaries;" **Tom Eickbush, "**Retrotransposons that insert into rRNA genes;" **Allen Orr, "**The genetics of speciation and adaptation."

Session III speakers were:**Bob Angerer, "**How to build a 'simple' deuterostome embryo;" **Jack Werren, "**Yet more interesting things about *Nasonia*;" **Adam Mason (Goldfarb Lab),** "The Intersection of nuclear transport, autophagy, apoptosis and lifespan in yeast."

Session IV speakers were: **John Jaenike, "**Mycophagous *Drosophila*;" **Don Kane**, "The three "M"s: Motility, Mutants, and Cadherins;" **Nitin Phadnis (Fry Lab), "**The genetic basis of an ecological adaptation in *Drosophila*."

The dinner buffet from 6:00 to 8:00 was open to spouses, friends and staff who wished to join the group.

(Velthuis, from p. 6) studying adaptation, as derived (and often times contrived) measures of fitness are not necessary for us to make sense of the deeper purpose of a female's behaviors. Which, let's face it, still eludes many of us men.

In the Werren lab, I now focus on a different aspect of female behavior: their mate choice. A *Nasonia* female typically mates upon emergence from the host on which she and her siblings developed. (Sibmating is the rule rather than the exception in *Nasonia*.) After mating, she promptly leaves her natal patch and is unlikely to ever meet another male, as males are short-lived and remain in the patch, waiting for what's still to come. This situation is rather different from that of e.g. *Drosophila*, where both sexes disperse before mating. Because in *Nasonia* there is (Continued on p. 17)

Biology Department and their Families Had Fun at the Yearly Holiday Party

What is everybody watching? (Those who can drag themselves away from the food that is.)

They're watching Zach Sia cringing while the jugglers toss balls—and then clubs—back and forth past him. Brave boy! He did emerge unscathed. The jugglers are all UR undergraduates who belong to "Strong Jugglers," a Student Association supported club. (See their web site for more information.)

Special thanks to Cindy Landry who found the jugglers and booked them for the party. Cindy also did all the party planning, enlisted volunteers for various tasks and shopped for the gifts for the children.

Santa Claus (aka Alan Dietsche) handed out a gift to every boy and girl who attended the party, even to 7 week old John Pellett, son of Nida Meednu and Jason Pellett.

Santa's Elf, Macy Eickbush, 17, assisted Santa by making sure he gave the right gift to each child. Alex Jiang looks a bit skeptical about the package Santa is handing to him.

Undergraduate Poster Symposium Features Summer Research

The twenty-first annual Undergraduate Program in Biology and Medicine (UPBM) Poster Symposium was held in Hutchison Lounge on Friday, October 10, 2003, in conjunction with the Chemistry Department as part of Meliora Weekend. The session featured the summer research of the eight 2003 de Kiewiet Summer Fellows as well as posters by five Chemistry majors.

There was a continuous flow of faculty, parents, undergraduates, lab personnel and alumni viewing the posters and asking the presenters for explanations of their projects.

de Kiewiet Fellows

Evan Kingsley, BCD
Retinal pathology of the *Cln3*$^{-/-}$mouse, a model for Batten Disease
Mentor: David Pearce, Center for Aging and Developmental Biology

Matthew Maurer, BMG
Protein factors involved in mismatch repair of the mitochondrial genome in *Saccharomyces cerevisiae*
Mentor: Elaine Sia, Biology

Mark O'Hara, BMG
Analysis of *TWI4*: a homologue of *TWI1*
Mentor: Martin Gorovsky, Biology

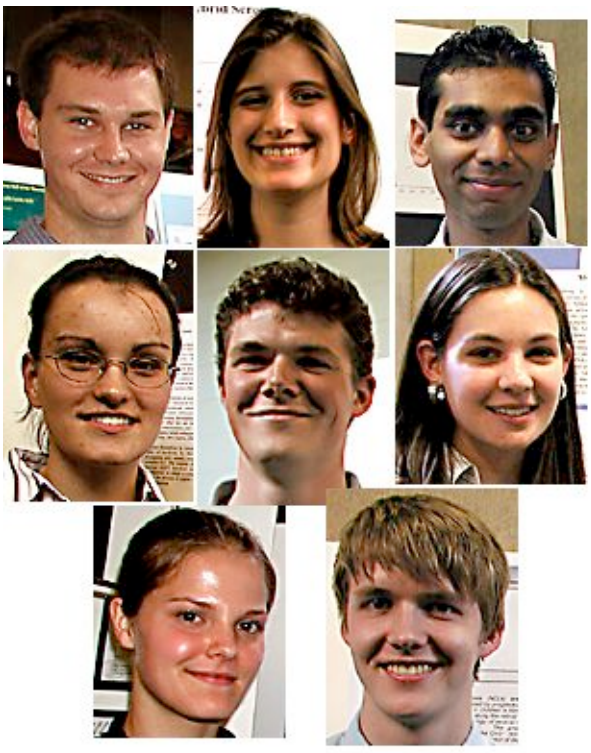
Niraj Patel, BBC
MTS1 binding research
Mentor: Ravi Basavappa, Biochemistry and Biophysics

Rebecca Porter, BBC
Genomic screening of *Saccharomyces cerevisiae* for pre-mRNA splicing factors
Mentor: Yi-Tao Yu, Biochemistry and Biophysics

Anne Stey, BNS
Excitotoxic intracellular and mitochondrial calcium regulation
Mentor: Shey-Shing Sheu, Pharmacology and Physiology

Kelly Wentworth, BIO
Identification of the interacting proteins of the protein kinase PKK by a yeast two-hybrid system
Mentor: Luojing Chen, Center for Human Genetics and Pediatric Disease

Cornelia Zorca, BMG
Attempts to generate a germline *HHP1* knockout in *Tetrahymena thermophila*
Mentor: Martin Gorovsky, Biology



From top left to right: Matthew Maurer, Kelly Wentworth, Niraj Patel, Cornelia Zorca, Mark O'Hara, Rebecca Porter, Anne Stey, Evan Kingsley.

Congratulations

Thesis Defenses

On May 27, 2003, **Yuhua Shang** defended her thesis "*In vivo* functions of gamma-tubulin in *Tetrahymena thermophila*." Yuhua did her predoctoral work in the laboratory of Martin Gorovsky. She is currently a postdoc with Gero Miesenbeock at Sloan Kettering Institute, Department of Biochemistry and Biophysics.

Adam Mason, who did his research under the direction of David Goldfarb, defended his thesis "*In vivo* analysis of the *Drosophila melanogaster* importin gene family" on June 18, 2003. Adam is currently a postdoc in Dave Goldfarb's lab.

Yifan Liu defended his thesis "Genetic studies of RNA-mediated DNA elimination in the developing macronuclei of *Tetrahymena thermophila*" on July 16, 2003. Yifan did his graduate studies in Martin Gorovsky's lab and is now a postdoc with Dr. C. David Allis at The Rockefeller University, Department of Biochemistry, Structural Biology and Chemistry.

On July 17, 2003, **Liam Casey** defended his thesis "Muscle microtubule-associated protein 4 (mMAP4), an early myogenic marker, is neither necessary nor sufficient for muscle development." His research was conducted under the direction of Joanna Olmsted. He is now a postdoctoral fellow with Rulang Jiang in the University of Rochester Center for Oral Biology.

Kathy Clark, who did her research under the guidance of Martin Gorovsky, defended her thesis "Functional analysis of the -tubulin-like gene, BLT1, in *Tetrahymena thermophila*" on August 6, 2003. Kathy is a postdoc in the University of Rochester's Center for Human Genetics/Molecular Pediatric Disease where her sponsor is Mark Dumont.

Karen DelKanic McFarland, whose research advisor was Don Kane, defended her thesis "Toward an understanding of zebrafish epiboly: characterization and molecular identification of the epiboly mutant *half baked*" on December 18, 2003. Karen is enjoying married life and spending time with her husband Nick while she is looking for a research position.

Awards and Grants

At a dinner on October 18, **Martin Gorovsky** received the 2003 Davey Memorial Award from the James P. Wilmot Cancer Center at the University of Rochester. The Davey Memorial Award, established in 1997, is given annually to a UR faculty member who has made outstanding contributions to cancer research. Marty was chosen to receive the award because of his breakthrough research which showed that a class of RNA molecules called small RNAs function in many of the cell's controls such as proper silencing of genes, cell division and possibly development and disease. (See the December, 2002, *Nonsense Suppressor* where the findings by Gorovsky and his postdoc Kazufumi Mochizuki were featured. Their studies were proclaimed by the journal *Science* #1 winner of "Breakthrough of the Year".)

In May, 2003, **Marty** received the University of Rochester Award for Graduate Teaching and spoke at the Graduate Commencement. (See May, 2003, *Nonsense Suppressor*.)

Allen Orr has been chosen as a Fellow of the Center for Advanced Study in the Behavioral Sciences at Stanford (Palo Alto, CA) and, as a fellow, is eligible for a Center-sponsored sabbatical fellowship any time in 2003-2009.

David Goldfarb received a grant of $700,000 direct for 2003-2007 from NIH for his research "Gating the Nuclear Pore Complex Translocon."

John Jaenike's grant proposal, "Evolutionary ecology of male-killing *Wolbachia* in *Drosophila innubila*," was funded by NSF for the years 2003-2006.

Jack Werren recently received a $5-million, 5-year grant from NSF to study the Biology of *Wolbachia*, intracellular bacteria common in arthropods. The grant is part of the Frontiers in Integrative Biology program at NSF, and involves 6 different institutions, with the UR being the lead institution and Jack as PI.

Marriages and Births

Nitin Phadnis (graduate student in the Orr and Fry labs) and **Naina Rao** (graduate student in the Sia lab) were married July 20, 2003.

From **Marty Gorovsky**. I became a first-time biological grandfather, of twins Max and Meg Hausser, born June 14, 2003, to Marcie (Gorovsky) Hausser and Mark Hausser. (I also have a step-grandson, Matthew Hausser.) Not only are they beautiful (anyone who wishes can check that out for themselves on my office door) but they are also a marvel of modern biomedical science, having been created by in vitro fertilization.

They (and 12 other potential Gorovsky grandchildren) were incubating in a Petri dish while my daughter and son-in-law were dancing at a wedding in Rochester. The four best embryos were implanted, 2 survived and Joyce and I are ecstatic.

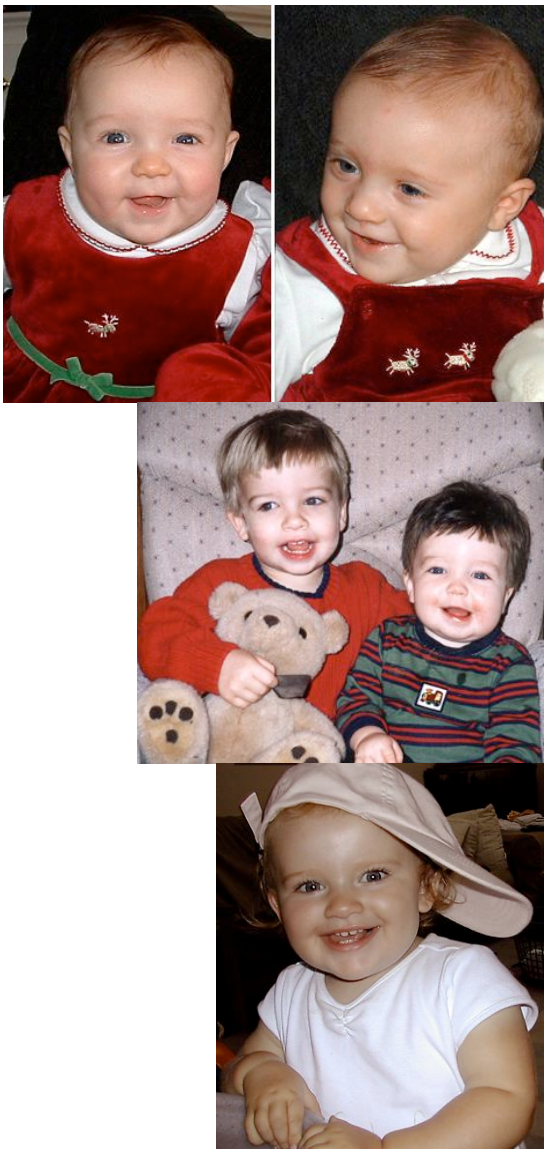
A son, John Pellett, was born to graduate student **Nida Meednu** and Jason Pellett on October 25.

Alan Dietsche's daughter Jennifer and her husband Ernie Bugbee made Alan a third-time grandfather with the birth on October 24, of McKayla Ashley. Granddaughters one and two are McKayla's twin sisters Madison and Megan who were 3 years and 7 months when the new baby arrived.

Doris Kist's daughter Anne and her husband Eric Beyer made Doris and Glenn second-time grandparents with the birth of Matthew Benjamin on December 4. Matthew's big brother Brian was 2 years and 10 months at that time.

Graduate student **Andrea Betancourt** became an aunt on December 27, when her sister gave birth to a girl.

The Baby Gallery



Meg and Max Hausser, Gorovsky grandchildren; Gregory and Ryan Zuill, Cindy Landry's nephews; Elise Hinkle McCamant, Hinkle grandchild.

Matthew and Brian Beyer, Kist grandchildren; McKayla Bugbee, Dietsche grandchild; John Pellet, Meednu child.

Austin Stull, Lynn Stull's grandson; Brittany and Michael Pink, Barbara Yunker's grandchildren; Jenovia Anne Levine, Betancourt neice.

Arrivals and Departures

The Werren lab has had several short-term members over the past several months. **Laura Baldo**, a graduate student from the University of Milan, visited the lab for 6 months to study recombination in *Wolbachia*. **Candace Collmer**, a faculty member at Wells College, conducted summer research on courtship behavior in *Nasonia*, as part of her sabbatical. **Caroline Agrawal**, an undergraduate at Boston University, conducted summer research on the genetics of female mate preference as part of an NSF Research Experiences for Undergraduates. **Lyndsey Thompson** worked over the summer as a laboratory technician, investigating intracellular bacteria in arthropods. She is now in graduate school at Yale University.

Jennifer Traggis started working in the Werren lab in June investigating various aspects relating to wing size evolution and *Wolbachia*. Originally from Connecticut, Jenn graduated from RIT in May, 2003, with a B.S. in Biology. She is applying to graduate schools for behavioral ecology and hopes to work with reptiles. To practice for her future carreer, she has a boa constrictor named Siren at home.

Laramy Enders, technician in the Werren laboratory, left at the end of the summer to go to graduate school at the University of California, Riverside.

Joe Sandmeier, lab tech in Xin Bi's lab, arrived from Nebraska in July to help with setting up Bi's lab at UR. Joe started his career as a lab tech in Jeff Smith's lab at UVA in 2000, and moved his family to Lincoln, Nebraska, where he started to work for Dr. Bi in October, 2002. Joe and his wife Jill met at Hastings College in Nebraska and have been married for nearly five years. They have two children—Alyssa Jane, 2 years, and Jacob Theodore, 10 months.

In September **Bob Minckley** joined the UR Biology Department as an Adjunct Assistant Professor. Bob has lab space in Hutch and in the spring will teach a new non-majors course, "How Bugs Rule." His wife is a faculty member in the Warner School of Education. They have two children, aged 17 and 14.

Bob grew up mainly in Arizona (Phoenix and Tucson) and received his B.Sc. in Ecology and Evolutionary Biology and M.Sc. in Entomology from the University of Arizona. His Ph.D. in Entomology was from the University of Kansas. He has had post-doctoral positions at the University of Kansas and at Auburn University and before moving to Rochester was at the University of Utah in the Department of Biology. Bob works on solitary bees—their relationships with plants, phylogeny and community ecology. Most of his work the last 4 years has been in Sonora, Mexico.

Lynn Stull joined the front office staff on September 22. She comes to the Biology Department after several years in the Medical Center. Lynn and her husband Ken live in West Irondequoit with their two cats, Barney and Pebbles, who rule the house. Lynn and Ken have two sons, Jeremy and Craig, and an eight month old grandson, Austin. Jeremy has recently completed his Class A, Passenger and Hazardous Material training requirements which allows him to drive various vehicles. Craig is waiting to be accepted into the fire department and is an EMT.

Lynn's hobbies include reading, doing crafts, gardening and traveling. One of her favorite travel destinations is Cozumel, Mexico, where she has been three times. During the months of April through October every spare moment of her time is spent on the family's boat "Lapse of Reason." She and Ken hope to take the boat to Alexandria Bay, Clayton and Cape Vincent this summer.

Sam Schlagman, longtime Research Associate in the Hattman lab, retired at the end of September.

Hengping Xu moved to Rochester with his wife and daughter from the University of Nebraska-Lincoln in October. Hengping is a postdoctoral research associate in Xin Bi's lab. He received his Ph.D. from the College of Life Sciences, Peking University. His previous research field is plant biology, focusing on specific molecules involved in the unique fertilization of flowering plants. To investigate this issue further the knowledge and techniques in the study of chromatin are essential. Therefore, Hengping chose for his current project chromatin-mediated regulation of gene expression in higher organisms with concentration on chromatin domain boundary elements.

Rong Xie joined the Gorovsky lab in October. He received his Ph.D. from the Chinese Academy of Science, Shanghai Institute of Plant Physiology and Ecology. His current research focuses on the functional study on tubulin gene in *Tetrahymena*. Rong's hobbies are soccer, swimming and reading books.

Eight Graduate Students Joined the Biology Department in Fall 2003

Chun Chen received her Bachelor of Medicine (B.M.) degree in Clinical Medicine in 2000, and her M.S. in Biochemistry in 2003 from Fudan University. She came to UR to study cell biology. Chun likes to swim and to travel.

Susan Elizondo earned a B.S. in Genetics at Texas A&M University in 2003, and is studying evolutionary biology at UR. She likes swing dancing and reading.

Lu Gao received a B.S. in Biochemistry in 1999, and a M.S. in Biochemistry and Molecular Biology in 2002, from Beijing Normal University. She is at UR to study molecular biology. Lu likes sports.

Rhitoban Ray Choudhury earned a B.S. in Zoology from Presidency College, Calcutta, in 1999, and an M.S. in Zoology from University of Calcutta in 2001. The focus of his UR studies is evolutionary genetics and molecular evolution. Rhitoban's hobbies are listening to classical music, reading non-fiction, studying freshwater fishes and turtles, eating and sleeping.

In 2003, **Deb Stage** received a B.S. in Microbiology with a minor in Chemistry at Northern Arizona University. At UR she is studying evolutionary biology. Her hobbies include painting, hiking, writing bad poetry and solving all the world's problems over a pint of beer.

Qun Yu transferred to UR from University of Nebraska-Lincoln where she was working with Xin Bi. Qun received a B.S. in Plant Pathology in 1998, and an M.S. in Molecular Biology in 2001, from China Agricultural University. The title of her thesis is "Transcriptionally silent chromatin and boundary elements in yeast." Qun's hobbies are watching movies and playing badminton. She thinks that Rochester is a beautiful city; however, it is too cold in the winter. She hopes to make more friends as she becomes acquainted with the campus and the city.

Jun Zhou earned a B.S. degree in Biology in 2001, and an M.S. in Ecology in 2003, from Nanjing University. At UR he will explore evolutionary biology. His hobbies are traveling, reading and watching movies.

Yanfei Zou transferred to UR from University of Nebraska-Lincoln where she has been working with Xin Bi. She earned a B.S. in Cell and Molecular Biology from University of Science and Technology of China in 2002. Her current thesis is "Silencing at HM loci in yeast." Yanfei likes reading novels and watching movies.

Off Campus

Recent outside talks given and meetings attended by **David Goldfarb** include: Gordon Conference: Autophagy in Stress, Development and Disease Autophagy, Colby College VT, 6/2; 2nd International Meeting on Yeast Apoptosis, Smolenice, Slovakia, 9/17; NIA sponsored International meeting on IGF, Aging, and Apoptosis, San Antonio, TX, 10/2/03; EURLIE nuclear transport meeting, Sicily, 10/31/03; Utica College, Asa Grey Society speaker, 11/17/03; Einstein College of Medicine, Dept. Anatomy and Structural Biol., 12/10/03.

Marty Gorovsky attended and gave an invited talk at the Ciliate Molecular Genetics FASEB meeting, July 19-25, 2003. His talk was entitled "H1 Phosphorylation Regulates Expression of CDC2 and Other Genes in Response to Starvation in *Tetrahymena thermophila*." Jody Bowen, Kazufumi Mochizuki, Che-Chia Tsao and Xiaoyuan Song also attended. Kaz and Xiaoyuan gave talks. Che-Chia presented a poster.

Marty Gorovsky attended and gave a talk at a one day (8/2) Cytoskeleton meeting at Woods Hole, MA, in honor of Dr. Joel Rosenbaum's 70th birthday. Marty says, "The title I submitted was 'Something about *Tetrahymena*.' The organizers added to that title 'Moves me like no other lover'. I did not show the title to my wife. (Actually, I did, but was quick to explain how it came about.)"

John Jaenike gave a seminar at Indiana University.

Allen Orr delivered The George C. Williams Lectures in Evolution at SUNY Stony Brook in November. The Williams Lectures recognize "individuals that have made truly outstanding contributions to the field of evolution." He spoke on "The genetics of speciation in *Drosophila*," and "Is a theory of adaptation possible?"

Orr also delivered a plenary lecture at the European Society for Evolutionary Biology annual meeting in Leeds, UK, in August. He spoke on "The theory of adaptation: what do we know?"

Orr was also an invited international speaker at Stazione Zoologica Anton Dohrn in Naples, Italy, in May.

Jack Werren gave the following seminars and presentations: a class and lectures at Dept. de Biologia, Univ. de Sao Paulo, BZ, on genetic conflict and cooperation in biological systems; an Opening Lecture on genetic conflict and development at Plant Gametophytes: Evolution, Development and Function, Ascona, Switzerland; the 2nd *Nasonia* Workshop, Schiermonnikoog, Netherlands; a seminar at BRIDGES (Biotic Resources: Integrating Development, Genetics, Evolution, and Systematics) Program, New York University; an invited lecture at the Keystone meeting on Natural Variation and Quantitative Genetics in Model Organisms.

Recent Publications

Bi

Bi, X., Q. Yu, J.J. Sandmeier and Y. Zou. 2004. Formation of boundaries of transcriptionally silent chromatin by nucleosome-excluding structures. Mol. Cell. Biol., in press.

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Fry

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Fry, J.D. 2003. Detecting ecological trade-offs using selection experiments. Ecology 84:1672-1678.

Fry, J.D. and S.V. Nuzhdin. 2003. Dominance of mutations affecting viability in *Drosophila melanogaster*. Genetics 163:1357-1364.

Messina, F.J. and J.D. Fry. 2003. Environment-dependent reversal of a life history trade-off in the seed beetle *Callosobruchus maculatus*. Journal of Evolutionary Biology 16:501-509.

Goldfarb

Roberts, P., S. Moshitz-Moshkovitch, E. Kvam, E. O'Toole, M. Winey and D. S. Goldfarb. 2003. Piecemeal microautophagy of the nucleus in yeast. Mol. Biol. Cell 14: 129-141.

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Gorovsky

Liu, Y., K. Mochizuki and M.A. Gorovsky. Histone H3 lysine 9 methylation is required for DNA elimination in developing macronuclei in *Tetrahymena*. Proc. Natl. Acad. Sci. USA, in press.

Hattman

Malygin, E.G., W.M. Lindstrom, V.V. Zinoviev, A.A. Evdokimov, S.L. Schlagman, N.O. Reich and S. Hattman. 2003. Bacteriophage T4 Dam DNA-(N6-adenine)-methyltransferase: single turnover kinetics on duplexes with native or modified sites. J. Biol. Chem. 278: 41749-41755.

Yang, Z., J.R. Horton, L. Zhou, X. Zhang, A. Dong, X. Zhang, S.L. Schlagman, V. Kossykh, S. Hattman and X. Cheng. 2003. Structure of the bacteriophage T4 DNA adenine methyltransferase. Nature Struct. Biol. 10:849-855.

Jaenike

Perlman, S.J. and J. Jaenike. 2003. Evolution of multiple components of virulence in *Drosophila*-nematode associations. Evolution 57: 1543-1551.

Perlman, S. J. and J. Jaenike. 2003. Evolution along the virulence spectrum: a case study of *Drosophila* and their nematode parasites. Nematology Monographs and Perspectives 2: 1-15.

Taylor, J. E. and J. Jaenike. 2003. Sperm competition and the dynamics of X chromosome drive in finite and structured populations. Annales Zoologici Fennici 40: 195-206.

Ross, C. L., K. A. Dyer, T. Erez, S. J. Miller, J. Jaenike, and T. A. Markow. 2003. Rapid divergence of microsatellite abundance among species of *Drosophila*. Molecular Biology and Evolution 20: 1143-1157.

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Miller

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Orr

Presgraves, D.C., L. Balagopalan, S.M. Abmayr and H.A. Orr. 2003. Adaptive evolution drives divergence of a hybrid inviability gene in *Drosophila*. Nature 423: 715-719. (See "News and Comment" by M. Noor. Nature 423:699-700; see also

news item in Nature Reviews Genetics 4:580.)

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Orr, H.A. 2004. Theories of adaptation: what they do and don't say. (For joint publication in the book *The Genetics of Adaptation*, ed. R. Mauricio and special issue of Genetica, vol. 21).

Orr, H.A. 2003. What's not in your genes. (Review of Matt Ridley's *Nature via Nurture*.) The New York Review of Books, August 14, 2003, pp. 38-40.

Sia

Sia, R.A.L., B.L. Urbonas and E.A. Sia. 2003. Effects of ploidy, growth conditions and the mitochondrial nucleoid-associated protein Ilv5p on the rate of mutation of mitochondrial DNA in *Saccharomyces cerevisiae*. Current Genetics 44:26-37.

Werren

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(Sethi, continued from p. 4)

analogs where the riboside moiety is substituted with a morpholine ring and the classic phosphodiester bond is replaced with a phosphodiamidate linkage. They are thought to bind to the 5′ untranslated region (5′UTR) and the initial part of the open reading frame of a target mRNA and block protein synthesis by preventing ribosomal loading. Although extremely powerful and versatile, morpholinos do have certain limitations. As of yet, inducibility is not really an option with morpholinos although photoactivation might provide a possible solution. This then does not allow for a contextual knockdown type analysis and it is well known that various signaling cascades and sometimes even the same signaling molecules are used reiteratively in development, often executing completely different functions at varying times. Furthurmore, tissue specific knockdowns remain an elusive holy grail for the same reasons using morpholinos. Another practical limitation is that the use of morpholinos requires extensive sequence information about the gene of interest including upstream sequence extending past the initiation codon and well into the 5′UTR of the gene. This is not always available and usually takes some time and often considerable effort to obtain. Additionally, morpholinos still remain fairly expensive on a per gene basis.

The recently discovered phenomenon of RNA based interference or RNAi has the potential to overcome some or all of the above limitations. In non vertebrate systems, the process is triggered by the introduction of double stranded RNA (dsRNA) precursors. These precursors are then enzymatically cleaved to yield short interfering double stranded RNA molecules or siRNAs usually 21-23 nucleotides long which execute post-transcriptional gene silencing or PTGS by seeking out and binding to homologous target mRNAs and degrading them. In vertebrate cells, direct introduction of dsRNA does not trigger RNAi since the cells invoke an interferon response resulting in a global translational arrest. However, even in these cells, direct introduction of the shorter final siRNAs will trigger PTGS. In theory then, introducing a DNA construct containing a hairpin or dsRNA precursor expressed under control of an appropriate promoter into an embryo should allow for temporal and spatial control of the knockdown process.

The sea urchin embryo, as a model system, is ideally suited to this promoter driven approach. Over the past few years, several key elements of the urchin endomesodermal gene network have been elucidated. There is also a large body of work centering around *cis* element analysis of the genes in the network thus potentially allowing for a number of different temporal and spatial co-ordinates by using the appropriate promoter to target a gene of interest through RNAi. We decided to test the viability of this RNAi approach using the promoter of a gene *Kruppel-like* (*Krl*), which has been worked on extensively in the lab before. Significantly, previous work in the lab has already isolated the minimal promoter region needed for correct spatial and temporal expression of an appropriate reporter driven by *Krl*. *Kruppel-like* has been shown to be a zygotic gene, and the initial phases of its expression can be detected at about the 16 cell stage, with a dynamic modulation of this pattern of expression taking place as embryogenesis proceeds.

All through its expression, *Krl* is vegetally distributed although the exact region of expression undergoes changes with time. As a preliminary experiment, we designed a snapback or hairpin construct wherein sense and antisense orientations of the coding region of Green Fluorescent Protein (GFP) were put under control of the *Krl* promoter previously characterized in the lab. The two arms of the GFP hairpin sequence were spaced using an intron to increase stability of the construct and also to improve silencing efficiency since in vivo splicing of the two arms of the GFP coding region would presumably allow for tighter annealing of the two arms of the dsRNA precursor molecule. The entire construct was cloned into a plasmid engineered to have a low copy origin of replication to overcome segregation loss. The finished plasmid was linearized and microinjected along with *in-vitro* transcribed GFP mRNA thus introducing the homologous target for the RNAi construct. Additionally the *in-vitro* transcribed GFP mRNA had a *lacZ* leader sequence which could be used as the target of a probe to check for actual gene silencing using whole mount *in-situ* hybridization. We consistently observed a very robust silencing effect with our GFP hairpin construct. Surprisingly, the silencing seems to have begun even before the initial zygotic expression of *Krl* has been previously reported, thus potentially uncovering the inherent sensitivity of the RNAi machinery. No significant non specific embryonic arrests were observed, indicating the viability of this approach for biologically relevant knockdown analyses.

As an extension of this work, we then tested whether microinjection of dsRNA itself would also effect silencing. An iteration of the above experiment was used wherein sense and antisense GFP mRNAs were synthesized *in vitro*, annealed and then microinjected into embryos along with their homologous target sequences as above. Preliminary experiments indicate that this approach is also workable, with very little non specific embryonic effects and a fairly large dose window in terms of injected dsRNA. This would potentially allow for high throughput genomic knockdown experiments analogous to those in the nematode *C. elegans* and analyses of the resulting phenotypes and correlating them with specific gene function. This is particularly valuable in light of the fact that the sea urchin genome project is nearing completion and should provide a valuable resource for investigations of gene function in the near future. This technique could be applied to both genes with homologues of known function in other systems and also completely novel genes. We are now in the process of extending this approach, getting finer dose titrations for the amounts of dsRNA needed and also applying this technique to recently isolated genes to work out their putative biological roles.

(Velthuis, continued from p. 7)

little opportunity for (repeated) sampling of males, a female's mate acceptance behavior again has direct implications for her lifetime fitness, and possibly far-reaching evolutionary consequences. Female mate discrimination is indeed well recognized as a potential driving force in processes such as sexual selection, speciation by sexual isolation or reinforcement, and the evolution of mating systems. We have a pretty good understanding of the consequences of female mate preferences. What is still largely lacking is a mechanistic understanding of how they "choose" a mate, so to speak. All the way from a genetic up to the behavioral level, females still remain mysterious.

Nasonia is an excellent experimental system to unravel at least some of this mystery. Anyone who has ever watched our wasps will recognize that *Nasonia* females are not cute. They are GORGEOUS! Their dark complexion, their long slender legs, their big/beady eyes, the mere curvature of their abdomen, not to mention the bouquet of fragrances they carry Oh my! Clearly, more than enough to excite not just any, but indeed every male! Understandably, in *Nasonia* (as in most species), the "beauty" perception threshold is rather low for males, although slight differences may well exist. Rather large differences, however, exist in various male courtship traits, both within, and more prominently between *Nasonia* species. In each of the three species, females actually prefer their own species male over that of males from either other species. We can thus utilize between species variation in male traits to truly put the underlying mechanism of female mate discrimination to the test and take it apart (as biologists like to do).

We study between species genetic and behavioral variation in female mate discrimination in the two *Nasonia* species for which male courtship traits are most extreme (*N. giraulti* and *N. vitripennis*). We also study within species genetic and behavioral variation in mate discrimination, but now utilizing females from the third species (*N. longicornis*, for which male courtship behaviors tend to be intermediate). In both cases, we use genetic tools to identify and study parts of the genome involved in the (initial) female rejection of a heterospecific male; i.e. genetic regions involved in sexual isolation. We study at a behavioral level how (yet unknown) allelic differences in those and other chromosomal regions may actually affect a female's mate acceptance behavior towards both heterospecific and conspecific males.

I have had the fortune to work closely with undergrads Michelle Powell, Jessica Berg, Elizabeth van Nostrand, Nadeem Hussain, Kathleen Svala, Caroline Agrawal and Crystal Rocha. Note how this sex ratio is not only appropriate for a *Nasonia* research lab, but that it gives us hope for tomorrow.