HHMI
HOWARD HUGHES MEDICAL INSTITUTE

Kirst King-Jones
Howard Hughes Medical Institute
Department of Human Genetics
15 N 2030 E, Room 5280
University of Utah
Salt Lake City
UT 84112-5331

phone: 801-581 2612
fax: 801-581 5374
e-mail: kirst@genetics.utah.edu

October 24, 2005

Yves Brun
Systems Biology/Microbiology Faculty Search
Department of Biology
Indiana University
Jordan Hall 142
1001 E 3rd Street
Bloomington
IN 47405-7005

Dear Dr. Brun and Members of the Search Committee,

I am writing to apply for one of the tenure-track positions in your Department that were advertised in the September 2 issue of *Science*. Currently, I am a postdoctoral researcher in the laboratory of Dr. Carl Thummel at the Howard Hughes Medical Institute, Department of Human Genetics, University of Utah.

I am studying regulatory networks that control metabolism, growth and development in a genetic model organism, the fruit fly *Drosophila*. More specifically, I have analyzed two previously uncharacterized nuclear receptor genes. One line of work revealed how nuclear receptors control maturation processes in response to steroid hormones and dietary status. In the second project, I discovered novel nuclear receptor pathways related to cholesterol homeostasis, lipid metabolism and detoxification responses.

For my future work, I plan to use *Drosophila* to study endocrine and metabolic pathways that control sterol homeostasis, growth, and maturation. I also plan to conduct genetic and genomic screens to identify novel genes involved in cholesterol and lipid metabolism, thus advancing our understanding of metabolic disorders and related diseases in humans.

Please find enclosed my *curriculum vitae*, my research plan, teaching philosophy and a list of four colleagues who have kindly agreed to write letters of recommendation. Thank you very much for your consideration. I look forward to hearing from you.

Sincerely,

Kirst King-Jones, Ph.D.

University of Utah
Eccles Institute of Human Genetics
15 North 2030 East, Suite 5200, Salt Lake City, Utah 84112-5331
801.581.2612 • Fax 801.581.5374

Introduction and Overview

The biological responses to dietary intake are remarkably complex and include processes such as growth, proliferation, metabolic homeostasis, and detoxification pathways. It is therefore not surprising that nutrients and metabolites have a fundamental impact on gene regulation and development, be it either through direct action or indirectly via hormones like insulin. Metabolites and nutrients often exert their effects on cellular physiology through members of the superfamily of nuclear receptors. This protein family – also known as steroid or nuclear hormone receptors – constitutes one of the central crossroads that connect small lipophilic compounds such as steroid hormones, nutrient metabolites and toxins to corresponding changes in gene expression. Nuclear receptors represent an ancient and widespread group of ligand-regulated transcription factors, which play fundamental roles in pathways controlling steroid hormone responses, lipid metabolism, detoxification processes and bile acid clearance[1]. Due to their unique biology, nuclear receptors have turned out to be excellent drug targets for the treatment of various diseases, but despite intense efforts, our understanding of the physiological processes underlying nuclear receptor action is still incomplete[2].

The fruit fly *Drosophila* harbors representatives of all six vertebrate nuclear receptor subfamilies, which establishes the fly with its powerful assembly of molecular and genetic tools as an ideal animal model system for studying the physiological, metabolic and developmental networks controlled by nuclear receptors[3]. To date, most work on *Drosophila* nuclear receptors has focused on their developmental roles, while virtually no studies have addressed their potential metabolic functions. Studying these receptors therefore holds the promise to discover novel endocrine and metabolic pathways, even if the ligand is initially unknown. For this reason, I decided to study two uncharacterized nuclear receptor genes during my time in Carl Thummel's lab, *DHR4* and *DHR96*. My work on *DHR4* represents the first report of a novel growth pathway that controls the timing of insect maturation: *DHR4* mutants display random and accelerated onset of maturation. This is because *DHR4* mutants stop growing before they have attained their optimal body size, resulting in smaller and precocious animals. These findings position *DHR4* as an ideal entry point to study a process we know very little about - the nature of the developmental determinant that triggers the onset of maturation. Evidence suggests that body mass plays a critical role in insects[4] as well as in humans[5], but we have no understanding of how such a threshold weight culminates in the endocrine cascades that trigger maturation in insects or puberty in humans.

In another line of work, I showed that the nuclear receptor DHR96 plays a critical role in the regulation of detoxification pathways. *DHR96* mutants are sensitive to the effects of phenobarbital, and subsequent microarray studies revealed an abnormal toxin and stress response in phenobarbital-treated mutant animals. The data gathered from this project are currently being prepared for publication.

In addition, I discovered that *DHR96* mutants are unable to tolerate suboptimal concentrations of dietary cholesterol, indicating that this receptor plays a role in cholesterol homeostasis. Biochemical studies performed by our collaborator showed that DHR96 binds cholesterol *in vivo*, suggesting that it is a ligand for this receptor. Furthermore, microarray analysis shows that many genes involved in lipid and cholesterol pathways are misregulated in *DHR96* mutants, including the fly homolog of the human Niemann-Pick Disease Type 1 gene, which plays a critical role in intracellular cholesterol trafficking. Although cholesterol and lipid metabolism have been studied extensively in humans, we do not have a complete understanding of all the processes involved. The discovery that DHR96 acts as a critical regulator of cholesterol metabolism allows us to genetically dissect this pathway and to potentially unearth novel players required for processes such as vesicle loading, extra- and intracellular trafficking and receptor-mediated endocytosis. Moreover, *Drosophila* can be utilized to design open-ended genetic screens to identify genes with hitherto unknown relevance to lipid and cholesterol pathways, thus advancing our understanding of critical human diseases such as diabetes, obesity and atherosclerosis.

Summary of Postdoctoral Research

DHR4 plays a key role during insect maturation. In most higher organisms, maturation is a dramatic, hormone-triggered developmental transition that transforms an immature juvenile form into a reproductive adult. In humans, this transition takes place during puberty and adolescence in response to steroid hormones. In *Drosophila*, maturation occurs during metamorphosis, a process that is controlled by ecdysone, also a steroid hormone. *DHR4* mutants mainly die as prepupae, an initial maturation stage. I showed that *DHR4* is directly induced by ecdysone just prior to the onset of metamorphosis. I also demonstrated that *DHR4* functions as a temporal bridge spanning the repression of "early" ecdysone targets and the induction of "late" response genes (Figure 1). The existence of such a factor has been postulated more than 30 years ago by Ashburner and colleagues[6], when they proposed a repressor of the early genes in their hierarchical model of ecdysone action. My data strongly support the idea that *DHR4* is at least one of these proposed repressors. In summary, my findings establish *DHR4* as an ideal tool for studying a complex transcription factor network that drives maturation in response to rapidly changing titers of a steroid hormone.

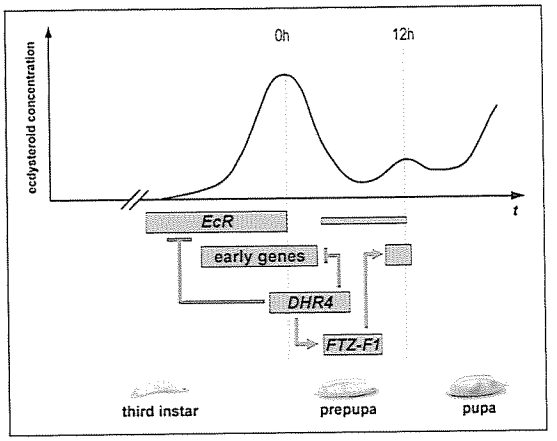

Figure 1. *DHR4* function at the onset of metamorphosis

DHR4 controls growth through a novel mechanism. In animals, growth is largely restricted to juvenile stages, but how it is terminated upon sexual maturation remains unclear. Insect larvae have to attain a certain critical body weight in order to mature[7-9], which triggers a small pulse of ecdysone that will suppress feeding and growth (Figure 2). The mechanisms by which this threshold mass is measured are not understood. In *DHR4* mutants, the onset of maturation occurs too early, resulting in abbreviated juvenile development and small animals. *DHR4* is expressed in the brain and the ecdysone-producing prothoracic gland during larval stages, suggesting that *DHR4* has a neuroendocrine function. Indeed, DHR4 appears to play a role in the control of feeding behavior, since mutant animals are unable to respond properly to nutritional cues. This suggests a model where *DHR4* promotes growth and feeding by repressing a rise in ecdysone levels in response to nutrients, which may occur directly or indirectly via signaling molecules from the fat body (insect adipose tissue and liver) (Figure 2). Taken together, my work has established *DHR4* as an excellent starting point to study how nuclear receptors control the onset of maturation and integrate growth, dietary intake, and feeding behavior to determine appropriate adult body size.

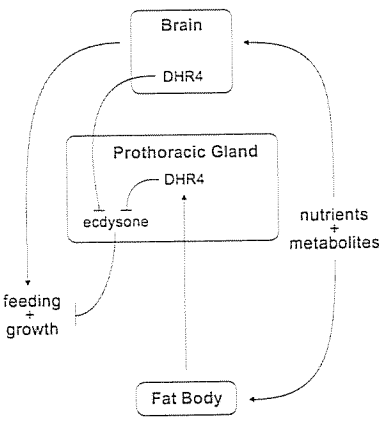

Figure 2. Model for *DHR4* function during larval growth.

DHR96 is required for responses to toxins and stress. No studies have addressed how insects respond to toxins on a genome-wide level, and how their detoxification processes may be regulated. In humans, foreign compounds bind to and directly activate the nuclear receptors SXR and CAR, which enables these factors to induce sets of detoxification genes. In flies, *DHR96* is the only close homolog of *CAR* and *SXR*. To study *DHR96* function in *Drosophila*, I generated a mutant allele using gene targeting[10]. Mutant flies are viable and fertile and display no obvious phenotypic defects when reared on a normal diet. However, when exposed to phenobarbital (PB), mutant flies are more effectively sedated than controls. This effect is specific to PB, since another sedative reveals no difference between mutants and wild type. Similar to *DHR96* mutants, PB-treated *CAR* knockout mice display a prolonged sleep phenotype[11] and are more sensitive to the effects of zoxazolamine, a muscle relaxant[12]. *DHR96* is expressed specifically in tissues

involved in nutrient traffic and metabolism, and thus ideally positioned to monitor exposure to toxins. I used microarray analysis of *DHR96* mutants and controls, in the presence or absence of PB, to describe the xenobiotic response on a genome-wide level in an insect model system. This study revealed that the detoxification machinery is highly conserved between humans and insects, with a few exceptions that appear to be insect-specific. In addition, I found that ~20% of the toxin response, as well as components of the stress response, are misregulated in *DHR96* mutants, and that PB appears to repress DHR96 activity. Taken together, these data suggest that DHR96 plays a critical role in the regulation of evolutionary conserved xenobiotic pathways, establishing *Drosophila* as an excellent model system to analyze these pathways and to study the genomic responses to toxic compounds.

DHR96 plays a crucial role in cholesterol homeostasis. Many components required for cholesterol metabolism appear to be highly conserved between insects and humans, with the exception that insects have not evolved the ability to synthesize cholesterol. This explains why *Drosophila* larvae are exceedingly efficient in retrieving trace amounts of cholesterol from their diet[13,14]. Interestingly, *DHR96* mutants are unable to survive on a diet that contains sufficient, but suboptimal levels of cholesterol, indicating an impaired ability to retrieve, transport or metabolize cholesterol. On low cholesterol food, mutant larvae do not progress beyond the second instar, and this lethality can only be rescued with cholesterol and some derivatives, but not with ecdysone, indicating a defect upstream of ecdysteroidogenesis. Our collaborator, Henry Krause (Univ. of Toronto), showed that a tagged version of full-length DHR96 from Sf9 cells co-purifies with cholesterol (determined by gas chromatography/mass spectrometry), suggesting that DHR96 is a cholesterol receptor. Microarray analyses of mutant larvae and adult flies reveal misregulation of at least two highly conserved LDL receptor genes as well as *NPC1b*, an ortholog of the human Niemann-Pick disease Type C1, and other genes involved in cholesterol and lipid metabolism. Interestingly, ectopic expression of DHR96 has opposing effects on some of these genes, suggesting that these genes may represent direct targets of this factor.

Although flies harbor orthologs of the mammalian sterol-sensing SREBP pathway (including SCAP, S1P and S2P), the insect pathway senses a phospholipid (phosphatidylethanolamine) instead of sterols, and does not appear to play a role in the regulation of cholesterol levels[15-17], but rather functions in lipid biosynthesis and membrane composition. For this reason, a different system must be in place in insects that senses sterols and regulates cholesterol pathways. Our data strongly suggest that DHR96 plays a central role in cholesterol homeostasis, setting the stage for dissecting this pathway in *Drosophila*.

Proposed research

Studying nuclear receptor biology is a powerful approach to uncover novel endocrine pathways, a fact that is highlighted by the term "reverse endocrinology"[18]. With the techniques and tools I have developed, I have laid out a path that allows me to study and dissect distinct nuclear receptor pathways that control central processes such as growth, maturation and metabolism in a highly tractable model organism. Furthermore, ample evidence exists indicating that many aspects of these pathways are conserved between *Drosophila* and humans. As such, the study of *Drosophila* metabolism has the potential to provide new insights into human physiology and related disorders. Therefore, I will exploit the genetics and biology of *Drosophila* to study endocrine and metabolic pathways controlling sterol homeostasis, growth, feeding behavior and maturation. Importantly, these pathways will be studied in the context of a developing animal, allowing the dissection of genetic networks that coordinate metabolic status with developmental processes.

Specifically, I will first focus on the study of DHR96-controlled networks that regulate cholesterol and lipid metabolism. In addition, my lab will conduct genetic screens designed to identify genes required for cholesterol and lipid pathways. My lab will also continue to study *DHR4* signaling pathways and investigate the mechanisms by which this factor coordinates growth and maturation, and how nutrients impinge on these processes. I expect this combined approach to provide us with a profound understanding of how fundamental metabolic events are regulated and integrated into developmental processes.

I. Dissecting cholesterol and lipid metabolism pathways in *Drosophila*.

1. To determine the metabolic defect in *DHR96* mutants. In this first aim, I plan to characterize the phenotypic defects that cause the lethality in *DHR96* mutants reared on a low cholesterol diet. This will greatly contribute to our understanding of how lipid metabolism pathways are regulated by DHR96. I plan to first determine which of the tissues that normally express DHR96 contribute to the lethality seen in *DHR96* mutants. For this, I will employ transgenic approaches to disrupt and rescue *DHR96* function in tissues where *DHR96* is normally expressed. Once I have identified the critical tissue(s), I will determine the phenotypic differences between tissues from mutants and controls using molecular, biochemical and microscopic techniques. For instance, I will generate lipid profiles of relevant mutant and control tissues, monitor trafficking of radiolabeled cholesterol and use filipin and Nile Red staining to detect local changes in cholesterol and lipid concentrations. In addition, my lab will generate molecular markers such as antibodies directed against proteins involved in intracellular cholesterol trafficking and reporter genes representing components required for lipid biosynthesis or transport, to facilitate phenotypic and molecular analyses. I also plan to generate mosaic animals in order to distinguish between systemic (e.g. low cholesterol levels) and cell-autonomous *DHR96* mutant phenotypes, ensuring that we can attribute certain phenotypes to a cellular requirement for DHR96. In summary, these approaches will improve our understanding of the metabolic processes that are controlled by *DHR96*.

2. Characterizing regulatory networks that control fat and cholesterol metabolism. To understand the role of DHR96 in cholesterol homeostasis my lab will identify direct and indirect target genes of this factor. We will also determine under which conditions these genes are activated and/or repressed by DHR96. For this, I plan to generate transgenic flies that express wild type DHR96 or a constitutively active version of DHR96 (VP16-DHR96) under the control of the Gal4/UAS system. These *DHR96* transgenes can be expressed with spatial and temporal specificity in either a wild type or mutant background and will form the basis for detailed microarray and other genomic studies. The *VP16-DHR96* transgenic line will facilitate the interpretation of microarray data, because this chimeric protein acts independent of potential DHR96 ligands. I plan to conduct tissue-specific quantitative PCR (qPCR) and microarray analysis to identify candidate target genes. This approach will be complemented by a combination of bioinformatics and SELEX[19] to identify DHR96 response elements. I will use antibodies directed against DHR96 and VP16 to carry out tissue-specific chromatin immunoprecipitation (ChIP) analysis on these potential target genes, with a particular emphasis on genes involved in cholesterol and lipid metabolism. Once I have identified target genes of DHR96, I will analyze them genetically and molecularly. This includes gene disruption by RNAi if mutants are not available, tests that look for defects in cholesterol or fat metabolism, as well as genetic interactions with *DHR96*. Using this strategy, we will start to unravel the transcriptional network that is controlled by DHR96, and in the process we will learn more about its roles in the control of cholesterol homeostasis and lipid metabolism.

3. Genomic and genetic screens to identify novel players required for cholesterol and lipid metabolism. I plan to conduct two types of screens: 1) an open-ended screen to identify genes that function in cholesterol and lipid metabolism and 2) modifier screens for *DHR96* mutants to isolate genes that function in DHR96 pathways. A simple genetic screen can be carried out utilizing the Zuker collection[20], an assembly of largely viable fly stocks that carry multiple EMS-generated mutations on the second or third chromosome. Essentially, mutants will be screened for reduced viability on a minimal diet when compared to a standard medium. Mutants will be kept if a minimal diet that contains cholesterol restores viability. *DHR96* mutants will serve as a positive control, and new *DHR96* mutant alleles should be isolated by this strategy since loss-of *DHR96* function results precisely in the characteristics required by the screen criteria.

This strategy will be complemented by a yeast-two-hybrid screen to identify proteins that modulate *DHR96* function, and thus impinge on metabolic pathways. In addition, I plan to monitor stage- and tissue-specific gene expression changes in response to various lipid diets, including low, high and

normal concentrations of cholesterol in wild type and mutant animals. This will be achieved by a combination of microarrays and qPCR of candidate genes. Taken together, these studies will lead to fundamental insights into the architecture of cholesterol and lipid metabolism pathways and thus provide a basis to advance our understanding of fatal metabolic disorders in humans, such as obesity, cardiovascular disease, diabetes or Niemann-Pick disease.

II. Characterizing the mechanisms that trigger the onset of maturation

1. To determine whether DHR4 affects ecdysone levels. The random onset of puparium formation in *DHR4* mutants suggests a possible mechanism where *DHR4* controls the amount and/or timing of released ecdysone from the prothoracic gland, which in turn terminates feeding (Figure 2). To address this issue, we will utilize transgenic approaches to disrupt *DHR4* function in the ecdysone-producing prothoracic gland as well as in the fat body and the brain. Effects on ecdysone biosynthesis and levels will be analyzed by three approaches: 1. I plan to measure ecdysone concentrations in staged *DHR4* mutants and animals that are *DHR4-/-* in specific tissues. 2. Using qPCR, I will monitor expression levels of ecdysone target genes as well as genes that are required for ecdysone production in wild type, *DHR4* mutants, and the transgenic lines discussed above. Finally, I will determine whether genes involved in ecdysteroid biosynthesis are affected cell-autonomously in *DHR4-/-* prothoracic gland cell clones. Should ecdysone levels be normal in *DHR4* mutants, I plan to identify the tissue that links DHR4 function to maturation, and determine the role of DHR4 pathways in this tissue (see next aim).

2. Dissecting the DHR4 signaling pathway. To identify downstream targets of DHR4 that are involved in maturation processes, I will utilize genomic, molecular and genetic tools to discover players that function in the *DHR4* signaling pathway and/or interact with DHR4 physically. Genomic approaches will be used to generate gene expression profiles of tissues that have lost *DHR4* function. To identify direct target genes of DHR4, I plan to utilize gene-specific or genome-wide chromatin immunoprecipitation (ChIP-chip) assays, EMSA studies and microarray analysis of *DHR4* gain-of-function lines. In addition, my preliminary data suggest that loss-of-*DHR4* function affects insulin and autophagic pathways, and therefore I will examine whether this occurs in a cell-autonomous or systemic manner. In summary, these approaches will reveal DHR4 target genes and potential crosstalk with other signaling pathways.

3. Characterization of DHR4 target genes and other pathways that contribute to maturation. Available mutants of DHR4 target genes will be further characterized by molecular and genetic means to determine whether they provide new insights into DHR4-dependent growth or maturation pathways. A long-term goal for this aim is to expand my studies to other endocrine pathways that control growth and maturation, for instance juvenile hormone (JH) controlled networks. JH pathways are poorly understood in *Drosophila,* and in one line of experiments, I plan to disrupt JH signaling in a temporally specific manner to analyze the effects on a genomic scale. Another interesting pathway is represented by the neuropeptide F (npf) gene. The npf pathway affects – just like its mammalian counterpart NPY – appetite and feeding behavior, and the mechanisms by which expression of this neuropeptide is controlled are completely unclear. Studying maturation processes in a genetic model organism will likely reveal pathways common to most or all higher organisms, thus advancing our understanding of the mechanisms that trigger and regulate maturation, such as puberty in humans.

Perspective

Through the study of two nuclear receptor genes, *DHR4* and *DHR96*, I have established *Drosophila* as an effective platform to genetically dissect metabolic pathways. I have laid out the groundwork to study the role of physiological pathways that govern processes such as cholesterol metabolism, growth, and maturation. In addition, I have generated ample preliminary data, including potential target genes, transgenic lines and other tools that allow me to hand over projects to potential undergraduate and graduate students as well as postdocs and to grow an independent research program.

References

1. Francis, G. A., Fayard, E., Picard, F. & Auwerx, J. Nuclear receptors and the control of metabolism. *Annu Rev Physiol* **65**, 261-311 (2003).
2. Maglich, J. M., Sluder, A. E., Willson, T. M. & Moore, J. T. Beyond the human genome: examples of nuclear receptor analysis in model organisms and potential for drug discovery. *Am J Pharmacogenomics* **3**, 345-53 (2003).
3. Laudet, V. Evolution of the nuclear receptor superfamily: early diversification from an ancestral orphan receptor. *J Mol Endocrinol* **19**, 207-26 (1997).
4. Nijhout, H. F. The control of body size in insects. *Dev Biol* **261**, 1-9 (2003).
5. Frisch, R. E. & Revelle, R. Height and weight at menarche and a hypothesis of critical body weights and adolescent events. *Science* **169**, 397-9 (1970).
6. Ashburner, M., Chihara, C., Meltzer, P. & Richards, G. Temporal control of puffing activity in polytene chromosomes. *Cold Spring Harb Symp Quant Biol* **38**, 655-62 (1974).
7. Nijhout, H. F. & Williams, C. M. Control of moulting and metamorphosis in the tobacco hornworm, *Manduca sexta* (L.): cessation of juvenile hormone secretion as a trigger for pupation. *J Exp Biol* **61**, 493-501 (1974).
8. Dominick, O. S. & Truman, J. W. The physiology of wandering behaviour in *Manduca sexta*. II. The endocrine control of wandering behaviour. *J Exp Biol* **117**, 45-68 (1985).
9. Davidowitz, G., D'Amico, L. J. & Nijhout, H. F. Critical weight in the development of insect body size. *Evol Dev* **5**, 188-97 (2003).
10. Rong, Y. S. & Golic, K. G. Gene targeting by homologous recombination in *Drosophila*. *Science* **288**, 2013-8 (2000).
11. Swales, K. & Negishi, M. CAR, driving into the future. *Mol Endocrinol* **18**, 1589-98 (2004).
12. Wei, P., Zhang, J., Egan-Hafley, M., Liang, S. & Moore, D. D. The nuclear receptor CAR mediates specific xenobiotic induction of drug metabolism. *Nature* **407**, 920-3 (2000).
13. Clayton, R. B. The utilization of sterols by insects. *J. Lipid Res.* **5**, 3-19 (1964).
14. Svoboda, J. A. & Feldlaufer, M. F. Neutral sterol metabolism in insects. *Lipids* **26**, 614-618 (1991).
15. Seegmiller, A. C. et al. The SREBP pathway in *Drosophila*: regulation by palmitate, not sterols. *Dev Cell* **2**, 229-38 (2002).
16. Rawson, R. B. The SREBP pathway--insights from Insigs and insects. *Nat Rev Mol Cell Biol* **4**, 631-40 (2003).
17. Dobrosotskaya, I. Y., Seegmiller, A. C., Brown, M. S., Goldstein, J. L. & Rawson, R. B. Regulation of SREBP processing and membrane lipid production by phospholipids in *Drosophila*. *Science* **296**, 879-83 (2002).
18. Kliewer, S. A., Lehmann, J. M. & Willson, T. M. Orphan nuclear receptors: shifting endocrinology into reverse. *Science* **284**, 757-60 (1999).
19. Drolet, D. W., Jenison, R. D., Smith, D. E., Pratt, D. & Hicke, B. J. A high throughput platform for systematic evolution of ligands by exponential enrichment (SELEX). *Comb Chem High Throughput Screen* **2**, 271-8 (1999).
20. Koundakjian, E. J., Cowan, D. M., Hardy, R. W. & Becker, A. H. The Zuker collection: a resource for the analysis of autosomal gene function in *Drosophila melanogaster*. *Genetics* **167**, 203-6 (2004).

Teaching statement

I have always taken pleasure in teaching and I enjoy interacting with students for a number of reasons. I find it gratifying to incite critical thinking and to instill curiosity. But interactions go both ways, and I like the process of being challenged with a problem I have not thought about, and to learn new things along the way. In addition, teaching provides an excellent opportunity for me to stay in touch with a wide spectrum of scientific topics, thus helping me to maintain a broad perspective. As an educator, I feel it is my obligation to train students to be able to communicate their ideas orally and in writing, since these skills are not only essential to the scientist, but are vital to succeed in any modern career. Therefore, communication skills need to be trained from early on during undergraduate instruction, refined through laboratory experiences and polished during graduate training.

At the undergraduate level, I feel that courses need to address fundamental problems in biology, and should be concept-oriented rather than relying on memorization alone. I believe that it is of critical importance to present the most recent research in these classes, since it illuminates the scientific method, confronts students with current problems as well as unanswered questions and provides opportunities to critically evaluate new ideas. I encourage all undergraduate students to participate in laboratory courses that teach the scientific method to gain experience and insights from working with a faculty member in an active research laboratory.

At the graduate level, I want to encourage students to tackle important scientific questions from different angles, and to employ multidisciplinary approaches. With the rapid advances in molecular biology and related fields, a questionable trend towards technique-driven rather than question-driven science has emerged. Through smaller classes and particularly within my own lab setting, I want to give students access to the latest techniques and experimental approaches, but also show them how to use different approaches to address important biological questions. Finally, I want to develop graduate courses that require critical reading of current literature, and would require my own graduate students to participate in journal clubs to not only hone their reading and presentation skills, but also to encourage them to ask questions and to engage in scientific discussions.

I have had several opportunities to teach undergraduate, master and graduate students during my career. Throughout my studies as a masters student (the german "Diplomand"), I had the chance to work as a teaching assistant (german: Tutor) in four lab courses with different teachers. During each class, my responsibility was to independently supervise six master students for 20 days (8 hour days). My task was to teach them basic and advanced molecular biology techniques, both in theory and practice. In addition, I assisted them in preparing their mandatory presentation and the course protocol. These classes required extensive preparation, since I had to provide all the necessary materials, plan the theoretical sections that were required for understanding the techniques, and read papers in advance to assist the students with the presentations. These classes were very important to me, because they represented an outstanding opportunity to acquire fundamental teaching skills. As a postdoctoral fellow at the University of Utah I have served as mentor to an undergraduate conducting research for a summer. I was also mentoring two rotating graduate students. Each one of these experiences was unique and all were rewarding for me, and I was thrilled to watch a student develop an

understanding of the scientific problem and acquire technical competence. I was always proud when they presented their results in front of our lab group.

I am qualified to teach courses in genetics, developmental biology, cell biology, animal physiology, introductory biology and genomics. I would really enjoy teaching upper-level undergraduate and graduate courses on *Drosophila* developmental genetics and on molecular techniques including genomics. In addition, I would like to give lectures on introductory biology, developmental biology and comparative physiology. However, should the need arise, I would welcome the challenge to teach other types of courses.