THE UNIVERSITY OF UTAH

Department of Human Genetics

2 January 2006

Dear Members of the Faculty Search Committee,

It is a pleasure to recommend enthusiastically Dr. Chris Cretekos for a faculty position in your Department. Chris performed some beautiful work as a graduate student with me in the Department of Human Genetics, University of Utah. He is talented and smart, and he was an original and independent thinker about his graduate work in my laboratory. Chris has unswerving dedication to his work, talents to match his drive, a broad grasp of pressing questions in developmental genetics, and a deep appreciation of and intuition about embryology. It is no surprise that even at such an early stage of his career Chris has had three of his publications heralded on front covers of journals – he has repeatedly tackled projects of fundamental and widespread interest in biology. Chris is a synthetic and critical thinker who loves biology and is motivated to think about the work of others. He will be a fine teacher and generous colleague.

Chris was centrally involved in two projects during his graduate career. On one of these Chris worked as part of a collaborative team in the lab to resolve an important controversy in our field that arose as a result of contradictory reports regarding the time and manner with which cells in the zebrafish embryo acquired restricted developmental potentials. The issue was important because it bore on the possible mechanisms by which cells were instructed to adopt a specific fate. Moreover, at a time when we were still very unclear about the degree to which developmental strategies were conserved among vertebrate embryos, this study ultimately rejected the proposal that zebrafish development differed fundamentally from that of other vertebrate embryos. One of the prevailing models proposed that there was no relation at all between cell lineage or cell position during early cleavage stages and eventual developmental fate, whereas a second model proposed that by the 8–cell stage each cell in the embryo had a predictable fate, akin to the pattern of development seen in C. elegans. To explain the contradictory reports, members of the lab developed a model reminiscent of the old story of the "Blind wise men and the elephant", suggesting that each model-proposing group had focused on a different portion of the embryo and that different portions of the embryo experienced different degrees of cell mixing. The effects of differences in early cell mixing would explain why some early cells give rise to descendants that are scattered among many tissues whereas other early cells give rise to descendants that populate a more restricted array of tissues. Chris was responsible for performing the cell lineage experiments required to test the model. Given that my lab had no prior experience with this type of analysis, I think it a significant accomplishment that Chris developed these techniques quickly, working completely on his own. The results of this study, published in *Science*, supported our model and clearly showed that the early cell divisions did not function to partition prospective fate in a predictable manner. Chris went on to ask why cells in different regions of the embryo displayed different scattering behaviors. In this study, Chris worked independently to design as well as execute experiments. These studies

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suggested that a morphogenetic change in the shape of the blastoderm (called "doming"), which occurs just prior to gastrulation, could account for all of the types of cell mixing seen in the embryo. Furthermore these studies showed clearly that the mesoderm arises from those early blastomeres that lie close to the yolk cell and undergo minimal scattering. This finding was especially intriguing because it allowed the hypothesis that mesodermal precursors become specified as a result of inductive signals emanating from the yolk cell (later proven to be true), in a process similar to the origin of mesoderm in other vertebrates. The work was reported in a special issue of *Developmental Genetics* devoted to vertebrate gastrulation. Chris' contribution to this report was primary, and I view him as a principal co-author of this paper.

Chris worked entirely independently on a second, long term project, the first results of which were published in *Developmental Biology*. This project was an extremely long haul, and the fact that it culminated in the isolation and characterization of a very exciting mutant is a reflection of Chris' persistence and his insight. Chris' idea was to generate a library of insertional mutations in the zebrafish by microinjection of DNA into fertilized eggs using gene-trap vectors that he had constructed. Chris selected one mutant, *alyron*, to evaluate in detail. *alyron* was the first zebrafish developmental mutation produced by DNA integration.

Although the mutant phenotype was highly complex, Chris demonstrated that the mutant defect was novel and interesting and that its pleiotropy could be traced to a single developmental defect: a block at the earliest stages of development of the neural crest, a multipotential cell type that arises at the border of the neural plate and non-neural ectoderm and that contributes to craniofacial skeleton, heart, pigment cells, portions of the nervous system and glia. Defects in neural crest development account for a broad spectrum of birth defects, and Chris' genetic analyses showed that *alyron* was a previously uncharacterized gene required for neural crest development. Chris then began work to molecularly identify the *alyron* gene. He was able to isolate genomic sequences bordering one side of the plasmid insertion, but was unable to complete molecular isolation of the gene. These unsuccessful efforts prolonged his tenure in my lab. Now we understand why. Our continued work on the project has shown that *alyron* is very close to the telomere of a chromosome and is embedded in highly repetitive sequences that continue to elude the genome sequence project. Only by analysis of YAC recombinants have we made headway in this region. Chris' initial mutation resulted in deletion of all sequences distal to the site of integration. The combination of highly repetitive sequences, a telomeric deletion, and few available genomic resources made molecular analysis of the gene particularly difficult. The gene appears to be a novel player in the FGF pathway. My expectation is that Chris will be a primary author on the forthcoming paper describing the gene.

Chris sought out Richard Behringer's lab because at heart he loves embryos and thinking about the embryonic processes that generate form. Once again he proved unafraid to tackle a highly ambitious project – an evolutionary and molecular genetic study of the genetic factors that contribute to modifying vertebrate form. Once again after many years, his work has proven to be novel and exciting and opening new possibilities. Chris' graduate and postgraduate studies demonstrate his technical range and emphasize his focus on the embryo. His staging series of bat development seems to me a work of love.

I expect Chris will continue to set high goals for himself and aspire to take on challenging and exciting projects. He will always be an interesting scientist. Clearly, Chris has moved his projects along slowly, and in the current pressured funding climate, he will need to develop a talent for creating short-range goals to complement his larger projects.

On a personal side, Chris is one of the most generous and affable persons I know. He is an extraordinarily dependable and patient person, and he has been an excellent teacher of others. My experience is that Chris whole-heartedly embraced the ethic of community interactions and inter-laboratory journal clubs and RIPs that characterize the developmental genetics groups at Utah. My expectation is that he will be an active intellectual contributor to your Department.

In sum, Chris is an exciting, intellectually ambitious scientist worthy of your consideration. Please contact me if I can be of further help in your evaluation of his candidacy.

Respectfully,

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