



HOWARD HUGHES MEDICAL INSTITUTE

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October, 20th, 2005

Dear Colleagues,

It is a pleasure for me to write a letter of recommendation in support of Dr. Jane Hubbard, who has applied for a faculty position at your institution. I am familiar with Dr. Hubbard's research project because both of our labs study germ line development, my lab in *Drosophila*, Dr. Hubbard in *C. elegans*. I know Dr. Hubbard as a colleague and teacher because she is part of the Developmental Genetics (DG) graduate program, a joint program between the Department of Biology and the School of Medicine at NYU.

Dr. Hubbard's research focuses on germ line stem cell biology. While stem cell biology has become a central theme in biology and medicine, we still know very little about the mechanisms that control stem cell maintenance and differentiation. Dr. Hubbard uses *C. elegans*, to study germ line development, where germ line stem cells can be recognized easily at the tip of the gonad and the differentiating products give rise to sperm first and then eggs. Dr. Hubbard studies how stem cell proliferation is controlled and how the pattern of proliferation and differentiation within the gonad is organized.

Dr. Hubbard made a number of significant contributions to the germ line stem cell field. It had previously been shown by others that germ line stem cell maintenance and continued proliferation required cell-to-cell interactions between a ligand expressed in somatic cells adjacent to the germ line and a receptor, Glp-1, expressed in the germ line. New results from the Hubbard lab now show that the receptor not only controls stem cell proliferation but also prevents differentiation. These studies also showed evidence for physical interaction between receptors, a novel finding for this type of receptor (*Genetics* 2003 and *Developmental Biology* 2003). This work is important beyond *C. elegans* first because it contributed to the functional interplay of stem cell maintenance and differentiation and further because it further defines the role of the conserved Notch/GLP1 receptor in the regulation of stem cell behavior. Dr. Hubbard continues to identify new mutations that affect germ line development, places them into genetic pathway and defines their role molecularly (*Genetics* 2005). In a recent study published in *Development* (2004), Dr. Hubbard and her graduate student Darrell Killian have identified the *pro-1* gene as a mediator of germ line proliferation acting in the somatic cells. *pro-1* as well as other "pro" genes identified in the Hubbard lab based on their specific gonadal phenotype encode highly conserved protein, with a role in ribosome biosynthesis. This suggests a link between the translational machinery and somatic

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gonad development possibly as a rate limiting regulator for the synthesis of proteins critical for gonadogenesis.

A second and similarly exciting aspect of Dr. Hubbard's work is her recent focus on mathematical modeling of *C. elegans* germ line development. Applying genetic understanding to mathematical modeling and developing predictive models of highly complex multicellular interaction in time and space is an important challenge in modern biology. Gonad development in *C. elegans* offers an excellent and at this point unique system for this type of study. In her studies on vulva development, computer models can be based and trained on the wealth of genetic and molecular data available in the worm and the predictive value of the emerging models can be tested using efficient worm genetics (PNAS 2005). This project as well as Dr. Hubbard's future plans to systematically test all worm genes for a function in germ line development by RNAi demonstrate that she is prepared to solve important developmental problem using whole genome and system approaches. The approaches she has chosen are not easy because they are not at all well developed. Her progress so far shows that she is determined to break new ground. This new project will foster the interface between model organism biology and informatic analysis. Dr. Hubbard was the driving force to bring together experts from different disciplines. This project has received funding by the NIH in a special initiative that aims to foster high-risk projects at the interface between developmental biology and computer assisted systems biology. I have been on study sections reviewing these types of grants and among the applications I have seen, I would rank Dr. Hubbard's proposal as one of the most promising and comprehensive; first, because she has chosen an excellent model for these studies and second, because she has assembled a group of researchers that brings together specialists in the areas of computer analysis, informatics, genetics and germ line biology.

In summary, Dr. Hubbard's detailed genetic, molecular and system biology approach has provided her with new insight into established signaling pathways, revealed new players and will ultimately lead to a systematic description of the gene network controlling gonad development. Each of Dr. Hubbard's publications is complete and thorough and published in highly regarded journals in the field of developmental biology and genetics. This scholarly style may not produce a large volume of publications but rather these publications will be of lasting impact. Dr. Hubbard is not only a scholarly scientist with a deep interest to pursue innovative research but she is also a dedicated teacher. She excels in her teaching assignments, in developing new courses and in mentoring students. Thus in considering Dr. Hubbard's scientific development one needs to see both her prospect for future research discovery and her outstanding role as a teacher and role model.

I enthusiastically support Dr. Hubbard's application. If I can be of any further assistance, please do not hesitate to contact me.

Sincerely,



Ruth Lehmann, Ph.D.
HHMI Investigator
Julius Raynes Professor of Developmental Genetics



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Re: Dr. Jane Hubbard

Dear Colleagues,

I would like to recommend Dr. Jane Hubbard most enthusiastically for a faculty position. I have known Jane for over three years, during which we have been collaborating extensively on a new and exciting way to model biological systems. (The third person in this collaboration is Prof. Michael Stern from Yale.) I have only praise for Jane's breadth, depth, scholarship, knowledge, talent and workmanship. She is extremely smart and clever, but also has the kind of wisdom one finds in much older and more experienced scientists. She brings to this collaboration her extensive knowledge of the *C. elegans* nematode worm, but her abilities and contributions to the project go far beyond that of a *C. elegans* expert. Jane has an incredible ability to grasp and put to work mathematical and algorithmic concepts as they relate and become relevant to biology. She is able not only to understand people like myself, who come from the other side of the 'fence', but to make solid suggestions within the computational framework too.

Jane has all the talent required of someone who is poised to make extremely valuable contributions to computational and systems biology in the next few years. I could say more than that: If I were to have tried to sketch, in my mind, the ideal collaborator for working with on a long-range approach to the computational modeling and analysis of complex biological systems, the sketch would have been of someone exactly like Jane.

I am also strongly in favor of her taking the lead in the long-term project I have been trying to outline in the last couple years, whereby the ultimate goal is to construct a fully-fledged 4-dimensional model of a multi-cellular organism; in particular, our proposal is to

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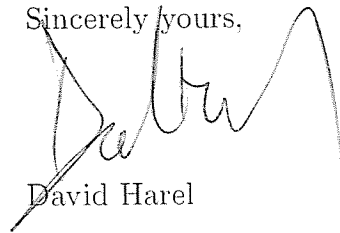
do this for *C. elegans*. Since my own work on this topic constitutes only about 30% of my research time, someone else must take the leadership of the entire project, someone who is vigorous and talented, who is an expert on one of the facets required of this effort but is sufficiently knowledgeable on the other side too. Jane is the perfect candidate for this, and I plan to do everything I can to help convince her to take upon herself this role.

Our joint work is quite new. We have published to date only a couple of papers and some abstracts, but these are already triggering much enthusiastic response, and there are several people from within Computer Science who can attest to her remarkable work and talents in the systems biology area. I'd be happy to supply some more names if you are interested. (Others would be able to supply names of people from Biology.)

To award Jane a position would — in my humble opinion — be one of the smartest moves you could make to strengthen and broaden a desire to deal with the system view of biology. Had she indicated to me a willingness to move to a foreign country, I'd not leave a stone unturned in an effort to convince her to join the Weizmann Institute as a tenured faculty member, though us being in a small country in the Middle East, and Jane being an American, means that such an idea doesn't have too much chance of succeeding...

In summary all I can say is: Take her. Nay — GRAB her!

Sincerely yours,

A handwritten signature in black ink, appearing to read 'David Harel', with a long, sweeping flourish extending to the right.

David Harel

DH/cw