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Dear Search Committee,

I would like to start by stating that this is a very strong recommendation for Dr. Yaroslava Yingling for an Assistant Professor in your Department. Yara is an exceptionally strong candidate. It is my opinion that in her current group she is the best post doc to have ever been there. Further, on the scale of the Laboratory she also ranks extremely high. (For clarification, I note that at the NIH a Laboratory is equivalent to a Department in a University). Her science is superb. Her thinking is clear. She is extremely creative, with deep understanding. And she is a very independent scientist, able to lead a group successfully.

Dr. Yingling joined the Laboratory in March 2004 as a postdoctoral fellow. Since our offices are located on the same floor, I had ample opportunity to meet Dr. Yingling on numerous occasions and to get acquainted with her and with her work on telomerase RNA. Yara came to the NCI from the Pennsylvania State University with an impressive background in Computational Material Science and expertise in developing a coarse-grained models representing laser ablation of organic and polymeric materials. At the NCI she undertook a completely different project on atomistic simulations of structure-function relationship of nucleic acids, particularly RNA. RNA folding and function are very close to my heart. My own Ph D involved developing a secondary structure prediction algorithm for RNA folding. I have subsequently worked on RNA for some 10 more years, until I switched to proteins. So, I have always been very interested to hear about her work.

Within her first year at the NCI she made a *remarkable* progress in elucidating the structure-function relationship of human telomerase RNA hairpin domain. *She has carried out a comprehensive study of nanosecond-scale implicit and explicit solvent molecular dynamics simulations of the wild-type telomerase RNA hairpin.* This is an extremely impressive work. She further studied the effects of various mutations on telomerase RNA dynamics. As might have been expected, she has observed that the human telomerase hairpin is a very flexible molecule. However, in particular,

periodically the molecule exhibits dramatic structural fluctuations represented by the opening and closing of a non-canonical base-pair region. These structural deviations correspond to significant disruptions of the direct hydrogen bonding network in the helix, widening of the major groove of the hairpin structure, and causing several U and C nucleotides to protrude into the major groove from the helix permitting them to hydrogen bond with, for example, the P3 domain of the telomerase RNA. This has led her to suggest that these structural fluctuations expose a nucleation point for pseudoknot formation. Moreover, the results show that the hairpin with dyskeratosis congenita mutations is more stable and less flexible than the wild-type hairpin due to base stacking in the pentaloop. The results from our molecular dynamics simulations are in agreement with experimental observations. This work was published in the prestigious *Journal of Molecular Biology*.

I found it very impressive that she was able to learn new concepts and techniques in biology and biophysics and simultaneously produce impressive results in such a short period of time. During last year, she has investigated the dynamic characteristics associated with the formation of a pseudoknot structure in human telomerase RNA and structural changes that are related to some genetic diseases. Since the structure of the pseudoknot was unknown, her project involved predicting the tertiary interactions in the pseudoknot formation. In order to obtain a three-dimensional pseudoknot telomerase structure she had creatively used concepts associated with molecular modeling. Not only did she obtain a high-resolution pseudoknot 3D structure using completely theoretical methodology, but also elucidated the critical importance of the bulge on the folding pathways and junction formation of the pseudoknot. These accomplishments will be reported in her recently submitted papers. In all her projects, Dr. Yingling showed a remarkable creativity; astonishingly fast pace of learning, and ability to tackle difficult problems. I was impressed by her ability to come up with interesting ideas and modeling solutions.

I should add that I myself am both a Professor at Tel Aviv University Medical School and a Principal Investigator at the NCI. I have large groups at both institutions: my joint group with Prof. Haim Wolfson (from the School of Comp. Science, at Tel Aviv) currently has 17 graduate students. Based on my experience, I would say that Yara is able to lead a group and be an excellent teacher. I see her explaining things to others, probably giving advice and guidance. She has excellent ideas; Her CV is also exceptional – I see that she has 16 papers (all since 2001!). In only 4 of these she is not the first author. I also know that her current mentor thinks extremely highly of her. Her contribution to the group is immense.

Recently, our Laboratory has been renamed Center of Cancer Research Nanobiology Program. This reflects an added dimension of our research. Dr. Yingling's background, expertise and accomplishments allow her to also merge extremely well into these design and application direction.

All in all, she is an extremely strong candidate, and I most strongly recommend her to you.

Best regards,

Ruth Nussinov
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