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Re: Santosh Kumar Paidi's nomination for Junior Fellowship in the Society of Fellows

Dear Members of the Junior Fellowship selection committee,

I am writing this letter to offer my strongest support for Santosh Paidi's nomination for Junior Fellowship in the Society of Fellows. I have known Santosh for the past five years and, at the very outset, he had struck me as a bright, independent and extremely motivated student. Working closely with him as his PhD advisor has greatly strengthened this first impression. I can attest to his problem-solving ability and unwavering dedication to tackling new and timely research questions. Santosh is an outstanding experimentalist and a strong quantitative thinker, who complements his expertise in basic measurements with the ability to turn such measurements into systematic, engineered and controlled procedures. Moreover, he is equally comfortable with employing advanced chemometric techniques for analysis of spectroscopic data and its integration into diagnostic models. Santosh is smart, well trained, and has excellent intuition both for the physical problems as well as the underlying biology. His training at some of the best schools in the world, at IIT Bombay as an undergraduate and currently at Johns Hopkins University as a graduate student, provides him with a stellar academic foundation to explore new research domains.

Since 2014, Santosh has been a doctoral researcher in my laboratory and has been working on a diverse array of basic scientific questions and clinical problems. That he has been able to handle this workload, in addition to graduate coursework, without exhausting his bandwidth speaks volumes of his tenacity, dedication and versatility. He has already published 12 important articles in journals such as *Cancer Research, Analytical Chemistry, Scientific Reports, Accounts of Chemical Research* and *Angewandte Chemie*, and is in the process of preparing several other manuscripts.

I would like to particularly highlight his work in unveiling the molecular composition of the pre-metastatic niche that resulted in a *Cancer Research* article (2017) and has sparked widespread interest in the oncology community. Through a series of rigorous experiments, Santosh demonstrated a spectroscopic method of pre-metastatic niche recognition with label-free Raman spectroscopy prior to seeding of tumor cells and, thus, in advance of conventional clinical manifestations. Here, by studying lungs of mouse models that recapitulate spontaneously disseminating breast cancer of low and high metastatic potential, he derived new biological insights into the nature of stromal modifications induced by factors secreted from the primary tumor. Utilizing the changes in the collagen architecture and proteoglycan content, as probed by their unique spectral markers, he employed a decision algorithm,

which accurately differentiated pre-metastatic lungs in mice with MDA-MB-231 (high metastatic potential) tumor xenografts from those in mice with MCF-7 (low metastatic potential) xenografts and normal controls. This approach could transform the exciting and emerging area of metastasis research that strives to elucidate the interplay between biochemical signals and morphologic features in the tumor microenvironment at distant secondary sites. In contrast to other approaches that attempt to identify differential markers to track metastatic changes, this approach is non-perturbing.

Motivated by this success, Santosh used label-free Raman spectroscopy to develop a minimally perturbative, quantitative tool that can reveal important radiation therapy-induced molecular changes in matched models of radiation-resistant lung tumors and head and neck tumors of known radiation sensitivity using xenograft models. He further showed that Raman spectroscopy was also able to identify hallmarks of radiation resistance in non-radiated control tumors. The determination of treatment resistance in tumors either prior to or immediately after commencing therapy would provide personalized treatment options for patients and would allow them to avoid the toxic side effects of ineffective therapy. The manuscript describing this work was recently accepted for publication in *Cancer Research* (2019) and the findings of this study have contributed to the award of a collaborative NIH R01 grant proposing the development of a multimodal optical approach for early and accurate identification of radiation resistance featuring two complementary label-free methods, namely diffuse reflectance and Raman spectroscopy, a diagnostic routine that focuses on the tumor microenvironment, and multivariate analysis of spectral data. Importantly, Santosh contributed to the writing of this proposal and, thus, demonstrates a degree of proficiency in grant-writing not commonly encountered in graduate students.

On the translational front, Santosh has been actively engaged in developing novel routes for identification of biotherapeutic drug products during various stages of their production using vibrational spectroscopic approaches that exploit both endogenous contrast and plasmonic enhancement strategies. Following the publication of these exciting results in *Analytical Chemistry* (2016), he worked closely with our collaborators at MedImmune, LLC to validate the developed approach for measurements on site. This is a major step towards employment of label-free Raman spectroscopy for rapid identification of very closely related biotherapeutic drug products using minimal sample volumes. For his efforts, he has been awarded the prestigious Tomas Hirschfeld award from the Federation of Analytical Chemistry and Spectroscopy Societies, only two of which are awarded annually to graduate students engaged in spectroscopy research. He was also the recipient of the SLAS Graduate Education Fellowship grant (one awarded annually) in 2018, which will support his research for the rest of his graduate program.

In addition to academic pursuits, Santosh is committed to advocating for high school STEM education and issues facing graduate student community. As an Advocacy Chair of Graduate Representative Organization, he played a key role in getting the voices of graduate student body heard, particularly in the wake of an announcement by the university administration supporting the proposed state legislation authorizing private police forces on private universities in Maryland, without consulting student community. He has worked actively to engage with the student body and to organize town hall meeting between students and university officials. Currently, as student representative of Whiting School

of Engineering on the Homewood Graduate Board, he is advocating for making the Graduate Board Oral examination and annual student review requirements uniform across the university so that the students can receive regular and timely feedback throughout their program.

Santosh has also been involved with SABES after-school program, an NSF-funded project aimed at improving STEM education in Baltimore public elementary schools. He is actively involved in holding lab tours to students ranging from high school students and freshmen in the department to prospective graduate students and encourages them to seek opportunities in the emerging area of biomedical optical spectroscopy. His recent trip to Capitol Hill with the goal of educating lawmakers about the need to continue funding research for optics and photonics, and science and technology in general, further substantiates his commitment to advancing science and technology.

In summary, I am very impressed by Santosh's professionalism, broad knowledge base and commitment to research and community. Clearly, he is part of the new breed of leaders that are well trained across the engineering/biology/spectroscopy domains and have a passion for touching human lives. I am confident that Santosh will boost the stellar legacy of Harvard Society of Fellows through his contributions in developing optical spectroscopy for label-free and real-time detection of primary and metastatic cancers and in gaining mechanistic insights into therapeutic intervention of these difficult-to-treat conditions. Hence, I sincerely hope that he will be the recipient of the Junior Fellowship. The full mailing addresses of the candidate and three additional researchers who have agreed to write a provide letters of recommendation are attached. In case I can be of any further assistance, please do not hesitate to contact me for additional information.

Yours sincerely,

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