January 27th 2015

The Origins Project Postdoctoral Prize Lectureship
Arizona State University
[redacted]

Re: Reference for Gopinath Sutendra, Ludwig Cancer Institute, University of Oxford.

Dear Committee Members,

I would like to offer my strongest possible support for **Gopinath Sutendra** for the Origins Project Postdoctoral Prize Lectureship competition at Arizona State University in the disciplines of *Biological Sciences and Medicine*. Over the past 17 years I have supervised many students that have received prestigious international awards, including several that have won the Cournard-Comroe Young investigator Award of the American Heart Association. Among those, Gopinath ranks in the top and I can comfortably say that he is the brightest and the most innovative and hard working student I have ever been associated with. Gopinath completed his PhD degree with me at the University of Alberta in June of 2012 and his thesis impressed me, as well as all the members of the defense committee. The external examiner was Dr. Marlene Rabinovitch, a senior professor of Pediatrics from Stanford University and perhaps one of the top 5 scientists in the history of pulmonary vascular biology. She has supervised myriads of students and her impressively positive comments on Gopinath's thesis were very important for both him and myself. Gopinath's thesis reflected his dedication, hard work as well as his innovative thinking that he has demonstrated continuously during his first steps in his academic career. It was not a surprise that, with Dr Rabinovitch's support, Gopinath's thesis was judged to be the best for the whole University of Alberta that year, not just the Medical School.

Overall his work is characterized by in-depth studies that include multiple techniques and several models, are mechanistic and explore fundamental mechanisms at multiple levels and in a highly translational manner, since they aim to answer important questions related to human disease. Despite the technical nature of his work, Gopi's research and thinking project an almost philosophical approach, as he tackles fundamental questions that have to do with decisions of life versus death and the decision making process behind them, only at the cellular level.

One of the challenges in pulmonary hypertension is the fact that there are many abnormal pathways that have been described (perhaps more than 20) and it is quite possible that almost all of them are actually present in human disease. This poses several therapeutic challenges as it suggests that it is unlikely that targeting one pathway will have important clinical benefits. Therefore it is important to identify and target integrative pathways that can address perhaps more than a few abnormalities. At the same time, all of these pathways result in one fact: suppression of cell death (which is normally activated to prevent excessive cell growth). This allows "proliferative" signals to be unopposed, resulting in the excessive growth of cells that characterizes the vascular obstruction seen in pulmonary hypertension. A similar paradigm characterizes cancer. The question is whether a comprehensive mechanism can put all of these pathways under one roof and whether unlocking this state of "resisting death" will be beneficial for pulmonary hypertension (and in that sense, for cancer as well).

Gopinath took this challenge upon himself and completed work that provided for the first time definitive molecular and genetic evidence for the critical role of metabolism in the pathogenesis of pulmonary

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hypertension. He proposed that mitochondria (the regulators of metabolism) can integrate many diverse decisions and activate or supress cell death accordingly. Paradoxically, while the mitochondria sustain life by generating the cell's fuel, at the same time they have the ability to activate cell death and kill their host cell. Gopi's work generated information that provided a unique integration of "pro-life" and "pro-death" mechanisms, according to availability of fuel, all orchestrated within mitochondria. His thesis included work that was published in at several prestigious journals. In the first 2 papers, that formed a part of his thesis, Gopinath studied knockout mice that lacked a critical gene and while they had an overall normal phenotype, they were completely resistant to the development of pulmonary hypertension.

With the **first paper**, Gopinath showed that lack of a specific mitochondrial enzyme involved in fatty acid oxidation in knockout mice (i.e. malonyl-CoA-decarboxylase) prevents the mitochondrial inactivation that has been shown to underlie animal and human pulmonary hypertension. It also completely prevents the disease in several models of pulmonary hypertension. This work exposed several therapeutic targets. Gopinath also inhibited these targets with clinically used metabolic modulators and was able to reverse mice and rat pulmonary hypertension, as well as reverse the disease phenotype in vitro in cells isolated from the pulmonary arteries of patients with pulmonary hypertension. This work was published in the prestigious ***Science Translational Medicine.***

In a similar manner, with the **second paper,** also published in ***Science Translational Medicine***, Gopinath showed how endoplasmic reticulum stress (which is linked to almost all conditions associated with pulmonary hypertension in humans and animals) could lead to metabolic remodelling and a suppression of mitochondrial function, resulting in a "paradoxical" cell proliferation despite a state of stress. He showed that a transcription factor and ER stress sensor, i.e. ATF6, is selectively activated in the pulmonary circulation and induces the expression of Nogo (*neurite outgrowth inhibitor*), a member of the reticulon family, that had previously only been implicated in spinal cord injury. Nogo expression selectively in the pulmonary circulation reshapes the ER and disrupts the strategic spatial relationship with mitochondria (i.e. disrupts the "ER-Mitochondria Unit") causing mitochondrial suppression and a switch to a cancer-like, non-mitochondria based metabolism in pulmonary vessels. Mice lacking Nogo also had a normal phenotype but were completely resistant to pulmonary hypertension.

The comprehensive nature of this work and the fact that it was the first definitive proof that metabolism and ER stress are critical in pulmonary vascular remodeling and are important therapeutic targets, was the basis for the acceptance of this work in high impact journals. Science Translational Medicine is a journal of the American Association for the Advancement of Science (the medical "sister" journal of Science). These papers both made the cover of this journal and had associated editorials in the same and other journals. For example, within a month after the publication of the first paper, the leading journal in the field of metabolism (*Cell Metabolism*, a sister journal of Cell) published a full editorial just on Gopinath's work, describing how it opens "a new window in pulmonary hypertension" (Rubin L, *Cancer Metabolism*, September 2010). It is overall unusual for a leading journal to publish a full editorial (not just under "news and views" sections) on a paper published in another journal. In addition, that month, *Nature Biotechnology* (a sister journal of Nature) published an article specifically describing the many therapeutic targets that Gopinath's paper exposed. Both Science Translational Medicine papers were also very positively reviewed at the Faculty 1000 web site in medicine and biology.

Gopinath has also recently published a paper on metabolism and epigenetics (currently a "hot" topic in the

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scientific community). Gopinath showed that the same protein complex that generates acetyl-CoA (the substrate for the Krebs' Cycle, a precursor for ATP production) in the mitochondria, can translocate to the nucleus in response to growth factors and mitochondrial stressors to generate acetyl-CoA for histone acetylation (an epigenetic modification) and regulate many genes that are needed for cell proliferation. In a sense he provided a very novel means by which the mitochondria can directly regulate the function of DNA, as until then, the source of acetyl-CoA in the nucleus, remained surprisingly unknown. This very influential biochemistry-oriented paper was published in ***Cell*** and was featured with an accompanying perspective in the same issue and as a highlight in *Nature Chemical Biology*. Not only was Gopinath first author, but he was also co-corresponding author on this publication.

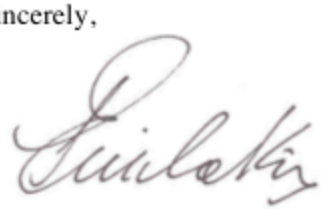
All of these papers represent hard work of many years for Gopinath. These are a very large manuscripts with many multi-paneled intense figures as well as >15 supplement multi-paneled figures. Gopinath always tries to develop complete and full "stories" in his papers. This strategy results in fewer but stronger papers that tell "a full story" and can thus have a major impact in the field.

I also have to point out that several experiments in his papers represent a methodological "tour de force". For example, Gopinath advanced a high fidelity catheter through the jugular vein into the pulmonary artery of mice in order to measure mean pulmonary artery pressure (as opposed to the less relevant but much easier to perform right ventricular pressure). This is one of a very small number of papers in the literature that present a full and appropriate right heart catheterization in mice. In addition, the images of the pulmonary vasculature in vivo (using our PET-SPECT-CT) were recognized by making the journal cover for Science Translational Medicine.

Gopinath will have a brilliant academic career and I strongly believe that he is already a rising star not only among his peers nationally but internationally as well. He came to me with a Masters in protein crystallography and was not afraid to dive into completely different areas in biology and physiology. He quickly mastered a number of challenging techniques, developed original methodologies and trouble-shooting strategies in complex procedures. He has won several awards already but still strikes one by his humility, modesty, and respect for colleagues. Going to Oxford University was a natural next step for him. I believe I can't see the end of the ladder for him. What I do know is that he will become better than me, fulfilling my goal as his mentor.

In summary, this is by far the best trainee I have ever been associated with. I believe his innovative thinking particularly around fundamental scientific questions, the quality of his work and his potential, make him worthy of this prestigious award.

Sincerely,



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