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To Whom it May Concern,

RE: Stephanie Berger's application for HHMI Hanna H. Gray Fellowship

I am writing to strongly support Stephanie Berger's application for a HHMI Hanna H. Gray Fellowship. I first came to know Stephanie in early 2015 when she approached me to assist with the characterization of a suite of high-affinity ligands she had designed and developed to target Bcl-2 family anti-apoptotic proteins. At that time, and it is probably still the case, those ligands were a unique resource as no one had ever previously been able to target every family member so effectively using similar approaches. The work conducted in my laboratory on the ligands subsequently showed that they functioned as expected in a cellular milieu.

To extend upon these studies, Stephanie obtained a scholarship to travel to Australia for 3 months at the end of 2015 to learn some more about cell death mechanisms, and how she could apply her ligands to cancer biology. During this time, Stephanie learnt all the required techniques very quickly and rapidly applied them to important questions about the best strategies to effectively kill cancer cells by targeting the cell death pathways. She was able to work independently to produce very high quality data that formed part of an outstanding publication in *eLife* in 2016.

Since returning to the USA, Stephanie has risen to the challenge of applying what she has learnt about targeting the Bcl-2 anti-apoptotic proteins to now targeting the pro-apoptotic family members. For various technical reasons, this is a significantly more difficult task, yet early studies in my laboratory on these molecules indicate she has managed to generate some of the most potent inhibitors of these proteins to date. This is a significant achievement as it has taken more than two decades of extensive research in this field for any laboratory to generate similarly-acting ligands. I have no doubt that when it is complete, this work will also be published in a prestigious journal and attract significant interest.

Stephanie's proposed research for the Fellowship is ambitious and demonstrates significant scientific maturity for a recent PhD graduate. It will build upon a solid foundation she has already built around

computational biology and design of medically important ligands, but take this into an entirely new realm where her methods can be universally applied to any ligand-receptor system. This design strategy will be coupled with newly developed screening methods to provide rapid insights into the best candidates in a massive library of variants. This is an original approach to protein engineering as the data generated from the screen(s) can then be fed back into her design algorithms to further improve their success. Moreover, such an approach is at the leading edge of computer-based protein engineering and demonstrates Stephanie's ability to address important scientific questions using the unique and powerful tools she has independently developed. The outcome of this research is likely to be significant and have wide-reaching impact.

As such, I believe that Stephanie has all of the hallmarks of top-grade scientist moving into the next stage of her career, and most strongly endorse her application for this HHMI Hanna H. Gray Fellowship. Please do not hesitate to contact me if you require further information.

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