Developing Cellularly Active Inhibitors of CARM1 for New Anti-Cancer Treatment

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Cancer is responsible for half a million deaths annually in the US. Tumor growth in breast and prostate cancers can be caused by unregulated CARM1 protein. Chemical inhibition of the CARM1 protein represents a promising anti-cancer treatment, but currently there are no compounds shown to be cellularly active in selectively inhibiting CARM1. I investigated five candidate inhibitory compounds that mimic a cofactor substrate of CARM1, SAM, using computational modeling, immunoassay and MALDI mass spectra, and developed a cell-based assay for CARM1 activity that reported siRNA CARM1 knockdown. Computational modeling calculated the binding affinity of each compound with CARM1 and initially predicted that compound #1 would have the highest binding affinity. The immunoassay provided antibody-based quantitative indications of inhibition for compound #1 and MALDI mass-based comparison validated these results. Finally, a new approach combining Western blot with substrate transfection indicated knockdown of CARM1 by siRNA. In summary, I developed and validated a cell-based activity assay, predicted binding affinity of five candidate compounds, and, using antibody and mass-based assays, discovered a new compound capable of inhibiting CARM1. Of the five compounds tested, compound #1 is promising as a prospective new cancer drug for the inhibition of tumor growth.

Awards Won: