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Synthetic sensing and signal transduction cascades based on artificial autoinhibited proteases

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The central tenet of the emerging field of Synthetic Biology is that biological components can be refined into a toolkit of plug-and-play building blocks. The experimental evidence supporting this idea has so far been limited to relatively slow synthetic gene expression circuits. Real-time events in biological process are mediated by protein-based signaling circuits that can operate up to the millisecond scale. Ability to design protein-based signaling circuits would in principle enable us to design of analytical and diagnostic tests for any analyte. To create orthogonal toolbox of protein-based signal detectors and amplifiers we combined structure-based engineering and directed evolution of proteins. This approach allowed us to create artificial auto-inhibited proteases with non-overlapping substrate specificities. These molecules are inactive in their ground state but are activated by changes in their structure that dislodge the inhibitor from the active site. Incorporation of a ligand-binding domain into such basic signaling unit allowed us to create an allostercally regulated receptor protease. It is demonstrated that a complete signal detection and amplification cascade can be assembled from such synthetic protein units. Such cascades are easily connectable to existing electronic detectors through engineered artificial zymogenes. Using this approach we created biosensors of cancer markers such as prostate specific antigen and several matrix metalloproteinases as well as proteases of the blood coagulation cascade. It has been demonstrated that the cascades operate effectively in biological fluids and can be used for developing POC applications.

Biography

Kirill Alexandrov obtained his Master's degree at the Leningrad State University, Russia in 1989 and completed his PhD in Cell Biology at EMBL Heidelberg, Germany in 1995. He went on to Postgraduate work at the Department of Physical Biochemistry at the Max-Planck Institute in Dortmund, Germany, and remained with the Institute for 12 years, becoming a group leader in 1999. He co-founded the German biotechnology company Jena Bioscience in 1998. He joined the Institute for Molecular Bioscience and the Australian Institute for Bioengineering and Biotechnology of the University of Queensland, Australia in 2008 as an Australian Research Council Future Fellow.

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