

Title of proposed program: Extracellular RNA Communication

Submitting Source: NIH

What is the major obstacle/challenge/opportunity that the Common Fund should address?

The concept of RNA as an endocrine signal has emerged over the past few years as RNAs have been discovered in extracellular vesicles or bound to lipids or proteins circulating in serum or other body fluids. The impact of extracellular RNAs (exRNAs) is largely unknown, but in cellular contexts where they have been analyzed, they have been demonstrated to modulate target cell function. For example, tumor-derived exRNAs can promote tumor growth, and endothelial cell-derived exRNAs have been demonstrated to regulate gene expression in smooth muscle cells. In addition, exRNAs from rice have been found in the circulation of humans and have been reported to modulate LDL levels. Microbes also secrete RNAs via extracellular vesicles; this may be a mechanism by which the microbiome may influence host cell function at a distance. These studies suggest a mechanism of inter-kingdom information exchange through exRNAs. An opportunity exists to establish entirely new paradigms of intercellular and inter-organismal communication by identifying fundamental principles of exRNA secretion, delivery, and impact. What RNAs are secreted into the circulation or into other body fluids? How are exRNAs in donor cells selected for secretion? How are they packaged, and what determines whether an exRNA will be exported via vesicles, lipid moieties, or via a protein complex? What is the functional impact of exRNAs in different cell types?

In addition to foundational biology, an opportunity exists to test the clinical utility of exRNAs as therapeutic molecules or as biomarkers. Can exRNAs or their carriers be engineered for targeted delivery? Vesicles have been shown to cross the blood-brain barrier; can exRNAs be selectively loaded into vesicles for delivery to the brain? Are exRNA profiles characteristic of health or specific diseases? Can changes in the profiles be useful as diagnostic or prognostic indicators?

These questions are exemplary of fundamental issues that need to be resolved with respect to exRNA communication. The challenges for this field are to develop profiles of exRNAs in different body fluids, to establish mechanisms through which exRNAs are generated and secreted, to identify mechanisms of delivery to recipient cells, and to demonstrate the potential for clinical utility.

What would the goals of the program be? What initiatives might be developed?

The overarching goals for this program would be to establish principles of exRNAs as endocrine signals and to demonstrate the potential for utility in the clinic. Specific goals would include:

- Develop tools/technologies/methods for isolation and analysis of various classes of exRNAs
- Establish a central repository for data collection and analysis for the community at large
- Develop profiles for human exRNAs in many tissues and body fluids to serve as reference data for analyses of exRNAs in disease conditions
- Support coordinated analyses to define fundamental biological principles of exRNA biogenesis, distribution, and uptake
- Support projects that demonstrate possible clinical utility of exRNAs as biomarkers or therapeutic delivery vehicles

Why is a trans-NIH strategy needed to achieve these goals?

Coordination among investigators who are working toward the stated goals for the program (above) will be essential to establish a core understanding of exRNAs and their function in many tissues and to establish methods for their use in the clinic. NIH staff from many ICs need to be involved in management of the program to bring perspectives from many diseases.

If a Common Fund program on this topic achieved its objectives, what would be the impact?

This program has the potential to create a new paradigm for intercellular and inter-organismal information exchange. It will lay the groundwork for many future investigator-initiated projects that will explore the function of specific exRNAs by providing tools for reliable isolation and analysis of exRNAs and by providing hypothesis-generating data. It will also provide a new avenue for

therapeutic delivery of exRNAs by developing methods for engineering and establishing the principles that govern target cell selection. It therefore has transformative impact for basic science as well as for the clinic.