

Title of proposed program: Zipcodes for Drug Delivery

Submitting Source: NIH and the Bethesda Meeting

What is the major obstacle/challenge/opportunity that the Common Fund should address? What would the goals of the program be? A major obstacle for drug development is unwanted side effects which are frequently caused by drug action on off-target tissues or cell types. This contributes to the high failure rate of developing preclinically effective compounds into medications as well as the withdrawal of medications from clinical use due to adverse effects. Recently, advances have been made in drug delivery systems that allow such medications to reach their designated targets and avoid targets that are not involved with the disease, alleviating undesirable side-effects. However, a major obstacle that prevents more targeted therapies is a lack of fundamental knowledge about cell surface markers that are specifically expressed in target sites that may be used in targeting approaches. These markers could serve as “zipcodes” for delivery - if they can be identified. Such molecules have been described in the vasculature, and vascular zip codes offer potential for targeted delivery to the vasculature of specific organs. However, a catalog of zip codes in the vasculature and elsewhere needs to be established, and a library of compounds that specifically bind these zip codes need to be established. The goals of this program are therefore to promote and implement targeted-drug delivery technologies through the identification and cataloging of zip code proteins, the development of binding reagents which specifically recognize these proteins and have the capacity to deliver therapeutic molecules, and a tracking system which will enable in vivo tracking of the binding reagents.

Why is a trans-NIH strategy needed to achieve these goals? What initiatives might form the strategic plan for this topic? A trans-NIH strategy could facilitate integration of knowledge across ICs on different organs, tissues and cells. Common Fund initiatives might include:

- “Zip code” identification – A catalog of cell type- or tissue-specific markers would be identified as “zip codes” for that cell or tissue. This catalog would be fully annotated and available to the public.
- “Packing Material” development – Therapeutic molecules will need to be “packed” for delivery through binding to molecules which will in turn bind to the “zip code” molecules. These “packing” molecules which will bind the zip codes may be developed via the Common Fund “Protein Capture” program, or it may require a separate activity.
- Development of Tracking methodologies – Just as packages can be tracked via UPS, targeted drugs will need to be tracked in vivo. Imaging methods which track the “packing” molecules will need to be developed.
- Demonstration Projects: Proof of concept projects will need to test the utility of the suite of compounds, including the ability of “packing” molecules to bind a therapeutic compound, its ability to deliver the compound specifically to the target zip code, and the ability of the tracking methods to follow delivery and clearance of the packing compound.

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

If the objectives of targeted drug delivery are achieved, it will increase the success rate of medication development and reduce the off-target toxicity. This in turn will significantly impact the efficiency of translating basic research discoveries to treatment of patients.