You Want to Build it Where? Using Electrochemistry to Solve Problems of Location

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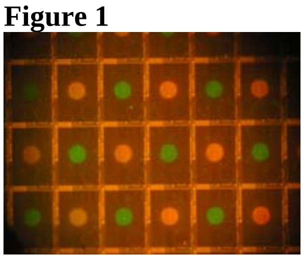
The development of spatially addressable libraries of small molecules has the potential to dramatically accelerate the pace at which the thousands of gene products typically produced by a cell can be isolated, identified, and probed for the factors that govern their binding to perspective ligands. This is especially true if the gene products can be evaluated simultaneously on a scale consistent with the tiny amounts of material generated by biological systems. To this end, chip-based microarrays of molecules have proven to be particularly useful.With this in mind, we have been working to establish the chemistry needed for building and analyzing molecular libraries on chips having arrays of microelectrodes. But how does one build the molecules in the library so that they are located next to the microelectrodes in an array? Our plan for answering this question calls for first using the electrodes in the array to construct molecules so that each unique set of molecules in a library is associated with an individually addressable electrode and then using the electrodes to monitor the behavior of the molecules in the library toward various biological receptors.

Synthetic efforts have been focusing on the development of site-selective transition metal reactions on the microelectrode arrays. In these reactions, the selected microelectrodes in an addressable array are used to transform a transition metal from an inactive form to an active catalyst by adjusting its oxidation state. The active catalyst is then confined to the region surrounding the electrode that generated it by a substrate in solution that reacts with the catalyst and returns it to its initial inactive form. To date, both mediated and catalytic processes have been confined to pre-selected sites on a chip in this manner and both oxidation and reduction reactions have been utilized in these efforts. As an example, Figure 1 illustrates the utility of a site-selective reductive amination strategy for placing amines next to the electrodes in a microarray containing 1024 electrodes/cm^2. In this experiment, the microelectrode array was covered with an agarose polymer and then the alcohols next to selected electrodes oxidized with the use of an anodically generated Pd(II) reagent. A reductive amination reaction then placed an amine containing a fluorescent indicator onto the chip. Two such reactions were done – one using a red fluorescent indicator and the second using a green fluorescent indicator – in alternating checkerboard patterns. The confinement of the oxidation reactions to specific electrodes in the array can be readily seen. This reaction represents only one of a variety of synthetic methods currently under development.[1-3]

Figure 1



In addition to the synthetic efforts, work is also underway to develop cleavable linker strategies so that the molecules constructed at any given electrode in a microarray can be characterized and to establish the capability of microelectrode arrays for monitoring in "real-time" the interactions between molecules on the chip's surface and a biomolecule in solution.

In the talk to be presented, recent progress concerning the development of new synthetic methods, the establishment of cleavable linker strategies, and the development of strategies for the electrochemical detection of binding events on the microelectrode arrays will be discussed.

For Leading References See:

1. "Building Addressable Libraries: The Use of Electrochemistry for Generating Reactive Pd(II) Reagents at Pre-Selected Sites on a Chip." Eden Tesfu, Karl Maurer, Steven R. Ragsdale, and Kevin D. Moeller. *J. Am. Chem. Soc.* **2004**, *126*, 6212-6213.
2. "Building Addressable Libraries: The Use of Electrochemistry for Spatially Isolating a Heck Reaction on a Chip." Jun Tian, Karl Maurer, Eden Tesfu, and Kevin D. Moeller. *J. Am. Chem. Soc.* **2005**, *127*, 1392-1393.
3. "Building Addressable Libraries: Spatially Isolated, Chip-Based Reductive Amination Reactions." Eden Tesfu, Karl Maurer, and Kevin D. Moeller *J. Am. Chem. Soc.* **2006**, *128*, 70.