

# Semiconductor-Neural Interfaces

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**Abstract- Continued advances in the design of prosthetic devices will demand increasingly smaller and more precise connections. We are developing a single cell device capable of specific molecular interactions using semiconductor quantum dots (qdots). The qdots are placed in direct proximity to individual cellular receptors using biorecognition molecules. These molecules may be incorporated into the passivation layer of the quantum dot or may be presented as an external molecule. In this manner, we have successfully created qdot-nerve cell interfaces utilizing both peptides and antibodies. Ultimately, the qdots will be excited optically, eliciting a change in the nerve cell membrane potential. The change in nerve cell membrane potential will be measured using a microelectrode array currently under development. These devices will allow researchers to determine the effect of electrical excitation on individual nerve-cell receptors and enhance development of molecular neuroprosthetics.**

**Keywords - semiconductor quantum dots, microelectrode arrays**

## I. INTRODUCTION

Current neuroprosthetic devices (i.e., cochlear implant, retinal implant) promote interaction between individual nerve cells and electronic components. Typically, cells from a nerve cable are placed in juxtaposition to a microelectrode array, composed of multiple micron-sized electrodes on a silicon or glass substrate [1]. While these devices have been successful, they form connections at the whole-cell level. However, the membrane potential of nerve cells arises from charge differences mediated by several types of receptors (i.e., ion channels) throughout the nerve membrane [2]. The ability to manipulate individual receptors through non-invasive electrical interactions will open doors to new therapeutic treatments for neurotransmitter based diseases (e.g., Parkinson's disease). Additionally, receptor-scale prosthetics could serve as the building blocks for novel bio-electric devices (e.g., neural memory devices).

*Receptor-scale devices:* Available neuroprosthetic devices create interfaces by culturing cells directly on electrical components. For cellular interactions this approach is successful. Electrode dimensions average 5  $\mu\text{m}$ ; and the cell itself averages 60  $\mu\text{m}$  in diameter [3]. As many as 64 electrodes may be placed on a 1 x 1 cm device. Therefore, a monolayer coverage of neurons will ensure that at least some of the electrodes make contact with an individual cell. However, due to the small size of receptors ( $\sim 1$  nm diameter) [4], culturing cells on a device cannot ensure contact. Instead, the device must be brought to the cell.

*Quantum dots (qdots):* Semiconductor qdots exhibit unique optical and electrical properties due to their small

size. In particular, when optically excited, they exhibit fluorescence, dipole moments, electron transfer, and thermal fluctuations that greatly exceed those found in bulk materials [5]. Sizes average from 1-60 nm, making qdots ideal electrical components for receptor interfaces. Further, qdots can be altered to contain a passivation layer that imparts water solubility and allows for surface chemistry modifications. We have exploited this layer to create qdots that bind to selected cellular receptors using biorecognition.

*Interface formation:* Biorecognition molecules (e.g., antibodies, peptides) create interfaces between a target and receptor through hydrostatic, electrostatic, Van Der Waals, or hydrogen bonding interactions. By incorporating these molecules into the passivation layer of qdots, we have created direct connections to cells. Because interactions mimic those that occur naturally in the body, harsh chemicals and syntheses may be avoided. We have already demonstrated the ability to use antibodies and monovalent peptides for qdot – cell binding [3]. Here we describe the use of a bivalent peptide recognizing *both* the qdot and the cell. The peptide was developed through the phage display technique. Using bivalent peptides, we can promote neuron-qdot interface formation, which will ultimately provide receptor-scale interfaces for neuroprosthetics.

## II. METHODOLOGY

### *Quantum Dot Synthesis*

Cadmium sulfide (CdS) quantum dots were prepared using  $10^{-2}$  M solutions of  $\text{CdCl}_2$  and  $\text{Na}_2\text{S}\cdot 9\text{H}_2\text{O}$  in water. Passivating ligand (i.e.,  $\beta$ -mercaptoethanol), up to 0.1 M, was added to the  $\text{CdCl}_2$  solution. The pH was raised to 7 with 1 M NaOH; then, an equal amount of  $\text{Na}_2\text{S}$  solution was added. The mixture was stirred for 1 hour. Next, 9.4 g/L phenol red free minimal essential media (MEM) and 1.5 g/L  $\text{Na}_2\text{HCO}_3$  was added. The pH of the solution was adjusted to pH 7.4, and the solution was sterile-filtered.

### *Bivalent Peptide*

CdS binding sequences were isolated following the method described by Whaley et al. [6]. Then, this sequence was altered to include a cellular recognition peptide, RGDS (arginine-glycine-aspartic acid-serine). RGDS is known to bind integrins, cellular receptors for extra-cellular matrix proteins, and was selected due to its short size and commercial availability.

### *Quantum dot- Neuron Interfaces*

Neuroblastoma cells (SK-N-SH) were incubated with 10  $\mu\text{g}/\text{ml}$  bovine serum albumin (BSA) for 1 hour. Cells were

then washed with phosphate buffered saline (PBS) three times (3x). Cells were then incubated with 300  $\mu\text{g}/\text{ml}$  bivalent peptide in PBS for 30 minutes, followed by washing 3x with PBS. Finally, cells were incubated with qdot – MEM mixture for 30 minutes and washed 3x with PBS. Cell-quantum dot interface formation was observed using oil immersion fluorescence microscopy.

#### Measuring cellular response

A microelectrode array will be used to measure the changes in cell firing patterns after qdot exposure. Traditional arrays, created with photolithography, require a separate mask for each electrode arrangement. To maximize flexibility in electrode placement, we are creating an array using electron beam lithography (EBL). EBL uses an electron sensitive polymer resist (i.e., poly (methyl methacrylate) PMMA). The resist is developed using an electron beam, typically provided by a modified scanning electron microscope (SEM) [7]. The pattern created in the resist is computer controlled and easily altered.

The array is manufactured using a three layer process. Gold bond pads are created using a barrier mask and metal deposition on a silicon substrate. Then, EBL is used to create an interior electrode PMMA mask, through which gold electrodes are deposited. PMMA is removed via sonication in acetone. A clean, insulating layer of PMMA is deposited on the device, and electrodes are exposed using EBL.

### III. RESULTS & DISCUSSION

#### Quantum Dots

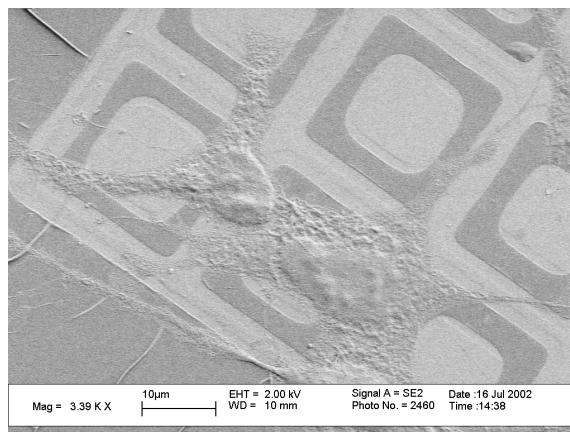
CdS quantum dots were prepared as described above. Qdots exhibited photoluminescence excitation at wavelengths  $<380$  nm with an emission maximum occurring at  $\sim 600$  nm. TEM images of the qdots demonstrated an average diameter of 55  $\text{\AA}$ . This size is well within the range needed to make contact with an individual receptor.

#### Bivalent Peptide

Following phage display, the seven amino acid sequence CHASNRLSC (cysteine-histidine-alanine-serine-asparagine-arginine-leucine-serine-cysteine) was identified as a positive binding sequence to CdS qdots. This peptide was combined with the RGDS sequence to create the bivalent peptide used in experiments (CHASNRLSCRGDS).

#### Microelectrode Array

The compatibility of cells with PMMA is demonstrated in Fig. 1. A test pattern containing 20  $\mu\text{m}$  boxes surrounded by 5  $\mu\text{m}$  lines was cultured with nerve cells in MEM for three days. Cells grow readily on the pattern. Also the film is relatively intact, showing its compatibility with saline.



**Figure 1.** SEM of neuroblastoma cells cultured on patterned PMMA surface. PMMA regions are dark gray; silicon substrate is light gray.

### IV. CONCLUSION

Qdots coupled with bivalent peptides form a model system for receptor-scale prosthetic devices. Qdots are small enough ( $\sim 5$  nm) to allow for direct coupling with receptors present in the cell membrane. This coupling is made possible through *dual* biomolecular recognition of *both* the qdot and the cell using a bivalent peptide identified through phage display techniques. Qdots will be excited optically to elicit cellular response. This response will be measured using a microelectrode array created with EBL. Ultimately, the coupling of qdot-cellular interfaces with current microelectrode array technology provides a method for constructing receptor-scale prosthetic devices.

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