THE NANOSTRUCTURE OF THE NERVOUS SYSTEM AND THE IMPACT OF NANOTECHNOLOGY ON NEUROSCIENCE

Gabriel A.Silva

Departments of Bioengineering and Ophthalmology, and Neurosciences Program, University of California, San Diego, USA

Keywords: Nanotechnologies, molecular organization, nanoengineering, nanometer, transmembrane proteins

Contents

Summary

Nanotechnologies involve materials and devices with an engineered functional organization at the nanometer scale. Applications of nanotechnoloy to cell biology and physiology provide targeted interactions at a fundamental molecular level. In neuroscience, this entails specific interactions with neurons and glial cells, which complements the cellular and molecular organization and structure of the nervous system. Examples of current work include technologies designed to better interact with neural cells, advanced molecular imaging technologies, applications of materials and hybrid molecules for neural regeneration and neuroprotection, and targeted delivery of drugs and small molecules across the blood-brain barrier.

1. Introduction

Nanotechnology and nanoengineering stand to produce significant scientific and technological advances in diverse fields including medicine and physiology. In a broad sense, they can be defined as the science and engineering involved in the design, syntheses, characterization, and application of materials and devices whose smallest functional organization in at least one dimension is on the nanometer scale, ranging from a few to

several hundred nanometers. A nanometer is one billionth of a meter, or three orders of magnitude smaller then a micron, roughly the size scale of a molecule itself (e.g. a DNA molecule is about 2.5 nm long, while a sodium atom is about 0.2 nm). To give an appreciation of just how significant an order of magnitude is, let alone three orders when going from micron to nanometer scales, consider that no one would ever walk from New York to San Diego; but, with a single order of magnitude change in speed, the equivalent of changing speed from walking to driving, you would get to San Diego in a few days. Flying, which would be two orders of magnitude faster than driving, would get you there in a few hours, and three orders faster than walking would take you minutes. (Walking a straight line between the two cities would take about 42 days at an average speed of 3 miles per hour.)

The potential impact of nanotechnology stems directly from the spatial and temporal scales being considered: materials and devices engineered at the nanometer scale imply controlled manipulation of individual constituent molecules and atoms in how they are arranged to form the bulk macroscopic substrate. This in turn, means that nanoengineered substrates can be designed to exhibit very specific and controlled bulk chemical and physical properties as a result of the control over their molecular synthesis and assembly.

For applications to medicine and physiology including neuroscience these materials and devices can be designed to interact with cells and tissues at a molecular (i.e. sub-cellular) level with a high degree of functional specificity, thus allowing a degree of integration between technology and biological systems not previously attainable. It should be appreciated that nanotechnology is not in itself a single emerging scientific discipline, but a meeting of traditional sciences such as chemistry, physics, materials science and biology in order to bring together the required collective expertise needed to develop these novel technologies. Bio-nanotechnology applications to the central nervous system (CNS) are designed to interact with cells and tissues at a sub-cellular molecular level, the functional building block level associated with the constituent protein elements that make up the functional cellular unit, such as cell surface receptors, transmembrane proteins, ion channels, and the cell's cytoskeleton. The complexity associated with the cellular heterogeneity, structure, and functional organization of the CNS present some unique challenges for designing and using bionanotechnologies, but the potential offered by the unique properties associated with nanoengineered materials and devices complement other neurobiological approaches and provide a significant opportunity to advance our basic understanding of cellular neurobiology and neurophysiology, and provide novel clinical treatments for neurological disorders.

2. The Micro- and Nanoscale Structure of the Central Nervous System (CNS)

2.1. The Organization of the CNS

As with all body systems, the fundamental functional scale of the central nervous system is at the micro- and nanoscales. This section begins with a review of the structure and organization of the CNS, working down in scale to the protein (i.e. nanoscale) level. For general reviews and further reading on neurophysiology the reader is referred to any of the several excellent texts which cover the subject to varying degrees and in different ways. The CNS essentially refers to three gross anatomical structures: The brain, spinal cord, and

neural retina, which is an extension of the brain itself. The entire CNS is separated from the rest of the body by the blood brain barrier (BBB), and in the case of the retina the blood retinal barrier. This makes the CNS immunologically privileged, in the sense that specific immune cells and factors (e.g. antibodies) circulating in the periphery do not have access to CNS structures. This also makes the local extracellular CNS environment, the cerebral spinal fluid (CSF), quite chemically unique. The CSF surrounds the brain and spinal cord and provides a degree of cushioning from the bony structures which protect them (i.e. the skull and vertebrae). The BBB, which controls the rate at which factors cross in and out of the CNS, is made up by the endothelial cells of the small blood vessels that feed it. The BBB provides both a mechanical mechanism of restricted access mediated by tight junctions between adjacent cells, and physiological mechanisms, mediated by specialized active transport processes.

In general, lipid soluble factors are able to cross the BBB much more readily than less lipid soluble factors, a fact that has been an important consideration for drug delivery into the CNS and is an important consideration for nanotechnological approaches that strive to do the same. Between the neural tissues and the bone that protect them a series of membranous covers collectively referred to as the meninges. The thick dura matter is closest to the bone, the arachnoid is next, and the very thin pia matter is immediately adjacent to the neural tissue. The subarachnoid space, between the arachnoid and the pia matter is where the CSF is.

During development the brain forms its main subdivisions, which consist of the cerebrum, diencephalon, cerebellum, and brainstem. The brain also has four cavities in which CSF is produced called the ventricles. The cerebrum and diencephalon together make up the fore brain, which include other key brain structures such as the basal ganglia, an area important in various aspects of behavior and movement, the thalamus, which is where much of the neural information passing on to the cortex is integrated, the hypothalamus, which is a small but critical region coordinating much of brain's functions, and the evolutionary primitive and complex limbic system, which lies deep in the brain and is involved in various aspects of learning, experience, behavior, and emotions. The cerebrum itself is where most of the complex neural processing occurs. The corpus collosum refers to the massive group of fibers that connect the two hemispheres of the brain. The cerebellum, which lies at the base of the brain towards the back, is involved in the coordination of posture, balance, and movement. The brainstem, which consists of the midbrain, the pons, and medulla oblongata, acts as the relay between the spinal cord and brain, but also has critical roles in basic life sustaining functions such as breathing. The spinal cord is made up of many complex ascending and descending pathways to the brain (afferent and efferent pathways, respectively) with specific off shoots along its length (the dorsal and ventral roots) that innervate all the structures outside the CNS that are controlled by the brain.

Most sensory and control information is shuttled through the spinal cord, with the exception of structures innervated by the twelve cranial nerves which connect to the brain directly. One of these nerves, the optic nerve, is made up by bundles of nerve fibers (properly called axons) that form the output from the neural retina on their way to the brain. The retina consists of several distinct anatomical and physiological layers of cells, and is where all visual sensory information begins as a result of a process called phototransduction in photoreceptor neurons where incoming light is transduced it into a

neuro-chemical signal. The axons formed by the last layer of neurons in the retina, the retinal ganglion cells, form the optic nerve. The retina is also responsible for a significant degree of pre-processing of neural information before it goes on to the brain. Neural structures outside of the CNS make up by definition the peripheral nervous system (PNS).

2.2. The Cellular and Molecular Structure of the CNS

Each of the CNS structures descried above consists of distinct anatomical and/or functional sub-structures that serve specific functions. All of these sub-structures are composed of a very complex interconnection of cells, which are the functional units responsible for all the information processing that occurs in the CNS (Fig. 1).
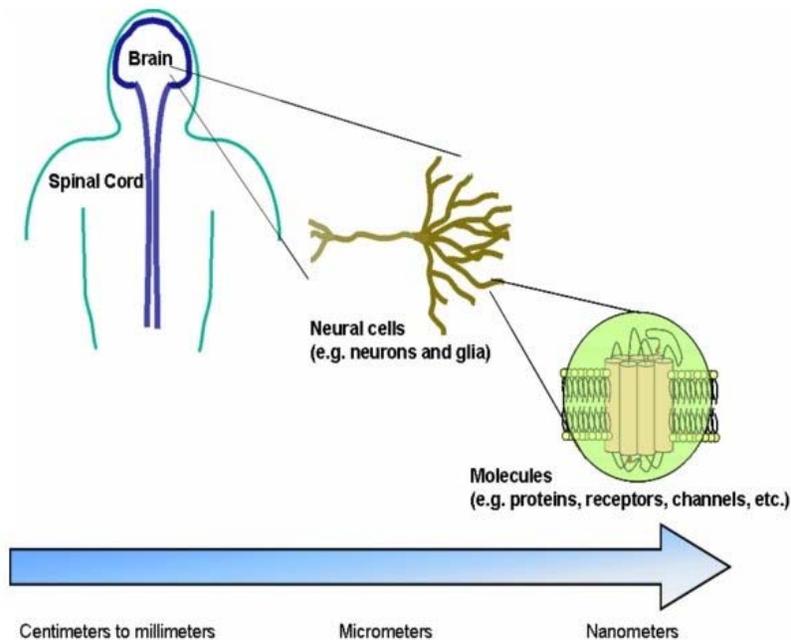

Figure 1: Overview of the structure of the central nervous system (CNS), from organs (i.e. the brain and spinal cord) to cells to molecules. The size scale progressively decreases from centimeter and millimeter sized anatomical and functional structures to micrometer sized cells, to nanometer sized molecules.

There are many different types and sub-types of cells in the CNS, each a highly specialized terminal phenotype cell designed to carry out a specific function. In general, there are two main classes of cells in the nervous system: neurons and glial cells. Neurons are the fundamental functional (i.e. information processing) unit of the nervous system. Neurons come in a tremendous variety of morphologies which reflect the vast number of specialized roles they are designed for. In general, however, an idealized neuron consists of dendrites, a cell body, an axon, and a synaptic terminal. The dendrites collect sub-threshold inputs from other neurons (i.e. presynaptic neurons) called excitatory postsynaptic potentials (EPSP's) or inhibitory postsynaptic potentials (IPSP's). If the temporal and/or spatial summation of these inputs reach a specific threshold level at the neuron's axon hillock, a specialized zone where the axon meets the cell body, an electrical event called an action

potential is generated that travels down the length the axon and terminates at the synaptic terminal where neurotransmitter molecules are released by the neuron and signal other downstream neurons by contributing to those neuron's EPSP's and IPSP's. Some neurons have up to 400,000 dendrites, and the complexity of the summating postsynaptic inputs both in space (e.g. as a function of where on the dendritic tree they are) and in time is staggering and represents the principal mechanism of computational processing in the CNS. The cell body, which contains the neuron's nucleus, carries out many of the typical life supporting processes of all cells, although in the neuron this is also where chemical-electrical processes result in an action potential being generated (or not). The axon is an elongated cellular process containing many intermediate filaments and microtubules that transport vesicles and other organelles up and down its length. It is also through which the action potential travels to signal a downstream neuron. Some neurons have very short axons, such the inter-neurons in the brain and spinal cord or the photoreceptors in the retina, while some axons can be almost a meter long, such as the spinal cord motor neurons that innervate the muscles of the leg.

The action potential is a self-propagating self-renewing chemical-electric event that begins at the axon hillock and travels the length of the axon uninterrupted. The molecular basis of the action potential is the movement of ions down strong electrochemical and diffusion gradients between the inside and outside of the neuron separated by the cell membrane of the axon. Na^+, which is actively pumped out of the neuron and is at much higher concentrations extracellularly, enters the cell through Na^+ specific ion channels while K^+, whose situation is reversed, flows out. Other ions, such as Cl^- are also involved. The ion channels are voltage sensitive, so that the activation of channels induces the opening of adjacent channels, thereby creating a self-propagating event. The amplitude and duration of the action potential are constant and very short, respectively, so that in engineering terms it can be regarded as a traveling or propagating delta function. It is important to appreciate that only a very thin shell of ions on either side of the axon's cell membrane are required to produce an action potential, so that the active pumping of ions by the transmembrane Na^+-K^+-ATPase pumps are only required to maintain these concentration gradients over long time scales, not over the millisecond time scale of an individual action potential. In fact, several thousand action potentials can occur following the chemical inactivation of the Na^+-K^+-ATPase pumps before any significant effect on the amplitude of the action potential can be measured. At the end of it all is the synaptic terminal of the presynaptic neuron which synapses with a dendrite of a postsynaptic neuron. We will pay particular attention to the molecular details of the synapse below as an example of a naturally occurring form of a nanoengineered structure. The action potential and synapse constitute the fundamental mechanisms by which information is transmitted through the nervous system. It should be noted that the term 'nerve', which everyone is familiar with, properly speaking refers to a bundle of axons running through the PNS. A similar bundle of axons running through the CNS is called a tract. Similarly, a collection of neuron cell bodies in the PNS is referred to as a ganglion (e.g. the dorsal root ganglia of the spinal cord which sit just outside the vertebral bodies); while in the CNS they are called a nucleus (e.g. the lateral geniculate nucleus in the brain which receives inputs from the retina). Note that this use of the term nucleus is not to be confused with a cell's nucleus. Some axons are 'insulated' by the processes of a type of specialized non-neuronal cell wrapping around them that give the axon a white appearance due to a high lipid content in these processes. This is referred to as myelination and results in increased speeds of action potential

transmission by a process called saltatory conduction, since the action potential 'jumps' from one spot on the axon to the next spot not covered by myelin, roughly equally spaced down the length of the axon (the nodes of Ranvier). The cells that do this insulating in the CNS are called oligodendrocytes, while their counterparts in the PNS are called Shwann cells. Both are types of glial cells, the second major cell type in the nervous system, described below. In contrast, unmyelinated axons and cell bodies appear grayish in color. This is the physical basis for the gray matter and white matter of the CNS. In the brain the gray matter is found on the surface, giving the brain a gray color, while the heavy myelinated tracts are hidden beneath. In the spinal cord it is the reverse, the white matter is in the periphery of the cord, with the butterfly shaped gray matter in the center.

The second major cell type in the nervous system are glial cells, which include several different distinct types of cells. As introduced above, oligodendrocytes in the CNS and Shwann cells in the PNS are primarily responsible for the myelination of axons. A break down in this process compromises the entire nervous system and is the pathological basis of multiple sclerosis. Another type of glial cell is the microglia, the CNS's phagocytic immune cells that are in part responsible for removing waste products. The third major classes of glial cells astrocytes in the brain and spinal cord and astrocytes and Muller cells in the neural retina. From a functional standpoint these cells are remarkably interesting. These cells were classically regarded as housekeeping cells that existed to support neurons by secreting growth factors and other trophic factors and maintaining a homeostatic extracellular environment. Relatively recently however, work by several groups have shown that astrocytes in particular are not just housekeeping cells, but also directly influence and participate in the regulation and transmission of information in the CNS by interacting with neurons, to the point that the concept of a synapse involving just pre-synaptic and post-synaptic neurons is being redefined to include an astrocytic process. These cells form highly complex signaling networks with each other and with neurons, although the molecular details are very different from those of the action potential. Astrocyte-astrocyte communication is mediated by intracellular calcium waves that spread throughout an astrocyte and results in the release of various extracellular signaling factors, including adenosine triphosphate among others, to signal both other nearby and relatively far away astrocytes . Astrocytes are able to signal neurons and neurons are able to signal astrocytes by a variety of different mechanisms that include direct cell-cell gap junctional coupling and over longer distances by chemical diffusion. Because a single astrocyte can have multiple processes associated with many neurons, neuronal-glial signaling adds a significant layer of computational complexity to information processing and flow in the CNS since these cells are able to 'short circuit' neuronal connections.

2.3. Membrane Proteins and Receptors

All cells, in a very real sense, are exquisitely engineered nanoscale machines designed to carry out many complex tasks in a coordinated way that respond, signal, and adapt to the environment in which they find themselves. The fundamental functional units that make up the cell are proteins and other molecules, the principal targets which nanoengineered materials and devices are designed to interact with. This can be achieved in one of two ways: One is to develop bio-nanotechnologies that target ubiquitous components of cellular and biochemical signaling systems. Depending on the specific cell with which the device interacts with, targeting a ubiquitous signaling pathway would affect one or more

specific downstream events. A good example would be targeting protein phosphorylation sites, which is a ubiquitous mechanism for modifying and altering the function of proteins. Targeting phosphorylation sites on β-tubulin III would produce specific affects in neurons, since it is a neuron specific microtubule, while doing the same thing on glial fibrillary acidic protein (GFAP) phosphorylation sites in astrocytes, a macroglial specific intermediate filament, would produce very different results. The second way would be to develop bio-nanotechnologies designed to target a cell specific signaling process in order to affect a known functional end point. This approach requires significant expertise in the physiological or biological system under consideration, and as such will most likely require interdisciplinary cross-training between fields and/or highly interdisciplinary collaborations. It should be appreciated that the former approach of developing nanotechnologies that target general or ubiquitous cellular processes would ultimately still require interdisciplinary collaborations to produce meaningful clinical or biological applications.

A particularly significant potential target for nanotechnologies designed to interact with neurons, for example, is the laminin family of proteins. The laminins have been used in micro- and nanoengineered systems with neurons both *in vitro* and *in vivo* particularly within the context of neural regeneration. Laminins are large multi-domain trimeric proteins made up of α, β, and γ chains (Fig. 2), of which there exist various isotypes due to proteolytic cleavage and alternative splicing post-translational modifications. The expression of different laminin isoforms varies both spatially and temporally between tissues and within a specific organ (e.g. the brain) during development and adulthood. In this way, the laminins play key roles in signaling and coordinating cell specific events from the outside world. The failure of laminin expression or their incorrect expression, either spatially or temporally, results in numerous pathologies of varying severity. For example, mutations in the laminin-5 genes LAMα3, LAMβ3, and LAMγ2 produce skin blisters, while mutations in the LAMα2 gene results in muscular dystrophy. A loss of function deletion of LAMα1 produces embryonic death in mice null mutants.
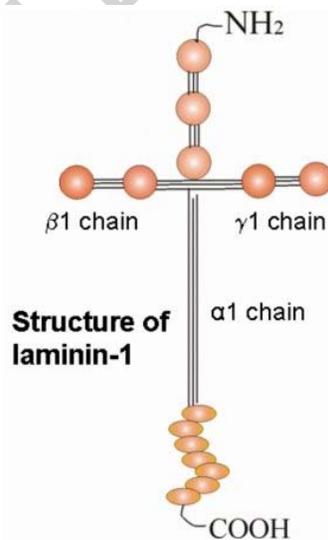

Figure 2: Schematic of the structure of laminin-1 showing its α1, β1, and γ1 component chains

To date, five different α chains have been identified, labeled α1 to α5, three different β chains, β1 to β3, and three different γ chains, γ1 to γ3. This allows forty five possible different combinations of trimeric isoforms, although in reality there are restrictions on the number of actual combinations that occur naturally, with specific chains interacting only with other specific chains. Twelve laminins have been identified, laminin 1 to 12, with laminin 1 being the most extensively studied. Ultrastructurally, laminin 1 has a cross shaped structure with the long arm ending in a G-domain formed by the C terminus of the α1 chain. The N terminus of the β1 and γ1 domains bend and form the short arms of the cross, while the N terminus of the α1 chain extends to form the top of the cross. Beyond the point where the three chains meet they form a α-helix that ends at the G-domain. The α1 chain is 400 kDa while the β1 and γ1 chains are 200 kDa each. In general, this is the structure of most of the laminins. Neurons in particular respond very strongly to the laminins and in particular to laminin-1, displaying strong cell adhesion and neurite outgrowth properties that are cell type and peptide dependent. A large variety of specific peptide sequences have been identified that affect neurons in different ways. Several groups, including our own, have recognized the advantages of engineering materials that not only provide mechanical and structural support to cellular systems, but that also express functional chemistry that promotes favorable cellular responses by incorporating extracellular matrix (ECM) signals. Nanoengineered systems provide an ideal opportunity to incorporate these molecular signals into novel materials that are designed to specifically interact with target cells.

-
-
-

TO ACCESS ALL THE **23 PAGES** OF THIS CHAPTER,
Visit: http://www.eolss.net/Eolss-sampleAllChapter.aspx

Bibliography

Ai, H. et al. 2001 - Biocompatibility of layer-by-layer self-assembled nanofilm on silicone rubber for neurons. J Neurosci Methods 128:1-8 . [Example of self-assembling nanofilm method.]

Akerman, M. E., Chan, W. C., Laakkonen, P., Bhatia, S. N. & Ruoslahti, E. 2002 - Nanocrystal targeting in vivo. Proc Natl Acad Sci U S A 99:12617-21 . [Demonstrates the potential of in vivo nanotechnology applications.]

Alyaudtin, R. N. et al. 2001 - Interaction of poly(butylcyanoacrylate) nanoparticles with the blood-brain barrier in vivo and in vitro. J Drug Target 9:209-21 .

Araque, A., Carmignoto, G. & Haydon, P. G., 2001 - Dynamic signaling between astrocytes and neurons. Annu Rev Physiol 63:795-813 . [Excellent review of neuronal-glial signaling in the CNS.]

Bezzi, P. & Volterra, A. 2001 - A neuron-glia signalling network in the active brain. Curr Opin Neurobiol 11:387-94 .

Bonneau, S., Dahan, M. & Cohen, L. D. 2005 - Single quantum dot tracking based on perceptual grouping using minimal paths in a spatiotemporal volume. IEEE Trans Image Proc 14:1384-1395 . [First work illustrating the ability to track individual quantum dots interacting with cells.]

Braydich-Stolle, L., Hussain, S., Schlager, J. & Hofmann, M. C. 2005 - In Vitro Cytotoxicity of
Nanoparticles in Mammalian Germ-Line Stem Cells. Toxicol Sci (2005).

Chan, W. C. & Nie, S. 1998 - Quantum dot bioconjugates for ultrasensitive nonisotopic detection.
Science 281:2016-8 . [One of the first publications describing cell labeling using quantum dots.]

Cheng, Y. S., Champliaud, M. F., Burgeson, R. E., Marinkovich, M. P. & Yurchenco, P. D . 1997 - Self-
assembly of laminin isoforms. J Biol Chem 272:31525-32 .

Dahan, M. et al. 2003 - Diffusion dynamics of glycine receptors revealed by single-quantum dot tracking.
Science 302:442-5 . [First publication showing a practical neuroscience result using quantum dot
tracking.]

Drummond, T. G., Hill, M. G. & Barton, J. K. 2003 - Electrochemical DNA sensors. Nat Biotechnol
21:1192-9 . [Example of bionanotechnology sensing application.]

Dugan, L. L. et al. 2001 - Fullerene-based antioxidants and neurodegenerative disorders. 7:243-246 .
[Description of an antioxidant nanoparticle that potentially be used to slow down neurodegenerative
diseases.]

Fan, H. et al. 2005 - Surfactant-assisted synthesis of water-soluble and biocompatible semiconductor
quantum dot micelles. Nano Lett 5:645-8 .

Fan, Y. W. et al. 2002 - Culture of neural cells on silicon wafers with nano-scale surface topograph. J
Neurosci Methods 120:17-23 . [Described how neurons can respond to nanoscale features on the substrate
on which they are growing.]

Frade, J. M., Martinez-Morales, J. R. & Rodriguez-Tebar, A. 1996 - Laminin-1 selectively stimulates
neuron generation from cultured retinal neuroepithelial cells. Exp Cell Res 222:140-9 . [Description of
laminin specific neuronal effects.]

Freire, E., Gomes, F. C., Linden, R., Neto, V. M. & Coelho-Sampaio, T. 2002 - Structure of laminin
substrate modulates cellular signaling for neuritogenesis. J Cell Sci 115:4867-76 . [Description of laminin
specific neuronal effects.]

Gagliardi, R. J. 2000 - Neuroprotection, excitotoxicity and NMDA antagonists. Arq Neuropsiquiatr
58:583-8 .

Gust, D., Moore, T. A. & Moore, A. L. 2000 - Photochemistry of supramolecular systems containing
C60. J Photochem Photobiol B 58:63-71 .

Hansma, H. G., Kasuya, K. & Oroudjev, E. 2004 - Atomic force microscopy imaging and pulling of
nucleic acids. Curr Opin Struct Biol 14:380-5 . [Demonstration of AFM application to the
characterization of biological molecules.]

Hartgerink, J. D., Beniash, E. & Stupp, S. I. 2002 - Peptide-amphiphile nanofibers: a versatile scaffold
for the preparation of self-assembling materials. Proc Natl Acad Sci U S A 99:5133-8 . [Description of
custom made molecules for bionanotechnology applications.]

Hartgerink, J. D., Beniash, E. & Stupp, S. I. 2001 - Self-assembly and mineralization of peptide-
amphiphile nanofibers. Science 294:1684-8 . [First paper describing nanoengineered molecules that self-
assemble into organized fibers.]

Hohenester, E. & Engel, J. 2002 - Domain structure and organisation in extracellular matrix proteins.
Matrix Biol 21:115-28 .

Howarth, M., Takao, K., Hayashi, Y. & Ting, A. Y. 2005 - Targeting quantum dots to surface proteins in
living cells with biotin ligase. Proc Natl Acad Sci U S A 102:7583-8 . [Good example of quantum dot
cellular labeling application.]

Jaiswal, J. K., Mattoussi, H., Mauro, J. M. & Simon, S. M. 2003 - Long-term multiple color imaging of
live cells using quantum dot bioconjugates. Nat Biotechnol 21:47-51 . [One of the first papers describing
the use of quantum dots for cell labeling.]

Jin, H. et al. 2000 - Polyhydroxylated C(60), fullerenols, as glutamate receptor antagonists and
neuroprotective agents. J Neurosci Res 62:600-7 .

Kandel, E. R., Schwartz, J. H. & Jessell, T. M. 2000 - Principles of neural science (McGraw-Hill Health Professions Division, New York,). [A classic and thorough text on neuroscience.]

Kasthuri, N. & Lichtman, J. W. 2004 - Structural dynamics of synapses in living animals. Curr Opin Neurobiol 14:105-11 .

Kreuter, J. et al. 2002 - Apolipoprotein-mediated transport of nanoparticle-bound drugs across the blood-brain barrier. J Drug Target 10:317-25 .

Kreuter, J. 2001 - Nanoparticulate systems for brain delivery of drugs. Adv Drug Deliv Rev 47:65-81 . [Review article on nanotechnology approaches for drug delivery.]

Lee, K. B., Park, S. J., Mirkin, C. A., Smith, J. C. & Mrksich, M. 2002 - Protein nanoarrays generated by dip-pen nanolithography. Science 295:1702-5 . [One of the original publications describing the method and use of dip pen nanolithography.]

Levene, M. J., Dombeck, D. A., Kasischke, K. A., Molloy, R. P. & Webb, W. W. 2004 - In vivo multiphoton microscopy of deep brain tissue. J Neurophysiol 91:1908-12.

Li, Z. & Sheng, M. 2003 - Some assembly required: the development of neuronal synapses. Nat Rev Mol Cell Biol 4:833-41 .

Liu, B. P., Fournier, A., GrandPre, T. & Strittmatter, S. M. 2002 - Myelin-associated glycoprotein as a functional ligand for the Nogo-66 receptor. Science 297:1190-3 .

Lo, E. H., Dalkara, T. & Moskowitz, M. A. 2003 - Mechanisms, challenges and opportunities in stroke. Nat Rev Neurosci 4:399-415 . [Review article summarizing the disease processes and potential therapeutic targets associated with stroke.]

Lockman, P. R., Mumper, R. J., Khan, M. A. & Allen, D. D. 2002 - Nanoparticle technology for drug delivery across the blood-brain barrier. Drug Dev Ind Pharm 28:1-13 .

Lyuksyutov, S. F. et al. 2003 - Electrostatic nanolithography in polymers using atomic force microscopy. Nat Mater 2:468-72 .

Michalet, X. et al. 2005 - Quantum dots for live cells, in vivo imaging, and diagnostics. Science 307:538-44 . [Review article on the use of quantum dots for live cell imaging.]

Mohammed, J. S., DeCoster, M. A. & McShane, M. J. 2004 - Micropatterning of nanoengineered surfaces to study neuronal cell attachment in vitro. Biomacromolecules 5:1745-55 .

Moxon, K. A. et al. 2004 - Nanostructured surface modification of ceramic-based microelectrodes to enhance biocompatibility for a direct brain-machine interface. IEEE Trans Biomed Eng 51:881-9 .

Murthy, V. N. & De Camilli, P. 2003 - Cell biology of the presynaptic terminal. Annu Rev Neurosci 26:701-28 .

Nomizu, M. et al. 1995 - Structure-activity study of a laminin alpha 1 chain active peptide segment Ile-Lys-Val-Ala-Val (IKVAV). FEBS Lett 365:227-31 .

Park, T. H. & Shuler, M. L. 2003 - Integration of cell culture and microfabrication technology. Biotechnol Prog 19:243-53 .

Pathak, S., Cao, E., Davidson, M. C., Jin, S. & Silva, G. A. 2006 - Quantum dot applications to neuroscience: new tools for probing neurons and glia. J Neurosci 26:1893-5. [Description of optimized protocols for labeling neural cells with quantum dots and description of the potential for artifactual labeling in neural cell systems.]

Phillips, G. R. et al. 2001 - The presynaptic particle web: ultrastructure, composition, dissolution, and reconstitution. Neuron 32:63-77 . [Characterization and description of the postsynaptic particle web.]

Powell, S. K. et al. 2000 - Neural cell response to multiple novel sites on laminin-1. Journal of Neuroscience Research 61:302 . [Review of neuronal effective laminin peptides.]

Saifuddin, U. et al. 2003 - Assembly and characterization of biofunctional neurotransmitter-immobilized surfaces for interaction with postsynaptic membrane receptors. J Biomed Mater Res A 66:184-91 .

Santos, N. C. & Castanho, M. 2004 - A. An overview of the biophysical applications of atomic force microscopy. Biophys Chem 107:133-49 .

Saxton, M. J. & Jacobson, K. 1997 - Single-particle tracking: applications to membrane dynamics. Annu Rev Biophys Biomol Struct 26:373-99 .

Schroeder, U., Sommerfeld, P., Ulrich, S. & Sabel, B. A. 1998 - Nanoparticle technology for delivery of drugs across the blood-brain barrier. J Pharm Sci 87:1305-7 .

Segura, J. L. & Martin, N. 2001 - New Concepts in Tetrathiafulvalene Chemistry. Angew Chem Int Ed Engl 40:1372-1409 .

Shenai, M. B. et al. 2004 - A novel MEA/AFM platform for measurement of real-time, nanometric morphological alterations of electrically stimulated neuroblastoma cells. IEEE Trans Nanobioscience 3:111-7 .

Silva, G. A. et al. 2004 - Selective differentiation of neural progenitor cells by high-epitope density nanofibers. Science 303:1352-5 . [First publication illustrating the use of self-assembling nanofibers for the regeneration of the CNS.]

Silva, G. A. in Introduction to Bioengineering (eds. Chien, S. & Chen, P. C. Y.) (World Scientific Publishers, in press).

Silva, G. A. 2004 - Introduction to nanotechnology and its applications to medicine. Surg Neurol 61:216-220 . [Review article summarizing the role of nanotechnology in biology and medicine.]

Silva, G. A 2006 - . Neuroscience nanotechnology: progress, opportunities and challenges. Nat Rev Neurosci 7:65-74 [Comprehensive review on the applications of nanotechnology to neuroscience.]

Silva, G. A . 2005 - Small Neuroscience: The nanostructure of the central nervous system and emerging nanotechnology applications. Curr Nanosci 3:225-236 .

Smyth, N. et al. 1999 - Absence of basement membranes after targeting the LAMC1 gene results in embryonic lethality due to failure of endoderm differentiation. J Cell Biol 144:151-60 .

Stang, F., Fansa, H., Wolf, G. & Keilhoff, G. 2005 -   Collagen nerve conduits--assessment of biocompatibility and axonal regeneration. Biomed Mater Eng 15:3-12 .

Stupp, S. I. & Braun, P. V.   1997 - Molecular manipulation of microstructures: biomaterials, ceramics, and semiconductors. Science 277:1242-8 .

Stupp, S. I. & Ciegler, G. W. 1992 - Organoapatites: materials for artificial bone. I. Synthesis and microstructure. J Biomed Mater Res 26:169-83 (1992).

Stupp, S. I. et al. 1997 - Supramolecular Materials: Self-Organized Nanostructures. Science 276:384-9 . [Review of supramolecular nanoengineered structures.]

Stupp, S. I., Mejicano, G. C. & Hanson, J. A. 1993 - Organoapatites: materials for artificial bone. II. Hardening reactions and properties. J Biomed Mater Res 27:289-99 .

Takano, H. et al. 2002 - Micropatterned substrates: approach to probing intercellular communication pathways. Anal Chem 74:4640-6 .

Tokumasu, F. & Dvorak, J.   2003 - Development and application of quantum dots for immunocytochemistry of human erythrocytes. J Microsc 211:256-61 .

Tunggal, P., Smyth, N., Paulsson, M. & Ott, M. C. 2000 - Laminins: structure and genetic regulation. Microsc Res Tech 51:214-27 .

Vinogradov, S. V., Batrakova, E. V. & Kabanov, A. V. 2004 - Nanogels for oligonucleotide delivery to the brain. Bioconjug Chem 15:50-60 .

Voura, E. B., Jaiswal, J. K., Mattoussi, H. & Simon, S. M. 2004 - Tracking metastatic tumor cell extravasation with quantum dot nanocrystals and fluorescence emission-scanning microscopy. Nat Med 10:993-8 .

Vu, T. Q. et al. 2005 - Activation of membrane receptors by a neurotransmitter conjugate designed for surface attachment. Biomaterials 26:1895-903 . [First publication illustrating the use of surface tethered nanoengineered structures used in the stimulation of neurons.]

Vu, T. Q. et al. 2005 - Peptide-conjugated quantum dots activate neuronal receptors and initiate downstream signaling of neurite growth. Nano Lett 5:603-7 .

West, J. L. & Halas, N. J. 2003 - Engineered nanomaterials for biophotonics applications: improving sensing, imaging, and therapeutics. Annu Rev Biomed Eng 5:285-92 .

Wewer, U. M. & Engvall, E. 1996 - Merosin/laminin-2 and muscular dystrophy. Neuromuscul Disord 6:409-18 .

Wheeler, B. C., Corey, J. M., Brewer, G. J. & Branch, D. W. 1999 - Microcontact printing for precise control of nerve cell growth in culture. J Biomech Eng 121:73-8 . [Use of surface micropatterning in order to control the placement and growth of neurons.]

Yang, F. et al. 2004 - Fabrication of nano-structured porous PLLA scaffold intended for nerve tissue engineering. Biomaterials 25:1891-900 (2004).

Yu, T. T. & Shoichet, M. S. 2005 - Guided cell adhesion and outgrowth in peptide-modified channels for neural tissue engineering. Biomaterials 26:1507-14 .

Zhang, S. 2003 - Fabrication of novel biomaterials through molecular self-assembly. Nat Biotechnol 21:1171-8 .

Biographical Sketch

Dr. Gabriel A. Silva is an assistant professor in the Departments of Bioengineering and Ophthalmology and the Neurosciences Program at the University of California, San Diego, USA. He received his undergraduate (1996) and masters (1997) degrees in human physiology and neuroscience, respectively, from the University of Toronto, Canada. After completing his PhD in neural bioengineering at the University of Illinois at Chicago, USA in 2001, he did a postdoctoral fellowship in applied nanotechnology to neuroscience at Northwestern University, Chicago until 2003. His research focuses on understanding how neurons and glial cells communicate across spatial scales — from the interactions between a few cells to the computational aspects of large networks — under normal physiological conditions, and how this communication changes following disease.