Evaluation of Monolayer Protected Metal Nanoparticle Technology

by

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ABSTRACT

Self assembling nanostructured nanoparticles represent a new class of synthesized materials with unique functionality. Such monolayer protected metal nanoparticles are capable of resisting protein adsorption, and if utilized as a coating could have broad application in a wide range of industries from consumer products to maritime shipping to medical instruments. The formation of proteic films can adversely affect the performance of materials and is often a limiting factor in device effectiveness. In many instances such as sensors or medical implants, regular cleaning or disposal of the instrument is not a viable option, thus there exists a demand for additional means to prevent nonspecific protein adsorption. Existing protein resistant coating options are still not completely effective, and monolayer protected metal nanoparticle coatings could be a superior means by which to prevent protein adsorption onto material surfaces.

This paper explores the commercialization potential of monolayer protected metal nanoparticle coatings for protein resistance; identifying application potential, evaluating potential markets, exploring intellectual property, analyzing the economics of monolayer protected metal nanoparticle synthesis, examining existing technologies, and assessing in depth the medical device industry and entry into the US cardiovascular device market.

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1. MPMN TECHNOLOGY

Here we present an investigation on the possibility of commercially introducing a novel protein resistant material recently developed in Professor Francesco Stellacci’s group at the Massachusetts Institute of Technology. It has been found that metal nanoparticles coated with a mixture of hydrophobic and hydrophilic ligands are able to resist protein nonspecific adsorption and thus could be used as coatings to create protein resistant coatings, i.e coatings able to prevent the formation of proteic films. [1] Protein adsorption is often a limiting factor for materials in a broad range of applications. It can adversely affect the performance of materials in everything from inexpensive toothbrushes to expensive small biosensors to large maritime vessels. Regular cleaning, periodic disposal, and “non stick” coatings are all techniques commonly used to avoid protein adsorption issues. In many cases, however, such as sensors and medical implants, the instrument cannot be readily cleaned or replaced, thus there exists a need for additional means to prevent nonspecific protein adsorption. The monolayer protected metal nanoparticles (MPMNs) created in Professor Stellacci’s group, if used in the form of a coating, could be a superior means by which to prevent protein adsorption onto materials. The purpose of this paper is to explore and assess the commercial potential of such nanostructured nanoparticle technology, with a focus on the cardiovascular medical market.

1.1 Background

Proteins are biological molecules that have the ability to adhere to almost any surface. The degree to which adsorption occurs is influenced a great deal by the nature of the surface. Proteins usually contain both hydrophobic and charged or hydrophilic parts; a combination of hydrophobic interactions and electrostatic attractions results in the nonspecific adsorption of proteins onto the surface. [2] Nonspecific protein adsorption is a problem that has been well documented in literature. Proteins have large degrees of freedom, they can change their conformation with a process called unfolding. When interacting with surfaces, proteins can alter their configuration to minimize or maximize the exposure of hydrophobic and hydrophilic segments. This property allows them to
adsorb on to a wide variety of surfaces, conforming to any type of surface, be it hydrophobic or hydrophilic. Thus, it is very difficult to stop adsorption entirely on a solid surface.

The creation of non-fouling surfaces that resist the uncontrolled adhesion of protein is of great importance for biomedical devices as well as any other area where the formation of a biofilm is detrimental to their performance. When the body interacts with an implant or other biomaterial it is interacting with or through the absorbed proteins. Upon adsorption a protein may unfold to a conformation that acts as a signal of damage and start inflammation. Thus, uncontrolled adhesion of protein in biomedical devices leads to harmful reactions in the body. For example, embolism formation is initiated by protein adsorption on to implanted biomaterials, and embolisms often result in strokes or heart attacks. The key to decreasing biofouling lies in the ability to reduce protein adsorption. Applications for protein resistant coatings include the control of wound healing around biomedical devices and the mitigation of bacterial infections on implants, catheters and contact lenses. For non-biomedical applications such as water purification, the build up of a biofilm leads to fouling of the filtration system.

In order to prevent protein adsorption on surfaces, we can turn to nature for clues, most notably the lotus leaf. The principle behind the lotus leaf affect is that the leaf contains ordered arrays of hydrophilic and hydrophobic regions that are spaced on the micron scale. When a water droplet hits the surface of the leaf, the droplet is attracted and repelled at the same time. The overall affect of such an interaction makes the droplet flow away thus achieving its self cleaning properties. The smallest size droplet of water is approximately 10 microns and thus the overall net interaction between the droplet and the hydrophilic and hydrophobic regions is zero. The sub-nanometer domains on the particle surfaces act similarly to this lotus leaf effect with respect to proteins. The ordered arrangement of hydrophobic and hydrophilic regions on the nanoparticle is so small compared to that of a protein (5 angstroms is approximately equally to 2 amino acids) that the protein is both attracted and repelled to the particle surface at the same time and consequently it is not thermodynamically favorable for protein adsorption to
occur. The following Figure 1 depicting the hydrophilic and hydrophobic regions is taken from Jackson et al., “Spontaneous assembly of subnanometer-ordered domains in the ligand shell of monolayer-protected nanoparticles” published in Nature Materials in April of 2004 regarding MPMNs:

![Figure 1](image)

**Figure 1.** Protein interaction with MPMN. A schematic drawing of a generic protein (top) interacting with and a domain phase separated nanoparticle (bottom). The pink and blue contour line on top of the nanoparticle show the hydrophobic and the hydrophilic regions of the particle respectively. The same colors are also used to represent the analogous regions in the protein. (Source: Jackson, et al. [1])

Different molecules in the ligand shell spontaneously self assemble, altering the outer shape and surface chemistry of the nanoparticle as shown in Figure 2 below. Such spontaneous self ordering of the ligand shell on such a small scale has not been observed prior to the aforementioned published paper. It is “the first synthesis materials class with controllable shape over a sub-nanometer length scale.” [3]
Figure 2. Images of MPMN. A) Scanning Tunneling Microscopy (STM) image of 2:1 octane thiol to mercaptopropionic acid coated gold nanoparticle. B) Another STM image of the 2:1 OT to MPA gold nanoparticle. C) Computer generated graphic of ordered domains on a 6nm in diameter nanoparticle. D) Section analysis of the line region on image B which shows phase separation between the longer hydrophobic OT molecules and the shorter hydrophilic MPA molecules. Domains are 5 angstroms wide encircling the nanoparticle. (Source: Jackson, et al. [1])

1.2 Benefits of MPMN

There are several benefits associated with MPMNs. A coating comprised of these nanoparticles would be transparent, nonconductive, biocompatible, and antimicrobial properties. That aside, the most notable benefit is the nanoparticle's ability to prevent nonspecific protein adsorption.

1.2.1 Protein Resistance

Proteins have the capability to attach to virtually any surface; the extent of adsorption is largely influenced by the character of the surface. Most proteins tend to adsorb in higher amounts on hydrophobic surfaces than on hydrophilic surfaces. Such a phenomenon has been studied by several research groups. Documented in Malmsten et al, proteins adsorbed at a considerably higher level on methylated silica versus non-methylated silica. The strong tendency for proteins to adsorb onto hydrophobic surfaces is due to the interactions between the substrate surface and the hydrophobic domains within a protein. [4,5] Electrostatic interactions also play an important role in protein adsorption when surfaces are charged. Most proteins have a net negative charge when in neutral pH, thus adsorption onto positively charged surfaces is strong. [2, 6] There are however examples
of strong adsorption of proteins onto surfaces of the same charge thus these electrostatic interactions alone cannot accurately describe the event of protein adsorption. [7]

Surfaces usually contain both hydrophobic and charged or hydrophilic regions, and a combination of hydrophobic interactions and electrostatic attractions results in the nonspecific adsorption on proteins onto the surface. [2] Of the two forces, hydrophobic interactions seem to be the dominating force.

Proteins are comprised of a long chain of smaller amino acid units which may be either hydrophilic or hydrophobic in nature. Proteins have a tremendous amount of conformational freedom to fold and refold according to its surrounds to minimize free energy. The amino acid unit of a protein is on the same scale of the domains on the nanoparticle, thus despite the conformational freedom of the protein, there will always be regions of attraction and regions of repulsion occurring during interaction with the nanostructured nanoparticle. As a result, the net attraction is zero, and no protein adsorption occurs.

Protein adsorption can be a desired event. For example, a bone scaffold implant that wants in growth of new bone into the structure. On the opposite end of the spectrum however, is the common case where protein adsorption onto surfaces is uncontrolled and undesirable. This is a major problem in medical and bio-technologies where nonspecific protein adsorption may interfere with specific interactions that occur with antigens, antibodies, haptens, ligands, etc. When nonspecific adsorption competes with specific interactions on a sensor for example, this may result in lower accuracy, low signal to noise ratio, and poor efficiency of the device. [2, 8] Another example of when undesired protein adsorption is a major issue are medical tubes and shunts that provide access to the interior of the body for a period of time. While the shunt may be temporary, protein adsorption occurs immediately and overtime the device may become clogged or the protein coat may provide a substrate for bacteria to proliferate.
In a time frame shorter than a second, proteins are already observed on biomaterial surfaces after implantation. [9] From seconds to minutes, a monolayer of protein is adsorbed onto most surfaces, then much later comes the arrival of cells. Adsorption of a protein layer onto a surface is often the precursor or first event of biofouling. Biofouling is the occurrence of cell, bacteria, and/or higher organism adhesion onto surfaces, an example of which is the build of plaque on teeth. [10] The build up of biological material onto implanted device surfaces may not only greatly reduce the effectiveness of the device, but also trigger a strong immune response. Associated with immune response may be acute or chronic inflammation, or bacterial infection which may ultimately result in the need to remove the implant. The inability to resist protein adsorption has been described as a major shortcoming in medical devices. [11]

1.2.2 Antimicrobial Effects

The antimicrobial effects of silver and copper core nanoparticles are an additional level of benefit. Silver ions have been repeatedly documented in literature as effective antimicrobials. [12-22] Active Ag⁺ ions are non toxic to human cells and are unique in being a long lasting biocide with high temperature stability and low volatility. [13] Should a protein actually manage to adsorb onto a MPMN coated surface, the metal core ions (of silver or copper) inhibit the growth of bacteria by deactivating the bacteria’s oxygen metabolism enzymes, essentially suffocating the bacteria as show in Figure 3 below.

![Figure 3. Activity of silver. Silver ions combine with the sulphydryl (-SH) groups of oxygenic metabolic enzymes to deactivate and block metabolism. (Source: Anson [23])](image)

The antimicrobial effect or activity of silver is dependent on the silver cation Ag⁺. Silver cations bind strongly to electron donor groups in biological molecules containing sulfur, oxygen, or nitrogen. Thus due to this antiseptic property, only few bacteria are intrinsically resistant to silver. [16] Silver, well known for this beneficial antimicrobial
property, has been applied to medical devices such as catheters. [17-19] Silver alloy-coated urinary catheters have been shown to reduce bacterial growth and be an effective agent in infection control. [17, 19]

1.3 Application Potential

There has been no commercialization of such monolayer protected metal nanoparticle technology as of yet. However, “antifouling-antimicrobial coating already represent a huge market that spans from military applications, to ships, stents, body implants and food containers.” [3] Potential applications are not limited to those described in this paper. The following examples do not constitute a complete list of all potential applications.

1.3.1 Medical Devices

Surfaces with protein resistance are very important in the context of blood contacting medical devices, contact lenses, and other products in contact with the human body. One of the major drawbacks of biomaterials after implantation is the biofilm that forms onto the surface enticing an immune response. Adhesion of protein and subsequent microorganisms leads to infections which are difficult to treat with antibiotics. [24] The following Table 1 details the incidence of infection amongst various medical implants and devices.

In a 1998 paper, Denstedt et al reports 100% infection for urinary tract catheters after three weeks use. [25] The only remedy after such an infection is the removal of the infected implant, a large expense in cost, time, and pain for the patient. Depending on the location of the implant in the body and the fluids it comes into contact with, potential for infection varies. An artificial vascular graft implant, for example, is in contact with blood or serum. Initially small proteins such as albumin, and immunoglobulin will likely absorb onto the surface creating a conditioning film. This conditioning film of proteins creates a favorable place for larger proteins such as fibrogen and fibronectin to adsorb. This may lead to the adhesion of blood cells and platelets initiating a blood coagulation
Table 1. Incidence of infection of various biomedical implants and devices (Source: Dankert et al. [2])

<table>
<thead>
<tr>
<th>Body site</th>
<th>Implant or device</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary tract</td>
<td>UT catheters</td>
<td>10-20</td>
</tr>
<tr>
<td>Percutaneous</td>
<td>CV catheters</td>
<td>4-12</td>
</tr>
<tr>
<td></td>
<td>Temporary pacemaker</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Short indwelling catheters</td>
<td>0.5-3</td>
</tr>
<tr>
<td>Peritoneal dialysis catheters</td>
<td>3-5</td>
<td></td>
</tr>
<tr>
<td>Subcutaneous</td>
<td>Cardiac pacemaker</td>
<td>1</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>Mammary prosthesis</td>
<td>1-7</td>
</tr>
<tr>
<td></td>
<td>Intrascleral lenses</td>
<td>0.13</td>
</tr>
<tr>
<td>Circulatory system</td>
<td>Prosthetic heart valve</td>
<td>1.88</td>
</tr>
<tr>
<td></td>
<td>Multiple heart valve</td>
<td>3.6</td>
</tr>
<tr>
<td></td>
<td>Vascular craft</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>Artificial heart*</td>
<td>40</td>
</tr>
<tr>
<td>Bones</td>
<td>Prosthetic Hip</td>
<td>2.6-4.0</td>
</tr>
<tr>
<td></td>
<td>Total knee</td>
<td>3.5-4</td>
</tr>
</tbody>
</table>

* From experiments in calves and sheep.

cascade resulting in thromobis, also known as a blood clot. [11] Regardless of location, the best means of addressing the issue is the prevention of infection in the first place which starts with the prevention of surface protein adsorption.

1.3.2 Biosensors

Literature exists in which non-specific protein adsorption is described as being an issue affecting the effectiveness of the biosensing device.

"A particularly common problem associated with glucose biosensors has been protein deposition and fibrous encapsulation known as biofouling limiting device lifetime. Protein deposition on biosensor membrane surfaces, a significant cause of biofouling, has been detrimental to biosensor performance. While this problem primarily affects long-term implants (more than 4 weeks), short-term implant (3-7 days) performance is impaired as well." [27]

As previously mentioned, when nonspecific protein adsorption competes with the specific interactions on a sensor, this may result in lower accuracy, low signal to noise ratio, and poor efficiency of the device. [2, 8] A thin protective layer that reduces or eliminates protein adsorption can help to prevent degradation of the measurement.
Specifically, sensors that measure intensity, wavelength, or electrical potential of an emission can benefit from a protective layer that is so thin that it does not interfere with the electrical potential.

1.3.3 Ocean & Maritime Transport

Fouling on the surface of sea going vessels results in corrosion of the surface, a decrease in hydrodynamic efficiency, and the introduction of foreign organisms to new locations. [28] Heavy fouling, such as barnacles, may reduce the responsiveness of a ship by causing it to sit lower in the water. The natural glues of attached organisms damage wood and fiberglass of hulls. Fouling also creates drag which slows the speed and efficiency of the vessel down and increases fuel costs. Fouling is a major problem and a priority of the marine shipping industry; tributyl tin (TBT) is one of the most common and effective chemical ingredients in antifouling paints. In recent years, however, due to concerns surrounding its toxicity and accumulation in the waters of harbors and shipping lanes, many countries around the world are phasing out the use of TBT. The International Maritime Organization (IMO) in 2003 called for a ban of TBT and other organotins for use on vessels to be banned in January 2008. [29] This leaves an opportune window in the marine coating industry to introduce new and effective antifouling coatings to market.

1.3.4 Additional Applications

Aside from the aforementioned major application areas, there are numerous uses for protein resistant coatings. MPMN coatings could be applied as a military grade coating to vehicles, equipment, and masks as a safeguard against biological warfare. Many miles of piping are subjected to fouling just like maritime vessels. Coated pipes may reduce the amount of maintenance and repaired required while increasing the quality of water that is delivered. Consumer products, everything from toothbrushes to socks and shoes to countertops could adopt the technology. Envision a line of products aimed for people with compromised immune systems. Friend Bob is has bacterial germs on his unwashed hands and comes to visit Jane, who is prone to illness at her home. The chair he sits in, the table they snack at, the counter tops he touches; Bob is potentially leaving a trail of
germs on all these objects that may infect Jane should she also touch the same areas, but if the chair, the table, and countertop were all coated with MPMN, the proteins on Bob’s hand would stay on his hand rather than transfer onto the given surface. Coating the most frequent germ spreading culprits, i.e. door knobs, public toilets, faucet knobs, bus/subway hand rails, could potentially help to minimize the spread of protein based illnesses. Potential applications are only limited by the imagination.
2. SYNTHESIS OF MPMNs

The MPMNs used in Prof. Stellacci’s laboratory were synthesized via a modified version of the Schriffin method where metal salt is dissolved into solution with targeted ligands mixed in. The nanoparticles are then precipitated out. By coating the nanoparticle with ligands, the result is a hybrid organic/inorganic material that is stabilized from coalescing and has good solubility properties. The advantages of this type of synthesis is that it creates a product that can be isolated, is stable in a solid phase, is soluble meaning it can be dried and redissolved many times, and can be dissolved and redispersed in many different matrices. The main disadvantage is that it is difficult to produce these materials on a large scale, potentially making it an expensive process.

Generally, what is happening is that the thiol terminated alkanes are dissolved in toluene, while the gold salt is dissolved in water. With vigorous stirring, the metal salt is transfers into the organic phase. The two solutions require a phase transfer agent, such as NaBH₄, which is soluble in both toluene and water. The agent is rapidly added to nucleate nanocrystals.

![Figure 4. Schematic of MPMN synthesis reaction](image-url)

Figure 4. Schematic of MPMN synthesis reaction

<table>
<thead>
<tr>
<th>H₂O</th>
<th>H₄AuCl₄ (gold salt)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toluene</td>
<td>HS [ S ] + H₄AuCl₄</td>
</tr>
<tr>
<td>Toluene, H₂O</td>
<td>nanoparticle</td>
</tr>
</tbody>
</table>

- add Sodium Borohydride, NaBH₄
Nanoparticles are formed through nucleation and growth, all the while influenced by stabilization. Stabilization of the nanoparticles occurs through two different means, first through electrostatic repulsion, and second through steric hindrance. Stabilization of the system is integral to the process. In the early stages, stabilization is a balance between competing forces, Van der Waals (VDW) and repulsion. If the electrostatic repulsion between the like charged components are not strong enough to counter the VDW attraction between neutralized gold atoms, then the gold will coalesce and precipitate out of solution. [30] Thus it is possible to "crash" an experiment by added too much sodium borohydride at once. The following series of Figure 5 depict the stabilization of the solution and formation process at various stages of nanoparticle synthesis.

Since the sulfilated thiol ligands form strong interactions with gold, there is a loose form of control over the size of the nanoparticles that can be achieved through the concentration of thiols added to the reaction. The more thiols added, the sooner stabilization switches to steric hindrance and the smaller the overall size of the gold nanoparticle core. [30] Figure 6 describes this nanoparticles size relationship.

\[
\text{[thiol]} = \# \text{ Au surface atoms} \quad \text{R = Radius of nanoparticle in terms of Au atoms}
\]

\[
\begin{align*}
\frac{\# \text{ surface atoms}}{\# \text{ total atoms}} &= \frac{\text{Surface Area}}{\text{Volume}} = \frac{4\pi R^2}{4/3 \pi R^3} = \frac{1}{R}
\end{align*}
\]

This relates the percentage of Au on the surface, and the thiol concentration.

Have a form of control over nanoparticle size; the concentration of the thiols can control overall radius.

**Figure 6.** Description of the relationship between thiol concentration and nanoparticle size.
Initial Stabilization

Figure 5a. Initial stabilization via repulsive forces. In the Toluene phase, negative forces from ligand ends and Br-, in the water phase, positive ions from Au+. Toluene and water are immiscible without a phase transfer agent.

Transition

Figure 5b. Addition of transfer agent. Presence of NaBH₄ allows 2 phases to mix and forms Na⁺ and BH₄⁻ ions.

Figure 5c. Interaction of phases. The ions from transfer agent NaBH₄ begin to neutralize Au⁺ ions and Br⁻ ions. Also thiolated ligands begin to form bonds with Au. Additionally Br⁻ ions begin forming diffuse layer around Au⁺ ions.

Final Stabilization

Figure 5d. Neutralized Au atoms begin to cluster and aggregate. Au becomes neutral via the ligands and/or NaBH₄. Aggregation occurs by VDW attraction, but slowed by the presence of other components experiencing electrostatic repulsion.

Figure 5e. Final stabilization through steric hindrance. Further continued clustering and growth of nanoparticle stopped by steric hindrance from the ligand chains that prevent more material from reaching the core.
Example:

Gold MPMNs can be synthesized with various material components in varying composition as detailed in Table 2. For each stoichiometry detailed, 354 mg (0.9 mmol) of HAuCl₄·3H₂O was dissolved in 50 ml of water and 2.187 (4 mmol) of BrN((CH₂)₇CH₃)₄ was dissolved in 80 ml of toluene. The two phases are then mixed and stirred for 30 minutes. Mixtures of the specific ligand composition as specified in Table 2 are then added into the solution after the color from the gold salt has transferred completely to the organic phase. Ligand abbreviations are detailed in Table 3. The solution is then allowed to react for ten minutes until it acquires a typically characteristic white in color appearance. A 10nM solution (30mL) of NaBH₄ is then added a drop at a time over the course of one hour. After this addition is complete, the solution is then stirred for two hours. The phases are separated and the organic phase is collected, reduced to 10 ml, diluted with 100 ml of absolute ethanol, and then placed in a refrigerator overnight. The precipitate is then collected via vacuum filtration using quantitative paper filters, and then washed thoroughly with water, acetone, and ethanol. This entire process should yield approximately 100 mg of collected black powder. Nanoparticles soluble in ethanol are collected via vacuum evaporation of the ethanol solution and then thoroughly rinsed with water, acetone, and toluene.
Table 2. Chart detailing the compositions for various ligand mixtures and the associated domain morphologies.

<table>
<thead>
<tr>
<th>Metal</th>
<th>Ligand 1</th>
<th>Ligand 2</th>
<th>Metal : Ligand Molar Ratio</th>
<th>Ligand 1 : Ligand 2 Molar Ratio</th>
<th>Morphology</th>
<th>Peak to Peak Spacing (nm)</th>
<th>Solubility</th>
<th>Solubility</th>
<th>Average Core Size (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Au</td>
<td>HT</td>
<td>MPA</td>
<td>1:1</td>
<td>2:1</td>
<td>Ripples</td>
<td>0.95</td>
<td>Highly soluble</td>
<td>Soluble</td>
<td>3.5</td>
</tr>
<tr>
<td>Au</td>
<td>OT</td>
<td>MPA</td>
<td>1:1</td>
<td>2:1</td>
<td>Ripples</td>
<td>1</td>
<td>Highly soluble</td>
<td>Insoluble</td>
<td>3.8</td>
</tr>
<tr>
<td>Au</td>
<td>DT</td>
<td>MPA</td>
<td>1:1</td>
<td>2:1</td>
<td>Ripples</td>
<td>1</td>
<td>Highly soluble</td>
<td>Slightly soluble</td>
<td>3.5</td>
</tr>
<tr>
<td>Au</td>
<td>DDT</td>
<td>MPA</td>
<td>1:1</td>
<td>2:1</td>
<td>Ripples</td>
<td>0.55-.75</td>
<td>Highly soluble</td>
<td>Insoluble</td>
<td>3.5</td>
</tr>
<tr>
<td>Au</td>
<td>OT</td>
<td>MUA</td>
<td>1:1</td>
<td>2:1</td>
<td>Ripples</td>
<td>1</td>
<td>Insoluble</td>
<td>Highly soluble</td>
<td>3.7</td>
</tr>
<tr>
<td>Au</td>
<td>DDT</td>
<td>MUA</td>
<td>1:1</td>
<td>2:1</td>
<td>Ripples</td>
<td>0.62</td>
<td>Insoluble</td>
<td>Soluble</td>
<td>3.7</td>
</tr>
<tr>
<td>Au</td>
<td>OT</td>
<td>MPA</td>
<td>1:1</td>
<td>1:2</td>
<td>Ripples</td>
<td>0.66</td>
<td>Highly soluble</td>
<td>Slightly soluble</td>
<td>3.6</td>
</tr>
<tr>
<td>Au</td>
<td>OT</td>
<td>MPA</td>
<td>1:1</td>
<td>2:1</td>
<td>Ripples</td>
<td>1</td>
<td>Highly soluble</td>
<td>Slightly soluble</td>
<td>3.8</td>
</tr>
<tr>
<td>Au</td>
<td>OT</td>
<td>MPA</td>
<td>1:1</td>
<td>10:1</td>
<td>Domains</td>
<td>N/A</td>
<td>Highly soluble</td>
<td>Slightly soluble</td>
<td>3.5</td>
</tr>
<tr>
<td>Au</td>
<td>OT</td>
<td>MUA</td>
<td>1:1</td>
<td>2:1</td>
<td>Ripples</td>
<td>1</td>
<td>Insoluble</td>
<td>Highly soluble</td>
<td>3.7</td>
</tr>
<tr>
<td>Au</td>
<td>OT</td>
<td>MUA</td>
<td>1:1</td>
<td>5:1</td>
<td>Domains</td>
<td>N/A</td>
<td>Slightly soluble</td>
<td>Highly soluble</td>
<td>3.6</td>
</tr>
<tr>
<td>Metal</td>
<td>Ligand 1</td>
<td>Ligand 2</td>
<td>Metal : Ligand Molar Ratio</td>
<td>Ligand 1 : Ligand 2 Molar Ratio</td>
<td>Morphology</td>
<td>Peak to Peak Spacing (nm)</td>
<td>Solubility</td>
<td>Average Core Size (nm)</td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>----------</td>
<td>----------</td>
<td>----------------------------</td>
<td>---------------------------------</td>
<td>------------------</td>
<td>--------------------------</td>
<td>----------------</td>
<td>------------------------</td>
<td></td>
</tr>
<tr>
<td>Au</td>
<td>OT</td>
<td>MUA</td>
<td>1:1</td>
<td>20:1</td>
<td>Domains</td>
<td>N/A</td>
<td>Highly soluble</td>
<td>Insoluble</td>
<td>3.6</td>
</tr>
<tr>
<td>Au</td>
<td>OT</td>
<td>MPA</td>
<td>1:1</td>
<td>2:1</td>
<td>Ripples</td>
<td>1</td>
<td>Highly soluble</td>
<td>Insoluble</td>
<td>3.8</td>
</tr>
<tr>
<td>Au</td>
<td>OT</td>
<td>MPA</td>
<td>2:1</td>
<td>2:1</td>
<td>Ripples</td>
<td>0.82</td>
<td>Highly soluble</td>
<td>Insoluble</td>
<td>4.3</td>
</tr>
<tr>
<td>Au</td>
<td>OT</td>
<td>MPA</td>
<td>5:1</td>
<td>2:1</td>
<td>Ripples</td>
<td>0.73</td>
<td>Highly soluble</td>
<td>Slightly soluble</td>
<td>5.1</td>
</tr>
<tr>
<td>Au</td>
<td>OT</td>
<td>MUA</td>
<td>1:1</td>
<td>2:1</td>
<td>Ripples</td>
<td>1</td>
<td>Insoluble</td>
<td>Highly soluble</td>
<td>3.7</td>
</tr>
<tr>
<td>Au</td>
<td>OT</td>
<td>MUA</td>
<td>3:1</td>
<td>2:1</td>
<td>Ripples</td>
<td>0.8</td>
<td>Insoluble</td>
<td>Highly soluble</td>
<td>4.9</td>
</tr>
<tr>
<td>Au</td>
<td>HT</td>
<td>APT</td>
<td>1:1</td>
<td>1:2</td>
<td>Ripples</td>
<td>0.6</td>
<td>Highly soluble</td>
<td>Insoluble</td>
<td>3.5</td>
</tr>
<tr>
<td>Au</td>
<td>OT</td>
<td>APT / MUA</td>
<td>1:1</td>
<td>1:1:1</td>
<td>Domains</td>
<td>N/A</td>
<td>Insoluble</td>
<td>Soluble</td>
<td>3.6</td>
</tr>
<tr>
<td>Au</td>
<td>OT</td>
<td>MPA</td>
<td>3:1</td>
<td>30:1</td>
<td>N/A</td>
<td>Highly soluble</td>
<td>Insoluble</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Au</td>
<td>OT</td>
<td>MPA</td>
<td>1:1</td>
<td>Substituted</td>
<td>Partial ripples</td>
<td>0.75</td>
<td>Insoluble</td>
<td>Insoluble</td>
<td>3.6</td>
</tr>
<tr>
<td>Ag</td>
<td>OT</td>
<td>MPA</td>
<td>1:1</td>
<td>2:1</td>
<td>Ripples</td>
<td>0.92</td>
<td>Slightly soluble</td>
<td>Slightly soluble</td>
<td>3.8</td>
</tr>
</tbody>
</table>
**Table 3.** Legend for ligand abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Ligand</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPA</td>
<td>HOOC-(CH(_2))(_2)-SH (mercaptopropionic acid)</td>
</tr>
<tr>
<td>MUA</td>
<td>HOOC-(CH(<em>2))(</em>{10})-SH (mercapto undecanoic acid)</td>
</tr>
<tr>
<td>APT</td>
<td>H(_2)N-C(_6)H(_4)-SH (4-amino thiophenol)</td>
</tr>
<tr>
<td>HT</td>
<td>CH(_3)-(CH(_2))(_5)-SH (hexanethiol)</td>
</tr>
<tr>
<td>OT</td>
<td>CH(_3)-(CH(_2))(_7)-SH (octanethiol)</td>
</tr>
<tr>
<td>DT</td>
<td>CH(_3)-(CH(_2))(_9)-SH (decanethiol)</td>
</tr>
<tr>
<td>DDT</td>
<td>CH(_3)-(CH(<em>2))(</em>{11})-SH (duodecanethiol)</td>
</tr>
</tbody>
</table>
3. INTELLECTUAL PROPERTY

As of Feb 28, 2005, inventors Francesco Stellacci and Alicia M. Jackson of MIT filed with the United States Patent and Trademark Office (USPTO) for a patent entitled “Nanoparticles Having Sub-Nanometer Features” with regards to MPMNs. [31] The field of invention claim is as follows:

“The present invention relates to nanoparticles having sub-nanometer surface features, and in particular to monolayer-protected nanoparticles that exhibit spontaneous assembly of ordered surface domains.”

In the public domain in monolayer protected metal nanoparticles are the following published papers. These papers are only a selection of related articles and do not represent a complete list of all relevant publications.


All the papers address the synthesis of ligand capped nanoparticles, however, only the first paper, Jackson et al relates specifically to MPMNs as described in the patent.

Due to the extent of intellectual property that exists regarding nanoparticle technology, this paper does not attempt to analyze any potential infringement or defensibility of the aforementioned filed patent. The focus is solely on describing the claims the filed patent has made.
Intellectual property aspects of the invention include the monolayer protected article and the method of creating a monolayer protected surface. An article has a surface, of which at least a portion has a local radius of curvature of approximately 1000nm or less and a monolayer coating on the portion. The monolayer contains a plurality of ligands that are organized in ordered domains which have a characteristic size of 10nm or less. Claims cover surface radius curvatures of between 1 to 10nm, 10 to 100nm, and 100-1000nm in scale. A surface is comprised of a metal, semiconductor material, a polymer, a ceramic, or any such composite of the above. Claims also cover the characteristic size of domains range 0.2 to 1nm, 1 to 5nm, and 5 to 10nm in scale. For example the surface could be a metal nanoparticle, and the surface may be textured. The ordered domains may align in parallel strips or a mosaic of roughly hexagonal domains on such a portion.

The monolayer coating may contain two ligands differing in length. Ligands, as listed in Table 4 below, may be independently selected and connected to the portion by a chemical group, as listed in Table 4 below, to be synthesized in any ligand to chemical group combination.

Table 4. Chart listing various ligand material independently selected to be combined with an independently selected chemical group.

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Chemical Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>mercaptobenzyl ether acid</td>
<td>silane</td>
</tr>
<tr>
<td>mercapto undecanoic acid</td>
<td>carboxylate</td>
</tr>
<tr>
<td>4-amino thiophenol</td>
<td>thiol</td>
</tr>
<tr>
<td>hexanethiol</td>
<td>phosphonate</td>
</tr>
<tr>
<td>octanethiol</td>
<td>nitrile</td>
</tr>
<tr>
<td>decanethiol</td>
<td>isonitrite</td>
</tr>
<tr>
<td>duodecanethiol</td>
<td>hydroxamate</td>
</tr>
<tr>
<td>acid chloride</td>
<td>anhydride</td>
</tr>
<tr>
<td>sulfonyle</td>
<td>sulfonyl</td>
</tr>
<tr>
<td>phosphoryl</td>
<td>phosphoryl</td>
</tr>
<tr>
<td>hydroxyl</td>
<td>amino acid</td>
</tr>
</tbody>
</table>

The ligand may also include an endgroups having a functionality characterized by one or more of the following: ionic, non-ionic, polar, non-polar, halogenated, alkyl, alkenyl.
alkynyl and aryl. The ligand may also have a tether characterized by one or more of the following: polar, non-polar, halogenated, positively charged, negatively charged, and uncharged. The tether might be, for example, saturated or unsaturated, linear or branched, alkyl group or aromatic group. The monolayer coating when deposited on a flat surface exhibit contact angles with water that differ by at least, 1 degree, 3 degrees, 5 degrees, or 7 degrees between two ligands. At least 2 of the plurality of ligands may have differing hydrophilicites.

The method of creating a monolayer protected surface includes providing a surface having a local radius of curvature of less than or approximately equal to 1000nm and attaching a first ligand and a second ligand to the surface. The first and second ligands are attached so as to form domains that have a characteristic size of less than or approximately equal to 10nm. Similar claims also cover surface radius curvatures of between 1 to 10nm, 10 to 100nm, and 100-1000nm in scale for this method. Also the characteristic size of domains range 0.2 to 1nm, 1 to 5nm, and 5 to 10nm in scale for this method. The provided surface may include textured surfaces, and providing a textured surface may involve sanding, chemical etching, sandblasting, or dewetting. Providing a surface may also include plasma etching the surface to generate hydroxyl groups.
4. ECONOMIC ANALYSIS

Application of MPMNs for the prevention of protein adsorption would be used in the form of a coating. The follow is a cost analysis for a coating comprised of octanethiol gold nanoparticles. In order to do an economic analysis of the costs associated with the synthesis of this MPNM, it is necessary to calculate the amount of surface area a single batch yield can cover. In order to do that calculation, coating thickness and the relative density of the nanoparticle coating must be determined. To calculate the relative density, a weighted density average is calculated by summing the mass of gold for its given volume and the mass of the ligand for its given volume then dividing by the total nanoparticle volume. The density of gold is 19,300 kg/m³ and the density of octanethiol is 843 kg/m³. The gold core of the nanoparticle is approximated at 5nm in diameter, while it is estimated that ligands add an addition 1.5nm in length all around. In a coating however, the ligands on the surface of the nanoparticles may interlock or weave into shared space like locked fingers of two hands. This phenomenon is known as interdigitation. 1nm is subtracted off the total nanoparticle size to reflect the occurrence of interdigitation. This leaves a relative nanoparticle size of 7nm in diameter or 3.5nm in radius, and yields an overall nanoparticle density of 7569 kg/m³. The calculation for the overall density is shown in Figure 7 below.

\[
\text{Overall nanoparticle density} = \frac{4/3\pi r_1^3 \rho_{\text{gold}} + 4/3\pi (r_2^3-r_1^3) \rho_{\text{ligand}}}{4/3\pi r_2^3}
\]

Relative nanoparticle size = 5 nm diameter gold core + (2 x 1.5 nm ligand) - 1 nm interdigitation

\( r_1 = 2.5 \text{ nm}, \ r_2 = 3.5 \text{ nm} \)
\( \rho_{\text{gold}} = 19,300 \text{ kg/m}^3 \)
\( \rho_{\text{ligand}} = 843 \text{ kg/m}^3 \)
\( \rho_{\text{overall}} = 7569 \text{ kg/m}^3 \)

**Figure 7.** Calculation of overall density of nanoparticles when in a coating.
Assuming the coating is 4 nanoparticle layers in thickness; (surface area) x (coating thickness) x (relative density) = mass needed to cover the given area. Thus for the given parameters:

\[ 1 \text{ m}^2 \times (7 \text{ nm} \times 4) \times 7469 \text{ kg/m}^3 = 0.212 \text{ g} \quad \text{(to coat area of 1 m}^2) \]

Each batch produces \( \sim 100 \text{ mg} = 0.1 \text{ g} \), therefore \( 0.212 / 0.1 = 2.12 \) batches to coat \( 1 \text{ m}^2 \) or equivalently, each batch can coat \( 0.472 \text{ m}^2 \).

Now that we know we require approximated 0.212 g of synthesized nanoparticle in order to coat a square meter of area, we can associate a cost to the production of these nanoparticles. The following Table 5 lists the prices associated with the purchase of each material component for the process and the amount needed to carry out the synthesis.

**Table 5. Cost of Materials needed for MPMN synthesis [32]**

<table>
<thead>
<tr>
<th>Material</th>
<th>Price</th>
<th>Quantity</th>
<th>Amount Needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Octanethiol</td>
<td>$48.00</td>
<td>2 liters</td>
<td>131.67 mg</td>
</tr>
<tr>
<td>Hydrogen tetrachloroaurate hydrate (HAuCl₄)</td>
<td>$363.50</td>
<td>5 grams</td>
<td>355 mg</td>
</tr>
<tr>
<td>Tetracetylammomium bromide (Br[N(CH₃(CH₂)₇]₄)</td>
<td>$72.40</td>
<td>25 grams</td>
<td>2187.2 mg</td>
</tr>
<tr>
<td>Sodium Borohydride (NaBH₄)</td>
<td>$176.80</td>
<td>100 grams</td>
<td>378 mg</td>
</tr>
<tr>
<td>Toluene</td>
<td>$39.00</td>
<td>2 liters</td>
<td>80 mL</td>
</tr>
<tr>
<td>Ethanol</td>
<td>$89.00</td>
<td>2 liters</td>
<td>100 mL</td>
</tr>
<tr>
<td>DI water</td>
<td>$29.99</td>
<td>1 gallon</td>
<td>80 mL</td>
</tr>
</tbody>
</table>

*Prices quoted from Sigma Aldrich catalogue*

With the pricing information and the amount of material needed per synthesis, cost per batch can be calculated in the following way:
If technician wage is $20/hr and batch process requires 4 hrs total, additional $80 per batch.

**Material + Labor = $112.615 / batch**

At $42.615 per batch and 2.12 batches, the pure materials cost associated with coating 1 m² is $90.34. Factoring labor into the cost and coating 1 m² becomes $259.94. This price only accounts for material and labor costs however. There are additional costs associated with producing MPMNs, some of which are fixed initial start up costs such as equipment, and some are continuous costs of equipment that needs to be restocked from time to time, such as filter paper. The following Table 6 lists some of the additional costs.

**Table 6.** Additional costs associated with producing MPMN [33]

<table>
<thead>
<tr>
<th>Equipment Cost</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Start-up costs</strong></td>
<td></td>
</tr>
<tr>
<td>1 roundabout flask</td>
<td>$ 52.00</td>
</tr>
<tr>
<td>3 cylinder beakers</td>
<td>$ 48.97/ 6 pk</td>
</tr>
<tr>
<td>1 titration apparatus</td>
<td>$ 100.00*</td>
</tr>
<tr>
<td>1 glass dish</td>
<td>$ 118.00/ 2 pk</td>
</tr>
<tr>
<td>1 stir machine / stir bar</td>
<td>$ 220 , $ 6.25 ea</td>
</tr>
<tr>
<td>3 pipettes</td>
<td>$ 285.39/ 6 pk</td>
</tr>
<tr>
<td>1 balance scale</td>
<td>$ 2945.00</td>
</tr>
<tr>
<td>1 RotoTap machine</td>
<td>$ 2000.00*</td>
</tr>
<tr>
<td>Refrigerator</td>
<td>$ 2625.00</td>
</tr>
<tr>
<td>Goggles</td>
<td>$ 6.00</td>
</tr>
<tr>
<td><strong>Continuous costs</strong></td>
<td></td>
</tr>
<tr>
<td>Filter paper</td>
<td>$ 141.00/ 100 sht</td>
</tr>
<tr>
<td>Latex gloves</td>
<td>$ 10.00/ 100 gl</td>
</tr>
</tbody>
</table>

*Prices quoted from Cole-Parmer Catalogue*

*price estimate
To reflect initial start up costs of equipment in addition to continual costs of material and labor, cost per batch can be calculated using the formula shown below:

\[
\text{Cost per Batch} = \frac{\text{Equip Cost} + \text{(#of Batches'x Mat'l & Labor Cost)}}{\text{#of Batches}}
\]

Table 7 below calculates the cost per batch in relation to the number of batches and takes into account fixed and continuous costs.

Table 7. Cost per Batch calculated with fixed and continuous costs

<table>
<thead>
<tr>
<th>Equipment Cost</th>
<th>Material &amp; Labor Cost</th>
<th>Number of Batches</th>
<th>Cost per Batch</th>
</tr>
</thead>
<tbody>
<tr>
<td>$ 6,557.61</td>
<td>$ 112,615</td>
<td>1</td>
<td>$ 8,670.23</td>
</tr>
<tr>
<td>(1 day)</td>
<td>6</td>
<td>$ 1,538.88</td>
<td></td>
</tr>
<tr>
<td>(1 week)</td>
<td>30</td>
<td>$ 397.87</td>
<td></td>
</tr>
<tr>
<td>(2 weeks)</td>
<td>60</td>
<td>$ 255.24</td>
<td></td>
</tr>
<tr>
<td>(1 month)</td>
<td>120</td>
<td>$ 183.93</td>
<td></td>
</tr>
<tr>
<td>(3 month)</td>
<td>360</td>
<td>$ 136.39</td>
<td></td>
</tr>
<tr>
<td>(6 month)</td>
<td>720</td>
<td>$ 124.50</td>
<td></td>
</tr>
<tr>
<td>(1 year)</td>
<td>1440</td>
<td>$ 118.56</td>
<td></td>
</tr>
</tbody>
</table>

Given the process requires 4 hrs of labor, at most 6 batches can be run in a day. The numbers chosen for number of batches reflect a time scale of a day, week, month, and year. Economies of scale are clearly in play, the more batches produced, the cost associated per batch is drastically reduced. Figure 8 below depicts this economy of scale.
While the costs associated with a batch production do not seem extraordinarily high, $90.34/m² in pure material costs is still high relative to that of alternatives such as PEG which has an estimated cost of ~$10/m². Despite this price disparity, the benefit and effectiveness of MPMN coatings at prevent protein adsorption in comparison to existing alternative technologies will likely trump the utility of cost.
5. ALTERNATIVE PROTEIN CONTROL TECHNOLOGIES

Control of nonspecific protein adsorption has been intensely studied for the years. The key requirement of a surface modification or coating that will come in contact with the body is that it must enhance the biocompatibility of the material without compromising the mechanical properties of the bulk material. MPMNs applied as a coating would satisfy this criterion. Use of poly(ethylene glycol), polysaccharides, and phospholipids are techniques that have all been used to modify surfaces that have achieved success in reducing protein adsorption. The main shortcoming of such surface modifications are that they have limited adhesion properties to many surface, are porous and may trap impurities over time, and react with many biomolecules making it less biocompatible. MPMN coatings address all these weakness in that it prevents protein adsorption better than any other known material, does not react with other biomolecules, and has optimal adhesion to a broad range of materials.

5.1 Poly(ethylene glycol)

Poly(ethylene glycol) (PEG) is hydrophilic and highly solvated in aqueous solutions. Established in work by Nagaoka et al, protein adsorption is dependent on the PEG chain length and brush density, and a dense, stable attached PEG layer on a surface can effectively reduce protein adsorption and cell adhesion. [34-36] Associated with chain length are exclusion effects, chain mobility, and protein size. For each molecular weight of PEG is a corresponding minimum surface density in order to significantly reduce protein adsorption. [37] If the PEG chain is too short, proteins can still sense the surface and come in contact with the surface or adsorb directly onto of the PEG layer as depicted below in Figure 9.

![Figure 9. Compression of PEG layer by protein adsorption. (Source: Bergström et al [38])](image-url)
The most common technique for PEG surface modification is through covalent attachment of a linear PEG chain. One end of the chain is modified with an active functional group such as methacrylate, and then attached to an insoluble surface. The result is a very stable surface modification due to the covalent bonding. [39] Another modification technique is through copolymerization of PEG with an anchor block such as (PEO)$_m$ – (PPO)$_n$ – (PEO)$_m$ where poly(ethylene oxide) or PEO is the same polymer as PEG but of a higher molecular weight. Poly(propylene oxide) or PPO is a hydrophobic block where its chain length largely determines the stability of the interaction between the surface and such a poloxamer surfactant. In this modification, however, the surface interaction is not covalent and the adsorption of PEO to the surface is reversible and potentially allows proteins to interact more strongly with the surface, leading eventually to the displacing of the PPO block. A method to increase the stability of PEO-PPO-PEO copolymer surface modification is to add a hydrophobic priming layer for the copolymer to covalently bind. [37, 40]

Figure 10. Schematic of PEO-PPO-PEO block copolymer grafting employing a COP350 priming layer. (Source: Einerson [37])

5.2 Polysaccharides

Another established method to reduce protein adsorption is surface modification with polysaccharides. Polysaccharides are both hydrophilic and noncharged in nature. Dextran, a polyglucose composed of 1,6-glucosidic linkages, and ethylhydroxyethylcellulose (EHEC), a nonionic cellulose ether are used commercially to improve surface protein resistance. A study by Osterburg et al compared dextran to PEG found that side-on attachment of dextran was equally effective at reducing the adsorption of fibrinogen on a hydrophobic surface. [41] Side on attachment is done by oxidizing the polysaccharide to generate aldehyde groups first, then coupling the oxidized polymer.
with a PEI treated surface. End on attachment of dextran is a direct coupling of the polysaccharide to the PEI treated surface. Such an attachment results in much inferior protein resistance capabilities because, while side-on attachment creates a thinner hydrophilic layer, it gives better overall surface coverage. EHEC is also exposed to a mild oxidation treatment to produce aldehyde groups prior to coupling with a PEI surface. Inefficiency of polysaccharide coatings to prevent protein adsorption is attributed to inadequate surface coverage. [42, 43] Layer thickness of the coating does not appear to be important in the effectiveness of polysaccharides preventing protein adsorption. [41]

5.3 Phospholipids
As in the case of PEG and polysaccharides, a tightly packed layer of phospholipids has been documented in literature to be effective in preventing protein adsorption on the modified surface. On hydrophobic surfaces, the amphiphilic phospholipids adsorb in a monolayer with the polar head oriented outwards the bulk solution and the hydrocarbon tail at the surface. The layer can be created by adsorption from an aqueous solution. [2] Phospholipids containing polymerizable groups, particularly synthetic polymers with polar group phosphorylcholine (PC), have been found to be highly successful at reducing protein adsorption. PC based coatings can be created in situ via polymerization of monomers at the surface or through the more tradition means of addition onto the surface. A study by Kingshott et al, showed a substantial drop in albumin adsorption and also reductions in corneal epithelial cell attachment, migration and proliferation, and platelet adhesion onto a silicone rubber substrate coated with poly(2-methacroylethyl phosphorylcholine (pMPM). [42] Despite these successes, it was also noted that there was still “significant bioadhesion” which occurred. In a process referred to as self assembled biomimetic membrane, such copolymers interact with phospholipids to form bilayer structures on top of MCM copolymer. [44] As shown in Figure 11 below, the interaction between the MCM copolymer needs to be stronger between the phospholipids than the proteins in order for such a bilayer to form. Ishihara et al proposed that the very high water content of the MCM based polymers is an important factor in the protein resistibility of such surfaces. [45]
5.4 Comparison of Effectiveness

Preliminary results show superior protein resistance by nanostructured nanoparticles comparatively to nanoparticles coated by PEG or Dextran. The following Figure 12 below depicts the results of the comparative study.

![Graph measuring the intensity of fluorescence tagged proteins on various nanoparticle surfaces](Source: Stellacci [3])

In this study, the first two nanoparticles were coated with PEG and dextran respectively. The next two particles are nanostructured nanoparticles that serve as control to understand the role of curvature and ripples in nanoparticles. The final three are
nanostructured nanoparticles with hydrophobic/hydrophilic ripples differing in size and ripple spacing. Equal amounts of coated gold nanoparticles were incubated with fluorescent labeled fetal bovine serum (FBS) which contains multiple proteins. After filtering and washing of the nanoparticles, fluorescence was measured. The higher the intensity of fluorescence is an indication of more adsorbed proteins on the nanoparticle surfaces. The nanostructured nanoparticles with ripples outperformed all other samples. From the control samples, we can see that curvature and ripples play a role in preventing protein adsorption, as these samples performed as well as PEG and dextran, however, this role is minor compared to the effect of the alternation of hydrophobic and hydrophilic domains. These results have also been confirmed with radio labeling tests.
6. MARKET ASSESSMENT

6.1 Overview

Although potential applications for MPMN coatings are extremely numerous, targeting high end products or serving as an enabler material would still provide the best revenue potential. A coating preventing protein adsorption would likely add the most value to products in the following three major markets:

1) Medical Device Implants
2) Biosensors
3) Marine Transport

6.1.1 Medical Device Implants:

According to a study by the Freedonia Group on the outlook of implantable medical devices, it states that in 2003, medical implants were a $14.6 billion industry, and is growing at approximately 11% annually through 2007. Amongst the best prospects for growth are implantable cardiac defibrillators (ICDs), drug-eluting stents, bioengineered tissue, neurological stimulators, and cochlear and retinal implants. [46]

6.1.2 Biosensors

According to a report by Fuji-Keizai studying the developments of the biosensor industry, the worldwide market for biosensors was $7.3 billion in 2003. The market is projected to grow to approximately $10.8 billion in 2007, a growth rate of about 10.4% annually. [47] While medical applications of biosensors dominate, a fast growing area of biosensor use includes Bio-Defense. Biosensors have also traditionally been used in bio/pharmaceutical research, food & beverage handling, and environmental detection.

6.1.3 Ocean & Maritime Transport:

The majority of global trade products are carried from destination to destination via marine shipping. The demand and growth of the marine shipping industry is cyclical and closely tied to the global economy. Due to global economic growth led by the United States, China, and Southeast Asian economies, global oil consumption experienced above
average growth for 2004. Forecasted by the International Energy Agency (IEA) is a 2.1% increase in oil demand. This should correspond to a 3.5 to 4.0% increase in tanker demand. [48] Additionally, strong economy should also correlate to increased exports and/or imports thus increasing the need for oceanic transport. Fouling is estimated to cost the marine shipping industry over $5 Billion each year. [28] In terms of the marine coating industry, according to the Freedonia Group, maintenance coatings for commercial ships remain the largest segment of the US marine coatings market at 70% of the market share. Other key segments of marine coatings are offshore drilling rigs and platforms at 20%, and yacht/recreational boats at 10%. Overall growth in the market has been pegged at 3.7% annually in 2002. [49]

6.2 Entering the Medical Device Industry
According to senior medical products analyst Robert C. Faulkner, observation of the medical device industry indicates three key points. 1) Valuable franchises are most likely to be derived from proprietary breakthrough products. 2) Barriers to a new technology's entry into the market, especially with regard to sales and distribution, are high for products that offer only incremental improvements over another competitors' products. 3) Most markets are too small to support a new company. [50]

Three main variables influence the likelihood of a technology’s success in the industry: clinical value, barrier to entry, and market size. Clinical value is the extent to which the technology addresses an unmet clinical need and is what overall drives the enter market. Barriers to entry include regulatory and proprietary issues that must be overcome. Market size is the extent to which there is demand for the given product. The following Figure 13 below plots clinical value versus barrier to entry to access the appeal of technologies.
“High” clinical value can be defined by the following characteristics:

- Quantified improvements in patient outcome such as increased lifespan, physical functionality, or the ability to function independently.
- Reductions in procedural risks such as mortality and morbidity.
- Improvements in recovery time measured in days or weeks, not hours.
- Value pricing at more than $1000 per device for a surgical procedure. (Source: Faulkner [50])

“High” for barriers to entry can be defined by the following assumptions:

- The ability to achieve critical mass in sales and distribution defines the midpoint of barriers to entry.
- Barriers that may be more important than achieving critical mass can be found in Quadrants #1 and #2 and include a significant lead to market or ownership of patents or know-how that blocks other companies from marketing a similar product.
- A technology that only provides a differentiated approach to an undifferentiated outcome is generally not novel enough to succeed; ease of use is generally not a sustainable competitive advantage. (Source: Faulkner [50])

Quadrant 1, where clinical value and barriers to entry are both high, is an ideal technology. Technologies that would fit into Quadrant 1 include implantable cardiac defibrillators (ICDs), pacemakers, and spinal fusion cages. Technologies on the border

---

Figure 13. Plot comparing Clinical Value (horizontal) versus Barrier to Entry (vertical) to access technologies. (Source: Faulkner, [50])
of Quadrant 1 and 3 could include abdominal aortic aneurysm (AAA) repair products. Quadrant 3 represents technologies with high clinical value, but low barriers to entry, thus price and market share degradation occur over time. Specialty disposable products such as interventional cardiology catheters, precutaneous myocardial revascularization (PMR) catheters and products, ablation catheters, and AVE stents would all fall into this quadrant. These products tend to have high profit margins, typically 60-70%, and due to the shifting nature of this market segment, quality and reputation are very important factors. [50]

Device companies such as Medtronic, Guidant, and Boston Scientific target Quadrant 1 and 3 technologies. Companies such as Ethicon and Becton Dickinson lie in Quadrant 4, where they rely on market share through critical mass. Quadrant 2, understandably has few players, but SafeSkin is an example, producing latex gloves that reduce allergic reactions; a market that is of low clinical value and barrier to entry, but can be economically valuable through critical mass. [50]

MPMN technology has great value when combined as an add-on to another high value product, such as a pacemaker. The most value to be added lie in Quadrant 1 and Quadrant 3 products. More specifically, since Quadrant 3 is so sensitive to changes in quality and reputation, companies producing such products are likely to all follow suit if any one company were to adopt the MPMN coating and prove successful. There are a number of major companies that lead the industry that span across quadrants that can be considered for partnership or patent licensing. Chapter 7 of this paper will examine these options in greater detail. Leading competing companies in the medical device industry include, but are not limited to: Medtronic, Guidant, Johnson & Johnson, Stryker, St. Jude Medical, Biomet, Zimmer, Mentor, Inamed Aesthetics, Bausch & Lomb, Advanced Medical Optics, and Cochlear Limited. [46]
6.3 Medical Device Market

6.3.1 Overview

The US is the largest market in the world for the medical sector, with $71.3 billion in sales in 2002. The US market generally represents about 50% of the world market, and Europe approximately 25%. [51] The pie chart below in Figure 14 depicts the breakdown of the medical device market worldwide.

![Pie chart showing medical device market breakdown by region for 2004](image)

*Figure 14. Breakdown of worldwide medical device market. (Source: MDDI [52])*

Given the importance of the United States in the medical device industry, from here on the focus of this section will be on the US market. The US market is expected to grow at an annual rate of 8% over the next three years. Fueling this expectation are the US economy and the population. The US economy is likely to still grow over the next few years. More notable however, is that the US population is aging. As of 2004, 35 million people were at or over the age of 65. By 2020, 55 million Americans will be age 65 and over. The trend of aging demographics will ultimately drive demand for medical products, especially in areas of cardiology, orthopedics, urology, neurology, and diagnostic imagining. [51] According to the US Department of Commerce, in 2002 the US consumed $69 billion in medical devices and $6 billion in diagnostic products. Figure 15 below shows the increasing growth trend in a variety of sectors from the medical industry.
6.3.2 Cardiovascular Implants

Heart disease and stroke are the number one and number three leading causes of death in the United States respectively. Cancer is the number two killer. These two significant areas of cardiovascular disease together accounted for 38.5 percent of all deaths in the US in 2001. In 2001, an estimated 931,000 Americans died from cardiovascular disease while an additional 64.4 million live with cardiovascular disease. [53] That number accounts for over one-fifth of the total US population and of which 25.3 million or nearly 40 percent of those living with disease are age 65 and older. While heart disease can be diagnosed at any age, it commonly occurs later in life, especially amongst those who are inactive and overweight or obese. Given the aging population of the “Baby Boom” generation as shown in Figure 16 and the country’s increasing obesity rates as shown in Figure 17 the incidence of heart disease is likely to increase significantly over the next 10 years. [51] By 2050, it is projected that nearly 12 percent of the US population will be over the age of 75. [54]
Cardiovascular disease includes both acute and chronic conditions. An example of an acute condition is a myocardial infarction, otherwise known as a heart attack. Examples of chronic conditions include congestive heart failure, atherosclerosis, and hypertension.

The economic impact of heart disease and stroke is estimated to be $226.7 billion in health care expenditures for 2004 by the American Heart Association. [52] The following Table 8 shows the prevalence of cardiovascular disease in the population.

Table 8. Breakdown of prevalence of cardiovascular disease in US population, 2001 (Source: Swiss Medtech [51])

<table>
<thead>
<tr>
<th>Type</th>
<th>Millions of Persons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular Disease</td>
<td>64.4</td>
</tr>
<tr>
<td>High Blood Pressure</td>
<td>50.0</td>
</tr>
<tr>
<td>Coronary Heart Disease</td>
<td>13.2</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>7.8</td>
</tr>
<tr>
<td>Angina Pectoris</td>
<td>6.8</td>
</tr>
<tr>
<td>Congestive Heart Failure</td>
<td>5.0</td>
</tr>
<tr>
<td>Stroke</td>
<td>4.8</td>
</tr>
<tr>
<td>Congenital CV Defects</td>
<td>1.0</td>
</tr>
</tbody>
</table>
Figure 17. Graph depicted overweight and obesity in the US by age from 1960 to 2002 (Source: American Heart Association [53])
The leading cause of death in the US amongst types of cardiovascular disease is coronary heart disease. In 2001, it accounted for approximately 460,000 deaths. Stroke is the second leading cause, accounting for approximately 163,000 deaths in that same year. Figure 18 below depicts a breakdown of percentages of associated with various cardiovascular diseases that cause death.

![Percentage Breakdown of Deaths From Cardiovascular Diseases - United States: 2002 Preliminary](image)

**Figure 18.** Percentage of deaths from cardiovascular Diseases, US 2002 (Source: American Heart Association [53], adapted from CDC/NCHS)

During the period from 1979 to 2001, the number of cardiovascular related procedures and operations increased by 417 percent. [51] The most common type of procedure performed in 2001 was cardiac catheterization. Over 1.2 million catheterization procedures were performed with a mean cost of $16,838 per procedure. Next most common procedure was Percutaneous Translumical Coronary Angioplasty (PTCA), performed 571,000 times at a mean cost of $28,558. Table 9 shows the number of and the mean cost of cardiovascular procedures.
Driving the growth in interventional cardiology devices are three primary device segments: stents, pacemakers, and implantable defibrillators. These three segments account for most of the cardiology device sales. In 2002, the market for Rapid Exchange Stents was valued at $1 billion with an expected growth rate of 46.6 percent to $3.2 billion in 2005 according to Frost & Sullivan. [51] Within the pacemaker segment, the market for double chamber rate responsive pacemakers was valued at $1.1 billion in 2002 and forecasted to be $1.45 billion in 2005. Finally, implantable defibrillators was valued at $1.95 billion in 2002 and expected to be have a market value of $3.0 billion in 2005. [51] Other segments also experiencing above average growth include Left Ventricular Assit Devices (LVAD) valued at $95 million in 2002, expected to grow to $150 million in 2005; and AAA Stem Grafts valued at $180 million in 2002, expected to grow to $400 million in 2005. Figure 19 provides an overview of the various segments that compose the interventional cardiology devices market and their corresponding market values.
<table>
<thead>
<tr>
<th>Segment</th>
<th>1999</th>
<th>2000</th>
<th>2001</th>
<th>2002</th>
<th>2003</th>
<th>CAGR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid Exchange Stents</td>
<td>647</td>
<td>825</td>
<td>915</td>
<td>1015</td>
<td>3200</td>
<td>46.6</td>
</tr>
<tr>
<td>Over the Wire Stents</td>
<td>737</td>
<td>545</td>
<td>425</td>
<td>325</td>
<td>200</td>
<td>-14.9</td>
</tr>
<tr>
<td>Over the Wire Balloons</td>
<td>237</td>
<td>203</td>
<td>175</td>
<td>150</td>
<td>100</td>
<td>-12.6</td>
</tr>
<tr>
<td>RX balloons</td>
<td>230</td>
<td>234</td>
<td>239</td>
<td>242</td>
<td>250</td>
<td>1.1</td>
</tr>
<tr>
<td>FW Balloons</td>
<td>7</td>
<td>6</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>-15.7</td>
</tr>
<tr>
<td>Perfusion Balloons</td>
<td>23</td>
<td>20</td>
<td>18</td>
<td>16</td>
<td>15</td>
<td>-2.1</td>
</tr>
<tr>
<td>Guiding Catheters</td>
<td>73</td>
<td>72</td>
<td>71</td>
<td>70</td>
<td>65</td>
<td>-2.4</td>
</tr>
<tr>
<td>Guidewires</td>
<td>104</td>
<td>103</td>
<td>102</td>
<td>100</td>
<td>96</td>
<td>-1.7</td>
</tr>
<tr>
<td>Other Accessories</td>
<td>39</td>
<td>39</td>
<td>38</td>
<td>36</td>
<td>30</td>
<td>-5.9</td>
</tr>
<tr>
<td>Interventional Atherectomy</td>
<td>75</td>
<td>75</td>
<td>75</td>
<td>74</td>
<td>70</td>
<td>-1.8</td>
</tr>
<tr>
<td>Interventional Thrombectomy</td>
<td>24</td>
<td>24</td>
<td>24</td>
<td>23</td>
<td>21</td>
<td>-3</td>
</tr>
<tr>
<td>Myocardial Revascularization</td>
<td>60</td>
<td>36</td>
<td>22</td>
<td>18</td>
<td>8</td>
<td>-23.7</td>
</tr>
<tr>
<td>Angiography Catheters</td>
<td>132</td>
<td>135</td>
<td>137</td>
<td>138</td>
<td>140</td>
<td>0.5</td>
</tr>
<tr>
<td>Inducer Sheaths</td>
<td>30</td>
<td>31</td>
<td>32</td>
<td>33</td>
<td>35</td>
<td>2</td>
</tr>
<tr>
<td>Angiography Guidewires</td>
<td>24</td>
<td>25</td>
<td>25</td>
<td>25</td>
<td>26</td>
<td>1.3</td>
</tr>
<tr>
<td>Mechanical Heart Valves</td>
<td>208</td>
<td>219</td>
<td>227</td>
<td>245</td>
<td>275</td>
<td>3.9</td>
</tr>
<tr>
<td>Tissue Heart Valves</td>
<td>168</td>
<td>183</td>
<td>202</td>
<td>230</td>
<td>250</td>
<td>2.8</td>
</tr>
<tr>
<td>Angioplasty Ring</td>
<td>16</td>
<td>17</td>
<td>17</td>
<td>18</td>
<td>19</td>
<td>1.8</td>
</tr>
<tr>
<td>Surgical Equipment &amp; Tools</td>
<td>392</td>
<td>419</td>
<td>446</td>
<td>472</td>
<td>600</td>
<td>8.3</td>
</tr>
<tr>
<td>Bypass &amp; Disposables</td>
<td>357</td>
<td>361</td>
<td>371</td>
<td>381</td>
<td>400</td>
<td>1.6</td>
</tr>
<tr>
<td>Mini CABG &amp; HV</td>
<td>26</td>
<td>26</td>
<td>27</td>
<td>27</td>
<td>30</td>
<td>3.6</td>
</tr>
<tr>
<td>Single Chamber Pacemakers</td>
<td>24</td>
<td>20</td>
<td>16</td>
<td>12</td>
<td>8</td>
<td>-12.6</td>
</tr>
<tr>
<td>Single Chamber Rate</td>
<td>303</td>
<td>321</td>
<td>339</td>
<td>354</td>
<td>400</td>
<td>4.2</td>
</tr>
<tr>
<td>Responsive</td>
<td>65</td>
<td>48</td>
<td>36</td>
<td>32</td>
<td>25</td>
<td>-7.9</td>
</tr>
<tr>
<td>Double Chamber Pacemakers</td>
<td>871</td>
<td>949</td>
<td>1034</td>
<td>1098</td>
<td>1450</td>
<td>9.7</td>
</tr>
<tr>
<td>Double Chamber Rate</td>
<td>255</td>
<td>272</td>
<td>284</td>
<td>296</td>
<td>315</td>
<td>2.1</td>
</tr>
<tr>
<td>Pacemaker Leads</td>
<td>1213</td>
<td>1468</td>
<td>1762</td>
<td>1950</td>
<td>3000</td>
<td>15.4</td>
</tr>
<tr>
<td>Implantable Defibrillators</td>
<td>288</td>
<td>346</td>
<td>415</td>
<td>478</td>
<td>750</td>
<td>16.2</td>
</tr>
<tr>
<td>Defibrillator Leads</td>
<td>303</td>
<td>333</td>
<td>366</td>
<td>399</td>
<td>550</td>
<td>11.3</td>
</tr>
<tr>
<td>External Defibrillators</td>
<td>105</td>
<td>110</td>
<td>116</td>
<td>118</td>
<td>125</td>
<td>1.9</td>
</tr>
<tr>
<td>IntraAortic Balloon Pumps</td>
<td>210</td>
<td>221</td>
<td>232</td>
<td>240</td>
<td>250</td>
<td>1.4</td>
</tr>
<tr>
<td>External Monitoring</td>
<td>26</td>
<td>43</td>
<td>74</td>
<td>95</td>
<td>150</td>
<td>16.4</td>
</tr>
<tr>
<td>Left Ventrical Assist Devices</td>
<td>220</td>
<td>249</td>
<td>285</td>
<td>325</td>
<td>446</td>
<td>11.1</td>
</tr>
<tr>
<td>Peripheal Vascular Stents</td>
<td>20</td>
<td>125</td>
<td>142</td>
<td>180</td>
<td>400</td>
<td>30.5</td>
</tr>
<tr>
<td>AAA Stem Grafts</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Cardiac Market</td>
<td>7512</td>
<td>8106</td>
<td>8694</td>
<td>9218</td>
<td>13700</td>
<td>14.1</td>
</tr>
</tbody>
</table>

6.4 Competitive Landscape of Cardiovascular Market

Adapted from the Swiss Medtech report on the “US Market for Medical Devices” is an updated summary of the various major market competitors specifically in the cardiovascular market.

6.4.1 Stent Market

The stent market has four major players, Guidant, Johnson & Johnson, Medtronic, and Boston Scientific. Guidant has been the market leader, closely followed by Johnson & Johnson. Medtronic and Boston Scientific have placed a distant third and fourth respectively. Figure 20 below shows the break down of market share in 2001.

<table>
<thead>
<tr>
<th>Company</th>
<th>Market Share</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guidant</td>
<td>43%</td>
</tr>
<tr>
<td>Johnson &amp; Johnson</td>
<td>36%</td>
</tr>
<tr>
<td>Medtronic</td>
<td>13%</td>
</tr>
<tr>
<td>Boston Scientific</td>
<td>7%</td>
</tr>
</tbody>
</table>

Figure 20. Stent market shares, 2001 (Source: Swiss Medtech [51])

The dynamics of the market has changed considerable since then, but an exact breakdown of the current market is not yet available. As of December 2004, Johnson & Johnson acquired Guidant, thus making Johnson & Johnson by far the largest player with considerable market share lead. Boston Scientific began gaining market share with their TAXUS drug eluting stent, however in July of 2004, they voluntarily recalled over 96,000 stents after cases of failure of the deployment balloon. This dropped their market share as many hospitals suspended the use of Boston Scientific stents. Boston Scientific has corrected the problem, and according to a February 2005 Wall Street Journal article, Boston Scientific is holding at a 65% market share for drug eluding stents in the US. [55] Johnson & Johnson’s drug eluting Cypher stent is the sole US competitor. According to Boston Scientific’s Chief Financial Officer Larry Best, “The U.S. market remains a two-horse race - Cypher versus Taxus.”
6.4.2 Pacemaker Market

The pacemaker market is dominated by Medtronic, St. Jude Medical, and Guidant. Barriers to entry in this market are very high due to the associated high R&D costs. Medtronic is the market leader with half of the entire market. Figure 21 below breaks down the percent market shares.

<table>
<thead>
<tr>
<th>Company</th>
<th>Market Share</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medtronic</td>
<td>50%</td>
</tr>
<tr>
<td>St. Jude Medical</td>
<td>25%</td>
</tr>
<tr>
<td>Guidant</td>
<td>22%</td>
</tr>
<tr>
<td>Other</td>
<td>3%</td>
</tr>
</tbody>
</table>

Figure 21. Pacemaker market shares, 2001 (Source: Swiss Medtech [51])

6.4.3 Defibrillator Market

The Implantable Cardiac Defibrillator (ICD) market is also dominated by Medtronic, St. Jude Medical, and Guidant. As in the case of pacemakers, Medtronic has half of the entire market. Figure 22 below breaks down the percent market shares.

<table>
<thead>
<tr>
<th>Company</th>
<th>Market Share</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medtronic</td>
<td>50%</td>
</tr>
<tr>
<td>Guidant</td>
<td>37%</td>
</tr>
<tr>
<td>St. Jude Medical</td>
<td>11%</td>
</tr>
<tr>
<td>Other</td>
<td>3%</td>
</tr>
</tbody>
</table>

Figure 22. Implantable Cardiac Defibrillator market shares, 2001 (Source: Swiss Medtech [51])

6.4.4 Cardiovascular Market Company Profiles

**Arrow International, Inc.** specializes in diagnosis and treatment products for heart and vascular disease patients. Their core line of product includes disposable critical care catheterization products which are primarily used to administer fluids, drugs, or blood into the central vascular system. A publicly traded company, Arrow’s net sales were $433.1 million in 2004, of which $279.9 million came from the United States. Net sales grew 13.9% worldwide over 2003, and increased 12% within the US.

[www.arrowintl.com](http://www.arrowintl.com)
**Boston Scientific** is a developer, manufacturer and marketer of medical devices. The company offers a broad range of products, technologies, and services across six medical specialties: Interventional Cardiology, Electrophysiology, Endoscopy, Oncology, Urology, and Neurovascular. Their most prominent presence is in Interventional Cardiology with the Drug-Eluting Coronary Stent called TAXUS. In 2004, Boston Scientific’s net sales reached $5.624 billion, an increase of 62 percent, and worldwide coronary stent sales reached $2.351 billion, an increase of 345 percent.

www.bsci.com

**Cordis Corporation**, a Johnson & Johnson company, is a leading developer and manufacturer of devices for treatment of circulatory diseases. Cordis has four business units: Cordis Cardiology, Cordis Endovascular, Cordis Neurovascular, Inc, and Biosense Webster, Inc. for developing cardiological, endovascular, neurological, and electrophysiological products respectively. Recent success is largely attributed to their drug-eluting CYPHER stent which directly competes with Boston Scientific’s TAXUS. In 2004 Cordis experienced $3.213 billion in sales.

www.cordis.com

**Guidant Corporation** is a leader in the treatment of cardiac and vascular disease. In 2003, 40 percent of the company’s revenue came from ICD systems, 36 percent from coronary stent systems, 18 percent from pacemaker systems, and the remaining from cardiac surgery, biliary, peripheral and carotid systems. Sales in 2004 exceeded $3.8 billion. Guidant was recently acquired by Johnson & Johnson in December of 2004.

www.guidant.com

**Medtronic** develops and produces technologies that focus on treating patients with chronic disease. Their main cardiovascular products are devices to treat bradycardia, tachyarrhythmia, heart failure, atrial fibrillation, coronary vascular disease, endovascular disease, peripheral vascular disease, and heart valve disease. Implantable defibrillators,
spinal products and insulin pumps have been fueling strong growth. In 2004, Medtronic reached over $9.087 billion in sales, an increase of 19 percent over 2003.

www.medtronic.com

**St. Jude Medical, Inc.** develops and manufactures cardiac resynchronization therapy devices; pacemakers and ICDs; diagnostic and therapeutic electrophysiology catheters; introducers, catheters, and vascular closure devices; and mechanical and tissue heart valves plus valve repair products. In 2004, St. Jude Medical had $2.294 billion in sales, an increase of 18.7 percent over 2003.

www.sjm.com

**Thoratec Corporation** is focused on the research, development, manufacturing and marketing of medical devices for circulatory support, vascular graft, blood coagulation and skin incision applications. Their HeartMate LVAS is the only FDA approved left ventricular assist system for use as both a bridge-to-transplant and for Destination Therapy. Product sales in 2004 were $172.3 million, an increase of 14.9 percent over 2003.

www.thermocardio.com

**WorldHeart Corporation** develops and manufactures technology for heart assist therapy for end stage congestive heart failure, such as their Novacor left ventricle assist system. The company generated $9.6 million in revenue in 2004, an increase of $2.8 million over the previous year. For 2005, WorldHeart has plans to acquire MedQuest Products, Inc., which is in final development stages of a magnetically-levitated, centrifugal flow rotary ventricular assist device.

www.worldheart.com

### 6.5 Medical Coating Companies

A growing number of companies or laboratories are pursuing a class of coatings called “hemocompatibles.” Hemocompatibles may or may not contain active agents such as heparin or other drugs. The purposes of such blood compatible coatings are to reduce
platelet adhesion and thrombus formation on devices, thus extending the device lifetime. Since protein adsorption is a precursor to platelet adhesion, MPMN coatings would serve the same purpose as hemocompatibles without the use of active biological agents. Since it is very difficult to bring a heparin coated devices to market due to concerns over the amount of drug release, there are a number of companies that are working to develop non-biological alternatives to heparin coatings. The following are profiles of some of these companies and does not represent a full list of those pursuing the development of hemocompatible coatings.

**AST Products, Inc.** is a provider of advanced surface coating technologies, plasma process equipment and contact angle analytical instruments for industry and research environments. Industries that they serve include biomedical, microelectronic, plastics, and semiconductor. In their Medical Coating business unit, they have developed a series of coatings that are lubricious, antimicrobial, antithrombogenic, and some incorporate drugs for control release. Their BioLAST™ platform technology is a water based polymer technology, deterring protein adsorption through its hydrophilic characteristic and in some instances the incorporation of heparin or other biological agents. Like MPMNs, their RepleaCOAT™ coating employs silver ions to act as an antimicrobial.

www.astp.com

**Surface Solutions Laboratories, Inc.** is a provider of products for commercial medical devices. The have been developing a formulation that combines heparin and different plastics to create a bioactive coating that can remain active for over a month while in contact with blood. Surface Solutions is currently in the process of applying for ISO certification. Their affiliate Coatings2Go.com develops, licenses, and supplies a wide range of coating technologies for the device industry. Provided coatings include ones that are antimicrobial, antithrombogenic, and or scratch resistant.

www.surfacesolutionslabs.com; www.coatings2go.com

**SurModics, Inc.** provides innovative surface modification and drug delivery technologies and products. They offer both heparin-based coatings and synthetic, non-
biological coatings to improve the blood compatibility of medical device surfaces. SurModic’s Bravo™ drug delivery polymer matrix is the coating applied to the drug eluting CYRHER™ stent (Cordis, J&J). Their non-heparin synthetic blood compatibility coating employs different techniques. One technique is masking the surface using hydrophilic molecules. The other approach is one where the coating actively recruits and binds native albumin to cover the surface and thus minimizing the adhesion of unwanted thrombogenic cells and proteins which elicit an immune response.

www.surmodics.com

STS Biopolymers, Inc. acquired in December of 2003 by Angiotech Pharmaceuticals, Inc, is now known as Angiotech BioCoatings Corp., as subsidiary of the mentioned parent company. STS has been developing and manufacturing biocompatible coatings for medical devices since 1991. Their coatings are in commercial use on a range of devices such as vascular, neurointerventional catheters, dilators, cannulae, gastroenteral feeding tubes, urinary catheters, blood filters, infusion catheters, and guidewires. Their lead product is the paclitaxel-eluting coronary stent, TAXUS® (Boston Scientific). Polymers used in their formulations include cellulose esters, polyurethane, methacrylates, and polyvinylpyrrolidone. While they are pioneering the addition of drugs in coatings, they also have and are capable of creating non-biological coatings as well.

www.angiotech.com
7. REVENUE MODELS

Given the filed patent “Nanoparticles Having Sub-Nanometer Features” is approved by the USPTO, there are several options towards commercializing the technology to generate revenue. Licensing is generally the most common commercialization pathway, but additional options include the establishment of an independent company, entering into a joint venture, or selling the technology, also known as patent assignment. Neither course is necessarily better than the other, but it is important to explore and consider various factors for each route to determine the proper avenue to pursue.

7.1 Establish Company

Amongst a host of considerations to take into account when forming a new company, the most critical issue is funding. The main sources of funding are from venture capital investors or angel investors.

Venture capital (VC) is a fund raising technique for companies that are willing to exchange equity in their company and the company’s management in return for money to grow and expand their business and can be sought at any stage of the company’s development. Venture capital firms usually require a high rate of return on their investment (20% or more per annum) and finance provided to the business is typically in the range of $500,000 to many millions of dollars. [56] Venture capital investors typically seek an exit from their investment in a three to five to seven year timeframe. [57] An exit opportunity includes listing the company upon a stock exchange, or trade selling the assets of the start up company. VCs strongly favor backing a company that owns its patents versus one that is merely licensing a technology patent because it is much easier to raise investment capital in the prelisting stage when the startup company owns its major assets. According to Philip Mendes, Partner at Innovation Law:

“Given that the start up company will typically develop new patents as its own asset, there is also a negative perception where the start up company’s patent is partly licensed in from the individual, university, research institute or government laboratory, and partly owned by the start
Angel investors are well off individuals who provide capital for business start-ups, usually in exchange for an equity stake. Money is typically not from a professionally-managed fund, however, angel investors often organize themselves in angel networks or angel groups to share research and pool investment capital. Unlike VCs, angel investors tend to require less control of the company and a slower return on invest, their criteria for investment however is still similar to that of VCs. Angel investor groups are excellent sources of private capital and frequently invest into new companies.

Often markets in the medical device industry are too small to support new companies, thus creating an independent company would be extremely risky. This risk can be mitigated through entering partnerships or joint ventures. Partnerships and joint ventures are very similar in nature except that joint ventures differ in that they are limited by time or activity.

7.1.1 Partnership & Joint Venture

Partnerships (long term) and joint ventures (short term) are business arrangements in which two or more parties undertake a specific economic activity together. A good synergy provides companies with the opportunity to obtain new capacity and expertise. The advantage of aligning with another company is the combining of forces in complementary R&D or technologies, sharing of scientists and professionals, utilizing of one another’s marketing and distribution, providing of financial support, sharing of economic burden for FDA approval, and sharing of financial risks and rewards. Factors to take into consideration when forming a joint venture are the “fit” of business strategy. This can be addressed by defining governance, accountability, decision making processes, conflict and issue resolution procedures, and preferred exit strategies. Approximately 80% of all joint ventures end in a sale by one party to the other. According to a recent survey highlighted on 1000ventures.com, only 44% of CEOs characterize their joint ventures as “very successful.” The most common reasons cited for failure were “poor or unclear leadership” and “cultural differences.”
partners for MPMN technology in the medical device industry include but are not limited to those profiled in Chapter 6 section 4.4 of this paper.

7.2 License Technology

If involvement in the actual production of the technology is not a desire, then licensing is an excellent option. Licensing occurs when the patent holder(s) grants exploitation rights over a patent to a designated licensee, a large established company for example. A license is a legal contract in which the terms of exploitations rights are granted and performance obligations set. Generally a license lasts for a set period of time and involves payment of some form of royalties to the patent holder. In an instance where the licensee fails compliance to the contract, such as a breech in royalty obligations, this may lead to the revoking and termination of the license. [57] Potential licensees for MPMN technology in the medical device industry include but are not limited to those profiled in Chapter 6 section 4.4 of this paper.

7.3.1 Royalties

Revenue generated from royalties involves risks of uncertainty. Over a long period of time there may be technical failure, market failure, regulatory failure, or new competing products or technologies that erode the revenue potential from royalties.

Royalties can be determined in a variety of ways. It could be based off a percentage of the revenue or sales, or on a flat rate per unit. The following Figure 23 is a chart that depicts the different means by which royalties can be based. Depending on the product and industry, royalty rates can range anywhere from 0.5% up to 30% of what the manufacturer sells. [59]
7.3.2 Exclusivity

Licenses may be “exclusive,” “limited exclusive,” or “non-exclusive.” [59] Exclusive is where sole rights are given to one party and one party only. Limited exclusive is where sole rights are given to one party of an industry, so for example MPMN technology could be licensed exclusively to Johnson & Johnson for medical devices, and exclusively to ExxonMobil for its oil tankers and deep sea pipes and platforms. Non-exclusive licensing is where multiple entities have the right to exploit the patent; thus, allowing Johnson & Johnson, Boston Scientific, and Medtronic to all use the technology would be an example of non-exclusive licensing.

Both limited exclusive and nonexclusive licensing have strong revenue producing potential. The technology could be licensed with royalties at a premium exclusively to Company X of the particular industry. Theoretically, this would allow Company X to have a superior product to that of Company Y and Company Z, thus gobbling up market share. As a result, the new dominant market share yields high returns. This path could be successful for a market segment that has limited competition with only two players with similar products fighting for market share. Allowing universal use of the patent could also return handsomely if many products and companies chose to adopt MPMNs. In a highly competitive market segment with many players, mass adoption of MPMN creates the possibility of becoming an industry standard. As a result, the universal

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**Figure 23.** Chart depicting examples of royalty basis for differing products (Source: PatentCafe [59])

<table>
<thead>
<tr>
<th>Product</th>
<th>Royalty</th>
<th>Based On</th>
<th>Total IP Investment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Software Product</td>
<td>10-40%</td>
<td>Retail Price or wholesale</td>
<td>N/A</td>
</tr>
<tr>
<td>Hard Goods Product Patent “A”</td>
<td>0%</td>
<td>50 cents per unit</td>
<td>N/A</td>
</tr>
<tr>
<td>Hard Goods Product Patent “B”</td>
<td>0%</td>
<td>0%</td>
<td>Flat Fee of $50,000 @ $10,000 per yr. for 8 years</td>
</tr>
<tr>
<td>Hard Goods Product Patent “C”</td>
<td>2-10%</td>
<td>Gross Revenues or Net Revenue</td>
<td>N/A</td>
</tr>
</tbody>
</table>
application of MPMNs would result in numerous royalty fees. Since the terms of the license can be set for any given duration, an alternative option would be some combination of the licensing types. The technology could be licensed only to one company for a short given period of time. This may allow MPMN to establish its value in the market, and after the exclusive agreement expires, it can then be licensed universally.

7.3.3 Performance Obligations

Licensing of a patent typically contains performance obligations to be met by the licensee. Failure to comply can result in revocation of the license. Performance obligations are of two types: pre-market entry milestones, and post-market entry sales targets. [57] Examples of pre-market entry milestones include the undertaking of trials or validation, producing a prototype, producing a pilot plant, meeting regulatory requirements, or progress through clinical trial phases. These milestones ensure that the licensee does not shelve the patent with no commercialization resulting in no financial benefits to the patent holder. Similarly, sales targets once market entry has occurred are performance obligations which ensure that the licensed patent will be exploited to at least a given extent. Performance obligations are appropriate when long term royalties is what the patent holder is seeking.

7.4 Assign Patent

Assigning or selling a patent is a desirable option if the patent holder(s) prefer to receive a lump sum price versus collecting royalties over a span of up to 20 years, thus minimizing risk. The disadvantage of assigning a patent is that the price paid is assessed on the value of the patent and that time and discounted for risk so you could lose more money in the long run. Unlike a license, assignment of a patent is irrevocable. An assignment involves the sale and transfer of ownership of the patent to a new assignee. As in the sale of any other good, once the asset is sold, the former owner is permanently divested of any ownership. Any assignment should be in writing and acknowledged before a notary public. [57] The assignment should be recorded in the USPTO within three months of the transfer. Failure to record the assignment in the USPTO can render
the assignment void to the subsequent purchaser of the patent. Potential assignees for MPMN technology in the medical device industry include but are not limited to those profiled in Chapter 6 section 4.4 of this paper.
8. FDA APPROVAL

Each country has their own regulations regarding medical devices. All medical devices manufactured and sold in the United States are regulated by the Food and Drug Administration to ensure their safety and effectiveness. A medical device as defined by the 1976 Medical Device Amendments is:

"...any instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part or accessory.

-which is recognized in the official National Formulary, or the US Pharmacopeia, or any supplement to them.

-which is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals; or intended to affect the structure or any function of the body of man or other animals.

-which does not achieve any of its principal intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its principal intended purposes." [60]

Whether a MPMN coating is added to an existing device, or to a new device, FDA approval must be obtained in order to market and distribute the product. The process for producing a coated device is essentially the same process as that for an uncoated device; however, additional testing is required for the coated device. Coated devices that include drugs or other biological agents are regulated as combination products by more than one of the FDA’s centers. Devices with coatings without drugs, however, are regulated by the Center for Devices and Radiological Health (CDRH) only. [61] Hydrophilic guidewires and catheters, and orthopedic implants with thermal spray metallic coatings are examples of such devices. [62] MPMN coated devices would fall under the jurisdiction of the CDRH. For devices with physical coatings, product development and regulatory risk is generally considered low. [62]

The following is an overview of the FDA approval process for a coated device. The approval process can be examined in much greater detail on the FDA and CDRH websites on the world wide web. [63]
8.1 Domestic Device Approval

Obtaining FDA approval varies from device to device depending on its classification. Three regulatory classes exist for medical devices which dictate the amount of control necessary to ensure safety.

8.1.1 Device Classification

Devices are allocated into Class I, II, or III; Class I being the lowest level of required control, and Class III the highest level of required control. Table 10 below shows examples of devices that fall into the different classifications.

Table 10. Examples of Class I, Class II, and Class III devices (Source: Ratner [9])

<table>
<thead>
<tr>
<th>Class I</th>
<th>Class II</th>
<th>Class III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Root canal post</td>
<td>Oxygen mask</td>
<td>Intraocular lens</td>
</tr>
<tr>
<td>Dental floss</td>
<td>Blood pressure cuff</td>
<td>Heart valve</td>
</tr>
<tr>
<td>Enema kit</td>
<td>Power wheelchair</td>
<td>Infant radiant warmer</td>
</tr>
<tr>
<td>Tongue depressor</td>
<td>Skull clamp</td>
<td>Ventricular bypass device</td>
</tr>
<tr>
<td>Surgeon’s glove</td>
<td>Obstetric ultrasonic imager</td>
<td>Automated blood cell separator</td>
</tr>
</tbody>
</table>

Class I is the least rigorous classification for devices. Devices in this category are subject to general controls that ensure safety and effectiveness detailed in 21 Code of Federal Regulations 860.3. General controls are basic requirements regarding adulteration, misbranding, banned devices, and restricted devices. These controls also require manufacturers register their facilities and to follow good manufacturing in practices maintaining records and reports to prove their device has not been adulterated or misbranded. All classes of devices are subject to these general controls.

Class II devices must comply with general controls and additionally must meet performance standards that ensure their safety and effectiveness as detailed in 21 Code of Federal Regulations 860.3. These additional standards and controls include post-market surveillance, patient registries, and the development of any additional guidelines necessary to ensure safety.
Class III is the most stringent classification. Devices that fall into this category are ones where there is insufficient information to show that general controls and performance standards would ensure their safety and effectiveness. Generally, Class III devices are defined as those that are implanted in the body, are life-sustaining or life-supporting, or pose unreasonable risk of injury or illness.

8.2 Approval Process
Regardless of the classification type of a medical device, the manufacturer may need to submit a premarket notification to the FDA at least 90 days prior to commercially distributing a new or substantially modified device. This notification is typically referred to as a “510(k) Submission” because it is mandated by Section 510(k) of the 1976 amendments. Class I devices, however, are commonly exempt from this requirement. Figure 24 is a flowchart schematic of the FDA regulatory approval process.

8.2.1 510(k) Submission
A 510(k) submission is a required premarket notification, registered at least 90 days in advance, of a manufacturer’s intent to market a medical device. [64] This allows the FDA to determine whether the device is equivalent to a predicate device from any of the three aforementioned classification categories. The submission also informs the FDA of “new” devices, be it first time distribution or reintroduction of a significantly changed or modified device to the extent that the safety and effectiveness could be affected. Such changes include modification to design, material, chemical composition, energy source, manufacturing process, or intended use. [64]

8.2.2 PMA Application
Use of MPMN coatings on implanted devices would require a Premarket Approval (PMA) application. A PMA application is a scientific, regulatory documentation to FDA to demonstrate the safety and effectiveness of the Class III device. PMA requires all Class III devices to file a full report of investigation containing data from both non-clinical and clinical studies. [9] Non-clinical laboratory studies include information on
Figure 24. FDA regulatory approval process flowchart. (Source: Swiss Medtech [51])
microbiology, toxicology, immunology, biocompatibility, stress, wear, shelf life, and any other lab or animal tests. All such studies need to be carried out in compliance with 21CFR Part 58, “Good Laboratory Practice for Nonclinical Laboratory Studies.” Information from clinical investigations should include study protocols, safety and effectiveness data, adverse reactions and complications, device failures and replacements, patient information, patient complaints, tabulation of data from individual subjects, results of statistical analysis, and any other relevant material. [64] Additionally, the device components and the principle of operations is to be described in detail. Manufacturing and quality control procedures, proposed labeling, and actual samples of the device are also required.

The review process for PMA applications is extensive: undergoing a filing review, an in depth scientific and regulatory review, a panel review by an advisory committee, and a final deliberation by the FDA. After the FDA has approved a PMA, if any changes are to be made which may affect the safety or effectiveness of the device, a PMA supplement must be submitted for review and approval by the FDA before such changes can take place. [64] After the PMA application is approved, there are no large regulatory roadblocks that exist between the device and the market.

8.3 Device Testing
In order to conduct clinical studies of a non-approved device in the US, an investigational device exemption (IDE) usually must first be obtained. Prior to the IDE, the device is categorized as presenting significant or non-significant risk. Significant risk is defined as a device that presents the potential for serious risk to a human subject and is either, an implant, used in supporting or sustaining life, or important in preventing the impairment of health in diagnosing, curing, or treatment of the disease. Non-significant risk devices do not require an IDE application. IDE applications must include manufacturing and quality control procedures, complete reports of non-clinical and prior clinical studies, a full investigational plan for the clinical study, and a list of committees to be involved in the study—designated by a university or institution to review biomedical research with human subjects. [9] If granted, an initial clinical study of a new product usually will
involve less than 100 people. If the results of the initial studies are promising, the FDA may let the manufacturer test the device on a larger scale. Results from clinical studies performed under an IDE may be used to support 510(k) submissions and PMA applications. [65]

8.4 Projected Timeline

In 2003, the FDA began undertaking a new goal for reducing device approval times. The metric for the goal is “FDA time to 50 percent approval” which is the number of days it took to reach 50 percent approval of PMAs filed in a fiscal year. “FDA time” is the total elapsed time from the date of a PMA is filed to the date of its approval. The time includes all instances where the PMA is under review by the FDA but does not include time it is on hold or being worked on by the applicant. During the three year period of 1999-2001, a total of 166 regular PMAs were filed and 119 were approved. An average of 363 days elapsed or 320 FDA days before reaching 50 percent approval during this time period. [65] The goal is to reduce FDA time to 50 percent approval by 30 days for the three year period of 2005-2007. IDEs are processed within 30 days, and once a PMA has passed a filing review the application is officially filed and a 180 day review session begins. The entire process, from IDE to PMA approval could take from three to six years or more. [66] Figure 25 is a timeline detailing approximate time frames associated with each phase of the approval process.

![Figure 25. Timeline of FDA approval process](image-url)
Due to the number of variables involved in obtaining FDA approval, such as number and duration of clinical trials, it is not possible at this time to accurately estimate the cost associated with gaining FDA approval for a MPMN coated device.
9. CONCLUSION

Recent advancements in nanotechnology have enabled Professor Stellacci and his group at MIT to create a new class of advanced materials. We have developed nanostructured nanoparticles which have added functionality. Due to the self assembling domains of hydrophobic and hydrophilic regions, these monolayer protected metal nanoparticles have the ability to resist protein adsorption onto its surface. Despite a protein’s ability to fold and unfold into endless configurations, the uniquely structured nanoparticle can attract and repel the individual units of a protein such that the net interaction is zero. Applied as a coating to existing devices or products, MPMNs have strong potential in a broad range of applications where nonspecific protein adsorption can be detrimental to device’s performance, as in the case of medical devices.

This study has shown that there is a need and a sizable market demand for protein resistant coatings. MPMN coatings would enable us to extend and improve the biocompatibility, effectiveness, and lifetime of implanted devices used to treat life threatening illnesses such as cardiovascular disease. While use in the medical device industry is just one of the many potential market applications of MPMN coatings, there are still several challenges to overcome on the road to commercialization.

MPMN technology is still in its infancy and the technology to produce high quality coatings out of MPMNs is still to be perfected. From there, questions like those that would be raised by the FDA regarding stress, wear, and lifetime, etc need to be addressed. Beyond the technology itself, there includes questions of patent defensibility, manufacturing, and regulatory approval. While many challenges still exist, application of monolayer protected metal nanoparticles as coatings hold much promise to dramatically improve the performance of a vast array of surfaces from all walks of industry.
REFERENCES:


[31] Stellacci, F. and Jackson, A.M. “Nanoparticles Having Sub-Nanometer Features” Patent filed Feb 28, 2005


[33] Cole Parmer catalogue: www.coleparmer.com


[63] Center for Devices and Radiological Health Homepage, www.fda.gov/cdrh

