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Thrombotic Inception at Nano-Scale

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1. Introduction

Seeing is believing, but the reverse, namely, disbelieving the unseen may often go against the spirit of scientific exploration. This is particularly true for nano-scale objects interacting almost invisibly with biological cells, tissues or organs. Interestingly many of the biological sub-cellular components (e.g. proteins, DNA) have nano-scale dimension. The apparently innocent (chemically inactive) and tiny particulate matter originating from various natural or artificial sources (e.g., pollutant) have been shown to be toxic at different physiological levels. The famous saying by Jeevaka, the legendary physician of the Jataka tales, that there is no herb in the world that is not a drug, however follows. What is toxic in some context have important therapeutic value elsewhere. Nanoparticles do interfere with the thrombo-static equilibrium. While this shift on one hand is a matter of concern, it may provide us a tool to handle or diagnose diseases in which such equilibrium is shifted. One of the finest models to test this dual aspect of the nano-scale objects is Acute Coronary Syndrome (ACS), a leading cause of death in the global scenario. What is known today regarding the effect of nanoscale objects may really be a tip of iceberg and with the advent of smarter nanoparticles one may think of more versatile use of nanotechnology in the management of ACS.

2. Role of platelets in Acute Coronary Syndrome (ACS)

ACS is a complex and multi-factorial disease (Badran et al., 2009). ACS is an umbrella like term which includes mainly three diseases i). **ST elevated myocardial infarction (STEMI)**, ii). **Non ST elevated myocardial infarction (NON STEMI)**, and iii) **unstable angina**. The patho-physiological event of ACS can be divided into four phases:

a. Atherosclerotic plaque formation.
b. Rupture of an unstable plaque.
c. The acute ischemic event.
d. Long term risk of recurrent coronary event.

2.1 Platelet basic physiology

Platelets play a pivotal in manifestation of ACS. Platelets are discoid in shape, with approximate number density 150,000-300,000/µl, and dimension of the order of 2000-4000 nm. Derived from megakaryocyte (figure 1) (Thompson, 1986) they contain mitochondria, peroxisomes, endoplasmic reticulum. They also contain granules and glycogen bodies.
Granules occur as i) **dense granules** (δ), ii) **alpha granules** (α). Dense granules mainly contain ATP, ADP, serotonin etc., whereas alpha granules contain fibronectin, fibrinogen, platelet activation factor (PAF) etc. (Marcus et al, 1966; Flaumenhaft et al, 2005). Ca\(^{++}\), one of the most important factors for platelet action, is stored in endoplasmic reticulum and released into the cytoplasm, during platelet activation (Nesbitt et al, 2003). Open canalicular system (OCS) is a channel like protrusion inside the platelet where granules release their contents (Escolar & White, 1991). Recently role of mRNA and mi-RNA has been shown to play important roles in platelet aggregation (Calverley et al, 2010; Rowley et al, 2011; Nagalla et al, 2011).

Fig. 1. Precursor megakaryocyte and progenitor platelets: Represents microscopic image (20X) of a megakaryocyte in the bone marrow. Platelets generated from the megakaryocyte can be seen in 12 o’clock position of the megakaryocyte.

When exposed to agonists, platelets become activated and this is followed by an aggregatory response (Patscheke, 1979). In systemic blood flow platelets remain in resting phase, without being activated (Marcus et al, 1991). Physiological agonists like collagen, thrombin, ADP, ATP etc. are not associated with the normal blood flow. Even if a trace amount of ADP and ATP are present, they are broken down by the phosphatase activity of CD39 (Marcus et al, 1997). At wound site, sub endothelial layers get ruptured. Hence Von Willebrand factor (vWF) and collagen get exposed causing activation of platelets (Nyman, 1980; Tschopp et al., 1980). After the primary phase of activation and aggregation, platelet granules are released, this leads to enhancement of local concentration of agonists (e.g. granule secreted ADP, ATP, serotonin etc.). This triggers irreversible secondary phase platelet aggregation with fibrinogen, which is further followed by cessation of bleeding (Decie and Lewis 2003) (figure 2).
Fig. 2. Schematic diagram of platelet activation and aggregation. In the resting conditions platelets, maintain their discoid form and flow in circulation. Upon injury, platelets become exposed to sub-endothelial collagen and vWF (1) adhered on it (2). This is followed by activation and shape changes (3). The next phase is granules release and secondary phase aggregation (4) and lastly the stable platelet plaque forms (5).

The detailed mechanism of platelet function depends on the complex intracellular signalling pathways. This leads to platelet activation by simulating a series of physiological events. Briefly, after binding of agonists, the corresponding receptors trigger downstream signalling cascades and initiates Ca^{++} mobilisation from endoplasmic reticulum. Platelet granules release (α and δ), platelet shape change and the thromboxane A2 (TXA2) production then follows. The cumulative effects of these events initiate activation of fibrinogen receptor (GPIIbIIIa) and triggering of primary phase aggregation. The released granules-content (ADP, ATP etc.) along with TXA2 activate other resting platelets resulting the secondary phase aggregation (Kroll & Schafer, 1989; Ashby, 1990) (figure 3). The important signalling molecules that help the above process through a complex interplay among different G-protein coupled receptors, integrin receptors, second messengers, kinases, phosphatase and Ca^{++} mobilisation etc (Dorsam & Kunapuli, 2004; Wu et al., 2006, 2010; Roberts et al., 2004; Karnigian et al., 1990; Farndale, 2006; Spalding et al., 1998; Patscheke, 1980; Clifford et al., 1998; Hoffman et al. 2009).
Fig. 3. Schematic diagram of agonists induced platelet activation. Binding of agonists with corresponding receptors, triggers downstream signalling cascade, and causes mobilisation of intracellular Ca\(^{++}\). The initial Ca\(^{++}\) flux branches itself into three major signalling events: A (alpha and dense granules release), B (platelet shape change), C (TXA\(_2\) production). The three signalling events cumulatively determine the activation and aggregation. The released chemicals (ADP, ATP etc) from granules and the TXA\(_2\), further activates other resting platelets and initiates the secondary phase of aggregation.
2.2 Platelet in ACS

It may be contextual to focus on the pathological role of platelets in ACS. Platelet thrombosis plays a central role in the pathogenesis of Acute Coronary Syndrome (ACS) by the formation of thrombi at the site of the ruptured atherosclerotic plaque (figure 4) (Massberg et al., 2003; Kottke-Marchant, 2009; Lakkis et al., 2004).

![Flow chart illustrating the role of platelets in thrombus formation.](image)

Thus, the main therapeutic regime for the treatment of ACS is use of anti-platelet drug that inhibits platelet hyper aggregation (Faxon, 2011; Guha et al., 2009; Aragam & bhatt, 2011; Born & Patrono, 2006). Table 1 describes a list of such drugs, while their mode of action is illustrated in figure 5.

In the normal platelet aggregation process, downstream signalling induces fibrinogen receptor activation (GpIIbIIIa). GpVI is the collagen receptor. P2X1 is the receptor of ATP and acts as Ca++ channel. P2Y1 is high affinity ADP receptor and P2Y12 is low affinity ADP receptor, where the former one is Gq and the later one is Gi coupled. Gz coupled alpha 2a are adrenergic receptors for epinephrine, where Gs coupled PGI2R are the receptors of prostaglandin I2 (PGI2) or prostaglandin E1 (PGE1), these being inhibitory receptors. Protease-activated receptor 1 (PAR1), protease-activated receptor 4 (PAR4), are coupled with Gq and G13 these being the receptors of thrombin. Thromboxane A2 (TxA2) receptor TP is also coupled with Gs and G13. Released TxA2 (b in figure 5) and ADP (a in figure5 ) further act on their corresponding receptors. The second messengers and other signalling mediators include, (DAG) diacylglycerol; (PLCβ) phospholipase C β; (PKC) protein kinase C; (PIP2)
<table>
<thead>
<tr>
<th>Mode of Action</th>
<th>Name of the drugs</th>
</tr>
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<tbody>
<tr>
<td>Cyclo-oxygenase inhibitors (COX1), (1)</td>
<td>Aspirin</td>
</tr>
<tr>
<td>P2Y12 receptor inhibitors(2)</td>
<td>Clopidogrel, Prasugrel, Ticlopidine</td>
</tr>
<tr>
<td>Phosphodiesterase inhibitors(3)</td>
<td>Cilostazole</td>
</tr>
<tr>
<td>Glycoprotein GPIIbIIIa inhibitors(4)</td>
<td>Abciximab, Eptifibatide, Tirofiban</td>
</tr>
<tr>
<td>Adenosine uptake inhibitors(5)</td>
<td>Dipyridamole</td>
</tr>
</tbody>
</table>

Table 1. List of anti-platelet drugs – their mode of action and generic names. The most common drugs are described in the first two rows.

Fig. 5. Target sites for anti-platelet drugs in platelet signalling pathway- different downstream signalling pathways are shown. The drug targets described in Table 1 are represented by the corresponding numbers (see text for elaboration).
phosphotidylinositol-4,5-biphosphate; (PLC$_{\alpha}$) phospholipase C $\gamma$; (PLC$_{\beta}$) phospholipase C $\gamma$; (IP$_3$) inositol triphosphate; (IP$_{3R}$) inositol triphosphate receptor; (PP) protein phosphorylation; (PLA$_2$) Phospholipase A$_2$; (AA) arachidonic acid; AkT and Rap1B (which are serine/threonine kinase); (PI3K) phosphatidylinositol 3-kinase; (AC) adenyl cyclase; (PKA) phosphorylase A; (cAMP) cyclic adenosine mono phosphate; (VASP) vasodilator stimulated phosphor protein; (P160 ROCK) a Rho activated kinase; (MLCK) myosine light chain kinase, (LIM-K) LIM kinase; (PGG2) prostaglandin G2; (PGH2) prostaglandin H2; (PL) membrane phospholipids; (COX1) cyclooxygenase 1; (TS) thromboxane synthetase and (PDEIII) phosphor di-esterase III. As platelets are the key player in ACS, any extra-physiological environmental materials that can alter platelet signalling circuit is of great challenge in combating the disease. This is the context where nanotechnology can come in picture.

3. Nano-interface

Nanotechnology has the potential to interfere with basic biological mechanisms because of their tunable electrical, magnetic and optical properties, and small size (Chen et al., 2005; Gobin et al., 2007; Fu et al., 2007). This tunability makes them potential tool in diagnostics (e.g. bio-imaging) therapy and a smart combination of both of these properties (Smith et al., 2008; Peng et al., 2000; Li et al., 2003; Murry et al., 2000).

Some of advancement of nanotechnology inspired application include improved imaging contrast agents by SPIONS (super-paramagnetic iron oxide nanoparticles), targeted delivery of drugs, molecular chaperons and agents to kill specific cancer cells (Yu et al., 2011; Petkar et al., 2011; Patra et al., 2007). Another exclusive application involve magnetic induction (radio frequency) heating or laser induced heating of designer particles, with desirable material and shape attributes (Peterman et al., 2003; Plech et al., 2004). The hyperthermic killing of tumor cells, is one of the most important examples (Rao et al., 2010; Huff et al., 2007). The recently reported chaperon properties of nanoparticles can also have important biomedical potential (Singha et al., 2010). Interestingly there are only few report on haematological (Elias & Tsourkas 2009; Baker, 2009; Walkey et al., 2009; Wickline et al., 2005) and cardiological applications (Lanza et al., 2006; Iverson et al., 2008) of nanotechnology.

4. Nanotechnology in ACS and platelet contexts

Nanotechnology is important in ACS because of several reasons. A simple application is imaging of plaques, conventional methods being grossly inadequate for such purpose (Nikolas, 2009; Wickline & Lanza, 2003). Secondly, the targeted delivery of therapeutic agents using nanoparticles to the areas of injured or dysfunctional vascular wall that inhibit the plaque progression is of significant importance in the ACS context (Nikolas, 2009).

Furthermore, nanoparticle based assay can be used for the detection of myocardial injury in patients with ACS (Wilson et al., 2009). In the therapeutic regime, an important use of nanotechnology is to increase the amount of HDL in circulation interning delivery of cholesterol to liver, thus minimizing the risk associated with ACS (Luthi et al., 2010).
In most of the above mentioned cases (diagnosis, drug delivery or treatment) the primary entry route of nanoparticle is through circulation where they interact directly with blood cells. Conversely exposure to unwanted nanoparticles (e.g. gas phase exhaust from car or industry) inhaled by human, that can penetrate the alveolar space and interfere with circulation may lead to cardiovascular diseases (Yamawaki & Iwai, 2006; Mohammad et al., 2011; Chen et al., 2008). In both cases such interaction deserves a special attention.

In case of ACS patients, if nanoparticles activate platelets then they may induce life threatening alarm. Till now there are a number of papers (Geys et al., 2008; Oberdörster et al., 2007; Deb et al., 2007, 2011; Wiwanitkit et al., 2009; Radomski et al., 2005; Shrivastava et al., 2009; Koziar et al., 2005; Mayer et al., 2009; Li et al., 2009; Ramtoola et al., 2010; McGuinness et al., 2010; Nemmar et al., 2003; Gulati et al., 2010; Cejas et al., 2007; Wilson et al., 2010; Rückler et al., 2007) about the effect of nanoparticles on platelets (Table. 2.) where most of the citations show that nanoparticles can induce platelet aggregation. What makes a nanoparticle pro-aggregatory (Geys et al., 2008; Oberdörster et al., 2007; Deb et al., 2007, 2011; Wiwanitkit et al., 2009; Radomski et al., 2005; Mayer et al., 2009; McGuinness et al., 2010; Nemmar et al., 2003; Cejas et al., 2007; Wilson et al., 2010; Rückler et al., 2007; Miller et al., 2009), inert (Li et al., 2009; Ramtoola et al., 2010; Gulati et al., 2010) or even anti-platelet in nature (Shrivastava et al., 2009; Koziar et al., 2005; Miller et al., 2009) is of great importance in development of ACS based nano-drugs, risk assessment in ACS, and also in evaluating resistance to ACS related drugs (Guha et al., 2009; Jogns et al., 2006; Michelson et al., 2006).
Table 2. Nanoparticle effects on platelets – the Table enlists how the platelet response varies with variation in nano-material as well as the corresponding nano-surface configuration. NP is nanoparticle.

5. Platelet nanoparticle interaction – A deeper insight

A different paradigm of nanotechnology application has recently got considerable interest. How thrombotic response is modulated by nanoparticles has recently become a new paradigm in nano-medicine. Till today, the exact mechanisms of how nano-surface exposure or uptake of nanoforms alter the platelet response are not known. Most of the metallic nanoparticles, carbon nanoparticles, aerosol and polymer nanoparticles induce platelet aggregation (Mayer et al., 2009; McGuinnes et al., 2011). A few nanoparticles remain inert for platelet or induce anti-platelet effect (Li et al., 2009; Ramtoola et al., 2010; Gulati et al., 2010). Interestingly in case of some polymer nanoparticles, surface conjugation induces varying response to platelets (McGuinnes et al. 2010). One needs deeper insights in induced platelet signalling to explain such varying response to nanoparticles with a characteristic surface property.
As mentioned earlier, anti-platelet drug therapy is the most important therapeutic regime for ACS patients. A major fall-out of the conventional therapeutic approach is the sizable incidence of drug resistance among ACS patients (Guha et al., 2009; Jogns et al., 2006; Michelson et al., 2006). There are indications that nanotechnology can help diagnosis of drug resistance (Deb et al. 2011).

Again, metallic nanoparticles can induce platelet aggregation depending on the physiological state of the platelets. For a given nano-drug, such response can show interindividual variations, and there is evidently a scope of judging the safety of such drugs depending on the extent of induced alteration in platelet function. It may be important to note that under certain conditions nanoparticles can be hazardous to both normal individuals as well as ACS patients. Table 3 summarises the overall ACS risk associated with nanoparticles:

<table>
<thead>
<tr>
<th>Phenomenon</th>
<th>Risk Factors</th>
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<tbody>
<tr>
<td>&lt; 60 nm nanoparticle.</td>
<td>Safe in context to thrombotic risk.</td>
</tr>
<tr>
<td>Resting platelets + nanoparticle.</td>
<td>No thrombotic risk.</td>
</tr>
<tr>
<td>Anti-platelet drug like clopidogrel or reo-pro.</td>
<td>No thrombotic risk.</td>
</tr>
<tr>
<td>Rupture plaque (where vascular bed is open) + Nanoparticle of any size.</td>
<td>High thrombotic risk.</td>
</tr>
<tr>
<td>Some special surface modification</td>
<td>tunable</td>
</tr>
</tbody>
</table>

Table 3. Overview of thrombotic risk factors of nanoparticles.

5.1 Excitability of the nanoparticle mediated pro-aggregatory response

Metallic nanoparticle (made of gold, copper, iron, cadmium sulphide and quantum dots) induced platelet aggregation is intriguing as the profile change of such aggregation fully depends on the physiologic conditions of the platelets (e.g. pre-activation) (Deb et al., 2007, 2011; Geys et al., 2008). Non-metallic carbon nano-tube or polymer based nanoparticles on the other hand induce platelet aggregation without any pre-activation, their pro-aggregatory effect depends mainly on hydrophobic collapses (Radomski et al., 2005) or charge-charge interaction among platelets and nanoparticles (McGuinnes et al., 2010). At critical concentrations of ADP or in presence of a threshold shear force, which mildly activates the platelets, they become most sensitive to nano-particles (figure 7). In other words, the nanoparticles in such cases serve as agonists. On the other hand, when platelets are in resting condition most of the metallic nano-forms seems to be inert.

Unlike optimal size response (of nanoparticles) observed in case of cancer cells, the nano-response in platelets increases monotonically with decreasing size of nanoparticles (Deb et al., 2011). This phenomenon occurs also in case of polystyrene nanoparticles (Mayer et al., 2009). This size attribute is similar to entry of the nanoparticles through inhalation. Smaller the size of the nanoparticle, lesser in the efficiency of the clearance by alveolar macrophages, which in turn increases their (nanoparticle) deposition in alveolar cell leading to entry into
circulation (Yamawaki & Iwai, 2006). Thus, smaller nanoparticles pose a higher risk in the ACS scenario.

Fig. 7. Nanoparticle Size Response. Gold Nanoparticle induced platelet response [see Deb et al. 2007, 2011] is dependent on nanoparticle size, smaller particle showing aggregatory effects.

Though the exact molecular mechanism of metallic-nanoparticle platelet interaction is yet to be established, systemic response like release of platelet granules (both α and δ) have been observed in presence of nano-particles. In presence of apyrase (scavenge ADP released from δ granules), or anti-platelet drug clopidogrel (block P2Y12 purinergic receptors, thus inhibit secondary wave of aggregation, which is the signature of granules release) nano-particle induced aggregation inhibited. In presence of Arg-Gly-Asp-Ser (RGDS) (a tetra-peptide, which binds to fibrinogen receptor GpIIbIIIa, mimicking the anti-platelet drug Reo-Pro), nano induced platelet aggregation is again inhibited. This reflects that nanoparticles induced aggregation is not due to any physico-chemical agglomerate formation. Consequently, metallic nano-forms are unlikely to activate platelets from patients under anti-platelet drug therapy (Deb et al., 2011). Alternatively, conjugation of anti-platelet drugs (or combined administration of such drugs) can help to reduce the thrombotic risk of nanoparticle based drug formulation.
5.2 Platelet Response as a measure for nano-safety
In the suspended condition, metallic nanoparticle induced platelet aggregation is highly dependent on the local ADP concentration. A transition of deaggregation to aggregation occurs at a threshold concentration of ADP. Interestingly, nanoparticle effect is most pronounced at this threshold concentration (Deb et al., 2007). This threshold nano-response is perhaps a manifestation of primary triggering of granules release which undergoes an auto-catalysis, ultimately leading to aggregation. As there is a considerable variation of platelet aggregation among individuals, the threshold ADP concentration and extent of enhancement of aggregation induced by the nanoparticle have an individual specific fingerprint. The parameters thus can be used as nano-safety indices. Higher the threshold value and lower the nanoparticle induced aggregation, safer is the nano-drug (Deb et al., 2011).

5.3 Nanoparticles and antiplatelet drugs
Aspirin and Clopidogrel are most widely used anti-platelet drugs for ACS. In many cases dual antiplatelet drug (both Aspirin and Clopidogrel) therapy is used for patient safety (Born et al., 2006, Guha et al., 2009, Faxon 2011, Aragam et al., 2011) Despite the benefits of dual antiplatelet therapy, many patients still suffer from cardiovascular disease due to resistance to such drugs. The drug resistance also increases the risk of the recurrent occurrence of ACS (Guha et al., 2009; Jogns et al., 2006; Michelson et al., 2006). It is thus important to have a quick sensor that will assess the resistance to aspirin or clopidogrel in patients in one step and also assess the equivalence of the drug effects with respect to variations in geographic populations (which may correspond to genetic variations of patient population) and variations in effective drug dose among different drug manufacturers (Deb et al., US patent application, 2011). Interestingly among the ACS patients, one’s showing resistance to the conventional anti-platelet drugs (e.g. aspirin or clopidogrel) respond differentially to gold nanoparticle (~20nm) as compared to one’s responding to it. This differential response can be used as a convenient classifier of responders and non responder to antiplatelet drugs (see figure 8).

5.4 Nano-material nano-surface and nano-response
Though most of the nano induced response is pro-aggregatory in nature, a few reports mention inert nature of some nanoparticles (Li et al., 2009; Ramtoola et al., 2010; Gulati et al., 2010). As most of the nano-particles induce platelet aggregation, so it can be said the aggregatory nature of nano surface depends on its diameter rather than its component material. But this conjecture is not applicable to all nano-forms. Charged surface (aminated - positively charged or carboxylated - negatively charged) polystyrene latex nano-forms are capable of inducing platelet aggregation, whereas unmodified latex beads are unable to do so. Interestingly, the modes of aggregation for positive and negatively charged nanoparticles are different. For carboxylated nanoparticle the aggregation is due to the upregulation of surface adhesion molecules, whereas aminated nanoparticles alter the platelet membrane and interact with the anionic phospholipid (Mayer et al., 2009; McGuinnes et al., 2010). Though both of the charged particles are capable of inducing platelet aggregation, the negatively charged larger particles (larger than 60nm) are shown to be less toxic in the platelet activation context (Mayer et al., 2009). The lesser toxicity of the such particle is probably due to less entry and charge repulsion between nano particles and platelets. Human cell derived nanoparticles that actually accentuate platelet granules
release, inhibit platelet aggregation. This paradox is possibly due to the reduction of platelet-platelet interaction in presence of nanoparticle (Miller et al., 2009). Negatively charged Polyethylene glycol (PEG) coated nanoparticles from Microemulsion precursor (PEG-E78) induces platelet inhibition (Koziara et al., 2005). Importantly, in both pro-aggregatory or antiplatelet responses, the nanoparticles are effective inducer when added in the pre-incubation stage. Neither the inhibition nor the aggregatory response are observed once the aggregation is initiated by an agonist (Koziara et al., 2005; Deb et al. 2007, 2010). Similar argument holds good for anti-platelet effect of silver nanoparticles prepared with a certain surface attributes (Shrivastava et al., 2009). Silver nanoparticles with a different surface conjugations again show pro-aggregatory effects (Deb et al., 2011 (in press)).

Fig. 8. Nanosensor for Drug Resistance in ACS [89]-Using Nanoparticle effect to discriminate between responder and non-responder of antiplatelet drugs (e.g. aspirin and clopidogrel).

The important question that crops up here is whether in the platelet context it is the nano-surface conjugation or the nano-material that play the lead role. It follows that by modulating
the nano-surface, one can tune the thrombotic level, the desirable level depending on the patient status. For ACS, the desired state is a nanoform that attenuates the aggregatory response, and in case of hemorrhage the situation may be complimentary in nature.

6. References


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Acute Coronary Syndromes
Edited by Dr. Mariano Brizzio

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This book has been written with the intention of providing an up-to-the-minute review of acute coronary syndromes. Atherosclerotic coronary disease is still a leading cause of death within developed countries and not surprisingly, is significantly rising in others. Over the past decade the treatment of these syndromes has changed dramatically. The introduction of novel therapies has impacted the outcomes and surviving rates in such a way that the medical community need to be up to date almost on a “daily bases”. It is hoped that this book will provide a timely update on acute coronary syndromes and prove to be an invaluable resource for practitioners seeking new and innovative ways to deliver the best possible care to their patients.

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