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CHALLENGES FOR ENGINEERS IN BIOMEDICAL AND CLINICAL SCIENCES

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NanoEngineering, using the smallest possible material conformations and related technology, is now being used to successfully address some of the world's greatest problems. New approaches for energy conversion and storage, advanced materials and performance, and smaller, more powerful electronics have all benefited from nanoengineering breakthroughs. More recently, nanoengineering is delivering similar benefits in biomedical sciences and health care where Nanoparticles (NP) for diagnosis and therapy hold the most achievable and significant hope for future improvement.

As part of the ASME Nanotechnology Institute, ASME's NanoEngineering for Medicine and Biology (NEMB) Steering Committee facilitates the exploration of challenging life science problems and to improve human health through nanoengineering. The Committee identifies challenges and opportunities for engineers in the emerging area of nanomedicine, and facilitates the cross fertilization among different fields by bringing engineers and biomedical scientists together.

Engineers have developed sophisticated methods and tools for predicting, controlling and directing systems behavior in response to external stimuli; indeed, this practice is one way to define "engineering." However, such tools, which have been developed over decades, have primarily targeted non-biological systems such as airplanes, nuclear power plants, and chemical manufacturing. Developing, applying and maximizing the benefits of engineering approaches to complicated biological processes holds a great promise and poses serious challenges.

On April 20, 2012, more than 25 experts from the nanoengineering and medical research communities met at ASME's Washington, DC office to identify the most pressing challenges that engineers and biomedical scientists must work together to solve. The workshop was organized around three thematic areas:

- Thematic Area 1: **Bioengineering and Biophysics of Wound Healing**
- Thematic Area 2: **Focal Therapy Enhancement with Nanoparticles**
- Thematic Area 3: **Rationally Designed Nanoparticles for Biomedical Imaging and Therapy**

The ultimate goal of the workshop and this white paper is to define key questions in each thematic area and possible solutions via the interdisciplinary alliance between engineers and biomedical scientists.

THEMATIC AREA 1: BIOENGINEERING AND THE BIOPHYSICS OF WOUND HEALING

Wound healing is an extremely complex process that involves multiple biological pathways and many interacting cell types. Researchers have demonstrated the ability of using mechanical, chemical, and electrical techniques to enhance wound healing, making it more effective in a shorter period of time. These bioengineering

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approaches show great promise in accelerating and improving wound healing.

To date, only very limited nanoengineering approaches have been developed for wound healing. Increased collaboration between medical and bioengineering experts in addressing the challenges presented by wound healing will enable a systems-level approach to the development of advanced techniques that exploit engineering and medical breakthroughs. Working together to educate future researchers about systems-level approaches, conduct interdisciplinary studies, and share information and challenges experienced along the way will help to effectively integrate engineering methods into the complex processes of wound healing.

KEY CHALLENGES

Medical and bioengineering experts must work together to share research experience and skills, and collaborate to understand wound healing mechanisms and develop advanced techniques that lead to better healing results. The success of these efforts is dependent on addressing three primary challenges:

- Establishing a better understanding of the biological processes that impact wound healing
- Determining how to accurately model, measure and control the wound healing processes using engineering techniques
- Developing and applying advanced engineering techniques for wound healing that incorporate mechanical, chemical and/or electrical approaches

Establishing a better understanding of the biological processes that impact wound healing

While medical researchers have made great strides in advancing wound healing, biological processes take place that are often unpredictable and can prevent techniques from working as intended, due in large part to *heterogeneity in cell-types, tissue-types and ages of cells*. For example, the variability of mononuclear phagocyte system (MPS)/reticulo-endothelial system (RES) function can affect wound healing and burns in different ways, as can the dynamics of protein–protein interactions in living cells.

Naturally occurring biological phenomena can also be used to the advantage of wound healing techniques. Medical researchers can learn from naturally occurring processes such as self-assembly, bone generation, and muscle atrophy; from the functionalities of different wound micro-environments; and from *similarities that may exist among wound healing, atherogenesis and tumor growth*.

To build more complete understanding, medical experts must determine how biological mechanisms such as myofibroblasts for wound contraction and the interactions of cells and scaffolds (e.g., migration, binding) can be used to the advantage of wound healing techniques. Developing a better understanding of the role of extra-cellular fluid, interactions between intra- and extra-cellular fluid-structures and the role of vascularity and oxygen is also important to improving wound healing, as are the identification of molecular paths and the identification of stress-sensitive genes and their regulators.

Determining how to accurately model, measure, and control the wound healing processes using engineering techniques

The complex interactions of the heterogeneous biological components of wound healing are difficult to model; animal models are often unable to accurately predict human reactions. Incorporating mechanical, chemical and/or electrical

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components into wound healing techniques adds another level of modeling difficulty, as there are currently *no constitutive laws or a mathematical model that links biological, chemical and electrical-signals to mechanical approaches*. Medical and engineering experts must work together to analyze patient statistics and use the findings to reveal new insights that can lead to more comprehensive models. For example, experts may be able to develop "living machines" to mimic behaviors for testing (e.g., climbing up glucose gradient while simultaneously detecting electrical, mechanical and chemical factors).

Experts must also determine ways to validate in silico and in vitro discoveries and techniques in vivo at the nano-micro level. To aid in the development of models and validation techniques, *experts need to develop tools that can more accurately measure biological effects and mechanisms*. Establishing a standard characterization of these tools, data and methods in the field will enable translation across studies or organizations.

Developing and applying advanced engineering techniques for wound healing that incorporate mechanical, chemical and/or electrical approaches

To create new wound healing therapies, medical and engineering experts need to explore novel applications of mechanical, chemical and electrical techniques and the potential synergies of these approaches into systems-level approaches. *Identifying the specific role of mechanical forces in the mediation of tissue organization* and as part of the optimal epigenetic milieu for tissue regeneration is important to the development of effective mechanical approaches. For example, determining the mechanisms and resonant frequencies for how vibrations influence wound healing could allow for innovative vibration-enhanced therapies. Other potential paths for exploration include mechanotransduction for extra-cellular matrix (ECM) expression, intracellular versus extra-cellular mechanical stress/translation and force-induced protein conformational changes in live cells.

To advance chemical approaches to wound healing, experts should investigate novel approaches and applications of wound cover for preservation. This investigation should include graft, de-cellular tissue, artificial tissue and other related options.

Electrical approaches have also shown promise for improving wound healing, making it important to explore the mechanism of electrotaxis and to bring electric healing advances to the wound healing clinic. Regardless of the approach, experts should investigate mechanisms to shift inflammatory response to healing without scarring, which may include developing a better understanding of cell-matrix interaction.

In addition to developing engineering-based approaches, researchers must also address the challenge of *developing methods and devices that can generate and deliver mechanical, electrical and chemical effects at the micro- and nano-scale*. Maintaining control at such a small scale is a difficult challenge to address. For example, ensuring that the right epidermal cells remain in the right locations (e.g., blood vessels) in skin regeneration, potentially using stem cell approaches, and upregulating certain cellular processes while interrupting homeostatic feedback are particularly challenging.

Experts will also need to determine how to control tumor resection site healing while managing the interaction of healing and radio or other adjuvant therapy and how to handle transient response to signals — not just instantaneous responses. Ultimately, modeling and improved control should

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enable researchers to optimize the field parameters, such as cycles, strains and surfaces, necessary to enhance wound healing rates.

Once these advanced techniques are developed, experts will also have to address *the challenge of scaling them up and implementing them to affect clinical outcomes*. A significant part of this process is *overcoming the regulatory hurdles and high initial costs to companies attempting to commercialize new practices*. To date, these barriers have made the development and manufacture of skin cell regeneration technologies unattractive. To help reduce manufacturing costs experts should determine and convey to manufacturers the size requirement variations needed for patient-specific devices.

THEMATIC AREA 2: FOCAL THERAPY WITH NANOPARTICLES

Focal electrochemical and thermal therapies, which have evolved over the past several decades, have shown the ability to effectively complement the existing front line cancer treatments of surgery, radiation and chemotherapy. These adjuvant therapies primarily enhance tumor cell cytotoxicity by changing the thermodynamic environment (thermal, mechanical, electrical or chemical) to provide a more targeted damage to the tumor, without sacrificing critical normal tissues. Such enhancement is essential for the success of any cancer therapeutic, primary or adjuvant, systemic or focal. The challenge in identifying and developing agents that satisfy this conceptually simple but essential criterion is and has been extremely challenging. An important recent development is the design and use of therapeutic NPs in combination with focal therapies. This new family of therapies allows for the specific delivery of increased therapeutic payload to tumor cells, but not normal tissues, thereby improving overall treatment efficacy.

To date, NP-mediated focal therapy experiments have produced some very promising results; however, significant modeling and in vitro/in vivo mechanistic and clinical trial type studies remain to be completed before the technology can be used effectively and safely to treat cancer and other diseases in patients. Understanding how these NP technologies work at the tumor, vascular and cellular level and at what additive or synergistic level is essential. For instance, will the NP be used as a heat source to kill the tumor by laser or radiofrequency excitation alone, or will the NP deliver a drug or molecular adjuvant to pre-condition the tumor environment to act synergistically with an existing focal therapy to destroy the tumor? Such enhanced understanding can only occur if the appropriate engineering, medical and biology expertise can be merged and used collaboratively to develop and translate these complex but highly promising novel NP techniques for improving patient outcome.

KEY CHALLENGES

Nanoparticles have the potential to improve and optimize both the initial destructive and the subsequent wound healing effects of focal therapies. Experts must address the following priority challenges to ensure the successful development and deployment of these advanced techniques:

- Characterizing nanoparticle therapies alone and in combination with focal therapies to establish safety, biodistribution, targeting and therapy enhancement/synergy.
- Developing and validating accurate nanoparticle therapy experimental models and protocols to study enhancement.

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- Theoretical modeling of nanoparticle delivery and activation in real-time for controlled therapeutic benefit. Determining methods for model validation that can be easily and accurately used for feedback and model improvement.

Characterizing nanoparticle therapy and defining its safety and advantages

Medical and engineering experts need to work collaboratively to characterize existing NPs and their functionalities in the context of focal therapies, including defining which NPs are most appropriate for certain therapies and why. Part of this work involves identifying a specific clinical application in which NPs are truly enabling; for example i) enhancing focal thermal therapies by synergistically increasing the treatment zone; ii) delivery of these NPs to specific locations to ensure the effect that is intended; iii) enhancing control of the treatment zone via specific drugs or adjuvants on the NP; iv) or using NP-mediated therapies to trigger sensitization instead of ablation. Appropriate treatment, dosimetry and follow-up biology, imaging and pathology co-registration studies will be essential for accurate validation of NP delivery and biomedical effect.

Understanding how to characterize NP-based therapies is essential to an enhanced treatment goal. Identifying the relative and specific characteristics of NP therapy alone compared to conventional, main stream therapies will enable medical experts to determine which treatments are better suited for specific scenarios. For example, researchers need to determine whether it is better to use tumor target effects such as NP based heat to enhance systemic anti-cancer therapy or use NP targeting of drug therapies that are conventionally used in a systemic or regional manner. Improving tumor cell delivery and reducing toxicity are key. Establishing the further benefit of "targeting" the NP with a ligand specific to the tumor and/or using focal heating or other "conditioning" of the tumor to enhance vascular uptake of NPs is also a very important and achievable goal. These and other experiments will help researchers understand when NP therapies can offer unique advantages and patient benefit.

There are several important aspects to demonstrate in the NP enhancement of focal therapies: i) defining uniformly acceptable and achievable *endpoints for terminal damage and subsequent healing at the treatment site*; ii) describing reproducible techniques and methods for evaluating the mechanisms of damage at the sub-cellular, cell, vascular and tissue level as a result of therapy; and iii) demonstrating long-term safety and the safety/therapeutic ratio of NP treatment to support its use in the clinic.

To aid in the characterization of NP therapies, experts must first develop a better understanding of thermal treatment effects. This may not be measurable by even with the most sophisticated conventional thermal measurement techniques and algorithms and dose approaches (e.g., low dose, long time vs. high dose, short time) as well as the relative efficacy of mono-therapy versus adjuvant NP therapy. If *combination therapies are determined to be most effective, researchers will need to work together to combine the therapies, including establishing mechanisms and timing*.

Developing and validating accurate nanoparticle therapy models and protocols

A major challenge to the implementation of novel focal therapies using NPs is to *develop models that accurately and consistently predict therapeutic outcomes*. Modeling the NP complexes for gene/drug delivery is best accomplished using

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combination of physical experiments both in vivo and in vitro and modeling in silico. To ensure efficiency, experts should consider conducting experiments in vitro, building models based on the experimental results, and then improving and ultimately validating the models using in ex vivo and in vivo techniques. It is important to include both animal and mathematical models that cross multiple-scales of sub-cellular, cellular, micro-environment, tissue and organs to provide complete, systems-level insights.

As part of this modeling effort, experts must address the influence of tumor biology and expected biological variation, especially on the delivery of the NP itself. For instance, while NPs can be locally injected into a tumor under image guidance, systemic injection of NPs is far quicker, cheaper and under some circumstances may yield not only a greater concentration of NPs but a more uniform distribution of NPs in the cells being targeted. Thus, understanding and measuring and quantifying the barriers to local and systemic delivery of NPs to tumors (i.e., vascular, interstitium, immune and cellular) is of great interest and importance to the field. In this context, experts should clearly identify the most appropriate models for tumor delivery and pharmacokinetics (PK), which affect simulations of dose and amount of NP delivery to tumors. Importantly, the vascular permeability (leakiness, enhanced permeability and retention effect) in human tumors is often different than in rodent tumors and also the tumor type (e.g., epithelial vs. mesenchymal) and growth kinetics also have a major influence on the ability of systemically delivered NPs to get to tumor cells. NP uptake by tumor cells is a critically important and understudied area that requires a diversity of expertise to be clarified in a manner that enhances therapy. Further, the blood and tissue biodistribution of NPs requires additional study. Specifically, the interaction of NPs in the cells of the blood (including circulating tumor cells and monocytes) and their behavior in metastatic vs. primary tumor tissue need to be carefully assessed to understand and harness NP tumor uptake for improved focal therapy of cancer.

Modeling nanoparticle delivery and activation in real-time for controlled therapeutic benefit

Key to the success of NP-mediated focal therapy is to deliver functional NPs to the targeted areas at the proper time followed by NP activation or delivery of an enhancing second modality, for improved treatment. Towards that end, it is necessary to develop capabilities to predict, manipulate and control location and biodistribution of NPs and their activation (i.e., heating or drug release) for improved therapeutic outcome.

To ensure that predictive theoretical models cover all aspects of the NP delivery system, experts should explore and account for mass and energy transport at the particle-blood or fluid interface in vascularized and realistic tissues with lymphatic drainage. *Models should also consider cell sensitization and sensitivity and resistance to heat* (e.g., for temperature based destruction: heat shock protein response, thermal dose and the impact of cell cycling). In developing computational models, mesh generation of complex biological systems needs to be addressed, especially in the case of patient-specific setting where NP-tumor biodistribution may need to be accurately assessed with imaging to obtain optimal treatment effect.

Researchers should be able to use these models to address the challenge of increasing the in vivo targeting efficiency of NPs, thereby enabling real-time imaging, surgical monitoring and control. Ultimately, the major challenge is to develop modeling capabilities that result in an NP treatment that enables the targeting of single cancer

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cells, or at least small groups of cells, without damage to healthy cells—essentially identifying the difference between healthy and cancer cells at the sub-cellular or molecular level, exploiting this with NPs to guide a physical process that destroys the cancer. It should also help to develop a systematic modeling approach for treatment optimization that includes i) aspecific patient geometry; ii) a specific cancer target; iii) a specific focal therapy with well understood and controlled temporo-spatial dosimetry parameters; and iv) a specific NP with well understood adjuvant treatment efficacy and toxicity parameters (therapeutic ratio).

THEMATIC AREA 3: RATIONALLY DESIGNED NANOPARTICLES FOR BIOMEDICAL IMAGING AND THERAPY

Nanoparticles (NPs) are small carriers that can be loaded with therapeutic and imaging agents and safely navigate within the circulatory system upon intravenous injection. Many classes of NPs have been developed for diverse biomedical applications, including the treatment and imaging of cancer and cardiovascular diseases. Over freely administered molecules, NPs offer several advantages such as (1) *multifunctionality:* multiple therapeutic and imaging molecules can be loaded within the same carrier and codelivered at the biological target; (2) *engineerability:* multiple parameters can be controlled during the manufacturing process to improve the in vivo performance (size, shape, surface properties, stiffness, etc.); (3) *remote controlling:* specific NP components can be activated through endogenous and/or exogenous energies and thus trigger the release of drugs or other signals at a specific site and time.

The rational design of NPs has the objective of developing carriers that could encompass all of the above features. This would generate an ideal carrier i) circulating within the body without being recognized by or stimulating the mononuclear phagocyte system (MPS – immune response), and ii) capable of identifying with high selectivity the biological target and accumulating thereof at high concentrations to release upon temporal command precious payloads. Indeed, this sequence of events and the spatio-temporal precision required would also describe the expected performance of a military unit on a mission.

Nanoengineers have a substantial role to play in rationally designing NPs. They must work with medical experts to determine how the many biological, biophysical and biomechanical differences between normal and abnormal tissues (the biological target) can be leveraged to maximize the in vivo performance of NPs.

KEY CHALLENGES

Improving nanoparticle design will aid in the optimization of biomedical imaging and therapy. To do this, the priority challenges that follow must be addressed:

1. Identifying the optimal NP feature combination via an integrated approach;
2. Understanding the interaction of NPs with the immune system
3. Improving the understanding and control of nanoparticle dosage, delivery and distribution

Identifying the optimal NP feature combination via an integrated approach.

The effect of NP size and surface properties on their in vivo behavior, therapeutic and imaging efficacy has been extensively studied and documented over the last two decades. More recently, novel

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nanofabrication strategies have been developed that allows us to synthesize particles with shapes other than spherical. This has fostered new theoretical, in vitro and in vivo studies that have confirmed the importance of NP shape in controlling the vascular behavior, cell internalization dynamics and differential organ accumulation. However, in addition to the size, shape and surface properties, a fourth parameter should be considered in a comprehensive approach to the rational design of NPs: stiffness, or the ability of particles to preserve their size and shape, at different degrees, under externally applied forces, such as hemodynamic, adhesive and electromagnetic forces.

Interestingly, the peculiar behavior of red blood cells and leukocytes in the vascular and extravascular compartment derives from the fine orchestration among their size, shape, surface properties and mechanical stiffness. The first challenge in the rational design of NPs is to *understand the role played in vivo by each of these four independent parameters (the 4S parameters), and their combination*. Is there any optimal combination that would maximize NP accumulation at the biological target? Is this combination depending on the type of biological target (tumor, atherosclerotic plaque) and on the site where the disease is developing (lungs, brain, abdominal cavity)?

An integrated approach is needed to address these questions, where mathematical modeling, in vitro assays and in vivo small animal experiments are combined. In this context, nanoengineers can contribute on modeling the transport and adhesion dynamics of NPs within the blood flow and in the extravascular space. But engineers would be also crucial in developing sophisticated microfluidic chips, resembling the complexity of the authentic normal and abnormal vasculature and in performing in vitro, microfluidic experiments with a high level of accuracy.

Another challenge for the 4S problem is in manufacturing, on a large scale, NPs with a precise control on size, shape, surface and stiffness. Methods for NP batch formulation and for controlling independently the 4S parameters during manufacturing (i.e., developing new approaches for the "accurate" synthesis of NPs with clinical grade and high yielding) are important challenges that must be addressed in this area, with the goal of facilitating the use of multifunctional NPs in vivo as soon as possible.

Understanding the interaction of NPs with the immune system.

Overcoming biological and pharmacological barriers in tumor biology alone is perhaps one of the most substantial challenges to improving the effectiveness of NP therapy. There exists such a high and clinically relevant inter- and intra-patient variability in pharmacokinetics (PK) and pharmacodynamics (PD) of drug molecules that even the greatest level of investment in NP design may not be able to overcome it. As a result, experts must explore this area before significant progress can be made.

This is particularly relevant for the NP interaction with the mononuclear phagocyte system (MPS), i.e., the large number of monocytes and macrophages accumulating in the lymph nodes, spleen and liver and dedicated to the continuous surveillance of our body. *High levels of inter- and intra-patient variability in MPS function exist, requiring experts to determine whether these variances are attributable to patient factors, mediators or other treatment variables, to gain a better understanding of how different types of NPs will interact.* Evaluating the variability of the MPS function on the PK and PD of NPs is critical,

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as is determining whether the MPS captures or hijacks the NPs.

For cancer applications, experts must also explore the actual occurrence and significance of endothelial fenestrations in the tumor microvasculature. Therefore, they should *clearly assess the relevance of the enhanced and permeation retention (EPR) effect in humans*. If EPR does occur in patients, researchers must determine how to quantify its relevance. If EPR is not relevant in humans, the current paradigm on designing sufficiently small particles (100 nm – 200 nm) with long circulation times could be responsible for the failure of many nanotechnological platforms in clinical trials.

Multi-scale imaging and mathematical modeling is one potential method for addressing the intrinsic variability of biological and pharmacological systems. Personalization via multi-scale imaging and modeling, including statistical tools within deterministic, validated modeling, can deliver high prediction accuracy. Assessing PK and PD at a multi-scale level can help overcome the issue that preclinical animal models do not predict PK and PD efficacy, and toxicity in patients.

Improving the understanding and control of nanoparticle dosage, delivery and distribution

Nanoparticles can be designed to deliver ideal dosages to eliminate tumors and enhance biomedical imaging. Determining when intervention is important is a critical first step in any treatment. Once assessed, meaningfully addressing allometric NP dosimetry issues and the predictability of dosage is critical to the success of the imaging or therapeutic treatment.

The improved delivery of NPs can also be addressed from a design standpoint. Exploring why monoclonal antibodies are more effective than current NP technology and how the aggregation of particles can be achieved through proteins or other methods is useful in developing a better understanding of designing NPs for optimal delivery. Addressing the multi-mode transport of NPs within their design is also a challenge to address.

In addition, *experts must determine whether active targeting of NPs is better than passive targeting, considering formulation and tumor biology issues*. Part of this effort should include examining passive versus active targeting, including demonstrating the active targeting of NPs and developing a method for localized activation of the warhead, and modulating actively and passively the 4S parameters in vivo.

NP partitioning into the heterogeneous tumor poses a substantial challenge to distribution that desperately needs new and creative ideas. Determining how to conquer the tumor micro-environment and defining the level of improved tumor accumulation regarding treatment versus toxicity that is sufficient to support nanomedical approval are both challenges that remain. Researchers must also ensure that spatial and temporal control of NP transport and clearance after the treatment can be maintained.

In addition to addressing the different functions of NPs through design, experts must also address the challenge of predicting the distribution of NPs at the whole animal/patient level as a function of the size, shape, surface and stiffness (4S parameters) modeling the transport of NPs and molecules over multiple spatial and temporal scales. *Imaging patients over multiple scales, from the molecular to the organ level, to extract parameters for accurate predictions via the development of clinical grade nano-based contrast agents with multimodal capability (PET/MRI; optical*

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imaging/MRI) is also a challenge for engineers and scientists to be addressed.

CONCLUSION

This summary of the April 20 meeting briefly identifies the most pressing challenges that engineers and biomedical scientists can effectively address by working together.

Developing a mechanistic understanding of medical processes over multiple scales, building predictive models for treatment options, rationally designing nano-based therapies using engineering approaches and integrating imaging over multiple scales using nano-based contrast agents are some of the challenges outlined in this paper that requires a strong, dedicated interdisciplinary effort.

The promise they hold merits a call to action on behalf of researchers and potential funding agencies looking to begin or expand funding nanoengineering and nanomedical research and development.

This has been the first such initiative organized by ASME and was focused on three specific thematic areas covering health treatment options and improved wound healing, cancer treatment and overall human health.

Future events supported under the NEMB umbrella will be the First Venice NEMB Workshop on Cancer Nanotechnology to be held in Venice (IT) on October 11 and 12, 2012 (http://nemb2012.cism.it/); and the 2nd Global Congress on Nanoengineering for Medicine and Biology to be held in Boston on February 4-6, 2013. (http://www.asmeconferences.org/NEMB2013).

The NEMB Steering Committee remains committed to its goal of advancing techniques for improving health through nanoengineering and welcomes suggestions for additional similar initiatives.

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