Editorial overview: Nanobiotechnology at a crossroads: moving beyond proof of concept
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Introduction

Interest within the scientific community for specific thematic areas can fluctuate, waxing or waning depending on the current scientific climate, the availability of new techniques, as well as changes in business cycles. Due to these factors, certain scientific disciplines are given more or less attention over time. So is the case for the interdisciplinary work encapsulated under the term ‘nanobiotechnology’. Inquiries into several bibliometric databases (e.g., ISI Web of Knowledge, Google ngram viewer, Google Scholar) indicate that the term came into use in the early 1990s, and maintained very low levels of usage until around 2001, when its use began to accelerate rapidly. In 2001, there were fewer than 200 articles published containing the term. By 2015, that number had ballooned to 5120.

The growth rate of the field, however, appears to be abating. Based on data from Google Scholar, from 2013 to 2015, the number of articles containing the term grew only 8.2%. A decade earlier from 2003 to 2005, the growth rate was closer to ~190%. This slowing of the growth rate indicates that a certain level of maturity is being reached in the field. We may be entering a period where most of the proof-of-concept studies have been done. The low hanging fruit has been plucked, and scientists are faced with solving the remaining hard problems. It is not without great resolve that the authors in this special issue are tackling these hard problems head on. We have assembled an impressive and broad list of topics, ranging from delivery of biologic drugs, to development of dynamic biomaterials and composites, to single-molecule characterization methods. As co-guest editors, we feel honored to be able to bring you this distinguished lineup of current topics.

Protein-based nanomaterials

Some of the most attractive features of protein-based nanomaterial is their plasticity and ability to modify specificity either by genetic engineering of their coding sequence or post-translation modification. Aghaei-Ghareh-Bolagh et al., demonstrate elastomeric protein alloys with silk fibroin as an effective tool to enhance biomechanical and biological properties leading to a new class of protein alloy materials with versatile properties. Dinjaski and Kaplan report on recent advances in recombinant protein blends: silk beyond natural design. Utilizing genetic engineering with computational modeling to analyze sequence–structure–function relationships while discussing current production methods limitations.

Domeradzka et al. report on recent progress in techniques for covalent bond formation between proteins and peptides. They identify several important strategies used by nature for covalent protein cross-linking, and describe...
systems that can be engineered to formulate non-natural protein structures (e.g., branched, Y-shaped) and to link polypeptides into higher order nanostructures. As this field develops, it will be interesting to see how non-natural protein topologies perform in biomedical settings, for example, as platform materials for protein gels and as drug delivery vehicles.

**Nanomedicine and drug delivery**

It became clearer in the recent years that nanotechnology offers great potential in medicine. The ability to increase target specificity, and delivery of drugs across biological barriers can change the way we treat patients while increasing efficacy and reducing side effects. Singh and Peer report on RNA nanomedicines: the next generation drugs. While the potential of RNA therapeutics could represent the next generation personalized medicine, the delivery of RNA molecules to their target is still one of the obstacles to realize this huge potential. In this paper the authors focus on the challenges and opportunities of the delivery of therapeutic RNAi molecules into cancer cells with special emphasis on solid tumors and tumor microenvironment.

Lühmann and Meinel are taking a different angle on this field and report on novel nanotransporters for drug delivery. They describe hybrid molecules made of albumin and various drug linkers for site specific release of the drug payload. This technology enable better use of very potent cytotoxic drugs that otherwise may have short residence time and severe side effects.

**Single-molecule analysis**

The 2014 Nobel Prize in chemistry awarded to Betzig, Hell, and Moerner for the development of super-resolved fluorescence microscopy indicates the high level of interest in far-field light microscopy that can break the diffraction limit. One recently developed method for achieving superresolution fluorescence imaging, highlighted in this issue by Molle et al., is referred to as superresolution by transient binding. Due to the ease with which biological molecules can be tuned to transiently bind and unbind specifically, and with controllable bound lifetimes, the transient binding method for superresolution imaging is particularly suitable for imaging of biological samples. The long term goal would be to quantify the positions and concentrations of specific biomolecules within the cell, to shed light on fundamental biological processes.

Schlichthaerle et al. provide an overview of DNA nanotechnology and fluorescence, focusing on tools to study a multitude of properties of well defined arrangements of biomolecules, enzymes, fluorophores and plasmonic nanoparticles. They describe the use of DNA nanotechnology as a ‘molecular breadboard’ for precise positioning of these objects, which can then be characterized and interrogated using superresolution microscopy.

Alternative approaches to single-molecule analysis also include utilizing the Coulter counting principle on the nanoscale to perform nanopore sensing and single-molecule DNA sequencing runs. For systems relying on biological nanopores embedded in lipid membranes, the system performance is limited in part due to issues such as membrane stability, longevity, and storage. Schmidt provides an overview of the current state-of-the-art in nanopore sequencing and of recent developments for addressing the shortcomings of membrane platforms to support single-molecule analysis. Banterle and Lemke highlight recent advances in single-molecule fluorescence imaging methods that do not require tethering of the molecules to a surface. This so called ‘linker-less’ approach has the advantage of increasing observation times, not requiring chemical immobilization, and allowing the
biomolecules to freely diffuse in a more ‘native’ environment, thereby expanding the number of systems that can be analyzed.

**Stimuli-responsive and polymeric materials**
As our ability to control linkages between proteins and synthetic materials improves, new hybrid systems are being enabled which combine synthetic and biological components. In this context, Malinowska and Nash provide an overview of synthetic polymerization reactions catalyzed or mediated by biological molecules. This approach shows promise for a number of important application, including non-instrumented biodetection and single-cell analysis.

**Bou et al.** describe the techniques and potential applications of ‘smart’ stimuli-responsive fibers. They organize the literature by classifying fibrous nanomaterials based on stimuli, methods of fabrication and application area. Some of the more modern applications of these materials include modulation of mechanical moduli of hydrogels, and cell encapsulation and release.

**Morris et al.** describe their vision for the field of dynamic biomaterials, which combines synthetic biology, gene expression control and micro-to-nanoscale biomaterials. This discipline represents an emerging category of ‘smart’ materials that are stimuli-responsive in a more complex way than conventional stimuli-responsive biomaterials. By implementing logics gates, feedback loops, triggered reactions and signaling cascades into nanoscale compartments, these systems provide new levels of control in potential biomedical applications. One of most challenging in almost any system which is exposed to the environment is prevention of biofilm development. **Nir and Reches** describe Bio-inspired antifouling approaches by combining bio inspired nano bio building blocks such as DOPA from the mussels with synthetic chemistry.

**Composite nanomaterials**
Composite materials have gained enormous interest in the last few decades, owing to the fact that they enable us to build light and strong airplanes, cars, boats, sport goods, personal shield, orthopedic implants and more. The ability to interface materials with different mechanical, spectral, electrical and biological properties at the nano scale is of great interest in almost any field of life. **Abitbol et al.**, describe in their report Nanocellulose, a tiny fiber with huge applications. Nanocellulose exhibits unique properties including its renewable nature, anisotropic particle shape, excellent mechanical properties, good biocompatibility, tailorable surface chemistries, and interesting optical properties. It represents one of the most important nanomaterials for or future. From flexible optoelectronics, structural composites to scaffolds for tissue regeneration. Another class of new nano composites is described by **Behrens and Appel**. Magnetic nanocomposites are multi-component materials, containing nanosized magnetic materials to trigger the response to an external magnetic stimulus. These materials include gels, liquid crystals, renewable polymers, among others. Magnetic nano composites has the applications in medical therapy and diagnosis, separations, actuation, and catalysis.

**Conclusion**
The promise of the scientific community to improve the wellbeing of the society while preserving our natural habitat may only be realized if we will have the wisdom to learn from billion years of evolution in nature. Noy Dekel, a young talented artist describes it so vividly in her piece of art displayed in our cover. The nano bio building blocks that are the makeup of all living materials is Nature’s Gift to us.

**Conflicts of interest**
None.