Bio-Nanotechnology Challenges for Intelligent Materials

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Introduction

The world is rapidly and drastically changing toward the knowledge-based society with accelerated globalization, where innovative efforts have been concentrated in creating new knowledge specifically through sciences and technology. It is recognized that the interdependence of different sciences and technology disciplines is effective on emerging innovative knowledge. In a last decade, there has been a significant nanotechnology initiative promoted throughout the world. It is noted that nanotechnology has made it possible to explore the biological information world in nanometer scale. Either Bio-Nanotechnology or Nano-Biotechnology has thus been evolved through these science and technology melding process of biotechnology and nanotechnology. New knowledge derived from the bio-nanotechnology challenges on the biological information world continues to emerge. Which seems to have a great concern with the achievements of safe and high quality living.

Bio-nanotechnology has made a profound progress on detecting, tracking and manipulating single biomolecules in an ambient environment, and visualizing the deep insight of a living cell which contains sophisticated biological information networks. A cell responds to either inner or outer stimuli by processing the information through the molecular information networks involving the signal transduction cascades and gene information processes. Bio-nanotechnology measures reveal that the informative information processing is conducted through the nanostructural changes of signal transduction molecules. It is amazing that a whole cell as well as the intracellular molecular assemble behave in an intelligent manner even though they have no brain.

Intelligent materials are modeled on such cellular and molecular response to stimuli. The bio-nanotechnology-based mechanisms may provide us with a possible design concept of intelligent materials in which the sensing, information processing and actuating functions are implemented. Intelligent materials may behave in an intelligent manner, facing extremely high performances such as human-friendliness, self-diagnosis, self-repair, self-control, adaptive, learning and other intelligent characteristics. In fabricating intelligent materials, the sensing, information processing and actuating functions should be integrated in such a fashion as to be interactive in nano-scale. The design concept of intelligent materials is schematically illustrated in Figure 1.

Promising bio-nanotechnology challenges have been emerging in designing various intelligent materials that are strongly supported by bio-nanotechnology progress including not only nano-scale measurement but nanoscale control and manipulation. Unique intelligent molecular intelligent biomaterials have been developed by bio-nanotechnology challenges, which involve nano-probes for molecular imaging, and nano-particles for mRNA replication.

Bio-nanotechnology is quite effective on enhancing intelligence of a living cell. Animal cells may respond to chemical stimuli through the receptors on the membrane surface. On the other hand, they are found responsive to such physical stimuli as electric and mechanical stresses. Since these stimuli modulate the gene expression processes, some physically responsive promoters have been surveyed out. Gene engineering makes it possible to enhance intelligence of animal cells to respond the electric signal in such a way as modulating the gene expression.

Challenges of bio-nanotechnology have also been emerging in developing either nano-scale or micro-scale biosensors for diagnostic, therapeutic, validating safety of chemicals, and drug discovery. Marked progress has been accomplished on developing nano-scale biosensors for intelligent drug delivery, which is capable of selective incorporation of drug into a targeted cell. It is stressed that a variety of cellular bio-devices have been under investigation for both therapeutic and diagnostics. These feature cellular bio-devices for pancreas alternative, on-demand drug delivery, and safety check of chemicals as animal test alternative.

The current aspects and perspectives of bio-nanotechnology challenges for intelligent materials and systems are overviewed with ongoing researches and developments.

Self-diagnosis, Self-repair, Self-control, Adaptive, Learning, Human friendliness, Extremely high performance with intelligence

Figure 1, Concept of Intelligent Materials

Bio-Nanotechnology Challenges (1) Intelligent Molecular Biomaterials : Nano-probes for Molecular Imaging

Recently molecular imaging in nano-scale has gained an increasing attention because of its powerful approaches to the real world of individual biomolecules in an ambient environment and even in a living cell. Molecular imaging is mostly based on optical, electrical and mechanical force measurements. Several categories of molecular imaging have intrinsically been investigated as listed below.

- Single molecular imaging
- In vivo, in vitro
- Intracellular Molecular imaging
- Distribution of individual moleculaes
- Conservation of individual molecules
- Dynamic molecular interaction
- Intracellular Molecular imaging
- Information processing in neuro-networks

Molecular imaging is carried out with or without probe. Although non-probe imaging is preferable, probe is required in most cases for enhancing sensitivity. Bio-luminescent enzymes and fluorescent protein are widely used as probe for molecular imaging. Intelligent nano-probes have been developed by gene and protein engineering.

Fusion protein of firefly luciferase and Protein A is a unique nano-probe which has a catalytic function of bio-luminescence at an end and a specific binding function at the other. The gene of the nano-probe is first synthesized by ligating luciferase and Protein A genes, which is followed by expressing it in bacterial cells. The nano-probe finds application in various highly sensitive analyses. Kobayashi et al show that the nano-probe of firefly luciferase and Protein A is effective on detecting local dynamic flow of ATP at the cellular membrane surface. The nano-probe is specifically anchored at immunoglobulin on the membrane surface and generates bio-luminescence from luciferase in presence of ATP. Bio-luminescence intensity reflects the local concentration of ATP.

Gene probe of Firefly luciferase or green fluorescent protein (GFP) is also a unique nano-probe, which is expressed in a living cell. The gene of firefly luciferase or GFP is inserted in adjacent promoter which is activated to be activated in gene expression.

Figure 1 Two types of nano-probes
Bio-Nanotechnology Challenges (2)
Engineered Cells for Enhancing Intelligence

A living cell behaves in an intelligent manner, when it is stimulated by either exterior or interior stress. The cellular response is restored from the information processing through the intricate information network. It was found that growth of a promoter on hsp70 is responsive to not only electric but also hydrostatic pressure stress. A small voltage and low frequency of electric stimulation activates hsp70 to trigger transcription of the corresponding gene. The promoter is also activated by extremely high hydrostatic pressure. These findings lead to design engineered cells which enhance intelligence with electric or mechanical direction.

A gene of target and a promoter of hsp70 are inserted into a plasmid, which is followed by transforming a cell of interest to enhance intelligence. The engineered cell may respond in such a way as segregating the gene of target with a direction of electric or mechanical stimulation. Schematic concept of such an intelligent cell is illustrated in Figure 3.

An example of the intelligent cell is a microchip alternative cell that secretes human insulin with electric direction. An animal cell of candidate is selected for a microchip alternative cell. The candidate cell is not required to produce human insulin, indicating that cells without human insulin gene may be selected. A fibroblast cell is, for instance, used for further research. The cell is transformed with a gene of human insulin and hsp70 promoter. Production of human insulin is switched ON and OFF by electric stimulation. Figure 3 illustrates the scheme of the electrically directed insulin production and secretion.

![Figure 3 Electrically directed insulin production and secretion](image)

Bio-Nanotechnology Challenges (3)
Biodetectors for Diagnosis and Prevention

Biodetectors are intelligent devices that molecular or cellular bio-components are implemented, although they may involve intelligent devices that biological function is controlled with artificially designed systems. Research and development of biodetectors for diagnosis and prevention have made an enormous progress in these decades, starting with an enzyme sensor for blood glucose. Extensive research has been extended over the wider range of community, resulting in biomarker innovation specifically for diagnosis and prevention.

In the early 1990's, a series of DNA chips have encouraged many students and engineers who are involved in research and development of biodetectors. During the 1990's, the DNA chip has revealed many potential applications. The technology is currently being utilized in research and development of biodetectors.

Bio-Nanotechnology Challenges (4)
Biodetectors for Therapeutics and Prevention

Biodetectors for Therapeutics and Prevention

A variety of micro-structured biodetectors for drug delivery have been under investigation by many researchers. Some have been reported in USP Program of Virtual Laboratory in Nanotechnology. Multi-functional Nano-structured Devices for Non-viral Gene Delivery, in which polymer microspheres nano-structured devices and envelope type micro-structured devices are under investigation.

Other bio-nanotechnology challenges are exemplified by cell sheet and cellular biodetectors for therapeutics and prevention. Okano and his colleagues are successful in development of cell sheet that is cultured cells on a thermo-responsive polymer sheet.

The perspectives of biodetectors for therapeutics and prevention are presented as follows.

- Intelligent cellular bio-materials for regenerative medicine
  - Regenerative materials
  - Tissue engineering
- Biodetectors with living cells
  - Tissue replacement
- Cellular biodetectors
  - Nanotechnology
- Biodetectors with nano-materials
  - Nano-structured devices for drug delivery
  - Nano-structured devices for gene delivery

Conclusion

Bio-nanotechnology challenges have been emerging in development of molecular and cellular intelligent bio-matrices, engineered cells for enhancing intelligence, biodetectors for diagnosis and prevention, and biodetectors for therapeutic and prevention. The perspectives of bio-nanotechnology challenges are overviewed.

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