

Drug and Gene Delivery



Thixotropic gel for 3D cell culture.

IBN
TECHNOLOGY PORTFOLIO



About IBN

The Institute of Bioengineering and Nanotechnology (IBN) is the world's first bioengineering and nanotechnology research institute. Since 2003, IBN has been conducting interdisciplinary research bridging science, engineering and medicine. The Institute's strengths lie in its synthetic capability for chemicals, materials and biologics. IBN has developed unique technology platforms that combine novel catalytic chemistry, biomaterials, nanofabricated devices and microfluidic systems with biological engineering. Its highly collaborative environment also promotes the sharing of ideas, expertise and infrastructural support, and a culture that encourages innovative research and the nurturing of young talents.

IBN's research activities are focused in the following areas:

Drug and Gene Delivery, where the controlled release of therapeutics involve the use of functionalized polymers, hydrogels and biologics for targeting diseased cells and organs, and for responding to specific biological stimuli.

Cell and Tissue Engineering, where biomimicking materials, stem cell technology, microfluidic systems and bioimaging tools are combined to develop novel approaches to regenerative medicine and artificial organs.

Biodevices and Diagnostics, which involve nanotechnology and microfabricated platforms for high-throughput biomarker and drug screening, automated biologics synthesis, and rapid disease diagnosis.

Pharmaceuticals Synthesis and Green Chemistry, which encompasses the efficient catalytic synthesis of chiral pharmaceuticals, and new nanocomposite materials for sustainable technology and alternative energy generation.

As of February 2011, IBN has filed over 1,168 patent applications on its inventions and the Institute is currently looking for partners for collaboration and commercialization of its suite of technologies.

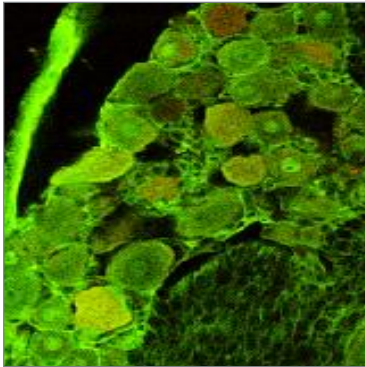
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Drug and Gene Delivery



▲ Confocal micrograph of DRG with luciferase expression.

Growth Factor Gene Delivery and Nerve Regeneration

The feasibility of gene transfer to the rat dorsal root ganglia (DRG) *via* lumbar intrathecal administration of gene delivery vectors is explored. The therapeutic effects of cDNA encoding growth factors delivered in this manner are examined in a nerve injury and regeneration model that uses nerve guide conduits to promote the outgrowth of transected rat sciatic nerves. The gene delivery method developed would be non-invasive to the nervous system and feasible for repeated administration of therapeutic genes. In addition to simulating re-growth of injured nerves, this method has the potential to be used in other clinical applications involving the peripheral nervous system.

Advantages:

- Effectively delivers genes *in vivo* to the DRG.
- Non-invasive to the nervous system and permits multiple administrations for gene delivery to the lumbar DRG, which receives sensory signals from the lower extremities.

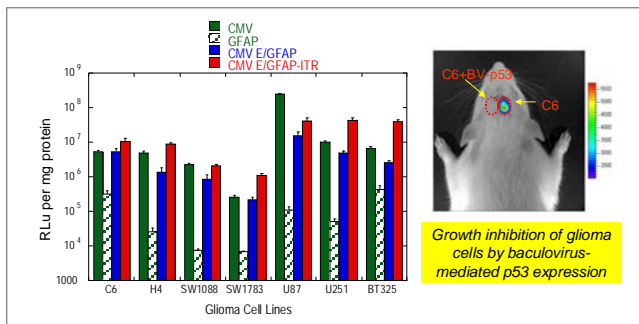
Applications:

- Non-invasive gene delivery in the nervous system.
- Stimulates regrowth of injured nerves.
- Clinical applications in the peripheral nervous system, including the treatment of diabetic neuropathy and other forms of peripheral neuropathies involving DRG neurons, the relief of pain caused by neuropathies, neural injury, inflammation or tumor invasions, and protection from neuronal degeneration caused by genetic mutations.
- Facilitate functional studies of genes that are involved in physiological processes of peripheral nerves.

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Baculovirus Vectors for Gene Therapy and Stem Cell Engineering in Treating Glioma and Neurodegenerative Diseases

Baculovirus-based vectors are recently introduced as a new type of delivery vehicle for transgene expression in mammalian cells. These viruses can enter, but do not replicate in mammalian cells. With mammalian expression promoters, recombinant baculoviruses provide high transduction efficiencies in many different types of cells and tissues, including neurons and tumor cells. IBN researchers have engineered baculovirus vectors to enhance their capability for gene transduction. Effective DNA delivery systems are being developed that will be applicable to the gene therapy of neurological disorders and brain cancers, as well as stem cell genetic engineering. In addition, a TMEM18 protein-encoding nucleic acid that regulates the migration of neural stem cells towards glioma cells has also been identified.



◀ Baculovirus/adeno-associated virus hybrid-mediated gene transfer for gene therapy of gliomas.

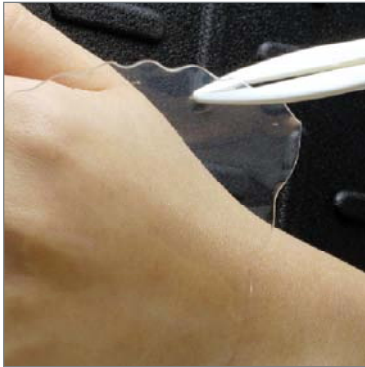
Advantages:

- Relatively safe. The virus will not recombine with pre-existing viral genetic materials in mammalian cells and produce little to no microscopically observable cytotoxicity inside mammalian cells, even at a high dosage.
- Large cloning capacity conferred by its 130 kb viral genome, which may be favorably used to deliver a large functional gene or multiple genes from a single vector.
- Easy construction of a recombinant viral vector and the simple procedure of purifying large quantities of viruses with high titers offers the possibility of scaling up this less labor-intensive process to pharmaceutical levels.
- Tackles the current failure of treatment (chemical or gene therapy) not reaching the glioma cells.

Applications:

- One of the newly developed baculovirus vectors may be used for glioma treatment, providing high-level and cell-type specific gene expression for safe and effective therapy.
- Another baculovirus vector developed by IBN can be used for gene delivery into neurons, offering the opportunity of gene therapy for neurodegenerative diseases, such as Alzheimer's and Parkinson's disease.
- The third type of baculovirus vectors was designed and developed for stem cell genetic engineering. This vector is effective in mediating gene transfer in human embryonic stem cells.

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▲ The transparent dressing can be used to treat different types of wounds.

Nanostructured Temperature-Sensitive Wound Dressing

IBN researchers have developed nanostructured polymeric membranes with temperature-dependent swelling properties. At lower temperatures, these transparent membranes swell and become less adhesive, allowing the dressing to be removed from the skin easily and without pain. In addition, these transparent membranes allow constant observation of the wound, while providing a moist wound-healing environment without an adhesive layer. When applied to an exuding wound, the membrane rapidly absorbs moisture and adheres to the surface without secondary retention materials. Therapeutics can be encapsulated within the membranes to accelerate the wound healing process. Cells also attach well onto the thermosensitive membranes at 37°C, but detach at low temperatures (e.g. 15°C). The detached cells are able to resume normal growth. In addition, the membranes have excellent durability and flexibility, demonstrating a great potential to be used as wound dressing or support for cell grafting.

Advantages:

- Allows easy monitoring of the wound healing process due to its transparency.
- Minimizes pain associated with conventional dressings and prevents damage to newly formed tissues, as the membrane adheres to the skin at body temperature without adhesive agents and detaches easily upon application of a cold press.
- Thin nanofilm allows air and moisture to circulate freely between the wound and the environment, while protecting the injury site from bacterial infection.
- Cells may be grafted onto the dressing to promote tissue regeneration, while drugs and antibacterial agents may be embedded in the nanoporous membrane to promote the healing process.
- Thermally stable up to 300°C, and is thus autoclavable and stable during storage and transport.

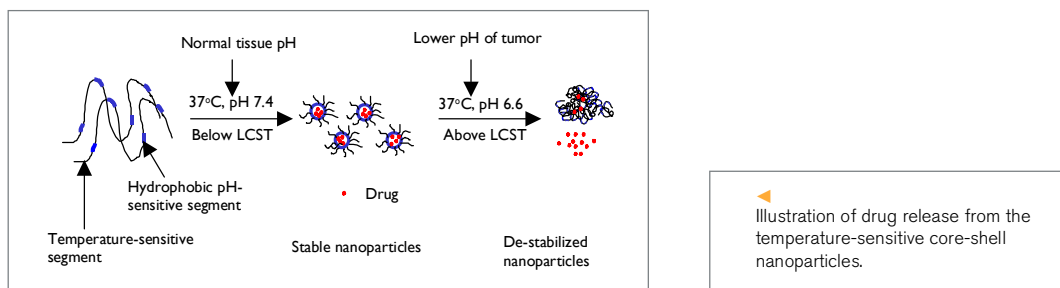
Applications:

- As wound dressing to treat different types of wounds, including burns, cuts, abrasions, lacerations and ulcers.
- Cell grafting applications.

Drug and Gene Delivery

Stimuli-Sensitive Core-Shell Nanoparticles for Targeted and Controlled Delivery of Bio-/Chemotherapeutics

IBN has developed smart and safe polymer-based carriers to target drugs specifically to cells. Novel core-shell polymer nanoparticles are designed with pH-dependent lower critical solution temperatures (LCST). This value is above the nominal physiological temperature of 37°C at pH 7.4, but decreases to a temperature below the physiological temperature with a small decrease in pH. The resulting change in LCST causes the core-shell nanoparticles to deform and precipitate in an acidic environment, triggering the release of chemotherapeutics at low pH. A number of amphiphilic copolymers with well-defined molecular weight and low polydispersity are being synthesized by novel approaches to fabricate pH-induced temperature-sensitive nanoparticles. A biological signal that can recognize tumor cells is chemically attached to the core-shell nanoparticles. These carriers may be employed to target drugs to tumor cells and release the drugs intracellularly. In addition, novel biodegradable cationic core-shell nanoparticles have also been developed whereby the hydrophobic core carries drug molecules while the hydrophilic shell binds DNA. This codelivery of drugs and nucleic acids or proteins allows synergy for higher efficacy of therapies. These cationic nanoparticles are a good vector for *in vitro* gene transfection, and display better performance compared to lipofectamine or polyethylenimine in many cell lines. These nanoparticles deliver proteins intracellularly much more efficiently than BioPorter, a commercial vector for protein delivery. Importantly, these nanoparticles are also less cytotoxic.



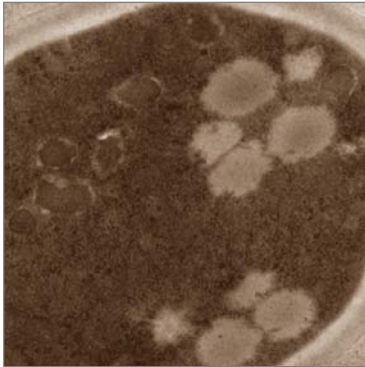
Advantages:

- Able to target drugs to deep tissues or tumors without external heating since the structural deformation and aggregation of the core-shell nanoparticles are triggered by pH changes in the environment.
- The change in LCST of the nanoparticles in slightly acidic environments leads to the formation of a hydrophobic shell, which exhibits good adhesion to tissues. This property facilitates drug targeting to specific tissues, and promotes endosomal/lysosomal escape.
- A biological signal can be conjugated onto the shell of the nanoparticles through the amine group of the polymer for specific tumor targeting.
- Codelivery of drugs and nucleic acids to achieve synergistic effect of drug and gene therapy.

Applications:

- Targeting drugs to cells or tissues with higher efficacy.
- *In vitro* applications and animal studies for drug discovery.
- Delivering drugs and nucleic acids simultaneously for cancer therapy.
- Transfecting genes *in vitro*.

Drug and Gene Delivery



▲
Micrograph of IBN's antimicrobial nanoparticles.

Cationic Nanoparticles as Efficient Antimicrobial Agents

The alarming rate at which microbes mutate against the limited backdrop of antibiotics and antifungal agents necessitates the search for more effective therapeutic agents. IBN's cationic core-shell nanoparticles, with their wide-ranging antimicrobial properties, have the potential of being an effective antimicrobial agent in the fight against multi-drug resistant microbes and fungus-induced brain infections. Their antimicrobial and antifungal properties have been evaluated in a mouse and rabbit model.

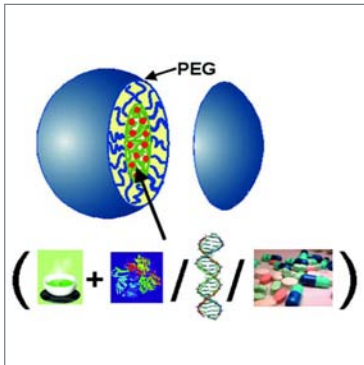
Advantages:

- Unique nanoformulation and self-assembly.
- Strong activity against bacteria, yeast and fungi.
- Animal model studies demonstrated that the nanoparticles crossed the blood-brain barrier and suppressed bacterial growth in the brain.
- Results from animal model studies did not show significant toxicity to the major organs caused by the nanoparticles.

Applications:

- Antimicrobial and antifungal therapeutic agent.
- Combat multi-drug resistant microbes and fungus-induced brain infections.

Drug and Gene Delivery



▲
Self-assembled green tea derivatives as carriers for proteins, genes and drugs.

Green Tea Derivatives as Drug Carriers

IBN researchers have developed core-shell micellar nanocomplexes comprised of epigallocatechin-3-O-gallate (EGCG) derivatives for drug delivery. These nanocomplexes are spontaneously self-assembled from EGCG and bioactive compounds. The complexes can be delivered in a controlled manner upon dissociation. These green tea-derived nanocomplex micelles present an unprecedented drug delivery system, which take advantage of the EGCG bioactivities. The synergistic effect of the micellar nanocomplexes loaded with therapeutic antibodies successfully killed cancer cells *in vivo*. No other drug carrier are known to form such micelles with different types of drugs.

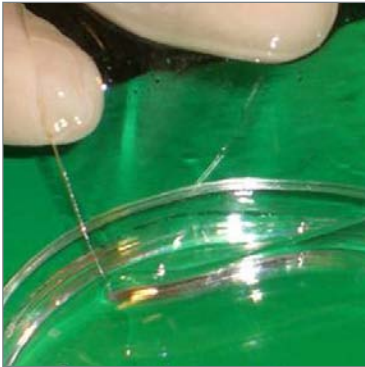
Advantages:

- Spontaneous self-assembly from EGCG (green tea component) and proteins into micellar nanocomplexes.
- Antioxidant, anti-inflammatory, anti-microbial and anti-aging properties.
- Synergistic effect of micellar nanocomplexes loaded with therapeutic antibodies successfully killed cancer cells *in vivo*.
- The only drug carrier that can form micelles with different types of drugs.

Applications:

- Therapeutic agent for wound healing and arthritis.
- Drug carrier for drug delivery.
- Scaffold for tissue engineering.
- Cosmetics.

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▲ Hydrogel composed of hyaluronic acid-tyramine conjugates using a peroxide-catalyzed reaction.

Injectable Biodegradable Hydrogels for Drug Delivery and Tissue Engineering

Hydrogels have been used extensively for the controlled release of bioactive molecules and the encapsulation of cells. In particular, the use of hydrogels as scaffolds for tissue engineering has shown potential for achieving tissue repair or tissue regeneration in the body. However, most existing hydrogels require surgical implantation, which often results in tissue irritation and damage. IBN researchers propose an alternative simple and biocompatible *in situ* gel-forming system composed of hyaluronic acid-tyramine (HA-Tyr) conjugates using a peroxidase-catalyzed oxidation reaction. This novel system allows hydrogels to be formed without any inflammation or reactions to the bioactive agents loaded in the hydrogels. Enzyme-mediated HA gel formation *in vivo* shows promise for achieving effective drug therapy and tissue regeneration. This involves controlled protein release from hydrogels, immunocancer therapy, hydrogel/inorganic compound composites for tissue engineering, and protein array fabrications in the hydrogel for cell migration and/or differentiation control. Furthermore, this injectable system may be used in bone cement applications. The technology allows for the regeneration of bone tissues at bone defects via the injection of a mixture of HA-Tyr conjugates, apatite, and/or collagen and growth factors. In particular, this material is well-suited for healing osteochondral defects as it contains mainly HA, collagen and apatites, all of which are native to bone and joint regions. This material has tunable mechanical properties and preliminary *in vivo* tests show that it is conducive to bone formation.

Advantages:

- This simple injection method allows the hydrogel to form safely in the body without surrounding tissue damage from heat release.
- Bioactive molecules such as protein and cells can be loaded into the gel without a loss in their activity.

Applications:

- Controlled protein release for disease treatment.
- 3D cell culture in hydrogels for tissue engineering.
- Bone regeneration.
- Wound healing.

Notes



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