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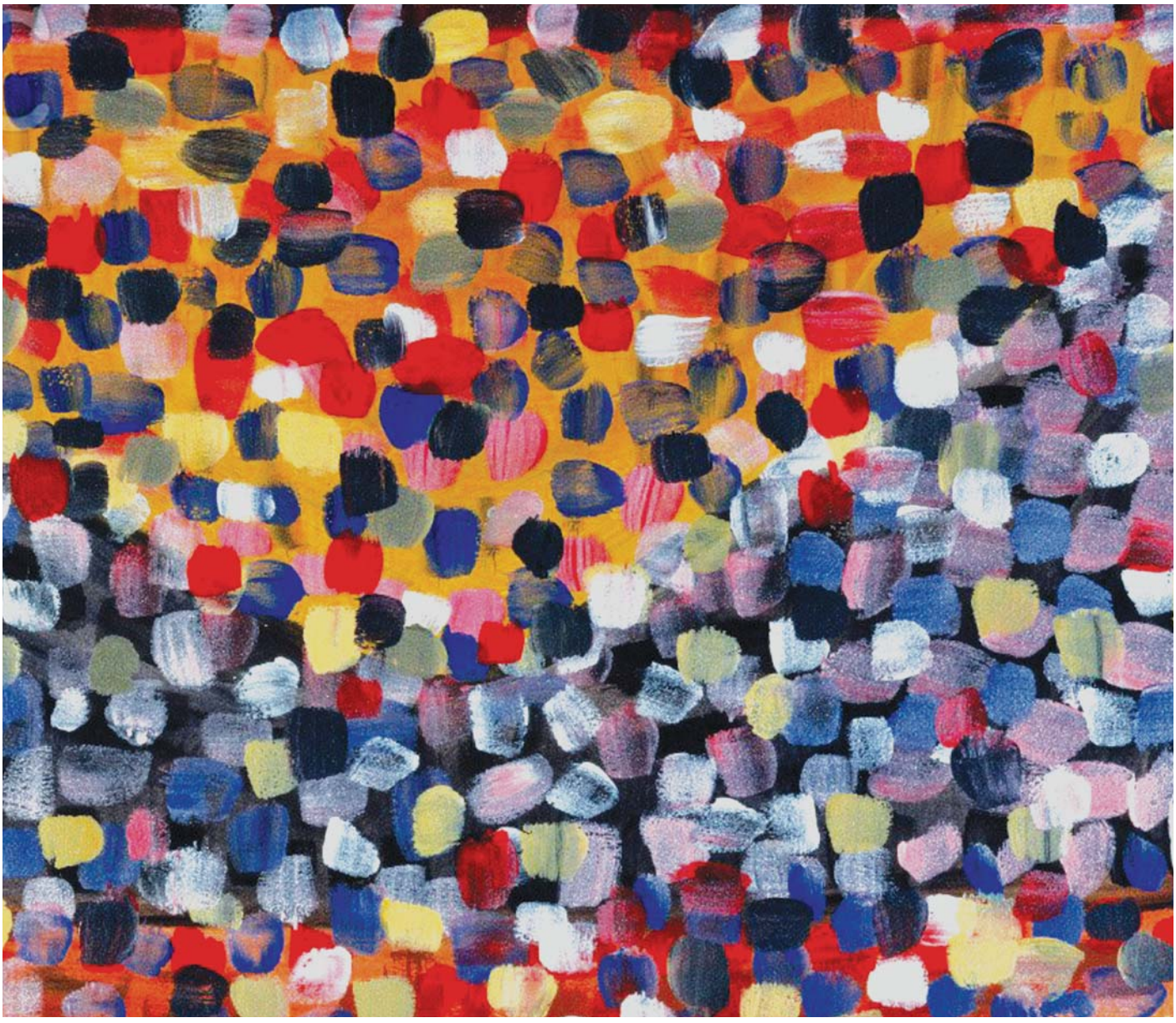
Cover story. Abstract #20 by Ong



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KIST Today

Leading to the world of tomorrow

contents

Foreword

The concept of a good quality of life has evolved significantly in the past few decades. People now consider living in good health in a safe and ecologically sound environment while having the leisure time to enjoy various activities to be a desirable way of living. However, with the improvements in health, safety and living conditions, the demand for consumer goods has gradually increased, placing a strain on society to adequately provide for its population.

The impact of an aging population is becoming a major global issue. As the proportion of elderly in the population has been increasing, the proportion of the young generation has been decreasing. With this shift in the distribution of a country's population towards older ages, there has been a real threat to economic growth and government welfare budgets. As a result, societies may soon find difficulty providing for the high quality of life people have come to expect.

I believe that science and technology can contribute toward easing some of the burdens associated with an aging population. In fact, KIST is focusing on research concerning "silver technology," which refers to technology designed specifically with the elderly in mind. This issue of *KISToday* features several ongoing projects for "silver technology," most notably in cognitive science and bionics. These projects also involve developing technologies for medical instruments and guidance systems for the elderly. The underlying aim of these projects is to improve the quality of life for individuals and societies. It is my sincere hope that the research conducted at KIST and its future initiatives will help sustain a high quality of life and thereby enrich human society.

President **Hong Thomas Hahn**

The use of Xenopus laevis oocytes in drug screening

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The study of ion channels has benefited greatly from the use of the Xenopus laevis oocyte expression system. Xenopus laevis oocytes offer a very convenient expression system for assaying the effect of candidate compounds on receptors, channels and transporters which have been cloned and characterized as potential targets for drug development. The well-established technique of voltage clamp recording from Xenopus oocytes makes it possible to perform high-throughput screening which is especially *useful in some cases for primary screening, as well as for determining the action and characterization of new drugs. Here we review the advantages, current methods, available recording systems and specific applications of the Xenopus* oocytes expression systems in drug *screening.*

INTRODUCTION

Numerous diseases have been linked to the dysfunction of ion channels, neurotransmitter receptors and transporters. Accordingly, research is increasingly focused on these areas as potential targets for drug discovery. Oocytes of the South African clawed frog, *Xenopus laevis* (Figure 1), have a long history in studies of oogenesis, fertilization, morphogenesis, and embryonic development. These oocytes have served as a reliable standard heterologous expression system for the study of cloned proteins. For example, the first demonstration of synthetic globin protein from foreign globin mRNA was with *Xenopus* oocytes (Gurdon et al. 1971). Since its initial development for the purpose of ion channel expression (Miledi et al.), the *Xenopus* oocyte system has been a valuable tool for screening drug candidates targeted at ion channels in a controlled environment.

Xenopus oocytes can be collected in very large numbers from a fully mature *Xenopus* frog (Figure 1). Hundreds of viable oocytes can be isolated synchronously and developed in a simple salt solution enabling exposure to almost any kind of compound. Their large size (~ 12 mm diameter) and relative ease of handling makes it possible to effectively inject naturally occurring mRNA, complementary RNAs transcribed *in vitro*, or complementary DNA without significantly compromising the health of the oocytes. As a result, functional expression and analyses can be accomplished quickly, within hours or days. Oocytes are also able to express multi-subunit proteins derived from exogenously-injected RNA or DNA with control of the expression level of each subunit. Electrophysiological recording from oocytes is relatively easy and requires only a basic recording setup. Well-established electrophysiological recording techniques, such as the two-electrode voltage clamp, the cell-attached patch, inside- or outside-out patch clamp recordings, and variable recording protocols from oocytes allow screening of potential drugs and determination of their action and parameters. The efficacies, affinities and kinetics of potential drugs can be evaluated against specific types of cloned ion channels. *Xenopus* oocytes express only a few endogenous ion channels and receptors, so exogenous protein can be tested without contamination from endogenous channels and receptors. Although oocytes express some channels and receptors, responses from endogenous protein are not usually a problem because the translation of messages is very efficient and the current from the injected

FIGURE 1. *Xenopus Laevis* and her oocytes

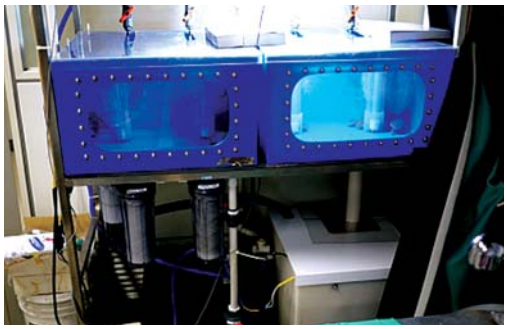
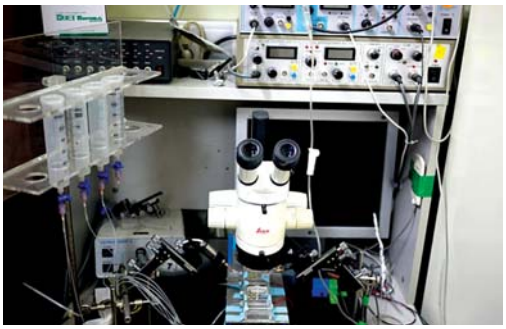


FIGURE 2. Aquariums for raising *Xenopus laev*



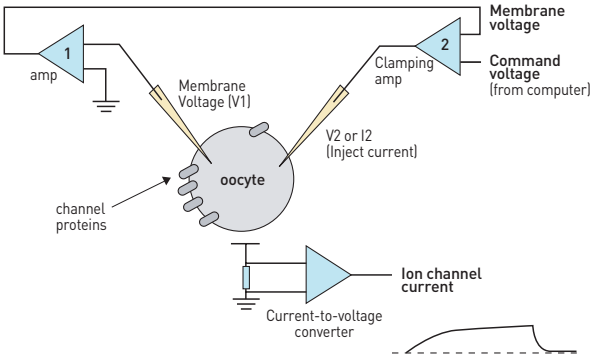


FIGURE 3. TEVC recording system and simplified electrical scheme of a TEVC setup

recombinant channels is usually much larger than the current from the endogenous channels. In some cases, endogenous channels and receptors themselves can be the target of drug screening, or endogenous response can be used as a second messenger system coupled to the exogenous expression.

Despite these important advantages, drug screening using a *Xenopus* oocyte system faces certain limitations. For example, oocytes are not the native cells in which the channels and receptors are normally expressed. Although exogenous proteins expressed in oocytes may be correctly post-translationally modified, the observed functional properties may not be identical to those that are characterized in native cells or tissues. Another drawback is that some pharmacological agents are less potent on channels in oocytes as compared to channels in mammalian cells or native tissue. In spite of such limitations, however, this system has helped to perform high throughput drug screening for various ion channels, including ligand-gated and voltage-gated ion channels. These studies have been made possible by the development of automated voltage-clamp devices.

1. SCREENING PROCEDURES

The following procedures are commonly used to investigate a potential drug for expressed target protein in oocytes: (1) preparation of nucleic acid encoding the protein of interest, (2) nucleic acid injection into prepared oocytes, and (3) electrophysiological recording.

Cytoplasmic injection of RNA that has been transcribed *in vitro* is the most common technique to express target protein in oocytes. This technique can lead to robust expression of ion channels and receptors in the oocyte membrane. *In vitro* synthesis of RNA can easily be performed from a cDNA clone within an appropriate expression vector containing a bacteriophage polymerase promoter such as T7, T3 or SP6 using a commercially available kit. The vector containing cDNA of the protein of interest must be linearized downstream of the cDNA insert prior to the *in vitro* transcription. It is also possible to inject cDNA directly into the nucleus of oocytes (Goldin, 1992). This approach is not time-consuming or expensive because there is no need to synthesize RNA *in vitro*. In this case, cDNA should be subcloned into a eukaryotic vector which contains a eukaryotic promoter such as Cytomegalovirus (CMV) promoter. The injection procedure is very similar to that used with mRNA, but requires a more sophisticated apparatus because cDNA must be injected into the oocyte nucleus. Using the injection of recombinant vaccinia virus carrying target cDNA driven by an early promoter, several ion channels and receptors are also expressed in oocytes (Yang et al., 1991). Because one can bypass the mRNA synthesis, this method is more rapid and convenient than the mRNA injection method. Alternatively, co-injection of T7- or SP6- driven cDNA and T7 or SP6 RNA polymerase into the oocytes recently resulted in the expression of functional proteins in the oocyte membrane (Geib et al., 2001).

To inject the prepared nucleic acid into the oocytes, freshly isolated oocytes are necessary. Ovaries of adult female frogs mainly contain stage V

and VI oocytes which are large round cells (~1.2 mm diameter) with a characteristic appearance: a dark-brown animal hemisphere and a yellowish vegetal hemisphere. After preparation by simple surgery (Wagner et al., *2000), the follicle cells are removed by treatment with collagenase or by individual* defolliculation using a binocular dissecting microscope. For ligand-gated ion channel receptor expression, large fully grown cells in the last two stages (V and VI) are preferred (Goldin, 1992; Yao et al., 2000). Oocytes in the best condition usually lead to the best results. Selection of the best oocytes is based on their appearance, i.e., size, color and shape. They should have minimal visual deformation or cytoplasm leaks. The procedure of cytoplasmic injection of cRNA is relatively easy and rapid, requiring only a few pieces of equipment, such as a dissecting microscope, a microdispenser and a micromanipulator. Recently, instead of manual injection, automated devices have been used for the injection, such as the *Roboocyte from Multichannel Systems* (Schnizler et al., 2003). This instrument was developed to perform automated two-electrode voltage clamp (TEVC) recording of oocytes, but it can also be used to inject nucleic acid into the oocytes.

In order to record and analyze the effect of new pharmaceuticals and those in development on the ion channel currents in oocytes as a measure of receptor function, TEVC is commonly used. This TEVC method seems simple and easy compared to the patch-clamp. Oocytes are impaled with a glass microelectrode instead of by using patching membrane with a recording pipette to form a gigaseal. Perfusion of the extracellular solution can easily be changed several times. If the oocytes are healthy and the quantity of injected cRNA is fixed, it is generally possible to obtain regular and stable responses from all recorded oocytes over long periods of time. Therefore, it is a very rapid, effective and reliable recording method providing high quality data with relatively simple apparatus.

Other recording methods, such as a macropath clamp, cell-attached patch, inside- or outside-out patch clamp, single channel recording and cut-open oocyte voltage-clamp, are used as occasion demands. For high-throughput drug screening, large-scale automated perfusion systems and patch clamp systems for oocytes have been developed. This has allowed investigators to test and analyze multiple channel variations in oocytes in parallel **[AJC1]**. As previously mentioned, the Roboocyte system performs automatic injection as well as TEVC recording from multiple oocytes located in a chamber of 96 well dishes. Another automation system, the OpusXpress system, is also used to test eight oocytes simultaneously in parallel. Other custom-made automated systems have been implemented and modified to smaller scale in laboratory settings (Baburin et al., Joshi et al., 2004)

MEMO [AJC1]. I'm assuming that your use of "in parallel" refers to something different than "simultaneously?" If it does, that's fine, leave it. Otherwise, use "simultaneously" instead.

2. EXAMPLES

As is evident from the discussion above, *Xenopus* oocytes have been widely used for drug screening in the field of ion channels and receptors. We next discuss several examples of drug screening using a *Xenopus* oocytes expression system.

2.1. Pharmaceutical screening of targeted compound libraries

The *Xenopus* oocytes expression system has been extensively used in performing the pharmaceutical screening of targeted compound libraries. For example, Yoneda et al. discovered AMPA receptor agonist using the *Xenopus* oocytes expression system. The AMPA receptor is one of the ionotropic glutamate receptors. These investigators designed and synthesized a series of polyamine derivatives based on the structures of prototype antagonist polyamines, including Joro spider toxin-3 (JSTX-3). Antagonist activities of the synthesized compound libraries for the Ca^{2+} permeable AMPA receptors were measured using TEVC with *Xenopus* oocytes which express the receptors after injection of rat brain mRNA. This same research team developed a novel potent Ca^{2+}-permeable AMPA receptor antagonist which showed neuroprotective effects in transient global ischemia models in gerbils (Yoneda et al., 2002).

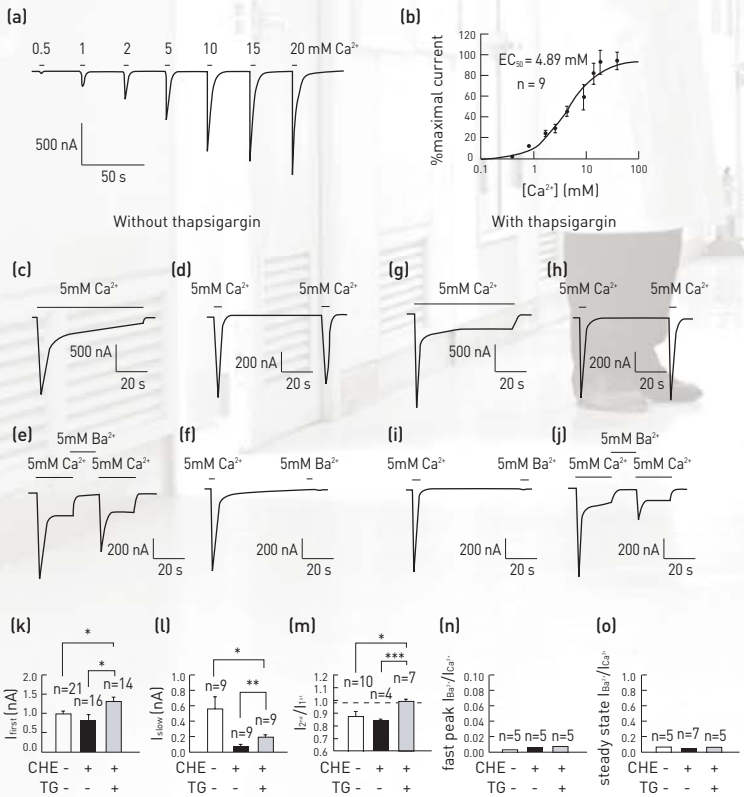


FIGURE 4. Endogeneous Ca^{2+} activated Cl^- channels in *Xenopus laevis* oocyte

A similar approach has been used by our research group at KIST. We discovered novel antagonist for Ca^{2+}-activated Cl^- channels (CaCCs) using endogenous CaCCs in *Xenopus* oocytes. First we optimized the recording conditions to obtain reliable and repeatable current responses mediated by CaCCs. We found that treating the oocytes with a cocktail of PKC inhibitor, SERCA inhibitor, and ionomycin reduced desensitization as well as run-down or run-up of current responses when activated repetitively (Figure 4). Then we designed and synthesized a series of the anthranilic acid derivatives based on the structures of several known blockers for CaCCs, including flufenamic acid and mefinamic acid. We examined the blocking effect of the synthesized compound libraries using TEVC with *Xenopus* oocytes (Table 1) and proposed a novel synthesized compound as improved CaCC blocker (Figure 5, Oh, et al, 2008).

TABLE 1. IC50s of known blockers for CaCC and anthranilic acid derivatives

Compound number	Chemical compound	IC_{50}*	IC_{50}	n
a-1	DIDS	48	10.7	6
a-2	NPPB (5-nitro-2-(3-phenylpropylamino)benzoic acid	22-68	32.3	6
a-3	9-AC (9-anthracene carboxylic acid)	10.3	94.3	5
a-4	Niflumic acid	28	37.3	7
a-5	Flufenamic acid (*N*-(*3*-Trifluoromethylphenyl)anthranilic acid)	-	35.4	6
a-6	Mefenamic acid	-	44.5	6
a-7	*N*-Phenylanthranilic acid	-	88.1	6
a-8	5-Nitro-*N*-phenylanthranilic acid	-	42.5	8
b-1	*N*-(2-Nitrophenyl)anthranilic acid	-	LP	7
b-2	*N*-(3-Nitrophenyl)anthranilic acid	-	32.1	7
b-3	*N*-(4-Nitrophenyl)anthranilic acid	-	17.8	6
b-4	5-Nitro-*N*-(4-nitrophenyl)anthranilic acid	-	15.4	5
b-5	*N*-(2-Trifluoromethylphenyl)anthranilic acid	-	29.5	6
b-6	*N*-(4-Trifluoromethylphenyl)anthranilic acid	-	6.0	6
b-7	*N*-(4-Fluoro-3-trifluoromethylphenyl)anthranilic acid	-	14.7	6
c-1	*N*-(4-Fluorophenyl)anthranilic acid	-	63.1	6
c-2	*N*-(4-Chlorophenyl)anthranilic acid	-	11.3	6
c-3	*N*-(4-Methylphenyl)anthranilic acid	-	55.3	7
c-4	*N*-(4-Isopropylphenyl)anthranilic acid	-	17.0	6
c-5	*N*-(4-tert-Butylphenyl)anthranilic acid	-	22.9	7
c-6	*N*-(4-Decylphenyl)anthranilic acid	-	LP	6
c-7	*N*-(4-Methoxyphenyl)anthranilic acid	-	102.3	5

The Xenopus oocytes expression system has been extensively used in performing the pharmaceutical screening of targeted compound libraries.

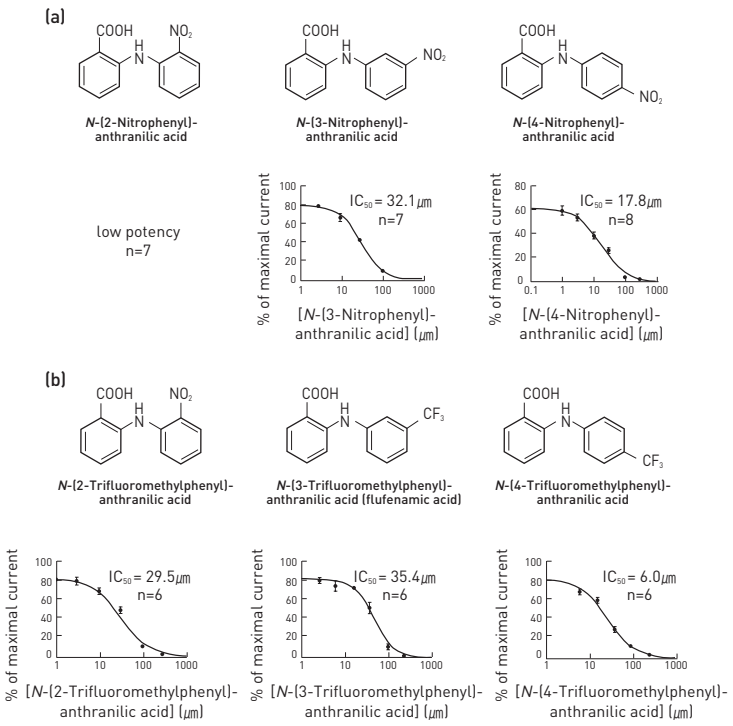


FIGURE 5. Positional effect of substituent group on the phenyl ring of blocker that affects block of Ca^{2+}-activated Cl^- current

Broad and his colleagues also explored three novel (2-amino-5-keto)thiazole compounds that act as selective potentiators of nicotinic acetylcholine receptors (nAChRs). nAChRs are ligand-gated ion channels formed by the assembly of five subunits. From this assembly process, seventeen distinct nAChR subunits have been identified. There is currently a significant interest in the development of selective nAChR agonists and positive allosteric modulators for the treatment of various neurological and psychiatric disorders. They **[AJC2]** first performed a high-throughput screen of a large chemical library on recombinant human nAChRs using a calcium dye and fluorescent imaging plate reader (FLIPR) technology. The activity of candidate compounds was confirmed using voltage-clamped *Xenopus* oocytes expressing exogenous nAChRs. The profile of these newly described compounds as selective potentiators of the two main central nAChR subtypes was verified in *Xenopus* oocytes and also confirmed in mammalian cells (Broad et al., 2006). However, many pharmacological agents are less potent on channels in oocytes compared to the channels in mammalian cells or native tissues. Therefore, testing in a mammalian expression system is essential for drug candidates which are first discovered using the *Xenopus* oocytes expression system.

MEMO [AJC2]. Who's "they?" Broad et al.?

2.2. Determining the potency and efficacy of a drug

A drug's effects can be evaluated in terms of strength (potency) or effectiveness (efficacy). Potency refers to the amount of drug (usually expressed in milligrams) needed to produce an effect. Efficacy refers to the potential maximum therapeutic response that a drug can produce. The effect of drugs such as antagonists and allosteric modulators can also be characterized with ion channels and receptors expressed in *Xenopus* oocytes. The potency of an antagonist (IC50) can be determined by testing a range of concentrations and assessing each concentration's ability to block the current induced by agonist in the oocyte. Andreev et al. showed that analgesic compound APHC from the sea anemone heteractis crispa had an inhibiting effect on transient receptor potential vanilloid type 1 (TRPV1) receptors. TRPV1 receptors are molecular integrators of pain stimulus and initiate neuronal response during inflammation. Screening a number of venoms and running tests of potent peptide APHC for TRPV1 inhibition activity were performed in *Xenopus* oocytes expressing TRPV1 receptors (Andreev et al., 2008).

The potency and efficacy of allosteric modulators acting at distinct binding sites can also be tested and characterized. An example of this process is the study of benzodiazepine compound modulation of GABAA **[AJC3]** receptor function. Sigel and Buhr quantitatively characterized the allosteric modulation of GABA currents by a number of drugs acting at the benzodiazepine binding site using *Xenopus* oocyte expression systems. (Sigel and Buhr, 1998) In this type of measurement studying the neuronal receptors of channels, the concentrations of ligand can be well controlled and there is no need to test the contribution from presynaptic uptake or release systems, or from possible endogenous ligands. Furthermore, in contrast to most studies performed on neuronal cell cultures, the oocytes containing neuronal ion channels may easily be investigated under voltage-clamp. In the case of GABAA receptors, it has been shown previously that GABA receptor channels expressed in *Xenopus* oocytes retain properties similar to those in the brain (Miledi et al., 1982; Smart et al., 1983; Gundersen et al., 1984), indicating that the *Xenopus* oocyte was the proper modeling system.

In determining the potency and efficacy of a drug as an antagonist for a target ion channel or receptor, a dose-response curve measures the effect of a range of drug concentrations. As previously mentioned, the potency of an antagonist is usually defined by its IC_{50} value. Dose-response data are typically graphed with the dose on the x-axis and the measured effect (response) on the y-axis. The IC_{50} can be calculated for a given antagonist by determining the concentration of antagonist needed to elicit half the inhibition of the maximum response of a target ion channel or a receptor recorded without antagonist. For example, we determined the blocking effect of the flufenamic acid for CaCC by elucidating an IC_{50} value (Figure. 6 Oh, et al, 2008). The lower the IC_{50}, the greater the potency of the drug and the lower the concentration of drug that is required to inhibit the maximum

biological response. Lower concentrations of drugs may be associated with fewer side effects.

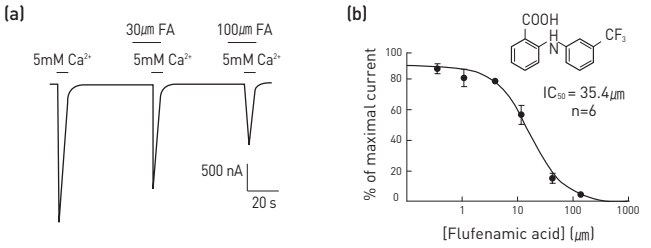


FIGURE 6. The blocking effect of the flufenamic acid for CaCC

The slope of the dose-response curve gives the apparent Hill coefficient. The Hill coefficient is commonly used to estimate the number of ligand molecules (in this case, blocker molecules) that are required to bind to an ion channel or a receptor to produce a functional effect. The Hill coefficient reflects the extent of cooperativity among multiple ligand-binding sites.

MEMO [AJC3]. I'm assuming that GABAA and GABA are different and it's not a typo? Just checking! (Same issue in Section 2.5)

2.3. Secondary screening of identified compound for subtype selectivity

The *Xenopus* oocyte expression system is also used to screen a compound for subtype selectivity in the case of an ion channel which has a few heteromer subtypes composed of different subunits. It was revealed that the NMDA receptor antagonist, ifenprodil, inhibited the NR1A/NR2B subtype NMDA receptor rather than the NR1A/NR2A receptor in Xenopus oocytes (Williams, 1993). Using an oocyte expression system, the subtype involved in a specific action of antagonist, as well as the potency of antagonist for ion channels and receptors, can be examined **[AJC4]**.

MEMO [AJC4]. This sentence seemed to be missing some words. It wasn't clear. I've filled in, but wasn't sure I was interpreting correctly. Please check.

2.4. Screening mutants of ligand-gated channels for changes in receptor function

It has been found that a large number of inherited diseases are caused by mutation of a protein. Particularly in the case of ion channels, the *Xenopus* oocyte expression system has been used to study the changes in receptor function caused by the mutation of ligand-gated channels. Claude et al. demonstrated that the serine residue of opioid receptor had a crucial role in opioid receptor activation (Claude et al., 1996). Opioid receptors have been reported to regulate many cellular effectors via pertussis toxin-sensitive G proteins. By electrophysiological recording using both *Xenopus* oocytes and mammalian cells for expressing mutant opioid receptors, Claude et al. showed that point mutation in opioid receptors 1 **[AJC5]** is sufficient to produce full agonist effects from antagonist **[AJC6]**. Similar studies have been carried out to analyze the effect of mutations in the SCN4A gene encoding the Nav1.4 skeletal muscle sodium channel. Taken together, these studies demonstrate that the *Xenopus* oocyte can serve as an effective modeling system to understand the mechanisms of receptor activation.

MEMO [AJC5]. Is this a typo or a kind of opioid receptor?
MEMO [AJC6]. I'm not sure I got this one right either---the original sentence had unclear phrasing.

2.5. Screening with Roboocyte

As previously mentioned, Roboocyte is the instrument that automatically performs cDNA injection as well as TEVC recording on *Xenopus* oocytes plated in a 96-well plate. Roboocyte makes high-throughput screening easy compared to manual recording, which needs a skillful person and more time because it is necessary to do one recording at a time. This fully automated system was applied to GABAA receptor (Pehl et al., 2004). Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the mammalian central nervous system. The GABA type A receptors are pentameric chloride channels which influence the pharmacological behavior of the receptor subtype and are targets for various clinically important drugs such as anxiolytics, anticonvulsants, anesthetics, sedatives, muscle relaxants, barbiturates, and benzodiazepines, such as valium. Utilizing the Roboocyte system, pharmacological properties of this ion channel, including modulation by GABA and the dose-dependent block of GABA-induced currents, were analyzed.

CONCLUSION

Xenopus oocytes have been widely used as a reliable heterologous expression system for the study of ion channels and receptors. Judging from numerous publications during the past few years, it is still effective as a standard expression system. Oocytes are particularly well-suited for high-throughput screening for agonist, antagonist and modulator of ion channels using instruments which have been developed specifically for oocyte research. In addition, in multidisciplinary studies of ion channels combining molecular biological and biochemical tools, oocytes are useful for looking at the effect of mutations and subunit compositions. One needs to be cautious, however, because oocytes are not the native cells in which the channels are normally expressed, so the effect of compounds needs to be tested in a mammalian system to confirm initial findings.

Bionics Emerges As A New Rehabilitation Technology for the Next Generation

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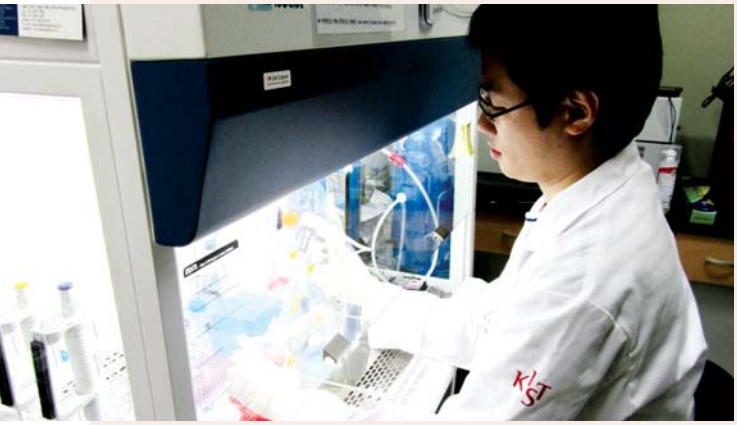

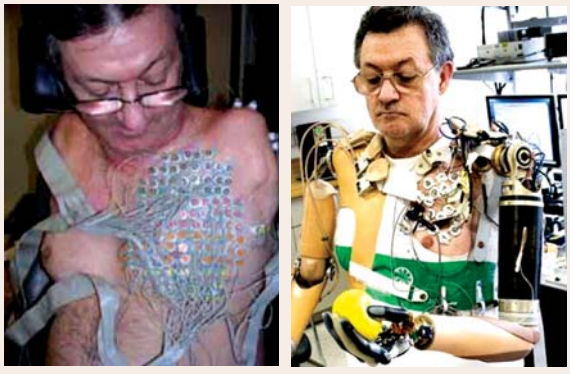

FIGURE 1. Jesse Sullivan with a new myoelectric prosthetic arm developed at the Rehabilitation Institute of Chicago, USA.

In May of 2001, Jesse Sullivan, a fifty-five-year-old power-company electrician, accidentally touched a live power line carrying 7200 volts of electricity, and had to have both his arms immediately amputated at the shoulder. Seven weeks later in November of 2001, Sullivan volunteered to be a guinea pig to test a new experimental myoelectric arm which had been developed by a joint team of physicians and biomedical engineers from Northwestern University and the Rehabilitation Institute of Chicago in the US. During the operative procedure, a surgeon on the team decided to reroute the ulnar, radial, median, and musculocutaneous nerves from Sullivan's left-shoulder stump to his pectoral muscle, which was of no use to Sullivan in its original form because he no longer had his arms. With the brain-muscle connection re-established at the pectoral muscle, the myoelectric signals for wrist and hand movement were detected from Sullivan's chest skin whenever he intended to move his nonexisting wrist and hand. Engineers on the team developed a prosthetic arm which could be controlled by the myoelectric signal acquired from Sullivan's chest. The result was that Sullivan became the world's first "bionic" man with an ability to move his prosthetic arm using nothing other than his own intuition (Figure 1). Although Sullivan's new prosthetic arm was still far from being as dexterous as Steve Austin's six-million-dollar bionic arm, it certainly represented a breakthrough as the first of its kind in rehabilitation technology using a man-machine interface.

As man-machine interface emerges as a new technology, a robotized human machine such as the Six-Million Dollar Man or RoboCop is no longer a futuristic fantasy, but has become, in some respects, closer to reality in a variety of applications in medicine and rehabilitation. A computer-controlled orthosis, called the C-Leg, successfully helped Andrew Lourake, a U.S. Air Force Lieutenant Colonel who underwent surgery for an above-the-knee amputation following a motorcycle accident, to return as a U.S. Air Force pilot in 2004. In fact, references to the use of artificial limbs to replace lost movement in the human body can be found long before the modern era; an artificial limb is described in Rigveda, an ancient Sanskrit text dating to around 1400 B.C., and later in Herodotus around the 5th century B.C. The earliest known prosthesis, dating to about 300 B.C., is made of bronze, iron, and wood and was recovered from the ruins of the city of Capua. However, it wasn't until much later in history, around 1960, that technological advancement in

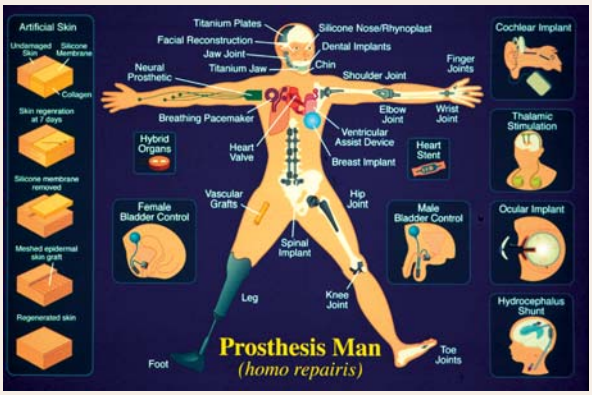

FIGURE 2. A variety of prosthetic implants currently either in clinical use or in development

FIGURE 3. Dr. Hyung Min Rho (1954 - 2009)

implantable medical devices exploded. In 1958, the first clinical implantation of a fully implantable cardiac pacemaker was performed at the Karolinska Institute in Sweden. In 1962, Sir John Charnley, a British orthopaedic surgeon, introduced a modern total hip implant, consisting of a steel stem and polyethylene socket liner. Over the course of the next forty years, a variety of implantable electrical devices have been developed in an attempt to treat patients with various neurological disorders, and many of them are now clinically used (Figure 2). Examples include treatment of urinary incontinence with electrical stimulation of the sacral nerves, reduction of visceral pain by electrical stimulation of the spinal cord, and restoring the mood of patients with depressive syndrome by electrical stimulation of the vagal nerves. Even electrical stimulation of the deep brain is now clinically used to undo the abnormal neuromuscular movements in patients with Parkinson's disease or essential tremor. These days, artificial cochlear implants are now widely used to restore hearing in the deaf by electrically stimulating the auditory nervous system, and artificial retinal implants to restore sight in the blind are currently under development at numerous institutions around the world, including in Korea.

According to a 2010 UN report on world population, the birth rate[1] of South Korea is 1.2, the lowest in the world! Korea is thus expected to become the "oldest" country in the world by 2050 with about one half of the total Korean population being non-working retirees at the age of 65 or older. This means that, on average, each member of the labor force[2] has to support at least one senior person, thus causing a tremendous socio-economic burden on society. Possible solutions for easing this burden are to convert the non-working senior population into participating workers or to increase the retirement age to 70 or above. Therefore, it is evident that bionics technology will be required to solve various age-related, degenerative disorders, thus restoring the capacity for activities daily life to the senior population. In fact, the development of bionics technology has been included in the National Agenda which targets future areas of growth for Korea. Recognizing the potential of this issue, KIST initiated bionics as a priority area of research and development in 2008 under the leadership of the late Dr. Hyung Min Rho (Figure 3), and hosted a series of KIST-sponsored bionics symposiums, one on October 7, 2008 and another on November 3 of 2009 (Figure 4).

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1. The birth rate is defined as the average number of children born to each woman over the course of her life.
2. The labor force of a country consists of everyone of working age, typically above a certain age (around 15) and below retirement (around 65) who are participating workers, that is people actively employed or seeking employment.
[AJC1]Are you sure these photos should be used? They're very repetitive, not very eye-catching, and there are tons of empty seats!!!

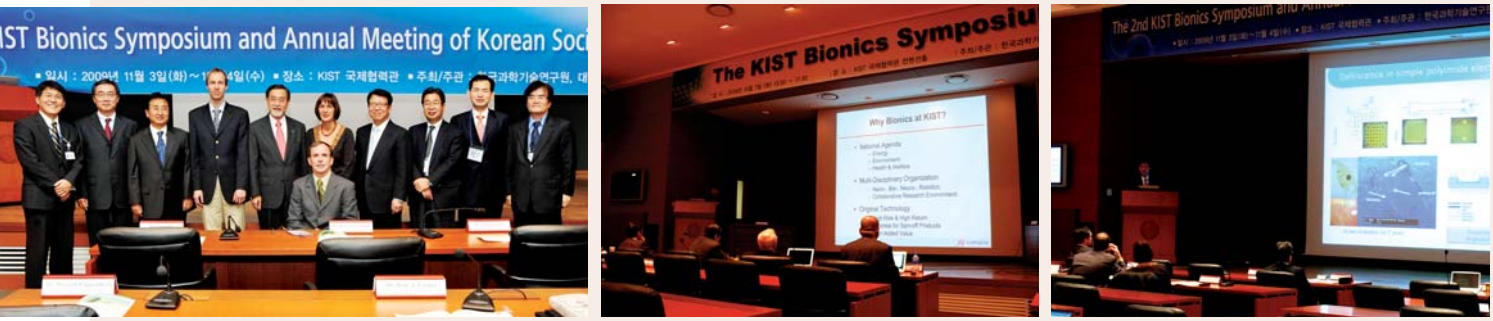

FIGURE 4. The second KIST Bionic Symposium held in 2009.

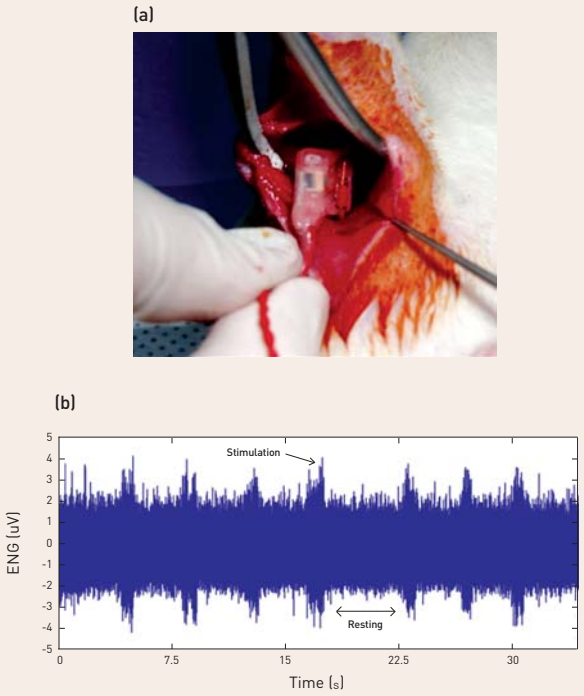

FIGURE 5. (a) An implantable nerve electrode developed by the KIST Bionics Group, and (b) the neural signal obtained from the sciatic nerve of a rat

In February of 2009, KIST officially launched its first bionics research project. The project is defined as development of a man-machine interface system for bionics rehabilitation technologies to aid the disabled and is intended as a showcase project in support of the National Agenda. To head the team, Dr. Jun-Kyo Francis Suh, a former Professor of Biomedical Engineering at Tulane University, USA, was recruited as the principal investigator of the project and named as Director of the Bionics Program at KIST. As part of this project, an implantable neural control system, consisting of an implantable nerve sensor and stimulator, implantable neural signal processor, implantable neural pulse generator, and external monitor and controller, is currently under development in an attempt to automatically modulate the human nervous system through the interface between the peripheral nerve and an external electronic device. Recently, we succeeded in acquiring a neural signal from the sciatic nerve of a rat using an implanted nerve electrode and a specially-designed low-noise amplifier system (Figure 5).

In 2010, we launched a second bionics project focusing on optogenetic deep brain stimulation in collaboration with Dr. Justin Changjoon Lee of KIST's Center for NeuroScience. In this research, optically sensitive ion channels, such as channelrhodopsin-2 (ChR2) and halorhodopsin (NpHR), are used as an interfacial medium between neurons and an external device. This second project is currently funded by the Korea Research Council of Fundamental Science and Technology.

As experience deepens with bionics projects such as these, scientists are becoming more comfortable with a field of technology first made popular by science fiction writers. Furthermore, the importance of research and development in bionics technology will only increase in the future with the successful clinical application of a wider range of bionic devices in patients worldwide.

Improving the Mechanical Stability of a NiTi Stent

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Introduction

Nitinol, an alloy of nickel and titanium, is highly biocompatible and its properties make it suitable for use in implants. These unique properties, as well as its tailorability, make Nitinol suitable for many applications such as orthodontic brackets and wires, underwire bras and medical stents.

It was the superelasticity of nitinol that first led to an interest in using it for stents, but it was also discovered that the elastic hysteresis of nitinol in the loading/unloading cycles involved in mechanical deformation could be exploited in stenting applications. An ideal stent should resist crushing during normal physiological processes (radial resistive force) yet exert a small outward force on the vessel wall during recovery (chronic outward force). Figure 1 demonstrates how the hysteresis of superelastic nitinol meets this requirement. The upper plateau represents the force required to deform the stent or the force that resists crushing (radial resistive force) and the lower plateau represents the force exerted on the vessel tissue during self-expansion.

Fatigue life, however, remains a fundamental risk of nitinol stents, and is one of the most discussed, yet least understood, aspects of NiTi alloys. The U.S.'s Food and Drug Administration (FDA) requires a fatigue life exceeding 400 million cycles for intravascular stents which means that a better understanding of the factors affecting fatigue life and the mechanism of crack initiation and growth is essential [1, 2].

The improvement of biocompatibility in stent designs may reduce stent-associated thrombosis and in-stent restenosis [3]. Thus, in an effort to improve mechanical properties to ensure sufficient radial strength and biocompatibility, metallic stents have been coated with various materials such as carbon, silicon carbide, or tantalum [4,5] . Among these materials, diamond-like carbon (DLC) has emerged as a promising coating material due to its excellent mechanical and biological properties such as high hardness, high wear and corrosion resistance, chemical inertness, excel-

Nitinol, an alloy of nickel and titanium, is highly biocompatible and its properties make it suitable for use in implants.

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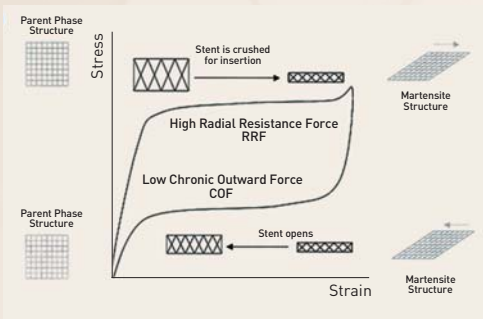

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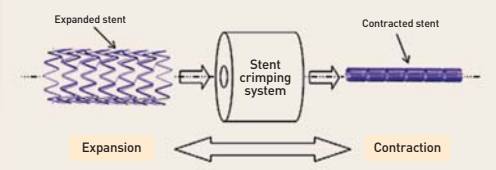

FIGURE 1. (a) Radial resistive force and chronic outward force as a function of the superelastic hysteresis loop; (b) Schematic diagram of a stent crimping system for applying a cyclic loading of contraction and expansion.

lent smoothness and low thrombogenicity [6]. However, it must be noted that a vascular stent may locally undergo a large deformation of tension, compression, or rotation as expansion and contraction occur during clinical operations, as illustrated in Fig. 1b. A large deformation could cause failures in the coating layer, such as cracking or spallation [7,8], which could result in a severe problem during the lifetime of the coated stent. The failure of the protective coating on self-expandable vascular stents is believed to relate to the cyclic loading process deployed in a stent crimping system which first subjects the stent to contraction and extension for clinical placement and subsequently to expansion once the stent is properly positioned.

This article describes the mechanical performance of a NiTi alloy stent coated with DLC to bring about improvement in the stability of the stent's structure and its coating materials.

Mechanical stability of a NiTi stent

Figure 2 shows a segment of a wire-woven stent which has undergone fatigue failure. This type of failure is usually attributed to either a microcrack on the surface or non-metallic inclusions. Fatigue resistance can be improved by preventing crack initiation through electropolishing; therefore, one of the main objectives of our research was to select the best conditions for electropolishing by varying electrolyte composition, current density, electrode gap and time. Using images from an atomic force microscope (AFM), Figure 3 shows the surface morphology of NiTi plates before and after electropolishing. The Ra (average roughness) of the non-electropolished NiTi plate was 11.2nm; however, Ra is reduced to 2.3nm by electropolishing. The effect of electropolishing on fatigue life was examined with a fatigue-testing machine made by Endura Tec, as shown in Fig 4a. This instrument was equipped with 12 mock vessels of latex which expanded and contracted at 70Hz with the inflow and outflow of water. Figure 4b exhibits the change in diameter of the mock vessels, one of which was loaded with an unpolished stent, the other with a polished stent . The vessel containing the unpolished stent underwent an increase in Dmax and decrease in Dmin at 70 million cycles, meaning that failure had occurred. On the other hand, the vessel containing the polished stent did not experience any change in diameter after 220 million cycles although its volume expanded up to 3.98%, indicating the onset of a crack after 25 million cycles [2]

Mechanical stability of a DLC-coated stent

A metallic stent made of NiTi or stainless steel may release its metallic elements causing allergic reaction, or it can generate thrombogenicity of blood in a physiological environment [1]. In order to improve mechanical properties and biocompatibility, metallic stent coatings of carbon, silicon carbide, titanium nitride, and tantalum have previously been tested. DLC coating has also been the subject of research testing due to its excellent mechanical and biological properties including high hardness, high wear and corrosion resistance, chemical inertness, excellent smoothness and low thrombogenicity [4]. It should be noted that a vascular stent may locally undergo a large amount of deformation resulting from tension, compression, or rotation as the extension and contraction process occurs during clinical operations. Significant deformation can cause

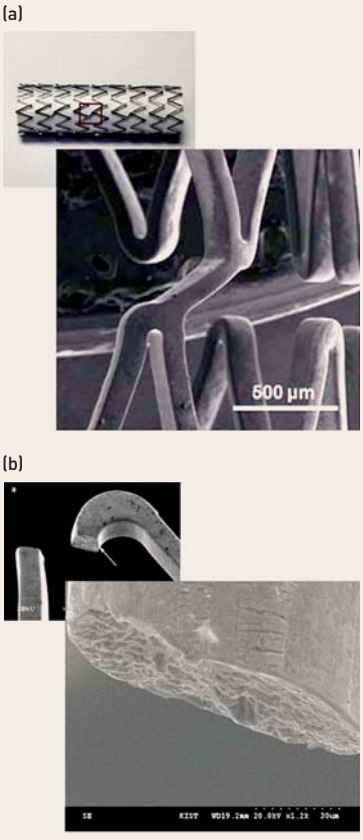

FIGURE 2. (a) Laser-cut NiTi stent; (b) Fatigue fracture on surface of nitinol stent after cyclic loading.

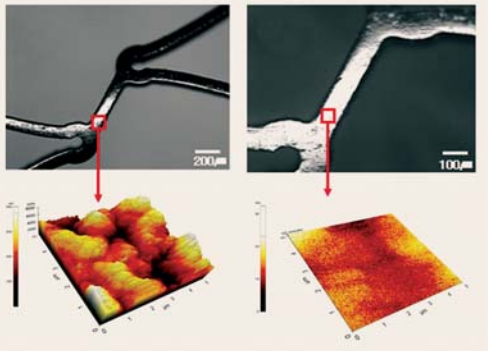

FIGURE 3. Optical images of electro-polished NiTi stent (a) before and (b) after electro-polishing.

failures in the coating layer such as cracking or spallation [8,9] drastically reducing the lifetime of a coated stent.

In our research, we used a stent crimping system to investigate the failure behavior of the coating layer on self-expandable vascular stents under cyclic loading conditions of contraction and expansion. The cohesive cracks and spallation in the film were explored by employing a focused ion beam (FIB) system. Since an amorphous Si (a-Si) buffer layer is widely used as an interlayer for improving adhesion between a thin film and substrate, we improved the adhesion strength of the DLC coating on our test stents with a-Si buffer layers.

The vascular nitinol stents of diameter 6 ㎜ and length 18 ㎜ consisted of V-shaped segments attached to each other at three sites, as shown in Fig. 2a. The coating conditions and analysis procedures we used are detailed in other literature [4]. The conditions we established to improve interfacial adhesion strength are as follows. Base pressure in the chamber was less than 5×10^{-3} ㎩ (^= superscript) and a radio frequency (RF) bias voltage was applied to the substrate holder. The Ar pre-cleaning and deposition of the a-Si buffer layer were performed for the improvement of interfacial adhesion strength between the stent and DLC film. The bare nitinol stents were cleaned for 30 min using an Ar ion gun at an anode voltage of 1.5 ㎸ with a pressure of 0.06 ㎩ and substrate bias voltage of −300 V. Sputtering of a silicon target (99.99% pure) was used for a-Si buffer layer deposition. Si was sputtered by Ar at a pressure of 0.26 ㎩ and target bias voltage of −590 V. The a-Si layer thickness was controlled by varying the sputtering time from 0 (no a-Si buffer layer), 15, 30, 60, to 300 s. The a-Si deposition rate was estimated to be about 6 Å/min as measured by both an atomic force microscope (Autoprobe CP research system, Thermo Microscope Inc, USA) and transmission electron microscope (TEM) cross-section microstructure. Finally, DLC film was coated on the stent by an ion beam deposition method using acetylene (C2H2) as the precursor gas. The ion gun was operated at an anode voltage of 1.5㎸ and gas pressure of 0.08 ㎩. During deposition, a bias voltage of −200 V was applied to the substrate. For producing a similar strain hysteresis in the DLC-coated stent inserted in the body conduit, a cycle of contraction and expansion at 100% maximum strain was applied to the stent using a stent crimping system, illustrated in Fig. 1b. The surface of the DLC-coated stent was then investigated under a FIB/SEM system (Nova 200, FEI Company) to observe the distribution of cohesive cracking and interface delamination of the DLC coating and its cross-section microstructure.

Figure 5 shows the cracking and delamination behavior of a DLC film using three different thicknesses for the a-Si buffer layer. In the absence of an a-Si buffer layer, the DLC film was delaminated and spalled across almost the entire region of the stent. Figures 5a to 5f show that the cracking and spallation of the coating predominate at the hinge regions connecting the V-shaped segments of the stent. Deformation due to contraction and expansion of the stent is highly localized in the vicinity of the hinge regions where there is high stretching strain. This result suggests that the strain distribution in the DLC film was localized at the specific region of the hinges, as indicated in the square inset boxes shown in Fig. 5.

Figure 5g shows the spalled area width normalized by varying the thickness of the DLC film by means of the a-Si buffer layer. The width of half-circular shaped spalla-

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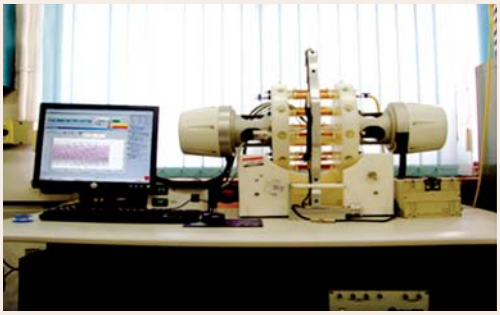

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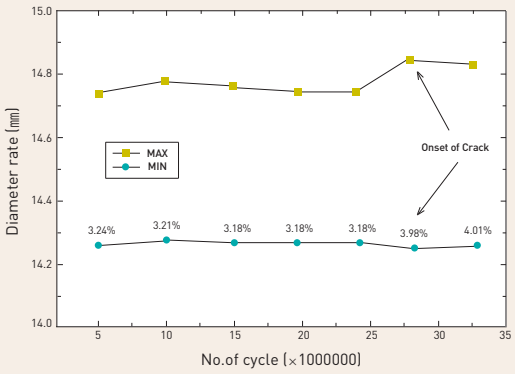
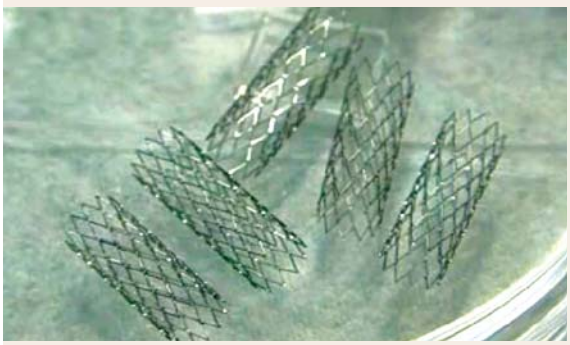


FIGURE 4. (a) Image of stent fatigue test machine; (b) Graph for long-term cyclic test.



tion was used to estimate the critical adhesion strength at the interface between the DLC film and the nitinol stent, as shown in previous research [9]. We observed no cracking when the a-Si buffer layer was deposited for more than 5 min. The condition for film cracking and spallation has generally been found in DLC-coated metallic substrate under external loading [3, 8]. The proper thickness of an a-Si buffer layer for eliminating film cracking and spallation was obtained at a deposition time over 1 min (over 6 Å thick), indicating that it is possible to deposit an a-Si layer on the entire surface of the nitinol vascular stent. However, a cautionary note should be added that the use of a thick a-Si layer can induce fracturing inside the buffer layer because of the brittle property of a-Si.

Biocompatibility of DLC-coated NiTi stent

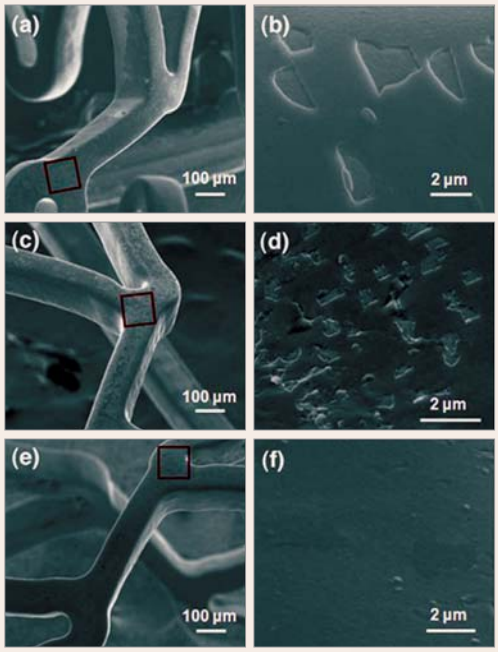
An important aspect of our research was to evaluate the efficacy of uncoated nitinol stents and DLC-coated nitinol stents for reducing neointimal hyperplasia formation in a canine iliac artery model. Detailed experimental conditions for film coating and animal testing are referenced in [5]. It was expected that DLC-coated nitinol stents would have superior biocompatibility as compared to uncoated nitinol stents due to the many advantages of DLC-coating described above. Therefore, it was hypothesized that the use of a DLC-coated nitinol stent could reduce the formation of neointimal hyperplasia, thereby improving the patency of stents with improved biocompatibility.

All experiments involving animal testing were performed in accordance with the National Institutes of Health's guidelines for the humane handling of animals and were approved by KIST's Committee of Animal Research. Under general anesthesia, a total of 24 stents were implanted, according to a fixed protocol, into the iliac arteries of six dogs (four stents in each → 25 ㎏ dog). After gross inspection of the periprosthetic, soft tissue appeared similar for all stents. Figure 6b shows the cross-sectional photomicrographs of representative serial pathology specimens from the two groups. In all cases, the majority of the neointimal hyperplasia was due to the overproduction of collagen secreted by proliferated fibroblasts (Fig 6b) in the NiTi stent. The mean percentage of neointimal hyperplasia was greater in the NiTi stent group than in the DLC-coated stent group. These results reflected in Fig. 6b indicate that DLC-coated nitinol stents may induce less neointimal hyperplasia than conventional nitinol stents after implantation in a canine iliac artery model [5].

Summary

In looking at the mechanical performance of NiTi stents and their functional DLC coatings, several important issues were considered. First was the issue of the fatigue resistance of laser-cut NiTi stents. It was found that our electropolishing technique improved fatigue resistance and extended the stent's lifetime. Secondly, biocompatibility and reduction in the release of metal ions into the body or blood stream was improved by using a functional coating of DLC for the mechanical stability of interfacial adhesion between the stent and DLC coating. By testing in the iliac arteries of six dogs, our work demonstrated that DLC-coated NiTi stents show more biocompatibility than bare NiTi stents due to their greater smoothness and the biocompatibility of DLC materials.

Most of the stents produced by domestic companies, some of which are sold on the world market, are limited to non-vascular stents. However, with coronary and carotid disease on the rise in Korea, the development of vascular stents made of NiTi or stainless



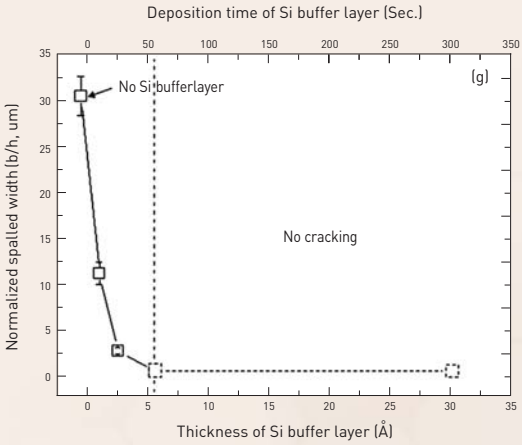


FIGURE 5. SEM images showing failure behavior as a function of the a-Si buffer layer: (a) Si buffer layer for 15 s; (b) Magnified image of square box in (a); (c) a-Si buffer layer for 30 s; (d) Magnified image of square box in (c); (e) a-Si buffer layer for 1 min; (f) Magnified image of square box in (e); (g) Spalled area width of the DLC films as a function of the a-Si buffer layer thickness: 'b' and 'h' indicate the half-width of spalled region and thickness of DLC film, respectively.

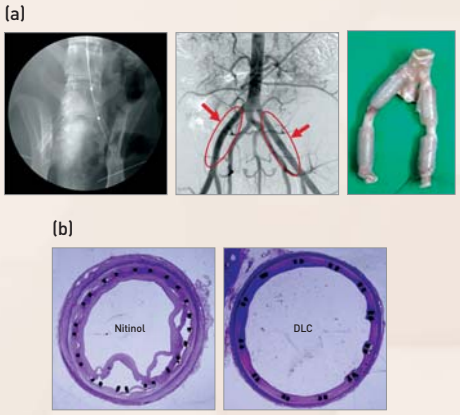


FIGURE 6. (a) Stents (arrows) are placed in both iliac arteries. Angiography immediately after stent placement (n = 4, two stents in each iliac artery) shows good position and expansions of the stents (arrows). (b) Cross-sectional photomicrographs of representative serial pathology specimens. Low microscopic findings show that the neointimal hyperplasia area was significantly less in the DLC-coated stent (right) compared with that in the nitinol stent (left).

steel is increasingly important for patients. Most of the coronary stents used in Korea are currently imported from international companies such as Boston Scientific or Johnson and Johnson. In 2007, this market was approximately 100 million dollars domestically and 5 billion dollars worldwide. The main reason Korean stent production has been lagging is that the existing technology does not meet the high standards required for FDA approval, but KIST's technology could change this situation. Our technique for the fabrication of stents from laser cutting, involving electropolishing and applying functionalized coating on the stent, could stimulate and support the efforts of domestic companies to develop a valuable market for improved stents.

REFERENCES

1. N. B. Morgan and C. M. Friend, Proc. of the Fifth European Symposium on Martensitic transformations and Shape Memory Alloys, Como, Italy, p.325 (2000).
2. 김윤배, 한준현, 박제민, 지광구, 김상호, *재료마당*, 22, 4 (2009)
3. B. Radeleff, L. Grenacher, P. Christoph, C. M. Sommer,U. Stampfl,S. Ramsauer et al. *J. Vasc. Interv. Radiol.*,20, 927-35 (2009).
4. H. J. Kim,M.-W. Moon, K.-R. Lee, H. K. Seok, S. H. Han, J. W. Ryu, et al. *Thin Solid Films*, 517, 1146-50 (2008).
5. J. H. Kim, J. H. Shin, D.H. Shin, M.-W. Moon, K. Park, T.-H.Kim, K.M.Shin, Y. H. Won, D.K. Han, & K.-R. Lee. *British J. Radio.*, In press (2010).
6. M. Allen, F. Law, N. Rushton, *Clin. Mater.* 17, 1 (1994).
7. S. Aisenberg, *J. Vac. Sci. Tcchnol.* A, 2, 369 (1984).
8. J. Franks, *J. Vac. Sci. Technol. A*, 7, 2307 (1989).
9. H.-J. Kim, M.-W. Moon, D.-I. Kim, K.-R. Lee, and K. H. Oh, *Scripta Mater.* 57, 1016-1019 (2007).

An Adaptive Process and Location Guidance System for the Elderly

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Korean society is aging at one of the most rapid rates in the world, a phenomenon that demands a response at many levels. Furthermore, the elderly of today have a different outlook than the elderly of the past. They prefer to remain active and participate in social activities without depending on other people. Development of information technology that can enable today's elderly to live independently is one example of the type of response needed to adapt to this new population pattern.

***myPAL** is an adaptive process and location guidance system that provides personalized assistance. This system can guide the elderly in public places such as hospitals and government offices by helping them find appropriate services and complete any required tasks. The system is composed of a mobile device, a sensor network and an information system. **myPAL** understands the user's needs in public places and offers guidance on where to go and what to do.*

Introduction

Many people get lost in public places such as hospitals or government offices where it is often difficult to find the right office or determine direction due to the complex structure of the buildings. Unfamiliar and/or complicated procedures can cause anyone difficulties, but these difficulties are compounded in the case of the elderly. Signs can be confusing and procedural guides difficult to understand. Although helpers or technical aids for the elderly are sometimes available, this help is often limited due to its high cost. In response, many context-aware systems have been developed, but most of the systems conceived thus far provide only fragmentary guidance. In order to be more effective, a system needs to provide general guidance about what to do, how to do it, and where to go. In addition, this guidance needs to be provided through a range of channels and formats so that it can be specifically tailored to users with different physical and mental capabilities.

This article describes a context-aware information service system, named *myPAL*, which is designed to help the elderly follow complicated procedures and accomplish tasks by providing relevant information through an adaptive interface.

Process and Location-Aware Information Service System

Location-based context-aware systems have been widely developed. However, their performance has been limited when it comes to providing effective guidance for complex processes. The process and location-aware information service system developed by KIST researchers is unique in this regard because it can understand

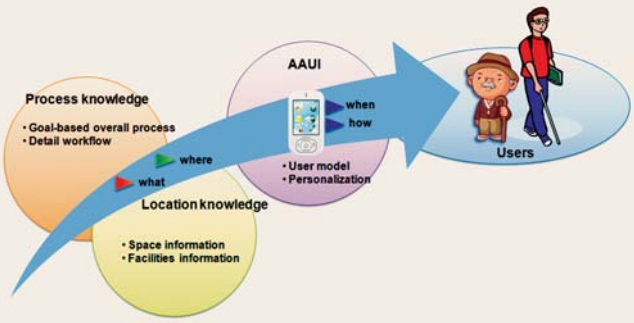

FIGURE 1. Process and location-aware information service system

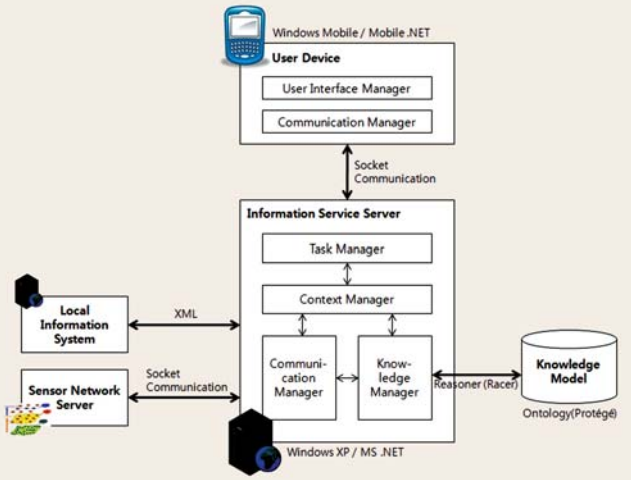

FIGURE 2. Architecture of the process and location-aware information service system

spatiotemporal context through a system that models a user's activities and location. In this case, the system selects a suitable process from its internal knowledge model based on what the user intends to do, and provides a detailed task flow that corresponds to the location of the user and the task log stored within the system. Users can also receive personalized guidance with the adaptive assistant user interface (AAUI) (Figure 1).

KIST's process and location-aware information service system includes the following components: a local information system, sensor networks, user devices and an information service server. The user device includes a user-interface manager and communication manager, and the information service server consists of a task manager, context manager, communication manager and knowledge manager that encompasses a knowledge base. The context manager, which obtains information from the communication manager and knowledge manager, directly infers the user's context from the contextual information. The communication manager communicates with the sensor network and local information system. The knowledge manager administers the knowledge base, and the task manager determines which contents are to be provided.

The local information system is a legacy information system. For example, in the case of a hospital, the system enables people to communicate with hospital personnel and manage various business processes such as billing. It also stores information such as hospital maps and patient data. The local information system also informs the user of impending events after a patient receives a medical examination and requires follow-up testing. The local information system recognizes that the exam has been completed and retrieves input from the doctor concerning the lab or other area that the patient should visit.

The sensor network consists of sensors and middleware. Low-level data gathered from sensors are converted into useful location information by the middleware, and the middleware sends this data to the information service server. The communication between systems or networks is accomplished via WLAN, a standardized communication channel. The local information system is loosely coupled with the information service server and exchanges XML documents, and the sensor network employs socket communication with the information service server.

The information service server plays a central role in the entire system. The information service server infers the user's context from the location information picked up by the sensor network, processes information from the local information system, and sends guidance content to the user's device. The reasoning steps of the information service server are as follows. First, the overall process is established based on the goal of the user. While the user is executing tasks, context information is gathered and the user context is set. If it is necessary to change the process, the information service server

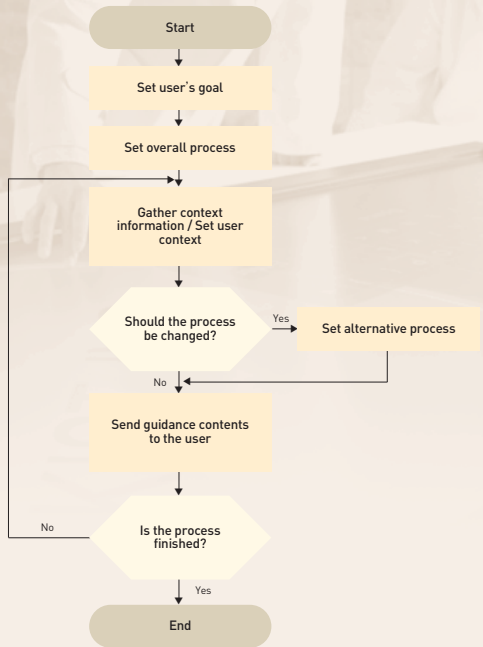

FIGURE 3. Flowchart of the information service server

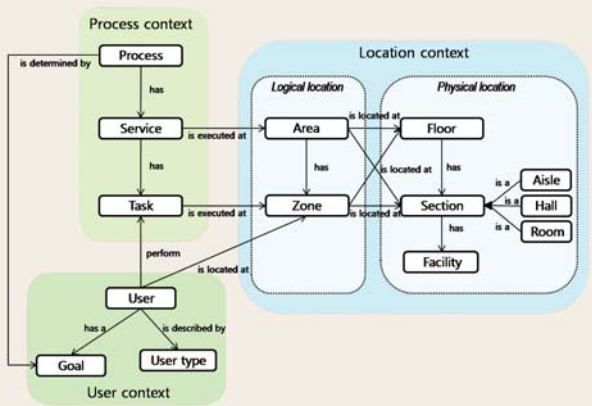

FIGURE 4. Structure of the knowledge model

sets an alternative process. The system continually sends guidance to the user until the process is completed. Figure 3 shows a flowchart of the process followed by the information service server.

The user device has two managers: the communication manager and user-interface manager. The communication manager takes charge of all communications through the user device. The user-interface manager converts guidance content based on the needs of the user. For instance, text content can be converted into aural content and small font can be magnified, adaptations which can be very helpful to an elderly individual.

A knowledge model has been designed to support the system. The knowledge model has three main parts: a process-context part, location-context part and user-context part. A process is selected based on the user's goal and defined as a flow of services; a service relates specifically to the agency/office/institution with which the user is dealing, and is defined as a flow of tasks. A task is defined as the standard unit that the user executes. In a hospital example, the project corresponds to "going to a hospital for treatments," a service might be "consulting a doctor," and a task might be "blood sampling." In the location-context part of the model, an area is defined as a group of zones, a zone being the standard unit covered by a sensor and in which a task is executed. The area and the zone are logical concepts and are connected to a physical structure, such as a floor, room, hall, aisle, or some part of a facility. The user, the user type, and the user's goal are also defined in the knowledge model. Figure 4 shows the structure of the knowledge model.

***myPAL*: An Adaptive Process and Location Guide System**

When we give people general guidance about where to go or what to do next, we usually consider their experience with the route or task. Similarly, *myPAL* gives guidance about tasks and routes considering a user's awareness level. In order to provide an adaptive process and location guide, *myPAL* uses a two-step process: 1) making a Guidance Map which represents a user's tasks, routes, and their relationships; and 2) making the level of the Guidance Map personalized to the user's capabilities.

myPAL's first step in making a Guidance Map, is to set a sequence of tasks that should be performed by the user to achieve his/her goal. After setting the task sequence, *myPAL* creates the user's routes based on the relationships between the tasks and zones that are defined in the knowledge model. The routes are

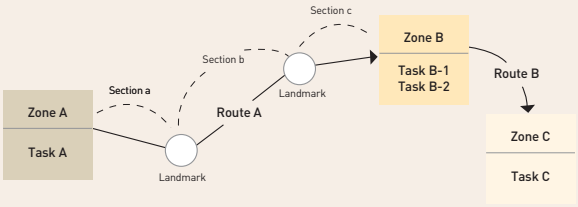

FIGURE 5. Example of a Guidance Map representing a user's task sequence, zones, routes, route sections and their relationships

FIGURE 6. Context-aware hospital guidance system

then divided into route sections, which are defined by landmarks. Figure 5 shows an example of a Guidance Map.

In the next step, *myPAL* provides personalized guidance by determining a level of guidance for each task and route in the Guidance Map. The level of route guidance is determined by the user's experience and his/her ability to follow directions. The level of task guidance is determined by the user's prior experience with the task. For example, assuming that a user has no experience with route A in Figure 5, but has previously been on route B, *myPAL* gives detailed guidance to the user about how to follow route A, but limits the information about route B to a simple indication of the destination without a detailed guide.

Example Application: A Context-Aware Hospital Guidance System

myPAL can be used in a variety of settings, but as an example application, the system was implemented in a setting which involves complicated processes and complex structures: a hospital. While a number of hospital information systems have been developed for hospital employees, *myPAL* focuses instead on the information needs of patients. The example application, a context- aware hospital guidance system, assumed a patient with disabilities, and provided guidance on what to do and where to go at the hospital.

Figure 6 shows the user device and implemented application. The user device was a PDA with an installed RFID reader. Communication with the information service server was via WLAN. The user interface was designed to be as simple as possible and allowed the user to switch between two screens, one which provided route guidance according to task name, and another with detailed service/task information.

The user interface illustrated in Figure 6 was specifically designed for the elderly. All possible guidance information was provided and the font size was selected for maximum visibility. For a person who is visually impaired, the interface can be changed into an aural interface.

Future Research

So far, KIST's process and location-aware information service system has been developed on a pilot test scale. Based on the results of the pilot study, future system functions will be examined and implemented. Plans are underway for a test system to be installed at the Seoul National University Bundang Hospital with support from the IT R&D program of the Ministry of Knowledge Economy / Korea Evaluation Institute of Industrial Technology.

Water Treatment Technology for People, Health, and Life

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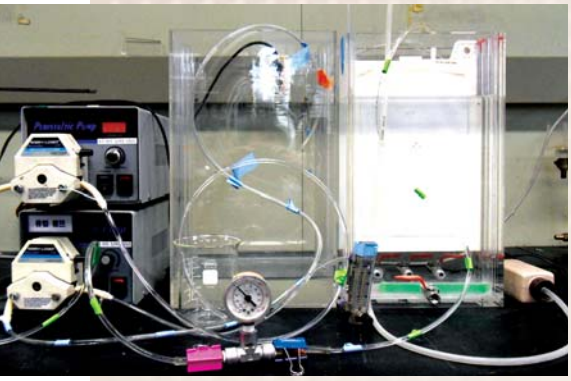
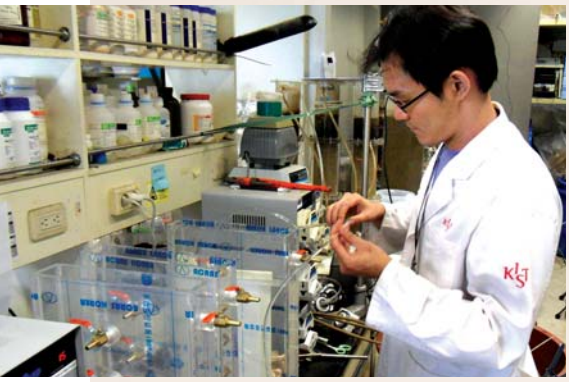




Introduction

Water is a necessity for human life. It is also essential for maintaining civilizations and cultures. We are well aware of its importance and cannot imagine life without a drop of water, yet our planet is increasingly suffering from water scarcity for many reasons including population growth, industrial development, global climate change and regional disparity of water resources. In 2008 the UN reported that about 2.7 billion people will face water shortages by 2025 [1].

It is natural to think that people are suffering from water poverty in other countries but that we still have sufficient water resources in Korea and will continue to have them. Unfortunately, many statistics indicate that Korea is also in danger. The Korean Ministry of Land, Transportation, and Maritime Affairs estimates that 2011 will see a shortfall of 1.8 billion ㎥ of water with the shortfall increasing to 2.6 billion ㎥ by 2020 because of increasing urbanization of the population and higher water demand [2]. Moreover, expensive energy resources make it imperative to use less energy in the treatment process.

Inadequate treatment of polluted water constitutes a serious threat to public health. A 2006 World Water Assessment Programme (WWAP) report showed about 1.1 billion people lacking access to safe water, 2.4 billion to adequate sanitation, 800 million suffering from malnutrition linked to the lack of clean water, and 1 million dying from malaria per year due to the lack of proper water treatment [3]. In addition, emerging micro pollutants such as endocrine-disrupting chemicals, personal care products, and pharmaceutical products, though very small in size and quantity, are very toxic and hazardous to the ecosystem. These micro pollutants should be treated more effectively in the drinking water treatment process.

None of the facts raised above are in dispute, and many policies, social movements, and technological solutions have been established to cope with "the era of water scarcity." This article introduces a leading-edge technology in water treatment processing: an advanced wastewater treatment process applying membrane technology. The main goal of this technology is to clean up wastewater on a large scale so that the treated wastewater can be reused. KIST's Water Environment Center has been conducting intensive research related to these technologies and recently initiated a project for developing an innovative water reuse process to produce clean, safe, and almost drinkable water from wastewater.

Using a membrane bioreactor in wastewater treatmen

Since the development of synthetic asymmetric membranes in 1960, interest in membrane processes for water and wastewater treatment has grown steadily. Recently, these technologies

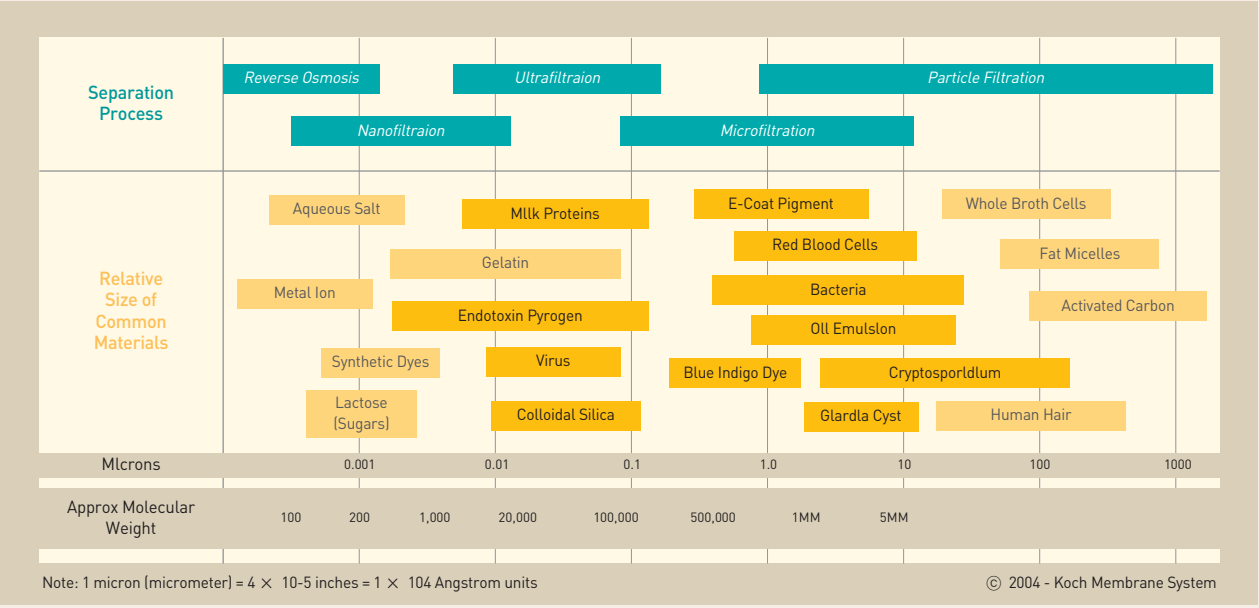


FIGURE 1. Microfiltration, ultrafiltration, nanofiltration, and reverse osmosis membrane process differing principally in the average pore diameter of the membrane filter and the different sizes of various solutes removed by each class of membrane separation (http://www.kochmembrane.com/ps_exmem.html).

have become the subject of substantial international research, development, commercial activity, and full-scale application. The increase in the use of membranes in water treatment applications is attributed to three factors: (1) increased regulatory pressure to provide better treatment for both drinking and waste waters; (2) increased demand for water requiring exploitation of water resources; and (3) market forces surrounding the development and commercialization of the membrane technologies and industries [4].

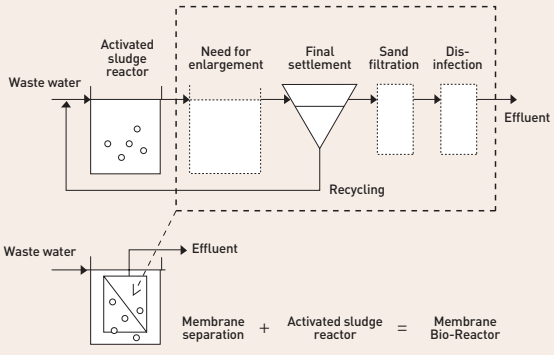
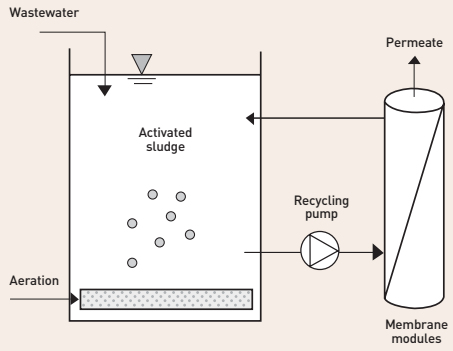


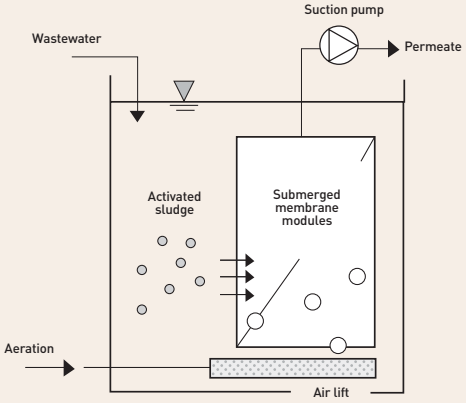
FIGURE 2. Figure 2 Application of membrane separation in a conventional wastewater treatment process in which many treatment steps (e.g., final settlement, sand filtration, and disinfection) can be replaced by a one-membrane filtration process.

Membrane separation (membrane operation or membrane process) can be defined as an operation that concentrates a suspension or purifies a solution (solvent-solute or particle separation) and fractionates a mixture (solute-solute separation) using a membrane. In water treatment technology which uses a membrane, *permeate* means clean or treated water/liquid and retentate implies pollutants or residual particles. Thus, after membrane separation, a feed stream is divided into two streams: permeate, containing matter which has passed through the membrane, and retentate or concentrate containing non-permeable species. Figure 1 classifies the membrane separation process according to different pore diameters of the membrane varying from microfiltration to reverse osmosis and the size of different solutes removed by each class of membrane.

In a conventional activated sludge process, wastewater purification takes place by suspending solids in an activated sludge tank. These suspended solids include inorganic particles as well as aerobic microorganisms, and in a secondary clarifier, these solids are separated from the treated water by gravitational sedimentation and recycled to the activated sludge tank. Accordingly, this sedimentation step depends on the properties of the sludge. Sludge bulking and foaming causes the washing out of the activated sludge from the system and a low quality of effluent. In order to prevent this failure, operation factors,



(a) Side-stream membrane filtration



(b) Submerged type MBR

FIGURE 3. General installations of side-stream (a) and submerged (b) membrane systems.

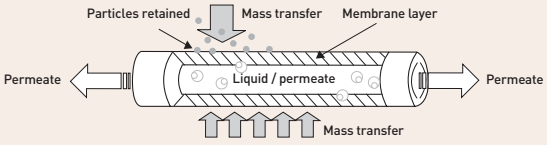


FIGURE 4. Schematic of the outside-in filtration process of a hollow fiber membrane. The flat-plate sheet membrane filtration process is essentially identical except that the membrane shape is a flat sheet rather than circular.

such as the dissolved oxygen concentration in the reactor, the organic substrate-loading rate to activated sludge, and the hydrodynamic design in the sedimentation tank should be considered. Also, the gravitational sedimentation step does not eliminate fine suspended particles nor germs in the effluent. The limitations inherent in the final separation step restrict the operation of a conventional activated sludge process because of the low sludge concentration (3,000-4,000 ㎎/ℓ). Consequently, a large-volume aeration tank should be constructed capable of a hydraulically long retention time. To remove enough nutrients and tertiary solids as well as sufficiently treat bacteria so that effluent is pure enough to be re-used as water, the conventional activated sludge process has to be expanded and combined with further tertiary treatment steps such as sand filtration, ultra-violet disinfection or chlorination.

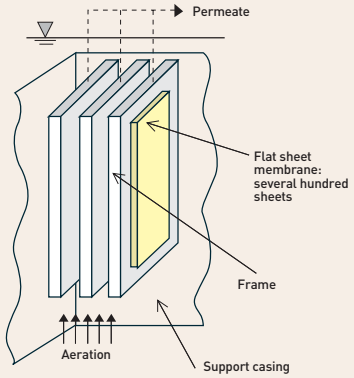
Applying membrane separation technology to an activated sludge system is a simple way to satisfy the high standards required for re-use of effluents. A membrane allows for perfect solid-liquid separation to produce particle-free effluent regardless of sludge setting conditions. Also, with mixed liquor suspended solids (MLSS) concentrations of 3 to 5 times higher than in a conventional system, activated sludge reactor volumes can be drastically reduced and hydraulic retention time decreased. The hydraulic and biological treatment capacity of existing treatment facilities can be increased without enlarging bioreactor volumes just by adding more membranes to the system. Figure 2 shows the application of membrane separation in an activated sludge process. This system, in which membrane filtration is combined with an activated sludge process, is termed a membrane bioreactor (MBR).

Types of membrane bioreactor systems

MBR processes are classified into two categories depending on the position in which the membrane filtration is operated; one is a side-stream (alternatively expressed as external) and the other is a submerged (alternatively expressed as immersed or internal) MBR. In a side-stream filtration system, the membrane is arranged outside the bioreactor. In this way, solids-liquid separation and pollutant purification take place independently. The mixed liquor suspended solids are recycled from an aerated bioreactor into a membrane filtration unit, and this recirculation is induced by means of a high pressurizing pump. Tubular and spiral wound membrane modules are usually equipped with this external filtration MBR system [5].

Recently, the submerged membrane bioreactor system (SMBR) has been receiving more attention for its compactness and low energy consumption compared with the side-stream membrane filtration system [6]. In this system, membrane modules are fully immersed in the bioreactor. Therefore, the biological purification and solids-liquid separation take place in an identical reactor. The membrane filtration process is usually driven by a permeate extraction pump, creating a pressure gradient between the inside and outside of the membrane. This pressure difference is called transmembrane pressure (TMP) and limited to the value less the atmospheric pressure (100 ㎪ at sea level) because a free water surface exists in the bioreactor. Only the permeate flows from out-

(a) Flat-plate membrane module



(b) Hollow fiber membrane module

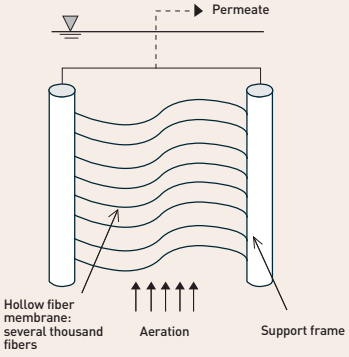


FIGURE 5. Schematics of flat-plate and hollow fiber membrane modules

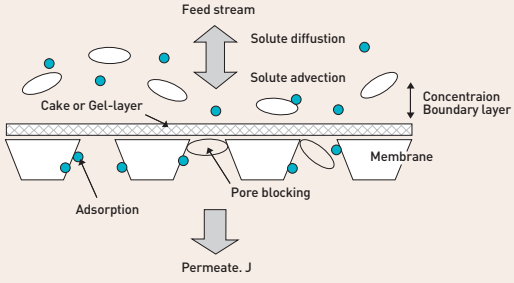


FIGURE 6. Membrane fouling phenomenon during pressure-driven separation.

side to inside the membrane, thereby retaining residuals in the bioreactor. Figure 3 illustrates the common installation of membrane in both side-stream and submerged type MBR systems. Figure 4 shows a schematic of the outside-in filtration process of a hollow fiber membrane. Almost all submerged membrane systems adopt this outside-in filtration regardless of the membrane module type, such as hollow fiber or flat-plate sheet.

A membrane module is a set of membranes which supports membrane sheets or hollow fibers with welded frames and provides the drainage system producing permeate (see Figure 5). Directly below the modules, air is supplied simultaneously to the membrane module and the reactor. The aeration supplies microorganisms with the oxygen needed for respiration. Also, uprising air generates turbulence in the air/liquid mixture, inducing shear strength on the membrane surface. This shear strength protects the membrane from fouling by controlling cake-layer formation on the membrane surface. When filtration is operated with shear strength, cross-flow filtration can be established and critical flux induced. Cross-flow filtration provides continuous and stable separation for a MBR system even with a high suspended solids concentration in the reactor.

Membrane Fouling in MBR System

Ultrafiltration (UF) and microfiltration (MF) have been considered promising technologies for enhancing particle separation in water treatment systems. Specifically, MF appears highly feasible in a membrane bioreactor system in which activated sludge is effectively removed from treated effluent by membrane separation. Nevertheless, one of the major obstacles preventing widespread application of MF is that the flux declines over time [7]. This phenomenon is generally termed *membrane fouling*. In terms of water treatment, fouling is the process in which a variety of species in the water increase hydraulic as well as membrane resistance by causing deposits to form on the membrane surface, causing adsorption on the pore surfaces within the bulk membrane material or by directly blocking pores. Membrane fouling reduces the permeate production rate, causes deterioration of membrane quality and increases operation costs because of the need to restore fouled membrane and eventually to replace it. Figure 6 represents the membrane-fouling phenomenon during pressure-driven separation using an asymmetric membrane.
Specifically, the bio-fouling caused by microbial action is a primary cause of membrane fouling in the MBR process. Bio-fouling is operationally defined as the biofilm formation resulting in an unacceptable degree of system performance loss [8]. Biofilms occur as a result of adhesion and growth of microorganisms on a membrane surface [9]. Transport of microorganisms to an interface may occur passively by diffusion, gravitational settling, or bulk fluid convection. Biofilm bacteria exhibit dynamic adhesion in which bonding to a membrane increases over time due to the biosynthesis of adhesive extracellular biopolymers. The biopolymers are frequently produced in amounts that completely envelop attached cells in a viscous hydrated gel [10, 11]. This gel matrix is referred to as the glycocoalyx [12], slime layer, capsule, or extracellular polymeric substance (EPS) [13]. Biofilm usually consists of multiple layers of living and dead cells and their associated extracellular products, which is a complex matrix including a variety of glycoproteins, humic acids, hetero-polysaccharides, and lipids [14]. Figure 7 shows SEM (scanning electron micro-

scope) images of a membrane surface which has been fouled by biofilm formation and fouling cake-layer growth.

To prevent fouling, many operating strategies have been applied such as chemical cleaning, surface flushing with clean water, and vigorous aeration at the membrane surface. Recently, many researchers have been applying specific materials as coatings on the membrane surface to improve resistance to membrane fouling, therby allowing the more widespread use of the membrane process in large-scale water treatment.

Membrane process development for water reuse at KIST

In 2010, KIST's Water Environment Center launched a 3-year project to develop a water re-use process to produce clean, safe, and almost drinkable water from wastewater. This project has three principal objectives: (1) to use an innovative desalination system employing both a reverse osmosis membrane process and a forward osmosis membrane process to remove all ionic matter from wastewater and thereby produce very clean, drinkable water; (2) to develop a resource recovery process to retrieve available resources such as metals, phosphorus, and fertilizer components from solid wastes or wastewater and to treat membrane filtration residuals that are very concentrated and toxic; and (3) to develop an energy efficient and highly advanced wastewater treatment system in which an advanced MBR system is used to obtain a highly efficient removal rate of organic, nitrogen, and phosphorus material from municipal wastewater while reducing energy consumption. Figure 8 represents a schematic describing the aims and research scope of this project. This system developed by KIST is expected to be applied to produce additional water resources and compensate for regional water demands during seasons of drought.

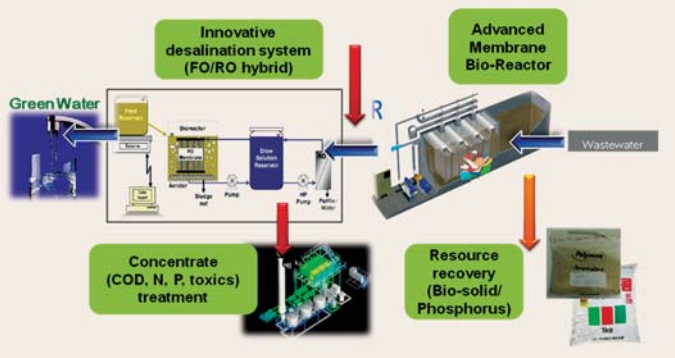


FIGURE 8. Advanced membrane process development plan for water reuse in KIST project.

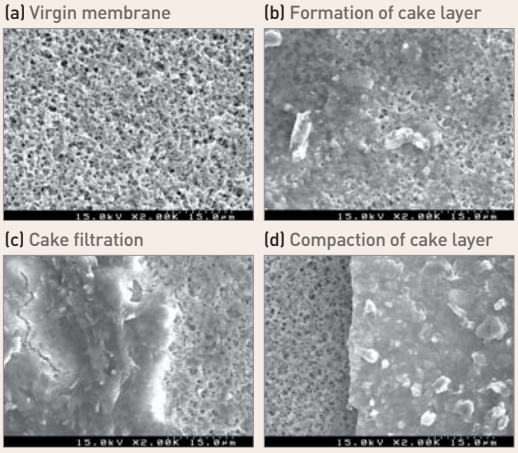


FIGURE 7. Scanning electron microscope images of membrane surfaces fouled by wastewater: (a) virgin membrane surface; (b) pore blocking is complete and cake layer (fouling layer) formation starts; (c) fouling cake filtration phase; and (d) fouling layer is concretely compacted.

REFERENCES

1. The United Nations, World Water Development Report 2 (2008)
2. Korean Ministry of Land, Transportation, and Maritime Affairs, Water Vision 2020 (2001)
3. UNESCO, World Water Assessment Programme (2006).
4. Mallevialle, J., Odendaal, P. E. and Wiesner, M. R., Water treatment membrane process, AWWA, 1.1-1.9 (1996).
5. Gunder, B. and Krauth, K., Water Science and Technology, 38(4-5), 383-393 (1998).
6. Gander, M. A., Jefferson, B. and Judd, S. J., Water Science and Technology, 41(1), 205-211 (2000).
7. Song, L., Journal of Membrane Science, 139, 183-200 (1998).
8. Characklis, W. G., Biofouling and Biocorrosion in Industrial Water Systems, 7-27 (1991).
9. Mallevialle, J., Odendaal, P. E. and Wiesner, M. R., Water treatment membrane process, AWWA, 1.1-1.9 (1996).
10. Flemming, H. C., Reverse Osmosis: Membrane Technology, Water Chemistry, and Industrial Applications, 163-209 (1993).
11. Geesey, G. G., Stupy, M. W. and Bremer, P. J., International Biodeterioration and Biodegradation, 30, 135-154 (1992).
12. Costerton, J. W. and Irvin, R. T., Ann. Rev. Microbiol., 35, 299-324 (1981).
13. Neu, T. R. and Marshall, K. C. , J. Biomaterials Applications, 5, 107-133 (1990).
14. Zydney, A. L. and Colton, C. K., Chemical Engineering Community, 47, 1-27 (1987).

Biodegradable Drug-Eluting Stents for Coronary Artery Intervention

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Coronary artery disease (CAD) is considered a major health threat worldwide because of its high fatality rate and the need for immediate intervention. Currently, the most dependable therapeutic approach to CAD is to use a stent, a circular mesh-type medical device with a very small diameter, to improve blood flow. Once arteries are clogged, stents are inserted to expand the constricted area so that blood flows without any blockages which are typically caused by atherosclerosis (Fig 1a). In fact, the lives of many patients are saved as a result of immediate stent implantation. Stents coronary arteries must be technologically superior to stents that do not come into contact with the blood. Even though the technology of development is advanced and ongoing, there are still many shortcomings to be addressed. The most serious one is the recurrence of CAD in which both restenosis and late thrombosis cause stent failure (Fig. 1b).

Numerous clinical cases and statistics have shown that while a bare metal stent (BMS) is vulnerable to restenosis (the re-narrowing of an inflated vessel), a drug-eluting stent (DES) can trigger late thrombosis (the formation of blood clots). For major stent manufacturers such as Johnson & Johnson, Boston Scientific, Medtronic, and Abbott, the technological trend in stent development is to utilize drugs in the stent design to prevent restenosis which is induced by the overgrowth of smooth muscle cells (SMCs). These drugs, typically rapamycin (sirolimus) and its derivatives as well as paclitaxel, are coated on the stent surface using non-biodegradable polymers. To deal with the problem of late thrombosis, biodegradable polymer-coated drug-eluting metal stents, and in particular, fully biodegradable drug-eluting polymer stents (Fig. 2), are receiving considerable attention because they eliminate the occurrence of neointimal hyperplasia and aggregation of blood clots, thereby making them attractive alternatives to BMSs and DESs. Given these findings, it is natural to

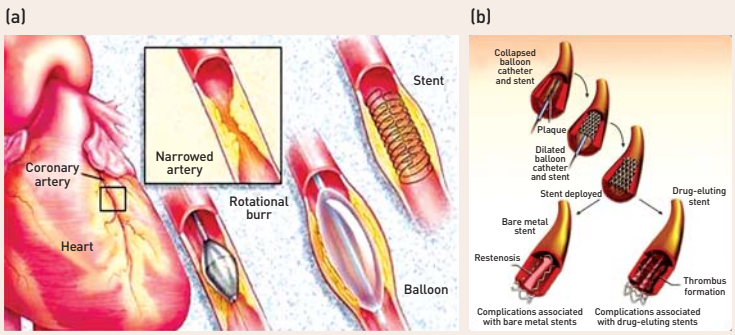


FIGURE 1. (a) Illustration of stent application for coronary artery intervention; and (b) bare metal stent (BMS) versus drug-eluting stent (DES). BMS can cause restenosis and DES can result in late thrombosis.

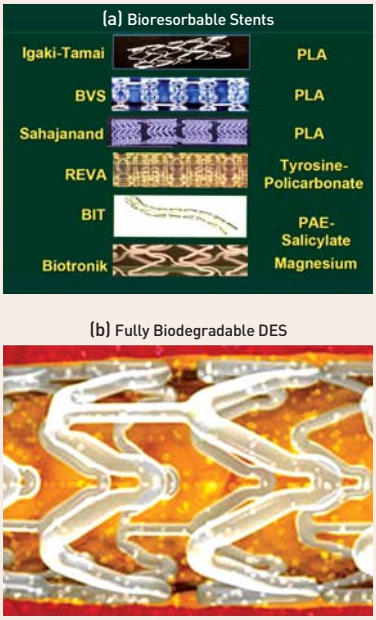


FIGURE 2. (a) Examples of bioresorbable stents and their base materials; and (b) a fully biodegradable DES.

postulate that multiple technologies should be combined to yield a perfect coronary artery stent design. The most relevant technologies are drug release control, surface coating technology, mechanical compliance of biodegradable stents, and strategies for re-endothelialization, a process of formation of a thin endothelium layer that regrows over the stent surface.

To provide the most viable solution for a CAD patient, we are now focusing on a fully biodegradable stent with a lifespan of less than 2 years. One of the core technologies for developing this type of stent is surface coating. A stent surface should be smooth and its thickness must be uniform throughout a 3D configuration of stent struts, otherwise its surface is the first target of blood clot formation. The present coating techniques are electrospraying (Fig. 3A) and ultrasonic nanocoating (Fig. 3b). Both can create a thin ($<10\ \mu m$) and smooth stent coating (Fig. 3c). Application conditions vary according to the type of polymer, solvents, and other related parameters. Therefore, it is of paramount importance that these factors be systematically controlled.

To maximize the benefits of any drugs loaded in the stent, it is critical to ensure control. Currently used drugs are mostly hydrophobic so that their release from a polymer matrix is hard to control. Some commercialized stents are designed to release most of the drug content within three months (Fig. 4a). Others such as Endeavor™ and TAXUS® use different concepts of release. Release profiles often fluctuate depending on the type of polymer matrix and drug (Fig. 4b). In some cases, several drugs are applied together to meet specific therapeutic purposes. Each drug shows a unique release pattern on a temporal basis (Fig. 4c).

Another important aspect of stent technologies is the methodology of stent re-endothelialization. Without this process, implanted stents are always to the risk of stent malfunction over time. Re-endothelialization is closely associated with complex biological chain reactions. Many novel strategies are being tested includ-

Another important aspect of stent technologies is the methodology of stent re-endothelialization.

FIGURE 3. Instruments for stent coating: (a) electrospraying; and (b) ultrasonic nanocoating. The coated surface (bottom photo (c)) is extremely smooth and uniform over all surface areas as compared to one with an uneven coating (top photo (c)).

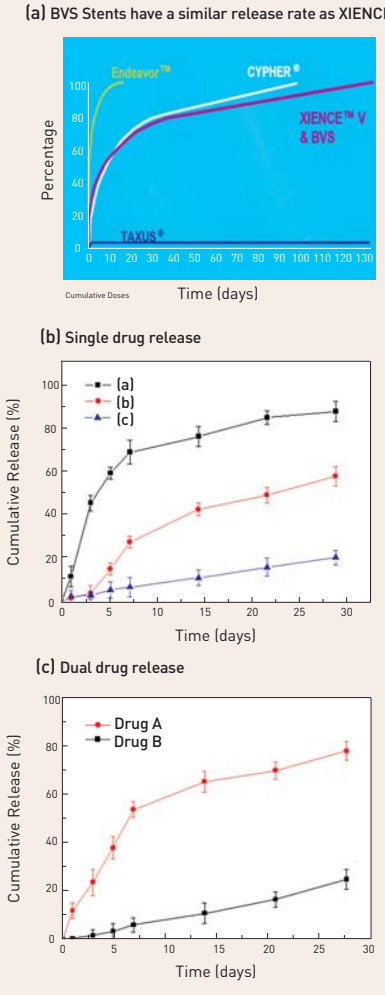


FIGURE 4. (a) Release profiles of commercialized stents; and (b) drug release patterns from different polymer matrices. (c) Two different drugs are released together from the polymer matrix and the released drug amount is different on a temporal basis.

ing: i) the capturing of endothelial progenitor cells (EPCs); ii) delivery of nitric oxide (NO); and iii) encapsulation of vascular endothelial growth factor (VEGF). In the first case, specific peptides, proteins or antibodies are grafted onto the stent surface and then utilized in capturing EPCs on the stent surface (Fig. 5a). In the second case, a NO- nanofibrous matrix covers the stent surface to recruit endothelial cells (ECs) (Fig. 5b). The goal of these approaches is to suppress the overgrowth of SMCs but boost the adhesion and proliferation of ECs.

Is a cutting-edge biomedical device that can save the lives of millions of people. To its performance and reliability, however, the core technologies described above must be carefully evaluated and effectively utilized to realize these essential improvements in the near future. KIST is working intensively to develop these technologies in the production of superior cardiac artery stents.

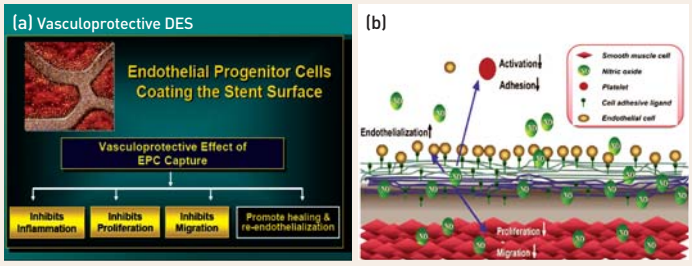


FIGURE 5. Strategies for the induction of stent re-endothelialization: (a) capturing of endothelial progenitor cells (EPCs); and (b) nitric oxide (NO) release from nanofibrous stent surface (Jun et al., *Biomaterials*).

PUBLICATIONS

1 Observational Fear Learning Involves Affective Pain System and $Ca_v1.2$ Ca^{2+} Channels in ACC

Nature Neuro Science 13, 4, 428~488

Daejong Jeon, Sangwoo Kim, Mattu Chetana, Daewoong Jo, H Earl Ruley, Shih-Yao Lin, Dania Rabah, Jean-Pierre Kinet, Hee-Sup Shin

Fear can be acquired vicariously through social observation of others suffering from aversive stimuli. We found that mice (observers) developed freezing behavior by observing other mice (demonstrators) receive repetitive foot shocks. Observers had higher fear responses when demonstrators were socially related to themselves, such as siblings or mating partners. Inactivation of anterior cingulate cortex (ACC) and parafascicular or mediodorsal thalamic nuclei, which comprise the medial pain system representing pain affection, substantially impaired this observational fear learning, whereas inactivation of sensory thalamic nuclei had no effect. The ACC neuronal activities were increased and synchronized with those of the lateral amygdala at theta rhythm frequency during this learning. Furthermore, an ACC-limited deletion of $Ca_v1.2$ Ca^{2+} channels in mice impaired observational fear learning and reduced behavioral pain responses. These results demonstrate the functional involvement of the affective pain system and $Ca_v1.2$ channels of the ACC in observational social fear.

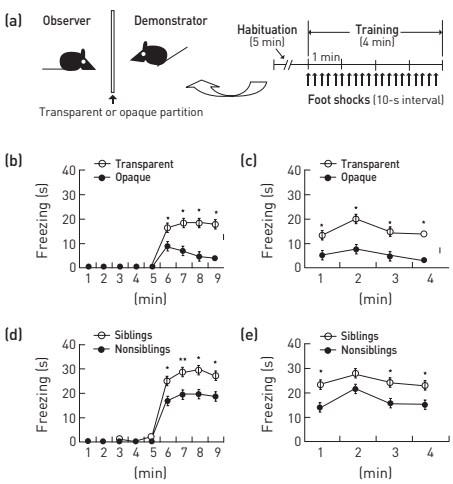


FIGURE 1. Observational fear learning in the mouse. (a) Diagram of the apparatus used for observational fear conditioning and the scheme of the behavioral assay. (b,c) Observational fear learning in the mouse (nonsiblings) using a transparent ($n = 21$) or opaque ($n = 8$) partition. A significant difference in the level of freezing behavior was apparent depending on whether a transparent or an opaque partition was used for the conditioning experiment on both the training day (b) and 24 h after training (c). *P < 0.01, Scheffe's post hoc test. (d,e) Observational fear learning with siblings. We examined freezing behavior on the day of training ($F1$, $45 = 9.41$, $P = 0.0036$, two-way repeated ANOVA, d) and 24 h after training ($F1$, $45 = 11.48$, $P = 0.0015$, two-way repeated ANOVA, e) in siblings ($n = 26$) and nonsiblings ($n = 21$) using a transparent partition. *P < 0.05, **P < 0.01, Scheffe's post hoc test. Error bars represent s.e.m.

2 Sonochemical Hybridization of Carbon Nanotubes with Gold Nanoparticles for the Production of Flexible Transparent Conducing Films

Carbon 48, 5, 1325~1330

HoSeok Park, Joon-Sung Kim, Bong Gill Choi, Seong Mu Jo, Dong Young Kim,
Won Hi Hong, Sung-Yeon Jang

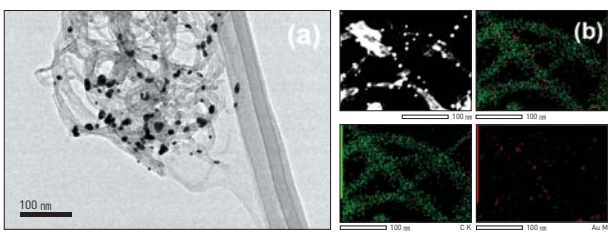


FIGURE 1. (a) TEM and (b) STEM images of Au-MWCNT-HBs. STEM image (top left), mass mapping of mixed C and Au (top right), C(lower left), and Au (lower right).

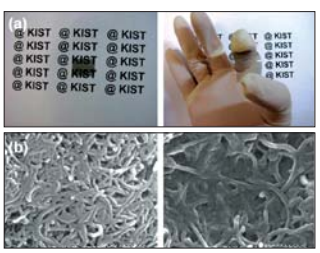


FIGURE 2. (a) Photo-images of Au NP-decorated MWCNT-HB films (Au-MWCNT-HB-2) and (b) SEM images of MWCNT (left) and Au-MWCNT-HB films (right).

We have demonstrated the fabrication of flexible, transparent, conducting multiwalled carbon nanotube (MWCNT)/gold nanoparticle hybrid films with improved optoelectronic properties by combining the ionic liquid-assisted sonochemical method (ILASM) for hybrid synthesis with the vacuum filtration (VF) method for thin film preparation. Au nanoparticles (NPs) with diameters of 10.3 ± 1.5 ㎚ were uniformly distributed onto the sidewalls of MWCNTs through ILASM, and flexible, transparent, conducting films of Au/MWCNT hybrids (HBs) were reproducibly fabricated by the VF method. In particular, the sheet resistance of Au-MWCNT-HB films was more than 2-fold lower than the sheet resistance of pristine MWCNT films due to the well-interconnected three-dimensional nanotube network structure and the synergistic effect of hybridization of MWCNTs with Au-NPs.

3 Electromagnetic Propagation From an Intestine-Ingested Source in a Human Body Model

IEEE 58, 5, 1683~1688

Ji-Hyun Jung, Sang-Wook Kim, Young-Sik Kim, and Se-Yun Kim

Electromagnetic fields radiated from an ingested source in the intestine of a human body model at point S, as illustrated in Fig. 1, are calculated using the finite-difference time-domain (FDTD) method. The propagation characteristics of the vertically polarized components of the electric fields (Ez) at the six receiving points vertically placed on the model surface (M1-M6) are analyzed in the frequency range of 100 MHz to 700 MHz. As the receiving point moves away from the ingested source, the received electric fields show relatively lower attenuation above 400 MHz and generate an unusual dip pattern at a particular frequency below 400 MHz, as shown in Fig. 2. The above two interesting features may occur due to the surface wave propagating along the boundary of the human body model. The effects of the surface wave are illustrated clearly in the homogeneous circular cylinder as a simplified model of the human body

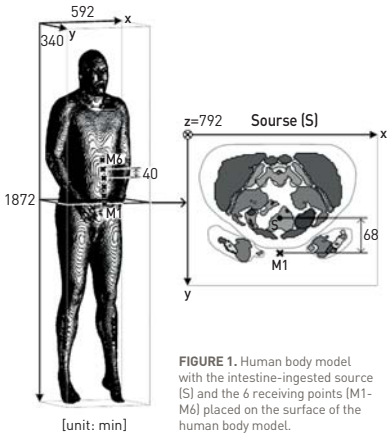


FIGURE 1. Human body model with the intestine-ingested source (S) and the 6 receiving points (M1-M6) placed on the surface of the human body model.

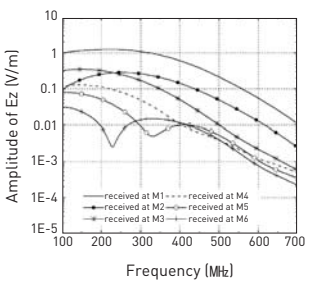
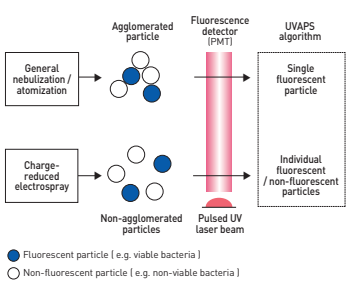


FIGURE 2. Amplitude variations of the normalized z-components of the electric fields radiated from the ingested source at S in the intestine of the human body model.

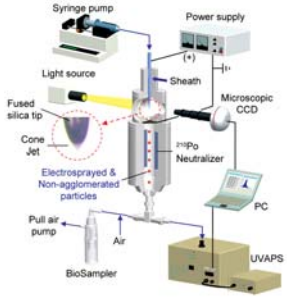
4 Electrospray-Assisted Ultraviolet Aerodynamic Particle Sizer Spectrometer for Real-Time Characterization of Bacterial Particles

Chemistry of Materials 22, 8, 2411~2413

Jae Hee Jung, Jung Eun Lee, Gi Byoung Hwang, Byung Uk Lee, Seung Bok Lee, Jong Soo Jurng, Gwi Nam Bae



Response algorithm of the UVAPS with respect to particle agglomeration.



Experimental configuration of the electrospray-assisted UVAPS system.

Real-time in situ monitors of biological particles not only enhance characterization efficiency but also improve the accuracy of data, as compared with conventional methods. The Ultraviolet Aerodynamic Particle Sizer (UVAPS) spectrometer is a novel, commercially available aerosol counter for real-time, continuous monitoring of viable bioaerosols based on the fluorescence induced from living microorganisms. We investigated the real-time characterization of bacterial particles using an electrospray-assisted UVAPS system. The charge-reduced electrospray technique can be used to produce stable aerosolization of bacterial particles without particle agglomeration, owing to the repulsive electrical forces generated with the system. Our results indicate that the agglomeration of particles resulting from general atomization can markedly affect the real-time characterization by UVAPS. The electrospray-assisted UVAPS system allows more accurate and quantitative characterization of bacterial particles in real-time and has potential applications in the control of bioaerosols and in bioengineering research. The results presented in this paper enhance the understanding of the UVAPS, particularly its performance with non-agglomerated particles, and thus assists in developing methodologies for routine application in various environments, including air and liquid-based media. In addition, this recommended system may also be useful for designing new detection methods for biological materials in real-time.

5 Targeted Delivery of Low Molecular Drugs Using Chitosan and its Derivatives

Analytical Chemistry 82, 2, 664~671

Jae Hyung Park, Gurusamy Saravanakumar, Kwangmeyung Kim, Ick Chan Kwon

Chitosan has prompted the continuous impetus for the development of safe and effective drug delivery systems because of its unique physicochemical and biological characteristics. The primary hydroxyl and amine groups located on the backbone of chitosan allow for chemical modification to control its physical properties. When the hydrophobic moiety is conjugated to a chitosan molecule, the resulting amphiphile may form self-assembled nanoparticles that can encapsulate a quantity of drugs and deliver them to a specific site of action. Chemical attachment of the drug to the chitosan throughout the functional linker may produce useful prodrugs, exhibiting the appropriate biological activity at the target site. Mucoadhesive and absorption enhancement properties of chitosan increase the *in vivo* residence time of the dosage form in the gastrointestinal tract and improve the bioavailability of various drugs. The main objective of this review is to provide an insight into various target-specific carriers, based on chitosan and its derivatives, towards low molecular weight drug delivery. The first part of the review is concerned with the organ-specific delivery of low molecular drugs using chitosan and its derivatives. The subsequent section considers the recent developments of drug delivery carriers for cancer therapy with special focus on various targeting strategies.

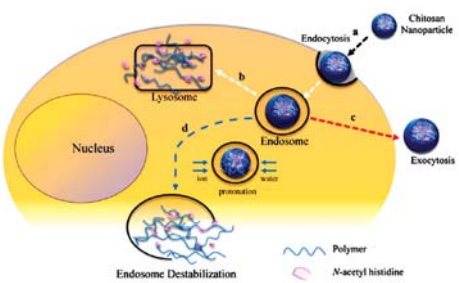


FIGURE 1. Schematic representation of a proposed model for the cellular internalization and drug release of NAcHis-GC nanoparticles. (a) Internalization of NAcHi-GC nanoparticles is initiated by nonspecific interactions between nanoparticles and cell membranes. (b) A part of the nanoparticles is exocytosed. (c)Without a specific mechanism for endosomal escape, drug-loaded nanoparticles are trafficked to lysosomes,where a high level of lysosomal enzymes is present. Drugs sensitive to these enzymes are degraded and lose their activity. (d) Under the slightly acidic environments found in endosomes, the imidazole group of histidine is protonated, causing the disruption of endosomal membranes and simultaneous delivery of drugs into the cytosol.

6 Ultrathin Crosslinked Perfluoropolyether Film Coatings from Liquid CO2 and Subsequent UV Curing

Advanced Drug Delivery Reviews 62, 1, 28~41

Jaehoon Kim, Jason P. Rolland, Ruben G. Carbonell, Joseph M. DeSimone

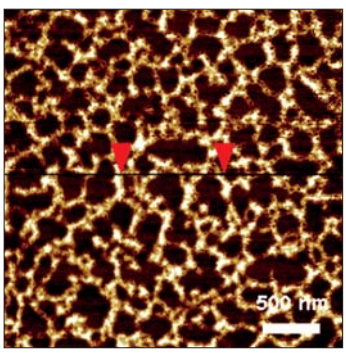


FIGURE 1. AFM image of Ultrathin film coatings of PFPE (~ 8 ㎚ in thickness) using (l-CO_2 as a coating solvent

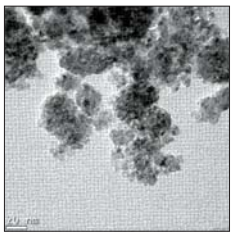
Low surface energy films have a variety of applications such as oil and water repellents, low adhesion and friction coatings, self-cleanable coatings, biocompatible coatings, and antibiofouling coatings. Thin film coatings of traditional fluoropolymers such as poly(tetrafluoroethylene) (PTFE), fluorinated ethylene propylene (FEP) and poly(vinyl fluoride) (PVF) are challenging because of poor solubility in conventional organic solvents, low melt flowability, and poor weldability. Recently, thin fluorinated polymer coatings from liquid carbon dioxide (l-CO_2) or supercritical carbon dioxide (scCO_2) have been widely investigated because of the high solubility of fluoropolymers in the compressed CO_2 medium, unique coating conditions, environmental benignity, and high film qualities. In this study, we demonstrate that ultrathin fluorinated films with optically clear and chemically resistant characteristics are produced by first depositing photocurable perfluoropolyether from l-CO_2 high-pressure free-meniscus coating (hFMC) and subsequent curing of the deposited films. Film thickness ranging from 3-13 ㎚ was controlled by adjusting solution concentration ranging from 5-15 wt%. Highly robust, solvent-resistant films were produced by UV curing of the deposited films. Contact angles of the coated substrate after acetone washing were in the range of 105 - 115 ℃.

PATENTS

METHOD OF FORMING TITANIUM NITRIDE POWDERS

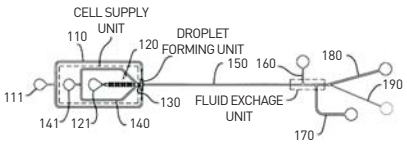
Patent No. **10-0959931** Contact Info. **SHIM, Jae-Hyeok** (jhshim@kist.re.kr)

Nano-sized titanium nitride powder can be prepared by a simple process comprising subjecting mixed powder of titanium trichloride and lithium nitride to high-energy ball milling using a plurality of balls in an airtight reactor vessel under an inert gas atmosphere to form composite powder and recovering the titanium nitride powder therefrom.



APPARATUS AND METHOD FOR FABRICATING MICRO-CAPSULE

Patent No. **10-0942184** Contact Info. **Kang, Ji Yoon** (jykang67@gmail.com)

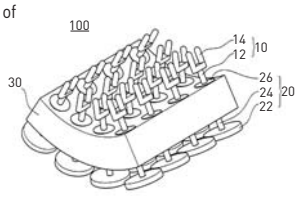


The present invention relates to an apparatus and method for fabricating a micro-capsule which enable encapsulation of a uniform cell number in a micro-capsule through cell distribution, improve cell viability in the micro-capsule through fluid exchange, and ensure uniform micro-capsule size.

TACTILE DISPLAY APPARATUS AND METHOD THEREOF

Patent No. **10-0958908** Contact Info. **Kang, Sung Chul** (kasch@kist.re.kr)

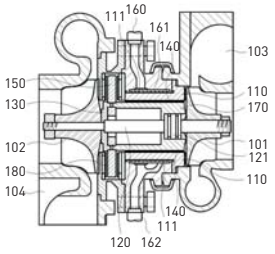
A tactile display apparatus which includes a plurality of stimulation pins in contact with a skin, an operating unit for vertically moving the stimulation pins, and a housing accommodating the stimulation pins and the operating unit, the housing having an opening in one surface such that the stimulation pins protrude outward. The plurality of stimulation pins is arranged such that a contact area occupied by front ends of the stimulation pins is smaller than an area occupied by rear ends of the stimulation pins.



OIL-FREE TURBOCHARGER ASSEMBLY

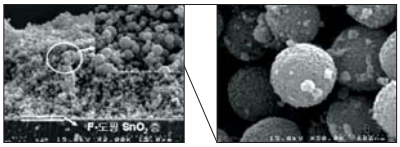
Patent No. **10-0937901** Contact Info. **LEE, YONG BOK** (lyb@kist.re.kr)

The present invention relates to an oil-free turbocharger assembly using an airfoil bearing that may be useful in high speed conditions. The assembly can be cooled easily. A heat-proof coating can also be easily applied to the turbo charger's rotating shaft.



DYE-SENSITIZED SOLAR CELL WITH METAL OXIDE NANOBALL LAYER AND PREPARATION METHOD THEREOF

Patent No. **10-0958920** Contact Info. **KIM, Dong Young** (dykim@kist.re.kr)



A dye-sensitized solar cell comprising a semiconductor electrode prepared by spraying a metal oxide nanoparticle dispersion on a conductive substrate using an electric field to form a metal oxide nanoball layer which is composed of agglomerated metal oxide nanoparticles and has a high porosity and specific surface area. A DSSC prepared by this method exhibits improved photoelectric properties even when a gel or solid electrolyte is used.

THE PHARMACEUTICAL COMPOSITION CONTAINING GLIONITRINS OR PHARMACEUTICALLY ACCEPTABLE SALT THEREOF AS AN ACTIVE INGREDIENT

Patent No. **10-0936277** Contact Info. **YANG, HYUN OK** (hoyang@kist.re.kr)

The present invention relates to a co-culture method of Sphingomonas sp. bacterial strain and Aspergillus sp. fungus strain, in which the novel Sphingomonas sp. bacterial strain KMK-001 is cultured in a liquid medium and the novel Aspergillus sp. strain KMC-901 separately cultured in a liquid medium is added to the above culture solution, a novel glionitrin biosynthesized therefrom and a pharmaceutical composition comprising the glionitrin or its pharmaceutically acceptable salt as an active ingredient.

KIST
NEWS

KIST Develops Housemaid Humanoid Robot Mahru-Z (January 15, 2010)

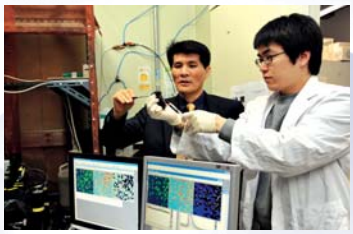
The Cognitive Robotics Center at KIST, headed by Dr. Bum-Jae You, has invented the humanoid Mahru-Z, which operates home appliances and is controlled by a remote control system in real time. Developed with highly advanced technology, Mahru-Z has the ability to walk with self-regulation and is able to find targets to operate various household machines using its own two feet and hands. Mahru-Z can also imitate a human's full body movement using a motion-capture system.

Using[AJC1] the network, the two different robots can be assigned to different tasks. For example, Mahru-Z can put fruit in a basket and place it on the dinner table, while Mahru-M, which has an advantage in mobility, can locate the owner and bring him the fruit directly.

Mahru-Z is compelling because it invented the market[AJC2] for working service robots that can live and interact with humans. "Utilizing its real time remote control technology, Mahru-Z can be used under conditions that are too difficult or dangerous for humans," Dr. You said.

The research on cognitive humanoid robots will be expanded to develop a working cognitive service robot which will be able to assist with household chores as well.

KIST Team is First to Identify a Link between Caffeine and Brain Cancer (Glioblastoma) (February 2, 2010)



A KIST research team has found for the first time that caffeine taken from coffee or green tea inhibits the growth of fatal brain cancer (glioblastoma) cells.

Dr. Changjun Justin Lee's research team at KIST's Neural Science Center has documented for the first time that caffeine can contain the movement and permeability of brain cancer (glioblastoma) cells. This discovery was made through joint research conducted with Seoul National University, Inha University, and Emory University (U.S.A.) and included the collaboration of Professor Sang Soo Kang of Gyeongsang National University.

The glioblastoma form of brain cancer forms highly malignant tumors, graded WHO 4, and is usually a fatal disease resulting in less than a one-year life expectancy after diagnosis. Glioblastoma is impossible to cure even through surgical intervention because its cells have active movement and permeability, killing various cells in the brain, including neurons, and expanding rapidly. The current treatment method is to use a drug therapy, Temodar, but this helps extend life expectancy by only 2.5 months.

Calcium plays an important role in transferring and activating the glioblastoma. The chemoreceptor involved in calcium secretion is the IP3R, which exists within the endoplasmic reticulum.

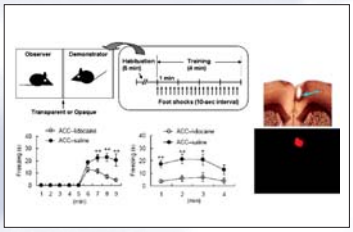
This research was the first to make the following discoveries: (1) IP3R consists of three types of subunits; (2) IP3R3 is particularly manifested in mostly glioblastoma, which is found by

using a variety of advanced techniques[AJC3] including calcium imaging, permeation measurements, molecular experimental techniques, and survival measurements in animal models; and (3) caffeine reduces the calcium concentration in glioblastoma by selectively containing IP3R3 and restraining the glioblastoma from transferring to and acting in other cells.
The research team applied this molecular cell mechanism to animal models, and results showed that the experimental group taking caffeine did not exhibit transfer of glioblastoma while the survival rate increased about twofold. The amount of caffeine used in the animal model was equivalent to consuming about 2-5 cups of coffee a day on a human scale.
"The findings of this research, which identities for the first time that caffeine inhibits the mechanisms of glioblastoma, have important meaning in that they have opened up the possibility of developing medicine for treatment. Follow-up research is required to validate the efficacy by clinical trials." Dr. Lee said.
This research was published on February 1, 2010 in the world-renowned journal, Cancer Research.

KIST Leaps Forward with New Vision (February 10, 2010)

KIST held a commemorative ceremony on February 10, 2010, at its Johnson Auditorium to celebrate the 44th anniversary of its founding. Many distinguished guests attended, including Dr. Jung Hyun Kim, Vice Minister of Education, Science and Technology, Prof. Dong-Pill Min, Chairman of the Korea Research Council of Fundamental Science and Technology, and three foreign ambassadors to Korea.
At the ceremony, KIST showcased its new vision "World eminent KIST we are proud of, where our dreams are made and realized[AJC4]", which is to transform itself into a world-renowned research institute by emphasizing S&T entrepreneurship and leading in the fields of green and silver technologies.

Empathy of Fear and Mechanisms of the Brain Circuit Investigated at KIST (March 3, 2010)



KIST disclosed that the Head of the Center for Neuroscience, Dr. Hee-Sup Shin, and his research team, had investigated, for the first time, the mechanisms of the brain circuit that is involved with the ability to empathize with others' fears. The research team found that the medial pain system of the cranial nerve is associated with the empathy of fear and the L-type Ca^{2+} channel plays an important role.


Observational fear learning involves affective pain system and $Ca_v1.2$ Ca^{2+} channels in ACC

Using a laboratory rat, the research team developed a new behavioral experiment that can elicit an emotion of fear. In this experiment, a laboratory rat exhibited fear after seeing other rats receive electric shocks, though it never received any of the simulation itself. They also discovered that the level of empathy of fear increased depending on the type of relationship it had with the other rat.

KIST
NEWS

This research project was carried out under the Ministry of Education, Science & Technology's National Scientists Support Project as joint research with the CEO of ProCell Therapeutics, Inc, Dr. Dae-Woong Jo, as well as researchers from Harvard Medical School and Vanderbilt Medical School. An article on this research project was published online on March 1, 2010, in the world renowned journal, Nature Neuroscience.

KIST Europe Completes Construction of Second Research Building (April 30, 2010)

A ceremony to celebrate the inauguration of a second research building at KIST Europe (based in Germany) was held on April 30, 2010. Among the over 100 attendees were Mr. Christoph Hartmann, Minister of Economy and Science of Saarland, Prof. Dr. Alexander Baumeister, Vice-President for Planning and Strategy of Saarland University, Prof. Dr. Hans-Juergen Warnecke, Former President of Fraunhofer-Gesellschaft, Mr. Tae-Young Moon, Korean Ambassador to Germany, Mr. Euy-Taek Kim, Consul General, Bonn Office of Korean Embassy in Germany, Mr. Kidong Song, Director General of the International Cooperation Bureau, Ministry of Education, Science and Technology (MEST) of Korea, Dr. Kwang Ho Kim, Institute Director of KIST Europe, and other distinguished guests from Korea and Germany.
As the first overseas research institute established by a Korean public institution, KIST Europe has carried out full-fledged research projects in its first research building, which was completed in 2000, and since 2007 has pushed forward with the construction of a second research building.
With the completion of this second research building of 2,069 ㎡, KIST Europe has secured the research infrastructure it needs to further develop into one of the premier research institutions in the EU region. In addition, these expanded facilities will provide Korean universities, research institutes and industry with lab facilities and offices for research and education which can be used for promoting research contracts and collaborations.
On April 29, 2010, immediately prior to the building inauguration, KIST Europe held its second KESTCAP Top-Down Forum covering issues in the fields of energy & environment technology and bio & nano technology.
*KESTCAP (Korea-EU Science and Technology Cooperation Advanced Program.

KIST Green Technology Fair 2010 (May 25, 2010)

The 2010 KIST Green Technology Fair, whose theme was "Cooperative Research between KIST and Industry and Transfer of Green Technology," was held on May 25th at the International Cooperation Building. The purpose of these KIST-sponsored technology forums, the first of which was held in 2009, is to establish an innovative and collaborative open network with companies in the industrial and corporate sectors to look for technology transfer possibilities associated with emerging technologies.
Establishing stronger links between KIST's R&D capabilities and industry's needs is considered of paramount importance in effectively responding to emerging changes in the industrial

environment and global marketplace. Topics discussed at these consortium forums center on technology commercialization, R&D cooperation, technology support and other cooperative measures under consideration.

At this year's event, 17 core technologies in the areas of energy, environment, materials/devices, and natural substances were discussed with participating companies, and possibilities for technology transfer were highlighted. During discussion of future developments, many promising new technologies of interest to the corporate world, such as alternative eco-friendly energy technologies and environment/health technologies, were outlined. These included technologies for military telecommunications equipment, portable fuel cell power packs for everyday and leisure use, and high-efficiency dye-sensitized solar cells which can be applied to glass windows, automobile sunroofs and battery chargers. Other technologies discussed as potential candidates for commercialization included a toxic air cleaning technology which does not generate secondary pollutants like ozone or aldehyde, multipurpose renewable energy technology that replaces single biofuels like gasoline, diesel and jet fuel, and natural anticancer material technology using bacterial strains.

Executives from over 100 small- to mid-sized domestic firms attended the Green Technology Fair, where Mi-nam Shin, from the Full[AJC5] Cell Power Corporation, delivered a special lecture on entrepreneurship in the field of science and technology. In his own remarks to the forum, KIST President Hong Thomas Hahn stated, "KIST plans to provide more information of its technologies and will continue to disseminate its technologies by utilizing the Forum attended by many corporations." He also confirmed his determination to make KIST a birthplace of S&T entrepreneurship.

Meanwhile, plans were made to hold the KIST Technology Forum twice a year on a regular basis, the first having been held in 2009. The forum in November will have "Silver Technology" as its theme and will continue to promote open innovation in the field of science and technology.

WCI's Center for Functional Connectomics Holds International Symposium (May 17, 2010)

The World Class Institute's (WCI) Center for Functional Connectomics held an international symposium on "Functional Connectomics" at KIST's Johnson Auditorium on May 17, 2010. Experts in the field of neural science from Duke University, Yale University, and Tokyo University along with researchers from the KIST Neural Science Center attended the symposium.

The WCI program, a project initiated by the Ministry of Education, Science and Technology, was introduced to the participants at the symposium, which offered a great opportunity to promote the Center for Functional Connectomics and to attract interest from overseas scientists.

Awards

* **Mr. Nam Kee Dal, Bioactive Molecules Center**
  - KIST Staff of the Month (KIST, April 27, 2010)
* **Dr. Song Soo Chang, Biomaterials Center**
  - Excellence Professor Awards (University of Science & Technology, March 18, 2010)
* **Dr. Shin Hee Sup, Neural Science Center**
  - Excellence Professor Awards (University of Science & Technology, March 18, 2010)
* **Dr. Koo Hyun Cheol, Nano Convergence Devices Center**
  - Excellence Professor Awards (University of Science & Technology, March 18, 2010)
* **Dr. Kim Soo-Kil, Fuel Cell Center**
  - KIST Staff of the Month (KIST, February 19, 2010)
* **Dr. Jo Seong Mu, Polymer Hybrid Center**
  - KIST Alumni Association Awards (KIST, February 10, 2010)
* **Dr. Koo Hyun Cheol, Nano Convergence Devices Center**
  - KIST Staff of the Year 2010 (KIST, February 10, 2010)
* **Dr. Kim Jaehoon, Clean Energy Center**
  - The Won Hee Park Award (KIST, February 10, 2010)
* **Mr. Kang Dae Shin, Unit of Research Information**
  - KIST Excellence Staff Awards / Korea Research Council of Fundamental Science & Technology (KRCF) (KIST, February 10, 2010)
* **Dr. Lee Ju Young, Natural Product Research Center**
  - KIST Excellence Staff Awards / Korea Research Council of Fundamental Science & Technology (KRCF) (KIST, February 10, 2010)
* **Dr. Kim Kwang Meyung, Biomedical Science Center**
  - KIST Excellence Staff Awards / Korea Research Council of Fundamental Science & Technology (KRCF) (KIST, February 10, 2010)
* **Dr. Chang Moon Ho, Neuro-Medicine Center**
  - A Man of Merit Awards (Korea Drug Research Association, February 26, 2010)

A Sign of the Times!

1. KIST site before construction in 1966

2. KIST site under construction (site grading) in 1967

3. Construction headquarters and partially-completed L2 building in 1968

4. L0, L2, and L3 buildings under construction in 1968

5. Front view of KIST after first phase of construction had been completed in 1969

Alumni Update

Being in Korea was a highlight of my life. For two years I studied and conducted research in the Imaging Media Research Center as part of the master's program at KIST's International R&D Academy. It was my first experience leaving my home country, Indonesia, and I found it very exciting.

Honestly, I knew nothing about Korea except that it was a little country squeezed between Japan and China, and I expected a weird culture as a blend of those two Asian giants. I knew no Korean words before I bought a guide book and language learning CD from a local bookstore. What I knew best from Korea was a childhood memory of Hodori, the mascot cat of the 1988 Summer Olympics.

So I came to Korea with great excitement. After extensive surfing of the internet and some guidance from some seonbae who came earlier, I prepared myself to come to this country. I stepped on Korean soil, my first step on mainland Asia, a day before Valentine's Day. Since it was one of the coldest times in winter, I expected to see snow for the first time. Together with three other newcomers who had also spent their whole lives in their home countries, we expected quite a lot from this new promised land.

What did we get? We got a lot more than we expected.

For me, a warm welcome from fellow countrymen picking us up from the airport made my thick coat seem useless. The weather suddenly seemed warmer. And the Koreans I met were no different. In contrast to my first perception about Koreans, they could communicate well with me, and we understood each other. But the best thing was that they were friendly.

During the first days in the lab, I began to adapt to their working pace. No different than what I expected, in Korea everyone works hard. Unlike popular 9-to-5 days, here they work 9-to-9, or even longer. No wonder a lot of great things come from Korea.

Korean superiority in science and technology was no longer a fiction or rumor for me.

Besides my labwork, I also explored the "outside world." I wanted to know more about how Korean people live. I joined several cultural activities arranged by KIST and also some other cultural exchange programs such as the one arranged by UNESCO. What I found out about Korean culture is that it is original and unique. So my expectation of a weird blend between Japan and China was wrong. Koreans have their own distinct culture and fight to preserve their unique ways. They love their country very much.

Since graduation I have been working in a European company. Although my job is not directly related to my studies at KIST, I still bring the Korean spirit and work ethic to my work. Studying in Korea gave me much confidence in international relations. In some cases being a Korean graduate is an advantage for me either in work or social life. All my colleagues and friends know that living in Korea is a great thing and a lot can be learned from Koreans.

My two-year life in Korea was a life-changing moment. What I feel now after living among Koreans is that I love my country more than ever, just like Koreans love their country. And Korean life is now undeniably integrated into my life. No day without listening to K-pop songs.

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