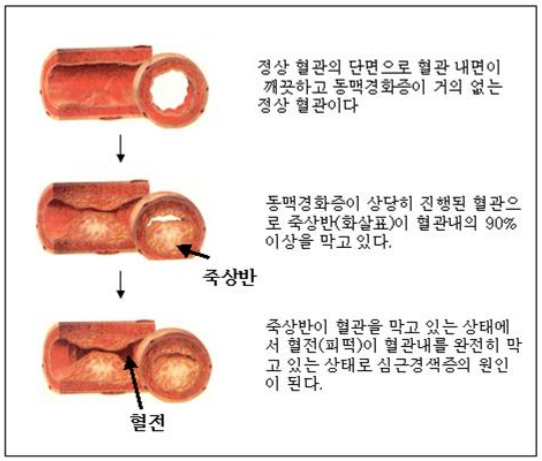
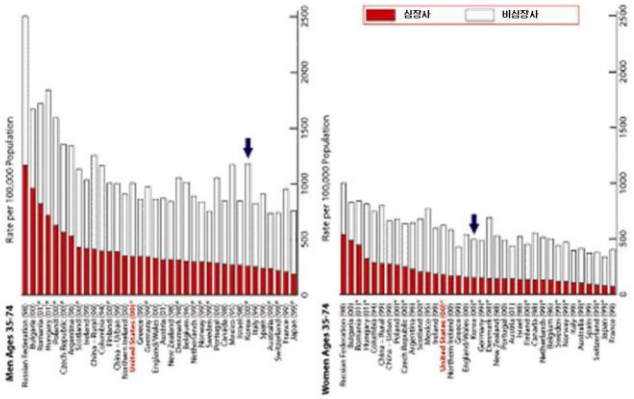
CARDIOTEC CO., LTD

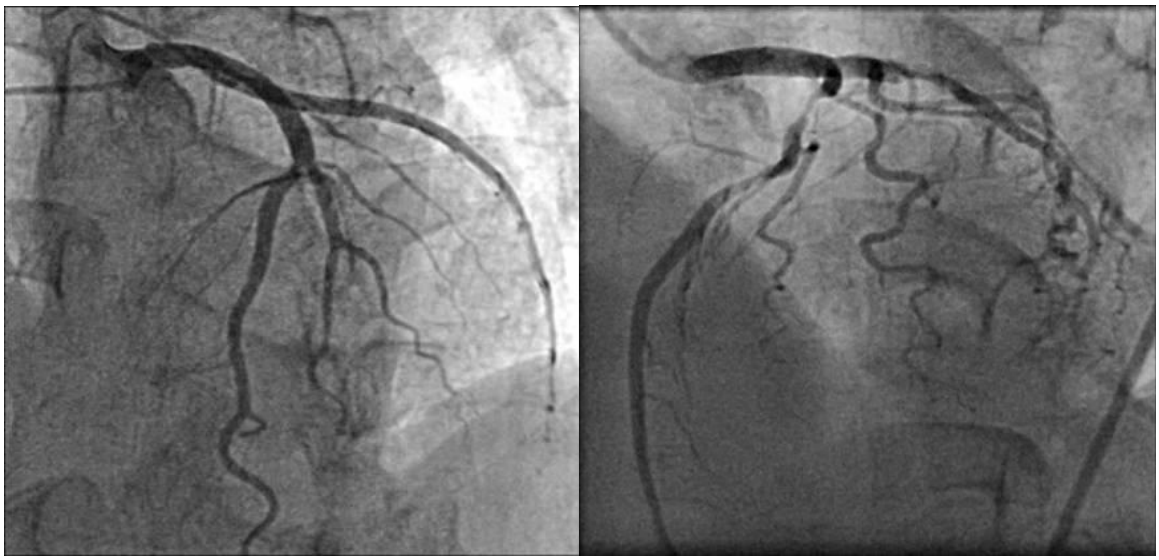
Key Technology Highlights

Ischemic heart disease is growing worldwide phenomenon of the World Health Organization (WHO), according to a survey of cardiovascular disease in 2002 died in 1.6 million people worldwide, cardiovascular disease, cancer, Coronary vascular disease as the cause of death along with three considered.





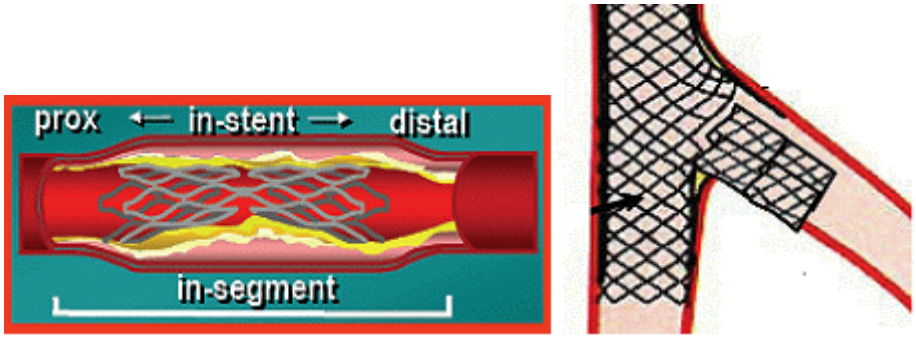
(Pic. 2-1) Diagram of coronary artery disease
(Pic. 2-2) The world cause of death statistics in 2004 (WHO data)



(Pic. 2-3) Normal vessels (left). Advanced vascular obstruction (right)

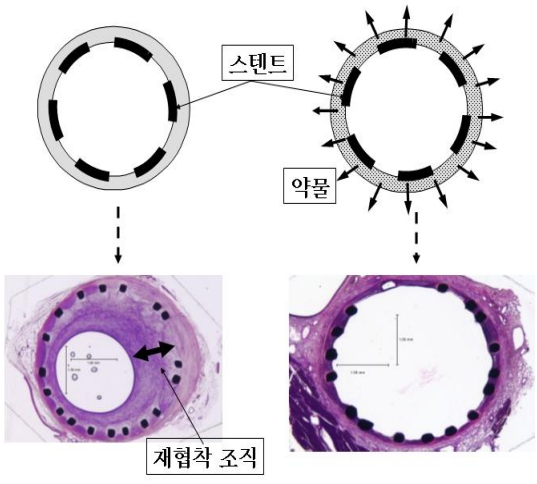
Last 10 years ischemic heart disease in the field of therapeutic intervention is most common with conventional treatment has been recognized. These developments contributed to the development of Coronary stent is one thing. Stent and Characterization intervention of the development intervention occur in the various complications, dissection or flap caused by acute obstruction quickly and safely overcome the intervention and a safe, a generalized procedure to be used to make a significant contribution. However, coronary stenting and one-step intervention to increase the contribution of restenosis, but new problems were faced, on average, approximately 20-30% after the procedure or showing the incidence of restenosis, particularly lesion long lesion, bifurcation lesion , ostial lesion, and small vessel

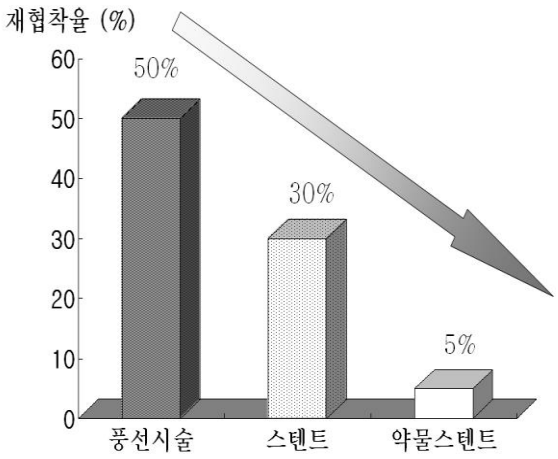
lesion showed a higher incidence of restenosis.
Stent Anti-thrombosis and Anti-proliferation increases biocompatibility improving measures of the recent international best issue and polymer-coated stent directly to the medication insert, this vessel passed to the short period of time appropriate topical medication mechanism to maintain the concentration has been widely utilized. Moreover, recently obtained approval from KFDA foreign multinational companies entering the domestic market of the product as the earnest domestic research in this area in the country has emerged as a very urgent issue.



(Pic. 2-4) Vascular stent insertion structure

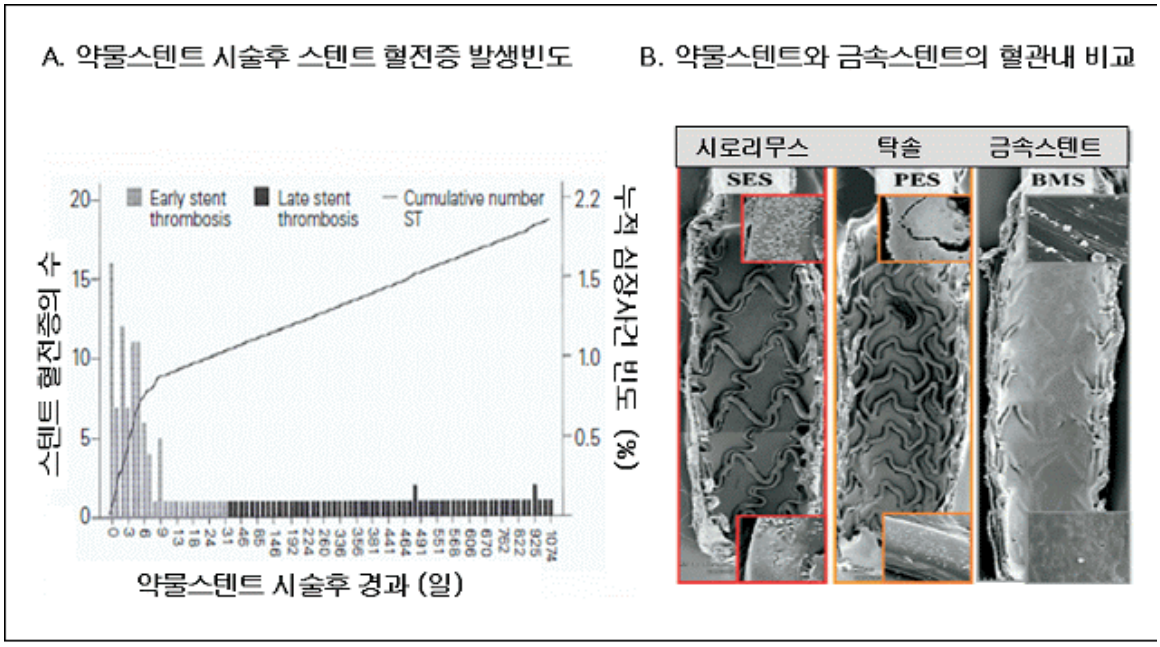
Coronary artery disease is already known in the West are the most common cause of death in our country because of the growing trend of food is in the Western fireplace. More than 80% of coronary artery disease using stents to treat, and most expensive is priced at $ 1,100 with the use of stents has been imported. In particular, a recently developed drug-coated stent priced at $ 2,500 or more to quote, but the manufacturing technology of domestic appliances and the treatment of restenosis after treatment, staying at research level is still insufficient.
In-stent restenosis is characterized by a neointimal hyperplasia, vascular smooth muscle cell intima from the media by going to the results it appears as proliferated. Restenosis related stimuli that (1) endothelial barrier layer damage (2) medial smooth muscle layer compromise, SMC proliferation and migration stimulated to act as a stimulant, mechanical factors (3) neointimal hyperplasia of the damage to start contact with circulating blood factors and mitogen floor will include.





(Pic. 2-5) The change of restenosis after coronary intervention
(Pic. 2-6) General comparison of Bare stents and DES.

Focusing on the United States in recent years, and to prevent long-term assessment of localized drug administration and for the improved stent that has been actively trying to develop. Drug coated stent drug loading in the polymer matrix of the configuration methods for non-biodegradable polymer matrix or a biodegradable polymer matrix for drug loading, delivered in a manner that is largely distinct.
Non-biodegradable polymer matrix that is generated in the polymer matrix with fine spatial diffusion and dissolution of the drug through the implementation of the drug and Sustained, biodegradable polymer matrix dissolution of the drug, as well as the spread of drug release through the degradation of matrix itself , due to residual thrombus deposition polymers have a concern that has been the subject of recent research. Drug coated stents currently being used by anti-proliferative and anti-thrombosis drug rapamycin to include Taxol (paclitaxel) is known as a representative.
Coronary artery disease is already known in the West are the most common cause of death in our country due to aging and dietary hearth of the Western trend is growing patient.



(Pic. 2-7) Incidence of stent thrombosis, DES treatment of pathologic findings and follow up

This technology is in response to these international trends, while technically a step compared to conventional dual drug system was upgraded using stents coated with a sustained released delivery system is developed. In particular, the early release of the drug to prevent blood and exert long-lasting drug can dramatically improve the restenosis drug coated stent in the development of the world's first "Dual Drug System" was introduced.
In other words, on the surface of the stent restenosis neointima acting as a cause of action to inhibit the growth of paclitaxel containing polymer layer and inhibited platelet aggregation and thrombosis, including anti-drug cilostazol works with containing polymer layer to multilayer by stacking of the drug dissolution rate constant and long-term restenosis of blood vessels that can dramatically improve the development of a new drug coated stent.
With cilostazol and effective drug paclitaxel to apply to the original idea of this team is due to the drug coated stent performance, upgrade to a stage role. In other words, antiplatelet and antithrombotic activity of cilostazol drugs represents the current intervention after stent thrombosis of blood vessels to the patient the purpose of preventing oral-administration has

been applied to drugs. However, as most of the drugs appearing in the oral approach through the liver first-pass effect of drug bioavailability and systemic problems that fall through the action of the drug has the disadvantage of side effects. Therefore, local delivery method by applying it between the lines due to the reduction of drug concentrations to minimize obstruction of blood vessels occurred in areas intensively by increasing concentrations of the drug therapy that can maximize the advantages are. In addition, the anticancer drug paclitaxel that elevate the boosting effect can be expected.
The configuration of the drug coating, in what "Multilayer" by adopting much of the drug is released abruptly in the early "initial burst" effect of the drug to suppress the constant and sustained plasma concentration is designed for continuous long-term effect of drugs Through the persistence of drug release can be secured is an important skill.

Technology Overview

Technology platform

▫ Product Name: Cilotax™ Dual Drug Eluting Coronary Stent System (Class Ⅲ)

▫ Device description : Cilotax™ Dual Drug Eluting Coronary Stent System is designed to treat coronary artery disease by opening clogged arteris and restoring blood flow. The stent provides support to the artery after angioplasty. The system also release medication to limit excess cell growth while artery heals.

This system consists of four subsystems.
A. Active Drugs – Paclitaxel & Cilostazol
B. Drug eluting Polymer system
C. Bare metal stent – a pre mounted L605 cobalt chromium alloy based stent.
D. Delivery system (Blackhawk ™ PTCA stent delivery balloon catheter)

▫ Indication for Use : The Cilotax™ is indicated for improving coronary luminal diameter and reducing restenosis in patients with symptomatic ischemic heart disease in de novo coronary artery lesions in native coronary arteries with a reference vessel diameter 2.25mm to 4.0mm

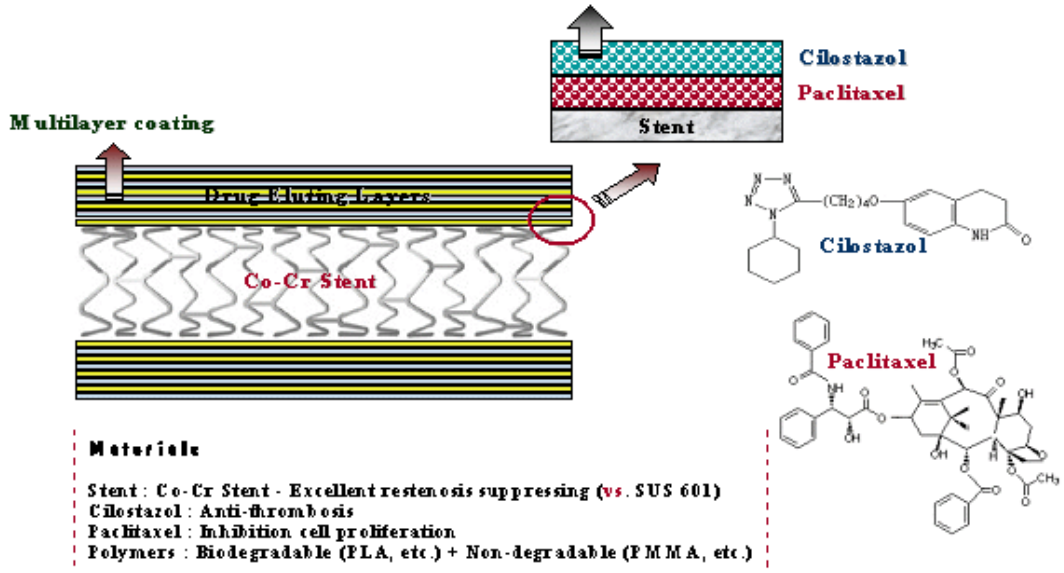
▫ Intended use: The Cilotax™ is intended for use in patients eligible for percutaneous transluminal coronary angioplasty (PTCA) with a reference vessel diameter 2.25mm to 4.0mm.
This system is intended to improve coronary luminal diameters as an adjunct to coronary interventions and reduce restenosis. The stents are intended as permanently devices.

- Active drug A : Paclitaxel “Anti-proliferative effect makes Lower restenosis”
- Active drug B : Cilostazol “Anti-platelet effect makes Lower stent thrombosis”
  Cilostazol have potential synergism with Paclitaxel
- Drug eluting biodegradable polymer system
- Greater tissue penetration
- Longer residency and better release kinetic
- Proven performance of drugs (Paclitaxel & Cilostazol) and drug eluting polymer system

supported by the rigor of the CILOTAX clinical program

- L605 Cobalt chromium alloy based stent is thinner (strut thickness 0.0035 inch), Stronger and more Biocompatible than 316L
  Stainless Steel stent and also provides the foundation for improved clinical outcomes.
- Thin struts and enhanced stent delivery system improve deliverability
- High radial strength, low recoil
- Excellent Stent retention even through the most tortuous vessels
- Exceptional flexibility and uniform scaffolding

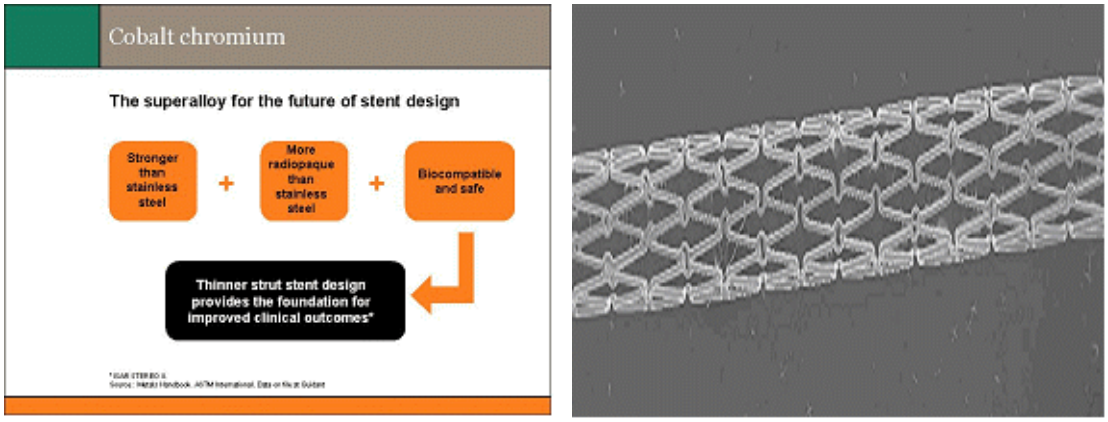
- Ultra low profile balloon with flexible bonds
- Trifold balloon with memory, excellent re-wrap and firm stent retention



(Pic. 3-1) Diagram of Drug coated stent

(A) Mare metal stent / Co-Cr Alloy stent

: Bare stent include rate of restenosis 316L stainless steel, much better than the L605 COBALT CROMIUM material applied



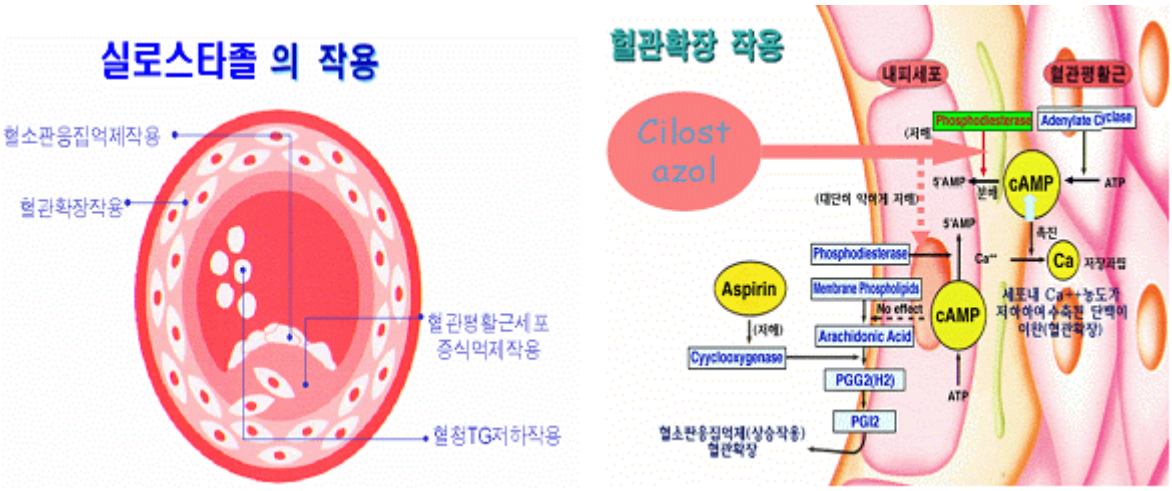
(Pic. 3-2) L605 COBALT CROMIUM Alloy

(B) Active drug A / Cilostazol

: Platelet aggregation inhibition, vasodilation, smooth muscle cell proliferation and inhibition

6 - [4 - (1 - cyclohexyl-1H-tetrazol-5-yl) butoxy] -3,4-dihydro-2 (1H) - quinolinone

Molecular formula C20H27N5O2, M.W = 369.47



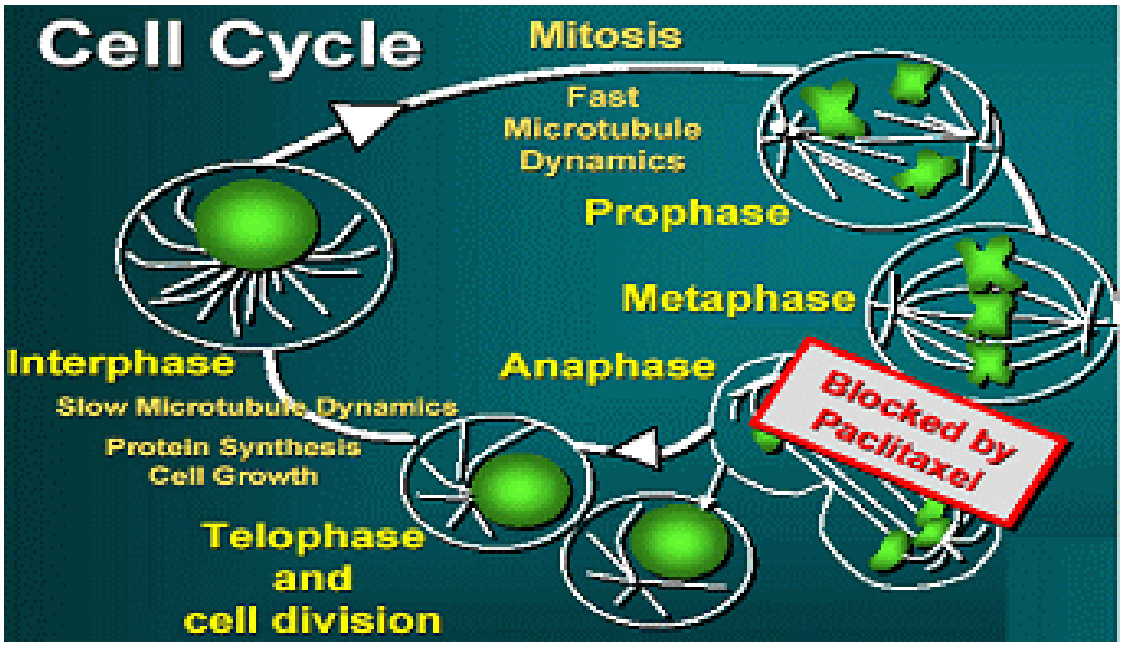
(Pic. 3-3) Cilostazol

(C) Active drug B / Paclitaxel

Anti-cancer therapy, Boston Scientific's Taxus, such as used in drug release stent.

Paclitaxel (C47H51NO14 molecular formula and molecular weight is 853.9, melting point 213 ℃ -216 ℃)

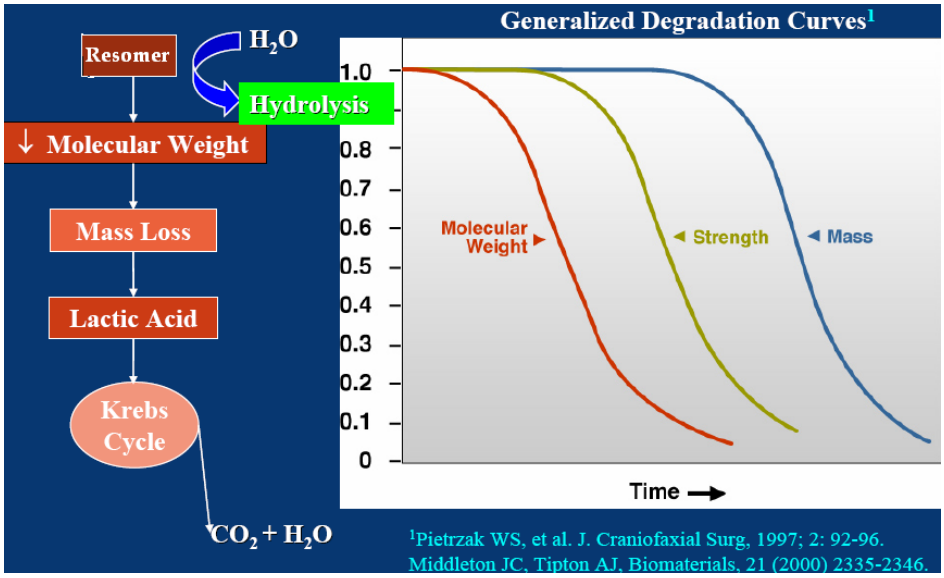
* Paclitaxel (Genexol, Samyang Genex Products Co., Ltd.)



(Pic. 3-4) Paclitaxel system model

(D) Polymer

: Biocompatible polymers PLGA 100% (Resormer RG504H)



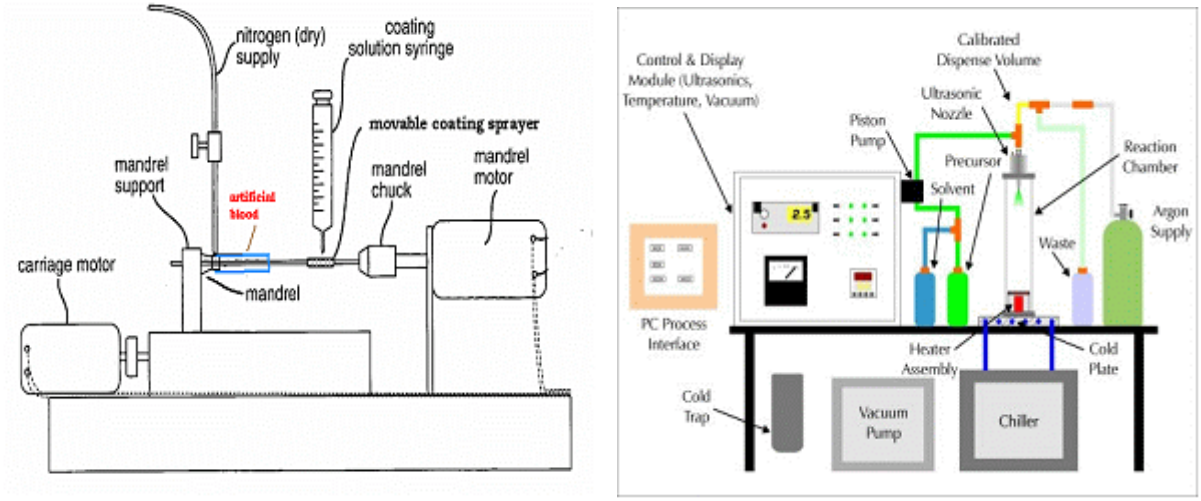
(Pic. 3-5) Resomer Metabolic Pathway

On the surface of the stent with drugs to form multi-layer coating method include a dip coating method and conventional spray coating method can be used. However, the dip coating method in terms of mass-produced drugs available by adjusting the thickness of the constantly active in order to ensure the reproducibility of the process has a lot of problems.

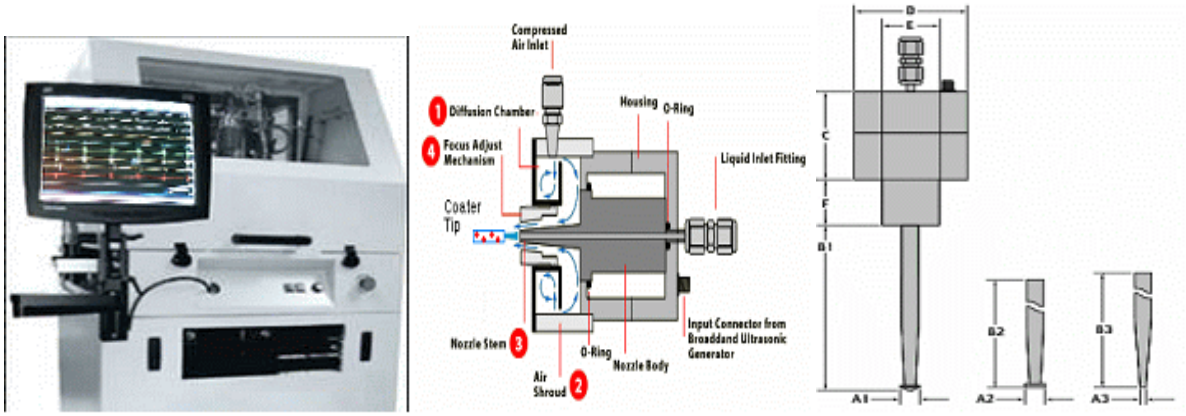
Therefore, in this project include spray coating method, coating method is to take precedence. Spray coating of the spray coating method can be divided depending on the variety, this technology is applied to the ultrasonic spray coating. Ultrasonic spray coating film-forming process in which the thickness of the coating, the coating to form a certain level of quality is a very effective way. Specifically, the drug at a constant rate drug layer from the glass, is active in homeostasis to maintain the drug polymer matrix in a certain domain with uniformly subject to, and the "dual-drug system" maximize the benefits that can process technology.

The technology applied in controlled drug release, biocompatibility of the amorphous polymer and a mixture of biodegradable polymers and drug use as a binder of materials to optimize the efficacy of the drug.

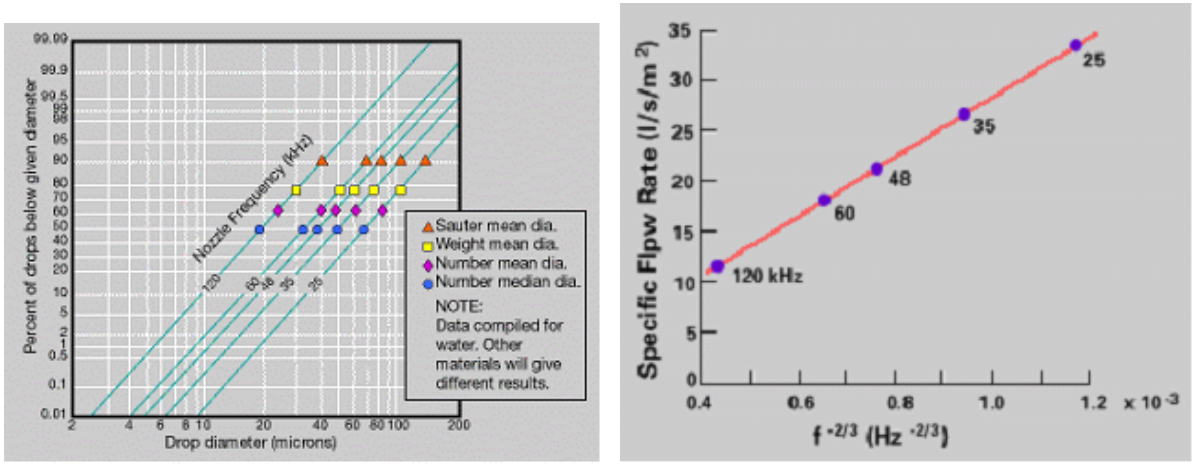
Optimizing the coating process the viscosity and surface tension of the main parameters determining, coating layer thicknesses determined, Curing temperature must be controlled to determine the main parameters, such as. The selection of solvents, especially for drugs that can be distributed throughout the solvent properties may need to have. The coating solutions contain traces of drugs and biocompatible polymers, including the configuration, and the above drug scaffolds applied to the coating layer thin that therapeutic agent composition of the fast release and thick that slowly release, and about the residual risk of because of certain maintenance of coating thickness required.



(Pic. 3-6) Ultrasonic Coating System Diagram



(Pic. 3-7) Ultrasonic Spray Coating Process



< Frequency vs. Drop Size > < Frequency vs. Flow rate >

(Pic. 3-8) Frequency of Drop size and Flow rate

Technology Development Status

To maximize drug efficacy drug over time, differentiating the current global emissions control mechanisms have not been any research is the field.
Therefore, through this project through the local approval to increase domestic market share, qualify for future international cases, sufficient in the global marketplace can be a competitive product.

CARDIOTEC commercialization of the sustained released drug eluting system is currently being supplied to the world market between Boston Scientific and J & J products, in contrast to the single-drug systems, to optimize the efficacy of the drug has drug release system, and the Republic of Korea is already registered giteukheo , including the United States, Japan and Europe for an international patent pending technology becomes, the world is not the product is a technology with which to compare.

	J & J Cypher	Boston scientific Taxus	Cardiotec Cilotax	Comparative advantage
Bare metal stent	316L stainless steel	316L stainless steel	(A) L605 Co-Cr alloy	Improved BMS application
Active Drug	Sirolimus (Rapamycin)	Taxol (Paclitaxel)	(B) Cilostazol (C) Paclitaxel	Dual drug system.
Polymer	Polyethylene-co-vinyl acetate(PEVA) + Poly n-butylmethacrylate(PBMA)	Poly(styrene-b-isobutylene-b-styrene) (SIBS)	(D) PLGA(Resormer RG504H)	100% Biodegradable polymer

Stage of development

1. Summary of Clinical Trial / Animal Trial

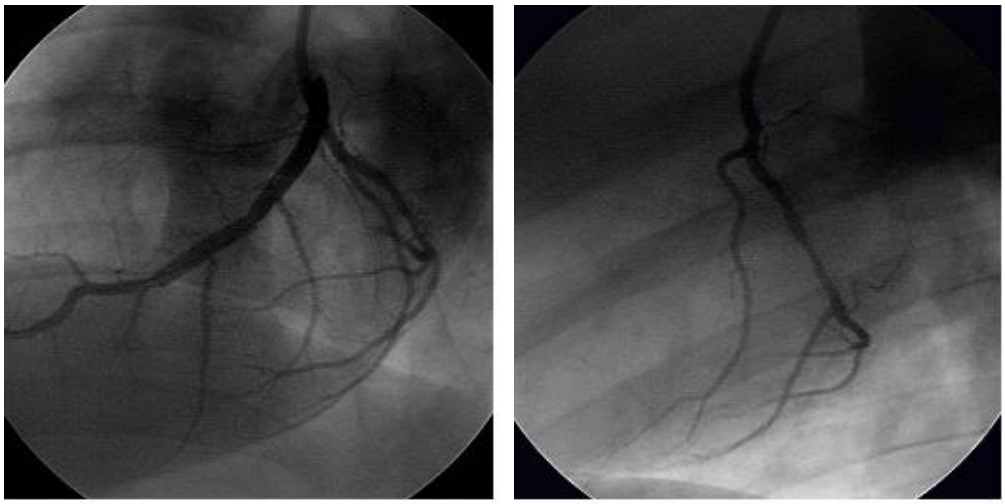
- Object: Testing CilotaxTM stent system is safe & effective at preventing neointimal proliferation compared with BMS in a porcine model of restenosis.
- Study Director: Seung-Jung Park, MD, PhD.
  Division of Cardiology A SAN Medical Center Seoul Korea.
- Histopathomorphometric Analysis : Renu Virmani, MD. Medical Director, CV Path Institute, Inc.
- Analysis: Angiography (QCA) and IVUS -1 month, 2 month follow-up
  Histopathomorphometric study - 1 month follow-up

Statistical analysis - nonparametric Kandall's W, Wilcoxon/Kruskal-Wallis test

Significance: p value<0.05

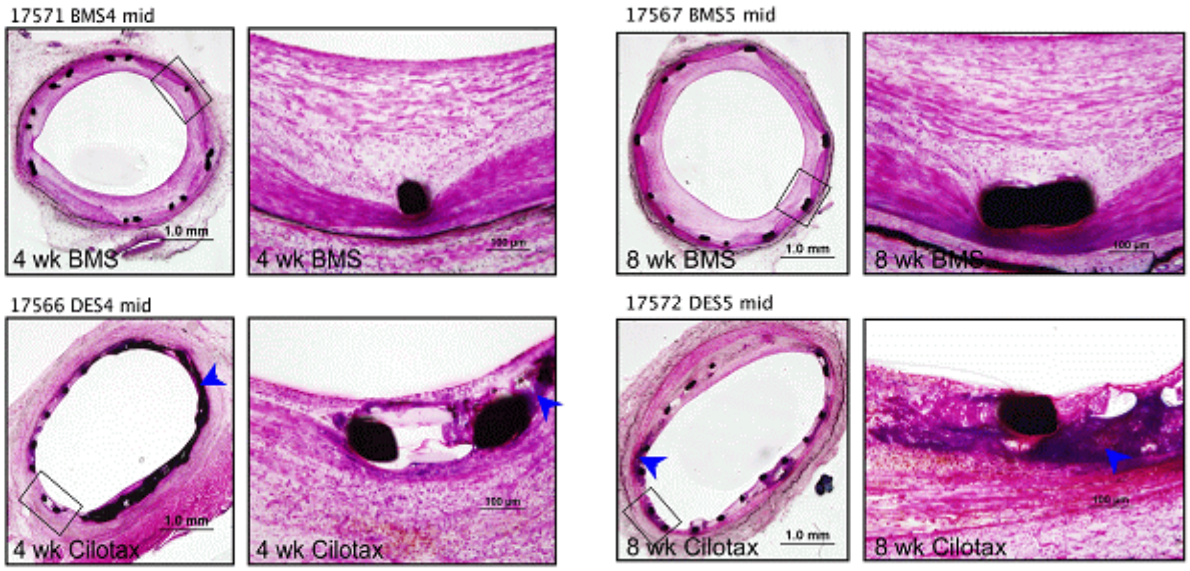
▫ Angiography (QCA) & IVUS Result:

	Bare Metal Stent	Cilotax™	P-Value	Valuation
QCA / Late loss	1.26 ± 0.47	0.009 ± 0.08	< 0.001	Cilotax™ comparison advantage
IVUS / % stent area stenosis	51.8 ± 19.4	6.6 ± 10.4	< 0.001	Cilotax™ comparison advantage



< Ciolotax stent > < BMS stent >

(Pic. 3-9) After the procedure, compared vessel



(Pic. 3-10) Histopathomorphometric study (Cilotax stent vs. BMS stent)

2. Summary of Korean Clinical Trial

▫ Hypothesis: The co-drug formulation of cilostazol plus paclitaxel (CilotaxTM stent / Cardiotec co) may attenuate the risk of stent thrombosis and potentially reduce the risk of restenosis as compared with paclitaxel alone (Taxus / Boston scientific inc)

▫ Object: To assess safety and efficacy of the Cilotax™ stent in de novo native coronary lesions. To compare the performance of a dual DES with that of a standard paclitaxel-eluting stent.

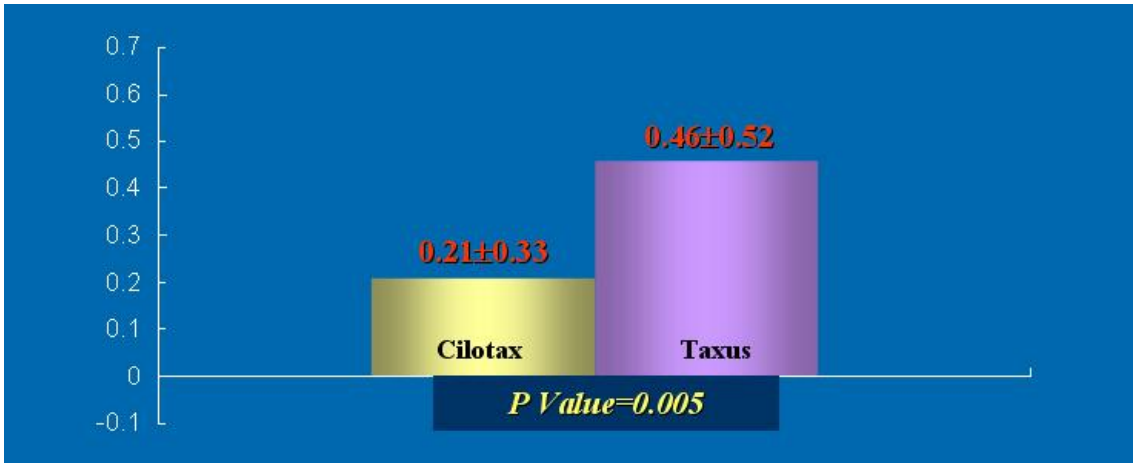
▫ Study Director: Seung-Jung Park, MD, PhD.
Division of Cardiology ASAN Medical Center Seoul Korea.
Ki-Bae Seung, MD,Phd.
Division of Cardiology Catholic University of Korea, Seoul St Mary's Hospital.

▫ Prospective randomized study 110 patients in 2 Sites in Korea
(Asan & Catholic Medical Center)

▫ Analysis: Angiography (QCA) and IVUS - 8 month follow-up

	Cilotax™	Taxus	P-Value	Valuation
QCA / Diameter stenosis, In segment	24.38 ± 12.33	30.51 ± 16.81	0.041	Cilotax™ comparison advantage
QCA / Diameter stenosis, In stent	15.72 ± 10.72	26.22 ± 16.84	< 0.001	Cilotax™ comparison advantage
IVUS / MLS mm2	-1.0 ± 1.5	-2.3 ± 1.5	0.001	Cilotax™ comparison advantage
IVUS / IH volume, %	10.7 ± 5.8	20.2 ± 13.9	0.001	Cilotax™ comparison advantage
IVUS / Normalized lumen vol, mm2	-0.7 ± 1.2	-1.7 ± 1.4	0.002	Cilotax™ comparison advantage
TLR, TVR	1 (1.8%)	3 (5.4%)	-	
Stent Thrombosis	0 (0%)	0 (0%)	-	
Stent Thrombosis	1 (1.8%)	4 (7.1%)	-	

Significance: p value < 0.05



(Pic. 3-11) In-segment Late Loss at 8 Months

* Study Conclusion :

- Clinical trials showed excellent efficacy and safety, in which study the in-stent late loss was 0.19mm at 8 month & no stent thrombosis was observed.

- Cilotax™ stent was superior to conventional PES, representing a promising alternative DES system.

- Cilotax™ stent is expected to be not only a safe but also effective next generation DES. It can be useful for complex lesions expecting higher late loss.

- Large randomized trials involving the Cilotax™ stent with clinical endpoints will be initiated in the future.

Specific Patent Information

U.S.A Application & Resistration	Multilayer-coated Stent for controlled drug release and manufacturing method thereof
	Application No. : 11/210,807 Application Date : 25 Aug 2005
PCT Application	-