Communications

Development of Technology Commercialization by International Collaboration

Organized by Ajou Research-Driven Hospital
Ajou Research Institute Innovative Medicine
G.B. Elyakov Pacific Institute of Bioorganic Chemistry

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Ministry of Health and Welfare, Republic of Korea

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Ajou Research-Driven Hospital

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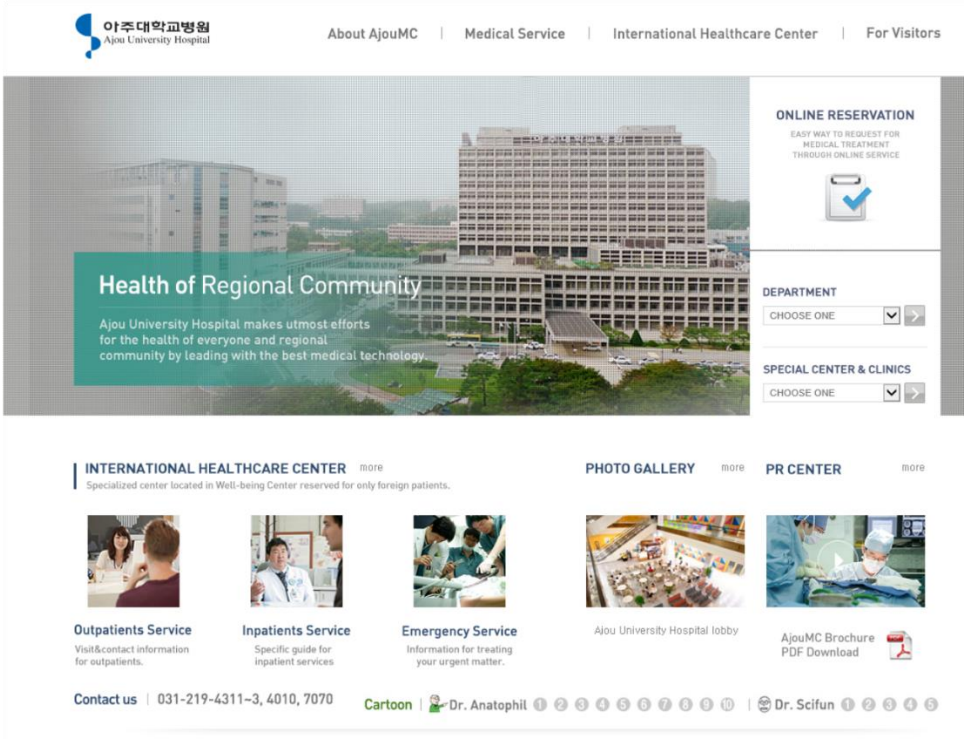

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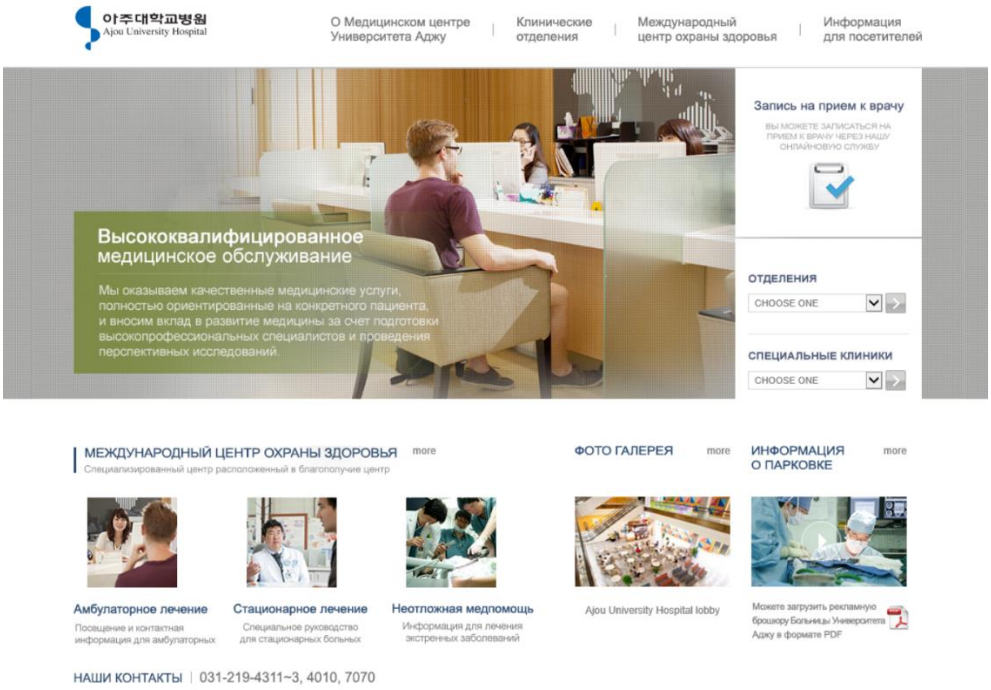

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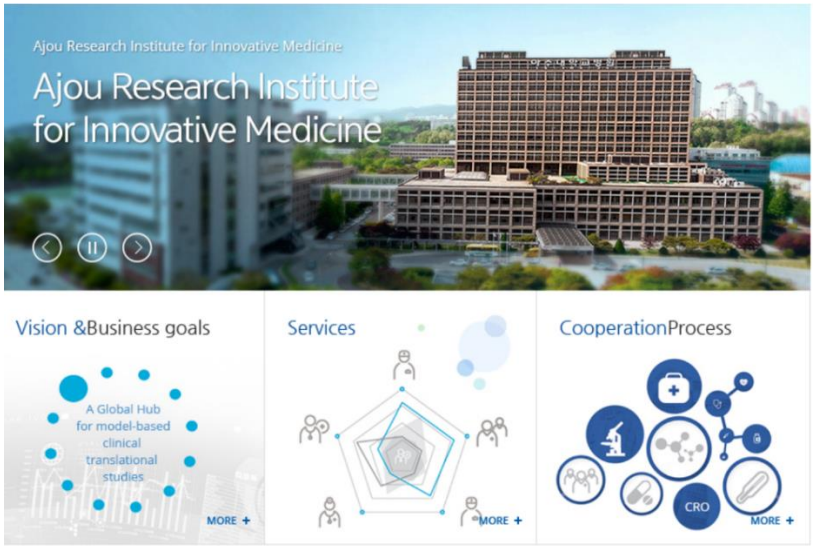


Welcoming Remarks

Home > Who We are > Welcoming Remarks

Thank you for visiting the Ajou Research Institute for Innovative Medicine homepage.

Ajou University Medical Center has grown to be known as an institute that has reached world-class status in the field of research capabilities, with over 20 years experience in health care, education, and research based on medicine and the development and progress of a sustainable R&D program.

Large-scale national research centers such as Bk21PLUS project, SRC, MRC and so on are used as base centers for where basic medical research is done. Through animal experiment research centers, cell therapy centers, medical records research centers, and clinical research centers vigorous clinical research studies are done. After formally being recognized in April of 2013 by the Ministry of Health and Welfare as an official 'research-driven hospital,' we have strived to build a foundation and an ideal base for fusion research combining clinical studies, and we are currently affiliated with 12 other research centers. The research team are also preparing for other trials, taking on the responsibility of intellectual property management and industrial cooperation.

The aim and vision of ARIM is to be a 'A top-tier research-driven hospital, searching for cures for incurable diseases.' As an intensive research hospital, through systematic clinical research we plan to identify unmet medical needs of clinical practice and practical development of new drugs, medical devices, as well as promote the bio- industry.

The ARIM' s future plans are to be a HT R&D platform in creating value within the bio-medical industry.
In addition, we will do our best to contribute to the national health promotion by becoming a hub for collaboration with Gwang-gyo Techno Valley and Global pharmaceutical companies.

We appreciate your constant support.

Thank you

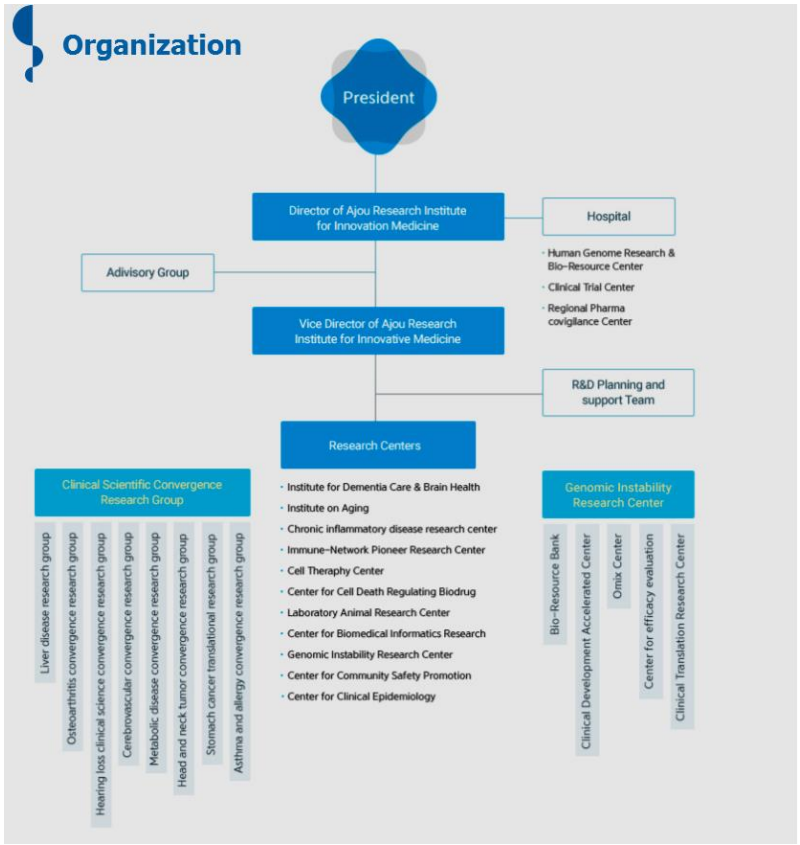
Visions and Business Goals

A Top Tier Hospital Leading the Way to
Overcome Incurable Diseases

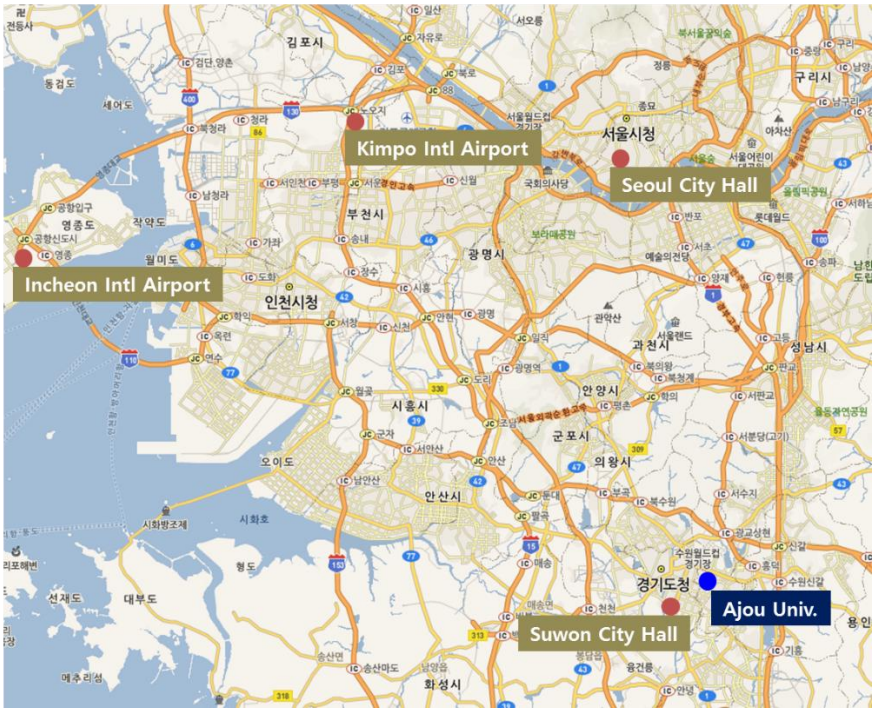
Establishing the Foundation for Sustainable R&D

Creating a Synergy through Academic-Industial-Research-Medical Cooperation

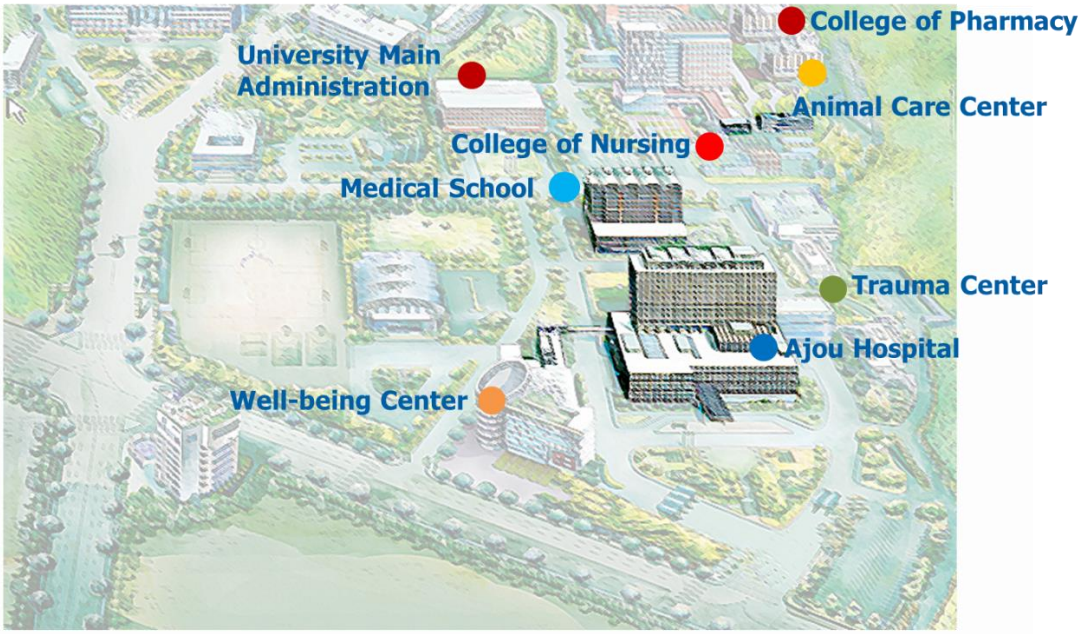
Organization



Human City, Suwon



Medical Campus

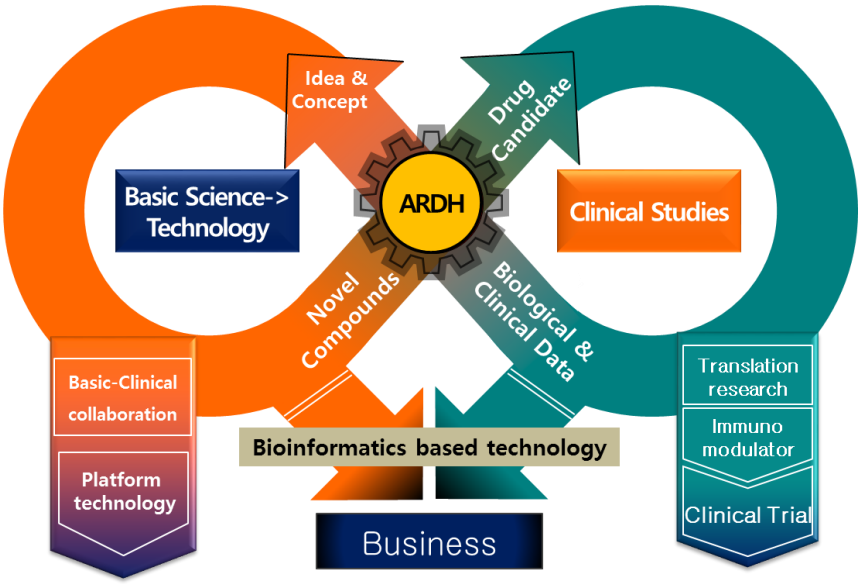


17 Research Centers & Institutes

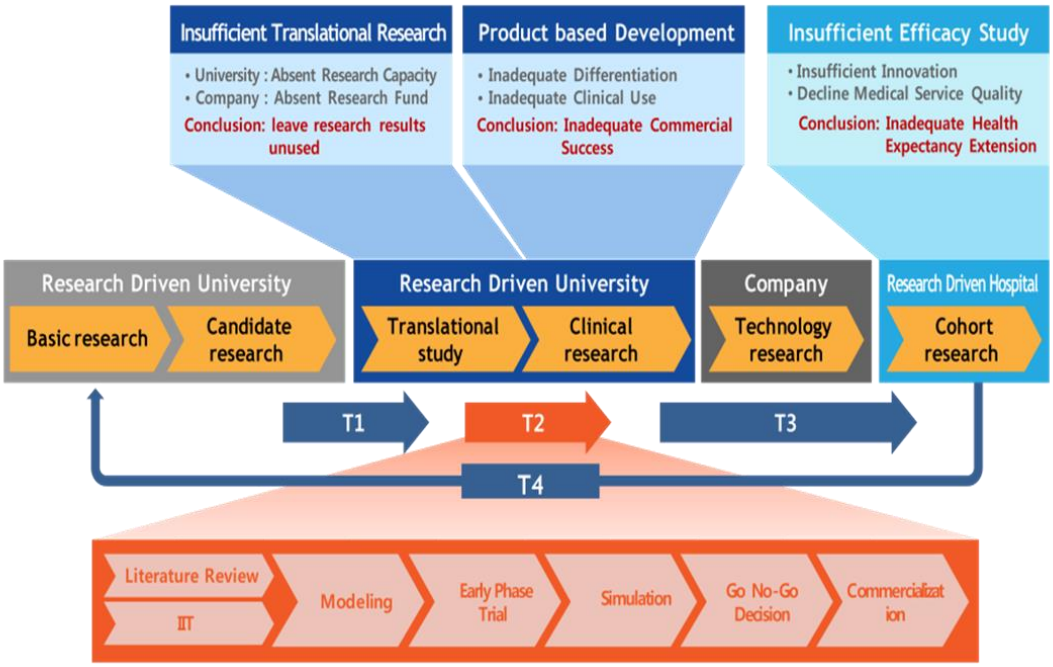
- BK21 Cell Transformation and Restoration, Institute for Medical Sciences
- Cell Therapy Center
- Center for Cell Death Regulating Biodrug
- Immune network Pioneer Center
- Center for Injury Prevention & Community Safety Promotion
- Chronic Inflammatory Disease Research Center
- Genomic Research Center for Gastroenterology
- Health Policy Institute
- Institute for Dementia Care & Brain Health
- Institute for Neuroregeneration & Stem Cell Research
- Institute for U-health Information Research
- Institute of Mental Health
- Institute on Aging
- Research Institute for Neural Science & Technology
- Ajou Translational Omics Center

- Global Clinical Trial Center for Medicine and Medical Device
- Laboratory Animal Research Center

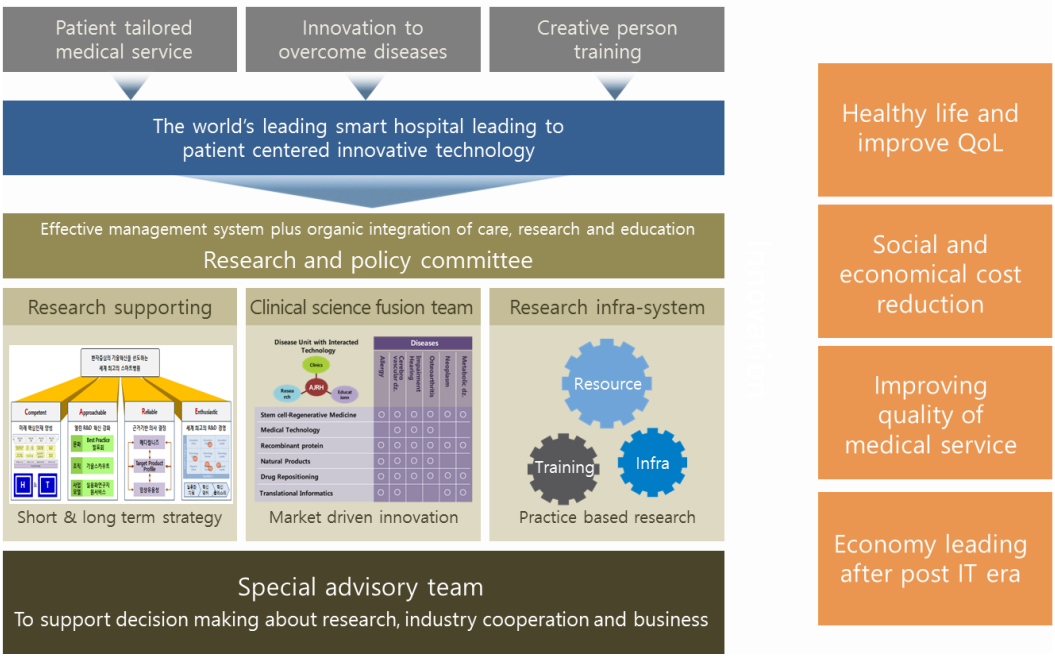
Mission of AJOU Research Driven Hospital: R&BD



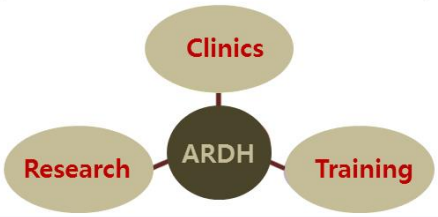
Accelerate Translational Research



Vision and key components of R&BD

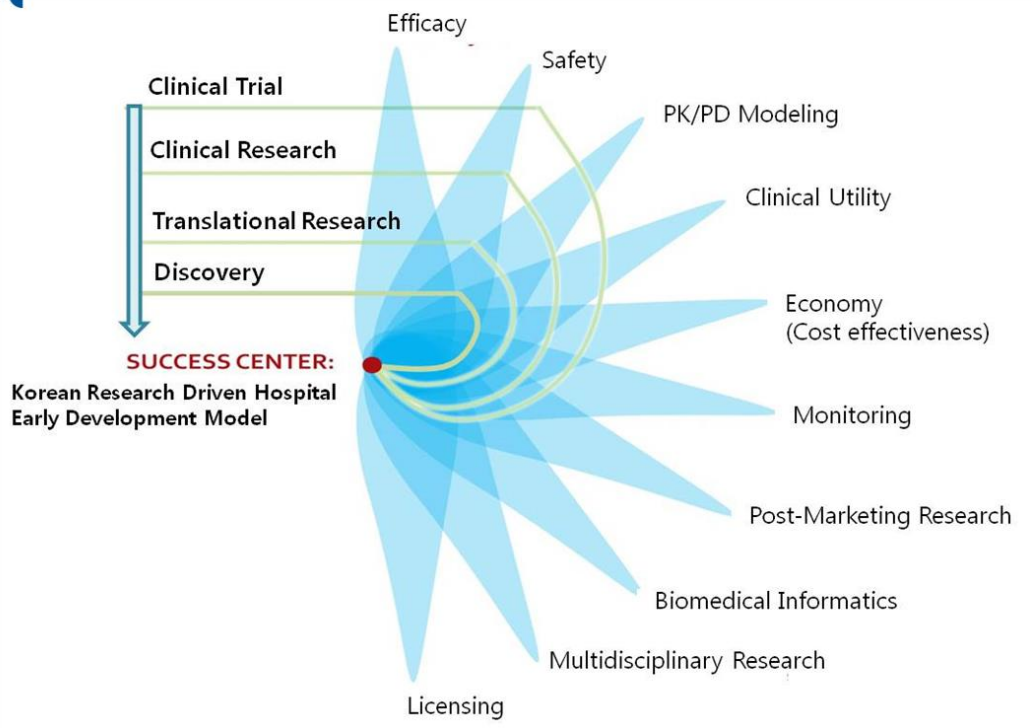


Disease Units with Interacted Technology



	Diseases					
	Allergy	Cerebro vascular dz.	Impairment Hearing	Osteoarthritis	Neoplasm	Metabolic dz.
Stem cell·Regenerative Medicine	○	○	○	○	○	○
Medical Technology		○	○	○		
Recombinant protein	○	○	○	○	○	○
Natural Products	○	○	○	○		
Drug Repositioning	○	○	○	○	○	○
Translational Informatics	○	○			○	○

Market Driven Research



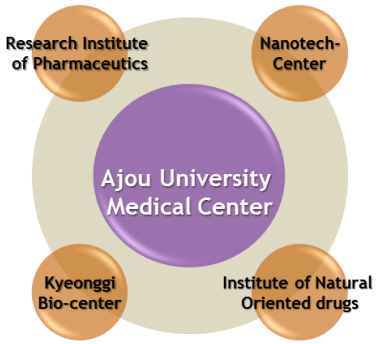
The Gear of Regional HT-ICT Research Cluster

- ✓ Close co-works with local government: Gyeonggi institute of science and technology /Gwangyo technovalley
- ✓ Pharmaceutical companies and institutes
  : Local and global companies

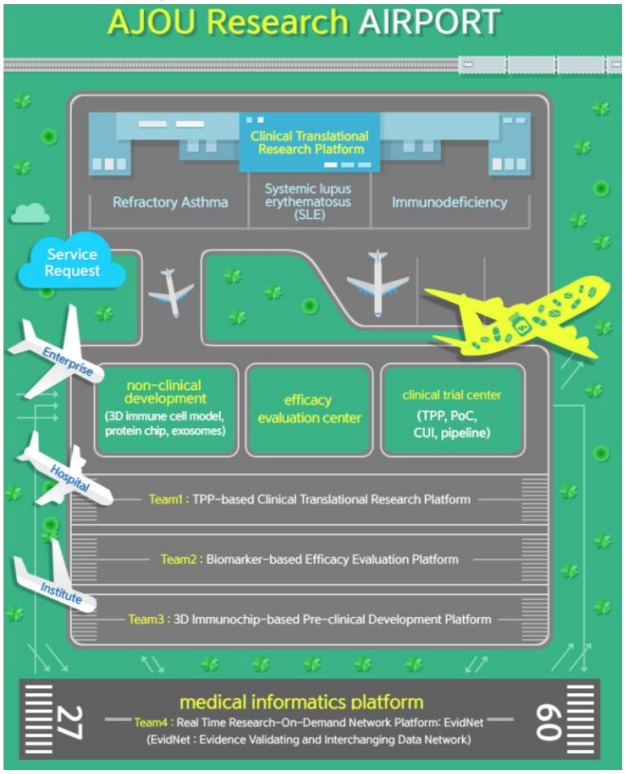
" Ajou Research Driven Hospital"

Global clinical trial center
Outcome research center

Basic Science/Medical School & Pharmacy College



R&D project of Ajou Research-Driven Hospital



Partnership between ARDH & PIBOC

Partnership between ARDH & PIBOC-1

1. **Researcher & Affiliation**

Seung-Hyun Kim, PhD
Translational Research Laboratory for Inflammatory Disease,
Clinical Trial Center,
Ajou University Medical Center,
Suwon, 16499
South Korea.
Tel: +82-31-219-4264; Fax: 82-31-219-4265, E-mail: kimsh@ajou.ac.kr

2. **Proposal:**

Therapeutic application of novel anti-inflammatory molecules for asthma and allergic rhinitis

3. **Research Background:**

Translational Research Laboratory for Inflammatory Disease (TRID) in Ajou University Medical Center plays a hub for the translational research of inflammatory disease by translating research processes from bench to bedside. The AJOU-TRID is aimed to foster the improvement the current health care environment and develop novel biomedical-pharmaceutical industry by providing a collaborative research of inflammatory disease between basic and clinical research.

Our research team has focused on clinical pathological research, pharmacogenomics study, and immunological research for asthma and allergic disease. The final goal of our research is to develop novel anti-inflammatory therapeutics through a high-throughput screening of

candidates and evaluation of the therapeutic potential for asthma and allergic rhinitis.

4. Research Target No.1: Steroid derivatives

Even if new target therapeutics have been introduced alongside with our increasing understanding of the mechanisms of asthma and allergic disease, corticosteroid therapy still remains the most effective treatment for allergic airway diseases including asthma and allergic rhinitis. Therefore, development of novel anti-inflammatory steroid derivative seems to be a challenge filed. The collaborative research between AJOU-TRID and PIBOC will be focused on the development of corticosteroid derivatives by considering the structure-activity relationships of glucocorticoids and the binding affinity to the glucocorticoid receptor. Thus I'd like to propose high throughput screening novel steroid derivatives in PIBOC and in vitro/ in vivo efficacy testing in AJOU TRID.

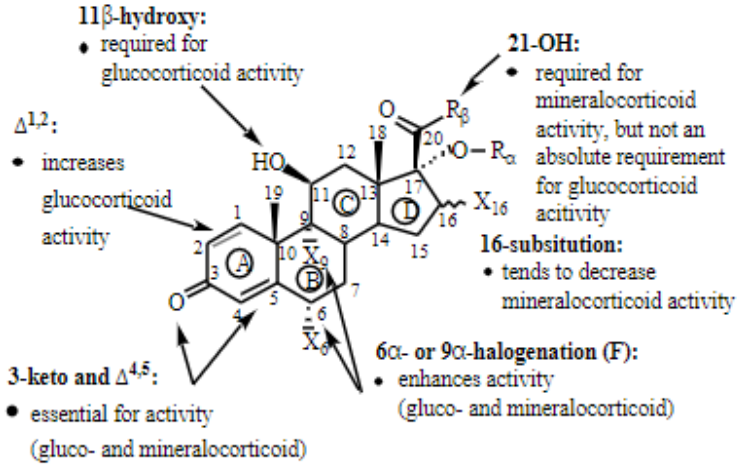


Figure 1. Structure-activity relationship of steroid

Research Target No.2: SPHK1 inhibitor

Considering multiple cellular process such as cell division, differentiation, apoptosis and autophagy of sphingolipids, the metabolic change of sphingolipids has been targeted as novel therapeutics for the management of allergic and inflammatory disease including asthma. The potential role of sphingosine-1-phosphate (S1P) in asthma has been discussed. S1P can initiate mast cell activation and chemotaxis as well as induce airway hyperreactivity by interacting with S1P receptors. Moreover, several sphingosine-1-phosphate kinase (SPHK) inhibitor has been introduced for the management of asthma. Therefore, I'd like to propose high throughput screening novel SPHK1 inhibitor in PIBOC and in vitro/ in vivo efficacy testing in AJOU TRID. The in vitro/ in vivo efficacy assessment platform in AJOU TRID will foster the collaborative research between AJOU-TRID and PIBOC for the development of novel therapeutic technology.

5. Recent publications:

Kim SH et al. Integrative information theoretic network analysis for genome-wide association study of aspirin exacerbated respiratory disease in Korean population. BMC Med Genomics. 2017

Kim SH et al. Identification of phenotypic clusters of nonsteroidal anti-inflammatory drugs exacerbated respiratory disease. Allergy. 2017

Kim SH et al., Neutrophil autophagy and extracellular DNA traps contribute to airway inflammation in severe asthma. Clin Exp Allergy. 2017

Kim et al., Exploration of the Sphingolipid Metabolite, Sphingosine-1-phosphate and

Sphingosine, as Novel Biomarkers for Aspirin-exacerbated Respiratory Disease. Sci Rep. 2016

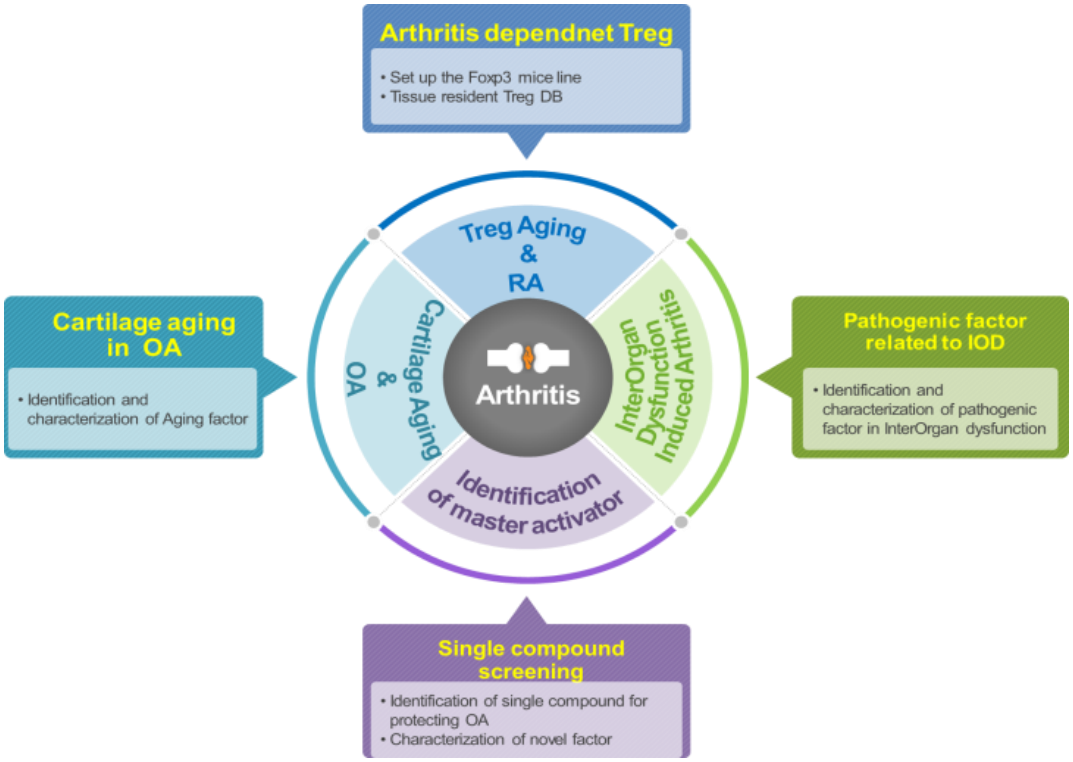
Partnership between ARDH & PIBOC-2

1. Researcher & Affiliation

Siyoung Yang, Ph.D,
Department of Pharmacology,
Ajou University School of Medicine,
Suwon, 16499,
Republic of Korea,
Tel: +82-31-219-5065; Fax: +82-31-219-5069; e-mail: yangsy@ajou.ac.kr

2. Research target and compounds

The final goal of our lab is doing translational research and developing the therapy technique for arthritis and autoimmune diseases. We are mainly focused on three projects;1) Understanding of molecular pathogenic mechanism of arthritis, 2) Development of therapy techniques for arthritis, and 3) the function of tissue resident Treg in autoimmune diseases. Most of project are investigated with in vivo mouse model (TG/KO mouse) and in vitro cell culture system. To develop the therapy techniques, we basically use a potential single compound drug and are collaborated with pharmaceutical company.



3. Major Publications

Kang LJ, Kwon ES, Lee KM, Cho C, Lee JI, Ryu YB, Youm TH, Jeon J, Cho MR, Jeong SY, Lee SR, Kim W, Yang S. 3'-silayllactose as an inhibitor of p65 phosphorylation ameliorates the progression of experimental rheumatoid arthritis. **British Journal of Pharmacology** 2018 In press.

Jeon J, Kang LJ, Lee KM, Cho C, Song EK, Kim W, Park TJ, **Yang S**. 3'-silayllactose protects against osteoarthritic development by facilitating cartilage homeostasis. **J Cell Mol Med** 2018 Jan 1.

Yang S, Fujikado N, Benoist C, Mathis D. Regulatory T cells generated early in life play a distinct role in maintaining self-tolerance. **Science** 2015 May:589-594.

Yang S, Ryu JH, Oh H, Jeon J, Kwak JS, Kim JH, Kim HA, Chun CH and Chun JS. NAMPT (visfatin), a direct target of hypoxia-inducible factor-2α, is an essential catabolic

regulator of osteoarthritis. **Annals of the Rheumatic Diseases** 2015 Mar;74(3):595-602.

Yang S, Bansal K, Lopes J, Benoist C, Mathis D. Aire's plant homeodomain(PHD)-2 is critical for induction of immunological tolerance. ***Proc Natl Acad Sci U S A***. 2013 Jan 29;110(5):1833-8.

Yang S, Kim J, Ryu JH, Oh H, Chun CH, Kim BJ, Min BH and Chun JS. Hypoxia-inducible factor-2α is a catabolic regulator of osteoarthritic cartilage destruction. ***Nature Medicine***. 2010 Jun;16(6):687-93

Partnership between ARDH & PIBOC-3

1. Researcher & Affiliation

Jung-Soon Mo, Ph.D,
Genomic Instability Research Center (GIRC),
Ajou University School of Medicine,
Suwon, 16499,
Republic of Korea,
Tel: +82-31-219-7803; Fax: +82-31-219-7802; e-mail: j5mo@ajou.ac.kr

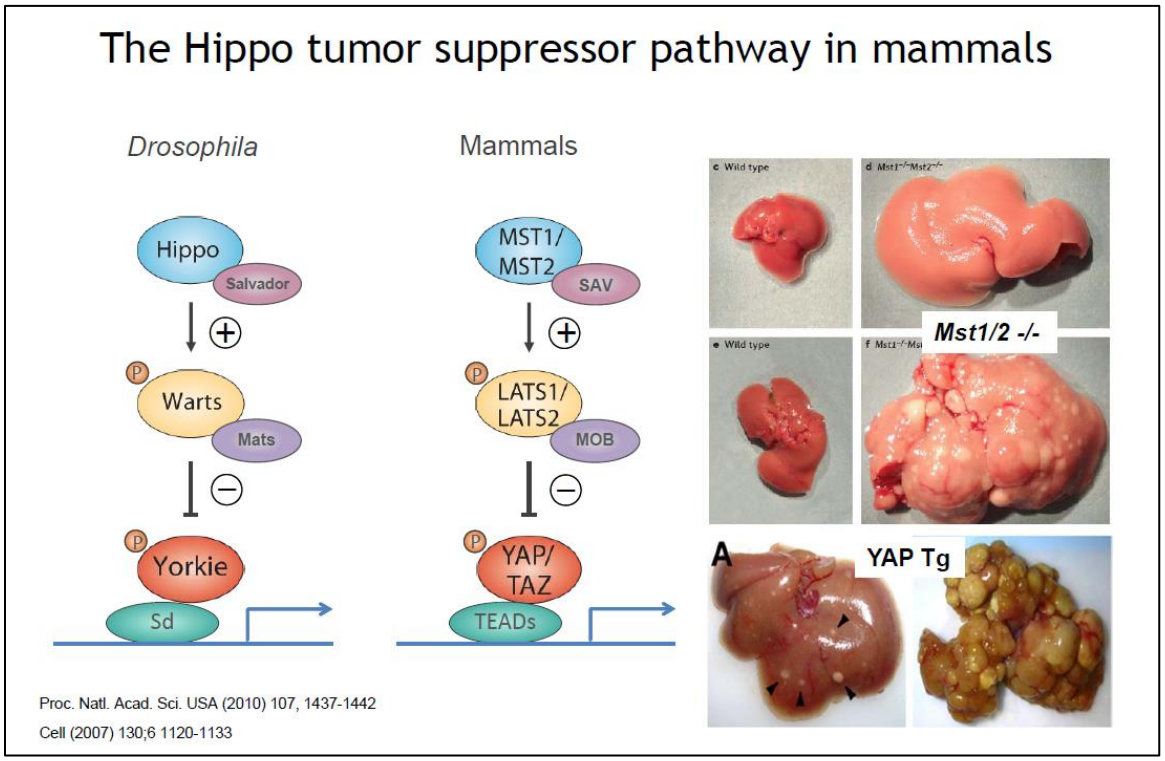
2. Research target and compounds

Our lab's research is focused on the physiological role for the Hippo-YAP cascade in growth control and its dysregulation in tumorigenesis. The Hippo tumor suppressor pathway plays a key role in regulating organ size and tumorigenesis by inhibiting cell proliferation, promoting apoptosis, and regulating stem cell expansion. Development of targeted anti-cancer therapeutics based on pathway specific inhibitors has proven to be an effective approach in the field of oncology research. Thus I would like to identify a compound as a novel Hippo-YAP pathway activator or inhibitor via cell based High throughput screening.

3. Research Background

The Hippo-Yap pathway has been well established as a regulator of development, organ size, and tissue regeneration under physiological conditions; deregulation of this pathway is known to contribute to tumorigenesis. Core components of the mammalian Hippo pathway include the Mst kinase and its regulator Sav, the Lats kinases and their regulator Mob, and the downstream effector Yes associated protein (YAP) and TAZ. The Yes associated protein (YAP) is a

transcription co-activator and an important downstream effector of the Hippo pathway. TAZ is a YAP paralog in mammals and is also regulated by the Hippo pathway in a similar manner. The phosphorylated forms of TAZ and YAP tend to localize to the cytosol decreasing tumor growth, whereas unphosphorylated YAP and TAZ are localized mainly in the nucleus promoting the growth of tumors. Inhibition of YAP and TAZ represents the major signaling output of the Hippo tumor suppressor pathway. As expected, abnormal activation of YAP and TAZ correlates with human cancer. Inhibitors and activators of the Hippo effector YAP may emerge as new tools for cancer intervention.



4. Major Publications

Mo JS. The role of extracellular biophysical cues in modulating the Hippo-YAP pathway. BMB Rep. 2017 Feb;50(2):71-78

Cosset É, Ilmjärv S, Dutoit V, Elliott K, von Schalscha T, Camargo MF, Reiss A, Moroishi T, Seguin L, Gomez G, **Mo JS**, Preynat-Seauve O, Krause KH, Chneiweiss H, Sarkaria JN, Guan KL, Dietrich PY, Weis SM, Mischel PS, Cheresh DA. Glut3 Addiction Is a Druggable Vulnerability for a Molecularly Defined Subpopulation of Glioblastoma. Cancer Cell. 2017 Dec 11;32(6):856-868.e5. doi: 10.1016/j.ccell.2017.10.016.

Mo JS, Meng Z, Kim YC, Park HW, Hansen CG, Kim S, Lim DS, Guan KL. Cellular energy stress induces AMPK-mediated regulation of YAP and the Hippo pathway. Nat Cell Biol. 2015 Apr;17(4):500-10. doi: 10.1038/ncb3111.

Mo JS, Park HW, Guan KL. The Hippo signaling pathway in stem cell biology and cancer. EMBO Rep. 2014 Jun;15(6):642-56. doi: 10.15252/embr.201438638.

Mo JS, Yu FX, Gong R, Brown JH, Guan KL. Regulation of the Hippo-YAP pathway by protease-activated receptors (PARs). Genes Dev. 2012 Oct 1;26(19):2138-43. doi: 10.1101/gad.197582.112

Partnership between ARDH & PIBOC-4

1. Researcher & Affiliation

Min Sook Ryu, PhD

Dept. of Allergy and clinical Immunology,

Dept. of Biochemistry and Molecular Biology,

Ajou University School of Medicine

Suwon, 16499,

Republic of Korea,

Tel: +82-31-219-4525; e-mail: msryubio@aumc.ac.kr

2. Research target and compounds

Target organ: skeletal muscle;

Target disease: Muscle atrophy;

Target gene: TIS21/BTG2, PGC1α, MEF2c; Target signal: HDAC, mTOR/Akt

3. Research Background

Skeletal muscle atrophy is characteristic of starvation and a common consequence of aging. It also complicates a wide range of severe human illnesses. However, we currently lack medical therapies to prevent or reverse skeletal muscle atrophy in humans. Many group used a histone deacetylase inhibitors as potential treatment for muscular atrophy (Mohseni et al., Genetics and Molecular Biology 2013 36(3) ; Aging Cell 2015 14(6): 957-70; Physiol Rep. 2018 May;6(10):e13706). Skeletal muscles of vertebrates contain myofibers that differ in contractile function, mitochondrial content and metabolic properties. The oxidative slow-twitch (type I) myofibers contain high concentration of mitochondria for oxidative metabolism to get the chief

energy source. In contrast, the glycolytic fast-twitch myofibers (type IIb) generate ATP mainly through glycolytic metabolism. PGC-1α, expressed in skeletal muscle, is a master transcriptional co-regulator of mitochondrial function and powerfully induces mitochondrial biogenesis when expressed ectopically in skeletal and cardiac myocytes. The transcription factor myocyte enhancer factor 2 (MEF2) is a key regulator of muscle development, and that is preferentially activated in the oxidative slow-myofibers. TIS21 (12-*O*-tetradecanoylphorbol-13-acetate-inducible sequence)/BTG2 (B-cell translocation gene 2) is a member of BTG/Tob family that belongs to anti-proliferative (APRO) genes. TIS21$^{/BTG2}$ acts as a key regulator of cellular machinery including cell growth, differentiation, death, and survival. }. It has been reported that TIS21$^{/BTG2}$ is stimulated by hypoxia, genotoxic stress, metabolic changes, and retinoic acid, however, it is attenuated by insulin, estrogen, and growth factors.

To explore TIS21 expression in the several skeletal muscles, its mRNA expression was measured in soleus, extensor digitorum longus (EDL), tibialis anterior (TA), and gastrocnemius (GA). Expression of TIS21 was marked in soleus as compared with the other muscles. TIS21 gene expression regulates formation of oxidative slow-fibers in soleus. TIS21 enhances HDAc4 degradation in proteasome, which increase the interaction of MEF2c with PGC1α along with mitochondrial oxidative metabolism, finally turning to switch myofibers from glycolytic to oxidative type in skeletal muscles. (submitted)

I expect that TIS21 have a function for specific HDAC4 inhibitor in skeletal muscle. It is important for formation the oxidative muscle.

The Akt/mTOR pathway was upregulated during hypertrophy and downregulated during muscle atrophy. My group reported several papers that TIS21/BTG2 can regulate a mTOR/Akt sinal pathways at cancer cell lines. So I also expect that TIS21 have a function for regulator mTOR/Akt in skeletal muscle.

When I use a component from PIBOC, the research purpose is divided into two point. First, what kind of natural component induce a TIS21 and specific MyHC gene expression in skeletal muscle? Second, what kind of natural component induce a oxidative fiber-specific gene expression in skeletal muscle? I will use a C2C12 myoblast cells and primary muscle cells from Wt or TIS21KO C57BL6 mice. And I will confirm the effect of component using Wt or TIS21KO C57BL6 mice.

4. Major Publications

Sundaramoorthy S, Devanand P, ***Ryu MS***, Song KY, Noh DY, Lim IK. TIS21$_{/BTG2}$ inhibits breast cancer growth and progression by differential regulation of mTORc1 and mTORc2-AKT1-NFAT1-PHLPP2 signaling axis. J Cancer Res Clin Oncol. 2018 May 28.

Hong AE, ***Ryu MS***, Kim SJ, Hwang SY, Lim IK. PPARα-Target Gene Expression Requires TIS21$_{/BTG2}$ Gene in Liver of the C57BL/6 Mice under Fasting Condition. Mol Cells. 2018 Feb 28;41(2):140-149.

Lim IK, Choi JA, Kim EY, Kim BN, Jang S, ***Ryu MS***, Shim SH. TIS21$_{/BTG2}$ inhibits doxorubicin-induced stress fiber-vimentin networks via Nox4-ROS-ABI2-DRF-linked signal cascade. Cell Signal. 2017 Jan;30:179-190.

Choi OR, ***Ryu MS***, **Lim** IK. Shifting p53-induced senescence to cell death by TIS21(/BTG2/Pc3) gene through posttranslational modification of p53 protein. Cell Signal. 2016 Sep;28(9):1172-85.

Ryu MS, Woo MY, Kwon D, Hong AE, Song KY, Park S, Lim IK. Accumulation of cytolytic CD8+ T cells in B16-melanoma and proliferation of mature T cells in TIS21-knockout mice after T cell receptor stimulation. Exp Cell Res. 2014 Oct 1;327(2):209-21.

Partnership between ARIDH & PIBOC-5

1. Researcher & Affiliation

So Hee Kim, Ph.D.

Lab of Pharmacology and Pharmacokinetics

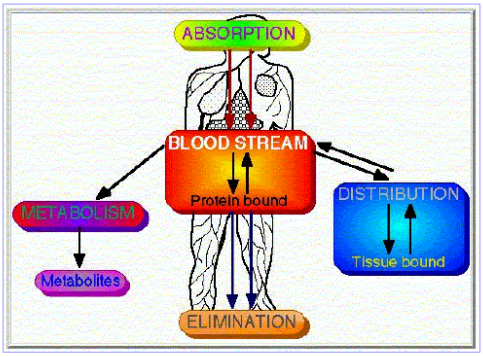
College of Pharmacy, Ajou University

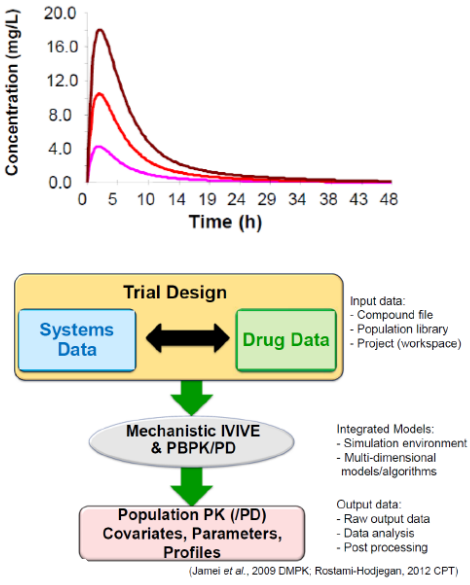
Suwon, 16499, Republic of Korea

Tel: 82-31-219-3451; Fax: 81-31-219-3435; e-mail: shkim67@ajou.ac.kr

2. Research target and compounds

Our lab is investigating the characteristics of drug metabolism and pharmacokinetics (DMPK) of small molecules and natural substances in the process of new drug development, drug-drug or drug-natural substance interaction, disease effects on the DMPK of drugs and physiologically based pharmacokinetics (PBPK) modeling & simulation. Our lab also studies the drug repositioning on cancer therapy and the mechanism of chemoresistance in solid tumor models.





3. Research Background

It takes about 15 to 20 years to develop a new drug. While a myriad of candidates is pouring out in the non-clinical phase, less than 1% will be approved as new drugs. Why the majority of candidates fail to succeed as new drugs. There are many reasons, such as toxicity problems, unexpected side effects, less efficacy and poor DMPK profiles. Among them, the frequency of failure due to the poor DMPK profiles varies a little by the statistical data, but it is almost up to 40%. Therefore, it is necessary to understand the DMPK characteristics of candidate and to overcome the issues raised. A good DMPK profile can not be achieved if the absorption is poor due to poor water solubility, if the plasma protein binding rate is too high, or if almost all of the dosage is metabolized. That is, they become too serious factors of failure to approve as new drugs. Therefore, it is very important to evaluate DMPK characteristics in the developmental process of new drugs. In addition, interactions between the coadministered drugs can not be ignored. Drug-drug interactions are expected to be somewhat predictable in the case of drugs that are highly metabolized and thus drug interaction studies are also required to be evaluated. These interactions have been reported in considerably more natural products than thought, and interactions studies of natural products and drugs need to be continued. This is also true for marine natural products. Since many natural products on land are already known, interest in marine natural products is increasing, and interaction between marine natural products and drugs should be considered.

4. Major Publications

Lee JM, Lee JW, Jung TS, Bang ES, **Kim SH** (2018) Low meropenem concentration in brain-dead organ donors: a single-center pharmacokinetic study and simulation. Antimicrob

Agents Chemother (http://DOI:10.1128/AAC00542-18)

Hong SS, Choi JY, Kim JO, Lee MK, **Kim SH***, Lim SJ* (2016) Development of paclitaxel-loaded liposomal nanocarrier stabilized by triglyceride incorporation. Int. J. Nanomed. 11:4465-4477 (* equally contributed as corresponding authors)

Hong SS, **Kim SH***, Lim SJ* (2015) Effects of triglycerides on the hydrophobic drug loading capacity of saturated phosphatidylcholine-based liposomes. Int. J. Pharm. 483:142-150. (* equally contributed as corresponding authors)

Ramnath N, Nadal E, Jeon CK, Sandoval J, Colocino J, Rozek LS, Christensen PJ, Esteller M, Beer DG, **Kim SH** (2014) Epigenetic regulation of vitamin D metabolism in human lung adenocarcinoma. J. Thorac. Oncol. 9:473-482.

Kim SH, Chen G, King AN, Jeon CK, Christensen PJ, Zhao L, Simpson RU, Thomas DG, Giordano, TJ, Brenner DE, Hollis B, Bee DG, Ramnath N (2012) Characterization of vitamin D receptor (VDR) in lung adenocarcinoma. Lung Cancer 27:265-271.

Chen G*, **Kim SH***, King AN, Zhao L, Simpson RU, Christensen PJ, Wang Z, Thomas DG, Giordano TJ, Lin L, Brenner DE, Beer DG, Ramnath N (2011) *CYP24A1* is an independent prognostic marker of survival in patients with lung adenocarcinoma. Clin. Cancer Res. 17:817-826. (* equally contributed as first authors)

Partnership between ARDH & PIBOC-6

1. Researcher & Affiliation

Jong-Young Kwak, M.D., Ph.D,
Immune-network Pioneer Research Center,
Ajou University School of Medicine,
Suwon, 16499,
Republic of Korea,
Tel: +82-31-219-5604; Fax: +82-31-219-5609; e-mail: jykwak@ajou.ac.kr

2. Research target and compounds

Our lab's research is focused on the development of functional 3D cell and tissue culture system. Natural and synthetic polymers have been used as a fundamental materials for scaffold of 3D culture system. Natural polymers from marine resources can be developed as biocompatible and biodegradable scaffold.

3. Research Background

3D cell culture leads to more predictive models for drug discovery and tissue regeneration. An ideal 3D culture model has not been defined due to loss of extracellular matrix-like scaffold although various 3D cell culture model systems need scaffold for 3D cell growth. Marine origin polymers have been used as scaffolds for 3D cell culture and will be developed as biomaterials for bioink in bioprinting. Thus, many polymers such as alginates, carrageenans, fucoidans, and chitosans from marine resources, including fish, algae, crustaceans, bacteria, cyanobacteria, actinobacteria, and fungi, are considered to be promising biomaterials for 3D cell and tissue

culture. In addition, the biological assays of bio-active materials from marine resources using 3D culture rather than 2D culture have been expanded. This Special Issue aims to provide an overview of the current research in 3D culture system with marine natural products as biomaterials. Innovative 3D culture systems to assay marine drugs also are one of the focus of future researches.

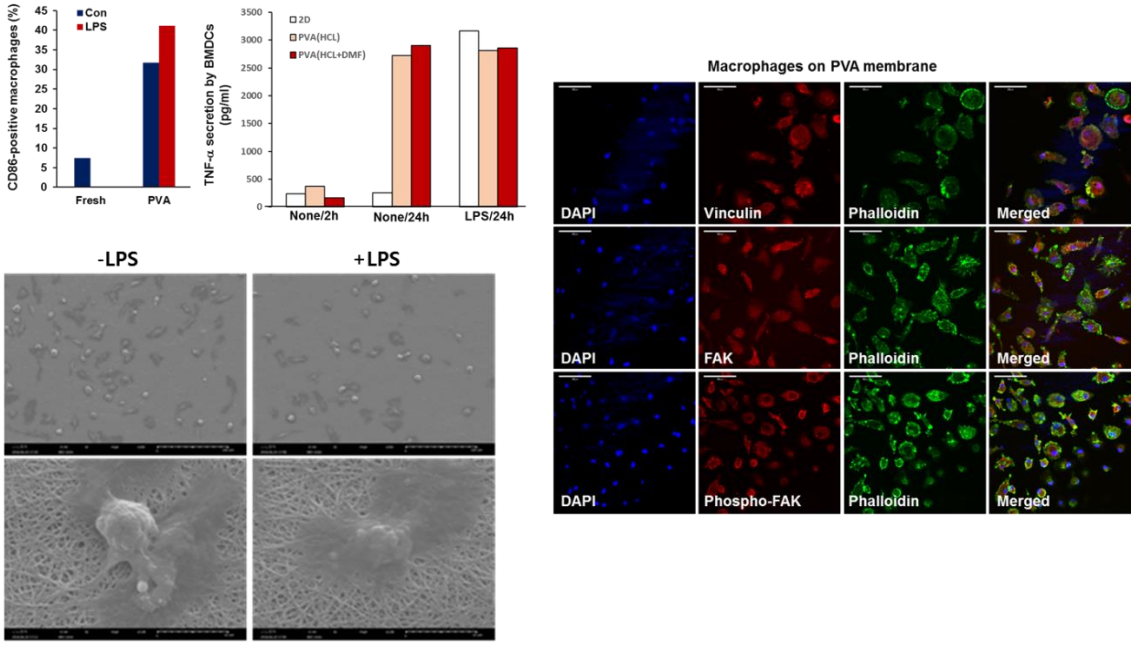


Figure. 3D Culture of dendritic cells on PVA nanofiber membrane

4. Major Publications

Kim TE, Kim CG, Kim JS, Jin S, Yoon S, Bae HR, Kim JH, Jeong YH, **Kwak JY**. Three-dimensional culture and interaction of cancer cells and dendritic cells in an electrospun nano-submicron hybrid fibrous scaffold. Int J Nanomedicine. 2016 Mar 2;11:823-35.

Kang D, Kim JH, Jeong YH, **Kwak JY**, Yoon S, Jin S. Endothelial monolayers on collagen-coated nanofibrous membranes: cell-cell and cell-ECM interactions. Biofabrication.

2016 May 17;8(2):025008.

Kwak JY et al., NANOFIBER STRUCTURE FOR CELL CULTURE, METHOD FOR MANUFACTURING THE NANOFIBER STRUCTURE, AND CELL ANALYSIS DEVICE INCLUDING THE NANOFIBER STRUCTURE. US patent application Number: 160623055, Application date: 06. 15. 2018, PCT number: PCT/KR2016/014384

Kwak JY et al., METHOD OF MANUFACTURING A POLYVINYL ALCOHOL NANOFIBERS TRUCTURE FOR CELL CULTURE. PCT/KR2017/000393, PCT application date: 16. 01. 2017

Kwak JY et al., MANUFACTURING METHOD OF NANOFIBER STRUCTURE COMPRIGING FUCOIDAN WITH ENHANCED CELL ADHESION AND NANOFIBER STRUCTURE COMPRIGING FUCOIDAN MADE BY THE SAME. PCT/KR2017/009136, PCT application date: 08. 22. 2017.

R&D of Botanical Drugs in Korea

Botanical Drugs

- Market, Players and Regulations Overview

Hoijong Jung
CEO, Assist Bio Inc.
Tel: +82)31 712-5431
Mobile: +82)10-4937-5431
Email: assistbio7@gmail.com

Education

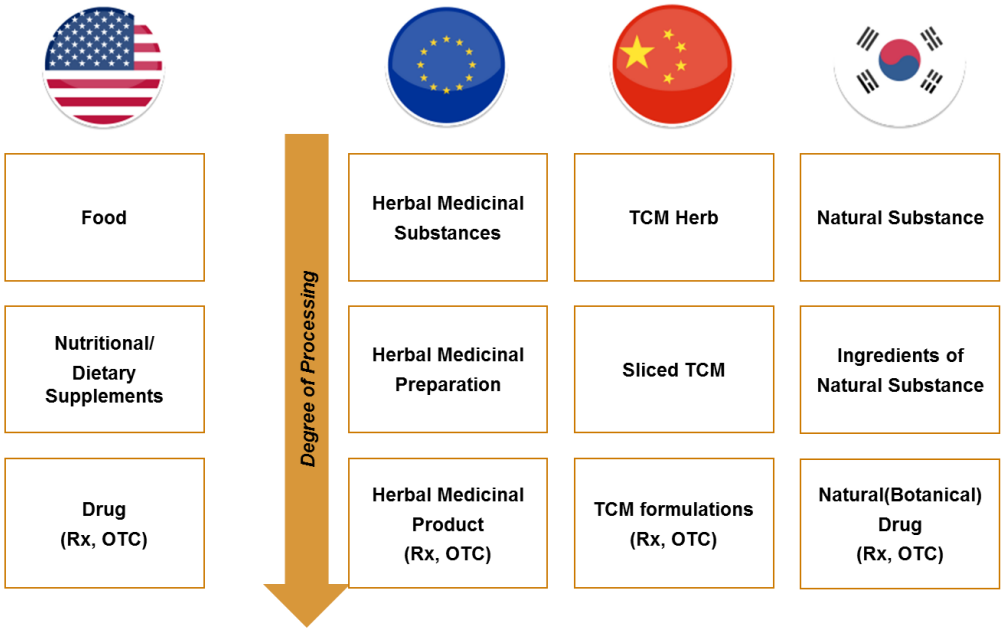
2002~2006 Feb Ph.D., Dept. of Life Science, GIST
2001~2002 Aug M.S., Dept. of Life Science, GIST
1993~2001 Feb B.S., Dept. of Genetic Engineering, Chonnam National University

Professional experience

2018~ CEO, Assist Bio Inc.
2014~2018 Team Leader, Commercializaions Promotion Agency for R&D Outcomes
2010~2014 Team Leader, Korea Institute of Planning and Evaluation for Technology in Food, Agriculture and Forestry
2008~2009 Post-Doc, Korea Institute of Ocean Science & Technology
2006~2008 Senior Researcher, Korea Institute of S&T Evaluation and Planning

Definition & Characteristics

Differences depending on the geographic region



Botanical Drug Market

China occupies the largest market share of Botanical Drug

	Market Share of Botanical Drug (2017 Estimation)	Remarks
	Estimated Total Market 352.5.2 Bn USD Chemical/ Biotech (56.9%) Botanical/ TCM product (43.1%) 151.0 Bn USD	▪ 23.1% CAGR in TCM drugs (02~11) ▪ 13.4% for Botanical OTC products (28.7Bn USD) ▪ Occupies largest market share of botanical drug
	Estimated Total Market 747.8 Bn USD Chemical/Biotech (98.9%) Botanical (1.1%) 8.2Bn USD	▪ 90.5% for Botanical OTC products (8.1Bn USD) ▪ 1,319 traditional herbal medicines registered (2004~2014) ▪ 622 Herbal medicines authorized (2004~2014)
	Estimated Total Market 1,736.6 Bn USD Chemical/Biotech (99.99%) Botanical (0.01%) 0.17Bn USD	▪ Two Rx products (Veregen® and Fulyzaq®) are now marketed

Source: Morgan Stanly Report, EMA Report, IMS data, KHIDI Review (2016)

Key players in Botanical Drug Market

Major Botanical Rx Products & Pipeline in US

No.	Product	Company	Indication	Origin	US Status
1	Veregen	Medigene AG	Genital warts	Green tea leaves	Marketed
2	Fulyzaq	Napo Pharma	Relief of Diarrhea in HIV patients	Croton lechierl	Marketed
3	MF-101	Bionovo	Flush in menopausal woman	Scutellaria barbata	Phase 3
4	BNO-1016	Bionorica	Chronic sinusitis	Gentian root	Phase 3
5	EISO	Viroxis	Wart	East Indian sandalwood Oil	Phase 2
6	HMPL-004	Hutchison Medipg	Crohn's disease	Andrographis paniculata	Phase 3

Botanical Product targeting US market (1st & 2nd generation products)

No.	Product	Company	Indication	target indication in US	US Status	Sales
1	Danshen	Tasly	Angina pectoris	Angina pectoris	Phase 3	110 Mil USD
2	Kang Lai Te Inj.	Kang Lai Te	NSCLC	Pancreatic cancer	Phase 2/3	118 Mil USD
3	TU-100	Tsumura	Postoperative Ileus	Postoperative Ileus	Phase 2	84 Mil USD
4	HMPL-004	Hutchison	Crohn's disease	Crohn's disease	Phase 2	298 Mil USD
5	Fuzheng Huagu	Shanghai Sundise	Hepatitis B	Hepatitis C	Phase 2	N/A
6	EISO	Viroxis	Commom wart		Phase 2	
7	MF-101	Bionovo	Flush in menopausal woman		Phase 3	
8	AOBO-001	AOB	Overactive bladder		Phase 2	

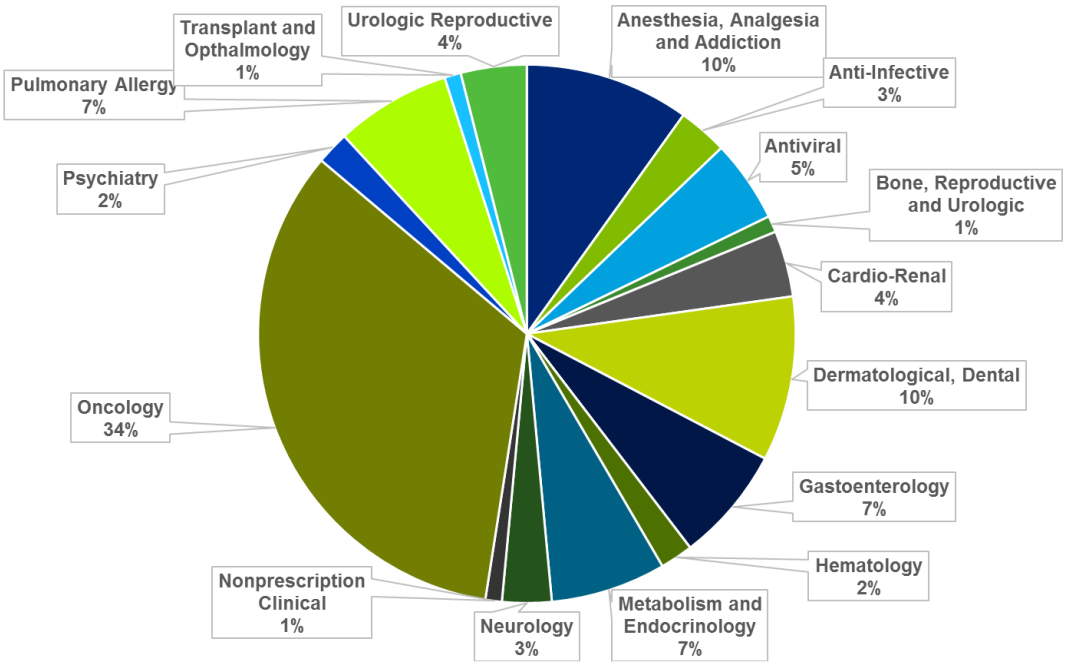
FDA Regulatory Overview

Botanical Review Team in FDA

1. Review of Botanical Drug Products
2. Performs pharmacognosy review
3. Making decisions on Botanical Drugs – PIND, IND, NDAs
4. Responding to general botanical drug development questions
5. Responding to general botanical drug development questions and meeting requests
6. Serving as an expert resources for CDER on all botanical issues
7. Promoting and enhancing botanical drug product development and knowledge

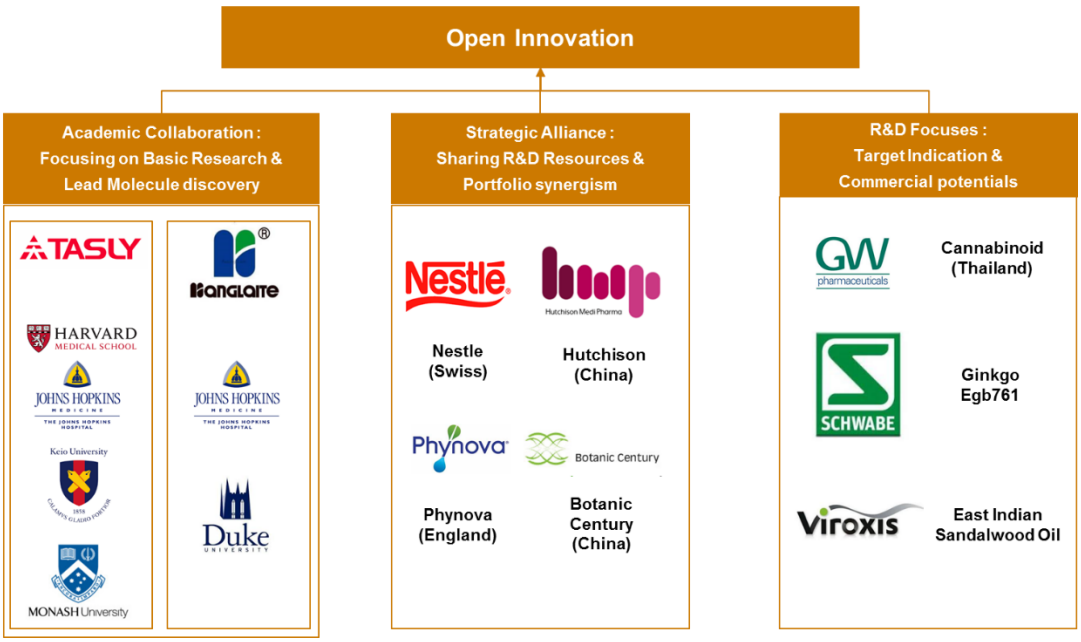
FDA Regulatory Overview

Botanical INDs by the Therapeutic Areas



Globalization Strategy

Open Innovation is a key to success



Presentation of ARDH Researches

Protective effects of ‘Loganin’ isolated from Corni fructus on postmenopausal osteoporosis and obesity

Seon-Yong Jeong, Ph.D

Professor/Vice-Dean, Ajou University School of Medicine
President/CEO, NINE B Co., Ltd.
E-mail: jeongsy@ajou.ac.kr

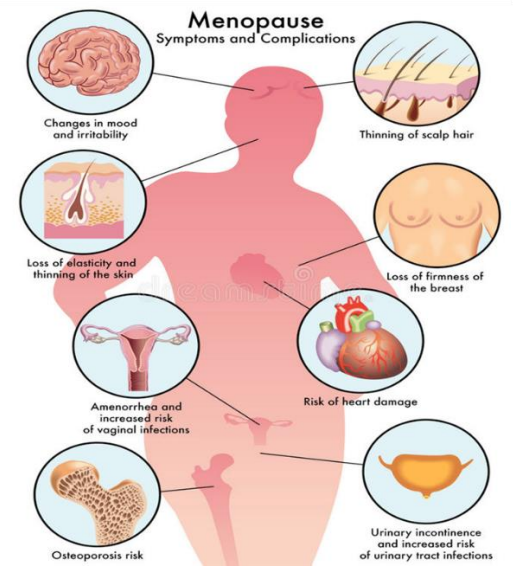
Education

Feb. 1991: B.S., Dept. of Biotechnology, Yeungnam University, Republic of Korea
Mar. 1997: Ph.D., Dept. of Applied Biotechnology, The University of Tokyo, Japan

Professional experience

1997.4 - 2001.8: Post-doc. Fellow, Dept. of Neurology, Tokyo Univ. Med. School, Japan
2001.9 - 2004.8: Post-doc. Fellow, Dept. of Biochemistry, NINDS, NIH, USA
2004.9 - present: Assistant Professor/Associate Professor/Professor,
Dept. of Medical Genetics, Ajou Univ. School. Med., Korea
2016.8 - present: President/CEO, NINE B Co., Ltd.

Symptoms and Complication of Woman's Menopause



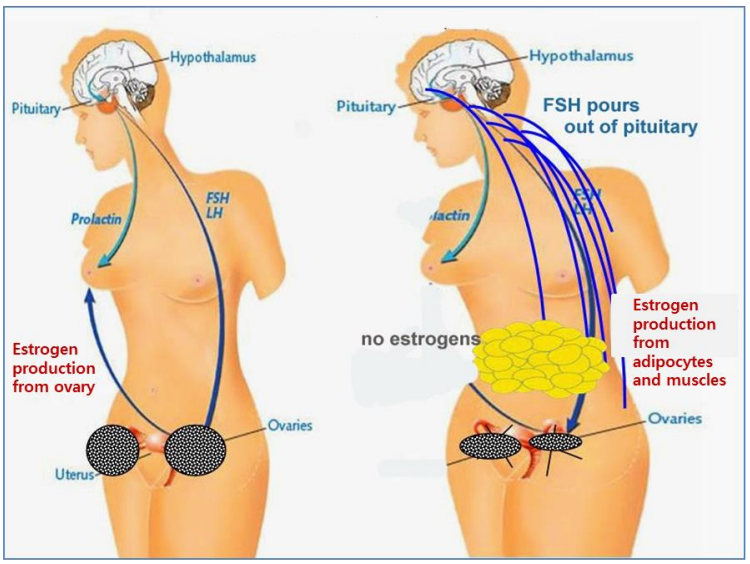
Hot flashes

Depression

Osteoporosis

Obesity

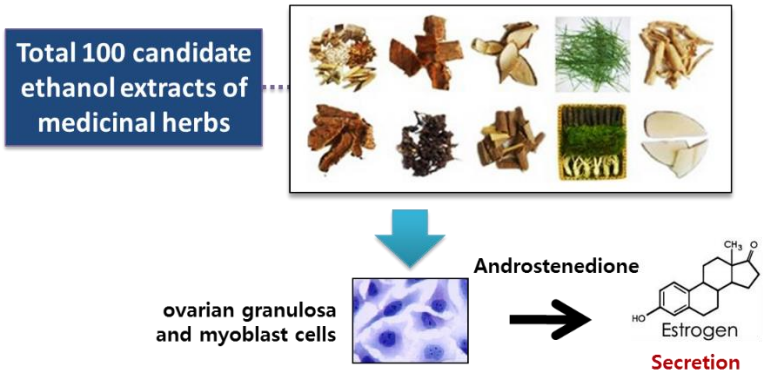
Cause of menopausal obesity in women



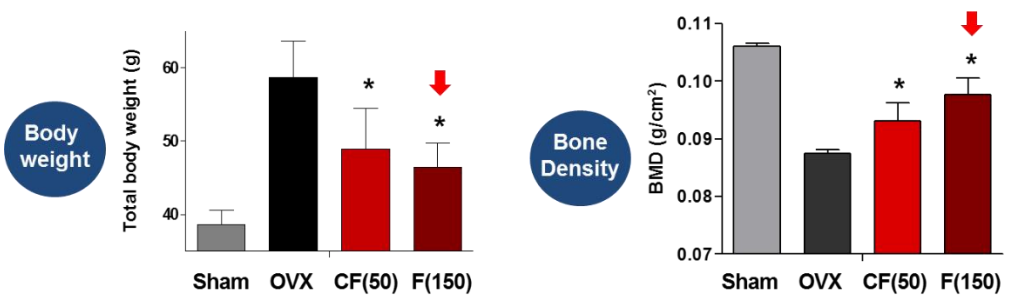
❖ **Requirement of appropriate estrogen level during postmenopause**

- ✓ New estrogen production from adipocytes and muscles after menopause
- ✓ Relatively easy increase in a risk of abdominal obesity because of augmented activation of abdominal fat tissues after menopause

Screening of ethanol extracts of medicinal herbs for enhancing estrogen secretion in ovarian granulosa and myocyte cells



Anti-obesity and anti-osteoporotic effect of Corni fructus extract in menopausal mouse model



Fractionation and isolation of the bioactive constituent responsible for the estrogen enhancing effect of Corni fructus

Corni fructus
(92brix, 75.7g)

Diaion HP20

100% H_2O fraction
EtOH fraction

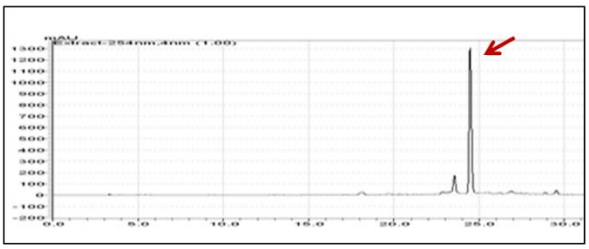
30% EtOH fraction

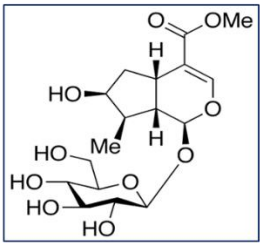
70% EtOH fraction

MPLC_RP18

1 2 3 **4** 5

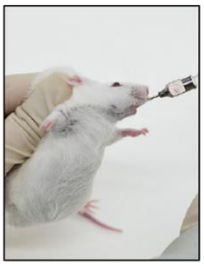
Bioactive fraction

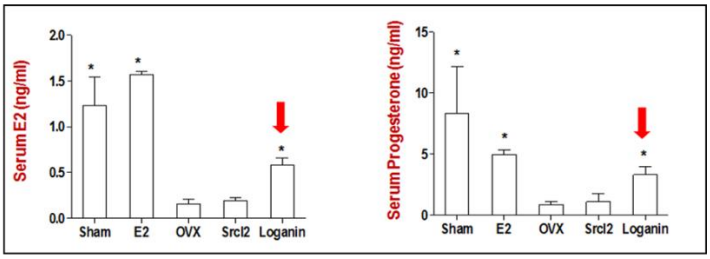


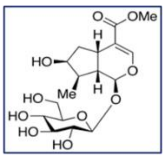


"Loganin"

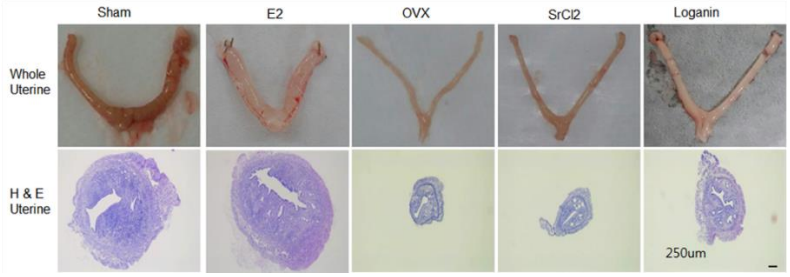
Effects of Loganin on inhibition of a decrease in serum estrogen and progesterone levels and uterus atrophy in OVX mice



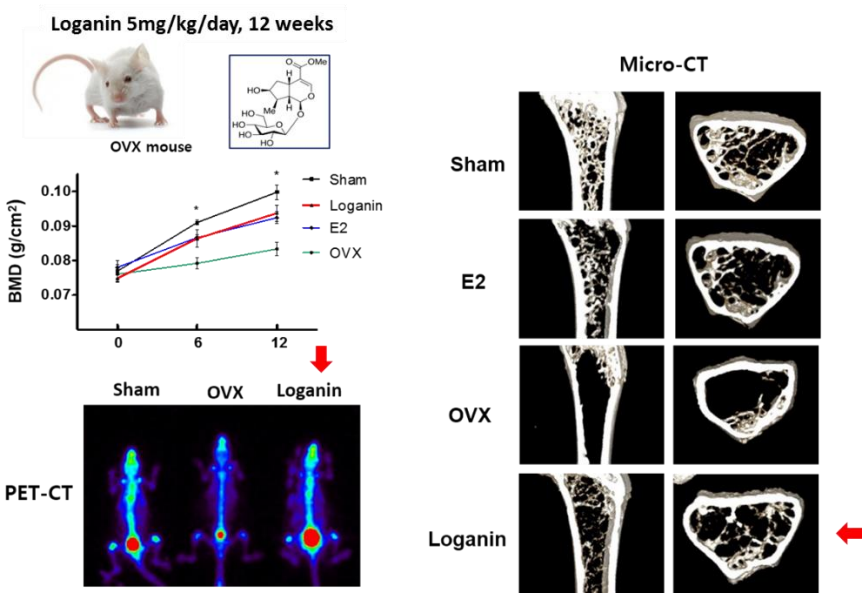




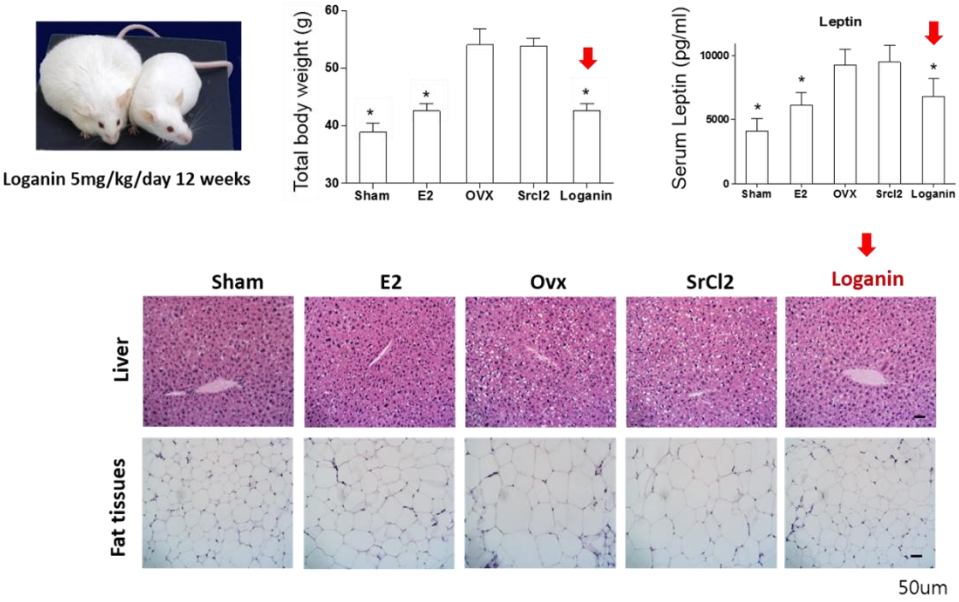
Loganin 5mg/kg/day
12 weeks



Effects of Loganin on inhibition of a decrease in bone mineral density and bone strength in OVX mice



Effects of Loganin on inhibition of weight gain and lipid accumulation & enlargement of adipocytes in OVX mice



Summary & Future plan

- **Corni fructus extract was screened as a candidate of medicinal herbs for treatment of woman's menopausal symptoms.**
- **Loganin was isolated from Corni fructus extract and identified as a bioactive ingredient responsible for estrogen enhancing in ovarian granulosa and myocyte cells.**
- **Loganin reveals to have an significant effects on menopausal complications including bone loss, weight gain, lipid accumulation in liver and abdominal fat tissues.**
- **Further researches include: (1) synthesis of Loganin derivatives, (2) evaluation of the derivatives for their effect and toxicity in animals, and (3) clinical trials in menopausal women.**

✓ **Patent:** Composition for preventing, improving or treating female menopause symptoms comprising Loganin or its derivatives

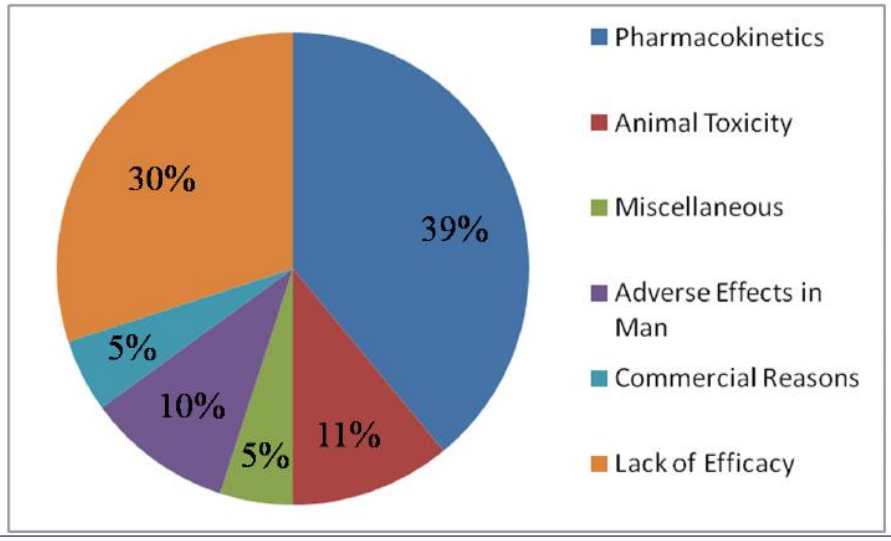
✓ **Patent registration:** Republic of Korea

✓ **Patent application:** Russia, US, EU, China, Japan, Canada, Australia, India, Brazil

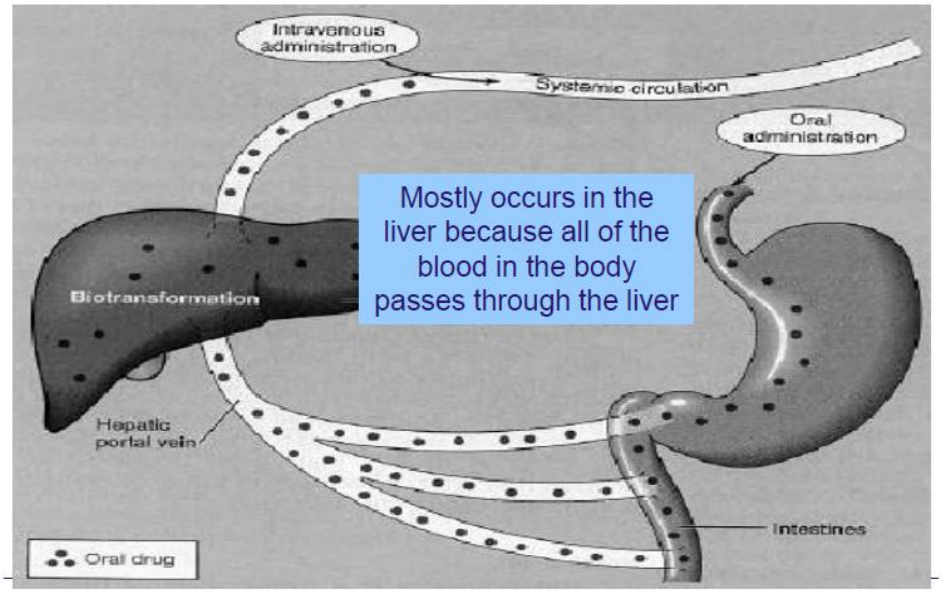
Biography

Dr. Kim is a professor at Department of Pharmacy, Ajou University College of Pharmacy, Korea. She is currently a Head of Pharmacy Department, Ajou University College of Pharmacy. She is a Chief of Academic Affair in Korean Society of Pharmacology in 2018. She completed her BS, MS and PhD degee in Seoul National University, Korea. She studied the pharmacokinetics of small molecules in the process of new drug development during her Ph.D. course. After Ph.D. degree, She became a professor in Department of Pharmacology, Kangnung National University School of Dentistry, Korea from 2001 to 2011. She moved to Institute of Environmental Health and Sciences (IEHS), Wayne State University, USA in 2004 as a visiting professor and researched the breast cancer biology for 2 years. She also had research experience in Comprehensive Cancer Center, University of Michigan School of Medicine, USA in 2010 and studied the epigenetic regulation of CYP24A1, a metabolizing enzyme of vit D, as a prognostic marker in lung cancer for 2 years. Her current research interests are drug-drug or drug-disease interaction, drug metabolism and pharmacokinetics (DMPK) of drug candidates, physiologically based pharmacokinetics (PBPK) modeling & simulation, and chemoresistance. Recently, she joined a venture company, Nanofaenetech, as a director.

Why drugs fail?



Drug Metabolism



Drug - Drug Interactions

Risks associated with CYP enzyme inhibition or induction

Inhibition of CYP enzymes

↓

Decreased degradation of comedicated drugs

↓

Increased drug plasma concentrations

↓

Risk of severe adverse events

Induction of CYP enzymes

↓

Increased degradation of comedicated drugs

↓

Decreased drug plasma concentrations

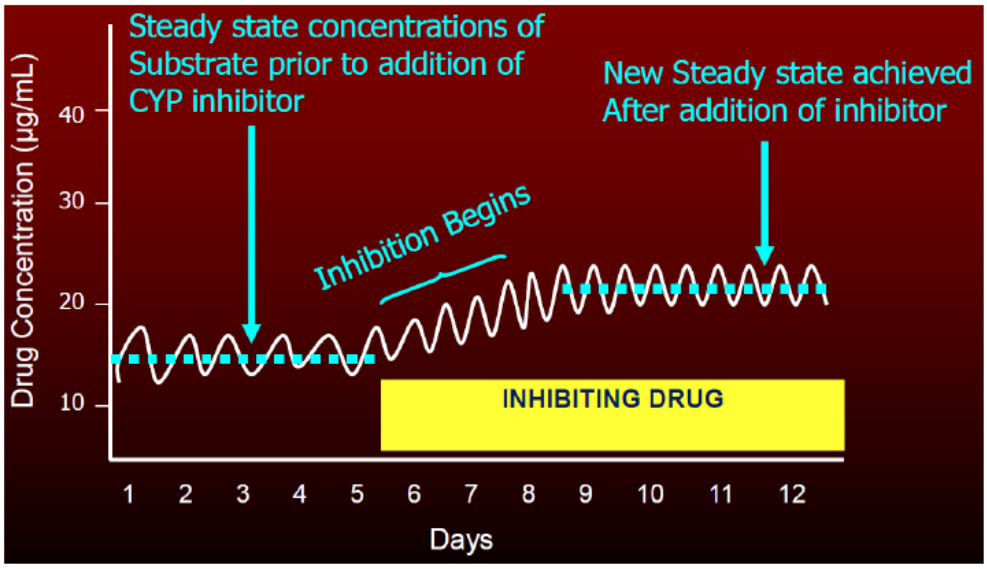
↓

Loss of pharmacological effect

↓

Risk of severe secondary effects

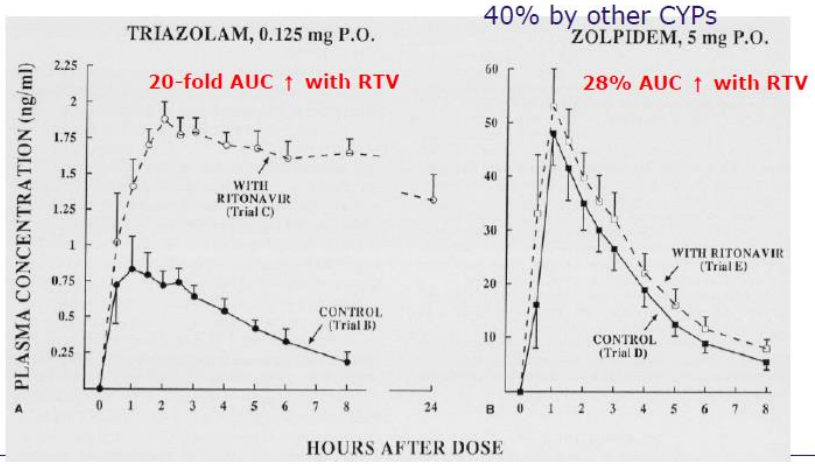
Drug Metabolism Interactions: Inhibition



Drug Metabolism Interactions: Inhibition

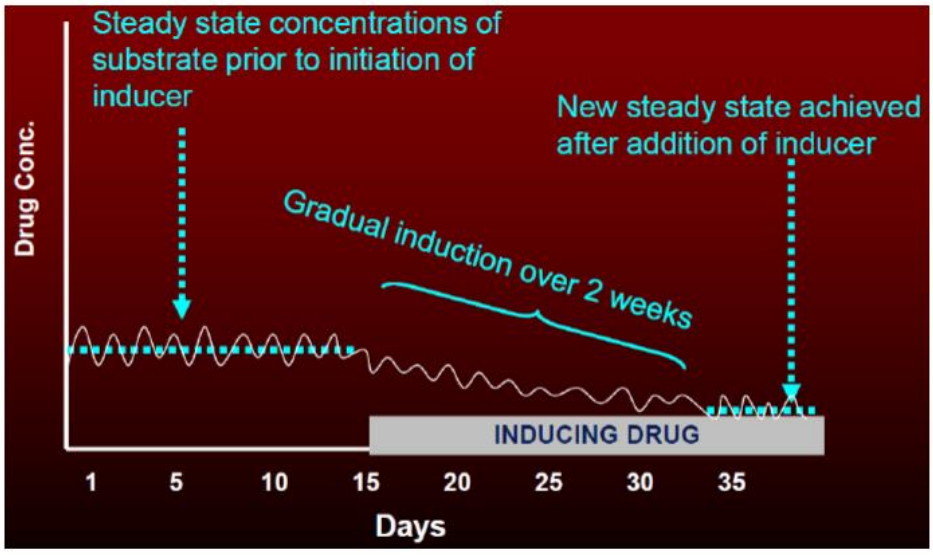
TRIAZOLAM
100% metabolized by CYP3A

ZOLPIDEM
60% metabolized by CYP3A
40% by other CYPs

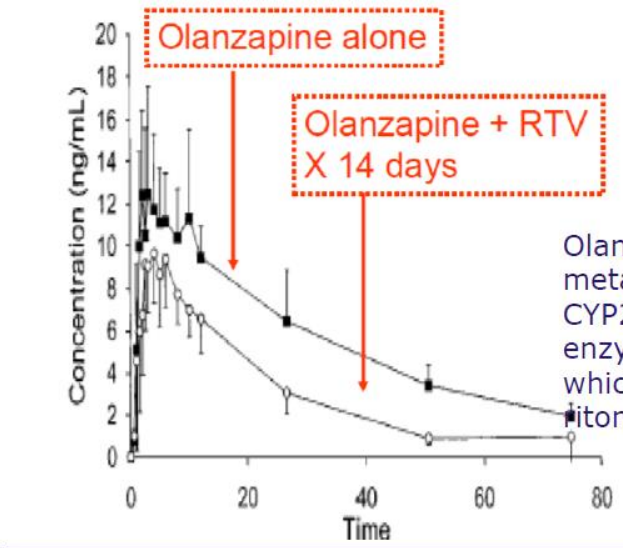


Greenblatt et al, J Acquir Immune Defic Syndr, 24:129-136 (2000)

Drug Metabolism Interactions: Induction



Drug Metabolism Interactions: Induction



Olanzapine is metabolized by CYP2D6 and UGT enzymes; Both of which are induced by ritonavir

Penzak SR et al, J Clin Psychopharm 22:366-370 (2002)

Natural Substances-Drug Interaction

	Food	Drug	What happens?
	Kale, broccoli (vitamin K)	**blood thinners** such as warfarin	Foods that are rich in vitamin K can reduce the effectiveness of blood thinners.
	Grapefruit	**statins** such as atorvastatin, lovastatin, simvastatin	Grapefruit can increase statin levels in your body, thereby increasing statin-related side effects.
	Bananas (potassium)	**ACE inhibitors** such as captopril, enalapril and lisinopril	ACE inhibitors increase potassium in your body. Too much potassium can cause an irregular heartbeat and heart palpitations.
	Walnuts, soybean flour (high fiber)	**thyroid medications** such as levothyroxine	High-fiber foods can prevent the body from absorbing thyroid medications.
	Dairy products (calcium)	**quinolone antibiotics** such as ciprofloxacin and levofloxacin	Calcium reduces the level of these antibiotics in your blood. Avoid eating dairy and calcium-fortified products alone.
	Salami, aged cheese (tyramine)	**oxazolidinone antibiotics** (such as linezolid) and **MAOI-type antidepressants** (such as phenelzine)	Eating a tyramine-rich diet while taking certain meds can cause a sudden, dangerous increase in blood pressure.

www.fda.gov/drugs

Education

2005~2010 Aug 18. Ph.D., Dept. of Life Science, GIST

2003~2005 Feb 25. M.S., Dept. of Molecular Medicine, Chonnam National University

1995~2003 Feb 25. B.S., Dept. of Food Science & Technology, Chonnam National University

Professional experience

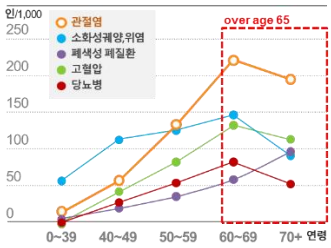
2016~ Assistant Professor, Department of pharmacology, Ajou University School of Medicine

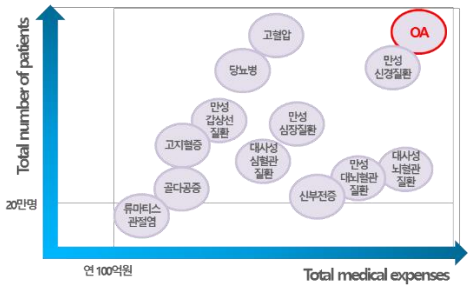
2013~2016 Researcher, Aging Intervention Research Center, KRIBB

2010~2013 Post-Doc., Dept. of Microbiology and Immunobiology, Harvard Medical School, USA (Advisor: Diane Mathis)

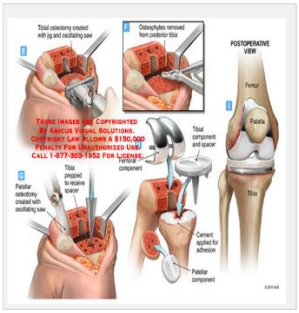
Osteoarthritis

Patients with joint disease

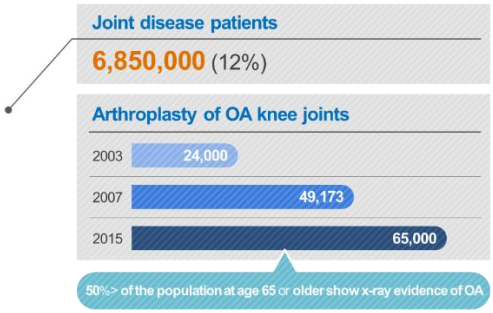




Arthroplasty

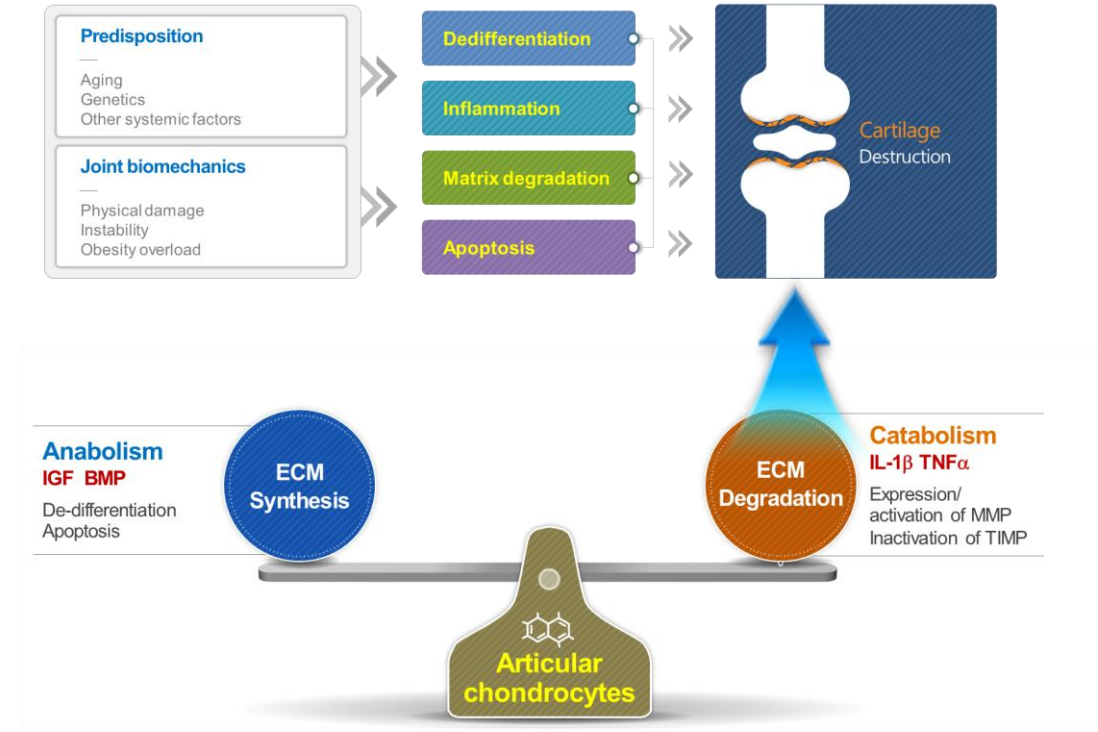


A chronic irreversible degenerative disease of articular cartilage



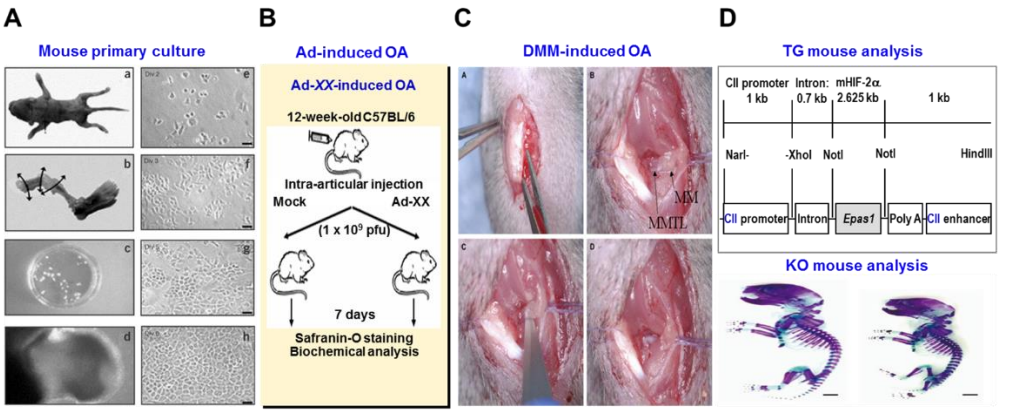
Molecular mechanism of osteoarthritis (OA)

Molecular mechanism of osteoarthritis



Human Milk Oligosaccharides (HMO)
&
Sialyllactose

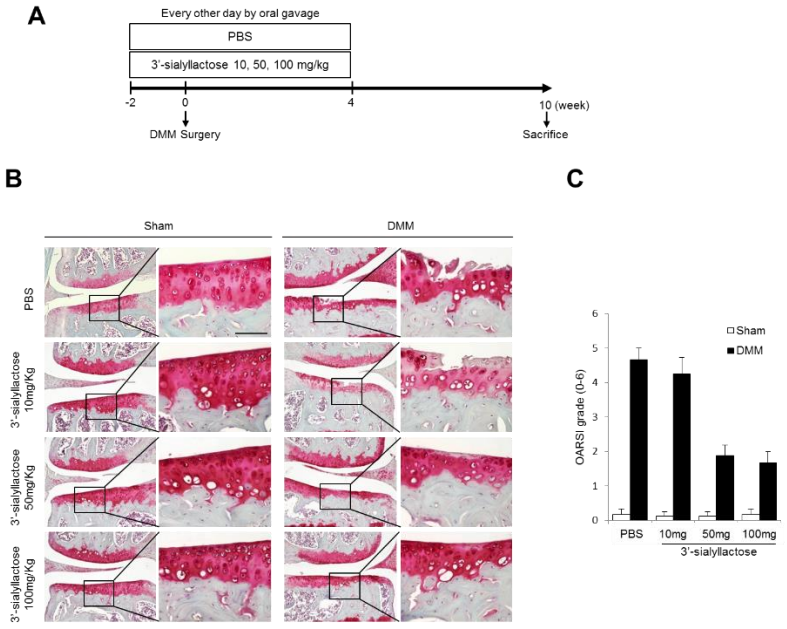
in vitro & in vivo analysis



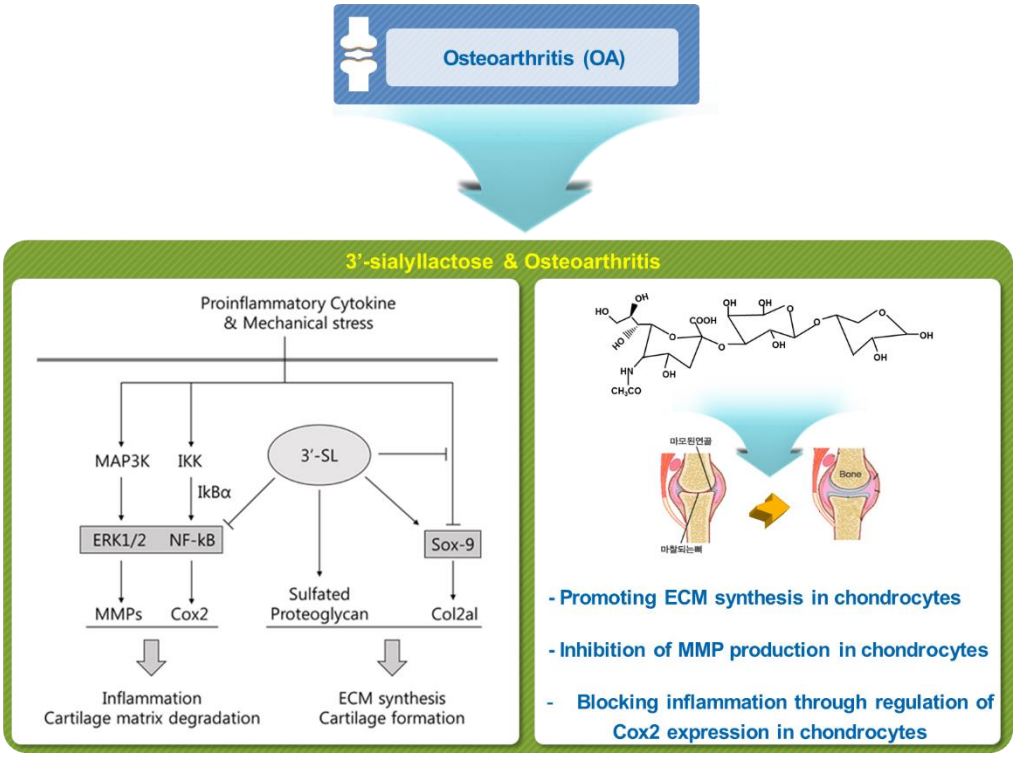
A	B	C	D
➔Gain/Loss of function - qRT-PCR - WB - Activity assay and etc.	➔IHC analysis ➔ Histology - Safranin O staining - Grade scoring & etc	➔IHC analysis ➔ Histology - Safranin O staining - Grade scoring & etc	➔IHC analysis ➔ Histology - Safranin O staining - Grade scoring & etc

The function of silayllactose in OA development

Oral administration of 3′-sialyllactose protects against cartilage destruction in OA development

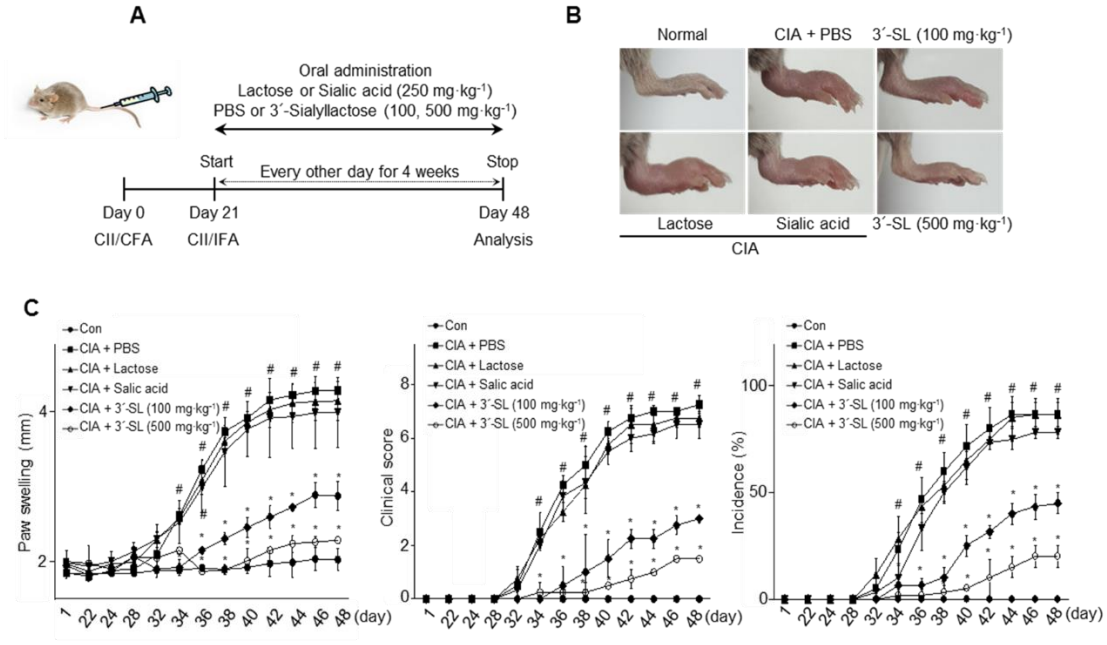


Summary of 3′-sialyllactose in OA

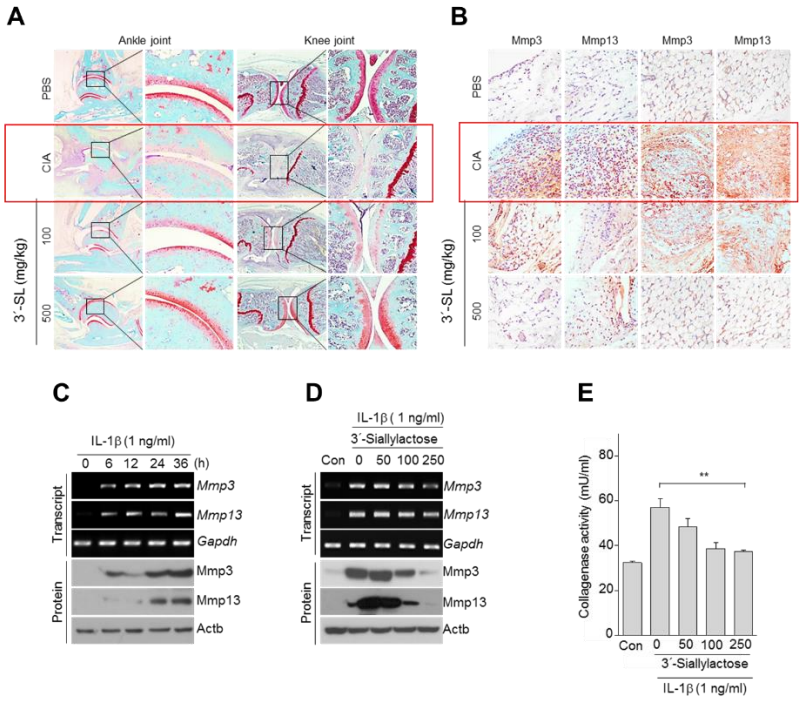


Human Milk Oligosaccharides (HMO)
&
Rheumatoid arthritis

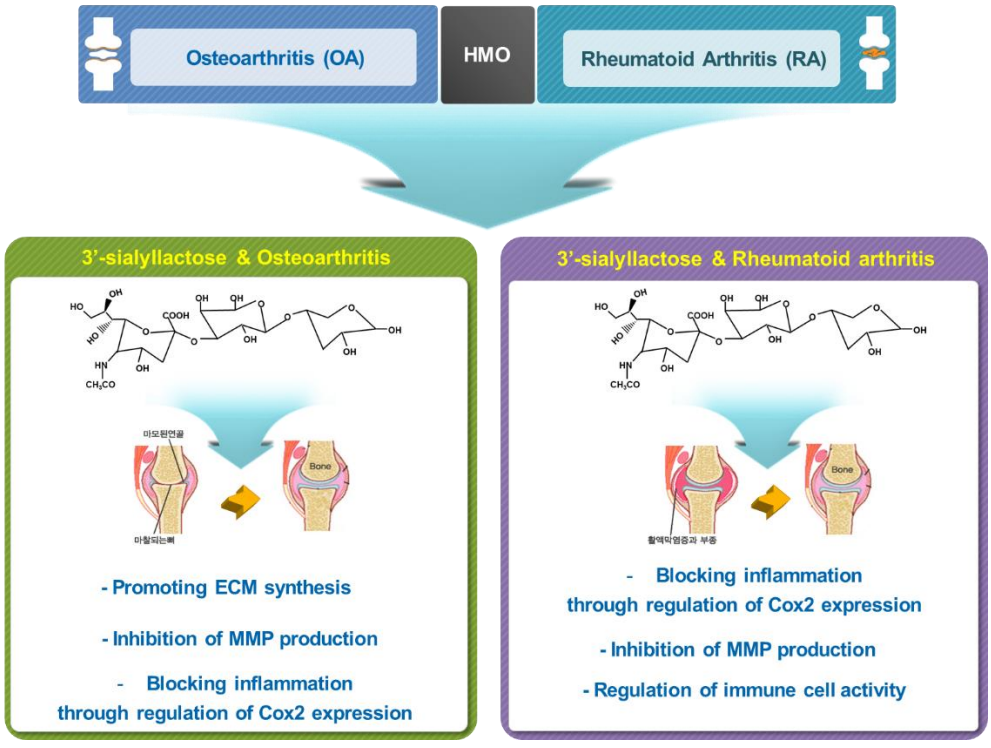
Oral administration of 3′-sialyllactose protects against RA development

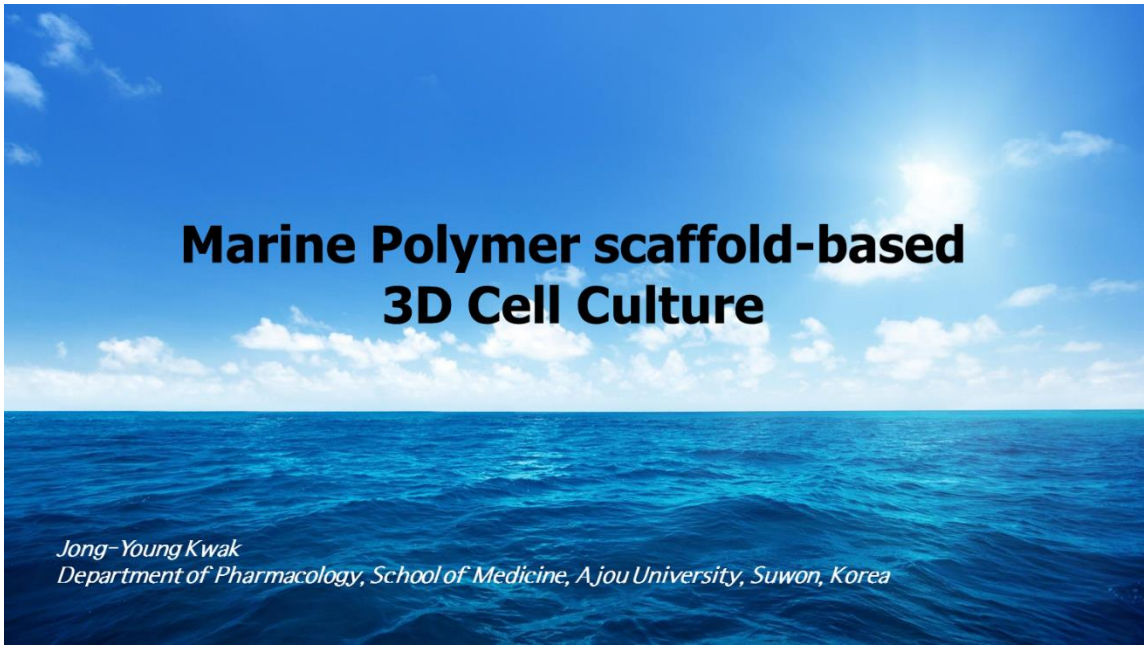


Inhibition of Mmp3 and Mmp13 by 3′-sialyllactose



Summary

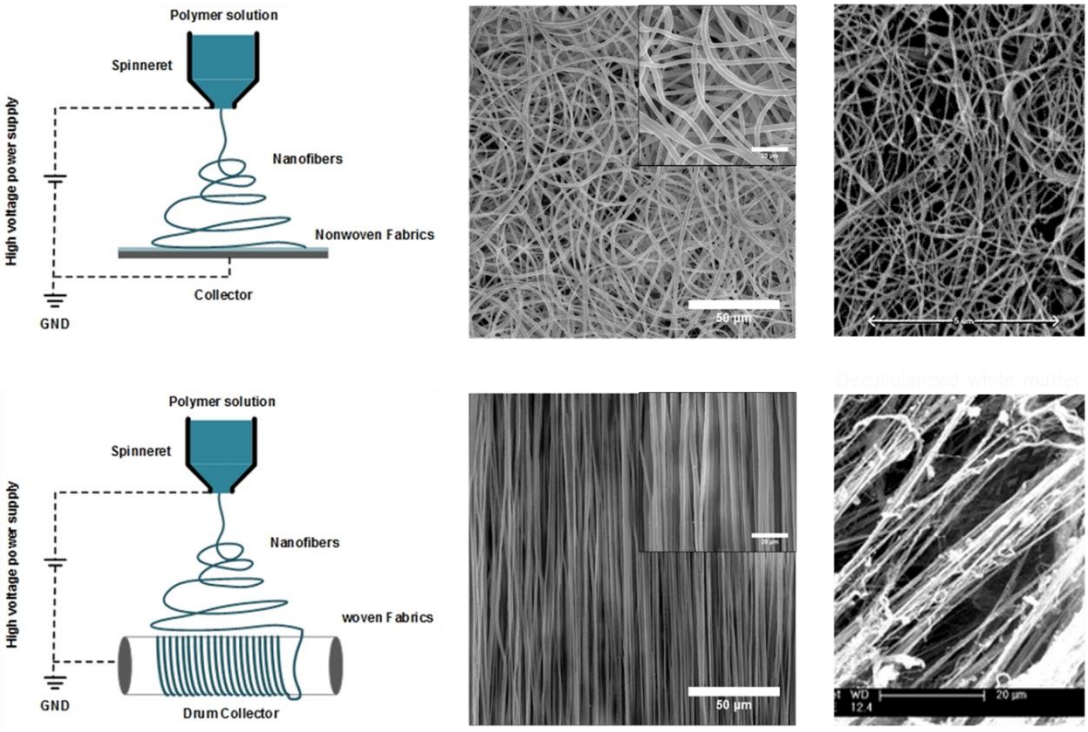




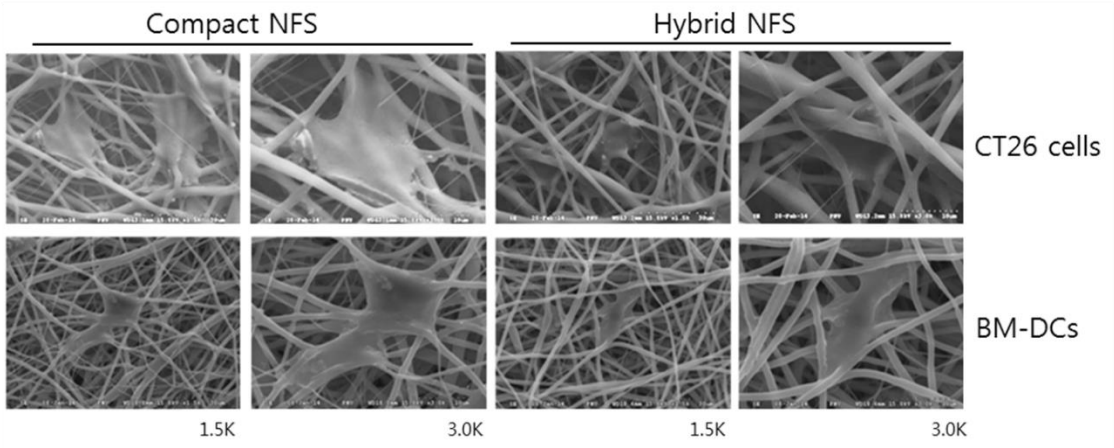
Biography

Dr. Kwak is professor at Department of Pharmacology, Ajou University School of Medicine, Korea. He is currently the Director of Immune-network Pioneer Research Center, Ajou University Medical Center. He became a vice-president of Korean Society of Biochemistry and Molecular Biology in 2015 and is a Doctor Honoris Causa in Russian Academy of Science since 2012. He completed his doctorate in Medical Biochemistry with neutrophil activation and signal transduction pathways at the Pusan National University, Korea in 1991. After his study of activation of neutrophils in Emory University as a post doctorate, he directed his research to dendritic cell analysis. Current research topic in his laboratory is immunogenic responses in 3D culture of immune cells and tissues. He is CEO of venture company, Nanofaentech Inc. in Korea.

● Fabrication by Electrospinning

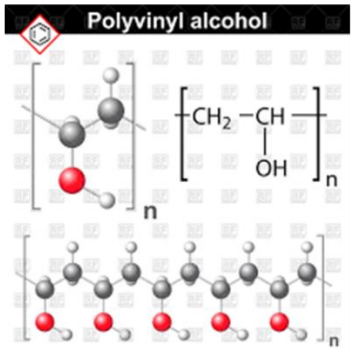


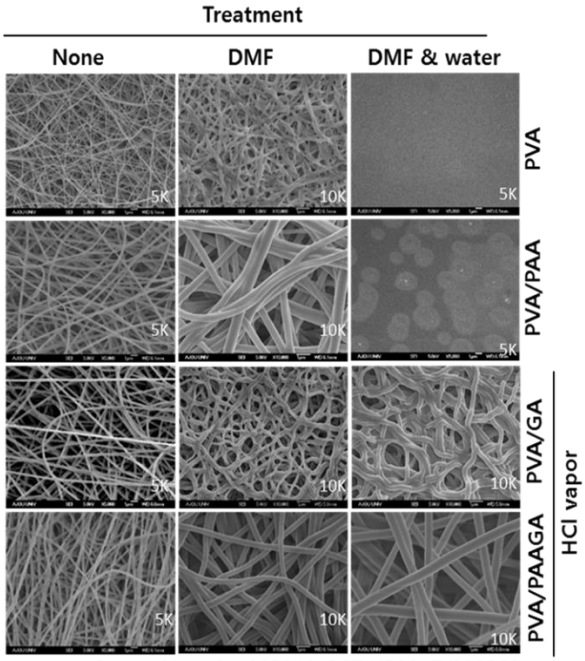
● Conventional nanofibers vs. Nano-submicron Hybrid nanofibers



● Water stable, optically transparent and cell adhesive poly(vinyl) alcohol (PVA) scaffold for cell culture

Transparent skeleton flower

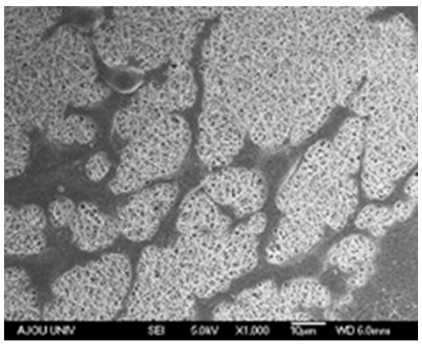




Patent No: 10-1665918, PCT/KR2017/000393

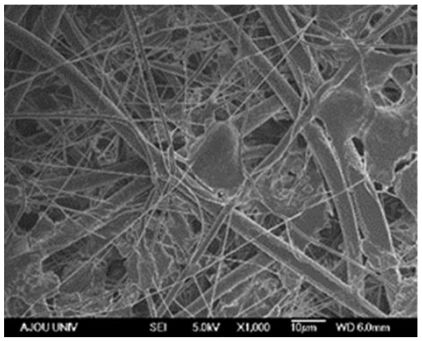
3D Epithelial Cell culture scaffold

- Electrospun PVA nanofiber
  - water stable
  - transparent
  - cell adhesive
- Single layer adhesion of epithelial cells
- 100–200 nm diameters and micropores
- 3D structural scaffold

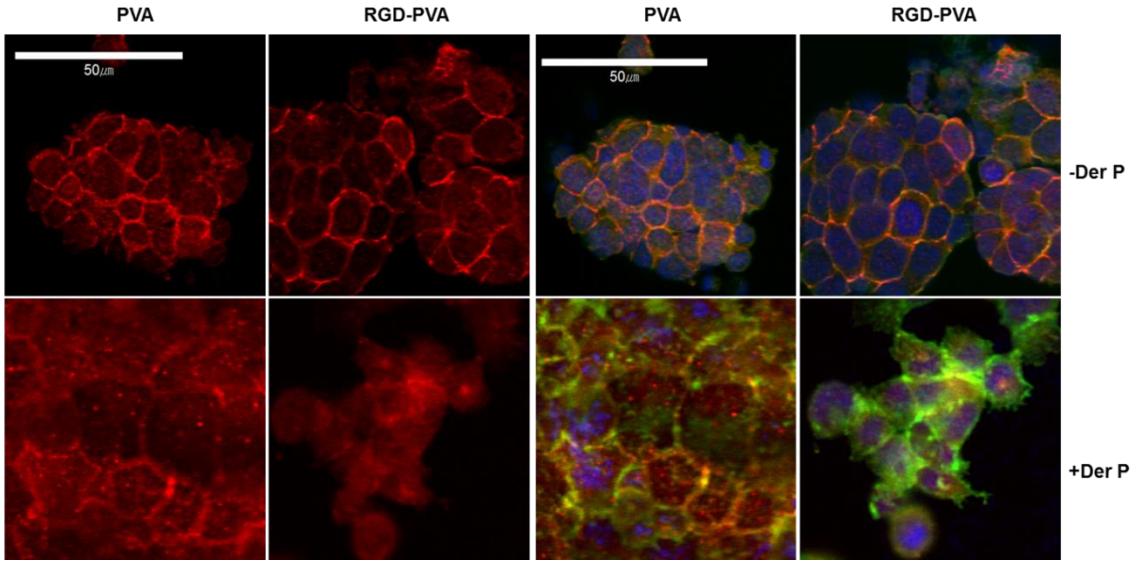


3D fibroblast culture scaffold

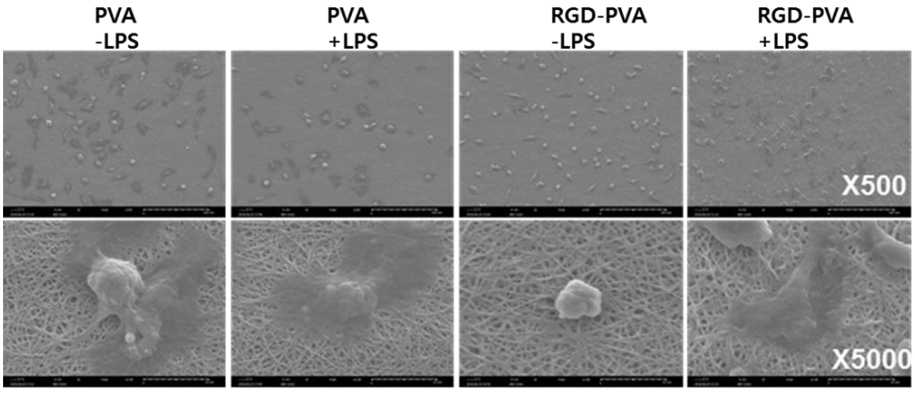
- Electrospun Polycaprolactone (PCL) nanofiber
  - Biocompatible
  - cell adhesive
  - cell infiltration
- Multiple layer adhesion of fibroblasts
- 400–1500 nm diameters & 10–50 μm micropores
- 3D structural scaffold

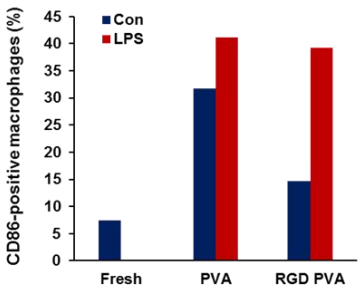


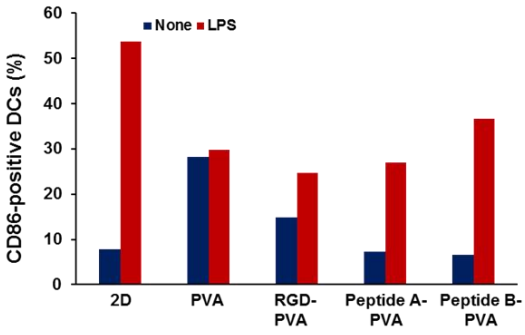
● Effects of dust mites on lung epithelial cells in 2D and 3D culture

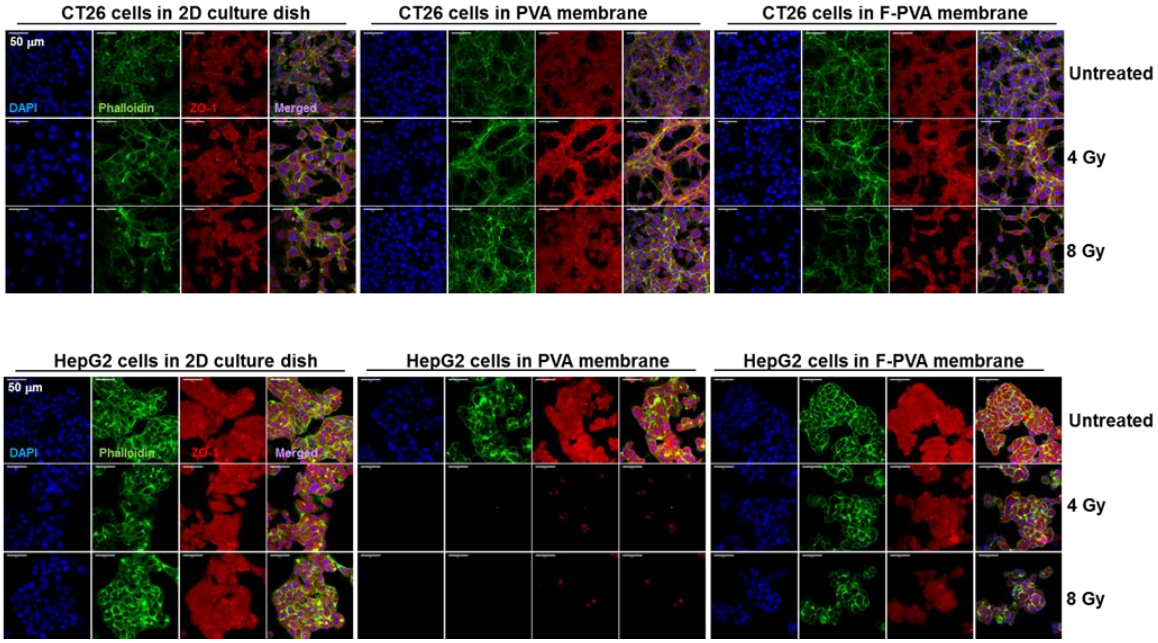


● Inactive Culture of Immune Cells on Fibronectin-PVA membrane

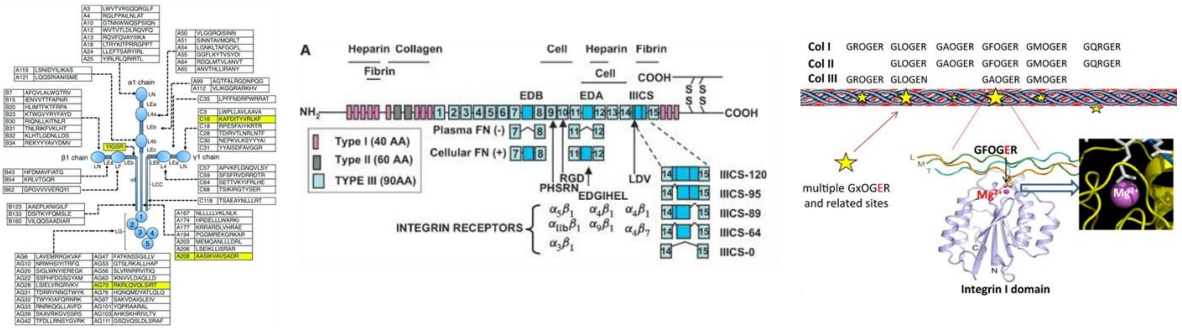




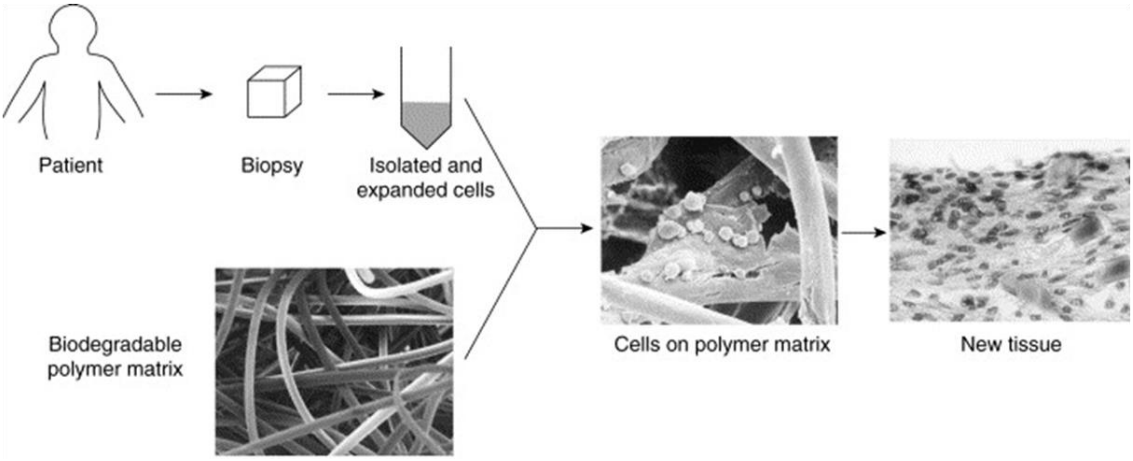




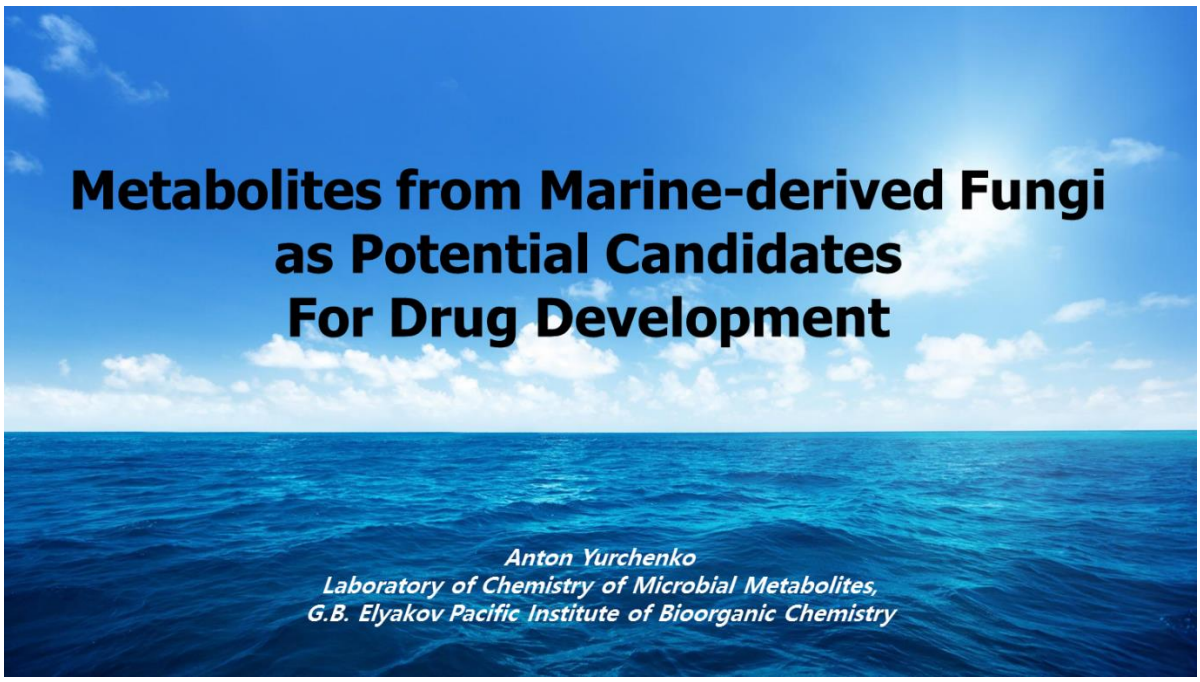
● Development of Artificial Extracellular Matrix



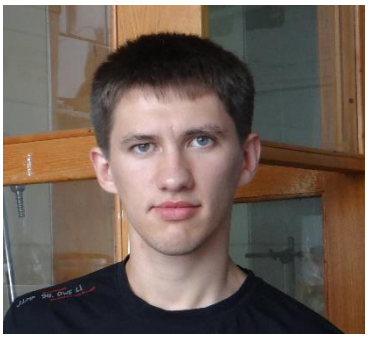
- **The tissue-engineering approach to developing organ replacements**



Presentation of PIBOC Researches



1. Researcher & Affiliation



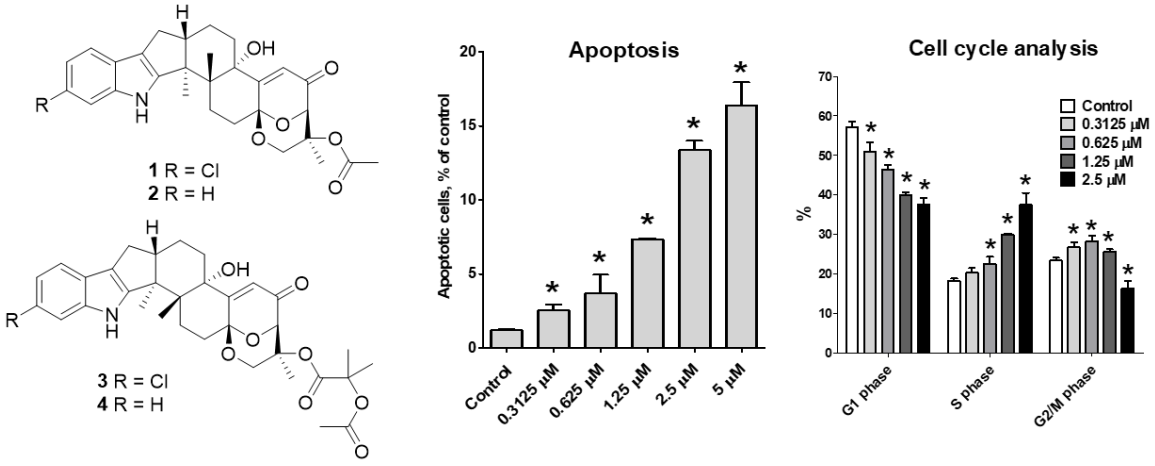
Anton Yurchenko, Ph.D,
Laboratory of chemistry of microbial metabolites,
G.B. Elyakov Pacific Institute of Bioorganic Chemistry,
Vladivostok, 690022,
Russian Federation
Tel: +7-423-231-11-68; Fax: +7-423-231-40-50; e-mail: yurchant@ya.ru

2. Research target and compounds

Our lab studies the low-molecular secondary metabolites from microfilamentous fungi isolated from various marine substrates. For stimulation of metabolites production, we use various nutrient media and mixed cultivation with other fungal strains. The isolated compounds are studied in cytotoxicity, antimicrobial, radical-scavenging and neuroprotective activity.

3. Research Background

The study of secondary metabolites of marine fungi is a relatively young but rapidly developing field of bioorganic chemistry. Starting with the discovery of cephalosporin C, isolated from the culture of *Cephalosporium* sp. in 1949, and up to 1992 only 15 metabolites from marine fungi were described. Intensive study of fungi-micromycetes as producers of biologically active compounds was started at the beginning of 2000-s. To date, more than 3,000 new metabolites from fungi isolated from marine sources have been described. The physical factors affecting marine fungi are high sodium ion content, low temperatures, oligotrophic type of food, high hydrostatic pressure are cause the ability of marine fungi to synthesize unusual in structure metabolites, which often have diverse biological activity. From marine fungi were isolated structurally unique biologically active compounds, which were not found in terrestrial fungi, despite the more than 70-year history of such studies.



4. Major Publications

Ivanets, E. V.*; **Yurchenko, A. N.*;** Smetanina, O. F.; Rasin, A. B.; Zhuravleva, O. I.; Pivkin, M. V.; Popov, R. S.; von Amsberg, G.; Afiyatullov, S. S.; Dyshlovoy, S. A., Asperindoles A–D and a p-terphenyl derivative from the ascidian-derived fungus *Aspergillus* sp. KMM

4676. *Mar. Drugs* **2018,** *16* (7). (* equally contributed)

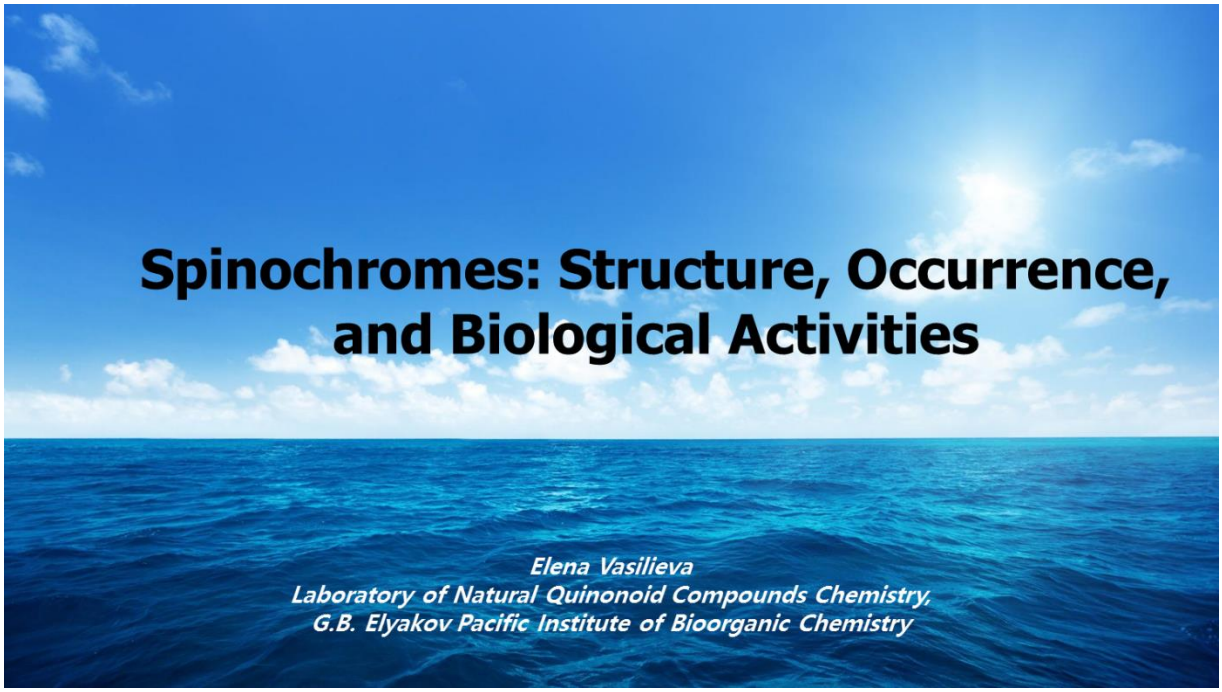
Afiyatullov, S. S.; Zhuravleva, O. I.; Antonov, A. S.; Berdyshev, D. V.; Pivkin, M. V.; Denisenko, V. A.; Popov, R. S.; Gerasimenko, A. V.; von Amsberg, G.; Dyshlovoy, S. A.; Leshchenko, E. V.; **Yurchenko, A. N.,** Prenylated indole alkaloids from co-culture of marine-derived fungi *Aspergillus sulphureus* and *Isaria felina*. *J. Antibiot.* **2018**, in press

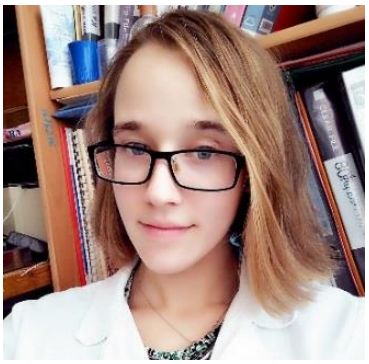
Smetanina, O. F.*; **Yurchenko, A. N.*;** Ivanets, E. V.; Kalinovsky, A. I.; Khudyakova, Y. V.; Dyshlovoy, S. A.; Von Amsberg, G.; Yurchenko, E. A.; Afiyatullov, S. S., Unique prostate cancer-toxic polyketides from marine sediment-derived fungus *Isaria felina*. *J. Antibiot.* **2017,** *70* (7), 856-858. (* equally contributed as first author)

Yurchenko, A.; Smetanina, O.; Ivanets, E.; Kalinovsky, A.; Khudyakova, Y.; Kirichuk, N.; Popov, R.; Bokemeyer, C.; von Amsberg, G.; Chingizova, E.; Afiyatullov, S.; Dyshlovoy, S., Pretrichodermamides D–F from a Marine Algicolous Fungus *Penicillium* sp. KMM 4672. *Mar. Drugs* **2016,** *14* (7), 122.

Yurchenko, A. N.; Smetanina, O. F.; Kalinovsky, A. I.; Pushilin, M. A.; Glazunov, V. P.; Khudyakova, Y. V.; Kirichuk, N. N.; Ermakova, S. P.; Dyshlovoy, S. A.; Yurchenko, E. A.; Afiyatullov, S. S., Oxirapentyns F-K from the Marine-Sediment-Derived Fungus *Isaria felina* KMM 4639. *J. Nat. Prod.* **2014,** *77* (6), 1321–1328.

Smetanina, O. F.*; **Yurchenko, A. N.***; Afiyatullov, S. S.; Kalinovsky, A. I.; Pushilin, M. A.; Khudyakova, Y. V.; Slinkina, N. N.; Ermakova, S. P.; Yurchenko, E. A., Oxirapentyns B-D produced by a marine sediment-derived fungus *Isaria felina* (DC.) Fr. *Phytochem. Lett.* **2012,** *5* (1), 165-169. (* equally contributed)





1. Researcher & Affiliation

Elena A. Vasileva, Junior Researcher
Laboratory of Natural Quinonoid Compounds Chemistry,
G.B. Elyakov Pacific Institute of Bioorganic Chemistry,
Far Eastern Branch of the Russian Academy of Sciences,
Vladivostok, 690022, Russia
Tel. +7 9025272055; Fax: +7 (4232) 314050; e-mail: vasilieva_el_an@mail.ru

2. Proposal

Spinochromes: structures, occurrence, and biological activities

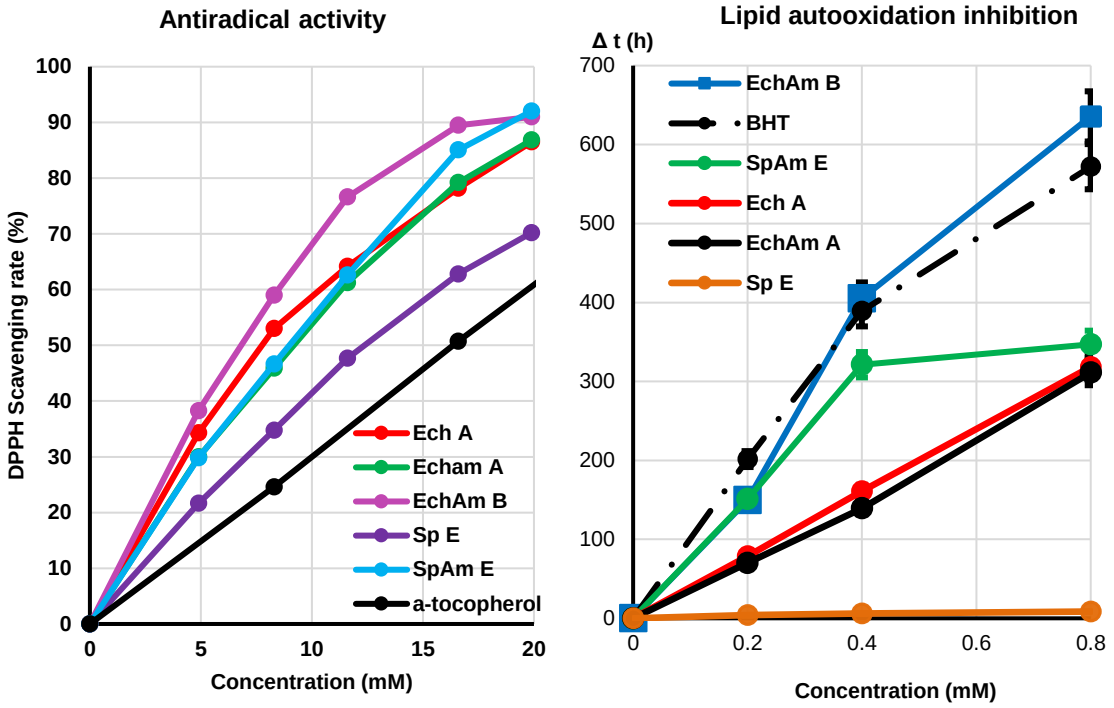
3. Research background

Oxidative stress has been implicated in a wide variety of degenerative processes, diseases and syndromes, due to a weakening of the antioxidant defense or excess production of radicals. The

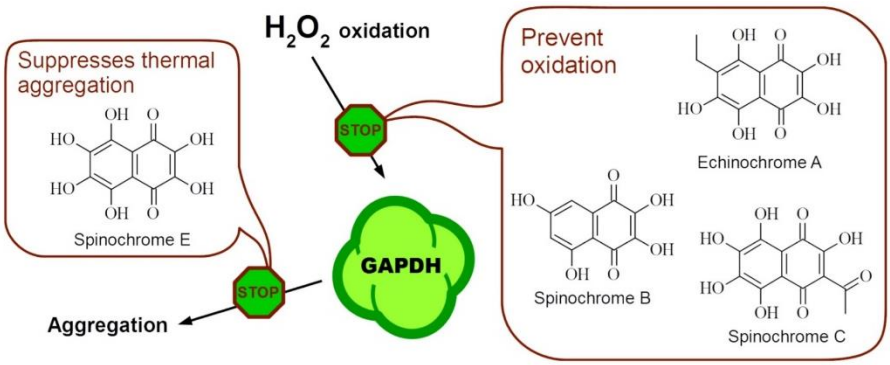
human body has several mechanisms to counteract oxidative stress by producing antioxidants, or they can be externally supplied through foods and supplements. Therefore, one of the important problems of modern biomedicine is the study of possibilities of regulation of redox processes in the body. One of the ways of its solution could be the use of exogenous natural antioxidants that can have a beneficial effect on the organism under conditions of oxidative stress.

Polyhydroxylated derivatives of either juglone (5-hydroxy-1,4-naphthoquinone) or naphthazarin (5,8-dihydroxy-1,4-naphthoquinone) are called spinochromes and are specific secondary metabolites of sea urchins. The most common well studied in the terms of physiological activities pigment of sea urchins echinochrome A exhibits antioxidant, cardioprotective, anti-inflammatory, anti-diabetic, anti-allergic, gastroprotective, and mitochondria-protective activities. Since echinochrome A exhibits so many different effects, it is interesting to study the biological activity of other spinochromes.

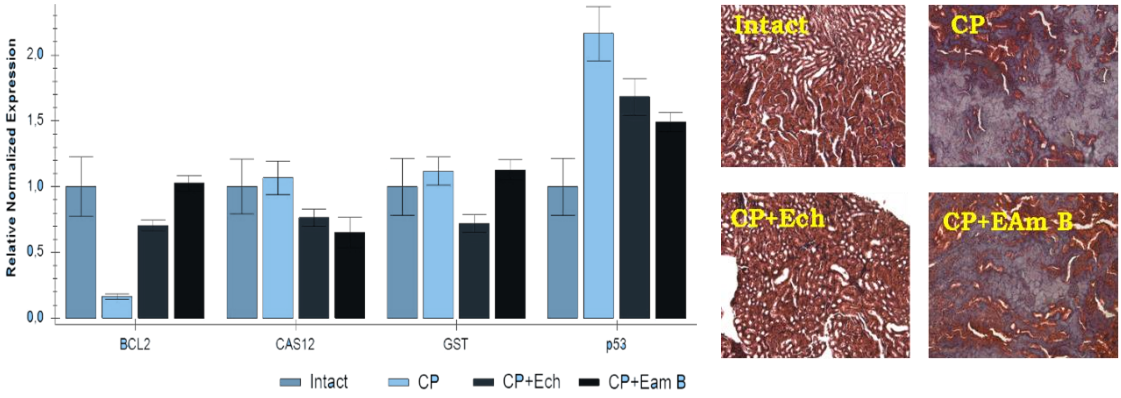
We performed comparative investigations of antioxidant activity of spinochromes on different *in vitro* and *in vivo* models.



Antioxidant and antiaggregant activity of spinochromes towards GAPDH:



Nephroprotective effects of spinochromes on the model of cisplatin-induced nephrotoxicity:

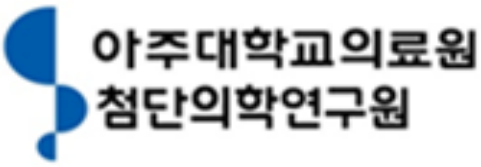


4. Major publications

1. Mishchenko N. P., Vasileva E. A., Fedoreyev S. A. // Mirabiquinone, a new unsymmetrical binaphthoquinone from the sea urchin *Scaphechinus mirabilis*. Tetrahedron Letters, 2014, Vol. 55, P. 5967-5969.
2. Vasileva E. A., Mishchenko N. P., Zadorozhny P. A., Fedoreyev S. A. // New Aminonaphthoquinone from the Sea Urchins *Strongylocentrotus pallidus* and *Mesocentrotus nudus*. Natural Product Communications, 2016, Vol. 11, No. 6, P. 821-824.
3. Vasileva E. A., Mishchenko N. P., Fedoreyev S. A. // Diversity of polyhydroxynaphthoquinone pigments in North Pacific sea urchins. Chemistry&Biodiversity, 2017, Vol. 14, N 9, P. e1700182[1-9].
4. Muronetz V. I., Asryants R. A., Semenyuk P. I., Mishchenko N. P., Vasilieva E. A., Fedoreyev S. A., Schmalhausen E. V. // Natural quinones: antioxidant and antiaggregant action towards glyceraldehyde-3-phosphate dehydrogenase. Current Organic Chemistry, 2017, Vol. 21, N 20, P. 2125-2133.
5. Hou Y., Vasileva E. A., Mishchenko N. P., Carne A., McConnell M., Bekhit A. E. A. // Extraction, structural characterization and stability of polyhydroxylated

naphthoquinones from shell and spine of New Zealand sea urchin (*Evechinus chloroticus*). Food Chemistry, 2019, 272, p. 379–387.

6. Hou Y., Vasileva E. A., Carne A., McConnell M., Bekhit A. E. A., Mishchenko N. P. // Naphthoquinones of the spinochrome class: occurrence, isolation, biosynthesis and biomedical applications. RSC Advances, 2018, 8, p. 32637-32650.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KOREA RESEARCH-DRIVEN HOSPITALS


아주대학교병원
Ajou University Hospital


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Ministry of Health
and Welfare