KORUS Symposium 2017

MEOW

Marine
Effective compounds
Open
Wellness

June 28 (Wed) - 29 (Thu), 2017
Busan, Korea

June 28 (Wed)

Symposium
- Busan National Science Museum

June 29 (Thu)

Open Discussion
- Inje University

Secretariat | The PLAN B Co.,Ltd.

TEL. 82-51-742-8407 FAX. 82-51-746-8407
E-MAIL. info.theplanb@gmail.com

Biomedical Sciences Laboratory, Pukyong National University, Brain Korea 21 Plus, Gimhae-si, Busan Society for Stem Cell Research, Busan Tourism Organization, Cardiovascular and Metabolic Disease Center, Inje University, Ministry of Education, Nano Bio Medicine Laboratory, Pukyong National University, National Research Foundation of Korea, PIBOC(Pacific Institute of Bioorganic Chemistry), The PLAN B Co.,Ltd.

CONTENTS

KORUS Symposium 2017

June 28-29, 2017, Busan, Korea

Invitation

Greetings!

Dear researchers interested in discovering new biomaterials at Korea and worldwide.

Sea is the origin of life, and marine Bio-resource is the treasury of new drug development. For the development of marine Bio-resource, the researchers of Korea and PIBOC in and Russia have been active in research exchanges including 6 times of KORUS symposiums over the last 10 years and have achieved academic and industrial economic performance. 2017 KORUS Marine Effective compounds Open Wellness (KORUS-MEOW) symposium will be held in Busan, an international maritime city.

2017 KORUS is a unique symposium for discovering the novel biomaterials to develop new drugs. For the development of the fourth industrial revolutionary business, there will be a place to provide alternatives and share innovation to transform our difficulties into industrial success.

The symposium will be attended by researchers from industry and academia, who selected domestic and overseas researchers, and selected different themes for the development of new therapeutic agents based on marine bio resources. Through this KORUS symposium, we will introduce the therapeutic effects of effective substances discovered to date and expand our international research and development capacity through sharing information on new substances.

In June 2017, we look into the role of marine biotechnology in addressing the global problems facing mankind and hope that your expertise and wisdom will be utilized.

We look forward to working with all researchers interested in discovering novel marine bio-resource for the development of therapeutic drugs at the 2017 KORUS symposium in Busan.

2017.06.

Co-chair of KORUS 2017 symposium

Korea Research Institute of bioscience and biotechnology ***Yong-Kyung Choe***

Cardiovascular and Metabolic Disease Center, Inje University ***Jin Han***

Invitation

국내외 해양 바이오 신 물질 발굴에 관심을 두고 있는 연구자 여러분, 안녕하십니까?

바다는 생명의 기원이며, 해양 바이오 자원은 신약개발의 보고입니다. 해양 바이오 자원의 개발을 위하여 대한민국과 러시아 PIBOC의 연구자들은 지난 10년간 6번의 KORUS 심포지엄을 포함한 활발한 연구교류를 진행해왔으며, 학술적 산업 경제적 성과를 이룩했습니다. 우수한 성과를 소개하고 확산하고자 2017 KORUS - Marine Effective compounds Open Wellness (KORUS-MEOW) 심포지엄을 국제 해양 도시 부산에서 개최하게 되었습니다.

2017 KORUS 심포지엄은 부산 유일 해양 바이오 신 물질 발굴 심포지엄입니다. 4차 산업혁명적 사업의 전개를 위해, 우리의 어려움을 산업적 성공으로 전환시킬 수 있도록 대안을 제공하고 혁신을 공유하는 자리가 마련될 것입니다.

본 심포지엄은 국내외 산학연 우수연구자들을 모시고, 해양 바이오 자원 기반 신규 치료제 개발에 대한 차별화된 주제를 선정하였습니다. 본 심포지엄을 통해 현재까지 발굴된 유효물질의 치료 효과를 소개하고 신규물질들에 대한 정보공유를 통한 국제연구 및 개발 역량을 확장하고자 합니다.

2017년 6월, 인류가 직면한 전지구적 문제를 해결하기 위한 해양생명공학의 역할을 고찰하며 전문가 여러분들의 경험과 지혜가 활용되기를 바랍니다.

부산에서 열리는 2017 KORUS 심포지엄에서 치료제 개발을 위한 해양 바이오 신 물질 발굴에 관심있는 모든 연구자들과 함께하기를 기대하겠습니다.

2017.06.

2017 KORUS 심포지엄 공동조직위원장

한국생명공학연구원 **최 용경**

인제대학교 심혈관 및 대사질환센터 **한 진**

History

History of Korea-Russia Collaboration	
2004. 5.	Joint Meeting between PIBOC and Korean team, Korea
2005. 7.	Joint Symposium, Busan, Korea
2005. 9.	MOU between PIBOC and Korean team
2007. 8.	Joint Symposium, Vladivostok, Russia
2008. 9.	Far-East Symposium of PIBOC, Vladivostok, Russia
2009. 5.	Joint Symposium, Keo-Je, Korea
2013. 11.	KORUS 2013 symposium, Busan, Korea
2014. 6.	MOU between PIBOC and CMDC and IPRC
2014. 11.	KORUS 2014 symposium, Busan, Korea
2016. 8.	KORUS 2016 symposium, Vladivostok, Russia
2017. 6.	KORUS 2017 symposium, Busan, Korea

2013 KORUS, Korea

2014 MOU, Russia

2014 KORUS, Korea

2016 KORUS, Russia

Organization

Organizing Committee

Yong-Kyung Choe (KRIBB, Daejeon, Korea)
Jin Han (Inje University, Busan, Korea)
Valentin A. Stonik (PIBOC, Vladivostok, Russia)
Jong-Young Kwak (Ajou University, Suwon, Korea)
Nari Kim (Inje University, Busan, Korea)
Dong Hyun Kim (Inje University, Busan, Korea)
Hyoung Kyu Kim (Inje University, Busan, Korea)
Jae Ho Kim (Pusan National University, Busan, Korea)
Sik Yoon (Pusan National University, Busan, Korea)
Jee-Yeong Jeong (Kosin University, Busan, Korea)
Jin Woong Chung (Dong-A University, Busan, Korea)
Ji Hoon Lee (The Plan B Co., Ltd., Busan, Korea)

Scientific Program Committee

Jong-Young Kwak (Ajou University, Suwon, Korea)
Nari Kim (Inje University, Busan, Korea)
Hyoung Kyu Kim (Inje University, Busan, Korea)
Valentin A. Stonik (PIBOC, Vladivostok, Russia)
Nikolay E. Nifantiev (Russian Academy of Sciences, Moscow, Russia)

Organized by

- Nano Bio Medicine Laboratory, Pukyong National University, Busan, Korea
- Biomedical Sciences Laboratory, Pukyong National University, Busan, Korea
- Busan Society for Stem Cell Research, Korea
- Gimhae-si

Organization

Advisory Board

Byoung Doo Rhee (Inje University, Busan, Korea)
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Yoon Chung (Korea Science Academy of KAIST, Busan, Korea)
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Nam Gyu Park (Pukyong National University, Busan, Korea)
Minseok Kwak (Pukyong National University, Busan, Korea)
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Hoi Young Lee (Konyang University, Daejeon, Korea)
Kang Dae Lee (Kosin University Gospel Hospital, Busan, Korea)
Byungjoo Lee (Pusan National University, Busan, Korea)

International Advisory Board

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Motohiro Nishida (Okazaki Institute for Integrative Bioscience, Okazaki, Japan)
Sookja Kim Chung (The University of Hong Kong, Hong Kong, China)
Valentin A. Stonik (PIBOC, Vladivostok, Russia)
Nikolay E. Nifantiev (Russian Academy of Sciences, Moscow, Russia)
Tatyana N. Makarieva (PIBOC, Vladivostok, Russia)
Svetlana P. Ermakova (PIBOC, Vladivostok, Russia)
Mikhael V. Pivkin (PIBOC, Vladivostok, Russia)
Natalia M. Shepetova (PIBOC, Vladivostok, Russia)
Oleg Chernikov (PIBOC, Vladivostok, Russia)

Special Lecture

10:20-10:40
From Neopetroside to New So-called Hidden Vitamin B3

Valentin A. Stonik, Ph.D., DSc.
Director, Head of the Laboratory of Marine Natural Products Chemistry, PIBOC

Session 1

10:40-10:50
A Discovery of New Natural Products as Potential Medicines from Marine Organisms

Tatyana N. Makarieva, Ph.D., DSc.
Major Researcher, Laboratory of the Marine Natural Products Chemistry, PIBOC

10:50-11:10
Steroidogenic Acute Regulatory Protein (StAR)-related Lipid Transfer (START) Domain-Containing Protein 13 (STARD13), Rho GTPase-Activating Protein: Mutant Mice as a Model for Drug Discovery?

Sookja K. Chung, Ph.D.
Professor, Department of Anatomy, The University of Hong Kong

Session 2

13:00-13:10
Marine Derived Fungi of the Northeastern Pacific. Taxonomy, Ecology and Metabolites

Mikhael V. Pivkin, Ph.D., DSc.
Senior Researcher, Laboratory of Microbiology, PIBOC

13:10-13:30
Semaphorin3E is a Novel Therapeutic Target for Unhealthy Obesity and Diabetes

Ippei Shimizu, M.D., Ph.D.
Associate Professor, Department of Cardiovascular Biology and Medicine, Niigata University Graduate School of Medical and Dental Sciences

Session 3

14:30-14:40

Brown Algae as a Source of Biologically Active Polysaccharides

Svetlana P. Ermakova, Ph.D., DSc.

Head of the Laboratory of Enzyme Chemistry, PIBOC

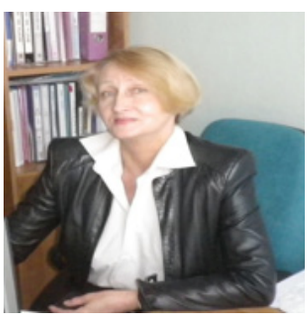
14:40-15:00

Metabolic Detoxification of Environmental Electrophile by Reactive Cysteine Persulfides

Motohiro Nishida, Ph.D.

Professor, Division of Cardiocirculatory Signaling, Okazaki Institute for Integrative Bioscience, National Institutes of Natural Sciences

Session 4



16:00-16:10

30 years of International Collaboration: the people and events

Natalia M. Shepetova

Assistant Director for Foreign Relations, PIBOC

Session 5

17:30-17:40

Gal/GalNAc-specific Lectin from the Mussel Crenomytilus grayanus Causes Tumor Cells Death and modulates immune response

Oleg Chernikov, Ph.D.

Head of the Laboratory of Chemistry of Noninfectious Immunity, PIBOC

17:40-18:00

What New Glycochemical Methods Can Contribute to Glycobiology Studies?

Nikolay E. Nifantiev, Ph.D., DSc.

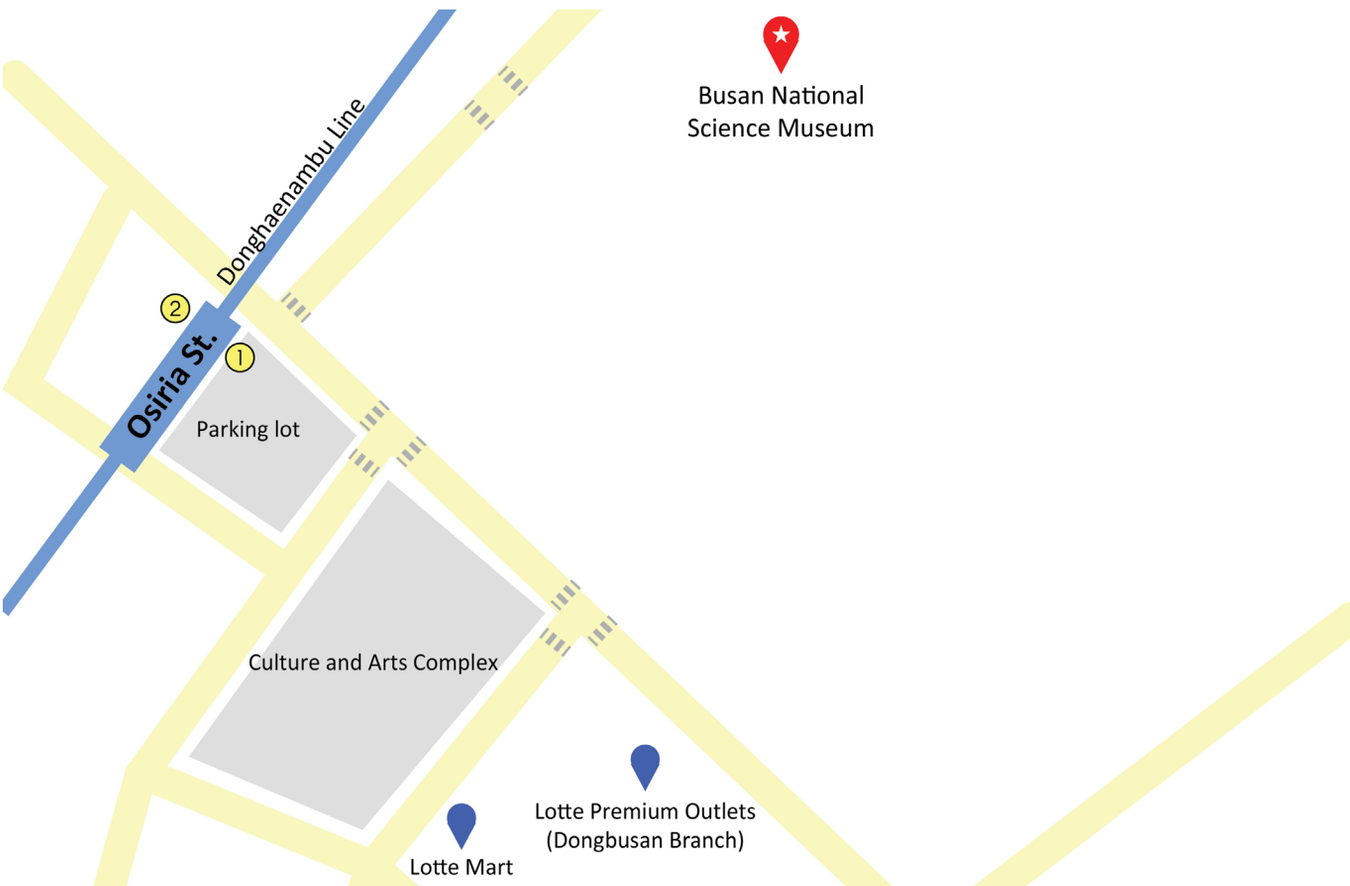
Head of the Laboratory of Glycoconjugate Chemistry, Russian Academy of Sciences

Registration Schdule

Pre-Registration: May 1 (Mon) – June 16 (Fri)

Abstract Submission: May 1 (Mon) – June 9 (Fri)

Conference Hall Information



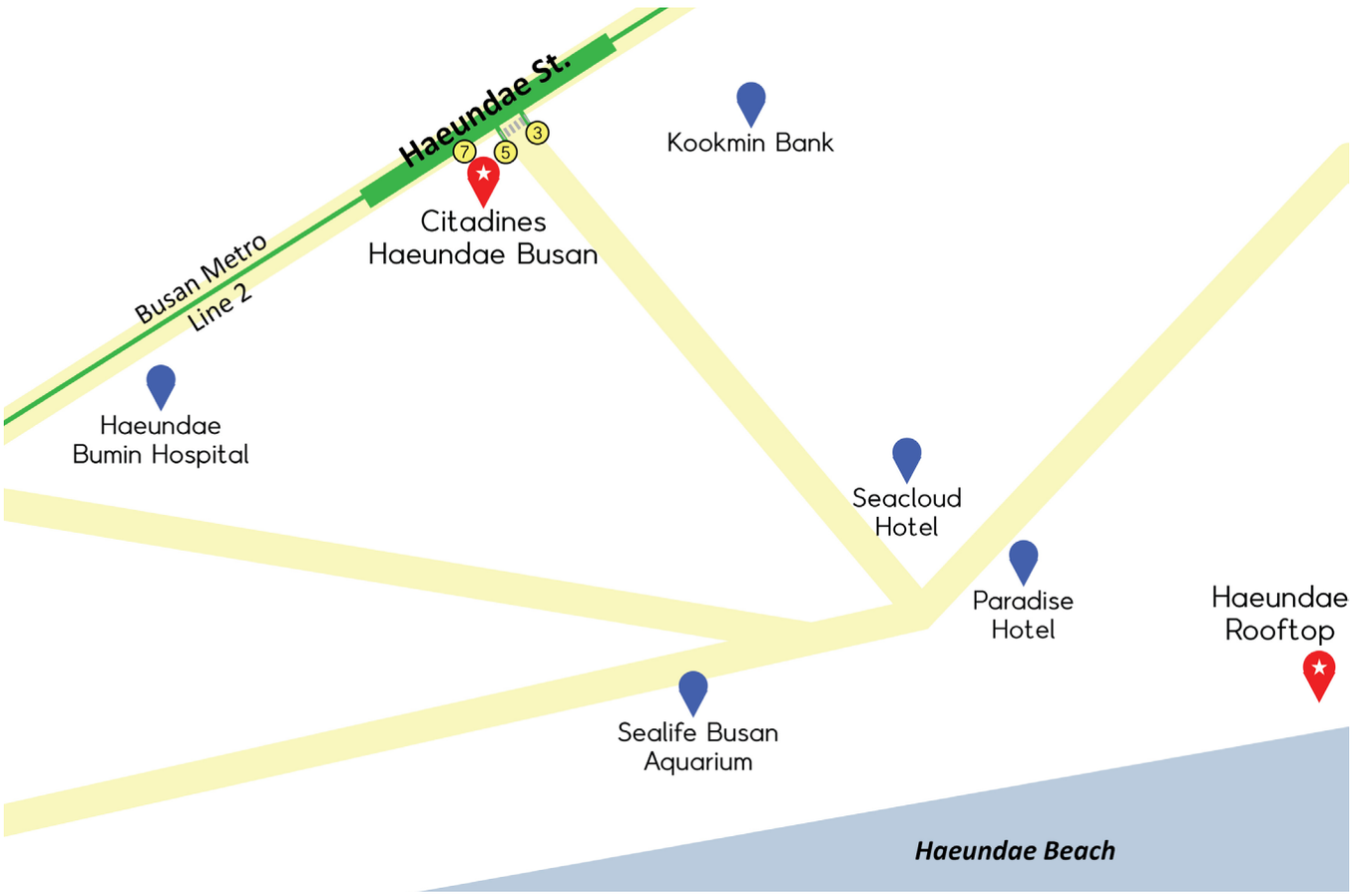
Date: June 28, 2017 (Wed) 9:00 ~ 18:40

Venue: Busan National Science Museum 1F Conference room

Address: 59, Dongbusangwangwang 6-ro, Seoksan-ri, Gijang-eup, Gijang-gun, Busan, Korea

Tel: +82-51-750-2300

Transportation
1. Bus 185, 100, 38, 39, 40, 63, 139, 182, 200
2. Busan Metro Line2 > Jangsan St. > Bus 185
3. Donghaenambu Line > Osiria St. > Bus 185



Accommodation

Venue: Citadines Haeundae Busan

Address: 620, Haeun-daero, Haeundae-gu, Busan, Korea

Tel: +82-51-662-8888

Transportation: Busan Metro Line2 > Haeundae St. > 1 min on foot

Banquet Dinner

Venue: Haeundae Rooftop

Address: 28, Dalmaji-gil 62beon-gil, Haeundae-gu, Busan, Korea

Transportarion Plan

Departure Time	Route
09:00	Citadines Haeundae Busan > Osiria St. (Donghaenambu line)
09:30	Osiria St. > Busan National Science Museum
19:00	Busan National Science Museum > Haeundae Rooftop
22:00	Haeundae Rooftop > Citadines Haeundae Busan

Secretariat

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Schedule - Symposium

- **Date: June 28 (Wed)**
- **Venue: Busan National Science Museum**
- **Symposium Moderator: Nari Kim (Inje University)**

9:00 - 10:00	**Registration**
10:00 - 10:20	**Opening Remark** Valentin A. Stonik, PIBOC, Russia Yong-Kyung Choe, KRIBB, Korea **Welcome Address** In June Cha, Inje University, Korea **Congratulatory Remarks** Sang Hun Oh, Busan Baik Hospital, Korea Chul-Gu Min, BISTEP, Korea
	Special Lecture
10:20 - 10:40	**From Neopetroside to New So-called Hidden Vitamin B3** Valentin A. Stonik (PIBOC, Russia)
	Session 1 From marine to Idea Chairs: Nam Gyu Park, Pukyong National University, Korea Sookja K. Chung, The University of Hong Kong, China
10:40 - 10:50	**A Discovery of New Natural Products as Potential Medicines from Marine Organisms** Tatyana N. Makarieva (PIBOC, Russia)
10:50 - 11:10	**Steroidogenic Acute Regulatory Protein (StAR)-related Lipid Transfer (START) Domain-Containing Protein 13 (STARD13), Rho GTPase-Activating Protein: Mutant Mice as a Model for Drug Discovery?** Sookja K. Chung (The University of Hong Kong, China)
11:10 - 11:20	**Comparison of Proteomic Profiling and Contractility of the Left and Right Ventricles in Rat Heart** Nari Kim (Inje University, Korea)
11:20 - 11:30	**Echinochrome A Improves Exercise Capacity During Endurance Exercise in Rats** Dae Yun Seo (Inje University, Korea)
11:30 - 11:40	**Identification of Dedifferentiation Factors Through the Proteomic Studies of the Reptile Tissue Regeneration Mechanisms** Jin Woong Chung (Dong-A University, Korea)
11:40 - 12:10	**Discussion & Poster Session 1**

12:10 - 13:00	**Lunch**
	Session 2 From marine to Invention Chairs: Valentin A. Stonik, PIBOC, Russia Hoi Young Lee, Konyang University, Korea
13:00 - 13:10	**Marine Derived Fungi of the Northeastern Pacific. Taxonomy, Ecology and Metabolites** Mikhael V. Pivkin (PIBOC, Russia)
13:10 - 13:30	**Semaphorin3E is a Novel Therapeutic Target for Unhealthy Obesity and Diabetes** Ippei Shimizu (Niigata University Graduate School of Medical and Dental Sciences, Japan)
13:30 - 13:40	**Neopetroside A, a Novel Pyridine Nucleoside, Protects Heart Against Ischemia/ Reperfusion-injury** Hyoung Kyu Kim (Inje University, Korea)
13:40 - 13:50	**The Anti-Oxidative, Anti-Inflammatory, and Protective Effects of Fish Scale Collagen Peptides on Human Keratinocytes** Sik Yoon (Pusan National University, Korea)
13:50 - 14:00	**Thrombolytic Fucoidan Activates Plasma Tissue-type Plasminogen Activator by Inhibiting tPA-PAI-1 Complexation: molecular mechanism of fucoidan-mediated thrombolysis** Jong-Ki Kim (Catholic University of Daegu)
14:00 - 14:30	**Discussion & Poster Session 2**
	Session 3 Novel Drug Development: targets and applications Chairs: Nikolay E. Nifantiev, Russian Academy of Sciences, Russia Dong Hyun Kim, Inje University, Korea
14:30 - 14:40	**Brown Algae as a Source of Biologically Active Polysaccharides** Svetlana P. Ermakova (PIBOC, Russia)
14:40 - 15:00	**Metabolic Detoxification of Environmental Electrophile by Reactive Cysteine Persulfides** Motohiro Nishida (Okazaki Institute for Integrative Bioscience, Japan)
15:00 - 15:10	**Polysiphonia Japonica Promotes Pancreatic β-cell Regeneration** Seon-Heui Cha (Gachon University, Korea)
15:10 - 15:20	**Improvement Characteristics of Bio-active Materials Coated Fabric on Rat Muscular Mitochondria** Jae Hong Ko (Chung-Ang University, Korea)
15:20 - 15:30	**Prostanoid as a Therapeutic Target for Atherosclerosis** Sun Sik Bae (Pusan National University, Korea)

15:30 - 16:00	**Discussion & Poster Session 3**
	Session 4 Past, Present and Future collaboration I Chairs: Sang Hong Baek, The Catholic University of Korea Jong-Young Kwak, Ajou University, Korea
16:00 - 16:10	**30 years of International Collaboration: the people and events** Natalia M. Shepetova (PIBOC, Russia)
16:10 - 16:30	**Development of Immune-modulating Natural Compounds by Korean and Russian Groups** Jong-Young Kwak (Ajou University, Korea)
16:30 - 16:40	**Necrotic Inflammation: A Novel Necrosis Inhibitor NecroX-7 with Therapeutic Potential for Necrosis-Associated & Inflammatory Diseases** Soon Ha Kim (LG Life Sciences Ltd., Korea)
16:40 - 16:50	**Stem cells for Ischemic Tissue Regeneration** Jae Ho Kim (Pusan National University, Korea)
16:50 - 17:00	**Effects of Exercise on Cardiac Contractility and Ca^{2+}-handling** Jae Boum Youm (Inje University, Korea)
17:00 - 17:30	**Discussion & Poster Session 4**
	Session 5 Past, Present and Future collaboration II Chairs: Hyun-Young Park, Korea National Institute of Health, Korea Jung Hwan Oh, Pukyong National University, Korea
17:30 - 17:40	**Gal/GalNAc-specific Lectin from the Mussel Crenomytilus grayanus Causes Tumor Cells Death and modulates immune response** Oleg Chernikov (PIBOC, Russia)
17:40 - 18:00	**What New Glycochemical Methods Can Contribute to Glycobiology Studies?** Nikolay E. Nifantiev (Russian Academy of Sciences, Russia)
18:00 - 18:10	**Effects of Imatinib on PDGFR-Positive Diffuse Large B Cell Lymphoma (DLBCL) Cells** Jee-Yeong Jeong (Kosin University, Korea)
18:10 - 18:20	**Therapeutic Application of MSC-derived Exosome** Woochul Chang (Pusan National University, Korea)
18:20 - 18:30	**Stem Cell Therapy for Immune Disorders: Harnessing the Immunomodulatory Capability of Adult Stem Cells** Hyung-Sik Kim (Pusan National University, Korea)
18:30 - 18:40	**Closing Remark & Poster Award** Jin Han (Inje University, Korea)

Schedule - Poster Session

- **Posting Time 09:00-10:00**
- **Presentation Time**
  1) 11:40-12:10
  2) 14:00-14:30

	Discussion & Poster Session 1 Moderator: Dae Yun Seo, Inje University, Korea	
	Hye-Jin Go (Pukyong National University, Korea)	A-01
	Hye Young Oh (Pukyong National University, Korea)	A-02
	Ara Jo (Dong-A University, Korea)	A-03
11:40 - 12:10	Soon Yong Park (Dong-A University, Korea)	A-04
	Joo Eon Lee (Dong-A University, Korea)	A-05
	Marquez Jubert (Inje University, Korea)	A-06
	Nguyen Thi Tuyet Anh (Inje University, Korea)	A-07
	Discussion & Poster Session 2 Moderator: Hyoung Kyu Kim, Inje University, Korea	
	Darya Tarbeeva (PIBOC, Russia)	B-01
	Elena Vasileva (PIBOC, Russia)	B-02
	Hye-Jin Go (Pukyong National University, Korea)	B-03
14:00 - 14:30	Hye Young Oh (Pukyong National University, Korea)	B-04
	Ye Seon Lim (Pusan National University, Korea)	B-05
	Seon Yeong Hwang (Pusan National University, Korea)	B-06
	In Hwa Cho (Pusan National University, Korea)	B-07

Schedule - Poster Session

- **Posting Time 09:00-10:00**
- **Presentation Time**
  3) 15:30-16:00
  4) 17:00-17:30

	Discussion & Poster Session 3 Moderator: Woochul Chang, Pusan National University, Korea	
	Alexey Belik (PIBOC, Russia)	C-01
	Darya Tarbeeva (PIBOC, Russia)	C-02
	Hye-Jin Go (Pukyong National University, Korea)	C-03
15:30 - 16:00	Hye Young Oh (Pukyong National University, Korea)	C-04
	Seon-Heui Cha (Gachon University, Korea)	C-05
	Jae Hong Ko (Chung-Ang University, Korea)	C-06
	Jung Joo Kim (Inje University, Korea)	C-07
	Discussion & Poster Session 4 Moderator: Hyung-Sik Kim, Pusan National University, Korea	
	Hye-Jin Go (Pukyong National University, Korea)	D-01
	Jung Min Kim (Kosin University, Korea)	D-02
	Woochul Chang (Pusan National University, Korea)	D-03
17:00 - 17:30	Yoojin Seo (Pusan National University Hospital, Korea)	D-04
	Hee Jun Cho (KRIBB, Korea)	D-05
	Tae Hee Ko (Inje University, Korea)	D-06
	Yeon Hee Noh (Inje University, Korea)	D-07

Schedule - Open Discussion

Date: June 29, 2017 (Thu) 14:00 ~ 18:00

Venue: Cardiovascular and Metabolic Disease Center, Inje University

Title: What We Have, How To Share

- **Korean Participants**

  Jin Han (Inje University)
  Nari Kim (Inje University)
  Jae Boum Youm (Inje University)
  Hyoung Kyu Kim (Inje University)
  Sookja Kim Chung (The University of Hong Kong)

- **Russian Participants**

  Valentin A. Stonik (PIBOC)
  Tatiana N. Makarieva (PIBOC)
  Svetlana P. Ermakova (PIBOC)
  Mikhael V. Pivkin (PIBOC)
  Oleg Chernikov (PIBOC)
  Natalia M. Shepetova (PIBOC)
  Nikolay E. Nifantiev (Russian Academy of Sciences)

- **Japan Participants**

  Ippei Shimizu (Niigata University Graduate School of Medical and Dental Sciences)
  Motohiro Nishida (Okazaki Institute for Integrative Bioscience)

Time	Discussion Topic
14:00 - 15:00	Novel Marine Compounds
15:00 - 16:00	Metabolic Disease Applications
16:00 - 17:00	Cardiovascular Disease Applications
17:00 - 18:00	Cancer Applications

Special Lecture

1. General Information

Name	Valentin A. Stonik		
Affiliation	G.B. Elyakov Pacific Institute of Bioorganic Chemistry, Far-Eastern Branch of the Russian Academy of Sciences		
Phone (Office)		**E-mail**	stonikiv@mail.ru

2. Educational background & professional experience

Year	Education / Degrees
1960-1965	Far East State University, Department of Chemistry, Vladivostok, Russia
1969	Ph.D.
1988	DSc.
1995	the Russian Academy of Sciences M.M. Shemyakin Prize Winner
1997	Corresponding Member of the Russian Academy of Sciences
2000	Full Mermber of the Russian Academy of Sciences (Academician)
present	Director, Head of the Laboratory of Marine Natural Products Chemistry, PIBOC

3. Research interests

1. Nnatural products chemistry and chemistry of physiologically active compounds

4. List of major publications

1. Diep C.N., Lyakhova E.G., Berdyshev D.V., Kalinovsky A.I., Tu V.A., Cuong N. X., Nam N.H., Minh C.V., Stonik V. A. Structures and absolute stereochemistry of guaiane sesquiterpenoids from the gorgonian Menella woodin // Tetrahedron Letters. 2015. Vol. 56, N 50. P. 7001–7004.
2. Dyshlovoy S.A., Hauschild J., Amann K., Tabakmakher K.M., Venz S., Walther R., Guzii A.G., Makarieva T.N., Shubina L.K., Fedorov S.N., Stonik V.A., et al., Marine alkaloid Monanchocidin a overcomes drug resistance by induction of autophagy and lysosomal membrane permeabilization // Oncotarget. 2015. Vol. 6, N 19. P. 17328–17341.
3. Kicha A.A., Kalinovsky A.I., Malyarenko T.V., Ivanchina N.V., Dmitrenok P.S., Menchinskaya E.S., Yurchenko E.A., Pislyagin E.A., Aminin D.L., Huong T.T.T., Long P.Q., Stonik V. A. Cyclic steroid glycosides from the starfish Echinaster luzonicus: structures and immunomodulatory activities // Journal of Natural Products. 2015. Vol. 78, N 6. P. 1397–1405.
4. Stonik V., Stonik I. Low-molecular-weight metabolites from diatoms: structures, biological roles and biosynthesis // Marine Drugs. – 2015. – Vol. 13, N 6. – P. 3672–3709.
5. Stonik V.A., Stonik I.V. Toxins produced by marine invertebrate and vertebrate animals: a sho¬rt review // Marine and Freshwater Toxins, Toxinology. 2016. P. 405–419.
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From Neopetroside to New So-called Hidden Vitamin B3

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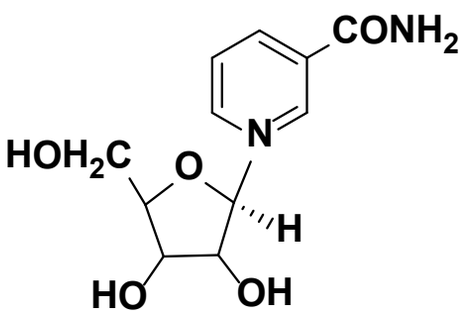
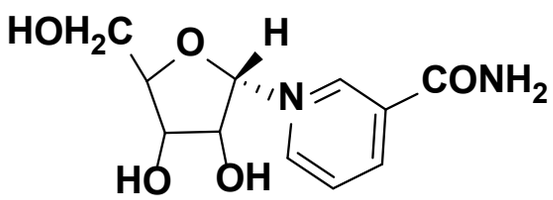
The finding and studying of a new unusual derivative of pyridine nucleoside, Neopetroside A from the sponge Neopetrosia sp., have shown that this compound has alpha-N-glycoside bond (in contrast with all of the previously studied pyridine nucleosides) and increases mitochondrial ATP production and NAD+/NADH ratio. Therefore, the change in configuration of N-glycoside bond does not always prevent mitochondrial myopathy and probably demonstrates other useful properties of some pyridine nucleosides [2].

Recently, a new vitamin B3, nicotinamide beta-riboside, a NAD+ precursor has been found in yeast and milk. Among precursors of NAD+, nicotinamide (60%) and nicotinamide riboside (40%) have been identified in cow milk as [2]. Previously unknown as vitamin, nicotinamide-beta-riboside demonstrates a series of useful effects at the peroral application. For example, it stimulates the growth of yeasts, participates in biosynthesis of NAD+, enhances sirtuins functions, and eliciting insulin sensitivity. The vitamin possesses positive effects against obesity, diabetes, and improves cognitive functions.



Nicotinamide β–riboside



Nicotinamide α–riboside

We suggest that nicotinamide alpha-riboside might be the second hidden vitamin belonging to a series of B3 vitamins. For a long time alpha–derivatives of pyridine nucleosides have been known as a components of biological liquids, although their function in many cases have been still unknown [3,4]. Recently the first enzyme transforming alpha-riboside precursors into NAD+ has been discovered [5]. The catalytic activity of renalase as NAD(P)H oxidase/anomerase has been shown, whereby alpha-anomer of NADPH and NADH initiates a rapid reduction of the renalase flavin cofactor. The reduced cofactor reacts then with dioxygen to form hydrogen peroxide and releases nicotinamide dinucleotide product in the beta-form.

We have started the studies to compare vitamin-like activities of alpha- and beta-nicotinamide ribosides and are going to report our results in the nearest future.

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Session 1
From marine to Idea

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1966-1974	Department of Chemistry, Far East State University, Vladivostok, Russia
1986	Ph.D.
1997	DSc.
1995	Russian Academy of Sciences M.M. Shemyakin Prize Winner
2010	G.B. Elyakov's Award of the Far-Eastern Branch of the Russian Academy of Sciences
present	Major Researcher, Laboratory of Marine Natural Products Chemistry, PIBOC

3. List of major publications

1. Guzii A.G., Makarieva T.N., Denisenko V.A., Dmitrenok P.S., Kuzmich A.S., Dyshlovoy S.A., von Amsberg G., Krasokhin, V.B., Stonik V.A., Melonoside A: an ω-Glycosylated Fatty Acid Amide from the Far Eastern Marine Sponge Melonanchora kobjakovae. Organic Letters. 2016. V.1. N.14. P.3478–3481.
2. Shubina L.K., Makarieva T.N., Denisenko V.A., Dmitrenok P.S., Dyshlovoy S.A., von Amsberg G., Glazunov V. P., Silchenko A. S., Stonik I. V., Lee H. S., Lee Y. J., Stonik V. A. Absolute Configuration and Body Part Distribution of Alkaloid 6-epi-Monanchorin from the Marine Polychaete Chaetopterus variopedatus. Natural Product Communications. 2016. V. 11. N 9. P. 1253–1257.
3. Guzii A.G., Makarieva T.N., Fedorov S.N., Denisenko V.A., Dmitrenok P.S., Kuzmich A.S., Krasokhin, V. B., Lee H. S., Lee Y. J., Stonik V. A. Gramine-derived bromo-alkaloids activating NF-kB-dependent transcription from the marine hydroid Abietinaria abietina. Natural Product Communications. 2016. V. 11. N. 9. P. 1263–1265.
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5. Dyshlovoy S.A., Venz S., Hauschild J., Tabakmakher K. M., Otte K., Madanchi R., Walther R., Guzii A. G., Makarieva T.N., et al., Anti-migratory activity of marine alkaloid monanchocidin A – proteomics-based discovery and confirmation. Proteomics. 2016. V. 16. P. 1590–1603.
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8. Kudryavtsev D., Shelukhina I., Vulfius C., Makarieva T., Stonik V., Zhmak M., et al., Natural Compounds Interacting with Nicotinic Acetylcholine Receptors: From Low-Molecular Weight Ones to Peptides and Proteins. Toxins. 2015. V. 7. N. 5. P. 1683-1701.

A Discovery of New Natural Products as Potential Medicines from Marine Organisms

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Marine organisms are a vast frontier for discovery of new natural products. Many marine organisms contain biochemical secret that, if unlocked, can provide new insights and understanding of human diseases and their treatment. In the course of our continued investigations on new natural products from marine organisms we have collected 1745 samples of marine organisms during the scientific cruises of the research vessel “Akademik Oparin” at the period from 2010 to 2016 near the Kuril and Bering Islands. It was showed that the Far-Eastern marine sponge Monanchora pulchra are a richest source of new guanidine alkaloids. Twenty of these were isolated in our laboratory from different samples of the sponge M. pulchra and various biological activities for the natural compounds have been reported. This is of particular interest that the alkaloids from different samples differ from each other in the structural elements. Probably, their structural variety is a result of synthesis with participation different symbiotic microorganisms.

For example, we recently found that bicyclic guanidine alkaloids from the cosmopolitan bioluminescent marine tube polychaete Chaetopterus variopedatus were biosynthesized by bacterium Vibrio hangzhouensis sp. nov. The microorganism was isolated by us from secreted mucus of the worm.

Three novel 6-azaindoles with inhibitory activities against an alkaline phosphatase were isolated from a marine Esperiopsis sp. sponge. The structures of the 6-azaindoles were elucidated by spectroscopic and chemical methods.

The diversity of new natural products as potential medicines in marine organisms is discussed as well as details of their structure elucidation, and peculiarities of biological action.

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2. Educational background & professional experience

Year	Affiliation	Position
1987	Department of Anatomy & Cell Biology, College of Medicine, University of Illinois, Chicago, USA	Ph.D.
1987-1988	Northwestern University Medical Center, Chicago, USA	NIH Postdoctoral Fellow
1988-1991	The Rockefeller University, New York, USA	Norman and Rosita Winston Foundation Fellow
1991-present	The University of Hong Kong	Research Officer to Profess (2006)
2007-present	The Fourth Military Medical University	Visiting Professor
2007-present	Eye Institute, HKU	Honorary Professor

3. Research interests

1. Metabolic and neurodegenerative diseases
2. Drug discovery for diabetic complications and neurodegeneration and regeneration
3. Stem cell strategies against stroke, Alzheimer's disease, Parkinson's disease and depression

4. List of major publications

1. Zhang X, Yeung PK, McAlonan GM, Chung SS, Chung SK. Transgenic mice over-expressing endothelial endothelin-1 show cognitive deficit with blood-brain barrier breakdown after transient ischemia with long-term reperfusion. Neurobiol Learn Mem. 2013 Jan 11;101C:46-54. doi: 10.1016/j.nlm.2013.01.002. [Epub ahead of print] PubMed PMID: 2331361
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Steroidogenic Acute Regulatory Protein (StAR)-related Lipid Transfer (START) Domain-Containing Protein 13 (STARD13), Rho GTPase-Activating Protein: Mutant Mice as a Model for Drug Discovery?

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Steroidogenic Acute Regulatory protein (StAR)-related lipid transfer (START) Domain-containing protein 13 (STARD13), also known as Deleted in Liver Cancer 2 (DLC2), is a member of the family of DLC/STARD genes. This gene encodes a protein containing 1,113 amino acids that shares 51% identity and 65% similarity with the amino acid sequence of DLC1. The DLC2 has a sterile alpha (SAM) domain, a START domain and a Rho GTPase activating protein (RhoGAP) domain. An additional functional domain was identified in residues 322-329 as an ATP/GTP-binding site. The DLC2 was first thought to be a tumor suppressor gene, since it is located on chromosome 13q12.3, a region often deleted in hepatocellular carcinoma (HCC). In addition, DLC2 expression is reduced in 18% of human HCC samples. The DLC2 exhibited RhoGAP activity specific for RhoA, cdc42 and Rac1, which may modulate stress fiber formation. The increased expression of its RhoGAP domain inhibited the proliferation of breast cancer cells and HepG2 cells by inactivating RhoA. In addition, increased expression of its GAP domain inhibited the migration of HepG2 cells. Therefore, we expected the deletion of DLC2 would lead to higher rate of liver tumor. However, our previous study showed that a DLC2-deficient mice appeared to be smaller with less visceral fat and did not lead to the increase the rate of spontaneous liver tumor formation or diethylnitrosamine (DEN)-induced hepatocarcinogenesis. Various detailed phenotypes of these DLC2-deficient mice will be discussed and their potential use as models for various human disease conditions.

1. General Information

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Year	Affiliation	Position
1996	Inje University College of Medicine, Busan, Korea	M.D.
2003	Inje University College of Medicine, Busan, Korea	Ph.D.
2002	Department of Physiology, College of Medicine, Inje University	Assistant Professor
2007	Bioengineering Institute and Department of Physiology, University of Auckland, NewZealand	Visiting Scientist
2010	Department of Physiology, College of Medicine, Inje University	Associate Professor
2015	Research group of Next Generation Biotechnology	Leader
2016	Department of Physiology, College of Medicine, Inje University	Professor

3. Research interests

1. Cardiovascular and metabolic disease
2. Physiological virtual human
3. Mitochondrial signaling

4. List of major publications

1. FOXM1-Induced PRX3 Regulates Stemness and Survival of Colon Cancer Cells via Maintenance of Mitochondrial Function. Gastroenterology. 2015
2. Low abundance of mitochondrial DNA changes mitochondrial status and renders cells resistant to serum starvation and sodium nitroprusside insult. Cell Biol Int. 2015
3 Echinochrome A protects mitochondrial function in cardiomyocytes against cardiotoxic drugs. Mar Drugs. 2014
4. B7-H4 downregulation induces mitochondrial dysfunction and enhances doxorubicin sensitivity via the cAMP/CREB/PGC1-α signaling pathway in HeLa cells. Pflugers Arch. 2014
5. NecroX-5 suppresses sodium nitroprusside-induced cardiac cell death through inhibition of JNK and caspase-3 activation. Cell Biol Int. 2014
6. Effects of the novel angiotensin II receptor type I antagonist, fimasartan on myocardial ischemia/reperfusion injury. Int J Cardiol. 2013
7. Glucocorticoids and their receptors: insights into specific roles in mitochondria. Prog Biophys Mol Biol. 2013
8. Mitochondrial modulation decreases the bortezomib-resistance in multiple myeloma cells. Int J Cancer. 2013
9. The angiotensin receptor blocker and PPAR-γ agonist, telmisartan, delays inactivation of voltage-gated sodium channel in rat heart: novel mechanism of drug action. Pflugers Arch. 2012
10. Non-genomic effect of glucocorticoids on cardiovascular system. Pflugers Arch. 2012

Comparison of Proteomic Profiling and Contractility of the Left and Right Ventricles in Rat Heart

Julius Ryan D. Pronto, Hyoung Kyu Kim, Kyung Soo Ko, Byoung Doo Rhee, Jin Han, Nari Kim

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Differences of the left (LV) and right ventricles (RV) have been described across different species, and the complexity of recent methods in cardiac research revealed differences down to the molecular level. However, differences in proteins involved in excitation-contraction coupling remain controversial. The present study aims to provide a molecular basis for the differences in Ca^{2+} handling and contractile properties between LV and RV. We characterized the rat interventricular proteome by 1D-LC-MS/MS, and expression level of the protein of interest was verified by immunoblotting. Functional analyses on Ca^{2+} handling and contractility were also performed on isolated rat cardiomyocytes. The proteomic analysis revealed 728 unique proteins; 47 of these were differentially expressed between the ventricles. Interestingly, the protein abundance of ryanodine receptor 2 (RyR2) was higher in the RV than that in the LV, and this result was verified using immunoblotting of isolated sarcoplasmic reticulum (SR) fraction. A majority of the Ca^{2+} used for contraction comes from the SR so other SR Ca^{2+} handling proteins were also assessed. FKBP12.6, SERCA2a, and phospholamban (PLB) showed higher protein expressions in the RV. PLB phosphorylation was also examined, which was higher on the Thr17 residue of PLB in the LV. Ca^{2+} transient analysis showed shorter time to peak and faster Ca^{2+} decay in LV myocytes than RV myocytes. RyR2 was inhibited by keeping it in an open subconductance state using ryanodine, and this significantly reduced time to peak in LV, but not in RV. Measurement of sarcomere shortening also showed show greater contractility in LV myocytes, but RV myocytes displayed shorter shortening and relaxation times. Taken together, variations in protein levels of SR Ca^{2+} handling proteins could explain the differences in Ca^{2+} handling and contractile properties between LV and RV myocytes. Differences in protein expression could be useful in improving therapeutic strategies for region-specific cardiomyopathies.

This research was supported by the Bio & Medical Technology Development Program of the NRF funded by the Korean government, MSIP (2015M3A9B6029133 and 2011-0028925).

1. General Information

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Year	Affiliation	Position
1999-2005	Division of Leisure & Sports Science, Dongseo University, Busan, Korea	B.S.
2005-2007	Department of Physical Education, Pusan National University, Busan, Korea	M.S.
2008-2011	Department of Physical Education, Pusan National University, Busan, Korea	Ph.D.
2011-2013	Cardiovascular and Metabolic Disease Center, Inje University, Busan, Korea	Post-Doc
2013-2015	Division of Leisure & Sports Science, Dongseo University, Busan, Korea	Adjunct Professor
2013-present	Cardiovascular and Metabolic Disease Center, Inje University, Busan, Korea	Research Professor

3. Research interests

1. Cellular and Molecular Control of Skeletal Muscle Metabolism
2. Mitochondrial Bioenergetics
3. Nutrition Metabolism for Enhancement of Physical Activity

4. List of major publications

1. Seo DY, Lee SR, Kim N, Ko KS, Rhee BD, Han J. Age-related changes in skeletal muscle mitochondria: the role of exercise. Integrative Medicine Research. 5(3): 182-186, 2016
2. Seo DY[#], Lee SR[#], Kwak HB, Seo KW, McGregor RA, Yeo JY, Ko TH, Bolorerdene, Saranhuu, Kim N, Ko KS, Rhee BD, Han J. Voluntary stand-up physical activity enhances endurance exercise capacity in rats. Korean J Physiol Pharmacol. 20(3):287-95, 2016
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5. Seo DY[#], Lee SR[#], Kim N, Ko KS, Rhee BD, Han J. Humanized animal exercise model for clinical implication. Pflugers Arch. 466(9):1673-1687, 2014

Echinochrome A Improves Exercise Capacity During Endurance Exercise in Rats

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Echinochrome A (Echi A) improves mitochondrial function in the heart; however, its effects on skeletal muscle are still unclear. We hypothesized that Echi A administration during short-term exercise may improve exercise capacity. Twenty-four male Sprague-Dawley rats were randomly divided into the following groups: control group (CG), Echi A-treated group (EG), aerobic exercise group (AG), and aerobic exercise treated with Echi A group (AEG) (n=6 per group). Echi A was administered intra-peritoneally (0.1 mg/kg of Echi A in 300 µL phosphate-buffered saline) daily 30 min before each exercise training. The AG and AEG groups performed treadmill running (20 m/min, 60 min/day) 5 days/week for 2 weeks. The exercise capacity was significantly higher in the AG and AEG groups compared to other groups. Interestingly, the exercise capacity increased more effectively in the AEG group. The body weight in the EG tended to be slightly lower than that in the other groups. There were no significant changes in the plasma lipids among the groups. However, the gastrocnemius muscle mitochondria content was greater in the EG and AEG groups. These findings show that Echi A administration after short-term endurance training enhances exercise capacity, which was associated with an increase in skeletal muscle mitochondrial content.

Keywords: marine drug, echinochrome A, exercise, skeletal muscle, mitochondria.

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2. Educational background & professional experience

Year	Affiliation	Position
1987-1992	Dept. of Biology, Korea University	B.A.
1993-1995	Dept. of Biology, Illinois Institute of Technology	M.S.
1995-2000	Dept. of Biology, Illinois Institute of Technology	Ph.D.
2000-2003	Johns Hopkins University, School of Medicine	Post-doctor
2003-2004	Dept. of Biology, Korea University	Research Professor
2004-2009	Korea Research Institute of Bioscience and Biotechnology	Senior Scientist
2009-present	Dong-A University	Associate Professor

3. Research interests

1. Anti-cancer therapy
2. Cancer stem cell
3. Drug delivery therapy
4. Anti-aging & Tissue regeneration

4. List of major publications

1. Synergistically enhanced selective intracellular uptake of anticancer drug carrier comprising folic acid-conjugated hydrogels containing magnetite nanoparticles. Kim H, Jo A, Baek S, Lim D, Park SY, Cho SK, Chung JW*, Yoon J*. Sci Rep. 2017 Jan 20;7:41090
2. Spot the difference: Solving the puzzle of hidden pictures in the lizard genome for identification of regeneration factors. Chung JW. BMB Rep. 2016 May;49(5):249-54.
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4. Bae KS, Kim SY, Park SY, Jeong AJ, Lee HH, Lee J, Cho YS, Leem SH, Kang TH, Bae KH, Kim JH, Jung YW, Jun W, Yoon SR, Lee SC, Chung JW. (2014) Identification of lactoferrin as a human dedifferentiation factor through the studies of reptile tissue regeneration mechanisms. J Microbiol Biotechnol. 13. 24(6), 869–878
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Identification of Dedifferentiation Factors Through the Proteomic Studies of the Reptile Tissue Regeneration Mechanisms

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Induced pluripotent stem cells (iPSCs) are an emerging technology that could replace embryonic stem cell (ESCs) without the associated ethical problems. However, iPSCs still have several technical limitations that must be solved for clinical applications, including low efficiency and the use of oncogenes. Thus, new strategies are required to improve the efficacy and safety of iPSC technology. In this study, we addressed this issue by the biomimetic approaches to identify the dedifferentiation factors, and identified a leech-derived tryptase inhibitor as a natural regeneration factor in lizards based on proteomic studies of reptile tissue regeneration mechanisms. The mammalian homologue lactoferrin, also a tryptase inhibitor, was specifically expressed in various stem cell lines and enhanced the efficiency of iPSC generation approximately 7-fold relative to the control. Furthermore, lactoferrin increased the efficiency by 2-fold without enforced expression of *Klf4*, a commonly used oncogene in iPSC generation, suggesting that lactoferrin may induce dedifferentiation at least partly by increasing the expression of *Klf4*.

Session 2
From marine to Invention

1. General Information

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2. Educational background & professional experience

Year	Education / Degrees
1978-1982	Primorskaja Academy of Agriculture
1987-1990	Biological Department of Moscow State University, Chair of Mycology and Algology (Mycology); Central Genetic Laboratory, Mytchurinsk, (Genetics);
1991	Ph.D. in Biology (Mycology)
1996	Senior Researcher
2010	DSc. in Biology (Mycology)
present	Senior Researcher, Laboratory of Microbiology, PIBOC

3. Research interests

1. Mycology (Hirsch index 10, citation 482)

4. List of major publications

1. Slinkina N.N., Pivkin M.V., Polokhin O.V. Filamentous fungi of the submarine soils of the Sakhalin Gulf (Sea of Okhotsk) // Russian Journal of Marine Biology. November 2010, Volume 36, Issue 6, pp 413–418
2. Kirichuk N.N., Pivkin M.V. Marine fungi associated with brown algae of the Sargassum genus of Peter the Great Bay (Sea of Japan) // “Mikologiya I fitopatologia” (in Russian). 2015. V. 49. Pt. 3. P. 146-150.
3. Chikalovets I.V., Chernikov O.V., Pivkin M.V., Molchanova V.I., Litovchenko A.P., Li W., Lukyanov P. A. A lectin with antifungal activity from the mussel Crenomytilus grayanus // Fish and Shellfish Immunology. 2015. V. 42. P. 503-507.
4. Kirichuk N.N., Pivkin M.V. Filamentous fungi associated with the seagrass Zostera marina Linnaeus, 1753 of Rifovaya Bay (Peter the Great Bay, the Sea of Japan)// Russian Journal of Marine Biology September 2015, Volume 41, Issue 5, pp 351–355.
5. Kirichuk N.N., Pivkin M.V., Matveeva T.V. Three new Penicillium species from marine subaqueous soils // Mycological Progress. 2017, V. 16. P. 15–26.

Marine Derived Fungi of the Northeastern Pacific. Taxonomy, Ecology and Metabolites

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Marine fungi involve ecologically defined group of primarily filamentous ascomycetes, basidiomycetes and their anamorphs. The ecological importance of filamentous fungi in marine systems is often underestimated or ignored completely, and yet these organisms represent a diverse range of saprobes, pathogens and symbionts that form an integral part of coastal systems.

The interactions between microbial diversity and ecosystem function are not well understood. In particular, it is unclear how population stability and metabolic function are related to diversity. Assessing fungal diversity accurately, encompassing phylogenetic diversity, species richness and evenness, is the first step towards modeling fungal assemblages dynamics in terms of species redundancy, species spatial and temporal distributions, and nutrient cycling. Such models are essential for the efficient management and conservation of agrarian, forest and marine environments that are economically important. Similar limitations also apply to the identification, isolation and quantification of fungi from marine environments, with the additional complication of distinguishing between transitory and native forms. Fungi isolated from marine environments have been considered traditionally to be either obligate, where growth and reproduction occur exclusively in a marine system, or marine-derived (facultative). The distinction between these states is not always clear. However, as many marine- and maritime-derived fungi can grow in saline conditions. Defining a fungus as an obligate marine species, therefore, has relied upon direct microscopic observation of morphological, particularly reproductive structures, growing on the substrata. Diversity assessments based on the identification of sexual and asexual fruiting bodies alone are likely to be incomplete for several reasons: the inability of some fungi to grow or fruit in culture or on substrata, differential rates of sporulation, the presence of unrecognized multiple life cycle forms, and the limitations of distinguishing between species with similar morphologies.

The procedure for distinguishing between transitory and native facultative marine fungi has been developed from the germination of marine isolate in the natural, not sterile sea water and in the fresh water, as well as incubation fungi in the sea. At present 32 species of 11 genera ascomycetes, 249 species of 57 genera anamorphic fungi were defined. It has been established that marine-derived fungi are more diverse in temperate waters than in tropical zone. More than 300 producers of new antibiotics, anticancer substances, and inhibitors of enzyme were obtained and structures of these substances were elucidated. About 50 producers of new enzymes were obtained.

Taxonomic and chemical studies of marine-derived fungi demand more attention and will be very promising.

1. General Information

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Year	Affiliation	Position
1996-2002	Chiba University faculty of medicine, Chiba, Japan	Medical student
2006-2010	Doctoral coarse, Chiba university graduate school of medicine, Chiba, Japan	Ph.D. student
2010-2012	Chiba University Hospital Department of Cardiology	Postdoctoral fellow
2012-2014	Boston University School of Medicine, Whitaker Cardiovascular Institute, Molecular Cardiology	Postdoctoral fellow(1st year), Research Instructor of Medicine (2nd year)
2014-present	Department of Cardiovascular Biology and Medicine, Division of Molecular Aging and Cell Biology, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan	Associate Professor

3. Research interests

Cardiology, Heart failure, Insulin resistance, Chronic inflammation, Metabolism, Aging, Brown and white adipose tissue

4. List of major publications

1. Kinoshita D, Nagasawa A, Shimizu I, Ito T, Yoshida Y, Tsuchida M, Iwama A, Hayano T and Tohru Minamino. Progerin impairs vascular smooth muscle cell growth via the DNA damage response pathway. Oncotarget. (in press)
2. Shimizu I*, Minamino T*. Physiological and pathological cardiac hypertrophy. J Mol Cell Cardiol. 2016 Jun 2;97:245-262 *Co-corresponding author
3. Shimizu I, Yoshida Y, Minamino T. Hypertens Res 2016 Feb 18, A role for circadian clock in metabolic disease.
4. Shimizu I, Yoshida Y, Minamino T. Diabetes. 2015 (Commentary) Dec;64(12):3984-6. Maintenance of subcutaneous fat homeostasis improves systemic metabolic dysfunction in obesity.
5. Yoshida Y*, Shimizu I*, Katsuumi G*, Suda M, Hayashi Y, Minamino T. J Mol Cell Cardiol. 2015 June 85:183-198. p53-induced inflammation exacerbates cardiac dysfunction during pressure overload. *Co-first author
6. Shimizu I, Yoshida Y, Suda M, Minamino T. Cell Metab. 2014 Dec 2;20(6):967-977. DNA damage response and metabolic disease.
7. Suzuki H, Kayama Y, Sakamoto M, Iuchi H, Shimizu I, Yoshino T, Katoh D, Nagoshi T , Tojo K, Minamino T, Yoshimura M, Utsunomiya K. Diabetes. 2015 Feb;64(2):618-30. Arachidonate 12/15-lipoxygenase-induced inflammation and oxidative stress are involved in the development of Diabetic Cardiomyopathy

Semaphorin3E is a Novel Therapeutic Target for Unhealthy Obesity and Diabetes

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Semaphorins and their receptors (plexins) were initially characterized according to their roles in repulsive axon guidance that also regulate the development of vascular network during embryogenesis. Semaphorin3E (Sema3E) is one of the class 3 semaphorins which binds to its specific receptor, plexinD1. Our previous study demonstrated that increased p53 signal in obesity induced adipose inflammation that lead to systemic insulin resistance. Recently we showed that p53 positively regulates Sema3E in the visceral fat under metabolic stress. Importantly, we found Sema3E was a chemo-attractant for inflammatory macrophages, inducing adipose tissue inflammation and systemic insulin resistance in obese model. Sema3E and plexinD1 expression were increased in adipose tissue of diet-induced obesity (DIO) model. Inhibition of the Sema3E-plexinD1 axis with genetic models or soluble form of the receptors markedly improved adipose tissue inflammation and systemic insulin resistance. Conversely, forced expression of sema3E in adipose tissues provoked inflammation and systemic insulin resistance. The genetic disruption of adipose p53 down-regulated the expression of Sema3E and improved adipose tissue inflammation in DIO model. Sema3E increased the infiltration of macrophages in the migration assay, and this effect was inhibited with the disruption of plexinD1 expression in macrophages. These results indicate that Sema3E functions as a chemo-attractant for macrophages and p53-induced increase of Sema3E-plexinD1 signals provokes adipose tissue inflammation and systemic insulin resistance in DIO model. Inhibition of the Sema3E-plexinD1 axis will become a new therapeutic target for unhealthy obesity and diabetes.

1. General Information

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1993-1997	Department of Animal Husbandry, Konkuk University	B.S.
1997-2000	Department of Animal Husbandry, Konkuk University	M.S.
2005-2008	Inje University, Colleage of Medicine	Ph.D.
2008-2009	Department of Physiology, College of Medicine, Inje University, Busan, Korea	Post Doc
2009-2012	Cardiovascular and Metabolic Disease Center, Inje University, Busan, Korea	Research associated professor
2012-present	Cardiovascular and Metabolic Disease Center, Inje University, Busan, Korea	Assistant Professor

3. Research interests

1. Biological mechanism and treatment of Ischemia/reperfusion heart injury
2. Mitochondrial physiology in health and diseases
3. Mitochondria Proteome in cardiovascular and metabolic diseases

4. List of major publications

1. Kim HK, Jeong YJ et al. Glucocorticoid receptor positively regulates transcription of FNDC5 in the liver. Scientific Reports 2017
2. Park JH, Kim HK, Jung H, Kim KH, Kang MS, Hong JH, Yu BC, Park S, Seo SK, Choi IW, Kim SH, Kim N, Han J, Park SG. NecroX-5 prevents breast cancer metastasis by AKT inhibition via reducing intracellular calcium levels. Int J Oncol. 2016 (Co-first)
3. Kim HK, Ko TH, Nyamaa B, Lee SR, Kim N, Ko KS, Rhee BD, Park CS, Nilius B, Han J. Cereblon in health and disease. Pflugers Arch 2016.
4. Kim H, Nilius B, Kim N, Ko K, Rhee B, Han J: Cardiac Response to Oxidative Stress Induced by Mitochondrial Dysfunction. In: Rev Physiol Biochem Pharmacol Springer Berlin Heidelberg; 2016: 1-27.
5. Song IS, Jeong YJ, Jeong SH, Heo HJ, Kim HK, Bae KB, Park YH, Kim SU, Kim JM, Kim N et al: FOXM1-induced PRX3 Regulates Stemness and Survival of Colon Cancer Cells via Maintenance of Mitochondrial Function. Gastroenterology 2015.
6. Kim HK, Youm JB, Jeong SH, Lee SR, Song IS, Ko TH, Pronto JR, Ko KS, Rhee BD, Kim N *et al*: Echinochrome A regulates phosphorylation of phospholamban Ser16 and Thr17 suppressing cardiac SERCA2A Ca reuptake. Pflugers Arch 2014.

Neopetroside A, a Novel Pyridine Nucleoside, Protects Heart Against Ischemia/Reperfusion-injury

Hyoung Kyu Kim[1,2,3], Seung Hun Jeong[1,3], Min Kim[1,3], Tae HeeKo[2,3], Yeon Hee Noh[2,3], In-Sung Song[1,2,3], Larisa K. Shubina[4], Tatyana N. Makarieva[4], Dmitry V. Yashunsky[5], Nikolay E. Nifantiev[5], Valentin A. Stonik[4] and Jin Han[1,2,3]

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[4]George B. Elyakov Pacific Institute of Bioorganic Chemistry, Far-Eastern Branch of the Russian Academy of Science, Vladivostok, Russian Federation
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Recently, an unprecedented nicotinic acid riboside neopetroside A (NPS A) was isolated from a sponge Neopterosia sp. and later synthesized. It differs from the well-known nucleoside and nucleotide biosynthetic precursors of NAD^+ and NADH in configuration of N-glycoside bond (α- instead of β-) as well as in substitution of hydroxyl group at 5′-position of ribose moiety by a hydroxybenzoyl substituent. Herein, we tested the biological function of NPS A in energy metabolism and heart protection by using cell line and animal models. NPS A treatment increased oxidative phosphorylation and glycolysis in the rat cardiomyoblast H9c2 cell line and isolated rat heart mitochondria. Specifically, NPS A enhanced NADH dehydrogenase complex (complex 1) activity in isolated cardiac myocyte resulting increase the ratio of NAD/NADH. Using in vitro direct kinase activity assays, it was figured out that NPS A directly inhibits the activity of GSK-3α and β-, a serine/threonine protein kinase playing a key role in many biological processes including cardiac energy metabolism and cell death. Based on those beneficial biological effects, NPS A treatment effectively protect hearts against global ischemia/reperfusion-injury and coronary artery occlusion-induced myocardial infarction in animal models. The NPS A treatment preserves the heart rate and contractility after global ischemia/reperfusion (I/R) and reduces the myocardial infarction size and fibrosis region in the animal heart. In conclusion, our data figure out that NPS A has a potential to enhance mitochondrial energy metabolism and protect heart against I/R-damage via inhibition of GSK-3 activity and enhanced mitochondria energy metabolism.

Keywords: NPS A, marine pyridine α-nucleoside, mitochondria, ischemia/reperfusion injury, inhibition of GSK-3

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2. Educational background & professional experience

Year	Affiliation	Position
1981-1987	College of Medicine, Pusan National University, Busan, Korea	M.D.
1987-1989	Graduate School, Pusan National University, Busan, Korea	M.A. (Anatomy)
1989-1993	Graduate School, Pusan National University, Busan, Korea	Ph.D. (Anatomy)
2001-2006	College of Medicine, Busan National University, Busan, Korea	Associate Professor
2005-2006	Washington University School of Medicine, St. Louis, MO, USA	Visiting Professor
2006-present	Dept. of Anatomy, Pusan National University School of Medicine, Busan, Korea	Professor
2012-present	Anatomy & Cell Biology (ISSN: 2093-3673)	Section Editor
2014-present	Korean Journal of Physical Anthropology (ISSN: 2287-626X)	Editor

3. Research interests

1. Nano-engineering of cells for regenerative medicines
2. Development and application of 3D technology for drug discovery and diagnostic tools
3. Molecular mechanisms of T cell regeneration, and development of therapeutic strategies to modulate immune function

4. List of major publications

1. Subhan F, Kang HY, Lim Y, Ikram M, Baek SY, Jin S, Jeong YH, Kwak JY, Yoon S : Fish scale collagen peptides protect against CoCl2/TNF-a-induced cytotoxicity and inflammation via inhibition of ROS, MAPK, and NF-B pathways in HaCaT Cells. Oxid. Med. Cell. Longev. 2017(in press)
2. Shin S, Ikram M, Subhan F, Kang HY, Lim Y, Lee R, Jin S, Jeong YH, Kwak JY, Na YJ, Yoon S : Alginate–marine collagen–agarose composite hydrogels as matrices for biomimetic 3D cell spheroid formation. RSC Adv 6:46952-65, 2016
3. Song IJ, Ikram M, Subhan F, Choi DJ, Lee JR, Kim HS, Lim YT, Yoon S : Molecular characterization and expression analysis of mouse epidermal growth factor-like domain 8. Int J Mol Med 36:541-550, 2015
4. Choi da J, Choi SM, Kang HY, Min HJ, Lee R, Ikram M, Subhan F, Jin SW, Jeong YH, Kwak JY, Yoon S : Bioactive fish collagen/polycaprolactone composite nanofibrous scaffolds fabricated by electrospinning for 3D cell culture. J Biotechnol 205:47-58, 2015
5. Subhan F, Yoon TD, Choi HJ, Muhammad I, Lee J, Hong C, Oh SO, Baek SY, Kim BS, Yoon S : Epidermal growth factor-like domain 8 inhibits the survival and proliferation of mouse thymocytes. Int J Mol Med 32:952-958, 2013
6. Kim KH, Park JK, Choi YW, Kim YH, Lee EN, Lee JR, Kim HS, Baek SY, Kim BS, Lee KS, Yoon S : Hexane extract of aged black garlic reduces cell proliferation and attenuates the expression of ICAM-1 and VCAM-1 in TNF-α-activated human endometrial stromal cells. Int J Mol Med 32:67-78, 2013

The Anti-Oxidative, Anti-Inflammatory, and Protective Effects of Fish Scale Collagen Peptides on Human Keratinocytes

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Skin diseases associated with inflammation or oxidative stress represents the most common problem in dermatology. The present study demonstrates that fish collagen peptides (FCP) protect against CoCl2-induced cytotoxicity and TNF-α-induced inflammatory responses in human HaCaT keratinocyte cells. Our study is the first to report that FCP increase cell viability and ameliorate oxidative injury in HaCaT cells through mechanisms mediated by the downregulation of key pro-inflammatory cytokines, namely, TNF-α, IL-1β, IL-8, and iNOS. FCP also prevent cell apoptosis by repressing Bax expression, caspase-3 activity, and cytochrome c release and by upregulating Bcl-2 protein levels in CoCl2- or TNF-α-stimulated HaCaT cells. In addition, the inhibitory effects of FCP on cytotoxicity and the induction of pro-inflammatory cytokine expression were found to be associated with suppression of the ROS, MAPK (p38/MAPK, ERK, and JNK), and NF-κB signaling pathways. Taken together, our data suggest that FCP are useful as immunomodulatory agents in inflammatory or immune-mediated skin diseases. Furthermore, our results provide new insights into the potential therapeutic use of FCP in the prevention and treatment of various oxidative- or inflammatory stress-related inflammation and injuries.

Keywords: fish collagen, HaCaT cells, cytotoxicity, inflammation

1. General Information

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Year	Affiliation	Position
1978-1982	Seoul National University, Astronomy & Physics	B.S.
1982-1984	KAIST, Physics	M.S.
1987-1992	State University of New York at Buffalo	Ph.D.
1992-1994	Memorial Sloan-Kettering Cancer Center	Fellow
2012-2013	UC Berkeley, Biomedical Engineering	Visiting professor
1995-present	Catholic University of Daegu, School of Medicine	Professor

1. Nanomedicine
2. Medical Imaging
3. Biomaterials

4. List of major publications

1. Se-Hee Lee, Won-Seok Chang, Sung-Mi Han, Duck-Hyun Kim, Jong-Ki Kim, Three-dimensional nanoscale imaging analysis of pore structure in nanoporous polymeric membranes. J of Membran Sci (2017) 535: 28–34.

2. Jae-Kun Jeon†, Sung-Mi Han†, Soon-Ki Min, Seung-Jun Seo, Kyuwook Ihm, Won-Seok Chang, and Jong-Ki Kim*, Coulomb nanoradiator-mediated, site-specific thrombolytic proton treatment with a traversing pristine Bragg peak, Scientific Reports (2016) 6:37848

3. Jae-Kun Jeon, Sung-Mi Han and Jong-Ki Kim, Fluorescence imaging of reactive oxygen species by confocal laser scanning microscopy for track analysis of synchrotron X-ray photoelectric nanoradiator dose: X-ray pump–optical probe, J. Synchrotron Rad. (2016). 23, 1191–1196.

4. Wonseok Chang, Jong-Ki Kim, Jin-Ho Cho, Jae-Hong Lim*, Wave Propagation Simulation Based on the Fourier Diffraction Integral for X-Ray Refraction Contrast Imaging-Computed Tomography, J Kor Phys Soc (2016) 69, 1098-1104.

5. Soon-Ki Min†, Sung-Mi Han†, Jae-Seok Jang, Jong-Ki Kim*, Stimulatory effect of an algal fucoidan on the release of vascular endothelial tissue-type plasminogen activator as a mechanism of fucoidan-mediated thrombolysis, Blood Coagulation and Fibrinolysis (2016) July, 27(5) 594–596.

6. S.-M. Han, J.-I. Chikawa, J.-K. Jeon, M.-Y. Hwang, J. Lim, Y.-J. Jeong, S.-H. Park, H.-T. Kim, S. Jheon, and J.-K. Kim, “Synchrotron Nanoscopy Imaging Study of Scalp Hair in breast Cancer Patients and Healthy Individuals: Difference in Medulla Loss and Cortical Membrane Enhancements,” Microscopy Res. Tech. 79, 23-30 (2016).

Thrombolytic Fucoidan Activates Plasma Tissue-type Plasminogen Activator by Inhibiting tPA-PAI-1 Complexation: molecular mechanism of fucoidan-mediated thrombolysis

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Identifying a pharmacological means for increasing the production of t-PA is always desirable to cure impaired production of this enzyme in various atherothrombotic diseases. An fucoidan from Korean Undaria pinnatifida sporophylls (UF) has been shown to exhibit novel thrombolytic effects, and demonstrated enhancement of the plasma levels of active t-PA in mouse arterial thrombus models. Thrombolytic activity and binding affinity with PAI-1 of various fucoidan fractions from Russian marine alga were examined in mouse arterial thrombus models and in tPA-PAI-1 coated well, respectively. Thrombolytic activities comparable with UF were found among various fucoidan fractions with relatively difference in sensitivity and the time for reperfusion between 30-90 min. More importantly, competitive binding of fucodian with t-PA-complexed plasminogen activator inhibitor-1 (PAI-1) enabled releasing free t-PA, in which relative amount was estimated reciprocally among various fucoidan fractions by measurement of remained tPA-PAI 1 complex. The tPA-activating properties of fucoidan fractions were found accordingly with the result of thrombolytic activities in vivo.

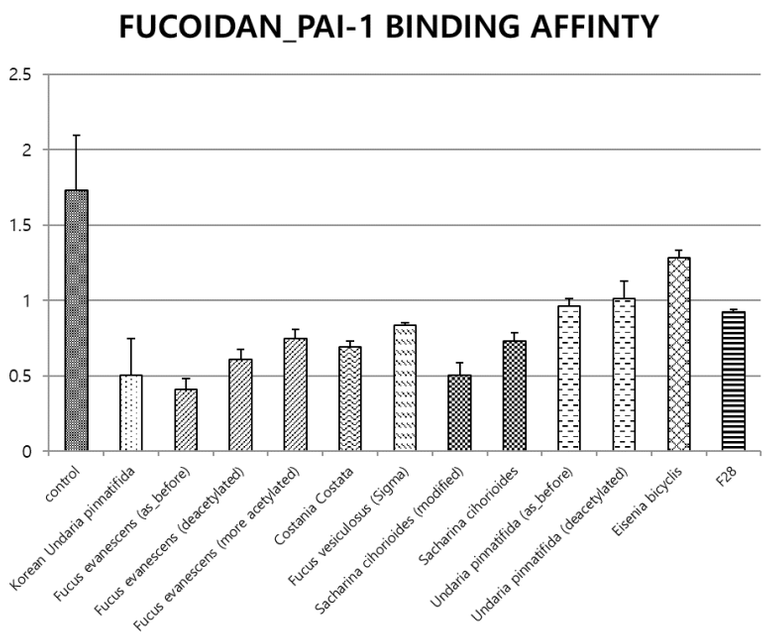

Fig1. Fucus evanescens and Korean Undaria pinnatifida fucoidans showed largest affinity with PAI-1, and resulting in relatively most fast thrombolysis in vivo

Session 3
Novel Drug Development : targets and applications

1. General Information

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2. Educational background & professional experience

Year	Education / Degrees
1982-1987	M.S., Moscow State Academy of Light Industry, Moscow, Russia
2002	Ph.D.
2014	DSc.
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3. Research interests

polysaccharides from seaweeds (purification, structures, biological activity); transformation of polysaccharides, molecular mechanisms and the signal transductions regulated by natural compounds

4. List of major publications

1. O.S. Vishchuk, S.P. Ermakova, T.N. Zvyagintseva, Sulfated polysaccharides from brown seaweeds Saccharina japonica and Undaria pinnatifida: isolation, structural characteristics, and antitumor activity. Carbohydr Res 346 (2011) 2769-2776.
2. O.S. Vishchuk, D.V. Tarbeeva, S.P. Ermakova, T.N. Zvyagintseva, Structural characteristics and biological activity of fucoidans from the brown algae Alaria sp. and Saccharina japonica of different reproductive status. Chem Biodivers 9 (2012) 817-828.
3. S. Ermakova, S. Men'shova, O. Vishchuk, C. Kim, B. Um, V. Isakov, T. Zvyagintseva, Water-soluble polysaccharides from the brown alga Eisenia bicyclis: Structural characteristics and antitumor activity. Algal Res 2 (2013) 51–58.
4. O.S. Vishchuk, S.P. Ermakova, T.N. Zvyagintseva The effect of sulfated 1,3-alpha-L-fucan from the brown alga Saccharina cichorioides Miyabe on resveratrol-induced apoptosis in colon carcinoma cells. Mar Drugs 11 (2013) 194–212.
5. R.V. Menshova, S.P. Ermakova, S.D. Anastyuk, V.V. Isakov, Yu.V. Dubrovskaya, M.I. Kusaykin, B.H. Um, T.N. Zvyagintseva Structure, enzymatic transformation and anticancer activity of branched high molecular weight laminaran from brown alga Eisenia bicyclis // Carbohydr Polym. 99 (2014) 2 101–109.

Brown Algae as a Source of Biologically Active Polysaccharides

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Brown algae have drawn worldwide attention due to their involvement in many industrial applications. Polysaccharides of algae are especially valuable substances. At the moment polysaccharides synthesized by brown algae (laminarans and especially fucoidans) are of greatest interest because they processed broad spectrum of beneficial biological activities. A laminarans are low molecular weight analogs of 1,3-β-D-glucans of terrestrial organisms. It should be noticed that fucoidans are truly marine polysaccharides. The general term "fucoidan" is used to integrate the molecules, differenced in composition, structure, and in degree of sulfation, acetylation, etc.

The structural investigation of laminarans, their sulfated derivatives and fucoidans from brown algae Saccharina cichorioides Miyabe, and Fucus evanescens C. Agardh and their anticancer activity and molecular mechanism will be presented.

Studies of the fucoidan content in F. evanescens, which depends on the location of algal harvest and on the conditions of the polysaccharide extraction procedure, were performed by our group. We found that this alga contained the highest fucoidan content compared to that of other brown algae harvested from the Sea of Okhotsk and Sea of Japan: Saccharina cichorioides, Saccharina japonica, and Saccharina gurjanovae. Fucoidan was shown to be a regular molecule containing disaccharide repeating units, with a linear main chain of alternating 2-sulfated 1,3- and 1,4-linked α-L-fucose residues. Fucoidan had a small amount (approximately 2%) of single 1,4-linked fucose residues in the branches at C-4 of 1,3-linked fucose residues of the main chain. Acetyl groups occupied the free C-3 of 1,4-linked residues and/or the C-4 of 1,3-linked fucose residues.

Fucoidan from Saccharina cichorioides was almost pure fucan, containing the main chain of 1,3-linked α-L-fucopyranose residues with a small degree of 1,4-linked α-L-fucopyranose residues. A small amount of single α-L-fucose residues were in the branches at the C2. Sulfate groups occupied position 2 and 4 of fucopyranose residues.

The laminaran from F. evanescens consisted of not only β-(1,3)-linked D- glucopyranose, but also includes single β-(1,6)-linked D-glucose residues. The branches at C6 are presented as glucose or as gentiobiose. The laminaran from S. cichorioides was confirmed to contain a main chain of β-(1,3)-D-glucopyranose with single branches at C6. The sulfated laminarans with different degree of sulfation were obtained by the chlorosulfonic acid - pyridine assay. In modified polysaccharides the positions of sulfates are directly predetermined by the structure of native laminarans.

The laminarans, their sulfated derivatives, and fucoidans inhibited proliferation, colony formation, and migration of human colorectal adenocarcinoma, melanoma, and breast adenocarcinoma cells in different manner.

1. General Information

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2. Educational background & professional experience

Year	Affiliation	Position
2001.3.	University of Tokyo, Graduate School of Pharmaceutical Sciences	Ph.D.
2001.4.	JSPS Research Fellow	Post Doc
2001-2003	National Institute for Physiological Sciences, Okazaki National Institutes	Assistant Professor
2003-2013	Kyushu University, Graduate School of Phamaceutical Sciences	Associate Professor
2013-present	Okazaki Institute for Integrative Bioscience, National Institutes of Natural Sciences	Professor
2015-present	Kyushu University, Graduate School of Pharmaceutical Sciences	Concurrent Professor

3. Research interests

1. Cardiovascular remodeling
2. Redox biology
3. Calcium signaling
4. Drug repositioning

4. List of major publications

1. Akaike T, Ida T, Wei F-Y, Nishida M, Kumagai Y, Alam MM, Ihara H, Sawa T, Matsunaga T, Kasamatsu S, Nishimura A, Morita M, Tomizawa K, Nishimura A, Watanabe S, Inaba K, Shima H, Tanuma N, Jung M, Fujii S, Watanabe Y, Ohmuraya M, Nagy P, Feelisch M, Fukuto JM, Motohashi H. Cysteinyl-tRNA synthetase governs cysteine polysulfidation and mitochondrial bioenergetics. Nature Commun. provisionally accepted.
2. Numaga-Tomita T., Kitajima N., Kuroda T., Nishimura A., Miyano K., Yasuda S., Kuwahara K., Sato Y., Ide T., Birnbaumer L., Sumimoto H., Mori Y. and Nishida M. TRPC3-GEF-H1 axis mediates pressure overload-induced cardiac fibrosis. Sci. Rep. 6, 39383 (2016); doi: 10.1038/srep39383.
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4. Nishimura A, Sunggip C, Tozaki-Saitoh H, Shimauchi T, Numaga-Tomita T, Hirano K, Ide T, Boeynaems J-M, Kurose H, Tsuda M, Robaye B, Inoue K and Nishida M. The purinergic P2Y6 receptor heterodimerizes with the angiotensin AT1 receptor to promote angiotensin II-induced hypertension. Science Signal.. 9(411), ra7 (2016). doi: 10.1126/scisignal.aac9187.
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Metabolic Detoxification of Environmental Electrophile by Reactive Cysteine Persulfides

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Exposome, a new concept that explicitly incorporates the body's response to environmental influences and also includes the endogenous metabolic processes that can alter or process the chemicals to which humans are exposed, is recently attracted attention as key predictive factors for disease development. These chemicals mostly have electrophilic and/or nucleophilic properties. Electrophilic signaling is precisely regulated by endogenous electrophilic substances that are generated from reactive oxygen species, nitric oxide, and its derivative reactive species during stress responses, and/or exogenous electrophiles including in foods and environmental pollutants. We found that exposure of healthy mice to sub-neurotoxic dose of methylmercury (MeHg), an environmental pollutant biologically concentrated in seafood, increased cardiac vulnerability to pressure overload through dynamin-related protein 1 (Drp1)-mediated mitochondrial hyper-fission, without showing any abnormal behavior. Reactive persulfide species such as cysteine persulfides that are enzymatically produced in cells are likely involved in electrophile metabolism. Protein persulfide detection assay revealed that endogenous Drp1 protein abundantly formed Cys persulfide in rat cardiomyocytes, and MeHg exposure markedly reduced Drp1 persulfide level through depriving sufur to form $(MeHg)_2S$. Treatment of rat cardiomyocytes with NaHS as a sulfur substrate for 24 hours completely canceled MeHg-induced sulfur deprivation of Drp1 as well as Drp1 activation and mechanical stretch-induced cardiac injury. These results strongly suggest that deprivation of sulfur from Cys persulfides of Drp1 underlies induction of mitochondrial remodeling (i.e., hyperfission) and cardiac vulnerability to pressure overload by MeHg, and supplementary intake of sulfur, such as garlic and onion, with seafood will be a benefit to improve the prognosis after heart failure.

1. General Information

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2005	Jeju National University, Marine Biotechnology	B.Sc
2010	Jeju National University, Aquatic Medicine	Ph.D.
2011	Korea Basic Science Institute	PostDoc Fellow
2011-2012	Georgia Institute of Technology (GA Tech)	PostDoc Fellow
2012-2016	Ajou University School of Medicine	Research Associates
2017-present	Gachon University Department of Pharmacy	Research Professor

1. Marine alage
2. Neuroscience
3. Diabetes
4. Senescence
5. zebrafish

1. Seon-Heui Cha*, Soo-Jin Heo, You-Jin Jeon, Sang Myun Park. Dieckol, an edible seaweed polyphenol, retards rotenone-induced neurotoxicity and α-synuclein aggregation in human dopaminergic neuronal cells.*Corresponding. RSC Advances. 2016.
2. Ji-Hyeok Lee, Ju-Young Ko, Eun-A Kim, Eun-Kyoung Hwang, Chan Sun Park, Jung-Suck Lee, Chul-Young Kim, Hyi-Seung Lee, Hee-Kyoung Kang, Seon-Heui Cha*, You-Jin Jeon*. *Corresponding. Identification and large isolation of an anti-inflammatory compound from an edible brown seaweed, Undariopsis pterersenianа and evaluation on its anti-inflammatory effect in in vitro and in vivo, zebrafish.*Corresponding. Journal of Applied Phycology. 2016.
3. Seon-Heui Cha, Yu Ree Choi, Cheol-Ho Heo, Seo-Jun Kang, Eun-Hye Joe, Ilo Jou, Hwan-Myung Kim and Sang Myun Park. Loss of parkin promotes lipid rafts-dependent endocytosis through accumulating caveolin-1: implications for Parkinson's disease. Molecular Neurodegeneration 10,63, 2015.
4. Seon-Heui Cha, Min-Cheol Kang, W.A.J.P. Wijesinghe, Sung-Myung Kang, Seung- Hong Lee, Eun-A Kim, Choon Bok Song, You Jin Jeon. Protective effects of marine algae polyphenol, phlorotannins against AAPH-induced oxidative stress in zebrafish embryo, Food chemistry 138, 950-955, 2013
5. Patent: Composition for preventing or treating diabetes comprising the extraction of Polysiphonia japonica. 2016.12

Polysiphonia Japonica Promotes Pancreatic β-cell Regenerationy

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Diabetes can be controlled with insulin injections, but a curative approach that restores the number of insulin-producing β cells is still needed. Using a zebrafish model of diabetes, it screened ~50 seaweed crude extracts to identify enhancers of β cell regeneration. The extracts identified converge on the bone morphogenesis protein (BMP) signaling pathway that inhibit endogenously BMP signaling. The most potent enhancer of β cell regeneration was the Polysiphonia japonica (PJ) extract, which acting through the BMPRⅡ, increased β cell proliferation in zebrafish. Despite markedly stimulating β cell proliferation during regeneration, PJ had only a modest effect during development. With this whole-organism screen, it identified component of the BMP pathway that could be therapeutically targeted for the treatment of diabetes.

Keywords: seaweeds, zebrafish, polysiphonia japonica, beta-cells regeneration, regenerative medicine

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Year	Affiliation	Position
1990-1996	College of Veterinary Medicine, Cheju University	DVM
1999-2003	College of Veterinary Medicine, Hokkaido University	Ph.D. Course
2003-2006	Department of Physiology, College of Medicine, Seoul University	Post Doc
2006-2008	Department of Physiology, College of Medicine, Inje University	Post Doc

3. Research interests

1. Molecular Physiology
2. Mitochondrial Gene Discovery
3. Cellular Immunity

4. List of major publications

1. Higher maternal vitamin D concentrations are associated with longer leukocyte telomeres in newborns. Maternal & Child Nutrition. 2017
2. Expression profile of mitochondrial voltage-dependent anion channel-1 (VDAC1) influenced genes is associated with pulmonary hypertension. Korean J Physiol Pharmacol. 2017
3. Cordycepin induces human lung cancer cell apoptosis by inhibiting nitric oxide mediated ERK/Slug signaling pathway. Am J Cancer Res. 2017
4. Functional and Structural Consequence of Rare Exonic Single Nucleotide Polymorphisms: One Story, Two Tales. Genome Biol Evol. 2015
5. Ion channel gene expression predicts survival in glioma patients. Sci Rep. 2015
6. Improvement Characteristics of Bio-active Materials Coated Fabric on Rat Muscular Mitochondria. Korean J Physiol Pharmacol. 2015
7. Expression profiling of mitochondrial voltage-dependent anion channel-1 associated genes predicts recurrence-free survival in human carcinomas. PLoS One. 2014
8. The role of RNA structure at 5' untranslated region in microRNA-mediated gene regulation. RNA. 2014
9. The impact of RNA structure on coding sequence evolution in both bacteria and eukaryotes. BMC Evol Biol. 2014
10. Ion channel gene expression in lung adenocarcinoma: potential role in prognosis and diagnosis. PLoS One. 2014

Improvement Characteristics of Bio-active Materials Coated Fabric on Rat Muscular Mitochondria

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This study surveys the improvement characteristics in old-aged muscular mitochondria by bio-active materials coated fabric (BMCF). To observe the effects, the fabric (10 and 30%) was worn to old-aged rat then the oxygen consumption efficiency and copy numbers of mitochondria, and mRNA expression of apoptosis- and mitophagy-related genes were verified. By wearing the BMCF, the oxidative respiration significantly increased when using the 30% materials coated fabric. The mitochondrial DNA copy number significantly decreased and subsequently recovered in a dose-dependent manner. The respiratory control ratio to mitochondrial DNA copy number showed a dose-dependent increment. As times passed, Bax, caspase 9, PGC-1α and β-actin increased, and Bcl-2 decreased in a dose-dependent manner. However, the BMCF can be seen to have had no effect on Fas receptor. PINK1 expression did not change considerably and was inclined to decrease in control group, but the expression was down-regulated then subsequently increased with the use of the BMCF in a dose-dependent manner. Caspase 3 increased and subsequently decreased in a dose-dependent manner. These results suggest that the BMCF invigorates mitophagy and improves mitochondrial oxidative respiration in skeletal muscle, and in early stage of apoptosis induced by the BMCF is not related to extrinsic death-receptor mediated but mitochondria-mediated signaling pathway.

Keywords: apoptosis, bio-active materials coated fabric, mitochondria, mitophagy, oxidative respiration

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1989-1993	Pohang University of Science and Technology	B.S.
1993-1995	Pohang University of Science and Technology	M.S.
1995-1998	Pohang University of Science and Technology	Ph.D.
1996-1997	DUKE Medical School	Visiting Scholar
1998-2001	Pohang University of Science and Technology	Post Doctor
2001-2004	University of Pennsylvania (HHMI)	Research Associate
2004-present	Pusan National University	Professor

3. Research interests

1. Angiogenesis
2. Atherosclerosis
3. Hypertension
4. Cancer Metastasis

4. List of major publications

1. Ha JM, Baek SH, Kim YH, Jin SY, Lee HS, Kim SJ, Shin HK, Lee DH, Song SH, Kim CD, Bae SS. Regulation of retinal angiogenesis by phospholipase C-β3 signaling pathway. Exp Mol Med. 2016 Jun 17;48(6):e240.
2. Kim YH, Baek SH, Kim EK, Ha JM, Jin SY, Lee HS, Ha HK, Song SH, Kim SJ, Shin HK, Yong J, Kim DH, Kim CD, Bae SS. Uncoordinated 51-like kinase 2 signaling pathway regulates epithelial-mesenchymal transition in A549 lung cancer cells. FEBS Lett. 2016 May;590(9):1365-74.
3. Yun SJ, Ha JM, Kim EK, Kim YW, Jin SY, Lee DH, Song SH, Kim CD, Shin HK, Bae SS. Akt1 isoform modulates phenotypic conversion of vascular smooth muscle cells. Biochim Biophys Acta. 2014;1842(11):2184-92.
4. Jin SY, Kim EK, Ha JM, Lee DH, Kim JS, Kim IY, Song SH, Shin HK, Kim CD, Bae SS. Insulin regulates monocyte trans-endothelial migration through surface expression of macrophage-1 antigen. Biochim Biophys Acta. 2014;1842(9):1539-48.
5. Kim EK, Ha JM, Kim YW, Jin SY, Ha HK, Bae SS. Inhibitory role of polyunsaturated fatty acids on lysophosphatidic acid-induced cancer cell migration and adhesion. FEBS Lett. 2014;588(17):2971-7.
6. Ha JM, Kim YW, Lee DH, Yun SJ, Kim EK, Hye Jin I, Kim JH, Kim CD, Shin HK, Bae SS. Regulation of arterial blood pressure by Akt1-dependent vascular relaxation. J Mol Med (Berl). 2011 Dec;89(12):1253-60.
7. Selective activation of Akt1 by mammalian target of rapamycin complex 2 regulates cancer cell migration, invasion, and metastasis. Kim EK, Yun SJ, Ha JM, Kim YW, Jin IH, Yun J, Shin HK, Song SH, Kim JH, Lee JS, Kim CD, Bae SS. Oncogene. 2011 Jun 30;30(26):2954-63.

Prostanoid as a Therapeutic Target for Atherosclerosis

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Since chronic inflammation and intimal thickening is accompanied during the pathogenesis of atherosclerosis, inflammatory cytokines may contribute to phenotypic modulation of VSMCs. The present study was designed to explore the effect of tumor necrosis factor α (TNFα) on phenotypic change of VSMCs. Especially, we screened responsible prostaglandins generated by cyclooxygenase-2 (COX-2) and defined the signaling pathways that leads to the phenotypic change of VSMCs. TNFα facilitated phenotypic change of contractile VSMCs into synthetic phenotype as judged by either expression of marker proteins or collagen gel contraction assay. Western blot analysis and promoter assay of COX-2 showed induction of COX-2 upon TNFα stimulation. Silencing or pharmacological inhibition of COX-2 significantly attenuated TNFα-induced phenotypic conversion. Among the tested prostaglandins, only prostaglandin D_2 (PGD_2) significantly induced phenotypic conversion. PGD_2 markedly activated ERK and inhibition of ERK blunted PGD_2-induced phenotypic conversion. However, antagonists or agonists of PGD_2 receptors did not affect PGD_2-induced phenotypic conversion. By contrast, spontaneously dehydrated form of PGD_2 such as PGJ_2, Δ^{12}-PGJ_2, and 15-d-PGJ_2 strongly induced phenotypic conversion. Reporter gene assay showed that TNFα, PGD_2, and 15-d-PGJ_2 significantly activated transcriptional activity of PPARγ. In addition, overexpression of PPAR-γ significantly facilitated PGD_2- and 15-d-PGJ_2-induced phenotypic conversion. Finally, neointima formation was significantly attenuated in mice lacking TNFα. In addition, feeding mice with celecoxib completely blocked carotid artery ligation-induced neointima formation. This study demonstrates that PGD_2 regulates phenotypic conversion of VSMCs through generation of endogenous agonist of PPARγ, leading to induction of neointima formation during occlusive arterial diseases.

Keywords: prostanoid; inflammation; atherosclerosis; phenotype; neointima

Session 4
Past, Present and Future collaboration I

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2. Educational background & professional experience

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1968-1973	Far East State University, Department of Chemistry, Vladivostok, Russia
1973-1979	Junior researcher, G.B. Elyakov Pacific Institute of Bioorganic Chemistry, the Far-Eastern Branch of the Russian Academy of Sciences
1985-1986	Institute of Patents and Licences, Moscow
1989-1990	State Central School of Foreign Languages, Moscow
1979-1992	Department of Patents and Exhibitions, G.B. Elyakov Pacific Institute of Bioorganic Chemistry, the Far-Eastern Branch of the Russian Academy of Sciences
1992-present	Assistant Director for Foreign Relations, G.B. Elyakov Pacific Institute of Bioorganic Chemistry, the Far-Eastern Branch of the Russian Academy of Sciences

3. Research interests

1. patents and lisences; scientific translation into English

4. List of major publications

Author and co-author of three publications in the Russian and international journals; one patent,

Translator (into English) of 33 scientific articles and manuscripts

30 years of International Collaboration: the people and events

Natalia M. Shepetova

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During 53 years our Institute has been engaged in the comprehensive studies of natural compounds. We started from a little laboratory in order to study natural biologically active ginseng root glycosides. Some years later we began investigations of unique biological resources of the World Ocean including marine microorganisms. The principal scientific trends of our research have been defined as bioorganic chemistry, molecular immunology, molecular biology, biotechnology, microbiology, and related fields. Our studies are not only fundamental ones, but pursue practical goal: to create new products for medicine, biotechnology, microbiology, and agriculture. These trends have proved reasonable and now our results in these fields are well-known and widely recognized by our foreign colleagues which show the interest in the collaboration with our Institute. So since the very beginning, our international relations have become very important for the development of our Institute.

For all of these years in order to demonstrate our achievements we have participated in more than twelve international exhibitions, including the exhibitions at the XIV Pacific Congress (1979, Russia), IX Pacific Science Inter-congress (1998, Taiwan), Expo-93 in Daejeon (1993, Republic of Korea), and Ocean Festival in Qingdao (2001, China). We have organized 20 international marine expeditions aboard the research vessel “Akademik Oparin”, which are very important not only to search for new natural resources of biologically active compounds, but also to widen and strengthen our international relations. Many our foreign colleagues participated in these expeditions in the Pacific, Atlantic, and Indian Ocean and successfully worked together with us in the territorial waters of Africa, Australia, Cuba, France, Italy, Madagascar, the Seychelles, Taiwan, and Vietnam. Among them there were outstanding scientists such as: Prof. Joe Baker, a Director of the Australian Institute of Marine Sciences in Townsville (Australia) and his colleagues; Prof. Carl Djerassi from Stanford University (USA); Prof. George Pettit and his team from Arizona State University (USA); Dr. Sang-Jin Kim from the Korea Ocean Research and Development Institute (Republic of Korea), and others.

Very important persons also visited our Institute: Deputy Assistant Secretary General for Scientific and Environmental Affairs at NATO Dr. Paul Rambaut (Brussels); Prof. Rolf Zinkernagel the Nobel Prize Winner; the President of the Vietnamese Academy of Science and Technology Prof. Dang Vu Minh; the President of the Korea Academy of Science and Technology Prof. Myung-Chul Lee.

All of our foreign colleagues have become our very good and reliable friends for many years to come.

1. General Information

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Year	Affiliation	Position
1980-1987	Pusan National University, College of Medicine	M.D.
1987-1991	Pusan National University, Graduate School	Ph.D.
1994-1996	Emory University School of Medicine	Post Doc
1996-1997	Keon-Yang University, College of Medicine	Assistant professor
1997-2014	Dong-A University, College of Medicine	Professor
2015-present	Ajou University School of Medicine	Professor

1. 3D cell culture
2. Immune cell regulation
3. Tumor immunity

1. 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. Nanomed. 2016;11:823-835.
2. Kwak JY. Fucoidan as a marine anticancer agent in preclinical development-review. Mar Drugs. 2014;12(2):851-70.
3. Yun SH, Park ES, Shin SW, Na YW, Han JY, Jeong JS, Shastina VV, Stonik VA, Park JI, Kwak JY. Stichoposide C Induces Apoptosis through the Generation of Ceramide in Leukemia and Colorectal Cancer Cells and Shows In Vivo Antitumor Activity. Clin Cancer Res. 2012;18(21):5934-48.
4. Jin JO, Song MG, Kim YN, Park JI, Kwak JY. The mechanism of fucoidan-induced apoptosis in leukemic cells: involvement of ERK1/2, JNK, glutathione, and nitric oxide. Mol Carcinog. 2010;49(8):771-82.
5. Jin JO, Park HY, Xu Q, Park JI, Zvyagintseva T, Stonik VA, Kwak JY. Ligand of scavenger receptor class A indirectly induces maturation of human blood dendritic cells via production of tumor necrosis factor-alpha. Blood. 2009;113(23):5839-47.

Development of Immune-modulating Natural Compounds by Korean and Russian Groups

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Department of Pharmacology, School of Medicine, Ajou University and Immune Network Pioneer Research Center, Ajou University Medical Center

Recently, Korean side has been testing two compounds from PIBOC. First, fucoidan, which is anion polysaccharide and can bind to many kinds of cell receptors, was evaluated whether it action is dependent on binding to receptors and endocytosis of fucoidan to cells. Among the various receptors, scavenger receptors and selectin are the most well-known binding receptors of fucoidan. We developed fucoidan-blended polycaprolactone and poly(vinyl) alcohol nanofibers. The binding of phagocytes to nanofibers is enhanced by fucoidan. In addition, lipopolysaccharide-stimulated macrophages in fucoidan-blended nanofibers produced higher amounts of nitric oxide than those cultured with fucoidan and lipopolysaccharide in culture dish. Second, an extract isolated from Chaga mushroom was tested whether it has immune-modulating activity. The extract down-regulated secretion of IL-6 by tumor necrosis factor-□-stimulated neutrophils, macrophages, dendritic cells, and T cells. In contrast, the extract had no effects on the production of other cytokines in cytokine and chemokine arrays. Thus, we can develop fucoidan and extract of chaga mushroom as immune-modulating drugs.

1. General Information

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2. Educational background & professional experience

Year	Affiliation	Position
1984	Biochemistry, College of Science, Yonsei University	B.S.
1984	Biochemistry, College of Science, Yonsei University	M.S.
1986	Molecular Pathology, Seoul National University College of Medicine	Ph.D.
1999.2-2003.2	The Scripps Research Institute (TSRI), USA	Research Fellow

3. Research interests

1. Discovery & development of new chemical entities (NCEs)
   - Cardiac diseases: myocardial infarction (MI), atherosclerosis
   - Metabolic diseases: type 1 & 2 diabetes, obesity
   - Hepatic diseases: NAFLD, NASH, fibrosis
   - Cancer: Immuno-Oncology, Adoptive T cell therapy
   - Compartmentalized therapy for mitochondrial diseases
   - Inflammatory (autoimmune) diseases: RA, GvHD, asthma, allergy, pancreatitis, sepsis
2. Biologics
   - Development of attenuated & therapeutic vaccines
   - Development of therapeutic Ab & antibody-drug conjugate (ADC)

4. List of major publications

1. A New Chemical Compound, NecroX-7, Acts as a Necrosis Modulator by Inhibiting High-Mobility Group Box 1 Protein Release during massive ischemia-reperfusion Injury. Lee JH, Park KM, Lee YJ, Kim JH, Kim SH. Transplant Proc. 2016. 48: 3406-3414.
2. NecroX-5 prevents breast cancer metastasis by AKT inhibition via reducing intracellular calcium levels. Park JH, Kim HK, Jung H, Kim KH, Kang MS, Hong JH, Yu BC, Park S, Seo SK, Choi IW, Kim SH, Kim N, Han J, Park SG. Int J Cancer. 2016. 50: 185-192.
3. Neuroprotective effect of NecroX-5. Kim HI, Paik SS, Kim GH, Kim M, Kim SH, Kim IB. Neuroreport . 2016. 27: 1128-1233.
4. NecroX-7 reduces necrotic core formation in atherosclerotic plaques of Apoe knockout mice. Mandy O.J. Grootaert, Dorien M. Schrijvers, Hanne Van Spaendonk, Annelies Breynaert, Nina Hermans, Viviane O. Van Hoof, Nozomi Takahashi, Peter Vandenabeele, Soon Ha Kim, Guido R.Y. De Meyer, Wim Martinet. Atherosclerosis. 2016. 252: 166-174.
5. Thu VT, Kim HK, Long le T, Thuy TT, Huy NQ, Kim SH, Kim N, Ko KS, Rhee BD, Han J. NecroX-5 exerts anti-inflammatory and anti-fibrotic effects via modulation of the TNFα/Dcn/TGFβ1/Smad2 pathway in hypoxia/reoxygenation-treated rat hearts. Korean J Physiol Pharmacol. 2016. 20: 305-314.

Necrotic Inflammation: A Novel Necrosis Inhibitor NecroX-7 with Therapeutic Potential for Necrosis-Associated & Inflammatory Diseases

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Necrosis is tremendously important in the pathogenesis of multiple diseases. In the case of necrosis, the organelles that need protection are the mitochondria, which sustain considerably more advantage than in apoptosis. In the last decade, mitochondria have provided a vast area of research for the pharmacologist, with potential targets for drug action. We identified a novel class of mitochondria-targeted ROS scavenger, NecroX (Archives of Pharmacal Research, 2010), and tested NecroX-7 in the unique in vitro and in vivo necrosis models to verify the notion that inhibition of mitochondrial defects are indispensable for preservation of mitochondrial function, which is critical for necrotic cell viability. Here we demonstrated that blockade of mitochondrial ROS generation with NecroX-7 treatment inhibited various types of necrotic cell death in vitro & in vivo against oxidative stress and ischemia-reperfusion injury (IRI) accompanied by inhibition of mitochondrial permeability transition (mPT) & mPT pore opening, and intracellular cytosolic & mitochondrial calcium overload, which are key features of necrotic cell death. Now the clinical phase 2a of STEMI patients with acute myocardial infarction (AMI) are undergoing in Korea.

These findings suggest that mitochondrial ROS play a key role in necrotic cell death, and identify a previously undescribed necrotic cell-death pathway as well as offer a new therapeutic target for IR injury with an extended window for necrosis-associated human pathologies.

Keywords: necrosis, mitochondrial ROS, ischemic-reperfusion injury

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2. Educational background & professional experience

Year	Affiliation	Position
1987-1991	Seoul National University, Dept. of Animal Science	B.S.
1991-1993	POSTECH, Dept of Life Science	M.S.
1993-1997	POSTECH, Dept of Life Science	Ph.D.
1997-1999	POSTECH, Dept of Life Science	Post-doctoral fellow
1999-2002	Johns Hopkins University, School of Medicine	Post-doctoral fellow
2002-present	Pusan National University, School of Medicine	Professor
2009-2010	University of Virginia, School of Medicine	Visiting professor
2013-present	PNU BK21 Plus Biomedical Science Education Center	Director
2015-present	Department of Physiology, School of Medicine, Pusan National University	Chair

3. Research interests

1. Application of mesenchymal stem cells for vascular regeneration
2. Development of new chemicals or ligands stimulating the therapeutic efficacy of stem cells
3. Proteomic identification of pararcine factors secreted from stem cells for drug development
4. Reprogramming of somatic cells to induced pluripotent stem cells
5. Cardiac and endothelial differentiation of pluripotent stem cells for drug screening and disease therapy

4. List of major publications

1. Jeon, E. S. et al. (2008) Cancer-derived lysophosphatidic acid stimulates differentiation of human mesenchymal stem cells to myofibroblasts-like cells. Stem Cells. 26(3): 789-797
2. Jeon, E. S. et al. (2008) A Rho Kinase/MRTF-A-Dependent Mechanism Underlies the Sphingosylphosphorylcholine-Induced Differentiation of Mesenchymal Stem Cells into Contractile Smooth Muscle Cells. Circ. Res. 103(6):635-42.
3. Kim, M. R., et al. (2009) Thromboxane A2 Induces Differentiation of Human Mesenchymal Stem Cells to Smooth Muscle-Like Cells. Stem Cells. 27(1):191-9.
4. Heo, S. C., et al. (2011) Tumor Necrosis Factor-α-Activated Human Adipose Tissue-Derived Mesenchymal Stem Cells Accelerate Cutaneous Wound Healing through Paracrine Mechanisms. J. Invest. Dermatol. 131(7):1559-67.
5. Yoo, C. H., Na, H. J., Lee, D. S., Heo, S. C., An, Y., Cha, J., Choi, C., Kim, J. H., Park, J. C., Cho, Y. S. (2013) Endothelial progenitor cells from human dental pulp-derived iPS cells as a therapeutic target for ischemic vascular diseases. Biomaterials 34(33):8149-60.
6. Lee MJ, et al. (2012) Macrophages Regulate Smooth Muscle Differentiation of Mesenchymal Stem Cells via a Prostaglandin F2α-Mediated Paracrine Mechanism. Arterioscler. Thromb. Vasc. Biol. 32(11):2733-40

Stem cells for Ischemic Tissue Regeneration

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Cardiovascular diseases are major causes of mortality and morbidity. The application of cel therapy to promote angiogenesis is a novel concept to treat ischemic cardiovascular diseases. Endothelial progenitor cells (EPCs) are mobilized from the bone marrow (BM) into peripheral blood and homed to sites of injury where they participated in the vascular recovery. However, the molecular mechanism associated with the mobilization and homing of endothelial progenitor cells in myocardial infarction has not been clarified yet. The G-protein-coupled formyl peptide receptors (FPRs) have been implicated in regulation of inflammation and angiogenesis, while the role of FPRs in mobilization of EPCs and neovascularization in infarcted heart have not been fully defined. Intraperitoneal injection of WKYMVm, a selective FPR2 agonist, stimulated mobilization of EPCs from BM into peripheral blood (PB). Administration of WKYMVm potentiated MI-induced mobilization of EPCs from BM into PB and resulted in reduced infarct size, apoptosis, and fibrosis. Moreover, cardiac performance after MI was improved by increased recruitment of BM-derived EPCs into the ischemic myocardium. WKYMVm-induced stimulation of EPCs mobilization and functional recovery of infarcted heart were completely attenuated in FPR2 knockout mice, but not in FPR1 knockout mice. Collectively, these results suggest that WKYMVm promotes repair of ischemic tissues by stimulating mobilization of EPCs from BM into PB, homing of circulating EPCs into injured tissues, and subsequent neovascularization via a FPR2-dependent mechanism.

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2. Educational background & professional experience

Year	Affiliation	Position
1987-1993	Seoul National University College of Medicine	M.D.
1996-2001	PhD in Physiology, Seoul National University	Ph.D.
2000-2004	Cheju National University College of Medicine	Assistant Professor
2004-2017	Inje University, College of Medicine	Assistant/Associate Professor
2017-present	Inje University, College of Medicine	Professor

3. Research interests

1. Mitochondrial Signaling Mechanism
2. Cardiac arrhythmias by mechanical stretch
3. Biophysical study of HERG and IKr channel in cardiac myocytes
4. Pacemaker mechanism of ICC (interstitial cell of Cajal)
5. Effect of physical exercise on the heart

4. List of major publications

1. Zhao ZH, Youm JB, Wang Y, Lee JH, Sung JH, Kim JC, Woo SH, Leem CH, Kim SJ, Cui L, Zhang YH. Cardiac inotropy, lusitropy, and Ca(2+) handling with major metabolic substrates in rat heart. Pflugers Arch. 2016 Nov;468(11-12):1995-2006. Epub 2016 Oct 28. PubMed PMID: 27796576; PubMed Central PMCID: PMC5138277.
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3. Wang Y, Youm JB, Jin CZ, Shin DH, Zhao ZH, Seo EY, Jang JH, Kim SJ, Jin ZH, Zhang YH. Modulation of L-type Ca^{2+} channel activity by neuronal nitric oxide synthase and myofilament Ca^{2+} sensitivity in cardiac myocytes from hypertensive rat. Cell Calcium. 2015 Sep;58(3):264-74. doi: 10.1016/j.ceca.2015.06.004. Epub 2015 Jun 10. PubMed PMID: 26115836.
4. Youm JB, Leem CH, Lee SR, Song IS, Kim HK, Heo HJ, Kim BJ, Kim N, Han J. Modeling of stochastic behavior of pacemaker potential in interstitial cells of Cajal. Prog Biophys Mol Biol. 2014 Sep;116(1):56-69. doi: 10.1016/j.pbiomolbio.2014.09.002. Epub 2014 Sep 17. PubMed PMID: 25238716.
5. Youm JB, Park KS, Jang YJ, Leem CH. Effects of streptozotocin and unilateral nephrectomy on L-type Ca^{2+} channels and membrane capacitance in arteriolar smooth muscle cells. Pflugers Arch. 2015 Aug;467(8):1689-97. doi:10.1007/s00424-014-1604-1. Epub 2014 Sep 9. PubMed PMID: 25196539.

Effects of Exercise on Cardiac Contractility and Ca^{2+}-handling

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Exercise is well known as an alternative therapy for cardiovascular diseases. However, effects of exercise on cardiac function and Ca^{2+} homeostasis are still controversial. The aim of this study was to investigate whether exercise alters cardiac function and Ca^{2+}-handling.

C57BL/6 mice (7-week-old) were divided into two groups; control (Con) and exercise (Ex) groups. Ex groups were trained on treadmill for 8 weeks (15m/min for 45 minutes a day). After 8 weeks of exercise, the effects of exercise on cardiac function and Ca^{2+}-handling were investigated by echocardiography, edge detection, Ca^{2+} transient, patch clamp, and western blot. After exercise, Ex groups showed lower body weight and white adipose tissue compared to Con groups. In vivo, Ex groups significantly enhanced cardiac contraction (EF and FS) and performance (SV) compared to Con groups. Improved cardiac contraction is likely to be related to increased time constant of Ca^{2+} transient and longer action potential duration (APD). Expression of Ca^{2+}-handling proteins such as FKBP12.6, p-PLB (Thr-17), troponin was significantly increased by exercise, although L-type Ca^{2+} current density was decreased in Ex compared to Con groups. Our data shows that exercise enhances cardiac contractility via higher expression of Ca^{2+}-handling proteins despite lower L-type Ca^{2+} current density. Therefore, the changes in cardiac contraction by exercise may be associated with other Ca^{2+} influx-related channels rather than L-type Ca^{2+} channel.

Keywords: exercise, cardiomyocyte, cardiac contraction, Ca^{2+}-handling, Ca^{2+}-handling proteins, L-type Ca^{2+} channel, Ca^{2+} transient

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Session 5
Past, Present and Future collaboration II

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present	Head of the Laboratory of Chemistry of Noninfectious Immunity, G.B. Elyakov Pacific Institute of Bioorganic Chemistry, Far-Eastern Branch, the Russian Academy of Sciences

3. Research interests

Isolation and purification of proteins, lectins. Protein sequencing. Study of glycosylation. Diagnosticum development. Cell adhesion. Lectinology. Glycobiology

1. Chernikov O.V., Molchanova V.I., Chikalovets I.V., Kondrashina A.S., Li W., Lukyanov P.A. Lectins of marine hydrobionts // Biochemistry (Moscow), 2013. V. 78, No. 7, P. 760-770.
2. Kovalchuk S.N., Chikalovets I.V., Chernikov O.V., Molchanova V.I., Li W., Rasskazov V.A., Lukyanov P.A. cDNA cloning and structural characterization of a lectin from the mussel Crenomytilus grayanus with a unique amino acid sequence and antibacterial activity // Fish Shellfish Immunol. 2013. V. 35. P. 1320-1324.
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4. Liu Sh., Li L., Tong Ch., Zhao Q., Lukyanov P.A., Chernikov O.V., Li W. Quantitative proteomic analysis of the effects of a GalNAc/Man-specific lectin CSL on yeast cells by labelfre LC-MS // International Journal of Biological Macromolecules. 2016. V. 85. P. 530-538.
5. Chikalovets I.V., Kovalchuk S.N., Litovchenko A.P., Molchanova V.I., Pivkin M.V., Chernikov O.V. A new Gal/GalNAc-specific lectin from the mussel Mytilus trossulus: Structure, tissue specificity, antimicrobial and antifungal activity // Fish Shellfish Immunol. 2016. V. 50. P. 27-33.

Gal/GalNAc-specific Lectin from the Mussel Crenomytilus grayanus Causes Tumor Cells Death and modulates immune response

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Marine biological resources are increasingly being used as sources of new physiologically active substances and objects for basic and applied biomedical research. The biological properties of GalNAc/Gal-specific lectin (CGL) from the edible mussel Crenomytilus grayanus were studied.

Glycan array assay revealed that CGL was able to bind both α and β anomer of galactose, but interaction with the αGal-terminated glycans was stronger. Analysis of most common glycan motifs for CGL showed high affinity to Galα1-4Galβ1-4GlcNAc motif similar to globotriose structure (Gb3: Galα1-4Galβ1-4Glc), the epitope of globotriaosylceramide. CGL recognized Gb3 on the surface of Burkitt`s lymphoma Raji cells (high Gb3 expression), leading to dose-dependent cytotoxic effect, G2/M phase cell cycle arrest and apoptosis. Lectin had no effect on erythroleukemia K562 cells (no Gb3 expression). The activity of CGL was specifically blocked by α-galactoside.

We demonstrated that CGL can activate immune responses in vitro and in vivo. In the in vitro cell models, CGL induced tumor necrosis factor-α and interleukin-6 (IL-6) secretion in mouse macrophages. The CGL-mediated cytokine production was regulated by reactive oxygen species, mitogen activated protein kinases, protein kinase C-α/δ and NF-κB. Interestingly, in LPS-activated macrophages, CGL induced endotoxin tolerance via the downregulation of IRAK2 expression, JNK1/2 phosphorylation and the activation of NF-κB. CGL also increased the bactericidal activity of and induced cytokine production in the macrophages in the mouse model in vivo.

Overall, our data indicate that CGL has the potential to be used in cancer diagnosis and treatment and as a modulator or adjuvant in immunotherapy.

1. General Information

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2. Educational background & professional experience

Year	Affiliation	Position
1975-1980	M.V. Lomonosov Moscow State University	Student
1980-1983	N.D.Zelinsky Institute of Organic Chemistry	Post-graduate student
1983-1991	N.D.Zelinsky Institute	Research Scientist
1991-1994	N.D.Zelinsky Institute	Senior Research Scientist
1989-1990	MPI for Immunbiology, Freiburg, Germany	Visiting scientist and visiting Professor
1990	Carlsberg Laboratory, Department of Chemistry, Copenhagen	Visiting scientist and visiting Professor
1993-4, 1996	MPI for Medical Research	Visiting scientist and visiting Professor
1999	Institute of Chemistry, Academia Sinica, Taipei	Visiting scientist and visiting Professor
1994-2004	N.D.Zelinsky Institute - Head of the Group of Glycoconjugates	
2004-present	N.D.Zelinsky Institute - Head of the Laboratory of Glycoconjugate Chemistry	

3. Research interests

Has published 350+ papers mainly within the area of the synthesis, NMR, and conformational studies of oligo- and polysaccharides. Recent interests have focused on the development of the computer-assisted method of structural analysis of regular polysaccharides, elaboration of new materials of practical importance from natural polysaccharides (chitosan, fucoidans, fucosylated chondroitin sulfates, arabinogalactan, cyclooligosaccharides), the synthesis of complex oligosaccharides and neoglycoconjugates of medical interest, study of the topology of carbohydrate-protein binding and computer design of the inhibitors of carbohydrate binding proteins, development of glycoconjugate vaccines and diagnostic test-kits.

4. List of major publications

1. CInfect. Immun., 78 (2010) 764.
2. Proc. Natl. Acad. Sci. USA, 110 (2013), E2209.
3. Chem. Eur. J., 19 (2013) 9272-9275.
4. Chem. Eur. J., 20 (2014) 16516.
5. Chem. Eur. J., 21 (2015) 1029-1035.
6. Chem. Eur. J., 21 (2015) 1749-1754.
7. Chem. Eur. J., 21 (2015) 17445-17452.
8. Org. Lett. 18 (2016) 5504.
9. Cell. microbiol., 18 (2016) 1294-1307.
10. Front. Immunol., (2016) 7:248. doi: 10.3389/fimmu.2016.00248.
11. Front. Immunol., (2017) 8:659. doi: 10.3389/fimmu.2017.00659.
12. Q. Rev. Biophys. 50 (2017) e9, doi:10.1017/S0033583517000075.

What New Glycochemical Methods Can Contribute to Glycobiology Studies?

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Glycobiology is one of most dynamic area of modern life sciences. New studies in this field are dependent from efficiency and sensitivity of available analytical methods while novel chemical approaches can open the access to synthetic oligosaccharides and glycoconjugates thereof which can be used in a variety of biological assays as molecular probes, haptens, immunogens and other indispensable tools.

Several years ago we discovered new process in carbohydrate chemistry, namely the pyranoside-into-furanoside (PIF) rearrangement [1] which opened straight access towards a variety of biologically important oligosaccharides which are structurally related to bacterial and fungal antigens and seaweed fucoidans. In this communication we summarize the examples of glycobiology investigations which were based on the use of synthetic furanosylated oligosaccharides and glycoconjugates thereof. For selected publications see refs. [2-7].

Supported by Russian Science Foundation (grant 14-23-00199).

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[2] V.B. Krylov, A.G. Gerbst, D.A. Argunov, A.S. Dmitrenok, A.S. Shashkov, Z. Kaczynski, J. Huebner, O. Holst, N.E. Nifantiev, “Definitive structural assessment of Enterococcal diheteroglycan”, Chem. Eur. J., 21 (2015) 1749-1754.

[3] D.A. Argunov, V.B. Krylov, N.E. Nifantiev, "The Use of Pyranoside-into-Furanoside Rearrangement and Controlled O(5)→O(6) Benzoyl Migration as the Basis of Synthetic Strategy to Assemble (1→5)- and (1→6)-linked Galactofuranosyl Chains" Org. Lett. 18 (2016) 5504–5507.

[4] D. Z. Vinnitskiy, V. B. Krylov, N. E. Ustyuzhanina, A. S. Dmitrenok and N. E. Nifantiev “The synthesis of heterosaccharides related to the fucoidan from Chordaria flagelliformis bearing α-L-fucofuranosyl unit”, Org. Biomol. Chem. 14 (2016) 598 – 611.

[5] D.A. Argunov, V.B. Krylov, N.E. Nifantiev “Convergent synthesis of isomeric heterosaccharides related to the fragments of galactomannan from Aspergillus fumigatus”, Org. Biomol. Chem. 13 (2015) 3255-3267.

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1. General Information

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Year	Affiliation	Position
1990, 1992	Department of Biochemistry, Yonsei University, Seoul, Korea	B.S., M.S.
1992-1996	Biotech Research Institute, LG Chemicals, Daejon, Korea	Research Scientist
2002	Biochemistry and Molecular Biology Program, Purdue University, West Lafayette, IN, USA	Ph.D.
2003-2012	Beth Israel Deaconess Medical Center / Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA	Research Fellow/ Instructor
2012-present	Kosin University College of Medicine, Busan, Korea	Professor

3. Research interests

1. Translational Research
2. Hematopoietic Stem/Progenitor Cells
3. Cancer Cell Biology

4. List of major publications

1. Park GB, Chung YH, Jeong JY*, and Kim D*. (2017) A p110delta-specific inhibitor combined with bortezomib blocks drug resistance properties of EBV-related B cell origin cancer cells via regulation of NF-kappaB. Int J Oncol, 50 (5): 1711-1720. (*co-corresponding authors)
2. Jeong JY*, Kim J*, Kim B, Kim J, Shin Y, Kim J, Ryu S, Yang YM, Song KS. (2016) IL-1ra secreted by ATP-induced P2Y2 negatively regulates MUC5AC overproduction via PLC□3 during airway inflammation. Mediators Inflamm, 2016 (Article ID 7984853), 1-10. (*equal contribution)
3. Nam SJ*, Jeong JY*, Jang TW, Jung MH, Chun BK, Cha HJ, Oak CH (2016) Neuron-specific enolase as a novel biomarker reflecting tuberculosis activity and treatment response. Korean J Intern Med, 31 (4): 694-702. (*equal contribution)
4. Jeong JY*, Levine MS, Abayasekara N, Berliner N, Laubach J, and Vanasse GJ. (2015) The non-peptide thrombopoietin receptor agonist eltrombopag stimulates megakaryopoiesis in bone marrow cells from patients with relapsed multiple myeloma. J Hematol Oncol, 8: 37. (*corresponding author)
5. Jeong JY*, Zhou JR, Gao C, Feldman L, and Sytkowski AJ. (2014) Human selenium binding protein-1 (hSP56) is a negative regulator of HIF-1alpha and suppresses the malignant characteristics of prostate cancer cells. BMB Rep, 47 (7): 411-6. (*corresponding author)

Effects of Imatinib on PDGFR-Positive Diffuse Large B Cell Lymphoma (DLBCL) Cells

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#Equal contribution

Imatinib is a chemotherapeutic medication that has successfully been used to treat the Philadelphia chromosome-positive (Ph+) chronic myelogenous leukemia (CML). Originally, imatinib was developed by its ability to inhibit the Bcr-Abl, a fusion protein tyrosine kinase expressed in Ph+ CML cells, but it has a variety of other molecular targets, including c-kit, the platelet-derived growth factor receptor (PDGFR) α and PDGFRβ, of which the expression status was not fully elucidated in lymphomas. Imatinib was reported to suppress the growth of diffuse large B cell lymphoma (DLBCL) in vivo, but not directly, rather by targeting PDGFRβ-positive pericytes surrounding the tumor. In this study, we found that Pfeiffer cells, a DLBCL cell line, express PDGFRα and investigated the effects of imatinib on these cells. PDGF treatment induced phosphorylation of PDGFRα, Akt and Erk that was effectively inhibited by imatinib treatment in Pfeiffer cells, but not in PDGFRα-negative cells such as OCI-Ly1 and Su-DHL2. Importantly, imatinib augmented the rituximab-mediated complement-dependent cytotoxicity, suggesting that a combination therapy of imatinib together with rituximab may be useful for the treatment of patients with PDGFR-positive lymphoma. (NRF-2015M3A9B6073646, 2015R1D1A1A01058387)

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2. Educational background & professional experience

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2002	Korea University, Seoul, Korea	B.S.
2004	Korea University, Seoul, Korea	M.S.
2009	Yonsei University, Seoul, Korea	Ph.D
2012	Yale University School of Medicine	Postdoctoral Associate
present	Pusan National University	Associate Professor

3. Research interests

1. Therapeutic application of adult stem cells in cardiovascular and cerebrovascular diseases.
2. Endothelial-mesenchymal transition (EndoMT) in the pathogenesis of fibrotic disorders
3. Drug development in cardiovascular diseases and genetic disorders

4. List of major publications

1. Seo HH, Lee SY, Lee CY, Kim R, Kim P, Oh S, Lee H, Lee MY, Kim J, Kim LK, Hwang KC, Chang W. Exogenous miRNA-146a Enhances the Therapeutic Efficacy of Human Mesenchymal Stem Cells by Increasing Vascular Endothelial Growth Factor Secretion in the Ischemia/Reperfusion-Injured Heart. (2017) Journal of Vascular Research 54(2):100-108
2. Kim R, Park SI, Lee CY, Lee J, Kim P, Oh S, Lee H, Lee MY, Kim J, Chung YA, Hwang KC, Maeng LS, Chang W. Alternative new mesenchymal stem cell source exerts tumor tropism through ALCAM and N-cadherin via regulation of microRNA-192 and -218 (2017) Molecular and Cellular Biochemistry
3. Lee CY, Kim R, Ham O, Lee J, Kim P, Lee S, Oh S, Lee H, Lee M, Kim J, Chang W. Therapeutic Potential of Stem Cells Strategy for Cardiovascular Diseases. (2016) Stem Cells International
4. Lee CY, Kang JY, Lim S, Ham O, Jang DH, Chang W. Hypoxic conditioned medium from mesenchymal stem cells promotes lymphangiogenesis by regulation of mitochondrial-related proteins. (2016) Stem Cell Research and Therapy 7(1):38
5. Chang W, Kim R, Park SI, Jung YJ, Ham O, Lee J, Kim JH, Oh S, Lee MY, Kim J, Park MS, Chung YA, Hwang KC, Maeng LS. Enhanced healing of rat calvarial bone defects with hypoxic conditioned medium from mesenchymal stem cells through increased endogenous stem cell migration via regulation of ICAM-1 targeted-microRNA-221. (2015) Molecules and Cells. 38(7):643-50
6. Ham O, Lee CY, Kim R, Lee J, Oh S, Lee MY, Kim J, Hwang KC, Maeng LS, Chang W. Therapeutic potential of differentiated mesenchymal stem cells for treatment of osteoarthritis. (2015) International Journal of Molecular Sciences. 16(7):14961-78
7. Ham O, Lee CY, Kim R, Lee J, Lee MY, Kim J, Hwang KC, Chang W. Differentiation of adult mesenchymal stem cells into chondrogenic cells using small molecules or microRNA. (2015) RNA & Disease. 2:e458

Therapeutic Application of MSC-derived Exosome

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Over the last decades, mesenchymal stem cells (MSCs) have been extensively studied with regard to their potential applications in regenerative medicine. MSCs possess the unique potential for use in cell-based therapy of heart diseases, especially in ischemic heart disease. The therapeutic potential of MSCs in myocardial regeneration is based on the ability of MSCs to directly differentiate into cardiac tissue and on the paracrine actions of factors released from MSCs. The predominant mechanism by which MSCs participate to tissue repair is through a paracrine activity. Via the production of a multitude of trophic factors with various properties, MSCs can reduce tissue injury, protect tissue from further degradation and/or enhance tissue repair. That is, the collected types of molecules released by the stem cells, called the secretome, or stem cell released molecules (SRM), number in the 100s, including proteins, microRNA, growth factors, antioxidants, proteasomes, and exosomes, and target a multitude of biological pathways through paracrine actions. Especially, exosomes have been identified as a new type of major paracrine factor released MSCs. They have been reported to be an important mediator of cell-to-cell communication. The diameter of exosomes ranges from 30 to 100 nm which contain an abundance of bioactive substances, such as mRNA, microRNA, and protein. In a myocardial infarction model, MSC-derived exosome had significantly better cardiomyocyte survival, enhanced capillary density, reduced cardiac fibrosis, and restored long-term cardiac function. These therapeutic effect of MSC-derived exosomes were mainly dependent on exosomal microRNAs. Taken together, MSC-derived exosome will be used for therapeutic delivery of miRNA targeted at cardiovascular disease.

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2002-2008	Collgege of Veterinary Medicine, Seoul National University	B.S.
2008-2010	Collgege of Veterinary Medicine, Seoul National University	M.S.
2010-2014	Collgege of Veterinary Medicine, Seoul National University	Ph.D.
2014-2015	Kangstem Biotech, Co., Ltd.	Senior Investigator
2015-2016	Collgege of Veterinary Medicine, Seoul National University	Post Doc.
2016-present	Pusan National University Hospital	Assistant Professor

1. Immune / Epigenetic Regulation of Stem Cell Function (Stemness & Immune Function)
2. Development of Stem Cell Therapeutics based on Immunoregulatory Function
3. Direct Reprogramming (Hematopoietic Stem Cells)
4. Hematopoietic Stem Cell Aging & Immunosenescence (Inflammasome Analysis)

1. Kim HS* et al. Clinical Trial of Human Umbilical Cord Blood-derived Stem Cells for the Treatment of Moderate-to-Severe Atopic Dermatitis: Phase I/IIa Studies. Stem Cells. 35(1):248-255, 2017 Jan
2. Shin TH, Lee BC, Choi SW, Shin JH, Kang I, Lee JY, Kim JJ, Lee HK, Jung JE, Choi YW, Lee SH, Yoon JS, Choi JS, Lee CS, Seo Y, Kim HS*, Kang KS*. Human adipose tissue-derived mesenchymal stem cells alleviate atopic dermatitis via regulation of B lymphocyte maturation. Oncotarget. 8(1):512-522, 2017 Jan
3. Seo Y*, Kim HS*, Kang I* et al. Cathepsin S contributes to microglia-mediated olfactory dysfunction through the regulation of Cx3cl1-Cx3cr1 axis in a Niemann-Pick disease type C1 model. Glia. 64(12): 2291-2305, 2016 Dec
4. Kim HS*, Yun JW*, Shin TH* et al. Human umbilical cord blood mesenchymal stem cell-derived PGE2 and TGF-β1 alleviate atopic dermatitis by reducing mast cell degranulation. Stem Cells. 33(4): 1254-66, 2015 April
5. Kim HS* et al. Human Umbilical Cord Blood Mesenchymal Stem Cells Reduce Colitis in Mice by Activating NOD2 Signaling to COX2. Gastroenterology. 145(6):1392-1403, 2013 Dec

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Stem Cell Therapy for Immune Disorders: Harnessing the Immunomodulatory Capability of Adult Stem Cells

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Mesenchymal stem cells (MSCs) are multipotent adult stromal cells that can self-renew and differentiate into various cell types of mesodermal lineage. Moreover, MSCs are recently known to possess regulatory function on immune cells which makes them a promising tool for the treatment of inflammatory and autoimmune diseases. The interaction between MSCs and immune cells through soluble factors and adhesion molecules has been reported to be crucial for the immunomodulatory effect of MSCs. However, MSC-based cell therapy still has potential limitations and the underlying mechanisms on specific disease remain largely unknown. The main purpose of this study is to provide the better understanding of immune regulatory mechanisms focused on allergic immune responses and autoimmunity and to suggest the new insight available for bridging the current gap between scientific findings and clinical applications. Several murine models for immune disorders including inflammatory bowel disease (IBD), atopic dermatitis (AD) and rheumatoid arthritis (RA) were established and the efficacy of mesenchymal stem cells was determined. Administration of hMSCs reduced the severity of colitis, atopic dermatitis and arthritis in mice through the regulation of disease exacerbating immune cells. Therefore, these results might suggest novel therapeutic strategies for the treatment of allergic disorders and autoimmune diseases.

Keywords: mesenchymal stem cells, immunomodulation, inflammatory bowel disease, atopic dermatitis, rheumatoid arthritis

Poster Session
1 - 4

Discovery of Novel Antibiotics with Low Molecular Weight from Urechis unicinctus

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Since the discovery of penicillin in 19030s, many antibiotic drugs have been discovered from natural products. However, the rapid increase in the emergence and the occurrence of resistant bacteria demands new antibiotics be developed constantly. A novel antibacterial organic compound has been isolated from viscera of Urechis unicinctus. Viscera were collected and extracted in 5% acetic acid and separated using Sep-Pak C18 cartridge and step-wise elution (ultrapure water, 10%, 60%, and 100% methanol in 0.1% trifluoric acid). Materials eluted with 60% methanol exhibited potent antibacterial activity and was subjected to a cation-exchange HPLC and a number of reverse phase HPLC (CAPCELL-PAK C18). The antibacterial activity of this compound digested with trypsin, chemotrypsin, and pronase did not show any decrease suggesting that this was not proteinaceous. LC-MS analysis revealed this compound's molecular weight as 360.1743 Da. Antimicrobial activity of this compound was investigated through ultrasensitive radial diffusion assay using several strains: Bacillus subtilis KCTC 1021, Staphylococcus aureus KCTC 1621, MRSA (methicillin resistant staphylococcus aureus) KCCM 40510, Streptococcus iniae FP 5228, Escherichia coli D31, Pseudomonas aeruginosa KCTC 2004, Aeromonas hydrophila KCTC 2358. Further investigation about the structure and activities of this compound is in progress.

Keywords: novel antibiotics, urechis unicinctus, antimicrobial activity

Asterocins, the First Starfish Antimicrobial Peptides Isolated from Starfish, Patiria Pectinifera

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Two novel cationic antibacterial peptides were purified through a series of HPLC steps from the tube feet and the coelomic epithelium of starfish, Patiria pectinifera, respectively. These peptides were designated Asterocin-1 and 2, in accordance with the phylogenic classification of P. pectinifera: class Asteroidea. The molecular weights and the primary structures of Asterocin 1 and 2 determined via ESI-Q-TOF-MS analysis, Edman degradation method, and rapid amplication of cDNA Ends-polymerase chain reaction (RACE-PCR) were 3715 Da $[M+H]^+$ and 4027 Da $[M+H]^+$ and GKKRNAYFNCDDEW GNPGCICKLVRGKKSTLNC-OH and GRKGRKGVRGNPFFNCEDEFGNPGCV CDKRKGGAAVTC-NH_2, respectively. The nucleotide sequences encoding Asterocin 1 precursor and Asterocin2 precursor comprised 5' untranslated region(UTR) of 78 bp and 81 bp, 3'UTR of 234 bp and 240 bp, and open reading frame (ORF) of 766 bp and 605 bp, respectively. Asterocin1 and 2 contain 76 and 78 amino acids composed of signal peptide of 19 and 21 amino acids, prosequence of 24 and 19 amino acids, and mature peptides of 33 and 38 amino acids. According to the deduced amino acid sequences, these peptides contain four cysteine residues that likely form two disulfide bridges. The difference in the molecular masses of the native Asterocin 2 and the deduced amino acid sequence suggests the Cys38 is likely amidated. The genomic DNA structure analysis revealed structural similarity between that of Asterocin 1 and that of Asterocin 2. Both peptides contained one intron, of 766bp and 896bp, in between two relatively short exons, 154bp and 80bp (Asterocin 1) and 164bp and 71bp (Asterocin 2). The results of real time-quantitative PCR(RT-qPCR) using the tube feet and the apical muscle of starfish suggest these peptides are not induced by immune challenge but produced constitutively.

Study of Targeted Drug Delivery System to Human Cervical Cancer Cells using Folic Acid conjugated Magnetite Nanoparticles

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Targeted drug delivery systems have received attention as a specific and effective chemotherapy. Notably, The use of nanoparticles as a drug delivery system has the potential to improve the specificity of anticancer drugs. In this study, we developed hydrogel nanoparticles that respond to temperature and magnetic field using folic acid (FA) as an external ligand. FA specifically binds to GP38 receptor on human cervical cancer cells. We observed higher cellular uptake of nanoparticles in human cervical cancer cells (HeLa cells) compared to human breast cancer (MDA-MB 231 cells) and human fibroblast cells (Nuff cells). When the nanoparticles loaded with doxorubicin were treated on human cervical cancer cells, we observed apoptosis of human cervical cancer cells in a time and dose dependent manner. Moreover, drug release was controlled by temperature and magnetic force. In conclusion, our results demonstrated that FA conjugated nanoparticles have potential as a carrier for specific drug delivery tool for anti-cancer therapies.

Keywords: nanoparticles, drug delivery system, human cervical cancer cells

Lizard Tail Extracts Induce the Apoptosis of Bladder Cancer 5637 Cells by Inhibiting Akt and Activating the Intrinsic Caspase Pathway

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Lizard Tail Extracts (LTE) have long been used as anti-tumor agents in oriental medicine, without any scientific background. Although anti-tumor effects of LTE on several cancers were recently reported, their effect on bladder cancer has not been investigated. Thus, we explored the anti-tumor effect of LTE and its cellular mechanisms in human bladder cancer 5637 cells. LTE significantly reduced the viability of 5637 cells without any cytotoxic effect on normal cells. LTE increased the Annexin-V staining and the amount of condensed chromatin, demonstrating that the LTE induced cell death was caused by apoptosis. LTE suppressed Akt activation, and the overexpression of constitutively active form of myristoylated Akt prevented LTE-induced death of 5637 cells. Furthermore, LTE activated caspase 9 and caspase 3/7. Taken together, our data demonstrated that LTE suppressed the Akt pathway and activated the intrinsic caspase pathway, leading to the apoptosis of bladder cancer cells.

Keywords: lizard tail extracts, anti-cancer, apoptosis, Akt, caspase

Lizard Tail Extracts induce the apoptosis of lung cancer cells by inhibiting Akt and activating the intrinsic caspase cascade

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Lizard Tail Extracts (LTE) have been used as oriental medicine for a variety of diseases without any scientific background. Recent studies have revealed that lizard extract inhibits proliferation, migration, angiogenesis of various cancer cells. However, the effects of lizard extract on lung cancer has not been investigated. Thus, we explored the anti-tumor effect of LTE and its cellular mechanisms in human and mouse lung cancer cells. LTE significantly reduced the cell viability of lung cancer cells without any cytotoxic effect on normal cells. In addition, we found that LTE induced apoptotic cell death in lung cancer cells. These extract increased the Annexin-V and single-stranded DNA. Furthermore, LTE induced the activation of caspase-9 and caspase-3 leading to apoptotic death of lung cancer cells. Studies of signaling pathway showed that LTE exerts anti-tumor effect on lung cancer cells via inhibition of Akt activation. In conclusion, our findings suggest that LTE can be a promising therapeutic candidate for the development of an anti-cancer drug for lung cancer.

Keywords: lizard tail extracts, anti-cancer, apoptosis, lung cancer

Pharmacologic activation of PGC-1α via AKT/mTOR signaling improves mitochondrial biogenesis in skeletal muscle cell mouse model

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In this study, we focused on targeting the mitochondria to regulate energy homeostasis through HS1793, a novel and potent analogue of resveratrol. We first determined the most effective dosage at which HS1793 takes effect in mouse myoblast C2C12 cells. Dosage screening was performed by evaluating for cytotoxicity and cell proliferation, which showed that higher than 10 μM are were anti-proliferative and detrimental to the cells. The succeeding experiments used dosages lower than 10 μM. Mitochondrial mass, mitochondrial membrane potential, reactive oxygen species (ROS) level, and mitochondria biogenesis-regulated genes were analyzed to determine the effects on mitochondrial biogenesis. HS1793 reduced ROS generation, but treatment did not interfere with cellular viability at low dosages. HS1793 also enhanced mitochondrial biogenesis function by increasing cellular and mitochondrial ATP synthesis function, but induced multinucleation in cells as an adaptive response. HS1793 also upregulated vital mitochondrial biogenesis-related genes such as PGC1-α, activated by AKT and mTOR, which are considered as important regulators of skeletal muscle function. When taken altogether, it shows the viability of HS1793 as a compound that can improve restore mitochondrial function and promote myogenesis and hypertrophy.

Keywords: mitochondria, mitochondria biogenesis, resveratrol, HS1793, muscle

Necrox-5 Exerts Anti-inflammation and Regulates Mitochondria Biogenesis in Hypoxia-reoxygenation (HR) Treated Rat Hearts

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NecroX compounds have been shown to protect the liver and heart from ischemia-reperfusion injury. In this study, we verified whether the Necrox-5 modulates cardiac proteomic alteration and mitochondrial biogenesis, inflammation and fibrosis responses in a hypoxia-reoxygenation (HR) treated rat heart. Necrox-5 treatment (10μM) and non-treatment were employed on isolated rat hearts during hypoxia/reoxygenation treatment using an ex vivo Langendorff system. Level of mitochondrial biogenesis related proteins has dramatically decreased and level of pro-inflammatory proteins was increased in HR treatment heart. However, treated with NecroX-5 significantly attenuated those HR-induced proteomic alterations, practically which are involved in oxidative phosphorylation and metabolic function. NecroX-5 treatment improved mitochondrial complex activities, markedly higher peroxisome proliferator-activated receptor-gamma coactivator-1α (PGC1α) expression levels were observed in NecroX-5-treated group. In addition, HR- or LPS-induced TNF-α and TGF-β1 and phosphorylation of Smad2 productions were reduced with NecroX-5 supplement. The findings suggested the cardio-protective effect of NecroX-5 against cardiac HR injuries by modulating mitochondrial biogenesis and exerting anti-inflammation actions.

Biologically Active Polyphenolic Compounds From Maackia Amurensis Roots

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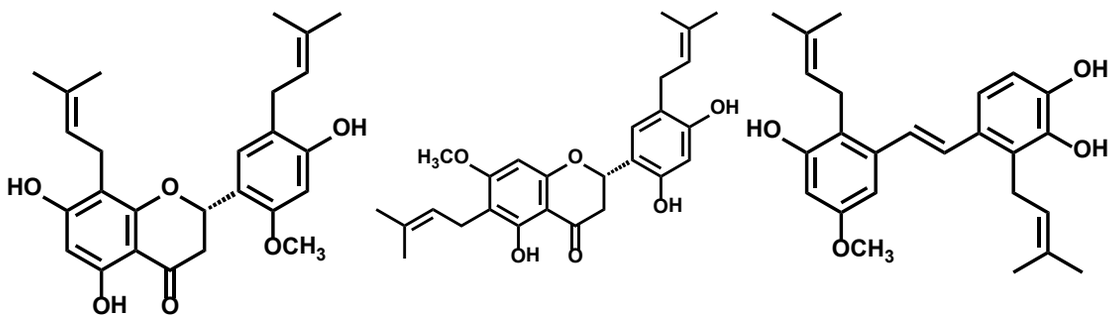
Maackia amurensis is widespread in the southern part of the Russian Far East and is a rich source of polyphenolic metabolites possessing significant hepatoprotective, antioxidant and antiplatelet properties. Previously, the roots of this tree have been shown to contain gentiobiosides, primverosides and glucosides of isoflavones and pterocarpans [1]. However, prenylated polyphenolic compounds of M. amurensis roots have not been investigated so far.

In this study eight polyphenolic compounds, including two new prenylated flavanones 1 and 2 and a new prenylated stilbene 3 have been isolated from M. amurensis roots using column chromatography on silicagel, LH-20 and C-18.



1 **2** **3**

The structures of these compounds were established as (2S)-4',5,7-trihydroxy-2'-methoxy-5',8-di-(3-methylbut-2-enyl)-flavanone (1) (2S)-2',4',5-trihydroxy-7-methoxy-5',6-di-(3-methylbut-2-enyl)-flavanone (2) and (E)-3,3',4'-trihydroxy-5-methoxy-2,2'-di-(3-methylbut-2-enyl)-stilben (3) by NMR, CD, HPLC–PDA–MS and HR-ESI-MS data analyses.

Along with the new compounds, five known prenylated flavanones, maackiaflavanone (4), maackiaflavanone A (5), maackiaflavanone B (6), abyssinone V (7) and 5-hydroxysophoranone (8) have been isolated and identified by comparison of their physical and spectroscopic data reported previously [2]. We showed that these polyphenols are present not only in M. amurensis stems, but also in the root bark of this plant.

The cytotoxicity of compounds 1, 2 and 4–8 against two human cancer cell lines HeLa and SK-MEL-5 was detemined by MTS method. Cisplatin was used as a reference compound. All tested polyphenols inhibited tumor cell growth. Compounds 4, 6 and 8 showed the strongest cytotoxic activity among the compounds tested with IC50 values of 6.5, 8.8 and 7.7 μM, against SK-MEL-5 cells and 8.2, 18.8 and 12 μM against HeLa cells, respectively.

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Complexes of Echinochrome A with Carrageenans, Their Properties and Biological Activity

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Secondary metabolites specific to sea urchins are known as spinochromes or polyhydroxynaphthoquinone pigments. The most well-known sea urchin pigment echinochrome A exhibit a wide range of pharmacological activities, for example antioxidant, anti-diabetic, anti-allergic, cardioprotective, and also protects mitochondrial functions against cardiotoxic drugs. In addition, echinochrome A is the active substance in the cardioprotective and ophthalmic drug Histochrome®, produced in Russia from the sand dollar Scaphechinus mirabilis.

One of the main obstacles to the wide use of echinochrome A is its insolubility in water. Histochrome is available only in ampoules in the form of echinochrome A di- and trisodium salts, which dissociate and oxidize by air oxygen easily. After the opening of ampoules, histochrome quickly undergoes oxidative destruction. Therefore, it is very important to investigate abilities of echinochrome A to form complexes with biopolymer matrices that can increase the solubility of echinochrome, protect its hydroxyl groups from oxidation, preserving or enhancing its pharmacological properties.

Due to diverse physiological activity, safety and biocompatibility, natural polysaccharides represent a promising for biomedicine class of polymers that can be used as carriers for pharmacological agents. In this investigation as such a carrier carrageenans (sulfated polysaccharides of red algae) were used. The combination of gelling and mucoadhesive properties of carrageenans together with their biological activity makes them prospective for drug delivery and prolonged release. It has been established that echinochrome A interacts with kappa- and lambda-carrageenans forming complexes in a wide range of concentrations of both components. These complexes prevent oxidation of echinochrome A and save its antioxidant properties.

Complex of echinochrome A with kappa-carrageenan in ratio 1:5 exhibited ex vivo cardioprotective action on isolated atria of rats comparable to that of echinochrome A. This complex also demonstrated strong gastroprotective activity on the indomethacin-induced gastric ulcer model that was two times higher than that of echinochrome A.

This study was supported by the Grant No. 16-14-00051 from Russian Science Foundation.

Antibacterial and Lysozyme Activities of an Invertebrate-type Lysozyme from Spoon Worm, *Urechis unicinctus*

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An invertebrate-type lysozyme has been isolated and characterized from nephridia of Urechis unicinctus. Nephridia were collected and extracted using 5% acetic acid (AcOH) which then were subject to further purification process using step-wise elution on Sep-Pak C18 cartridge, series of high performance liquid chromatographis (HPLC), and ultrasensitive radial diffusion assay (URDA) as a bioassay system. Finally, a pure antibacterial peak has been eluted at 27-28% acetonitrile with 0.1% trifluoric acid (TFA) on ZORBAX 300SB C18 column. The molecular mass and primary structure of the purified material studied using LC-MS and Edman degradation method were 13kDa and a partial sequence of AISNNXlAXIXQVEGXESQVGKXRMDRGSL respectively. The full amino acid and nucleotide sequences were found using rapid amplification cDNA end polymerase chain reaction (RACE PCR). The nucleotide sequence for the purified protein was comprised of 3' UTR of 208 bp, ORF of 483 bp (160 amino acid residues), and 5'UTR of 784 bp. NCBI Blast of the full amino acid sequence showed high homology to invertebrate type lysozymes purified from several annelids in destabilase domain. The purified protein was then named UuLysI. Recombinant UuLysI (rUuLysI) was produced using pET-28a(+) expression vector and Escherichia coli BL21 (DE3). Antibacterial activity against Bacillus subtilis KCTC 1021, Staphylococcus aureus KCTC 1621, and Salmonella enterica ATCC 13311 was observed. Additionally, potent lysozyme activity of both the native and recombinant UuLysI was present. The transcriptional expression level of UuLysI in different tissues of U. unicinctus was studied through quantitative real-time PCR using the LightCycler system (Roche, Basel, Switzerland). Among the five tissues that were sampled, hemocytes, nephridia, body wall, intestine, and anal vesicle, nephridia which was the source of the purified protein showed the highest expression level.

Isolation and Molecular Cloning of Hepcidin-like Antimicrobial Peptide from the Skin of Puffer Fish, *Takifugu pardalis*

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Mucosal immunity is the primary defense system which plays an important role in the survival of fish in aquatic environment with rich microbial flora. In this context, antimicrobial peptides (AMPs) are crucial components to defense system against infectious bacteria. Hepcidin is a group of cysteine-rich AMPs and plays a crucial role in innate immune system of teleost fish. In this study, we have isolated Hepcidin-like AMP from skin mucus of puffer fish, Takifugu pardalis, using series of reverse-phase (RP)-HPLC and cation-exchange HPLC. Finally, single observance peak with antimicrobial activity was obtained from RP-HPLC with isocratic 23 % acetonitrile/0.1%TFA elution. And antimicrobial activity was tested against Bacillus subtilis using ultrasensitive radial diffusion assay (URDA). The primary structure of the purified peptide was determined by automated N-terminal sequencer and MALDI-TOF MS. The results showed the purified peptide comprises 23 amino acid residues, RKRXRFXXNXXPGKQGXVFXXGF, where X is unidentified residue, and molecular mass is 2609.7 Da as the protonated molecular ion $(M+H)^+$. Alignment of primary structure of purified peptide with other known AMP reveals that purified peptide share sequence homology with other hepcidins. we designated the purified peptide, Takifugu pardalis hepcidin-like AMP (TpHepcidin-like AMP). To clone precursor protein Rapid amplification of cDNA ends (RACE) was conducted. cDNA encoding TpHepcidin-like AMP precursor contains an open reading frame(ORF) of 141bp encoding 46 amino acids with 93 bp located in the 5' untranslated region(UTR) and 219 bp in the 3'UTR. The ORF encoded a signal peptide of 23 amino acids and mature peptide of 23 amino acids and we confirmed the unidentified residues in N-terminal sequencing were cysteine residues. Base on the structural analyses and cDNA cloning, the peptide has 8 cysteine residues forming four disulfide bridges. Collectively, these suggest that hepcidin is involve in mucosal immunity such as a primary defense molecule in fish skin.

Fish Collagen Protect Against $CoCl_2$/TNF-α Induced Cytotoxicity and Inflammation through Inhibition of ROS/MAPK/NF-κB Pathway in HaCaT Cells

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Skin diseases associated with inflammation or oxidative stress represents the most common problem in dermatology. The present study demonstrates that fish collagen peptides (FCP) protect against $CoCl_2$-induced cytotoxicity and TNF-α-induced inflammatory responses in human HaCaT keratinocyte cells. Our study is the first to report that FCP increase cell viability and ameliorate oxidative injury in HaCaT cells through mechanisms mediated by the downregulation of key pro-inflammatory cytokines, namely, TNF-α, IL-1β, IL-8, and iNOS. FCP also prevent cell apoptosis by repressing Bax expression, caspase-3 activity, and cytochrome c release and by upregulating Bcl-2 protein levels in $CoCl_2$- or TNF-α-stimulated HaCaT cells. In addition, the inhibitory effects of FCP on cytotoxicity and the induction of pro-inflammatory cytokine expression were found to be associated with suppression of the ROS, MAPK (p38/MAPK, ERK, and JNK), and NF-κB signaling pathways. Taken together, our data suggest that FCP are useful as immunomodulatory agents in inflammatory or immune-mediated skin diseases. Furthermore, our results provide new insights into the potential therapeutic use of FCP in the prevention and treatment of various oxidative- or inflammatory stress-related inflammation and injuries.

Keywords: fish collagen, HaCaT cells, cytotoxicity, inflammation

Fabrication of Cytocompatible Marine Collagen-Based Nanofibrous Scaffolds for 3D Cell Culture

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Bioactive electrospun nanofibrous scaffolds have been gaining increasing attention as a promising strategy for 3D cell culture and for tissue engineering applications. We constructed a novel composite marine collagen-based (MC/PCL) nanofibrous scaffold by electrospinning method to develop scaffolding materials with outstanding biocompatibility and favorable mechanical strength for 3D culture of thymic epithelial cells (TECs). Nanofibrous scaffolds were characterized using a scanning electron microscope (SEM), and it was revealed that the nanofiber diameters decreased with increasing MC content in the MC/PCL composite nanofibers. The cytocompatibility of the MC/PCL scaffolds was evaluated by SEM, WST-1 assay, confocal microscopy, western blot, and RT-PCR. It was found that the scaffolds not only facilitated the adhesion, spreading, protrusions, and proliferation of TECs but also effectively stimulated the expression of genes and proteins involved in cell adhesion and T cell development. Therefore, these results suggest that the composite MC/PCL nanofibrous scaffolds will be a useful model of 3D cell culture for TECs, and may have wide applicability in the future for 3D cell culture of various cell types and for tissue engineering.

Keywords: nanofiber, marine collagen, electrospinning, 3D cell culture

Marine Collagen-Based Biomimetic Hydrogels for Efficient 3D Cell Culture

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Hydrogels are prototypical matrices for 3D cell culture, of which alginate hydrogels are extensively used. However, ionic crosslinking agents, such as Ca^{2+}, are required to form alginate hydrogels, but introduce Ca^{2+}-associated cytotoxicity and long-term stability issues. Collagen is a promising biomaterial for 3D cell culture scaffolds primarily due to its biocompatibility. In the present study, the authors designed and fabricated a calcium-free, physically crosslinked, efficient, and bioactive hydrogel composed of alginate, marine collagen, and agarose (AmCA) for use in 3D cell cultures. This AmCA hydrogel was assessed by FTIR, swelling property, scanning electron microscopy, phase contrast microscopy, cell proliferation, cell viability, confocal microscopy, transparency and RT-PCR analyses. The gel was found to exhibit excellent cytocompatibility with various tumor and non-tumor cells, to generate high yields of multicellular spheroids, and to promote cellular activity. Furthermore, the transparency of the AmCA hydrogel suggests it can be used without cell-tracking chemicals in morphological studies of cell cultures. Taken together, it would appear that the described physically crosslinked AmCA hydrogel could provide a novel platform for the development of customizable, transparent, biocompatible, functional, easy-to-produce, and cost-effective scaffolds for use in 3D cultures of various cell types.

Keywords: hydrogel, 3D cell culture, collagen

1,3-β-D-GLUCANASES: Distribution, Structure, Properties and Application

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1,3-β-D-glucanases are widely distributed class of enzymes, that can be found in bacteria, fungi, plants, invertebrates, and viruses. At present, there are about 436 enzymes with experimentally detected 1,3-β-D-glucanase activity. According to classical nomenclature of enzymes, 1,3-β-D-glucanases are divided into 4 subclasses: EC 3.2.1.58 (exo-glucanases), EC 3.2.1.6 (split in β-1,3;1,4-glucans not only β-1,3-linkages but also β-1,4-linkages adjacent to the β-1,3-linkages), EC 3.2.1.73 (lichenases, split in β-1,3;1,4-glucan only β-1,4-linkages adjacent to the β-1,3-linkages) and EC 3.2.1.39 (specific to β-1,3-linkages and require the presence of at least two adjacent β-1,3-linkages). Alternative classification is based on structural homology (CAZy – Carbohydrate Active Enzyme). It should be noted that these enzymes possess not only hydrolysing but also transglycosylating activity. Active centers of all 1,3-β-D-glucanases have two key amino acid residues: one of them plays the role of proton donor, another – of nucleophile. The topology of catalytic domains belongs to “pocket” type for exo-glucanases and to “cleft” type for endo-enzymes. The enzymes can be structurally divided into bigger ones (have C-terminal carbohydrate-binding domain with mass about 10 kDa) and smaller ones (without this domain). 1,3-β-D-Glucanases are fibrolytic enzymes, playing irreplaceable role in hydrolysis of carbohydrates for the purposes of consuming of nutrients and production of energy in bacteria and fungi. They are already used in brewing and feeding industries, conversion of algal biomass to fermentable sugars etc. In the same time, because of the special role of 1,3-β-D-glucans in fungal cell walls, they find a range of specialized applications. For instance, 1,3-β-D-glucanase from micelle of Trichoderma harzianum inhibited proliferation of pathogenic fungus Crinipellis perniciosa, a dangerous phyto-pathogen of cocoa trees. Previously this enzyme had been successfully used in vine-making industry for removing the precipitate of 1,3-β-D-glucan of fungus Botrytis cinerea, which hampered filtration. 1,3-β-D-Glucanase from Pseudomonas aeruginosa MCCB 123 was used for isolation of DNA from a range of fungi. 1,3-β-D-Glucanases from Bacillus clausii NM-1 and Vigna aconitifolia were used in immobilized condition in sensors to determine the concentration of laminaran in solutions. The using of 1,3-β-D-glucanases is safe, taking in account the fact, that they have no cytotoxic effect in relation to animal cells, and in big amounts even promote their proliferation.

Keywords: endo-1,3-β-D-glucanase, laminarinase, laminaran, transglycosylation

Biotransformation of Fromononetin Gentiobioside From Maackia Amurensis Roots

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Relict Far Eastern plant Maackia amurensis contains significant amounts of isoflavonoids possessing antioxidant, hepatoprotective, anticoagulant properties. Experiments in vitro and in vivo showed that isoflavones and pterocarpan glycosides including formononetin gentibioside (GBF) from M. amurensis roots can influence the processes of vascular platelet and coagulation hemostasis [1]. The hypocoagulation effect of GBF at a concentration of 50 mM was comparable to that of 0.2-0.5 IU/ml heparin in tests on volunteer blood plasma. After 10-day GBF oral administration to rats at a dose of 25 mg/kg, a 10-fold decrease in ADP-induced platelet aggregation was observed, as well as an increase in activated partial thromboplastin time (APTT), prothrombin clotting time (PT) and thrombin clotting time (TT) in comparison to the control group of animals. Anticoagulant activity of GBF was due to the inhibition of internal and external blood coagulation ways, a decrease in the fibrin formation rate and its density. However, when GBF was injected intraperitoneally to rats at the same dose, we did not observe any similar effect. This is why the study of GBF metabolic transformation ways after oral and intraperitoneal administration to animals was necessary.

GBF was administered to rats a dose of 150 mg/kg. Identification of GBF metabolites in rat blood, urine and liver tissues was carried out by HPLC-PDA-MS and HR-ESI-MS spectrometry. The chemical compositions of GBF metabolites in urine after enteral and intraperitoneal administration of this compound differed significantly. Along with GBF traces, the urine collected within 8 hours after GBF was given to animals orally contained significant amounts of formononetin and daidzein as well as their glucuronides and sulfates.

At the same time, when GBF was injected to rats intraperitoneally, it almost did not undergo any transformations and was excreted from the body with urine unchanged. In addition to GBF, we identified only traces of formononetin, daidzein and glucuronylformononetin in urine.

GBF traces were detected in the blood plasma of animals after 2 and 4 hours after oral administration. In addition, daidzein, one of the products of formononetin conversion by large intestine microflora, were detected in the blood plasma after 4 hours after GBF was given to rats orally. A significant amount of GBF was detected in blood after two hours after intraperitoneal injection of this compound. After four hours only its trace amounts were identified. It should be noted that we did not found even trace amounts of GBF metabolites in blood plasma after intraperitoneal administration of this compound to rats.

Thus, the routes of administration and, hence, biotransformation processes have an impact on the pharmacological activity of GBF in experiments in vivo.

These results show that GBF preparation is converted into formononetin, daidzein and then into their glucuronides and sulfates by intestine microflora β-glucosidases. Finally, we believe that formononetin and daidzein are prodrugs that have extensive anticoagulant and antithrombotic properties.

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Purification of a Novel Neuropeptide from the Whole Body of Starfish, *Patiria pectinifera*

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A novel hexadeca-neuropeptide (HNP) was purified from the whole body of Patiria pectinifera using the apical muscle of the P. pectinifera as a bioassay system. Based on an automated amino acid sequencing, LC/MS/MS analysis, and cDNA cloning results, the amino acid sequence of this peptide revealed FGKGGAYDPLSAGFTD with free carboxyl terminus. This peptide showed threshold response at 10-11 M, and potently relaxed an apical muscle induced the contraction by acetylcholine. In addition, HNP also relaxed the cardiac stomach and tube feet of starfish, P. pectinifera and A. amunensis, in vitro. The precursor HNP cDNA was comprised of 1682 bp, starting with a 5'-UTR of 123 bp, followed by an open reading frame (ORF) of 1305 bp, a 5'-UTR of 253 bp, and the poly-A tail. This peptide has no structural homology with any other previously identified invertebrate or vertebrate neuropeptide family.

Isolation of a Novel Antimicrobial Peptide from the Starfish, *Patiria Pectinifera*

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A novel antibacterial peptide was purified from the tubefeet of starfish, Patiria pectinifera, using HPLC system for fractionation. The tubefeet were extracted with water containing 1 % acetic acid. The extract was tested for antimicrobial activity against Bacillus subtilis using ultrasensitive radial diffusion assay. The antimicrobial peptide was purified through three steps of RP-HPLC and ionexchange HPLC. This material was treated with trypsin for 60min at 37. The treatment caused decrease in antibacterial activity against B.subtilis, indicating that the activity of substance was due to proteinaceous nature. The molecular weight of this peptide was determined to be 3715 Da by the LC/MS/MS analysis. This peptide was composed of 33 amino acids. The primary sequence of the peptide was obtained from Edman degradation and RACE-PCR. This peptide showed potent antibacterial activities against Gram-positive and –negative bacteria. Moreover, this peptide has no structural homology with any other previously identified invertebrate or vertebrate antibacterial peptide family.

Keywords: purification, starfish, antibacterial peptide.

Polysiphonia Japonica Promotes Pancreatic β-cell Regenerationy

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Diabetes can be controlled with insulin injections, but a curative approach that restores the number of insulin-producing β cells is still needed. Using a zebrafish model of diabetes, it screened ~50 seaweed crude extracts to identify enhancers of β cell regeneration. The extracts identified converge on the bone morphogenesis protein (BMP) signaling pathway that inhibit endogenously BMP signaling. The most potent enhancer of β cell regeneration was the Polysiphonia japonica (PJ) extract, which acting through the BMPRⅡ, increased β cell proliferation in zebrafish. Despite markedly stimulating β cell proliferation during regeneration, PJ had only a modest effect during development. With this whole-organism screen, it identified component of the BMP pathway that could be therapeutically targeted for the treatment of diabetes.

Keywords: seaweeds, zebrafish, polysiphonia japonica, beta-cells regeneration, regenerative medicine

Improvement Characteristics of Bio-active Materials Coated Fabric on Rat Muscular Mitochondria

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This study surveys the improvement characteristics in old-aged muscular mitochondria by bio-active materials coated fabric (BMCF). To observe the effects, the fabric (10 and 30%) was worn to old-aged rat then the oxygen consumption efficiency and copy numbers of mitochondria, and mRNA expression of apoptosis- and mitophagy-related genes were verified. By wearing the BMCF, the oxidative respiration significantly increased when using the 30% materials coated fabric. The mitochondrial DNA copy number significantly decreased and subsequently recovered in a dose-dependent manner. The respiratory control ratio to mitochondrial DNA copy number showed a dose-dependent increment. As times passed, Bax, caspase 9, PGC-1α and β-actin increased, and Bcl-2 decreased in a dose-dependent manner. However, the BMCF can be seen to have had no effect on Fas receptor. PINK1 expression did not change considerably and was inclined to decrease in control group, but the expression was down-regulated then subsequently increased with the use of the BMCF in a dose-dependent manner. Caspase 3 increased and subsequently decreased in a dose-dependent manner. These results suggest that the BMCF invigorates mitophagy and improves mitochondrial oxidative respiration in skeletal muscle, and in early stage of apoptosis induced by the BMCF is not related to extrinsic death-receptor mediated but mitochondria-mediated signaling pathway.

Keywords: apoptosis, bio-active materials coated fabric, mitochondria, mitophagy, oxidative respiration

Preliminary Study of Dermal Fibroblasts on Different Substrates Under Mechanical Stimulus

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The skin is a multilayer organ and can endure an incredible range of external mechanical, chemical, and biological forces owing to its physical robustness. In the skin, many possible mechanisms exist for the transmission of external forces from epidermis to dermis such as cell-to-cell interactions, cell-to-extracellular matrix interactions. Fibroblasts (skin cells) found in the dermis show a mechanical association with collagen fibril surfaces and cell-to-cell connections are sometimes evident. It is also announced that mechanical loading on collagen fibrils entail changes in the fibrils interactions with some proteins, however, no clear explanation for this mechanobiological phenomenon has been published. Therefore, external forces on the skin not only stretch various cell and membrane junctions, but also cause lower level stretching of elastin and collagen fibril networks. The mechanical properties of collagen fibres and cell's behaviour under mechanical stimuli must be well understood as the fundamental basis of the mechanobiology of the skin.

To generate mechanical stimulus, the cell stretching device should be employed, however, currently existing cell mechanical devices are not capable of achieving the accuracy required in this study. This prompted us to develop own customized apparatus with unique driving and clamping mechanisms for skin research. In this study, rubber-like silicone materials were mainly used to culture the fibroblasts. It is also demonstrated that cell response to mechanical stimuli depend on the cell orientation. Therefore, micro-patterning was performed to have a correct cell orientation, especially the parallel patterns in longitudinal direction. Cells were isolated from dermal tissue and separately seeded into both smooth and micro-patterned surfaces of the customized stretchable culture wells with density of 37.5k cells /ml and 2ml of the solution. These smooth and micro-patterned surfaces were coated with type I collagen to enhance the cell attachment. The mechanical stimuli condition was 4% of stretching in 0.5Hz for 12 hours.

In the result of cell morphology, only few focal adhesions were formed. In the result of gene expression, however, the expressions of SCX, TNC and MMP13 were increased. This preliminary study can be a signpost for studying a stretching induced molecular mechanobiology of skin tissue engineering.

Novel Defensin-like Antimicrobial Peptides Involved in the Innate Immunity Induced by Vibrio Challenge in the Clam, *Cyclina sinensis*

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Antimicrobial peptides, the important components of the innate immune system, play a pivotal role in the invertebrate defense system against pathogenic bacteria. Novel defensin-like antimicrobial peptides, CsDLPa and its analogue, have been isolated and characterized from the hemolymph of Vibrio challenged clam, Cyclina sinensis. CsDLPa (Cyclina sinensis defensin-like peptide a) has a molecular weight of 3838.30 Da and comprises 35 amino acids, of which 6 are cysteine residues that form 3 disulfide bridges, as a mature peptide. The full nucleotide and amino acid sequences determined through rapid amplification of cDNA ends were consisted of 560 bp, starting with a 5'-UTR of 76 bp, ORF of 411 bp, and a 3'-UTR of 101 bp. The ORF encoded a precursor of 136 amino acids that comprises a 15 residue-long signal peptide, a 86 residue-long propeptide region, and a mature peptide of 35 amino acids. NCBI blast of the mature CsDLPa sequence revealed that this peptide holds no significant homology to any known antimicrobial peptides. Comparison of cysteine arrangements of CsDLPa and other known defensins from invertebrates showed conserved cysteine residues suggesting CsDLPa is an invertebrate defensin-like antimicrobial peptide. To further investigate and characterize CsDLPa, recombinant peptide was produced using a heterologous expression system. The recombinant CsDLPa, which has the same molecular mass as the native, has antimicrobial activity against Gram positive bacterium Bacillus subtilis KCTC 1021. Comparison of the recombinant and the native on reverse-phased high performance chromatography demonstrated the two have different retention times indicating that the cysteine connectivity may not be crucial in exerting antimicrobial activity. CsDLPa which was isolated from C. sinensis after Vibrio challenge may contribute to the innate immunity of C. sinensis in aquaculture and may be utilized in the development alternative antimicrobial agents for aquaculture in the future.

Effects of Imatinib on PDGFR-Positive Diffuse Large B Cell Lymphoma (DLBCL) Cells

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#Equal contribution

Imatinib is a chemotherapeutic medication that has successfully been used to treat the Philadelphia chromosome-positive (Ph+) chronic myelogenous leukemia (CML). Originally, imatinib was developed by its ability to inhibit the Bcr-Abl, a fusion protein tyrosine kinase expressed in Ph+ CML cells, but it has a variety of other molecular targets, including c-kit, the platelet-derived growth factor receptor (PDGFR) α and PDGFRβ, of which the expression status was not fully elucidated in lymphomas. Imatinib was reported to suppress the growth of diffuse large B cell lymphoma (DLBCL) in vivo, but not directly, rather by targeting PDGFRβ-positive pericytes surrounding the tumor. In this study, we found that Pfeiffer cells, a DLBCL cell line, express PDGFRα and investigated the effects of imatinib on these cells. PDGF treatment induced phosphorylation of PDGFRα, Akt and Erk that was effectively inhibited by imatinib treatment in Pfeiffer cells, but not in PDGFRα-negative cells such as OCI-Ly1 and Su-DHL2. Importantly, imatinib augmented the rituximab-mediated complement-dependent cytotoxicity, suggesting that a combination therapy of imatinib together with rituximab may be useful for the treatment of patients with PDGFR-positive lymphoma.
(NRF-2015M3A9B6073646, 2015R1D1A1A01058387)

Therapeutic Application of MSC-derived Exosome

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Pusan National University, Korea

Over the last decades, mesenchymal stem cells (MSCs) have been extensively studied with regard to their potential applications in regenerative medicine. MSCs possess the unique potential for use in cell-based therapy of heart diseases, especially in ischemic heart disease. The therapeutic potential of MSCs in myocardial regeneration is based on the ability of MSCs to directly differentiate into cardiac tissue and on the paracrine actions of factors released from MSCs. The predominant mechanism by which MSCs participate to tissue repair is through a paracrine activity. Via the production of a multitude of trophic factors with various properties, MSCs can reduce tissue injury, protect tissue from further degradation and/or enhance tissue repair. That is, the collected types of molecules released by the stem cells, called the secretome, or stem cell released molecules (SRM), number in the 100s, including proteins, microRNA, growth factors, antioxidants, proteasomes, and exosomes, and target a multitude of biological pathways through paracrine actions. Especially, exosomes have been identified as a new type of major paracrine factor released MSCs. They have been reported to be an important mediator of cell-to-cell communication. The diameter of exosomes ranges from 30 to 100 nm which contain an abundance of bioactive substances, such as mRNA, microRNA, and protein. In a myocardial infarction model, MSC-derived exosome had significantly better cardiomyocyte survival, enhanced capillary density, reduced cardiac fibrosis, and restored long-term cardiac function. These therapeutic effect of MSC-derived exosomes were mainly dependent on exosomal microRNAs. Taken together, MSC-derived exosome will be used for therapeutic delivery of miRNA targeted at cardiovascular disease.

Cathepsin S Contributes to Microglia-Mediated Olfactory Dysfunction Through the Regulation of Cx3cl1–Cx3cr1 Axis in a Niemann–Pick Disease Type C1 Model

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Microglia can aggravate olfactory dysfunction by mediating neuronal death in the olfactory bulb (OB) of a murine model of Niemann–Pick disease type C1 (NPC1), a fatal neurodegenerative disorder accompanied by lipid trafficking defects. In this study, we focused on the crosstalk between neurons and microglia to elucidate the mechanisms underlying extensive microgliosis in the NPC1-affected brain. Microglia in the OB of NPC1 mice strongly expressed CX3C chemokine receptor 1 (Cx3cr1), a specific receptor for the neural chemokine C-X3-C motif ligand 1 (Cx3cl1). In addition, a high level of Cx3cl1 was detected in NPC1 mouse-derived CSF due to enhanced catalytic activity of Cathepsin S (Ctss), which is responsible for Cx3cl1 secretion. Notably, nasal delivery of Cx3cl1 neutralizing antibody or Ctss inhibitor could inhibit the Cx3cl1–Cx3cr1 interaction and support neuronal survival through the suppression of microglial activation, leading to an improvement in the olfactory function in NPC1 mice. Relevant in vitro experiments revealed that intracellular cholesterol accumulation could act as a strong inducer of abnormal Ctss activation and, in turn, stimulated the Cx3cl1–Cx3cr1 axis in microglia via p38 mitogen-activated protein kinase signaling. Our data address the significance of Cx3cl1–Cx3cr1 interaction in the development of microglial neurotoxicity and suggest that Ctss is a key upstream regulator. Therefore, this study contributes to a better understanding of the crosstalk between neurons and microglia in the development of the neurodegeneration and provides a new perspective for the management of olfactory deficits and other microglia-dependent neuropathies.

Keywords: cathepsin s, olfaction, cx3cl1–cx3cr1 interaction, microglia, niemann–pick disease type c

EphrinB1 Promotes Cancer Cell Migration and Invasion Through the Interaction with RhoGDI1

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The Eph receptor tyrosine kinases and their membrane-bound ligands, the ephrins, have been implicated in regulating cell adhesion and cell movement, and thus play important roles in many biological processes such as tissue morphogenesis and homeostasis, as well as pathogenesis of several diseases. Deregulation of the Eph/ephrin system is associated with the promotion of aggressive and metastatic tumors in various human cancers. Here, we show that a Rho family GTPase regulator, Rho-specific guanine nucleotide dissociation inhibitor 1 (RhoGDI1), can interact with ephrinB1, and this interaction is enhanced upon binding the cognate EphB2 receptor extracellular domain. Deletion mutagenesis revealed that amino acids 327~334 of the ephrinB1 intracellular domain are critical for the interaction with RhoGDI1. Stimulation with an EphB2 extracellular domain-Fc fusion protein (EphB2-Fc), induces RhoA activation, and enhances cancer cell migration and invasion in wildtype-ephrinB1 expressing cells. In contrast, these Eph-Fc-induced effects were markedly diminished in cells expressing the mutant ephrinB1 construct (D327-334) that is ineffective at interacting with RhoGDI1. Our study reveals that the binding of RhoGDI1 and ephrinB1 promotes cancer cell progression and may be a therapeutic target in cancers that express ephrinB1.

Resistance Exercise Ameliorates Diabetic Cardiomyopathy by Improving Mitochondrial Function in OLETF Rats

Tae Hee Ko, Seung Hun Jeong, Hyoung Kyu Kim, Jubert C. Marquez, SungRyul Lee, Jae Boum Youm, Dae Yun Seo, Byoung Doo Rhee, Kyung Soo Ko, Nari Kim, and Jin Han*

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Diabetic cardiomyopathy (DC) is a hallmark complication of long-standing hyperglycemia caused by various metabolic and mitochondrial disturbances. Physical activity such as exercise not only enhances the condition of healthy individuals but could also improve the status of those with disease. However, the beneficial effects of resistance exercise (RE) in the prevention of DC and cardiac mitochondrial dysfunction are uncertain. Therefore, this study investigated whether RE attenuates DC by improving mitochondrial function using an in vivo rat model of diabetes. Fourteen Otsuka Long-Evans Tokushima Fatty rats were assigned to sedentary control (SC, n=7) and RE (n=7) groups at 28 weeks of age. Long-Evans Tokushima Otsuka rats were used as the non-diabetic control. The RE rats were trained by 20 repetitions of climbing a ladder 5 days per week. The RE rats exhibited higher glucose uptake and lower lipid profiles, indicating enhanced energy metabolism. RE significantly increased the ejection fraction and fractional shortening compared with the SC rats. The RE rats had more cardiac mitochondria, which increased mitochondrial biogenesis via higher expression of PGC-1α and TFAM. RE reduced proton leakage and reactive oxygen species production, with increased membrane potential. These results were accompanied by higher SOD2 and lower UCP2 and UCP3 levels in the RE group. These data suggest that RE is effective at ameliorating DC by improving mitochondrial function, which may contribute to the maintenance of diabetic cardiac contractility.

Key words: diabetic cardiomyopathy, resistance exercise, cardiac contraction, mitochondrial function

Zinc Deficiency Induces Cardiacdysfunction by Altering Phosphorylation of Phospholamban

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Zinc (Zn^{2+}) is multifaceted element which contains about 2-3g in adult body. Zn^{2+} is found most of organ even though blood and cells. It is essential for diverse biological functions and plays a role in large number of enzyme catalytic action. The present study was undertaken to determine whether zinc deficiency mediates Ca^{2+} handling protein regulation and whether changed Ca^{2+} regulation may lead to generation of cardiac dysfunction in the rat heart. Male wistar rats were pair fed with the control or low zinc food for 1month. Zinc deficiency group decreased aortic pressure, left ventricular developing pressure. In isolated ventricular myocytes, sarcomere shortening and cell shortening was decreased. Our data demonstrate that zinc deficiency results in a significant increase in the phosphorylation of phospholamban at Ser16, Thr17 leading to increased Ca^{2+} uptake into SERCA2A and decreased $[Ca^{2+}]i$ followed by decreased the cardiac contractility. These results suggest that zinc deficiency decrease cardiac contractility, which, in turn, increases phospholamban phosphorylation. Taken together, our data show that zinc ion regulates cardiac contractility byregulating PLB phosphorylation, which leads to a reduction in cardiac function.

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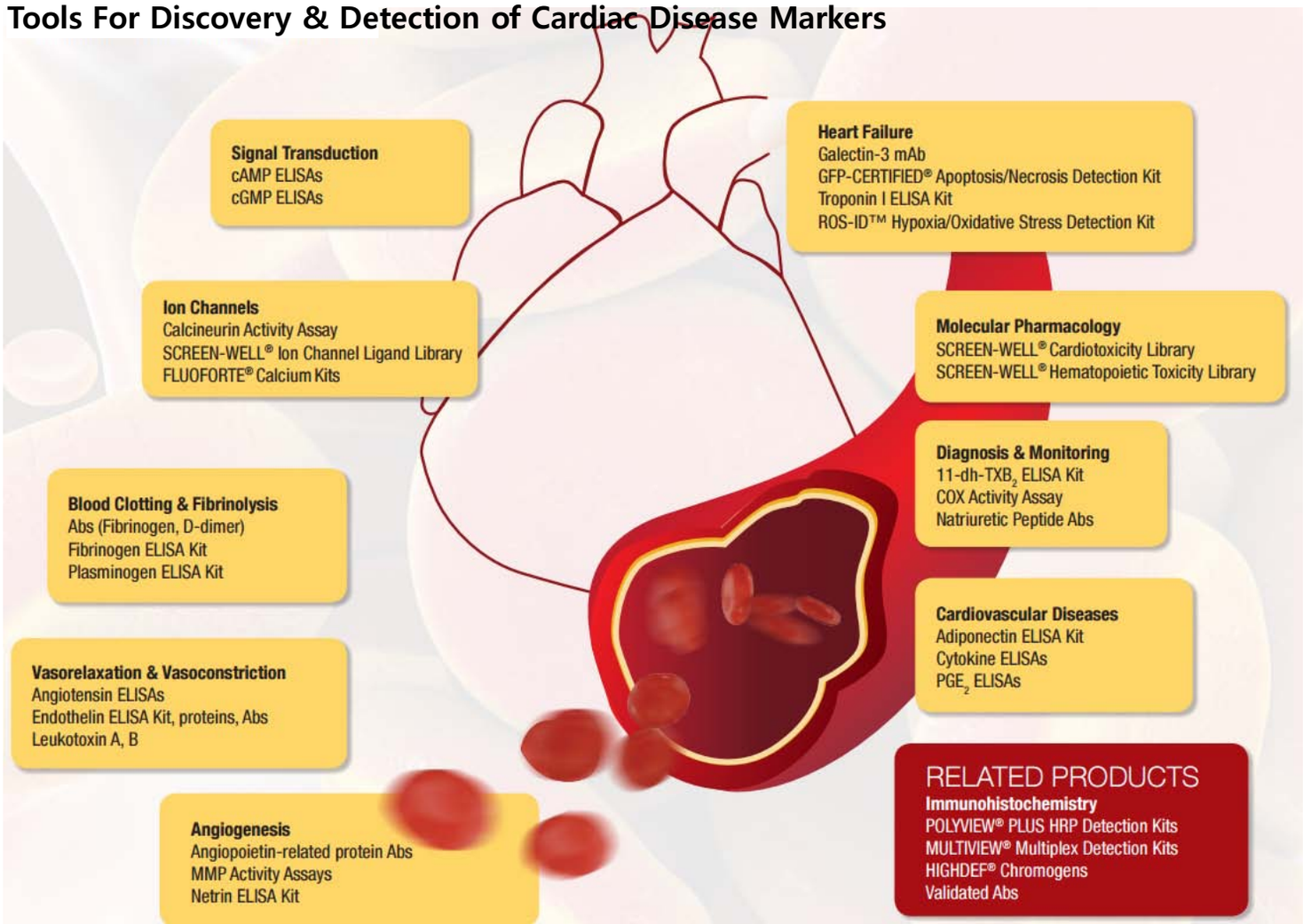

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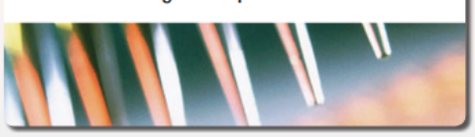

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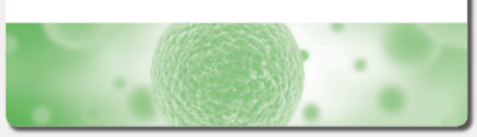

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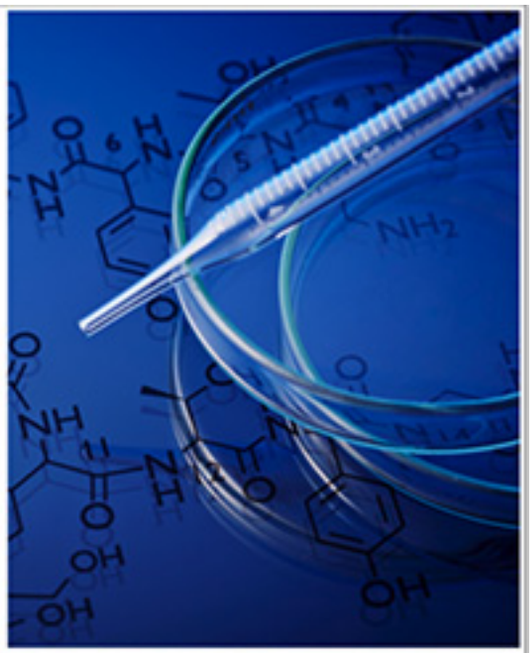

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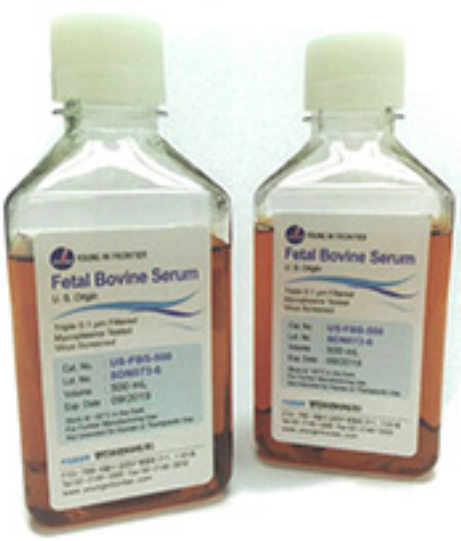

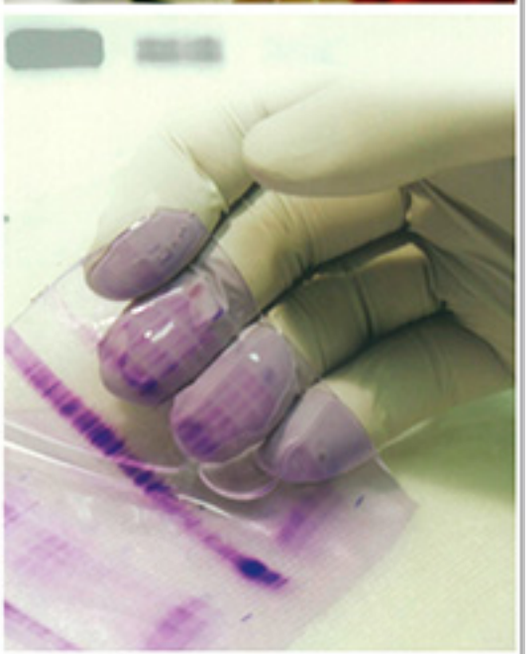

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