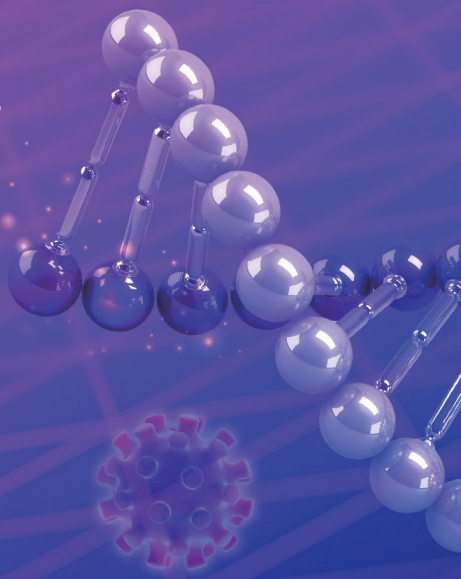
연세대학교 약학대학 대학중점연구소 심포지엄 2021

난치성 질환 치료를 위한 트랜스포톰 제어 기술 개발

Center for Innovative Drug Research on Transportome Modulation, CIDT

일시: 2021년 8월 25일(수) 9:00~13:00

장소: 온(Zoom)/오프라인 하이브리드
연세대학교 국제캠퍼스 진리관D 회의실
Zoom 접속: https://yonsei.zoom.us/j/83739460357
(회의 ID: 837 3946 0357, 암호: 별도발송)



연세대학교 약학대학 대학중점연구소

연세대학교 약학대학 대학중점연구소 심포지엄 2021

난치성 질환 치료를 위한 트랜스포톰 제어 기술 개발

Center for Innovative Drug Research on Transportome Modulation, CIDT

좌장: 김영수 교수(연세대학교 약학대학)

Opening Session		
9:00–9:10	Welcome Address	**강혜영 약학대학 학장** 연세대학교 약학대학
Session 1		
9:10–10:00	Keynote Lecture **"How do we sense pungent and cool compounds? Structural insights from TRP channel studies"**	**이석용 교수** Duke University 의과대학
10:00–10:30	Invited Lecture 1 **AI-powered drug discovery and development**	**남호정 교수** GIST 전기전자컴퓨터공학부
10:30–11:00	Invited Lecture 2 **KCNA4 variants significantly contribute to hearing impairment in population**	**지헌영 교수** 연세대학교 의과대학
11:00–11:10	Break	
Session 2		
11:10–11:40	Invited Lecture 3 **Identification and characterization of novel modulators of protease-activated receptors**	**남궁완 교수** 연세대학교 약학대학
11:40–12:00	Young Scientist 1 **Exploring the molecular mechanisms linking amino acid metabolism and anticancer drug response**	**유희찬 박사** 연세대학교 약학대학
12:00–12:20	Young Scientist 2 **Rhizolutin to reverse the aggregation of Alzheimer pathogenic proteins**	**신지수 박사** 연세대학교 약학대학
12:20–12:50	Panel Discussion	연자 및 참석자
Closing Session		
12:50–13:00	Closing Remarks	**황성주 중점연구소장** 연세대학교 약학대학

Keynote Lecture

“How do we sense pungent and cool compounds? Structural insights from TRP channel studies”

이석용 교수

Duke University School of Medicine

Ion channels are the fundamental components of a multitude of cellular processes. Our group are interested in the transient receptor potential (TRP) ion channels that play central roles in sensory transduction. In my talk, I will cover two key TRP channels: TRPM8 and TRPA1. TRPM8 is the primary cold and menthol sensor and TRPA1 is a primary irritant sensor in human. They are both targets for novel analgesic development. Many intriguing questions remained concerning the design principles of these sensors. For example, menthol generates chemically induced cool sensation in human by activating cold-activated ion channel TRPM8 and this menthol sensing is highly dependent of the signaling lipid PI(4,5)P2 but the mechanism by which this channel senses cooling agents and lipid was not clear. Regarding TRPA1, many TRPA1 agonist irritants are electrophiles that are recognized via covalent bond modification of cysteine residue(s) in TRPA1. Although it was known that TRPA1 possesses a high-performing and versatile electrophile sensing apparatus, which is critical for human nociception, the design principle of this sensor apparatus was unclear. I will discuss our recent cryo-EM and functional studies to address these questions.

연자정보

- 학사, 연세대학교 생화학과(1998)
- 박사, U.C.Berkeley Biophysics(2003)
- 교수, Duke University School of Medicine(2009-현재)

대표논문

- Science. 2019;363(6430):eaav9334. https://doi.org/10.1126/science.aav9334
- Neuron. 2020;105(5):882-894.e5. https://doi.org/10.1016/j.neuron.2019.11.023
- Nat Struct Mol Biol. 2021;28(7):554-563. https://doi.org/10.1038/s41594-021-00616-3

Invited Lecture 1

AI-powered drug discovery and development

남호정 교수

GIST 전기전자컴퓨터공학부

The process of drug discovery is a challenging process considering its required time and efforts. Traditionally, developing one promising drug requires more than 10,000 initial compounds to be selected as candidates. Then these candidates undergo pre-clinical and clinical tests to be passed for several years. In recent years, the paradigm in drug development has been re-shaped in several ways. Many studies have shown the efficiency of artificial intelligence (AI) based drug development approaches that further increase the ability to predict and model the most relevant pharmacokinetic, metabolic, and toxicity endpoints, thereby accelerating the drug discovery process. This talk covers studies about developing AI models for hit compound discovery and lead optimization. The first part of the talk is about the AI model that suggests hit compounds. We employ a convolutional neural network (CNN) on target protein raw sequences to capture local residue patterns participating in drug-target interactions. Our model shows improved prediction performance with the engineered features using CNN on protein sequences than previous protein descriptor-based models and the previous deep learning model. The second part of the talk is about drug repurposing. We describe an interpretable AI model of use in predicting drug responses in cancer cells at the gene, molecular pathway, and drug level. We found that the model shows better accuracy in predicting drugs having efficacy against a given cell line than other state-of-the-art methods. We also confirmed that the model gives high attention to drug-target genes and cancer-related pathways when predicting a response. The validity of predicted results was proven by in vitro cytotoxicity assay. Overall, we propose that our hierarchical and interpretable AI-based model is capable of interpreting intrinsic characteristics of cancer cells and drugs for accurate prediction of cancer-drug responses.

연자정보

- 학사, 서강대학교 컴퓨터공학과(2001)
- 석사, KAIST 컴퓨터공학과(2003)
- 박사, KAIST 바이오및뇌공학과(2009)
- 포스트닥, UCSD Bioengineering(2009-2013)
- 조교수, GIST 전기전자컴퓨터공학부(2013-2018)
- 부교수, GIST 전기전자컴퓨터공학부(2019-현재)

대표논문

- PLoS Comput Biol. 2019;15(6):e1007129. https://doi.org/10.1371/journal.pcbi.1007129
- Comput Biol Chem. 2020;87:107286. https://doi.org/10.1016/j.compbiolchem.2020.107286
- J Chem Inf Model. 2021. https://doi.org/10.1021/acs.jcim.1c00706

Invited Lecture 2

KCNQ4 variants significantly contribute to hearing impairment in population

지헌영 교수

연세대학교 의과대학

Potassium voltage-gated channel subfamily q member 4 (KCNQ4) is a voltage-gated potassium channel that plays essential roles in maintaining ion homeostasis and regulating hair cell membrane potential. KCNQ4 is frequently mutated in autosomal dominant nonsyndromic hearing loss, a typically late-onset, initially high-frequency loss that progresses over time (DFNA2). In addition, variants of KCNQ4 have also been associated with noise-induced hearing loss and age-related hearing loss. To understand the contribution of KCNQ4 variants to hearing loss, we examined public genomic databases and found missense KCNQ4 variants which were present at a low frequency in the population and of unknown significance. We characterized the functional impact of these variants, which, interestingly, induced a reduction in potassium channel activity without altering expression or trafficking of the channel protein, being functionally similar to DFNA2-associated KCNQ4 mutations. Therefore, these variants may be risk factors for late-onset hearing loss, and individuals harboring any one of these variants may develop hearing loss during adulthood. Some KCNQ4 variants responded to KCNQ activators, suggesting the possibility of medical intervention. For variants which are not rescued by KCNQ activators, gene editing utilizing CRISPR/Cas9 could be an alternative. Our results indicate that KCNQ4 variants may contribute more to late-onset hearing loss than expected, and therefore, genetic screening for this gene is important for the prevention and treatment of hearing loss.

연자정보

- 학사, KAIST 생물과학과(2000)
- 석사, KAIST 생물과학과(2002)
- 학사, 연세대학교 의학과(2006)
- 박사, 연세대학교 의과학과(2011)
- 포스트닥, 미시간대학교 소아과(2011-2012)
- 강사, 보스턴아동병원 & 하버드의과대학(2013-2015)
- 부교수, 연세대학교 의과대학(2015-현재)

대표논문

- Exp Mol Med. 2019;51(8):1-12. https://doi.org/10.1038/s12276-019-0300-9
- Clin Transl Med. 2021;11(3):e322. https://doi.org/10.1002/ctm2.322
- Allergy. 2021. https://doi.org/10.1111/all.14952

Invited Lecture 3

Identification and characterization of novel modulators of protease-activated receptors

남궁완 교수

연세대학교 약학대학

Protease-activated receptors (PARs) are a subfamily of G-protein coupled receptors and activated by the proteolytic cleavage of its amino terminal sequence that exposes a tethered ligand. PAR subtypes (PAR1-4) play an important role in many inflammations. For example, PAR1 activation plays a crucial role in the process of skin wound healing such as thrombosis, inflammation, proliferation and tissue repair, and PAR2 activation by serine proteases in the kidney initiates and accelerates kidney injury and collagen synthesis. We identified the first positive allosteric modulator (PAM) of PAR1 (GB83) and a novel potent PAR2 antagonist (Punicalagin, a major polyphenol enriched in pomegranate), and investigated the effect of GB83 on skin wound healing and evaluated the effects of PCG on lupus nephritis (LN). Interestingly, GB83 did not activate PAR1 by itself but strongly enhanced PAR1 activation by thrombin and PAR1-activating peptide. GB83 significantly promoted PAR1-mediated cell viability and migration. In addition, the enhancement of PAR1 activity by GB83 strongly increased gene expression of TGF-β, fibronectin and type I collagen in vitro and promoted skin wound healing in vivo. Punicalagin (PCG) potently inhibited PAR2 (IC50 = 1.5 ± 0.03 μM) and significantly reduced the PAR2-mediated activation of ERK1/2 and NF-κB signaling pathway. In addition, PCG significantly decreased PAR2-induced increases in ICAM-1 and VCAM-1 as well as in IL-8, IFN-ɣ, and TNF-α expression. Notably, the intraperitoneal administration of PCG significantly alleviated kidney injury and splenomegaly and reduced proteinuria and renal ICAM-1 and VCAM-1 expression in NZB/W F1 mice. Our results revealed that GB83 and PCG could be potential therapeutic agents for skin wound healing and LN, respectively.

연자정보

- 학사, 연세대학교 생물학과(2001)
- 석사, 연세대학교 의과대학(2003)
- 박사, 연세대학교 의과대학(2006)
- 포스트닥, 연세대학교 의과대학(2006-2007)
- 포스트닥, Department of Medicine & Physiology, University of California-San Francisco(2007-2010)
- 연구원, Department of Medicine & Physiology, University of California-San Francisco(2010-2012)
- 교수, 연세대학교 약학대학(2012-현재)

대표논문

- J Allergy Clin Immunol. 2019;144(5):1425-1428.e12. https://doi.org/10.1016/j.jaci.2019.07.016
- Int J Mol Sci. 2020;21(14):4975. https://doi.org/10.3390/ijms21144975
- Theranostics. 2020;10(22):9913-9922. https://doi.org/10.7150/thno.46417

Young Scientist 1

Exploring the molecular mechanisms linking amino acid metabolism and anticancer drug response

유희찬 박사

연세대학교 약학대학

It is now well established the tumors alter their metabolism to meet their energetic and metabolic needs. One common feature of many cancer cells is their enhanced uptake and increased dependency on amino acids. Growing evidence indicates that amino acid metabolism is interconnected to drug response in cancer cells. However, factors that connect amino acid metabolism to drug response remain incompletely understood. We recently reported that a variant of SLC1A5 is mitochondrial glutamine transporter in cancer cells and controls intracellular metabolism and drug responses. New possibilities for targeting glutamine metabolism for cancer therapy will be discussed.

연자정보

- 학사, 연세대학교 약학과(2014)
- 박사, 연세대학교 약학과(2020)
- 포스트닥, 연세대학교 약학과(2020–2021)
- 연구교수, 연세대학교 약학과(2021–현재)

대표논문

- Science. 2020;367(6474):205–210. https://doi.org/ 10.1126/science.aau2753
- Cell Metab. 2020;31(2):267–283.e12. https://doi.org/10.1016/j.cmet.2019.11.020
- Exp Mol Med. 2020;52(9):1496–1516. https://doi.org/10.1038/s12276–020–00504–8

Young Scientist 2

Rhizolutin to reverse the aggregation of Alzheimer pathogenic proteins

신지수 박사

연세대학교 약학대학

Rhizolutin, a natural product derived from ginseng–rhizospheric Streptomyces sp. WON17., was discovered with unprecedented structure. Its novel structure was characterized as 7/10/6–tricyclic dilactone carbon skeleton elucidated on the basis of spectroscopic analysis and chemical derivatizations. The potential therapeutic effects of rhizolutin on both amyloid–β (Aβ) and tau, two pathogenic proteins of Alzheimer's disease (AD) were investigated through unbiased in vitro screening followed by animal study using APP/PS1 double transgenic mice model. In the hippocampus of rhizolutin–treated mice brain, significant removal of Aβ was observed. Rhizolutin effectively inhibited the aggregation of both proteins, more importantly, dissociated Aβ and tau aggregates, thereby reducing Aβ–induced apoptosis and inflammation in neuronal and glial cells. Our findings reveal that the novel natural product with unique structure regulates both Aβ and tau simultaneously by therapeutic and preventive means, representing this tricyclic dilactone is attractive as a new scaffold for AD drug discovery.

연자정보

- 학사, 차의과학대학교 의생명과학과(2016)
- 박사, 연세대학교 약학과(2021)

대표논문

- Angew Chem Int Ed Engl. 2020;59(28):11491–11500. https://doi.org/10.1002/anie.202002574
- Angew Chem Int Ed Engl. 2020;59(51):22994–22998. https://doi.org/10.1002/anie.202009294
- Sci Rep. 2021;11(1):1617. https://doi.org/10.1038/s41598–021–81304–6