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KSSFN
대한정위기능신경외과학회
2022 정기학술대회

The Korean Society of Stereotactic and
Functional Neurosurgery

2022. 9. 3.
SAT 08:30~17:20

그랜드 하얏트 인천 (웨스트 타워 그랜드볼룸)

대한정위기능신경외과학회
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그랜드 하얏트 인천 (웨스트 타워 그랜드볼룸)

PROGRAM

08:30~08:50	Registration	
08:50~08:55	Opening Remarks	**전상용** (대한정위기능신경외과학회 회장)
08:55~09:00	Congratulatory Address	**장진우** (세계정위기능신경외과학회 회장)
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09:00~09:20	Pain and Emotion	**최진규** (가톨릭대) ····· 2
09:20~09:40	Epilepsy	**이승훈** (성균관대) ····· 4
09:40~10:00	Parkinson's Disease	**이재민** (부산대) ····· 5
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10:10~10:20	Pseudoprogression and Peritumoral Edema Due to Intratumoral Necrosis after Gamma Knife Radiosurgery for Meningioma	**정인호** (단국대) ····· 9
10:20~10:30	A Predictive Model for 3-Months Survival after Gamma Knife Surgery in Patients with Brain Metastasis from Non-small Cell Lung Cancer with a Karnofsky Performance Status Scale of ≤ 70	**이은정** (서울대) ····· 10
10:30~10:40	Clinical Efficacy of Pulsed Radiofrequency Neuromodulation for Post-stroke Shoulder Pain in Patients with Hemorrhagic Stroke	**나도영** (한림대) ····· 11
10:40~10:50	Aducanumab Delivered to the Hippocampus with Focused Ultrasound Promotes Neuropathology and Cognitive Function in a Model of Alzheimer's Disease	**공찬호** (연세대) ····· 12
10:50~11:00	Retrospective Review of Stereotactic Surgery Using Kymero Robotic Device in Severance Hospital	**장경원** (연세대) ····· 13
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12:20~12:40	Enabling Personalized Patient Care with Sensing Technology	**Shah Saurabh** ····· 24 (Global Sr. Marketing Director, Medtronic)
12:40~13:00	PRECISION IN SIGHT: Future Directions and Development of BSC DBS	**Nicholas Maling** ····· 25 (DBS Scientist, Boston Scientific)

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PROGRAM

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16:50~17:20	총회 및 감사패 증정	
17:20~	경품 추첨 및 만찬	

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YFNS Session
Disease Related Subcortical Pathways

좌장: **최혁재** (한림대), **장원석** (연세대)

대한정위기능신경외과학회
The Korean Society of Stereotactic and Functional Neurosurgery

Pain and Emotion

가톨릭대

최 진 규

CURRICULUM VITAE

Carrier

2018-	Clinical Assistant Professor, Department of Neurosurgery, Yeouido St. Mary's Hospital, Seoul, Republic of Korea
2017-2018	Clinical Assistant Professor, Department of Neurosurgery, Seoul St. Mary's Hospital, Seoul, Republic of Korea
2015-2017	Clinical Fellowship of Stereotactic and Functional Neurosurgery, Seoul St. Mary's Hospital, College of Medicine, the Catholic University of Korea
2012-2014	General Neurosurgeon, Gangwon-do Sokcho Medical Center (Public Health Doctor, Ministry of Health & Welfare)
2008-2012	Residency, Department of Neurosurgery, Seoul St. Mary's Hospital, College of Medicine, the Catholic University of Korea
2007-2008	Internship, Kangnam St. Mary's Hospital & St. Vincent's Hospital, College of Medicine, the Catholic University of Korea

Education and Qualifications

2015-2019	Neurosurgery, Graduate School of Medical Science, the Catholic University of Korea (PhD)
2012	Neurosurgical board, Korean Academy of Medical Sciences
2001-2007	Chungnam National University School of Medicine (MD)

Memberships

Member of Korean Society of Stereotactic and Functional Neurosurgery (KSSFN)
Member of Korean Society of Peripheral Nervous System (KPNS)
Member of World Society for Stereotactic and Functional Neurosurgery (WSSFN)
Member of International Neuromodulation Society (INS)
Member of Korean Society of Neurological Surgeons (KNS)
Member of Korean Society of Stereotactic and Functional Neurosurgery (KSSFN)
Member of Korean Neurotraumatology Society (KNTS)
Member of The Korean Society of Geriatric Neurosurgery (KGNS)

초록

통증이란 "실제적 또는 잠재적인 조직 손상과 관련되거나, 그와 유사한 불쾌한 감각 및 감정적 경험(an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage)"으로 정의된다(international association for the study of pain, IASP, 2020). 따라서 통증은 통각(nociception)과는 다른 현상이며, 감각 뉴런의 활성만으로 설명되지 않고, 개인의 주관적 정서적 경험이 포함된다. 따라서 통증을 이해하는데 있어 신경계의 감정영역과, 관련 회로를 아는 것은 필수적이다.

통증의 감각-식별성 부분(sensory-discriminative component)은 강도, 위치, 통증 양상 등으로 이해될 수 있으며, 정서-동기적 부분(affective-motivational component) 은 불쾌감(unpleasantness)으로 표현되고, 동기적 영역을 통해 우리 몸을 보호하도록 조치를 취하게 한다. 이러한 통증의 두 영역은 일부 임상 연구에서도 밝혀진 바 있는데, 예를 들면, 본인의 통증이 건강에 큰 위협이 된다고 생각하는 사람은, 그렇지 않은 사람에 비해 비슷한 통증강도에서도 불쾌감은 더 높게 나타난다. 하지만 여러 노력들에도 불구하고, 두 영역을 분리하여 임상에 적용하는 것은 아직 쉽지 않다.

말초 및 척수로부터 전달받은 통각정보는, 뇌의 피질과 일부 피질하 영역에서 처리과정을 겪는다.이 통증관련영역을 소위 "pain matrix" 라고 하는데, 그 정확한 범위에 대해서는 아직 논란이 있지만, 현재까지 여러 연구들에서 제1차, 2차 체성감각피질(primary and secondary somatosensory cortices), 섬이랑(insula), 전대상피질(anterior cingulate cortex), 전전두피질(prefrontal cortex), 시상(thalamus)의 일부 핵들 등이 지속적으로 주목되어 왔다. 이 "Pain matrix"는 위에 언급한 것 처럼, 통증의 감각-식별(sensory-discriminative)과 연관된 '외측 통로(lateral pathway)'와 통증의 정서적 부분(affective component)과 관련된 '내측 통로(medial pathway)'로 나눌 수 있다.

통증의 신호전달체계는 고도로 조직화되어 있으며 다양한 특성으로 나타난다. 대뇌 피질로의 체성감각신호는 시상의 체성감각중계뉴런들(VPL, VPM)과 뇌줄기, 중뇌에서 프로젝션하는 3차 신경원(3rd order neuron)을 통한다. 미만성이 아닌 특정뇌피질영역으로만 정보를 전달하는 경우를 예로 들면, VPL의 중심부분에 위치한 세포들은 시상의 외측 후측 영역의 뉴런들은 척수후주-내측섬유대(dorsal column-medial lemniscus) 섬유에서 신호를 받아 대뇌 피질 SI, SII로 프로젝션한다. 시상의 외측 후측 영역의 뉴론 들은, 전외측시스템(anterolateral system)으로부터 받은 신호를 SII와 섬이랑뒷부분(retrpinsular area)으로 프로젝션하고, 시상의 내측핵들은 전대상회피질(anterior cingulate cortex)로 신호를 전달한다. 또한, 중뇌 팥옆핵(midbrain parabrachial nucleus)의 중계뉴런들은 신피질(neocortex)의 편도핵으로 신호를 보낸다. 반면에 넓은 영역으로 미만성 신호를 보내는 경우도 있다. 척수망상체로(spinoreticular tract)으로부터 받은 입력신호는 뇌간의 망상활성계(reticular activating system)가 받아 신피질 전체영역으로 보낸다.

이와 같이, 우리 뇌의 통증전달체계 및 처리과정에는 다양한 피질 및 피질하 영역이 신호를 주고 받는다. 저자는 이번 발표를 통해 통증의 정서적 영역과 관련된 대뇌 피질 및 피질하 부분의 신호전달체계에 중점을 두어 리뷰해 보고자 한다.

Epilepsy

성균관대

이 승 훈

CURRICULUM VITAE

Education

2021	Ph.D. Neurosurgery, Sungkyunkwan University School of Medicine
2012	M.S., Neurosurgery, Sungkyunkwan University School of Medicine
2006	M.D., Sungkyunkwan University School of Medicine

Professional Experience

2022-	Associate professor, Samsung Medical Center, Sungkyunkwan University School of Medicine
2020-	Assistant professor, Samsung Medical Center, Sungkyunkwan University School of Medicine
2018-2020	Clinical Assistant Professor, Samsung Medical Center, Sungkyunkwan University School of Medicine
2015-2018	Clinical Fellow, Functional neurosurgery & Neuro-oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine
2008-2012	Resident, Neurosurgery, Samsung Medical Center, Sungkyunkwan University School of Medicine

Parkinson's Disease

부산대

이 재 민

CURRICULUM VITAE

Academic Education

2006	MD. degree from Pusan National University College of Medicine, Busan, Korea
2017	Master degree from Pusan National University College of Medicine, Busan, Korea
2021	PhD candidate from Gwangju Institute of Science and Technology, Gwangju, Korea

Professional Activities

2010-2014	Resident of Neurosurgery in Pusan National University Hospital, Busan, Korea
2014-2015	Clinical Fellow in Pusan National University Hospital, Busan, Korea
2015-2017	Clinical Fellow in Seoul National University Hospital, Seoul, Korea
2017-	Assistant Professor in Pusan National University Hospital, Busan, Korea

Parkinson's disease (PD) is a complex, multi-system neurodegenerative disorder. Functional changes in basal ganglia circuitry are responsible for the major clinical features of PD such as tremor, bradykinesia, and rigidity. As a result of the investigating the connectivity of basal ganglia networks from the substantia nigra pars compacta (SNc) in PD, The SNc had decreased connectivity with basal ganglia networks. We will also show the basal ganglia-thalamocortical circuit, the network of PD-related circuit dysfunction. Additionally, we suggest some important remaining problems for this field and new neuromodulation strategies such as deep brain stimulation.

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Session I.
Free Paper I

좌장: **김무성** (인제대), **이태규** (가톨릭대)

대한정위기능신경외과학회
The Korean Society of Stereotactic
and Functional Neurosurgery

The Role of Gamma Knife Radiosurgery for Ruptured Cavernous Malformation; Clinical Presentation and Review of Articles

건국대학교병원

조호성

Introduction: Cavernous malformation is a type of an abnormally large collection of "low flow" vascular channels without brain parenchyma intervening between the sinusoidal vessels. Those are occult lesions, known as cryptic vascular malformations. There are different treatment options, including watch and wait, microsurgery and Gamma knife radiosurgery. The purpose of this presentation is to find the role of GKS in treatment of CM and review of articles on ruptured cavernous malformation.

Methods: We performed CM patient medical record review, retrospectively. From 2018 to 2022, 38 patients were involved in this study. Patients presented with headache, and dizziness and blurred vision. Each CM located in right middle cerebellar peduncle and left medial occipital area. To prevent hemorrhagic adverse radiation effects, margin of radiation was limited in high signal on T2WI, GRE. The radiation dose was 13~15Gy(median:14Gy) at 55% isodose line, 14~16Gy(median:15Gy) at 53% isodose line.

Results: Follow up of post-GKS MRI was done in three months and a year after GKS. Mean follow up duration was 42months. During the follow up period, patients' medical history of seizure, hemorrhage and neurologic deficits were not presented. There was no observed adverse radiation effect. Patients\' symptoms were relieved and there was no evidence of recurrent hemorrhage.

Conclusions: Neurosurgical CM removal is recommended for symptomatic lobar CM. When symptomatic CM is present in deep, eloquent areas, the use of GKS for CMs should be considered. Radiation dose prescription for CM should be considered lower than other vascular malformation, such as arteriovenous malformation(AVM).

Pseudoprogression and Peritumoral Edema Due to Intratumoral Necrosis after Gamma Knife Radiosurgery for Meningioma

[1]단국대학교병원, [2]신촌세브란스, [3]영남대학교병원

정인호[1], 장경원[2], 박소희[3], 정현호[2], 장진우[2], 장원석[2†]

Introduction: Peritumoral cerebral edema is reported to be a side effect that can occur after stereotactic radiosurgery. We aimed to determine whether intratumoral necrosis (ITN) is a risk factor for peritumoral edema (PTE) when gamma knife radiosurgery (GKRS) is performed in patients with meningioma. In addition, we propose the concept of pseudoprogression: a temporary volume expansion that can occur after GKRS in the natural course of meningioma with ITN.

Methods: This retrospective study included 127 patients who underwent GKRS for convexity meningioma between January 2019 and December 2020. Risk factors for PTE and ITN were investigated using logistic regression analysis. Analysis of variance was used to determine whether changes in tumor volume were statistically significant.

Results: After GKRS, ITN was observed in 34 (26.8%) patients, and PTE was observed in 10 (7.9%) patients. When postoperative ITN occurred after GKRS, the incidence of postoperative PTE was 18.970-fold (p=0.009) greater. When a 70% dose volume ≥1 cc was used, the possibility of ITN was 5.892-fold (p<0.001) higher. On average, meningiomas with ITN increased in volume by 128.5% at 6 months after GKRS and then decreased to 94.6% at 12 months.

Conclusions: When performing GKRS in meningioma, a 70% dose volume ≥1 cc is a risk factor for ITN. At 6 months after GKRS, meningiomas with ITN may experience a transient volume expansion and PTE, which are characteristics of pseudoprogression. These characteristics typically improve at 12 months following GKRS.

A Predictive Model for 3-Months Survival after Gamma Knife Surgery in Patients with Brain Metastasis from Non-small Cell Lung Cancer with a Karnofsky Performance Status Scale of ≤ 70

[1]Department of Neurosurgery, Seoul National University Hospital, Seoul, Republic of Korea
[2]Gamma Knife Radiosurgery Center, Seoul National University Hospital, Seoul, Republic of Korea
[3]Seoul National University College of Medicine, Seoul, Republic of Korea

Eun Jung Lee, MD, PhD[1,2,3], Hangeul Park, MD[1], Hyun-Tai Chung, PhD[1,2,3], Sun Ha Paek[1,2,3]

Background: Gamma Knife surgery (GKS) for brain metastasis (BM) has been generally advocated for patients with with a Karnofsky performance status (KPS) scale of ≥ 70. However, some patients with poor KPS scale of 〈 70 are recoverable after GKS and show tenacious survival.

Objective: To devise a 3-month survival prediction model to screen for the patients with BM with a KPS of ≤ 70 in whom GKS is needed.

Methods: A retrospective analysis for 67 patients with a KPS scale of from 50 to 70 undergoing GKS for BM of NSCLC from 2016 to 2020 in our institute was performed. Univariate and multivariate logistic regression analyses were performed to investigate on factors related to survival for more than 3 months after GKS. The probability (p) prediction model was designed by giving weight corresponding to the odds ratio of the variables.

Results: The overall survival was 9.9 ± 12.7 months (range, 0.2-53.2), with a 3-months survival rate of 59.7% (n = 40). In multivariate logistic regression analysis, extracranial disease (ECD) control (p = .033), focal neurological deficit (FND) (p = .014), and cumulative tumor volume (Σ TV) (p = .005) were associated with 3-month survival, generating the prediction model of 3-months survival as below (Harrell' C index = 0.767).

$$p = \frac{\left(exp^{-0.2505} \times \left(4^a \times 5^b \times 0.9^c\right)\right)}{1+\left(exp^{-0.2505} \times \left(4^a \times 5^b \times 0.9^c\right)\right)}$$

where a for ECD (1 or 0); b for FND (1 or 0); and c for Σ TV.

Conclusions: GKS for BMs is recommended in selected patients despite a KPS scale of ≤ 70 if the patients have BM-related FND, small intracranial tumor burden, and controlled ECD.

Clinical Efficacy of Pulsed Radiofrequency Neuromodulation for Post-stroke Shoulder Pain in Patients with Hemorrhagic Stroke

Department of Neurosurgery, Chuncheon Sacred Heart Hospital, Hallym University, College of Medicine, Korea

Doyoung NA, MD, Hyukjai Choi, MD, PhD†, Jinseo Yang, MD, PhD, Yongjun Cho, MD, PhD, Jinpyeong Jeon, MD, Ph.D

Introduction: Post-stroke shoulder pain (PSSP) is a common, painful complication of stroke. PSSP causes severe pain and range of motion (ROM) limitation that affects patients' quality of life (QOL). Pulsed radiofrequency (PRF) neuromodulation of the suprascapular nerve is a safe and efficient modality for chronic shoulder pain with long-term effects. This study aimed to evaluate the long-term clinical efficacy of PRF neuromodulation of the suprascapular nerve in patients with PSSP after a hemorrhagic stroke.

Methods: This retrospective case series was conducted at a single center. From 2013 to 2021, 13 patients with PSSP underwent PRF neuromodulation of the suprascapular nerve. The primary outcome was the visual analog scale score. The secondary outcomes were the shoulder ROM, disability assessment scale, modified Ashworth scale, modified Rankin scale, and EuroQol-5 dimension-3L questionnaire scores. These parameters were evaluated before,immediately after PRF modulation, and every 3 months until last f/u.

Results: Six men and seven women were enrolled. All patients were followed up for at least 12 months. The mean VAS score was 7.07 points before PRF neuromodulation, and it markedly decreased to 2.38 points immediately after the procedure. Shoulder ROM for abduction and flexion, DAS for pain, mRS, and EQ-5D-3L demonstrated marked improvement. No complications were reported.

Conclusions: PRF neuromodulation of the suprascapular nerve is an efficient modality to reduce pain and improve QOL in patients with hemorrhagic stroke.

Aducanumab Delivered to the Hippocampus with Focused Ultrasound Promotes Neuropathology and Cognitive Function in a Model of Alzheimer's Disease

[1]연세대학교 의과대학, [2]서울대학교 의과대학

공찬호[1], 양은정[2], 신재우[1], 박준원[1], 장원석[1], 이창한[2], 김현주[2], 김혜선[2], 장진우[1†]

Introduction: In previous studies, it has been shown that focused ultrasound (FUS)-induced BBB opening enhanced the penetration of therapeutic agents. Aducanumab (Adu), which has recently attracted attention as the first disease-modifying therapeutic for Alzheimer\'s disease (AD), is a human IgG1 monoclonal antibody that targets oligomer and fibril forms of beta-amyloid. We investigated the effects of combined treatment with FUS and a low dose of Adu (3 mg/kg) compared with FUS or Adu alone in AD animal model.

Methods: The FUS was targeted to four focal spots in the hippocampus bilaterally. Aducanumab (3 mg/kg in saline) was injected intravenously at the end of FUS sonication. It was delivered three times in total and each treatment was performed every two weeks. To investigate a spatial working memory, spontaneous alternation in the Y-maze was observed in experimental animals.

Results: The combined treatment significantly restored cognitive impairment and decreased the level of Aβ plaques in the hippocampi. We also found that the combined treatment increased phagocytosis in microglia and astrocytes and neurogenesis in the hippocampi. Furthermore, RNA sequencing identified 4 enriched canonical pathways such as phagosome formation, neuroinflammation signaling and CREB signaling and reelin signaling suggesting that the combined treatment may have beneficial effects.

Conclusions: The combined therapy was shown to be effective even with the minimal dose of drug by increasing the BBB penetration rate with FUS while excluding the possibility of side effects. This study provides better insight into establishing a solid therapeutic strategy for the treatment of AD as well as other neurodegenerative diseases.

Retrospective Review of Stereotactic Surgery Using Kymero Robotic Device in Severance Hospital

세브란스병원

장경원, 홍승우, 장원석, 정현호, 장진우†

Introduction: Recent advances in technology allowed a new era for robotic surgery. Especially for stereotactic surgery which needs high preciseness, robotic surgery can reduce the error which can occur in manual surgery. Here we retrospectively overlooked our 3 year experience using the kymero robotic device.

Methods: We retrospectively reviewed patients who underwent surgery using the kymero robotic device. The study includes surgery from our first patient in November 2020 to July 2022. We collected the data from type of surgery, surgery time, complications,

Results: 78 patients underwent stereotactic robot surgery during our study period. No robot related complications occured. Mean target error were below 5mm. 41 patients underwent stereotactic biopsy, 17 patients underwent SEEG. 14 patient underwent depth EEG electrode insertion, Other surgeries included DBS, Ommaya catheter insertion, ICH catheter insertion.

Conclusions: Using robotics in stereotactic surgery is a safe and accurate method, and for multiple electrode insertion such as SEEG or multi target biopsy, robotics can increase efficacy by reducing surgical time.

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대한정위기능신경외과학회
2022 정기학술대회

Symposium I.
Cutting Edge Technologies

좌장: **홍석호** (울산대), **김종현** (고려대)

대한정위기능신경외과학회
The Korean Society of Stereotactic
and Functional Neurosurgery

Brain-Machine Interfaces: Present and Future Perspectives

고려대 뇌공학과

민 병 경

CURRICULUM VITAE

학력 및 대표 경력

2007년	독일 막데부르그 대학교, 박사 (뇌파, 인지 신경과학)
2009-2011년	미국 Harvard 의과대학 / 브리검 병원 방사선과 연구원
2012년 - 현재	고려대학교 뇌공학과 교수
2018-2019년	미국 MIT 방문 학자 (맥거번 뇌 연구소)
2020 – 2022년	고려대학교 뇌인지과학 융합전공 주임교수
2022년- 현재	고려대학교 뇌공학연구소 소장

학술지 편집 위원 (Editor) 활동

Frontiers in Human Neuroscience (Associate Editor) Frontiers in Neuroimaging (Associate Editor)
Frontiers in Neurology (Associate Editor)

기술 위원 (Technical Committee) 활동

IEEE Systems, Man, and Cybernetics Society
Brain-Machine Interface Systems (Technical Committee)

학술지 및 연구비 심사 위원 (Reviewer) 활동

Scientific Reports (Nature.com)
Communications Biology (Nature.com)
Trends in Biotechnology (Cell.com)
NeuroImage
PLOS ONE
Frontiers in Neuroscience
Journal of Ultrasound in Medicine
Journal of Computing Science and Engineering
BMC Neuroscience
Ergonomics

Physiology & Behavior
Social Neuroscience
Journal of Clinical Neurophysiology
Journal of Psychosomatic Research
IEEE Transactions on Cybernetics
IEEE International Conference on Systems, Man, and Cybernetics
IEEE Transactions on Information Forensics and Security
IEEE Access
IEEE International Winter Conference on Brain-Computer Interface
Journal of Cognitive Science
International Journal of Psychophysiology
International Journal of Imaging Systems and Technology
Swiss National Science Foundation
Bulletin of the Polish Academy of Sciences: Technical Sciences

연구 관심

뇌파(EEG, MEG, fMRI)의 인지적 속성 및 의식의 신경생리학적 연구
비침습적 신경/인지 기능 제어 연구 (경두개 전류 자극, 집속 초음파 자극)
전전두엽(PFC) 기반의 인지적 Brain-Machine Interface 연구

기존의 뇌-기계 인터페이스 (Brain-machine interface: BMI) 연구는 뇌의 감각 정보 처리를 담당하는 후두엽이나 연합 정보 처리를 담당하는 두정엽 등에 기반한 기초적인 접근 연구가 일반적이었고, 사용되는 인지 과제 패러다임 역시 전형적이고 다소 진부한 방법에서 크게 벗어나지 못했다. 이는 기계학습이나 딥러닝 등의 뇌파 신호 기반의 BMI 디코딩 방법의 최근 혁신적인 발전에 비교하면, 상대적으로 미흡한 면이 있다. 따라서, BMI용 뇌파 신호를 의도적으로 뇌의 특정 영역에서 손쉽게 끌어낼 수 있도록, 신경생리학에 기반한 특화된 인지 처리 실험 패러다임을 새롭게 개발하는 접근법도 필요한 상황이다. 예를 들어, 전전두엽(prefrontal cortex: PFC)은 인간의 고차원적 인지 기능을 담당하여, 그곳의 뇌파 신호가 BMI 구동의 핵심 역할을 할 인간의 의도를 담고 있음에도 불구하고, 그 동안 BMI 분야에서 해당 뇌파 신호를 고차원적인 인지 기능별로 분리해 내기 어려운 기술적 이유로, 의도 기반 BMI 기술 개발이 지체되고 있었다. 최근, 인간의 의도를 반영하는 전전두엽-기반의 BMI 연구도 가능성이 있다는 연구 결과도 발표되는 등, 인간의 의도가 직접적으로 반영된 BMI 뇌파 신호 추출이 고무적이란 측면에서 BMI 기술에 희망이 있고, 나아가, 앞으로의 연구는 BMI가 뇌의 비침습적 신경제어 (neuromodulation) 기술과 결합하여, 뇌-뇌 인터페이스 (brain to brain interface) 기술이 가능해지고, 이는 그동안 주목을 받지 못하던 뇌심부의 피질하(subcortical) 영역의 특정 인지 처리 네트워킹에 대한 선택적 자극과 함께 미래의 BMI 기술로서 새로운 방향을 제시할 수 있다.

Machine Learning with Super Computer

율리히 연구소

고 성 룡

CURRICULUM VITAE

Education

1998.09-2004.02	Dept. of Mechanical Engineering, Korea University, Seoul, Korea Ph.D. degree, dissertation title: "Aeroacoustic Computations of Subsonic Turbulent Flows over Open Cavity"
1994.03-1997.08	Dept. of Mechanical Engineering, Korea University, Seoul, Korea Master of Science in Engineering, thesis title: "Numerical Analysis of Turbulent Flow on Turbine Cascade with an Endwall Fence"
1990.03-1994.02	Dept. of Mechanical Engineering, Korea University, Seoul, Korea Bachelor of Science in Engineering

Professional Experience

2018.08-present	Juelich Supercomputing Centre (JSC), Forschungszentrum Juelich, Juelich, Germany Research Scientist (CS Division/SDLFSE) - SiVeGCS: SC technical support team / project mentor - R&D management: Biomechanics/AI/CFD - Industry Relation Team: Development of cooperation with external partners
2007.01-2018.07	Institute of Aerodynamics, RWTH Aachen University, Aachen, Germany Research Scientist (Numerical Research Department)
2006.01-2006.12	Institute of Aerodynamics, RWTH Aachen University, Aachen, Germany Visiting Research Scientist funded by Korea Research Foundation
2004.03-200612	Research Institute of Engineering and Technology, Korea Univ., Seoul, Korea Senior Research Scientist
1997.09-1998.08	Research Institute of Engineering and Technology, Korea Univ., Seoul, Korea Research Scientist

Area of Expertise

- Computational fluid dynamics (CFD)
- Aeroacoustics
- Turbulent flow modeling/control
- Biofluid
- High-performance computing
- Machine learning/Deep learning
- GPU programming

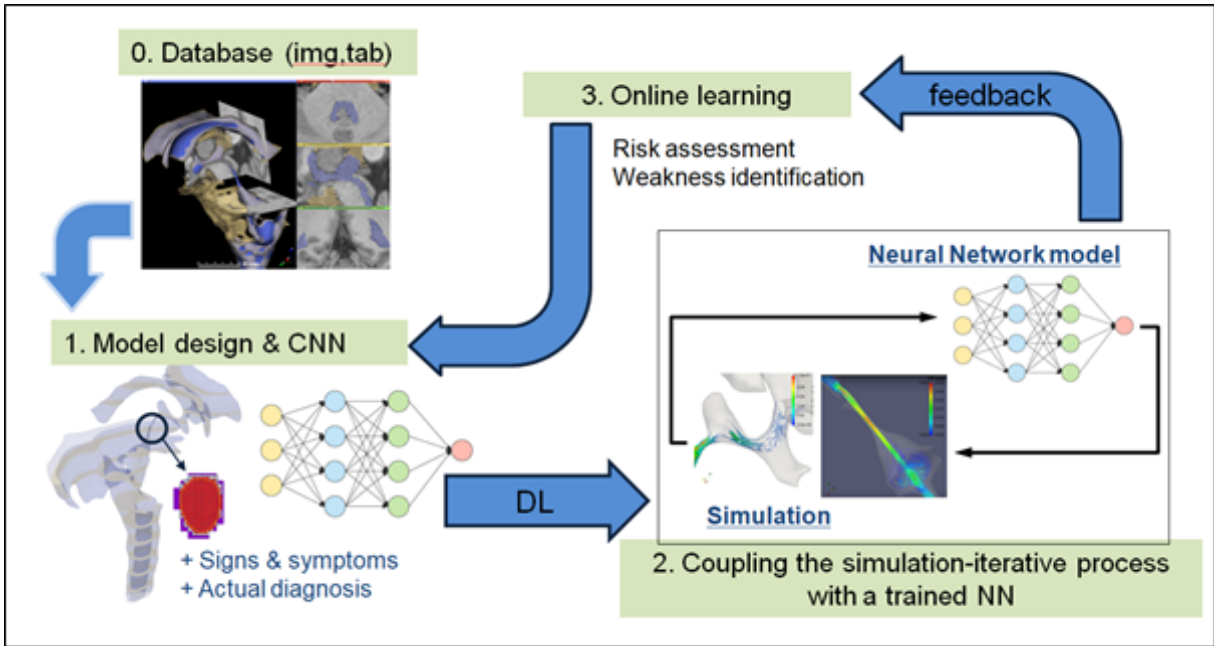
Research Projects

2022-01-present	HAI_TBIDIA Helmholtz AI research project
2019.01-present	Cooperation with Korea University College of Medicine (KUCM) AI-based diagnosis and prognosis of trauma brain injuries
2018.08-present	SiVeGCS Koordination und Sicherstellung der weiteren Verfügbarkeit der Supercomputing-Ressourcen des Gauss Centre for Supercomputing im Rahmen der nationalen Höchstleistungsrechner-Infrastruktur
2016.01-2018.07	European Space Research and Technology Centre (ESA-ESTEC) “Prediction of acoustic loads on space structures”
2014.07-2015.12	EU Framework Program, COPA-GT “Coupled Parallel Simulation of Gas Turbines”
2014.01-2015.12	Deutsche Forschungsgemeinschaft (DFG), FOR1779 “Active drag reduction via wavy surface oscillation”
2012.09-2015.08	Deutsche Forschungsgemeinschaft (DFG), Öko-effizientes Fliegen “Numerical optimization of porous surface to reduce trailing-edge noise generation”
2011.01-2012.12	Deutsche Forschungsgemeinschaft (DFG), Research grant “Trailing-edge noise reduction using fluid injection”
2008.01-2009.12	Deutsche Forschungsgemeinschaft (DFG), FREQUENZ “Prediction of slat-wing noise”
2006.01-2008.12	EU Framework Program, CoJeN “Prediction of coaxial jet noise”

Teaching Experience

2019.11-present	Juelich Supercomputing Centre, FZJ, Juelich, Germany Lecture: ANSYS CFD on HPC
2016.04-2018.07	Institute of Aerodynamics, RWTH Aachen University, Aachen, Germany Lecture: Computational Aeroacoustics (Sonderprobleme der Strömungsmechanik)

The high-performance computing (HPC) knowledge obtained from general computational fluid dynamics (CFD) applications has been expanded to bio-fluid mechanics problems in neurosurgical diseases. For example, the disorders of a human central nerve system disrupt the cardiac circulation of cerebrospinal fluid (CSF) that fills brain ventricles and spinal cord. The CSF circulation is involved in a number of vital functions of the human body. Progressing HPC technologies the numerical simulations are performed to build up a basis for testing and optimizing the therapeutics via understanding of the CSF pathophysiology. The CFD analysis is able to quantify the functional interactions of the components of the central nerve system. Recently artificial intelligence (AI)-based analysis has been effectively applied to various examinations of diseases such as epilepsy and Parkinson's disease which are hard to detect via an image-based diagnosis even in the recent significant improvement of diagnostic imaging technique. Furthermore, the disease caused by traumatic brain injuries is another important topic that AI-based approaches can be used to in such a practical way as the non-invasive prediction of intracranial pressure or the prediction of prognosis from multiple clinical variables. To obtain the sufficient accuracy, the simulations require high resolution numerics, i.e., an enormous amount of computer memory and a high-performance numerical solver are mandatory to deal with complex geometries. Scaling up the processing data, the HPC simulation with deep neural network (DNN) models is expected to enhance the in-situ treatment of patients via the accurate prediction. The outcomes are able to bring benefits to the scientific researches via the reciprocal actions which will develop the advanced method in AI-based medical diagnosis.



Workflow of a biofluid simulation supported by deep neural network (DNN) models

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Luncheon Symposium

좌장: **조 준** (건국대)

대한정위기능신경외과학회
The Korean Society of Stereotactic
and Functional Neurosurgery

Enabling Personalized Patient Care with Sensing Technology

Global Sr. Marketing Director, Medtronic

Shah Saurabh

PRECISION IN SIGHT: Future Directions and Development of BSC DBS

DBS Scientist, Boston Scientific

Nicholas Maling

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2022 정기학술대회

Invited Lecture

좌장: **전상용** (대한정위기능신경외과회장)

대한정위기능신경외과학회
The Korean Society of Stereotactic
and Functional Neurosurgery

Functional Imaging Signatures are Key to Guide Deep Brain Stimulation for Consciousness Restoration

Paris-Saclay Univ., France

Bechir Jarraya

CURRICULUM VITAE

Bechir Jarraya is both a neurosurgeon and neuroscientist. He graduated from the Sorbonne medical school of Paris (France), and trained as a resident in neurosurgery at Paris hospitals. He has been board certified in neurosurgery since 2005. He also trained in neuroscience research and obtained a Master's degree then a PhD degree in neuroscience in 2006 from Paris VI University (UPMC). In 2006-2007, he worked as a research fellow at Harvard medical school and the Massachusetts general hospital (Boston, USA). Back in Paris, he was granted the competitive Inserm Avenir program, with the support of the Bettencourt Schueller Foundation, to mount the laboratory of cognitive and translational neurosciences that he is currently leading, in Neurospin neuroimaging center at CEA Saclay (French atomic energy research commissariat, life science division). He also pursued neurosurgery as clinical chief in the functional neurosurgery unit at Henri Mondor hospital, Paris greater area, where he specialized further in neuromodulation, cell and gene therapies for neurological disorders.

In November 2011, he was appointed associate professor in the medical school of Versailles university, and as responsible for the neuromodulation unit, in the department of neurosurgery, Foch hospital, Paris greater area. This unit is dedicated to treating patients with neurological disorders using advanced neurotechnologies. He also received the European prize Aesculap for the best scientific work among young European neurosurgeons, the Fondation Bettencourt Schueller award for young scientists and a prize from the French National Academy of Medicine. In 2012, he was selected in the Young Leaders program of the French American Foundation. In 2014 he was appointed as full professor at the medical school of Université-Paris Saclay. He has published several neuroscience and neurosurgical studies in international journals. He is also co-inventor of a new gene therapy for Parkinson's disease. His main interests are neurodegenerative diseases such as Parkinson's disease, consciousness disorders, neurological rehabilitation, and functional neuroimaging, using high field magnetic resonance imaging (MRI). He also serves as a scientific expert of the French Parliament panel commission for science and technology.

A major challenge in medicine is the rehabilitation of severely injured patients who "recover" from the acute phase of severe neurological injury, but experience chronic impairment of consciousness, such as minimally conscious state or vegetative state, now called unresponsive wakefulness syndrome. Although substantial progress has been made toward more precise diagnosis of disorders of consciousness, there are literally no validated therapeutic interventions to ameliorate the consciousness state of these patients. So far, clinical trials that investigated deep brain stimulation (DBS), mainly relied on clinical features to select patients, adjust and evaluate DBS. However, clinical features hold limitations to quantify and characterize consciousness. In this lecture, I will present the key role of cognitive neuroscience, functional MRI (fMRI) signatures of consciousness and computational models to guide the development of DBS for consciousness restoration in a translational perspective.

Consciousness can be studied at two different levels: arousal, emerging from brainstem ascending reticular systems and basal forebrain, and awareness, mainly characterized by the conscious access to a specific piece of information. So far, DBS of the thalamus has been reported to improve arousal in patients with disorders of consciousness. However, restoring awareness and conscious access is key for a clinically relevant approach in patients with disorders of consciousness. We tested the hypothesis that deep brain stimulation of central thalamus, with adequate settings, might restore both arousal and awareness following consciousness loss.

We modelled unconsciousness using finely tuned anesthesia in non-human primates, a model in which the signatures of loss of consciousness were also found to reflect the clinical status of patients with disorders of consciousness. Functional MRI was performed at 3T with a phased array multi-channel coil. The anatomical localization of the DBS lead was checked with both Lead-DBS toolbox (non-human primate version) and histology. Under propofol anesthesia, the implanted DBS leads stimulated either central thalamus or a control structure, the ventro-lateral thalamic nucleus. We monitored the effects of DBS on both behavior and brain activity using fMRI and EEG. We investigated two fMRI signatures of consciousness: (1) the cortical dynamics of spontaneous resting-state fMRI activity, which evaluates the richness of the repertoire of brain states and the function-structure similarity; and (2) the brain evoked activity by the “local-global” auditory paradigm, which dissociates two hierarchical levels of auditory regularities.

During anesthesia, central thalamic stimulation induced arousal in an on-off manner and increased fMRI activity in prefrontal, parietal and cingulate cortices. Moreover, DBS restored a rich dynamic repertoire of spontaneous resting-state activity and reduced function-structure similarity, previously described as a signature of consciousness. None of these effects were obtained during the stimulation of the control site in the ventro-lateral thalamus. Finally, DBS restored a broad hierarchical response to auditory violations, an important biomarker of awareness, that was disrupted under anesthesia.

We demonstrated that electrical stimulation of central thalamic nuclei could recruit large-scale thalamo-cortical networks and restore the signatures of arousal and awareness in the non-human primate model of loss of consciousness, paving the way to its therapeutical translation in patients with disorders of consciousness. From a theoretical point of view, our findings fit with several theories of consciousness including the

"Thalamo-Cortical Loops and Sensorimotor Couplings" theory, the "Global Neural Workspace" theory and the recently proposed "Dendritic Information" theory of consciousness. Functional MRI based signatures of consciousness hold the potential to guide future clinical trials that investigate DBS effects on disorders of consciousness.

We are currently applying deep learning models and mechanis These new approaches based on computational analysis of global fMRI dynamics and specific task evoked fMRI maps, can potentially profit to the refinement of DBS to treat patients with movement disorders or psychiatric diseases.

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Symposium II.
Revisit Cell Therapy in Parkinson's Disease

좌장: **이정일** (성균관대), **허 륭** (가톨릭대)

대한정위기능신경외과학회
The Korean Society of Stereotactic and Functional Neurosurgery

Update of Cell Therapy on Parkinson's Disease

연세대 신경과

이 필 휴

CURRICULUM VITAE

Education

1994	Yonsei University College of Medicine, MD
2004	Yonsei University College of Medicine, PhD, Neuroscience
1999	Sevrance Hospital, Resident, Neurology

Positions and Honors

Professional Experience

2014-2021	Professor, Department of Neurology and Severance Biomedical Science Institute, Yonsei University, Korea
2008-2013	Associate Professor, Department of Neurology and Severance Biomedical Science Institute, Yonsei University, Korea
2007-2008	Visiting Scholar, Department of Neuroscience, UC San Diego, USA
2004-2007	Assistant Professor, Department of Neurology, Ajou University, Korea, Korea

Current

Professor, Department of Neurology and Severance Biomedical Science Institute, Yonsei University, Korea

Honors and Awards

2022	The Best Professor Award in Yonsei University College of Medicine
2022	Kim Ki Whan Research Award
2017	Pfizer Medical Research Award
2015	Adult Stem Cell Award from Archdiocese of Seoul
2014	The Grand Prize in Korean Movement Disorders Society
2014	The Best Professor Award in Yonsei University College of Medicine
2007	Young Investigator in Korean Neurological Association
2006	Young Investigator in Korean Movement Disorders Society

SEVERANCE

Stem cell therapy in Parkinsonian diseases

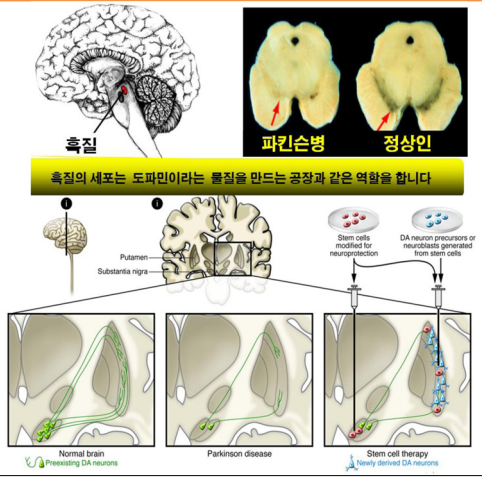
Phil Hyu Lee, MD, PhD

Yonsei Parkinson Center
Department of Neurology, Yonsei University
Severance Biomedical Science Institute, Yonsei University

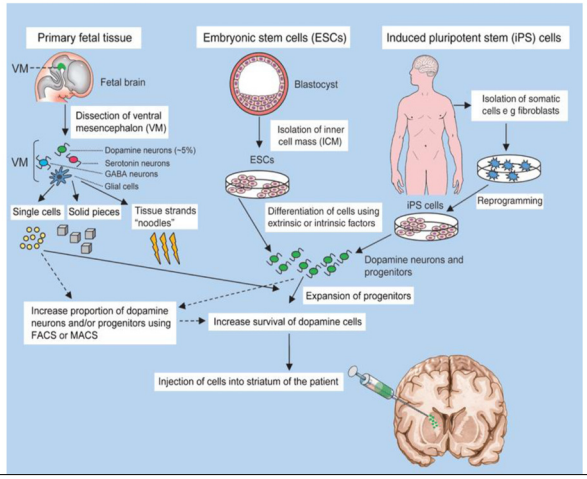
Contents

- Concepts of stem cell therapy
- Issues in stem cell therapy
- Current advances in stem cell therapy
- Perspectives

1. Replacement of DA neurons

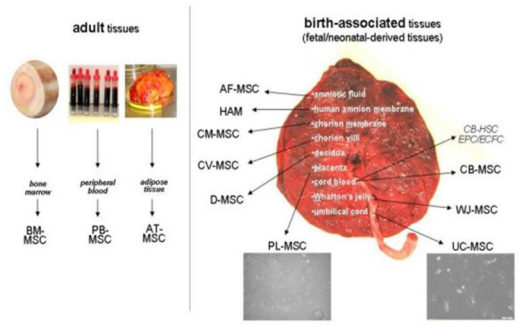


Variable sources of DA neurons



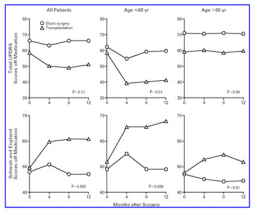
2. Disease modifying strategy

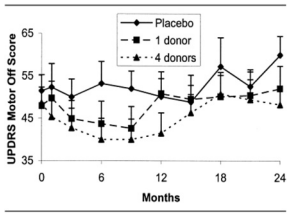
- *Environmental enrichment via stimulation of host plastic responses*
- *Cytotrophic factor secretion*
  - stimulation of plastic response & improved survival & function of host neuron
- *Modulation of neurogenesis*



Considering issues in replacement therapy of DA

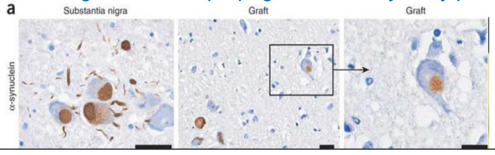
1. No effective in double-blind placebo trials





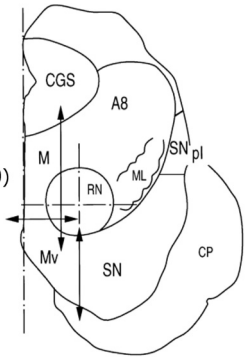
2. Off dyskineisa, 56% of transplanted patients

3. Host-to-graft disease propagation of Lewy body pathology



Summary of embryonic mesencephalic tissue implantation

- Different effect according to
  - the number of donor cell
    ;survival DA neuron of 3-5%, DA of 5-10% in transplanted cells
    ;7000-40,000 in the Denver-Columbia trial vs 80,000- 135,000 surviving DA neurons in open-label trial
  - the use of immunosuppressant
  - method of cell preparation (A9 >> A10)
- Mismatch between clinical and radiological or pathological findings
- Less effectiveness than DBS
- No convincing evidence of L-dopa resistant symptoms
- Emerging "off" dyskinesia



➔ *currently, far from optimal therapeutic strategy (vs DBS)*

Extensive graft-derived dopaminergic innervation is maintained 24 years after transplantation in the degenerating parkinsonian brain

PNAS

Wen Li[a], Elisabet Englund[b], Håkan Widner[c], Bengt Mattsson[d], Danielle van Westen[e], Jimmy Lätt[e], Stig Rehncrona[f], Patrik Brundin[g], Anders Björklund[d,1,2], Olle Lindvall[c,h,1,2], and Jia-Yi Li[a,1,2]

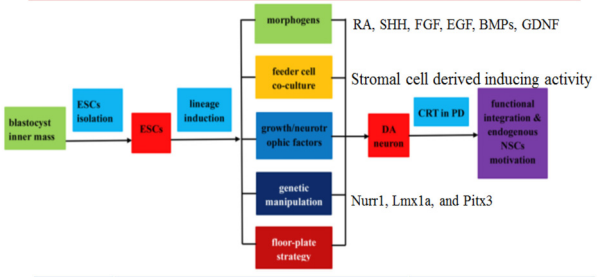
- A patient with Parkinson's disease who 24 y earlier underwent unilateral transplantation of embryonic dopaminergic neurons in the putamen and subsequently exhibited major motor improvement and recovery of striatal dopaminergic function
- After a quarter of a century, complete graft-derived dopaminergic reinnervation was still evident in the transplanted putamen
- The clinical improvements were gradually lost from 14 y posttransplantation with PDD conversion
- α-Syn–positive inclusions were present in 11–12% of the grafted dopaminergic neurons
- Even a viable dopaminergic graft giving rise to extensive striatal reinnervation may lose its efficacy if widespread α-synucleinopathy and major degenerative changes develop in the host brain.

Future issues in replacement therapy of DA

1. *How to select pure DA neurons <- off dyskineisa*
2. *How to be free from immunological issues <- DA survival*
3. *How to be free from safety issues <- tumorigenesis and mutagenesis*
4. *How to select best candidates <- like DBS*

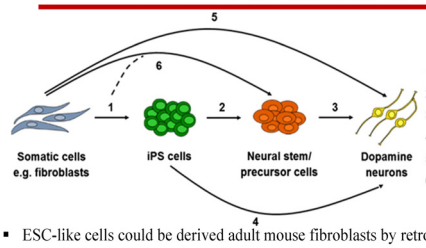
(A) Manufacturing process	(B) Safety	(C) Efficacy
• **In process Quality Control (QC) and Release Criteria (RC) to ascertain quality of cells and comparability between batches** Eighty percent of cells co-expressing midbrain markers such as FOXA2, LMX1A, EN1 and CORIN Absence of pluripotency markers Low expression of non-neural markers Low numbers of forebrain and hindbrain progenitors (i.e. PAX6⁺, FOXG1⁺, GBX2⁺) (Kirkeby et al., 2017b; Studer, 2017; Takahashi, 2017)	• **Tumorigenicity** Rule out pluripotent cells or other contaminants *in vitro* and ensure no tumor formation *in vivo* can be done in nude mice or rats at certified contract research organization • **Biodistribution** Standard *in vivo* testing at certified CRO • **Toxicology** Standard *in vivo* testing at certified CRO (Kirkeby et al., 2017b; Studer, 2017; Takahashi, 2017)	• **Yield** Estimate the number of mature dopaminergic neurons obtained per 100,000 grafted cells • **Ability to restore motor function** Full recovery of amphetamine-induced rotations in 6-hydroxydopamine lesion model • **Long-range target specific innervation** Intranigral grafting in rat model, or intrastriatal grafting in a large animal model (Barker et al., 2017; Grealish et al., 2014; Kikuchi et al., 2017)

ESC-derived DA



ESCs	Advantage	Disadvantage
	Totipotent differentiation	Tumor formation
	Maintain pluripotency after expansion	Ethical issue
	Generating midbrain DA neurons	Immuno-rejection
	Rescue functional deficits	

iPSC-derived DA



1. *OSKM* reprogramming
2. Neural induction & patterning
3. Terminal differentiation
4. Transgene-mediated differentiation
5. Direct-to-iN/iDA reprogramming
6. Direct-to-iNS/iNP reprogramming

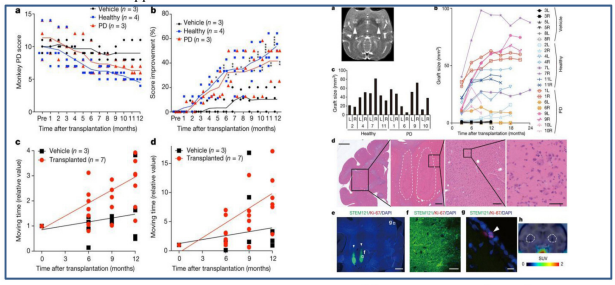
- ESC-like cells could be derived adult mouse fibroblasts by retrovirally introducing OSKM (Oct3/4, Sox2, Klf4, and c-Myc) gene transcription factors
- Potential risks posed by genome-integrating viruses, producing insertional mutations or tumorigenesis (c-Myc oncogene)
- Mutagenesis-and integration-free iPSCs using other non-viral vector

Vectors	Crews
mRNA	OSKM
	Oct4, Sox2, Klf4, c-Myc, or GLIS1
miRNA	miRNA302/367cluster
	miRNAfamily(miRNA200c, miRNA302s, miRNA369s)
Protein	CPP, OSKM, VPA
	CPP,OSKM
	ESC-derived proteins
Small molecules	VPA, Oct4, Sox2
	Oct4, Klf4, BIX-01294
	Oct4, VPA, CHIR99021, 616452
	Wholly small-molecule compounds

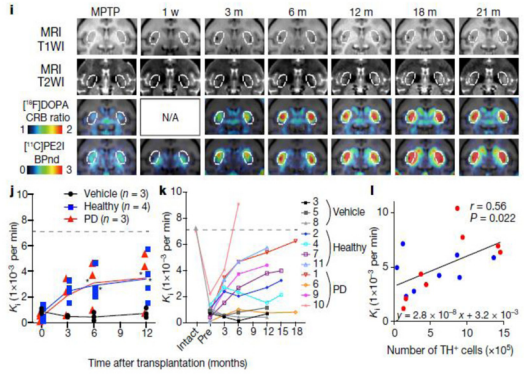
Human iPS cell-derived dopaminergic neurons function in a primate Parkinson's disease model

Tetsuhiro Kikuchi[1], Asuka Morizane[1], Daisuke Doi[1], Hiroaki Magotani[1], Hirotaka Onoe[2], Takuya Hayashi[2], Hiroshi Mizuma[2], Sayuki Takara[2], Ryosuke Takahashi[3], Haruhisa Inoue[4], Satoshi Morita[5], Michio Yamamoto[5], Keisuke Okita[6], Masato Nakagawa[6], Malin Parmar[7] & Jun Takahashi[1,8]

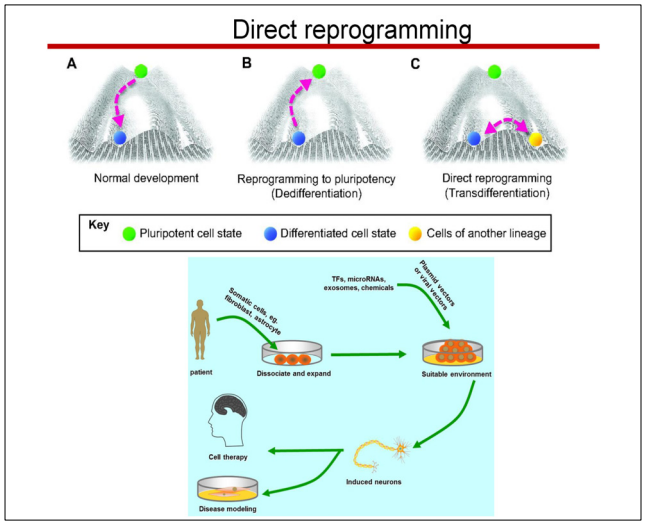
- 87.5 % of cells were FOXA2(a floor plate marker)+TUJ1+, and 16.4 expressed NURR1
- On day 26, the expression levels of pluripotent cell markers (OCT4, NANOG, LIN28A) was 1% or less
- With immunosuppressant

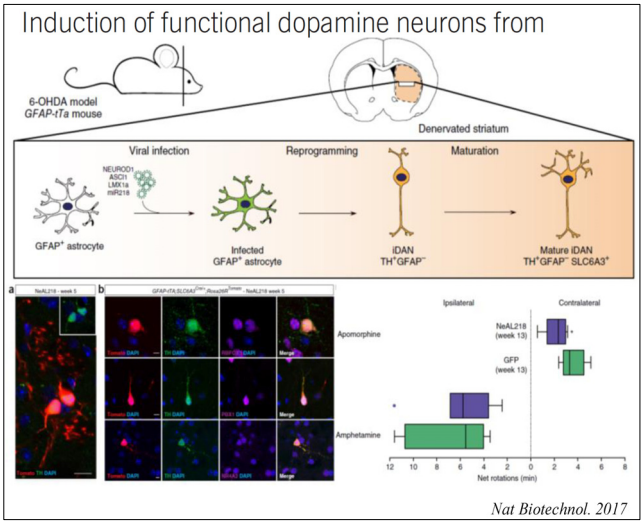


- ~ 50% improvement of PD sx (Healthy~PD)
- No tumor or mass formation

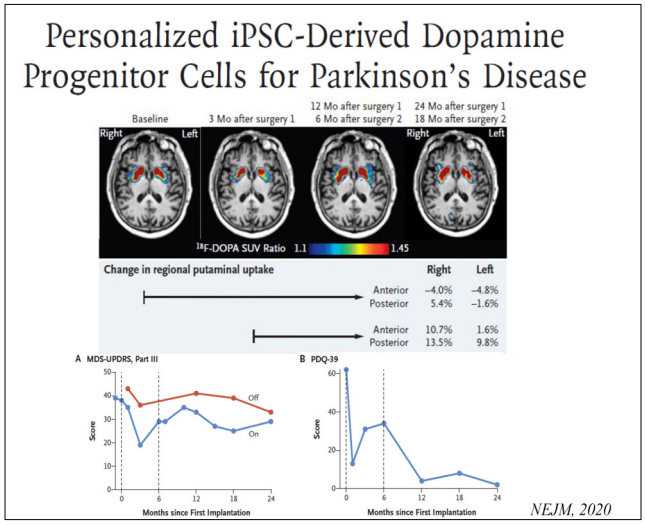


- ~ 16,000 TH+ cells, equivalent to about 100,000 TH+ cells in humans
- No serotonin+ cells in the grafts
- No microglial activation on PET imaging
- The number of surviving dopaminergic neurons differed between monkeys, suggesting that unknown characteristics that vary between cell lines may affect cell survival or differentiation





Nat Biotechnol. 2017

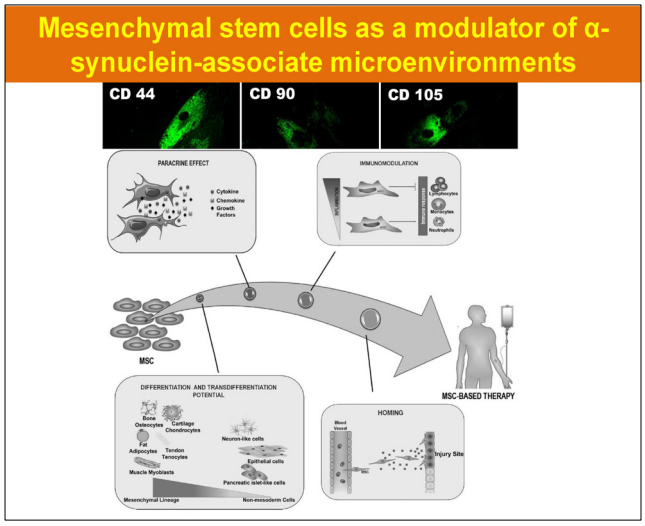


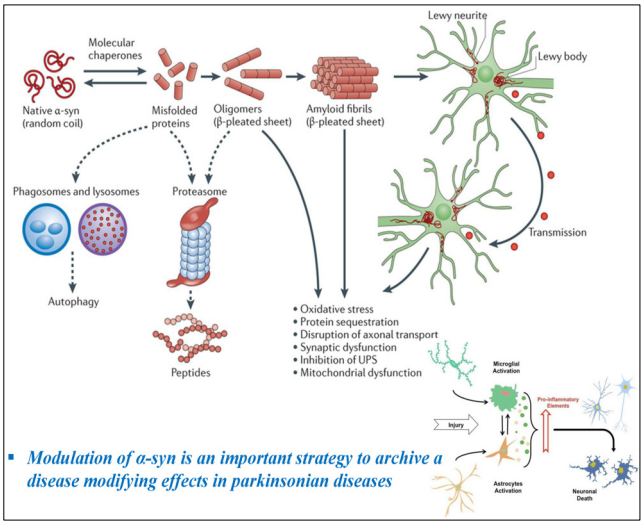
NEJM, 2020

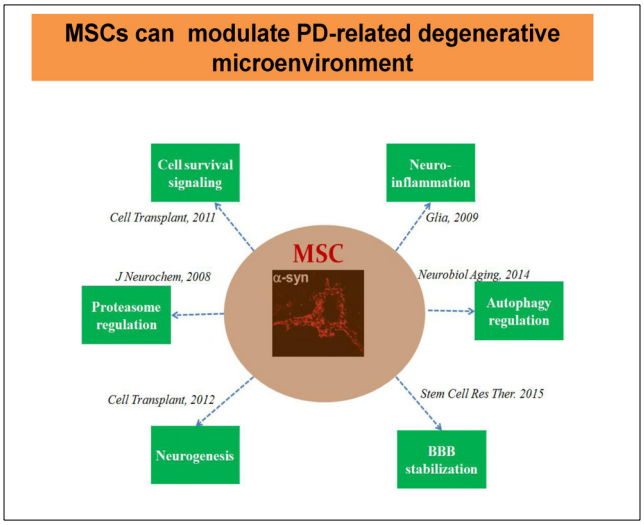
GForce-PD Partners' Clinical Trials

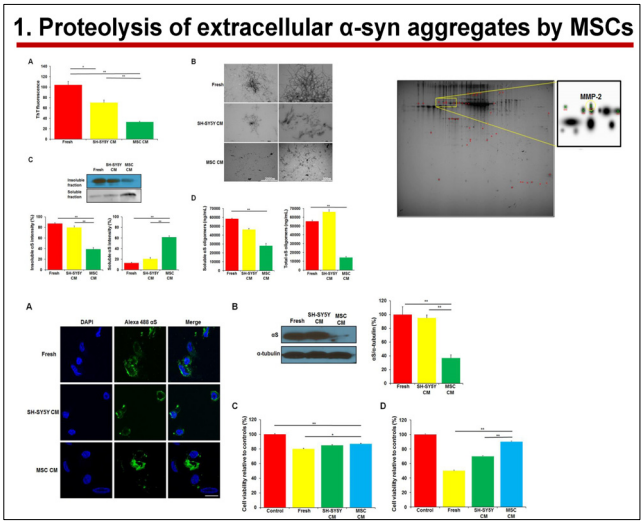
	EUROPEAN STEM-PD[a]	NYSTEM-PD	CIRA Trial	Summit for PD Trial
Cell source	ESCs	ESCs	allogeneic iPSCs	autologous iPSCs
Cryopreserved cell product?	yes	yes	no	yes
Genetic testing of cell product	TBD	karyotype / + TBD	sequencing for certain genes	full genome sequencing
Cell delivery method	"Rehncrona" instrument previously used in fetal VM trials	MRI/Clearpoint system	purpose made needle	MRI/Clearpoint system
Dosing?	low dose, high dose	low dose, high dose	one dose	low dose, high dose
Immunosuppressive regime	yes, at least 12 months; probably CiclosporinA; Azathioprine; steroids	yes, 12 months; FK506; Basiliximab; TBD ± mycophenolate	yes, 1–2 years; FK506	none
Patient characteristics				
Age	<70 years old	40–70 years old	50–70 years old	45–70 years
Disease duration	<12 years	5–12 years	>5 years	>5 years
Significant LIDs?	no	no	no	no
L-dopa response?	>30%	>50%	>30%	>20%
Pre-transplant run-in period	>1 year	>1 year	TBD	>1 year
Follow-up period	indefinitely	at least 2 years	at least 2 years	at least 1 year
PET imaging	F-dopa; PE2i	F-dopa; PE2i; DPA 713	F-dopa; DAT-SPECT; FLT GE180	F-dopa; DAT-SPECT FLT GE180
Primary end point	adverse events	adverse events	adverse events	adverse events
Secondary clinical end points (changes in)	UPDRS motor 3 in defined "off"; PDQ39; Addenbrooke's Cognitive Examination (Revised)	UPDRS motor 3 in defined "off"; PDQ39; Montreal Cognitive Assessment	UPDRS motor 3 in defined "off"; "off" time period PDQ39; Mini Mental State Examination score	UPDRS motor 3 in defined "off"; PDQ39; Mini Mental State Examination Score
Date for planned first-in-human study	2019–2020	2018	2018	2019

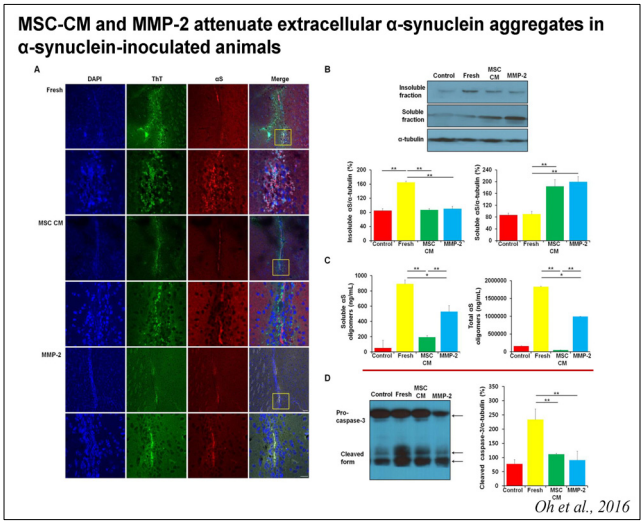
Cell stem cell, 2017

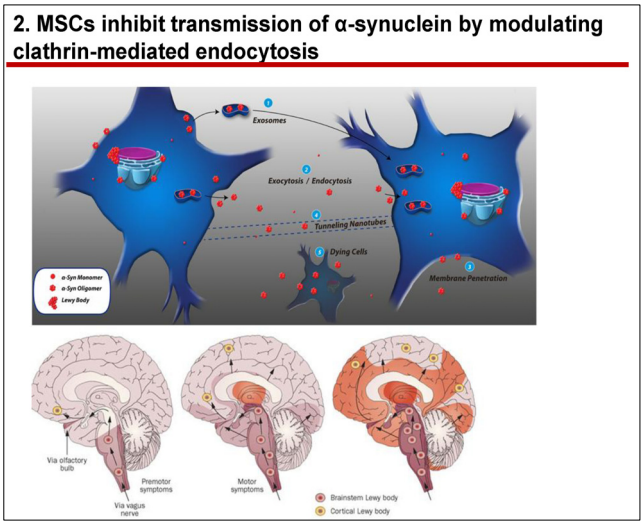


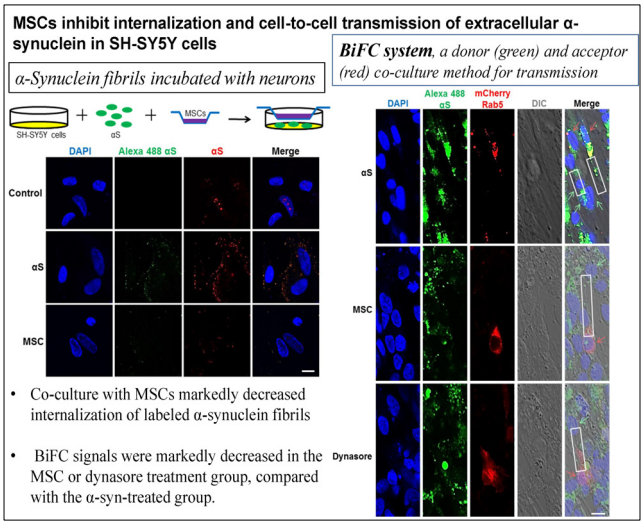

Molecular chaperones
Native α-syn (random coil)
Misfolded proteins
Oligomers (β-pleated sheet)
Amyloid fibrils (β-pleated sheet)
Lewy neurite
Lewy body
Phagosomes and lysosomes
Proteasome
Transmission
Autophagy
Peptides
• Oxidative stress
• Protein sequestration
• Disruption of axonal transport
• Synaptic dysfunction
• Inhibition of UPS
• Mitochondrial dysfunction
Microglial Activation
Pro-inflammatory Elements
Injury
Astrocytes Activation
Neuronal Death
Modulation of α-syn is an important strategy to archive a disease modifying effects in parkinsonian diseases


MSCs can modulate PD-related degenerative microenvironment
Cell survival signaling
Neuro-inflammation
Cell Transplant, 2011
Glia, 2009
MSC
α-syn
J Neurochem, 2008
Neurobiol Aging, 2014
Proteasome regulation
Autophagy regulation
Cell Transplant, 2012
Stem Cell Res Ther. 2015
Neurogenesis
BBB stabilization

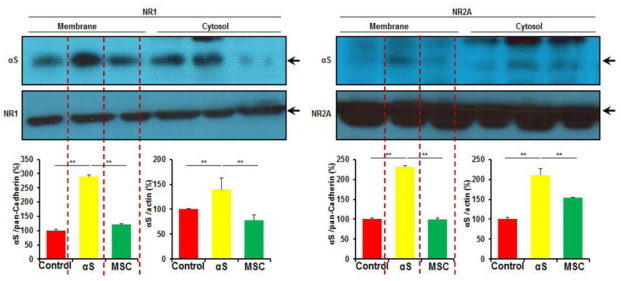

1. Proteolysis of extracellular α-syn aggregates by MSCs
MMP-2
DAPI
Alexa 488 αS
Merge
Fresh
SH-SY5Y CM
MSC CM
αS
α-tubulin
Control
Cell viability relative to control (%)


MSC-CM and MMP-2 attenuate extracellular α-synuclein aggregates in α-synuclein-inoculated animals
DAPI
ThT
αS
Merge
Fresh
MSC CM
MMP-2
Control
Insoluble fraction
Soluble fraction
α-tubulin
Pro-caspase-3
Cleaved form
Oh et al., 2016


2. MSCs inhibit transmission of α-synuclein by modulating clathrin-mediated endocytosis
Exosomes
Exocytosis / Endocytosis
Tunneling Nanotubes
Dying Cells
Membrane Penetration
α-Syn Monomer
α-Syn Oligomer
Lewy Body
Via olfactory bulb
Premotor symptoms
Via vagus nerve
Motor symptoms
Brainstem Lewy body
Cortical Lewy body

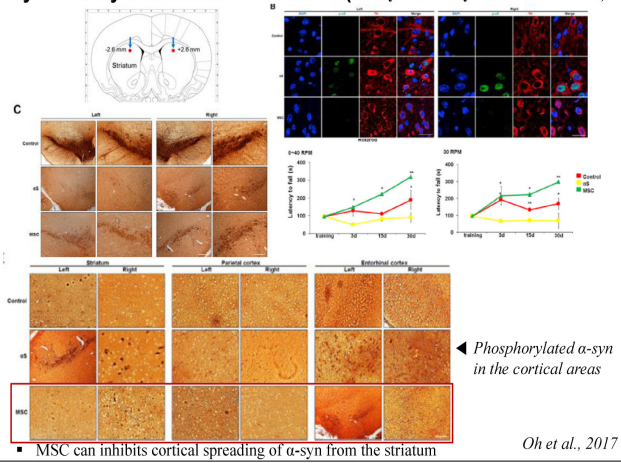

MSCs inhibit internalization and cell-to-cell transmission of extracellular α-synuclein in SH-SY5Y cells
α-Synuclein fibrils incubated with neurons
BiFC system, a donor (green) and acceptor (red) co-culture method for transmission
SH-SY5Y cells
αS
MSCs
DAPI
Alexa 488 αS
Merge
Control
αS
MSC
Co-culture with MSCs markedly decreased internalization of labeled α-synuclein fibrils
BiFC signals were markedly decreased in the MSC or dynasore treatment group, compared with the α-syn-treated group.
Alexa 488 αS
mCherry Rab5
DIC
Dynasore

MSCs inhibit endocytosis of extracellular α-synuclein fibrils through modulation of surface NMDA receptors



- An IP assay showed that α-synuclein treatment increased the amount of NR1 or NR2A immunoprecipitated with α-synuclein
- The amount of NR1 or NR2A interacted with α-synuclein was significantly decreased in the MSC-treated group
- MSC inhibits interaction of α-synuclein and NR1 and NR2A.

Long-term effect of MSCs on transmission of extracellular α-syn in α-syn-inoculated animals (30 days after α-synuclein inoculation)

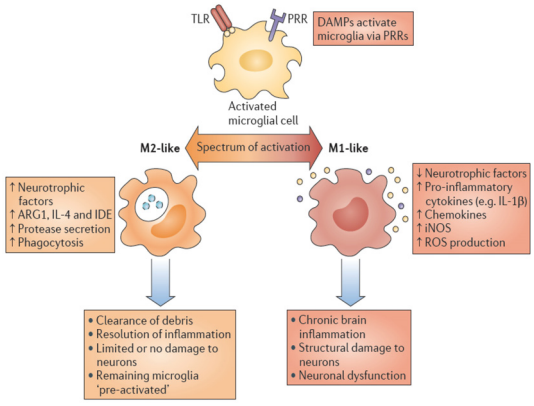


◀ *Phosphorylated α-syn in the cortical areas*

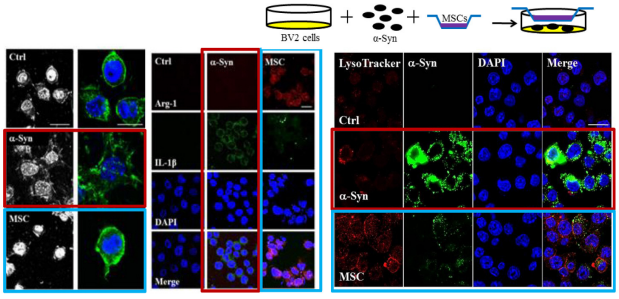
- MSC can inhibits cortical spreading of α-syn from the striatum

Oh et al., 2017

3. Phagocytic clearance of α-synuclein by MSCs

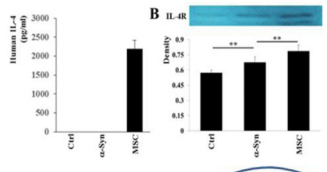


Microglia polarization in α-synuclein-treated BV2 cells

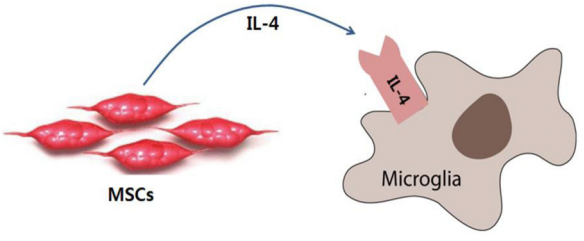


- BV2 cells treated with α-synuclein displayed numerous lamellar processes/ increased IL-1 expression/decreased lysosomal activity with increased α-syn levels in microglia
- MSC treatment displayed Arg-1 expressing M2 phenotype/ increased lysosomal activity with decreased α-syn levels in microglia

Microglia M2 polarization is induced by IL-4 secreted from MSCs



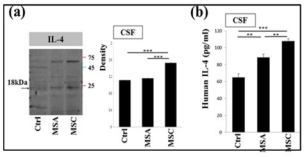
- Human specific IL-4 was only detected in responded media of hMSC treatment

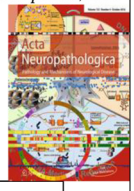


IL-4 secreted from MSCs modulates M2 polarization by binding IL-4R in microglia

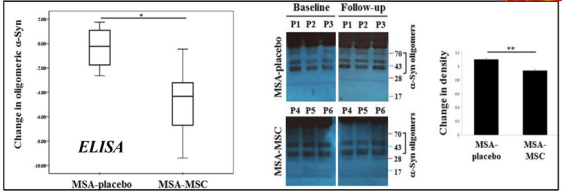
IL-4 in CSF from MSC-transplanted MSA patients modulates M2 polarization

Park et al. Acta Neuropathol, 2016

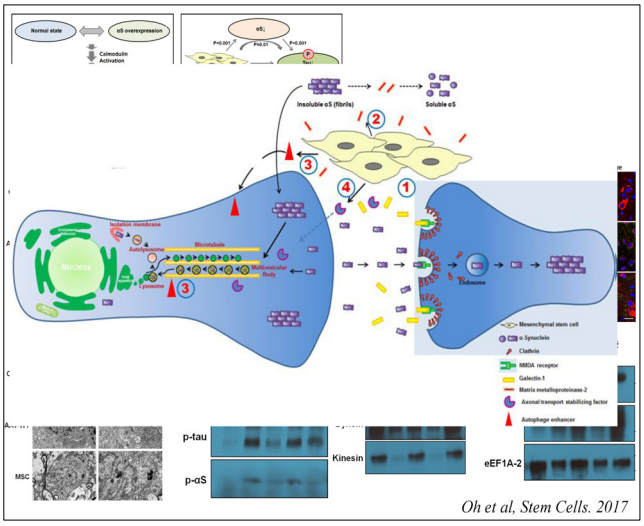




M2 polarization by MSCs leads to enhanced α-synuclein clearance

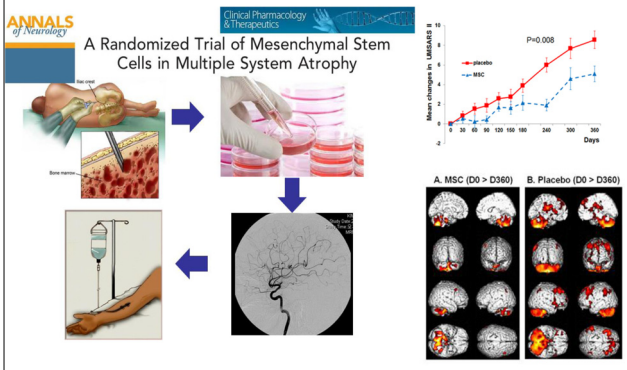


- Longitudinal changes in oligomeric α-synuclein and total α-synuclein during follow-up period were lower in MSC-transplanted MSA patients compared with placebo-transplanted patients
- *MSC treatment reduces the protrusion of α-syn into the CSF, possibly by enhancing α-synuclein clearance in the brain*



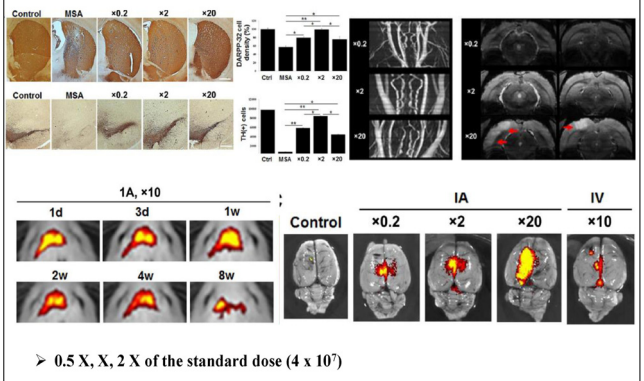
Oh et al, Stem Cells. 2017

Mesenchymal stem cell as a α-synuclein modulator ; *a MULTITARGET disease-modifying strategy*



STEM CELLS TRANSLATIONAL MEDICINE

Feasibility and Efficacy of Intra-Arterial Administration of Mesenchymal Stem Cells in an Animal Model of Double Toxin-Induced Multiple System Atrophy



➢ **0.5 X, X, 2 X of the standard dose (4 x 10^7)**

Kim et al, 2018

Clinical trials of MSCs in Parkinsonian disorders

1. NCT02315027, Phillip Low, Mayo Clinic

- Intrathecal Autologous Mesenchymal Stem Cell Therapy in Multiple System Atrophy (MSA) - Effect of Dose and Natural History.
- The primary aim is to evaluate the safety and tolerability of intrathecal injection of autologous MSCs in a dose escalation study in patients with MSA.
- Safety secondary goals include to monitor changes in peripheral blood and in components of CSF, and monitor for any changes of nervous system structures using MRI.

2. Phase I trial, SIT (CS10BR05)

- Intraarterial autologous mesenchymal stem cell therapy in MSA-C.
- The primary aim is to evaluate the safety and tolerability of intraarterial injection of autologous MSCs in a dose escalation study in patients with MSA-C.
- Safety secondary goals include to monitor changes in UMSRA, structural and functional patterns, and CSF biomarkers.

Chung et al, Stem Cells Int. 2021

Intrathecal administration of autologous mesenchymal stem cells in multiple system atrophy

Wolfgang Singer, MD, Allan B. Dietz, PhD, Anita D. Zeller, Tonette L. Gehrking, James D. Schmelzer, Ann M. Schmeichel, Jade A. Gehrking, Mariana D. Suarez, David M. Sletten, Karla V. Minota Pacheco, MD, Elizabeth A. Coon, MD, Paola Sandroni, MD, Eduardo E. Benarroch, MD, Robert D. Fealey, MD, Joseph Y. Matsumoto, MD, James H. Bower, MD, Anhar Hassan, MB, BCh, Andrew McKeon, MD, Anthony J. Windebank, MD, Jay N. Mandrekar, PhD, and Phillip A. Low, MD

Abstract

Objective
This phase I/II study sought to explore intrathecal administration of mesenchymal stem cells (MSCs) as therapeutic approach to multiple system atrophy (MSA).

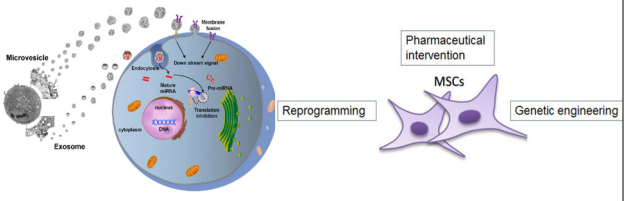
Methods
Utilizing a dose-escalation design, we delivered between 10 and 200 million adipose-derived autologous MSCs intrathecally to patients with early MSA. Patients were closely followed with clinical, laboratory, and imaging surveillance. Primary endpoints were frequency and type of adverse events; key secondary endpoint was the rate of disease progression assessed by the Unified MSA Rating Scale (UMSARS).

Results
Twenty-four patients received treatment. There were no attributable serious adverse events, and injections were generally well-tolerated. At the highest dose tier, 3 of 4 patients developed low back/posterior leg pain, associated with thickening/enhancement of lumbar nerve roots. Although there were no associated neurologic deficits, we decided that dose-limiting toxicity was reached. A total of 6 of 12 patients in the medium dose tier developed similar, but milder and transient discomfort. Rate of progression (UMSARS total) was markedly lower compared to a matched historical control group (0.40 ± 0.59 vs 1.44 ± 1.42 points/month, $p = 0.004$) with an apparent dose-dependent effect.

Conclusions
Intrathecal MSC administration in MSA is safe and well-tolerated but can be associated with a painful implantation response at high doses. Compelling dose-dependent efficacy signals are the basis for a planned placebo-controlled trial.

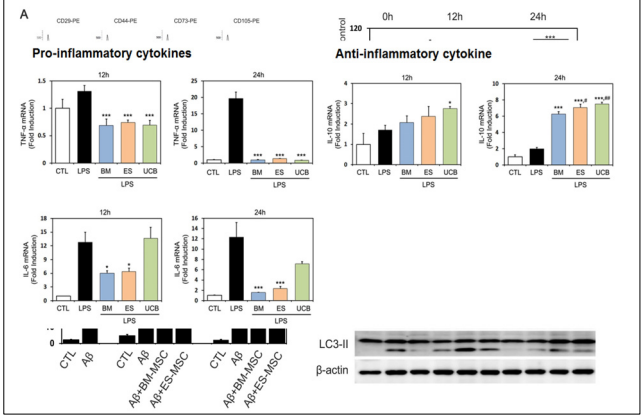
Perspectives: adult stem cells

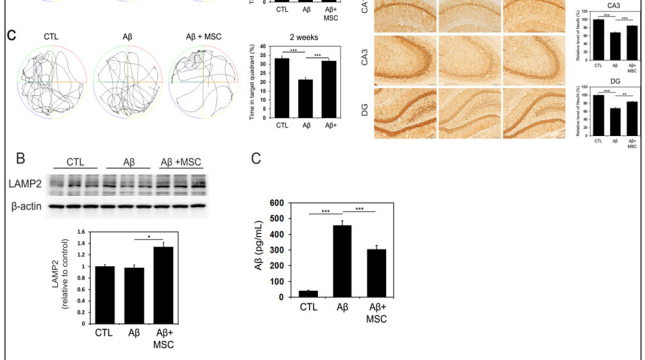
- Potency
- Stemness
- Mass manufacturing
- Injection routes



1. Mass production

Feasibility and efficacy of intra-arterial administration of ESC derived-mesenchymal stem cells in Alzheimer disease

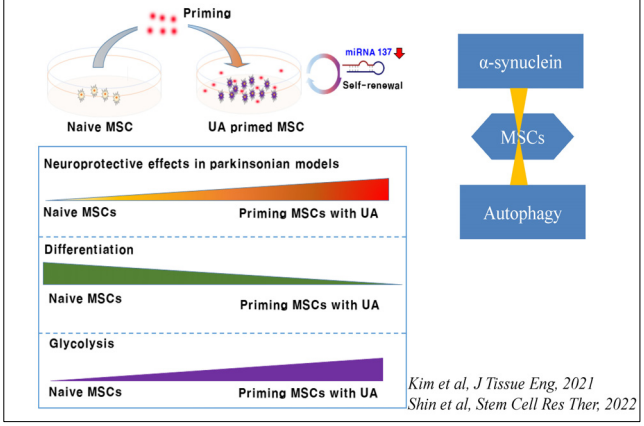




- ES-MSCs had a comparable prosurvival effect against Aβ-induced cell death relative to different cell sources of MSCs

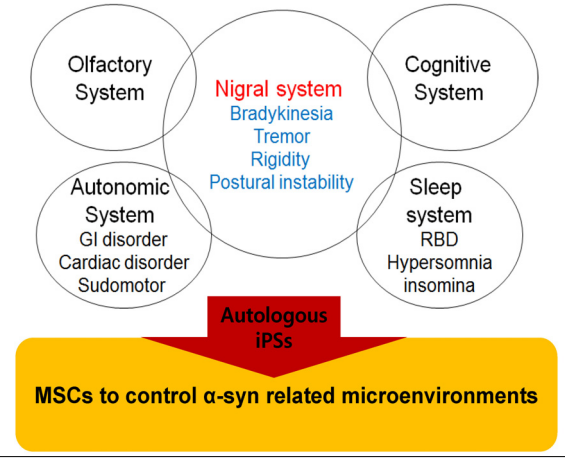
2. Stemness

Priming mesenchymal stem cells with uric acid enhances neuroprotective properties in parkinsonian models



Kim et al, J Tissue Eng, 2021
Shin et al, Stem Cell Res Ther, 2022

Perspectives



Neurosurgeon's Role in Cell Therapy for Parkinson's Disease

차의대

김 주 평

CURRICULUM VITAE

Education

1995-2001	Kyunghee University, College of Medicine, Seoul, Korea; M.D.

Postdoctoral Training

2018-	Associate Professor, Bundang CHA Medical Center
2013-2018	Assistant Professor, Bundang CHA Medical Center
2012-2013	Researcher, Department of Neurologic Surgery, Mayo Clinic, Rochester, MN, USA
2010-2012	Clinical Fellow, Yonsei University College of Medicine, Seoul, Korea
2009-2010	Clinical Fellow, Kyunghee University, College of Medicine, Seoul, Korea
2005-2009	Resident, Kyunghee University, College of Medicine Seoul, Korea
2001-2002	Internship, Kyunghee University, College of Medicine, Seoul, Korea

(Clinical trial in Parkinson's disease using human fetal mesencephalic dopamine neuronal precursor cells in a GMP-compliant, serum-free, long-term cultivation process: A dose-escalation open-label phase I/IIa trial)

Since human fetal ventral mesencephalic tissue graft provided promising results in ameliorating motor dysfunction of patients with Parkinson's disease (PD), human fetal midbrain derived dopamine neuronal precursor cells (hFMD-NPCs) are hailed as a good candidate for a cell-based therapy for PD in that large quantities of cells can be supplied through a good manufacturing practice-compliant system. In order to assess their safety and therapeutic efficacy for the PD treatment, we conducted a "first in human" dose-escalated, open-label phase I/IIa clinical trial for idiopathic PD patients with hFMD-NPCs. In this study, 15 patients were assigned to receive three different dosages of the cells, low ($4x10^6$), medium ($12x10^6$) or high dose ($40x10^6$) respectively, and completed a 12-month follow up. The primary outcome monitored adverse effects of grade 3 or higher according to National Cancer Institute guidelines and the secondary ones measured motor and neurocognitive functions as well as a level of dopamine transporter by positron emission tomography-computed tomography. During 12 months after transplantation., both the medium- and high-dose treated groups exhibited the significant improvement in Unified Parkinson's Disease Rating Scale, part III, up to 26.16% and 40% respectively, and a pronation-supination and a hand/arm movement performance was remarkably enhanced in all three groups (all $p < 0.05$) without any serious clinical complication nor graft-induced dyskinesia in all patients. Especially restoration of dopamine transporter became more prominent in higher dose groups compared to the low. Our results first demonstrate the safety and plausible dose dependent efficacy of hFMD-NPCs for idiopathic PD.

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2022 정기학술대회

Session II.
Free Paper II

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대한정위기능신경외과학회
The Korean Society of Stereotactic
and Functional Neurosurgery

Early experience of MRI-guided focused ultrasound thalamotomy for essential tremor in Korea, single center study

삼성서울병원

전우진

Introduction: Essential tremor (ET) is one of the most common neurological diseases affecting about 0.9% of the world population. Treatment is primarily medical management, but medication resistant ET patients presents. And surgical treatments should be considered. Recent advances led to development of non-invasive treatment option, especially MRI-guided focused ultrasound (MRgFUS). Here, we summarize single center ET patient registry focusing on effectiveness of MRgFUS unilateral thalamotomy.

Methods: From October 2021 to May 2022, 13 patients with intractable essential tremor in our institute were enrolled. Briefly, all procedures were performed using an ExAblate NeuroTM (InSightec, Haifa, Israel). All patients' target lesion was left.VIM nucleus. Clinical endpoints evaluated at baseline and during study follow-up timepoints include: Clinical Rating Scale for Tremor (CRST), The Essential Tremor Rating Assessment Scale (TETRAS), Clinical Global Impression of change (CGI-C).

Results: As of date, a total of 14 patients got MRgFUS Lt.VIM thalamotomy (age = 64.9 ± 8.0 years) with a disease duration of 18.7 years. Comparison data of baseline CRST and 1 month follow-up CRST was obtained in 9 patients. Baseline score was 45.44, 1 month follow up score was 13.33 and reduction rate was 70%. Comparison data of baseline TERTAS and 1 month follow-up TERTAS was obtained in 11 patients. Baseline score was 26.9, 1month follow up score was 4.18. All patients reported improvement on CGI-C.

Conclusions: This on-going, prospective, preliminary registry data of single center Significant reduction in tremor severity was reported compared to baseline (TERTAS, CRST). All subjects and clinicians reported improvement (CGI-C)

The data collected so far can be confirmed to show significant clinical improvement in short term follow-up, allowing long-term follow-up data to be expected. It is expected that it will be the start point of a large scale multi-center study in Korea.

Intrinsic Functional Networks Differ in Good and Poorly Respondent Essential Tremor Patients after Thalamotomy Using MRI-Guided Ultrasound

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Introduction: Thalamotomy at the VIM nucleus using MRgFUS has been an effective treatment method for essential tremor (ET). However, this is not true for all cases. How the brain differs in patients with ET between those with long-term good and poor outcomes is not clear. To analyze the functional connectivity difference between thalamotomy-effective and -ineffective patients and its prognostic role in ET treatment, we evaluated preoperative resting-state functional MRI in thalamotomy-treated patients.

Methods: Preoperative rsfMRI data of 85 ET patients, who were in tremor relief at the time of treatment and followed up for a minimum of 6 months after the procedure, were collected for the study. We conducted a graph-independent component analysis of the functional connectivity matrices of tremor-related networks. We divided the patients into thalamotomy-effective and -ineffective groups and compared network components between groups.

Results: Seventy-two (84.7%) of the 85 patients showed more than 50% tremor reduction from baseline at six months after thalamotomy. The network analysis shows significant suppression of functional network components with connections between the areas of the cerebellum and the basal ganglia and thalamus but enhancement of those between the premotor cortex and supplementary motor area in the non-effective group, compared to the effective group.

Conclusions: The present study demonstrates that non-effective patients have suppressed functional subnetworks in the cerebellum and subcortex regions and have enhanced functional subnetworks among motor-sensory cortical networks compared to thalamotomyeffective patients. Therefore, we suggest that functional connectivity pattern might be a possible predictive factor for outcomes of MRgFUS thalamotomy.

Outcome of Pallidal Deep Brain Stimulation for Treating Pure Blepharospasm

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Introduction: Blepharospasm(BSP) is a disease in which the closure rate of the bilateral eyelids increases, mainly due to involuntary contraction of the orbicularis oculi, procerus and corrugator muscles. The objective of this study was to report our results about postoperative outcome after deep brain stimulation (DBS) in total of 10 cases of pure BSP after at least 12 months follow-up.

Methods: Ten patients with pure blepharospasm who underwent GPi DBS at Incheon St. Mary\'s Hospital, The Catholic University of Korea between 2019 and 2021 were included in this study. Burke-Fahn-Marsden Dystonia Rating Scale, Blepharospasm Disability Index and Jankovic Rating Scale were used for analysis before surgery, at 6 months follow-up as short term outcome, and at follow-up over one year (12 months to 37 months) as long-term results.

Results: The median age of patients at surgery was 56.5 (IQR range, 50.5-65.8) years and the median length of time from disease onset to the time of surgery was 58.0 (IQR range, 46.8 – 64.3) months. The median post-operative follow-up period was 22.5 (IQR range, 15.3 – 29.0) months. The median of Burke- Fahn- Marsden Dystonia Rating Scale at the three time points (preoperative baseline, 6 months, and over one year of follow-up) were 7.0(6.0-8.0),4.5(4.5-5.6, 25.0% improvement, p = 0.002),respectively.

Conclusions: Bilateral GPi DBS in pure blepharospasm can be effective if conservative treatment options fails. Its benefit is not only observed in a short-term, but also maintained with a long-term follow-up.

High Cervical Medial Branch Blockade for Craniofacial Pain

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Craniofacial pain is one of the most common medical condition compromising activities of daily life. It was reported that 48.9% in the general population experience headache in their life. Around 1.3－2.4% of these patients suffered from chronic pain in spite of medical treatment. The author performed high cervical medial branch blockade (hcMBB) for craniofacial patients who did not respond to medical treatments. From Jan. 2019 to Mar. 2022, 107 patients with craniofacial pain underwent hcMBB. It was performed bilaterally or unilaterally depending on the patient's symptoms, and the levels of the hcMBB were C2 and/or C3 according to dermatomal distribution of patients' pain. The most common symptom accompanied by patients was eyeball pain except for occipital pain. Treatment effects were measured using patients' self-report, which are excellent (〉 90% of pain relief), good (50－90%), fair (10－50%), and poor (〈10%). Excellent pain reliefs were found in 40.2%, 25.2%, and 23.4% of patients in acute (up to 3 days after blockade), subacute (3－7 days), and delayed (up to 3 months) period, respectively. Good pain relief was identified in 30.8%, 31.8%, and 20.6% of patients in acute, subacute, and delayed period, respectively. It indicates that somewhat favorable pain relief was found in 44% of patients who underwent hcMBB up to 3 months after injection. There was no side effect after the procedure except for transient sensory loss around occipital nerve distribution areas. In conclusion, hcMBB is a simple procedure with few side effects, and may provide acceptable clinical benefits for patients with chronic craniofacial pain.

Effect of Optogenetic Inhibition of Reactive Astrocytes on the GABA Secretion and Recovery of Parkinsonism in A53T Parkinson's Disease Rat Model

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Objective: A recent study revealed the presence of the dormant DA neurons that are functionally inactive by aberrant tonic GABA secretion by the reactive astrocyte but are rescuable. Thus, we aimed to verify the impact of functional inhibition of the reactive astrocytes in the alpha-synuclein (a-Syn) overexpression PD rat model on GABA secretion and parkinsonian motor symptoms using optogenetic technology.

Methods: AAV2-CMV-α-synuclein (A53T)-EGFP was injected into the dorsal border of substantia nigra pars compacta (SNpc) of 16 Wistar rats to establish an a-Syn overexpressing PD model. After 2 weeks, the experimental group (n = 8) was injected with AAVDJ-GFAP104-eNpHR3.0-mCherry to transduce a halorhodopsin (NpHR) into reactive astrocytes, and phosphate-buffered saline was injected into the control group (n = 8). After 2 weeks, optical fibers were inserted in all animals, and after 1 week, light with a wavelength of 590 nm was applied for 1 hour at 50 Hz and 10 ms pulse duration. Changes in contralateral forelimb akinesia before and after light stimulation, TH expression, glial fibrillary acidic protein (GFAP), GABA, and a-Syn levels were compared between the experimental group and the control group.

Results: In the experimental group, contralateral forelimb akinesia after light stimulation was significantly improved by 81.4±7.2 (71.6–90.9) % compared to the pre-light stimulation state ($p = 0.0002$), while in the control group, the motor symptom was worsened by 49.5±23.2 (9.3–85.1) % ($p = 0.0003$). There was no statistical difference in GFAP expression between the two groups, but the amount of GABA was significantly reduced in the experimental group by 72.6% ($p = 0.0486$). Also, after illumination, the amount of pathological a-Syn aggregates in SNpc in the experimental group was significantly reduced by 67.5% ($p < 0.0001$) compared to the control group.

Conclusions: Functional inhibition of reactive astrocytes by optogenetic stimulation of NpHR decreased GABA production and a-Syn aggregates in the DA neurons, improving parkinsonian motor symptoms. These implicate that the restored DA neuronal activity via disinhibition by decreased astrocytic GABA might enhance the clearance of the -Syn aggregates, resulting in motor improvement.

Mfsd2a Downregulation during Focused Ultrasound-Induced Blood-Brain Barrier Opening and Peak Time Difference Compared with Tight Junction Proteins

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Introduction: The blood-brain barrier (BBB) is the interface between the CNS and blood vessels. However, because of this BBB, there is a problem in the treatment of brain diseases due to difficulties in the delivery of drugs to the brain. Meanwhile, some studies have shown that when focused ultrasound (FUS) is used to open the BBB. Past studies have often focused on the tight junctions of endothelial cells. In this study, transcytosis and tight junction mechanisms were compared.

Methods: In this study, male Sparague-Dawley rats (230-250g) were used. Low intensity focused ultrasound (LoFUS) was applied to parameters of 0.25Mpa, 120s (Targeted hippocampal region: AP -3.5, ML ±2.5). They were sacrificed 1, 4, 24 and 48 hours after sonication, respectively.

Results: As a result of comparing the sonicated brain regions of the sacrificed group at each time point after FUS, Major facilitator superfamily domain-containing 2a(Mfsd2a) is a transmembrane transport protein, which decreased the most in the 4hour group. And endothelial caveolae vesicle formation increased the most in the 4hour group. Meanwhile, it was confirmed that tight junction proteins ZO-1 and occludin were expressed the least in the 1hour group.

Conclusions: Focused ultrasound is a non-invasive and safe way to open specific brain areas. The results of this study show that there is a time gap between paracellular and transcellular pathways. Therefore, when delivering a drug after opening the BBB using ultrasound, it is suggested that different injection times should be considered depending on the characteristics of the drug. However, further studies are needed a more diverse and detailed study of the mechanism of BBB opening.

Spontaneous Repositioning of DBS Electrodes after Burr Hole Drainage for Chronic SDH : A Case Report

고려대학교 구로병원

이동한

Introduction: Deep brain stimulation(DBS) is an effective treatment option for advanced Parkinson\'s disease(PD). Since it modulates hyperexcitation of basal ganglia output by transmitting electrical currents to highly specifics area such as subthalamic nucleus(STN) or globus pallidus interna(GPi), migration of DBS electrodes may incur treatment failure and necessitates repositioning. We report a case of spontaneous repositioning of DBS leads after Burr hole drainage for chronic SDH.

Methods: A 62-year-old male patient who underwent bilateral STN DBS in 2010 was diagnosed with left convexity chronic SDH. Brain CT showed SDH along with brain edema caused midline shift about 20.4mm and subfalcine herniation with dextrad migration of DBS leads. We performed left side Burr hole drainage. and follow up CT on 2nd postoperative day(POD) noted only a small amount of hemorrhage remained, so drainage was removed and he was discharged on 5th POD

Results: On 19th POD, he visited outpatient clinic and reported no difference in Parkinson's disease-related symptoms without modulating pulse generator settings. Furthermore, follow-up CT scan showed spontaneous repositioning of leads to their previous location.

Conclusions: This case shows the possibility of spontaneous repositioning of DBS leads after removing hemorrhage, suggesting that maintaining them during hematoma evacuation operation and waiting for their repositioning can be an option rather than removing them in the first place.

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Poster Session

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Effects of rAAV-shmTOR to Nerve Injury-Induced Neuronal Hyperexcitability in the Dorsal Root Ganglion.

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Introduction: The activation of mammalian target of rapamycin (mTOR), a serine/threonine protein kinase, has been known as a one of the contributing factors in nociceptive sensitization after peripheral injury. Notably, its activation followed by the phosphorylation of downstream effectors causes the hyperexcitability of primary sensory neurons located in DRG. We investigated whether the inhibition of mTOR activation may decrease neuronal hyperexcitability in the DRG.

Methods: Adult male Sprague-Dawley rats were used. Rats were assigned into 4 groups: shmTOR, shCON, Sham, Normal. On post-operative 16th day (POD), shmTOR and shCON group were injected with rAAV-shmTOR and rAAV-shCON, respectively. Behavioral responsiveness was measured using von Frey test before modeling SNI, on POD14, PID3, 7, 14, 21, and 28 (PID: post-injection day). Rats were sacrificed on PID 21, and both spinal cord and DRG tissues were harvested for western blot analyses.

Results: The differences in mechanical withdrawal threshold were remarkable between shmTOR and shCON group. shmTOR group showed gradually increased threshold compared to shCON group. Consistent with the behavioral data, western blot analysis showed that mTOR complex 1 and complex 2 were both downregulated in DRG compared to shCON and sham group on PID 21. For its downstream effectors, p-4EBP1 and p-PKCα were also highly downregulated compared to shCON.

Conclusions: This research has a significance in that we observed AAV treatment effects on a long-term basis and consequently showed downregulation of both mTORC1 and mTORC2 as well as behavioral hypersensitivity. This study may provide a new insight into understanding the underlying pathological mechanism of mTOR in neuropathic pain and bring us one step closer to establish clinical strategy for gene therapy in neuropathic pain.

Alteration of Parvalbumin Interneuron by Baclofen treatment in TBI Mouse Model

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Introduction: Traumatic brain injury(TBI) causes neuroinflammation, and motor and cognitive disorders. Some studies show that TBI not only enhances cortical excitability but also induces loss of synaptic inhibition on excitatory neurons and decreased the expression of several interneurons. Disruption of the excitatory glutamate cycle leads to deficits in motor and cognitive functions. In this study, we will use baclofen which reduces the release of the excitatory neurotransmitter and compare with parvalbumin.

Methods: A TBI mouse model was prepared by inducing CCI in C57BL/6N mice. They were divided into Control, TBI, and TBI-BAC groups, and baclofen was injected into the TBI-BAC group for 7 days after modeling. Each group confirmed the recovery of TBI through the modified Neurological Severity Score test (mNSS test). This procedure lasted a total of 8 days and mice were sacrificed. For immunohistochemistrical analysis, brain were harvested.

Results: The histological results of the TBI and TBI-BAC groups were compared with the control group, the density of parvalbumin interneuron was significant in the TBI group, but not in the TBI-BAC group. In the behavioral experiment conducted to compare with functional recovery, the function of the TBI-BAC group was numerically better, but there was no significance.

Conclusions: Disruption of the excitatory glutamate cycle results in deficits in motor and cognitive functions. It shows that the effect of baclofen can a result that it can have an effect on the prevention of reduction of interneuron expression in TBI. In further studies, a longer period will be checked to confirm the change of parvalbumin interneuron, and additionally, the fast-spiking of parvalbumin will be compared using a neurophysiological method.

Brain-Machine Interface Based Analysis of Neural Signals in Somatosensory Cortex with Virtual Reward

연세세브란스

김태준

Introduction: Neural signal changes in the brain can be detected by BMI in order to control external machines or computers. In this experiment, neural signals from the somatosensory area in rats were analyzed in real-time and used as a control signal for external device. Providing visual feedback followed by stimulation of MFB enables the animal to learn how to control the mechanical unit, a cursor. This study implemented a design of BMI that can be controlled by visual feedback and analyze neural signals.

Methods: Customized electrodes are implanted into the somatosensory barrel cortex and the MFB of SD rats for chronic neural recording and electrical stimulation. For operant conditioning, rats were trained for 6 days in the skinner box for self-stimulation training. After addiction process, the machine control session starts with getting used to the monitor setting for a day, then training lasted 5 days. To validate the system, total 10 sessions for each rat were recorded for further analysis.

Results: The success rates were gradually increased from day 1 to day 7 (62.0 ± 6.49%, 89.0 ± 4.69 %, respectively; p* <0.05), which shows that the animal effectively learned how to control the object (circular figure) on the monitor. The gamma power between right and left barrel cortex showed differences in trials and it was used for control signal.

Conclusions: This study showed the possibility that somatosensory cortex can be an effective alternative region for BMI when the motor region is impaired. It has been demonstrated that rats are able to move the cursor with stimulation-based visual feedback without any physical movements.

Neuroprotective Role of Baclofen on Secondary Injury Induced by Traumatic Brain Injury in Mice Model

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Introduction: Traumatic brain injury is reported as a major cause of death and disability in worldwide. The secondary injury from TBI deteriorates brain damage continuously. Chronic neurological dysfunction can arise from neuroinflammatory process. Baclofen has been explored for its neuroprotective effects in diverse disease animal models involving inflammatory pathways. The purpose of this study was to confirm neurological recovery by reducing activated glial cells after baclofen treatment.

Methods: 10weeks male C57BL/6 mice were established to moderate-severe controlled cortical impact model, velocity:5m/s, depth: 1mm, dwelling time: 100ms. The target area was AP: posterior 1mm, DV: 2mm. Baclofen was dissolved in saline and was administrated with intraperitoneal (i.p.) injection. Daily injections were performed from 24hours after CCI modeling to 3weeks. After the injections were completed, an additional observation period was given to test neurological severity scores and Y-maze.

Results: Compared with TBI, modified neurological severity score were decreased in baclofen groups. In histological results, Iba-1 which represents microglia decreased in TBI group whereas reduced in baclofen groups. The relative band intensity of IL-1 beta, one of the main proinflammatory cytokines decreased in baclofen groups in compared with TBI group. GFAP, a marker of astrocytes, also was significantly down regulated in the cortex of baclofen groups in both of immunohistochemistry and western blot.

Conclusions: Baclofen has been emerged as a therapeutic drug for neurodegenerative diseases. Baclofen improved motor and cognition deficits in TBI. Moreover, baclofen reduced activated glial cells and proinflammatory cytokine in cortex region. Baclofen might be able to regulate secondary injury induced by post traumatic brain injury. However, in order to support neuroprotective effect, further analysis is required. Additionally, more research is needed on the detailed intervention mechanism.

Strategies to Treat Glioblastoma with Photodynamic Therapy and Focused Ultrasound in Rat Model

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Introduction: Glioblastoma (GBM) is a typical intractable disease, and various treatments have been attempted to date, but with slight effect. Photodynamic therapy (PDT) is a way to treat tumors under certain conditions. Similar to PDT, Sonodynamic therapy (SDT) generates reactive oxygen species by ultrasonic excitation, ultimately killing tumor cells. Based on this background, we conducted studies to demonstrate the possibility of combined therapy to treat glioblastoma.

Methods: C6 cells were transplanted into the brain of SD rats. 5-aminolevulinic acid hydrochloride (60 mg/kg) was intravenously injected 6 h before treatments. Treatments were administered 9 days after tumor transplantation. The acoustic power used for the SDT was 5.5 W/cm2 using a 0.5-MHz single-element spherically focused transducer for 20 min. The 633 nm laser was illuminated at 100 J/cm2. Magnetic resonance imaging and FDG-PET was performed to observe the status of tumor after the transplantation.

Results: In MRI image, there were differences on day 21, which showed a significant decrease in the PDT group (p<0.05) compared with the 5-ALA and SDT groups. In PET image, activation of metabolism at the tumor site was observed in the 5-ALA and SDT groups. In addition, high expression rates of reactive oxygen species-related factors in SPDT were observed through Immunohistochemistry (p<0.01, p<0.001).

Conclusions: Our results suggest that the PDT regimen of 5-ALA combined with laser therapy can significantly inhibit tumor growth in the rat brain. The tumor increased in size in SDT due to the misapplication of ultrasound. However, in SPDT, a decrease in tumor size and high oxidative stress due to treatment were observed. This indicates that SPDT has great potential as a therapeutic method for GBM. Further studies are needed to investigate the safety parameters to improve this combination method.

Effect of Ventrolateral Periaqueductal Gray (vlPAG) Stimulation with Low Frequency in an Animal Model of Neuropathic Pain

연세대학교

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Introduction: The periaqueductal gray (PAG) is one of the major centers of the descending pain inhibitory system. It has been known that the of PAG alleviates mechanical allodynia and the activity of nociceptive neurons in spinal cord. This study aimed to understand whether long-term PAG stimulation in neuropathic pain model may attenuate mechanical allodynia.

Methods: Male Sprague-Dawley rats were used and grouped into 3 groups: Normal, sham, stimulation group. Rats with spared nerve injury were implanted with customized tungsten microelectrodes in the vlPAG. Stimulation was delivered for 9 hours and behavioral responses were measured every 1 hour using von Frey test. This procedure lasted total 5 days and rats were sacrificed immediately after the last day of the stimulation. For immunohistochemical analysis, brain and spinal cord were harvested.

Results: Mechanical allodynia was decreased in stimulation group and it was remarkably effective 6 hours after the stimulation (PreStim: 1.584 ± 0.35, 6hr Stim: 6.665 ± 0.82, *p<0.05) Immunohistochemical analysis showed a decrease in glial activation in the spinal dorsal horn.

Conclusions: This study demonstrated that stimulation of vlPAG remarkably alleviated pain responses by long-term stimulation. It is noteworthy that neuropathic pain could be effectively modulated with extremely low frequency. These results suggest that stimulation of vlPAG may be one of the promising therapeutic options in neuropathic pain.

A Novel Neural Electrode Based on Liquid Metal

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Introduction: Metal based electrodes are rigid and stiff, which enables to reach the target region in implanting surgery. However, brains are normally submerged in cerebrospinal fluid so highly rigid electrodes could damage the adjacent soft brain tissues. This can cause immune responses resulting in glial scars, which hinders the long-term and stable stimulation and recording processes. To overcome the conventional limitation of electrodes, we presented facile Gallium-Indium eutectic electrodes.

Methods: Liquid metal electrode was made using EGAIn and polyimide tubing. The tip of the electrodes was coated with platinum black for higher electrochemical properties and biocompatibility. Its neural signal recording capability and implantation stability were verified through in vivo animal study by recording the nucleus accumbens (NAcc) and long term stimulation of ventral posterolateral nucleus of thalamus (VPL).

Results: EGAIn has comparable Young's modulus to the neural tissues, which minimizes the formation of inflammation and glial scars compared to conventional rigid metals. We demonstrated the in-vivo tests for electrical stimulation and in-situ recording of neural signals from the rat brain. In vivo recording of NAcc, the firing rate of neurons were increased following medial forebrain bundle stimulation (pre stimulation: 21.8 ± 3.6 Hz, post stimulation: 36.45 ± 4.4 Hz, respectively).

Conclusions: Collectively, this liquid electrode can be advantageous to long-term, stable recording and stimulation to treat neurological disorders.

Low Intensity Focused Ultrasound-Induced Endogenous Neural Stem Cell Activity.

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Introduction: Endogenous neural stem cells (eNSCs) distributed in subgranular zone (SGZ) and subventricular zone (SVZ), are important role in endogenous neurogenesis of adult brain. Meanwhile, some studies have shown that neurogenesis occurs when focused ultrasound (FUS) used to open the blood-brain barrier is irradiated into SGZ with hippocampus. In this study, FUS stimulation was given to the hippocampus to investigate the activation and lasting effects of eNSCs.

Methods: In this study, male Sparague-Dawley rats (230-250g) were used. Low intensity focused ultrasound (LIFUS) was applied to parameters of 0.25Mpa, 120s (Targeted hippocampal region: AP -3.5, ML ±2.5). Before the sonication, microbubble was injected into the tail vein of the rats. Each group was divided into 5 groups, which were non-treat control group, sonication after 3 days, 1, 2 and 4 week-groups, and sacrificed, respectively.

Results: As a result of confirming through immunohistochemistry method with Nestin and Sox2, which are markers of stem cells, significant activity values could be verified in 1 week-group. Comparing the groups at each time point after LIFUS with Western Blot. There is no noticeable difference with normal group and 3 days-group, but it can be seen that the activity in 1 week-group increases, and it decreases in 2 weeks and 4 weeks-groups. In the end activation rate becomes similar to that of normal group.

Conclusions: LIFUS is a way to activate eNSCs and cause neurogenesis. The results of this study show that able to visualize the degree of activation after FUS treatment and duration. Based on this, it is possible to set an effective repetitive treatment cycle when FUS treatment is recommended to patients with brain diseases in clinical fields. However, further studies are needed a more diverse and detailed study of repeated treatment effects and the mechanism of cell differentiation.

Effect of 915 MHz Long-Term Evolution Radiofrequency Radiation on the Body Temperature of Rat

[a]Ajou University School of Medicine and Hospital, [b]Electronics and Telecommunications Research Institute

Hye Sun Kim[a], Sung-Ae Cho[a,0], Hyung-Do Choi[b], and Young Hwan Ahn[a]

Introduction: The body temperature can be influenced by radiofrequency radiation (RFR) in animal. In this study, we evaluated how continuous or intermittent exposure modes of exposure to RFR induce rises of body temperatures in rats.

Materials and Methods: The Sprague-Dawley rats (300g, 10-week old) were exposed to the 915 long-term evolution (LTE) signals. An RFR reverberation chamber system was used. The implantable IPTT chip was implanted to monitor the body temperature continuously. The rectal thermometer was also used to measure the body temperature.

The pattern of body temperature change was compared between continuous mode and intermittent mode of RF exposure. The rats in two groups (0 W/kg, n=4 and 8 W/kg, n=6) were exposed to the intermittent exposure mode of 10 min on/off schedule for 10 hours.

Results: The body temperatures were not changed in rats exposed to wbSAR at 4 W/kg and 6 W/kg but was increased by more than 1 ˚C in rats exposed to 8 W/kg.

The pattern of body temperature rise in wbSAR of 8 W/kg was different between continuous exposure and intermittent exposure. In the continuous exposure mode, the body temperature rose by more than 1˚C after 3 hours of exposure, and in the intermittent exposure mode, 6 hours after exposure. After cessation of exposure, the increased body temperature was recovered in all.

Conclusion: The thermal effect was induced at the exposure to 915 MHz LTE signals of 8 W/kg Wb SAR in healthy male rats. And according to the mode of RF exposure, the pattern of thermal effect was different.

ACKNOWLEDGMENTS

This work was supported by the ICT R&D program of MSIT/IITP [2019-0-00102, A Study on Public Health and Safety in a Complex EMF Environment]

Reference

[1] Kim, H.S., Lee, Y.H., Choi, H.D., Lee, A.K., Jeon, S.B., Pack, J.K., Kim, N., and Ahn, Y.H., "Effect of exposure to a radiofrequency electromagnetic field on body temperature in anesthetized and non-anesthetized rats." Bioelectromagnetics. vol. 41, pp. 104-112, 2020.

대한정위기능신경외과학회
2022 정기학술대회

인 쇄 일 | 2022년 8월 31일

발 행 일 | 2022년 9월 3일

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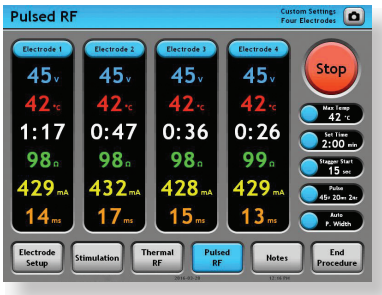

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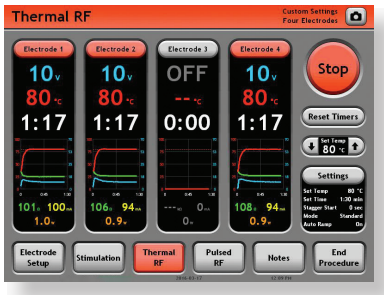

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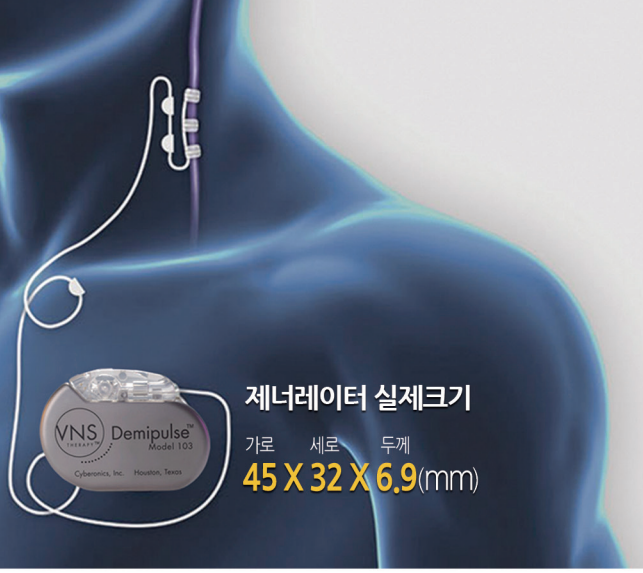

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Step 02 미주신경자극기 체내 삽입

Step 03 2주후 테스트 검진
전기자극 시작

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- **전극선**
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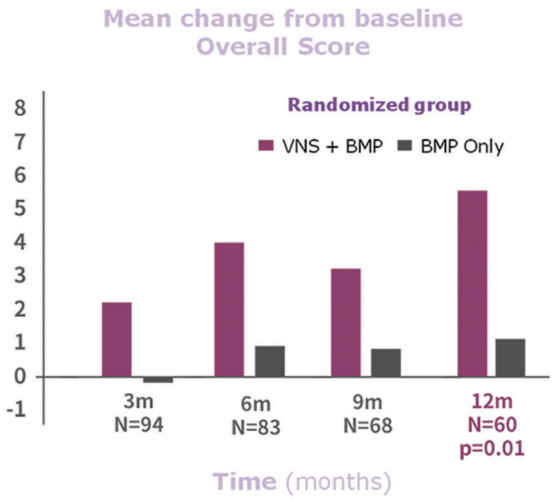
출처

Ryvlin P, et al. Epilepsia 2014; 55(6):893–900.



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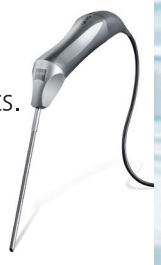

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Reference 1. Knee Surg Relat Res 2014;26(1):33-42 2. 진통소염제 클란자 CR정의 안전성 조사를 통한 안전성,유효성 평가 결과보고서, 2014

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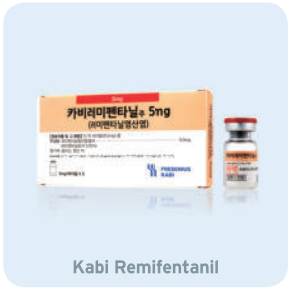

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