루게릭병 진단과 치료에 대한 최신 지견

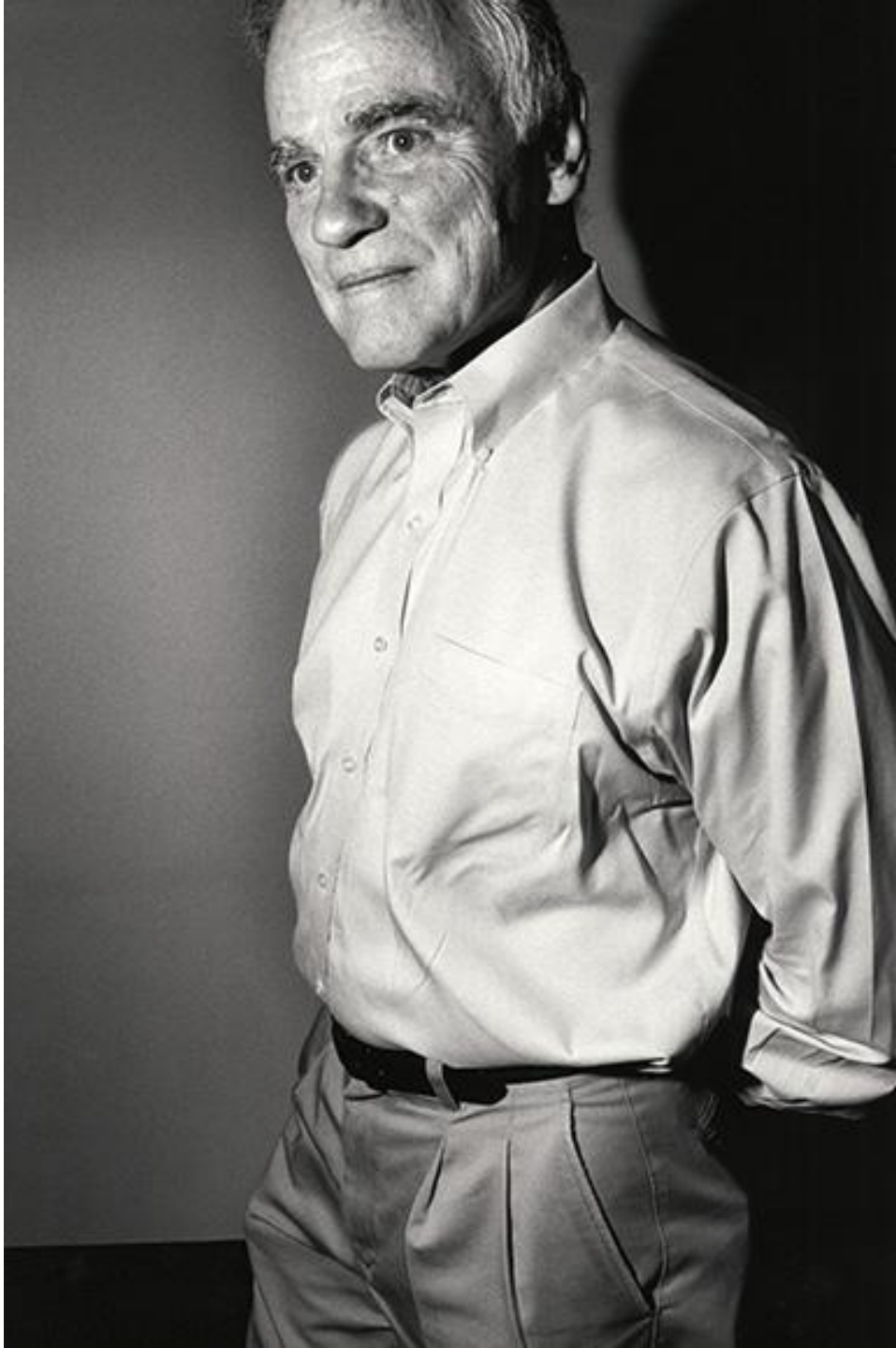
한양대학교병원 신경과

임상조교수 최원준

루게릭병 진단에 대한 최신 지견

미래 의학은
유전자 정보를 기초로한
개인 맞춤형 의학입니다.

LEROY HOOD, MD, PHD



루게릭병의 진단

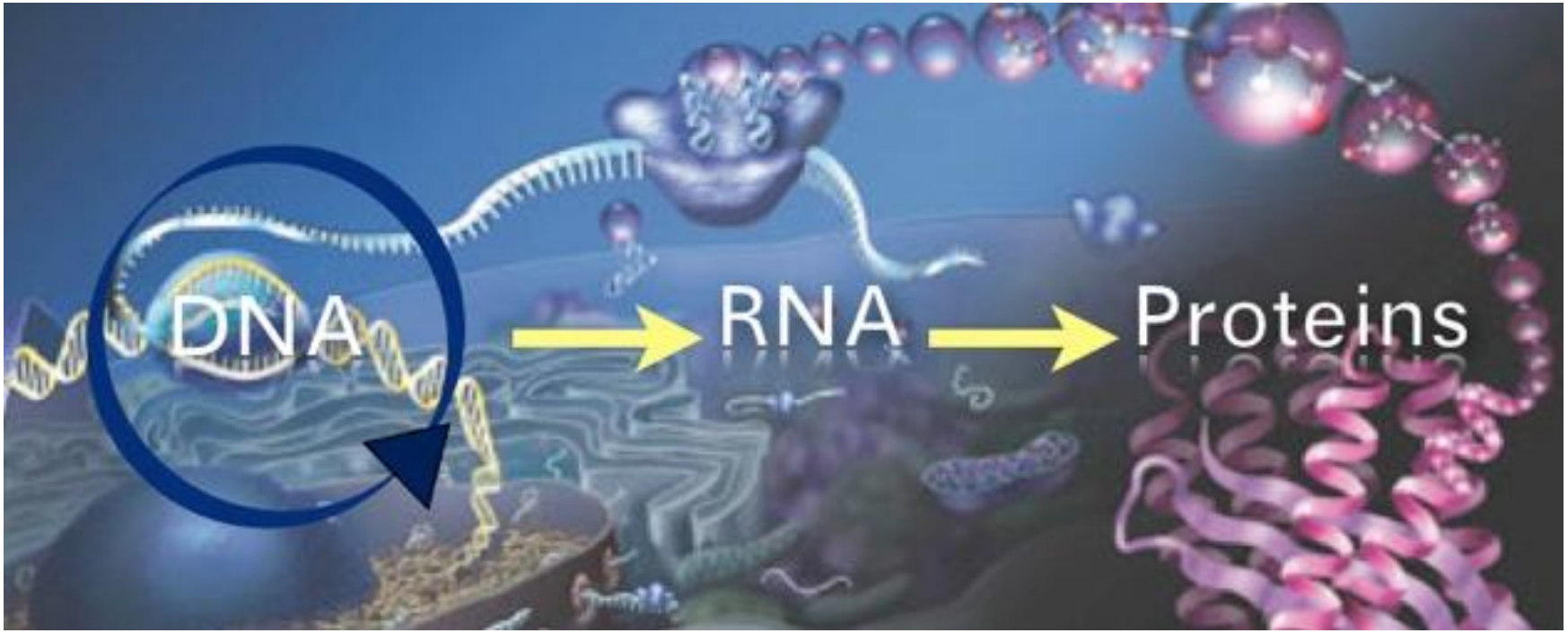
임상적 진단

병리학적 진단

유전학적 진단

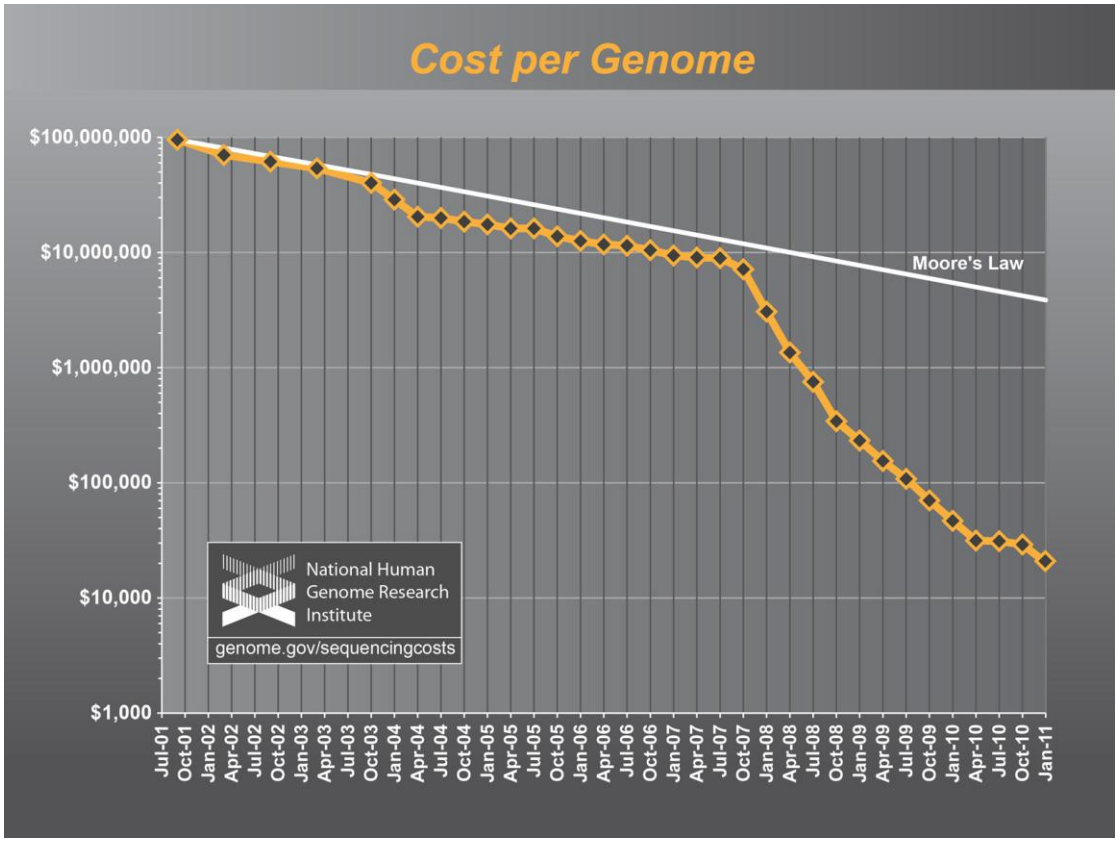
유전자란 ?

DNA 유전자 RNA Protein 단백질



획기적 유전자 분석 방법이 도입되어,

유전자 분석 비용이 급감하고 있습니다.



최근, 유전학적 진단 결과,

루게릭병은 다양한 유전자 이상과 연관됨이 [illegible]

Table 1 Genotype–phenotype correlations for ALS-FTD genes

Years	Gene	Locus	Phenotype	Pleiotropy/features	UMN, LMN, Bulbar	Mean AOO	AOO range	M:F ratio	Mode of inheritance	Refs.
1993	SOD1	21q22.11	ALS ≫ FTD	PMA, PBP, BFA, CI, CA, AuD, FTD	UMN, LMN, Bulbar	47	13–19	58:43	AD, AR, De Novo	[96]
1998	NEFH	22q12.1-q13.1	ALS ≫ FTD	–	UMN, LMN, Bulbar	60	46–73	2:3	AD	[1, 109]
2001	ALS2	2q33.2	ALS	jPLS, jALS, iHSP	UMN, LMN, Bulbar	1	1–3	7:3	AR	[46]
2003	DCTN1	2p13	ALS-FTD	CA, FTLD	UMN, LMN, Bulbar	55	48–64	2:1		[93]
2004	PRPH	12q12	–	–	LMN, Bulbar	–	–	–	–	[43, 68]
2004	SETX	9q34.13	ALS	AOA2, CA, MN	UMN, LMN, Bulbar	18	1–73	13:9	AD	[17]
2004	VAPB	20q13.33	ALS	MN, SMA, PBP, PMA	UMN, LMN, Bulbar	44	18–73	2:1	AD	[82]
2006	CHMP2B	3p12.1	ALS-FTD	PMA, Park, FTLD	UMN, LMN, Bulbar	–	–	–	AD	[89]
2006	ANG	14q11.1	ALS-FTD	Park, PBP,FTLD	UMN, LMN, Bulbar	55	21–83	4:3	AD	[42]
2008	TARDBP	1p36.22	ALS-FTD	PSP, Park, FTLD, Ch	UMN, LMN, Bulbar	55	30–77	45:26	AD, AR	[40, 55, 103]
2009	FIG4	6q21	–	HSP, PLS	–	55	29–77	5:4	AD	[20]
2009	FUS	16p11.2	ALS > FTD	Park, FTLD	UMN, LMN, Bulbar	46	13–80	39:31	AD, AR, De Novo	[58, 122]
2009	OPTN	10p13	ALS-FTD	POAG, FTLD	LMN, UMN	51	24–83	10:9	AD, AR	[74]
2010	ATXN2	12q23-q24.1	ALS	CA	LMN, UMN	57	21–87	2:3	AD[a]	[33]
2010	DAO	12q24	–	–	UMN, LMN, Bulbar	44	42–55	–	–	[75]
2010	SPG11	15q21.1	ALS ≫ FTD	jALS	UMN, LMN, Bulbar	16	7–23	11:12	AR	[85]
2010	VCP	9p13	FTLD > ALS	Dem, Pag, FTLD	UMN, LMN, Bulbar	49	37–53	–	AD	[52]
2011	C9orf72	9p21.2	ALS-FTD	FTLD, Psych, Park	UMN, LMN, Bulbar	56.8	27–80	1:1	AD	[27, 94]
2011	SIGMAR1	9p13	ALS ≫ FTD	jALS, FTLD	LMN, UMN	1	1	–	AD	[4]
2011	TAF15	17q11.1-q11.2	–	–	LMN, UMN	50	45–55	0:4	AD and AR	[107]
2011	UBQLN2	Xp11.21	ALS > FTD	Dem, FTLD	UMN, LMN, Bulbar	41	16–71	22:13	SD	[29]

PMA progressive muscular atrophy, *PBP* progressive bulbar palsy, *BFA* benign focal amyotrophy, *CI* cognitive impairment, *CA* cerebellar ataxia, *AuD* autonomic dysfunction, *j* juvenile, *PLS* primary lateral sclerosis, *HSP* hereditary spastic paraparesis, *AOA2* oculomotor apraxia type 2, *MN* motor neuropathy, *SMA* spinal muscular atrophy, *PBP* pseudo bulbar palsy, *Park* parkinsonism, *PSP* progressive supranuclear palsy, *Ch* chorea, *HSP* hereditary spastic paraparesis, *POAG* primary open angle glaucoma, *Dem* dementia, *Pag* Paget's Disease, *Psych* psychosis, *AOO* age of onset, *M:F* male:female. Mode types: *AD* autosomal dominant, *AR* autosomal recessive, *SD* sex-linked dominant

[a] *ATXN2* is regarded as autosomal dominant because heterozygosity for an intermediate allele is associated with ALS. It is classified as a dominant variation by OMIM

View Details	Causative	Gene	Gene name	Chromosome
Select		AGT	angiotensinogen (serpin peptidase inhibitor, clade A, member 8)	1q42-q43
Select		ALAD	d-Aminolevulinic Acid Dehydratase	9q33.1
Select	ALS 2	ALS2	amyotrophic lateral sclerosis 2 (juvenile) homolog (human). Alsin	2q33.2
Select	ALS 9	ANG	Angiogenin	14q11.1
Select		APEX1	Apurinic endonuclease	14q11.2
Select		APOE	Apolipoprotein E	19q13.2
Select		AR	Androgen receptor	Xq11.2
Select	ALS 13	ATXN2	ataxin 2	12q23-q24.1
Select		B4GALT6	UDP-Gal:betaGlcNAc beta 1,4- galactosyltransferase, polypeptide	18q12.1
Select		BCL11B	B-cell CLL/lymphoma 11B (zinc finger protein)	14q32.2
Select		BCL6	B-cell CLL/lymphoma 6	3q27
Select		C1orf27	chromosome 1 open reading frame 27	1q25
Select	ALS-FTD 2	C9orf72	chromosome 9 open reading frame 72	9p21.2
Select		CCS	Copper chaperone for superoxide dismutase	11q13
Select		CDH13	cadherin 13, H-cadherin (heart)	16q24.2-q24.3
Select		CDH22	cadherin 22, type 2	20q13.1
Select	ALS-FTD 3	CHMP2B	chromatin modifying protein 2B	3p12.1
Select		CNTF	Ciliary neurotrophic factor	11q12
Select		CNTN4	contactin 4	3p26.3
Select		CNTN6	DOC2B double C2-like domains, beta	3p26-p25
Select		CRIM1	cysteine rich transmembrane BMP regulator 1 (chordin-like)	2p21
Select		CRYM	crystallin, mu	16p
Select		CSNK1G3	casein kinase 1, gamma 3	5q23
Select		CST3	cystatin C	20p11.21
Select		CYP2D6	Cytochrome p450, subfamily IID, polypeptide 6	22q13.1
Select	ALS	DAO	D-amino-acid oxidase	12q24
Select	ALS	DCTN1	Dynactin	2p13
Select		DIAPH3	diaphanous homolog 3 (Drosophila)	13q21.2
Select		DISC1	disrupted in schizophrenia 1	1q42.2
Select		DOC2B	double C2-like domains, beta	17p13.3
Select		DPP6	dipeptidyl-peptidase 6	7q36.2
Select		DYNC1H1	Dynein heavy chain	14q32
Select		EFEMP1	EGF-containing fibulin-like extracellular matrix protein 1	2p16.1
Select		ELP3	elongation protein 3 homolog (S. cerevisiae)	8p21.1
Select		EPHA4	EPH receptor A4	2q36.3
Select		EWSR1	Ewing sarcoma breakpoint region 1	22q12.2
Select		FEZF2	FEZ family zinc finger 2	3p14.2
Select		FGGY	FGGY carbohydrate kinase domain containing	1p32.1
Select	ALS 11	FIG4	FIG4 homolog, SAC1 lipid phosphatase domain containing (S. cerevisiae)	6q21
Select	ALS 6	FUS	fusion (involved in t(12;16) in malignant liposarcoma)	16p11.2
Select		GARS	Glycyl tRNA synthetase	7p15
Select		GRB14	growth factor receptor-bound protein 14	2q22-q24
Select		HEXA	Hexosaminidase A	15q23

그러므로,

루게릭병은 하나의 질환이 아니라,

다양한 유전자 이상에 의한,

다양한 발병 기전을 가진,

다양한 질환의 집합체로 이해되기 시작했습니다.

미래에는,

루게릭병은 유전자에 따라 또는 발병기전에 따라

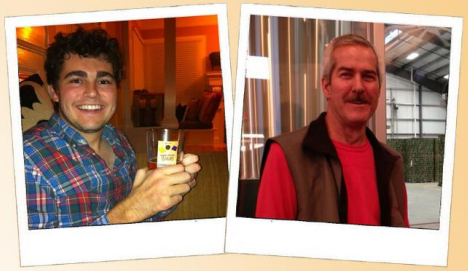
세부진단 되어야하며,

그 세부진단에 의한 맞춤치료가 시행될 것으로

예측됩니다.

Great Beer Ales for ALS Great Cause

Loftus Ranches and Hopunion have created Ales for ALS to support a very worthy cause – ALS research. They have offered participating brewers access to a proprietary hop blend, free of charge, in exchange for participation in Ales for ALS™. Participating brewers are brewing special beers with these hops and will donate a portion of the sales to ALS TDI, the world's leader in ALS research.



Ales for ALS inspired by Corey Reich, the Hanses family, and all others living with ALS

Target Brew Time: JUNE / JULY 2013

Blend designed by Russian Rivers' Vinnie Cilurzo and Bell's Brewery's John Mallet

WHAT IS ALS? (AKA: LOU GEHRIG'S DISEASE)

Amyotrophic lateral sclerosis (ALS, Lou Gehrig's disease) is a progressive neurodegenerative disease that leads to paralysis,
due to the death of motor neurons in the spinal cord and brain.

- There is no known cure for the disease.
- The average person survives only 2-5 years following diagnosis.
- About 5,000 people in the US are diagnosed with ALS each year.
- There are about 30,000 people in the US diagnosed with ALS today.
- The worldwide population of ALS patients is estimated at 450,000.

ABOUT ALS THERAPY DEVELOPMENT INSTITUTE

The ALS Therapy Development Institute (ALS TDI) is the world's leading ALS research organization and aims to discover and develop effective treatments and a cure for ALS. Built by and for patients, the Cambridge, MA based drug development institute operates as a 501c3 nonprofit: combining the optimal entrepreneurial practices of a biotechnology and pharmaceutical company with the passion and urgency of a nonprofit mission. For more information, please visit us online at www.als.net.

루게릭병 치료에 대한 최신 지견

: 근접한 루게릭병 치료제 개발에 대한 기대

신경퇴행성 질환 국내 유병률

루게릭병: 2000 명 (추정)

파킨슨병: 50000-100000 명 (추정)

알츠하이머병: 541000 명 (2012 년 보건복지부 자료)

루게릭병은 희귀 질환으로 분류됩니다.

하지만,

치료제 개발을 위한 연구자의 노력은 결코 희귀하지 않습니다.

1. 루게릭병: 운동신경 세포의 가속화된 노화; 노화 연구의 한 분야
2. 루게릭병: 치매와 공통 발병기전; 치매 연구의 한 분야
3. 루게릭병 치료제 개발만을 목표로 한 비영리회사 인 TDI 의 적극적 노력

신경퇴행성 질환은 가속화된 노화 현상이며,

루게릭병은 주로 운동신경세포의 가속화된 노화로 이해됩니다.

한국 사회의 고령화 추이에 따라,

스마트 에이징에 대한 관심이 지대합니다.

미래 고령화 사회 10 대 유망 기술
한국과학기술기획평가원 (KISTEP)

1. 신경줄기세포 치료기술… 새로운 뇌세포 생성, 치매 치료
2. 라이프케어 서비스 로봇… 로봇이 환자의 재활 의사로
3. 생체신호 인터페이스… 눈빛과 손짓으로만 컴퓨터 제어
4. 초고속 유전체 해독기술… 싸고 빠르게 유전자 해부
5. 근력지원 로봇 수트… 로봇 입고 무거운 짐도 거뜬하게
6. 무인 자율주행 자동차… 노인·장애인도 쉬운 운전
7. 실감형 스마트워크 기술… 거동 힘들어도 회의 참석 가능
8. 나노바이오 의료센서… 침 한방울로 암·뇌경색 자가 진단
9. 분자영상 질병진단 기술… 파킨슨병·치매 조기 발견
10. 대화형 자연어 처리기술 말 정확히 알아듣는 IT

신경줄기세포로 할머니 치매 정복　시력 나쁜 할아버지도 운전 척척　100달러로 유전자 진단·맞춤 진료

최근, 한 유전자 이상이

루게릭병과 전두엽성 치매를 공통적으로 발병시킬 수 있음이

밝혀졌고, 치매 연구자들 상당수가

루게릭병 연구에 관심을 가지게 되었습니다.

Our Mission:

Secure funding, develop potential treatments, end ALS

Donate

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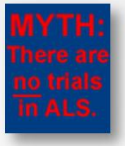
Research Center

90 mins on Stem Cell Clinical Trials (Recorded 5/8/13)
Co-hosts: Rob Goldstein (TDI) & Dr. Yael Gothelf (BrainStorm) discuss current an...

TDI and Gladstone Join Forces
Partners will leverage Nobel Prize winning technology to identify potential trea...

TDI adds to-BBB as Partner
Getting drugs across the blood brain barrier using cutting-edge drug delivery to...

ALS Community



Looking for a clinical trial?
Our database is unbiased, international and updated daily.

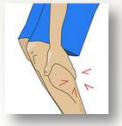
May Update from TDI
Not registered with TDI? Click here to see our latest e-update.

Craft Brewers Unite to End ALS
30+ craft brewers to donate sales of special brews this summer to ALS TDI

In The Spotlight

Diaphragm pacing explained
SUNY's Kirsten Gruis MD talks about the NeuRx DPS including the upcoming trial

A Go for anti-NogoA
AP-HP's Pierre-François Pradat MD PhD talks GSK's ozanezumab, now at phase II



A pain reliever for pALS?
An upcoming trial asks whether mexiletine can help reduce muscle cramps in pALS.

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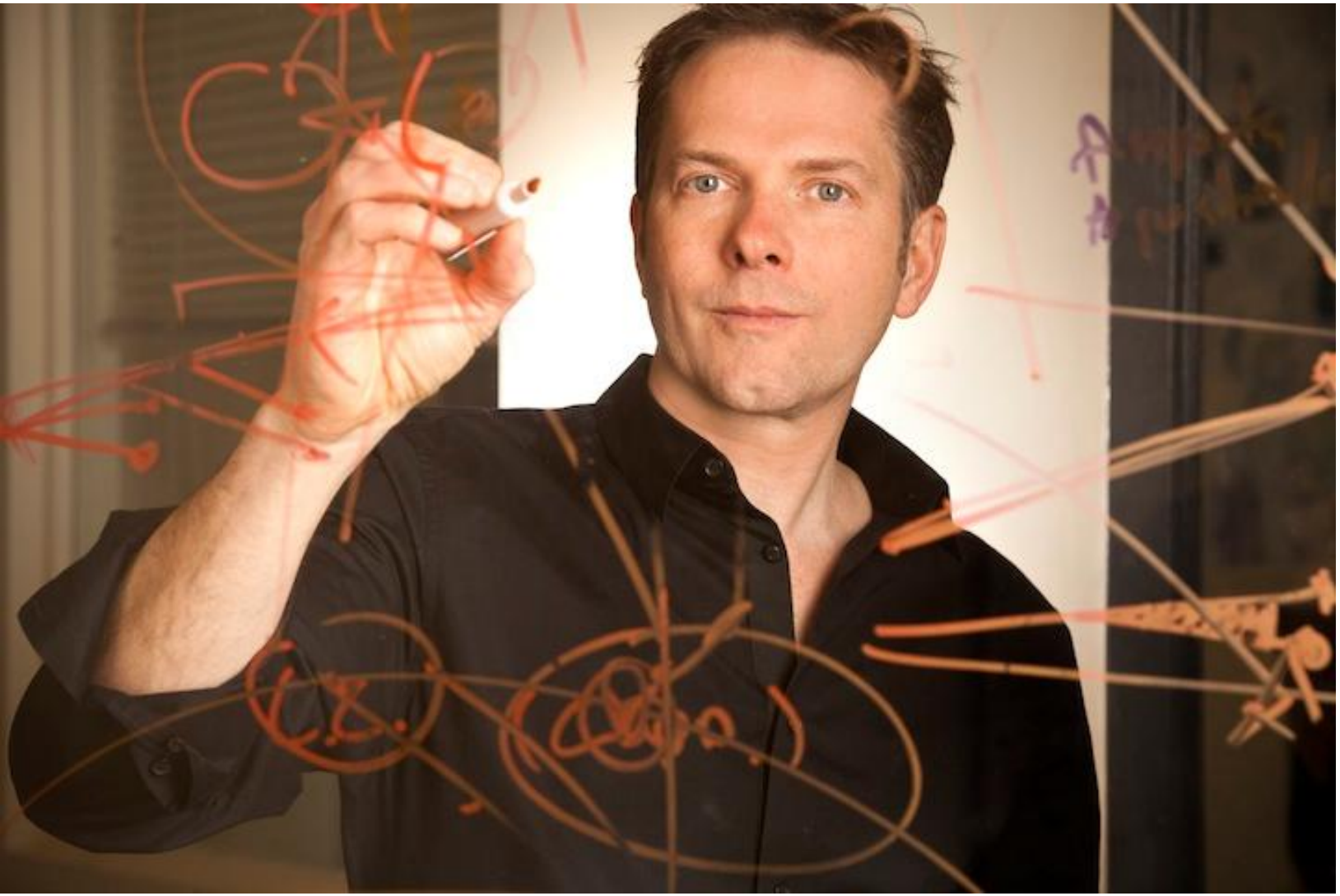

제임스 헤이우드

Augie Nieto

Augie Nieto is the founder and retired chief executive of Life Fitness and the chairman of Octane Fitness. He and his wife, Lynne live in Carona Del Mar, California and have four children. Wikipedia

Born: 1960

Books: Augie's Quest: One Man's Journey from Success to Significance

오기 니에토

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IT'S TIME TO CURE ALS

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Augie's Quest

MDA's ALS research initiative, is an aggressive, cure driven effort focused on finding treatments and cures for ALS.

Join the Quest.
It's time to cure ALS.

Total Raised Since 2006: $36,996,009.53

Augie's Golf & Wine Extravaganza

Our 6th Annual Augie's Quest Golf & Wine Extravaganza held on April 30, 2013, at Big Canyon Country Club was a huge success raising $130,000 for ALS research! Thank you // Learn More…

Featured Video

AQ-BigNews

TDI Timeline

ALS TDF becomes ALS Therapy Development Institute (ALS TDI) following the annoucement of a three-year, $18 million grant from MDA's Augie's Quest.

One-of-a-kind bioinformatics and laboratory management system, "KnowledgeSphere", is built at ALS TDI allowing for seamless data analysis and management of the world's largest drug discovery effort dedicated to treating ALS.

Steve Milne Fund reaches its $1 million goal. Commits to hitting its next target in half the time.

Steve Perrin, Ph.D., becomes the organization's first chief scientific officer.

2007

ALS TDI completes the first ever comprehensive gene expression database of the SOD1 mouse in partnership with GeneLogic.

ALS TDI purchases a Laser Capture Microdisection (LCM) to investigate cell-specific changes in gene and protein expression.

3rd Annual Leadership Summit fills the room at the Museum of Science in Boston. Drs. Ray Onders, Dale Lange and Hans Kiersted make presentations.

After eight years leading ALS TDI, Jamie steps down as CEO and joins the board.

ALS TDI raises an astonishing $9,687,302 in 2007 - making the Institute one of the best funded private research organizaitons in the world focused on a single disease.

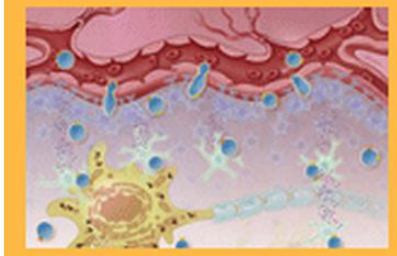
For the second year in-a-row, the DOD funds ALS TDI, awarding a $1 million grant.

"Yoda" and "Darth," two BioMek automation robots become permanent members of the team at ALS TDI. They are tasked with speeding up the processing of RNA and genotyping.

ALS TDI launches novel gene therapy pipeline and partners with Microbix to develop targeted vectors.

FDA Approves Clinical Trial of TDI-132 (Gilenya) in ALS Patients

02/11/2013



Gilenya, giving ALS the fingo?

Categories: Podcast

Posted By Michelle Pflumm, Ph.D. February 12, 2013

An upcoming phase IIA trial asks whether Gilenya might have the potential to slow ALS by reducing T cell-mediated inflammation.

February 11, 2013 – CAMBRIDGE, MA – The ALS Therapy Development Institute (ALS TDI) announced today that it has received FDA approval to conduct a clinical trial of TDI-132 (aka: fingolimod, Gilenya™) in ALS. Fingolimod is currently being marketed by Novartis AG as Gilenya™ as a treatment for some forms of multiple sclerosis.

This clinical trial is being launched as a Phase IIA with the primary purpose of determining the safety and tolerability of TDI-132/Gilenya in people with ALS. ALS TDI, a non-profit biotech, is the sole funding sponsor of this clinical trial, thanks to the support it received from the ALS community. Current enrollment sites include Massachusetts General Hospital in Boston; University of California, Irvine in Orange; Georgia Health Sciences University in Augusta; and Methodist Neurological Institute in Houston, TX.

“It was exciting to see how expeditious the FDA reviewed our application to test Gilenya in ALS patients,” comments Steve Perrin, Ph.D., CEO and CSO of ALS TDI. “We are eager to start enrolling patients in the clinical trial of TDI-132 and take this important step toward understanding whether or not Gilenya is a potential treatment for ALS.”

루게릭병 치료 임상시도 분류

1. 줄기세포 치료: 한양대학교병원 신경과
2. 약물 치료
3. 임플란트 치료
4. 단일항체 치료: GSK NoGoA antibody
5. 리보핵산 억제재 RNAi 치료
6. 보톡스 치료
7. 두뇌 접속

루게릭병

오기 치료