Rare Genetic Disorders; Beyond the Diagnosis, Development of Orphan Drugs for the Cure

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Numbers related with orphan diseases

8,000	8,000 diseases
80	80%가 Genetic Disorder
20,000	20,000 명 미만의 유병인구
5	최종진단시까지 5년의 시간경과
30	소아병원 입원환자의 30%

Definition, number, and cumulative prevalence of rare diseases

Definition, number, and cumulative prevalence of rare diseases	References
Definition	Richter et al., 2015
United States: <200,000 people (1 in ~1,630)	
European Union: <5/10,000 (<1/2,000)	
Japan: <50,000 (1 in ~2,500) Korea : <20,000 (~1 in 2,500)	
Global average: 1 in 2,500	
Number of rare diseases: 9,603	Orphadata: Free access data from Orphanet
Percentage of rare diseases with a genetic etiology: 39%	This study
Minimal cumulative prevalence: 1.5–6.2%	Chiu et al., 2018; Walker et al., 2016; this study

	Rare disorders	Ultra-rare disorders
Prevalence	<1:2,000	<1:2,000,000
		Korea : < 200 (~1 in 250,000)
Number of affected newborns/disorder in Europe	5,000 or less	5 or less
Diagnosis	centers of expertise (national) e-mail consulting	electronic database (international) e-mail consulting
Follow-up	centers of expertise	local healthcare professionals virtual centers of expertise
Provision of information	text books; literature; sites (OMIM; Orphanet; etc)	Wiki sites
Support groups	national	international
Research	grants difficult	grants extremely difficult

Am J Med Genet. 2019;179A:885–892.
Eur J of Med Genet 2011;54:220-224.

Statistics of Orphan drugs

Orphan drugs	statistics	References
Annual worldwide expenditure on orphan drugs	$125 billion	EvaluatePharma's Orphan Drug Report 2018
Percentage of worldwide orphan drug expenditure compared to non-generic prescribed drug expenditure	15.9%	EvaluatePharma's Orphan Drug Report 2018
Number of orphan drug approvals since the Orphan Drug Act of 1983	744	FDA's Orphan Drug Product database
Percentage of orphan drug approvals compared to all novel drug approvals	39–53%	FDA's Orphan Drug Product database
Percentage of rare diseases treated with an FDA-approved orphan drug indication	2.4% (226/9,603)	Am J Med Genet. 2019;179A:885–892.
Percentage of orphan drug approvals among the FDA orphan drug designations since the Orphan Drug Act of 1983	15.6 % (744/4,780)	Am J Med Genet. 2019;179A:885–892.

Big chasm between diagnosis and curative therapy in genetic disorders

Photo credit: modified from Google image

왜 희귀약품개발에 관심을 가지게 되나?

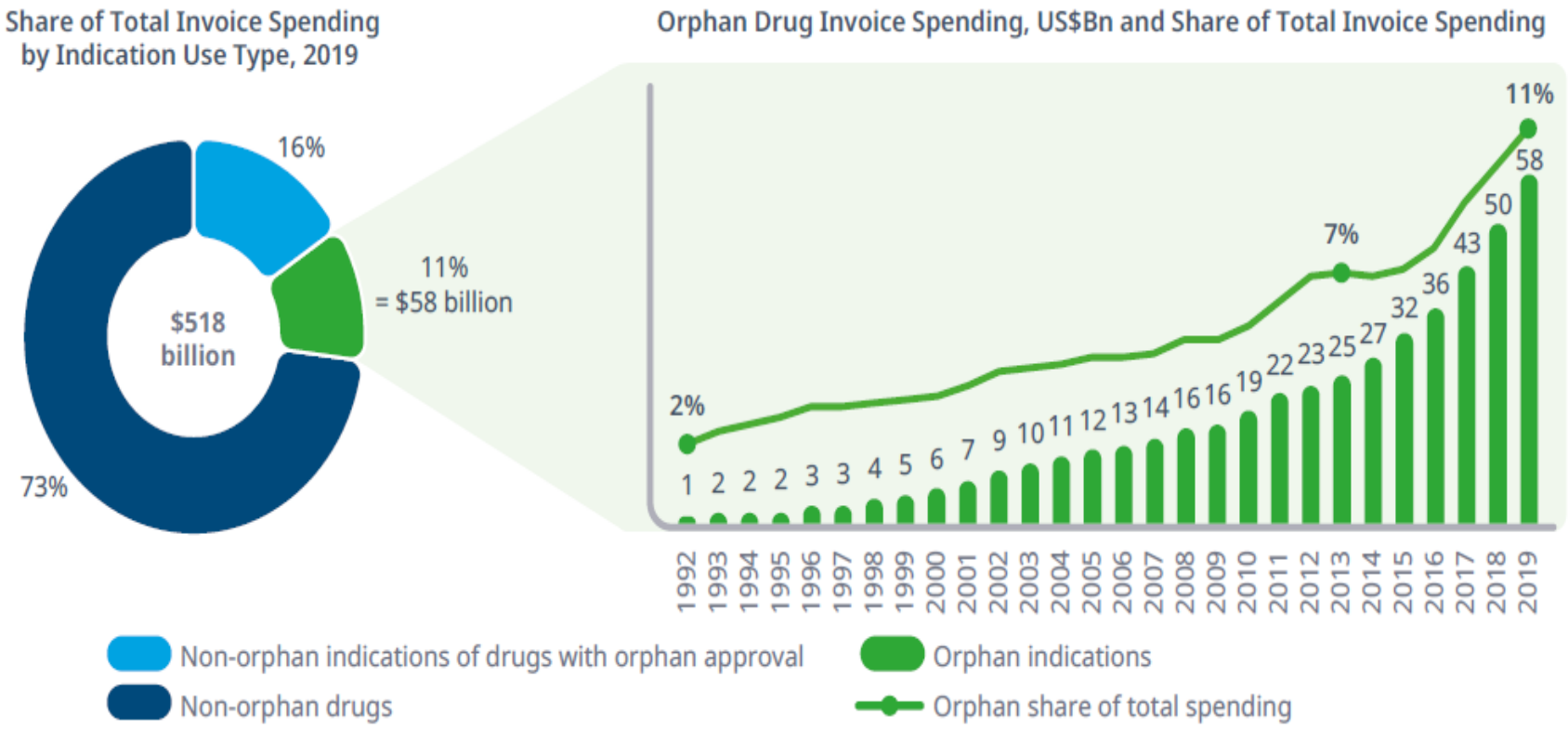
▣ 지속적인 성장률 예상 (CAGR(compound annual growth rate)

- ◆ 시장 독점권 (미국 7년/유럽 10년)
- ◆ 상대적으로 적은 개발 비용
- ◆ 보험 지원 및 高價의 약가 구조

	Orphan	Non-Orphan
시장 독점권	미국 7년/유럽 10년	5년
임상 3상 (환자수/비용)	731 명/99M$	3,540 명/188M$
치료비용/환자1名/1年	137,782 $	20,875 $
투자 회수율 (NPV/임상 3상 비용)	14.9 (86 B$/5.8 B$)	7.9 (180 B$/22.8 B$)

Source; Evaluate Pharma Success Rates (2014)

Invoice Spending on Orphan Drugs in the United States 1992–2019, US$Bn

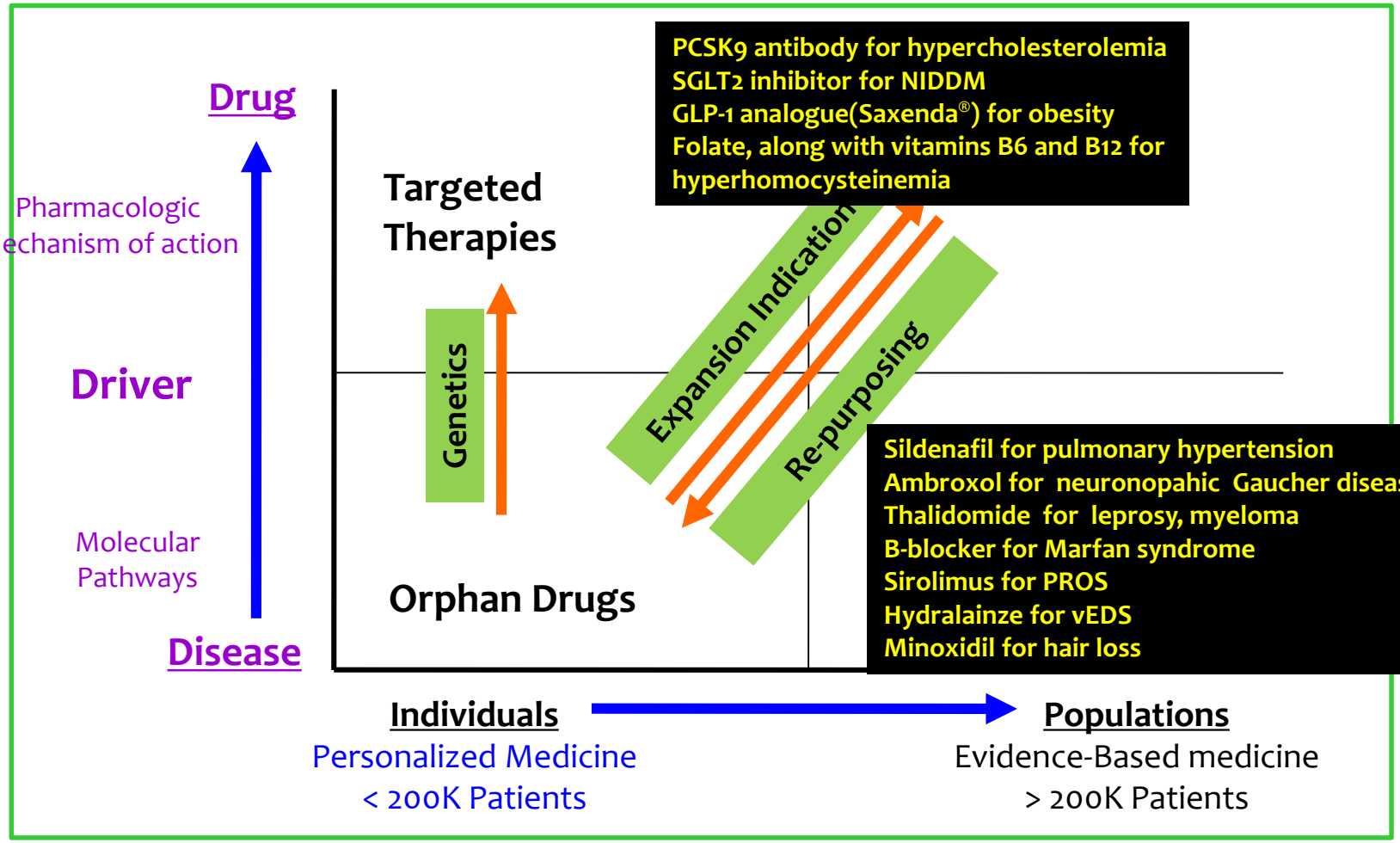


Source: IQVIA Institute, Aug 2020;
FDA Orphan Drug Designations and Approvals;
IQVIA National Sales Perspective, Jan 2020

Epoch making events of FDA approved orphan drug

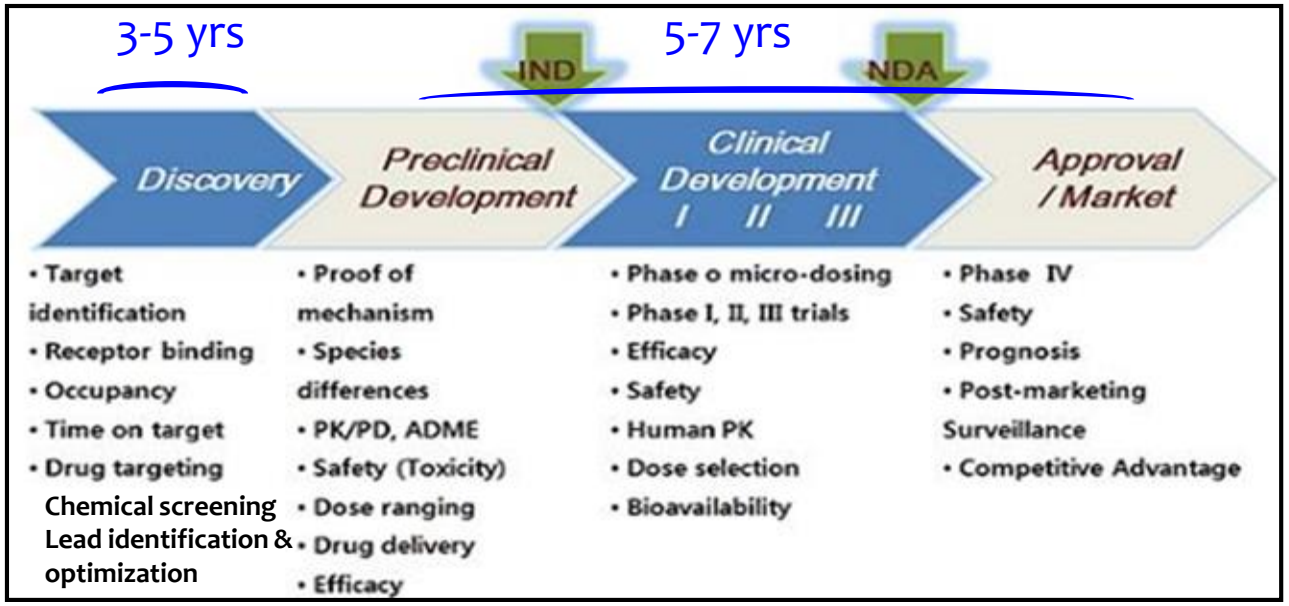
- 1955 PKU: Diet therapy
- 1982 Type I DM: Insulin
- 1985 Growth hormone deficiency: recombinant human growth hormone
- 1991-1995 Gaucher disease: Ceredase, Cerezyme, enzyme replacement therapy
- 1992 Hemophilia A: recombinant Factor VIII
- 2012 Cystic fibrosis: Ivacaftor (CFTR potentiator)
- 2016 Duchenne muscular dystrophy: Eteplirsen (Exondys 51) , antisense oligonucleotide therapy
- 2017 Retinal dystrophy: LUXTURNA™
- 2017 B-cell precursor ALL: CD-19 directed genetically modified autologous T-cell immunotherapy (KYMRIAH)
- 2018 Adult PKU: Palynziq (pegvaliase-pqpz), enzyme replacement therapy
- 2019 Spinal muscular atrophy: most expensive gene therapy product (25억원), Zolgensma
- 2020, 2022 Spinal muscular atrophy: Evrysdi (risdiplam)

Product Development: Disease-driven vs Drug driven



Modified from PharmBio Sciences 2010 ; 4:290-299

Process of drug development



- Disease epidemiology
- Number of patients & clinical experiences
- Disease phenotype delineation
- Natural history of the disease
- Mechanism & pathophysiology
- In vitro & In vivo model (cell model, animal model):
  - but not always animal study results ≠ human study results

Major challenges in orphan drug development

Group	Specific challenges
Clinical trial design and execution	Poor understanding of natural history of disease because of few observational studies studying disease progression Heterogeneous populations with variable phenotypes and clinical courses Lack of clinically relevant endpoint definitions and validations Geographical dispersal of patients and researchers Lack of prior clinical studies to establish template for study execution
Patient recruitment	Small number of patients Low disease awareness Ill-defined therapeutic approach by physicians
Regulatory	Lack of comprehensive evidence Need to meet standard criteria for approval
Others	Reimbursement scrutiny Pediatric trials Ethical concerns

"N of 1 clinical trial"

Drug Discovery Today 2019;24:867-872.

Treatment strategies of genetic disorders at various levels

Level of intervention	Treatment strategies
Epigenetics	Epigenetic therapy/ Gene expression modulation
Genes	Organ/tissue/cell therapy
	Gene therapy (ex vivo/in vivo) , genome editing
	Modulation of gene expression by chemicals
RNA	Anti-sense oligonucleotide / iRNA therapy
	Stop codon read-through therapy
	Exon skipping by phosphorodiamidate morpholino oligonucleotide(PMO)
Proteins	Protein replacement therapy
	Enhancement of residual enzyme by pharmacological chaperone

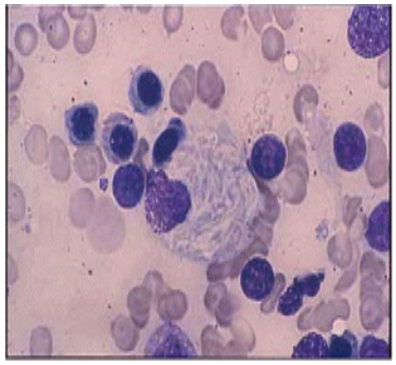
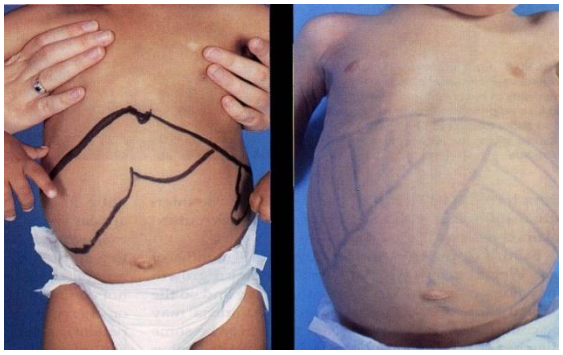
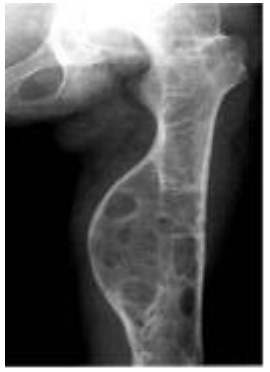
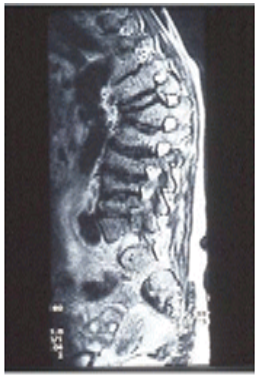
Current approved gene therapy product

1. Gendicine: 2003, Chinese FDA, head and neck squamous cell carcinoma
2. Oncorine: 2005 Chinese FDA, refractory nasopharyngeal cancer
3. Glybera: 2012 EMA, lipoprotein lipase deficiency
4. Imlygic: 2015 FDA, 2015 EMA, melanoma
5. Zalmoxis: 2016 EMA, add-on treatment in adults who have received a haematopoietic stem cell transplant
6. Strimvelis: 2016 EMA, ADA-SCID (Severe Combined Immunodeficiency due to adenosine deaminase deficiency).
7. Luxturna: 2017 FDA, 2018 EMA, retinal dystrophy by RPE65 gene defect
8. Kymriah: 2017 FDA, 2018 EMA, CAR-T for B-cell ALL
9. Yescarta: 2017 FDA, 2018 EMA, CAR-T for Non-Hodgkin's lymphoma
10. Zolgensma: 2019 FDA, spinal muscular atrophy
11. Zynteglo : 2019 EMA, β-thalassemia

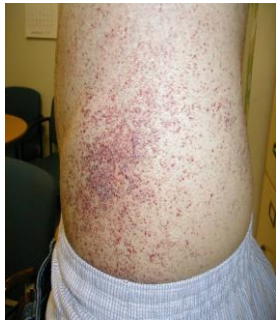
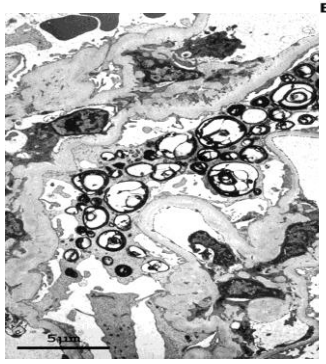
https://www.genetherapynet.com/

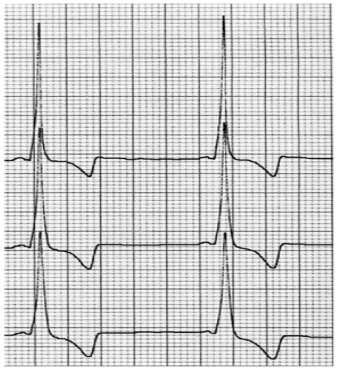
효소대치요법이 가능한 리소솜 축적 질환

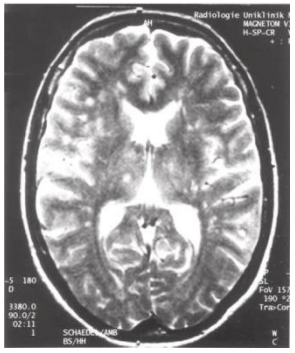
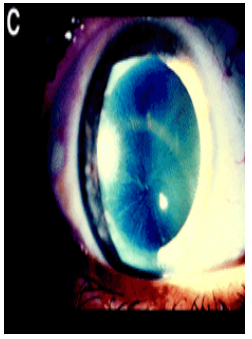
Gaucher disease

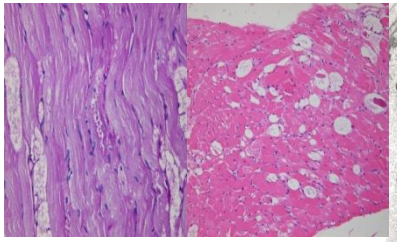
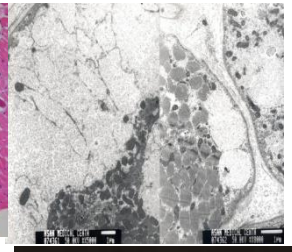
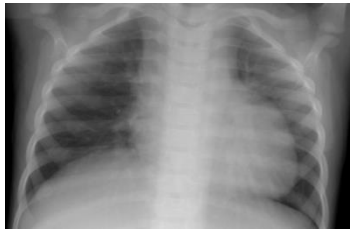
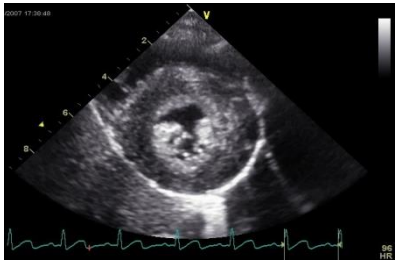
Fabry disease

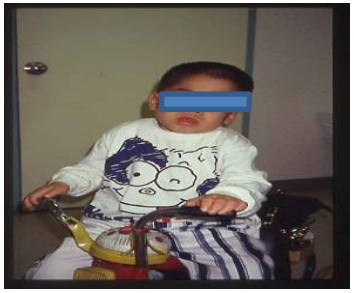


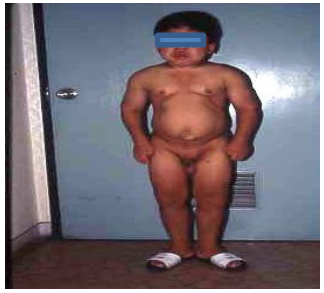
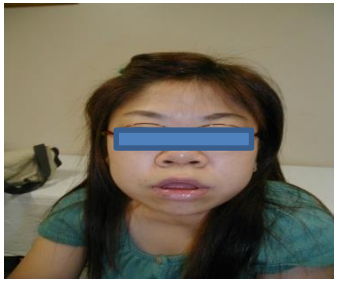



Pompe disease

Hunter/ Hurler/ Morquio diseases



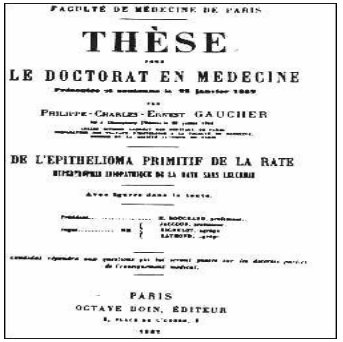
Current status of FDA approved enzyme replacement therapy (ERT) in lysosomal storage disorders(LSD)

LSDs	Gaucher Disease	Fabry Disease	MPS I	MPS II	MPSIVA	MPSVI	MPS VII	Pompe Disease	CESD	CLN2	Alpha-Mannosid-osis
Product	Cerezyme	Fabrazyme	Aldurazyme	Elaprase	Vimizim	Naglazyme	Mepsevii	Myozyme Lumizyme Nexviazyme®	Sebelipase alfa (KANUMA)	Brineura™ (cerliponase alfa)	
Year of FDA/EMA Approval	1995	2001	2003	2007	2014	2006	2017	2006 2021	2015	2017	2018
Year of Initiation In Korea	1994	2003	2004	2008	2015	2008		2005	2016		
Financial Coverage In Korea	1998	2004	2004	2009	2015	2010		2009 (infantile) 2011 (late onset)			
	Abcertin (2012) Velaglucerase (2015) Taliglucerase (2016)	Fabagal (2014) Replagal (2014)		Hunterase (Green Cross) 2012						Intraventricle infusion	

ERT: enzyme replacement therapy, LSD: lysosomal storage disease, MPS: mucopolysaccharidosis, CESD: cholestryl ester storage disease
CLN2: neuronal ceroid lipofuscinosis type 2

Gaucher Disease

Time Line



FACULTÉ DE MÉDECINE DE PARIS

THÈSE

POUR

LE DOCTORAT EN MÉDECINE

Présentée et soutenue le 28 janvier 1882

PAR

PHILIPPE-CHARLES-ERNEST GAUCHER

DE L'EPITHELIOMA PRIMITIF DE LA RATE

HYPERTROPHIE IDIOPATHIQUE DE LA RATE SANS LEUCHÉMIE

Avec figures dans le texte.

Président ..... M. DOCKARD, professeur.

Suffrages ..... MM. { JACCOUD, professeur. / HANOT, agrégé. / RATHERY, agrégé.

Les propositions imprimées à la suite de la thèse sont relatives aux matières qui y sont traitées.

Vu et permis d'imprimer :

Le Vice-Recteur de l'Académie de Paris,

GRÉARD.

PARIS

OCTAVE DOIN, ÉDITEUR

8, PLACE DE L'ODÉON, 8

1882

1882, Phillipe Charles Ernest Gaucher
Doctoral Thesis: description of 32 yr old woman with splenomegaly

1905, Brill NE
premortem diagnosis "Gaucher disease"

1955, de Duve C,
Discovery of lysosome

1966, Brady RO, concept of ERT in Gaucher disease

1974, Brady RO, first clinical trial with purified glucocerebrosidase in human

1984, Genzyme begins aglucerase clinical trial

1991, Ceredase (placentally derived aglucerase) approved by FDA

1994, Cerezyme approved by FDA , First ERT in a Korea patient

2003, Substrate reduction therapy (miglustat) –FDA approval

2010, Velaglucerase alfa

2012, Taliglucerase alfa

2013, Abcertin

2014, Cerdelga(Eligustat)

Structural Elucidation

1. Primary structure of CHO cell derived, human macrophage-targeted recombinant human β-glucocerebrosidase

- Amino acid sequence and composition
- Disulfide bridge and Free sulfhydryl group
- N-glycosylation site

Disulfide bridge

Free sulfhydryl group

```
1    ARPCI PKSFG YSSVV CVCNA TYCDS FDPPT FPALG TFSRY ESTRS GRRME
51   LSMGP IQANH TGTGL LLTLQ PEQKF QKVKG FGGAM TDAAA LNILA LSPPA
101  QNLLL KSYFS EEGIG YNIIR VPMAS CDFSI RTYTY ADTPD DFQLH NFSLP
151  EEDTK LKIPL IHRAL QLAQR PVSLL ASPWT SPTWL KTNGA VNGKG SLKGQ
201  PGDIY HQTWA RYFVK FLDAY AEHKL QFWAV TAENE PSAGL LSGYP FQCLG
251  FTPEH QRDFI ARDLG PTLAN STHHN VRLLM LDDQR LLLPH WAKVV LTDPE
301  AAKYV HGIAV HWYLD FLAPA KATLG ETHRL FPNTM LFASE ACVGS KFWEQ
351  SVRLG SWDRG MQYSH SIITN LLYHV VGWTD WNLAL NPEGG PNWVR NFVDS
401  PIIVD ITKDT FYKQP MFYHL GHFSK FIPEG SQRVG LVASQ KNDLD AVALM
451  HPDGS AVVVV LNRSS KDVPL TIKDP AVGFL ETISP GYSIH TYLWH RQ
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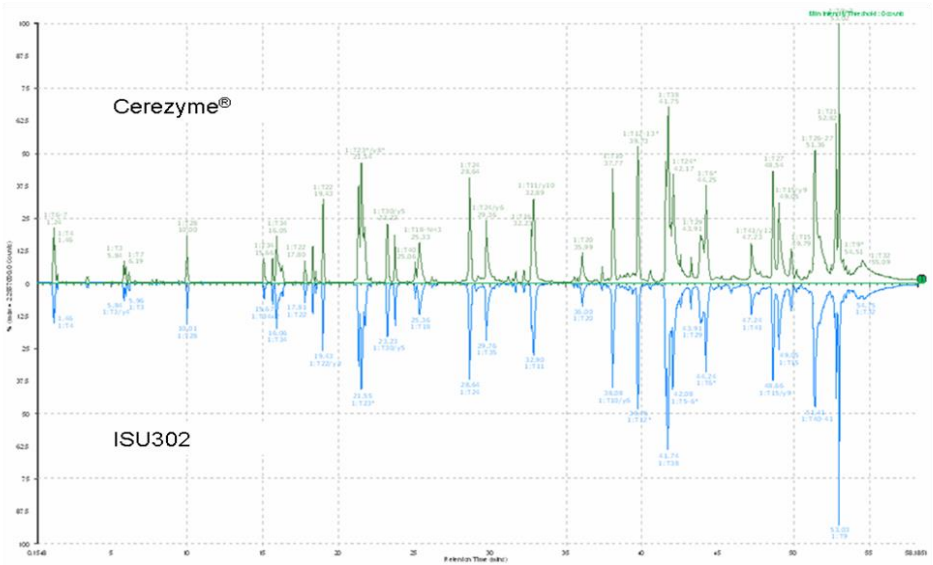
- Amino acid: 497 A.A
- Disulfide bridge:
  Cystine 4 = Cystine 16
  Cystine 18 = Cystine 23
- Free sulfhydryl group
  Cysteine 136
  Cysteine 248
  Cysteine 342
- N-Glycosylation site
  N19, N59, N146, N270

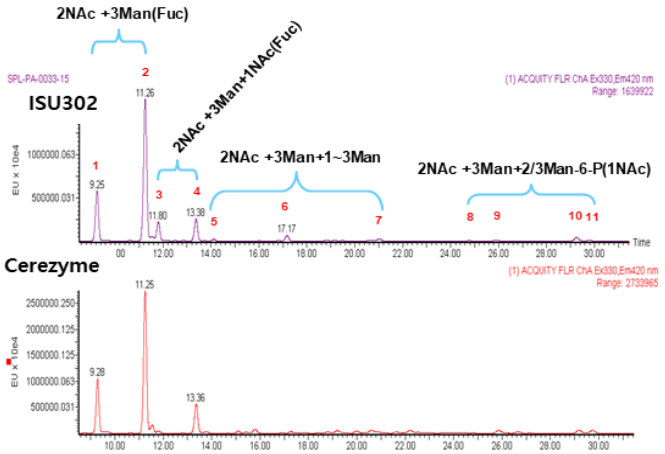
- **Peptide mapping (LC-MS with mirror image analysis)**

Cerezyme® vs. ISU302 Peptide mapping profile



- Oligosaccharide profile
- Monosaccharide composition

Oligosaccharide profile (biantenary structure)



Monosaccharide composition

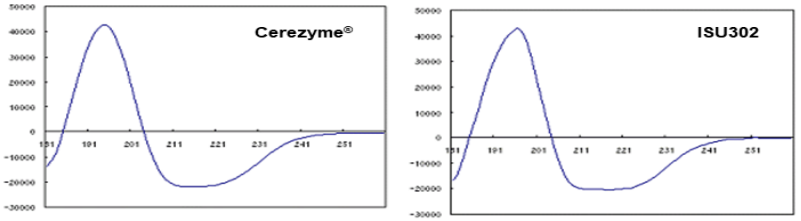
(unit; mol/mol protein)

samples/sugars	ISU302	Cerezyme® (A7030A05)	SD	CV(%)
fucose	2.0±0.1	2.3±0.0	0.2	9.9
galactosamine	0.4±0.0	0.3±0.0		
glucosamine	9.9±0.2	10.3±0.7	0.3	2.8
galactose	0.2±0.0	0.6±0.0		
glucose	0.4±0.5	0.4±0.0		
mannose	12.3±0.6	12.9±0.2	0.4	3.4
Sugar (%, w/w)	7.4±0.3	7.8±0.2		

High order structure

- Circular Dichroism
- Differential Scanning Calorimeter

Circular Dichroism



	Method	HELIX	BETA	TURN	PP2	Others
Cerezyme®	Self Selcon3	64.1 %	6.7 %	8.4 %	2.2 %	21 %
ISU302	Self Selcon3	63.6 %	5.5 %	9.5 %	1.2 %	18 %

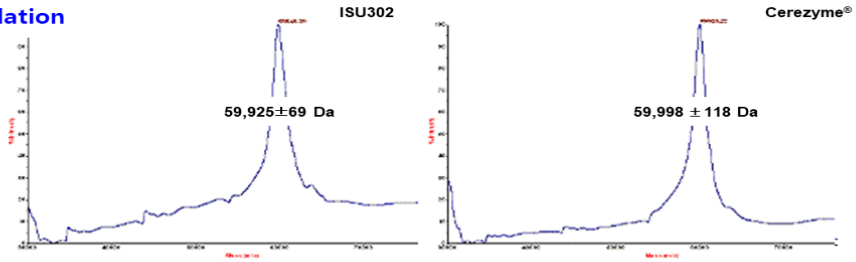
Differential Scanning Calorimeter

	Melting temperature (℃)
Cerezyme®	56.8
ISU302	56.5

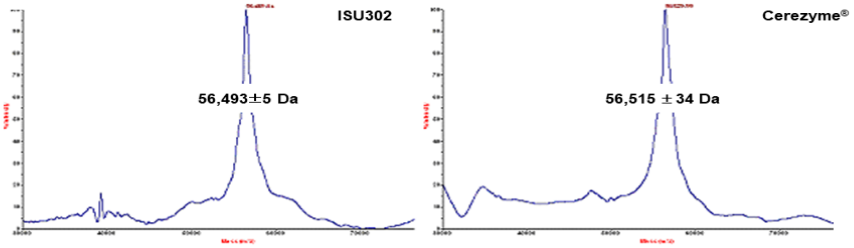
Physicochemical Properties

1. Intact Mass and size (analyzed by MALDI-TOF MS)

w/ glycosylation

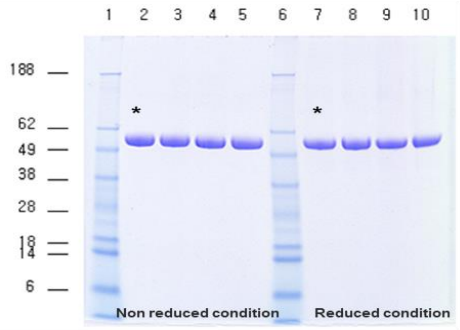


w/o glycosylation



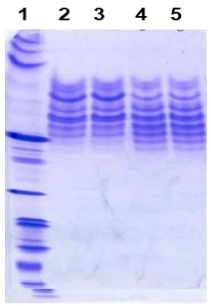
2. Electrophoretical Properties and Spectroscopic profiles

SDS-PAGE



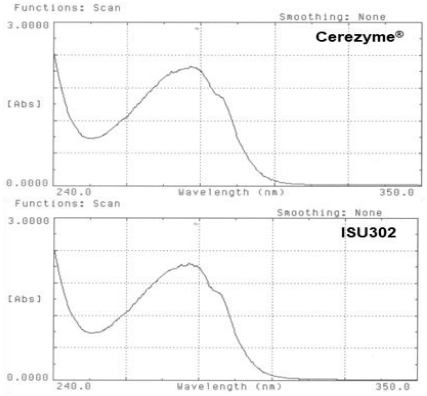
Lane 2,7 *: Cerezyme®
Lane3-5/8-10 ISU302

Isoelectric Focusing (pI 6.9~8.0)



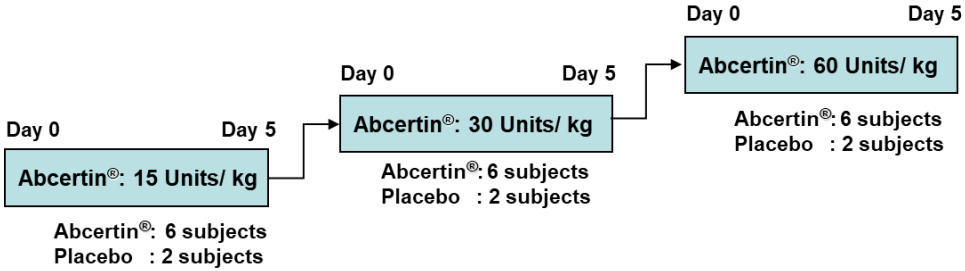
Lane2,3: ISU302
Lane4,5: Cerezyme®

UV Spectrum



Phase 1 (Stand-alone in Korea)

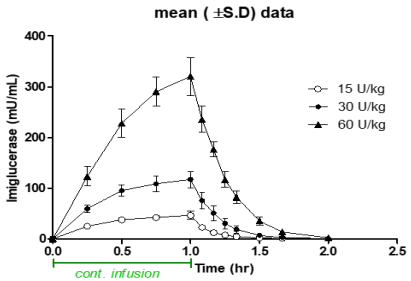
Double-Blind, Placebo-controlled, Single Ascending Dose (SAD) phase 1 clinical trial in Healthy Subjects

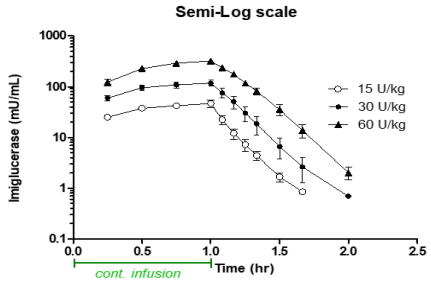


- **Primary objective: To determine the safety and tolerability of single ascending dose of Abcertin® in healthy subjects**
- **Secondary objective: To evaluate pharmacokinetics of single ascending doses of Abcertin® in healthy subjects**

Pharmacokinetics; Pharmacokinetic linearity was observed

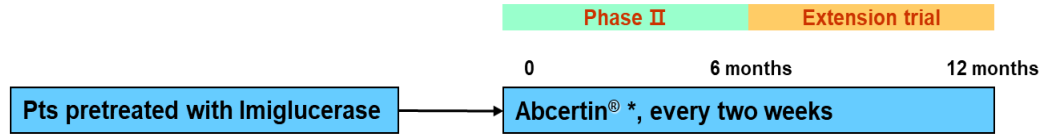
	15 units/kg		30 units/kg		60 units/kg	
	mean	SD	mean	SD	mean	SD
Half life (hr)	0.12	0.02	0.11	0.01	0.2	0
T_{max} (hr)	0.96	0.1	1	0	1	0
C_{max} (mIU/mL)	46.59	7.72	116.9	15.95	319.96	37.68
AUC_{all} (hr*mIU/mL)	37.95	4.29	101.53	15.53	275.6	30.45
CL (mL/hr)	28,285.26	5,383.15	20,695	3,259.36	14,602.73	1,819.13





Phase 2: Switch-over study

A multicenter, open label phase 2 study of Abcertin® in patients with Type 1 Gaucher disease previously treated with Imiglucerase



Type I Gaucher patients stably treated with Cerezyme® during at least past 6 months

The dose of Abcertin® will be equal to each patient's previous Cerezyme® dose.

Primary objective: To evaluate the safety of every other week dosing of Abcertin® in patients previously treated with Imiglucerase

Secondary objective: To evaluate the efficacy

Assessment criteria

Safety

√ Laboratory evaluation, Vital sign, ECG, Adverse event, Anti-drug antibody

Efficacy

Primary endpoint

√ Changes in hemoglobin concentration

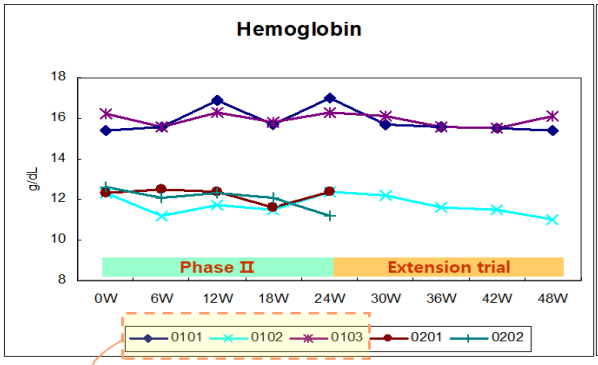
√ Changes in platelet counts

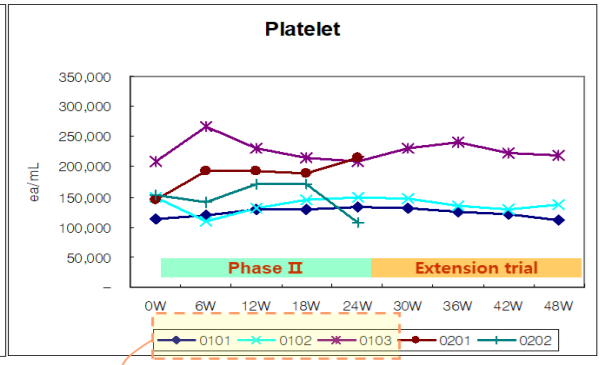
Secondary endpoint

√ Changes in liver and spleen volume and liver function

√ Changes in biomarkers: acid phosphatase, angiotensin converting enzyme, and chitotriosidase

√ Changes in skeletal status and bone mineral density





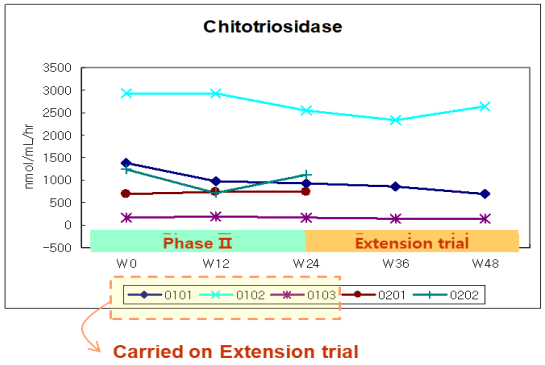
Hemoglobin concentration and Platelet count were ranged within ±1g/dL and ±20%, respectively, at all measurement points.

▶ **Abcertin® maintained the efficacy of Cerezyme® throughout the administration period.**


서울아산 유한욱 교수, 허귀유전병 치료제 개발

Secondary endpoint

1. **Changes in liver and spleen volume: No significant changes**
2. **Changes in liver function (ALT, AST): No significant changes**
3. **Changes in skeletal status: No significant changes**
4. **Changes in bone mineral density: No significant changes**
4. **Changes in biomarkers (ACE, Acid phosphatase, and Chitotriosidase): No significant changes**



	Biomarkers		
	ACE (U/L)	ACP (IU/L)	Chitotriosidase (nmol/mL/hr)
Baseline	79.42±31.77	18.68±8.71	1,279.82±1,041.47
Week 24	81.50±45.84	17.10±4.77	1,103.76±884.36
Changes (%)	-2.59±20.61	-0.92±22.97	-9.11±15.53
p-value	0.7927	0.933	0.2598

Clinical Trial/Experimental Study

Medicine®

OPEN

A multicenter, open-label, phase III study of Abcertin in Gaucher disease

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Abstract

Background: Gaucher disease (GD) is caused by a deficiency in the lysosomal enzyme glucocerebrosidase. Enzyme replacement therapy (ERT) is recommended for clinical improvement.

Methods: The efficacy and safety of a new imiglucerase, Abcertin, were assessed in 7 Egyptian patients with treatment-naïve type 1 GD. Each patient was administered a biweekly 60 U/kg dose of Abcertin for 6 months. The primary endpoint was the change in hemoglobin concentration. The secondary endpoints were changes from baseline in platelet counts, spleen and liver volumes, biomarker levels, skeletal parameters, and bone mineral density.

Results: The hemoglobin concentration increased by a mean of 1.96±0.91 g/dL (range 1.11–2.80 g/dL) or 20.6% (P=.001). Statistically significant increases in the platelet count and decreases in the spleen volume and biomarker levels were also observed. There were no severe drug-related adverse events. One patient developed anti-imiglucerase antibodies without neutralizing activity.

Conclusion: Our study results demonstrate the efficacy and safety of Abcertin in patients with type 1 GD. This suggests that Abcertin can be an alternative ERT option for type 1 GD.

Abbreviations: ACE = angiotensin-converting enzyme, ACP = acid phosphatase, AUC_{last} = last measurable concentration, BMD = bone mineral density, CCL-18 = chemokine ligand 18, CL = serum clearance, C_{max} = maximum concentration of drug, ERT = enzyme replacement therapy, GD = Gaucher disease, MN = multiple of normal, MRI = magnetic resonance imaging, PK = pharmacokinetic, $t_{1/2}$ = half-life, T_{max} = time to C_{max}, V_d = volume of distribution.

Keywords: enzyme replacement therapy, Gaucher disease, imiglucerase


서울아산 유한욱 교수, 희귀유전병 치료제 개발

Algorithm for Rare Disease Research (e.g. Wilson disease)

- Introduction: What are unmet needs? (screening, diagnosis, treatment and monitoring marker)
- How common is it in Korea?
- Natural history study & genetic epidemiology
  - Clinical characteristics of Korean patients with Wilson disease & prognostic factor of hepatic outcome
  - Mutation spectrum of *ATP7B* gene & functional analysis of mutant *ATP7B* & genotype-phenotype correlation
- Understanding of pathophysiology
  - Proteome & transcriptome analysis of liver and brain of LEC rat model for Wilson disease during the disease progression
- Search for new biological marker for newborn screening, confirmative diagnosis, and treatment
  - Proteomic approach
  - iPS cell model

ACADEMIC PRESS

Molecular Genetics and Metabolism 76 (2002) 133–136

Molecular Genetics and Metabolism

www.academicpress.com

Pilot study of mass screening for Wilson's disease in Korea

GENETIC TESTING
Volume 12, Number 3, 2008
© Mary Ann Liebert, Inc.
Pp. 395–400
DOI: 10.1089/gte.2008.0016

Estimation of Wilson's Disease Incidence and Carrier Frequency in the Korean Population by Screening *ATP7B* Major Mutations in Newborn Filter Papers Using the SYBR Green Intercalator Method Based on the Amplification Refractory Mutation System

Liver International ISSN 1478-3223

CLINICAL STUDIES

Distinct clinical courses according to presenting phenotypes and their correlations to *ATP7B* mutations in a large Wilson's disease cohort

ORIGINAL ARTICLE

Biochemical and molecular characterisation of neurological Wilson disease

Seo GH, *et al*. *J Med Genet* 2018;**55**:587–593.

HUMAN MUTATION 11:275–278 (1998)

RESEARCH ARTICLE

Identification of Three Novel Mutations and a High Frequency of the Arg778Leu Mutation in Korean Patients With Wilson Disease

Identification of novel mutations and the three most common mutations in the human *ATP7B* gene of Korean patients with Wilson disease

Genet Med 2002:4(6, Supplement):43S–48S.

HUMAN MUTATION 0, 1–6, 2007

RESEARCH ARTICLE

Identification of Novel *ATP7B* Gene Mutations and Their Functional Roles in Korean Patients With Wilson Disease

Metallomics

RSC Publishing

PAPER

Cite this: DOI: 10.1039/c3mt20243g

The early molecular processes underlying the neurological manifestations of an animal model of Wilson's disease†

Proteomics Clin. Appl. 2009, *3*, 1185–1190 DOI 10.1002/prca.200800057 1185

RESEARCH ARTICLE

Proteomic analysis of sera of asymptomatic, early-stage patients with Wilson's disease

Journal of proteome research

Article

pubs.acs.org/jpr

Quantification of ATP7B Protein in Dried Blood Spots by Peptide Immuno-SRM as a Potential Screen for Wilson's Disease

ATP7B Peptide Analysis in Wilson's Disease

Direct measurement of ATP7B peptides concentration can help identify patients with Wilson's disease.

Gastroenterology 2021;160:2231–2233

cells

MDPI

Article

Human Embryonic Stem Cell-Derived Wilson's Disease Model for Screening Drug Efficacy

Fair pricing of “old” orphan drugs

Fair pricing of “old” orphan drugs: considerations for Canada’s orphan drug policy

Eve A. Roberts MD MA, Matthew Herder LLM JSM, Aidan Hollis PhD

The trientine story

Wilson disease was first described in 1912; at the time, it was an invariably fatal neurologic disorder associated with liver cirrhosis. In the 1950s and 1960s, D-penicillamine (1956) and trientine (1969) were developed as oral treatments, largely by researchers in the United Kingdom.[3] Now, medical treatment is highly effective in

CMAJ, April 7, 2015, 187(6)

- 2010, the pharmaceutical company Valeant purchased Aton Pharma, which had previously acquired the US license for Syprine from Merck.

- Around November 2013, Valeant Canada announced that, as of January 2014, the price of Syprine would match the US price: roughly Can $13,244 per month ($158, 928 per year),which is about 13 times the previous price.

Total Number of Orphan Designations and Approvals

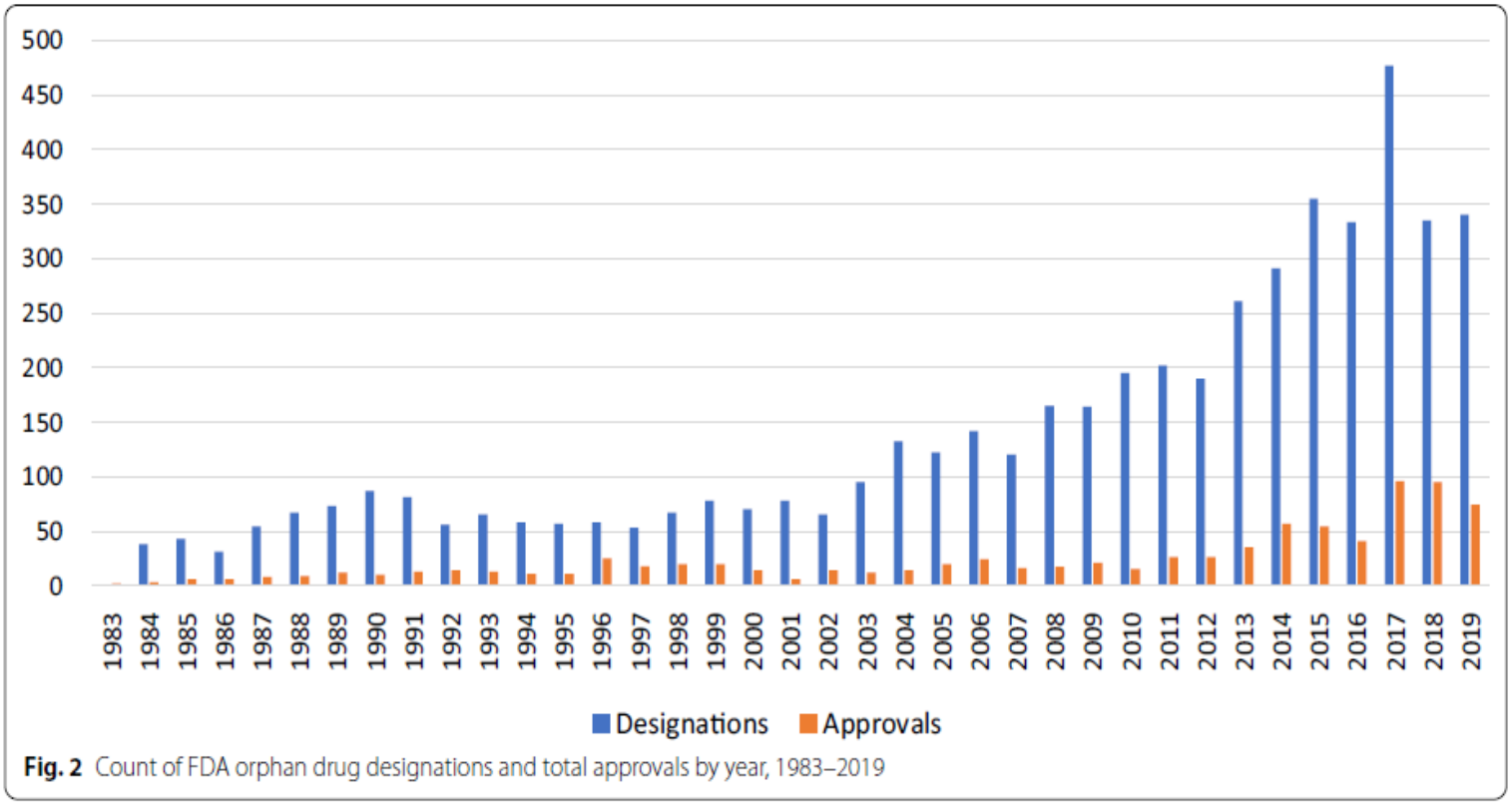
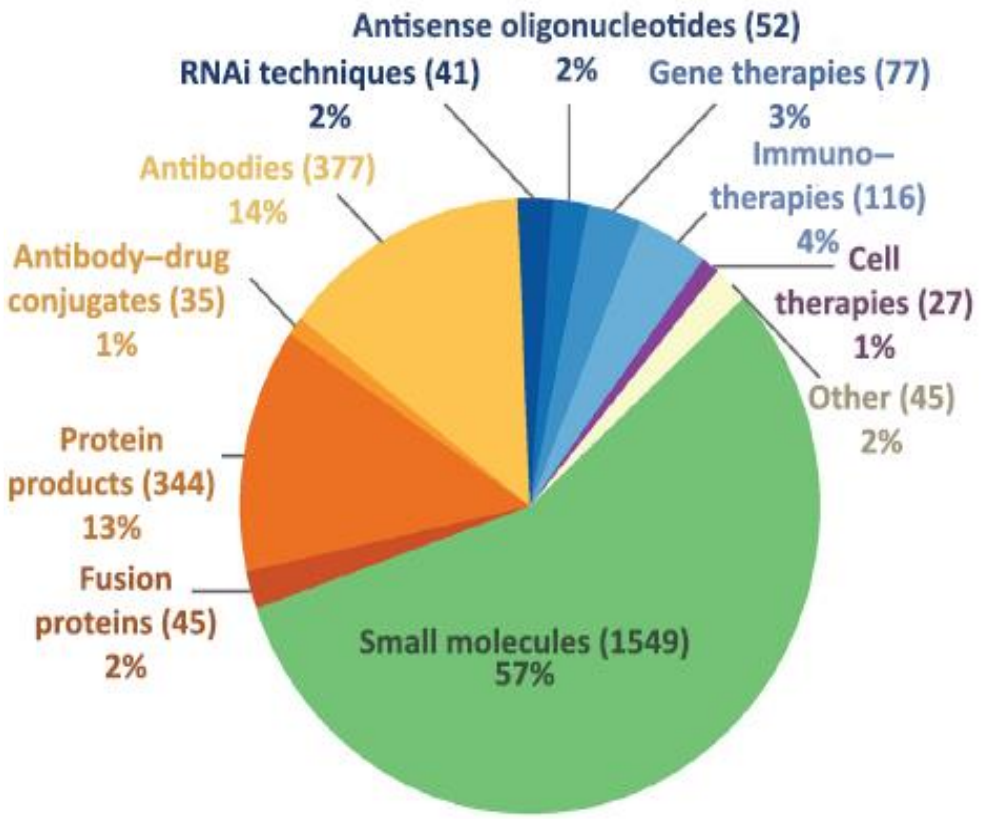
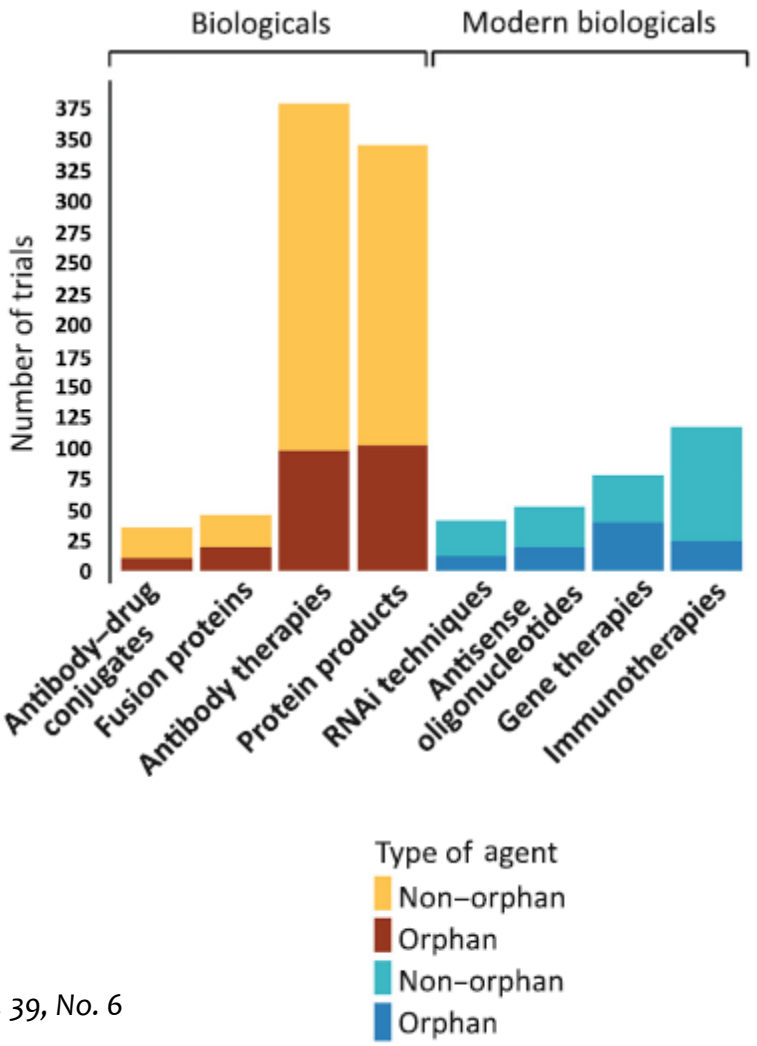


Fig. 2 Count of FDA orphan drug designations and total approvals by year, 1983–2019

Orphanet J Rare Dis 2021;16:265-74.

Classification of clinical trial agents as of 2017

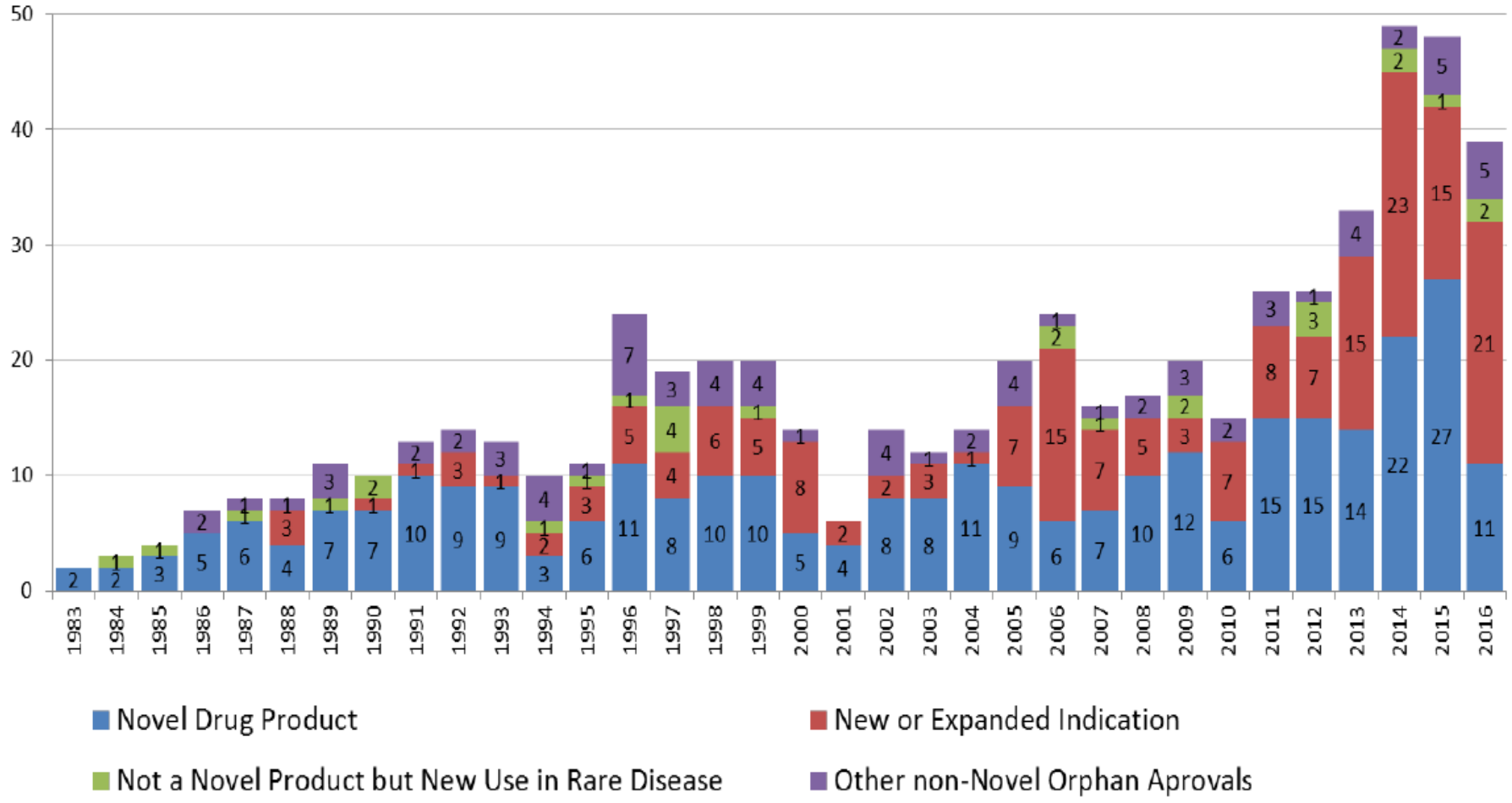




Trends in Pharmacological Sciences, June 2018, Vol. 39, No. 6

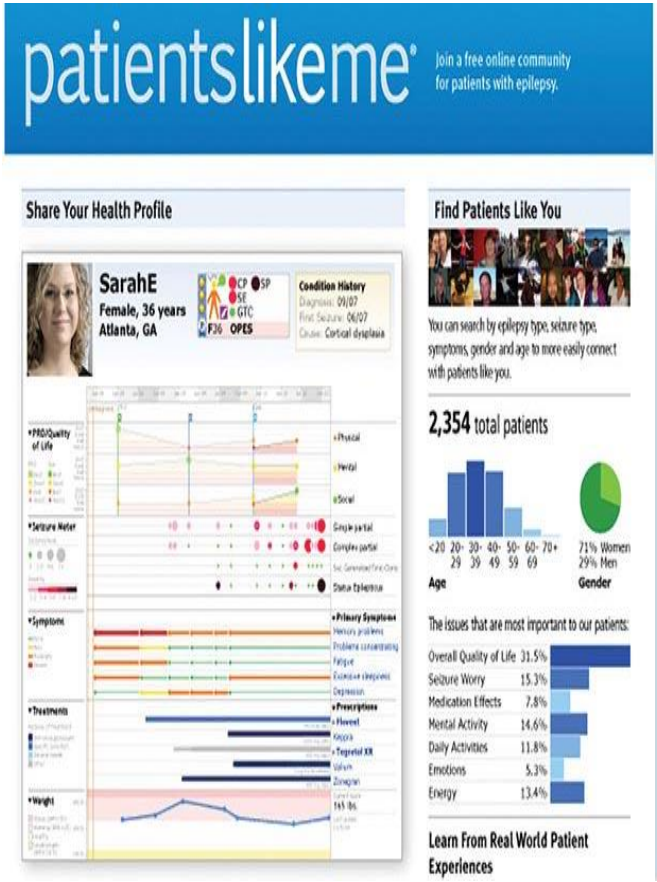
FDA Orphan Drug Approval Trends in U.S.A

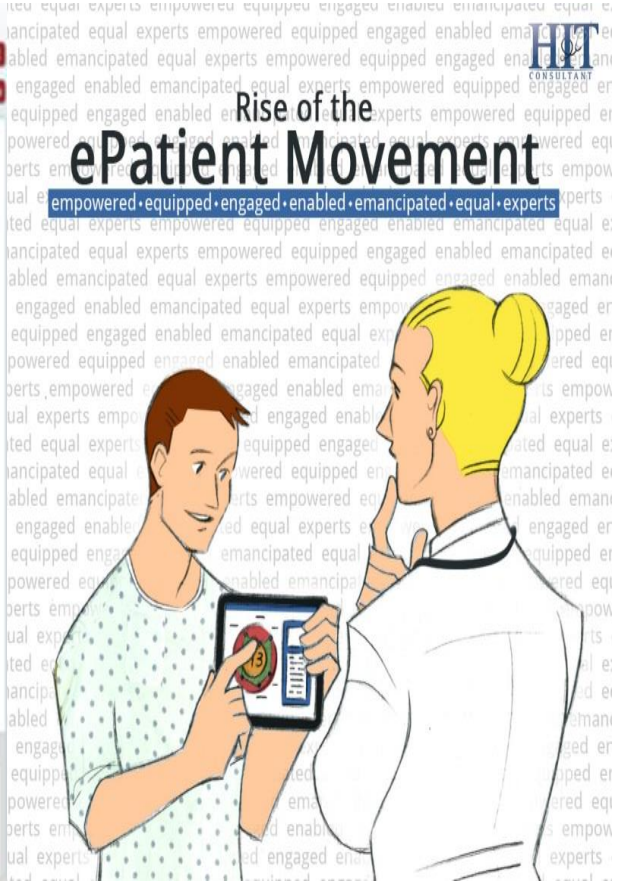
Since 1983: 600+ orphan drug indications approved from 450+ distinct drug products



www.fda.gov

e-Patient movement





국가 간 희귀약품개발 정책의 비교

	미국	유럽연합	일본	한국
개발촉진법	Orphan drug act (1983)	Orphan drug regulation(2000)	약사법에 희귀약품지정에 관한 규정(1993)	약사법에 희귀약품지정에 관한 규정(1998) 희귀약품센터(1999) 희귀질환관리법(2016)
시장독점권	7 년	10 년	10 년	10 년
인허가특권	신속허가제도 임상시험계획서작성자문	임상시험전과정자문	연구개발 전과정자문 신속허가제도 재인가 기간연장	신속허가제도 재심사면제
인센티브	허가 심사비 면제	임상시험계획서 심사비면제, 허가심사료 반액 면제, 허가전 현장 실사료 면제		심사비 할인
조세혜택	임상시험경비 50%	가맹국마다 다름	법인세 10%, 연구개발비 6% 조세감면	연구 및 인력개발비용의 20%(중소기업은 30%) 소득세 또는 법인세에서 공제
연구개발비 지원	임상시험 경비 지원(직접비 및 간접비)	가맹국마다 다름	임상시험경비 50%지원	국가과제연구비 수혜 시 일부 혜택

Take Home Message: Multidisciplinary integrative efforts

- Clinician: phenotype clarification, clear and identifiable symptom & signs, natural history of disease, creative idea, clinical study design
- Patient organization: enhancement of awareness & education regarding clinical trials, e-patient movement
- Researcher: elucidation of disease pathophysiology, demonstration of proof-of-concept, linkage between drug and target, drug mechanism of action
- Pharmaceutical company: funding for research & development
- Regulatory agency: balancing between urgency of development & safety issues, funding , legal issue
- Networking: ex) GARD, RDCRN, Orphanet, ERN….

Q & A