Drug Discovery and Development - Diabetes-Curing Prusogliptin (DBPR108)

新藥研究與開發 - 糖尿病治療藥物 Prusogliptin (DBPR108)

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November 16, 2024 (15:50-16:20)

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國家衛生研究院, 代理主秘 (2011), 實驗動物中心主任 (2005-2009)
中華實驗動物學會, 理事/常務理事 (2004-present), 副理事長 (2012-2015), 理事長 (2016-2019)
千禧生技創業投資股份有限公司, 董事 (2003-2005)

h-index 49
Stanford University's Top 2% Scientists Listed, 2024
Stanford University's Top 2% Scientists (Career Impact) (1960-2022) Listed
Coauthor of 167 peer-reviewed scientific papers, coinventor of 36 patents allowed/pending.

Disclaimers

All materials and information delivered are not representing the opinions of IBPR nor NHRI.

OUTLINE

Introduction of Drug Discovery & Development

Discovery & Development of Prusogliptin, DBPR108 for Treating Type 2 Diabetes

Purposes of Drug Discovery and Development

1. To **save lives** – Life threatening disease, pandemic
2. To improve health and living standards:
   -- **Unmet medical needs**
3. To **make profits**:
   -- Pharmaceutical industry → profits pursuing
   (10-12% health care spent on prescription drugs in US)

US$1,000,000,000/yr for a blockbuster drug
(US$ 1 billion/yr) US$ ≒ 2.74 millions/day

NT$ ≒ 77,000,000 (7.7千萬)/day

($$$$$$) Exclusive market protected w/ **patents**
($$$$) Followers in the class (Me Too) protected w/ patents
($) Copiers after patent expiration (Generic)

Oliver Browning | June 28, 2021
Wimbledon crowd gives standing ovation to Covid-19 vaccine developer
Dame Sarah Gilbert received a standing ovation from the crowd at Wimbledon on Monday afternoon. Professor Gilbert is a co-developer of the Oxford-AstraZeneca Covid-19 vaccine.
https://www.independent.co.uk/tv/news/wimbledon-vaccine-standing-ovation-video-vfee82333

Oxford University surprised and pleased advocates of overhauling the vaccine business in April by promising to donate the rights to its promising coronavirus vaccine to any drugmaker.
A few weeks later, Oxford -urged on by the Bill & Melinda Gates Foundation- reversed course.
It signed an exclusive vaccine deal with AstraZeneca that gave the pharmaceutical giant **sole rights and no guarantee of low prices**-with the less-publicized potential for Oxford to eventually make millions from the deal and win plenty of prestige.
By **Jay Hancock** AUGUST 25, 2020. https://khn.org/news/rather-than-give-away-its-covid-vaccine-oxford-makes-a-deal-with-drugmaker/

To save more lives, Generosity → Generics

PHARMALOT

Gilead signs licenses for generic companies to make and sell remdesivir in 127 countries

By Ed Silverman May 12, 2020

PHARMALOT

First generic version of Gilead's remdesivir will be sold by a Bangladesh drug maker

By Ed Silverman May 22, 2020

Following an emergency decree issued by the Bangladesh government, Beximco Pharmaceuticals is donating copies of the Gilead Sciences (GILD) medicine to state-run hospitals free of charge, but will sell the intravenous treatment to private clinics. Moreover, the company is reportedly willing to export its version if other governments request the drug, although it does not have a license from Gilead to do so.

Beximco is able to take this step under provisions of a World Trade Organization agreement, which permits a "least-developed" country to grant a public agency or a company a license to copy a patented medicine without the consent of the patent holder. As a result, Bangladesh is not required to grant pharmaceutical patents until 2033.

https://www.statnews.com/pharmalot/2020/05/22/gilead-remdesivir-covid19-coronavirus-beximco-patent/

To save more lives, Generosity → Generics

HEALTH • COVID-19

Merck says poorer countries can produce its new COVID pill without paying royalties

BY DAVID MEYER
October 27, 2021 9:11 PM GMT+8

Molnupiravir

a prodrug of the synthetic nucleoside N^4-hydroxycytidine, introducing errors during viral RNA replication.

https://fortune.com/2021/10/27/merck-covid-pill-molnupiravir-royalty-free-generic/

COVID-19

Pfizer to allow generic versions of its Covid pill for poor countries

Issued on: 17/11/2021 - 05:02

Paxlovid (PF-07321332 + ritonavir)

Nirmatrelvir (PF-07321332) inhibits the SARS-CoV-2 3CL protease acting as a substrate for the virus protease in the cell, blocking its replication.
Ritonavir, selective cytochrome P450 3A4 inhibitor.

https://www.france24.com/en/americas/20211117-pfizer-announces-deal-to-allow-generic-versions-of-its-covid-pill-for-world-s-poor

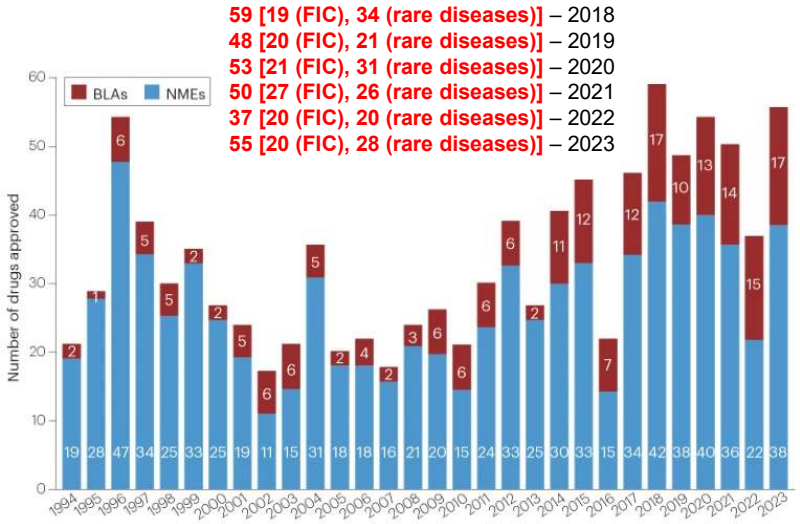

Fig. 1 | 30 years of novel FDA approvals. Annual numbers of new molecular entities (NMEs) and biologics license applications (BLAs) approved by the FDA's Center for Drug Evaluation and Research (CDER). See Table 1 for new approvals in 2023. Products approved by the Center for Biologics Evaluation and Research (CBER), including vaccines and gene therapies, are not included in this drug count (Table 2).
2023 FDA approvals, Nature Reviews Drug Discovery, Jan. 02, 2024.

US-FDA CDER Approved Drugs in 2020

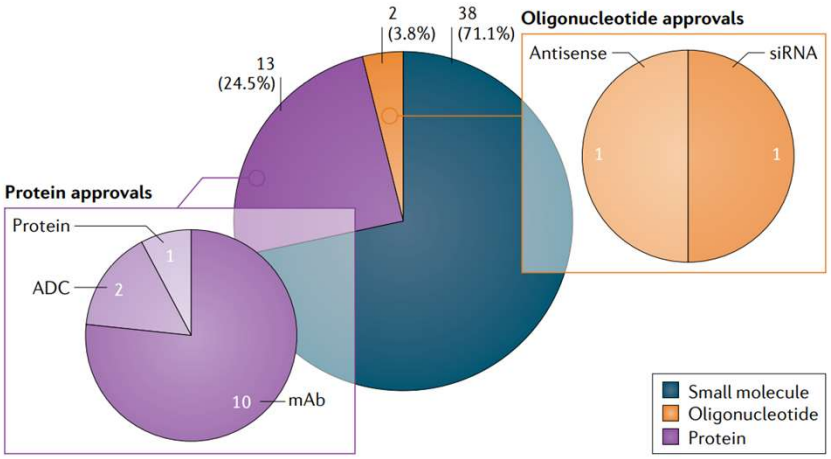

Fig. 3 | **CDER approvals by modality.** 'Small molecules' includes all peptides of up to 40 amino acids in length. Small molecules and oligonucleotides are approved as new molecular entities (NMEs). Protein-based candidates are approved through biologics license applications (BLAs). ADC, antibody–drug conjugate; mAb, monoclonal antibody. Source: *Nature Reviews Drug Discovery*.

US-FDA CDER Approved Drugs in 2021

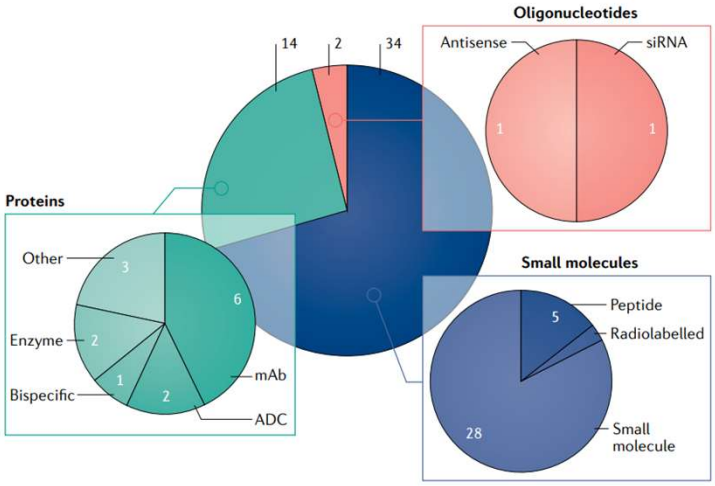

Fig. 3 | **CDER approvals by modality.** Small molecules, including peptides of up to 40 amino acids in length, and oligonucleotides are approved as new molecular entities (NMEs). Protein-based candidates are approved through biologics license applications (BLAs). ADC, antibody–drug conjugate; mAb, monoclonal antibody. Source: *Nature Reviews Drug Discovery*.

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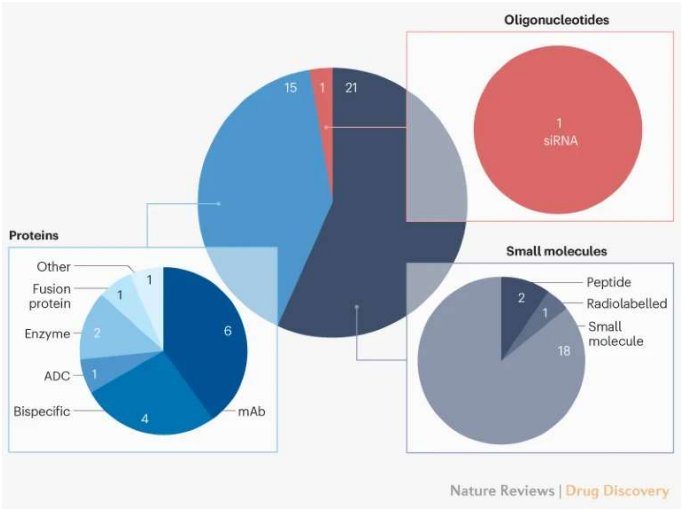
US-FDA CDER Approved Drugs in 2022



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US-FDA CDER Approved Drugs in 2023

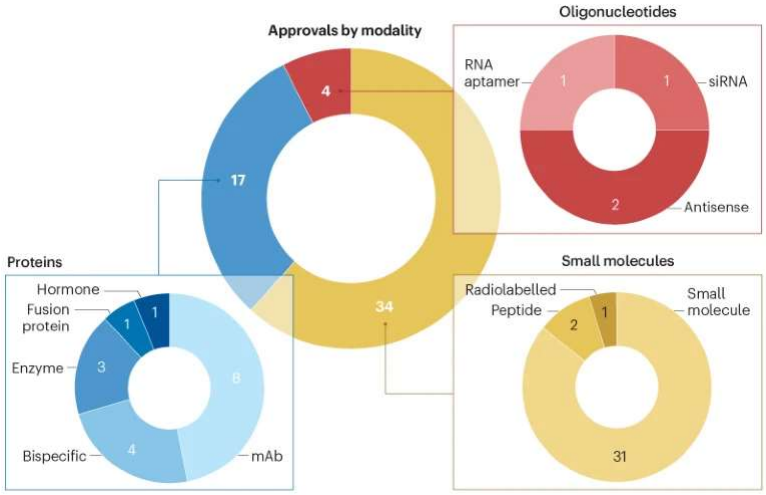

Fig. 3 | CDER approvals by modality. Small molecules, including peptides of up to 40 amino acids in length, and oligonucleotides are approved as new molecular entities (NMEs). Protein based candidates are approved through biologics license applications (BLAs). mAb, monoclonal antibody; siRNA, small interfering RNA. 2023 FDA approvals, Nature Reviews Drug Discovery, Jan. 02, 2024.

Development of Protein Biosimilars

FDA approves Amjevita, a biosimilar to Humira

For Immediate Release: September 23, 2016

The U.S. Food and Drug Administration today approved Amjevita (adalimumab-atto) as a biosimilar to Humira (adalimumab) for multiple inflammatory diseases.

Amjevita is approved for the following indications in adult patients:

- moderately to severely active rheumatoid arthritis;
- active psoriatic arthritis;
- active ankylosing spondylitis (an arthritis that affects the spine);
- moderately to severely active Crohn's disease;
- moderately to severely active ulcerative colitis; and
- moderate to severe plaque psoriasis.

FDA Approves Cyltezo, the First Interchangeable Biosimilar to Humira

Second Interchangeable Biosimilar Product Approved by Agency

For Immediate Release: October 18, 2021

The U.S. Food and Drug Administration approved the first interchangeable biosimilar product to treat certain inflammatory diseases. Cyltezo (adalimumab-adbm), originally approved in August 2017, is both biosimilar to, and interchangeable with (may be substituted for), its reference product Humira (adalimumab) for Cyltezo's approved uses. Cyltezo is the second interchangeable biosimilar product approved by the agency and the first interchangeable monoclonal antibody. Once on the market, approved biosimilar and interchangeable biosimilar products can play a role in facilitating access to treatments for many serious health conditions.

Biosimilar

Amgen, September 23, 2016
https://www.fda.gov/news-events/press-announcements/fda-approves-amjevita-biosimilar-humira

Interchangeable Biosimilar

Granted to Boehringer Ingelheim on October 15, 2021
https://www.fda.gov/news-events/press-announcements/fda-approves-cyltezo-first-interchangeable-biosimilar-humira

To check for biosimilars and/or interchangeable biosimilars in **Purple Book**

Purple Book
Database of Licensed Biological Products

The Purple Book database contains information on all FDA-licensed (approved) biological products regulated by the Center for Drug Evaluation and Research (CDER), including licensed biosimilar and interchangeable products, and their reference products.

The Purple Book also contains information about all FDA-licensed allergenic, cellular and gene therapy, hematologic, and vaccine products regulated by the Center for Biologics Evaluation and Research (CBER).

https://purplebooksearch.fda.gov/

Development of bsAbs

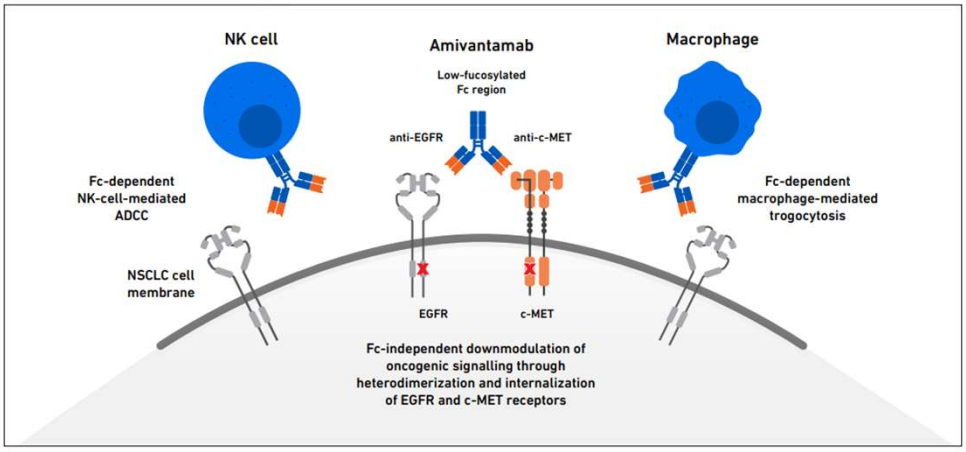

Figure 2: Mechanisms of action of the bispecific antibody amivantamab. EGFR: epidermal growth factor receptor, MET: mesenchymal-epithelial transition receptor, NK cell: natural killer cell, ADCC: antibody-dependent cell-mediated cytotoxicity.[17]

New Advances in Cancer Drug Discovery, Mariana Gil, PhD. Technology Networks

siRNA Drug

NOVARTIS Search Menu

FDA approves Novartis Leqvio® (inclisiran), first-in-class siRNA to lower cholesterol and keep it low with two doses a year

Inclisiran, a PCSK9 siRNA to lower low-density lipoprotein cholesterol (bad cholesterol or LDL-C)

Dec 22, 2021

https://www.novartis.com/news/media-releases/fda-approves-novartis-leqvio-inclisiran-first-class-sirna-lower-cholesterol-and-keep-it-low-two-doses-year

PCSK9 (proprotein convertase subtilisin/kexin type 9), identified in 2003, is a proprotein convertase which is involved in the degradation of low-density lipoprotein (LDL) receptors in the liver.

Inhibition of PCSK9 activity reduces the degradation of LDL receptors and increases the clearance of LDL cholesterol.

Small Molecule - Protein - RNA Drugs

Characteristics of inorganic and small-molecule organic compound drugs, as well as macromolecule protein and nucleic acid therapeutics

Properties	Inorganic Compound Drugs	Small-Molecule Organic Compound Drugs	Protein Therapeutics	RNA Therapeutics
Chemistry	Typical mol. wt. < 200 Da; ionic	Typical mol. wt. < 500 Da; hydrophobic	Typical mol. wt. > 100 kDa; positive/negative/neutral	Typical mol. wt. > 7 kDa; negative charge
Dosing	Primarily oral; often daily	Primarily oral; often daily	Mainly intravenous and subcutaneous; weekly to monthly	Intravenous, subcutaneous, intrathecal, intravitreal (various); weekly to once every 3–6 mo
ADME/PK properties	Orally bioavailable; distributed to all organs and tissues, cell permeable; usually not metabolized; excreted primarily in urine	Orally bioavailable; distributed to all organs and tissues, cell permeable; metabolized by phase I and II enzymes; excreted mainly in bile and urine	Not orally bioavailable; distributed mainly in plasma or extracellular fluids, cell impermeable; catabolized extensively to peptides or amino acids; limited excretion	Not orally bioavailable; Distributed extensively to kidney and liver, cell impermeable; catabolized extensively by nucleases to (oligo)nucleotides; limited excretion
Molecular targets	Proteins	Mainly proteins	Proteins	Mainly RNAs, besides proteins and DNAs
Site of action and PD	Extra-/intracellular; direct or indirect relationship to blood PK	Extra-/intracellular; Direct or indirect relationship to blood PK	Extracellular/membrane; direct or indirect models linked to blood PK	Primarily intracellular; more relevant to tissue PK, whereas PD can be linked to blood PK
Safety/ toxicity	Risk of off-target effects	Risk of off-target effects	Risk of immunogenicity	Risk of immunogenicity

ADME, absorption, metabolism, distribution, and excretion.

Yu et al, Pharmacol Rev, 2020

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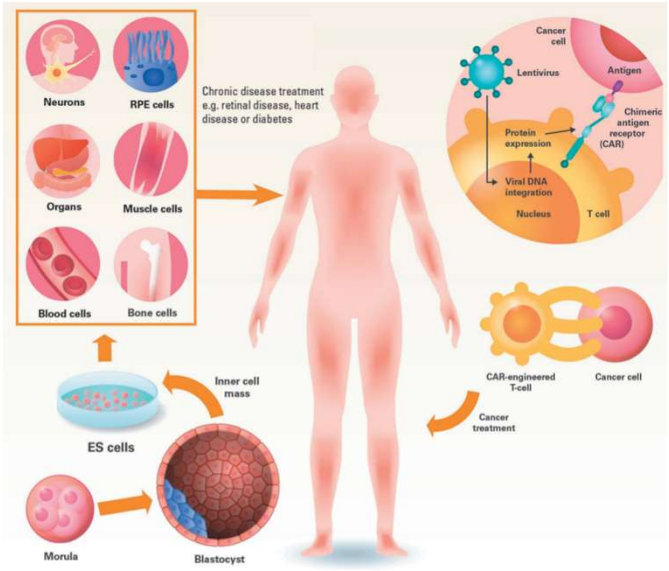
Development of Cell / Gene Therapies



Drug Target Review Cell Gene Therapy eBook 2021, 17 June 2021

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Kymriah (tisagenlecleucel) 新萊亞® **$US475,000. Nov. 1, 2023 納健保**

August 30, 2017 US FDA approved

A historic action making the first gene therapy available in the US.
A **cell-based gene** therapy, new approach to the treatment of cancer and other serious and life-threatening diseases.

A genetically-modified **autologous** T-cell immunotherapy, for certain patients up to 25 years of age w/ B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse.

The patient's T-cells are collected and sent to a manufacturing center where they are genetically modified to include a new gene that contains a specific protein (a chimeric antigen receptor or CAR) that directs the T-cells to target and kill leukemia cells that have a specific antigen (CD19) on the surface. Once the cells are modified, they are infused back into the patient to kill the cancer cells.

https://www.fda.gov/news-events/press-announcements/fda-approval-brings-first-gene-therapy-united-states

FDA approves 1st Gene Therapy for hemophilia A

Hemophilia A, also called FVIII deficiency or classic hemophilia, is an X-linked genetic disorder caused by missing or defective FVIII, a clotting protein. Although it is passed down from parents to children, about 1/3 of cases are caused by a spontaneous mutation, a new mutation that was not inherited. Approximately 1 in 10,000 people have hemophilia A.

BioMarin Pharmaceutical's ***ROCTAVIAN***™ **(valoctocogene roxaparvovec-rvox)**, an adeno-associated virus vector-based gene therapy, is the first and only gene therapy approved for the treatment of adults with severe hemophilia A (congenital factor VIII deficiency with factor VIII activity < 1 IU/dL) without antibodies to adeno–associated virus serotype 5 (AAV5) detected by an FDA–approved test. The one-time infusion works by delivering a functional gene that is designed to enable the body to produce FVIII on its own, reducing the need for ongoing prophylaxis.

A 134-patient Phase 3 study showed a 50% reduction in annual bleeding incidents among treated patients. The one-time, single-dose infusion was first approved by the ***EMA*** in August 2022.
In 2023, BioMarin has indicated that Rocktavian will be priced at $**2.9** million.

*In 2022, **FDA** approved the first gene therapy for adults with* **hemophilia B**, *a less common form of hemophilia — CSL Behring's **Hemgenix®** — and it quickly became the world's most expensive drug, priced at $**3.5** million for the one-time treatment.*

https://www.pharmamanufacturing.com/development/drug-approvals/news/33007499/fda-approves-first-gene-therapy-for-hemophilia-a?utm_source=PHAR+Daily+Dose&utm_medium=email&utm_campaign=CPS230630050&o_eid=5731J4492678C2Z&rdx.ident[pull]=omeda|5731J4492678C2Z&oly_enc_id=5731J4492678C2Z
https://www.fda.gov/news-events/press-announcements/fda-approves-first-gene-therapy-adults-severe-hemophilia June 29, 2023

Most Expensive Drugs in the US in 2023

1 **Hemgenix** *By Zoey Becker*
Company: CSL Behring, uniQure
Disease: Hemophilia B
Cost per dose: $3.5 million

2 **Skysona** *By Kevin Dunleavy*
Company: Bluebird bio
Disease: Cerebral adrenoleukodystrophy
Cost per dose: $3 million

3 **Zynteglo** *By Kevin Dunleavy*
Company: Bluebird bio
Disease: Transfusion-dependent thalassemia
Cost per dose: $2.8 million

4 **Zolgensma** *By Angus Liu*
Company: Novartis
Disease: Spinal muscular atrophy
Cost per dose: $2.25 million

5 **Myalept** *By Zoey Becker*
Company: Chiesi Farmaceutici
Disease: Leptin deficiency
Cost per year: $1.26 million

https://www.fiercepharma.com/special-reports/priciest-drugs-2023?utm_medium=email&utm_source=nl&utm_campaign=LS-NL-FierceLifeSci&oly_enc_id=9163H0043434B8D

6 **Zokinvy** *By Fraiser Kansteiner*
Drug name: Zokinvy
Company: Eiger BioPharmaceuticals
Disease: Hutchinson-Gilford progeria syndrome and processing-deficient progeroid laminopathies
Cost per year: $1.07 million

7 **Danyelza** *By Eric Sagonowsky*
Company: Y-mAbs Therapeutics
Disease: Relapsed or refractory high-risk neuroblastoma
Cost per year: $1.01 million

8 **Kimmtrak** *By Angus Liu*
Company: Immunocore
Disease: Uveal melanoma
Cost per year: $975,520

4&9 2項罕病藥物納健保

9 **Luxturna** *By Fraiser Kansteiner*
Company: Spark Therapeutics
Disease: Biallelic RPE65-mediated inherited retinal disease
Cost per treatment: $850,000

10 **Folotyn** *By Eric Sagonowsky*
Company: Acrotech Biopharma
Disease: Relapsed or refractory peripheral T-cell lymphoma
Cost per year: $842,585

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Top 10 Best-Selling CGTs in 2023

1 **Yescarta** Kite, a Gilead Company
(axicabtagene ciloleucel) 2nd CAR-T Cell Therapy Oct. 18, 2017
Adults with large B-cell lymphoma (LBCL) refractory to/ relapsed from 1st-line chemoimmunotherapy, relapsed/ refractory LBCL, including DLBCL, primary mediastinal LBCL, DLBCL arising from follicular lymphoma. 1st for certain types of NHL.
$1.498 billion

2 **Zolgensma** Novartis
(onasemnogene abeparvovec-xioi) May 24, 2019
Spinal muscular atrophy
$1.214 billion

3 **Kymriah** Novartis 1st CAR-T Cell Therapy
(tisagenlecleucel) August 30, 2017
Patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia refractory/relapsed; Adults w/ relapsed/ refractory LBCL, including DLBCL including DLBCL, primary mediastinal LBCL, DLBCL arising from follicular lymphoma.
$508 million

4 **Carvykti** Janssen Biotech (J&J) & Legend Biotech
(ciltacabtagene autoleucel) February 28, 2022
Adults w/ relapsed/refractory multiple myeloma after 4 or more prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 mAb.
$500 million

5 **Abecma** Bristol Myers Squibb and 2seventy bio
(idecabtagene vicleucel) March 26, 2021
Adults w/ relapsed/refractory multiple myeloma after 2 or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 mAb.
$472 million

6 **Tecartus** Kite, a Gilead Company
(brexucabtagene autoleucel) July 24, 2020 (accelerated approval)
Adults w/ relapsed/refractory mantle cell lymphoma, relapsed/refractory B-cell precursor acute lymphoblastic leukemia.
$370 million

7 **Breyanzi** Bristol Myers Squibb
(lisocabtagene maraleucel) Feb. 5, 2021 (accelerated approval)
Adults with LBCL, including DLBCL not otherwise specified (including DLBCL arising from indolent lymphoma), high-grade BCL, primary mediastinal LBCL, and follicular lymphoma grade 3B who have refractory to/relapsed after first-line chemoimmunotherapy…..
$364 million

8 **Elevidys** Sarepta Therapeutics
(delandistrogene moxeparvovec-rokl) June 22, 2023 (accelerated approval)
Ambulatory pediatric patients aged 4 through 5 years with Duchenne muscular dystrophy with a confirmed mutation in the Duchenne muscular dystrophy gene.
$200.356 million

9 **MACI** Vericel
(autologous cultured chondrocytes on porcine collagen membrane) December 13, 2016
Repair of symptomatic, single, or multiple full-thickness cartilage defects of the knee with or without bone involvement in adults
$164.8 million

10 **Luxturna** Spark Therapeutics (Roche)
(voretigene neparvovec-rzyl) December 18, 2017
Disease: Biallelic RPE65-mediated inherited retinal disease
Approximately $51 million

Top 10 Best-Selling Cell and Gene Therapies
By **Alex Philippidis** April 30, 2024
www.genengnews.com/a-lists/top-10-best-selling-cell-and-gene-therapies

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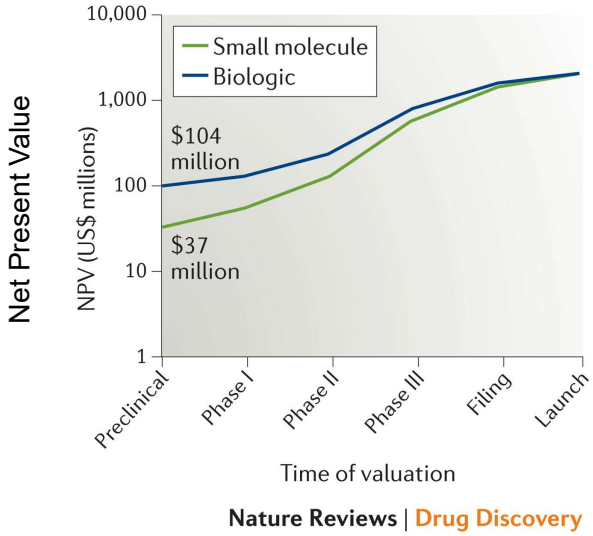
Small Molecule (小分子藥) Drugs

or

Biologics (大分子/生物藥) Drugs

or…. Better?!

Value of Small Molecule and Biologics Projects



Nature Reviews Drug Discovery **15**

Drug Discovery & Development

Pre-Clinical Discovery (研究) and
Pre-Clinical Development (開發)

&

Clinical Development (開發)

Drug Discovery and Development

Development

Discovery

			Pre-Clinical	*Clinical*
Basic Research	Assay Development	Selective *in vitro/in vivo*	Preclinical Toxicology	Clinical Trials
	Hit Screening	Safety Pharmacology	Safety Pharmacology	Phase 0, I ~ III
Mol. Target Identification & Validation	Lead Optimization, Characterization & Validation	Pre-formulation	Pharmacokinetics	
		Exploratory	Metabolism	Post-Marketing Surveillances (Phase IV)
		Pharmacokinetics	Pre-formulation	
		Metabolism	Formulation	Phase V
		Toxicology	Chemistry, Manufacturing & Controls	

Discovery → Development

Basic Research
Mol. Target
Identification
& Validation

Assay Development, Hit Screening
Lead Optimization,
Characterization & Validation

Selective *in vitro/in vivo* Safety
Pre-formulation, Pharmacology
Exploratory Pharmacokinetics
Metabolism & Toxicology

Integrated efforts of multi-disciplines

Biology: To identify, characterize and validate molecular targets of disease relevance

Intimate Collaborations!!!

Chemi

(combinatorial chemistry, computational chemistry, purification, physical-chemical characterization, computational modeling, …etc)

Hit Screening: To develop assays, perform high throughput screening and manage data base
(enzymatic, cellular, or chemical assays in high content primary screening, computational data base management and analysis, …etc)

Lead Optimization, Validation: To improve quality of and validate leads
(medicinal chemistry, computational modeling, secondary bioassays, pharmacology, pharmacokinetics, toxicology, …etc.)

Pharmacokinetics, Pharmacology: To identify and validate leads
(*in vitro/ex vivo/in vivo* pharmacokinetics and pharmacology, …etc.)

Pre-Clinical Development

Primary/Secondary Pharmacodynamics

Pharmacokinetics and/or Drug Metabolism

Pre-Formulation/Formulation

Feasible/Economic chemical manufacturing process

Safety pharmacology

Toxicology

Chemistry, manufacturing and controls (CMC)

Preparation of clinical study batches
(Investigational Product, IP)

Clinical Development

Clinical Trials: Study Phases 0 ~ 5 -(GCP/GLP/GDP)

Each phase is designated based on the type of questions that the study is seeking to answer, i.e., by its functional purpose.

Phase 0 – microdosing for sub-therapeutic preliminary PK/PD
Phase 1 – human safety/tolerability/dose range/PK
Phase 2 – initial efficacy dose response (pilot trial)
Phase 3 – definitive efficacy/safety (pivotal trial)
Phase 4 – risk benefits/pharmacogenomics
Phase 5 – new formulation, regimen, indication, comparison w/ others

http://ClinicalTrials.gov as on September 1, 2024

ClinicalTrials.gov is a Web-based resource that provides patients, their family members, health care professionals, researchers, and the public with easy access to information on publicly and privately supported clinical studies on a wide range of diseases and conditions. The Web site is maintained by the National Library of Medicine (NLM) at the National Institutes of Health (NIH). ClinicalTrials.gov contains information about medical studies in human volunteers. Most of the records on ClinicalTrials.gov describe clinical trials (also called interventional studies). A **clinical trial** is a **research study** in which human **volunteers** are assigned to interventions (for example, a medical product, behavior, or procedure) based on a protocol (or plan) and are then evaluated for effects on biomedical or health outcomes.

ClinicalTrials.gov also contains currently 507,578 records describing observational studies and programs providing access to investigational drugs outside of clinical trials (expanded access). Studies listed in the database are conducted in all 50 States and in 220 countries.

Quality Control assured by Good Project Management & the followings

Discovery

Standard Operating Procedure (SOP)

Good Laboratory Practice (GLP)

Development

Standard Operating Procedure (SOP)

Good Laboratory Practice (GLP)

Good Manufacturing Practice (PIC/S-GMP)

Good Clinical Practice (GCP)

Good Distribution Practice (GDP)

Documentation, Documentation, Documentation


法規名稱：藥物優良製造準則 EN
修正日期：民國 102 年 07 月 30 日
法規類別：行政 > 衛生福利部 > 食品藥物管理目
所有條文 編章節 條號查詢 條文檢索 沿革
第 一 編 總則
第 1 條 本準則依藥事法（以下簡稱本法）第五十七條第五項規定訂定之。
第 2 條 藥物製造工廠之廠房設施、設備、組織與人事、生產、品質管制、儲存、運
事項，應依本準則之規定；本準則未規定者，適用其他法令之規定。
第 二 編 藥品優良製造規範
第 一 章 西藥
第 3 條 西藥藥品含外銷專用產品之製造、加工、分裝、包裝、儲存及運銷，應符合
醫藥品稽查協約組織（PIC/S）其規範所訂定之西藥藥品優良製造規範，該規
其分階段施行之項目、時程，由中央衛生主管機關公告之。
第 二 章 中藥

Professional Partners

CRO, CMO, CDMO, CRA

Contract **Research Organization (CRO)**
(PreClinical/Clinical studies implementation)

Contract **Manufacturing Organization (CMO)**
(API/formulation/IP)

Contract **Development and Manufacturing Organization (CDMO)**
(API/formulation/IP)

Contract clinical research associate (contract CRA) is a person who manages clinical trials and scientific research projects.

Strategies of Drug Discovery

Repurpose approved drugs
老藥新用
Discover new drugs 新藥研發

I. Cell-based cytotoxicity → (HTP) screening against compound library, natural or synthetic compounds.

eg. paclitaxel – microtubule stabilizing agent; virus infected cells; reporters for virus infection; virus-like particle infection; replicon cells

II. Modification of existing active chemical entities.

eg. camptothecin → CPT-11, topotecan – topoisomerase I inhibitors

III. Valid protein/molecule target-based → virtual screening (pharmacophore/3D structure) or biological (functional/binding) activity screening against compound library.

eg. Imatinib – TKs: bcr-abl, c-kit, PDGFR, CML, GISTs (2001 US-FDA)
eg. Crizotinib – ELM4-ALK, c-Met, Lung Cancer (2011 US-FDA)

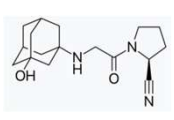
IV. AI Strategy

Discovery and Development

Prusogliptin, DBPR108

a dipeptidyl peptidase-4 (DPP-4) Inhibitor

for treating Type II Diabetes



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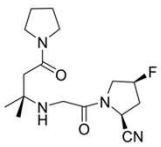
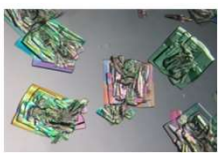




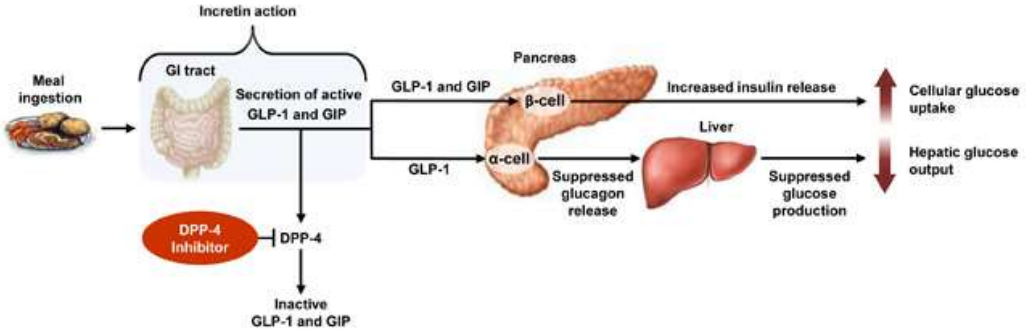
LAF-237
Vildagliptin, Galvus® (2009)

DBPR108

Dipeptidyl Peptidase 4 (DPP4)

Target for Type II diabetes drug discovery

Glucose Homeostasis



Incretin:
GLP-1: Glucagon-like peptide 1
GIP: Glucose-dependent insulinotropic peptide

***Cobble, J Fam Pract.* 2009 58(10).**

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Discovery

Pharmacokinetics, Pharmacology, Toxicology

In vitro mechanistic models

In vivo pharmacodynamic and pharmacology studies

Preliminary single/repeated dose range finding toxicity studies

in 2 species; at least 1 non-rodent (rat & dog, or …)

Specificity of DBPR108, Januvia and Galvus against DPP family

Inhibitor	DPP4 IC_{50} (nM)	DPP8 IC_{50} (μM)	DPP2 IC_{50} (μM)	DPP9 IC_{50} (μM)
Sitagliptin (Januvia, Merck)	23	>100	>100	>100
Vildagliptin (Galvus, Novartis)	56	18.5	>50	1.2
DBPR108	15	>100	>100	>100

Plasma DPP4 inhibition by DBPR108 & Januvia (*in vitro*)

DPP4 Sample	DBPR108 IC_{50} (nM)	Januvia IC_{50} (nM)
Human plasma	5.5	17.6
Rat plasma	9.5	45.5
Mouse plasma	13.8	64.4
Dog plasma (male)	20.4	34.5
Rhesus Monkey plasma	4.8	12.9
Cynomolgus Monkey plasma	4.1	12.3

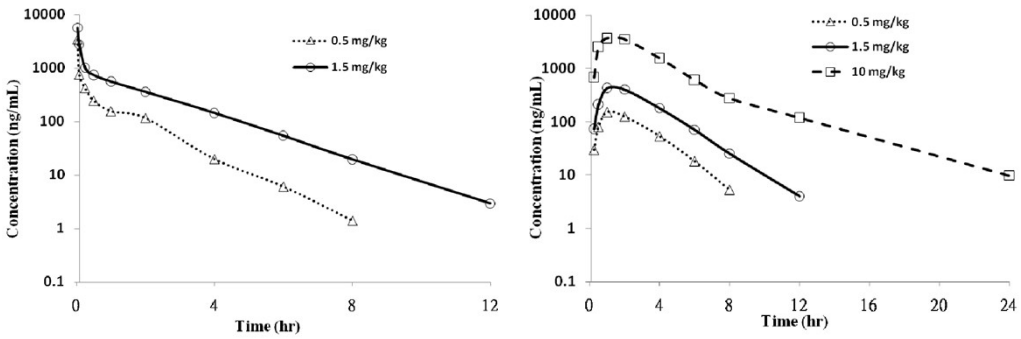
Table 1. Pharmacokinetic parameters of DBPR108 in SD rats.

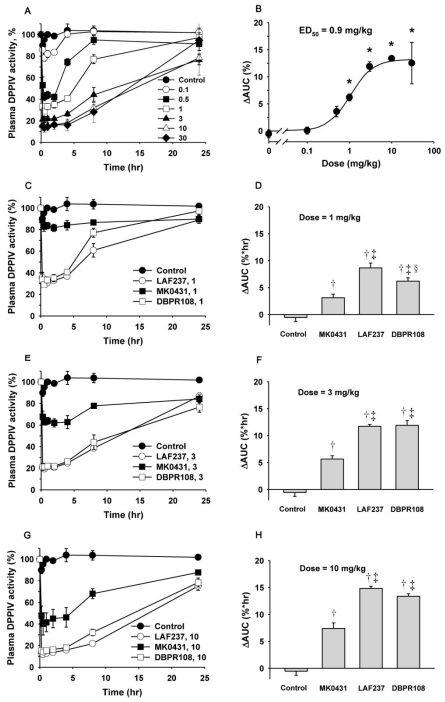
C_{max} (ng/mL)	T_{max} (h)	$AUC_{(0\text{-}inf)}$ (ng/mL * h)	$T_{1/2}$ (h)
108 ± 8	1.8 ± 1.0	410 ± 46	3.8 ± 0.4

Data from 3 rats dosed via oral gavage at 5 mg/kg.

Yeh et al, Life Sciences 2021

Plasma profiles of DBPR108 in dogs

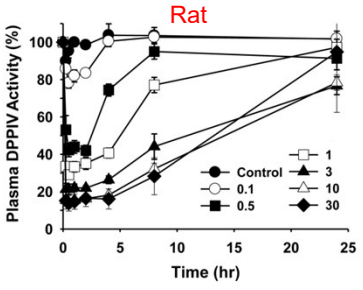


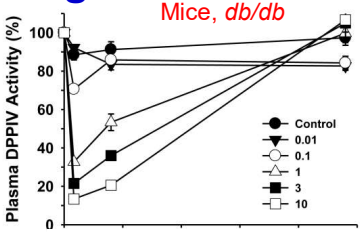


DBPR108 dose-dependently inhibits plasma DPP4 activities in rats

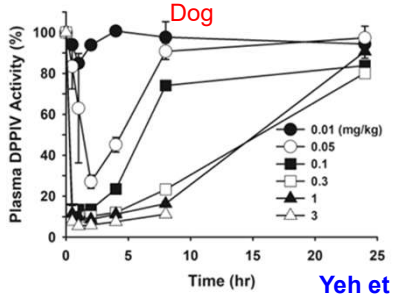
Yeh et al, Life Sciences 2021

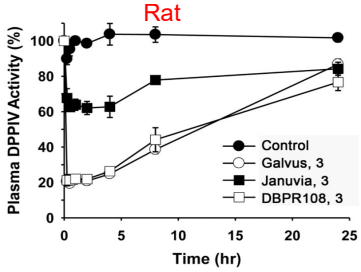
DBPR108 inhibits plasma DPP4 activities in mice/rats/dogs





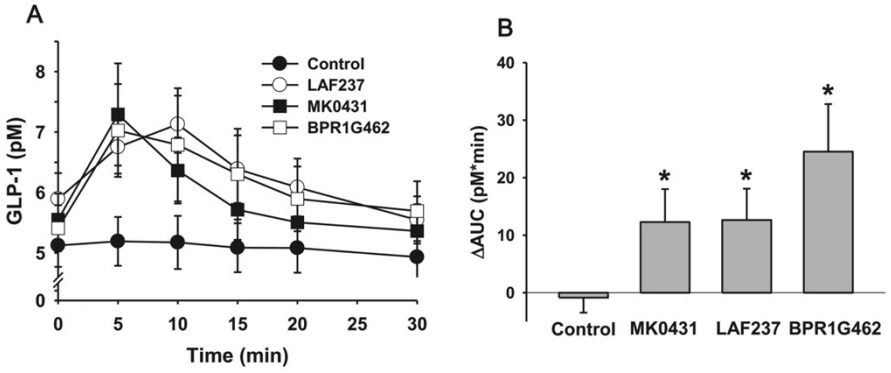
DBPR108 is superior to Januvia and is equally potent as Galvus in rats.





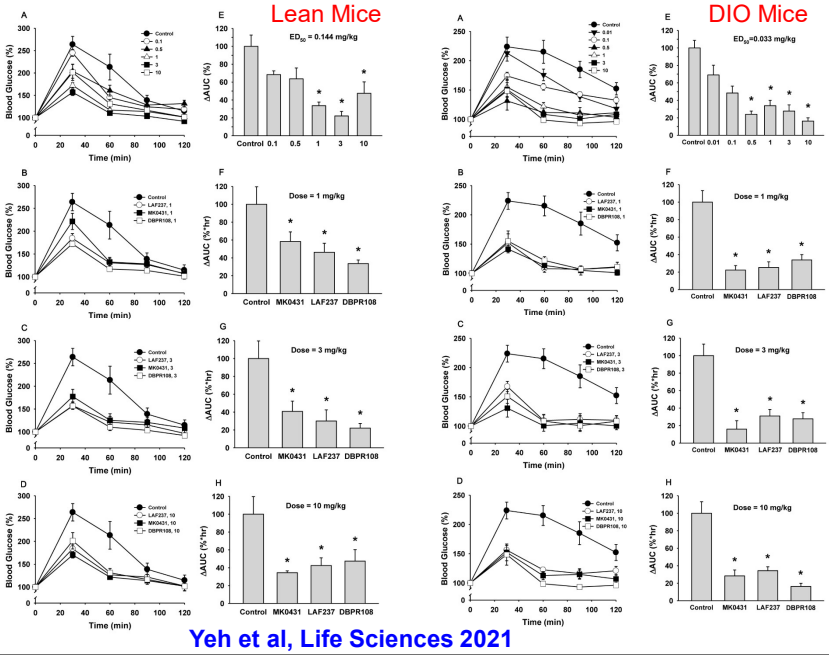
Yeh et al, Life Sciences 2021

DBPR108 increases plasma active GLP-1 levels in rats



Yeh et al, Life Sciences 2021

DBPR108 increases oral glucose tolerability

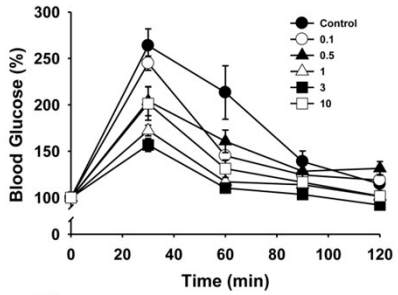


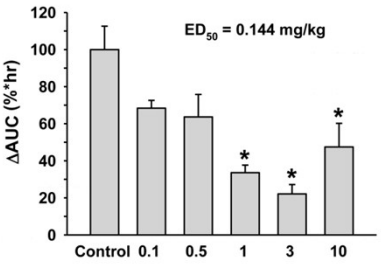
Yeh et al, Life Sciences 2021

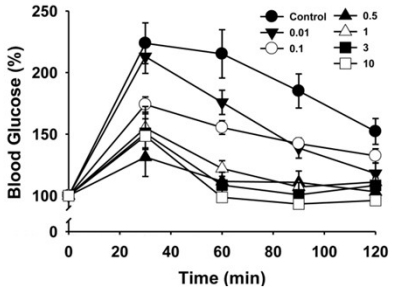
DBPR108 increases oral glucose tolerability

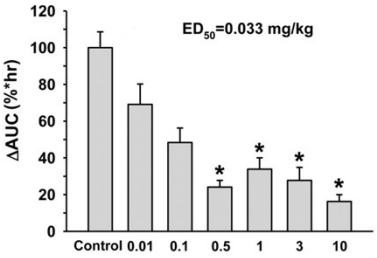
Lean Mice

DIO Mice





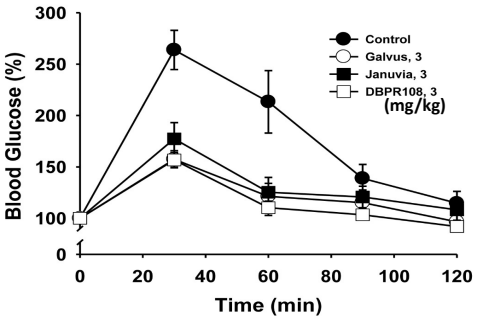




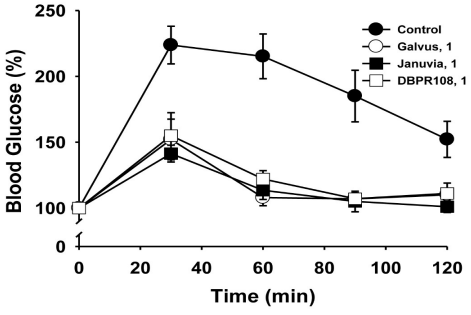
Yeh et al, Life Sciences 2021

DPP4 Inhibitors increase oral glucose tolerability

Lean Mice



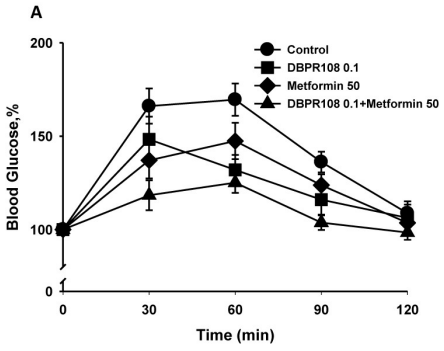
DIO Mice

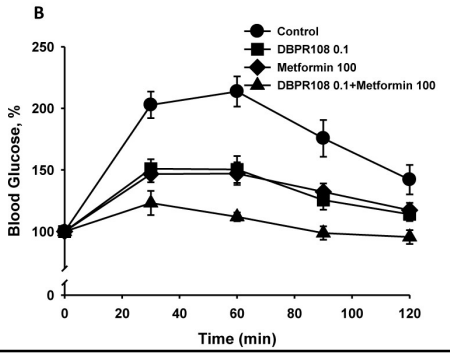


(Study site: NHRI)

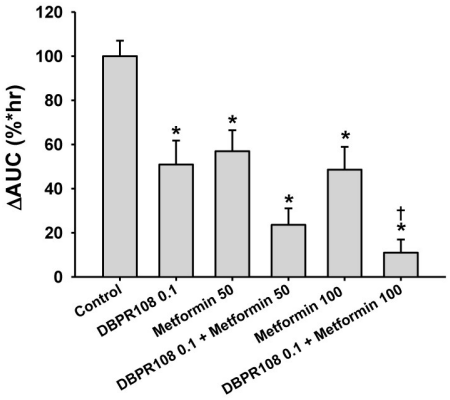
DBPR108 is as potent as Januvia and Galvus in these models.

Yeh et al, Life Sciences 2021





DBPR108 + Metformin increase oral glucose tolerability



Yeh et al, Life Sciences 2021

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Pre-Clinical Development

Pre-Clinical Development

Toxicology and Safety Pharmacology - (GLP)

In vitro genotoxicity studies
- – Ames test (*Salmonella*); Chromosome aberration test (CHO, HuPeBlLymphocy)

In vivo genotoxicity study
- – Micronucleus test in mice (micronucleated polychromatic erythrocytes in BMarrow/PeBL)

Single/Repeated dose range finding toxicity studies
Repeated-dose toxicology/toxicokinetic studies

in 2 species; at least 1 non-rodent (rat & dog, or …)

Safety pharmacology studies (rats/dogs)
- Central nervous system effects
- Respiratory effects
- Cardiovascular effects

Reproductive (DRF) toxicology studies (rats/rabbits)

DBPR108 - *Ames* Test

SALMONELLA-E. COLI/MAMMALIAN MICROSOME REVERSE MUTATION ASSAY

DBPR108 was evaluated for mutagenic activity in the *in vitro Salmonella-E. coli*/mammalian microsome reverse mutation assay using the plate incorporation and pre-incubation methods.
Four tester strains of *Salmonella typhimurium* (TA1537, TA98, TA100, and TA1535) and one *Escherichia coli* strain (WP2 uvrA) were used. Mutagenicity testing was performed in triplicate at each concentration with and without an Aroclor™1254-induced rat liver S9 metabolic activation system.

In the initial assay, DBPR108 (prepared at 50 mg/mL) was tested at 25, 50, 100, 250, 500, 1000, 2500 and 5000 µg/plate using the plate incorporation method. Precipitates and cytotoxicity (i.e., reduction in the background lawn and/or mean number of revertant colonies) were not observed in any strain with or without metabolic activation.
In the confirmatory assay, DBPR108 was tested at 100, 250, 500, 1000, 2500 and 5000 µg/plate using the pre-incubation method. Precipitates and cytotoxicity (i.e., reduction in the background lawn and/or mean number of revertant colonies) were not observed in any strain with or without metabolic activation.
In both assays, criteria for a negative response were met for all tester strains with and without metabolic activation. Mean number of revertant colonies was comparable to historical control ranges at all concentrations for all tester strains with and without metabolic activation.
The data from the vehicle and positive controls demonstrated the validity and sensitivity of this test system for detecting chemical mutagens with and without metabolic activation.

DBPR108 is negative for mutagenic activity in the *Salmonella* strains TA1537, TA98, TA100, and TA1535 and in the *E. coli* strain WP2 uvrA, with and without metabolic activation, under the conditions of this assay.

DBPR108 - Chromosome Aberration Test

Table 2. Cytotoxicity and Aberration Summary: 3-Hour Incubation without Metabolic Activation

Treatment	% Mitotic Reduction	% Cells w/Abs	% Cells w/>1 Abs	% Endo Cells	% Polyploid Cells
PBS (10%)	0	0.5	0.0	0.0	0.0
MMC 0.6 µg/mL	44	54.5 *	30.9 *	0.0	0.3
DBPR108					
1000 µg/mL	0	1.5	0.0	0.0	0.0
2000 µg/mL	-2	0.0	0.0	0.0	0.0
3250 µg/mL	-8	1.0	0.0	0.0	0.5

Endo = Endoreduplicated cells PBS = Dulbecco's Phophate Buffered Saline
Abs = Aberrations MMC = Mitomycin C
Percent Aberrant cells: * $p \leq 0.01$ using Fisher's Exact Test

Table 3. Cytotoxicity and Aberration Summary: 22-Hour Incubation without Metabolic Activation

Treatment	% Mitotic Reduction	% Cells w/Abs	% Cells w/>1 Abs	% Endo Cells	% Polyploid Cells
PBS (10%)	0	0.5	0.0	0.0	0.0
MMC 0.3 µg/mL	44	85.7 *	54.3 *	0.0	0.0
DBPR108					
2000 µg/mL	-2	0.0	0.0	0.0	0.5
2500 µg/mL	16	1.0	0.0	0.0	0.0
3250 µg/mL	36	4.5 **	0.0	0.0	0.8

Endo = Endoreduplicated cells PBS = Dulbecco's Phophate Buffered Saline
Abs = Aberrations MMC = Mitomycin C
Percent Aberrant cells: * $p \leq 0.01$, ** $p \leq 0.05$ using Fisher's Exact Test

Table 4. Cytotoxicity and Aberration Summary: 3-Hour Incubation with Metabolic Activation

Treatment	% Mitotic Reduction	% Cells w/Abs	% Cells w/>1 Abs	% Endo Cells	% Polyploid Cells
PBS (10%)	0	0.0	0.0	0.0	0.0
CP 10 µg/mL	66	58.8 *	37.3 *	0.0	0.0
DBPR108					
2250 µg/mL	5	0.5	0.0	0.0	0.0
2500 µg/mL	2	1.0	0.0	0.0	0.3
3250 µg/mL	8	1.0	0.0	0.0	0.0

Endo = Endoreduplicated cells PBS = Dulbecco's Phosphate Buffered Saline
Abs = Aberrations CP = Cyclophosphamide
Percent Aberrant cells: * $p \leq 0.01$ using Fisher's Exact Test

DBPR108 was negative under the conditions of this test system for inducing numerical chromosome aberrations with or without metabolic activation. DBPR108 was negative for inducing structural chromosome aberrations with or without metabolic activation with the exception that a statistically significant increase in the percentage of cells with aberrations was observed at 3250 µg/mL in the 22-hr treatment without metabolic activation; however, this increase did not meet the criteria of a positive response.

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DBPR108 - Micronucleus Test

Bone Marrow Micronucleus Test in SD Rats

Detailed physical examinations were performed on Study Day 0 and prior to the scheduled euthanasia. Individual body and food weights were recorded on Study Day 0 (prior to dosing) and prior to the scheduled euthanasia. Bone marrow collection for micronucleus evaluation was performed for 5 of 6 animals/sex/group at the scheduled euthanasia (Study Day 3). All animals were discarded without necropsy. Bone marrow smears were prepared and the coded slides were counted for polychromatic, normochromatic, and micronucleated polychromatic erythrocytes (PCEs) following the final bone marrow sample collection on Study Day 3.

DBPR108 did not induce an increase in micronucleated PCEs in either males or females when compared to the vehicle control group. No bone marrow cytotoxicity (decreases in the ratio of polychromatic to total erythrocytes, PCE:TE ratio) was noted in any test article-treated group. Therefore, DBPR108 met the criteria for a negative response for bone marrow cytotoxicity and clastogenicity under the conditions of this assay.

Based on the results of this study, oral administration of DBPR108 once daily to Crl:CD[SD] rats for 3 consecutive days at 100, 300, and 1000 mg/kg/day showed a negative response for bone marrow cytotoxicity and clastogenicity at all dosage levels examined under the conditions of this study.

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DBPR108 - 28-Day Toxicity/TK Study in SD Rats

CONCLUSION:
No test article-related mortality or adverse effects were noted following oral administration of DBPR108 to Crl:CD(SD) rats over a period of up to 29 days.

The **no-observed-adverse-effect level** (NOAEL) was 1000 mg/kg/day with a corresponding AUC(0-24h) of 119,000 and 159,000 ng/mL*hr for males and females, respectively.

DBPR108 - 28-Day Toxicity/TK Study in Dogs

No reduction of exposure was observed in dogs that were given 100 mg/kg/day dose for the same duration.

Oral (gavage) administrations of DBPR108 to Beagles resulted in a no-observed-adverse-effect level (NOAEL) of 1000 mg/kg/day.

At NOAEL of 1000 mg/kg/day, mean Cmax values were 238 and 224 µg/mL and the mean AUC0-24h values were 1040 and 990 µg•hr/mL for males and females, respectively.

DBPR108 - 13-Week Toxicity/TK Study in Monkeys

DBPR108 at oral doses 20, 60, and 200 mg/kg/day for 91 consecutive days was well tolerated by cynomolgus monkeys.

No morbidity.

No test article-related effects identified in clinical observations, food consumption, body weights, hematology, coagulation, or serum chemistry during the dosing phase and in postmortem assessments of organ weights or in gross and microscopic examinations of tissues.

No adverse reactions were observed following oral administrations of DBPR108 to cynomolgus monkeys at doses up to 200 mg/kg once a day for 91 consecutive days, a NOAEL under the conditions of this study was considered to be 200 mg/kg/day.

DBPR108 - Safety Pharmacology
CNS Effects (Irwin Test) in SD Rats

To evaluate the effects of DBPR108 at single oral dose by gavage to 6 male SD rats/dose group on the gross behavioral, physiological, and neurological state of the rats using a modification of a primary observation test, specifically the Irwin test (Irwin, 1968).

Group	Treatment	Dose Level (mg/kg)	Dose Concentration[a] (mg/mL)	Dose Volume (mL/kg)	Number of Males
1	Vehicle	0	0	10	6
2	DBPR108	100	10	10	6
3	DBPR108	300	30	10	6
4	DBPR108	1000	100	10	6

CONCLUSIONS: A single oral (gavage) administration of DBPR108 to male Sprague Dawley rats at dose levels of 100, 300, or 1000 mg/kg resulted in no effects on the gross behavioral, physiological, or neurological state of the animals.

DBPR108 - Safety Pharmacology Respiratory Effects in SD Rats

Group	Treatment	Dose Level[a] (mg/kg)	Dose Concentration[a] (mg/mL)	Dose Volume (mL/kg)	Number of Males[b]
1	Vehicle	0	0	10	8
2	DBPR108	100	10	10	8
3	DBPR108	300	30	10	8
4	DBPR108	1000	100	10	8

CONCLUSIONS: A single oral (gavage) administration of DBPR108 to male SD rats at 100, 300, or 1000 mg/kg resulted in no effects on respiratory functions (respiratory frequency, tidal volume, or the resulting minute volume).

DBPR108 - Safety Pharmacology CVS Effects in Beagle Dogs

A single oral gavage of DBPR108 to radiotelemetry-implanted male Beagle dogs at 100, 300, or 1000 mg/kg resulted in soft feces.

No DBPR108-related changes in body temperature, ECG waveform morphology, QRS and PR interval were observed at any dose level.

Slightly higher heart rate and subsequent shorter RR, QT, and QTcV intervals were attributed to DBPR108 administration at 300 or 1000 mg/kg.

DBPR108 administration at 1000 mg/kg resulted in lower arterial blood pressures (systolic, diastolic, mean arterial pressure, and pulse pressure) through 6 hr post-dosing.

These changes were of small magnitude; therefore, none of the changes attributed to DBPR108 administration were considered adverse.

Pre-Clinical Development Timeline of DBPR108

Items \ Year	2009	2010	2011	2012-2015
Production of API		—	—	
Production of Clinical Product			—	
DMPK	—	—	—	
A 13-week toxicity study and skin lesion evaluation study in cynomolgus monkey	—	—	—	
Single dose phase studies and 28-day toxicity studies in rats and dogs	—	—	—	
Genotoxicity studies	—	—		
Safety pharmacology studies	—	—		
Application for IND				▲
Phase I clinical trial				→

— Active study period

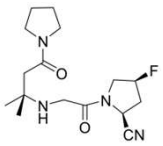
Galvus

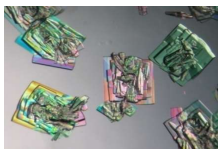
Clinical Development

Clinical Development
Prusogliptin (DBPR108), a DPP4 Inhibitor

Manufacturer of API: ScinoPharm Taiwan

Manufacturer of Investigational Drug Product: SinPhar Pharmaceutical Group





Yeh et al, Life Sciences 2021

Tsu et al, J Med Chem. 2006; Tsai et al, Bioorg Med Chem Lett. 2009.

Clinical Development
Prusogliptin (DBPR108), a DPP4 Inhibitor
Phase 1a/1b Clinical Studies

Wang-Fang Hospital (1a)/TMU Hospital (1b)
Clinical trial identifiers: NCT01650324/NCT02163278

- A double-blinded, randomized, placebo-controlled, dose-ranging study of the safety, tolerability, pharmacokinetics, and pharmacodynamics of DBPR108 in healthy male subjects.
- Objectives:
  - Primary: safety and tolerability of oral doses of DBPR108
  - Secondary: pharmacokinetics (PK) and pharmacodynamics (PD) of DBPR108

Table 1. Demographics and baseline characteristics of the Asian healthy male volunteers

Characteristics	Placebo (N=8)	DBPR108 25 mg (N=6)	DBPR108 100 mg (N=6)	DBPR108 300 mg (N=6)	DBPR108 600 mg (N=6)
	Single Dose Study				
Age, years	31 ± 8 (22, 42)	26 ± 2 (22, 29)	24 ± 2 (22, 28)	27 ± 5 (23, 37)	26 ± 6 (20, 36)
Height, cm	170.5 ± 3.9 (165.0, 176.5)	175.0 ± 5.4 (169.4, 182.3)	171.3 ± 7.7 (163.8, 185.1)	177.0 ± 5.4 (170.6, 186.5)	174.7 ± 4.5 (168.2, 178.3)
Weight, Kg	71.4 ± 7.3 (62.2, 86.3)	69.5 ± 11.3 (54.1, 86.8)	71.9 ± 16.3 (54.9, 95.9)	76.2 ± 15.6 (54.9, 102.9)	74.9 ± 9.3 (65.2, 87.3)
BMI, Kg/m^2	24.5 ± 2.6 (21.2, 28.4)	22.6 ± 2.5 (18.6, 26.1)	24.3 ± 4.0 (20.4, 30.0)	24.1 ± 4.0 (18.1, 29.5)	24.5 ± 2.5 (21.5, 27.4)
	Multiple Dose Study				
Age, years	31.8 ± 1.5 (30.4, 34.8)	28.7 ± 4.5 (21.0, 34.5)	29.6 ± 6.6 (21.7, 37.3)	32.2 ± 5.2 (26.1, 41.6)	29.2 ± 3.5 (22.1, 31.7)
Height, cm	172.1 ± 3.4 (167.8, 176.9)	172.2 ± 3.6 (167.3, 175.3)	172.1 ± 5.9 (162.6, 178.6)	174.8 ± 6.7 (165.2, 182.1)	174.6 ± 4.9 (169.5, 182.2)
Weight, Kg	68.4 ± 3.5 (64.0, 72.7)	64.3 ± 6.5 (55.3, 73.5)	64.6 ± 8.0 (53.1, 74.0)	67.8 ± 7.6 (59.5, 78.5)	68.7 ± 6.1 (58.9, 76.3)
BMI, Kg/m^2	23.1 ± 0.4 (22.6, 23.9)	21.6 ± 1.7 (19.6, 23.9)	21.7 ± 1.4 (20.1, 23.2)	22.1 ± 1.4 (20.5, 23.7)	22.5 ± 1.4 (19.7, 23.9)

Data are represented as mean ± S.D.; Minimum and maximum values are shown in the parenthesis.

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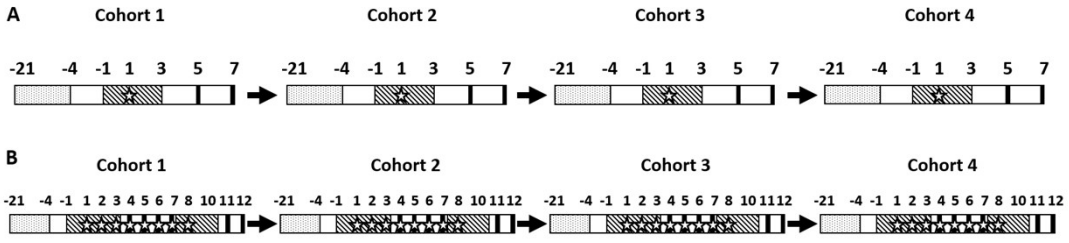
Design of Phase I study of DBPR108



Phase 1 study of orally ingested DBPR108 is consisted of a single-dose (1A) and a follow-up multiple-dose (1B) study phases. Cohorts 1-4 were healthy male volunteers given oral doses of 25, 100, 300, and 600 mg, respectively, to which each cohort consisted of 6 DBPR108-treated and 2 placebo-treated subjects double-blinded and randomized. Study activities including pre-enrollment screening period from Day -21 to Day -4 (▨), hospital visits (▌), hospital residential stays (▧) and oral ingestions (☆) of the Phase 1 study are indicated. The oral ingestion of DBPR108 was started from the lowest single dose level at 25 mg and the safety and tolera bility were evaluated and confirmed before going up to the next higher single dose level gradually up to the highest dose level at 600 mg (Figure 1A). Analogously, the same study design, study activities and safety confirmations for the dose increments bet ween cohorts were applied to the multiple-dose study phase, in which DBPR108 was ingested once daily by the healthy male volunteers from Day 1 to Day 8 (Figure 1B).

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DBPR108 - Phase I Clinical Study

Plasma concentration-time profiles of DBPR108

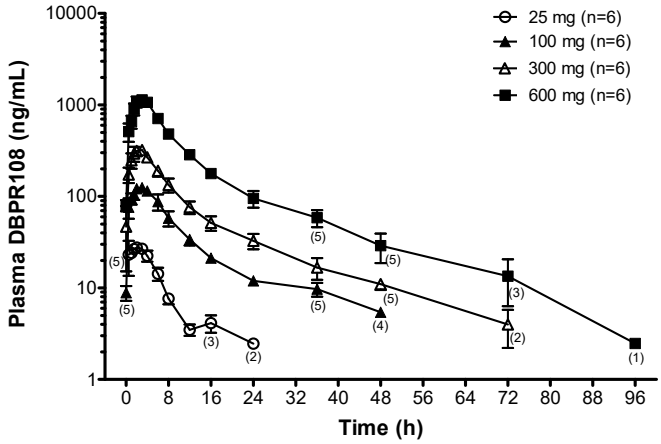

Figure 2. Mean plasma concentration-time profiles of DBPR108 in healthy male subjects.
Healthy male volunteers received one single oral dose of DBPR108 at different dose levels as 25 mg (■, N=6), 100 mg (□, N=6), 300 mg (●, N=6) and 600 mg (○, N=6).
The number in the parentheses means the number of data available and presented. Data are presented as mean ± S.D.

Note: The number in the brackets means the time point only has less data because of the quantifiable limit (<2.00 ng/mL).

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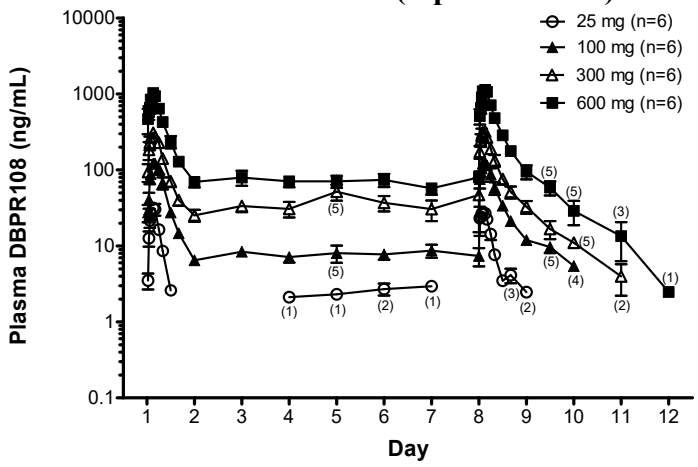
DBPR108 - Phase I Clinical Study

Plasma concentration-time profiles of DBPR108 (repeated doses)



Plasma concentration-time profiles of DBPR108 in healthy male subjects.

Repeated once daily oral doses for 8 consecutive days of DBPR108 at different dose levels as 25 mg (■, N=6), 100 mg (□, N=6), 300 mg (●, N=6) and 600 mg (○, N=6).
It is noted that the plasma DBPR108 concentrations were able to be maintained in a dose dependent manner during the daily visits (Days 4 to 7) between the 2 hospital stays. The number in the parentheses means the number of data available and presented. Data are presented as mean ± S.D.

Note: The number in the brackets means the time point only has less data because of the quantifiable limit (<2.00 ng/mL).
Unlabeled portions were described as follows:
(5) at 0.5 hr after 1st treatment (25 mg) on Day1, and (5) at 0.5 hr after 2nd treatment (25 mg) on Day8.
(4) at 0.5 hr on Day1 and (5) on Day8 after 1st treatment (100 mg).

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Table 3. Pharmacokinetic parameters of DBPR108 after once daily multiple oral administrations in healthy human male subjects.

Parameter	Dose Cohort			
	25 mg	100 mg	300 mg	600 mg
Day 1				
$AUC_{0\text{-}24h}$ (ng*h/mL)	179 ± 41	1,050 ± 181[a]	2,620 ± 393[ab]	8,340 ± 1,070[abc]
$AUC_{0\text{-}inf}$ (ng*h/mL)	182 ± 41	1,090 ± 174[a]	2,840 ± 488[ab]	8,990 ± 1,200[abc]
C_{max} (ng/mL)	34 ± 14	141 ± 31	349 ± 88[ab]	1,100 ± 233[abc]
T_{max} (h)	3.17 ± 0.75	4.33 ± 1.37	3.17 ± 1.69	2.92 ± 1.28
$T_{1/2}$ (h)	2.28 ± 0.18	5.06 ± 0.75[a]	5.77 ± 0.99[a]	6.60 ± 0.90[ab]
CL/F (L/h)	142 ± 29	93 ± 15[a]	108 ± 20[a]	68 ± 10[abc]
Vz/F (L)	469 ± 108	689 ± 195	895 ± 180[a]	651 ± 159
$Ae_{0\text{-}24h}$ (mg)	1.4 ± 0.7	10.7 ± 2.1	36.2 ± 7.8[ab]	95.8 ± 14.0[abc]
$fe_{0\text{-}24h}$ (%)	5.7 ± 2.7	10.7 ± 2.1[a]	12.0 ± 2.6[a]	16.0 ± 2.3[abc]
CL_R (L/h)	8.0 ± 2.4	10.2 ± 0.6[a]	13.7 ± 1.7[ab]	11.5 ± 0.9[ac]
Day 8				
$AUC_{0\text{-}24h}$ (ng*h/mL)	193 ± 46	1,170 ± 261[a]	2,820 ± 642[ab]	9,890 ± 1,210[abcd]
$AUC_{0\text{-}last}$ (ng*h/mL)	190 ± 47	1,350 ± 333	3,310 ± 960[ab]	11,400 ± 1,900[abc]
$AUC_{0\text{-}inf}$ (ng*h/mL)	206 ± 52	1,440 ± 358	3,440 ± 942[ab]	11,600 ± 2,130[abcd]
C_{max} (ng/mL)	36 ± 12	141 ± 29	372 ± 111[ab]	1,220 ± 330[abc]
T_{max} (h)	1.92 ± 0.97	2.25 ± 1.17	2.33 ± 0.75	3.17 ± 0.75
$T_{1/2}$ (h)	4.61 ± 3.12	12.20 ± 4.57[ad]	13.50 ± 6.45[ad]	10.30 ± 5.79
CL/F (L/h)	139 ± 46	88 ± 17[a]	111 ± 24	62 ± 8[ac]
Vz/F (L)	863 ± 505	1,530 ± 622	2,120 ± 1,070[ad]	888 ± 462[c]
$Ae_{0\text{-}24h}$ (mg)	1.4 ± 0.3	13.2 ± 2.3	42.0 ± 4.0[ab]	113.0 ± 30.9[abc]
$fe_{0\text{-}24h}$ (%)	5.6 ± 1.3	13.2 ± 2.3[a]	14.0 ± 3.1[a]	18.9 ± 5.1[abc]
$Ae_{0\text{-}48h}$ (mg)	1.5 ± 0.4	14.4 ± 2.5	47.9 ± 11.3[ab]	130.0 ± 34.4[abc]
$fe_{0\text{-}48h}$ (%)	5.8 ± 1.4	14.4 ± 2.5[a]	16.0 ± 3.8[a]	21.6 ± 5.7[abc]
CL_R (L/h)	7.4 ± 0.9	10.8 ± 1.3[a]	15.0 ± 2.0[ab]	11.6 ± 2.4[ac]
AR (%)	**110 ± 28**	**114 ± 27**	**107 ± 19**	**120 ± 18**

Data are represented as mean ± S.D. a: p<0.05 vs. 25 mg; b: p<0.05 vs. 100 mg; c: p<0.05 vs. 300 mg; d: p<0.05 vs. Day1 of the equal dose, by one-way ANOVA analysis following by Student-Newman-Keuls multiple comparison test.
AUC0-24h: area under the concentration-time curve from time 0 to 24 h; AUC0-inf: area under the concentration-time curve from time 0 to infinity; AUC0-last: area under the concentration-time curve from time 0 to last sampling time; Cmax: maximum concentration observed in plasma; Tmax: time to reach maximum concentration observed in plasma; T1/2: terminal elimination half-life; CL/F: apparent clearance; VZ/F: apparent volume of distribution; Ae0-24h: cumulative amount of unchanged drug excreted in urine from time zero to 24 h; fe0-24h: fraction of unchanged drug excreted in urine from time zero to 24 h; Ae0-48h: cumulative amount of unchanged drug excreted in urine from time zero to 48 h; fe0-48h: fraction of unchanged drug excreted in urine from time zero to 48 h; CLR: renal clearance; AR: accumulation ratio.

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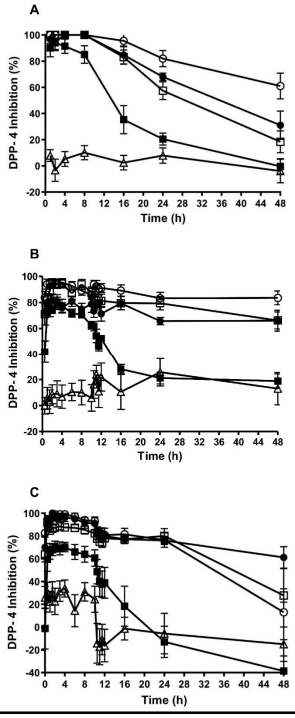

Inhibition of plasma DPP-4 activities after oral administrations of DBPR108 in healthy male subjects.

Healthy male volunteers received single dose (A) or repeated doses (Day 1, B; Day 8, C) of DBPR108 via oral ingestion at different dose levels:
0 mg, (Placebo, △, N=8), 25 mg (■, N=6), 100 mg (□, N=6), 300 mg (●, N=6) and 600 mg (○, N=6).

Within a time period from pre-dose to 48 h after an oral ingestion, plasma samples were collected at the time points indicated for measurements of the DPP-4 activities.

A significant dose-dependent inhibitory effect of DBPR108 on the plasma DPP-4 activity was observed on both Day 1 after one single dose administered and Day 1 and Day 8 after the administrations of repeated oral doses.
Data normalized in percentage to the maximum inhibition of the plasma DPP-4 activity are presented as mean ± S.D.

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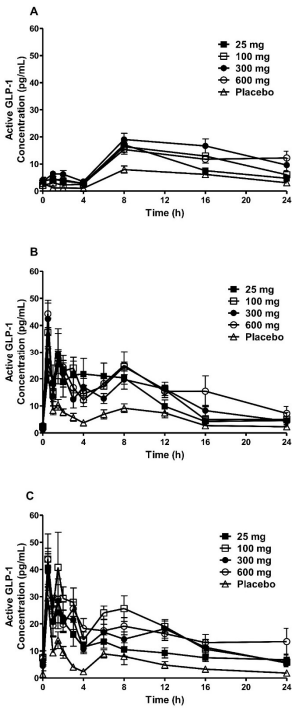

Increase of the circulating active form of GLP-1 after oral administration of DBPR108 in healthy male subjects.
Healthy male volunteers received oral dose(s) of DBPR108 at different dose levels; 0 mg, (Placebo, △, N=8), 25 mg (■, N=6), 100 mg (□, N=6), 300 mg (●, N=6) and 600 mg (○, N=6). The circulating levels of GLP-1 of active form were increased in response to the DBPR108 administration in the single-dose study (A), and in the multiple-dose study on Day 1 (B) and Day 8 (C).
The subjects in the single-dose study were fasted with restriction of food and water for at least 10 h before the DBPR108 dosing and for another fasting period of 4 h after the DBPR108 dosing. On the other hand, the subjects in the multiple-dose study were non-fasted and served with a total of 4 standardized test meals as breakfasts and dinners on the 2 dosing days, Day 1 and Day 8, during the 2 hospital stays. Breakfast test meals were given approximately 5 min after the DBPR108 dosing.
A significant dose-dependent induction activity of DBPR108 on the circulating active GLP-1 level was observed in both study phases. Data are presented as mean ± S.D.

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Clinical Development

Prusogliptin (DBPR108), a DPP4 Inhibitor

- A double-blinded, randomized, placebo-controlled, dose-ranging study of the safety, tolerability, pharmacokinetics, and pharmacodynamics of DBPR108 in healthy male subjects.

Completed @ Wang-Fang Hospital (1a)/TMU Hospital (1b)!!

  - Primary: safety and tolerability of oral doses of DBPR108
  - Secondary: pharmacokinetics (PK) and pharmacodynamics (PD) of DBPR108

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→ **Genovate** → **CSPC PHARMA**
(mainland China territory only)

Wang et al, (2020) Current Medical Research and Opinion.
Xu et al, (2022) & Wang et al, (2024) Diabetes, Obesity and Metabolism.

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Discovery & Development of DBPR108

Drug Discovery/Research: NHRI/NSTC Projects → **Drug Development:** NHRI/Industry Collaborative Project

- Target Validation & Mechanism Studies
- Assays Development
- High Throughput Screening
  In vitro Screening
  Molecular Modeling
- Medicinal Chemistry
  Rational Design
  Lead Optimization
- Animal Efficacy & Pharmacology Pharmacokinetics
- Development Candidate DBPR108
- Pharmacokinetics
  Drug Metabolism
  Pre-formulation
- Safety Pharmacology Studies
  Toxicology Studies
  Scale-up Synthesis of API
  Early-phase Formulation
  Pharmaceutical Development
  GMP Production
- Planning for FIH Clinical Trial
- IND Applied: TFDA & US-FDA
- Phase I Clinical Trials **in Taiwan Completed.**
- **Phase I/II Clinical Trials in Mainland China** completed in 2019
  Phase III done in 2021
  NDA filed: NMPA in April 2023

- 20 papers published
- Patent Applications in Taiwan, USA and PCT
- 7 Patents granted up to now: US(3), ROC(1), AU(1), KR(1), China(1)

- IND applications approved by US-FDA and TFDA in 1/2012.
- Phase Ia initiated in Q2/2012
- Phase Ia/Ib completed in 2015

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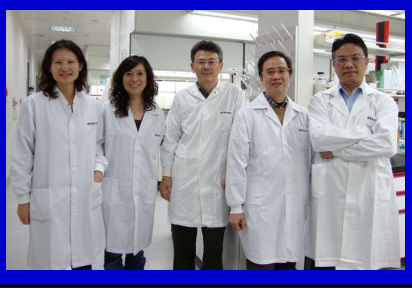
DBPR108- THE Discovery and Development Team



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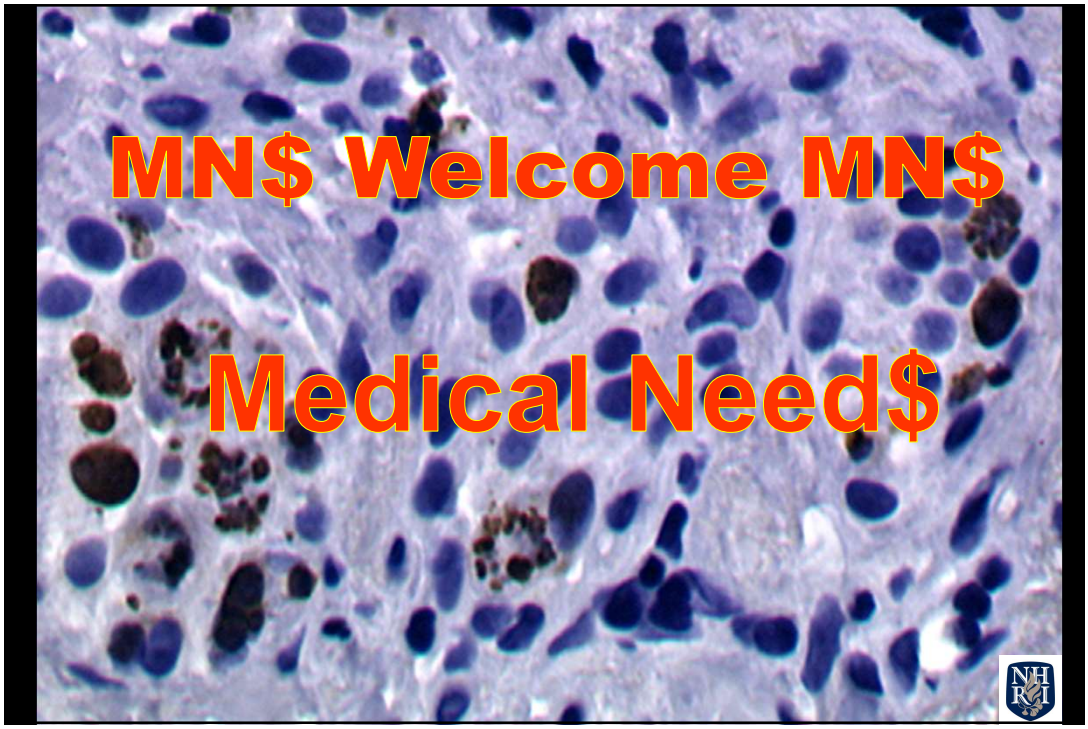
Conflict of Interest Declaration

PI & Co-PI of the Pre-clinical/Clinical development projects for DBPR108.



Drug Discovery and Development - Diabetes-Curing Prusogliptin (DBPR108)

Q & A

陳 炯 東
Chiung-Tong Chen, Ph.D.
生技與藥物研究所 研究員
國家衛生研究院

中國醫藥大學 水湳校區 國際會議廳 卓越B201
November 16, 2024 (15:50-16:20)