GM-60106 is a Clinical Drug Candidate for Non-alcoholic Steatohepatitis (NASH)

JD BIOSCIENCE

GM-60106 Highlights

- **GM-60106 is a first-in-class drug candidate for NASH.**
- **GM-60106 blocks the novel target 5-hydroxytryptamine receptor 2A (HTR2A) that is directly connected to fibrosis and correlated steatosis.**
- **Preclinical and toxicology studies were completed and showed that the compound can improve both hepatosteatosis and liver fibrosis and is not permeable to blood-brain barrier (BBB); thus, it does not induce any central nervous system (CNS) mediated side effects.**
- **A clinical study started in September 2022 in Australia to assess the safety, tolerability, and pharmacokinetics of GM60106**

Overview of GM-60106

JD Bioscience (JDB) is a South Korean-based venture company currently developing GM-60106, a novel therapeutic compound for NASH with potent efficacy in liver fat accumulation and fibrosis by blocking of HTR2A in serotonin pathway.

Experts estimated that about 2~5% of US population has NASH and 20~30% of these patients progress to liver fibrosis in 7 years. However, there are no drugs commercially approved for NASH and off-target drugs are currently used for treatment. There are drug candidates for NASH treatment in phase 2 or 3 clinical trials, but majority of them only can improve fatty liver and lipotoxicity but cannot improve liver fibrosis.

Preclinical studies have shown that GM-60106 improved NASH-related fibrosis and steatosis effectively by directly suppressing HTR2A in translatable preclinical animal models. According to the preclinical data, GM-60106 showed superior pharmacokinetics (PK) profiles and minimized blood-brain barrier permeability, thus it can directly inhibit the target only in the peripheral tissues but not in the brain.

Conclusively, the novel mechanism for liver fibrosis and superior pharmacokinetics can differentiate GM-60106 from the current clinical drug candidates for NASH.

Differentiated Profile of GM-60106

Direct mechanism for NASH-related fibrosis

- Suppressing HTR2A with GM-60106 can directly deactivate hepatic stellate cells (HSCs), which is critical for liver fibrosis.

Superior efficacy, kinetics, and safety

- GM-60106 has stronger efficacy for liver fibrosis and inflammation compared to other drug designs in vivo.
- The compound shows optimal PK profiles for an oral administrative drugs.
- Safe from CNS-mediated safety issues.

IP protection

JDB filed patents for a composition of matter (10-2020-0143809) and a back up scaffold compound (10-2021-0048761) in US/Europe/Asia/South America.

Partnering interest

JDB is seeking an exclusive (including geographical right) out-licensing opportunity of GM-60106 after its phase 1 clinical study.

Summary of a Preclinical Study

Pharmacokinetics, safety, and efficacy of GM-60106 Analysis

- PK values of GM-60106 are optimal for oral medication development.
- GM-60106 appears to be a safe compound, judged by the toxicity and safety pharmacology data in preclinical animal studies. It is not expected to have CNS-related adverse effects since it is not permeable to blood brain barrier(BBB).
- It showed stronger effect on liver fibrosis and inflammation compared to prevailing drug candidates for NASH.

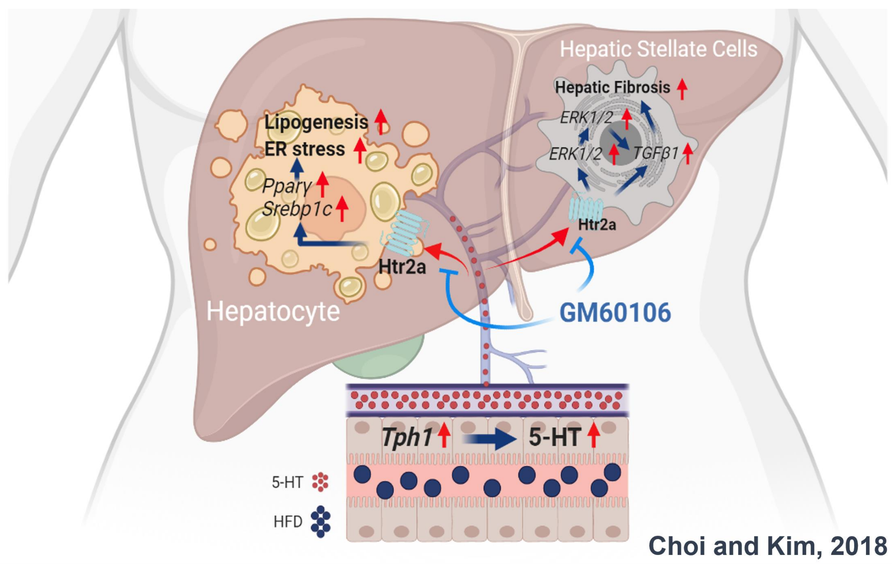
Summary of chemical profiles and pharmacology of GM-60106

Assays	Results
Physicochemical Property studies	✓
In vitro assays	✓
Pharmacokinetic assays	✓
In vivo efficacy assays	✓
Metabolic stability assays	✓
CMC studies	✓
Preclinical toxicity studies	✓

Novel Mechanism of Action (MOA)

- High fat diet increases both serotonin levels and HTR2A expressions in the liver that induces signaling important for lipogenesis, inflammation, and fibrosis.
- The expression of HTR2A is increased during hepatic stellate cells (HSC) activation that is directly connected to the progression of liver fibrosis. The inhibition of HTR2A deactivates the HSCs.
- Blocking of HTR2A with GM-60106 can improve steatosis, inflammation, and liver fibrosis in the liver.

MOA of GM-60106 during hepatic steatosis and liver fibrosis



Choi and Kim, 2018

JDB-106001 Phase I Clinical trial (NCT05517564)

Sep 2022	Apr 2023	Sep 2023	Nov 2023
Part A (SAD Cohort 1 to 8)	Part B (MAD Cohort 1 to 3)	Part C (MAD Cohort 4 to 5)	

Phase 1A SAD
- 8 cohorts (n=8)
- Sentinels included
- QD dosing, 1 day

Phase 1A MAD
- 3 cohorts (n=8)
- QD dosing, 14 days

Phase 1B MAD
- 2 cohorts (n=8)
- Healthy adults with increased BMI & markers of NAFLD
- QD dosing, 28 days

SAD: Single Administration Dosing; MAD: Multiple Administration Dosing

For more information, please contact:

Sungmin Song, Ph.D. (+82-62-974-9380, seaflow@jdbiosci.com)

Peter Goughnour, Ph.D. (+82-2-406-9380, petergoughnour@jdbiosci.com)

GM-10395 is a Novel Drug Candidate for Inflammatory Bowel Disease (IBD)

JD BIOSCIENCE

GM-10395 Highlights

- **GM-10395 is a first-in-class drug candidate for IBD, targeting a novel molecule that is important for cell metabolism.**
- **GM-10395 inhibits pyruvate dehydrogenase kinase (PDK) that is tightly connected to chronic inflammation by modulating CD4⁺ T cell activity.**
- **Preclinical studies are being performed, and they show that the compound can improve both ulcerative colitis (UC) and Crohn's disease (CD)**
- **A tox study is planned for Q4 of 2022 to assess the safety, tolerability, and pharmacokinetics of GM-10395**

Overview of GM-10395

JD Bioscience (JDB) is a South Korean-based venture company currently developing GM-10395, a novel therapeutic compound for IBD with potent efficacy to reduce inflammation caused by CD4⁺ T cells.

Experts estimated that about 1.2% of US population has IBD and the incidence rate of this population has been rapidly rising. Even though corticosteroids and aminosalicylates are currently used along with monoclonal antibodies for treatment of IBD, a considerable fraction of patients do not respond well to the available treatments or lose response. In addition, the U.S. FDA warned about safety concerns, including serious heart problems and cancer, related to Janus kinase (JAK) inhibitor-based UC drugs recently. Thus, unmet medical needs for an effective drug with strong safety profile is increasing.

One of the main reasons for not finding effective drugs for IBD is the lack of understanding of pathogenesis. Our preclinical studies have elucidated a novel mechanism that can suppress the activity of CD4⁺ T cells. According to the preclinical data, GM-10395 was highly selective to the target and block PDK, and it effectively ameliorated murine colitis.

Conclusively, the novel mechanism of inhibiting PDK with GM-10395 mitigated colitis that differentiates it from the currently approved drug candidates for IBD.

Differentiated Profile of GM-10395

Direct mechanism for reducing colitis

- Suppressing PDK with GM-10395 can directly suppress CD4⁺ T cells which is important for IBD progression.

Superior efficacy and safety

- GM-10395 is highly selective for the PDK target and also shows stronger efficacy for ameliorating colitis compared to other drug designs.
- The compound can be used as an oral administrative drug.
- Animal model showed no adverse side effects.

IP protection

A patent for a composition of matter (10-2021-0150928) and a patent for a back up scaffold compound (10-2021-0150929) were filed.

Partnering interest

JDB is seeking an exclusive (including geographical right) out-licensing opportunity of GM-10395 at the preclinical stage.

Summary of a Preclinical Study

Pharmacokinetics, safety, and efficacy of GM-10395 Analysis

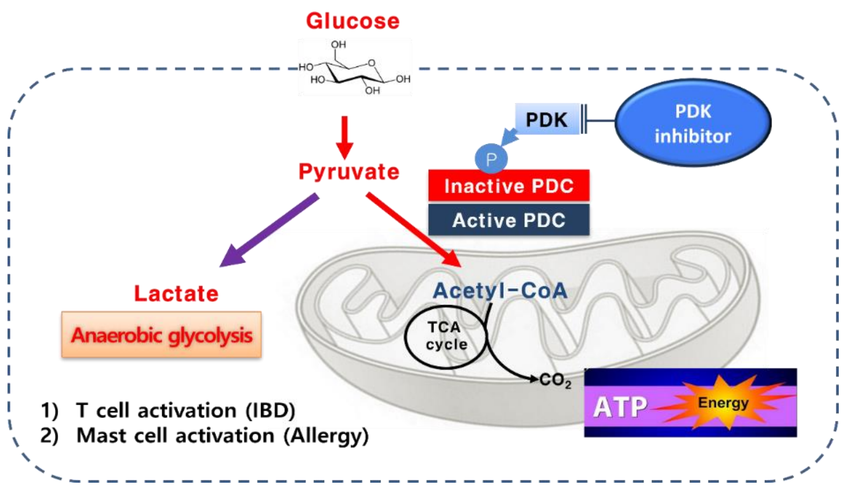
- PK values of GM-10395 are optimal to be developed as an oral medication.
- GM-10395 is a safe compound, judged by a strong target selectivity and a minimum toxicity in animal models.
- It showed stronger effect on intestinal inflammation compared to commercially available drugs for IBD.

Summary of chemical profiles and pharmacology of GM-10395

Assays	Results
Physicochemical Property studies	✓
In vitro assays	✓
Pharmacokinetic assays	✓
In vivo efficacy assays	✓
Metabolic stability assays	✓
CMC studies	In progress
Preclinical toxicity studies	In progress

Novel Mechanism of Action (MOA)

- The percentage of intestinal CD4+ T cells is highly induced in the patients with active IBD compared to the patients with inactive IBD.
- When the intestinal CD4⁺ T cells are activated, secretion of inflammatory cytokines is significantly increased, leading to the disruption of gut integrity and colitis initiation.
- According to our finding, the activity of T cells is strongly correlated with the PDK –mediated metabolic machinery, i.e., when PDK expression is induced, anaerobic glycolysis becomes dominant to the oxidative phosphorylation (OXPHOS) and this causes mitochondria dysfunction that is tightly connected to functional characteristics of pathogenic T cells such as cytokine secretion.
- Thus, pharmacological inhibition of PDK have potential to suppress gut inflammation that is due to the activated gut-infiltrating CD4⁺ T cells



A word from KOLs in the field of hepatology

"A considerable fraction of patients do not respond to available treatments or lose response for IBD."

"Number of patients fail to achieve clinical remission after treatment with current available medication."

"With the deepening of research, new therapies for IBD treatment are coming into view, but there is no clear front candidate."

For more information, please contact:

- **Sungmin Song, Ph.D (+82-62-974-9380, seaflow@jdbiosci.com)**
- **Peter Goughnour, Ph.D (+82-2-406-9380, petergoughnour@jdbiosci.com)**

JD-X is a Novel Drug Candidate for Dravet Syndrome

JD BIOSCIENCE

JD-X Highlights

- **JD-X is a best-in-class drug candidate for the treatment of Dravet syndrome (DS).**
- **The compound has been shown to increase serotonin levels, which activates the GABAergic interneurons.**
- **Compared to current therapeutics for Dravet syndrome, JD-X demonstrated strong efficacy.**
- **Its pharmacokinetic (PK) value suggests that it is suitable candidate for development into an orally administered drug.**
- **Non-GLP toxicology studies have validated the safety of JD-X.**

Overview of JD-X

JD Bioscience (JDB) is a South Korean-based venture company currently developing JD-X, a novel therapeutic compound for DS that shows potent efficacy in reducing seizure-like behavior caused by mutations in the sodium voltage-gated channel alpha subunit 1 (*SCN1A*) gene.

DS is a rare and fetal hereditary interstitial childhood encephalopathy characterized by prolonged seizures in infancy, accompanied by intellectual and behavioral disorders. It affects an estimated 1 in 15,700 individuals globally, with 85% of those affected having a mutation in their SCN1A gene. While several treatments are available for patients with DS, including recently approved medications by the US FDA such as Cannabidiol, Stiripentol, and Fenfluramine, these drugs have a diverse range of adverse effects, such as vomiting, fatigue, sedation, and insomnia.

JDB's new drug candidate, JD-X, was developed through collaborative research and has shown strong anti-epileptic effects in genetic zebrafish and Pentylenetetrazole (PTZ)-induced kindling mice models. Its efficacy is comparable to existing drugs for DS, and it has optimal PK values for orally administered drugs as well as good safety profile.

Before commencing the GLP-toxicology study, JDB intends to apply for FDA Orphan Drug Designation (ODD) and Rare Pediatric Disease Designation (RPDD) for rare diseases.

Differentiated Profile of JD-X

Orphan Drug for Rare Disease

- JD-X may qualify for fast-track, ODD and RPDD for regulatory agencies such as the FDA or MFDS.

Superior efficacy and safety

- JD-X has demonstrated strong efficacy in reducing seizure-like behaviors in various animal models, with safe dosing levels. Additionally, it has optimal PK properties for oral administration.
- MOA is involved the activation of GABAergic neurons through a significant increase in the synthesis of 5-HT and GABA.

IP protection

A patent for a composition of matter and patents for a back up scaffold compounds will be filed Q3 2023.

Partnering interest

JDB is seeking an exclusive (including geographical right) out-licensing opportunity JD-X at the preclinical stage.

Summary of a Preclinical Study

Pharmacokinetics, safety, and efficacy of JD-X Analysis

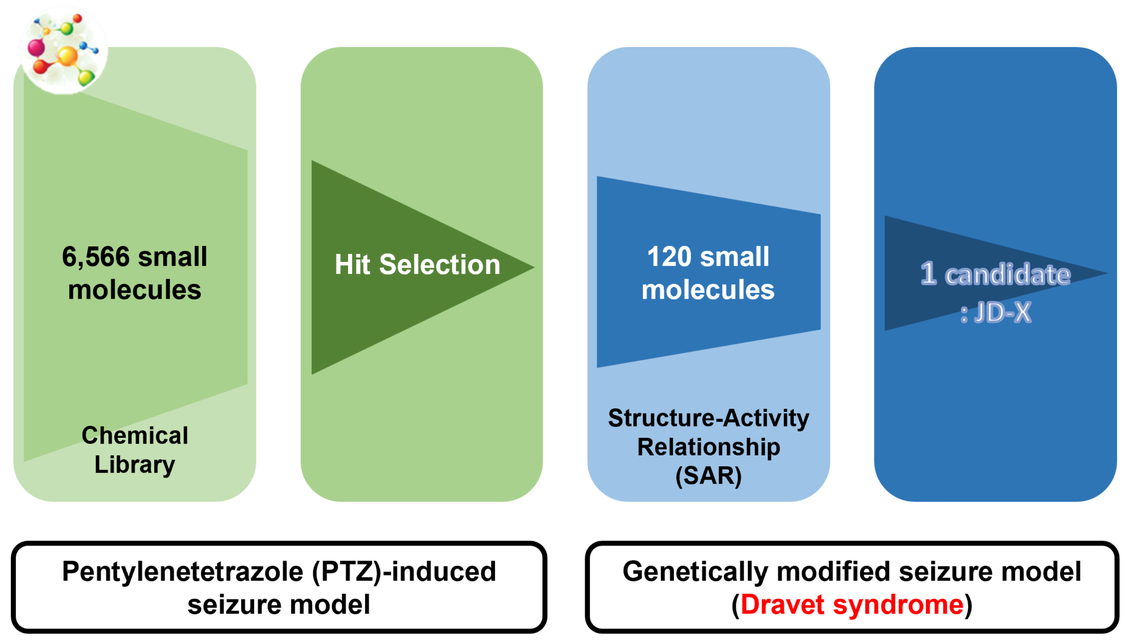
- The efficacy of JD-X was evaluated in zebrafish, mouse, and cerebral organoid models and the neurochemical profile was analyzed to understand the MOA of JD-X.
- PK was analyzed in mice, rats, and monkeys; membrane & blood brain barrier permeabilities were also analyzed.
- The safety of JD-X was evaluated through in vitro assessment, including cardiac toxicity testing, as well as in vivo safety evaluation.

Summary of chemical profiles and pharmacology of JD-X

Assays	Results
Physicochemical Property studies	✓
Neurochemical profiling	✓
Pharmacokinetic assays	✓
In vivo efficacy assays	✓
Metabolic stability assays	✓
CMC studies	In Progress
Preclinical toxicity studies	In Progress

Drug Screening method using a Zebrafish-based Disease Model

- A hit compound was selected from a chemical library using a PTZ-induced kindling model.
- Over 100 derivatives were synthesized using a structure-activity relationship approach based on the hit scaffold.
- A Lead compound was identified using a genetic zebrafish model, and its anti-epileptic efficacy was confirmed in a mouse model and human cerebral organoid.
- The lead compound has been optimized to enhance its druggability.



A word from KOLs in the field of hepatology

"There is a strong unmet medical needs for therapies that can modify the course of the disease and potentially prevent or delay the onset of seizures.."

"Although certain drugs can help reduce seizures in people with DS, a significant number of individuals continue to experience frequent and severe seizures. Thus, there is a need for new drugs with more effective seizure control.

For more information, please contact:

- **Sungmin Song, Ph.D (+82-62-974-9380, seaflow@jdbiosci.com)**
- **Peter Goughnour, Ph.D (+82-2-406-9380, petergoughnour@jdbiosci.com)**

Novel Designs for Antibody Drug Conjugates & Proteolysis Targeting Chimera

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Medicinal Chemistry Overview of JD Bioscience

JD Bioscience (JDB) is a South Korean-based venture company has the core technology and experience to design small molecules for the treatment of a variety of diseases that can be applied to antibody drug conjugate (ADC) or proteolysis targeting chimera (PROTAC). JBD is currently collaborating with ~15 different companies in South Korea and abroad assisting them in their research. We are seeking to expand our collaborative research with companies that have novel antibodies for ADC and novel targets for PROTAC that can increase tremendously the market potential.

Antibody Drug Conjugate (ADC) highlights

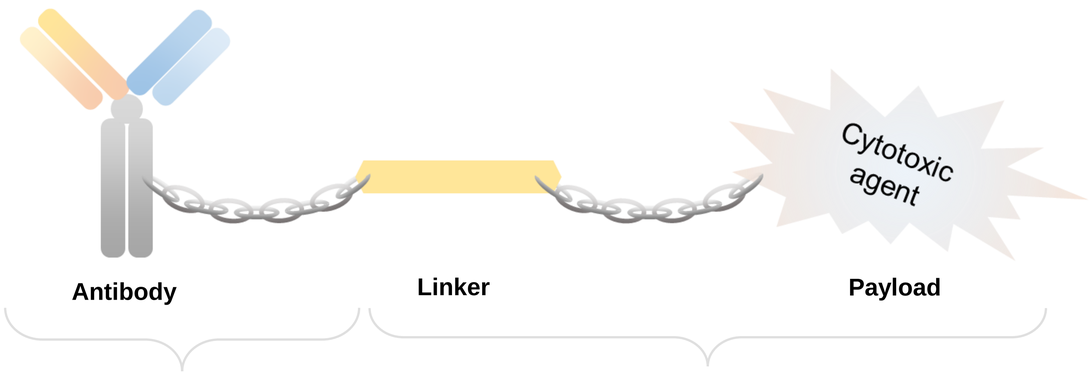
- **Design novel payloads and linkers**
- **Identified new Seco-Duocarmycin (DUBA) and Camptothecin (SN-38 and Dxd) payloads**
- **ADC with a DAR of 8 showed better toxicity than commercial payload**
- **All patentable**

Proteolysis Targeting Chimera (PROTAC) highlights

- **Design novel warheads and E3 ligases**
- **Identified new celerbron (CRBN) and Von Hippel-Lindau (VHL) binders**
- **Good DC_{50} value**
- **Good Metabolic stability and can be used orally**
- **All patentable**

Schematic

Antibody Drug Conjugate (ADC)

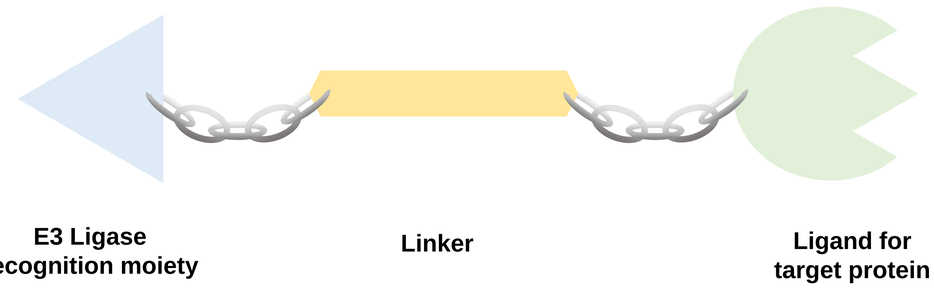


Collaboration Company

JD BIOSCIENCE

Schematic

Proteolysis Targeting Chimera (PROTAC)



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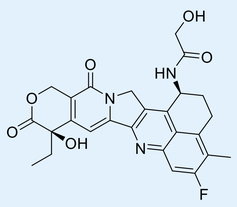
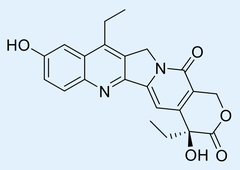
We are developing new payloads for ADC

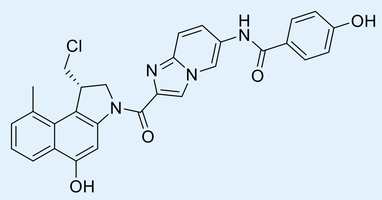
DXD



SN-38

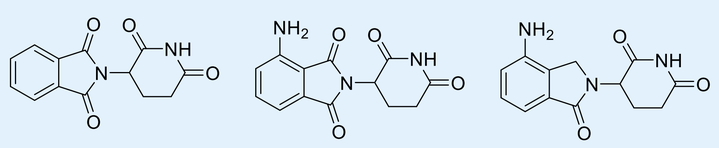


Seco Duocarmycin (DUBA)



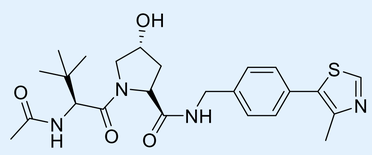
We are developing new CRBN and VHL binders for PROTAC

CRBN

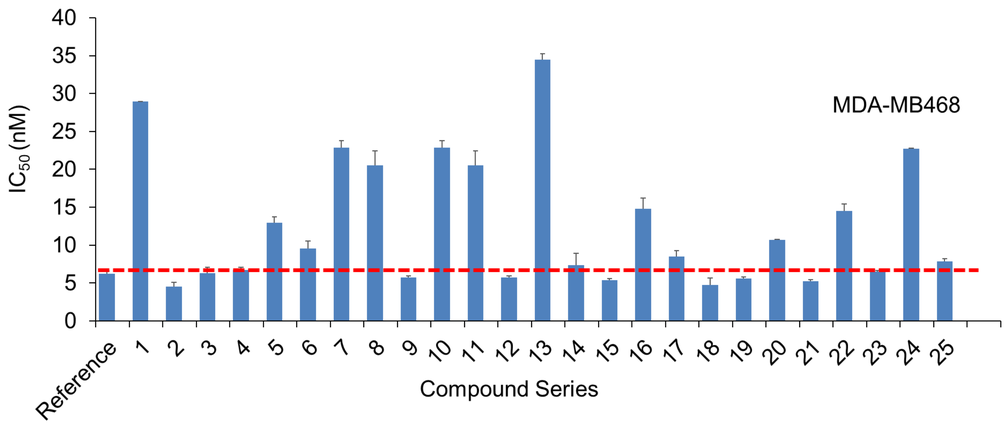


Thalidomide Pomalidomide Lenalidomide

VHL

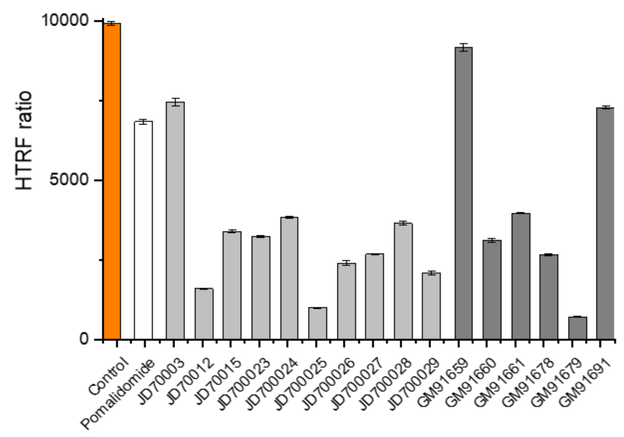


CCK-8 cell viability assay of JDB Compounds

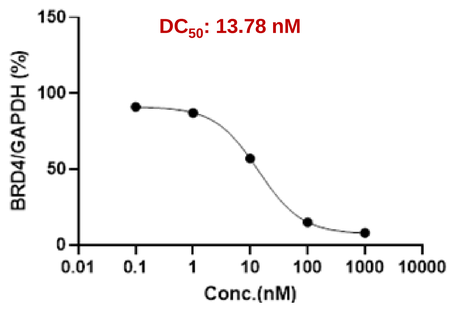


JDB payloads show improved toxicity

Binding affinity of JDB ligand



Degradation Concentration of JDB PROTAC



JDB binders showed higher binding affinity compared to Pomalidomide and excellent degradation

IP protection

Patents for scaffold compounds will be filed Q4 this year.

Partnering interest

JDB is seeking collaborative research partners that are interested in novel linkers and payloads for ADC and binders for PROTAC

For more information, please contact:

Sungmin Song, Ph.D. (+82-62-974-9380, seaflow@jdbiosci.com)

Peter Goughnour, Ph.D. (+82-2-406-9380, petergoughnour@jdbiosci.com)