New 21st Century Cures from

KDDF

KDDF
Korea Drug Development Fund

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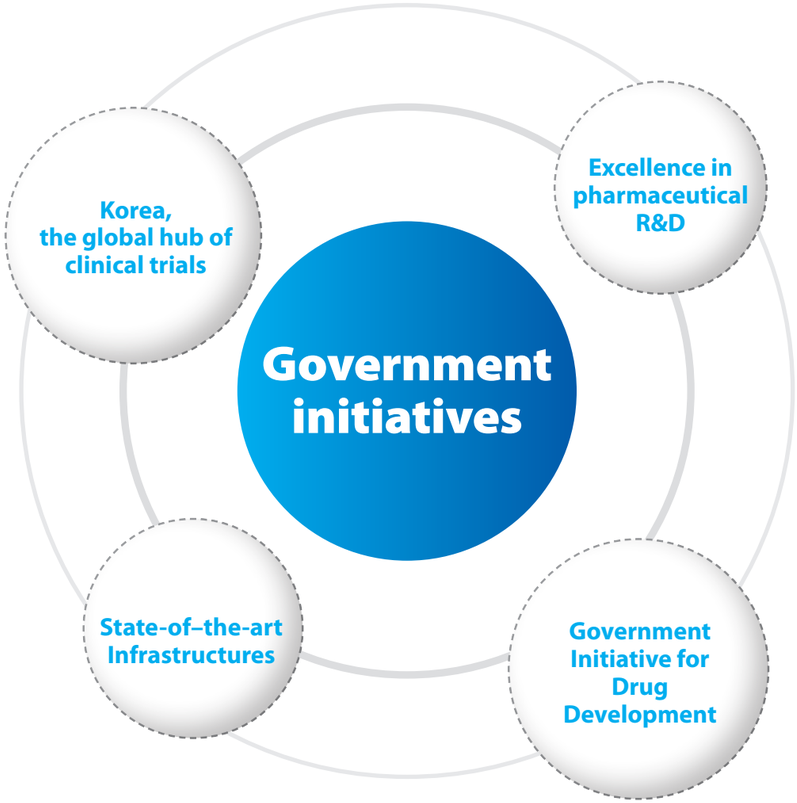
Korea Drug Development Fund

Why

"KOREA" is the perfect place for new drug development



Geographical Advantage

Korea is strategically located at the center for transportation in Northeast Asia

- 61 cities with a population of more than 1 million within a 3-hour flight from Seoul
- Korea, Japan and China boast a combined GDP of about $14 trillion
- Total population of Korea, Japan and China exceeds 1.52 billion, or 22% of the global population, and total trade volume is $5.32 trillion, or 17.6% of total world trade.
- Established the APEC Harmonization Center for regulatory harmonization within ICH guideline.
- Efforts for Regulatory Harmonization across Korea, China, Japan – Established AHC (APEC Harmonization Center, www.apec-ahc.org) and holds tripartite forum to elicit the right policy environment for life sciences innovation.

Government initiatives

The government selected the bio industry as a new growth engine and launched various initiatives to galvanize pharmaceutical industries

- **Government Initiative for Drug Development** : The government of the Republic of Korea launched the **Korea Drug Development Fund (KDDF)** in 2011 to transform Korea into the global leader for new drug development with a budget of US$1 billion.
- **State-of–the-art Infrastructures** : Korea National Enterprise for Clinical Trials(KoNECT), Korea Research Institute of Bioscience & Biotechnology(KRIBB), Korea Institute of Technology(KIT), Korea Research Institute of Chemical Technology (KRICT), Two high-tech medical clusters (Osong, Daegu)

Excellence in pharmaceutical R&D

Korea has strong human capital & research capability

- **Large pool of R&D experts** : 22,817 workers in the bio industry (36.7% of them having master's or doctor's degrees)
- **Strong Competitiveness in Basic Research**

▶ 28 Korean researchers' papers related to biotechnology published in the top 3 global science magazines (Nature, Science, Cell)
▶ Ranked 5th for number of patents (9,689 patents Statistics from the World Intellectual Property Organization in 2010)
▶ Registered 520 patents in the bio sector of the United States between 2006 and 2010, and recorded 166 in technology strength, ranking 14th.

Korea Drug Development Fund (KDDF)

We openly welcome foreign investment and partnerships with international organizations who seek to gain a competitive edge in the next ten years!

About the KDDF

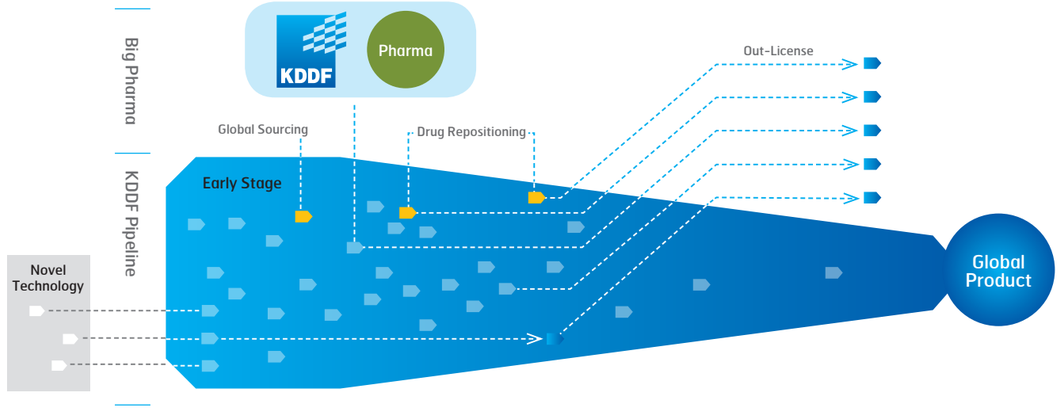
Korea Drug Development Fund (KDDF) is a government-initiated drug development program that manages a total budget of US $1 billion, backed by a collaborative effort of healthcare related Korean ministries. KDDF supports new drug development projects across discovery to clinical stage and actively builds local and global networks that will drive innovation in biopharmaceutical industry.

Acting as a neutral third party in reviewing proposals from local companies and academia, KDDF selects projects and operates through close project management linking with monetary support for developing its pipelines to be global products. KDDF currently manages over 70 selected projects (Pipeline information on http://eng.kddf.org/).

KDDF actively focuses on business development activities to commercialize its pipelines through R&D partnerships & collaborations with international organizations who seek to gain a competitive edge in the next ten years.

- Government Fund / Non-profit organization
- Global New Drug Development support
- Develop experts human resources for new drug R&D
- International networking of experts from Industry-Academia-Institute
- Business Development activities across the portfolio

KDDF Business Models



Big Pharma Customized Model

KDDF selects and manages pipelines aligned with in-license demand of Global Pharmaceutical Companies who can distribute and sell products globally.

Connect & Development Model

Adapting Open Innovation Strategy, KDDF seeks promising drug candidates to co-develop with international organizations via Global Sourcing Program and Drug Repositioning Program.

Novel & Innovative Track

Novel & Innovative Track is designed to accelerate novel and innovative technologies into pharmaceutical pipelines. Projects are guided through one of KDDF's experienced Project Manager to develop viable research-stage technologies into innovative medicines.

Selection process

- Proposal
- 1st : Applicant Presentation
- 2nd : Due diligence
- 3rd : Investment Decision
  - Technical Feasibility, Commercial Viability, IP, etc
- 4th : Milestone/Budget Adjustment
- Contract (Agreement)

KDDF Performance (As of May 2015)

266 — Proposals Received
- Industry: 146, Academia: 84, Institute: 36
- Discovery: 164, Pre-clinical: 39, Clinical: 63

72 — Funded Projects
- Industry: 49, Academia: 18, Institute: 5
- Discovery: 40, Pre-clinical: 12, Clinical: 20

9 — Licensing-Out
- Global:2, Domestic: 7
- 30M USD in Deal Value

160 — Due Diligence
- Due diligence for project selection
- 1 project/1 day

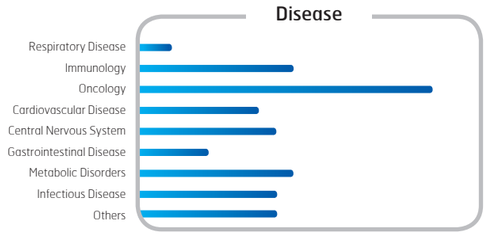
13 — Moved to Next Phase

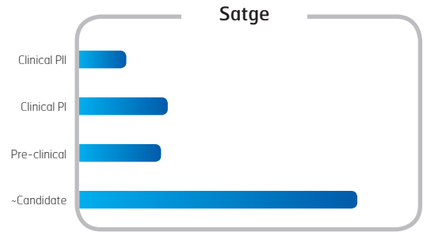
220 — Pre-Application Meeting

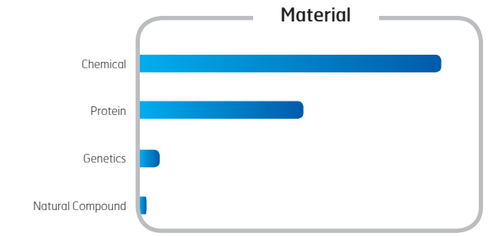
161 — Patents
- Global: 121, Domestic: 40

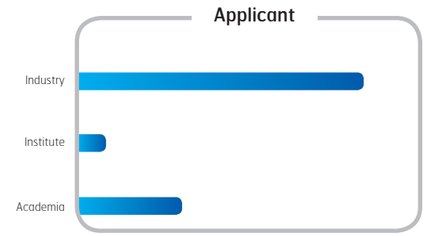
10 — Global/Domestic MOU
- Global: 6, Domestic: 4

Statistics of the Funded Projects (As of May 2015)









KDDF Pipeline (As of May 2015)

On-going (37)

Discovery (40)	Non-Clinical (12)	Phase1 (13)	Phase2 (7)
Hallym Univ. — CIPN			
Inje Univ. — T-cell lymphoma			
Asan Medical Center — NASH	HanAll — Autoimmune Disease		
Sookmyung Women's Univ. — Rheumatoid arthritis	Handok — Glaucoma		
Cellinbio — Rheumatoid arthritis	National Cancer Center — Cancer		
SNU — HIV	BIONEER — Pulmonary fibrosis	Enzychem — Neutropenia	Yungjin Pharm — COPD
Yonsei University — Osteoporosis	IPK — HCV	OliX — Hypertrophic scar	JEIL Pharm — Stroke
Ewha Womans Univ. — Diabetes	AbClon — Gastric Cancer	Hoseo Peptide — Skin infection	JW Pharm — Multiple Myeloma
Hanyang Univ. — Atopic dermatitis	ST Pharm — Anti-coagulant	CJ Healthcare — Acid Related Disorder	DINONA — Acute leukemia
UNIST — Lung Cancer	ImmuneMed — HCV, HBV	Yuhan — Degenerative disc disease	CKD — Dyslipidemia
Medytox — Diabetes	Chung-Ang Univ. — NSCLC	Oscotec — Rheumatoid arthritis	Handok — Autoimmune Disease
			Yuhan — Degenerative disc disease
			LGLS — Myocardial infarction
			SK Biopharm — Constipation/IBS
			Hanmi — Diabetes
			SK Biopharm — Epilepsy

Completed (35)

Discovery (40)	Non-Clinical (12)	Phase1 (13)	Phase2 (7)
Hallym Univ. — CIPN	NeoPhram — Lung cancer	Qurient — MDR/XDR-TB	Bukwang — Solid Cancer
CNU — Myocardial infarction	Hanmi — Diabetes	Oscotec — Rheumatoid arthritis	Daewoong — Alzheimer
Duksung Women's Univ. — Breast cancer	UAI — Melanoma	Genexine — Human Growth Hormone	LegoChem — Antibiotics
SNUH — Alzheimer	Scripps Korea — Solid Cancer	CKD — Dyslipidemia	Genexine — Human Growth Hormone
Korea Univ. — Duchenne muscular dystrophy	CNU — Blindness	LegoChem — Antibiotics	JEIL Pharm — Stroke
KIST — Depression	HanAll — Autoimmune disease	JW Pharm — Multiple Myeloma	PharmAbcine — Glioblastoma
	AEON Medix — Vaccine	Shin Poong — Osteoporosis	Green Cross — Anti-coagulant
	Kangwon Univ. — Cholangiocarcinomas		
	Ajou Univ. — Diabetic macular edema		
	Shin Poong — Myocardial infarction		
	Hyundai Pharm — Diabetes		
	KRIBB — Liver Cancer		
	Handok — Cololectal cancer		
	DINONA — Allo-islet Transplantation		

★ Licensing-Out (9)
○ Next Phase (13)

- Oncology (17)
- CV (7)
- Metabolic Disease (9)
- CNS (8)
- Infection (8)
- Immunology (9)
- GI (4)
- Respiratory Disease(2)
- Others (8)

Total : (72)

Government Initiative

Korea Drug Development Fund

Contents

JW Pharmaceutical Corporation

Clinical phase 1 Study of CWP291 in Relapsed Patients with Multiple Myeloma

Code Number : KDDF-201408-09

Development and Market Objectives

- To receive fast-track FDA approval for CWP291, a potent β-catenin inhibitor that has shown excellent antitumor activity in multiple myeloma models, as a therapeutic agent and conduct multinational clinical trial research in patients suffering from relapsed and refractory multiple myeloma in Korea and the US.
- Future commercialization through licensing and developmental collaboration with a multinational pharmaceutical company.

Unmet Medical Need & Target Patients

Target patients

- Relapsed or refractory multiple myeloma patients who have failed standard therapies.

Unmet Medical Needs

- Poor prognosis for many multiple myeloma patients, with high rates of relapse after receiving standard of care.
- Targeted therapies with lowered toxicity are needed, particularly because the majority of multiple myeloma patients are seniors.
- Novel approaches that can synergize with standard therapies are needed to increase the therapeutic options available to physicians.

Status

- Preclinical studies have revealed that CWP291 demonstrates outstanding in vitro, and in vivo anti-tumor effects through the inhibition of β-catenin, a major factor implicated in relapsed and refractory multiple myeloma cases. CWP291 also demonstrated synergism when treated in combination with standard therapies.
- In order to increase translational relevance, we conducted and confirmed CWP291's antitumor activity in additional preclinical models including mesenchymal stem cell co-culture system, patient-derived (PD) xenografts and standard treatment resistant cells.
- A phase 1 study to assess the safety, tolerability, pharmacokinetics and efficacy of CWP291 in subjects with relapsed or refractory myeloma patients has been filed and received FDA IND approval in July 2014. MFDS IND approval in Feb 2015.

Intellectual Property

- CWP291 compound-patents are granted in major markets valid until 2028.

Competitive Advantages

- First-in-class drug with potent β-catenin inhibitory effects at an early development stage in comparison to competing candidates
- Exhibits outstanding in vitro/in vivo anti-cancer effects in resistant multiple myeloma models and demonstrates synergism in co-administration with standard therapy
- Lower toxicity profile when compared to standard therapy and existing cytotoxic drugs
- Indications may be expanded to various solid tumor types that display drug tolerance due to β-catenin overexpression
- Strong patent position and guaranteed monopoly period

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AbClon Inc.

Novel HER2 targeted therapeutic antibody against Gastric Cancer

Code Number : KDDF-201408-02

Development and Market Objectives

- By successfully completing optimization studies for efficacy, pharmacokinetics and single-dose toxicity studies of an innovative antibody drug targeting HER2 for the treatment of patient with gastric cancer, our final objective is to enter preclinical development.

Unmet Medical Need & Target Patients

- Gastric cancer is third leading cause of cancer deaths worldwide, and the fifth most common cancer, with a 5-year survival rate for progressive gastric cancer patients at diagnosis of only 7%. HER2 is overexpressed in 22% of gastric cancer patients and is known to be involved in the development and progress of malignant growth. The blockbuster breast cancer treatment Herceptin was approved as a targeted treatment for HER2 overexpression in gastric cancer patients but compared to existing chemotherapy, the average survival rate is only extended for 2.7 months and the response rate is 47%, indicative of a limited effect. Therefore, new drugs that can increase the survival and response rates of gastric cancer patients with HER2 overexpression are urgently needed.

Status

- Development of stable cell lines for pharmacokinetics and toxicity studies.
- Efficacy profiling in HER2-expressing cancer cells.
- Studies for mechanism of action.

Intellectual Property

- National patent registered (10-1453462, HER specific-binding antibody): Specific CDR listed antibody and/or antigen binding fragment and pharmaceutical composition which includes use for preventing or treating breast cancer or gastric cancer.
- National patent applied (10-2014-0109642, HER specific-binding antibody): CDR listing, antibody with specificity for the CDR3 area in light and heavy chains and/or its antigen binding fragment and pharmaceutical composition which includes its use for preventing or treating breast cancer or gastric cancer.
- PCT application (PCT/KR2014/004317, HER specific-binding antibody): Combined antibody with a specific CDR listing and/or antigen binding fragment and pharmaceutical composition which includes its use for preventing or treating breast cancer or gastric cancer.

Competitive Advantages

- Limited therapeutic options are available for the treatment of patients with gastric cancer, so there is a big potential for clinical development and a large market size.
- Novel anticancer activity based on distinct mechanism of action compared to the existing antibody therapeutics.
- Shows superior anticancer efficacy in combination with Herceptin compared to Herceptin single treatment and combination treatment of Herceptin and Perjeta.
- Shows anticancer activity in some HER2-positive and Herceptin-resistant cancer cells.

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National Cancer Center

Anti-cancer antibody therapeutics, anti-AITR

Code Number : KDDF-201408-11

Development and Market Objectives

- Anti-AITR has been characterized in human PBMC and humanized mouse model. It polarized Teff to Th1 and converted Treg to Th1, and suppressed human cancers in HLA-match humanized mice. We plan to develop the antibody as an anti-cancer drug by taking steps of nonclinical and clinical trials.

Unmet Medical Need & Target Patients

- Our newly developed anti-AITR converts Treg to Teff cells, and then activates effector T cells, which enables to trigger potent and comprehensive anti-tumor activities, and thus provide therapeutic effects for all types of hematologic and solid cancers.

Status

- The antibodies are being validated and optimized.

Intellectual Property

- Patents are being applied.

Competitive Advantages

- Polarization of Treg to Th1 and activation of $CD8^+$ T cells.

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Dinona Inc.

Phase I study of a novel therapeutic antibody, DNP001 in acute leukemia

Code Number : KDDF-201406-09

Development and Market Objectives

Target patients

- JL1-positive acute leukemia patients and myelodysplastic syndrome (MDS) patients.

Unmet Medical Needs

- Adult patients with ALL and AML have a long term disease-free survival rate of only 30-40%, and 20-30%, respectively, even with chemotherapy and bone-marrow transplantation. Of particular note, the 5-year survival rate for patients over 65 years of age in the AML patient group remains below 10%, and has not improved for decades (Lancet 2013;381:484-495).
- The primary reasons for the prevailing unsuccessful treatment of acute leukemia are due to recurrence of the disease, and the side effects of chemotherapy and bone-marrow transplantation, which contribute to a high mortality. Bone-marrow transplantation in particular is only attempted for leukemia patients that cannot be treated with chemotherapy. However, for high-risk AML and ALL, patients only survive long term and disease-free at rates of 20-30% and 30-40%, respectively, even after bone-marrow transplantation (Bone Marrow Transplant. 2005, 36_1021).
- To increase the long term survival rate and number of effective treatments for acute leukemia, we need to develop a curative alternative to bone-marrow transplantation and develop therapeutics that can reduce toxicity and retain remission. Novel therapies to overcome multidrug resistance without increasing toxicity are also needed, as well as techniques that can effectively destroy minimal residual disease with a high risk of recurrence and effective medicines for relapsed patients.

Status

- Clinical phase 1 testing for DNP001, a new antibody treatment for acute leukemia, is currently in progress at Seoul Asan Hospital in KOREA and is expected to be completed by the end of 2015.

Intellectual Property

- 28 patent registrations approved, 4 applications under examination
- Registered Countries: South Korea, United States of America, Japan, Australia, Mexico, Singapore, Canada, Europe, Germany, Indonesia, Philippines, India
- Countries where application has been lodged and is under examination: Brazil, Israel, Vietnam
- Title of Patent: Acute leukemia and lymphoma-specific CD43 epitope and use thereof.
- Patent Registration Number/ Registration Date

- USA, 7,622,560 / 2005.12.20
- USA, 8,426,555 / 2009.10.09
- USA, 8,753,636 / 2013.03.15
- KOREA, 10-0738401 / 2005.08.24

Competitive Advantages

- Epitope-specific antibody that selectively binds to leukemia cells, while leaving other cells unaffected.
- FIH (First-in-Human) trial antibody with a novel target for acute leukemia.
- An ADCC-reinforced antibody via defucosylation.
- There is a market with high unmet needs and potential for sustainable growth.

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Inje University

Validation of synthetic small-molecule lead compound to develop anti-cancer drug for T-cell lymphoma and finding its mechanism of action

Code Number : **KDDF-201406-06**

Development and Market Objectives

- Validation of synthetic small-molecule lead compound to develop anti-cancer drug for T-cell lymphoma and finding its mechanism of action.

Unmet Medical Need & Target Patients

- Patients with peripheral T-cell lymphomas have often been relapsed or refractory about conventional therapy. Since their 5-year survival rate is below 30%, effective first-line treatments are needed. Vincristine, a well-known microtubule inhibitor, is widely used but its effective capacity is restricted due to severe peripheral neurotoxicity. The development of new therapeutic drug targeting microtubule with low peripheral neurotoxicity and a strong cytotoxic effect toward T-cell lymphoma is urgently needed.
- The development of new drug with minimal side effects and that can be used in combination with other therapies is needed.

Status

- Efficacy against T-cell lymphoma has been confirmed with the lead compound that induces microtubule depolymerization.
- We are currently analyzing the effectiveness of the lead compound, together with multilateral evaluation of peripheral neurotoxicity and investigating the mechanism of action.

Intellectual Property

- Domestic patent and PCT application have been completed.

Competitive Advantages

- Can effectively eliminate T-cell lymphoma that exist within both lymphatic and non-lymphatic organs
- Has high drug selectivity for not only for T-cell lymphoma, but also tumor cells arising from other lymphocytes
- Has low peripheral neurotoxicity at effective concentrations
- Has strongly cytotoxic effects toward multidrug-resistant T-cell lymphoma
- Can be used in combination with other therapies

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Ulsan National Institute of Science and Technology (UNIST)

Development of cancer therapeutics targeting mitochondrial TRAP1

Code Number : **KDDF-201312-06**

Development and Market Objectives

- To identify a lead compound from mitochondria-targeted TRAP1 inhibitors with a drug delivery mechanism.

Unmet Medical Need & Target Patients

Target patients:

- Cancer patients with malignancies exhibiting a TRAP1 overexpression phenotype

Unmet medical needs:

- Despite increases in cancer incidence due to an aging population, the development of effective anti-cancer drugs remains elusive.
- Anti-cancer drugs with noble mechanism of action are required for the treatment of patients who do not respond to conventional anticancer therapeutics and to overcomedrug resistance to conventional chemotherapy.
- Novel therapeutics are required for combination treatment with conventional anticancer drugs.

Status

- The inhibitor development program has been initiated lately and analysis protocols to examine target protein inhibition and action mechanism-of drugshave been established. In addition, high-resolution protein 3D structural informationhas been obtained from the inhibitor-TRAP1 co-crystals.
- Design and synthesis of TRAP1 inhibitors are currently progressing in order to select a lead compound with outstanding safety and efficacy parameters.

Intellectual Property

- Patents have already been filed for a first-in-class mitochondria-targeted TRAP1 inhibitor showing anticancer activities in vitro and in vivo. Ourdrug development program aims for not only an effective cancer drug but also a patentable drug that does not infringe any existing intellectual property.

Competitive Advantages

- First-in-class cancer drug development with novel mechanism of action delivering inhibitory compounds to the organelle
- Structure-based drug design, using high resolution protein crystal structures ofhuman TRAP1 protein complexed with its inhibitors
- A novel approach to increase drug efficacy by, incorporating both the target inhibitory moiety and drug delivery system to the relevant organelle.
- Drug combination with various anti-cancer drugs currently used in clinic could synergistically enhance their therapeutic potential.

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Chung-Ang University

Optimization of reversible small molecule inhibitors for EGFR T790M

Code Number : 201208-07

Development and Market Objectives

- Our objective is to develop an effective anti-cancer drug for Non-small cell lung cancers (NSCLC) that express the EGFR T790M mutation, with resistance to tyrosine kinase inhibitors.
- We aim to develop a preclinical candidate substance and reversible small molecule inhibitor with specificity for EGFR T790M.

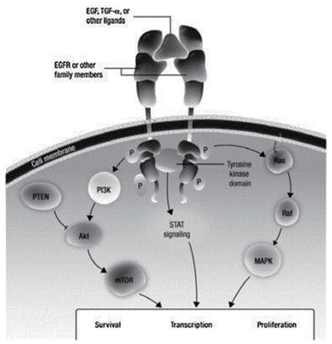

Figure 1. EGFR signal transduction pathways. With the binding of ligands such as EGF, the EGFR family receptors form homo- and heterodimers for full activation (Lung Cancer, 2012, 131).

Unmet Medical Need & Target Patients

- EGFR is a receptor tyrosine kinase involved in cell survival and proliferation. The overexpression of EGFR and activating mutations are associated with the occurrence of several cancers. One prominent example is non-small cell lung cancer (NSCLC).
- EGFR overexpression can be identified in approximately 40-80% of patients with non-small cell lung cancer and is closely associated with a very poor prognosis. Approximately 90% of patients exhibiting abnormal expression of EGFR harbor a deletion of Exon 19 or the L858R mutation. Of these, NSCLCs with acquired resistance to first-line EGFR TKIs expressing the EGFR T790M mutation constitute our target patient population.
- Gefitinib (Iressa) and erlotinib (Tarceva) are Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitors (EGFR-TKIs) with high initial efficacy as anti-cancer drugs. However, the emergence of resistance remains a major problem and no available treatment exists for resistant cancers arising from the T790M mutation.

Frequency of acquired resistance mechanisms for EGFR-TKI

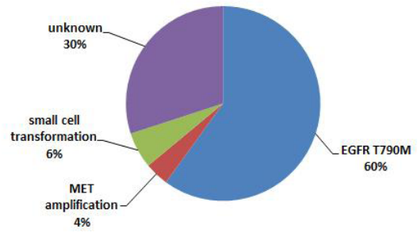

Figure 2. Frequency of resistance mechanisms against EGFR TKIs (Clinical Cancer Research, 2011, 5530).

- Resistance occurs within an average of 6-14 months after administration of EGFR-TKIs to patients with NSCLC. Approximately 60% of resistance arises through the T790M point mutation and no treatment options exist for this condition.
- Recent studies on pan-HER inhibitors and irreversible EGFR T790M inhibitors have been conducted. However these candidates inhibit the wild-type form of the receptor, leading to significant cytotoxicity.
- Therefore, a selective inhibitor for the EGFR T790M (EGFR Mutant-Selective Inhibitor, EMSI) is urgently needed to suppress first & second-line NSCLCs. The development of irreversible inhibitors has the advantages of lower development costs and increased development speed.

Status

- We will ensure mutant selectivity for our TKI candidates (via in vitro kinase assays) and select compounds that exhibit a binding affinity for T790M that is at least 500 times higher than existing drugs.
- By analysing changes in IC50 dependent upon ATP concentrations, candidates that are reversible inhibitors can be identified and excluded.
- Candidates that exhibit inhibitory effects against cell proliferation in the H1975 line with T790M mutation will be selected for further studies in other cell lines.

Intellectual Property

- Among our candidate compounds, some were registered for patents, with additional patents to be applied for based on future research results.

Competitive Advantages

- The existing irreversible panHER inhibitor effectively inhibits T790M, but shows little efficacy in clinical settings. If the dosages are increased for effective treatment, side effects (including rash and diarrhea) are very serious, due to the irreversible inhibition of wild-type EGFR.
- Currently, two candidates that are T790M selective and irreversible inhibitors are being prepared for clinical Phase 1, but some difficulties in development are expected due to concerns with unpredictable side effects and the absence of PK parameters.
- Our candidate is highly selective to T790M and importantly, exhibits extremely low affinity for EGFR wild-type. Therefore, less concern exists regarding dose-limiting toxicity which is a major issue for EGFR-TKIs.
- In addition, as opposed to reversible inhibitors, there is relatively less concern about the expected drawbacks of irreversible inhibitors. This enhances the competitiveness of our candidate.

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DUKSUNG WOMEN'S UNIVERSITY

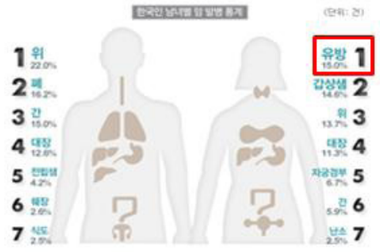
Development of Innovative Drugs for Breast Cancer

Code Number : KDDF-201110-12

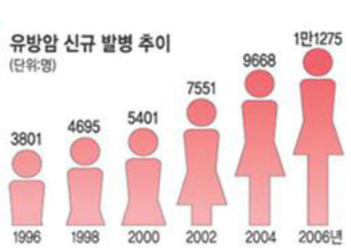
Development and Market Objectives

- We previously identified the membrane protein DS-20, which plays a key role in the growth of breast cancer and infiltrative induction, as a novel target for breast cancer. The final goal of this research is to derive a DS-20 inhibitor candidate for the development of innovative breast cancer treatment. We also aim to enter the pre-clinical stage by deriving DS-20 inhibitor candidate material, before entering the clinical stage.
  - Chemical library screening for DS-20 inhibitors
  - Development of leading material and optimization
  - Determination of pharmacology and pharmacodynamics parameters
  - Development of pre-clinical candidate material.

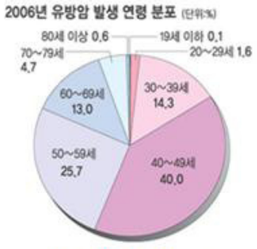
Unmet Medical Need & Target Patients



보건복지가족부 중앙암등록본부, 2008



대한유방암학회, 2008



대한유방암학회, 2008

- Breast cancer is the most common cancer affecting women in Korea. (Data: Central Cancer Registration Office of the Ministry of Health, Welfare and Family).
- Recently, the Korea Breast Cancer Academy reported that 1 in 25 Korean women will experience breast cancer during their lifetime, a 3.5-fold increase from 1996 to 2008. This increase in the incidence of breast cancer is the highest among the OECD countries at 91% (Based on research by the Korea Breast Cancer Academy in 2011).
- When examining the risk of breast cancer by age, more than half of patients are under 40 (55.7%), showing that the age of breast cancer patients in Korea is very young compared with patients in the USA and Europe (Based on research by the Korea Breast Cancer Academy in 2008).
- Breast cancer also exhibits a high reccurrence rate, and no treatments exist for Triple Negative Breast Cancer (TNBC; ER, PR, Her-2 negative) patients.

Current status of breast cancer treatment

- The most basic breast cancer treatment is surgery, and this is applied to patients who do not exhibit metastasis in other organs. For breast cancer, the effects of adjuvant therapy after operation are generally good, and these therapies can include chemotherapy, radiation treatment, antihormone therapy and molecular target inhibition. The use of these adjuvant therapies is decided based on the stage of cancer, relevance of receptor status and the type of operation (source: Seoul University Hospital).
- Problem and requirements for current breast cancer treatment: Insufficient options for TNBC patients
- Among breast cancer patients, 75% are in the ER-positive patient group, 20-25% are in the HER2 (Human Epidermal Growth Factor Receptor 2)-positive patient group, and 10-17% are in the triple negative patient group.
- The majority of current breast cancer treatments target ER and HER2. These include herceptin, an antibody, and tamoxifen, antihormone therapy. Tamoxifen obstructs the estrogen receptor while herceptin obstructs overexpressed HER2 in breast cancer.
  - However, no distinctive treatment for TNBC patients exists
- Need to develop targeted therapies that only attack cancer cells: Anticancer drugs target constantly dividing cancer cells, causing side effects in other organs that also require cell proliferation in order to function. Targeted therapy protects normal cells, selectively controlling specific target factors in cancer cells. Current targeted treatments include treatment for chronic myelocytic leukemia (Gleevec) which targets BCRABL and breast cancer treatment (Herceptin) that targets HER2, as well as a new vessel creation inhibitor (Avastin) that targets VEGF. However these are still insufficient for many patients.
  - As the biggest cause of death for cancer patients is metastasis, the development of a targeted treatment for the core factors that induce metastasis is needed, as well as the development of targeted molecules for the treatment for TNBC.

Status

- We are currently conducting 1st hit through 1st screening, based on the chemical library provided by Dong-a Pharmaceutical Company and we are also processing in vitro biological assays for identified 1st hits.
- We have produced a mutant to induce the core domain that contributes to a breast cancer transformation mechanism, based on structural research of DS-20.
- We are performing virtual screening by constructing the DS-20 homology structure, based on similar proteins.

Intellectual Property

- Subject of invention: Anticancer composition.
- Name of inventors: Aree Moon, Myoung Ok Kim, Jin Sun Hwang.
- Contents of invention: This invention is for an anticancer compound including DS-20, which is a protein involved in the lower signal passing course of the Ras protein and inhibitors of the coding gene, useful for the prevention and treatment of cancer.

Competitive Advantages

- Candidate materials targeting DS-20 discovered through leading research will represent a new mechanism of breast cancer control. This creates the potential for an original anticancer drug to be developed.
- There is room to apply and expand our research results for other kinds of cancer in addition to breast cancer.
- Through the experience of developing original anticancer candidate material, our team will be better able to develop new drugs in future.
- Our research team will contribute to the development of innovative breast cancer treatments by deriving successful DS-20 inhibitor candidate material, with the goal of entering into the pre-clinical phase.
- This research will proceed with the close cooperation of Dong-A Pharmaceutical Company, a leading company in Korea's pharmaceutical industry, and a company that has successfully developed novel medicines in the past.

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Bukwang Pharmaceutical Co.,Ltd.

BUKWANG PHARM. CO., LTD.

Evaluation of the Safety, Pharmacokinetics and Efficacy of YN968D1 in Subjects with Solid Tumors

Code Number : KDDF-201112-03

Development & Market Objectives

- YN968D1, a small molecule anti-cancer drug candidate, inhibits the growth and metastasis of tumors by selectively binding to VEGFR-2, thereby inhibiting the angiogenesis necessary for the growth of cancer cells. Its biggest advantage is its significantly fewer side-effects and superior anti-cancer efficacy in comparison to existing chemotherapy. Preclinical trials in animal models, as well as clinical trials in humans have proven superior efficacy and lower toxicity. Based on this evidence, we aim to develop YN968D1 as an anti-cancer drug with superior efficacy and lower toxicity compared to other angiogenesis inhibitors.
- In the US and Korea, clinical Phase 1 assessments in patients with solid tumors are underway.

Unmet Medical Need & Target Patients

- In the US, the cases of patients with solid tumors are approximately 1.3 million per year. Worldwide, approximately 6 million patients are diagnosed with solid tumors on an annual basis (Source, American Cancer Society; Center for Disease Control).
- The market for targeted anti-cancer drugs is continuously growing and is expected to exceed $24,821 million in 2020 (Source, Datamonitor 2011)
- Current chemotherapy drugs are often associated with serious side effect such as nausea, vomiting, alopecia, hepatotoxicity, renal toxicity, leukopenia and thrombocytopenia.
- In recent years, the development of targeted anti-cancer drugs that are different from conventional chemotherapy has been a focus of renewed attention. Targeted therapy using monoclonal antibodies have a high unit cost for production and low stability and patients are required to visit hospitals for intravenous administration.
- In order to solve these problems, low molecular weight targeted anti-cancer drugs with low production costs, excellent stability and oral administration are being developed, however, various side-effects are still observed due to multi-kinase receptor targeting.
- Therefore, the development of small molecule angiogenesis inhibitors with less side-effects and higher specificity is urgently needed.

Status

- In China, clinical Phases 2/3 for YN968D1 have been completed with advanced or metastatic gastric cancer patients and clinical Phase 3 on advanced or metastatic gastric cancers is underway. Currently, YN968D1 is at the stage of product licensing and it is expected to receive SFDA approval for gastric cancer and enter the market in the middle of 2013.
- In order to increase the number of diseases for which the drug is efficacious, a total of six clinical trials, including two trials of non-small-cell lung cancer and triple-negative breast cancer, and one trial of liver cancer and colorectal cancer, are underway in China.
- Additionally, in order to enter the global market, clinical Phases 1/2a for solid tumors are underway in the US and Korea.

Intellectually Property

- Developer: Advenchen Laboratories (US)
- License: Hengrui (China), LSK BioPartners (US), Bukwang Pharmaceutical Co., Ltd (Europe, Korea, Japan)
- Information on Patents

Country	Patent No.	Patent title
US	US 7,129,252 B2	Six Membered Amino-Amide Derivatives as Angiogenesis Inhibitors
WO	WO2005/000232 A2	
Europe	EP 1633712 A0	
Japan	JP 5046643	
Canada	CA 2568608	
Korea	KR 10-1159034	

Competitive Advantages

- High potent and specific VEGFR-2 inhibitor (IC_{50}, 1 nM)
- Low production cost, as synthetic small molecule
- Broad spectrum and potent anti-cancer activities (CRC, NSCLC, HCC, Gastric, Breast)
- Product licensing is underway in China

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Scripps Korea Antibody Institute

SKAI 스크립스코리아항체연구원 Scripps Korea Antibody Institute

Identification of candidate antibody molecules for inhibiting tumor angiogenesis

Code Number : KDDF-201210-05

Development and Market Objectives

- This project aims to develop optimized anti-angiogenic antibody lead substances through a three-step optimization process, using in vitro characterization and efficacy analysis to identify the final candidate antibodies.

Unmet Medical Need & Target Patients

Target patients

- Patients with malignant tumors (inhibition of tumor angiogenesis).

Unmet medical needs

- Bevacizumab (Avastin®) is a U.S. Food and Drug Administration-approved anti-angiogenic therapeutic antibody currently used in clinics and occupied a market share of $590 million in 2012.
- However, Bevacizumab has the following limitations:
  - No significant efficacy as a single therapeutic agent.
  - Distinct side effects, including hypertension, proteinuria, bleeding, and gastrointestinal perforation.
  - Limitations of cancer therapy due to drug resistance issues.

Status

- Target validation and selection of anti-angiogenic antibody lead substances have been completed in previous studies. A three-step optimization process is currently under development.

Intellectual Property

- U.S. provisional application: Targeted inhibition of angiogenesis by C-type lectin domain specific human antibodies against clec14a tumor endothelial cell marker 61/659,654
- PCT application: Novel antibody specific for clec14a and uses thereof PCT/KR2012/008618
- Provisional application for the patent was lodged on June 14, 2012, with conversion to a PCT patent on October 19, 2012. The broad scope of rights includes the lead substances (antibodies) and epitopes, diagnostic and therapeutic compositions, kits, and methods for cancers and angiogenesis-related diseases

Competitive Advantages

- Higher likelihood of development of a first-in-class drug through preclinical and clinical trials due to no development of therapeutic antibodies against the target molecule.
- A broad range of intellectual property rights have already been secured, including development of antibodies and epitope identification.
- Superior anti-angiogenic treatment efficacy is expected through mechanisms distinct from the existing therapeutic antibody, Bevacizumab.
- Developed antibodies are expected to have fewer side-effects because human antibodies have lower immunogenicity and exclusively target tumor blood vessel-specific antigens for specific targeted therapy.
- Because the developed antibodies will be functional domain-specific antibodies that build on existing therapeutic antibodies and surpass their limitations, the time, effort, and costs associated with development are reduced. It is therefore expected that the wide range of industrial applications for the developed antibodies will enable a ripple effect superior to existing therapeutic antibodies.
- Treatment can be applied to a variety of cancers through specific targeting of tumor blood vessels.
- Treatment can be applied to several other diseases that require inhibition of angiogenesis, such as glaucoma and macular degeneration.
- The antibodies under development can induce endocytosis through the cross-linking of antigen, underscoring an original technology for novel anti-cancer drug development that may be used as a platform technology for antibody-drug conjugates.

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PharmAbcine

PharmAbcine
Antibody Therapeutics for Life

Completion of phase II clinical trial with Tanibirumab, a Novel Anti-cancer Therapeutic Antibody

Code Number : KDDF-201210-14

Development and Market Objectives

- The safety and tolerability of the monoclonal antibody Tanibirumab with be examined in Phase1 in targets of patients with advanced or metastatic cancers. subsequently, the safety and tolerability of the drug will be further examined in phase 2a Clinical trial in Patients with recurrent brain tumors (glioblastoma, GBM) If successful, additional disease application study will be conducted in the global market.

Unmet Medical Need & Target Patients

- Glioma is a type of malignant tumor that accounts for 60% of all primary brain tumors. Except radiotherapy, no specific treatment currently exist. In particular, Gliobalstomas (GBM) are classified as the most malignant, and are often highly resistant to radiotherapy and chemotherapy. Major reasons for a lack of effective treatment options include a poor understanding of neurobiology and the fact that drug delivery is hampered by the blood- brain barrier.
- Despite rapid development over the past 30 years and the introduction of new anti-cancer drug Temozolomide, the median overall survival rate for patients with GBM is only 14.6 months with some patients exhibiting significant resistant to Temozolomide. Thus, GBM remains a largely incurable disease and the development of novel anti-cancer drug is urgently needed.
- The majority of existing anti-cancer are unable to pass through the blood-brain barrier and their efficancy remains are not to be. Verified The unmet medical needs for the treatment of GBM can be summarized as follows. ① Development of novel therapeutic strategies. ② Development of drugs that are effective in lowering resistance to Temozolomide. ③ Development of personalized treatments for patients who exhibit different clinical benefits

Status

- Tanibirumab an anti-cancerdrug candidate is currently in phase 1 clinical trial for patients with advanced or metastatic cancers in Korea. This phase 1 is excepted to be completed by the second half of 2013.

Intellectual Property

Registration Date	Registration No.	Applicant	Title
2009.02.05	10-0883430 Korea	PharmAbcine /KRIBB	HUMAN MONOCLONAL ANTIBODY NEUTRALIZING VASCULAR ENDOTHELIAL GROWTH FACTOR RECEPTOR AND USE THEREOF
2012.09.14	5086430 (Japan)	PharmAbcine /KRIBB	HUMAN MONOCLONAL ANTIBODY NEUTRALIZING VASCULAR ENDOTHELIAL GROWTH FACTOR RECEPTOR AND USE THEREOF
2012.12.05	2012113000071360 (China)	PharmAbcine /KRIBB	HUMAN MONOCLONAL ANTIBODY NEUTRALIZING VASCULAR ENDOTHELIAL GROWTH FACTOR RECEPTOR AND USE THEREOF

- Patent registration has been completed in Korea, Japan and China. The patent application is currently under review in the us, Canada, Australia, singapore and at the European Patent Office

Scope of rights

- ScFv and IgG molecules neutralizing vascular endothelial cell growth factor receptor (VEGFR) with combinations of 19 species in the light chain variable region, including the light chain of Tanibirumab as well as the heavy chain variable region.
- Composition of the molecule for the inhibition of angiogenesis in paragraph 1.
- Composition of the molecule for cancer treatment containing molecule in paragraph 1.

Competitive Advantages

- A strong market cap exists in the field of angiogenesis inhibitors.
- Tanibirumab is a fully human antibody therapeutic agent, the most suitable antibody type for therapeutic application in humans
- Due to selective binding affinity to the vascular endothelial growth factor receptor-2 (VEGFR-2) a primary regulator of tumor angiogenesis, minor side-effects are anticipated. In addition, due to its IgG1 subtype, it is expected to exhibit enhanced therapeutic efficacyvia antibody dependent cell mediated cytotoxicity(ADCC)
- It is the only therapeutic antibody containing cross species reactivity for VEGFR-2 in rodents Translational research opportunities are therefore available and selection of optimal indications can be determined. As a result, the success rate in clinical trials is expected to increase.
- Through process development, the yield has been improved (> 1.5 g/L).

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Kangwon National University

KNU 강원대학교 KANGWON NATIONAL UNIVERSITY

Preliminary non-clinical study of a therapeutic antibody candidate for the treatment of cholangiocarcinomas

Code Number : KDDF-201212-12

Development and Market Objectives

- Our developmental goal is to analyze the pharmacokinetics, single-dose toxicity, and antitumor activities of Ab417 human monoclonal antibody that binds to both human and mouse L1CAM with high affinity. We aim to conduct single-dose toxicity tests in mice and carry out research to optimize antitumor efficacy using mouse models of human bile duct cancers. Our immediate goal is to enter the pre-clinical stage.

Unmet Medical Need & Target Patients

- Target patients include those with intrahepatic bile duct cancer, extrahepatic bile duct cancer and gallbladder cancer.
- The survival rate for bile duct cancer patients is less than 5 percent. Although bile duct cancer is not as prevalent as many other types of cancer, the 5-year overall survival rate is among the lowest, after pancreatic, lung and liver cancer.
- As of 2012, only 13 out of 144 clinical tests being conducted worldwide on bile duct cancer are EGFR/VEGFR targeted therapy tests. In order to improve bile duct cancer treatment, various targeted therapies must be further developed.

Status

- We are currently in the stages of cell line development for mass production of human monoclonal antibody that will be used for conducting PK, toxicity and efficacy studies.

Intellectual Property

- A novel monoclonal antibody specific to the L1CAM, A hybridoma producing the same and a method producing the same (licensed number 0756051, license date 2007.08.30).
- A composition for treating L1CAM-expressing cancer comprising an inhibitor of activity or expression of L1CAM and anticancer agent (application number 2008-0118921, application date: 2008.11.27 PCT/KR2009/007056).
- A pharmaceutical composition for treating cholangiocarcinoma, a method for inhibiting growth or invasion of cholangiocarcinoma and a method for treating cholangiocarcinoma.

Country of Application	Date of Application	Application Number	Date of Registration	Registration Number
Australia	2009.3.12	2007288620		
Brazil	2009.2.25	0715844-0		
Canada	2009.2.23	2,661,669		
China	2009.4.21	200780039170.9		
Europe	2013.11.27	2054083		
Indonesia	2009.2.23	W00200900471		
India	2009.3.6	474/MUMNP/2009		
Philippines	2009.2.23	1-2009-500353		
Japan	2009.2.23	2009-525498		
Mexico	2009.2.23	MX/A/2009/002064	2012.4.9	297926
USA	2009.2.20	12/438,354	2012.4.10	8153122
Vietnam	2009.3.23	1-2009-00568		
Korea	2007.7.1	2007-0084868	2009.12.07	931976

- Humanized antibody against human L1CAM and method for preparing the antibody (application number 10-2012-00092965, application date 2012.8.24)
- Antibodies specifically binding to L1CAM in humans and mice, and use thereof (application number: 10-2011-0130590, application date: 2012.11.16).

Competitive Advantages

- Currently holding patents for targets of bile duct cancer treatment and antibodies.
- Antibody binding to both human and mouse L1CAM provides efficient testing of toxicity, PK, and efficacy in mouse models.
- Bile duct cancer therapeutics are categorized as orphan drugs, reducing the time for clinical studies and leading to faster market penetration.
- The L1CAM targeting antibody may have applications in bile duct cancers as well as the treatment of other tumors expressing L1CAM.

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ST PHARM, Co., Ltd.

Development of oral low molecular weight heparin, STP02-3725, as an anticoagulant drug

Code Number : KDDF-201408-03

Development and Market Objectives

- To develop a new orally absorbable anticoagulant by performing efficacy study, process development and manufacture, PK/PD/TK study, and by verifying mechanism of action for preclinical studies.

Unmet Medical Need & Target Patients

Target Patients

- Deep vein thrombosis & pulmonary thromboembolism
- Atrial fibriliation
- Cancer associated thrombosis

Unmet Medical Need

- Explore orally absorbable anticoagulants to replace the intravenous regimen of heparin.
- High demands for new anticoagulants to replace vitamin K antagonist warfarin showing severe toxicity, drug-drug interactions and slow reaction rate.
- Improved antithrombotic effect and safety than FXa inhibitors' (aka Xaban series).

Status

- A novel low molecular weight heparin used in the treatment of venous thrombosis and the prevention of thromboembolic events has been developed by adopting bile acid derivatives.
- Excellent Factor Xa activity
- Good PK properties in rodent
- POC PD assay in DVT rodent model completed
- No toxicity issues observed in 14-day DRF studies (rat & monkey)

Intellectual Property

- Strong IP positions of the lead substances and ready for the advanced and process patent filings of the back-up series.

Competitive Advantages

- New oral delivery technology of low-molecular weight heparins using tetraDOCA.
- Planning high efficacy and de-risk on the bleeding side-effect.
- Ample network with global pharmaceutical and biotech companies and diverse business development experience.

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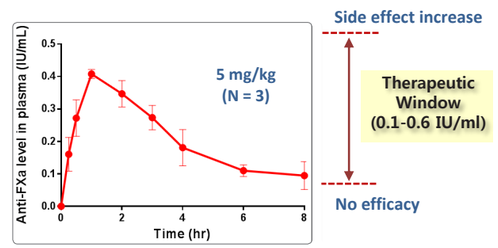
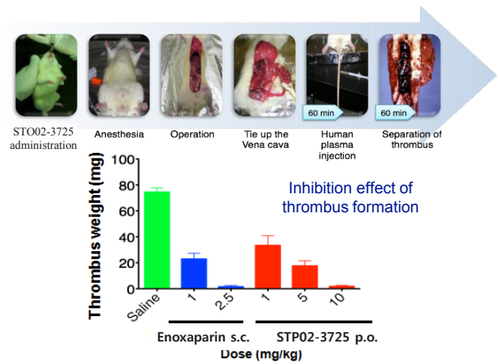


▲ Pharmacokinetic Study in rat



▲ Pharmacodynamic Study

Chong Kun Dang Pharmaceutical Corp.

Development of the CETP inhibitor CKD-519 for the treatment of dyslipidemia

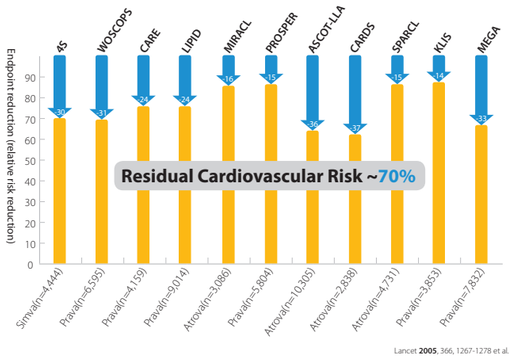
Code Number : KDDF-201406-01

Development and Market Objectives

- CKD-519 is developed by CKD Pharmaceutical Corp, is a CETP inhibitor that finished pre-clinical and is waiting for IND approval. It increases in-vivo HDL-C levels, subsequently slowing the progression of atherosclerosis and decreasing overall cardiovascular risks through the inhibition of CETP.

Unmet Medical Need & Target Patients

- The ability to increase HDL-C levels via the inhibition of CETP can reduce the residual risks of cardiovascular diseases (CVDs).
- CVDs are responsible for over 17.3 million deaths per year and remain the leading cause of deaths worldwide. Dyslipidemia features prominently as one of the major determinants of CVD risk.
- Over the past two decades, pharmacological prevention strategies for atherosclerotic CVDs have focused on reducing levels of low-density lipoprotein cholesterol (LDL-C). In practice, however, full compliance with statin therapy and the achievement of current LDL-C goals corresponds to only a ~30% risk reduction for major cardiovascular events, leaving a ~70% residual risk.



Lancet **2005**, 366, 1267-1278 et al.

▲Statin Effects on CV Event Reduction and Residual Risk

- A promising alternative target is HDL-C. Genetic and epidemiologic data support the hypothesis that pharmacological intervention to raise HDL-C can translate into significant reductions in cardiovascular events in dyslipidemic patients.
- Cholesterol ester transfer protein (CETP) is responsible for the transfer of neutral lipids (cholesteryl ester and triglyceride) between HDLs and apoB-containing lipoproteins (VLDL & LDL).
- Generally, physician satisfaction is the lowest with high-density lipoprotein cholesterol (HDL-C)-raising treatment, as this lipid type exhibits uncontrolled levels for the highest reported proportion of patients (at around 30%) in the 7 major pharmaceutical markets.
- The current treatments available for increasing HDL-C include nicotinic acid (+30%) and fibrates (+20%), both of which are unsatisfactory. In addition, nicotinic acids cause adverse effects (including flushing) which limit adherence.
- In contrast, CETP inhibition with anacetrapib or evacetrapib raises HDL-C levels by approximately 138% while decreasing LDL cholesterol (LDL-C) levels by approximately 40%. Physicians have reported that the ability to raise HDL-C levels using antidyslipidemics is their greatest need in the treatment of dyslipidemia.
- Cholesterol ester transport protein inhibitors represent a novel class of antidyslipidemics with the potential to provide significant opportunities in the dyslipidemic market.

Status

- GLP toxicity study and ADME study was finished in 4Q, 2013 and there is no significant findings in oral GLP_Tox.
- Human clinical phase I study package has been conducting and will be completed in 1Q 2016.

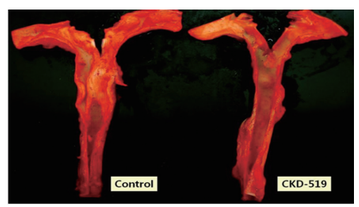
Pharmacology

- CKD-519 has shown remarkable efficacy in elevating HDL-C levels, inhibiting CETP in a dyslipidemic animal model, as well as a panel of normolipidemic animal models:
  - In vitro (CETPi) IC_{50} = 2.3 nM
  - In vivo efficacy (po, qd)

	Model		Period (day)	Doses (mpk)	Results
CETP / HDL-c / LDL-c	Hamster	Normal	5	1, 3, 10, 30	% change of HDL-C levels (16~60%) % change of LDL-C levels (-5~-13%)
		Dyslipidemic	1	3, 10, 30	PK/PD, EC_{50} = 31 nM
			14	1, 3, 10	% change of CETP activity (-33~-71%) % change of HDL-C levels (45~89%)
	TG Mouse	Hu man CETP /Apo-AI	28	3, 10, 30	% change of CETP activity (-29~-60%) % change of HDL-C levels (16~41%)
	Cyno M.	Normal	1	1, 5, 30	PK/PD, EC_{50} = 83 nM
			14	30, 100	Decreased CETP activity by 90% @ D14 % change of HDL-C levels (13, 25%)
Function	Rabbit	Dyslipidemic	12 wks	10, 30, 60	Decreased CETP activity by 89% @ 12 wks Increased HDL-C levels by 229% @ 12 wks Significantly inhibited lipid deposition in aorta
	Hamster	Dyslipidemic	14	30, 60	Increased in cholesterol efflux from macrophages (RCT)
				30	Increase in fecal chelesterol excretion in dyslipidemic hamster (FCR)

- Anti-atherosclerotic effects of CKD-519 in rabbit

In a diet-induced atherosclerosis rabbit model (10/30/60 mg/kg, po, 12 wks), CKD-519 significantly reduced the extent of aortic lesions. These results strongly underline the firm potential for CKD-519 to be developed for the effective treatment of atherosclerotic cardiovascular disease.



▲ Comparison of aortic lesions in control and CKD-519-treated rabbit

Pharmacokinetics

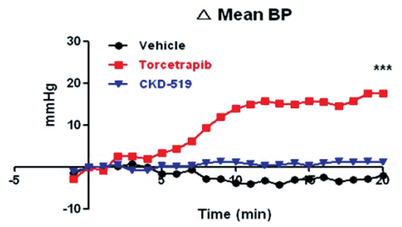
- CKD-519 is a low clearance compound that exhibits long half-life values in tested species. Oral administration of CKD-519 resulted in sufficient exposure for maximal efficacy. The candidate is projected to be an once-a-day drug in human.

Species	$T_{1/2}$ (h)	Vd (L/kg)	Cl (mL/h/kg)	AUC (ng.hr/mL, po)	%F
Hamster	6.7	0.37	38.7	11,000 (3 mpk)	14.2
Rat	8.7	0.82	58.4	3,700 (5 mpk)	4.0
Dog	9.2	0.003	100.3	5,355 (10 mpk)	6.1
Cyno M.	100	1.16	10	14,129 (1 mpk)	11.3

- Excellent microsomal stability and without detectable gender or species bias.
- No detectable inhibitory effects toward CYP isozymes up to ~10 uM concentrations.

Toxicology and Safety Pharmacology

- No inhibitory effects against alternate lipid transfer proteins (including LCAT, MTTP, PLTP)
- No effect on plasma levels of aldosterone/corticosterone and BP in anaesthetized rats.



▲ CKD-519 does not induce blood pressure elevation in rats

- Does not induce aldosterone or cortisol synthase mRNA production in vitro
- No genetic toxicity (AMES, Chromosomal Aberration)
- GLP_Tox NOAEL (4weeks-repeated toxicity): 300 mg/kg (hamster, monkey, rat)

Clincal Trial

- First in Human study was finished in 1Q 2015.
- CKD-519 showed dose-dependent increase of inhibition of CETP activity (EC_{50}=20 ng/ml)
- There was no significant safety issue in all group.

Chong Kun Dang Pharmaceutical Corp.

Intellectual Property

- A Korea patent & PCT have been published(4Q, 2012).
- Pending : USA, Japan, India, Vietnam, Brazil, Mexico, China, Canada, Philippins, New Zealand, Australia, Russia, EU.
- Additional Patent Application has been filed (PCT, 2014,1Q).

Competitive Advantages

- No CV issues observed with Torcetrapib (Blood pressure, aldo/cortico).
- Based upon efficacy, PK and safety profiles, CKD-519 is expected to become one of the leading HDL therapies for the treatment of atherosclerotic cardiovascular diseases.

Drug		CKD-519	Anacetrapib	Evacetrapib	Dalcetrapib	Torcetrapib
Company		CKD	Merck	Eli Lilly	Roche	Pfizer
CETPI (IC_{50})		2.3 nM (hCETP, buffer)	21.5 nM[1] (rhCETP, buffer)	5.5 nM[1] (rhCETP, buffer)	204.6 nM[1] (rhCETP, buffer)	23.1 nM[1] (rhCETP, buffer)
Normolipidemic hamster	HDL-c	35% (3 mpk, 5d)	-	-	40%[9] (100 mpk, 7d)	-
dyslipidemic hamster	HDL-c	83% (3 mpk, 14d)	47%[3] (60 mpk, 2wks)	130%, Tgm[1] (30 mpk, 1d)	49%[2] (300 mpk, 21d)	72%[2] (10 mpk, 21d)
RCT (hamster)		Promotes RCT (cholesterol Efflux & fecal excretion)	Promotes RCT (dyslipidemic Hamster)[3]	-	Promotes RCT (normolipidemic)[4]	Promotes RCT (CETP/Apo-B100 tg mice)[5]
Anti-atherosclerotic effects (rabbit)		reduced the aortic lesions	-	-	reduced the aortic lesions[6]	reduced the aortic lesions[7]
Blood pressure (in vivo)		No effect	No effect[8]	No effect[8]	No effect[8]	Increase[8]
Clinical trials	HDL-c ↑	-	138% (100mg)	132, 98, 57% (500, 100, 30mg)	31% (600mg)	61% (60mg)
	LDL-c ↓	-	40%	40, 26, 18	3	24
	CVD risk factor		-39%, Lp(a)		+17%, LP-PLA2	
Development phase		P1 (2014, 2Q)	Phase 3	Phase 4	discontinued	discontinued

(1) J. Lipid Res. **2011**, 52, 2169-2176.
(2) Atherosclerosis **2011**, 219, 761–767.
(3) J. Lipid Res. **2011**, 52, 1965-73.
(4) J. Lipid Res. **2010**, 51, 3443-54.
(5) Clin Transl Sci. **2011**, 4, 414-20.
(6) Nature **2000**, 406, 203-207.
(7) J. Lipid Res. **2007**. 48, 1263–1272.
(8) Drugs **2012**, 72, 491-507.
(9) Eur J. Pharmacol **2003**, 466, 147–154

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LG Life Sciences, Ltd.

LG Life Sciences, Ltd.

Development of an Anti-myocardial Infarction Agent against Ischemia-Reperfusion Injury with A Novel Necrosis Inhibitor, LC28-0126

Code Number : KDDF-201210-07

Development and Market Objectives

- Development of a cardio-protective agent through successful completion of clinical Phases 1 & 2 using a novel class of necrosis inhibitor, LC28-0126 (CYCL001 Ver. 1.0 approved by KFDA) by demonstrating safety & tolerability in clinical Phase 1 as well as its suppressive effect on infarct size against lethal ischemia-reperfusion injury during percutaneous coronary intervention (PCI) in ST-segment elevation in myocardial infarction (STEMI) patients in clinical Phase 2.

Unmet Medical Need & Target Patients

Target Patients

- STEMI patients have been selected as the primary target to clearly demonstrate the efficacy of LC28-0126 in Phase 2.
- Non-STEMI patients will be tested after completion of Phase 2 in STEMI patients.

Unmet Medical Needs

- More than 1,000,000 cases of myocardial infarction occur in the US every year and the high prevalence rate of 600 cases/100,000 population has been reported. However, no drug is currently available to effectively treat this condition.
- Patients with myocardial infarction typically exhibit a 70% size of infarct area, causing death from heart attack.
- PCI administrated to patients with myocardial infarction ultimately extends the life of the patient, but paradoxically, 30% of the infarct area still remains due to lethal reperfusion injury caused by excess blood and oxygen provided at the time of the procedure.
- Consequently, 5~10% of patients may die within a year of PCI, or incur significant medical expenses due to serious clinical complications.
- Several clinical trials performed in patients with myocardial infarction have failed as they did not demonstrate fundamental reductions in size of the myocardial infarct. The underlying reason is that due to the size of infarct is decisively influenced by the degree of necrosis of myocardial cells.
- Therefore, the development of a treatment drug which can reduce the infarct area of 30% post PCI, down to < 5% serves a significant unmet medical need. LC28-0126, a strong necrosis inhibitor-which specifically targets the mitochondria-has been developed by LG Life Sciences. The world's first clinical trial using LC28-0126 has clinical implications in the area of myocardial infarction for which there are no adequate treatments.

Status

- A clinical Phase 1 study with healthy volunteers is underway in Korea, which will be followed by clinical Phase 2 with STEMI patients in Korea, 1Q 2014.
- A backup study of chemical synthesis is also underway.
- Out-licensing or collaborative research opportunities including a necrosis program are available.
- Partnership for MI is possible.

Intellectual Property

- 4 PCTs are pending.

Competitive Advantages

- Thus far, anti-platelet agents have been used as secondary drugs to vasodilatation in PCI. Two candidates that are known to inhibit apoptosis of myocardial cells are under clinical development as myocardial infarction inhibitors: cyclosporin A-immunosuppressant, Phase 3) and TRO-40303 (Phase 2).
- A Drug that can effectively decrease the size of PCI-induced lethal ischemia reperfusion injury (myocardial infarct) in myocardial infarction patients does not yet exist. No candidates have been able to demonstrate fundamental blocking of myocardial cell necrosis, which is the main cell-death mechanism of myocardial infarction.
- Therefore, our compound LC28-0126 which effectively reduces the size of infarction through strong inhibitory effects on necrosis in a rat MI model is expected to demonstrate fundamental reduction of the size of infarct caused by lethal reperfusion injury in clinical trials.

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Green Cross Corporation

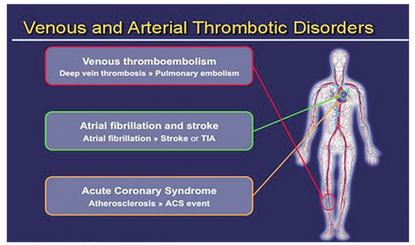
Development of a novel anti-coagulant Factor Xa inhibitor, GCC-4401C

Code Number : KDDF-201210-04

Development and Market Objectives

- Green Cross Corporation is developing an orally available direct Factor Xa inhibitor, GCC-4401C, which has shown an excellent safety profile during Phase I clinical study. After completion of Phase II and III studies for the prevention of venous thromboembolism (VTE) on hip or knee replacement surgery patients, we will explore additional indications for the treatment of acute coronary syndromes and the prevention of stroke in patients with atrial fibrillation.

Unmet Medical Need & Target Patients



- GCC-4401C may prove its greatest impact in providing a much-needed and attractive alternative to warfarin in various indications. Prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism in patients undergoing hip or knee arthroplasty, is considered to be a primary unmet medical need. It is the most common cause for rehospitalisation in this patient group. Each year in the United States, between 350,000 and 600,000 people experience a blood clot in the legs or in the lungs. The US and European hip and knee implant markets are the two largest, accounting for nearly 80 percent of total procedures conducted worldwide. The 2005 revenues for hip and knee implants in the US and Europe were $6.5 billion. Demand driven by an aging population and an increasing number of younger patients are contributing to the continuous growth of hip and knee replacement procedures.
- Thromboembolism involving arterial or venous circulation is a common cause of morbidity and mortality. As an anticoagulation therapy, heparin and Vitamin K antagonists (VKAs) such as warfarin have been used in clinical settings for more than 50 years, but both are associated with several limitations requiring frequent coagulation monitoring due to unpredictable effects of anticoagulant . Therefore, there is an urgent need for novel, oral agents with a predictable anticoagulant action. The greatest unmet medical need in anticoagulation therapy is to find a replacement for VKAs for long-term therapy, particularly stroke prevention in patients with atrial fibrillation (a heart rhythm disorder). Recently, Factor Xa has emerged as an attractive target for novel anticoagulants and a number of Factor Xa inhibitors are currently under development as oral anticoagulants for long-term use.
- A major unmet medical need is for direct FXa inhibitors that are simpler to administer than VKAs, with fewer strokes and less intracranial bleeding compared with warfarin and less bleeding yet similar or better efficacy with a lower-dose regimen. In addition, the availability of simple, fixed-dose, unmonitored therapies should increase the use of direct FXa inhibitor therapy in patients with atrial fibrillation at risk for stroke.

Status

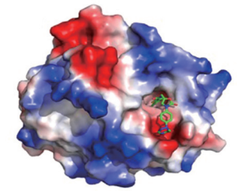
Phase I Clinical Study

- To investigate the safety, tolerability and pharmacokinetics (PK) of multiple doses of GCC- 4401C in healthy male subjects, a Phase Ib study was recently completed in the United States under the conditions of randomized, double-blind, placebo-controlled, and multiple ascending dose. The study consisted of 5 cohorts given either 10, 20, 40, 60 or 80mg GCC-4401C or matching placebo, comprising 8 subjects per cohort. In the 20mg cohort, 6 additional subjects were to be given rivaroxaban 20mg as an active comparator in open-label fashion. GCC-4401C was well-tolerated without any significant adverse events, and was detected in blood plasma dose-proportionally across the dose range of 10 mg to 80 mg per patient. The pharmacodynamic variables were also statistically correlated with GCC-4401C plasma concentrations.
- We plan to be identified an appropriate dose and dosing regimen of oral GCC- 4401C from subsequent clinical trials on VTE patients.

Intellectual Property

- Material patent for GCC-4401C, covering a wide range of chemical structures, was awarded in early 2008 within S. Korea, followed by its production method patent in early 2011. Moreover, patent applications for both material and production method, are in progress in 21 and 5 overseas countries including the US, respectively.
  - KR811865 : Pyrimidinone derivatives or pyridazinone derivatives for inhibition of factor VIIa activity
  - KR109594 : FXa inhibitors with cyclic amidines as P4 subunit, processes for their preparations, and pharmaceutical compositions and derivatives thereof
  - KR898361 : FXa inhibitors with cyclic amidoxime or cyclic amidrazone as P4 subunit, processes for their preparations, and pharmaceutical compositions and derivatives thereof
  - KR1037051 : Method for preparing of (S)-5-chloro-N-((3-(4-(5,6-dihydro-4H-1,2,4-oxadiazin-3-yl)phenyl)-2-oxooxazolidin-5-yl) methyl)thiophene-2-carboxamide derivatives
  - KR1037052 : Method for preparing 5-chloro-N-(((5S)-2-oxo-3-(4-(5,6-dihydro-1,2,4-triazin-1(4H)-yl)phenyl)-1,3-oxazolidin-5-yl)methyl)thiophen-2-carboxamide derivatives, and their intermediates
  - PCT/KR2010/004420 : Method for preparing (S)-5-chloro-N-((3-(4-(5,6-dihydro-4H-1,2,4-oxadiazin-3-yl)phenyl)-2-oxooxazolidin-5-yl)methyl)thiophene-2-carboxamide derivatives
  - PCT/KR2010/004421 : Method for preparing 5-chloro-N-{{(5S)-2-oxo-3-[4-(5,6-dihydro-4H-[1,2,4]triazin-1-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)thiophene-2-carboxamide derivative and intermediate used therein.

Competitive Advantages



- From the recent Phase Ib clinical study, GCC-4401C did not show any significant sign of adverse events. PK parameters and PD markers were predictable dose-proportionally across the all dose ranges. GCC-4401C is expected to show excellent safety profiles, less bleeding and less liver toxicity through human clinical studies.

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Jeil Pharmaceutical Co., Ltd.

JEIL PHARMACEUTICAL CO.,LTD.

Phase IB Clinical Study of JPI-289 for the Treatment of Stroke

Code Number : KDDF-201410-08

Development and Market Objectives

- The aim of this project is to accomplish phase IB clinical trial including evaluation of safety/tolerability and PK/PD profiles of JPI-289, and to proceed phase IIA clinical development of the PARP-1 inhibitor, as a first-in-class drug for the treatment of acute ischemic stroke.
- Ultimately, after rapid completion of Proof of Concept (POC, Phase IIA) clinical studies, Jeil Pharmaceutical is planning to license out, co-develop, and co-commercialize JPI-289 with global big companies.

Unmet Medical Need & Target Patients

- Stroke is a debilitating condition, with the highest death rate as a single organ disease. Incidence is expected to keep increasing over the next 20 years despite the progress in modern medical science and technology. This is largely due to a global increase in the aging population.
- No clinically effective therapies currently exist although the stroke incident rate in Korea remains high. Developments of new therapeutic strategies and standards of medical care are imperative.
- Currently, treatment for ischemic stroke with cerebral blood vessel occlusion predominantly employs a thrombolytic agent combined with surgery and further agents including anticoagulants and platelet aggregation inhibitors for secondary prevention. Any new therapy for stroke is expected to be highly marketable, as the only thrombolytic agent, tPA (tissue Plasminogen Activator) has been approved by the FDA with limitations.
- Jeil Pharmaceutical will develop JPI-289, a PARP-1 inhibitor, on a commercial scale after acquiring Proof-of-Concept data via a combination therapy with tPA in Phase IIA clinical trials. This will be followed by licensing-out and co-development with multinational partners.
- A homogeneous patient group will be selected for the tPA co-administration for NDA approval, with the range of subjects and indications further expanded through PMS clinical trials.

Status

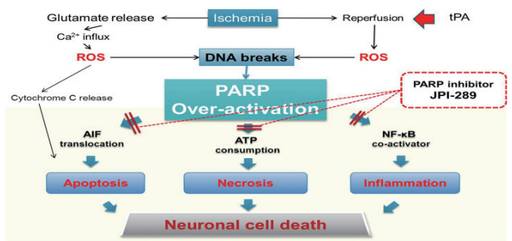
- A clinical protocol for a phase IB clinical trial of JPI-289 was approved by Ministry of Food and Drug Safety (MFDS) and Institutional Review Board (IRB) of Asan Medical Center, and the MAD (Multiple Ascending Dose) clinical trial in healthy male subjects is currently in progress.
- A clinical protocol for a phase IIA clinical trial in stroke patients will be developed by the end of 2015. After acquiring IND/IRB approvals for the phase IIA clinical trial of JPI-289, Jeil Pharmaceutical will enter the POC trial in early 2016.

Intellectual Property

- Patent applications covering materials and preparation methods were submitted in 2008 and approved in 2011 in Korea (10-0968175), as well as in the US, Europe, China, Japan, Australia, Canada, and Russia during 2011 and 2014.
  - PCT: WO 2010/056038
- Application for the JPI-289 crystalline structure patent was submitted in 2012.
- In summary, one application in Korea and seven international applications have been registered, and registration processes for another application in Korea and seven international applications are currently underway.

Competitive Advantages

- The majority of previous stroke candidates have been designed to inhibit apoptosis mechanisms; however, the clinical results have been inconclusive as most of the brain damages were caused by necrosis during the first 10 hours after the stroke occurs.
- JPI-289 inhibits the damages caused by necrosis, apoptosis and inflammation, at the same time, and is expected to exert significant benefits in the treatment of stroke.



① Inhibition of PARP-1 is a significantly distinct mechanism of action when compared to other candidates and is expected to show high efficacy in clinical trials with ischemic stroke patients through the neuroprotective effects.

② Effective PARP-1 inhibition and the mechanism of action by MP-124 have been proven in a monkey model, which is the closest stroke primate animal model to human so far. In a monkey tMCAO stroke model, JPI-289 showed 49% decrease in infarction volume, which is the best result in the world when compared with that of 21% decrease in infarction volume by MP-124. Therefore, JPI-289 among PARP inhibitors is considered as one of the most promising agents for the treatment of stroke.

③ Safety of JPI-289 has been confirmed in healthy volunteers because there were no critical compound-related adverse events during phase IA study. AUCs of JPI-289 in the blood were increased dose-proportionally.

④ JPI-289 is highly soluble with excellent PK parameters. Single doses of JPI-289 significantly decreased infarct volume in an SD rat stroke model. Therefore, it is expected to be suitable for acute ischemic stroke patients who are required a prompt administration and onset of efficacy (JPI-289 iv infusion over 1 h vs MP-124 iv infusion over 24 h).

⑤ When JPI-289 was co-administered with tPA in the rat embolic tMCAO models, the infarction volume and hemorrhage area were significantly decreased compared to those of tPA single treatment group.

⑥ Because JPI-289 can be taken as an oral administration due to relatively high bio-availability (rat: 66%, dog: 100%) as well as an injection, treatment of stroke with JPI-289 after discharge is predicted to be maximized.

⑦ JPI-289 has shown excellent safety profiles in non-clinical studies, leading to IND approval for Phase I clinical trials in healthy male subjects. This is in favorable contrast to MP-124, another leading candidate that has been in Phase I since 2009. Acquisition of clinical POC via rapid completion of Phase IIA is expected to endow an advantageous position in licensing-out to global big pharmaceutical companies.

⑧ After secure of clinical POC, the drug value will be maximized by expanding its application for other diseases (e.g. myocardial infarction) and patient groups.

⑨ S100B, NSE will be scrutinized further to develop as a bio-marker of stroke in upcoming studies.

⑩ The synthetic process of JPI-289 has been established with DS/DP production in cGMP facilities for Phase I trials. As a result, mass production for commercial purposes is tangible.

⑪ A huge market value has been established with monopolistic right until 2029

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HALLYM UNIVERSITY

Development of analgesic compounds for the treatment of chemotherapy-induced peripheral neuropathy

Code Number : KDDF-201406-15

Development and Market Objectives

- The development of 2 candidate substances for the treatment of chemotherapy-induced neuropathic pain, using FY-304, a derivative of 5-membered heterocyclic compounds and FY-504, the lead candidate from the Korean government's new therapeutic development project [KDDF201304-06] in order to synthesize a new compounds with excellent efficacy, high stability and fewer side effects, and which is also appropriate for broad indications.

Unmet Medical Need & Target Patients

Chemotherapy-induced Peripheral Neuropathy, CIPN

Drug/Combination Tested	Study Result
Lyrica®	Failed
Lidoderm®	Failed
Procrit®	Failed
Amitriptyline/ketamine/baclofen	Limited efficacy

▲ **Clinical research data for existing and combination CIPN therapies**

Neuropathic Pain : Issues with existing medication

- Analysis of currently-available medications highlights issues related to their efficacy and side effects. Improved pain alleviation and decreased side effects related to the central nervous system are the most important factors for the development of a new medication for the neuropathic pain.
- Gabapentin, pregabalin and similar drugs are allopathic medications used to ease neuropathic pain, but their level of efficacy is currently low effective for less than 30% of patients → an improvement of more than 50% is needed).
- Side effects such as dizziness and drowsiness are associated with CNS-targeted medications and none are currently capable of addressing the underlying cause of the disease.
- High-capacity administration is currently not possible with low stability candidates.

Status

- In vitro and in vivo data show that FY-304 inhibits the TTX-resistant Na channel, highlighting the possibility for development as a CIPN alleviator.
- Using the properties of FY-304 and FY-504 from previous research efforts as the foundation, and via the synthesis of novel compounds, we are developing new substances for chemotherapy-induced neuropathic pain with excellent efficacy, high stability and fewer side effects, and which is also appropriate for broad indications.

Intellectual Property

- Patent Title: 5-membered heterocyclic derivatives, their method of manufacture and the pharmaceutical compositions arising from it (Patent No: 10-2013-0046117)
- Extent of Rights: 5-membered heterocyclic derivatives and their hydrates or pharmacologically active substances including pharmaceutical compositions that decrease pain including acute pain, chronic pain, neuropathic pain, post-operative pain, migraine, and arthralgia.

Competitive Advantages

- Patent: Extensive literature analysis suggests that the potential for exclusive patent rights is very high with no intellectual property issues identified worldwide. As a highly novel candidate, broad patent rights are expected.
- Efficacy: Potentially broad indications.
- Mechanism of Action: The potential for development as a CIPN alleviator via the inhibition of TTX-resistant Na channels has been validated.
- Toxicity: 5 g/kg of the compound had been administered orally in mice, with analysis of viability, weight, defecation, behavior and internal organs including liver, spleen, stomach and intestines showing no signs of toxicity after one week of treatment. In comparison to gabapentin, side effects are greatly reduced.

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SK Biopharmaceuticals

YKP3089, an Innovative Drug for the Treatment of Epilepsy: Late-Phase Global Clinical Development

Code Number : KDDF-201110-14

Development and Market Objectives

- SK Biopharmaceuticals is currently running a worldwide Phase 2b dose-range finding trial in epilepsy as well as other studies supporting Phase 2 and further exploring the mechanism of action of the molecule.
- Our goal is to complete clinical development of YKP3089 in the United States and establish it as the first product of our Specialty Pharmaceutical company there. In addition, we are seeking to co-develop and co-commercialize it with a global partner or regional partners while our clinical trials in epilepsy are ongoing. Furthermore, with the NDA approval in epilepsy we plan to conduct clinical trials to expand YKP3089's indication to include neuropathic pain and bipolar disorder. Ultimately, we anticipate that YKP3089 will have multiple therapeutic uses in the burgeoning area of central nervous system (CNS) diseases.

Unmet Medical Need & Target Patients

Unmet medical need

- Epilepsy is the most common neurological disorder and can be life-long. With the overall improvement in worldwide life expectancies, the patient pool is expected to expand markedly. The various types of seizures are difficult to control with a single drug. Despite the availability of many antiepileptic drugs acting by a variety of molecular mechanisms, approximately 30 percent of patients across all types of seizures are still not seizure-free on their current combination drug regimens. In addition, the use of many of the currently-available drugs is compromised by their inconvenient dosage regimens or deleterious side effects, such as sedation, cognitive deficits, weight gain, and behavioral changes.

Target patients

- Epilepsy is categorized into two major seizure types: partial and generalized seizures. Partial seizures are the more common, representing 53 percent of all epilepsy patients; 30 to 40 percent of patients who are refractory to their current drug regiments also suffer from partial seizures. Therefore, for its first indication, we will confirm the efficacy of YKP3089 in the treatment of refractory partial-onset seizures in patients whose medical needs are urgent and unmet. Later we will expand into research in other epilepsy syndromes including generalized seizures.

Status

- YKP3089 represents a new approach to the treatment of seizure disorders; its identification was the result of the phenotypic-driven discovery of its broad efficacy in a variety of preclinical seizure models. Early clinical studies established its oral availability, its safety in normal volunteers with regard to sedation, cognitive effects, and behavioral changes, and confirmed its convenience in having an acceptable once-a-day dosing regimen. It has also been shown to be free of drug-drug interactions with a number of common, troublesome concomitant drugs used clinically. A Proof-of-Concept study in epileptic patients demonstrated its ability to diminish or abolish photosensitive pro-convulsant syndromes. Recent Phase 2 Proof-of-Efficacy trial in refractory patients with partial onset seizures successfully showed robust efficacy compared to placebo in reducing frequency of partial onset seizures, regardless of seizure type.

Intellectual Property

- Composition of Matter Patent:
  - US : issued as US 7,598,279 (parent case filed April 2005)
  - Pending : Canada, Mexico, Brazil, Chile, Argentina, Europe, South Africa, Russia, India, Indonesia, Malaysia, Thailand, Taiwan, China, Korea, Japan, Australia
  - Process patent (A) : filed June 2009
  - Pending : WorldwideProcess patent (B) (EZ process): filed October 2009
  - Pending: Worldwide

Competitive Advantages

- Broad efficacy across seizure types:
  - YKP3089 exhibits efficacy in many preclinical epilepsy models, in particular those that reflect refractory seizure types; this efficacy is potent and frequently superior to currently marketed drugs considered to be the Gold Standard. As preliminary shown P2a POE study, It is expected that YKP3089 will be used clinically in a variety of epilepsy types.

SK Biopharmaceuticals

- Facilitates uncomplicated combination therapy:
  - YKP3089 exhibits no or minimal interaction with existing drugs (oral contraceptives, other antiepileptic drugs such as divalproex sodium or carbamazepine) in clinical studies. Its novel mechanism of action can be expected to complement the effects of currently-available therapeutic agents without augmenting any of their current side effects.

- Convenient once-a-day dosing:
  - Numerous studies have identified patient compliance as a significant issue in the treatment of epileptic disorders. The ability to take YKP3089 on a once-a-day dosing schedule is expected to increase patient compliance and outcomes and improve social benefits (less frequent hospitalizations and societal costs).

- Long patent life
  - Worldwide composition of matter exclusivity to 2025; in the US, Hatch-Waxman extension possible for up to five additional years. In European states, 10 years of market exclusivity is the minimum for a new chemical entity.

- Expansion to indications in addition to epilepsy:
  - Extensive preclinical testing is suggestive of utility in neuropathic pain and bipolar disorder.

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Yungjin Pharm. Co., Ltd.

US FDA Phase 2a Completion and KFDA Phase 2b Approval of YPL-001 (Chronic Obstructive Pulmonary Disease Drug)

Code Number : KDDF-201410-05

Development and Market Objectives

- YPL-001 is a natural product developed by Yungjin pharm for COPD treatment. It is the 1st Koran natural products with phase I IND approved by FDA and has been government funded project since 2011. Phase IIa is undergoing in 3 USA hospitals now and we are looking for licensing out partners or co-development partner after phase IIa

Unmet Medical Need & Target Patients

Unmet Medical Needs

- Efficacy
  - The primary unmet medical need of COPD is to find a treatment preventing the disease progression from stage 2 or 3 to stage 3 or 4
- Steroid sensitivity
  - COPD patients have a tendency of reduced responsiveness to steroids as their disease progresses. So symptoms get worse even using steroids especially for stage 3 or 4 patients. Thus to reduce corticosteroid resistance in patients is important in acute or frequent COPD exacerbations..
- Safety
  - COPD requires long-term treatment. Most of existing treatments for COPD have safety issues. Development of product with less side effects is needed.
- Formulation
  - Most COPD are inhalant type which need patient education for usage. Oral dosage form is easy and convenient for dosing, usually cheaper than device type drug which is helpful especially in underdeveloped country.

Target patients

- COPD patients are classified based on their degree of severity - Mild (Stage 1), Moderate (Stage 2), Severe (Stage 3), Very severe (Stage 4). The ultimate and primary goal of treatments is to prevent exacerbation of COPD. For such purpose, long term safety and prevention the development of resistance should be secured. None of the existing drugs have been proven to stop the disease progression from Stage 1 or 2 to Stage 3 or 4. YPL-001 is for stage 2 or 3 patients to prevent COPD exacerbation.

Status

- Yungjin has completed Phase 1a (Single Ascending Dose Study) and 1b study (Multiple Ascending Dose Study). The IND and IRB have been done Phase IIa and currently patients recruiting are ongoing.

Intellectual Property

- Patent registered: total 17 patents completed
  - Korea(4), USA(2), Europe(6), Japan(1), China(1), India(1), Canada(1), Australia(1)
- Patent pending: Korea(1), US(1), PCT(2)
  - Covering worldwide

Competitive Advantages

- Unique MoA
  - Reduce inflammatory response and increase steroid sensitivity as HDAC2 activator (First In Class)
- Well- controlled CMC
  - Phytoequivalence established
  - Identified components (> 90 % (w/w))
  - Standardized API by GAP*
- Formulation
  - Oral dosage form: easy compliance compared to inhalants
- Exclusivity
  - Well protected intellectual property through several patent application

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Bioneer Corporation

BIONEER
Innovation • Value • Discovery

Selection of optimized lead compounds for preclinical studies for idopathic pulmonary fibrosis using a novel RNAi-based nanoparticle technology SAMiRNA™, with a goal of IND application

Code Number : **KDDF-201312-11**

Development and Market Objectives

- Our objective is to develop the effective therapeutic drugs for the treatment of Idiopathic Pulmonary Fibrosis (IPF), a respiratory fibrotic diseases. It will be the first siRNA-based therapeutic drug against IPF, fatal respiratory diseases with no available efficient drugs yet. We are developing multiple preclinical candidate substances for idiopathic lung fibrosis with overall evaluations of efficacy and PK/PD analysis, applying the SAMiRNA™ RNAi nanoparticle technology covered by patent protection.

Unmet Medical Need & Target Patients

Unmet medical need

- The mortality rate for lung fibrosis is extremely high, with a 5-year survival rate lower than 30%.
  - Esbriet® (Pirfenidone) and Ofev® (Nintedanib), which are approved by FDA in 2014, is expensive and exhibits limited efficacy. Urgent need for the development of new effective drug which can actively reverse the process of fibrosis
  - By developing potent antifibrotic agents, applications can be extended to diseases that are frequently accompanied by fibrosis (such as NASH, systemic scleroderma, etc).

Target patients

- Patients aged 50 and older, with lung fibrosis confirmed by high resolution computed Tomography (HRCT) or by surgical biopsy, with mild to moderate symptoms between 50% to 80% on a post-bronchodilator forced vital capacity pulmonary function test.

Status

- ***In-vitro* screening**: Several hundreds of siRNA molecules were in-vitro screened to find highly specific and potent siRNAs against these target genes. Hundreds of SAMiRNA™ have been synthesized and screened for the highly potent therapeutic candidates.
- ***PK/PD***: PK/PD analysis of SAMiRNA was performed by in vivo imaging of biodistribution and real-time qPCR-based quantification of gene knock-down in various organs. SAMiRNA-IPF is delivered to lung only in the IPF induced model animals both of Bleomycin-induced and TGF-b transgenic model, consequently knock down.
- ***in vivo* efficacy test**: The efficacy of the SAMiRNA-IPF drug has been evaluated with TGF-ß transgenic & Bleomycin induced mouse models of pulmonary fibrosis. Based on these comprehensive evaluations, the candidates show the more significant therapeutic potential for IPF treatment than Pirfenidone of InterMune, Inc and FG-3019 (CTGF mAb) of Fibrogen, Inc.

Intellectual Property

Country	Application Date	Application Number	Registration Date	Registration Number	Name of Invention
KR	2009-05-14	10-2009-042297	2013-01-16	1224828	siRNA conjugate and preparing method thereof
KR	2009-05-14	10-2012-0069988	2013-03-05	1241852	
KR	2009-05-14	10-2012-0114011	2014-04-30	10-1392973	
US	2010-05-13	13/319885	2014-07-15	8779114	
US	2010-05-13	13/613071	2014-07-08	8771976	
EP	2010-05-13	10775118			
EP	2013-03-15	13159602.5			
JP	2010-05-13	2012-510752			
CN	2010-05-13	201080021324.3			
CN	2010-05-13	201210301551.2			
CA	2010-05-13	2761794			
AU	2010-05-13	2010248239			
IN	2010-05-13	2336/MUMNP/2011			
RU	2010-05-13	2011150787			
KR	2012-10-05	10-2012-0110559			Composition for the prevention or treatment of respiratory diseases including gene-specific double strand oligo-RNA
PCT	2013-10-07	PCT/KR2013/008949			
KR	2013-07-05	10-2013-0079311			Respiratory disease related genes-specific siRNA, double-stranded oligo RNA molecules comprising the siRNA, and composition for the prevention or treatment of respiratory diseases comprising the same
PCT	2014-07-04	PCT/KR2014/006033			
PCT	2013-10-07	PCT/KR2013/008949			Gene-specific double strand oligo-RNA, double-stranded oligo RNA molecules comprising the double strand oligo-RNA, and composition for the prevention or treatment of respiratory diseases comprising the same

- Patents for the SAMiRNA™ RNAi drug platform (siRNA conjugate and preparing method thereof) have been filed for domestic and major international markets, including patents for specific fibrosis-related genes. The period of monopoly by 2035 will be obtained in the major markets by follow-up patent applications with further studies.

Competitive Advantages

- Robust SAMiRNA™ technology fundamental patents for lung fibrosis-related siRNA sequences
- Synergy for the lung fibrosis treatment effect will be verified by administration of an siRNA cocktail simultaneously targeting two critical genes.
- Favorable comparisons for therapeutic effect in various animal models (TGF-β transgenic mouse model, smoking model, bleomycin-induced lung fibrosis mouse model)
- Market assessment will be faster due to a shorter clinical trial period, as idiopathic lung fibrosis medicines are classified as orphan drug.
- Potential extended applications for the diseases in other organs which are frequently accompanied with fibrosis symptoms (hepatocirrhosis, kidney fibrosis, etc).

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ImmuneMed Inc.

Development of newly defined antiviral drug that selectively acts on the virus infected cells

Code Number : KDDF-201406-08

Development and Market Objectives

- Virus Suppressing Factor (VSF) is an antiviral protein that inhibits various pathological activities essential to viral replication. It specifically targets on receptor of virus infected cells and have been classified as an investigational new drug following lead candidate nomination and preclinical trials through the optimization of humanized VSF (HzVSF), providing a new concept for the treatment of viral diseases.

Unmet Medical Need & Target Patients

Target patients

- This candidate is under development for the treatment of hepatitis B and C. Infected patients with clinical symptoms caused by immunophathologic phenomena, such as inflammation arising from viral infection will be prioritized.
- Initial target indication
  Hepatitis C: There are an estimated 170 million international patients (with more than 350 thousand people dying from the disease each year), and more than 600 thousand domestic patients.
- Secondary target indication
  Hepatitis B: There are an estimated 400 million international patients (with more than 1 million people dying from the disease each year), and more than 2 million domestic patients.
- Tertiary target indication
  Other serious viral diseases that cause clinical symptoms arising from inflammation by virus infection.

Unmet medical needs

- The existing antiviral therapies are only effective for specified viral strains.
- There is a strong unmet need for new therapies that can reduce the excessive immune reaction, such as inflammation caused by viral infection.
- Novel treatments with a wide range of anti-viral and anti-inflammatory activity are needed for the treatment of patients who do not receive therapeutic benefit from existing drugs.
- A new drug that can synergize with existing treatment options for combination therapy is needed.

Status

- The developmental candidate for hepatitis B and C is currently being optimized by Epibase in vitro screening, and the development of a cell line to produce the candidate in larger quantities is in progress.

Intellectual Property

- Patent Name: Novel anti-viral VSF protein and hybridoma producing same
  - 2 registration patents, 1 public PCT
  - Registration Countries: Korea, USA
  - Patent Registration Number / Registration Date
    United States of America, 7,514,082 / 2009.04.07.
    Republic of Korea, 0425030 / 2004.03.17.
    PCT, WO 2003064461 A1 / 2003.01.30.
- Patent for preparing application: Humanized VSF
  - Expecting date of application: October, 2014
  - Countries for application: Korea, USA, Europe, China, Japan, India, Indonesia

Competitive Advantages

- In contrast to existing treatment options, we are developing a first–in-class humanized antibody that exhibits dual properties of antiviral and anti-inflammatory effects, which can selectively act on virus infected cells.
- There is a high likelihood for success, because the drug is phenotype-based, rather than target-based therapeutic.
- It is expected to have synergy with both anti-viral and anti-inflammatory effects when used in combination with currently available antiviral therapies.

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Hoseo Peptide Inc.

Pre-Clinical Study on Novel Anti-Microbial, MycosTericin, for Treatment of Skin Infections

Code Number : KDDF-201406-04

Development and Market Objectives

- MycosTericin containing an antimicrobial peptide (named HG1) as a main ingredient, is a topical candidate for the treatment of recalcitrant skin infections. Our objective is to conduct pre-clinical tests of MycosTericin for evaluating its toxicity and stability, and then to obtain approval as an indicant for clinical trials.
  (* The bioactive peptide HG1 has already been approved as an IND for the treatment of stomatitis by the Korea Food and Drug Administration)

Unmet Medical Need & Target Patients

Target Patient Group

- Skin infections caused by a wide range of pathogenic bacteria and/or fungi (impetigo, ecthyma vulgare, candidiasis, tinea versicolor, acne vulgaris etc)
- Chronic inflammatory skin diseases with secondary infections, which are commonly due to a defective epidermal barrier and dryness of the skin resulted from inheritable immunologic abnormality (atopic dermatitis).

Unmet Medical Needs

- As has been observed in a number of systemic infectious diseases, rapidly emerging antimicrobial resistant microbes also pose a serious threat to the treatment of skin and soft tissue infections. In addition, skin diseases are frequently associated with poly-microbial infections caused by a variety of pathogenic bacteria and fungi. Accordingly, it is imperative to develop novel antimicrobial agents that possess a mode of action distinctly different from conventional drugs and a broad antimicrobial spectrum.
- Biofilms are complex poly-microbial communities attached to a surface and embedded in an extracellular matrix. Up to 80% of all chronic skin infections are known to be caused by biofilms. For several reasons, biofilms are highly resistant to killing by microbicidal agents and thereby biofilm infections are difficult to eradicate with currently available antimicrobial treatment. Therefore, there is an urgent need for novel therapeutic to cope with biofilm involved in skin infections.

Status

- It was previously determined that HG1 had no toxicity upon administering unto the skin. As a result, HG1 was approved as an IND for mouthwash to manage oral mucositis.
- MycosTericin containing HG1 was named in accordance with the meaning that it could exert both fungicidal (Mycos) and bactericidal (Tericin) activity. MycosTericin has been confirmed to be highly effective in a model of animal infected with MRSA or Candida albicans.
- Experiments for toxico-kinetics of MycosTericin have been preparing to verify its safety when being administered onto the skin. The pilot toxicity experiment of HG1 in rodents has been completed.

Intellectual Property

- We currently hold a patent for materials based on a halocidin structure as an original and newly developed material and this also covers some halocidin isomers including HG1 generated by substitutions or the addition of amino acids to the halocidin structure.
- Antimicrobial peptides have entirely distinct biochemical features to existing therapies and the strategies employed in existing external preparations cannot be used. A patent for MycosTericin covering the efficacy of antimicrobial peptides may be feasible.

No.	Type	Title	Registration (YYMMDD)	Patentee	status
1	INTERNATIONAL	Antimicrobial peptide isolated from halocynthia aurantium	07504380 Reg Date (2009.03.17)	Hoseo Peptide Inc.	Registered
2	INTERNATIONAL	アカボヤから分離された抗菌ペプチド	JP4226555 Reg Date (2008.12.05)	Hoseo Peptide Inc.	Registered
3	DOMESTIC	Antimicrobial Peptide Having Reduced Hemolytic Activity	1008491620000 Reg Date (2008.07.23)	Hoseo Peptide Inc.	Registered
4	DOMESTIC	Antimicrobial peptide isolated from Halocynthia aurantium	1004914230000 Reg Date (2005.05.17)	Hoseo Peptide Inc.	Registered
5	DOMESTIC	New bacteroides and use of antibacterial peptide derived from silk-sea squirt	1020140064369 Reg Date (2014.05.28)	Hoseo Peptide Inc.	Applied

Hoseo Peptide Inc.

- The duration of the material patent is until 2027. Exclusivity in major markets is secured.

Competitive Advantages

- As a promising candidate for new drug based on antimicrobial peptide (AMP), HG1, major component of MycosTericin, has critical advantages over hitherto-known AMPs that had entered clinical trials for development as a topical antibiotic. HG1 exerts its profound antimicrobial activity even in the presence of a range of proteases and anionic components of extracellular matrix that might occur in a skin infection lesion, which is an essential property for AMPs to be developed as a clinically available drug.
- MycosTericin could become an effective antimicrobial for treatment of multiple infections with a wide range of pathogenic microbes including recalcitrant strains resistant to conventional antimicrobial drugs.
- MycosTericin exhibited a strong anti-biofilm effect against microbial biofilms generated by bacteria and/or Candida albicans.
- As has been observed in many AMPs, MycosTericin also has a fast and distinct mode of action in killing microbes.

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Seoul National University

Development of Anti-HIV peptides against Tat-TAR interaction

Code Number : **KDDF-201404-07**

Development and Market Objectives

- One of our research teams has discovered an active material against HIV-1 virus with a novel mechanism of action, by screening a self-synthesized peptide library. This peptide has been found to suppress the Tat-TAR interaction in nanomolar concentration of which has not been previously described previously. Our candidate is potentially the first new therapeutic againt the target.

Unmet Medical Need & Target Patients

- HIV-1 is one of the most common viruses that has spread worldwide, and according to 2012 statistics, more than 35.3 million people are infected. Approximately 1.8 million patients died from AIDS-related complications in 2010, and although this number has decreased from 2.2 million in 2005, it is still regarded as a global pandemic viral disease.
- Since its first recognition in 1981, AIDS has taken more than 30 million lives (2009 estimate). Although the mortality rate is rapidly decreasing in some areas where medical facilities and medicine is available, there remain many people infected by the virus across the globe.
- New medicines for HIV virus targets, such as Stribild (elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate) which was approved by the FDA as a new HIV medicine in 2012, are being developed, targeting active virus with cocktail therapy using combinations of new medicines (known as highly active anti-retroviral treatment; HAART).
- HIV-1 virus encodes a trans-activating regulatory protein (Tat), which is essential for increased transcription of all HIV genes to cause explosive viral generation. However there is also a high possibility that the virus can become active again after an incubation period. The mechanism of virus reactivation after the incubation period is due to a viral protein called Tat, which activates viral transcription. The Tat protein plays the role of a molecular switch that shifts between the latent period and the active period. Subsequently, the Tat protein is essential for active viral replication and absolutely critical while the incubation period is transitioning to the active period. Tat therefore represents a promising HIV target for both acute and chronic conditions.
- Of particular note, the transcription process initiated by this protein involves multiple viral proteins and transcription factors from the host cell. It is expected that the possibility of virus appearance with resistance to the drug that can suppress this process is very low. From this perspective, targeting Tat is expected to have a unique effect and our HIV-1 candidate that is being developed will be applicable for acute cases, carriers or patients who are suspected to be carriers and chronic stages as well.

Status

- We are currently in the stage of discovery and optimization of active ingredients. Ongoing efforts are focused on establishing a peptide library that can suppress Tat-TAR interaction and verification of activity. At the same time, we are progressing with peptide modification to increase cell permeability and stability.

Intellectual Property

- Patent Application Date: Oct. 2013
- Trustee: Seoul National University. University-Industry Cooperation
- Patent Application No: 10-2013-0123709
  - Patent Title: The production method of cytopermeability peptide by using disulfide composition and its usage.
- Inventor: Jaehoon Yu and others.

Competitive Advantages

- Clear differentiation against competitors for licensing-out
- The active peptide obtained can be used during both active and incubation periods of the HIV virus and inhibits viral replication with a new mechanism of action.
- No mutation of Tat-TAR has yet been identified and the possibility of viral drug resistance is expected to be low.of the 4-week rat toxicity test. As a result, limited side effects and toxicity during clinical testing are expected.

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Institut Pasteur Korea (IP-K)

Lead optimization of TU: A new hepatitis C virus drug candidate with a novel mechanism of action

Code Number : KDDF-201312-10

Development & Market Objectives

- Institut Pasteur Korea (IP-K) identified TU a novel hepatitis C virus (HCV) inhibitor by phenotypically screening of small molecule libraries using infectious virions. Mechanism of action (MoA) studies demonstrated that IPK ES-1 inhibits at least early steps of the HCV life cycle. During structure-activity-relationship studies (SAR) a Lead molecule was identified with good antiviral efficacy and good DMPK properties.
- After Lead optimization our goal is to move towards a pre-clinical candidate, and together with an industrial partner we aim to enter pre-clinical stage to further develop a global novel drug candidate for a market size exceeding 15 billion USD annually.

Unmet Medical Need & Target Patients

- More than 200 million patients worldwide are chronically infected with HCV and are at risk of developing life-threatening liver diseases. There are no vaccines available yet and despite the recent approval of direct-acting antiviral agents (DAAs), the standard of care is a therapy with pegylated interferon-alpha (PEG-IFNα) and ribavirin (RBV), associated with an unsatisfactory sustained virologic response rates (SVR) of only 70-80 % and accompanied by serious side effects. Furthermore, DAAs have high economic burden to patients which will significantly limit access to therapy. In anticipation of potential therapy concerns like drug intolerability, viral drug resistance, etc. therapeutic options for patients and clinicians (personalized therapy) are needed.
- Targeted patients are all chronic HCV carrier by combinatorial therapy of IPK ES-1 together with other DAAs, and because of the MoA, our drug will be potentially particular suitable for pregnant women and liver transplant patients preventing mother to child transmission and re-infection of the new organ, respectively.

Status

- IPK ES-1 represents a new approach to the treatment of chronic hepatitis C. Identified by a phenotypic target free screening campaign IPK ES-1 is currently undergoing lead optimization by further improving already acceptable DMPK properties. Because IPK ES-1 has a novel MoA, inhibiting early and late steps in the HCV life cycle, in-depth characterization and confirmation of the putative molecular target envelope glycoprotein E1 is ongoing.

Intellectually Property

- Patent filed: April 2014
- Assignee: Institut Pasteur Korea
- US provisional application No. 61/980,940: PCT
- Title: Inhibitory molecules targeting HCV
- Subject of invention: Composition of matter (chemical compounds) and their method of use (treatment of HCV)
- Inventors: Windisch *et al.*

Competitive Advantages

- IPK ES-1 is a first-in-class HCV inhibitor interfering with of early and late steps in the viral life cycle.
- Outstanding antiviral potency.
- Inhibition of all major HCV genotypes and its subtypes.
- Synergy with selected DAAs in cell culture.
- Accumulation in target organ (>40-fold accumulation in liver).

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Qurient

Non-clinical development of Q203: A novel drug candidate against MDR/XDR tuberculosis

Code Number : KDDF-201302-01

Development and Market Objectives

- Completion of preclinical trials and entering phase 1 clinical trial for the development of a novel drug candidate against MDR(Multi Drug Resistant)/XDR(Extensively Drug Resistant) tuberculosis.

Unmet Medical Need & Target Patients

Target Patient Group

- Patients infected with MDR/XDR tuberculosis bacillus who are not receiving first or second line standard medication.
- Patients infected with TB which has susceptibility to existing drugs.

Unmet Medical Needs

- Tuberculosis (TB) is a common infectious disease worldwide. TB infection has been challenging to control due to concurrent infections with HIV/AIDS and the rapid emergence of multi-drug resistant/extensively drug resistant (MDR/XDR) tuberculosis bacillus, despite continuous improvements in medical treatment and health care management systems.
- According to a WHO and TB alliance report, two billion people, one-third of world's population, are thought to have been infected by tuberculosis bacillus. In 2010, there were an estimated 1.4 million associated deaths.
- The development of novel drugs has been delayed largely because tuberculosis has been regarded as a third world disease for the last fifty years. In addition, the market attractiveness for pharmas has been low due to low cost historical medicines such as isoniazid. However, the overall market size of anit-tuberculosis drugs is rapidly increasing due to economic growth in high burden countries including China, India and Russia The need for novel drugs against MDR/XDR tuberculosis is also increasing due a growing incidence rate of MDR/XDR TB in Western countries,.

Status

- Q203 has shown strong efficacy in TB animal model.
- Q203 has shown strong bactericidal efficacy against MDR/XDR TB in clinical isolates.
- The mechanism of action - targeting the QcrB subunit of the cytochrome bc1 complex in the TB electron transfer system has been identified.
- Q203 has been shown safety through preliminary toxicity tests in rodent and non-rodnet species.
- Preclinical studies are now in progress to support human clinical study.

Intellectual Property

No.	Patent Title	Published to	Publication Date	Published to	Publication Number
1	ANTI-INFECTIVE COMPOUNDS	PCT	2011-03-11	PCT	PCT/EP2011/001345

Competitive Advantages

- **First-in-Class** : Q203 has novel mechanisms of action and inhibits the cytochrome bc1 complex and ATP synthesis in TB.
- **Strong efficacy** : Even at low concentrations, Q203 exhibits strong efficacy in chronic tuberculosis experimental models. Low dosages of the compound are sufficient for effective treatment.
- **Efficacy against resistant strains** : The candidate has proven its strong efficacy against MDR/EDR TB using clinical isolates.
- **High selectivity** : Q203 has high selectivity against TB and minimizes side-effects such as eneteric bacterium elimination.
- **Improvement of quality of life for patients** : Q203 has been proven to reduce post-infection inflammation via animal testing and minimizes lung damage.
- **Medical cost reduction** : A short synthesis pathway enables significant reductions for the cost of production and its related expenses.

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Legochem Biosciences

Clinical development of novel Oxazolidinone antibiotics LCB01-0371

Code Number : KDDF-201112-02

Development and Market Objectives

- To complete Phase 1 study for a new oral oxazolidinone (LCB01-0371), for the treatment of Methicillin-resistant Staphylococcus Aureus (MRSA) and Vancomycin-Resistant Enterococci (VRE) infections.
- To develop an intravenous (IV) formulation and license to global pharmaceutical companies following Phase 2a clinical studies

Unmet Medical Need & Target Patients

- Since it was first discovered in the 1960s, the increase in methicillin resistance in the human pathogen S. *aureus* (known as MRSA) has increased sharply from 2% of cases in 1974, to 22% in 1995 and 50% in 1997. According to the US Center for Disease Control, 94,000 patients were infected with MRSA in 2005, of which 19,000 died. In 2009, there were 1.10 million reported cases of MRSA infection in seven main countries around world, including 738,000 in the US alone.
- As bacterial resistance to antibiotics like methicillin increases, the need to develop more effective treatments has become a global health challenge. The IDSA (Infectious Diseases Society of America) is currently engaged in a campaign to secure 10 new antibiotics by the year 2020. A portion of this campaign is aimed at lobbying for government support to ease FDA regulations, with the ECDC (European Centre for Disease Prevention and Control) in agreement.
- MRSA, VRSA (Vancomycin-resistant Staphylococcus aureus) and VRE are a series of multi-drug resistant strains which exhibit resistance to most first-line antibiotics, including beta-lactams and quinolones. For highly resistant bacterial strains, the only existing treatments are Vancomycin, Zyvox, Cubicin and Synercid, and the only oral medicine is Zyvox. However, Zyvox cannot be used for more than two weeks due to side-effects of marrow toxicity, while Cubicin exhibits low efficacy toward infections of the respiratory tract and causes side-effects in skeletal muscle.
- A number of pharmaceutical companies have attempted to develop new antibiotics that can overcome the side-effects and disadvantages of Zyvox, but as yet there have been no significant breakthroughs. Two Oxazolidinone candidates have entered the clinical stage, but have failed to show distinctive improvements in safety. Therefore, the development of a second generation antibiotic that can overcome the disadvantages of Zyvox with rapid efficacy and minimal side-effects has the potential to become a blockbuster product.

Status

- LCB01-0371 has completed Phase I SAD (Single Ascending Dose) and MAD (Multiple Ascending Dose) for 21 days clinical trial in healthy adults and is currently preparing Phase IIa.

Intellectual Property

- 5 patents applied originally in Korea, all registered.
- PCT registered in ten countries including the US, Europe, Japan, China.
- PCT pending in three countries

Competitive Advantages

- Significant problems exist with current Oxazolidinone antibiotics: There is a need to improve the time course of myelosuppression and solubility.
  Linezolid (Zyvox®) is an oxazolidinone antibiotic marketed by Pfizer since 2000, and has maintained its position in the spotlight as the first member of a new class of antibiotics in over 35 years. However, it cannot be injected during long term treatment using a time course approach for myelosuppression, and can only be used by infusion injection due to low solubility.
- The distinct advantages of our current candidate can be divided broadly into five features:
  - Excellent safety: Can be injected long-term for short time courses of myelosuppression.
  - Superior effect: Exhibits superior effects in animal tests and is effective against some strains of gram negative bacillus.
  - Improved solubility: Can be used both orally and through injection, due to excellent water-solubility.
  - Excellent pharmacodynamics: Exhibits long post-antibiotic effects for extended efficacy duration.
  - Possibility to expand indications into multiple-resistance tuberculosis treatments (MDR-TB) with distinct safety advantages: Exhibits excellent effects against multiple-resistance tubercle bacillus. 30-day injection periods in animal testing showed the resultant concentration of tuberculosis bacilli to be 50 times lower than that achieved by Linezolid, with sterilizing power 4 times higher (MBC 99).

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Legochem Biosciences

Development of New Antibiotics against Gram Negative Pathogens LCB10-0200

Code Number : KDDF-201212-13

Development and Market Objectives

- Enter clinical Phase I after completion of preclinical studies. After completion of Phase I, the candidate will be developed for co-administration with a beta-lactamase inhibitor, a number of which are currently under development by global pharmaceutical companies.

Unmet Medical Need & Target Patients

- With the recent emergence of multiple drug-resistant bacteria, the focus on gram-positive bacteria (especially MRSA) has increased. However, research into strains of gram-negative bacteria, which more frequently infect elderly and severely ill patents, has been relatively low.
- Currently, very few effective drugs for gram-negative bacteria exist, particularly for Pseudomonas aeruginosa and Acinetobacter baumannii in particular, develop resistance to multi-drugs. In addition, resistance is becoming a serious problem for drugs targeting individual strains.
- The Infectious Diseases Society of America (IDSA) has been emphasizing the need to develop antibiotics, initiating a campaign to secure 10 new drugs by 2020. This underlines the current lack of efficacious drugs, particularly those concerning gram-negative bacteria. The IDSA has underlined the magnitude of the current need by stating that while "better drugs" are needed for gram-positive bacteria, for gram-negative bacteria "any drug" will do, at least for now.

Status

- Samples are currently in production for preclinical trials, with GLP-Tox (rat, dog) studies scheduled for the latter half of this year.
- Efficacy was evaluated with systemic infection model and thigh infection model in mouse. Additionally, various animal model studies are underway (including respiratory organ infection, urinary tract infection and skin infection)
- PBP binding assays are being conducted to identify the mode of action
- Beta-lactamase stability tests are in progress to identify effects on resistant bacteria
- Combination effects with BLI are awaiting confirmation

Intellectual Property

- 1 patent applied originally in Korea, currently pending
- PCT registered in the US
- PCT pending in ten countries including Europe, Japan and China

Competitive Advantages

- Candidate LCB10-0200 is effective against key gram-negative bacteria, particularly P. *aeruginosa* and A. *baumannii*. When used in combination with beta-lactamase inhibitors, the compound is effective against the key gram-negative species including K. *peumoniae*, and E. coli.

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Asan Medical Center

Development of lead candidates for non-alcoholic steatohepatitis and liver cirrhosis using natural compound analogues

Code Number : KDDF-201406-03

Development and Market Objectives

- Non-alcoholic steatohepatitis (NASH) and liver cirrhosis are prevalent and serious diseases, but effective treatment options have yet to be developed. In this study, we are focusing on the development of an innovative new therapeutic that will inhibit the generation and progression of NASH and cirrhosis.

Unmet Medical Need & Target Patients

- Along with the rise in obesity due to the increasing popularity of the Westernized diet, non-alcoholic liver disease (NAFLD) is increasing. The prevalence of NAFLD is approximately 20% and it is the most common cause of liver dysfunction. Some forms of NAFLD appear in the form of NASH that involves the destruction of liver cells and can proceed to cirrhosis or liver cancer via liver fibrosis.
- NASH is one of the most significant causes of cirrhosis and liver cancer in developed countries where viral hepatitis is decreasing. Approximately 20 percent of NASH patients progress to cirrhosis that leads to death, due to failure of the liver or malignancy. According to a recent meta-analysis, NASH, compared to simple fatty liver disease, has a 5.7-fold higher risk of death, which increases to 10-fold if accompanied with liver fibrosis.
- However, there are no evidence-based treatments for the clinical effects on NAFLD available, especially therapeutics that can prevent the generation of NASH or the progression to cirrhosis.

Status

- We found that a natural compound can inhibit the generation of NASH and the progression to cirrhosis via activation of NLRP3 inflammasome. With potency from at least 10-fold lower concentrations of the natural compound derived from structural analogs of that compound, 8 leading candidates have been identified that inhibit the activation of NLRP3 inflammasome. We are planning to select 2-3 optimized lead candidates through studies of:
  - Target validation
  - In vitro efficacy and in vitro DMPK/ toxicity
  - In vivo PK
  - In vivo efficacy

Intellectual Property

- A patent application has been submitted

Competitive Advantages

- Structural analogs of the natural compound, with potent efficacy confirmed by our researchers, are highly novel and excellent candidates for patent protection.
  - Structurally, they belong to a class of novel compounds that have not been previously reported and related compounds have not been developed for therapeutic purposes for the treatment of NAFLD, NASH and liver cirrhosis.
  - Accordingly, patent protection for the compounds' structural aspects and their usage is highly likely, and activity of the lead candidate is significantly superior to the natural compound. Both Korean and international PCT applications are planned upon finalization of the lead substance.

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CJ HealthCare

Global Development of CJ-12420, the next generation acid suppressant

Code Number : KDDF-201404-10

Development and Market Objectives

- CJ-12420 belongs to a new class of acid secretion inhibitors called potassium-competitive acid blockers (P-CAB). Based on the outstanding pharmacology results of pre-clinical and phase 1 clinical studies, we would like to maximize the licensing value of CJ-12420 by executing preclinical and clinical studies for differentiated efficacy and long-term safety. CJ-12420, the next generation acid suppressant, is expected to be a global blockbuster drug with clinical development in the world's key "pharmerging" markets including China.

Unmet Medical Need & Target Patients

Target Patient Population:

- Target patients of CJ-12420 are people with acid related diseases such as peptic ulcer, gastroesophageal reflux disease, and H.pylori infection.

Unmet Medical Needs:

- Acid-related diseases means various digestive disorders associated with gastric acid including gastric ulcer, duodenal ulcer, erosive esophagitis, and non-erosive reflux disease, etc. Acid related diseases can be cured, or at least the symptoms can be alleviated significantly by inhibiting gastric acid secretion.
  It has been reported that these diseases are increasing due to aging, obesity, alcohol, and caffeine. We expect more than 250 million patients occur in world pharmaceutical market by 2020. There is more than $ 30 billion prescription drugs for gastrointestinal disorders by 2020, which is the largest market in the entire drug treatment industry.
- Especially, gastroesophageal reflux disease(GERD) is a disease type in developed countries and it's incidence in the developed world is very high at about 20%. By increasing factors such as aging, obesity, and mental stress, GERD incidence is continuously growing. GERD is the conditions that result in discomfort or complications due to The contents of the stomach to reflux into the esophagus. It is classified into erosive esophagitis (EE) and non-erosive reflux disease (NERD), and caused complications in severe condition. Heartburn and acid reflux symptoms are typical symptoms. Chronic pain is most often and recurrence rate of the disease is very high
- Acid suppressants have been the biggest-selling drugs worldwide since the release of H2 receptor antagonists in 1970s and introduction of proton pump inhibitors in late 1980s. Proton pump inhibitor(PPI) currently holds the major part of acid suppressant market, but has identifiable limitations related to its mode of action; it requires several days to achieve maximum suppression, is less efficacious when administered post-prandially, and has large individual differences. The purpose of this study is to develop CJ-12420, the next generation acid suppressant as a global blockbuster drug that overcomes the limitations addressed by currently available PPI.

Status

- CJ-12420 showed potent inhibitory effect on H+/K+-ATPase from human, pig, and dog. We also confirm the high selectivity between Na+/K+-ATPase and H+/K+-ATPase.
- CJ-12420 totally suppressed acid secretion in Heidenhain pouch (HP) dog compared to 80% inhibition of Revaprazan at 3mg/kg. Phase 1 results showed dose dependent acid suppression, potent efficacy and fast onset time. We are doing phase 2 study in EE patients, and have a plan to perform phase 3 in EE patients after completion of phase 2.

Intellectual Property

- Patent registration was completed in the major countries in Korea, China, Honkong, and the United States

Competitive Advantages

- PPIs, current mainstay of acid related disease, are acid-activated pro-drugs that require consumption of food for stimulation of proton pumps because they only bind to active proton pumps. CJ-12420, on the other hand, binds to both resting and stimulated pumps, which exerts potent efficacy under any gastric conditions.
- **Pharmacology**
  - Inhibition of both resting and activated gastric H+/K+-ATPase
  - Highly selective inhibition of gastric H+/K+-ATPase
- **Pharmacokinetics and Drug Metabolism**
  - Rapid absorption
  - Low risk for drug-drug interaction
- **Safety**
  - Safe and well tolerated in various clinical studies including 300 patients
  - No clinically significant liver toxicity reported
- **Pharmacokinetics/Pharmacodynamics**
  - Rapid absorption within 0.5 to 1.5 hour
  - Rapidly increased median pH>4
  - Complete control of NAB upon administration before bed
  - Remarkably similar acid suppression profile in both fed and fasting state

- We are planning to conduct preclinical and clinical studies for demonstrating distinctive efficacay/safety data in parallel with our own domestic phase 3 trial. Via those study results, we are expecting to enhance licensing value and to establish stable business foundation for global market entry. The important thing for licensee would be not only differentiated pharmacology and development risk but also domestic market entry of drug. Quicker market entry can make them achieve profit more. Therefore, the fast launch to their market make the drug very attractive and increase licensing value. We are also striving to maximize the licensing value through preemptive execution of long-term toxicity studies, and initiation of clinical development in China.

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SK Biopharmaceuticals

YKP10811, A Drug for Functional Gastrointestinal Disorder : Global Clinical Phase 2b Development

Code Number : KDDF-201402-12

Development and Market Objectives

- SK Biopharmaceuticals Co., Ltd. has developed a partial agonist for the 5-HT4 receptor and completed extensive preclinical efficacy tests for chronic idiopathic constipation (CIC) and irritable bowel syndrome with constipation (IBS-C). Phase I clinical trials have verified its excellent safety and tolerability. Phase IIa clinical trial have focused on its ability to improve motility in the upper and lower gastrointestinal tract in patients with CIC, and further confirmed its efficacy and safety. On the basis of these results, phase IIb clinical trial is currently in progress to determine the optimal dosage.
- A technology transfer agreement is currently planned, by entering into a partnership with a multinational corporation or a professional pharmaceutical company specializing in gastroenterology at the completion of phase IIb trial, so that the candidate can enter the market with maximal sales potential.

Unmet Medical Need & Target Patients

Unmet medical needs

- Propulsid (cisapride) and Zelnorm (tegaserod), accelerate gastrointestinal motility and received considerable attention when first marketed. However, due to issues with potential side effects on the cardiovascular system, they were withdrawn in 2001 and 2007, respectively. Unmet medical needs then increased for IBS-C, CIC and gastroparesis. Existing laxatives, bulk agents and stool softeners retain many issues including lack of potency, potential side effects and a lack of long-term efficacy. Recently launched secretogogues(Amitiza/Linzess)) have made some progress in the CIC field by increasing moisture content in the colon, but disadvantages include lack of efficacy for an approximate 20% of patients with very slow intestinal movement, or no improvement in upper bowel movement and questionable efficacy for reducing pain in patients with CIC. Therefore, new therapeutic options that will provide significant and effective improvement in both upper/lower gastrointestinal motility, less side effects, and long term efficacy is strongly needed.

Target patient group

- The target patient groups for YKP-10811 are CIC and IBS-c patients. In regards to CIC, there are currently 92 million patients in the world's 7 major markets, including the USA, which includes approximately 14% of the adult population. For IBS-c, approximately 15% of the adult population suffer from IBS-C.

Status

- The development of a prokinetic drug is currently in progress to optimize a selective partial agonist of the 5-HT4 receptor which can address the unmet medical needs described above.
- Through various preclinical tests, its efficacy has been verified with extensive and strong improvements in upper/lower gastrointestinal motility and lasting effects during long term treatment. Phase I trials verified its excellent in pharmacodynamic properties, favorable side effects, and its tolerability safety margin is at least 50 times higher than its effective dose range.
- A phase IIa trial (http://www.clinicaltrial.gov/, NCT01523184) verified its efficacy in human, while safety parameters were confirmed for long-term treatment via preclinical long-term toxicity tests (six months in rats, six and nine months in dogs).
- Currently, a phase IIb trial is underway (http://www.clinicaltrial.gov/, NCT01989234) to determine the optimal dosage, in addition to carcinogenicity testing as mandatory requirements for approval. Phase II trials are also in progress for Korean patients with IBS-c through a domestic technology transfer agreement with SK Chemical Co., Ltd. (http://www.clinicaltrial.gov/, NCT02082457). Business development is in progress to seek a global technology transfer agreement at the completion of the phase IIb trials.

Intellectual Property

- Current patent status: International patents applied for in 2008.
- Patent coverage: substance patent including YKP10811

Competitive Advantages

Superior efficacy compared to existing medications

- YKP10811 exhibits a superior effect in animal models compared to existing medications such as tegaserod and prucalopride, suggesting the potential for strong efficacy in clinical trials.

Possibility of indication expansion

- ThPotential extensive efficacy in the entire gastrointestinal tract
  - Animal model tests and phase IIa results show that YKP10811 accelerates motility throughout the upper and lower gastrointestinal tracks. This underlines the potential for an expansion of indications to other disorders such as functional dyspepsia or gastroparesis.
- Reduction of abdominal pain
  - YKP10811 exhibits efficacy in an abdominal pain model, and is therefore expected to be efficacious for IBS-c, to be verified in clinical trials conducted by SK Chemical Co., Ltd.
- Safety
  - In comparison to existing drugs with identical mechanism of action including cisapride, YKP10811 exhibits high selectivity in terms of hERG and its QTc risk is very low. In addition, compared to tegaserod, it does not act on other subtype serotonin receptors (5-HT1B/1D, etc.) implying that the risk of cardiovascular ischemia would be relatively low.
- Long-term efficacy
  - Unlike existing 5-HT4 agonists in which efficacy is disappeared if treated for long-term, YKP-10811 has been confirmed to have long-term efficacy in animal models of abdominal pain.

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HanAll BioPharma Co., Ltd.

Development of New Antibody Therapeutics of Novel Mechanismfor the Treatment of Severe Autoimmune Diseases

Code Number : KDDF-201410-02

Development and Market Objectives

- The final objective of this project is to develop a novel antibody drug for the treatment of various autoimmune diseases mainly caused by autoantibodies.
- We aim to select the antibody candidate for the nonclinical study and conduct cell line development, production process development, animal efficacy study and non-GLP toxicity study and so on.

Unmet Medical Need & Target Patients

- The first target indications are pathogenic IgG-mediated autoimmune diseases like pemphigus vulgaris, neuromyelitis optica and myasthenia gravis. In addition, immune complex-mediated glomerular diseases like lupus nephritis and membranous nephropathy could be applied.
- There is no specific medicine for these indications. In the case of pathogenic IgG-mediated autoimmune diseases, high dose of steroid, high dose of IVIG therapy and plasmapheresis are current treatment option for the patients. However, current treatment options have significant limitations in terms of efficacy, safety and treatment cost. So, the development of a new treatment option is urgently required.

Status

- Two antibody candidates were selected through antibody screening study and in vitro and in vivo tests.
- The selected two antibody candidates showed excellent catabolism effect of decreasing endogenous IgG more than 70% in PK/PD studies in non-human primates.
- In order to select the final candidate antibody, PK/PD study in non-human primates is ongoing. In addition, we are conducting cell line development, production process development, formulation study, MOA study and animal model study and so on.

Intellectual Property

- We have applied several material patents related to the lead antibody
  - KR 2011-0139472
  - KR 2013-0071185
  - PCT/KR2014/005495
  - US61/986742

Competitive Advantages

- There are concerns over an imbalance between supply and demand of plasma-derived product, IVIG, due to an increased demand for plasma. However, this supply and demand issues for HL161 anti-FcRn monoclonal antibody will be stable because it will be produced by recombinant technology.
- In the case of IVIG, the price for a single treatment reaches $10,000~20,000 with standard dosage of 1~2g/kg, but the treatment cost of HL161 will be significantly lower than IVIG since it will be effective at 10~20mg/kg in the patients.
- HL161 can effectively suppress autoimmunity against autoantigens through increasing catabolism of pathogenic autoantibodies, thus exert therapeutic effect on various severe autoimmune diseases.
- HL161 shows excellent efficacy in comparison with IVIG and anti-FcRn antibodies that other companies are developing

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HANDOK INC.

Clinical Development of Therapeutic Agent for Auto-Inflammatory Diseases

Code Number : KDDF-201404-05

Development and Market Objectives

- The final research goal is approval in Korea for 3 rare disease indications by 2017 and global or local licensing-out .

Unmet Medical Need & Target Patients

Target Patients

- Prevalence rate has been reported as 1/1,000,000. Approximately 300-500 patients are reported to be in the USA.
- Incidence rate is 0.4-0.8/100,000.
- According to overseas data, the prevalence rate is 0.16-1.47/100,000.

Unmet Medical Need

- No drugs have been approved for the treatment of A, B, or C in Korea. However, A disease can be treated with Anakinra which imported through Rare Disease Centre and covered by insurance. Anakinra is inconvenient as it should be injected in every day. The anti-IL-1 therapeutics such as neutralizing antibody and receptor typed biologics are not importing to Korea and too expensive. B and C cause more severe symptoms than general r?rheumatoid arthritis and have a higher severity. There is no standard therapy in B and C, and also, the response rates for TNF-blocking biologics are not good. However, IL-1 blockade are expected to be effective in treatment of B and C based on several investigator initiated studies.

Status

- A clinical Phase I study has completed in healthy adults at Seoul National University Hospital.

Intellectual Property

No.	Registration number	Register	Patent Title	Country	Domestic/ Overseas	Registration Date
1	10-1333958	HANDOK INC	Human interleukin-1 acceptor antagonist-hybrid F c fusion protein	Korea	Overseas	Nov. 21, 2013
2	PCT/ KR2011/007809	HANDOK INC	Human interleukin-1 acceptor antagonist-hybrid F c fusion protein	Overseas	Overseas	Oct. 19, 2011
3	8883134	HANDOK INC	Human interleukin-1 acceptor antagonist-hybrid F c fusion protein	US	Overseas	Nov. 11, 2014

Competitive Advantages

- Inhibits both Interleukin 1-alpha and Interleukin 1-beta.
- With new hybrid Fc technology, in vivo half- life of the fusion protein is increased, and safety and convenience for patients has been improved significantly by eliminating ADCC and CDC function while retaining fusion protein activity levels.

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Sookmyung Women's University

Development of lead componds for rheumatoid arthritis therapy by using cytokine-derived peptide SIS-1

Code Number : KDDF-201404-04

Development and Market Objectives

- The development objective is to generate lead compounds as a novel therapy to treat rheumatoid arthritis based on a Erdr1-derived peptide SIS-1 that has been observed to exhibit anti-inflammatory effects and improvement of rheumatoid arthritis in CIA mouse model.

Unmet Medical Need & Target Patients

- Currently prescribed drugs to treat rheumatoid arthritis include TNF inhibitors, which are primarily focused on easing of symptoms rather than a cure of the disease. The percentage of patients reporting a 70% improvement in terms of symptoms is only around 15%, while that of the patient group with very low reactivity (patients who do not reach ACR20) is approximately 30%. In addition, considering drug resistance issues and severe side effects, the developments of new medicines that address these problems are critically needed.
- Recently, interest in the use of biologicals with a different mechanism-of-action to TNF inhibitors has been increasing. Therefore, needs of new developmental therapeutics with novel mechanisms has been recognized by the medical community.
- Our research team attempts to develop therapeutic lead compounds for rheumatoid arthritis therapy by using Erdr1-derived peptide SIS-1 with novel mechanism-of-action. It targets a novel inflammatory cytokine control mechanism by focusing on the fact that the amount of inflammatory cytokines such as IL-17 remains high after treatment in TNF-refractory patient groups. Evidence suggests that the amount of inflammatory cytokines such as IL-18/IL-32 increases in rheumatoid arthritis patients.

Status

- Establishment of the optimal efficacy of SIS-1 for RA therapy in CIA mouse model.
- Verifying the inhibitory function of Erdr1/SIS-1 toward inflammatory cytokines.
- Target identification and validation of relevant mechanisms are in progress.

Intellectual Property

- Domestic application 10-2012-0072513
- PCT application PCTKR20131005912
- Securing of substance patent
- Progressing with patent protection in 10 major countries.

Competitive Advantages

- Development of a novel therapeutic target that is highly effective on TNF inhibitor refractory patients by targeting a different mechanism to that of TNF inhibition.
- 'First-in-class' investigation of the therapeutic potential of Erdr1 which has been implicated with anti-cancer and anti-inflammatory effects.
- Domestic licensing-out is in progress via joint research with domestic and overseas pharmaceutical companies through continuous contact. The possibility of a successful international licensing deal is high.

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Cellinbio co., ltd

Lead development: Development of drug candidates for rheumatoid arthritis using immunomodulatory cytokine

Code Number : KDDF-201404-02

Development and Market Objectives

- Rheumatoid arthritis (RA) is characterized by pathogenic mechanisms that include synovial inflammation as well as the progressive destruction of cartilage and bone.
- Particularly, CD4+ T-helper cells that express interferon (IFN)-γ and interleukin (IL)-17 (TH1 and TH17 cells) and macrophages, which are infiltrated in synovium, are considered to be the main drivers in the pathogenesis of RA.
- Recently, various approaches, such as specific monoclonal antibodies against inflammatory cytokines and chemical inhibitors, have been widely undertaken for RA treatment.
- However, they have not yet been sufficient unmet medical need, because the targets usually are end product and/or involved in only one pathway function at the downstream.
- We previously reported that immunomodulatory cytokline, CIB13034H transiently affected MHC class II expression on B cells via increasing cAMP.
- Here we demonstrated that CIB13034H, which may function at upstream, ameliorated RA symptom in a mouse model in vivo via suppressing differentiation of TH1 and TH17 cells as well as activation of macrophage.
- Moreover, CIB13034H generally inhibited LPS-triggered inflammation.
- Our observation suggests that tIK cytokine can systemically function as a counterbalance against inflammatory cells, which are related with RA induction, and thus, it could become new therapeutic agent for the treatment of RA.

Unmet Medical Need & Target Patients

Target Patient

- Rheumatoid arthritis is a chronic auto-inflammatory disease characterized by polyarthritis. The inflammation at joint membrana sinovial cause destruction of cartilage and bone that leads to destruction and modification of joint. The anemia, scleratitis, pulmonary diseases, vasculitis and osteoporosis may occur as a result.
- Rheumatoid arthritis has been shown that 0.2 male per 1,000 and 0.4 female per 1,000 annually and has relatively even prevalence of 0.4%~1.0% around the world.

Unmet Medical Needs

- Current rheumatoid arthritis drugs such as non-steroidal anti-inflammatory drugs (NSAID), steroids, conventional disease modifying anti-rheumatic drugs (DMARD) and biological disease modifying anti-rheumatic drugs (bDMARDs) are unsatisfying to maintaining low disease activity and may cause side effect after long-term medication.
- Most of current rheumatoid arthritis are antibody therapeutics that shows no medical effects approximately at 30% of rheumatoid arthritis patient. Also, very high priced and may occur complications with pneumonia, tuberculosis, herpes zoster and suppuration.
- Therefore, the new rheumatoid arthritis therapeutic agent with less or none side-effects is urgently needed.

Status

- A new peptide candidates derived from immune response control cytokine has been secured.

Intellectual Property

- Korean patent application No.10-2014-0038809 (2014. 01. April)
- PCT application No. PCT/KR2014/003282 (2014. 24. April)

Competitive Advantages

- As existing drugs of rheumatoid arthritis have several controversial points such as 1) efficacy avoidance 2) high price 3) side effects, the effect of treatment is limited.
- CIB13034H drug has a new meaning as a biological drug aims new target over antibody drugs for inflammatory cytokine.

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Oscotec Inc.

Oscotec Inc.

Development of SYK inhibitor for Rheumatoid Arthritis

Code Number : **KDDF-201402-05**

Development and Market Objectives

- SKI-O-703 (mesylate salt of SKI-O-592) is currently under development as a preclinical candidate for the treatment of rheumatoid arthritis. SKI-O-592 inhibits spleen tyrosine kinase (SYK), which is a characterized drug target for autoimmune diseases.
- Our market objective is to out-license SKI-O-703 to a global pharmaceutical company. Oscotec Inc. aims to conduct a phase I clinical trial in compliance with the US FDA based on existing data. Oscotec's data reveals high selectivity, superior efficacy in in vivo models and a high-level of safety in rodents.

Unmet Medical Need & Target Patients

Unmet medical needs:

- Low molecular weight drugs from the DMARDs family are the current gold-standard for treatment of rheumatoid arthritis. However, they suffer from low efficacy, frequent cases of non-responsiveness and a variety of adverse events.
- Biologics often exhibit reasonable efficacy, but many patients are non-responsive to them. Moreover, high costs, limited administration routes (injection is the only validated administration route) and potential tumor formation are points of concern in using biologics for anti-rheumatic applications. Therefore, the key unmet needs for rheumatoid arthritis medicines are summarized as follows:
  - Achievement of adequate therapeutic efficacy for patients who are non-responsive to existing medicines,
  - Management of adverse events to a low level coupled with high selectivity,
  - Maintenance of economic feasibility through low molecular weight synthetic drugs,
  - Improvement in convenience via oral administration.
- Target patient population: Patients with rheumatoid arthritis, those who are non-responsive to MTX and biologics.

Status

- The candidate SKI-O-703 is currently in preclinical development in preparation for an IND submission to the US FDA
- The preclinical study was completed at US CRO (2014). SKI-O-703 shows good Tox profile and excellent safety margin in rat and dog via oral administration (>30-fold margin of safety).
- The IND application will be submitted in the third-quarter of 2015.

Intellectual Property

- The legal groundwork has been laid for the development of SKI-O-592, which will protect its novelty and competitiveness. Key scaffolds are filed in the PCT application and in patent applications across 18 countries. Patent that includes SKI-O-592 has been filed for US and PCT patents.

Competitive Advantages

- Rigel Pharmaceuticals, Inc. (CA, USA) has been developing an SYK inhibitor called R788. However, its documented clinical performance, both in terms of efficacy and adverse events, has fallen below expectations due to low selectivity. P505-15, from Portola Pharmaceuticals, Inc. (CA, USA) exhibits high selectivity, but the experiments have also revealed a high level of toxicity and low bioavailability.
- The preclinical candidate SKI-O-703 demonstrates superior selectivity to SYK, improved bioavailability and a low level of toxicity. It has been established from in vivo models that SKI-O-592 and SKI-O-703 has better efficacy and safety characteristics when compared to existing SYK inhibitors. A leading pharmaceutical company has contacted Oscotec Inc. via an international conference. Currently, with a CDA in effect, publication strategies for the scientific data are being discussed.

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Hanyang University

HANYANG UNIVERSITY

(Hanyang University Department of Biology)

Generation of lead compound of transcutaneous delivery peptide (TDP) for atopic dermatitis

Code Number : **KDDF-201312-15**

Development and Market Objectives

- Our primary objective is to develop a safe and unique biomaterial for the treatment of intractable allergic disease (atopic dermatitis). A cell-penetrating peptide has been investigated with extensive research and developed into a transcutaneous delivery peptide, a drug delivery system that can penetrate the skin barrier.

Unmet Medical Need & Target Patients

Target Patients

- Atopic dermatitis is a chronically recurring typical allergy-type skin disease frequently accompanied by severe itchiness. The condition is widespread from toddlers to adults and the number of reported cases continues to rise. The primary target patients for our therapeutic are those with evident dermatitis symptoms including itching, dryness and eczema.

Unmet Medical Needs

- Common treatment modalities are prescribed according to treatment stage.

Degree	Treatment Stage	Treatment Method
Dry skin	1	Basic Treatment: Moisturization, inflammatory suppression, identification of allergen
Slight ~ Moderately Serious	2	Prescription of mild local steroid agents and a local calcineurin inhibitor
Moderately Serious ~ Serious	3	Prescription of a high potency local calcineurin inhibitor
Serious (incurable)	4	Systemic Treatment: systemic steroid prescription with cyclosporine A, UV treatment

Table 1. Common treatments for atopic dermatitis

- Progress in the development of safe and effective medicines for the treatment of atopic dermatitis has been limited (Datamonitor). This has been largely due to the fact that the modes of onset and pathological mechanisms have only been recently elucidated.
- Local steroid application is the most common treatment, but is only suitable for providing temporary relief due to side effects including skin shrinkage, blood vessel extension, bleaching, the appearance of purple spots and issues with the development of tolerance. Oral and intravenous steroid treatment is used for moderately serious atopic dermatitis. However, despite high efficacy, the steroid rebound effect is considered as a risk when prescribing this treatment. The side effect can manifest as growth impairment, obesity and other complications caused by an increased appetite. Similarly, high risks are associated with CyA and calcineurin inhibitors including red spots, flu symptoms and headaches when used continuously. As such, widespread dissatisfaction and considerable unmet medical needs exist for the treatment of atopic dermatitis.
- New treatments that are safer and address the underlying pathophysiology of atopic dermatitis are urgently needed.

Status

- We have confirmed a highly effective human cell-penetrating peptide sequence that can deliver functional biomaterial (both protein and peptide) into cells.
- Optimization of the cell-penetrating peptide is ongoing, to improve the delivery of functional biological payloads into cells through the epidermis and dermis with high efficiency.
- Two types of candidate protein have been selected, based on the mode of action characterized for atopic dermatitis.

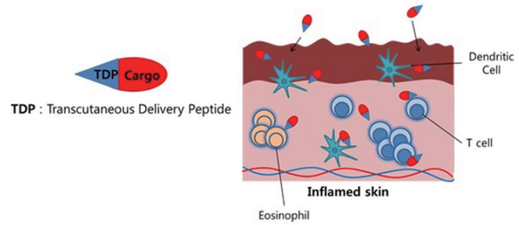
Intellectual Property

- Patents have been filed covering 6 types of cell-penetrating peptide, including sequence and domain information, as well as the cargo delivery functionality.
  (Application Numbers: 2012-0152966 / 10-2013-0120096 / 10-2013-0120095 / 10-2013-0120094).

Hanyang University

(Hanyang University Department of Biology)

Competitive Advantages



- This treatment is projected to deliver therapeutic proteins directly into cells safely and effectively using a cell-penetrating peptide based on a human protein sequence that is distinct from existing cell penetrating peptide methods (TAT, VP22: viral origin).
- Using proteins and peptides of human origin for skin treatment confers additional advantages in terms of safety and efficiency.
- The method for intracellular delivery of proteins and peptides for the inhibition of atopic dermatitis signalling is in an excellent competitive position because the market for atopic dermatitis treatment is still largely dependent on steroid agents, while the effect of newly-developed monoclonal antibodies have not been verified.
- In addition, the skin penetrating peptide currently under development has potential applications in diverse fields including not only atopic dermatitis, but also for other skin diseases and skin care needs.

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Dinona Inc.

Development and preclinical study of MD3 antibody therapeutics for induction therapy of allo-islet transplantation

Code Number : KDDF-201212-01

Development and Market Objectives

- To develop an induction treatment for the suppression of adverse reactions resulting from allo-islet transplantation.
- Pre-clinical efficacy tests for candidate antibodies, MD3 have been completed and IND approval is scheduled for completion in the near future.

Unmet Medical Need & Target Patients

The target Patient

- The target patient group consists of Type 1 diabetes patients who require islet transplantation, and includes patients with adverse reactions to islet or pancreatic transplantation, as well as patients who require islet transplantation after a kidney transplant. Severe Type 2 diabetes patients who require insulin injections may also be suitable.

Unmet Medical Needs

- The drop ratio for allo-islet transplants within one year or less has significantly improved to between 3 and 5 percent, as a result of the development of efficient immune modulation technology. However, long-term transplantation success over a period of one year remains disappointingly low. The ratio of insulin independent patients five years after islet transplantation drops to approximately 15 percent. A key cause of this phenomenon is toxicity arising from the prolonged injection of immunosuppressive preservers. There is a critical need for research and development to address this problem.

Status

- MCB was established, the whole processes related CMC was completely developed. GMP manufacturing for IND is going to conducted in Q3~Q4, 2015. Also, Non-human primate toxicity study will be ended up by Q1, 2016.

Intellectual Property

- Patents : 2 registered
- PCT Applications : 3
- Scope/extent analysis currently being conducted in different countries
  - Material: A candidate antibody highly specific for human ICAM-1 and an additional antibody that recognizes both primate and human ICAM-1.
  - Indication: Adverse reaction of cell or organ transplantation, graft-versus-host reaction, autoimmune diseases.

Competitive Advantages

- Succeeded in transplanting the world's longest pig islet into a diabetic monkey.
- Induced antigen-specific T-cell immune tolerance in non-human primates.
- Confirmed that the immune reaction toward infection in animals injected with MD-3 antibody was within the normal range and that CMV was not re-activated.
- Throughout repeated primate tests, excellent efficacy and safety confirmed.
- Treatment can be used for islet transplantation, and also as an indicant for solid-organ transplants, repression of the formation of anti-drug antibodies (ADA) and autoimmune diseases.

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School of Medicine, Yonsei University

Development and optimization of the novel sclerostin inhibiting lead compound with small molecules for the treatment of osteoporosis

Code Number : KDDF-201404-06

Development and Market Objectives

- The objective is to extract and optimize a lead compound that can accelerate osteogenesis by stimulating Wnt signal transmission in weakened and compromised bone as a new developmental concept. We aim to identify a small molecule or PPI which can selectively target sclerostin, a known endogenous Wnt signal transmission inhibitor, to promote LRP5/6 activity.

Unmet Medical Need & Target Patients

Target patient group:

- Osteoporosis patients:
  - a) Postmenopausal osteoporosis
    - Patients aged over 65 with loss of cortical bone density, increased porosity and patients with multiple fractures
    - Patients who do not respond to bisphosphonate treatment and those on drug holiday
  - b) Goal direct Rx, initial treatment
    - A new treatment strategy that dramatically increases bone density and decreases the risk of fracture at the initial stages, and maintains existing bone resorption suppressants; could be used as an initial stage medicine.
  - c) Osteoporosis, post steroid treatment
    - Sclerostin levels are high in patients on long-term steroid treatment.
  - d) Osteoporosis in males
  - e) Osteoporosis with diabetes
    - Sclerostin levels are increased in patients with diabetes.
  - f) Osteoporosis caused by limb movement disorders such as hemiplegia
    - Sclerostin is increased in all patients with immobilization.
- Fractures: Can be used for rapid recovery.
- Chronic periodontal diseases: No specialized medicines exist for periodontal diseases at present.
- Osteogenesis imperfect: Rare disease.

Unmet medical needs:

- Bisphosphonate is a typical bone resorption suppressant but causes severe side effects such as BRONJ and atypical femoral fractures, and thereby treatment is limited (3~5 years).
- Inadequate efficacy of SERM limits its effective treatment for fractures.
- Available bone resorption suppressants have already saturated the market to an extent that the development of new candidates is relatively insignificant.
  - Available bone resorption suppressants: Bisphosphonates, SERMs, Denosumab (RANKL inhibitor), and Odanakatib (Cathepsin K inhibitor).
- Treating all patients with a single medicine is impossible for chronic diseases like osteoporosis.
- The biggest limitation for existing osteoporosis medicines is the lack of effective promoters of bone formation. Therefore, such "Goal Direct Treatment" is impossible.
- Deficiency of medicines targeting cortical bones.
  - After the age of 65, cortical bone loss becomes most significant, and trabecularization of cortical bone becomes an issue.

Status

- Hit compounds are currently being identified and a lead substance is to be selected by Milestone 1 and will be optimized for Milestone 2.

Intellectual Property

- Registration of a patent is scheduled after identifying a lead substance.

Competitive Advantages

	Advantages	Disadvantages	Remarks
Bisphosphonate	Low cost Proven efficacy	Serious side effects (BRONZ and atypical femoral fracture). Stoppage after 3-5 years use (drug holiday)	Bone resorption inhibitor
Denosumab	Strong inhibition of bone resorption Continuous increase in bone density	Injected, expensive Side effects such as BRONZ	Bone resorption inhibitor Expected 2015 domestic release
Odanacatib	Bone resorption inhibition No inhibition of bone formation	Increased incidence of skin adverse events, infections and cancer	Bone resorption inhibitor Expected 2016 domestic release
PTH & Biased PTH (BA058)	Osteogenesis promoter Trabecular bone Endocortical bone	Trabecular bone Endocortical bone Treatment up to two years Bone-cancer risk Narrow therapeutic window Injected, expensive Endocortical porosity increases	Osteogenesis promoter - On the market (PTH) - Phase 3 (BA058)
Sclerostin Monoclonal Ab	Osteogenesis promoter Cortical bone Trabecular bone Cortical porosity reduction	2nd Ab generation Injected (monthly) No fracture data	Osteogenesis promoter Phase 3 started
Sclerostin Inhibitor OGX5-28 (small molecule)	Osteogenesis promoter (predicted) Can be administered orally	Lead substance No published data	Osteogenesis promoter In development

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Ewha Womans University

EWHA WOMANS UNIVERSITY

Development of intranasal insulin using TCTP-PTD

Code Number : KDDF-201402-01

Development and Market Objectives

- Our goal is to develop an alternative non-invasive method of insulin administration for diabetics who are treated with insulin injection. We are currently developing an insulin lead substance based on TCTP-PTD, originating from TCTP (translationally controlled tumor protein) which can facilitate the nasal delivery of insulin.

Unmet Medical Need & Target Patients

- Patients receiving long-term insulin therapy with invasive hypodermic injections can become averse to treatment due to pain, fear and issues related to discomfort. In addition, repeated injections can cause side effects including abnormal absorption and infections arising from skin damage. In particular, children and the elderly experience difficulty in self-administration using injectors. Therefore, the development of more user-friendly methods of insulin administration, alternative routes of insulin administration, is needed.

Status

- Using various analogues of TCTP-PTD, the development of an insulin lead substance that can be administered intranasally is underway.

Intellectual Property

- [Peptide having cell membrane penetrating activity] – Patent registered in Korea (2008), Patent registered in Japan (2013)
- [A composition for improving of insulin transmucosal ability] - Patent registered in Korea (2015)

Competitive Advantages

- Unlike PTDs derived from other virus transcription factors, TCTP-PTD (which is derived from human protein, TCTP), is expected to be a safe and versatile approach for intranasal or noninvasive delivery of bioactive molecules such as insulin. Nasal delivery of insulin using TCTP-PTD may serve the user-friendly medications that are safe and effective for the treatment of diabetes, thereby improving the clinical usefulness of insulin therapy.

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Medytox Inc.

Development of Novel T Cell Targeting Immuno-Modulators for Type 1 Diabetes Mellitus (T1DM)

Code Number : KDDF-201310-13

Development & Market Objectives

- We aim to develop a first-in-class disease-modifying medicine for Type 1 Diabetes Mellitus (T1DM) patients with minimized side effects.

Unmet Medical Need & Target Patients

- T1DM, juvenile-onset diabetes, is an autoimmune disease characterized by T cell-mediated destruction of pancreatic β cells, resulting in insulin deficiency and hyperglycemia. The incidence of T1DM has been growing rapidly, with an estimated 2 million T1DM patients worldwide and approximately 70 thousand in children under the age of 14 diagnosed annually. Although, injectable insulin therapy is an available life-saving first-line treatment, a significant unmet need exists for a highly reliable treatment option that can address the discomfort of daily subcutaneous injections and the side-effects of hypoglycemia.

Status

- We are currently developing human T cell-specific monoclonal antibodies (mAbs) and validating the candidates through in vitro/ in vivo efficacy and reliability assessments. For further pre-clinical tests on selected mAbs, generation of humanized transgenic T1DM mouse model is underway.

Intellectually Property

- Patent applications are under preparation

Competitive Advantages

- In contrast to insulin-therapy which only alleviates symptoms, our goal is to develop a disease-modifying therapy with long-term efficacy (> 6 months). Our humanized transgenic T1DM mouse model facilitates developing superior candidates . We shall develop innovative biological immuno-modulators free from non-specific activation or side effects.

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Hanmi Pharmaceutical Co., Ltd.

Study for Global Clinical Trials and Production of a next-generation diabetes drug, HM11260C

Code Number : **KDDF-201204-03**

Development and Market Objectives

- We are aiming to commercialize a next generation GLP-1 agonist that can be administered in single doses weekly or monthly, resulting in high efficacy and low side effects. This will be achieved through the development of a next generation long-acting GLP-1 agonist, which overcomes the disadvantages of existing long-acting types, through the development of a novel Exendin-4 derivative (Exendin-4 analog) combined with the use of long-acting Platform base technology.

Unmet Medical Need & Target Patients

- In 2010, the diabetes treatment market in 7 major countries recorded sales of approximately 22 billion USD (CAGR 9.9% 2006 ~ 2009).The diabetes market is expected to grow rapidly in the near future, with an increase in patients and the launching of new medicines. By 2019, it will reach a market cap of 35 billion dollars (Datamonitor, 2010).
- The ultimate goal of diabetes treatment is to maintain normal blood glucose levels. However, when taken for an extended period of time, oral medications that are widely used as treatments can irreversibly damage beta cells, which create insulin. They have also been known to cause various side effects including hypoglycemia, an increase in weight, excess lactic acid or hepatotoxicity. There are also many disadvantages of insulin usage, including a need to be injected 2-3 times daily, as well as weight gain or hypoglycemia. Accordingly, it is necessary to develop a treatment with excellent efficacy and safety, which can also solve the problem of insulin tolerance.

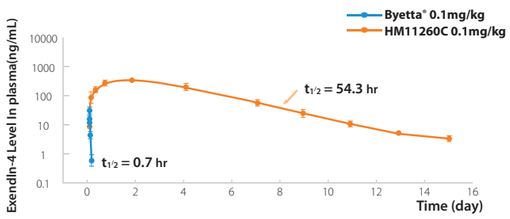
Status

- HM11260C has completed Phase 1 clinical trials with healthy adults in Korea and a Phase 1b clinical trial with diabetes patients in Europe. HM11260C has also completed 26 weeks repeat dose toxicity and Phase 2 clinical MAD (Multiple Ascending Dose) trial in the USA. The multinational Phase 2 dose finding study (US, Europe, and Korea) is currently ongoing.

Intellectual Property

- Our research team has completed patent applications by successively developing novel Exendin-4 derivatives that present excellent titers when made as a long-acting version, outside the scope of leading novel Exendin-4 derivatives. This was done while developing a next generation long-acting version. We also confirmed human translation in various proteins and peptides by securing a next generation, continued type peptide development platform technology (LAPSCOVERY, Long Acting Protein/Peptide Discovery) by using a novel bio-carrier. We are applying for patents for the materials, methods and the use of this technology, and it is already registered in both Korea and the USA (US 7737260: Protein complex using an immunoglobulin fragment and method for the preparation thereof, US 7736653: A pharmaceutical composition comprising of an immunoglobulin Fc region as a carrier)

Competitive Advantages



- **Securing Excellent Treatment Efficiency by Developing Exendin-4 Analog**
  - The majority of currently developed long-acting GLP-1 agonists exhibit low efficacy, compared with liraglutide (Victoza Novo), despite their relatively high use in once-daily medical administration. The Exendin-4 analog developed by our research team, and the resultant complex (HM11260C), demonstrate unique kinetics against the GLP-1 receptor. It has already proven its high efficacy at low doses in animal models, and is also expected to show excellent efficacy in humans.

- **Developing Weekly- or Monthly-dose Medicines with LAPSCOVERY Technology**
  - LAPSCOVERY technology, which is a next generation long-acting platform, can be applied not only for proteins such as human growth hormones, but also for peptides including synthetic amino acids.
  - The majority of GLP-1 agonists currently being developed or under clinical study are once-weekly versions. HM11260C is manufactured by applying LAPSCOVERY technology to an Exendin-4 analog, and it can be developed into a once-weekly or once-monthly version (70 times more effective when compared to natural type), since its safety in the blood has been increased.
  - Because it is slowly absorbed after injection, negative side effects such as vomiting and nausea caused by rapid release injections are expected to be substantially reduced.

- **Maximizing Convenience**
  - HM11260C has been confirmed as appropriate for a 31-gauge needle through verification of high solubility and low glide force. We are also planning to develop it into a form that patients can inject at their own convenience.

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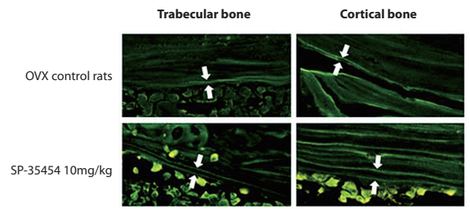
SHIN POONG PHARM CO.,LTD

New drug development study for osteoporosis with novel mechanism

Code Number : **KDDF-201212-10**

Development and Market Objectives

- Our aim is to develop a new drug for osteoporosis that acts through a novel mechanism targeting TAZ (transcriptional coactivator with PDZ-binding motif). This action triggers osteoblast proliferation and activation, while suppressing osteoclast activation. Research and development is currently underway to complete non-clinical and Phase I clinical trials using the candidate compound SP-35454. We then plan to initiate partnership with a global pharmaceutical company to jointly promote further development and commercialization.



Evidence of 10-day osteogenic effects in an OVX rat model of aging, marked with tetracycline

Unmet Medical Need & Target Patients

- Due to our aging society, the number of people suffering from osteoporosis has been rapidly rising. Approximately 40% of women and 13% of men over the age of 50 suffer from the condition. It is a serious disease with a 2.8% death rate, on par with breast cancer in the United States. The current medical need for osteoporosis treatment is a therapy that involves symmetrical bone formation and a deterrence of bone resorption, and preferably a convenient oral treatment rather than an injection, with no side effects.
- The osteoporosis therapeutic market was worth $7.3 billion in 2010 and by 2015, it is projected to be worth around $11.4 billion., Approximately 1.5 million fracture patients are annually expected worldwide with resultant health expenditures totaling more than $30 billion.

Status

- TAZ is a transcriptional modulator that promotes the differentiation of osteoblasts from mesenchymal stem cells. Our candidate SP-35454 activates TAZ, increasing ALP (a marker for osteoblast activation) and aiding calcium accumulation.
- After inducing osteoporosis in 6-week-old genetically-aged rats via OVX surgery, SP-35454 was orally administered for one year. Significant increases in bone density were detected in the 5 and 10 mg/kg treatment groups. In addition, the biomarkers ALP and osteocalcin were significantly affected, and increases in tetracycline double line gaps were observed, allowing us to detect bone growth in the thighbone and the shinbone. Further non-clinical research is currently underway.

Intellectual Property

- Material patents : Application was lodged in 2009 (PCT/KR 2009/0068085)
- Patent scope : Worldwide (COM patent) entitled : Indenone derivative and pharmaceutical composition comprising same (patent number : WO2011/030955A1). The patent was registered in 35 countries including the United States, Europe, Japan, China of 48 countries and the rest is under review in May 2015.

Competitive Advantages

- **Superior remedial effect** : As the treatment enables superior remedial effects in various animals with osteoporosis, we expect these results to be reflected in clinical trials.
- **Possibility of extended usage** : SP-35454 controls differentiation of mesenchymal stem cells, which may enable the suppression of differentiation to fat cell. This may have applications in the treatment of obesity.
- **Safety** : NOAEL was calculated at 1000 mg/kg/day for the duration of the 4-week rat toxicity test. As a result, Reduced side effects and toxicity during clinical trials are expected.
- **Convenient usage** : Our candidate is expected to retain remedial effects with a once-daily oral dosage.
- **Patent period** : Related patent applications were submitted in 2009 with an expiration date of 2029, with further periods of validity possible.

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Hyundai Pharm. Co., Ltd.

Development of HD-6277, a potent GPR40 agonist without hypoglycemic risk

Code Number : **KDDF-201306-07**

Development and Market Objectives

- Our objective is to develop HD-6277, a competitive therapeutic GPR40 agonist for the control of hypoglycemia, and generate the API for preclinical research.

Unmet Medical Need & Target Patients

- Type II diabetes mellitus is a widespread chronic disease. In 2010, 6.4% of the adult population was afflicted, and is projected to reach 7.7% by 2030, according to experts (Diabetes Research and Clinical Practice, 2010; Diabetes Care, 2004). The Korean domestic situation is more serious; the morbidity rate of the disease in 2009 was 9.9% of for 30~70 year old adults (Diabetes Metab. J., 2011).
- Commonly-used therapeutics for type II diabetes mellitus such as metformin, sulfonylurea, and rosiglitazone cause many adverse effects including diarrhea, stomach aches, hypoglycemic induction, weight increases and cardiovascular disorders. In addition, the long-term administration of sulfonylurea creates additional clinical issues, and type II diabetes typically requires long term administration of drugs for treatment.
- The islet beta-cell secretion capacity for insulin in most patients is often found to be decreased by more than 50% upon initial medical examination. This beta-cell secretion capacity of insulin, as well as the total number of beta-cells continues to decrease over time. Another drawback of sulfonylurea therapy is that it renders glycemic control difficult despite its effects on beta-cells. Currently, incretine hormone-based drugs that regulate blood glucose and protect beta-cells are being developed. However, evidence for real clinical effects on blood sugar levels and beta-cells over prolonged periods of time are needed in order for them to remain relevant when compared to metformin or sulfonylurea therapy.

Status

- GPR40 (G-protein-coupled receptor 40) is a membrane protein that develops in islet cells of the small and large intestine. GPR40 activation in islet beta-cells by GPR40 agonists is known to stimulate insulin secretion (Gromada J., 2006). Hyundai Pharmacy has created a lead backbone from a large number of chemical modifications and generated hundreds of new compounds. Each lead backbone-based compound has passed the primary screening process by in vitro methods, based on GPR40 agonist mechanism of action. Compound HD-6277 was identified to be the safest after 2nd round in vivo screening using normal and diabetic rodent models.
- HD-6277, a potent GPR40 agonist, has demonstrated its superiority and safety in PK profiling through cutting-edge research. The compound is highly effective for blood glucose control in a number of type II diabetes mellitus animal models with 2~4 week interval repeated administration and has shown excellent safety characteristics in non-GLP 2-week repeating toxicity tests. In addition, we have confirmed the outstanding HD-6277 bioavailability and safety in both rodents and non-rodent animal models and confirmed that there are no side effects such as hypoglycemia after repeated administration for 4 weeks. We are currently conducting additional research to consolidate its future superiority in the market and developing the HD-6277 API for GLP safety evaluation

Intellectual Property

- Hyundai Pharmacy has developed a unique scaffold and a GPR40 agonist library through the creation of hundreds of new compounds based on lead frames. A patent application is present in STN search, Registry database and the Marpat database.
- Application Number : 10-2013-0043100
- Name : Novel cyclohexene derivative, pharmaceutically acceptable salts thereof or optical isomer thereof, preparation method thereof and pharmaceutical composition for prevention or treatment of the metabolic diseases containing the same as an active ingredient

Competitive Advantages

- The mechanism of action of GPR40 agonists that target beta-cells is deeply related to blood glucose control and the fact that such agonists stimulate insulin secretion causing a drop in blood sugar levels to a greater extent than sulfonylurea (Lin DCH., 2011). Of particular note, GPR agonists are not only effective in potently downregulating blood sugar levels strongly, they can also counteract hypoglycemia because it has been shown that

Hyundai Pharm. Co., Ltd.

insulin secretion of beta-cells stimulated by GPR40 agonists only occurs during times of high blood sugar levels. Additionally, activation of GPR40 in L-cells spreads from the small and large intestine via cognate GLP-1 (glucagon-like peptide-1) secretion which is known to affect hypoglycemia. This protects beta-cells and has an effect on weight gain, so it is possible that GPR40 agonists can act to prevent deterioration of beta-cells in diabetic patients and provide a mechanism for control of weight gain (Luo J, 2012). HD-6277 has demonstrated an outstanding potential for glycemic control in diabetic animal models using Fasiglifam as a comparator, and GLP-1 secretion in the blood was increased with HD-6277 administration. Based on these research results, further experiments that will verify the possibility of anti-apoptotic effects in beta-cells and stimulation of neogenesis will be conducted. In addition, incretin's potency will be verified by confirming the blood sugar reduction ratios after food intake in relation to stable hypoglycemic capacity. Moreover, the practicality and safety of co-administration with HD-6277 will be confirmed via in vivo analysis of the metabolome.

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Genexine, Inc.

Conduct and Completion of a Global Clinical Phase I Trial of a Next-Generation Human Growth Hormone Product

Code Number : **KDDF-201308-07**

Development and Market Objectives

- The next generation recombinant human growth hormone (GX-H9) project, which was funded by KDDF, was approved to conduct Clinical Phase I study in Europe. Our goal is to conduct and complete Phase 1 study in EU and carry out monkey PK/PD study and hFcRn transgenic mice PK study to create higher value to the project.

Unmet Medical Need & Target Patients

- The global market for human growth hormone is continuously growing at an annual growth rate of 4.6% and with a sales figure of 3 billion US dollars in 2012. The primary target patients are those who suffer from growth hormone deficiencies (both adults and children) and indication is expected to expand to growth failures due to chronic renal insufficiencies, GSA, Prader-Willi Syndrome, Turner's Syndrome, Cachexia AIDS-related, Noonan Syndrome, ISS, Short Stature Homeobox containing gene deficiency, and Short Bowel Syndrome. Currently, 1st generation recombinant human growth hormone products have poor compliance due to daily injection. Many rhGH products is redeveloped by combining with medical devices to improve compliance, but once-daily injection still cause inconvenience and distress for patients. New generation of rhGH products with longer-acting characteristic such as weekly or monthly administration are under development to improve quality of life for patients.

Status

- GX-H9 was approved to conduct clinical phase 1 trial in The Netherlands in August 2013. A global CRO is now conducting a Phase I trial for GX-H9 in healthy male volunteers and plans to conduct further clinical trials in adults and children patients with growth hormone deficiencies.

Intellectual Property

- The hyFc, a proprietary platform technology developed by Genexine, Inc., is already protected by registered patents in many countries including the United States and Korea.

Competitive Advantages

- Development a bi-weekly or monthly administration product by using the hyFc technology
  - The hyFc was developed by hybridizing IgD and IgG4. The IgD portion of hyFc have characteristics of high hinge flexibility and IgG4 have long half-life by Fc region mediated by FcRn. It is also designed to remove ADCC and CDC functions. Long-acting mechanism of GX-H9 is mediated by FcRn recycling which allow bi-weekly or monthly administration.
  - GX-H9 has higher bioavailability when compared to Pegylation or other long-acting technologies. By using the hyFc technology, greater efficacy was shown with lower doses in animal models compared to existing products. Therefore, GX-H9 is expected to show superior efficacy in humans.

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Enzychem Lifesciences Corporation

ENZYCHEM LIFESCIENCES

The development of a new oral drug to treat Chemotherapy Induced Neutropenia (CIN)

Code Number : KDDF-201410-10

Development and Market Objectives

- Neutropenia is a common dose-limiting toxicity during treatment with myelosuppressive cancer drugs. Chemotherapy-induced neutropenia (CIN) often leads to a dosing delay and/or reduction of dose resulting in compromised chemotherapy. The current standard of care is a parenteral product (G-CSF), and it has a number of side effects and is limited to use in only the treatment of febrile neutropenia. Our goal is to develop an orally efficacious drug that can be generally applicable to both febrile and afebrile neutropenia with a profile that is excellent in safety.

Unmet Medical Need & Target Patients

- A recent review reported that 16.8% out of 2,131 patients who received various chemotherapies experienced febrile CIN (J Oncol Pharm Pract 20 (3): 190, 2014). Another review reported that 10.7% out of 2,692 cancer patients experienced febrile CIN, and 29.3% experienced Grade 3-4 CIN (febrile and afebrile combined). (J Natl Compr Canc Netw. 6:109, 2008.)
- In the clinic, G-CSF injection is the standard of care to increase the numbers of neutrophils and to prevent infection. However, G-CSF products are expensive, inconvenient to use, indicated for use on only febrile neutropenia, and problematic due to several side effects/toxicities such as pain, fever, rash and splenic rupture, etc. Therefore, a new therapeutic agent that can overcome the various issues of the current therapy (G-CSF) in terms of convenience, target patients, cost and safety is warranted.

Status

- The core battery of safety studies testing up to the maximum dose of 2000 mg/kg in nonclinical animals did not raise any safety concern. A variety of nonclinical studies and pilot proof-of-concept studies have demonstrated the efficacy of EC-18 after oral administration. The mechanism of the actions of EC-18 includes the activation of cell differentiation in the hematopoetic stem cells and a reduction of neutrophil migration from blood vessels. Currently, a Phase 1 clinical study is ongoing in Korea, and an IND to conduct Phase 1 in the US was submitted at the end of April, 2015. In addition, various investigations including formulation optimization, absorption mechanism, DMPK, and toxicity are ongoing.

Intellectual Property

- Method for treating, controlling or mitigating neutropenia comprising administration of a monoacetyldiacylglycerol
- Methods for treating, controlling or mitigating neutropenia and other conditions, comprising administration of a monoacetyldiacylglycerol simultaneously, sequentially or in combination with a granulocyte colony stimulating factor (G-CSF)
- Methods for treating, controlling or mitigating neutropenia and/or thrombocytopenia, in patients receiving chemotherapeutic agents, such as lenalidomide and monoacetyldiacylglycerol

Competitive Advantages

- Patient population: G-CSF is mostly indicated for febrile neutropenia whereas EC-18 can be used in both febrile and afebrile neutropenia (Grade 3-4).
- Route of administration: G-CSF is administered parenterally, whereas EC-18 is an oral drug.
- Efficacy (Prevention & Recovery): G-CSF cannot be administered until 24 hours after the completion of chemotherapy, whereas EC-18 can be administered prior to the initiation of chemotherapy to effectively prevent neutropenia.
- Safety: Common side effects of G-CSF include pain, fever, rash and splenic rupture unlike EC-18

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HANDOK INC.

Development of Anti-Glaucoma Drug with a Novel Mechanism of Action

Code Number : KDDF-201410-09

Development and Market Objectives

- To discover and develop a preclinical candidate with novel mechanism, good efficacy and excellent safety profile for novel treatment options for glaucoma patients.

Unmet Medical Need & Target Patients

- There are approximately 583,000 patients suffered from glaucoma in South Korea and about 66% of patients are over 50's in age. Various treatment options including prostaglandin derivatives are well-established, however, there are highly unmet medical needs in that significant percentage of glaucoma patient population does not respond to the standard medications in terms of IOP (IntraOcular Pressure) reduction, and some patient groups demonstrate a variety of side effects.
- Therefore, a novel therapeutics, as a single agent and/or combination with current drugs, in order to overcome the current issues is highly needed in the glaucoma market

Status

- We have identified a novel target as well as its new mechanism of action, and we have successfully validated a possibility that its antagonism would provide first-in-class therapeutics for glaucoma treatment. The current lead series compounds showed excellent efficacy in vitro and in vivo.
- Currently, the project is at the lead optimization stage, through which the compound profile is being improved and will be ready for preclinical candidate selection.

Intellectual Property

- Ready for patent filing in 2015

Competitive Advantages

- This is a first-in-class glaucoma therapeutics with the goal to have superior efficacy and lower side effect over current standard therapies.
- Due to its novel mechanism, which has never been explored in glaucoma therapeutics, it would show a good efficacy with sufficient IOP reduction especially in the patients who do not respond sufficiently to the current standards. And with the same reason, it may well have a synergistic efficacy in combination with standard therapies, which would provide another rationale to use this compound to the refractory patient groups. Overall, compounds having abovementioned features will generate a good market share in the glaucoma therapeutic sector.

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OliX Pharmaceuticals, Inc.

Preclinical study and IND approval of anti-scarring therapeutics BMT101, self-delivering RNAi molecule

Code Number : KDDF-201408-14

Development and Market Objectives

- Our objective is to obtain preclinical safety data and complete an IND application/approval for BMT101, a new preventive medicine for intractable hypertrophic scarring, developed by using OliX's self-delivering RNAi technology.

Unmet Medical Need & Target Patients

- In general, hypertrophic scarring has an incidence which is 3 times higher in Asians and other ethnicities, compared to the Caucasian population. In the US, it has been reported that approximately 45% of patients who suffer from illnesses, surgical operations and burns end up with scarring, and in Asians and other ethnicities, approximately 44.6% will develop a hypertrophic scar.
- Surgical interventions, laser treatment, ointments and patch-type treatments continue to remain the most common treatments. However, these treatments typically have limited effects on reducing the hypertrophic scar. For more effective treatment and prevention, a treatment that eradicates the formation of the hypertrophic scar is needed. Currently, no FDA approved drug exists for this indication.

Status

- After asymmetric siRNA library sequence screening for CTGF, a key gene for the information of hypertrophic scars, our self-delivering RNAi technology was introduced to the corresponding sequence for the development of a new candidate substance, BMT101, for an anti-scarring therapeuticBMT101's anti-scar efficacy was verified in-vitro through the confirmation of its selective silencing effects for CTGF and other fibrosis factors
- Through PK/PD testing, BMT101 has been determined as only topically active, and it has been confirmed that there are virtually no side effects with systemic exposure.
- Using animal models of scarring, we have demonstrated the efficacy of BMT101 as an anti-scarring therapeutic and are currently preparing for a preclinical study.

Intellectual Property

- A patent is held for 'Novel siRNA Structure for Minimizing Off-target Effects and Relaxing Saturation of RNAi Machinery and the Use Thereof' (issue no. 10-0949791, issue date March 19th, 2010(Korea), PCT issued. Patent issued or pending in Europe, Japan, China, and Australia)
- 'Nucleic Acid Molecules Inducing RNA interference with Cell-penetrating Ability and the Use Thereof (issue no. 10-2013-0057412, issue date May 21st, 2013(Korea). PCT issued. Patent pending in several key territories)

Competitive Advantages

- Our cp-lasiRNA technology enables self-delivery into cells without the need for delivery vehicles, such as cationic lipids or polymers,, so there are no delivery vehicle-related side effects. Additionally, via pharmacodynamics test and preliminary toxicity test of BMT101, we have confirmed the low possibility for side effects due to systemic exposure.
  - Unlike the conventional siRNA, when treated with BMT101, the quantity of IFN-α was almost identical to the negative control group, and this suggests that BMT101 does not elicit non-specific immune effects.
  - Through the development of a new intractable anti-hypertrophic scarring therapeutic, BMT101, it may be possible to expand its indication to other diseases that are related to fibrosis from overexpression of CTGF.

    BMT101 is 10 times more potent than other competing candidates and has outstanding competitiveness in terms of side effects and cost of production.

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Yuhan Co., Ltd.

Phase 2b study of YH14618 for degenerative disc disease

Code Number : KDDF-201408-07

Development and Market Objectives

- YH14618 is a novel peptide under development as an intradiscal injection for the treatment of patients with symptomatic lumbar degenerative disc disease, to achieve the treatment goals of improvement in chronic back pain and prevention of disease progression via its modulatory effect on TGFβ1.
- The initial safety, tolerability and therapeutic efficacy of YH14618 has been investigated in a Phase 1/2a clinical trial (YH14618-201). The current study (YH14618-202; ClinicalTrial.gov Identifier: NCT02320019) is a double-blind, placebo-controlled clinical trial designed to establish proof-of-concept for the safety and efficacy of YH14618, by comparing the proportion of VAS (Visual Analogue Scale) responders, defined as those who achieve a ≥ 50% reduction from baseline score for low back pain, at Week 12 following intradiscal injection. Patients diagnosed with one or two symptomatic lumbar degenerative discs with persistent low back pain despite at least 3 months of conservative therapy are eligible.

Unmet Medical Need & Target Patients

Target Patient Population

- Patients diagnosed with one or two symptomatic lumbar (L1/L2 ~ L5/S1) degenerative discs, defined as a Pfirrmann grade of 2 to 4 (on MRI). Patients must have suffered from persistent low back pain with VAS ≥4 cm and modified Oswestry disability index (mODI) of ≥30%, despite at least 3 months of conservative therapy.

Unmet Medical Needs

- Low back pain is a common condition with approximately 80% of the population reported to experience the condition at least once during their lifetime. Although an estimated 5% of this population will develop chronic low back pain, only 20~40% of these patients respond satisfactorily to currently available treatments. Many factors can contribute to the onset of chronic low back pain, however, discogenic factors are known to be the major cause, affecting 26~42% of patients. Discogenic low back pain is a serious medical and social problem, with total health care costs in the United States estimated to exceed $100 billion per year. Degenerative disc disease can arise from the natural process of aging, but eventually becomes irreversible, and can begin when adolescents are in their twenties. Pain and the impaired mobility associated with degenerative disc disease typically affect adults between the ages of 30 and 50.
- Current treatment options for discogenic low back pain range from medicinal anti-inflammatory and pain relief strategies to invasive procedures including spine fusion and spinal arthroplasty. However, these treatments are limited to relieving symptoms, with no attempt to restore the disc structure. Additionally, there are unsatisfactory outcomes with surgical intervention due to high cost, complications, and recurrence of pain. None of the currently available treatment options satisfactorily meet the treatment goals for DDD which include long-term improvement in chronic back pain and restoration of disc structure.

Status

- First-in-human phase 1/2a clinical trial (YH14618-201) has been completed in a total of 50 patients with symptomatic lumbar disc degenerative disease.
- Additional *in vitro* mechanistic study is ongoing
- *In vivo* study using a rabbit model of degenerative disc disease is underway to evaluate the synergistic effect of repeated dosing (KDDF-201404-09).

Intellectual Property

- Patents have been granted in approximately 20 countries including the Republic of Korea.

Competitive Advantages

- Currently, for patients with degenerative disc disease and chronic low back pain, there is no approved treatment that addresses the underlying pathophysiology responsible for the disease. Pain killers such as NSAIDs and other conservative analgesics have only temporary efficacy in general, with concerns for side effects related to long-term use. Surgical intervention is a significant undertaking and frequently does not comprehensively resolve the unmet needs of patients despite high costs. Therefore, a significant clinical demand exists for the development of safe and efficacious solutions that can modify the disease course and provide sufficient and sustainable pain control. YH14618,

Yuhan Co., Ltd.

a first-in-class disease modifying peptide for the treatment of degenerative disc disease, is being developed as a differentiated therapeutic offering clinical benefit for both long-term pain relief and prevention of disease progression.

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Yuhan Co., Ltd.

Preclinical in vivo study to evaluate the additional mechanism of action(MoA) and to demonstrate the enhanced therapeutic efficacy following the repeated dosing of YH14618

Code Number : KDDF-201404-09

Development and Market Objectives

- In a previous first-in-human study following single intradiscal injection of YH14618 in patients with degenerative disc disease suffering from chronic low back pain, YH14618 showed potential therapeutic efficacy. The objective of the current preclinical study is to generate robust molecular mechanistic data related to disc regeneration and pain control that may translate into enhanced clinical efficacy following repeated dosing of YH14618 in patients with degenerative disc disease.

Unmet Medical Need & Target Patients

Unmet Medical Needs

- Currently, there are no approved treatments that can modify degenerative changes in the disc.
- Pain killers have temporary efficacy, with concerns for side effects related to long-term use, while surgical intervention is not satisfying the needs of patients, despite high operation costs.
- Therefore, there is a high clinical demand for the development of safe and efficacious drugs that can modify the disease course and provide sufficient sustainable pain control.

Target Patient Population

- Patients with mild to moderate degenerative disc disease who have not experienced adequate control of chronic low back pain on NSAIDs or other conservative treatments.

Status

- A first-in-human clinical trial in patients with degenerative disc disease has been completed.
- An additional preclinical study is being carried out by a global CRO.
- A phase 2 clinical trial began in early 2015 to determine an optimal dose in patients with degenerative disc disease (YH14618-202; KDDF-201408-07).

Intellectual Property

- International patents in over 20 countries have been granted, including patent registration in Korea.

Competitive Advantages

- Competitors such as cell therapies and recombinant proteins are being developed but their pharmacological efficacy on disc regeneration and pain control in patients with degenerative disc has not been confirmed.
- YH14618, a first-in-class disease modifying therapeutic for the treatment of degenerative disc disease, offers clinical benefit for both long term pain relief and prevention of disease progression.
- YH14618 is a peptide composed of natural amino acids with excellent safety and commercially competitive qualities.

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Development of therapeutic agent for duchenne muscular dystrophy by targeting NMD

Code Number : KDDF-201304-03

Development and Market Objectives

- To develop a medicine for hereditary conditions including duchenne muscular dystrophy (DMD), a rare disease arising from nonsense mutations, by developing novel compounds through cellular-based screening and optimization.

Unmet Medical Need & Target Patients

- DMD is a rare disease, but affects more than 30,000 people in America and Europe. No lasting treatment for DMD currently exists on the market.
- The development of treatments that can improve dystrophin protein expression, a primary factor in DMD, is critically needed.
- Other hereditary diseases derived from nonsense mutations can potentially be diagnosed by genomic analysis, but current medicinal methods are very limited.
- Hereditary diseases that arise from nonsense mutations cause more serious symptoms than those of other genetic disorders. Therefore, radical treatments targeting these diseases are urgently needed.
- Prolonged treatment with a low molecular weight compound is ideal.

Status

- NMD / Researching and discovering inhibitor nonsense mutations
- Lead materialization of identified lead candidates
- Currently in progress with research to explore the possibility of clinical trials with DMD patients.

Intellectual Property

- The pathological cause of rare diseases derived from nonsense mutations and DMD is relatively simple. For the case of DMD, the function of dystrophin is downregulated, and therefore, the conduct of preclinical-clinical translation for radical treatments is expected to be easier than for other diseases. This allows project planning in the near future for the discovery of new compounds without patent infringement.

Extent of Patent

- New compounds that inhibit NMD specifically, and their derivatives.
- The new compounds in # 1, and protein translation inhibitors and their derivatives
- The new compounds in # 1 and hereditary disease medicines and their derivatives

Competitive Advantages

- Our research team is currently in the process of discovering NMD inhibitors by targeting all stages of NMD using an NMD-relevant cell line optimized for inhibitor screening. Inhibitors discovered from this process will have a big advantage in that we can apply it to DMD which arises from NMD, and many other hereditary diseases.
- This research will be undertaken through cooperation with the Green Cross Corp., a leading pharmaceutical company in Korea that has successful experience in developing new drugs, and Professor Chae Jong Hee's team from Seoul National University Hospital, whose primary research focus is in DMD clinical trials.

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