LegoChem Biosciences, Inc.

Ⅰ. Company Summary

Company Description

A leading chemistry-based venture company working on the discovery and development of new small molecule drugs. 7 original members came from LG Life Science Research Institute

- Company Name : LegoChem Biosciences, Inc.
- CEO : Yong Zu KIM (former New Drug Research Director, LG Life Sciences)
- Established : May 2, 2006
- Web site : www.legochembio.com

Products in the Pipeline

- Key Research Areas : antibiotics, anticoagulants, anticancer

Areas	Project	Lead generation	Lead optimization	Pre-clinical	Phase I
Anticoagulants	**Fxa Inhibitor**	■	■	■	
	FVIIa	■	■		
	FXIa	■	■		
Antibiotics	**Oxazolidinone**	■	■	■	
	Gram(-)	■	■		
Anticancer	HSP90	■	■		
	Mitochondrio-tropic(HSP90)	■	■		
Others	DDR 2	■	■		
	Wondonin	■	■		

Product in the market

- *NONE* -

Company History

2006	05	Established at DBVT (Daejeon BioVenture Town, Daejeon, Korea)
	11	Joint Research Contract with Yonsei Univ.(anticoagulants)
2007	02	Research Contract with Handong Univ.(antibiotics), Daejeon Univ. (anticoagulants)
	03	1st Round fund raising from korean venture capitals (4.5 billion koean ₩ ≈4 million US$)
	04	Research contract with Univ. Mass.
	07	3-year Joint Research Contract with NeoPharm (anti-Inflammation)
	08	Government Research Grant (anticoagulants)
	09	Posters presented (Antibiotics) at "2007 ICAAC" Conference , Chicago, U.S.A.
2008	01	2nd Research Contract with U. Mass
	02	Joint Research Contract with Newgex (anti cancer)
	04	Government Research Grant (Antibiotics for IND filing)
	07	Satellite Lab established at Young-nam Univ.
		Licence Agentship Contract with SPI(Sumitomo Subsidiary) for Japan Market
2009	02	Joint Research Contract with Hanmi Pharm (anticoagulants)
	03	Anti-cancer(HSP 90) paper published in JCI (Joint research with U.Mass)
	05	2nd Round fund raising from korean venture capitals (4.0 billion koean ₩ ≈3.8 million US$)
		Government Research Grant (gram- Antibiotics for IND filing)
	06	Anticoagulants (FXa Inhibitor) licensed out to GREEN CROSS
	09	Posters presented (Antibiotics) at "2009 ICAAC" Conference , San Francisco, U.S.A
	10	Entering Preclinical Study (Oxazolidinone antibiotics)
		Government Research Grant (Anti-cancer for IND filing)
	12	Received "Technology Commercialization Award "sponsored by DAEDEOK INNOPOLIS, (Fxa Inhibitor)

Ⅱ. Key Technology Highlights

- **Running three major active research area: total of 9 projects ongoing**
- **One program licensed out (Green Cross, a Korean pharmaceutical company)**
- **Oxazolidinone antibiotics in preclinical study (MPI, US); Two preclinical candidates expected this year**

Res. Area	Project	Summary
Antibiotics	Oxazolidinone	▪ 4 patents filed or registered including 1 PCT (National Research Fund) ▪ In preclinical study (MPI, US); IND-filing expected by 4Q, 2010 ▪ Expecting licensing-out or co-developing (preferably global partner) ▪ For more details, refer to the separate "executive summary"
	G-negative	▪ Nat'l PJT funded by Ministry of Education, Science & Technology ▪ Expecting preclinical candidate at the end of 2010
Anticoagulant	FXa	▪ Four patents filed with one registered (PCT) ▪ L/O to Green Cross; expecting 'sub-license out' to global company ▪ For more details, refer to the separate "executive summary"
	FVIIa	▪ Lead optimization stage with 1 PCT filed : Joint Research with Hanmi Pharm ▪ Found to be active in *in vivo* model with dose dependency ▪ Pre-candidate expected by the end of 2010
	FXIa	▪ Lead Optimization Stage ▪ Mainly operated by Fragment-based Drug Discovery approach ▪ Three novel fragments (~uM) under extensive optimization
Anticancer	HSP90 (1)	▪ Joint Research with Boram Pharm ; 3-Party J.R. in plan (with Asan Medical Center, Seoul) ▪ Small molecular approach; candidate soon-to-be selected
	HSP90 (2)	▪ Mitochondriotropic agent approach in Joint Research with Hanmi Pharm ▪ Selected as one of LEADER Program : Currently at pre-candidate stage ▪ For further scientific background, see JCI. 2009. 119(3). 454 and commentary in P445.
Others	HIF-1	▪ Extensive derivatization of natural product known to be a HIF-1 inhibitor ▪ Evaluating for ophthalmic therapy (The Catholic University of Korea, School of Medicine)
	DDR-2	▪ Precandidate inhibitors in hand : atopic application planned ▪ Joint Research with Korea Institute of Science & Technology

1. Oxazolidinone Antibiotics

<Antibiotics market >

- Characteristics of antibiotics market

1. Most big pharma companies are active in the market and there is no single market-leading drug or class. Instead, a number of blockbusters from different classes and for different indications are dominating the scene.

- *total sales : $25.5 billion (7 major markets in 2005), CAGR : 5.1% (2001~2005)*

2. The antibiotics market is highly genericized but branded products still account for the main part of sales.

- *branded products : 73% total sales achieved with as little as 19% of total prescription volume (US in 2005)*

3. Although the community market is still dominant, the hospital market is gaining importance.

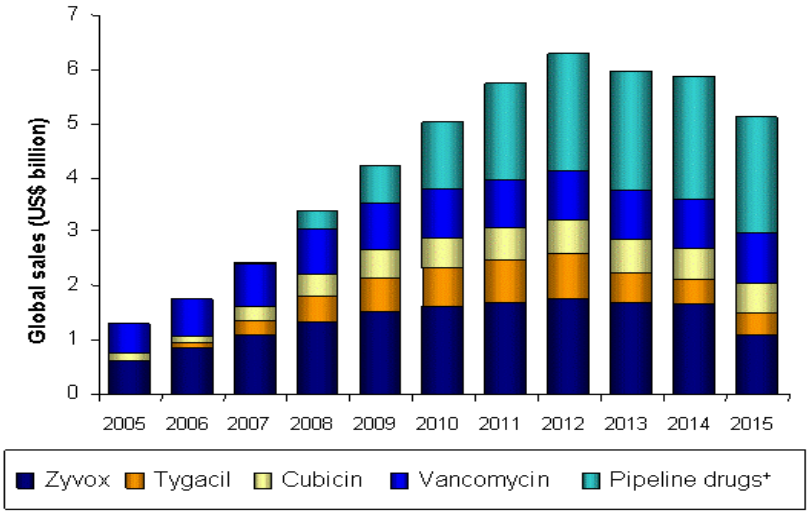
- *the hospital market has been gaining sales market share with a CAGR of 8.8% (2001~2005)*

- MRSA drugs are a main source of overall antibacterial market growth

Growth drivers : increasing incidence, emerging resistances, high drug prices

Expected CAGR 2005-2015 : 14.8%

Datamonitor forecast* for drugs mainly indicated for treatment of infections caused by MRSA



<Unmet need of antibiotics market>

1. Oral MRSA drugs: With MRSA incidence rising in the community, oral drugs have a large commercial potential.

2. Gram-negative resistance: Carbapenems and tigecycline are the only available treatment options for severe gram-negative infections. Upon emergence of resistances, novel drugs are a crucial need.

3. Compounds outside previous drug classes: Most compounds currently in development are derivatives of existing drugs with low potential to overcome resistances in the mid- to long term.

<Competitors in clinical stage>

	Linezolid(Zyvox)	Radezolid	Torezolid
status	Launched (2000)	Phase II	Phase II
Therapeutic targets	HAP, CAP, c&u-SSSI	CAP, u-SSSI	c-SSSI
Efficacy in animal model	Potent efficacies against MRSA, *S. pneumoniae*, VRE	Comparable or better than Linezolid (S.*pneumoniae* and respiratory tract pathogens)	Systemic infection *S. pneumoniae* (PR): PO : 2 times more potent than Lzd IV : 3-8 times more potent than Lzd Thigh infection, soft tissue infection MRSA : significantly more potent than Lzd
Target pathogen	Gram+ (MRSA, VRE)	*S.pneumoniae* MRSA	Gram+

Toxicity	NOAEL: 20mpk (PO,1 month, Rat, Dog, male, female)		NOAEL(rat, 4week) : 30mpk(male), 10mpk(female)
Dosing	600mg BID	300mg QD	200mg QD
Con and pros	Potent efficacy but low solubility, bone marrow toxicity, MAO inhibition	QD is possible but less effective against MRSA than linezolid	Potent and QD is possible but significantly toxic than linezolid

Owing to significant toxicity and low solubility of oxazolidinone moiety, only a few candidates are survive in clinic stage until now.

The goal : **To make 2nd generation oxazolidinone with improved efficacy and safety profile compared with Linezolid (Pfizer)**

- highly soluble , broad spectrum,
- potent efficacy and less toxicity (MAO inhibition, bone marrow toxicity)

<Profiles of our candidate, LCB01-0371>

1. Solubility : HCl salt form is freely soluble in water (>25%, Linezolid : 0.3%)

2. *Invitro* ADME-T and PK

1) In vitro ADME-T

Metabolic stable, No CYP inhibition, No cytotoxicity

Reasonable plasma protein binding (Human : 37%, Rat : 57%, mouse 69%)

2) MAO inhibition

Weak inhibition than Linezolid (more safe)

	MAO-A inhibition	MAO-B inhibition
Linezolid	12.6 uM	12.1 uM
LCB01-0371	4.0 uM	176 uM

3)Pharmacokinetic Profiles

Comparable to linezolid (BA : 100% in rat)

3. *Invivo* efficacies in animal models

1) Systemic infection model (ED50, mg)

More potent than Linezolid (1.5~4 times)

N=5~7, PO/SC	Linezolid	LCB01-0371

MSSA (PO)	8.05	4.54
MRSA (PO)	4.84	2.96
S. pneumoniae (PO)	9.10	2.28
H. Influenzae (PO)	21.4	9.96
MSSA (SC)	3.10	2.25
MRSA (SC)	2.61	1.96

2)Air pouch model (soft tissue infection)

LCB01-0371 showed 3 ~20 times (25~50 mpk) more reduction in CFU than Linezolid

4. Toxicity and Current Stage of Development

* Significantly reduced toxicity was seen than Linezolid in 2 week repeated dose (100 mpk and twice a day, no toxicity were seen at lower dose)
* Pre-clinical study is in progress: MPI (USA), October 2009~ July 2010. (4 weeks repeated dose, rat, dog and safety pharmacology)
* IND filing and preparing phase I will be done within 2010.

2. FXa Inhibitor (anticoagulants)

< Overview >

Factor Xa (FXa) plays a key role in the blood coagulation cascade, as it is activated by both the intrinsic and the extrinsic pathways. FXa catalyzes the conversion of prothrombin to thrombin through the prothrombinase complex, which consists of FXa, FVa, prothrombin, and Ca2+ on a phospholipid surface.

Inhibition of FXa produces antithrombotic effects by decreasing amplified generation of thrombin, thus diminishing thrombin-mediated activation of both coagulation and platelets, without affecting existing thrombin levels. Therefore, FXa is a particularly promising target for anticoagulant therapy and has attracted great interest in recent years. A significant advantage over current antithrombotic therapies should be provided by a small-molecule, direct FXa inhibitor that can be administered orally without the need for routine coagulation monitoring.

Rivaroxaban (Bayer) is an oral, direct factor Xa (FXa) inhibitor in advanced clinical development for the prophylaxis and treatment of thromboembolic disorders. it is a promising alternative to the pharmacological strategies currently available for prophylaxis against venous thromboembolism (VTE)- manifesting as deep vein thrombosis (DVT) or pulmonary embolism (PE).

Although Rivaroxaban is well recognized as a promising oral anticoagulant, its limited aqueous solubility and bleeding side effect leave the room for improvement. LCB02-0133 is a highly potent, selective, efficacious, and orally available FXa inhibitor that carries a significantly less bleeding side effect than Rivaroxaban.

< Market Forecast >

Pipeline	Taget	2008	2010	2012	2014	2016
ART-123	thrombomodulin (sc, iv)	15	29	16	14	15
Idraparinux	FXa/thrombin inhibitor (sc)	4	93	158	164	171
Rivaroxaban	FXa inhibitor (oral)	10	438	1663	2630	2812
Rendix(Dabigatran)	thrombin inhibitor (oral)	41	470	650	698	759
Prasugrel	ADP receptor antagonist (oral)	11	443	1075	777	323
Cangrelor	P2Y12 antagonist (iv)	4	124	207	104	74
Ticagrelor	P2Y12 antagonist (oral)	0	6	131	280	316

(2007, Datamonitor)

< Rivaroxaban : Strength and Limitation>

strength

- The first in a new class of oral direct FXa inhibitor
- Currently approved in Europe and Canada, but disapproved in USA
- Better efficacy
- Lower Side Effects
-

Limitation

- Solubility is not good
- Still some bleeding

< Project Goal >

1. **Efficacy**
   - Comparable in vivo efficacy compared to Rivaroxaban
2. **Solubility**
   - > 5x ~ 10x better than Rivaroxaban
3. **Bleeding Side Effect**
   - Should be significantly lower than Rivaroxaban

< Profiles of candidate : LCB02 - 0133 >

1. Aqueous Solubility

LCB02-0133 is > 400x more soluble in water than Rivaroxaban

Compound	Solubility in water (mM)
Rivaroxaban	< 0.05
LCB02-0133 (MSA Salt)	> 20

2. in vivo efficacy

In the AV shunt model in rats, LCB02-133 exerted antithrombotic effects dose-dependently and showed very comparable in vivo efficacy to Rivaroxaban.

Compounds	Thrombus formation Inhibition from AV-shunt model in rats (% vs. vehicle)				
	1.25 mpk	2.5 mpk	5 mpk	10 mpk	20 mpk
Rivaroxaban	32.82	46.41	55.33	72.67	74.09
LCB02-0133	32.60	44.21	49.47	67.16	78.14

3 . in vivo bleeding side effect

Compared to Rivaroxaban, LCB02-0133 showed significant advantage in rat tail-transection bleeding model.

Compounds	Bleeding Time Increase (x-fold±SD)				
	1.25 mpk	2.5 mpk	5 mpk	10 mpk	20 mpk
Rivaroxaban	2.12±1.28	1.48±0.40	2.35±1.13	2.96±1.22	3.95±0.11
LCB02-0133	1.39±0.62	1.52±0.59	1.65±0.75	2.03±1.08	2.71±1.30

Current Stage of development (by Licensee, : Green Cross Corp.)

- **CB02-0133 was out-licensed to Green Cross Corp. in June, 2009 (GC2107).**
- **Pre-clinical sample is being prepared at Dr. Reddy's (India).**
- **Pre-clinical study begins in June, 2010 and completes at 1st quarter of 2011.**

Ⅳ. Specific Patent Information

Project	Patent Title	Domestic(Korea) (Date applied) (Date registered) (Filed Number)	PCT (Date applied) (applied Number)
Antibiotics **(5)**	1. Novel Oxazolidinone derivatives, Process for preparing thereof and phamaceutical composition Containing the same	(2007.12.06) (2010.03.11) (10-0948345)	(2007.12.07) (PCT/KR2007/006364)
	2. Novel Oxazolidinone with amidoxime or hydroxamide and pharmaceutical compositions and derivatives thereof	(2007.02.21) (2008.11.28) (10-0872059)	
	3. Novel Oxazolidinone derivatives with cyclic amidoxime or cyclic amidrazone and Pharmaceutical Compositions thereof	(2008.09.24) (-) (10-2008-0093712)	(2009.09.22) (PCT/KR2009/005376)
	4. Novel Oxazolidinone derivatives cyclic th amidrazone ane pharmaceutical compositions thereof	(2010.01.29) (-) (10-2010-008379)	
	5. Method for preparing of (R)-3-(3-fluoro-4-(1-methyl-5,6-dihydro-1,2,4-triazin-4(1H)-yl)phenyl)-5-(substituted methyl)oxazolidin-2-one derivatives	(2010.03.08) (-) (10-2010-0020525)	
Fxa Inhibitor **(4)**	1. Fxa inhibitors with cyclic amidines as P4 subunit, processes for their preparations, amd pharmaceutical compositions and derivatives theirof	(2008.05.08) (-) (10-2008-0042740)	(2008.05.09) (PCT/KR2008/002619)
	2. Fxa inhibitors with cyclic amidoxime or cyclic amidrazone as P4 subunit, processes for their preparations, amd pharmaceutical compositions and derivatives theirof	(2008.07.03) (2009.05.12) (10-0898361)	(2008.12.12) (PCT/KR2008/007386)
	3. 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	(2009.07.08) (-) (10-2009-0062122)	
	4. 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	(2009.07.08) (-) (10-2009-0062090)	
FVIIa Inhibitor	1.Pyrimidinone derivatives or pyridazinone derivatives for inhibition of Factor VIIa activity	(2006.12.08) (2008.03.03) (10-0811865)	(2007.12.07) (PCT/KR2007/006341)
Anticancer **(2)**	1. Tyrosine kinase inhibitory compounds, isomers thereof or pharmaceutical acceptable salts Thereof, and pharmaceutical composition comprising the same	(2008.11.27) (-) (10-2008-0118850)	(2009.10.20) (PCT/KR2009/006050)
	2. Novel Compounds of Inhibiting Activity of Heat Shock Protein	(2009.2.20) (-) (10-2009-0014351)	(2010.02.19) (PCT/KR2010/001028)

Ⅴ. Specific Publication Information

No.	Journal	Title
1	JCI (The Journal of Clinical Invetigation) March 2009, Volumn 119	Combinatorial drug design targeting multiple cancer signaling networks controlled by mitochondrial Hsp90

☞ Dr. Song H.Y (Project Leader of LCB) as second author