AGM-130, a novel CDK inhibitor with a marked anti-tumor activity and reduced toxicity, targeting the triple negative breast cancer(TNBC) and tamoxifen-resistant estrogen receptor (ER) positive breast cancer

AnyGen Co., Ltd.

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Industry Sector	Academinc/Research, Drug Delivery, Pharmaceutical
Therapeutic Area	Oncology
Stage of Development	Phase I

1. Summary

- Code name : AGM-130
- Product name : Inditinib
- Therapeutic target : Oncology
- Indications : triple negative breast cancer (TNBC), Tamoxifen-resistant ER positive breast cancer
- Features

- AGM-130 is a highly selective, potent and reversible ATP-competitive inhibitor of cyclin dependent kinases (CDKs). CDKs have become emerging targets for the development of anti-cancer therapeutic drugs.

- CDKs affect cell growth and survival through several mechanisms, making the appropriate regulation of CDK activity important in various cellular processes. Inhibition of CDKs may provide an effective strategy for controlling tumor growth, making CDKs attractive targets for anticancer therapy.

- Molecular understanding has paved the way for the development of new agents that target pathogenic molecular alterations that drive tumor cell growth while sparing patients many of the traditional toxicities associated with chemotherapy. Ubiquitous to all cancer types is abnormal proliferation with dysregulation of normal cell cycle control. For this reason, inhibitors of key cell cycle regulators are attractive targets for novel cancer therapeutics. Selective CDK inhibition may provide therapeutic benefit against certain human neoplasia.

- Preclinical studies indicate that AGM-130 is a highly selective CDK inhibitor, which effectively inhibits CDKs signaling in tumors. Administration of AGM-130 in xenograft cancer animal models resulted in dramatic decrease of tumor progression with acceptable short-term and long-term animal toxicity profiles.

- Especially, AGM-130 is a cancer type specific anti-cancer agent, for triple negative, ER & PR+ breast cancers.

- Triple-negative breast cancer (TNBC) is a nasty form of the disease that does not respond to receptor-targeted therapeutics (Herceptin or Tamoxifen), as the receptors of interest (estrogen (ER), progesterone (PR), or HER-2) are not found in TNBC. The only marginally-effective treatments against TNBC are general chemotherapies, but overall response and survival rates are much lower in TNBC versus other breast cancers.

- AGM-130 development has been focused on an important group of solid tumors with unmet medical need, such as triple negative breast cancer, small lung cancer and melanoma, which will also benefit from this mechanism of action. These pathways affect disease progression and survival in solid tumors such breast cancer,

- AGM-130 is currently being evaluated in phase I clinical trial in patient with progressive or relapsing solid tumor in South Korea.

2. Applications

- The possible combination treatment of AGM-130 and other anti-cancer reagents - AGM-130 is intended for use as a single agent, or in combination with other anti-cancer agents, and will be used in patients with a variety of tumor types.
- Expansion of indication via adjustment of other cancers : non-small cell lung cancer etc.,
- Expansion of indication via the development of back-up drug candidates of AGM-130 (AGM-140, 145 and 147) : AGM-130 development can be used in the treatment of hematologic malignancies, including acute and chronic lymphocytic leukemia (CLL), based on the consistent anti-tumor activity that has been observed across a broad spectrum of cancer models, including those resistant to currently available therapies.

3. Market Feasibility

- Decision Resources, one of the world's leading research and advisory firms for pharmaceutical and healthcare issues, finds that the uptake of premium-priced agents will fuel 5 percent annual growth in the breast cancer market, with sales reaching more than $15 billion in 2022 in the United States, France, Germany, Italy, Spain, the United Kingdom and Japan

4. Type of Business Relationship Sought (include licensing availability)

- Out-licensing : AnyGen Inc. expects to receive licensing payments from as milestones are reached

5. Technical Advantages

- AGM-130 is a highly selective, potent and reversible ATP-competitive inhibitor of cyclin dependent kinases (CDKs). CDKs have become emerging targets for the development of anti-cancer therapeutic drugs.
- The validation of anti-proliferative activity of AGM-130 in breast cancer cell lines comparing with Pfizer's Palbociclib
- Palbociclib will eventually improve the cure rate for all patients with ER-positive, HER2-negative breast cancer, including those with early-stage disease whereas AGM-130 works against Triple-negative cancers.
- No adverse effect were observed based on general appearance, weight loss or reduction in weight gain after treatment of AGM-130 can be given in patients with metastatic triple negative breast cancer and tamoxifen-resistant ER-positive breast cancer

6. Technical Highlighted Summary

Method of Admin.	Test System	Results
In vitro	*In vitro* kinase reactions	*In vitro* kinase activities of CDK1, 2, 4, 5 and 6 was inhibited with an IC_{50} of 1.9 ~ 59.8 nM (AGM-130) and 0.2 ~ 0.5 nM (Roscovitine), 3.1 ~ 65.4 nM (Staurosporin)
	In vitro kinase reactions (40 different kinases)	*In vitro* kinase activity of Flt4(h), ckit(V560G)(h), CDK2,5,6, HIPK2(h), Fms(h) and ARK5(h) was inhibited by AGM-130 by more than 90 % at 100 nM
	NIH 60 cell lines screening	-In breast cancer cell lines, AGM-130 showed a good growth inhibition. In melanoma and lung cancer cell lines, AGM-130 showed lethality.
	18 Breast cancer cell lines screening	4 types of Her2 positive breast cancer cell lines showed relatively insensitive with IC50 values higher than 3 μM, whereas the growth of 3 types of ER positive and 7 of 10 types of triple negative cell lines was potently inhibited with IC50 values below 1 μM.
In vivo	The effect of AGM-130 on cell proliferation in HUVECs and mES cells	cell cytotoxicity was not observed (IC50 > 10,000 nM)
	anti-tumor effect of AGM-130 in various xenograft models	The anti-tumor activity of AGM-130 was not observed in KB (oral cancer cell line) and HCT116 (colon cancer cell line) xenograft experiments, but in A549 (lung cancer cell line) and MDA-MB-231 (triple negative breast cancer cell line) xenograft experiments. AGM-130 also significantly inhibited tumor progression in the xenograft animal model with MCF-7 cells in a dose-dependent manner. Consequently, AGM-130 is a cancer type specific anti-cancer agent, especially for triple negative, ER & PR+ breast cancers.

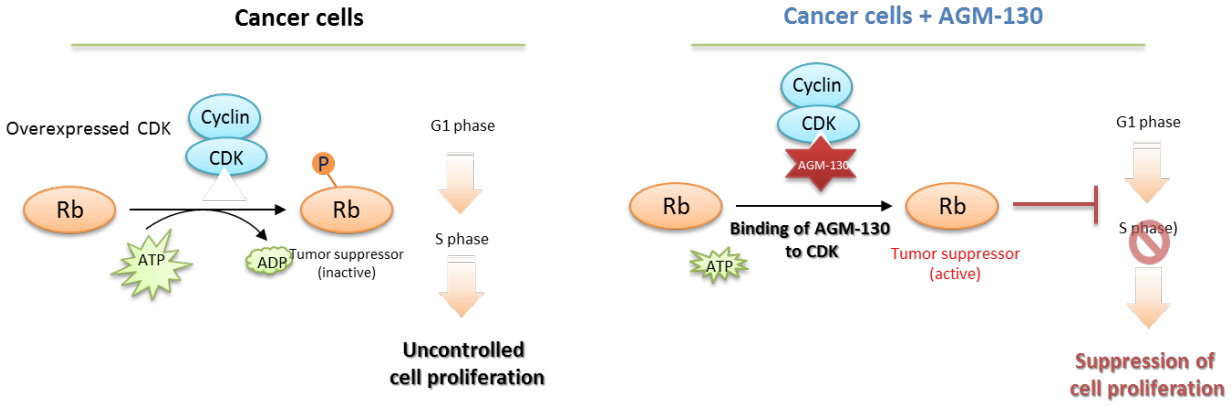
7. Mechanism (MOA)

The proof of concept that inhibition of CDK mediated signaling by AGM-130 results in growth inhibition and apoptosis of tumor cells was established in pre-clinical studies,

- To examine the effect of AGM-130 on the cell cycle regulation, we investigated cell cycles through the Flow cytometry analysis. As a result, decreased G1 phase and increased G2/M phase were observed upon treatment of AGM-130. Also, a western blot showed that cyclin B1 expression involved in G2/M phase was remarkably reduced, suggesting that G2/M phase arrest was induced by AGM-130 in MDA-MB-231 cells.

- We examined the apoptotic body stained with DAPI using a fluorescence microscope to investigate the induction of apoptosis by AGM-130. AGM-130 inhibited cell proliferation by the mechanism of mitochondria-dependent apoptosis.

- We analyzed the secretion of LDH (Lactate dehydrogenase) enzyme to media as a representative necrosis biomarker. Consequently, we concluded that apoptosis and necrosis were induced at the same time by AGM-130 in MDA-MB-231 cells.



8. Patent Information and Status

Nation	Appl number (Appl date)	Pub/Reg Number	Status	Description
United States of America	10/586,780 (2005.01.26.)	07572923 (2009.08.11.)	Registration	Indirubin derivatives having anticancer property against human cancer cell line
KOREA	10-2010-0010715 (2010.02.05.)	10-1180030 (2012.08.30.)	Registration	Indirubin-3'-oxime derivatives as potent cyclin dependent kinase inhibitors
EUROPE	11739972.5 (2011.01.28.)	EP02531488 A2 (2012.12.12.)	Pending	Indirubin-3'-oxime derivatives as potent cyclin dependent kinase inhibitors
United States of America	13/576,105 (2012.07.30.)	08859783 (2014.10.14.)	Registration	Indirubin-3'-oxime derivatives as potent cyclin dependent kinase inhibitors
JAPAN	2012-551909 (2012.08.06.)	25518874A (2013.05.23.)	Pending	Indirubin-3'-oxime derivatives as potent cyclin dependent kinase inhibitors

9. Patent Number(s)

Title	Country	Patent Application No.	Original Assignee	Filing Date	Inventors
Indirubin derivatives having anticancer property against human cancer cell line	United States of America	07572923	AnyGen Co., Ltd.	01-26-2005	Kim Yong-Chul; Kim Si Wouk; Kim Tae Sung; Lee Sang Kook; Kim Jae Il; Yoon Jung-Hoon; Ahn Sang-Gun; Moon Myoung Ju
Indirubin-3'-oxime derivatives as potent cyclin dependent kinase	KOREA	10-1180030	AnyGen Co., Ltd.	02-05-2010	Kim, Yong-Chul; Kim, Jae-Il; Ban, Soo-Ho; Jeong, Soon-Young; Choi, Soo-Jeong; Lee, Jung-Eun

Indirubin-3'-oxime derivatives as potent cyclin dependent kinase inhibitors	EUROPE	11739972.5	AnyGen Co., Ltd.	01-28-2011	Kim, Yong-Chul; Kim, Jae-Il; Ban, Soo-Ho; Jeong, Soon-Young; Choi, Soo-Jeong; Lee, Jung-Eun
Indirubin-3'-oxime derivatives as potent cyclin dependent kinase inhibitors	United States of America	08859783	AnyGen Co., Ltd.	07-30-2012	Yong-Chul Kim; Jae-Il Kim; Soo-Ho Ban; Soon-Young Jeong; Soo-Jeong Choi; Jung-Eun Lee
Indirubin derivatives having anticancer property against human cancer cell line	JAPAN	2012-551909	AnyGen Co., Ltd.	08-06-2012	Kim, Yong-Chul; Kim, Jae-Il; Ban, Soo-Ho; Jeong, Soon-Young; Choi, Soo-Jeong; Lee, Jung-Eun

10. Key Words

- Anti-cancer drugs, triple negative breast cancer (TNBC), tamoxifen-resistance, CDK inhibitors, indirubin derivatives, clinical trial

11. Company Description

AnyGen Co., Ltd. was founded in May 2000, as a laboratory venture company at Gwangju Institute of Science and Technology (GIST) and has been working in the fields of peptide APIs development and manufacturing for the past fifteen years.

- Peptides are widely used in medicine, cosmetics, and food products and since they have very little side-effects to the body, peptide markets are rapidly expanding worldwide.

- Leading the peptide market trend, AnyGen completed a peptide APIs factory over the course of three years that included through planning and construction. In addition, by receiving the first peptide BGMP certification and license in Korea, we have acquired the bridgehead for market entrance.

- Recently, we have expanded and relocated headquarters to the Jangseong NanoBio Research Center and have secured the latest research and manufacturing facilities to boost the peptide APIs and commercialization.

- To thrive as a successful bio-company with active R&D investment and globalization strategies based on a stable cash-flow of peptide APIs manufacturing, every member of AnyGen will strive for the best.