Neomics Co., Ltd.

Key Technology Highlights

1. Potent lung cancer suppressor associated to multiple-cancer signaling

: Our target AIMP2 is related to a couple of major cancer pathways. AIMP2 enhances cell death extrinsically and intrinsically. Further AIMP2 suppresses cellular proliferation via beta-catenin and c-myc pathways. Targeting this multifunctional protein can protect the clinical trial from acquiring drug resistance.

2. Targeting cancer -specifically inducible oncogene

: We suppress a splicing variant induced in tumor region. Therefore we can efficiently avoid side effect on normal cells.

3. Screening platform to optimize siRNA

: We should optimize siRNA to fit the lung cancer therapy and we developed a platform to screen siRNA. That techniques include monitoring transfection yield, calculating released cytokines and comparative method about siRNA stability.

4. Expert delivery skill of siRNA to lung

: We have designed several delivery system and carrier to lung.

5. Basic research infra to prove a value of novel therapeutic target

: We have studied the various functions of tRNA synthetases and the co-factors. Although now we are focusing on oncology, we have enough experiences with immunology and biochemistry. Moreover, because Dr. Kim’s Lab of Seoul National University also cooperate our researches, we can deal with several high techniques.

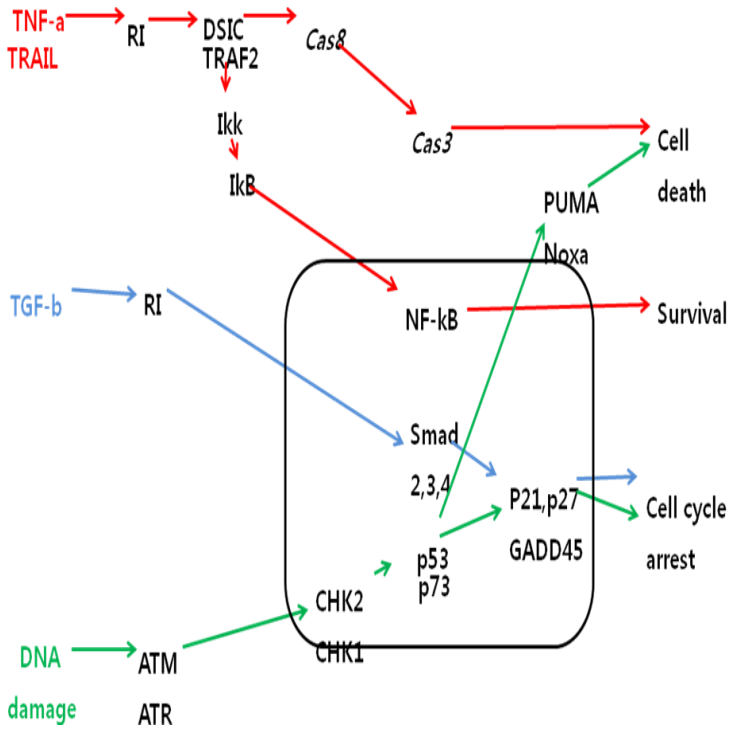
Technology Overview

1. AIMP2-DX2 siRNA targeting Lung Cancer (Non Small Lung Cancer Cells)

- AIMP2 is one of the scaffold proteins involved in protein synthesis machinery, aminoacyl tRNA synthetases with various ARSs for protein synthesis.

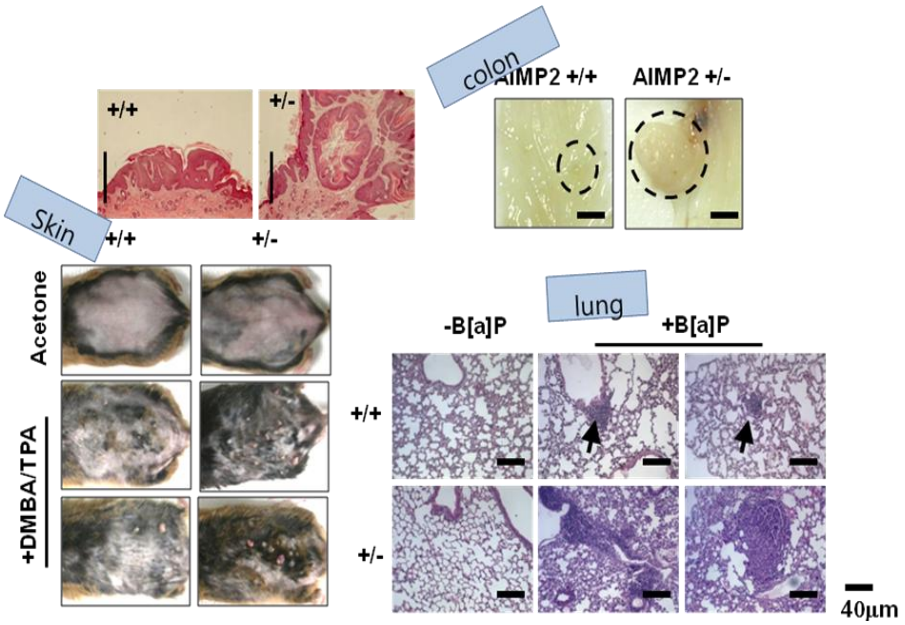
- AIMP2 is known to have tumor suppressive role obtained from the phenotypic characteristics of AIMP2-deficient mice.

- And cellular and molecular studies revealed that AIMP2 plays a critical role in the growth arresting signal by TGF-beta and enhances both intrinsic and extrinsic cell death via p53 and TNF-alpha pathway, respectively. Since TGF-beta, TNF-alpha and p53 are important factors in the regulation of tumorigenesis, the relationship of AIMP2 to these factors implies its potential as a novel tumor suppressor. - AIMP2 plays a key role in down regulation of c-myc expression that results in stopping cell proliferation and stimulating the cells into differentiation.



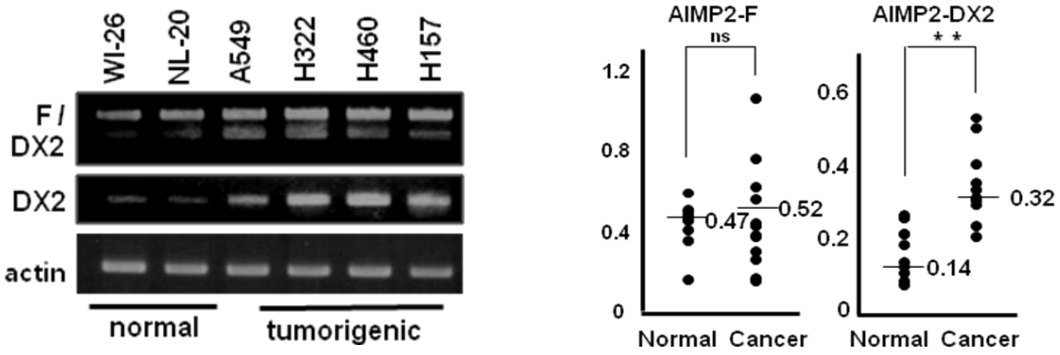
(AIMP2-related signaling pathway)

- the mice in which expression level of AIMP2 was reduced compared to wild type became more susceptible to chemical-induced carcinogenesis



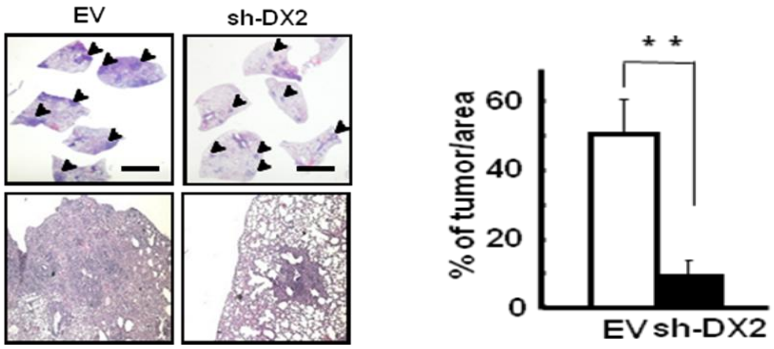
(High tumor susceptibility of AIMP2 heterozygous mice)

- Gene coding AIMP2 can produce exon2-deleted splicing variant specifically in tumor regions. We named the variant as AIMP2-DX2. Actually, AIMP2-DX2 variant are found to be specifically increased in a variety of cancer cells including lung, breast, liver, stomach cancer, etc.



(Cancer- specific induction of AIMP2-DX2)

-Furthermore, NCI-H460 with shRNA targeting AIMP2-DX2 showed significant reduction of the expression level of AIMP2-DX2 compared to control. Decreased expression of AIMP2-DX2 was closely correlated with reduced tumor size.

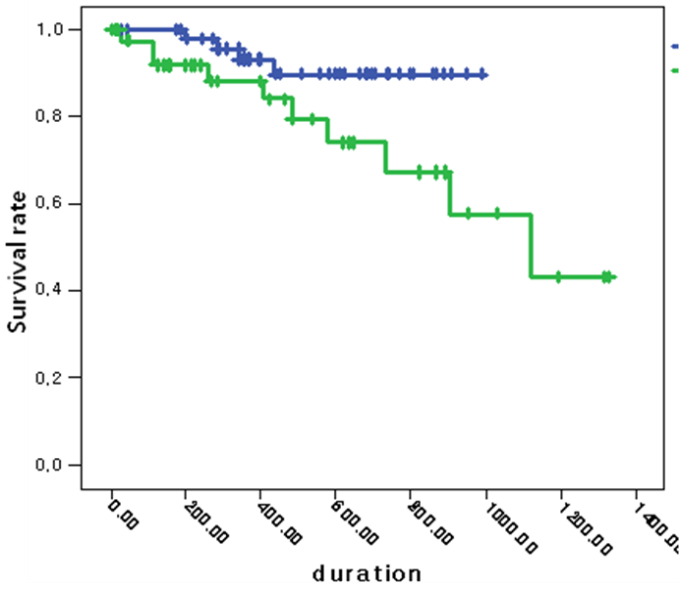


2. Development of Diagnostics using AIMP2-DX2 to select patients who are applicable to siDX2 therapeutics.

Rapid and accurate diagnostics are the most important factor to make a targeted therapy successful. We also need to develop an efficient diagnostic kit for correct quantization of AIMP2-DX2.

The quantitative reverse transcriptase polymerase chain reaction (q-PCR) method has proved to be useful in accurately measuring expression levels of specific gene transcripts. First, we developed the q-PCR- based the AIMP2-DX2 detection kit which can monitor the AIMP2-DX2 expression. This kit can be used to distinguish a proper group to ‘clinical trials using si-AIMP2-DX2’ among all lung cancer patients.

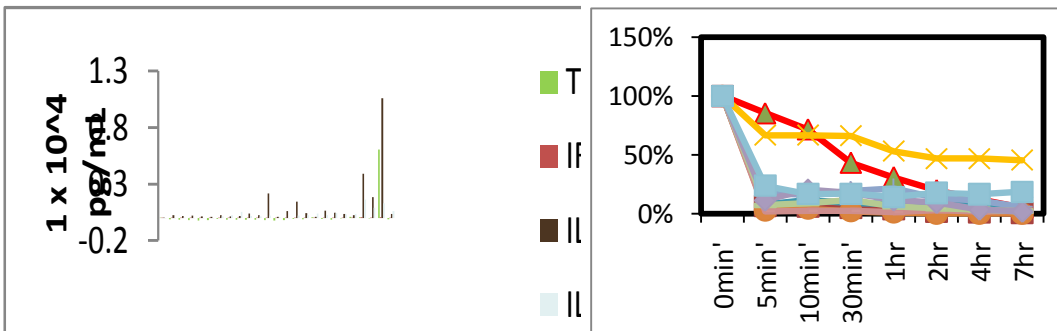
We already got interesting results when we analyzed the AIMP2-DX2 expression level in human lung cancer cells by this q-PCR kit. The AIMP2-DX2 expression is not only increased in lung cancer tissue compared to normal lung tissue but also high AIMP2-DX2 expressing lung cancer patients showed poor prognosis compared to low AIMP2-DX2 expressing lung cancer patients. We are trying to develop the AIMP2-DX2 detection kit by immunohistochemistry (IHC) to monitor the AIMP2-DX2 expression at protein level. Using our kit, it is proved that the high AIMP2-DX2/AIMP2 expressing lung cancer patients show poor prognosis compared to low AIMP2-DX2/AIMP2 expressing lung cancer patients.



(Increased DX2 level, Decreased survival)

3. Selection of an efficient chemical modification for siRNA

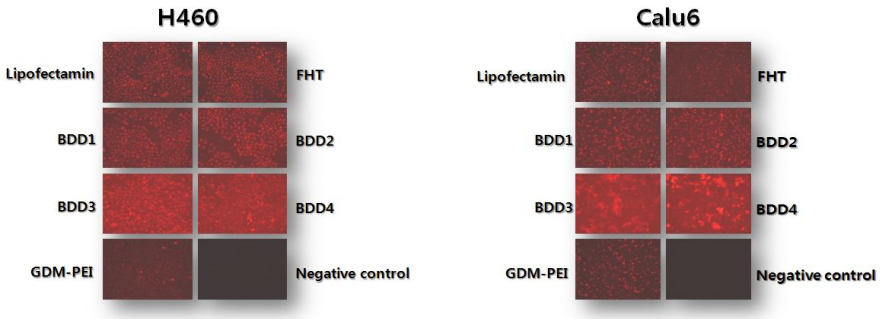
To increase the efficacy of siRNA therapeutics, siRNA can be modified chemically to be more stabilized even in serum and reduce immune surveillance of host system. We designed several chemical modification on targeted siRNA. We determined secretion of TNF-alpha, IL-6, 12 and IFN-gamma via ELISA methods after transfection of each modified siRNA forms. We then tested stability of them via gel running method. Finally, we calculated reduction of AIMP2-DX2 level 72h after transfection of 5 nM siRNA. Totally we decided final format of modified siRNA.



Decreased Immunogenicity Increased stability

4. Selection of proper delivery system for siRNA.

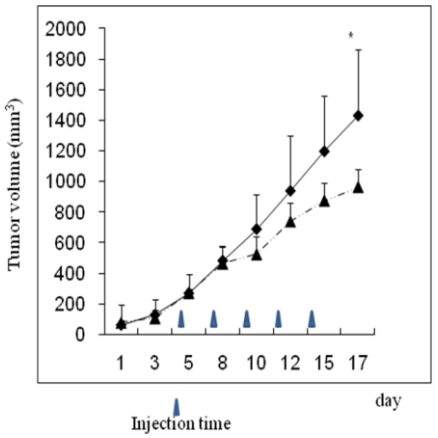
siRNA delivery is another barrier for siRNA therapeutics. Especially, targeting the specific organ and disease need to regulate the introduction of siRNA more finely. To overcome this problem, we had to gather and compare a couple of delivery carriers to find formulation which result in the best efficacy or transfection yield of ours. Additionally we tested their immunogenicity. Our test articles included peptide, liposome, polymer-originated carriers properly. Regarding these factors, we selected a final carrier.



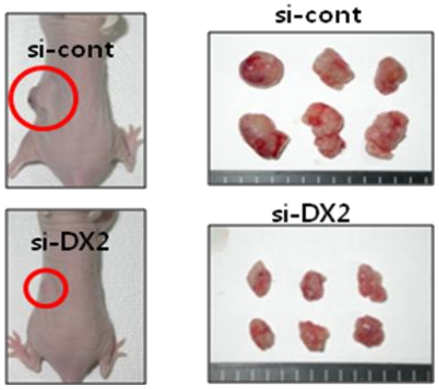
(Increased transfection yield)

5. The effect of final siDX2 format was proved in xenograft mouse moldel

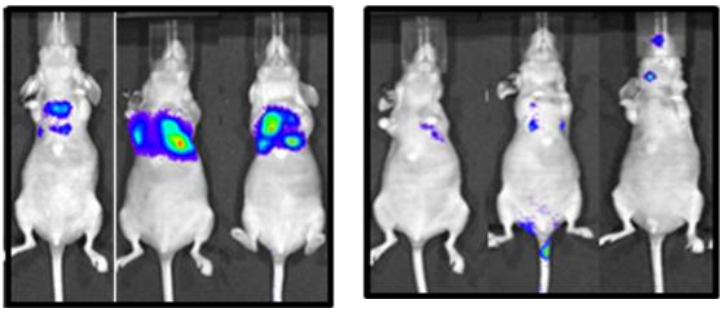
50ug/100ul/head intratumoral injection, twice a week, total 5 times at tumor size 300mm^2 statistically significantly reduced tumor size ($p<0.05$).



(Control group)



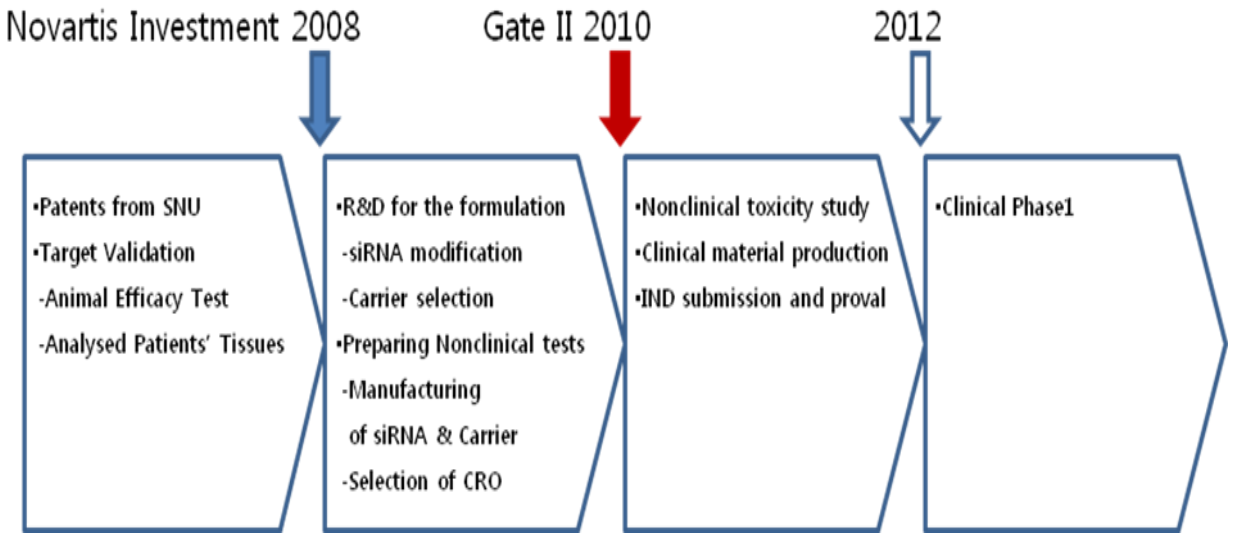
(siDX2 treated group)



(siDX2 RNA efficacy in lung cancer animal models by inhalation route)

5. Current Stage of Development : entering the nonclinical study

1) We finalized therapeutic format including chemically- modified siRNA and delivery carrier
2) We have a prototype companion diagnostic kit using q-PCR method.
3) We prepared all material for non-clinical toxicity study and expect the entry of nonclinical toxicity tests in this September.



R&D Plan & Cost in 2010 - 2013

Year 2010

Q2-Q4 : Large scale process development and Non-clinical toxicity material production
Q2-Q4 : Carrier particle optimization and efficacy optimization with clinical route
End of Q4 : pre-preIND meeting to discuss non-clinical study plan
Q4 : Initiation of Non-clinical toxicity studies

Year 2011

Q1- Q3 : Nonclinical toxicity study
Q2- Q3 Clinical material production
Q3- Q4 IND submission and approval

Year 2012-13

Complete siRNA Therapy Phase I & IIa clinical trials
IPO listing to raise funds for continuing trials of Chemical Drug candidates

R&D Cost Estimate

Manufacturing : 1 M USD

- process development and non-clinical and clinical siRNA synthesis

Carrier development and manufacturing :0.2 M USD

Non-clinical efficacy and formulation optimization : 0.15 M USD

Non-clinical toxicity studies : 2 M USD

Pre-preIND and IND approval : 0.18 M USD

Development of diagnostics : 0.3 M USD

Internal R&D cost : 1.2 M USD

Total 5 M USD for 2 years till phase I entry

Complete siRNA Therapy Phase I & IIa clinical trials : 6.0 M USD
Internal R&D cost : 1.5 M USD

Total 12.5 M USD for 4 years till phase IIa entry

Specific Patent Information

No.	Patent Name	Registration (Application) Number	Registration (Application) Date	Registration (Application) Country	Registration or Application
1	Pharmaceutical composition for treatment of cancercontaining p38/JTV-1 as an effective component andscreening method for pharmaceutical composition fortreatment of cancer	575251	2006.04.24	Korea	Registration
2	Use of AIMP2DX2 for the diagnosis and treatment of cancer	762995	2007.09.21	Korea	Registration
3	Use of AIMP2/p38 and AIMP2-DX for Regulation of TNF-a Signaling via TRAF2	10-2007-0114520	2007.11.09	Korea	Application
4	Use of AIMP2DX2 for the diagnosis and treatment of cancer	10-2006-0047831	2006.05.26	Korea	Application
5	Composition for preventing and treating inflammatory diseases comprising inhibitor of AIMP2-DX2 as an active ingredient	10-2008-0111109	2008.11.10	Korea	Application
6	Method for Treating Cancer Using p38/JTV-1 and Method for Screening Pharmaceutical Composition for Treating Cancer	4351896	2009.07.31	Japan	Registration
7	Method for Treating Cancer Using p38/JTV-1 and Method for Screening Pharmaceutical Composition for Treating Cancer	7,196,068	2007.03.27	USA	Registration
8	MEDICAL USE OF P38/JTV-1	1454628	2009.04.01	EPO	Registration
9	AIMP2-DX2 AND ITS USES	7459529	2008.12.02	USA	Registration
10	USE OF AIMP2DX2 FOR THE DIAGNOSIS AND TREATMENT OF CANCER	05 819 055.4	2007.04.04	EPO	Application
11	USE OF AIMP2DX2 FOR THE DIAGNOSIS AND TREATMENT OF CANCER	200580037802.9	2007.04.30	China	Application
12	USE OF AIMP2DX2 FOR THE DIAGNOSIS AND TREATMENT OF CANCER	2007-542907	2007.05.24	Japan	Application
13	AIMP2-DX2 GENE AND SIRNA TARGETING AIMP2-DX2	12/255,943	2008.10.22	USA	Application