Identifying Novel Targets for Non-Small Cell Lung Cancer

Just How Novel Are They?

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Solution Scientist

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Non-Small Cell Lung Cancer (NSCLC) is a larger cancer type

Stage I, the cancer is discovered in the lungs and has not affected outside.

Stage II, it has affected the nearby lymph nodes.

Stage III, the cancer has been discovered in the lymph nodes present in the middle of the chest and also the opposite side.

Stage IV, cancer is spread to both the lungs and also in other organs.
NSCLC global incidence and prevalence

United States
Aggressive tobacco-control programmes have caused a decline in smoking and the incidence rate is slowly falling.

Mexico
As in many other developing countries, low rates of tobacco use correlate with low rates of lung cancer.

Sub-Saharan Africa
Incidence rates are low but public-health officials predict an epidemic of lung cancer because of tobacco advertising campaigns.

Hungary
The country has an ageing population and in the past many Hungarians smoked. Even though an estimated 33% of men and 23% women now smoke, according to 2009 World Health Organization data, it will take some years for any decrease in the number of people smoking to be reflected in fewer cases of lung cancer.

China
More than half of men in the world’s most populous nation smoke, and lung cancer rates are soaring.
Incorporating chemotherapies, immunotherapy and targeted therapies into the management of NSCLC

Current strategies first look at actionable mutations in well-known genes to identify targeted therapies. For unknown or not detected mutation statuses, the standard chemotherapy is applied.

When well-known genes and/or mutations are not easily identifiable, there is a need to identify novel actionable hypotheses in order to conduct patient stratification and novel therapy development.
Systems Biology: from peer reviewed articles to signaling pathways

Manual annotation from publications
- Team of PhDs, MDs
- More than 10 years

Publications
- 208 publications for EGF-EGFR interaction

Molecular Interaction
- 1,600 CANONICAL AND DISEASE SIGNALING PATHWAYS

Global Network
- 1,800,000 molecular interactions
Flexibility in data analysis

11 Different Network Building Algorithms, all with written and visual descriptions

Choose building algorithm
- Analyze network
- Analyze network (transcription factors)
- Analyze network (receptors)
- Transcription regulation
- Shortest paths
- Trace pathways
- Direct interactions
- Self regulation
- Auto expand
- Expend by one interaction
- Manual expand

Multiple automated Workflows to save, share and export

Data Analysis Workflows
A set of simple step-by-step wizards for analysis of your data.
- Enrichment Analysis
- Analyze Single Experiment
- Compare Experiments
- Compare Compounds
- Toxicity Analysis
- Biomarker Assessment
- Interactome Analysis

But also One-Click analysis for instant answers

Enrichment Ontologies
- Pathway Maps
- Gene Families
- Process Networks
- Disease (Dr. Hyman)
- Disease Biomarker Networks
- Drug Target Networks
- Tumor Pathologies
- Drug and Xenobiotic Metabolism Enzymes
- Toxicity Networks
- Metabolic Networks
- Metabolic Networks (Redoxen)

Interactome
- Interactions by Protein Function
- Transcription Factors
- Significant Interactions Within Set
- Interactome Topology
- Enrichment by Protein Function
- Interactions Between Datasets (48)
- Interactions Between Datasets (78)
- Drug Lookup for Your Gene List and Datasets

Microarray Repository
- Similar search by Gene
- Similar search by Functional Descriptors

Causal reasoning algorithm to find key hubs
Genome-wide screening of transcriptional modulation in non-smoking female lung cancer in Taiwan

- **GSE19804** gene expression dataset from NCBI GEO
- 58 NSCLC female patients
- Each tumor gene expression simple is compared with corresponding normal lung tissue from the same patients

**NSCLC PATIENTS IN THE STUDY**

- Stage 1: 12 patients
- Stage 2: 13 patients
- Stage 3: 34 patients

PMID: 20802022
MetaCore analysis demo
MetaCore main page; dataset preparation

### Enrichment Ontologies
Scores and ranks entities in functional ontologies most relevant in activated dataset(s).

**Ontologies**
- Pathway Maps
- Gene Sets
- Process Networks
- Diseases (by Biomarkers)
- Disease Biomarker Networks
- Drug Target Networks
- Toxicity Networks
- Metabolic Networks
- Metabolic Networks (Endogenous)

### Interactome
Detailed analysis of interaction space for activated datasets and gene lists.
- Interactions by Protein Function
- Transcription Factors
- Significant Interactions Within Set(s)
- Network Topology
- Enrichment by Protein Function
- Interactions Between Datasets (all)
- Interactions Between Datasets (subset)
- Drug Lookup for Your Data

### Microarray Repository
- Similarity search by Genes
- Similarity search by Functional Descriptors

### A closer look at your datasets
Note that you should first activate your experimental data in the Data Manager by selecting the uploaded datasets and then clicking on the Activate button. You can also drag one or more experiments from the upper frame of the Data Manager and drop it in the lower one.

Enrichment Analysis (EA) is a common type of functional analysis which scores and ranks the most relevant cellular processes, disease targets, biomarkers, toxicity processes and molecular functions for your dataset(s). MetaCore™/MetaDrug™ features over 12 different functional ontologies that are applied in EA.

Interactome is a unique proprietary tool which evaluates the "local interactome" of your dataset(s) in the context of the "global interactome" (all links between the genes, proteins and compounds in MetaCore™/MetaDrug™ database).
- Interactions by Protein Function scores and ranks by relative connectivity transcription factors (TF), ligands, receptors, kinases, and other protein classes in your dataset(s).
- Transcription Factors tool lists interactions with the "transcription regulation" mechanism.
- Significant Interactions Within Set(s) tool lists proteins from the active experiment with its significant interactions.
Selecting analysis

Enrichment Ontologies
Scores and ranks entities in functional ontologies most relevant in activated dataset(s).

Ontologies
- Pathway Maps
- Data Sets
- Databases
- Molecular Networks
- Microarray Repository

Interactome
Detailed analysis of interaction space for activated datasets and gene lists.

Microarray Repository
- Similarity search by genes
- Similarity search by functional descriptors

A closer look at your datasets

Note that you should first activate your experimental data in the Data Manager by selecting the uploaded datasets and then clicking on Activate button. You can also drag one or more experiments from the upper frame of the Data Manager and drop it in the lower one.

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Interactions by Protein Function: scores and ranks by relative connectivity transcription factors (TF), ligands, receptors, kinases, and other protein classes in your dataset(s).

Transcription Factors: tool lists interactions with the "transcription regulation" mechanism.

Significant Interactions Within Set(s): tool lists proteins from the active experiment with its significant interactions.
Pathway map folders analysis

### Pathway Map Folders

#### Enrichment Save Enrichment

<table>
<thead>
<tr>
<th>Experiments</th>
<th>Species</th>
<th>Network Objects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Small-Cell Lung Carcinoma, Stage I vs. Surrounding Non-Tumor Lung</td>
<td>Homo sapiens</td>
<td>728</td>
</tr>
<tr>
<td>Non-Small-Cell Lung Carcinoma, Stage II vs. Surrounding Non-Tumor Lung</td>
<td>Homo sapiens</td>
<td>1118</td>
</tr>
<tr>
<td>Non-Small-Cell Lung Carcinoma, Stage III vs. Surrounding Non-Tumor Lung</td>
<td>Homo sapiens</td>
<td>1291</td>
</tr>
</tbody>
</table>

#### Experiments

<table>
<thead>
<tr>
<th>Experiment name</th>
<th>Species</th>
<th>Network Objects</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Homo sapiens</td>
<td>1291</td>
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</table>

#### Pathway Map Folders

<table>
<thead>
<tr>
<th>Map folders</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>12</th>
<th>14</th>
<th>-log(p-value)</th>
<th>pValue</th>
<th>min(pValue)</th>
<th>FDR</th>
<th>Ratio</th>
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<tbody>
<tr>
<td>Asthma</td>
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<td>1.046e-10</td>
<td>129/2626</td>
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<td>2.046e-18</td>
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<td>Neurofibromatoses</td>
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<td>Stem cells</td>
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<td>Systemic Lupus Erythematosus</td>
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<td>4.079e-6</td>
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</tr>
</tbody>
</table>

**Total results:** 50
Browsing lung cancer related pathway maps to get the insight on disease progression and mechanism

<table>
<thead>
<tr>
<th>Pathway Name</th>
<th>P-value</th>
<th>min(P-value)</th>
<th>FDR</th>
<th>Ratio</th>
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</thead>
<tbody>
<tr>
<td>Cell cycle. Role of APC in cell cycle regulation</td>
<td>2.77e-1</td>
<td>6.899e-1</td>
<td>5/52</td>
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</tr>
<tr>
<td>Cell cycle. Start of DNA replication in early S phase</td>
<td>2.658e-2</td>
<td>5.442e-1</td>
<td>6/52</td>
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<tr>
<td>Immune response. IL-17 signaling pathways</td>
<td>4.237e-1</td>
<td>9.969e-1</td>
<td>3/52</td>
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<tr>
<td>Cell adhesion. ECM remodeling</td>
<td>1.386e-4</td>
<td>8.893e-3</td>
<td>10/72</td>
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</tr>
<tr>
<td>Transcription. HIF-1 targets</td>
<td>1.21e-3</td>
<td>9.609e-1</td>
<td>6/50</td>
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<tr>
<td>Cell cycle. Initiation of mitosis</td>
<td>2.786e-3</td>
<td>9.949e-1</td>
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<tr>
<td>Immune response. CCL2 signaling</td>
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</tr>
<tr>
<td>Development. YAP/TAZ-mediated co-regulation of transcription</td>
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<td>10/75</td>
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<td>Main genetic and epigenetic alterations in lung cancer</td>
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<td>9.856e-1</td>
<td>3/50</td>
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<tr>
<td>Development. Regulation of epithelial-to-mesenchymal transition (EMT)</td>
<td>3.776e-3</td>
<td>9.856e-1</td>
<td>3/50</td>
<td></td>
</tr>
</tbody>
</table>

Clarivate Analytics
Main genetic and epigenetic alterations in lung cancer
Target Druggability analysis demo
Explore targets of interest

Select in *Drug Research Advisor* targets, condition(s) or drug(s) of your interest
Narrowing the search for a novel target for NSCLC

Filtering by “Condition” allows to identify those targets that have been associated with Lung Cancer

“Exploration view”

“The Table view”
**RECK** as a suitable novel target for NSCLC

**RECK** is a membrane-anchored protein that is downregulated in transformed cells and acts as a tumor suppressor. It negatively regulates matrix metalloproteinase-9 (MMP-9) by suppressing MMP-9 secretion and by direct inhibition of its enzymatic activity. **RECK** down-regulation by oncogenic signals may facilitate tumor invasion and metastasis. It also appears to regulate MMP-2 and MT1-MMP, which are involved in cancer progression.
RECK as a suitable novel target for NSCLC

Drugs

There is one drug in very early stage of development (Biological Testing) targeting RECK for treatment of Lung and Breast Cancers.
RECK as a suitable novel target for NSCLC

Drugs

<table>
<thead>
<tr>
<th>Entry Number</th>
<th>Sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>867566</td>
<td>dsRNA sequence:</td>
</tr>
<tr>
<td></td>
<td>UGGAAACACUGUGAGGCAGTT</td>
</tr>
</tbody>
</table>

**Chemical Name/Description**

Double-stranded RNA (dsRNA) activating the promoter region of human reversion-inducing-cysteine-rich protein with kazal motifs (RECK) gene, whose sequence is 5'-UGGAAACACUGUGAGGCAGTT-3'

**Standard InChI**

**Standard InChIKey**

**Code Name** | **Generic Name** | **Brand Name**
--- | --- | ---
RECK-82 | | |

**Molecular Mechanism**

RECK Expression Enhancers

**Cellular Mechanism**

**Product Category** | **Therapeutic Group** | **Prescription/Indication Type**
--- | --- | ---
Double stranded oligoribonucleotide (RNA) | Lung Cancer Therapy | |
Small Activating RNA (saRNA) | Breast Cancer Therapy | |

**Organization**

Osaka University (Originator)

**Product Summary**

**Related Information**

- Biomarkers: 2
- Targets & Pathways: 2
- Literature: 1
- Companies & Research Institutions: 1
**RECK** as a suitable novel target for NSCLC

**Genetic Evidence**

<table>
<thead>
<tr>
<th>Condition (Showing 10 of total 10)</th>
<th>Number of related records</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Drugs</td>
</tr>
<tr>
<td>Adenoma, pituitary</td>
<td></td>
</tr>
<tr>
<td>Amyotrophic lateral sclerosis</td>
<td></td>
</tr>
<tr>
<td>Cancer, breast</td>
<td>1</td>
</tr>
<tr>
<td>Cancer, head and neck (squamous cell carcinoma)</td>
<td></td>
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<tr>
<td>Cancer, liver (hepatocellular carcinoma)</td>
<td></td>
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<tr>
<td>Cancer, lung</td>
<td>1</td>
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<tr>
<td>Cancer, oropharynx</td>
<td></td>
</tr>
<tr>
<td>Cancer, pancreas (ductal adenocarcinoma)</td>
<td></td>
</tr>
<tr>
<td>Carcinoma, Pancreatic Ductal</td>
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</tr>
</tbody>
</table>

**Genetic evidence citations**

Filtered by: **Cancer, lung (non-small cell) (NSCLC)**

1 genetic evidence record related to the following 1 reference

**CONFERENCE**

A novel functional polymorphism in CIR1 gene is associated with the risk of lung cancer

Author: Jin, C., Jung, D.K., Park, J.Y.

Publication: World Conference on Lung Cancer - 2015-09-06 / 2015-09-08 - Denver, United States

Cancer, lung (non-small cell) (NSCLC) Relevance
RECK as a suitable novel target for NSCLC
Biomarkers

Examination of Biomarkers suggests that RECK is used as a biomarker for NSCLC and hence could be a valid target for the treatment of NSCLC.