**DSDHT FALL 2017**
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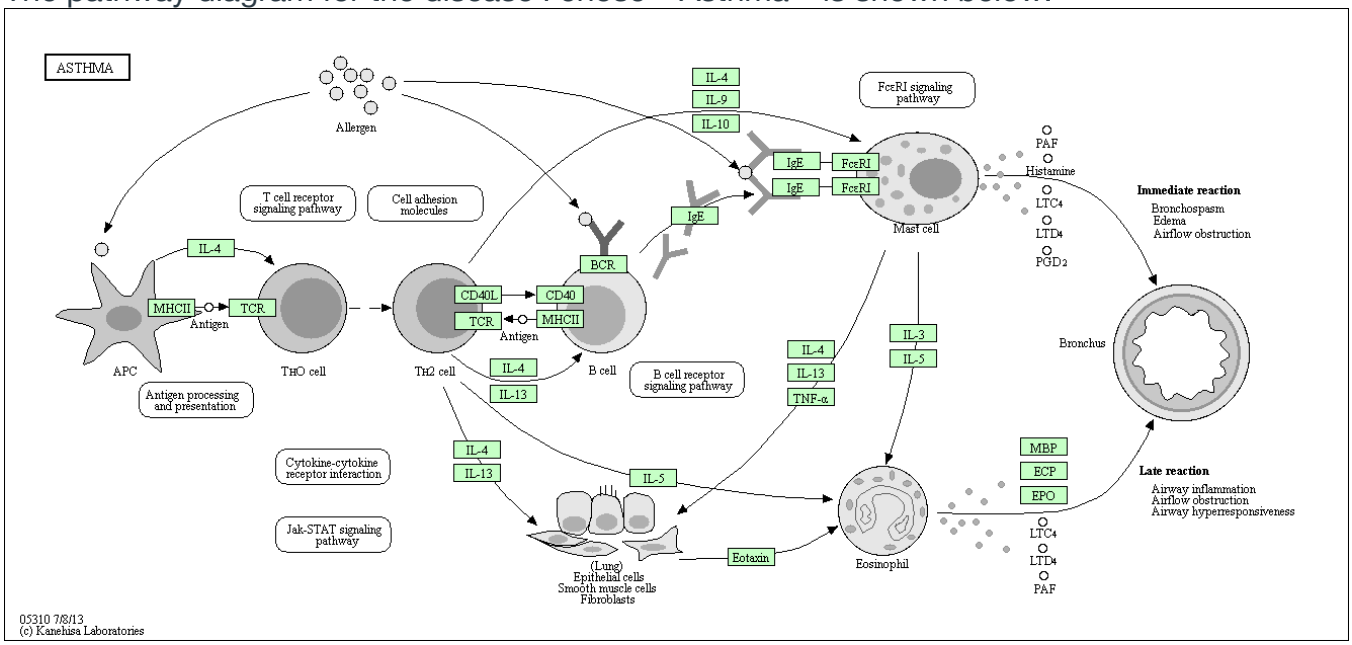
# Module 7 – Bioinformatics and Medicine

1. Go to KEGG, the Kyoto Encyclopedia for Genes and Genomes, at http://www.genome.jp/kegg/. Search for a disease (e.g. diabetes or cancer). Find one or more pathways associated with the disease query. Find the pathway diagram and copy into your assignment answer. List all the genes in this pathway (by gene symbol). Also describe in your own words what KEGG is telling us, associating molecular biology with medicine.

The pathway diagram for the disease I chose – Asthma – is shown below.




The entry in KEGG for the disease "Asthma" lists all genes in the pathway. They are: IL4, IL4RA, IL13, FCER1B, TNFA, ADAM33, CD14, HLA-DRB1, HLA-DQB1, ADRB2. A search to this gene list using the "Multi-symbol checker" in the HGNC website revealed all these symbols are approved symbols, except IL4RA. However IL4RA is found in the UniProtKB website.

| **Pathway** | hsa05310 Asthma |
|---|---|
| **Gene** | IL4 (polymorphism) [HSA:3565] [KO:K05430]<br>IL4RA (polymorphism) [HSA:3566] [KO:K05071]<br>IL13 (polymorphism) [HSA:3596] [KO:K05435]<br>FCER1B (polymorphism) [HSA:2206] [KO:K08090]<br>TNFA (polymorphism) [HSA:7124] [KO:K03156]<br>ADAM33 (polymorphism) [HSA:80332] [KO:K08616]<br>CD14 (polymorphism) [HSA:929] [KO:K04391]<br>HLA-DRB1 (polymorphism) [HSA:3123] [KO:K06752]<br>HLA-DQB1 (polymorphism) [HSA:3119] [KO:K06752]<br>ADRB2 (polymorphism) [HSA:154] [KO:K04142] |

The pathway describes how allergens interact with certain cells in the organism (e.g. antigen presenting cells - APC) triggering and/or contributing to a chain of biochemical events and reactions that culminates with the production of molecules or chemical compounds (e.g. PAF, histamine, LTC4, LTD4 and PGD2) as well as gene products (e.g. MBP, ECP and EPO) that ultimately affect the bronchus causing the symptoms that are known as "asthma", i.e., bronchospasm, airway inflammation, airway obstruction and airway hyper responsiveness.

A full description of the pathway available in the website is copied below:

| | |
|---|---|
| **Description** | Asthma is a complex syndrome with many clinical phenotypes in both adults and children. Its major characteristics include a variable degree of airflow obstruction, bronchial hyperresponsiveness, and airway inflammation. Inhaled allergens encounter antigen presenting cells (APC) that line the airway. Upon recognition of the antigen and activation by APC, naive T cells differentiate into TH2 cells. Activated TH2 stimulate the formation of IgE by B cells. IgE molecules bind to IgE receptors located on mast cells. The crosslinking of mast-cell-bound IgE by allergens leads to the release of biologically active mediators (histamine, leukotrienes) by means of degranulation and, so, to the immediate symptoms of allergy. Mast cells also release chemotactic factors that contribute to the recruitment of inflammatory cells, particularly eosinophils, whose proliferation and differentiation from bone marrow progenitors is promoted by IL-5. The activation of eosinophils leads to release of toxic granules and oxygen free radicals that lead to tissue damage and promote the development of chronic inflammation. |

Clearly, the understanding and documentation of biochemical pathways can only contribute to the advancement of medicine. Each link in the pathway, if broken via a drug, would disrupt the pathway and could potentially prevent the downstream effect of asthma. But other undesirable effects could ensue. The fact that the biochemical pathway for a common disease like asthma is captured on a rather complex graph, with links to six other pathways and a large number of gene products and chemical compounds brings to mind the integrative paradigm for drug discovery that we learned in module 5 of our class; it brings to mind the interconnectedness of biological systems in the body, and it provides evidence of the potential for data science to contribute to the advancement of medicine.

2. Go to Drug Central, at http://drugcentral.org/. Search for a drug target among the examples provided on the home page. For a drug found which is active on that target, drill down and find out whether this is the only target affected by this drug. Describe your findings.

I searched for target "P35372" which yielded 76 results. From the displayed results I selected the drug "codeine" which is described as an "opioid analgesic related to MORPHINE but with less potent analgesic properties and mild sedative effects…". Clicking on the "codeine" link I was able to view the "Bioactivity Summary" for this drug, which is seen in the next page.

**Bioactivity Summary:**

| Target | Class | Pharos | UniProt | Action | Type | Activity value (-log[M]) | Mechanism action | Bioact source | MoA source |
|---|---|---|---|---|---|---|---|---|---|
| Mu-type opioid receptor | GPCR | P35372 | OPRM_HUMAN | AGONIST | Ki | 6.14 | ☑ | CHEMBL | CHEMBL |
| Kappa-type opioid receptor | GPCR | P41145 | OPRK_HUMAN | AGONIST | Ki | 4.59 | | CHEMBL | |
| Delta-type opioid receptor | GPCR | P41143 | OPRD_HUMAN | AGONIST | Ki | 4.28 | | CHEMBL | |
| Opioid receptor | GPCR | | OPRD_RAT<br>OPRK_RAT<br>OPRM_RAT<br>SGMR1_RAT | | IC50 | 8 | | CHEMBL | |

New Search

The summary shows that the "mechanism of action" (MoA) for this drug is known and that the drug interacts at the molecular level with four different targets. The targets appear in the first column of the table in the screenshot.