Example of MANORAA Drug Design Platform Usage Report

Irosustat: Pharmacological treatment of hormone-sensitive cancers and endometrial cancer.

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Abstract

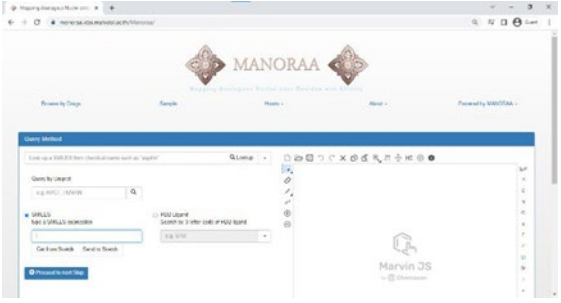
Diseases may be caused by several factors. The factors responsible for causing diseases can be extrinsic or intrinsic. Extrinsic factors are influences from outside. Examples include food or beverages (alcohol), smoking, malnutrition, water deprivation, the environment, etc. Intrinsic factors are those that are related to an individual. Age, gender, genetics, and disease states are examples of intrinsic factors. Extrinsic factors that can cause cancer, tobacco use, alcohol consumption, an unhealthy diet, physical inactivity, and air pollution are risk factors for cancer and other noncommunicable diseases. Nowadays, people are more likely to engage in risky behaviors that increase the risk of cancer. Cancer is a leading cause of death worldwide, accounting for nearly 10 million deaths in 2020, or nearly one in six deaths. Along with the situation in Thailand, cancer is a killer disease in Thailand. More than 122,000 new patients are diagnosed with cancer each year. This report focused on a drug in clinical trials called Irosustat. It has been used as a pharmacological treatment for hormone-sensitive cancers, i.e., breast, prostate, and endometrial cancers. The study shows that irosustat is an orally active, irreversible, nonsteroidal inhibitor for steroid sulfatase (STS), so it prevents the body from producing estrogen and androgen. In addition, the drug can bind to carbonic anhydrase II (CA II), thereby affecting various pathways in the body, which may lead to several side effects.

Introduction

During disease progression, hormone-sensitive cancers rely on sex hormones to develop and grow. Medical treatments can either stop your body from synthesizing sex hormones or prevent hormone receptors from binding to the hormones. Irosustat is a pharmacological treatment that prevents the body from producing estrogen and androgen. The research was done using bioinformatic tools and MANORAA, A machine learning platform to guide protein-ligand design by anchors and influential distances.

Methods

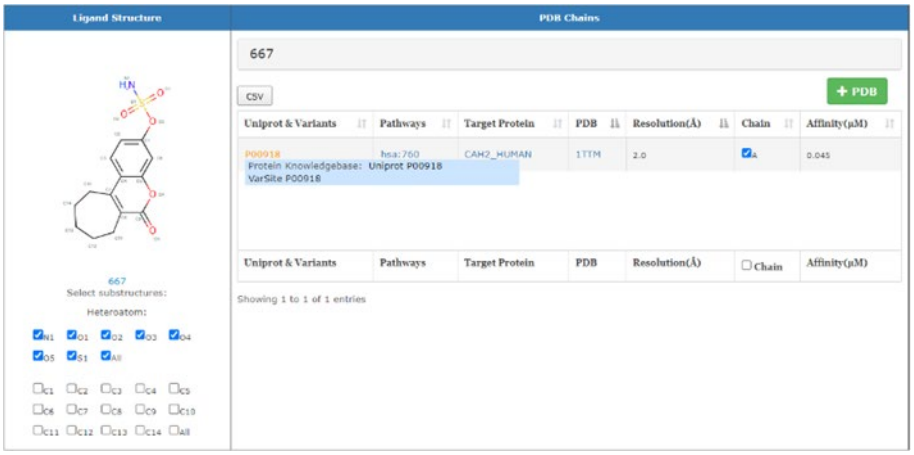
1. Search for Irosustat at https://manoraa.icbs.mahidol.ac.th/Manoraa/

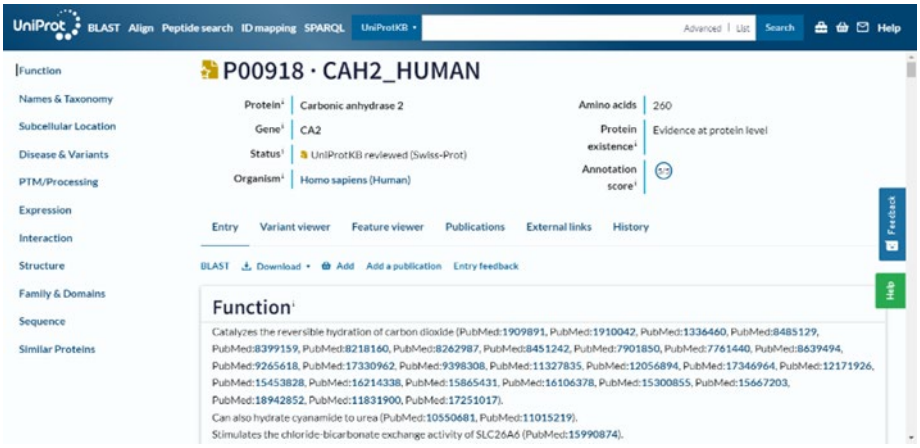


2. Click on 

3. Investigate the information of irosustat, which contains of:

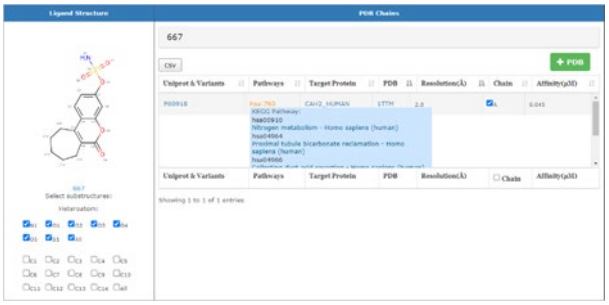
- UniProt: is high-quality, comprehensive and freely accessible resource of protein sequence and functional information.
    - After bringing the mouse cursor to the UniProt section, the pop-up shows the UniProt code, so you can click on the code to learn more information.



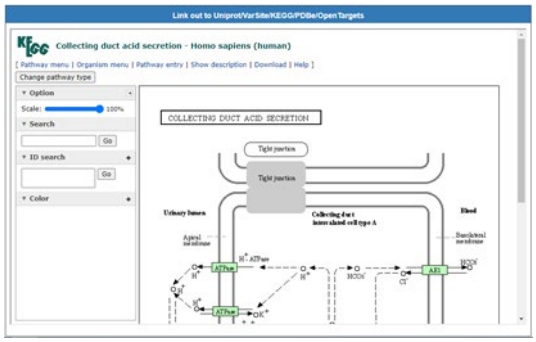


- KEGG Pathway: is a collection of pathway maps representing our knowledge of the molecular interaction, reaction and networks for:

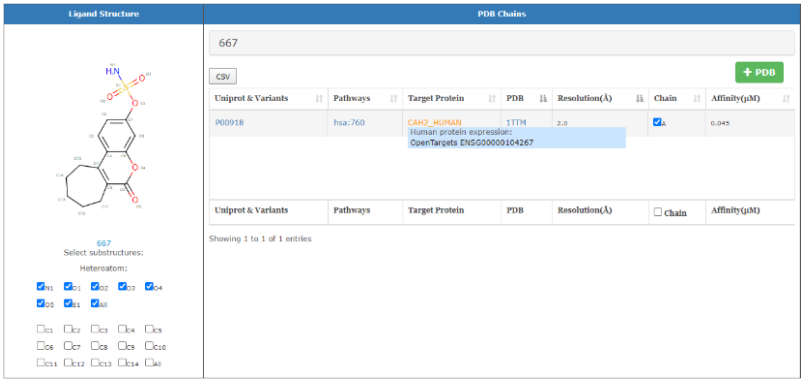
- Metabolism
- Genetic Information Processing
- Environmental Information Processing
- Cellular Processes
- Organismal Systems
- Human Diseases
- Drug Development



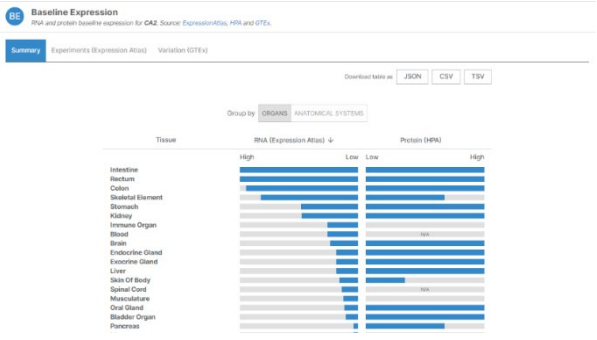
- After bringing the mouse cursor to the Pathway section, the pop-up shows the KEGG Pathway, so you can click on the pathway to learn more about the biological pathway that it consists of.



- Target protein: is a comprehensive tool that supports systematic identification and prioritization of potential therapeutic drug targets.
  - After bringing the mouse cursor to Target Protein section, the pop-up shows “Open Target Platform”, so you can click on each headline to learn more about the target protein.



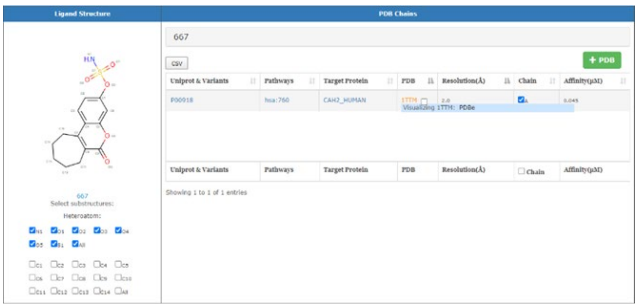
Or you may click on the headline "Baselines Expression" to see baseline RNA and protein expression data help us ascertain whether the target is expressed in all tissues or selectively in one or a few tissues or cell types. The availability of the target molecule in the location of interest is critical at different stages of the drug development process.

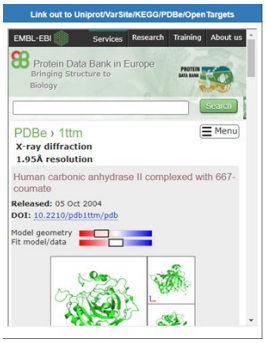


- PDB file: RCSB Protein Data Bank (RCSB PDB) enables breakthroughs in science and education by providing access and tools for exploration, visualization, and analysis of:

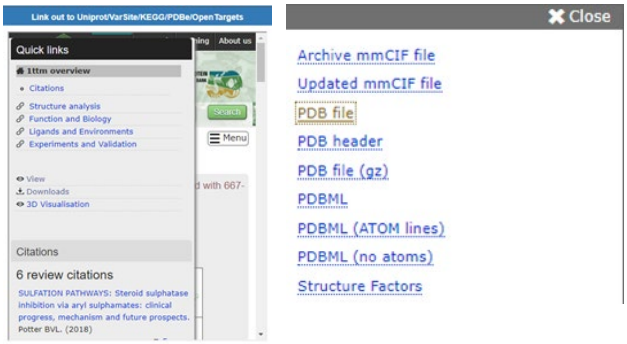
- Experimentally-determined 3D structures from the Protein Data Bank (PDB) archive
- Computed Structure Models (CSM) from Alpha Fold DB and Model Archive

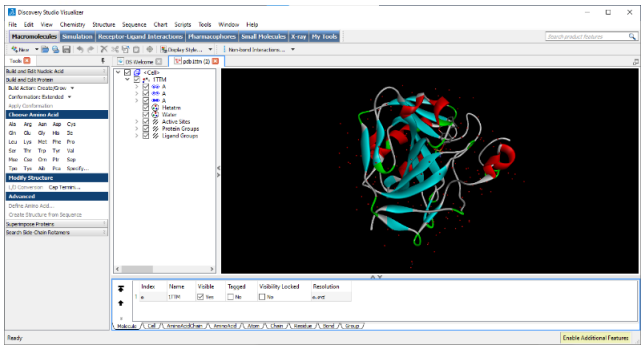
- After bringing the mouse cursor to the PDB file section, the pop-up shows a link out to the RCSB Protein Data Bank (RCSB PDB) for visualizing target proteins, so you can click on each headline to learn more about the target protein.

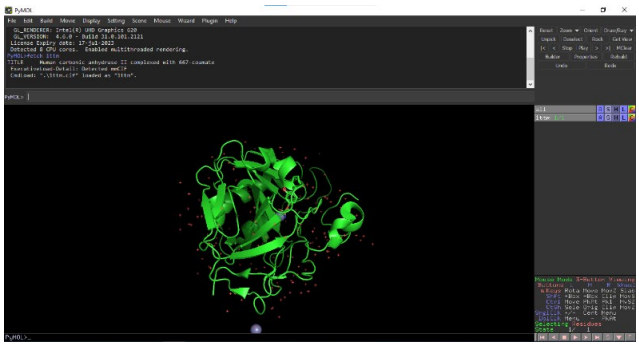


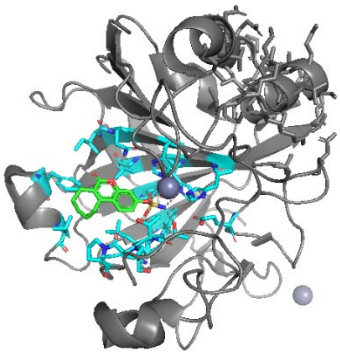


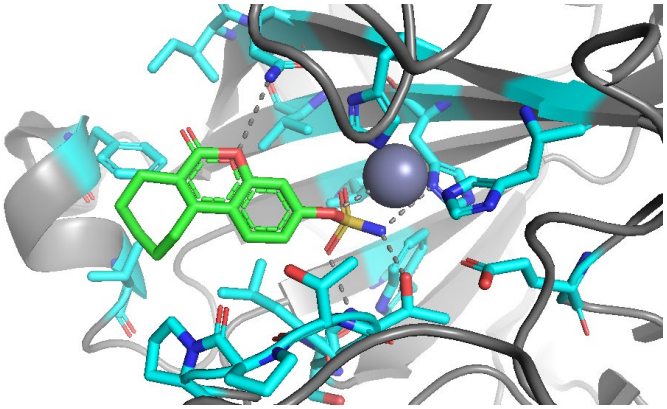
Or you may click on the menu button and click download PDF file. To open the file, you need to use an appropriate program for bioinformatics. In this study, Biovia: Discover Studio Visualizer and PyMOL were used together to analyze the structures of protein.

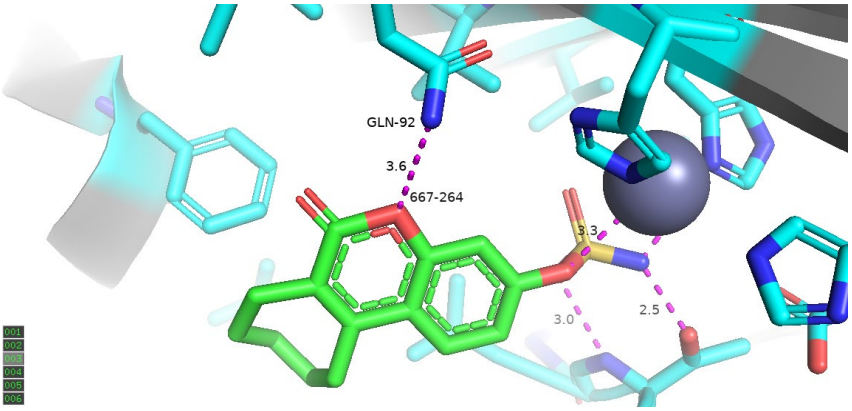








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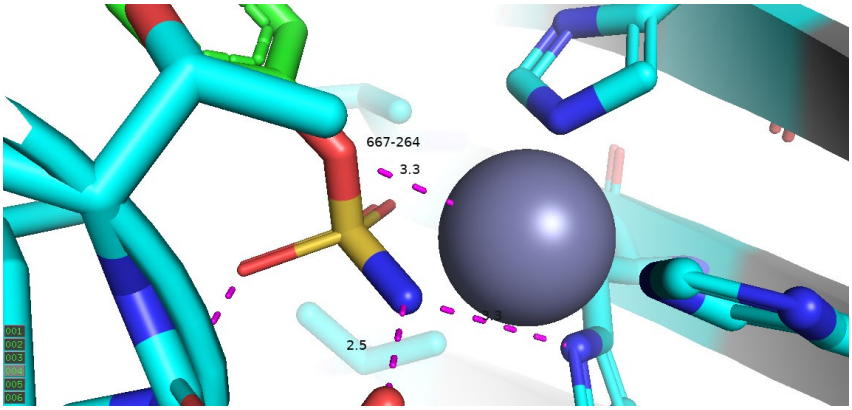
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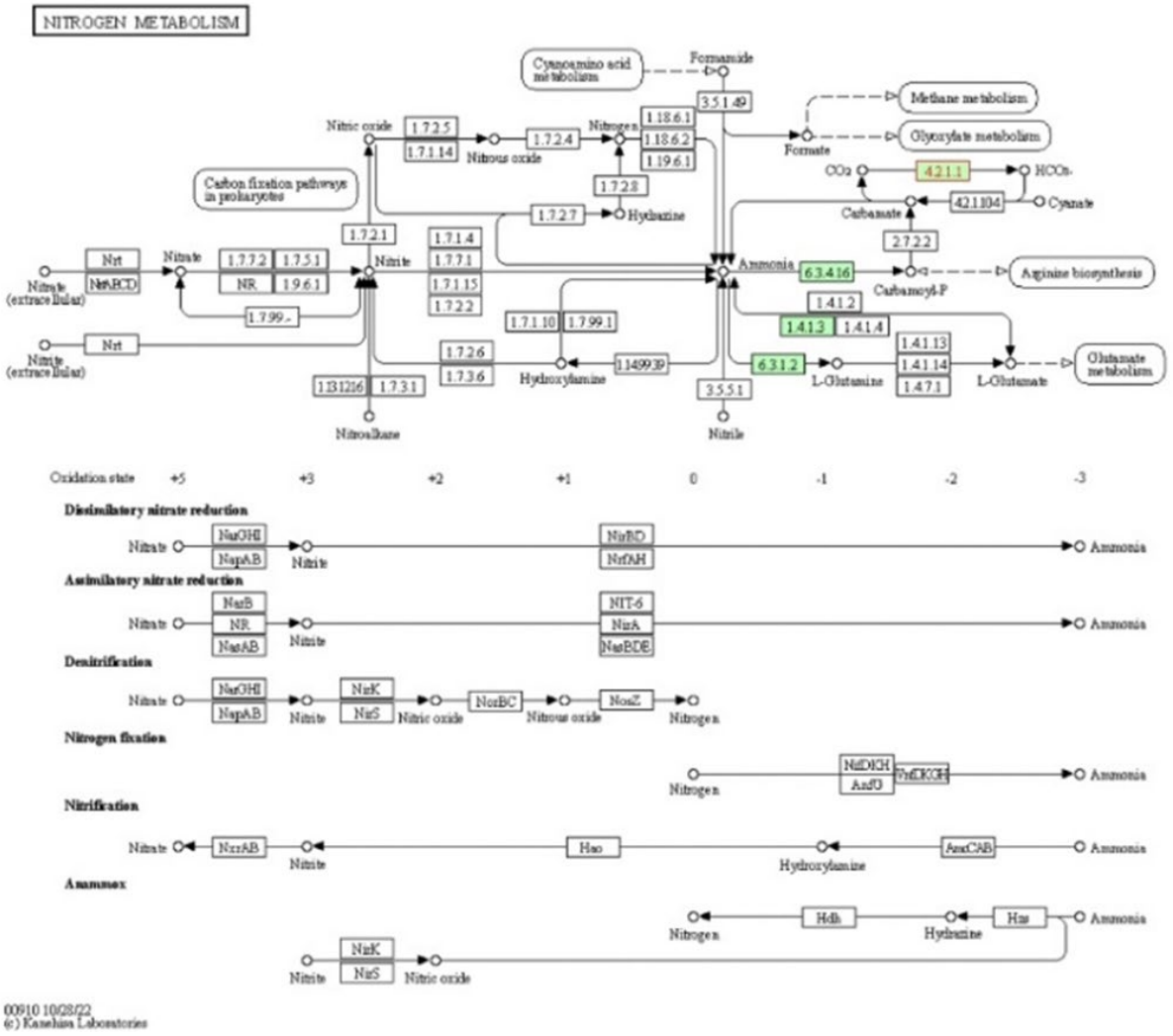
Result

Irosustat is an orally active, irreversible, nonsteroidal inhibitor for steroid sulfatase (STS). It is a clinical trial treatment for hormone-sensitive cancers, i.e., breast, prostate, and endometrial cancers. It prevents the body from producing estrogen and androgen by preventing the conversion of hormonally inactive steroid sulfates such as dehydroepiandrosterone sulfate (DHEA-S) and estrone sulfate (E1S) by STS into their respective active forms, i.e., DHEA and estrone. These precursor compounds can be transformed into more potent androgens and estrogens, respectively. In addition, the drug can bind to carbonic anhydrase II (CA II), thereby affecting various pathways in the body as follows: nitrogen metabolism, proximal tubule bicarbonate reclamation, collecting duct acid secretion, gastric acid secretion, pancreatic secretion, and bile secretion pathways.

Affected pathways:

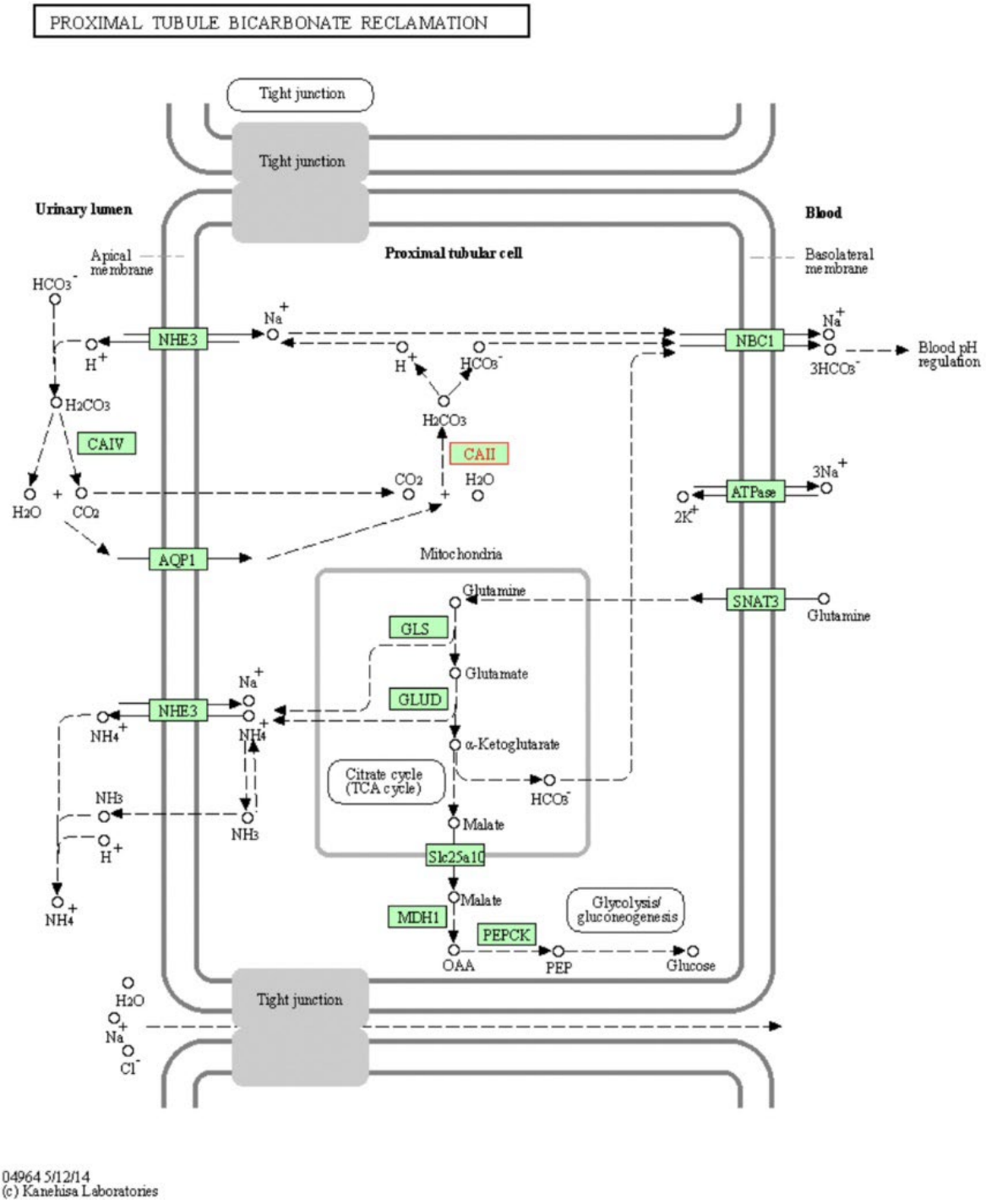
- Nitrogen metabolism pathway

The biological process of the nitrogen cycle is a complex interplay among many microorganisms catalyzing different reactions, where nitrogen is found in various oxidation states ranging from +5 in nitrate to -3 in ammonia. It is common knowledge that nitrogen is an essential element for protein composition, RNA and DNA. Therefore, the level of nitrogen in human body is generally used to assessing nutritional status. In many cases, decreased level of nitrogen is found in most cancer patients due to the consumption of tumor cell.



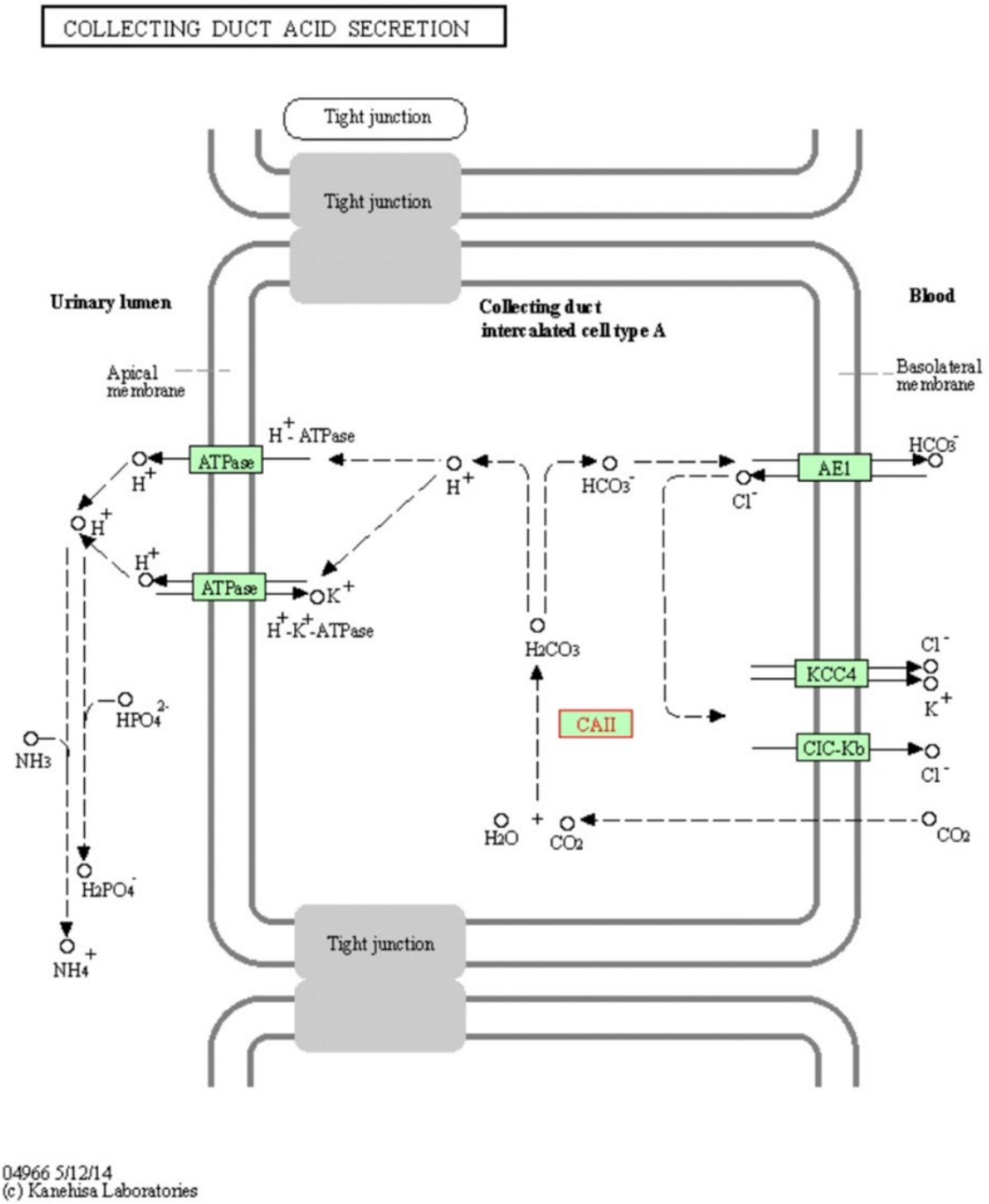
- Proximal tubule bicarbonate reclamation pathway

One of the major tasks of the renal proximal tubule (PT) is to secrete acid into the tubule lumen, thereby reabsorbing approximately 80% of the filtered bicarbonate (HCO^{3-}), as well as generating "new HCO^{3-}" for regulating blood ph.



- Collecting duct acid secretion pathway

One of the important roles of the collecting duct segment of the kidney nephron is acid secretion. As daily food intake loads acid into the body, urinary acid excretion is essential, and urine pH can drop as low as 4.5. The alpha-intercalated cell of collecting duct is the main responsible for hydrogen secretion into the urine. The carbon dioxide, which is generated in the cells and enters from the blood, is changed to carbonic acid. This carbonic acid is divided into hydrogen ion and bicarbonate ion. Intracellular CAII catalyzes the formation of these ions. The hydrogen ion is secreted into the lumen by the luminal H^+-ATPase. The bicarbonate ion is transported to the blood side by the anion exchanger type 1. Hydrogen ion in the lumen is trapped by urinary buffers. These include ammonium and phosphate



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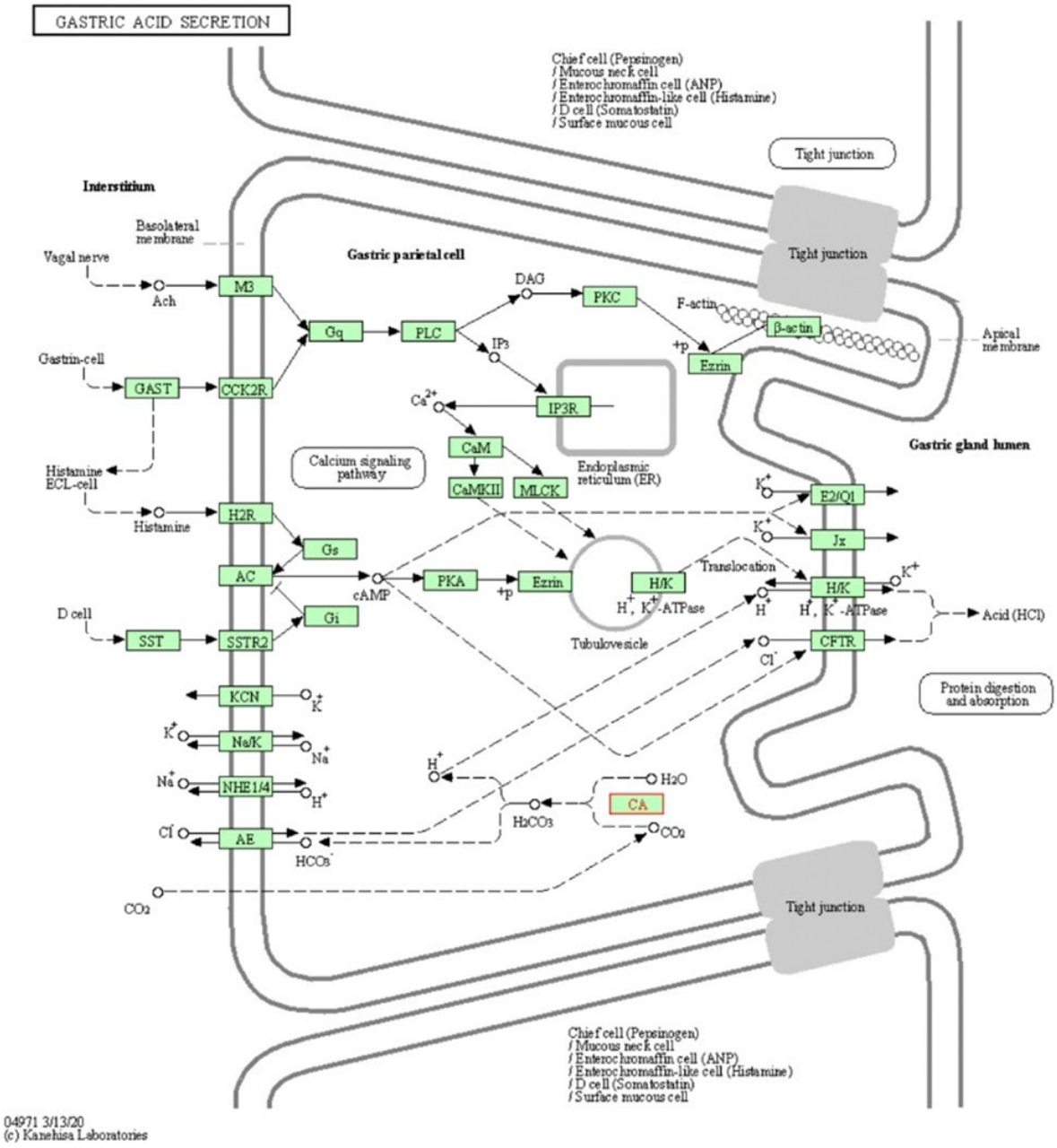
(c) Kanehisa Laboratories

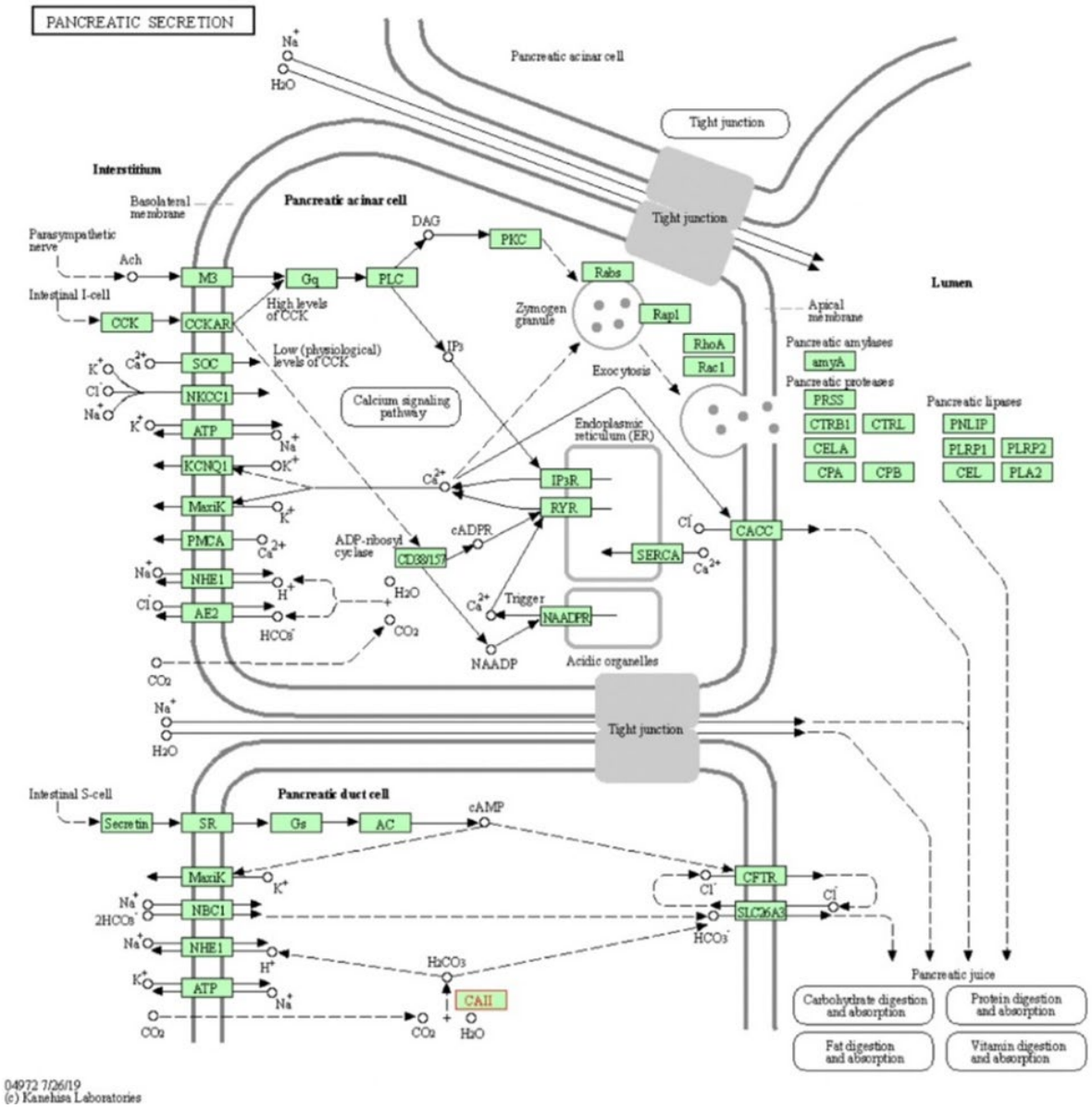
- Gastric acid secretion pathway

Gastric acid is a key factor in normal upper gastrointestinal functions, including protein digestion and calcium and iron absorption, as well as providing some protection against bacterial infections. The principal stimulants of acid secretion at the level of the parietal cell are histamine (paracrine), gastrin (hormonal), and acetylcholine (ACh; neurocrine). Stimulation of acid secretion typically involves an initial elevation of intracellular calcium and cAMP, followed by activation of protein kinase cascades, which trigger the translocation of the proton pump, H^+, K^+-ATPase, from cytoplasmic tubulovesicles to the apical plasma membrane and thereby H^+ secretion into the stomach lumen.



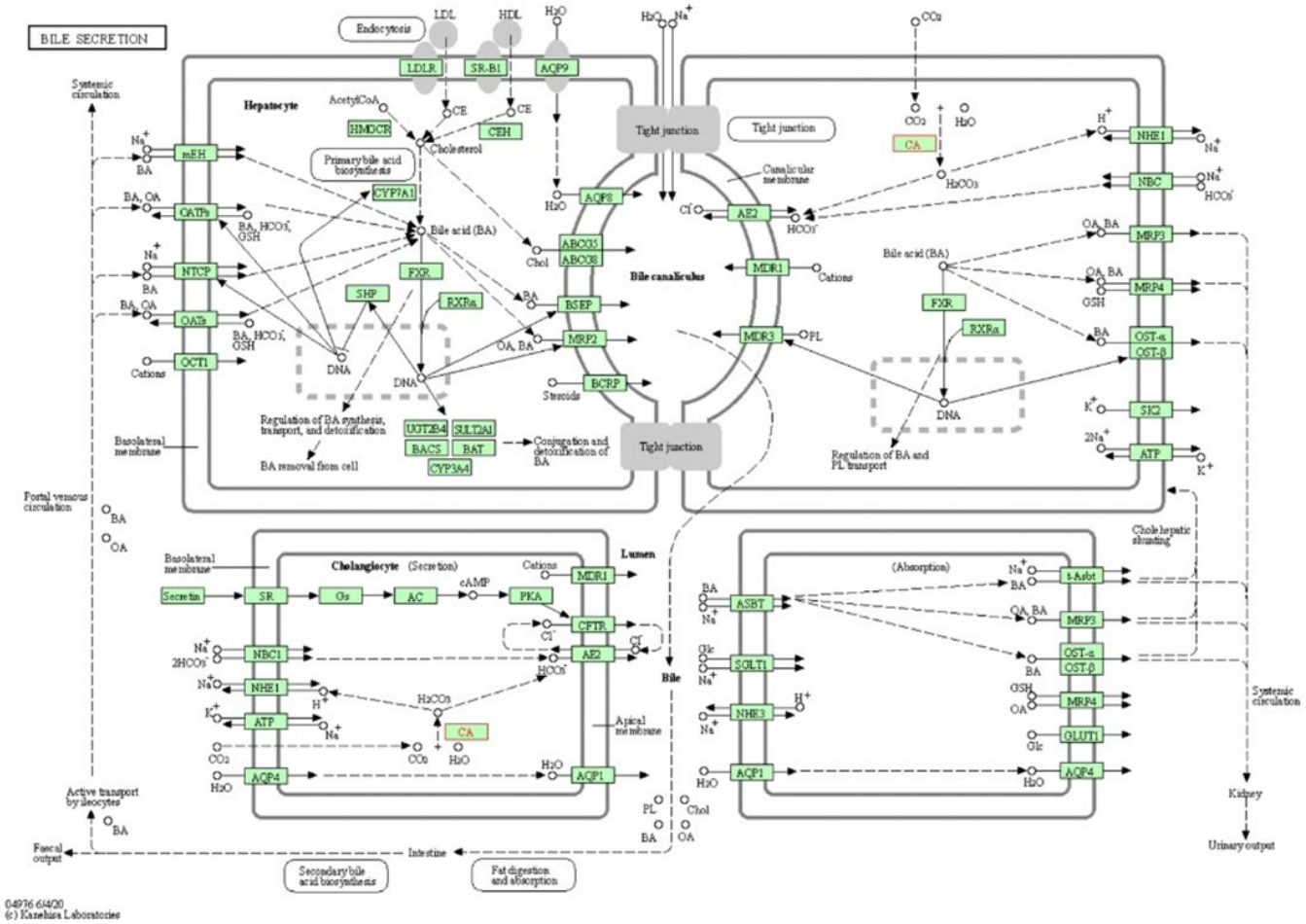
- Pancreatic secretion pathway

The pancreas performs both exocrine and endocrine functions. The exocrine pancreas consists of two parts, the acinar and duct cells. The primary functions of pancreatic acinar cells are to synthesize and secrete digestive enzymes. Stimulation of the cell by secretagogues such as acetylcholine (ACh) and cholecystokinin (CCK) cause the generation of an intracellular Ca^{2+} signal. This signal, in turn, triggers the fusion of the zymogen granules with the apical plasma membrane, leading to the polarized secretion of the enzymes. The major task of pancreatic duct cells is the secretion of fluid and bicarbonate ions (HCO^{3-}), which neutralize the acidity of gastric contents that enter the duodenum. An increase in intracellular cAMP by secretin is one of the major signals of pancreatic HCO^{3-} secretion. Activation of the cystic fibrosis transmembrane conductance regulator (CFTR) Cl^- channel and the CFTR-dependent Cl^-/ HCO^{3-} exchange activities is responsible for cAMP-induced HCO^{3-} secretion.



- bile secretion pathway

Bile is a vital secretion, essential for digestion and absorption of fats and fat-soluble vitamins in the small intestine. Moreover, bile is an important route of elimination for excess cholesterol and many waste product, bilirubin, drugs and toxic compounds. Bile secretion depends on the function of membrane transport systems in hepatocytes and cholangiocytes and on the structural and functional integrity of the biliary tree. The hepatocytes generate the so-called primary bile in their canaliculi. Cholangiocytes modify the canalicular bile by secretory and reabsorptive processes as bile passes through the bile ducts. The main solutes in bile are bile acids, which stimulate bile secretion osmotically, as well as facilitate the intestinal absorption of dietary lipids by their detergent properties. Bile acids are also important signaling molecules. Through the activation of nuclear receptors, they regulate their own synthesis and transport rates.



Discussion

Irosustat has a function as a nonsteroidal inhibitor of steroid sulfatase (STS). Inhibiting STS prevents the body from producing estrogen and androgen by preventing the conversion of hormonally inactive steroid sulfates. The drug has been beneficial since it is irreversible, so the patients can treat their hormone-sensitive tumor. The study shows that the drug can bind to carbonic anhydrase II (CA II). CAII is critical for acid-base homeostasis and bone remodeling; inhibition may cause alkalinization of urine resulting from increased bicarbonate excretion, which may promote development. Furthermore, by using this technique, it may help researchers discover the affected pathways by any kind of drug or may help pioneer any target in biological pathways with a low scientific trial cost.

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