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Life-saving drugs and GPCR in the eyes of scientists

By Dr. Andrew Huang, CSO on March 27, 2020

Someone once said that two places can teach people to cherish life, one is a hospital and the other is a crematorium because when you are healthy, you don't understand the torture of the illness and the despair of death.

Patients are so fragile and helpless when suffering from the deadly disease. In this case, both the patient's own mentality adjustment and the care and encouragement from family and medical professionals are needed. At the same time, the continuous efforts of medical scientific researchers are needed to develop more "life-saving drugs".

GPCR (G protein-conjugated receptor) is a seven-time transmembrane protein expressed on the cell surface, and it is closely related to many human diseases, for example, cardiovascular diseases, cancer, mental disorders, diabetes and obesity, various inflammatory diseases and so on. It can regulate a variety of physiological processes, and it is currently a large family of drug target proteins. Therefore, it is the drug target of most interest to researchers and a key research object of the pharmaceutical industry.

"If you have GPCR, you have the world." This is a sentence often spoken by Hualiang Jiang, director of the Shanghai Institute of Materia Medica, Chinese Academy of Sciences. According to statistics, there are more than 800 members of the GPCR protein family, and sales of drugs targeting GPCRs account for 27% of the global market.

The table below shows some GPCR-related prescription drugs that are already on sale. These drugs have reduced the pain and restore healthy life to many patients.

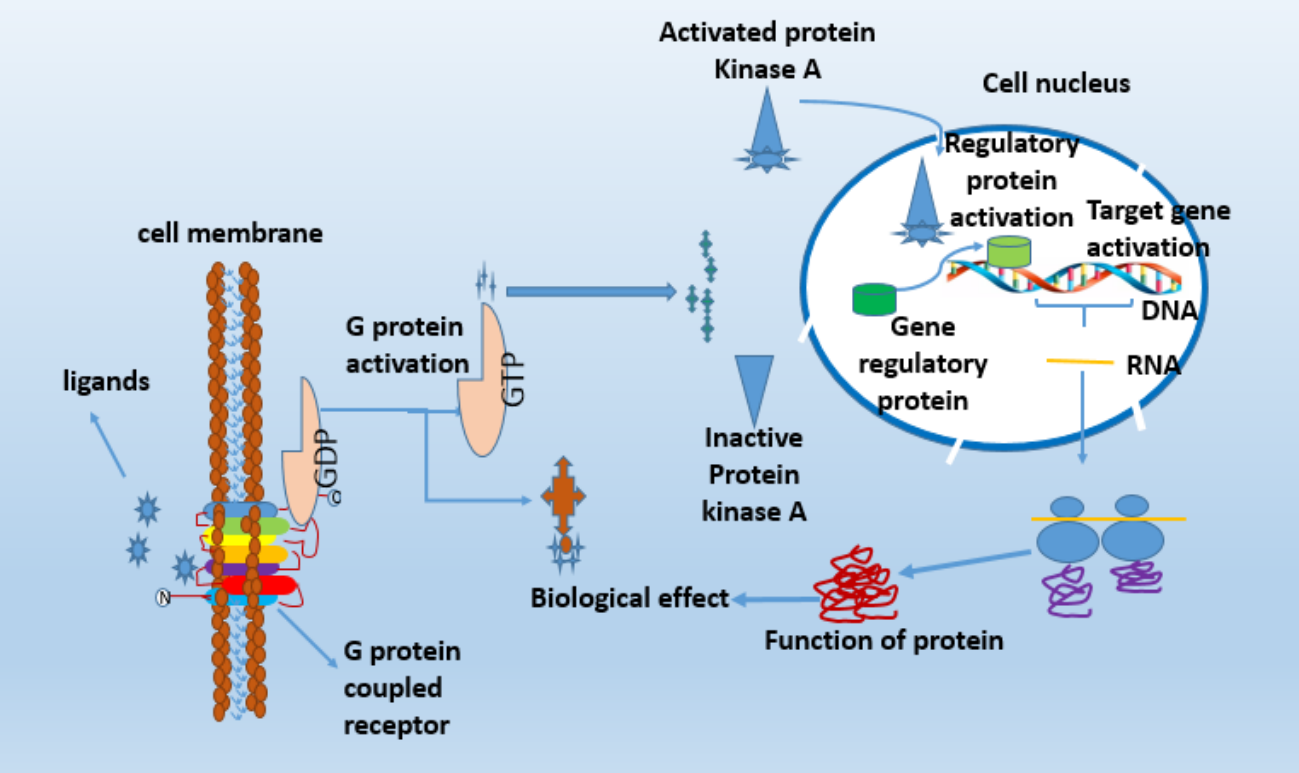
MabPlex USA, Inc.
10210 Campus Point Drive, Suite 100, San Diego, CA 92121
1-800-925-3608 info@mabplexinc.com

Cardiovascular diseases	Vasotec, Cozaar, Hytrin, Plavix, Toprol-X, Tenormin, Diovan, Carvedilol
Mental illness	Olanzapine, Prozac, Paxil, Zyprexa, Risperdal, Effexor, BuSpar, Wellbutrin
Stomach trouble	Pepcid, Ranitidilne
Prostate disease	Lupron, Zoladex
Respiratory diseases	Serevent, Atrovent, Ventolin, Singulair
Allergic disease	Claritin, Allegra
Others	Imitrex, Gaster, Depakote, Diprivan, Zyrtec, Xalatan

What are the contributions of scientists in recent years?

Through X-ray crystal diffraction technology, scientists have obtained many GPCR structures, such as β2 adrenergic receptors related to cardiovascular diseases, diabetes, etc., adenosine A2A receptors for tumor treatment, the chemokine receptor CCR5 for the regulation of the immune system, the purinergic receptor P2Y1R related to new drugs for the treatment of thrombotic diseases, the D3 dopamine receptor that regulates behavior and mood, etc., which are all important therapeutic targets that target various human diseases. This also provides a theoretical basis for the subsequent treatment of these diseases.

Without G protein-conjugated receptors, humans would simply not survive. Without β-adrenergic receptors, we would not be able to regulate blood sugar; without serotonin receptors, we would not even be able to experience happiness and so on. These are related to the signaling pathways regulated by GPCRs, and dysfunctions of signal pathways will cause various diseases



G protein-conjugated receptor physiological mechanism

More and more GPCR-related drugs have also been developed. Data as early as 2017 showed that the FDA had approved a total of 475 GPCR-targeted drugs, accounting for 34% of all FDA-approved drugs. There are 321 targeted GPCRs in clinical research drugs, of which 66 (20%) drugs target innovative GPCR targets.

The indications for targeted GPCR drugs are also expanding from traditional areas such as hypertension, allergies, anesthesia, and schizophrenia to new areas such as Alzheimer's disease and obesity. The developed drugs to target GPCR molecules are mainly small molecule drugs and low molecular weight peptide drugs. Monoclonal antibody drugs have many advantages over small molecule and peptide drugs. Therefore, the pharmaceutical industry is increasingly interested in the development of monoclonal antibody drugs targeting GPCR molecules.

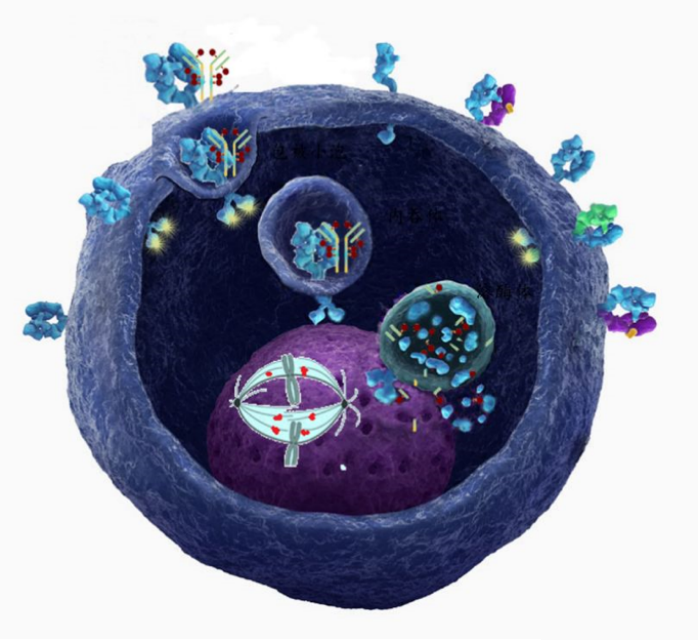
Advantages of monoclonal antibody drugs:

1. Better specificity, long half-life period, and can reduce immunogenicity through humanization;

2. Can kill cells through antibody-dependent cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and antibody-dependent cellular phagocytosis (ADCP);

3. There are different forms, such as single domain antibodies, bispecific or multispecific antibodies, and antibody-conjugated drugs (ADC).

As a different form of monoclonal antibody drugs, antibody-conjugated drugs (ADCs) have the advantages of monoclonal antibody drugs-identifying immune cells and diseased cells, and can also release conjugated chemical toxins to kill diseased cells. Therefore, ADC, as a new technology platform for classic antibody research and development pipelines, has been favored by more and more researchers, setting off a wave of research and development worldwide. LGR5 is the first GPCR member to be used for ADC drug targeting, and it is believed that good results will be achieved in the near future.



The action mechanism of ADC inside of a tumor cell

DS-6157 is a "first-in-class" ADC drug targeting GPR20. GPR20 is an orphan G protein-conjugated receptor (GPCR) specifically expressed in gastrointestinal stromal tumors (GIST). DS-6157 has a different mechanism of action than TKI and can be used to treat patients with GIST that develop resistance to TKI. It is currently entering phase 1 clinical trials.

ADC drugs are considered to be more effective in treating cancer and there are seven ADC

drugs have been approved by FDA so far. The next generation of ADC will become an important means of treating cancer in the future.

References:

Therapeutic antibodies directed at G protein-coupled receptors. MAbs. 2010 (6):594-606.doi: 10.4161/mabs.2.6.13420. http://www.biodiscover.com/news/research/730131.html

Trends in GPCR drug discovery: new agents, targets and indications
https://www.zhihu.com/question/20522960