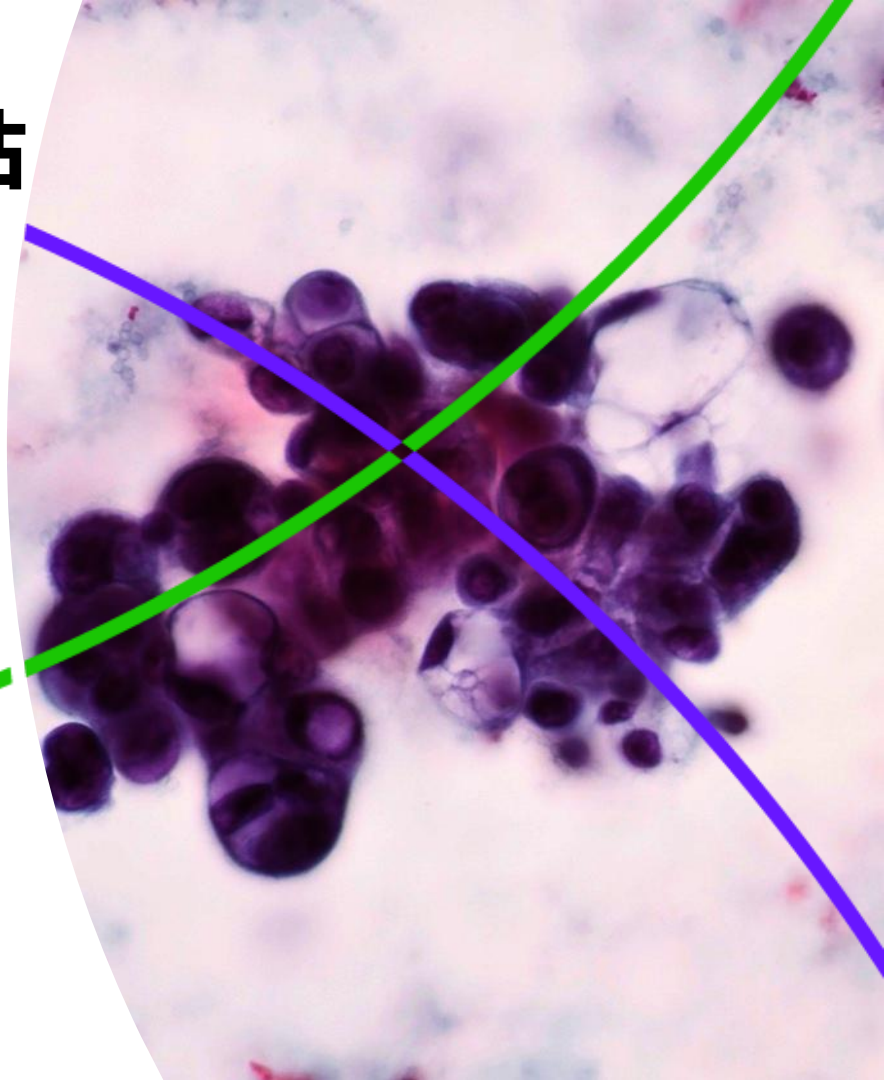


# 活用数据库，完善靶点评估

藏捷

科睿唯安 Clarivate Analytics

2017年11月2日



# 优质的数据库是如何炼成的？

The screenshot shows a search for 'iphone' on Taobao. The search results are filtered by '所有宝贝' (All Items) and '天猫' (Tmall). The results list various iPhone cases with detailed attributes such as brand, material, and style. The page also features a sidebar with navigation options and a search bar at the top.

**搜索关键词:** iphone

**筛选条件:** 所有宝贝, 天猫, 二手, 今日发现

**品牌:** Q果, BASEUS/倍思, QBQB, 第一卫, 以诺, Joyroom/其乐堂, Gview/景为, TORRAS/图拉斯, X-IT

**材质:** 硅胶, 塑料, tpu, 软胶, 亚克力, 仿皮, 金属, 树脂, 毛绒, 绒布, 铝合金, 牛仔布

**风格:** 简约, 日韩, 卡通, 欧美, 奢华, 中国风, 商务, 英伦

**相关分类:** 运动包/户外包/配件, 户外运动用品, 个性化定制/设计服务/DIY, 模玩/动漫/明星/COS/桌游, 五金/工具

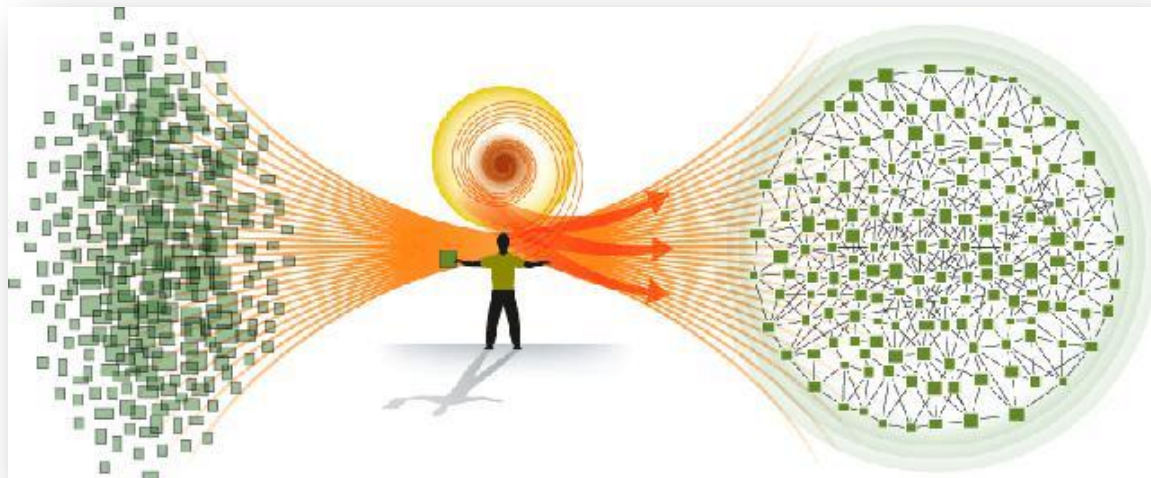
**商品列表:**

商品名称	价格	销量
苹果7plus手机壳防摔iPhone6透明磨砂硅胶软壳x气囊男女款plus翻盖	¥18.80 包邮	5992人付款
苹果6手机壳6Plus硅胶Phone6磨砂6s软胶潮男6新款透明套女超薄	¥9.90 包邮	93002人付款 994504条评论
倍思苹果6手机壳iPhone6s超薄磨砂六潮男plus全包防摔新款女	¥29.00 运费: 400.00	10823人付款 2444条评论

## 数据库标准:

- 可靠来源
- 收录标准
- 索引关联
- 易用程度
- 有效信息检索

# 实验未动，数据先行



## 临床试验中生物标志物的应用

Application Of Biomarkers Within Clinical Development

李寅

Yin.li@clarivate.com

010-57601261, 18911813699



- 生物标志物与临床研究

## 活用数据库 玩转立项评估

周峰 博士

科睿唯安 [Clarivate Analytics](#)

中国·南京

2017年9月21日



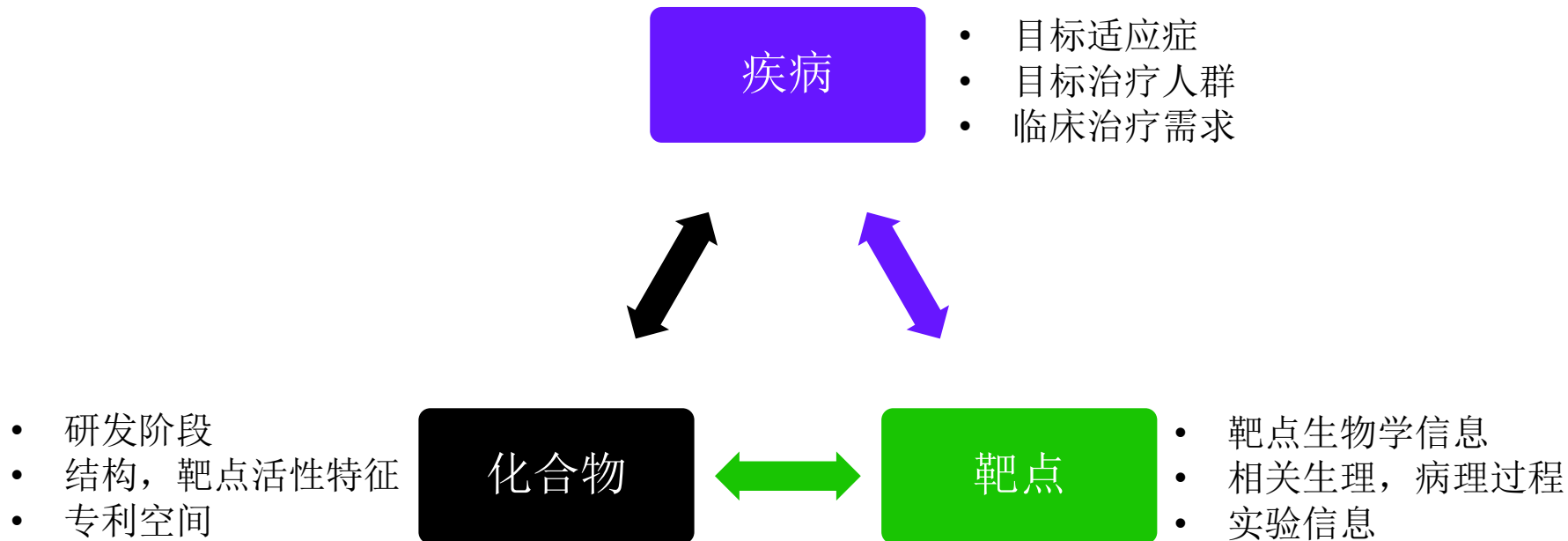
©2017 Clarivate Analytics. All rights reserved

- 运用多个数据库，完成系统立项



# 活用数据库，完善靶点评估

- 如何从研发的角度，对疾病，靶点，化合物进行评估？



# 提纲

明辨疾病格局，换个角度看疾病

从疾病到靶点，深入评估靶点

探宝数据库，围绕Pre-clinical看数据

# 第一部分

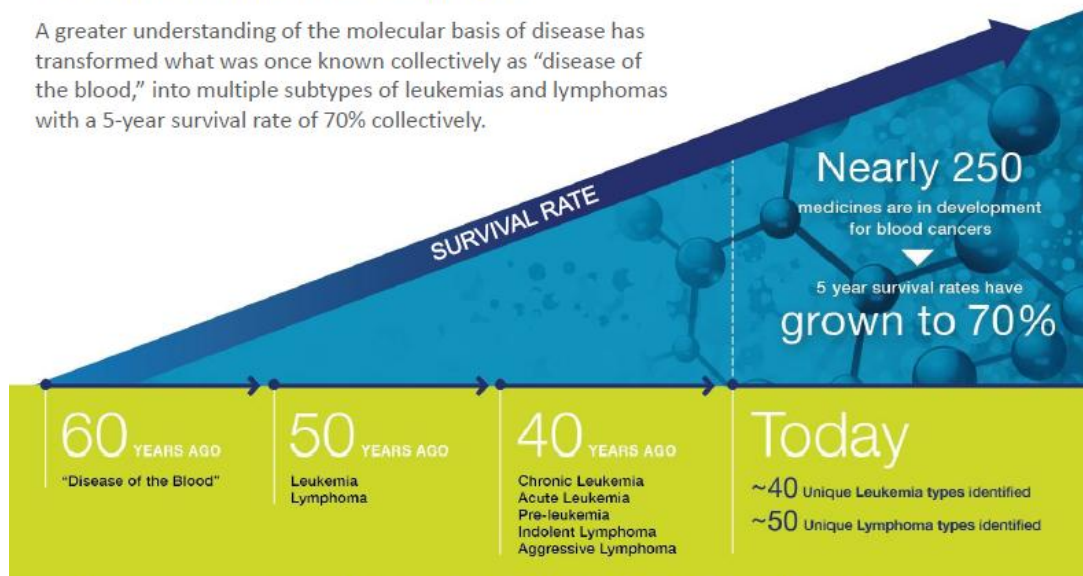
明辨疾病格局，换个角度看疾病

在疾病细分化趋势下，如何借助生物标志物信息了解疾病信息？

# “精准医疗”带来的挑战

## Advances in Personalized Medicine Improve Outlook for Patients with Blood Cancers

A greater understanding of the molecular basis of disease has transformed what was once known collectively as “disease of the blood,” into multiple subtypes of leukemias and lymphomas with a 5-year survival rate of 70% collectively.



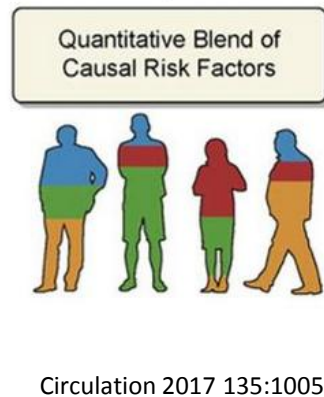
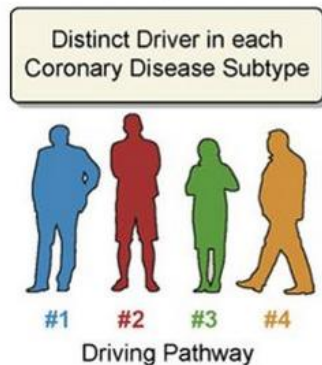
Source: M Aspinall, former President Genzyme Genetics [cited at [http://www.comtecmol.com/biomarker/2014/Uploads/Editor/PDF/jgpt/Edward%20Abrahams\\_Key%20Note%20Lecture.pdf](http://www.comtecmol.com/biomarker/2014/Uploads/Editor/PDF/jgpt/Edward%20Abrahams_Key%20Note%20Lecture.pdf)]; National Cancer Institute.; SEER Cancer Statistics Review, 1975-2011. [http://seer.cancer.gov/csr/1975\\_2011/](http://seer.cancer.gov/csr/1975_2011/), based on November 2013 SEER data submission, posted to the SEER web site, April 2014; PhRMA, “Medicines in Development for Leukemia & Lymphoma,” April 2015 [all cites accessed May 2015].

- 疾病-患者群体的细分
  - 疾病机理的深入认识
  - 诊疗流程的不断优化
  - 切实的临床获益
- 药物开发的挑战：
  - 患者人群比例变化
  - 治疗方案针对性
  - 更多的治疗方案
  - 临床需求 vs. 研发投入



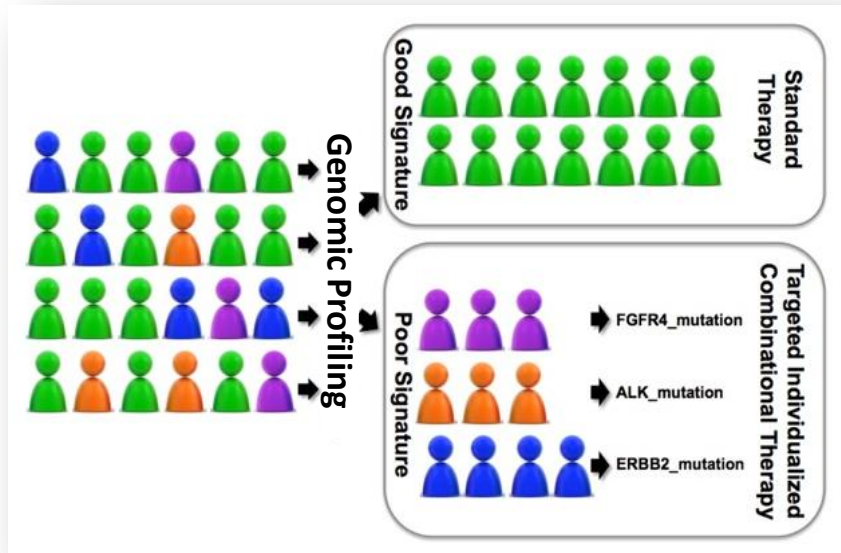
# “精准医疗”：两种观点

- “单一、主导因素诱发疾病”
  - 疾病存在不同亚型
  - 疾病由不同的单个，主要致病因素导致
    - “driver vs. Passenger mutations” 理论
  - 患者群体相对独立，需单独分析
  - 需要单独的诊断，治疗，预后评估
- 多因素复合作用诱发疾病
  - 疾病由多种致病因素，共同作用于与疾病相关的多个生理过程，信号通路
  - 个体间的致病因素有重叠，但影响程度存在差异
  - 可作为一个治疗群体，适用共同的治疗方案

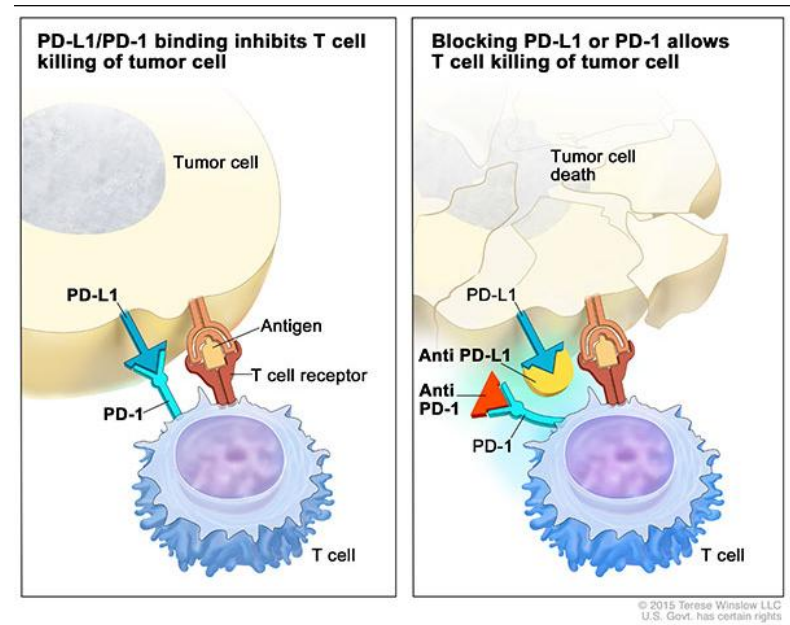


# “精准医疗”：两种观点，两种方向

靶向治疗：EGFRi, ALKi, HER2i



肿瘤免疫疗法：checkpoint inhibitors



Report “Biomarker Trends Are Auspicious for Pathologists and Clinical Laboratories” 2017  
NCI webpage” Immune Checkpoint Inhibitor”  
<https://visualsonline.cancer.gov/details.cfm?imageid=10396>

# 明辨疾病格局，换个角度看疾病



## Hepatitis B

**Facts about Hepatitis B**

Viral hepatitis is a necroinflammatory disorder which varies widely in presentation and severity (Chisari, F.V. et al., 2010). Hepatitis B virus (HBV) is the viral agent responsible for the disease, which differs in their mode of transmission and pathogenesis.

- 乙肝领域基础数据
- 诊断
- 预防
- 治疗
- 相关药物
- 相关靶点
- 最新新闻
- 相关网站资源
- 治疗指南

- 病毒结构和生命周期
- 传播
- 疾病历史、发病率、死亡率
- 流行病学
- HBV-HIV 的协同感染
- 治疗费用

- 抗病毒疗法：
  - 干扰素
  - 病毒酶抑制剂
  - 抗病毒药物的抗药性
- 非特异性免疫
- 天然化合物疗法
- 移植

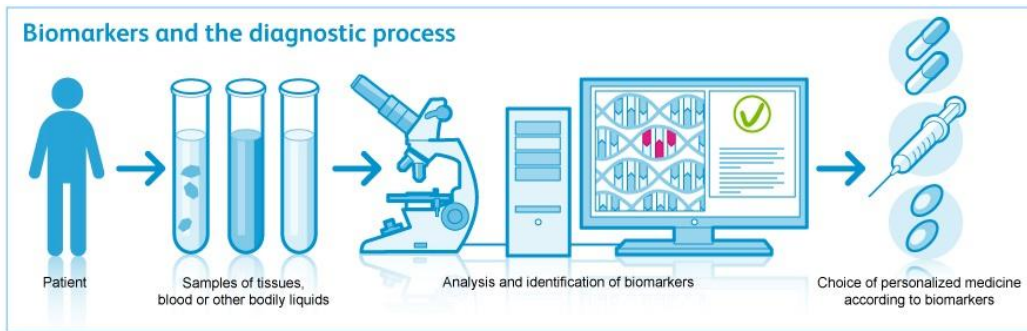
Dandri, M. and Locarnini, S. [PubMed](#) [OpenURL Full Text](#)  
New insight in the pathobiology of hepatitis B virus infection  
Gut 2012; 61(Suppl. 1): i6

- Integrity 疾病概览模块
- 基于靶点和药物出发
  - 疾病基础信息
  - 流行病学
  - 已知药物及靶点
- 基于生物标志物和治疗指南
  - 患者群体，治疗流程
    - 疾病风险
    - 预后情况
  - 潜在需求

# 生物标志物的定义和特点

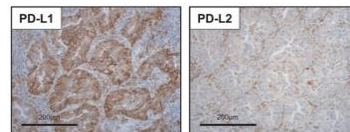
**Biomarker:** 能够客观测定和评价正常生理过程, 病理过程, 或治疗药理过程的某种特征性的生物指标。

- 能够客观测定
- 如实、专一的反映生理/病理特征
- 随着生理/病理过程动态变化
- 有可能作为药物靶点

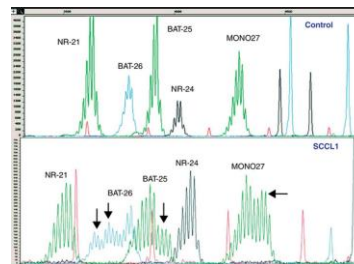


Pfizer Website: “[personalized\\_med](#)”

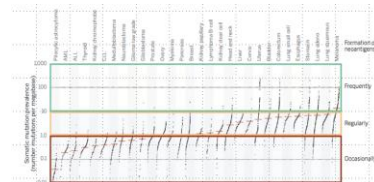
Schumacher and Schreiber, *Science*, 2015; 348(6230): 69-74.



Protein

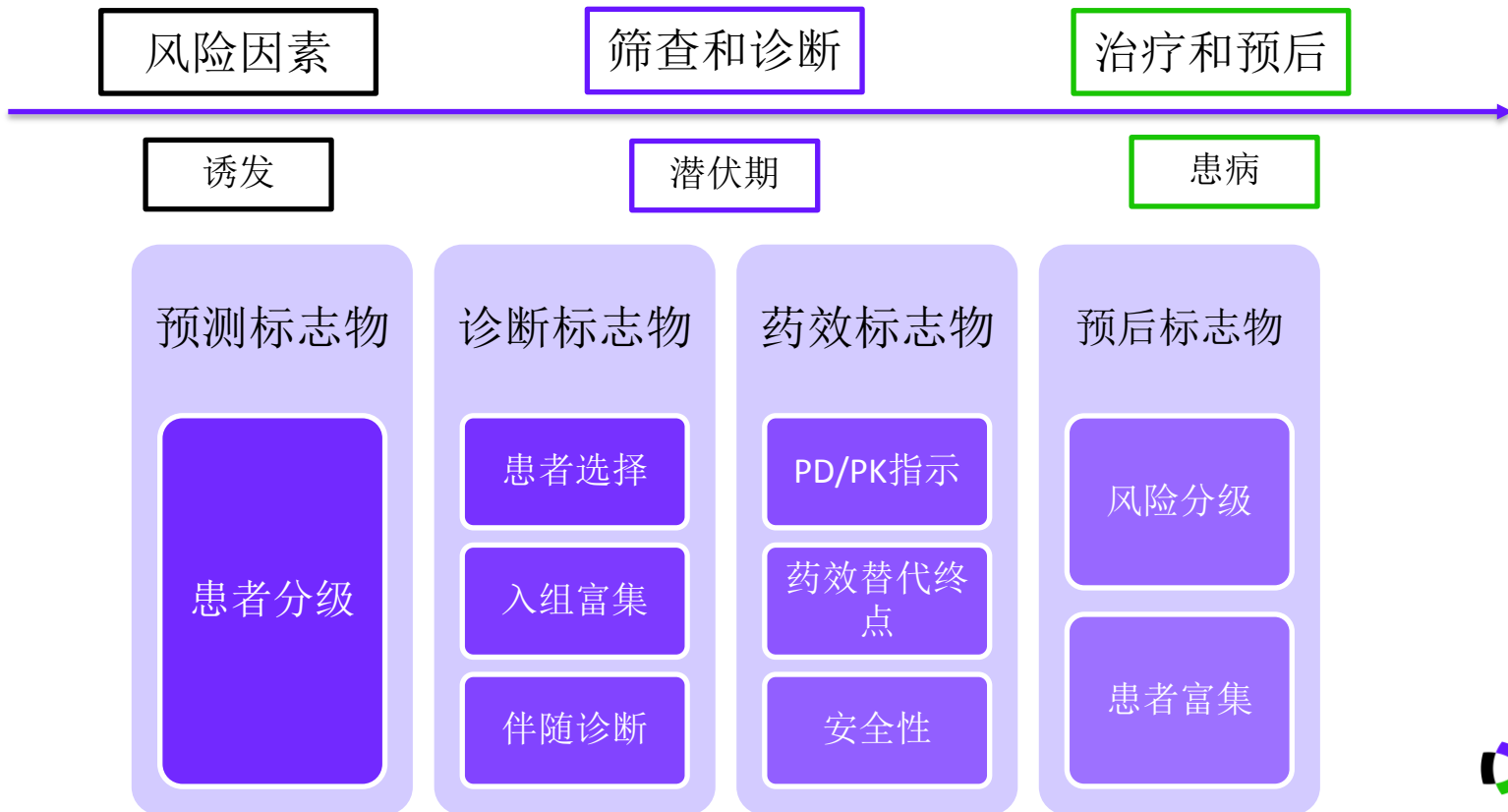


Genome



Tumor

# 生物标志物的分类



# 生物标志物的关键信息

## 生物标志物的验证程度

- 需经历早期概念，实验验证，人体验证及推荐批准

## 生物标志物的用途

- 疾病认识：正常和疾病状态下的生理活动差异
- 疾病诊断，预后：反映疾病存在与否，严重程度
- 疾病治疗：反映药效和毒性作用
  - 明确药物作用机制，代谢特征；提早预测不良反应
  - 调整给药方案和剂量；减少过度医疗

需一并考虑

# Integrity生物标志物模块



Integrity<sup>SM</sup> Biomarkers

Knowledge Areas Quick Search Home Support/Help Query Manager/Alert Center

37318 Records in Biomarkers

**BIOMARKERS User Resources**

The following resources are available to assist you with your discovery of the Biomarkers Module:

- Introduction to the Biomarkers knowledge area - Factsheet
- Find out more about our Biomarkers knowledge area
- Biomarkers knowledge area Frequently Asked Questions
- "Latest Enhancements"

**WHAT'S NEW**

- LATEST RELEASE INFORMATION
- IMPORTANT NOTICES
- MEETINGS AND REPORTS

**Advanced Search** Session History Clear Form Start

**Biomarker**

Select Value

Biomarker

Name

Type

Combination Biomarker (Y/N)

Combination Type

Biological Process

Description

Product Modifier

Mechanism Modifier

Highest Validity

Methods Papers

Review Type

Review Title

Last Updated

Available Since

Biomarker use

Use ID

Indication

Population

Role

Validity

Parameter

Technique

Substrate

Kit

Genetic Variation

Correlates to...

Product Name

Mechanism of Action

Product Category

Therapeutic Group

Authority

## 标志物研究进展

Select one or more terms from the list below to the Search Form.

Emerging  
Experimental  
Early Studies in Humans  
Late Studies in Humans  
Recommended / Approved

初始概念

试验研究

早期人体研究

晚期人体研究

批准应用

Select one or more terms from the list below to copy the term(s) to the Search Form.

Allelic loss  
Epigenetic change  
Gene amplification  
Gene deletion  
Gene duplication  
Polymorphism/mutation  
Short Tandem Repeats  
Variable Number of Tandem Repeats

## 标志物用途

Select one or more terms from the Search Form.

Diagnosis  
Differential Diagnosis  
Disease Profiling  
Monitoring Disease Progression  
Monitoring Treatment Efficacy  
Monitoring Treatment Toxicity  
Predicting Drug Resistance  
Predicting Treatment Efficacy  
Predicting Treatment Toxicity  
Prognosis  
Prognosis - Risk Stratification  
Risk Factor  
Screening  
Selection for Therapy  
Staging  
Toxicity Profiling

疾病诊断

疾病表征

疾病进展

预测药效

预测毒性

药物耐受

监视药效

监视毒性

Biomarker涉及的基因异常

- 全面获取疾病，药物相关的标志物信息

# 借助Biomarker发现高风险群体

## 在阿尔兹海默疾病中，APOE ε4 是一个高风险因子

### Alzheimer's Disease

#### Genetics

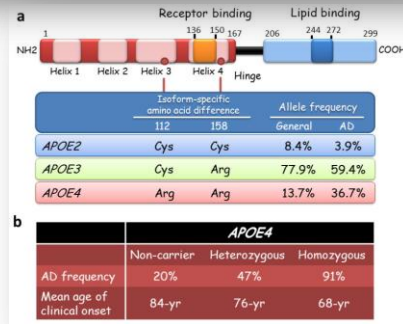
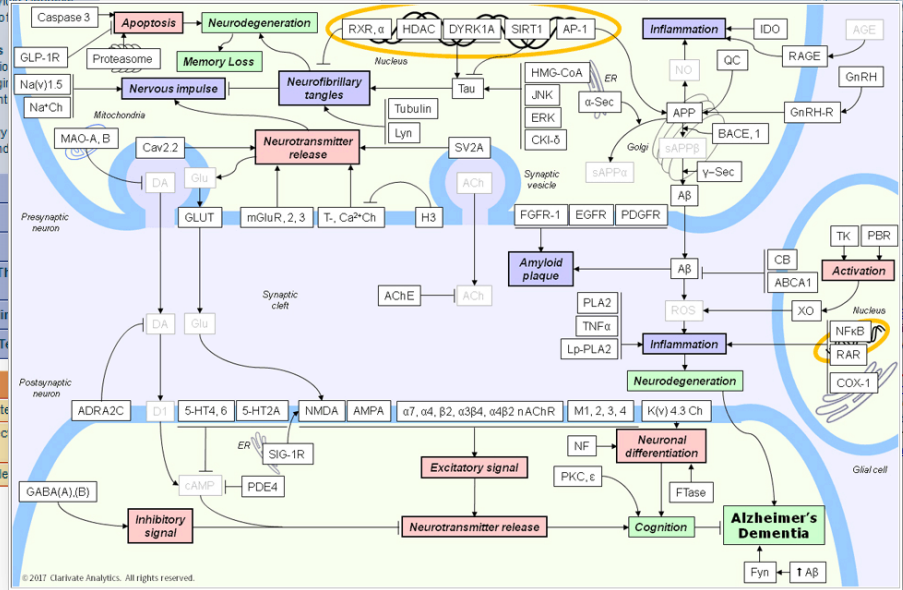
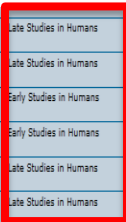
Dominantly inherited mutations in the presenilin-1 (*PSEN1*) and presenilin-2 (*PSEN2*) genes are located on chromosomes 14, 1 and 21, respectively, have been identified in patients with early-onset Alzheimer's disease (Waring, S.C. and Rosenberg, R.N., 2008; Avramopoulos, D., 2009). Autosomal dominant genes are implicated in one-third to one-half of early-onset Alzheimer's cases, underlining the importance of APP-modifying genes including *PSEN1*, *PSEN2* and *ADAM10* can also affect risk of late-onset Alzheimer's disease.

#### Apolipoprotein E

Alzheimer disease, late onset

Population	Role	Technique (Substrate)	Parameter	Validity (Authority)	Sources	+	-	All		
All	Disease Profiling	Genotyping (DNA)	NA	Experimental	Ref	1	0	0	1	<a href="#">View Use</a>
	Prognosis	RFLP-PCR (DNA)	NA		Ref	1	0	0	1	<a href="#">View Use</a>
	Risk Factor	Exome sequencing (DNA)	NA		Ref	1	0	0	1	<a href="#">View Use</a>
	Risk Factor	Genotyping (DNA)	NA	Late Studies in Humans	Ref	1	1	0	2	<a href="#">View Use</a>
	Risk Factor	Genotyping (DNA)	NA	Late Studies in Humans	Ref	1	0	0	1	<a href="#">View Use</a>
	Risk Factor	PCR (DNA)	NA	Early Studies in Humans	Ref	1	0	0	1	<a href="#">View Use</a>
	Risk Factor	PCR + DirectSeq (DNA)	NA	Early Studies in Humans	Ref	1	0	0	1	<a href="#">View Use</a>
	Risk Factor	RFLP-PCR (DNA)	NA	Late Studies in Humans	Ref	2	0	0	2	<a href="#">View Use</a>
	Risk Factor	Real Time PCR (DNA)	NA	Late Studies in Humans	Ref	1	0	0	1	<a href="#">View Use</a>

晚期人体验证阶段



### Clarivate Analytics



# 临床治疗指南

以小细胞肺癌“Small cell lung cancer”为例：

NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2018

NCCN Guidelines Index

STAGE

Extensive stage (See [ST-1](#) for TNM Classification)

Extensive stage with symptoms or brain metastases

Extensive stage with local symptoms

Extensive stage with brain metastases

• In patients with limited-stage disease, response rates of 70% to 90% are expected after treatment with EP plus thoracic radiotherapy, whereas in extensive-stage disease, response rates of 60% to 70% can be achieved with combination chemotherapy alone. Unfortunately, median survival rates are only 14 to 20 months and 9 to 11 months for patients with limited- and extensive-stage disease, respectively. After appropriate treatment, the 2-year survival rate is approximately 40% in patients with limited-stage disease, but less than 5% in those with extensive-stage disease.<sup>71</sup> Thoracic radiotherapy improves local control rates by 25% in patients with limited-stage disease and is associated with improved survival.<sup>52,53</sup> Data suggest that chemoradiotherapy may be indicated for patients with limited-stage disease who have cytologically negative pericardial fluid, whereas it is not indicated for those with pericardial effusion.

• 化疗响应率较好，但生存期较差，尤其其extensive阶段

- 诊断分析
- 患者分级
- 治疗路径
- 药物定位
- 预后信息

# 借助Biomarker发现目标患者群体



- 以小细胞肺癌“Small cell lung cancer”为例，在Integrity Biomarker模块中查询
- 查询条件：“SCLC + 晚期人体研究+风险因素”

**Advanced Search** | Session History | Clear Form | Start

**Biomarker**

Role	▶ "Risk Factor"	Index AND ▶
Validity	▶ "Late Studies in Humans"	Index AND ▶
Condition (Indication)	▶ "Cancer, lung (small cell) (SCLC)"	Index AND ▶

**Product**

Lead Compounds  Under Active Development

Select Value	▶	Index AND ▶
Optional Value	▶	Index AND ▶
Optional Value	▶	Index AND ▶

**Reference**

Select Value	▶	Index AND ▶
Optional Value	▶	Index AND ▶
Optional Value	▶	Index AND ▶

**Patent**

Select Value	▶	Index AND ▶
Optional Value	▶	Index AND ▶
Optional Value	▶	Index AND ▶

**Filter by Statistics**

**BIOMARKER**

- ▶ Biomarker Type
- ▶ Highest Validity
- ▶ Combination Type
- ▶ Component Biomarker
- ▶ Component Of
- ▶ Biological Process
- ▶ Product Modifier
- ▶ Mechanism Modifier
- ▶ Method Papers (Y/N)

**BIOMARKER USE**

- ▶ Indication Type
  - Major Condition
  - Condition
  - Safety/Tox
  - Experimental Pathology
- ▶ Population
- ▶ Role
- ▶ Technique
- ▶ Substrate
- ▶ Genetic Variation Type
- ▶ Parameter
- ▶ Validity
- ▶ Scientific Authority
- ▶ Source Evidence

**BIOMARKER KIT**

- ▶ Kit Name
- ▶ Organization
- ▶ Status
- ▶ Country / Area
- ▶ Regulatory Authority

过滤标签

基因扩增

文献支持

**Records Retrieved** | Records 1 to 10 of 79 retrieved | Options

**Biomarkers Search Results**

Query > Role = "Risk Factor" AND Validity = "Late Studies in Humans" AND Condition (Indication) = "Cancer, lung (small cell) (SCLC)"

# 借助Biomarker发现目标患者群体

结果从79个缩减为3个

Biomarker Name	IV
<input type="checkbox"/> <b>DNA topoisomerase 2-alpha</b> DNA gyrase; DNA topoisomerase (ATP-hydrolyzing); DNA topoisomerase II A; DNA topoisomerase II, 170 kD; DNA topoisomerase II, alpha isozyme; TOP2; TOP2A; TP2A; Topoisomerase (DNA) II alpha 170kDa	Pr
<input type="checkbox"/> <b>L-myc-1 proto-oncogene protein</b> L-myc protein; L-myc-1 proto-oncogene; LMYC; MYCL; MYCL1; bHLHe38; v-Myc avian myelocytomatosis viral oncogene homolog 1, lung carcinoma derived; v-myc myelocytomatosis viral oncogene homolog 1, lung carcinoma derived (avian)	Ge
<input type="checkbox"/> <b>Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha isoform</b> PI3-kinase subunit alpha; PI3K; PI3K-alpha; PI3Kalpha; PIK3CA; Phosphatidylinositol 4,5-bisphosphate 3-kinase 110 kDa catalytic subunit alpha; Phosphoinositide-3-kinase catalytic alpha polypeptide; Phosphoinositide-3-kinase, catalytic, alpha polypeptide gene; PtdIns-3-kinase p110; PtdIns-3-kinase subunit alpha; PtdIns-3-kinase subunit p110-alpha; Serine/threonine protein kinase PIK3CA; p110-alpha; p110alpha	Pr

- 借由PI3KCA 基因扩增筛选出特定SCLC患者人群

[Lung Cancer](#), 2014 May;84(2):139-44. doi: 10.1016/j.lungcan.2014.02.013. Epub 2014 Mar 3.

## Molecular profiling of small cell lung cancer in a Japanese cohort.

Wakuda K<sup>1</sup>, Kenmotsu H<sup>2</sup>, Serizawa M<sup>3</sup>, Koh Y<sup>3</sup>, Isaka M<sup>4</sup>, Takahashi S<sup>4</sup>, Ono A<sup>5</sup>, Taira T<sup>5</sup>, Naito T<sup>5</sup>, Murakami H<sup>5</sup>, Mori K<sup>6</sup>, Endo M<sup>7</sup>, Nakajima T<sup>8</sup>, Ohde Y<sup>4</sup>, Takahashi T<sup>5</sup>, Yamamoto N<sup>9</sup>.

### Author information

### Abstract

**OBJECTIVES:** Advances in the molecular profiling of lung adenocarcinoma over the past decade have led to a paradigm shift in its diagnosis and treatment. However, there are very few reports on the molecular profiles of small cell lung cancers (SCLCs). We therefore conducted the present Shizuoka Lung Cancer Mutation Study to analyze genomic aberrations in patients with thoracic malignancies.

**MATERIALS AND METHODS:** We collected samples of SCLC from a biobank system and analyzed their molecular profiles. We assessed 23 mutations in nine genes (EGFR, KRAS, BRAF, PIK3CA, NRAS, MEK1, AKT1, PTEN, and HER2) using pyrosequencing plus capillary electrophoresis. We also amplified EGFR, MET, PIK3CA, FGFR1, and FGFR2 using quantitative real-time polymerase chain reaction (PCR) and the fusion genes ALK, ROS1, and RET using reverse transcription PCR.

**RESULTS:** Between July 2011 and January 2013, 60 SCLC patients were enrolled in the study. Samples included eight surgically resected snap-frozen samples, 50 formalin-fixed paraffin-embedded samples, and seven pleural effusion samples. We detected 13 genomic aberrations in nine cases (15%), including an EGFR mutation (n=1, G719A), a KRAS mutation (n=1, G12D), PIK3CA mutations (n=3, E542K, E545K, E545Q), an AKT1 mutation (n=1, E17K), a MET amplification (n=1), and PIK3CA amplifications (n=6). EGFR and KRAS mutations were found in patients with combined SCLC and adenocarcinoma. No significant differences were detected in the characteristics of patients with and without genomic aberrations. However, serum neuron-specific enolase and progastrin-releasing peptide levels were significantly higher in patients without genomic aberrations than in those with aberrations (p=0.01 and 0.04, respectively).

**CONCLUSION:** Genomic aberrations were found in 15% SCLC patients, with PIK3CA amplifications most frequently observed. To further our understanding of the molecular profiles of SCLC, comprehensive mutational analyses should be conducted using massive parallel sequencing.

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# Biomarker的详细信息

Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha isoform							UPDATES
Last Updated Date		Oct 30, 2017					
Sy Cancer, lung (small cell) (SCLC)							10 kDa catalytic subunit alpha; Phosphoinositide-3-kinase catalytic alpha subunit alpha; PtdIns-3-kinase subunit p110-alpha; Serine/threonine protein kinase
Population	Role	Technique (Substrate)	Parameter	Validity (Authority)	Source	+ - All	
All	Predicting Treatment Efficacy	Genotyping (DNA)	NA	Experimental	Refs	1 0 0 1	<a href="#">VIEW USE ▼</a>
All	Disease Profiling	PCR + DirectSeq (DNA)	NA	Early Studies in Humans	Refs	1 0 0 1	<a href="#">VIEW USE ▼</a>
All	Diagnosis	Exome sequencing (DNA)	NA	Early Studies in Humans	Refs	1 0 0 1	<a href="#">VIEW USE ▼</a>
All	Predicting Treatment Efficacy	IHC (Tissue)	NA	Early Studies in Humans	Refs	0 0 1 1	<a href="#">VIEW USE ▼</a>
All	Risk Factor	ISH (DNA)	NA	Early Studies in Humans	Refs	1 0 0 1	<a href="#">VIEW USE ▼</a>
All	Risk Factor	Genotyping (DNA)	NA	Late Studies in Humans	Refs	3 0 0 3	<a href="#">VIEW USE ▼</a>
All	Risk Factor	Oligonucleotide array analysis (DNA)	NA	Early Studies in Humans	Refs	1 0 0 1	<a href="#">VIEW USE ▼</a>
All	Risk Factor	High Throughput Nucleotide Sequencing (DNA)	NA	Early Studies in Humans	Refs	5 0 0 5	<a href="#">VIEW USE ▼</a>
Advanced	Disease Profiling	High Throughput Nucleotide Sequencing (DNA)	NA	Experimental	Refs	1 0 0 1	<a href="#">VIEW USE ▼</a>
All	Predicting Treatment Efficacy	High Throughput Nucleotide Sequencing (DNA)	NA	Early Studies in Humans	Refs	3 0 0 3	<a href="#">VIEW USE ▼</a>
All	Differential Diagnosis	IHC (Tissue)	NA	Early Studies in Humans	Refs	1 0 0 1	<a href="#">VIEW USE ▼</a>
All	Disease Profiling	Array CGH (DNA)	NA	Experimental	Refs	1 0 0 1	<a href="#">VIEW USE ▼</a>
Advanced	Selection for Therapy	Genotyping (DNA)	NA	Early Studies in Humans	Refs	1 0 0 1	<a href="#">VIEW USE ▼</a>
All	Prognosis	Genotyping (DNA)	NA	Early Studies in Humans	Refs	0 0 1 1	<a href="#">VIEW USE ▼</a>
All	Risk Factor	PCR / MALDI-TOF-MS (DNA)	NA	Experimental	Refs	1 0 0 1	<a href="#">VIEW USE ▼</a>
All	Prognosis	IHC (Tissue)	NA	Early Studies in Humans	Refs	0 0 1 1	<a href="#">VIEW USE ▼</a>
All	Risk Factor	PCR + DirectSeq (DNA)	NA	Early Studies in Humans	Refs	5 0 0 5	<a href="#">VIEW USE ▼</a>
All	Diagnosis	IHC (Tissue)	NA	Early Studies in Humans	Refs	2 0 0 2	<a href="#">VIEW USE ▼</a>
All	Diagnosis	Real Time RT-PCR (mRNA)	NA	Early Studies in Humans	Refs	1 0 0 1	<a href="#">VIEW USE ▼</a>
All	Disease Profiling	Real Time PCR (mRNA)	NA	Experimental	Refs	1 0 0 1	<a href="#">VIEW USE ▼</a>
Advanced	Risk Factor	Genotyping (DNA)	NA	Early Studies in Humans	Refs	1 0 0 1	<a href="#">VIEW USE ▼</a>

[a polymorphism colorectal cancer panel](#)

[View full results list](#)

various phosphoinositide species and plays a crucial role in the control of cell

## Biomarker信息

- PI3KCA相关生理过程，调节机制
- PI3KCA作为标志物在不同适应症中的用途，进展

# 结合指南和标志物发掘临床需求



依据生物标记物信息：

- 高风险人群特征（潜在患病人群）
- 确诊患者类型（现有治疗需求，伴随诊断）
- 治疗方案（发现治疗空白）
- 治疗效果（现有药物不足）
- 高复发风险（后续治疗药物）

# 从研发角度评估靶点关键信息

## Gilead Shows Off Mid-Stage NASH Data

Published: Oct 24, 2017 | By Mark Terry



Gilead Sciences released results from a Phase II clinical trial of GS-0976 for nonalcoholic steatohepatitis (NASH).

GS-0976 is an oral inhibitor of Acetyl-CoA carboxylase (ACC). NASH, sometimes **called** the “silent liver disease,” resembles alcoholic liver disease, but appears in people who drink little or no alcohol. It can be quite severe and lead to cirrhosis. According to the **National Institute of Diabetes and Digestive and Kidney Diseases**, NASH affects 2 to 5 percent of people in the U.S. There are currently no specific treatments aside from weight loss, increased physical activity, and avoiding alcohol and unnecessary medications.

The clinical trial included 126 patients. Patients either received 20 mg (49 patients) or 5 mg (51 patients) of the drug, with the remainder (26 patients) receiving a placebo once a day for 12 weeks. All patients had been diagnosed with NASH and liver fibrosis stages F1 through F3 based on a biopsy or magnetic resonance elastography (MRE) and MRI proton density fat fraction (MRI-PDFF). The patients receiving the 20 mg dose showed significant decreases in liver fat content compared to placebo after 12 weeks. They also had a significant decrease in TIMP-1, a blood serum marker associated with liver fibrosis. The differences between placebo and patients receiving 5 mg doses of the drug were not statistically significant.

# 从研发角度评估靶点关键信息

信息:

- 疾病: 非酒精性脂肪肝  
炎伴随F1到F3级纤维化
- 靶点: ACC; 药物: GS-0976
- 研究方法: 影像学方法
- 指标: 肝脏脂肪分数,  
血清标志物TIM-1
- 结果: 给药12周, 高剂量组脂肪含量明显下降;  
低剂量差异统计不显著



- 靶点和疾病联系: 纤维化是否有改善未知。调节ACC是否只能满足部分治疗需求?
- ACC的具体功能
- 化合物的其他研发信息
- 靶点调节程度要求: 高剂量有效 (活性, PK)
- 药效评估: 影像学方法似乎不太适用于动物。TIM-1标志物如何反映纤维化程度? 是否可以在动物研究应用?

## 第二部分

从疾病到靶点，深入评估靶点

如何从研发角度评估靶点关键信息

借助Drug Research Advisor (Target Drugability)通过复合信息评估早期靶点成功率



# 靶点关键信息：研发信息需求

项目	意义
所属家族	靶点蛋白的性质，实验方法
亚型	功能区别，靶点选择性（安全性）
细胞定位	干预手段，e.g 抗体, 小分子, 基因治疗
组织表达	靶器官 vs. 其他组织，亚型分布，安全性
基因异常	基因异常对靶点自身功能的影响, 疾病关联
基因研究 (K.O, K.D, Overexpression)	靶点功能，靶点调节的安全性，疾病关联
分子生物学特征	化合物结合部位，胞外结构域，结构域功能
生理，病理过程	信号通路，标志物，疾病关联，安全性

# 靶点关键信息：靶点检索ACC

Targets & Pathways



Targets & Pathways

Advanced Search

Session History

Clear Form

Start

Targets & Pathways

Name (Target Name) > "ACCA" or "ACCB"

Index AND >

Optional Value >

Index AND >

Optional Value >

Index AND >

Product

Lead Compounds  Under Active Development

Drug Name > "GS-0976"

Index AND >

Optional Value >

Index AND >

Optional Value >

Index AND >

Product

Lead Compounds  Under Active Development

Mechanism of Action > "Acetyl-CoA Carboxylase (ACC) Inhibitors"

Index AND >

Optional Value >

Index AND >

Optional Value >

Index AND >

靶点及信号通路模块

多种靶点检索方式：

- 靶点名称
- 药物名称
- 作用机制

Target Name	Type
<input type="checkbox"/> <a href="#">Acetyl-CoA carboxylase 1 (isoform 1)</a>	Protein
<input type="checkbox"/> <a href="#">Acetyl-CoA carboxylase 2</a>	Protein

# 靶点关键信息：靶点概览

Acetyl-CoA carboxylase 1 (isoform 1)	
Last Updated Date	Jan 10, 2017
Type	Protein <span>靶点类型</span>
Related Names	ACAC; ACACA variant 1; ACACAD; ACC; ACC-alpha; ACC1; ACCA; Acetyl-CoA carboxylase 1; Acetyl-Coenzyme A carboxylase alpha; Acetyl-Coenzyme A carboxylase alpha, transcript variant 1
EC	6.4.1.2
Links	UniProtKB: <a href="#">Q13085</a> <span>分子生物学信息: 功能, 细胞定位, 结构域, 序列, 表达等</span>
MetaCore	<a href="#">ACACA</a> , acetyl-CoA carboxylase alpha
Description/Function	ACC1 is an enzyme that catalyzes the carboxylation of acetyl-CoA to malonyl-CoA a key step in the fatty acid synthesis. <span>基本生物功能</span>

Acetyl-CoA carboxylase 2	
Last Updated Date	Jan 10, 2017
Type	Protein
Related Names	ACACB; ACC-beta; ACC2; ACCB; Acetyl-Coenzyme A carboxylase 2; Acetyl-Coenzyme A carboxylase beta; HACCC275
EC	6.4.1.2
Links	UniProtKB: <a href="#">Q00763</a> PDB: <a href="#">2DN8</a> , <a href="#">2HJW</a> , <a href="#">2KCC</a> , <a href="#">3FF6</a> , <a href="#">3GID</a> , <a href="#">3GLK</a> , <a href="#">3JRW</a> , <a href="#">3JRX</a> , <a href="#">3TDC</a> , <a href="#">4HO6</a>
MetaCore	<a href="#">ACACB</a> , acetyl-CoA carboxylase beta
Description/Function	ACC2 is an enzyme that acts as a biotin carboxyl carrier, a biotin carboxylase and as a carboxyltransferase. It may be involved in the regulation of fatty acid oxidation, rather than fatty acid biosynthesis.

- 两个亚型的功能不重叠, 但有关联
- 进一步探索是否需要选择性靶向: 与疾病联系; 化合物靶向信息

# 靶点关键信息：疾病靶点格局

## Targetscape

### Cancer

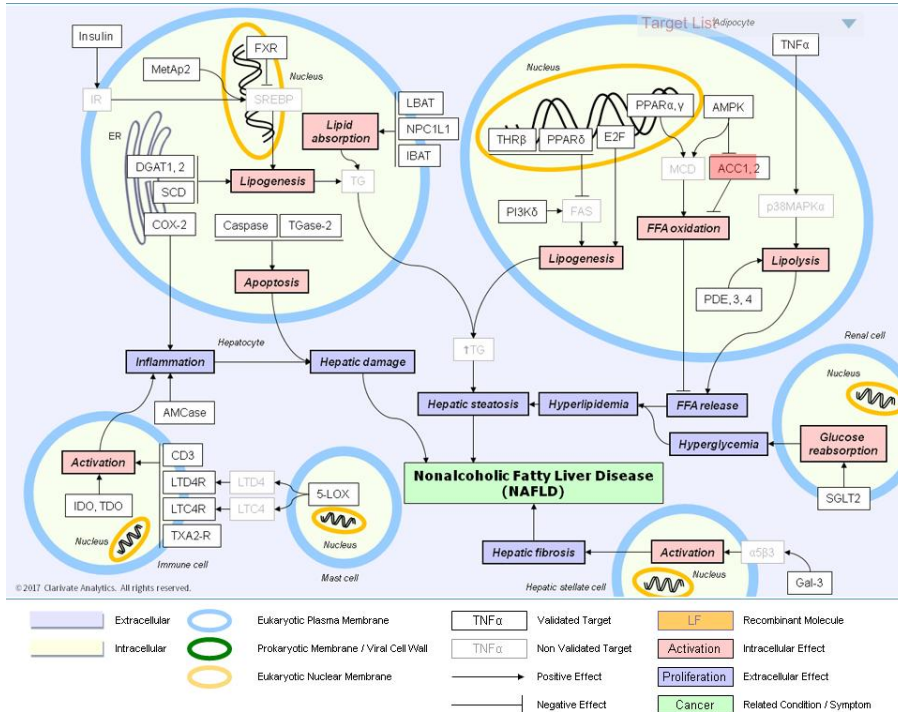
Liver Cancer Targetscape

### Gastrointestinal Disorders

Nonalcoholic Fatty Liver Disease (NAFLD) Targetscape

### Neurological Disorders

Parkinson's Disease Targetscape



- 疾病相关的生理/病理过程
- 疾病涉及的组织，细胞类型
- 靶点直接调节的细胞功能
- 其他疾病相关靶点的分布

# 靶点关键信息：靶点成熟度评估

Condition (Status)		
<input type="checkbox"/> Collapse All	<input type="checkbox"/> Expand All	<b>V 2 Conditions</b>
<input checked="" type="checkbox"/> Cancer	<input type="checkbox"/> C (View Drugs)	<b>C 5 Conditions</b>
<input checked="" type="checkbox"/> Cardiovascular Disorders		<b>E 14 Conditions</b>
<input checked="" type="checkbox"/> Endocrine Disorders		
<input checked="" type="checkbox"/> Gastrointestinal Disorders		
<input checked="" type="checkbox"/> Infections	<input type="checkbox"/> E (View Drugs)	
<input checked="" type="checkbox"/> Metabolic Diseases		
<input checked="" type="checkbox"/> Neurological Disorders		
<input checked="" type="checkbox"/> Other disorders (Systemic disorders)		

靶点在不同治疗领域中针对不同适应症的研发情况

V: 有活跃 (UAD) 的药物在临床前及之后的阶段

C: 有活跃 (UAD) 的药物在临床前及之后的阶段，但目前处于不活跃阶段 (NDR)

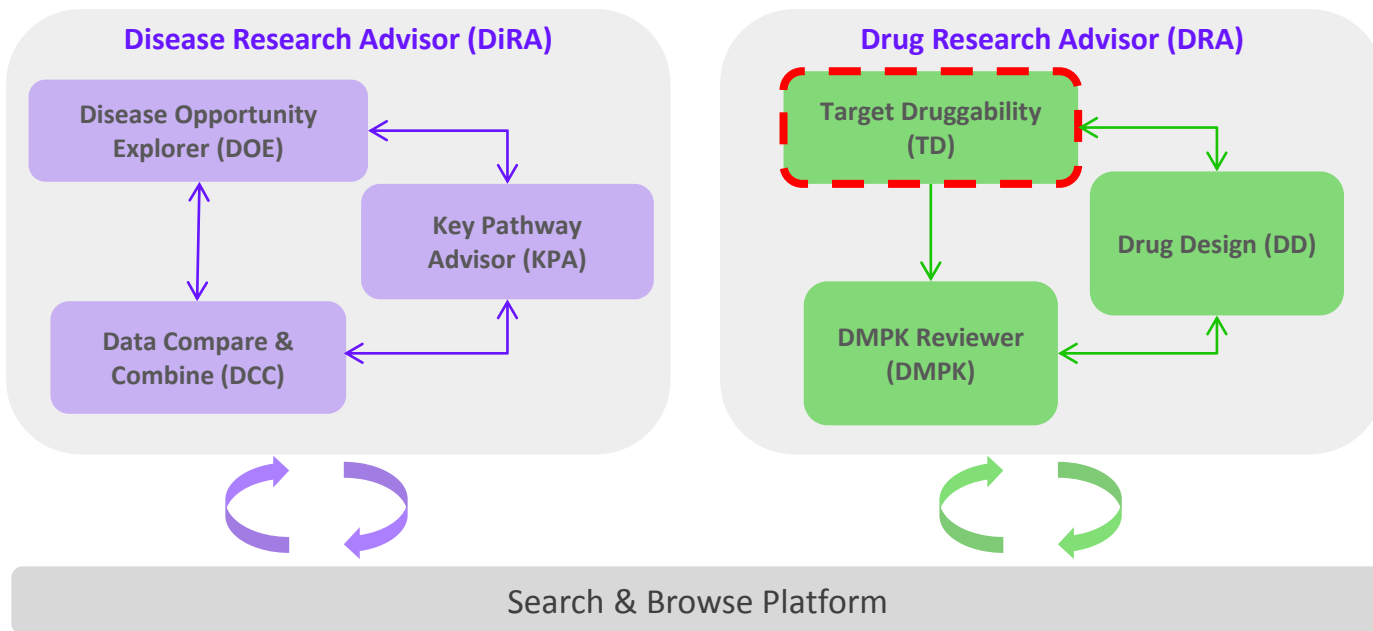
E: 药物都在早期活性测试阶段

- 探索靶点对应的其他适应症，及现有开发状态

Condition (Status)		
<input type="checkbox"/> Collapse All	<input type="checkbox"/> Expand All	<b>V 2 Conditions</b>
<input checked="" type="checkbox"/> Cancer	<input type="checkbox"/> C (View Drugs)	<b>C 5 Conditions</b>
<input checked="" type="checkbox"/> Cardiovascular Disorders		<b>E 14 Conditions</b>
<input checked="" type="checkbox"/> Endocrine Disorders		
<input checked="" type="checkbox"/> Gastrointestinal Disorders		
<input checked="" type="checkbox"/> Infections	<input type="checkbox"/> E (View Drugs)	
<input checked="" type="checkbox"/> Metabolic Diseases		
<input checked="" type="checkbox"/> Neurological Disorders		
<input checked="" type="checkbox"/> Other disorders (Systemic disorders)		

**可视化，交互型的靶点评估工具来了**

# 药物研究顾问靶点成药性工具 DRA-TD



- DRA（药物研发顾问）套件的首个应用工具
- 数据源支持：Integrity数据库和Meta系列数据库
- 交互呈现、可视化分析的靶点探索和评估工具
- 快速实现“探索-筛选-评级-评估”的靶点发现工作流程

# 药物顾问-靶点成药性工具

Explore targets ⓘ

Match all Match any

C Non-alcoholic steatohepatitis x

Enter a target, target family, condition or drug

Explore

Explore targets ⓘ

Match all Match any

D GS-0976 x

Enter a target, target family, condition or drug

Explore

Explore targets ⓘ

Match all Match any

T Acetyl-CoA carboxylase 1 x

Enter a target, target family, condition or drug

Explore

- 以疾病，药物，具体靶点（靶点家族）出发评估靶点信息
- 支持复合条件检索
  - 多种疾病：共同靶点
- 支持布尔运算符号 AND OR NOT



# DRA靶点评估：探索模式

Drug Research Advisor Target Druggability Search Saved work

Save search 192 targets for Non-alcoholic steatohepatitis

Filters

View targets by Reset

Group by  
Target families

Color by  
Drug highest phase

Size by  
Drug count

Legend

Color by  
● Phase III  
● Phase II / III  
● Phase I

Filter Data ⓘ

Target type 靶点类别

Target families 靶点家族

Pathway maps 信号通路

Target conditions 适应症关联

None  
Active / launched drugs (Y/N)  
Animal models (Y/N)  
Biomarker uses (Y/N)  
Drug highest phase  
Drugs (Y/N)  
Experimental pharmacology (Y/N)  
Genetic evidence (Y/N)  
Target families

None  
Active / launched drugs (Y/N)  
Animal model count  
Animal models (Y/N)  
Biomarker use count  
Biomarker uses (Y/N)  
Drug count  
Drug highest phase  
Drugs (Y/N)  
Experimental pharmacology count  
Experimental pharmacology (Y/N)  
Genetic evidence count  
Genetic evidence (Y/N)  
Target families

None  
Animal model count  
Biomarker use count  
Drug count  
Experimental pharmacology count  
Genetic evidence count

## 显示设置：分类，颜色，大小

Table Exploration

Back Select targets Deselect

- All Groups
- Enzymes (60)
- Other Proteins (60)
- Receptors (33)
- Carriers (10)
- Cytokines (8)
- Transcription Factors (7)
- Ion Channels (3)
- Others (3)
- Adaptor Proteins (2)
- Hormones (2)
- Adhesion Molecules (1)
- Lipoproteins (1)
- Molecular Chaperones (1)
- Untranslated RNAs (1)

## 靶点家族及数目

过滤标签：依照目标要求进行过滤

# DRA靶点评估：表格模式

Drug Research Advisor Target Druggability Search Saved work

Save search **192 targets for Non-alcoholic steatohepatitis**

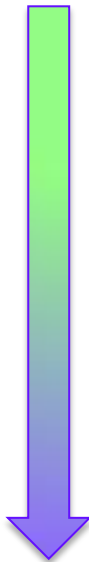
Filters **1**

Target prioritization Complete novelty Condition novelty Early development No prioritization **1**

[Table](#) [Exploration](#)

Target		Number of related records				
Target main name	Gene symbol	Drugs	Experimental pharmacology	Animal models	Biomarker uses	Genetic evidence
		filtered (total)		filtered (total)	filtered (total)	filtered (total)
<input checked="" type="checkbox"/> Select targets <input type="checkbox"/> Deselect						
<input checked="" type="checkbox"/> Acetyl-CoA carboxylase 1	[SYN] ACACA	3 (137)	185	0 (11)	5 (195)	0 (23)
<input checked="" type="checkbox"/> Acetyl-CoA carboxylase 2	[SYN] ACACB	2 (360)	375	0 (6)	1 (107)	0 (32)
<input checked="" type="checkbox"/> Acetyl-CoA Carboxylases (ACC) (nonspecified subtype)	[SYN] -	1 (183)	111	0 (11)		
<input checked="" type="checkbox"/> Acyl-CoA desaturase	[SYN] SCD	38 (653)	574	0 (24)	10 (323)	0 (15)
<input checked="" type="checkbox"/> Adenosine receptor A3	[SYN] ADORA3	1 (504)	1620	0 (6)	0 (106)	0 (8)
<input checked="" type="checkbox"/> Adiponectin receptor protein 2	[SYN] ADIPOR2	3 (9)	3	0 (9)	4 (140)	0 (34)
<input checked="" type="checkbox"/> ADP-ribosyl cyclase/cyclic ADP-ribose hydrolase 1	[SYN] CD38	7 (54)	73	0 (6)	0 (380)	0 (29)
<input checked="" type="checkbox"/> Advanced glycosylation end product-specific receptor	[SYN] AGER	0 (79)	36	0 (43)	3 (724)	1 (156)
<input checked="" type="checkbox"/> Alpha-1-antitrypsin	[SYN] SERPINA1	0 (7)		0 (9)	2 (868)	1 (83)
<input checked="" type="checkbox"/> Amine oxidase [flavin-containing] B	[SYN] MAOB	2 (876)	1777	0 (15)	0 (147)	0 (52)
<input checked="" type="checkbox"/> AMP-activated protein kinase (AMPK)	[SYN] -	2 (646)	847	0 (18)		
<input checked="" type="checkbox"/> Apolipoprotein E	[SYN] APOE	0 (4)	19	4 (757)	5 (783)	1 (1314)
<input checked="" type="checkbox"/> Arachidonate 5-lipoxygenase	[SYN] ALOX5	2 (511)	1036	0 (11)	0 (203)	0 (40)
<input checked="" type="checkbox"/> Beta-klotho	[SYN] KLB	1 (5)		0 (2)	0 (54)	0 (8)
<input checked="" type="checkbox"/> Beta-parvin	[SYN] PARVB				0 (60)	4 (22)
<input checked="" type="checkbox"/> Bile acid receptor	[SYN] NR1H4	51 (553)	734	4 (29)	3 (195)	0 (22)
<input checked="" type="checkbox"/> C-C chemokine receptor type 2	[SYN] CCR2	2 (1079)	966	0 (56)	5 (339)	0 (86)
<input checked="" type="checkbox"/> C-C chemokine receptor type 5	[SYN] CCR5	1 (1099)	610	0 (18)	1 (349)	0 (179)

靶点成药性级别



靶点名称

相关研究数量

# DRA靶点评估：靶点创新性优先评级

- 依照研发定位，对靶点潜力进行评级

Complete novelty    Condition novelty    Early development    No prioritization

全新靶点

已知靶点拓展  
新的适应症

已有化合物处在  
早期研究阶段

Drug Research Advisor Target Druggability    Search    Saved work

Save search    192 targets for Non-alcoholic steatohepatitis    Save search    192 targets for Non-alcoholic steatohepatitis

Filters 1    Filters 1    Filters 1

Target prioritization    **Complete novelty**    Condition novelty    Target prioritization    Complete novelty    Condition novelty    **Early development**    No prioritization    i

Hyperlipidemia

Rank	Target main name	Rank	Target main name	Rank	Target
	<input checked="" type="checkbox"/> Select targets    Deselect		<input checked="" type="checkbox"/> Select targets    Deselect		<input checked="" type="checkbox"/> Select targets    Deselect
1	<input checked="" type="checkbox"/> Methylenetetrahy	1	<input checked="" type="checkbox"/> Mu-type opioid receptor	1	<input checked="" type="checkbox"/> HLA class I histocompatibility antigen, A-1 alpha chain [SYN]
2	<input checked="" type="checkbox"/> Superoxide dismu	2	<input checked="" type="checkbox"/> Serine/threonine-protein kinase mTOR	2	<input checked="" type="checkbox"/> HLA class I histocompatibility antigen, A-11 alpha chain [SYN]
3	<input checked="" type="checkbox"/> Transcription fact	3	<input checked="" type="checkbox"/> Fibroblast growth factor receptor 1	3	<input checked="" type="checkbox"/> HLA class I histocompatibility antigen, A-2 alpha chain [SYN]
4	<input checked="" type="checkbox"/> HLA class I histoc	4	<input checked="" type="checkbox"/> C-C chemokine receptor type 5	4	<input checked="" type="checkbox"/> HLA class I histocompatibility antigen, A-23 alpha chain [SYN]
5	<input checked="" type="checkbox"/> HLA class I histoc	5	<input checked="" type="checkbox"/> Sodium/glucose cotransporter 2	5	<input checked="" type="checkbox"/> HLA class I histocompatibility antigen, A-24 alpha chain [SYN]
6	<input checked="" type="checkbox"/> HLA class I histoc	6	<input checked="" type="checkbox"/> Toll-like receptor 4	6	<input checked="" type="checkbox"/> HLA class I histocompatibility antigen, A-25 alpha chain [SYN]
7	<input checked="" type="checkbox"/> HLA class I histoc	7	<input checked="" type="checkbox"/> Mineralocorticoid receptor	7	<input checked="" type="checkbox"/> HLA class I histocompatibility antigen, A-26 alpha chain [SYN]
8	<input checked="" type="checkbox"/> HLA class I histoc	8	<input checked="" type="checkbox"/> Signal transducer and activator of transcription 3	8	<input checked="" type="checkbox"/> HLA class I histocompatibility antigen, A-29 alpha chain [SYN]
9	<input checked="" type="checkbox"/> HLA class I histoc	9	<input checked="" type="checkbox"/> cGMP-specific 3',5'-cyclic phosphodiesterase	9	<input checked="" type="checkbox"/> HLA class I histocompatibility antigen, A-3 alpha chain [SYN]
10	<input checked="" type="checkbox"/> HLA class I histoc	10	<input checked="" type="checkbox"/> Histone deacetylase 1	10	<input checked="" type="checkbox"/> HLA class I histocompatibility antigen, A-30 alpha chain [SYN]
11	<input checked="" type="checkbox"/> HLA class I histoc	11	<input checked="" type="checkbox"/> Phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit delta	11	<input checked="" type="checkbox"/> HLA class I histocompatibility antigen, A-31 alpha chain [SYN]

# DRA靶点评估：靶点概览

Acetyl-CoA carboxylase 1

ACACA [SYN]

Overview Drugs Experimental pharmacology Biomarker uses

## Description

ACCI is an enzyme that catalyzes the carboxylation of acetyl-CoA to malonyl-CoA a key step in the fatty acid synthesis.

## Condition evidence 3

- AIDS
- Cancer
- Cardiovascular Disorders
- Endocrine Disorders
- Eye Disorders
- Gastrointestinal Disorders
- Infections
- Metabolic Diseases
- Neurological Disorders
- Other disorders (Systemic [...])
- Psychiatric Disorders



## Main family

Acetyl-CoA Carboxylases (ACC)

## Main family group

Enzymes

## Protein/RNA description

Catalyzes the rate-limiting reaction in the biogenesis of long-chain fatty acids. Carries out three functions: biotin carboxyl carrier protein, biotin carboxylase and carboxyltransferase.

## Gene description

Acetyl-CoA carboxylase (ACC) is a complex multifunctional enzyme system. ACC is a biotin-containing enzyme which catalyzes the carboxylation of acetyl-CoA to malonyl-CoA, the rate-limiting step in fatty acid synthesis. There are two ACC forms, alpha and beta, encoded by two different genes. See more

### Molecular function

### Biological process

### Subcellular location

## Protein

Chromosomal location: 17q12

Molecular weight: 263554

Organism: Homo sapiens

## Lists

- Drugs
- Pathway maps
- Animal models
- Genetic evidence citations
- Patents
- References

## Crystallographic data



Protein Data Bank

## Tissue Expression



Human Protein Atlas

## Integrity

Targets and Genomics

## External links

EMBL

Ensembl Gene

Ensembl Protein

Ensembl Transcript

Entrez Gene

GenBank

HUGO

KEGG

OMIM

UniProtKB

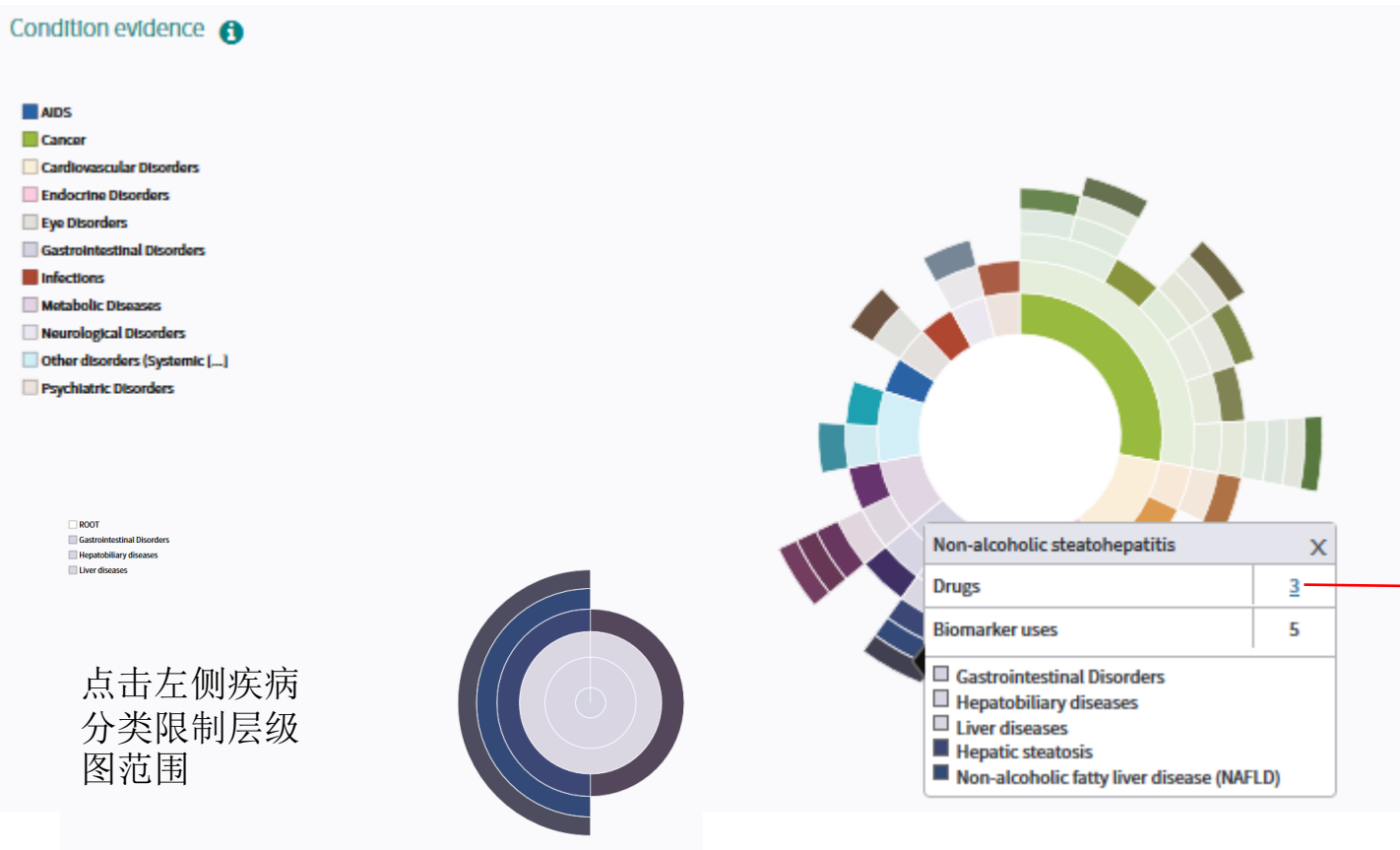
靶点相关家族，功能，细胞定位，生理过程

## 靶点相关信息

- 药物
- 信号通路
- 动物模型研究
- 基因研究证据
- 专利
- 文献

- PDB蛋白质数据库 靶点蛋白结构信息
- HPA蛋白表达数据库 靶点在不同组织表达信息
- Integrity数据库 靶点和基因信息
- 其他分子生物学数据库

# DRA靶点评估：靶点-适应症层级图



以层级图显示

- 内圈：主要疾病种类
- 外圈：细化适应症

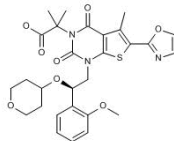
化合物和基因研究直接点击查看

# DRA靶点评估：相关药物

Drugs

Explore all drugs in Drug Design

Drug ID	Drug name	Highest phase	Experimental pharmacology	Animal models
912039 ACTIVE	GS-0976 <a href="#">↗</a>	[SYN] Phase II		
873586 ACTIVE	873586 <a href="#">↗</a>			
907330	BAY-ACC002 <a href="#">↗</a>			
857206	ND-646 <a href="#">↗</a>			
838626	838626 <a href="#">↗</a>			
836589	836589 <a href="#">↗</a>			

Entry Number	814008	UPDATE	Chemical Structure	STRUCTURE FEATURES
Former ID	822559			
Record Creation Date	Mar 18, 2014			
Last Updated Date	Dec 10, 2016			
Molecular Formula	C28 H31 N3 O8 S			
Molecular Weight	569.626			
Highest Phase	Preclinical			
Under Active Development				
				
			ND-630	
			Structure/Sequence Entry Date	Mar 18, 2014
<b>Chemical Name/Description</b>				
2-[1-[[[2R]-2-(2-Methoxyphenyl)-2-(tetrahydro-2H-pyran-4-yloxy)ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1,4-dihydrothieno[2,3-d]pyrimidin-3(2H)-yl]-2-methylpropanoic acid				
<b>Standard InChI</b>				
15C28H31N3O8S /c1-16-21-24(32)31(28(2,3)26(33)34)27(35)30(25)21)40-22(16)23-29-11-14-38-23)15-20(39-17-9-12-37-13-10-17)18-7-5-6-8-19(18)36-4/h5-8,11,14,17,20H,9-10,12-13,15H,2,14-H3,(H,33,34)20-/m0/s1				
<b>Standard InChIKey</b>				
ZZWWWXIBKLBMSCS-FQEVSTJZSA-N				
<b>Code Name</b>	<b>Generic Name</b>	<b>Brand Name</b>		
ND-630				
NDI-630				
<b>Molecular Mechanism</b>		<b>Cellular Mechanism</b>		
Acetyl-CoA Carboxylase 2 (ACC2) Inhibitors		Lipid Lowering Agents		
Acetyl-CoA Carboxylase 1 (ACC1) Inhibitors				
<b>Product Category</b>	<b>Therapeutic Group</b>	<b>Prescription/ Indication Type</b>		
	Antiobesity Drugs Liver and Biliary Tract Disorders, Treatment of Antidiabetic Drugs			
<b>Organization</b>				
<a href="#">Nimbus Therapeutics (Originator)</a>				

- 化合物的名称/研发代号，研发活跃度，最高研发阶段，实验数据
- 链接可跳转到Integrity数据库

# DRA靶点评估：相关信号蛋白相互作用网络

Pathway maps

Pathway map name

Adiponectin in pathogenesis of type 2 diabetes

Butanoate metabolism

Development\_Leptin signaling via PI3K-dependent pathway

Immune response\_The effect of INDO on T cell metabolism

Propionate metabolism p.2

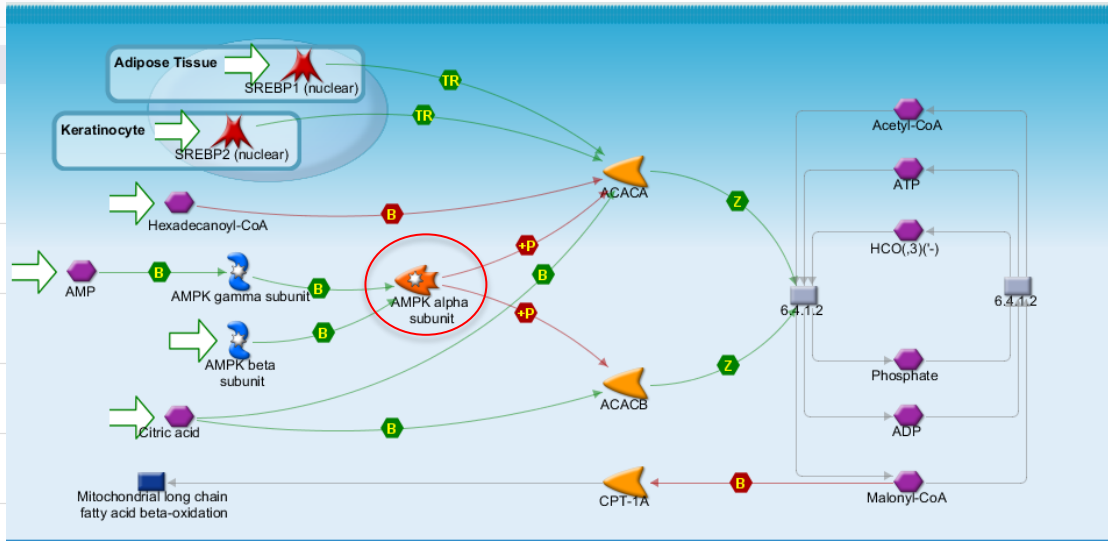
Regulation of lipid metabolism\_Insulin regulation of fatty acid metabolism

Regulation of lipid metabolism\_Regulation of acetyl-CoA carboxylase 1 activity

Regulation of lipid metabolism\_Regulation of lipid metabolism via LXR, NF-Y and SREBP

Regulation of metabolism\_Bile acids regulation of glucose and lipid metabolism via FXR

Regulation of metabolism\_Role of Adiponectin in regulation of metabolism



- 挖掘网络图中的其他靶点
- 探索靶点调节的生理功能
- 激动AMPKα是否也能抑制ACC活性？

# DRA靶点评估：依据关联类型快速锁定核心文献

## Patents

### Fatty acid elongation enzymes as targets for cancer diagnostics and therapeutics

Assignee: Katholieke Universiteit Leuven (KU Leuven)

Inventor: Lerut, E. | Marien, E. | Dehaers, J. | Rincon, N.R. | Berkers, J. | Machiels, J. | Bagadi, M.R. | Swinn

Publish date: 2013-10-03

WO 2013144325

Association type: Biomarker uses 生物标志物研究关联

### Substituted 3-(biphenyl-3-yl)-4-hydroxy-8-methoxy-1-azaspiro[4.5]dec-3-ene

Assignee: Bayer Intellectual Property GmbH

Inventor: Fischer, R. | Bömer, U. | Hilger, C. | Scholz, A. | Mönning, U. | Thede, K. | Liu, N.

Publish date: 2013-02-07

WO 2013017600

Association type: Experimental Pharmacology 实验药理学数据关联

### N1-Pyrazolospiroketone acetyl-CoA carboxylase inhibitors

Assignee: Pfizer Inc.

Inventor: Kung, D.W.-S. | Griffith, D.A. | Bagley, S.C.

Publish date: 2013-01-31

US 2013030181

Association type: Experimental Pharmacology Animal models

## References

### CONFERENCE

Acetyl-CoA carboxylase inhibition by ND-630 reduces hepatic steatosis and delays diabetes progression in ZDF rats

Author: Harriman, G. | Greenwood, J. | Bhat, S. | Westlin, W.F. | Kapeller, R. | Harwood, H.J.

Publication: Annual Meeting & Scientific Sessions of the American Diabetes Association (ADA) - 2015-06-05 / 2015-06-05 - Boston, United States

Association type: Experimental pharmacology

### CONFERENCE

Sitagliptin can be preventative drug for the development of hepatic steatosis due to inhibiting the expressions of hepatic acetyl-CoA carboxylase1 (ACC1) in high-fructose diet-fed ob/ob mice

Author: Fukunishi, S. | Yokohama, K. | Asai, A. | Tsuda, Y. | Higuchi, K.

Publication: Digestive Disease Week (DDW) - 2015-05-16 / 2015-05-16 - Washington, United States

Association type: Biomarker uses

### CONFERENCE

The genetic architecture of autism spectrum disorders in the faroe islands

Author: Carton, C. | Huguet, G. | Buratti, J. | et al.

Publication: Annual Meeting of the American Society of Human Genetics (ASHG) - 2015-10-06 / 2015-10-06 - Baltimore, United States

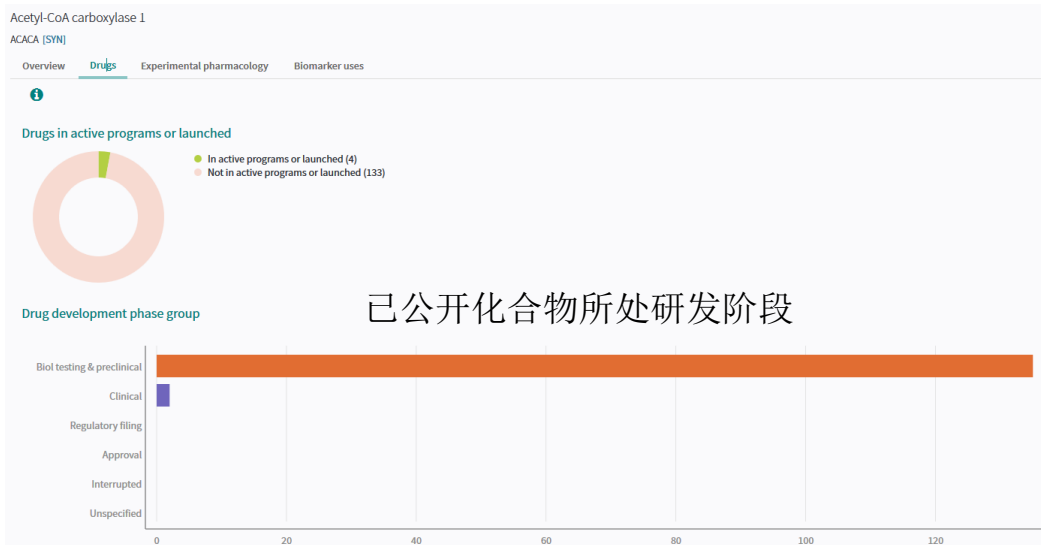
Association type: Biomarker uses

## 靶点相关基因研究，专利，文献

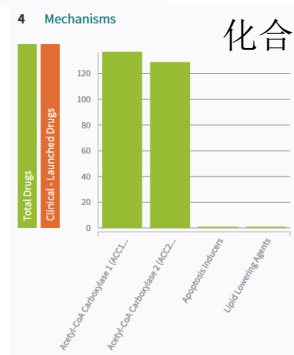
- 指明关联适应症
- 指明关联类型
- 提供Pubmed链接



# DRA靶点评估：靶点化合物研发概览



- 明确已知化合物的开发阶段分布
- 涉及的主要研发机构/公司
- 化合物涉及的作用机制
- 综合判断潜在竞争情况，确定主要竞争对手



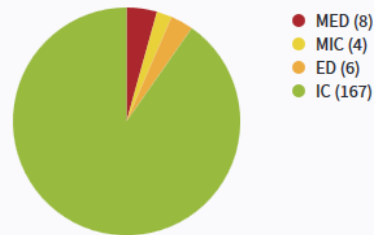
# DRA靶点评估：药理研究和标志物研究概览

Acetyl-CoA carboxylase 1

ACACA [SYN]

Overview Drugs Experimental pharmacology Biomarker uses

Experimental pharmacology by parameter



Experimental pharmacology by activity and compartment

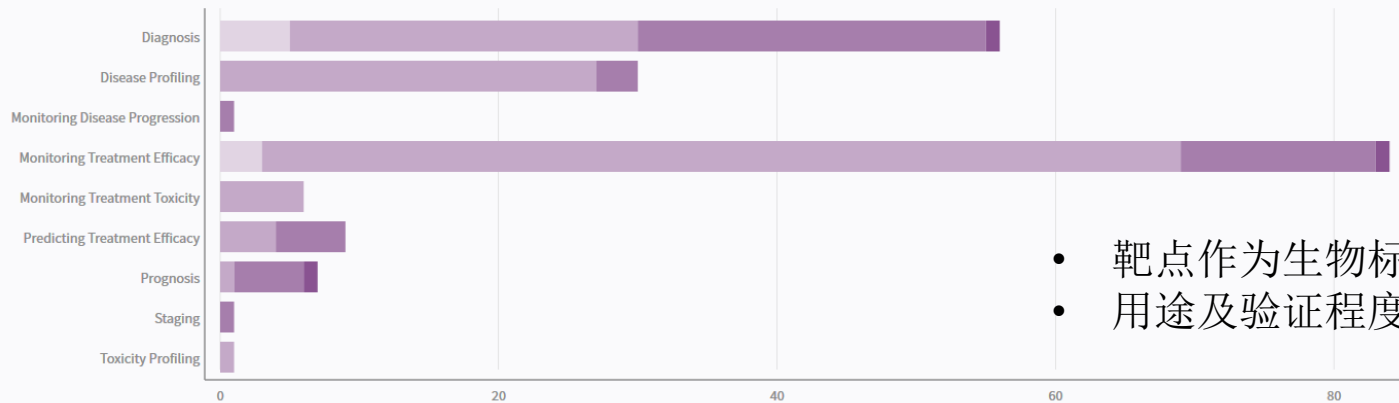
● in vitro (171) ● ex vivo (2) ● in vivo (12)



- 药理学试验类型及数据类型
- 明确主要化合物作用类型

Biomarker uses by role and validity

● Emerging (8) ● Experimental (130) ● Early Studies in Humans (54) ● Late Studies in Humans (3)



- 靶点作为生物标志物的相关研究
- 用途及验证程度

## 第三部分

探宝Clarivate Integrity，围绕Pre-clinical看数据

深入挖掘靶点信息：基因研究，药效生物标志物，实验模型

参考活性数据合理选择参考化合物；通过核心专利快速进行SAR分析

# 深入挖掘靶点信息

候选靶点



候选适应症

靶点细节

实验信息

化合物信息

- 相关基因异常（靶点覆盖范围）
- 基因研究类别（额外的适应症）
- 体内研究模型
- 体内研究模型
- 生物标志物
- 活性范围
- 典型分子的SAR
- 参考化合物

# 深入挖掘靶点信息：基因异常类型

The screenshot displays the Thomson Reuters Integrity Genomics search interface. The search criteria are: **Condition = "Cancer, breast" AND Variation Type = "Gene amplification"**. The results table lists various genes and their associated conditions.

Gene Symbol	Gene Name	Organism	Condition	Links	MetaCore
<input type="checkbox"/> AKT1_variant.2	V-akt murine thymoma viral oncogene homolog 1, transcript variant 2	Homo sapiens (human)	Cancer, breast Cancer, colorectal Cancer, ovary	Entrez Gene: 207 KEGG: 207	AKT1
<input type="checkbox"/> AKT1_variant.3	V-akt murine thymoma viral oncogene homolog 1, transcript variant 3	Homo sapiens (human)	Cancer, breast Cancer, colorectal Cancer, ovary Multiple hamartoma syndrome (Cowden's syndrome)	Entrez Gene: 207 KEGG: 207	AKT1
<input type="checkbox"/> AR_variant.1	Androgen receptor, transcript variant 1	Homo sapiens (human)	Androgen Insensitivity Cancer, prostate Spinal and bulbar muscular atrophy, X-linked	Entrez Gene: 367 KEGG: 367	AR
<input type="checkbox"/> ATM	ATM serine/threonine kinase	Homo sapiens (human)	Ataxia Cancer, breast Louis-Bar syndrome (ataxia telangiectasia) Lymphoma	Entrez Gene: 472 KEGG: 472	ATM
<input type="checkbox"/> C11orf30	Chromosome 11 open reading frame 30	Homo sapiens (human)	Cancer, breast	Entrez Gene: 55946 KEGG: 55946	C11orf30
<input type="checkbox"/> ERBB2_variant.4	Erb-b2 receptor tyrosine kinase 2, transcript variant 4	Homo sapiens (human)	Cancer, breast Cancer, ovary	Entrez Gene: 2064 KEGG: 2064	ERBB2
<input type="checkbox"/> KRAS_variant.a	v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog, transcript variant a	Homo sapiens (human)	Astrocytoma, pilocytic Cancer, bladder (adenocarcinoma) Cancer, breast (adenocarcinoma) Cancer, lung Cancer, pancreas Cancer, stomach Cardiofaciocutaneous syndrome Leukemia, acute myeloid Neurofibromatosis, type 1 Noonan syndrome Trigonocephaly	Entrez Gene: 3845 KEGG: 3845	KRAS
<input type="checkbox"/> NOTCH1	Notch 1	Homo sapiens (human)	Cancer, breast	Entrez Gene: 4851 KEGG: 4851	NOTCH1

On the right side of the interface, a list of gene variation types is shown with corresponding buttons:

- Allelic loss (缺失)
- Epigenetic change (表观遗传改变)
- Gene amplification (基因扩增)
- Gene deletion (基因删除)
- Diversity/Mutation (多样性/突变)



# 深入挖掘靶点信息：基因异常类型

## 以HER2为例

▲Cancer, ovary			
Variation Type	Variation Name	Association Variant	Effect / Source
Polymorphism/mutation	<b>rs121913470</b> (p.Leu755Ser;c.2264T>C;p.L755S)	C Allele	Carcinogenesis <a href="#">References (1)</a>
Polymorphism/mutation	<b>c.2524G&gt;A</b> (p.V842I;p.Val842Ile)	A Allele	Carcinogenesis <a href="#">References (1)</a>
Polymorphism/mutation	<b>c.955A&gt;G</b> (p.Asn319Asp;p.N319D)	G Allele	Carcinogenesis <a href="#">References (1)</a>
Polymorphism/mutation	<b>rs1057519816</b> (c.929C>T;p.S310F;p.Ser310Phe)	T Allele	Carcinogenesis <a href="#">References (1)</a>
Polymorphism/mutation	<b>c.2033G&gt;A</b> (p.Arg678Gln;p.R678Q)	A Allele	Carcinogenesis <a href="#">References (1)</a>
Gene amplification	<b>ERBB2amp</b>	Not specified Not specified	Carcinogenesis <a href="#">References (1)</a>
Polymorphism/mutation	<b>c.2305G&gt;T</b> (p.D769Y;p.Asp769Tyr)	T Allele	Carcinogenesis <a href="#">References (1)</a>
▲Cancer, ovary (epithelial)			
Variation Type	Variation Name	Association Variant	Effect / Source
Polymorphism/mutation	<b>rs121913470</b> (p.Leu755Ser;c.2264T>C;p.L755S)	C Allele	Carcinogenesis <a href="#">References (1)</a>
Polymorphism/mutation	<b>rs768974971</b> (c.2301C>G;p.I767M;p.Ile767Met)	G Allele	Carcinogenesis <a href="#">References (1)</a>
Polymorphism/mutation	<b>c.2299A&gt;T</b> (p.Ile767Phe;p.I767F)	T Allele	Carcinogenesis <a href="#">References (1)</a>
Polymorphism/mutation	<b>c.2305G&gt;T</b> (p.D769Y;p.Asp769Tyr)	T Allele	Carcinogenesis <a href="#">References (1)</a>
▲Cancer, ovary (adenocarcinoma)			
▲Cancer, ovary (clear cell carcinoma)			
Variation Type	Variation Name	Association Variant	Effect / Source
Gene amplification	<b>HER2amp</b>	Not specified Not specified	Carcinogenesis <a href="#">References (1)</a>
▲Cancer, ovary (borderline tumors)			
▲Cancer, ovary (mucinous borderline tumors)			
Variation Type	Variation Name	Association Variant	Effect / Source
Gene amplification	<b>HER2amp</b>	Not specified Not specified	Carcinogenesis <a href="#">References (2)</a>

全面收录靶点相关基因异常及其影响

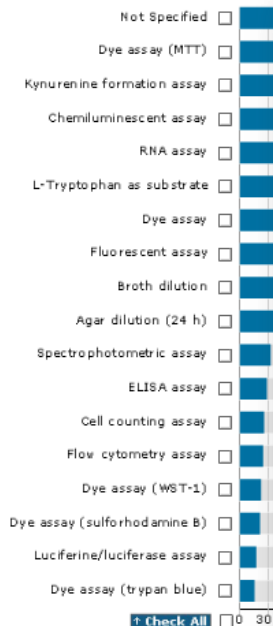
# 深入挖掘靶点信息：体外实验模型

Experimental Pharmacology



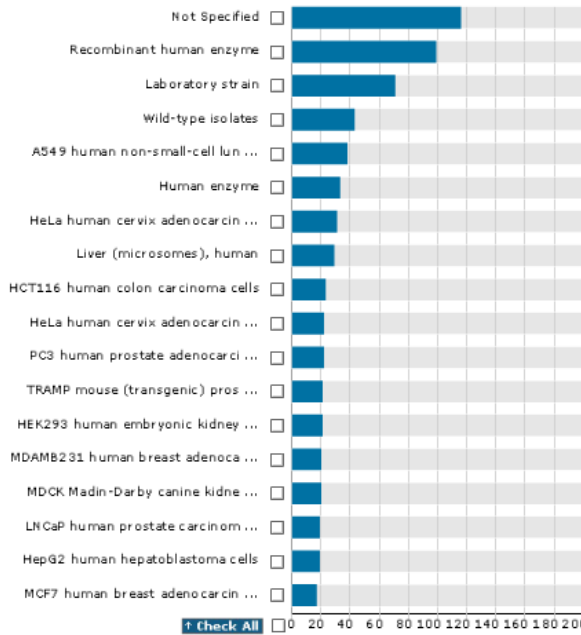
## Method

Include Literature Results = Y AND Include Patent Results = Y AND Lead Compounds AND Mechanism of Action = "Indolear"



## Material

Include Literature Results = Y AND Include Patent Results = Y AND Lead Compounds AND Mechanism of Action = "Indolear"



## Display Options

Horizontal Display Vertical Display Pie Chart Display

View Subset(s)

Print Chart

Help

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- 实验方法
  - 细胞，酶学
- 实验模型
  - 选取广泛应用的细胞株
  - 结合基因异常评估细胞株

# 动物实验模型：探索毒性评估模型及方法

- 获取特定毒性研究信息

Experimental Models



Experimental Models		
Toxicity	▶ "Kidney injury"	Index AND ▶
Species	▶ "Rattus norvegicus (rat)"	Index AND ▶
Optional Value	▶	Index AND ▶

**Kidney injury (adverse event), in rat (Sprague Dawley CD)**

Record ID	70213
Species	Rattus norvegicus (rat)
Strain	Sprague Dawley CD
Sex	Male; Female
Age	Not Specified

**Tam, V.H.; Ledesma, K.R.; Bowers, D.R.; Zhou, J.; Truong, L.D.**

[WEB OF SCIENCE CITING RECORDS](#) [WEB OF SCIENCE RELATED RECORDS](#) [OpenURL Full Text](#)

**Kidney injury associated with telavancin dosing regimen in an animal model**  
Antimicrob Agents Chemother 2015, 59(5): 2930

Drug Name	Exp. Pharma	Refs	Pats
<a href="#">Telavancin hydrochloride</a>	0	1	0

[View all 1 drugs tested on this model](#)

**Related Information**



# 深入挖掘靶点信息：生物标志物



Biomarkers Search Results

Query > Role = "Predicting Treatment Efficacy" AND Mechanism of Action = "Indoleamine 2,3-dioxygenase 1 (IDO1; IDO) Inhibitors"

Biomarker Name	Type	Use Indication Type and Validity							Source			
<input type="checkbox"/> <b>Apoptosis regulator BAX</b> BAX; BCL2L4; Bax Apoptosis Regulator Protein; Bax Protein	Proteomic; Genomic	Major Condition	EME	EXP	ESH	LSH	R/A	All	Ref	Pat	Kits	
		Cancer		1	1				2	2		
		All		1	1				2	2		
<input type="checkbox"/> <b>Apoptosis regulator Bcl-2</b> B-cell lymphoma protein 2 (alpha isoform); BCL2; BCL2 variant 1; Bcl-2; Bcl-2-like 12 protein	Proteomic; Genomic	Major Condition	EME	EXP	ESH	LSH	R/A	All	Ref	Pat	Kits	
		Cancer		1	1				2	2		
		All		1	1				2	2		
<input type="checkbox"/> <b>Apoptotic protease-activating factor 1</b> APAF-1; APAF-1L; APAF1; CED4; DKFZp781B1145; KIAA0413; apoptotic peptidase activating factor 1	Proteomic; Genomic	Major Condition	EME	EXP	ESH	LSH	R/A	All	Ref	Pat	Kits	
		Cancer		1					1	1		
		All		1					1	1		
<input type="checkbox"/> <b>Aquaporin-4</b> AQP4; Aquaporin type 4; HMIWC2; MGC22454; MIWC; Mercurial-insensitive water channel; WCH4	Proteomic; Genomic	Major Condition	EME	EXP	ESH	LSH	R/A	All	Ref	Pat	Kits	
		Neurological Disorders		2					2	1		
		All		2					2	1		
<input type="checkbox"/> <b>Baculoviral IAP repeat-containing protein 4</b> API3; Apoptosis inhibitor 3; BIRC4; E3 ubiquitin-protein ligase XIAP; HILP; IAP-like protein; IAP3; ILP1; Inhibitor of apoptosis protein 3; MIHA; X-Chromosome-Linked Inhibitor of Apoptosis Protein (XIAP); X-linked IAP; X-linked inhibitor of apoptosis; X-linked inhibitor of apoptosis protein; XIAP; XLP2	Proteomic; Genomic	Major Condition	EME	EXP	ESH	LSH	R/A	All	Ref	Pat	Kits	
		Cancer							-	-		
		All							-	-		
<input type="checkbox"/> <b>Bcl-2 binding component 3</b> BBC3; JFY1; PUMA; PUMA/JFY1 protein; p53 up-regulated modulator of apoptosis	Proteomic; Genomic	Major Condition										
		Cancer										
		All										
<input type="checkbox"/> <b>Bcl-2-like protein 1</b> BCL-X; BCL-XL/S; BCL2-like 1; BCL2L; BCL2L1; BCLX; Bcl-2-like 1 protein; Bcl-XL; Bcl-XS	Proteomic; Genomic	Major Condition										
		Cancer										
		All							1	1	1	
<input type="checkbox"/> <b>Cadherin-1</b> ARC-1; CAM 120/80; CD324; CDH1; CDHE; Cadherin 1; Cadherin 1, type 1, E-cadherin (epithelial); Calcium-dependent adhesion protein, epithelial; E-Cadherin; ECAD; Epithelial-cadherin; LCAM; UVO; Uvomorulin	Proteomic; Genomic	Major Condition	EME	EXP	ESH	LSH	R/A	All	Ref	Pat	Kits	
		Cancer		1					1	1		
		All		1					1	1		
<input type="checkbox"/> <b>Calcitonin receptor</b> CALCR; CRT; CTR; CTR1	Genomic	Major Condition	EME	EXP	ESH	LSH	R/A	All	Ref	Pat	Kits	
		Cancer		2					2	1		
		All		2					2	1		
<input type="checkbox"/> <b>Caspase-3</b> Apopain; CASP-3; CASP3 variant alpha; CPP-32; Caspase 3; Cysteine protease CPP32; Procaspase3; SCA-1; SREBP cleavage activity 1; Yama protein	Proteomic; Genomic	Major Condition	EME	EXP	ESH	LSH	R/A	All	Ref	Pat	Kits	
		Cancer		1	1				2	2		
		All		1	1				2	2		

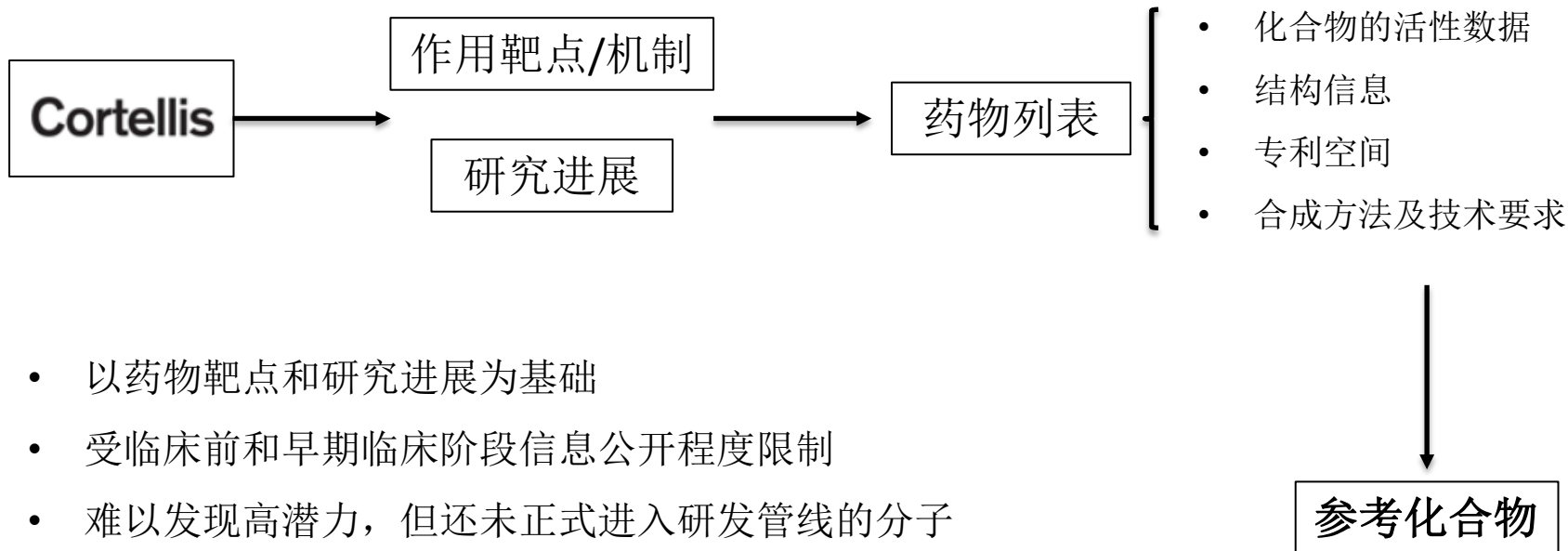
- 依照作用机制探索药效标志物，毒性标志物

- 可能用于预测IDO抑制剂药效的标志物
  - 细胞凋亡相关蛋白

# 选择参考化合物的目的

- 选取合适的化合物: 起始结构参考, 验证实验模型, 数据比较。
- 凭借已有信息证明化合物对靶点的调节, 靶点和疾病之间的关联
- 了解化合物的活性数据范围 (靶点本身对化合物活性的要求)
- 探索已知化合物的不足之处
- 额外的信息收集渠道:
  - 所属开发公司, 主要成员, 专利公开情况, 内部研发管线

# 选择参考化合物通常方法



- 以药物靶点和研究进展为基础
- 受临床前和早期临床阶段信息公开程度限制
- 难以发现高潜力，但还未正式进入研发管线的分子
- 需手工比较信息：不同专利间化合物的结构相似性和活性差异

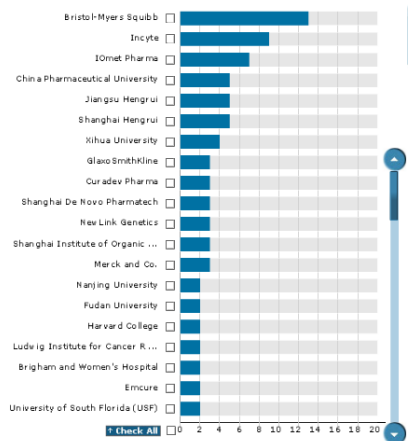
# 参考化合物的选择：从专利出发

- 检索以IDO1为靶点的化合物专利

Records Retrieved		99 in Patents		Options	
Patent Search Results					
Patents (Applicants)	Title	Subject Matter	Condition	Lead Compound	
<input type="checkbox"/> WO 2017173973 * (Peking University (PKU))	<a href="#">Nitrogen heterocyclic tryptamine ketone derivative and application as IDO1 and/or TDO inhibitor</a>	Drug Substances	Anxiety Autoimmune disease Cancer Dementia, Alzheimer's type Depression Infections	<a href="#">979038</a>	
<input type="checkbox"/> WO 2017152857 * CN 107176993 (Shanghai Institute of Organic Chemistry)	<a href="#">Indoleamine-2,3-dioxygenase inhibitor containing nitrogen substituted and arylated sulphoxide imine</a>	Drug Substances	Anxiety Autoimmune disease Cancer Cardiovascular Disorders Dementia, Alzheimer's type Eye Disorders Infection, HIV Neurodegeneration	<a href="#">976058</a>	
<input type="checkbox"/> WO 2017149468 * (Emcure Pharmaceuticals Ltd.)	<a href="#">Heterocyclic compounds useful as IDO and/or TDO modulator</a>	Drug Substances	Cancer Infection, viral Inflammation Neurodegeneration Pain Psychiatric Disorders Renal Disorders Transplant rejection	<a href="#">974268</a>	
<input type="checkbox"/> WO 2017143874 * (Shenzhen Targetrx Biotechnology Co., Ltd.)	<a href="#">Substituted oxadiazole chemical compound and composition containing said chemical compound and use thereof</a>	Drug Substances	Cancer Cardiovascular Disorders Cataract Depression Immunological Disorders Infections Inflammation Metabolic Diseases	<a href="#">974150</a>	
<input type="checkbox"/> WO 2017140272 * (Jiangsu Chia Tai Tianqing Pharmaceutical Group Co., Ltd., Medshine Discovery Inc.)	<a href="#">Triicyclic compound acting as immunomodulator</a>	Drug Substances	Immunological Disorders	<a href="#">974217</a>	
<input type="checkbox"/> WO 2017139414 * (Inventisbio Inc.)	<a href="#">Inhibitor of indoleamine-2,3-dioxygenase (IDO)</a>	Drug Substances	Cancer Infection, viral	<a href="#">972208</a>	
<input type="checkbox"/> CN 107033097 * (Jiangsu Hengrui Medicine Co., Ltd., Shanghai Hengrui Pharmaceutical Co., Ltd.)	<a href="#">Furodiazoles derivative, its preparation method and the upper application in medicine</a>	Drug Substances	AIDS Anxiety Autoimmune disease Cancer Cataract Dementia, Alzheimer's type Depression Myelodysplasia	<a href="#">978077</a>	

## Applicant/Assignee

Query definition not available for this operation.



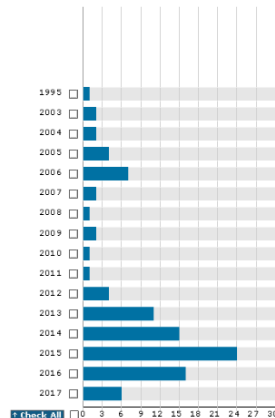
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专利申请人

- 领头企业，竞争对手
- 项目开展时间
- 确定专利分析范围

## Priority Date

Query definition not available for this operation.

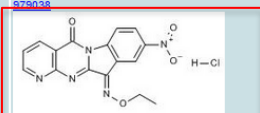
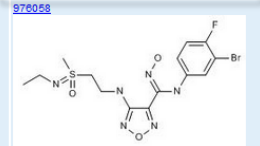
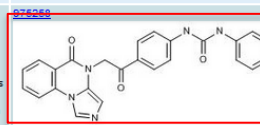
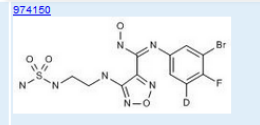
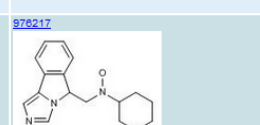
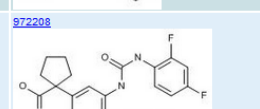


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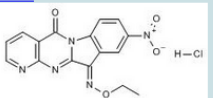
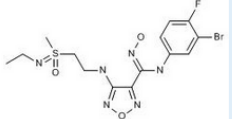
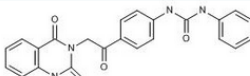
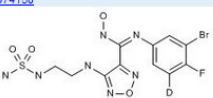
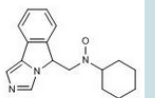
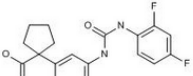
# 参考化合物的选择：典型结构

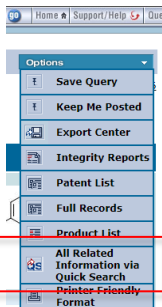


Records Retrieved 99 in Patents		Records Retrieved 99 in Patents		Options		
Patent Search Results		Patent Search Results		1 2 3 4 5 6 7 8 9 10		
Patents (Applicants)	Title	Patents (Applicants)	Title	Subject Matter	Condition	Lead Compound
<input type="checkbox"/> WO 2017173973 * (Peking University (PKU))	<a href="#">Nitrogen heterocyclic tryptamine ketone derivative and application as IDO1 and/or TDO inhibitor</a>	<input type="checkbox"/> WO 2017173973 * (Peking University (PKU))	<a href="#">Nitrogen heterocyclic tryptamine ketone derivative and application as IDO1 and/or TDO inhibitor</a>	Drug Substances	Anxiety Autoimmune disease Cancer Dementia, Alzheimer's type Depression Infections	
<input type="checkbox"/> WO 2017152857 * CN 107178933 (Shanghai Institute of Organic Chemistry)	<a href="#">Indoleamine-2,3-dioxygenase inhibitor containing nitrogen allylated and allylated sulphoxide imines</a>	<input type="checkbox"/> WO 2017152857 * CN 107178933 (Shanghai Institute of Organic Chemistry)	<a href="#">Indoleamine-2,3-dioxygenase inhibitor containing nitrogen allylated and allylated sulphoxide imines</a>	Drug Substances	Anxiety Autoimmune disease Cancer Cardiovascular Disorders Dementia, Alzheimer's type Eye Disorders Infection, HIV Neurodegeneration	
<input type="checkbox"/> WO 2017149468 * (Emcure Pharmaceuticals Ltd.)	<a href="#">Heterocyclic compounds useful as IDO and/or TDO modulators</a>	<input type="checkbox"/> WO 2017149468 * (Emcure Pharmaceuticals Ltd.)	<a href="#">Heterocyclic compounds useful as IDO and/or TDO modulators</a>	Drug Substances	Cancer Infection, viral Inflammation Neurodegeneration Pain Psychiatric Disorders Renal Disorders Transplant rejection	
<input type="checkbox"/> WO 2017143874 * (Shenzhen Targetrx Biotechnology Co., Ltd.)	<a href="#">Substituted oxadiazole chemical compound and composition containing said chemical compound and use thereof</a>	<input type="checkbox"/> WO 2017143874 * (Shenzhen Targetrx Biotechnology Co., Ltd.)	<a href="#">Substituted oxadiazole chemical compound and composition containing said chemical compound and use thereof</a>	Drug Substances	Cancer Cardiovascular Disorders Cataract Depression Immunological Disorders Infections Inflammation Metabolic Diseases	
<input type="checkbox"/> WO 2017140272 * (Jiangsu Chia Tai Tianqing Pharmaceutical Group Co., Ltd. Medshine Discovery Inc.)	<a href="#">Tryptic compound acting as immunomodulator</a>	<input type="checkbox"/> WO 2017140272 * (Jiangsu Chia Tai Tianqing Pharmaceutical Group Co., Ltd. Medshine Discovery Inc.)	<a href="#">Tryptic compound acting as immunomodulator</a>	Drug Substances	Immunological Disorders	
<input type="checkbox"/> WO 2017139414 * (Inventisbio Inc.)	<a href="#">Inhibitor of indoleamine-2,3-dioxygenase (IDO)</a>	<input type="checkbox"/> WO 2017139414 * (Inventisbio Inc.)	<a href="#">Inhibitor of indoleamine-2,3-dioxygenase (IDO)</a>	Drug Substances	Cancer Infection, viral	
<input type="checkbox"/> CN 107033097 * (Jiangsu Hengrui Medicine Co., Ltd. Shanghai Hengrui Pharmaceutical Co., Ltd.)	<a href="#">Furodiazoles derivative, its preparation method and the use application in medicine</a>					

- 通过Option选项中 patent list with structure 显示典型化合物结构
- 明确不同专利间的关联程度及参考关系
- 进一步通过其优先权和公开时间明确项目的开发顺序

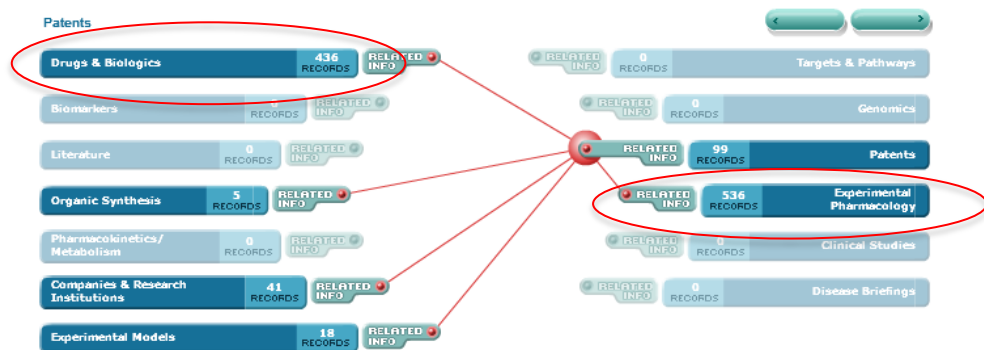
# 参考化合物的选择：由专利获取药物和活性数据

Records Retrieved		99 in Patents		Options	
Patent Search Results					
Patents (Applicants)	Title	Subject Matter	Condition	Lead Compound	
<input type="checkbox"/> WO 2017173973 (Peking University (PKU))	<a href="#">Nitrogen heterocyclic tryptamine ketone derivative and application as IDO1 and/or TDO inhibitor</a>	Drug Substances	Anxiety Autoimmune disease Cancer Dementia, Alzheimer's type Depression Infections	973038 	
<input type="checkbox"/> WO 2017152857 CN 107176933 (Shanghai Institute of Organic Chemistry)	<a href="#">Indoleamine-2,3-dioxygenase inhibitor containing nitrogen alkylated and arylated sulphoxide imines</a>	Drug Substances	Anxiety Autoimmune disease Cancer Cardiovascular Disorders Dementia, Alzheimer's type Eye Disorders Infection, HIV Neurodegeneration	974058 	
<input type="checkbox"/> WO 2017149469 (Emcure Pharmaceuticals Ltd.)	<a href="#">Heterocyclic compounds useful as IDO and/or TDO modulators</a>	Drug Substances	Cancer Infection, viral Inflammation Neurodegeneration Pain Psychiatric Disorders Renal Disorders Transplant rejection	974258 	
<input type="checkbox"/> WO 2017143874 (Shenzhen Targetx Biotechnology Co., Ltd.)	<a href="#">Substituted oxadiazole chemical compound and composition containing said chemical compound and use thereof</a>	Drug Substances	Cancer Cardiovascular Disorders Cataract Depression Immunological Disorders Infections Inflammation Metabolic Diseases	974150 	
<input type="checkbox"/> WO 2017140272 (Jiangsu Chia Tai Tianqing Pharmaceutical Group Co., Ltd. Medshine Discovery Inc.)	<a href="#">Tricyclic compound acting as immunomodulator</a>	Drug Substances	Immunological Disorders	976217 	
<input type="checkbox"/> WO 2017139414 (Inventisbio Inc.)	<a href="#">Inhibitor of indoleamine-2,3-dioxygenase (IDO)</a>	Drug Substances	Cancer Infection, viral	972208 	

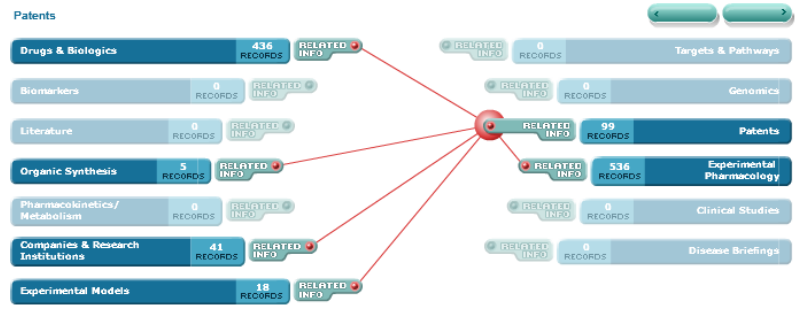


借助Integrity的关联性数据获取专利相关信息

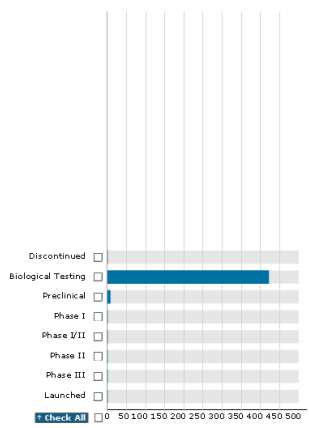
- 专利相关药物及活性分子
- 相关活性，实验模型信息



# 参考化合物的选择: 1.从研发状态出发筛选



- 从专利获取相关早期活性分子及管线药物信息



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Entry Number	Highest Phase	Code Name	Generic Name	Brand Name	Product Category	Therapeutic Group	Mechanism of Action	Organization
169220	Launched-1992	FI-7045 (free base)	Sertaconazole nitrate (Rac INNM)	Dermoflox Dermoseptic Ertacco Extens Fisdem Ginadermoflox Onabet Z-lain	Imidazoles, Antifungal Agents	Antifungal Agents	Immune Checkpoint Inhibitors Tryptophan 2,3-Dioxygenase (TDO) Inhibitors Indoleamine 2,3-dioxygenase 1 (IDO1; IDO) Inhibitors	Farrar (Originator) Valant Glenmark Pharmaceuticals Mylan
282732	Phase II	ARQ-501 CO-501 MB-12066 MB-660 NSC-26326	beta-Lapachone	R-1668	Cancer Immunotherapy	Sarcoma Therapy Antiobesity Drugs Ovarian Cancer Therapy Pancreatic Cancer Therapy Liver and Biliary Tract Disorders, Treatment of Head and Neck Cancer Therapy Solid Tumors Therapy	Immune Checkpoint Inhibitors Tryptophan 2,3-Dioxygenase (TDO) Inhibitors Indoleamine 2,3-dioxygenase 1 (IDO1; IDO) Inhibitors E2F Modulators Apoptosis Inducers DNA Topoisomerase I Inhibitors DNA Topoisomerase II Inhibitors	Beth Israel Deaconess Medical Center (Originator) Roche AstraZeneca Dana-Farber Cancer Institute (Originator) K1&S Life Sciences
686486	Phase III	INCB-024360 INCB-24360 715964SR13 (UNII code)	Epacadostat (Rec INN)		Cancer Immunotherapy	Myelodysplastic Syndrome Therapy Non-Small Cell Lung Cancer Therapy Melanoma Therapy Oncolytic Drugs Bladder Cancer Therapy Ovarian Cancer Therapy Female Reproductive System Cancer Therapy Digestive/Gastrointestinal Cancer Therapy Colorectal Cancer Therapy Renal Cancer Therapy Head and Neck Cancer Therapy	Immune Checkpoint Inhibitors Indoleamine 2,3-dioxygenase 1 (IDO1; IDO) Inhibitors	Incyte (Originator) Fox Chase Cancer Center
910778	Phase I/II	BMS-986205 ONO-7701			Cancer Immunotherapy	Non-Small Cell Lung Cancer Therapy Melanoma Therapy Oncolytic Drugs Hematological Cancer Therapy Solid Tumors Therapy	Immune Checkpoint Inhibitors Indoleamine 2,3-dioxygenase 1 (IDO1; IDO) Inhibitors	Bristol-Myers Squibb (Originator) Ono
920185	Phase I	EOS-200271 PF-06840003			Cancer Immunotherapy	Brain Cancer Therapy	Immune Checkpoint Inhibitors Indoleamine 2,3-dioxygenase 1 (IDO1; IDO) Inhibitors	Pfizer (Originator) Heska Therapeutics (Originator)

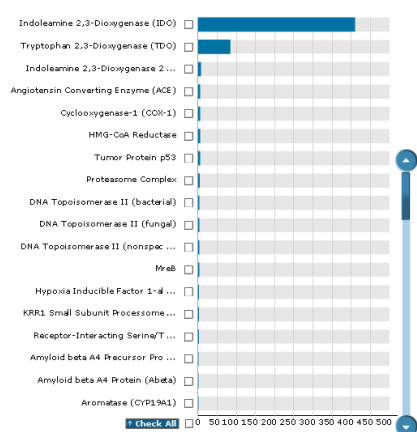


# 参考化合物的选择: 1.从研发状态出发筛选

Drugs & Biologics

## Target

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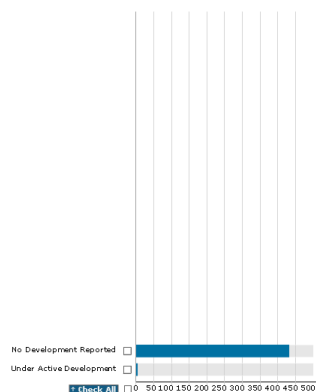


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靶点覆盖范围  
(化合物的选择性)

## Under Active Development / No Development Reported

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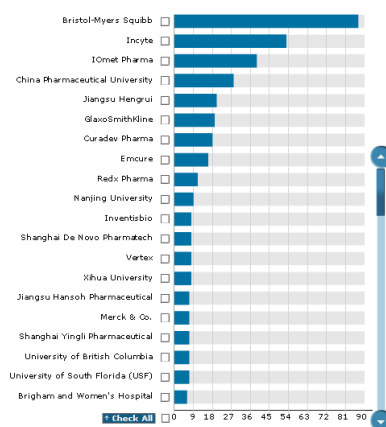


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研发活跃度

## Organization

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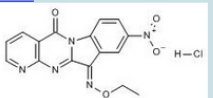
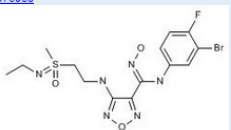
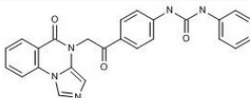
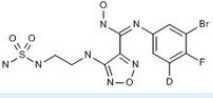
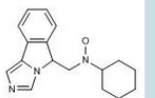
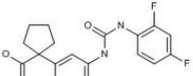


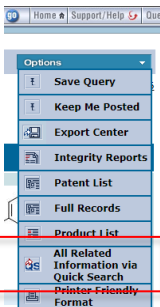
Source: Thomson Reuters Integrity  
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研发公司



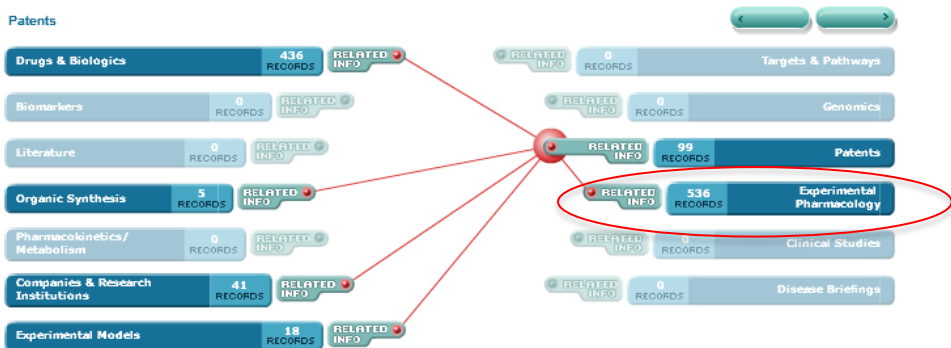
# 参考化合物的选择：2.由活性数据出发

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Patent Search Results					
Patents (Applicants)	Title	Subject Matter	Condition	Lead Compound	
<input type="checkbox"/> WO 2017173973 (Peking University (PKU))	<a href="#">Nitrogen heterocyclic tryptamine ketone derivative and application as IDO1 and/or TDO inhibitor</a>	Drug Substances	Anxiety Autoimmune disease Cancer Dementia, Alzheimer's type Depression Infections	973038 	
<input type="checkbox"/> WO 2017152857 CN 107176933 (Shanghai Institute of Organic Chemistry)	<a href="#">Indoleamine-2,3-dioxygenase inhibitor containing nitrogen alkylated and arylated sulphoxide imines</a>	Drug Substances	Anxiety Autoimmune disease Cancer Cardiovascular Disorders Dementia, Alzheimer's type Eye Disorders Infection, HIV Neurodegeneration	974058 	
<input type="checkbox"/> WO 2017149469 (Emcure Pharmaceuticals Ltd.)	<a href="#">Heterocyclic compounds useful as IDO and/or TDO modulators</a>	Drug Substances	Cancer Infection, viral Inflammation Neurodegeneration Pain Psychiatric Disorders Renal Disorders Transplant rejection	974258 	
<input type="checkbox"/> WO 2017143874 (Shenzhen Targetx Biotechnology Co., Ltd.)	<a href="#">Substituted oxadiazole chemical compound and composition containing said chemical compound and use thereof</a>	Drug Substances	Cancer Cardiovascular Disorders Cataract Depression Immunological Disorders Infections Inflammation Metabolic Diseases	974150 	
<input type="checkbox"/> WO 2017140272 (Jiangsu Chia Tai Tianqing Pharmaceutical Group Co., Ltd. Medshine Discovery Inc.)	<a href="#">Trioidic compound acting as immunomodulator</a>	Drug Substances	Immunological Disorders	976217 	
<input type="checkbox"/> WO 2017139414 (Inventisbio Inc.)	<a href="#">Inhibitor of indoleamine-2,3-dioxygenase (IDO)</a>	Drug Substances	Cancer Infection, viral	972208 	



借助Integrity的关联性数据获取专利相关信息

- 专利相关药物及活性分子
- 相关活性，实验模型信息



# 参考化合物的选择: 2.从活性数据出发



测试方法

已知化合物的活性范围

- 了解关键筛选实验
- 了解已知化合物分子的活性分布情况
- 明确化合物活性标准

# 参考化合物： 候选参考化合物










## Options: 选则 structure activity

Records Retrieved 3 in Experimental Pharmacology

Experimental Pharmacology Search Results

Pharmacological Activity: Indoleamine 2,3-Dioxygenase (IDO) inhibition, IN VITRO

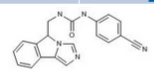
Parameter: IC50

Drug Name & Structure	Mechanism of Action	Material	Method	Value	Details
 851149	Immune Checkpoint inhibitors Indoleamine 2,3-dioxygenase (IDO1; IDO) inhibitors	HeLa human cervix papocarcinoma cells (interferon gamma-stimulated)	Kyrenine formation assay	↔ 0.100 μM	Pat. 1
 851151	Immune Checkpoint inhibitors Indoleamine 2,3-dioxygenase (IDO1; IDO) inhibitors	HeLa human cervix papocarcinoma cells (interferon gamma-stimulated)	Kyrenine formation assay	↔ 0.100 μM	Pat. 1
 851152	Immune Checkpoint inhibitors Indoleamine 2,3-dioxygenase 1 (IDO1; IDO) inhibitors	HeLa human cervix papocarcinoma cells (interferon gamma-stimulated)	Kyrenine formation assay	↔ 0.100 μM	Pat. 1
 851153	Immune Checkpoint inhibitors Indoleamine 2,3-dioxygenase 1 (IDO1; IDO) inhibitors	HeLa human cervix papocarcinoma cells (interferon gamma-stimulated)	Kyrenine formation assay	↔ 0.100 μM	Pat. 1
 851154	Immune Checkpoint inhibitors Indoleamine 2,3-dioxygenase (IDO1; IDO) inhibitors	HeLa human cervix papocarcinoma cells (interferon gamma-stimulated)	Kyrenine formation assay	↔ 0.100 μM	Pat. 1
 851155	Immune Checkpoint inhibitors Indoleamine 2,3-dioxygenase 1 (IDO1; IDO) inhibitors	HeLa human cervix papocarcinoma cells (interferon gamma-stimulated)	Kyrenine formation assay	↔ 0.100 μM	Pat. 1
 851157	Immune Checkpoint inhibitors Indoleamine 2,3-dioxygenase (IDO1; IDO) inhibitors	HeLa human cervix papocarcinoma cells (interferon gamma-stimulated)	Kyrenine formation assay	↔ 0.100 μM	Pat. 1
 851158	Immune Checkpoint inhibitors Indoleamine 2,3-dioxygenase (IDO1; IDO) inhibitors	HeLa human cervix papocarcinoma cells (interferon gamma-stimulated)	Kyrenine formation assay	↔ 0.100 μM	Pat. 1
 931654	Immune Checkpoint inhibitors Tryptophan 2,3-Dioxygenase (TDO) inhibitors Indoleamine 2,3-dioxygenase 1 (IDO1; IDO) inhibitors	HeLa human cervix papocarcinoma cells (interferon gamma-stimulated)	Kyrenine formation assay	↔ 0.100 μM	Pat. 2

Records Retrieved 1 in Drugs & Biologics

Drugs & Biologics Search Results

Entry Number: 931654

Chemical Structure: 

Record Creation Date: Sep 01, 2016

Molecular Formula: C19 H15 N5 O

Molecular Weight: 329.3553

Highest Phase: Biological Testing

Chemical Name/Description: (-)-N-(4-Cyanophenyl)-N'-[[5H-imidazo[5,1-e]sindol-5-yl)methyl]urea

Standard InChI: 1S/C19H15N5O/c20-9-13-5-7-14(8-6)12-19(20)10-11-15-16-4-2-1-3-15(16)17-19-21-12-24(17)18h1-8,10,12,18m,11h2 (H2,22,23,25)

Standard InChIKey: UXLPCQZDQWIMLN-UHFFFAQYSA-N

Code Name:

Generic Name:

Brand Name:

Molecular Mechanism: Tryptophan 2,3-Dioxygenase (TDO) Inhibitors

Cellular Mechanism: Immune Checkpoint Inhibitors

Indoleamine 2,3-dioxygenase 1 (IDO1; IDO) Inhibitors

Product Category: Therapeutic Group: Oncolytic Drugs, Antiviral Drugs, Prescription Indication Type: Treatment of Autoimmune Diseases

Cancer Immunotherapy

Organization: Shanghai De Nove Pharmaceutical (Originator)

Product Summary:

Related Information:

Drugs & Biologics: 2

Targets & Pathways: 2

Literature: 2

Patents: 2

Experimental Pharmacology: 7

Comparisons & Research Institutions: 7

Check All This Page / Reset All This Page

Check All Results / Reset All Results

- 高活性分子分别从属于2篇专利
- 针对候选参考化合物专利细致分析

# 参考化合物：公司信息

Companies & Research Institutions



## Companies & Research Institutions Search Results

Organization		Vertex	
Main Activity	Headquarters	<a href="http://www.vrtx.com">www.vrtx.com</a>	
Biotechnology	Cambridge, MA (US)	Fiscal Year Ends	Dec 31
Therapeutic Areas		Fiscal Year 2013	none
Specialty pharmaceuticals		Annual Revenues (M)	USD 1212
		Annual Sales (M)	USD 838
		R&D Investment (M)	USD 919
		R&D (% of Sales)	109.7
		Employees	1800
Marketed Products			
<a href="#">Fosamprenavir calcium</a>	Lexiva (BN)	Launched - 2003	Infection, HIV
<a href="#">Ivacaftor</a>	Kalydeco (BN)	Launched - 2012	Fibrosis, cystic <span>SALES</span>
<a href="#">Lumacaftor/ivacaftor</a>	Orkambi (BN)	Launched - 2015	Fibrosis, cystic
<a href="#">Telaprevir</a>	Incivek (BN)	Launched - 2011	Hepatitis C (HCV) <span>SALES</span>
Clinical Trials and Preclinical Research			
<span>none</span>			
<a href="#">BA-210</a>	Phase II/III	Injury, spinal cord	
<a href="#">Ivacaftor</a>	Pre-Registered - 2015	Fibrosis, cystic	
<a href="#">Ivacaftor</a>	Registered - 2015	Fibrosis, cystic	
<a href="#">Ivacaftor</a>	Phase III	Fibrosis, cystic	
<a href="#">Lumacaftor</a>	Phase III	Fibrosis, cystic	
<a href="#">Lumacaftor/ivacaftor</a>	Pre-Registered	Fibrosis, cystic	
<a href="#">Lumacaftor/ivacaftor</a>	Phase III	Fibrosis, cystic	
<a href="#">Tezacaftor</a>	Phase III	Fibrosis, cystic	
<a href="#">Tezacaftor/ivacaftor</a>	Phase III	Fibrosis, cystic	
<a href="#">Tezacaftor/ivacaftor</a>	Pre-Registered	Fibrosis, cystic	
Recent Patents			
<a href="#">DNA-PK inhibitors</a>	Cancer		
<a href="#">Mannose derivatives for treating bacterial infections</a>	Inflammatory bowel disease Infection, urinary tract		
<a href="#">Modulators of cystic fibrosis transmembrane conductance regulator</a>	Pain		
<a href="#">Pyrrolopyrrolidine-spirocyclic piperidine amides as modulators of ion channels</a>	Pain		
<a href="#">Pharmaceutical composition and administrations thereof</a>	Fibrosis, cystic Chronic obstructive pulmonary disease (COPD) Osteoporosis Dry eye		
<a href="#">Method for treating cancer using a combination of DNA damaging agents and ATR inhibitors</a>	Cancer		
<a href="#">Pyridone amides as modulators of sodium channels</a>	Pain		
<a href="#">Prodrugs of pyridone amides useful as modulators of sodium channels</a>	Pain		
<a href="#">DNA-PK inhibitors</a>	Cancer		
<a href="#">Heteroaryl derivatives as CFTR modulators</a>	Fibrosis, cystic		
Related Information			
Drugs & Biologics	2686	Patents	675
		Literature	85

WE ARE VERTEX

## Board of Directors

Our Board has been a source of stability and experience that has helped guide and direct Vertex's growth from a small research startup to a global S&P 500 company that launched three breakthrough medicines in five years.

Over time, the Board has evolved to meet Vertex's needs and help the company fulfill its mission. The Board's role in helping Vertex successfully transition into a sustainably profitable company with serious diseases.

**Jeffrey Leiden, M.D., Ph.D.**  
Chairman, President and CEO  
Dr. Leiden is the Chairman, President and Chief Executive Officer of Vertex Pharmaceuticals since 2009. Dr. Leiden has more than 20 years of pharmaceutical and biotechnology industry as well as clinical molecular biologist. Read more.

**Sangeeta N. Bhatia, M.D., Ph.D.**  
Dr. Bhatia joined the Vertex Board in June 2015. She currently is the Massachusetts Institute of Technology's (MIT) Institute for Data, Systems and Applications in Computer Science (IECS), where she has worked since 2005.

VERTEX < PIPELINE & MEDICINES

## Research and Pipeline

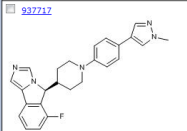
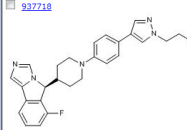
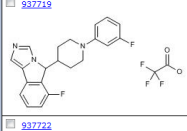
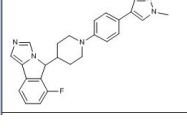
Vertex is focused on discovering, developing and commercializing innovative medicines so people with serious diseases can lead better lives. Our scientists don't see the impossible as an obstacle; they see it as a good place to start.

*These studies are investigating treatments or outcomes that have not received approval from a Health Authority. The information presented is not intended to convey conclusions of safety.*

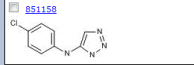
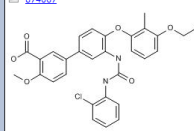
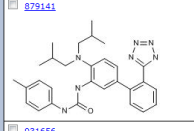
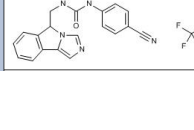
- 获取所属公司的研发概况（管线，专利）
- 公司网站提供的项目相关信息（会议海报，文献）
- 了解公司成员：额外的信息搜索参考

# 参考化合物：专利典型分子的SAR分析

- 如果不限活性范围：即可进行SAR分析

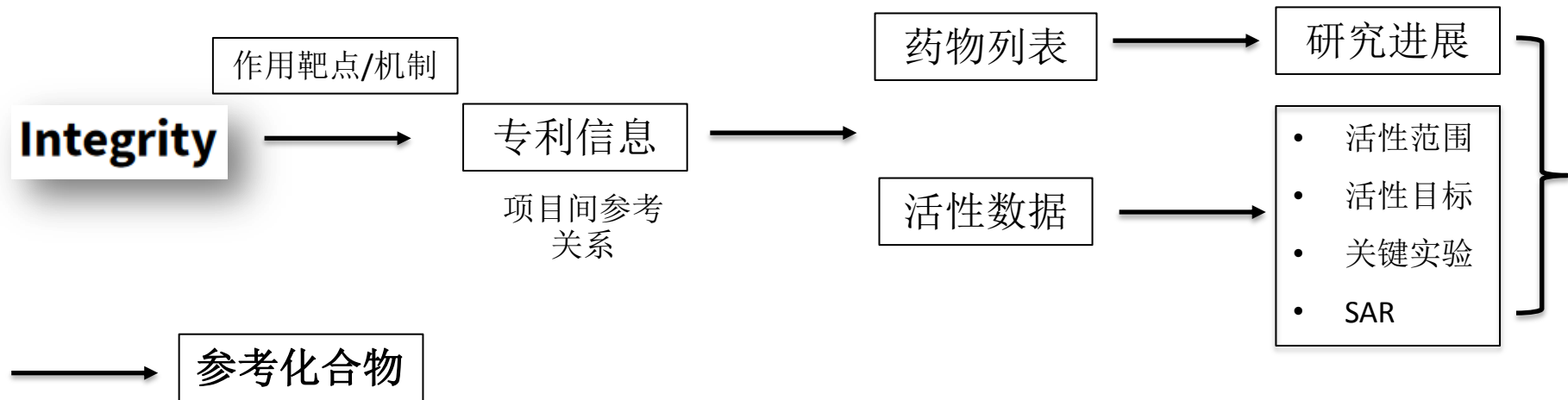
	Immune Checkpoint Inhibitors Tryptophan 2,3-Dioxygenase (TDO) inhibitors Indoleamine 2,3-dioxygenase 1 (IDO1, IDO) inhibitors	HeLa human cervix adenocarcinoma cells (interferon gamma-stimulated)	L-Tryptophan as substrate	85.2 nM	<a href="#">Pat. 15</a>
	Immune Checkpoint Inhibitors Tryptophan 2,3-Dioxygenase (TDO) inhibitors Indoleamine 2,3-dioxygenase 1 (IDO1, IDO) inhibitors	HeLa human cervix adenocarcinoma cells (interferon gamma-stimulated)	L-Tryptophan as substrate	47.7 nM	<a href="#">Pat. 15</a>
	Immune Checkpoint Inhibitors Tryptophan 2,3-Dioxygenase (TDO) inhibitors Indoleamine 2,3-dioxygenase 1 (IDO1, IDO) inhibitors	HeLa human cervix adenocarcinoma cells (interferon gamma-stimulated)	L-Tryptophan as substrate	0.167 μM	<a href="#">Pat. 15</a>
	Immune Checkpoint Inhibitors Tryptophan 2,3-Dioxygenase (TDO) inhibitors Indoleamine 2,3-dioxygenase 1 (IDO1, IDO) inhibitors	HeLa human cervix adenocarcinoma cells (interferon gamma-stimulated)	L-Tryptophan as substrate	0.101 μM	<a href="#">Pat. 15</a>

- 同一专利内：  
比较不同取代的影响

	Immune Checkpoint Inhibitors Indoleamine 2,3-dioxygenase 1 (IDO1, IDO) inhibitors	HeLa human cervix adenocarcinoma cells (interferon gamma-stimulated)	Kynurenine formation assay	≈ 0.100 μM	<a href="#">Pat. 6</a>
	Immune Checkpoint Inhibitors Indoleamine 2,3-dioxygenase 1 (IDO1, IDO) inhibitors	HeLa human cervix adenocarcinoma cells (interferon gamma-stimulated)	Kynurenine formation assay	20 nM	<a href="#">Pat. 7</a>
	Immune Checkpoint Inhibitors Indoleamine 2,3-dioxygenase 1 (IDO1, IDO) inhibitors	HeLa human cervix adenocarcinoma cells (interferon gamma-stimulated)	Kynurenine formation assay	1.30 nM	<a href="#">Pat. 8</a>
	Immune Checkpoint Inhibitors Indoleamine 2,3-dioxygenase 1 (IDO1, IDO) inhibitors	HeLa human cervix adenocarcinoma cells (interferon gamma-stimulated)	Kynurenine formation assay	0.100 - 0.500 μM	<a href="#">Pat. 5</a>

- 不同专利之间：  
比较不同母核结构的修饰空间

# 用Integrity选择候选参考化合物



- 了解现有分子活性范围，评估项目可行性，及明确差异化目标
- 探索高潜力分子，持续跟踪信息，确定竞争地位
- 快捷进行专利结构及活性比较，SAR分析比较

# 总结



# 常见问题1

Q: 针对某一适应症，检索处于临床二期研究的药物，用phase标签和highest phase标签检索，检索数量为什么不同？

A: Phase指代的是化合物对应任一适应症的研发状态，由于一个化合物可能针对多个适应症在不同地区进行开发，因此一个化合物会有多条不同的记录。

Highest Phase是指化合物的最高开发状态，每个化合物只有一条记录。

Drugs & Biologics Search Results

1 2 3 4 5 6 7 8 9 10 [Next>] [Last>>]

Query > Phase = "Phase II"

Entry Number	Main Name	Mechanism of Action	Organization	Condition	Phase	Country/Area	Admin. Route	Formulation
<input type="checkbox"/> <a href="#">070003</a>	Methylprednisolone		<a href="#">Vilnius University</a>	Leukemia, chronic lymphocytic	Phase II			
<input type="checkbox"/> <a href="#">070005</a> *	Metronidazole	Cytochrome P450 CYP1A2 Inhibitors	Institute for Drug Research	Conjunctivitis, infective	Phase II	United States		
<input type="checkbox"/> <a href="#">070005</a> *	Metronidazole	Cytochrome P450 CYP1A2 Inhibitors	<a href="#">National Institute Allergy Infect Dis</a>	Tuberculosis, multidrug resistant (MDR-TB)	Phase II	Korea, Republic of		





Q: 药物检索结果的过滤标签中的, Major therapeutic group和 therapeutic group, Major condition group和condition的区别?

A: Major therapeutic group对应的是药物的大治疗分类, 例如, 肿瘤用药, 神经类药物, therapeutic group是进一步的细分类别, 如治疗HIV药物, 其Major therapeutic group 是抗感染用药, therapeutic group 是抗HIV类药物。

Major condition group是对应疾病的分类, 同样Major condition group是上层概念, 如肿瘤, 心血管疾病; condition是细分的适应症, 如NSCLC, 高血脂症等

Table 1: definitions for the development phase terminology in Integrity

Development phase	Definition
Biological Testing	Products from patents are entered into this phase. Synthesis and preliminary pharmacology (in vitro testing) data may be available.
Preclinical	In-vivo testing; testing in animals has started.
IND Filed	Application has been filed with the competent authority requesting permission to test the drug in humans (IND - Investigational New Drug Application in US).
Clinical	Used when it is known that the drug is in clinical testing, but the exact phase is not known.
Phase 0	FDA approved studies that tests small quantities of experimental drugs on humans.
Phase I	Initial studies to determine the metabolism and pharmacologic actions of drugs in humans, the side effects associated with increasing doses, and to gain early evidence of effectiveness have started; usually conducted in healthy volunteers.
Phase I/II	Studies that combine certain aspects of phase I trials and phase II trials (e.g., a safety study in patients).
Phase II	Controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks.
Phase II/III	Studies that combine certain aspects of phase II trials and phase III trials.
Phase III	Expanded controlled and uncontrolled trials initiated after preliminary evidence suggesting effectiveness of the drug has been obtained. These are intended to gather additional information to evaluate the overall relationship of the drug and provide an adequate basis for physician labeling benefit-risk.
Pre-registered	Application to market the drug (e.g., New Drug Application or Marketing Authorisation Application) has been filed.
Recommended Approval	Approval of the drug has been recommended by the corresponding FDA Advisory Committee or a Positive Opinion has been issued by the CHMP.
Registered	The competent regulatory authority has approved the marketing, but the drug is not yet available on the market.
Launched	The drug is being marketed.
Discontinued	Development of the product has stopped before a registration application has been submitted.
Suspended	The product is stopped when undergoing regulatory review.
Withdrawn	The product is withdrawn from the market after launch.
Undetermined	Development status is unknown.
Not Applicable	A preparation or extract that is under study as a drug, but is already available on the market as an unregulated product.

**Getting Started**

- Frequently Asked Questions
  - English
  - Japanese
  - Biomarkers - English
  - Biomarkers - Japanese
- Learning Center
  - Live Training
  - Recorded Training
  - Quick Guides

Q: 研发状态具体的定义标准? Under active development 和no development reported是什么概念?

A: 研发状态的定义可在数据库主页的常见问题有详细的描述。

Under active development: 化合物处于临床前及更高阶段, 在过去的12-18个月内所属公司积极主动通过文献, 会议, 临床, 公司管线等信息披露化合物的研究进展。

no development reported: 在过去的18个月中通过公开的渠道未能发现任何关于该化合物的信息更新; 但不代表研发终止。

# 全方位售后服务

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- **可访问科睿唯安在线学院**：<http://clarivate.com.cn/e-Clarivate/>
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- **官方微信 扫描二维码 或搜索“科睿唯安 生命科学与制药”**

# 感谢参加本次会议！

