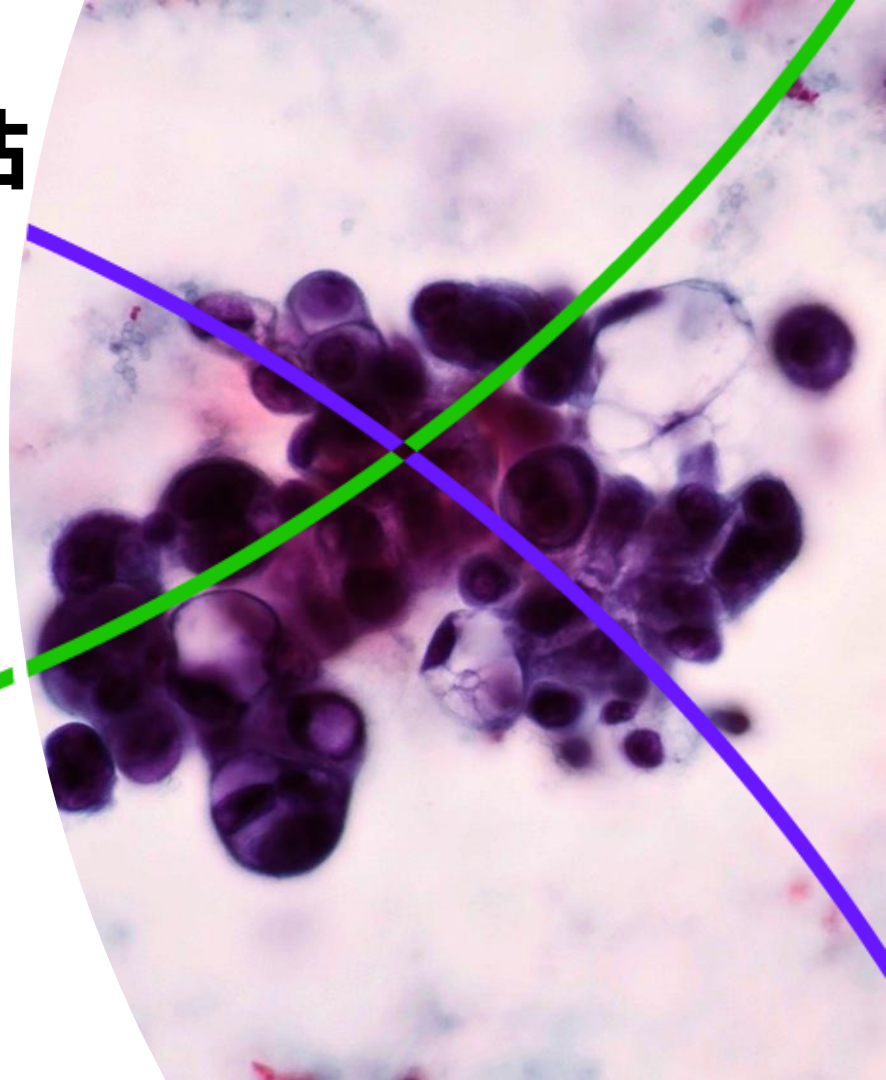
活用数据库，完善靶点评估

藏 捷

科睿唯安 Clarivate Analytics

2017年11月2日



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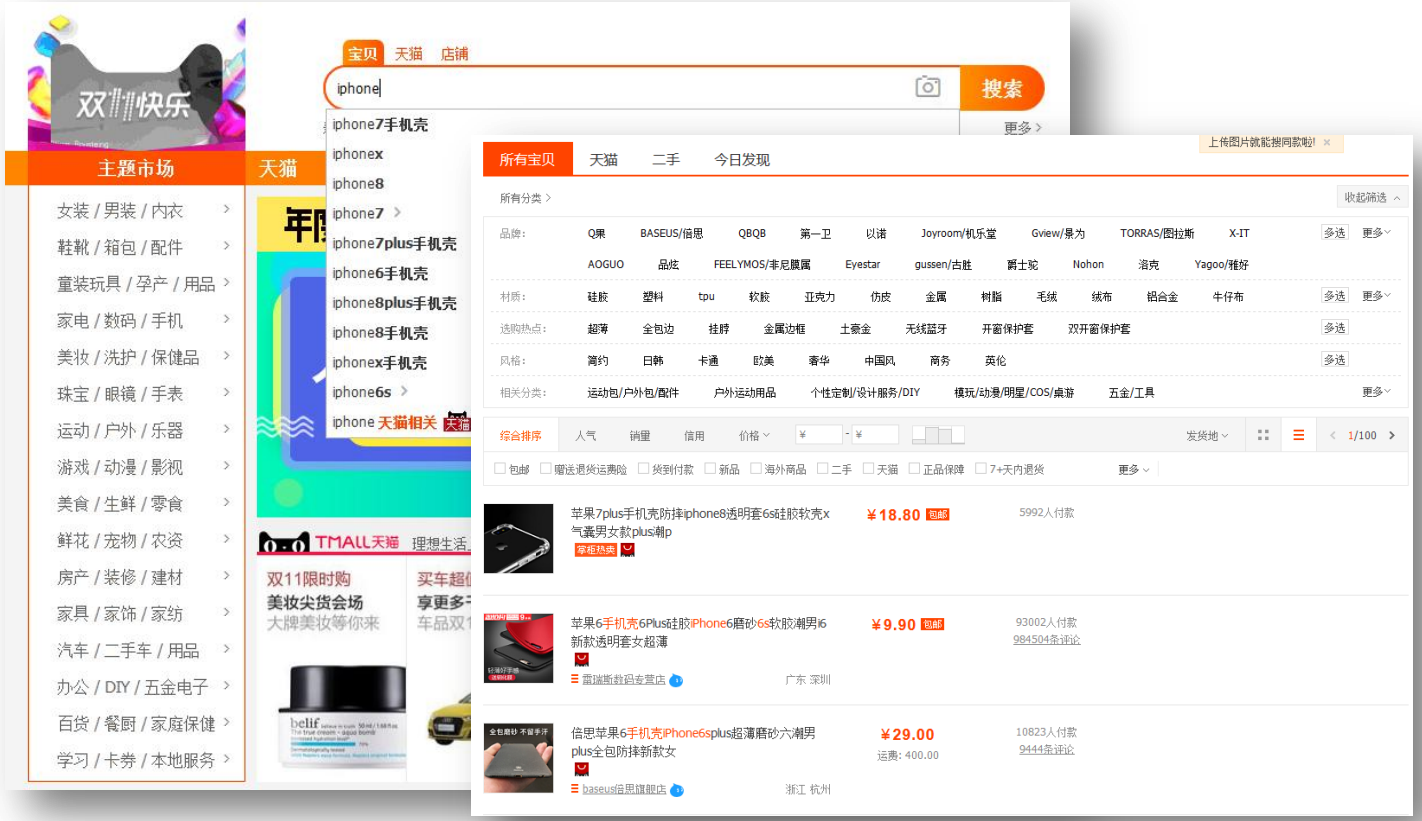
Analytics

优质的数据库是如何炼成的？



数据库标准：

- 可靠来源
- 收录标准
- 索引关联
- 易用程度
- <u>有效信息检索</u>

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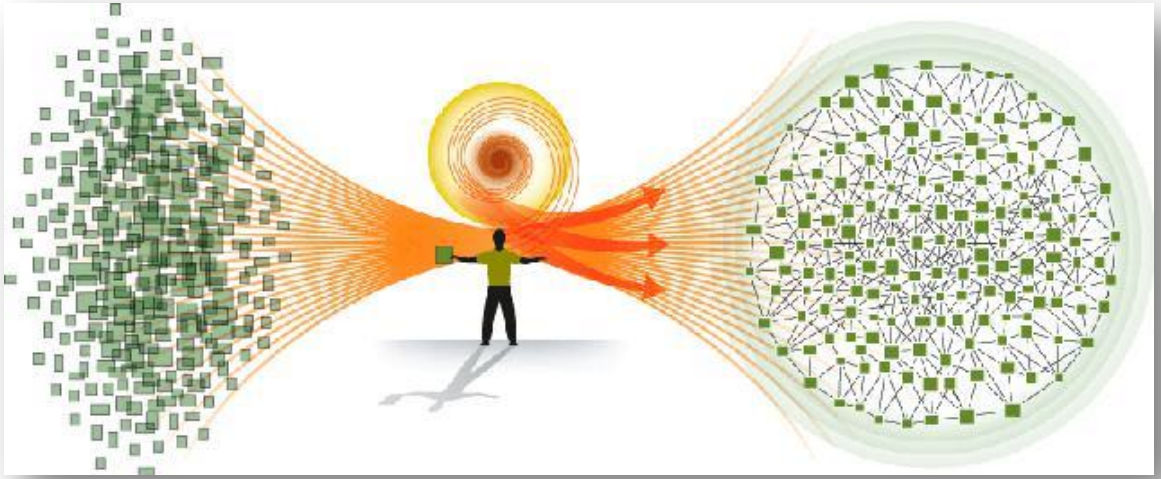
实验未动，数据先行



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- 生物标志物与临床研究
- 运用多个数据库，完成系统立项

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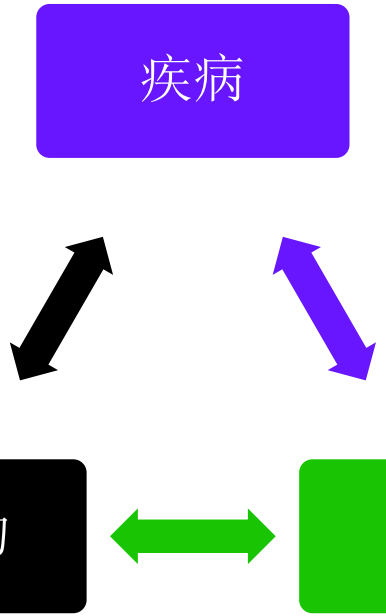
活用数据库，完善靶点评估

- 如何从研发的角度，对疾病，靶点，化合物进行评估？



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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

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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？

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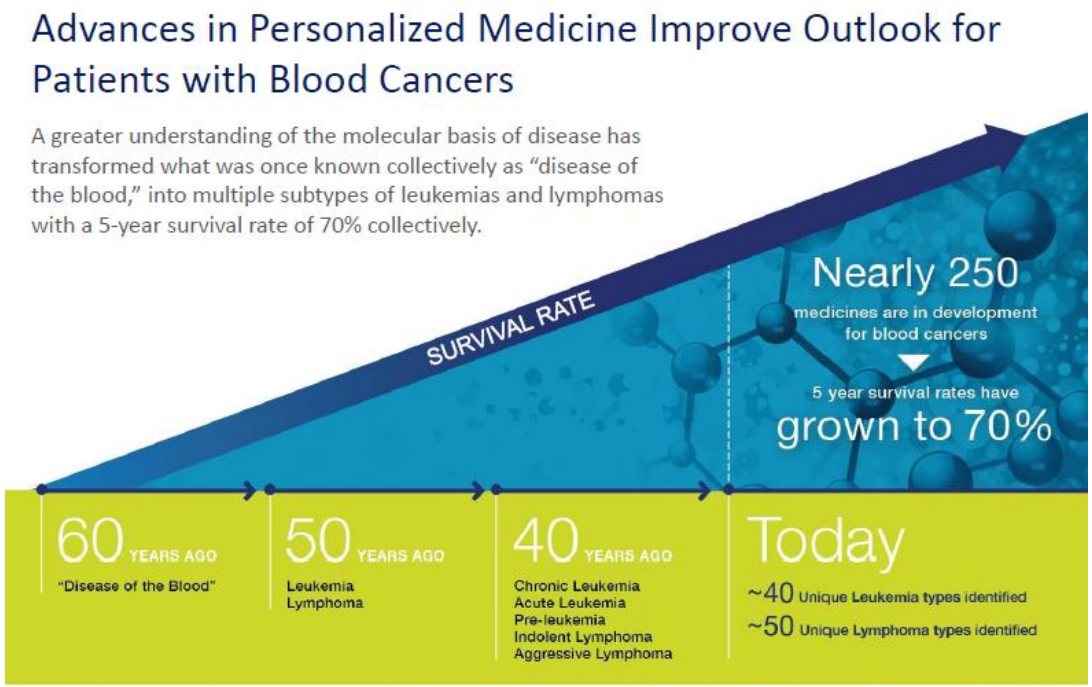
“精准医疗” 带来的挑战



Source: M Aspinal, former President Genzyme Genetics (cited at http://www.comtecmed.com/biomarker/2014/Uploads/Editor/PDF/ppt/Edward%20Abrahams_Key%20Note%20Lecture.pdf); National Cancer Institute,; SEER Cancer Statistics Review, 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

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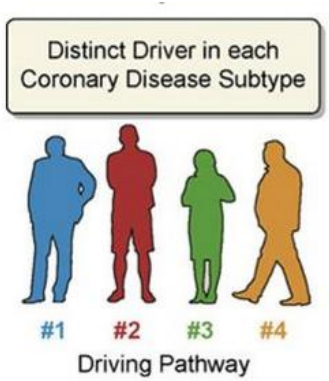
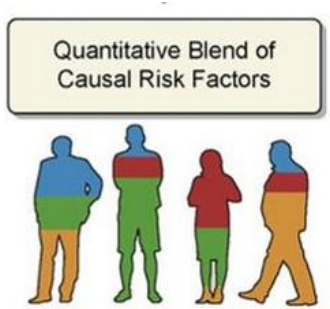
“精准医疗”：两种观点

- “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





Circulation 2017 135:1005

- 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

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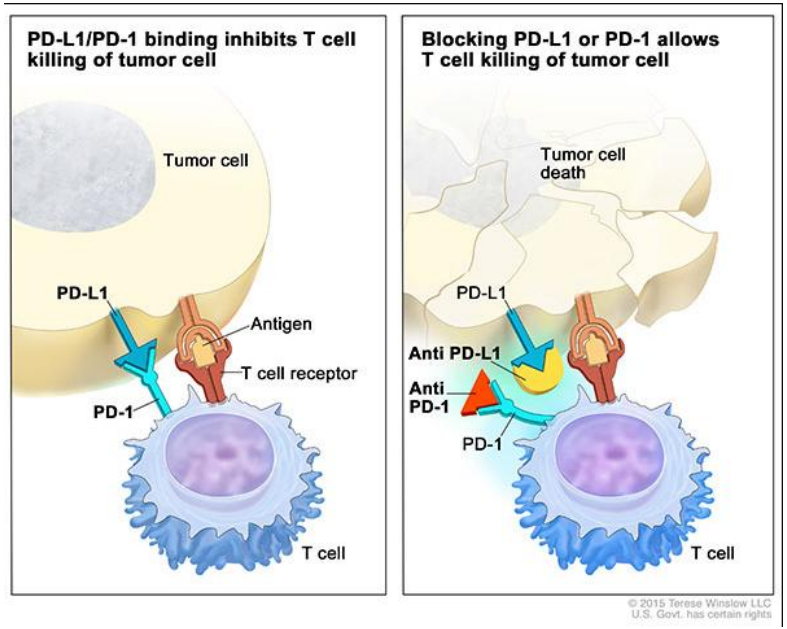
“精准医疗”：两种观点，两种方向

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

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明辨疾病格局，换个角度看疾病

Disease Briefings

- 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

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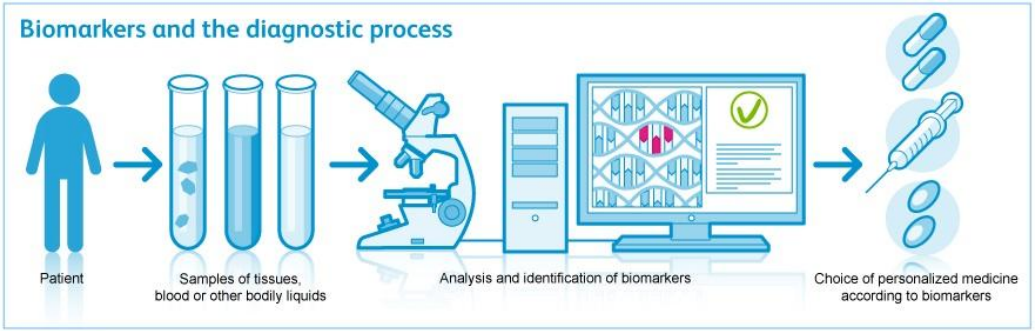
Source：Clarivate Analytics Integrity

生物标志物的定义和特点

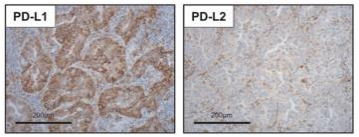
Biomarker：能够客观测定和评价正常生理过程，病理过程，或治疗药理过程的某种特征性的生物指标。

- 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

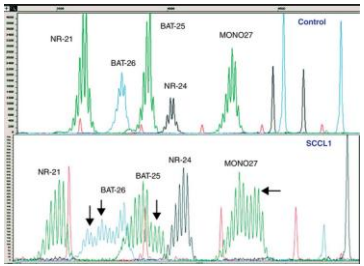


Pfizer Website： “personalized_med”

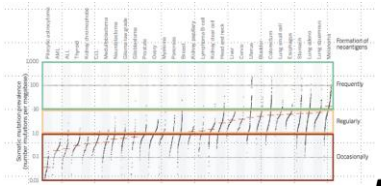
Schumacher and Schreiber, Science, 2015; 348(6230): 69-74.



Protein



Genome



Tumor

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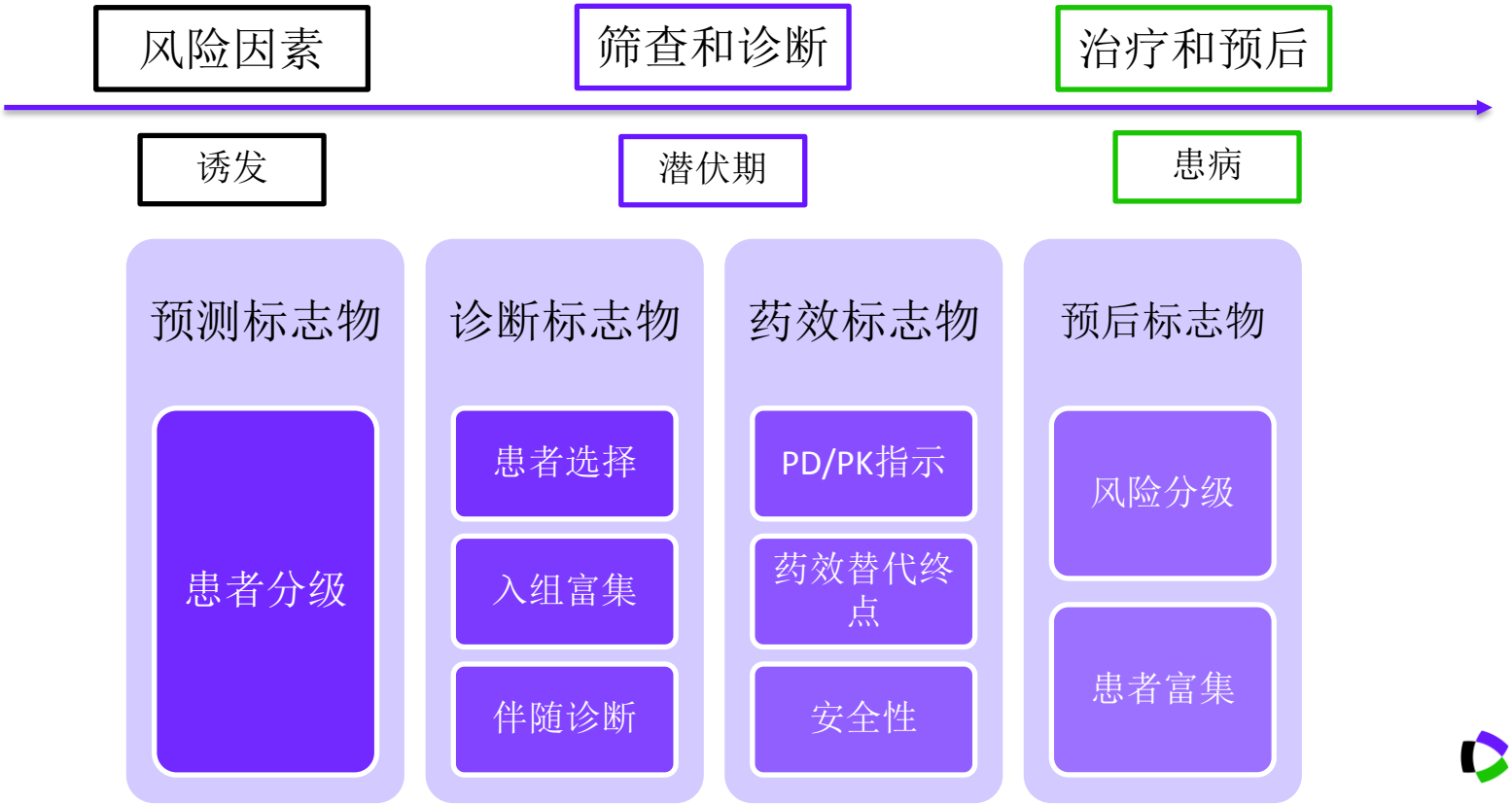
生物标志物的分类



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生物标志物的关键信息

生物标志物的验证程度

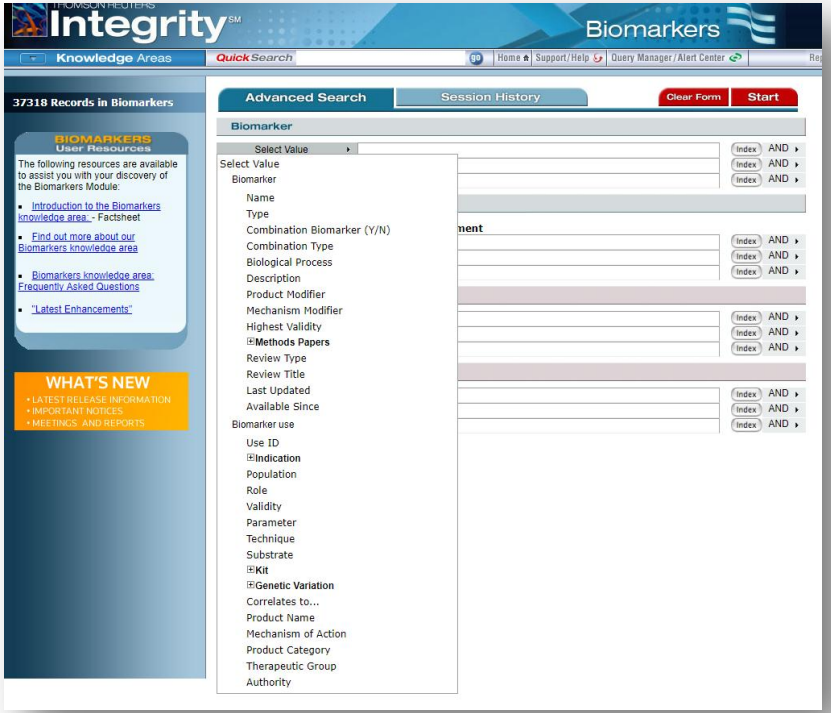
- 需经历早期概念，实验验证，人体验证及推荐批准

生物标志物的用途

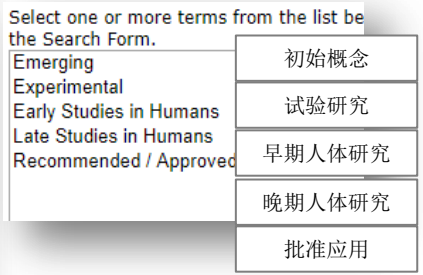
- 疾病认识：正常和疾病状态下的生理活动差异
- 疾病诊断，预后：反映疾病存在与否，严重程度
- 疾病治疗：反映药效和毒性作用
  - 明确药物作用机制，代谢特征；提早预测不良反应
  - 调整给药方案和剂量；减少过度医疗

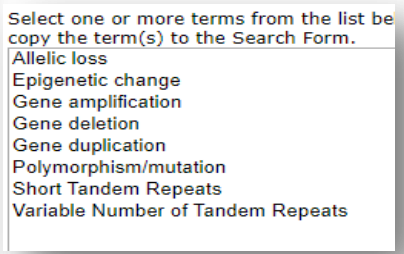
需一并考虑

Integrity生物标志物模块



标志物研究进展





Biomarker涉及的基因异常

标志物用途

- 全面获取疾病，药物相关的标志物信息

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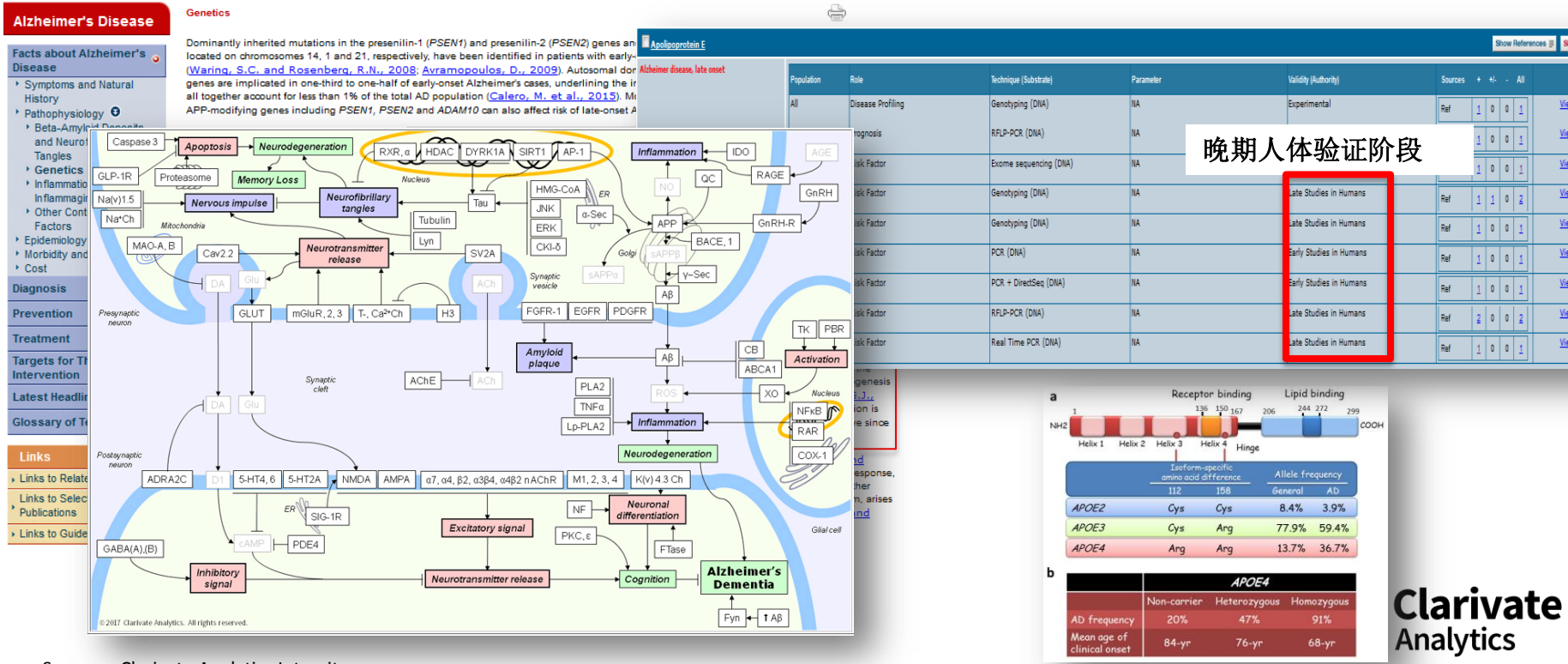
借助Biomarker发现高风险群体

在阿尔兹海默疾病中，*APOE* ε4 是一个高风险因子

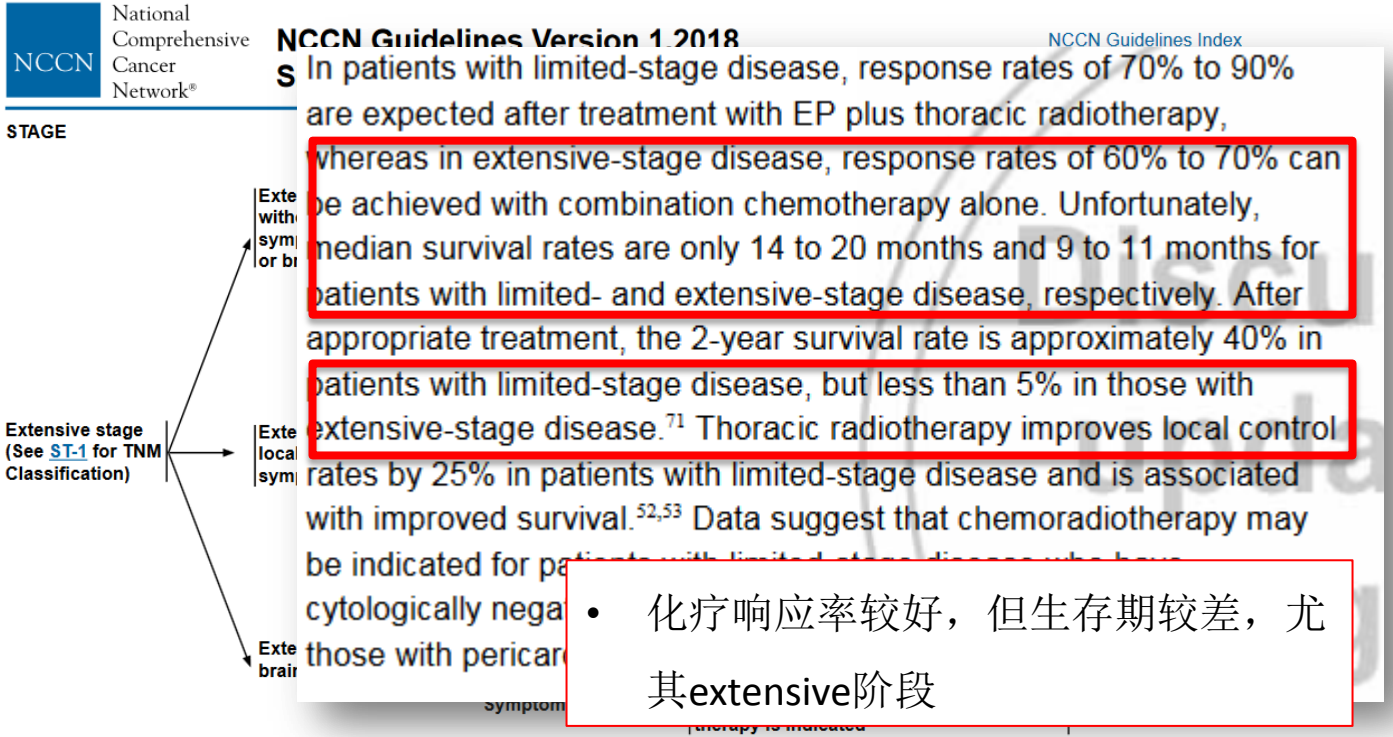


Source：Clarivate Analytics Integrity

Clarivate Analytics

临床治疗指南

以小细胞肺癌“Small cell lung cancer”为例：



- 诊断分析
- 患者分级
- 治疗路径
- 药物定位
- 预后信息

Small Cell Lung Cancer Version 1.2018 — September 18, 2017 NCCN.org

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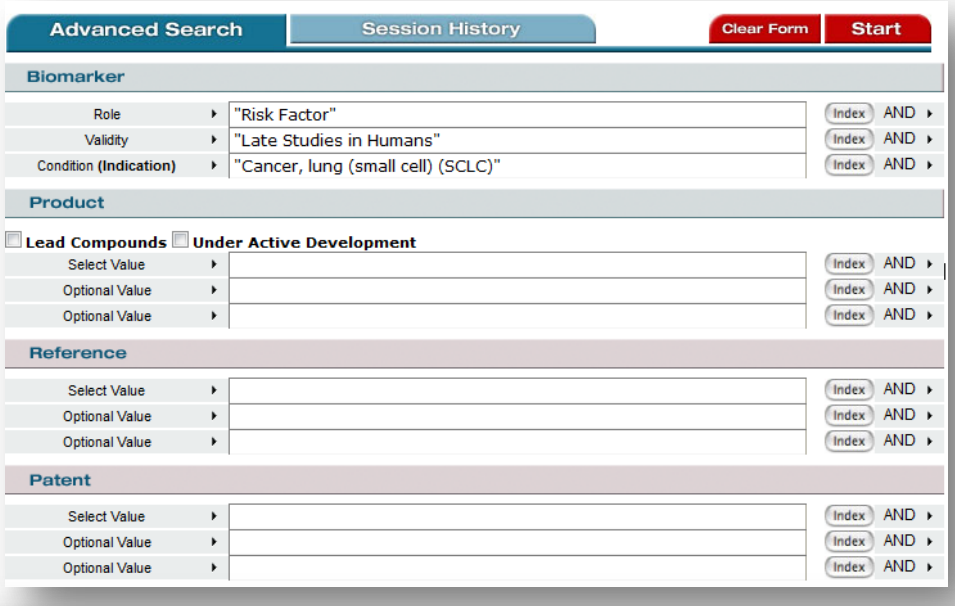
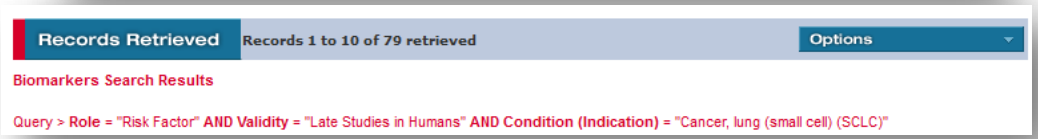
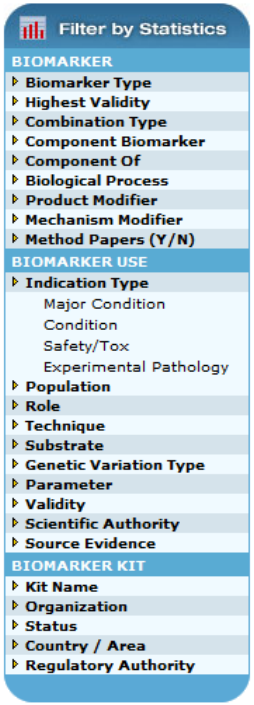
借助Biomarker发现目标患者群体

- 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”







过滤标签

基因扩增

文献支持

借助Biomarker发现目标患者群体

结果从79个缩减为3个

Biomarker Name	Ty
DNA topoisomerase 2-alpha 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
L-myc-1 proto-oncogene protein 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
Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha isoform 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[1], Kenmotsu H[2], Serizawa M[3], Koh Y[3], Isaka M[4], Takahashi S[4], Ono A[5], Taira T[5], Naito T[5], Murakami H[5], Mori K[6], Endo M[7], Nakajima T[8], Ohde Y[4], Takahashi T[5], Yamamoto N[9].

⊕ 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.

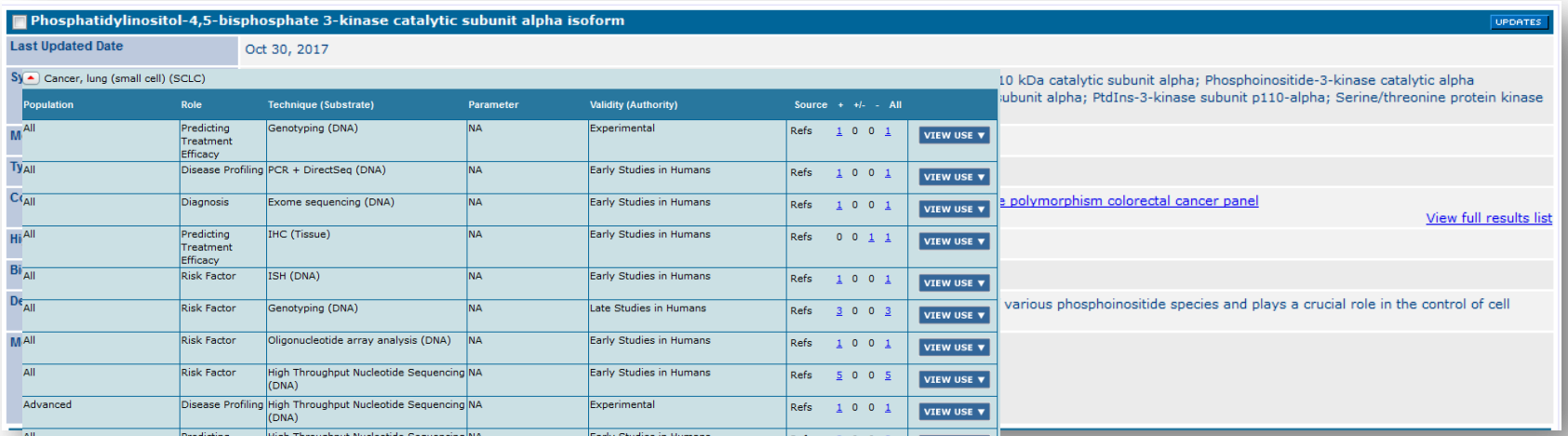
MATERIALS AND METHODS: We collected samples of SCLC from a biobank system and analyzed their molecular profiles. We assessed 23 mutations in nine genes (EGFR, KRAS, BRAF, PIK3CA, NRAS, MEK1, AKT1, PTEN, and HER2) using pyrosequencing plus capillary electrophoresis. We also amplified EGFR, MET, PIK3CA, 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.

Analytics

Biomarker的详细信息



Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha isoform

UPDATES

Last Updated Date: Oct 30, 2017

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

e polymorphism colorectal cancer panel

View full results list

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

Population	Role	Technique (Substrate)	Parameter	Validity (Authority)	Source	+	+/-	-	All	
All	Predicting Treatment Efficacy	Genotyping (DNA)	NA	Experimental	Refs	1	0	0	1	VIEW USE
All	Disease Profiling	PCR + DirectSeq (DNA)	NA	Early Studies in Humans	Refs	1	0	0	1	VIEW USE
All	Diagnosis	Exome sequencing (DNA)	NA	Early Studies in Humans	Refs	1	0	0	1	VIEW USE
All	Predicting Treatment Efficacy	IHC (Tissue)	NA	Early Studies in Humans	Refs	0	0	1	1	VIEW USE
All	Risk Factor	ISH (DNA)	NA	Early Studies in Humans	Refs	1	0	0	1	VIEW USE
All	Risk Factor	Genotyping (DNA)	NA	Late Studies in Humans	Refs	3	0	0	3	VIEW USE
All	Risk Factor	Oligonucleotide array analysis (DNA)	NA	Early Studies in Humans	Refs	1	0	0	1	VIEW USE
All	Risk Factor	High Throughput Nucleotide Sequencing (DNA)	NA	Early Studies in Humans	Refs	5	0	0	5	VIEW USE
Advanced	Disease Profiling	High Throughput Nucleotide Sequencing (DNA)	NA	Experimental	Refs	1	0	0	1	VIEW USE
All	Predicting Treatment Efficacy	High Throughput Nucleotide Sequencing (DNA)	NA	Early Studies in Humans	Refs	3	0	0	3	VIEW USE
All	Differential Diagnosis	IHC (Tissue)	NA	Early Studies in Humans	Refs	1	0	0	1	VIEW USE
All	Disease Profiling	Array CGH (DNA)	NA	Experimental	Refs	1	0	0	1	VIEW USE
Advanced	Selection for Therapy	Genotyping (DNA)	NA	Early Studies in Humans	Refs	1	0	0	1	VIEW USE
All	Prognosis	Genotyping (DNA)	NA	Early Studies in Humans	Refs	0	0	1	1	VIEW USE
All	Risk Factor	PCR / MALDI-TOF-MS (DNA)	NA	Experimental	Refs	1	0	0	1	VIEW USE
All	Prognosis	IHC (Tissue)	NA	Early Studies in Humans	Refs	0	0	1	1	VIEW USE
All	Risk Factor	PCR + DirectSeq (DNA)	NA	Early Studies in Humans	Refs	5	0	0	5	VIEW USE
All	Diagnosis	IHC (Tissue)	NA	Early Studies in Humans	Refs	2	0	0	2	VIEW USE
All	Diagnosis	Real Time RT-PCR (mRNA)	NA	Early Studies in Humans	Refs	1	0	0	1	VIEW USE
All	Disease Profiling	Real Time PCR (mRNA)	NA	Experimental	Refs	1	0	0	1	VIEW USE
Advanced	Risk Factor	Genotyping (DNA)	NA	Early Studies in Humans	Refs	1	0	0	1	VIEW USE

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

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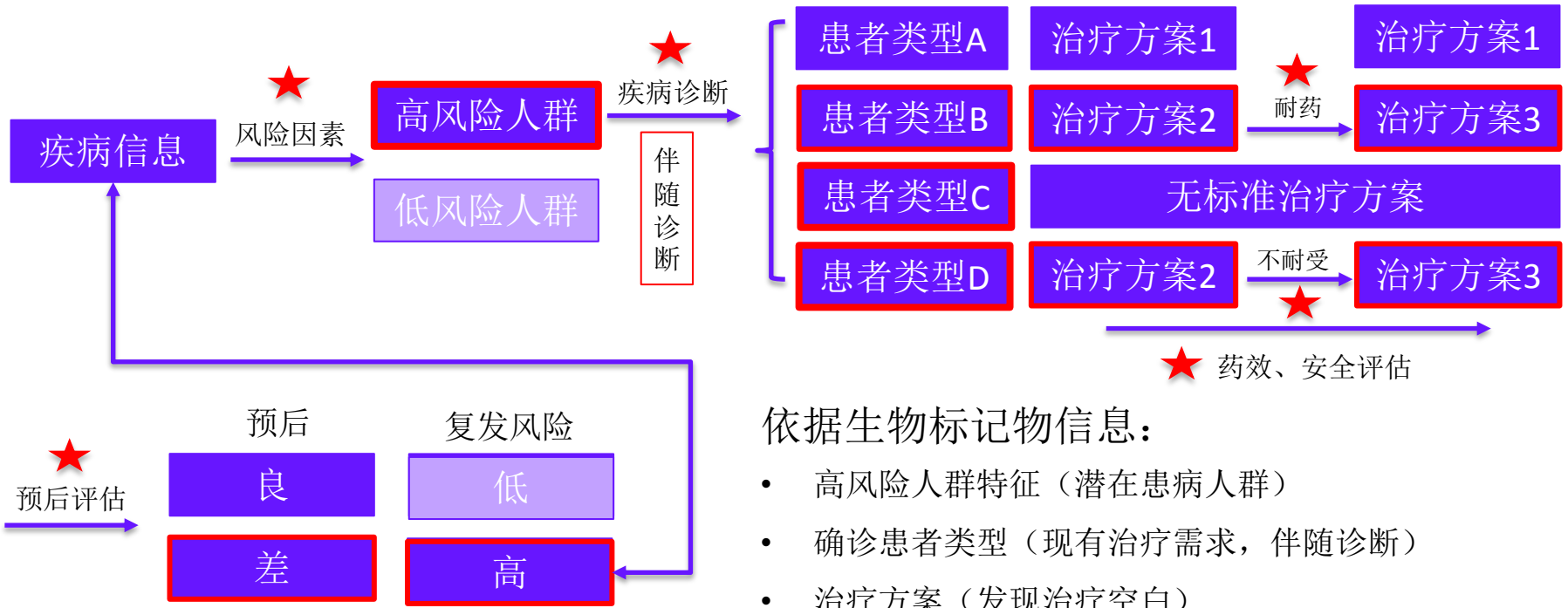
结合指南和标志物发掘临床需求



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）

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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 caroboxylase (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.

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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？

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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

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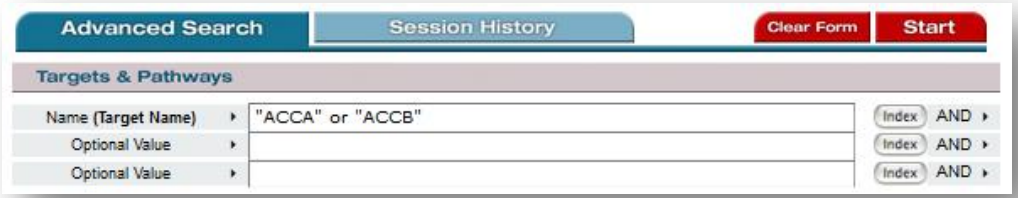
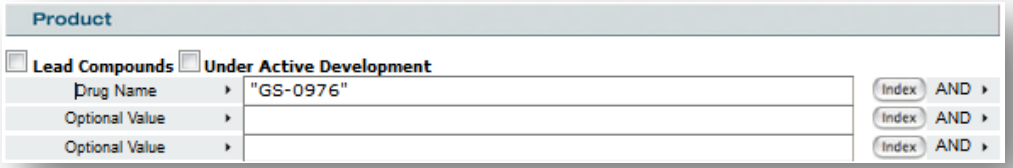
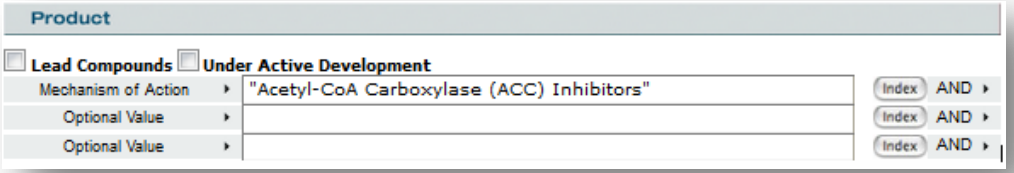
靶点关键信息：研发信息需求

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







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
Acetyl-CoA carboxylase 1 (isoform 1)	Protein
Acetyl-CoA carboxylase 2	Protein

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靶点关键信息：靶点概览

Acetyl-CoA carboxylase 1 (isoform 1)	
Last Updated Date	Jan 10, 2017
Type	Protein
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: Q13085
MetaCore	ACACA, 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.

靶点类型

分子生物学信息: 功能，细胞定位， 结构域，序列，表达等

基本生物功能

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; HACC275
EC	6.4.1.2
Links	UniProtKB: O00763 PDB: 2DN8, 2HJW, 2KCC, 3FF6, 3GID, 3GLK, 3JRW, 3JRX, 3TDC, 4HQ6
MetaCore	ACACB, 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

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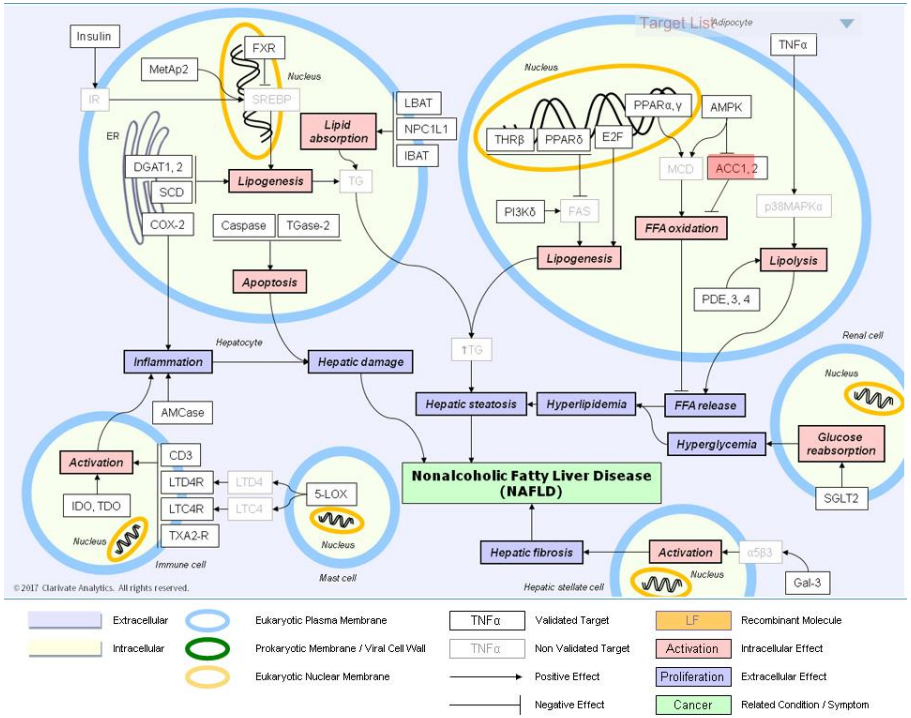
靶点关键信息：疾病靶点格局

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

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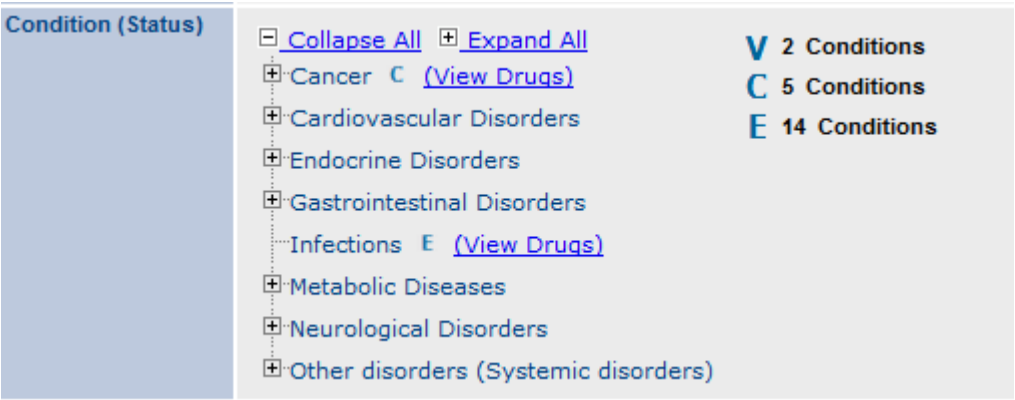
靶点关键信息：靶点成熟度评估



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

可视化，交互型的靶点评估工具来了

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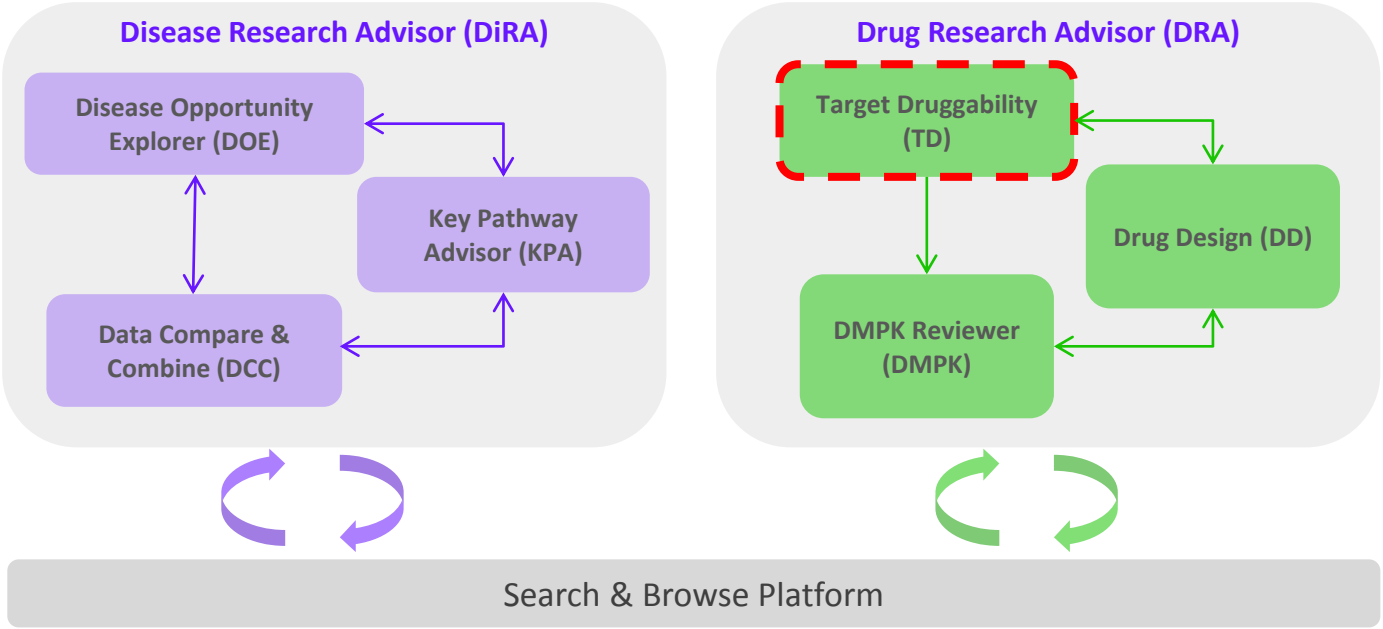
药物研究顾问靶点成药性工具 DRA-TD



- 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

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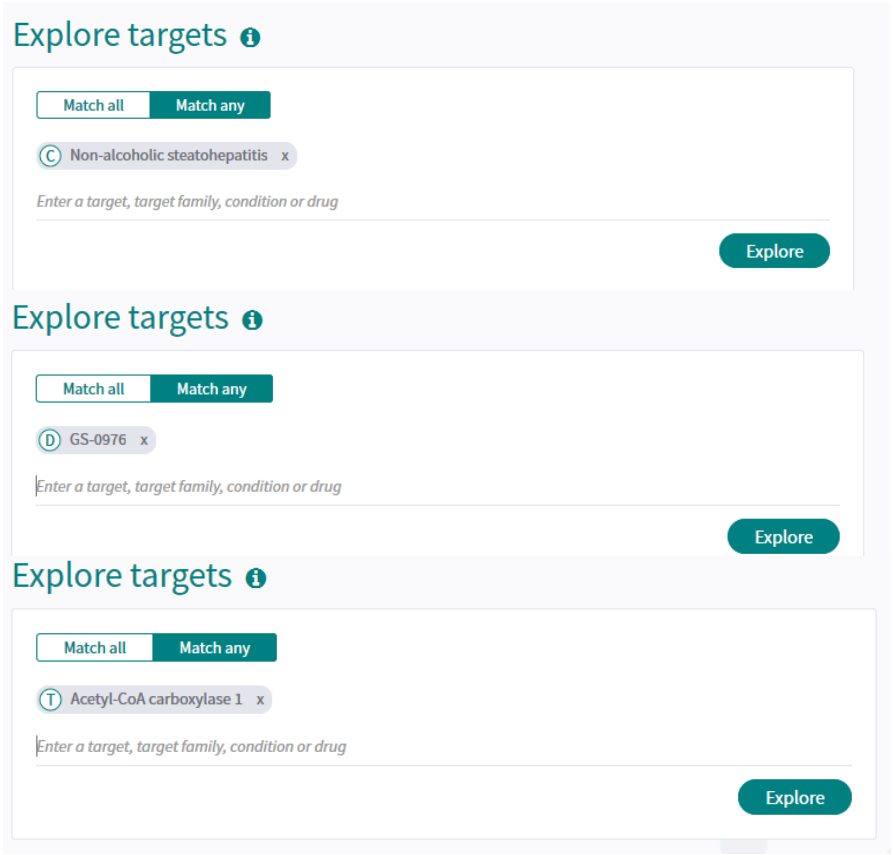
药物顾问-靶点成药性工具



- 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

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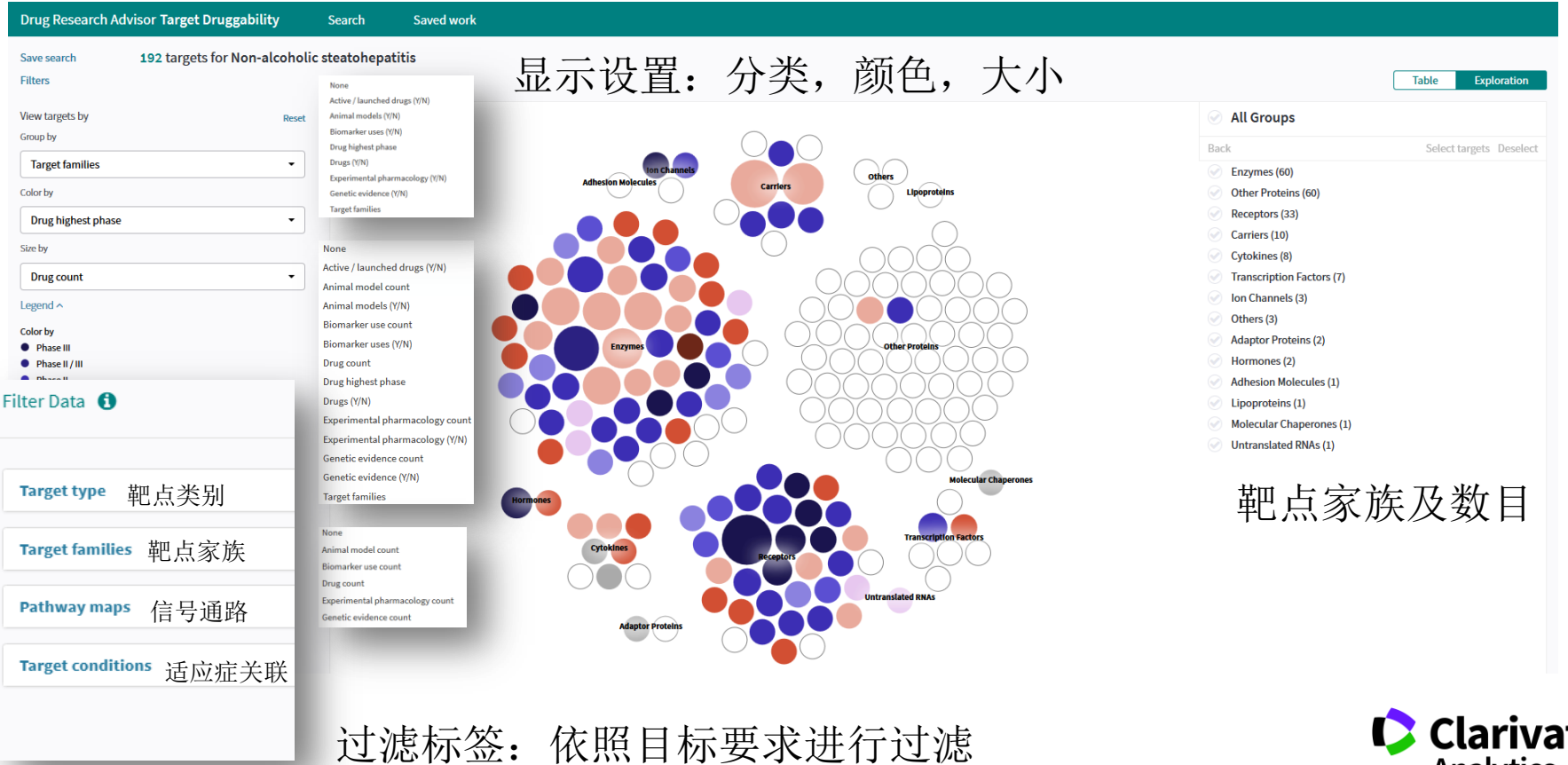
DRA靶点评估：探索模式



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DRA靶点评估：表格模式

Drug Research Advisor **Target Druggability** Search Saved work

Save search

Filters 1

192 targets for **Non-alcoholic steatohepatitis**

Table | Exploration

Target prioritization: Complete novelty | Condition novelty | Early development | **No prioritization**

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

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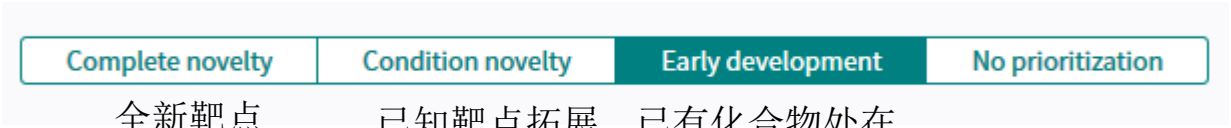
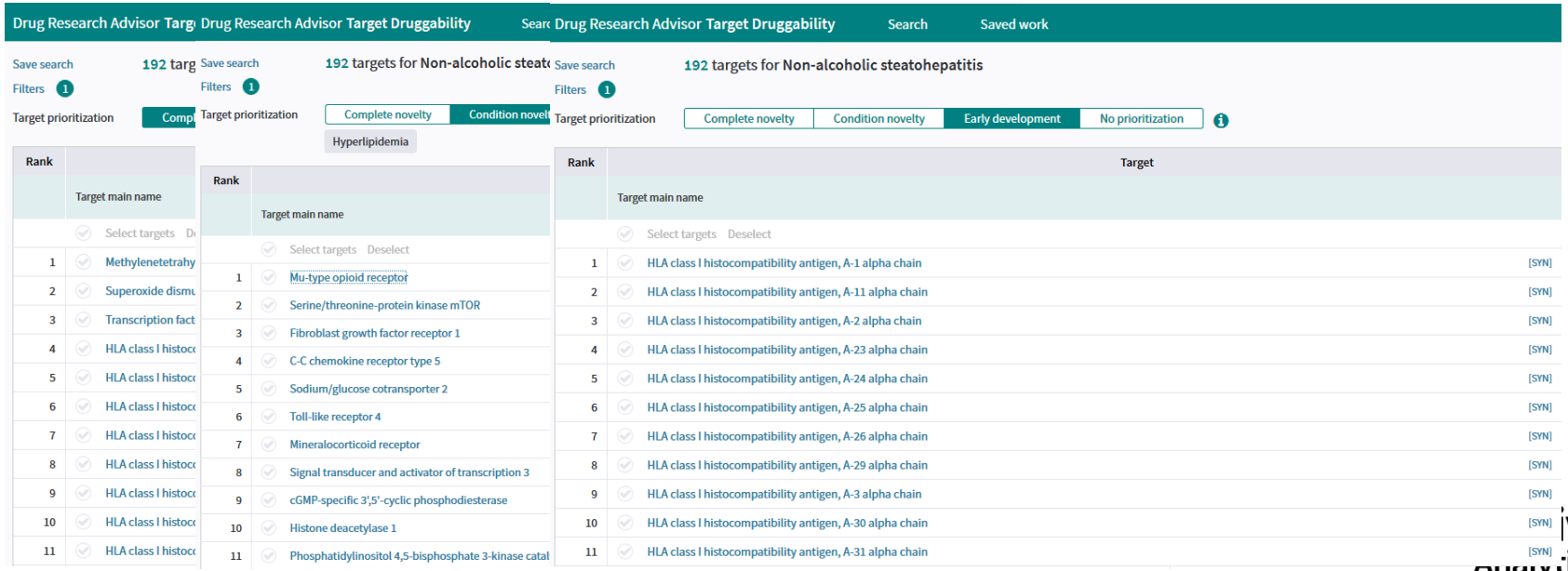
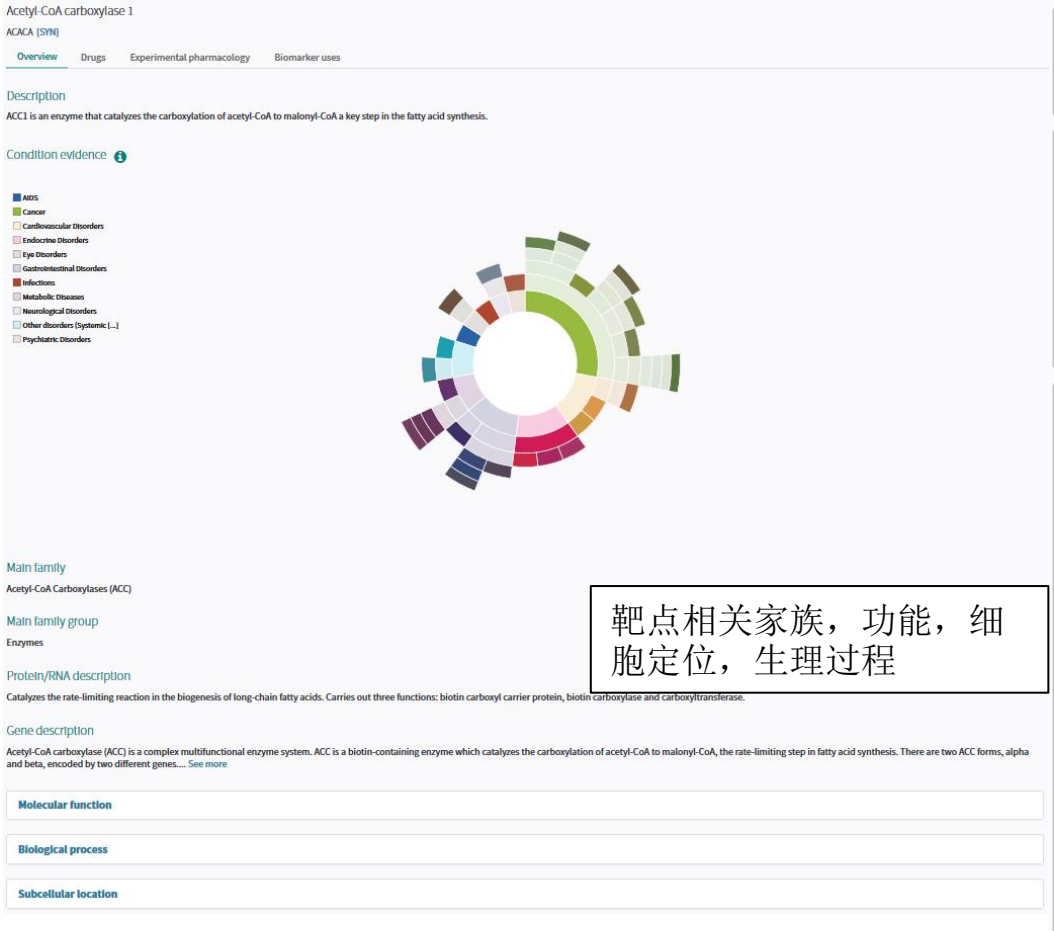
DRA靶点评估：靶点创新性优先评级



- 依照研发定位，对靶点潜力进行评级



DRA靶点评估：靶点概览



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

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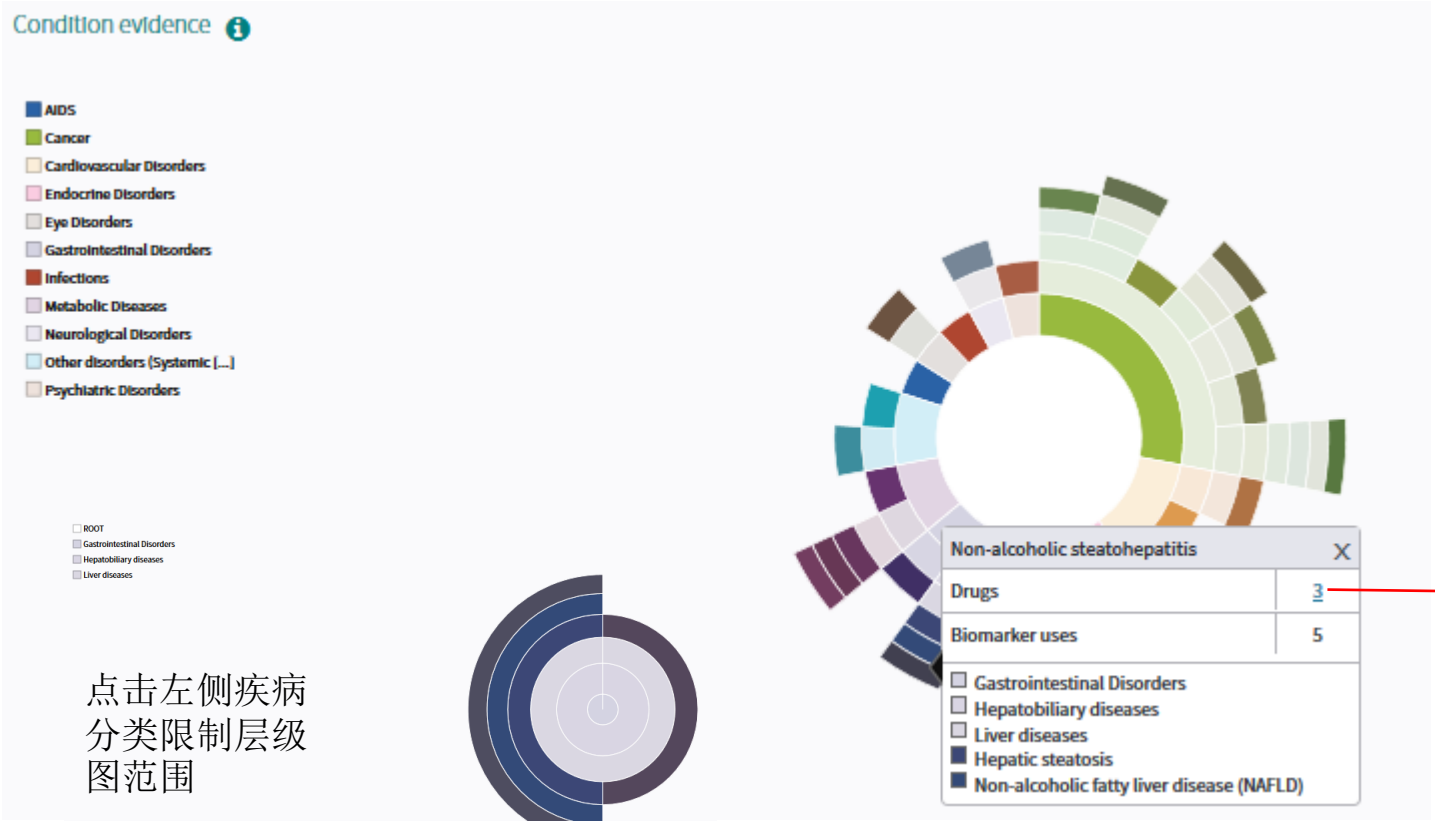
DRA靶点评估：靶点-适应症层级图



点击左侧疾病分类限制层级图范围

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

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DRA靶点评估：相关药物

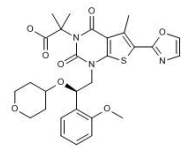
Drugs

Explore all drugs in **Drug Design**

Drug ID	Drug name		Highest phase	Experimental pharmacology	Animal models
912039 ACTIVE	GS-0976	[SYN]	Phase II		
873586 ACTIVE	873586				
907330	BAY-ACC002				
857206	ND-646				
838626	838626				
836589	836589				

Entry Number	814008 UPDATES
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	

Chemical Structure — STRUCTURE FEATURES



NDI-630

Structure/Sequence Entry Date: Mar 18, 2014

Chemical Name/Description

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

Standard InChI

1S/C28H31N3O8S
/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,9-10,12-13,15H2,1-4H3,(H,33,34)/t20-/m0/s1

Standard InChIKey

ZZWWXIBKLBMSCS-FQEVSTJZSA-N

Code Name	Generic Name	Brand Name
ND-630 NDI-630		

Molecular Mechanism	Cellular Mechanism
Acetyl-CoA Carboxylase 2 (ACC2) Inhibitors Acetyl-CoA Carboxylase 1 (ACC1) Inhibitors	Lipid Lowering Agents

Product Category	Therapeutic Group	Prescription/ Indication Type
	Antiobesity Drugs Liver and Biliary Tract Disorders, Treatment of Antidiabetic Drugs	

Organization

Nimbus Therapeutics (Originator)

- 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

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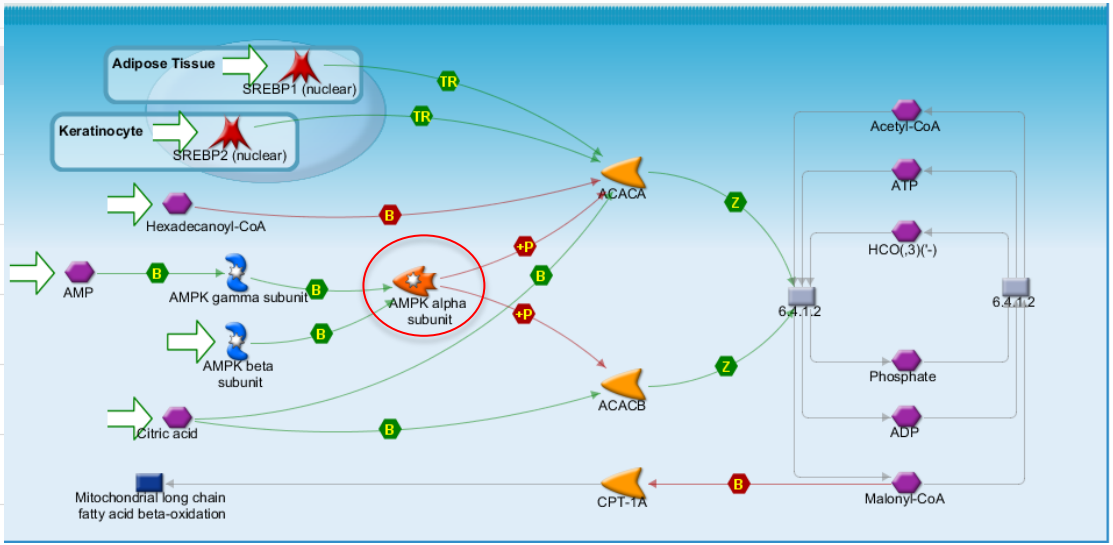
DRA靶点评估：相关信号蛋白相互作用网络

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AMPKa是否也能抑制ACC活性？

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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. | Dehairs, 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-€

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 carboxyrase1 (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.

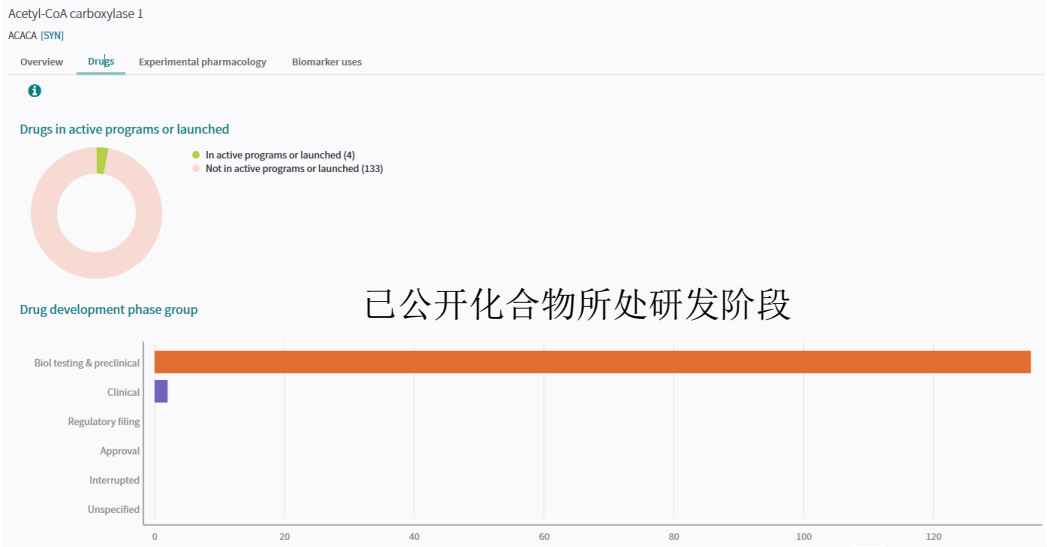
Publication: Annual Meeting of the American Society of Human Genetics (ASHG) · 2015-10-06 / 2015-10-06 · Baltimore, United States

Association type: Biomarker uses

靶点相关基因研究，专利， 文献

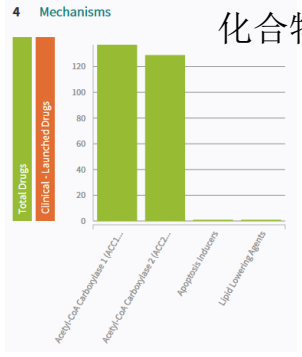
- 指明关联适应症
- 指明关联类型
- 提供Pubmed链接

DRA靶点评估：靶点化合物研发概览



已公开化合物所处研发阶段

开发公司及化合物数量

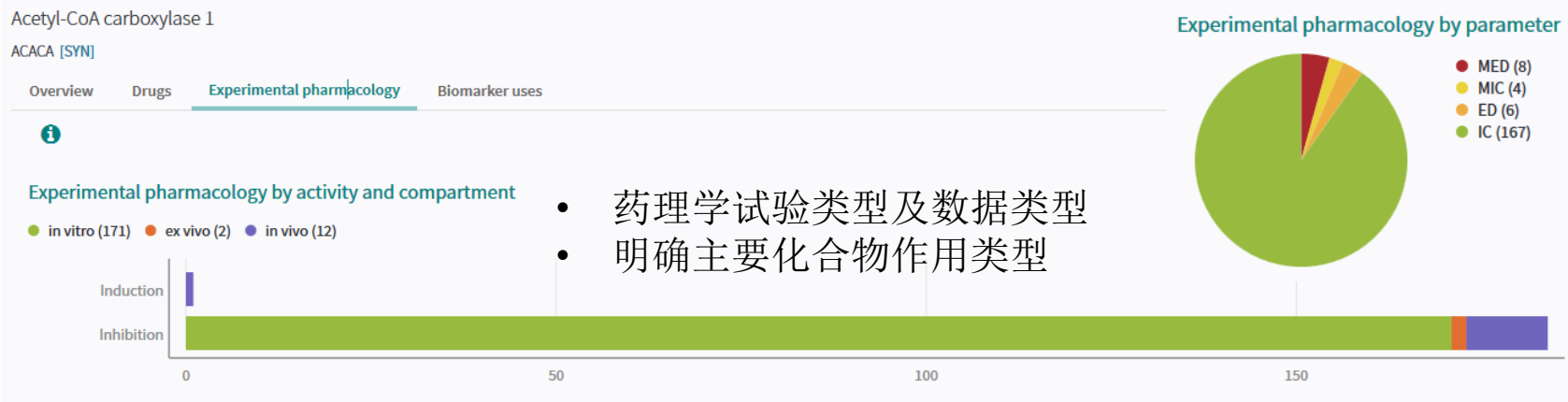


化合物作用机制

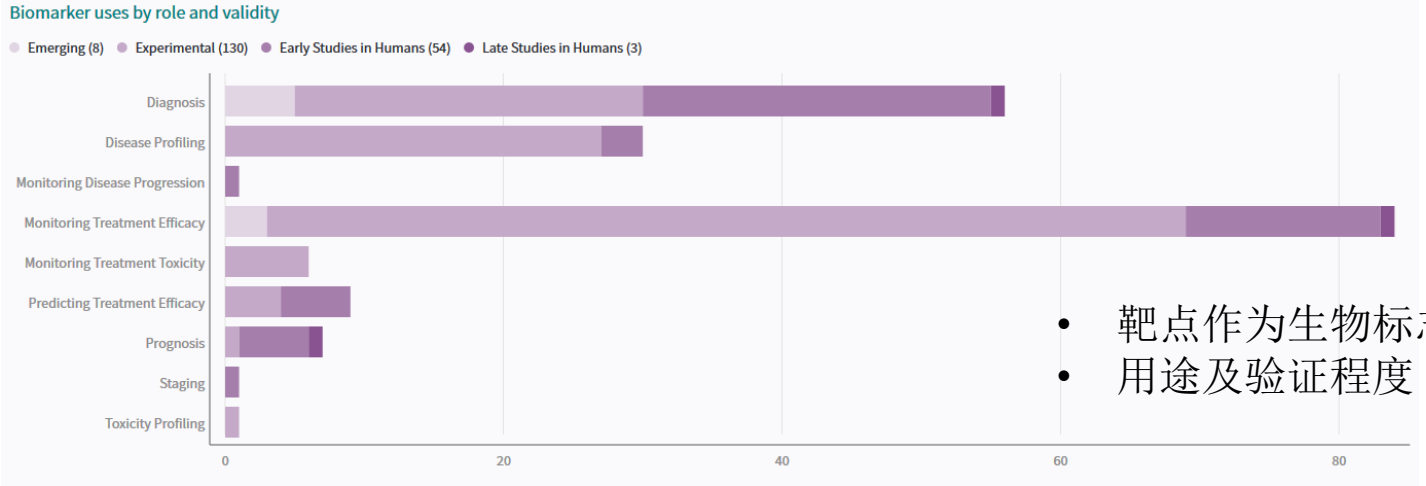
- 明确已知化合物的开发阶段分布
- 涉及的主要研发机构/公司
- 化合物涉及的作用机制

- 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



- 药理学试验类型及数据类型
- 明确主要化合物作用类型



- 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

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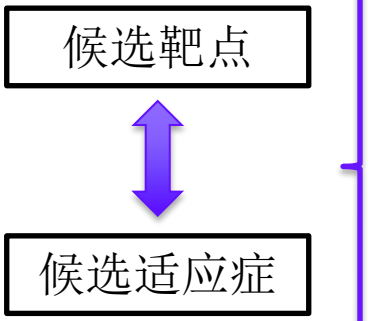
深入挖掘靶点信息



靶点细节

- 相关基因异常（靶点覆盖范围）
- 基因研究类别（额外的适应症）

实验信息

- 体内研究模型
- 体内研究模型
- 生物标志物

化合物信息

- 活性范围
- 典型分子的SAR
- 参考化合物

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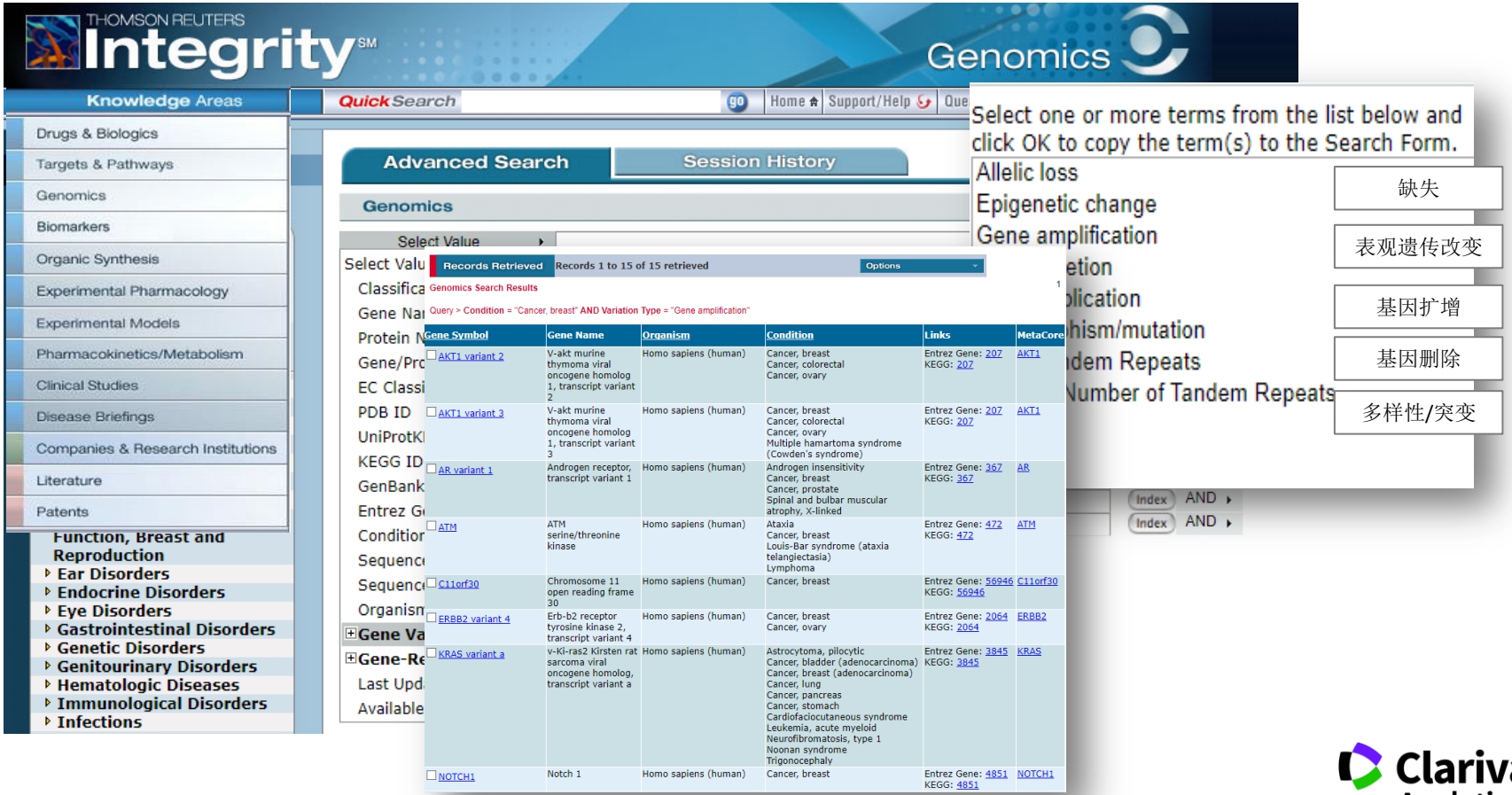
深入挖掘靶点信息：基因异常类型



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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	**rs121913470** (p.Leu755Ser;c.2264T>C;p.L755S)	C Allele	Carcinogenesis	References (1)
Polymorphism/mutation	**c.2524G>A** (p.V842I;p.Val842Ile)	A Allele	Carcinogenesis	References (1)
Polymorphism/mutation	**c.955A>G** (p.Asn319Asp;p.N319D)	G Allele	Carcinogenesis	References (1)
Polymorphism/mutation	**rs1057519816** (c.929C>T;p.S310F;p.Ser310Phe)	T Allele	Carcinogenesis	References (1)
Polymorphism/mutation	**c.2033G>A** (p.Arg678Gln;p.R678Q)	A Allele	Carcinogenesis	References (1)
Gene amplification	**ERBB2amp**	Not specified Not specified	Carcinogenesis	References (1)
Polymorphism/mutation	**c.2305G>T** (p.D769Y;p.Asp769Tyr)	T Allele	Carcinogenesis	References (1)

Cancer, ovary (epithelial)

Variation Type	Variation Name	Association Variant	Effect / Source	
Polymorphism/mutation	**rs121913470** (p.Leu755Ser;c.2264T>C;p.L755S)	C Allele	Carcinogenesis	References (1)
Polymorphism/mutation	**rs768974971** (c.2301C>G;p.I767M;p.Ile767Met)	G Allele	Carcinogenesis	References (1)
Polymorphism/mutation	**c.2299A>T** (p.Ile767Phe;p.I767F)	T Allele	Carcinogenesis	References (1)
Polymorphism/mutation	**c.2305G>T** (p.D769Y;p.Asp769Tyr)	T Allele	Carcinogenesis	References (1)

Cancer, ovary (adenocarcinoma)

Cancer, ovary (clear cell carcinoma)

Variation Type	Variation Name	Association Variant	Effect / Source	
Gene amplification	**HER2amp**	Not specified Not specified	Carcinogenesis	References (1)

Cancer, ovary (borderline tumors)

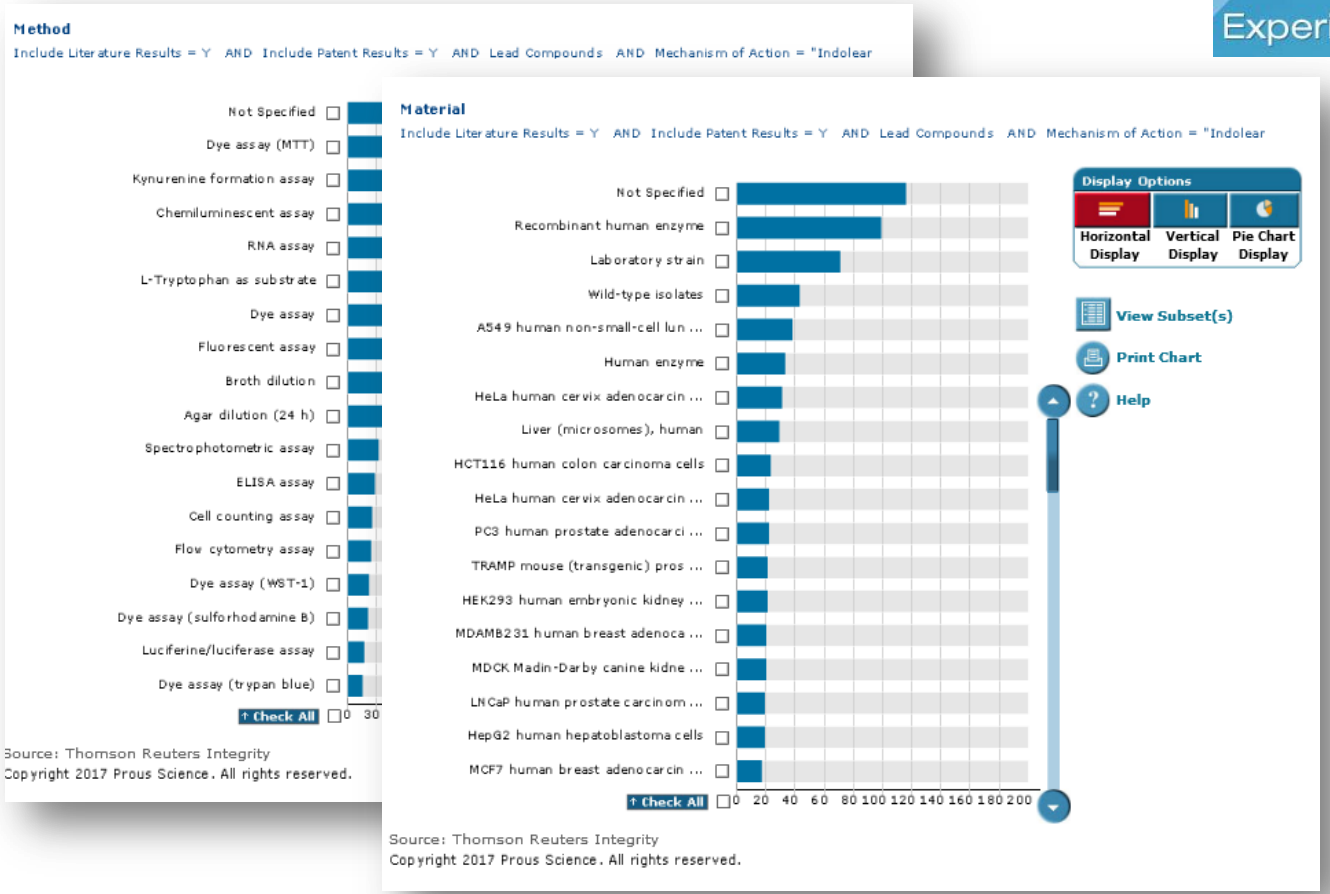
Cancer, ovary (mucinous borderline tumors)

Variation Type	Variation Name	Association Variant	Effect / Source	
Gene amplification	**HER2amp**	Not specified Not specified	Carcinogenesis	References (2)

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



- 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

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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

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

Applications

	Target/Condition/Toxicity
☐	Kidney injury

☐ Select/Deselect All 0 0 0

Drug Information

	Drug Name	Exp Pharma	Refs	Pats
☐	Telavancin hydrochloride	0	1	0
☐	Select/Deselect All	0	1	0

View all 1 drugs tested on this model

Related Information

Tam, V.H.; Ledesma, K.R.; Bowers, D.R.; Zhou, J.; Truong, L.D. PubMed crossref >> WEB OF SCIENCE RECORD

>> 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

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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
Apoptosis regulator BAX BAX; BCL2L4; Bax Apoptosis Regulator Protein; Bax Protein	Proteomic; Genomic	Major Condition: Cancer — EXP 1, ESH 1, All 2; All — EXP 1, ESH 1, All 2	Ref 2; All 2
Apoptosis regulator Bcl-2 B-cell lymphoma protein 2 (alpha isoform); BCL2; BCL2 variant 1; Bcl-2; Bcl-2-like 12 protein	Proteomic; Genomic	Major Condition: Cancer — EXP 1, ESH 1, All 2; All — EXP 1, ESH 1, All 2	Ref 3; All 3
Apoptotic protease-activating factor 1 APAF-1; APAF-1L; APAF1; CED4; DKFZp781B1145; KIAA0413; apoptotic peptidase activating factor 1	Proteomic; Genomic	Major Condition: Cancer — EXP 1, All 1; All — EXP 1, All 1	Ref 1; All 1
Aquaporin-4 AQP4; Aquaporin type 4; HMIWC2; MGC22454; MIWC; Mercurial-insensitive water channel; WCH4	Proteomic; Genomic	Major Condition: Neurological Disorders — EXP 2, All 2; All — EXP 2, All 2	Ref 1; All 1
Baculoviral IAP repeat-containing protein 4 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: Cancer; All	
Bcl-2-binding component 3 BBC3; JFY1; PUMA; PUMA/JFY1 protein; p53 up-regulated modulator of apoptosis	Proteomic; Genomic	Major Condition: Cancer; All	
Bcl-2-like protein 1 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; All — 1; Ref 1	
Cadherin-1 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: Cancer — EXP 1, All 1; All — EXP 1, All 1; Ref 1; All 1	
Calcitonin receptor CALCR; CRT; CTR; CTR1	Genomic	Major Condition: Cancer — EXP 2, All 2; All — EXP 2, All 2; Ref 1; All 1	
Caspase-3 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: Cancer — EXP 1, ESH 1, All 2; All — EXP 1, ESH 1, All 2; Ref 2; All 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

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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

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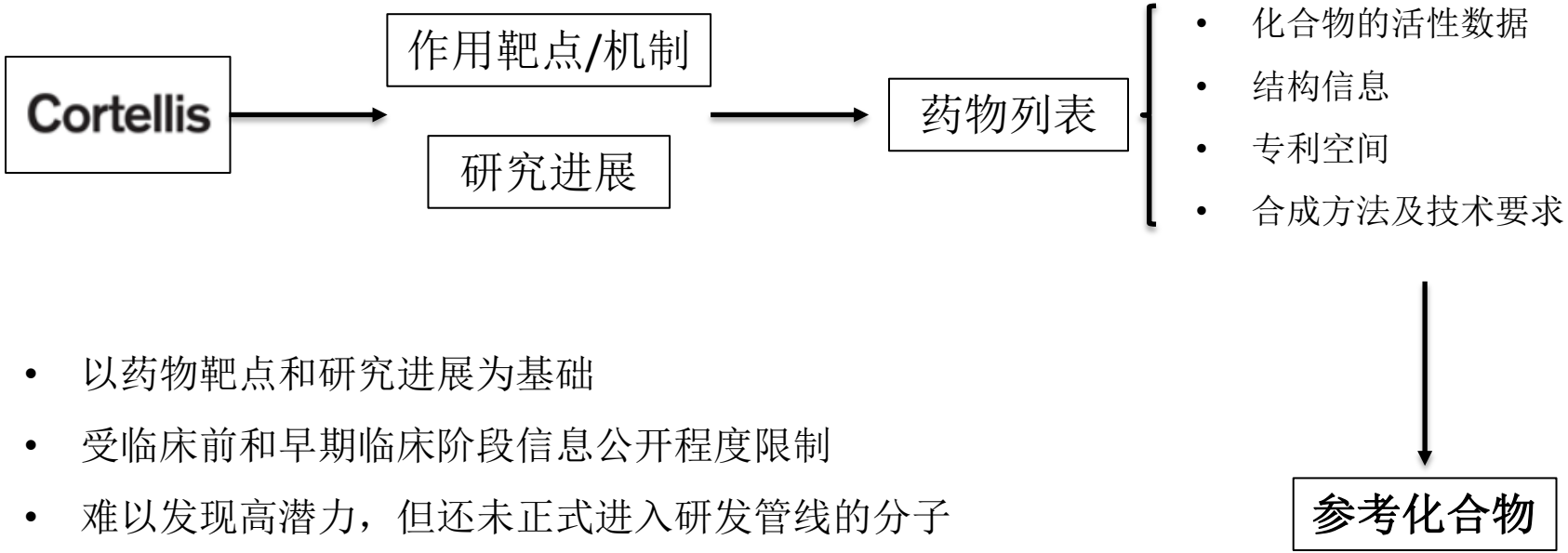
选择参考化合物通常方法



- 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

Clarivate Analytics

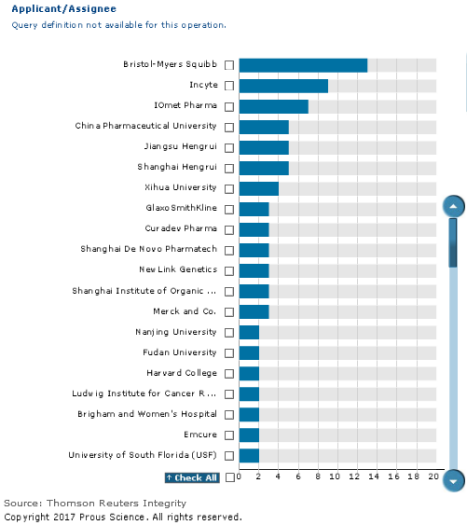
参考化合物的选择：从专利出发

- 检索以IDO1为靶点的化合物专利

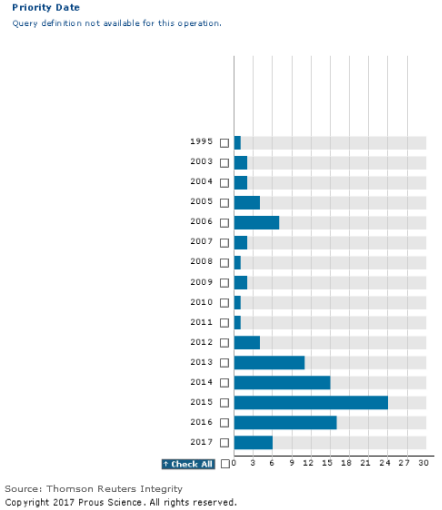
Records Retrieved 99 in Patents **Options**

Patent Search Results 1 2 3 4 5 6 7 8 9 10

Patents (Applicants)	Title	Subject Matter	Condition	Lead Compound
WO 2017173973 * (Peking University (PKU))	Nitrogen heterocyclic tryptamine ketone derivative and application as IDO1 and/or TDO inhibitor	Drug Substances	Anxiety Autoimmune disease Cancer Dementia, Alzheimer's type Depression Infections	979038
WO 2017152857 * CN 107176933 (Shanghai Institute of Organic Chemistry)	Indoleamine-2,3-dioxygenase inhibitor containing nitrogen alkylated and arylated sulphoxide imines	Drug Substances	Anxiety Autoimmune disease Cancer Cardiovascular Disorders Dementia, Alzheimer's type Eye Disorders Infection, HIV Neurodegeneration	976058
WO 2017149469 * (Emcure Pharmaceuticals Ltd.)	Heterocyclic compounds useful as IDO and/or TDO modulators	Drug Substances	Cancer Infection, viral Inflammation Neurodegeneration Pain Psychiatric Disorders Renal Disorders Transplant rejection	975258
WO 2017143874 * (Shenzhen Targetrx Biotechnology Co., Ltd.)	Substituted oxadiazole chemical compound and composition containing said chemical compound and use thereof	Drug Substances	Cancer Cardiovascular Disorders Cataract Depression Immunological Disorders Infections Inflammation Metabolic Diseases	974150
WO 2017140272 * (Jiangsu Chia Tai Tianqing Pharmaceutical Group Co., Ltd. Medshine Discovery Inc.)	Tricyclic compound acting as immunomodulator	Drug Substances	Immunological Disorders	976217
WO 2017139414 * (Inventisbio Inc.)	Inhibitor of indoleamine-2,3-dioxygenase (IDO)	Drug Substances	Cancer Infection, viral	972208
CN 107033097 * (Jiangsu Hengrui Medicine Co., Ltd. Shanghai Hengrui Pharmaceutical Co., Ltd.)	Furodiazoles derivative, its preparation method and the upper application in medicine	Drug Substances	AIDS Anxiety Autoimmune disease Cancer Cataract Dementia, Alzheimer's type Depression Myelodysplasia	978077



专利申请人



优先权日

- 领头企业，竞争对手
- 项目开展时间
- 确定专利分析范围

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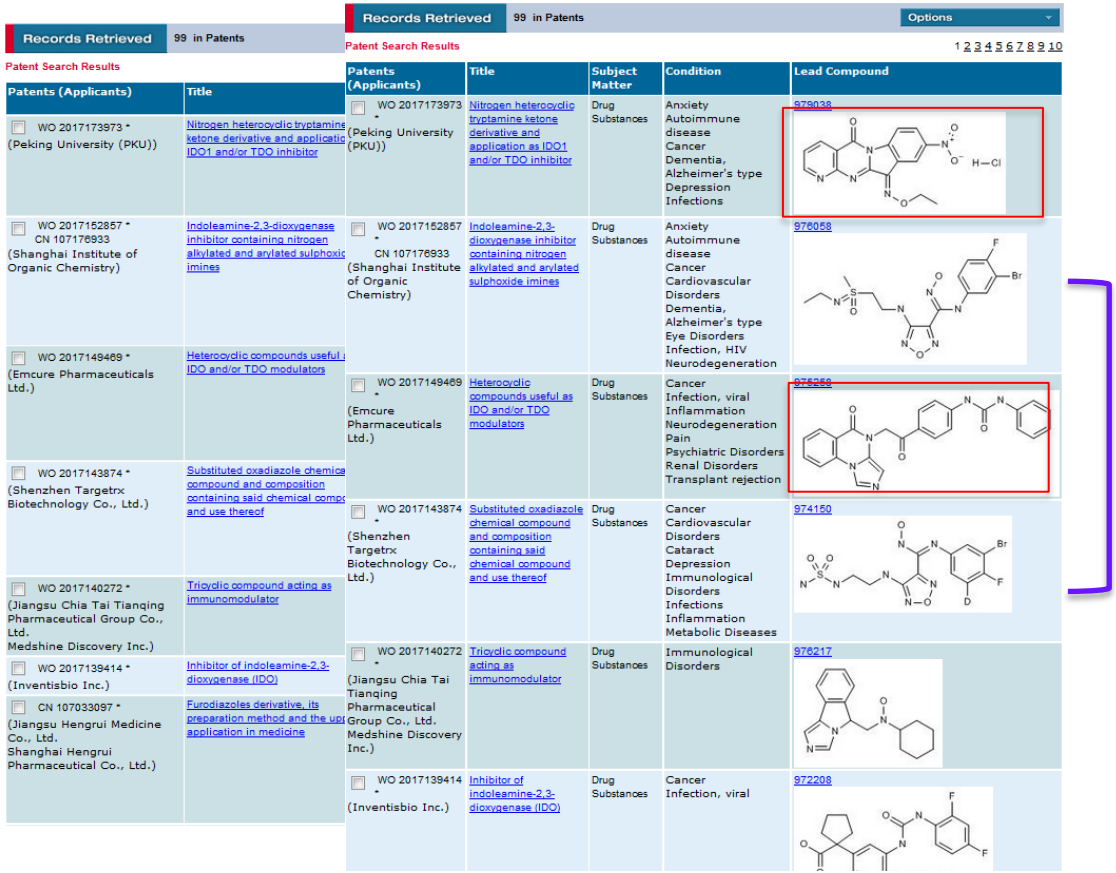
参考化合物的选择：典型结构



Records Retrieved 99 in Patents

Patent Search Results

Patents (Applicants)	Title
WO 2017173973 * (Peking University (PKU))	Nitrogen heterocyclic tryptamine ketone derivative and applicatio IDO1 and/or TDO inhibitor
WO 2017152857 * CN 107176933 (Shanghai Institute of Organic Chemistry)	Indoleamine-2,3-dioxygenase inhibitor containing nitrogen alkylated and arylated sulphoxi imines
WO 2017149469 * (Emcure Pharmaceuticals Ltd.)	Heterocyclic compounds useful i IDO and/or TDO modulators
WO 2017143874 * (Shenzhen Targetrx Biotechnology Co., Ltd.)	Substituted oxadiazole chemica compound and composition containing said chemical comp and use thereof
WO 2017140272 * (Jiangsu Chia Tai Tianqing Pharmaceutical Group Co., Ltd. Medshine Discovery Inc.)	Tricyclic compound acting as immunomodulator
WO 2017139414 * (Inventisbio Inc.)	Inhibitor of indoleamine-2,3-dioxygenase (IDO)
CN 107033097 * (Jiangsu Hengrui Medicine Co., Ltd. Shanghai Hengrui Pharmaceutical Co., Ltd.)	Furodiazoles derivative, its preparation method and the up application in medicine

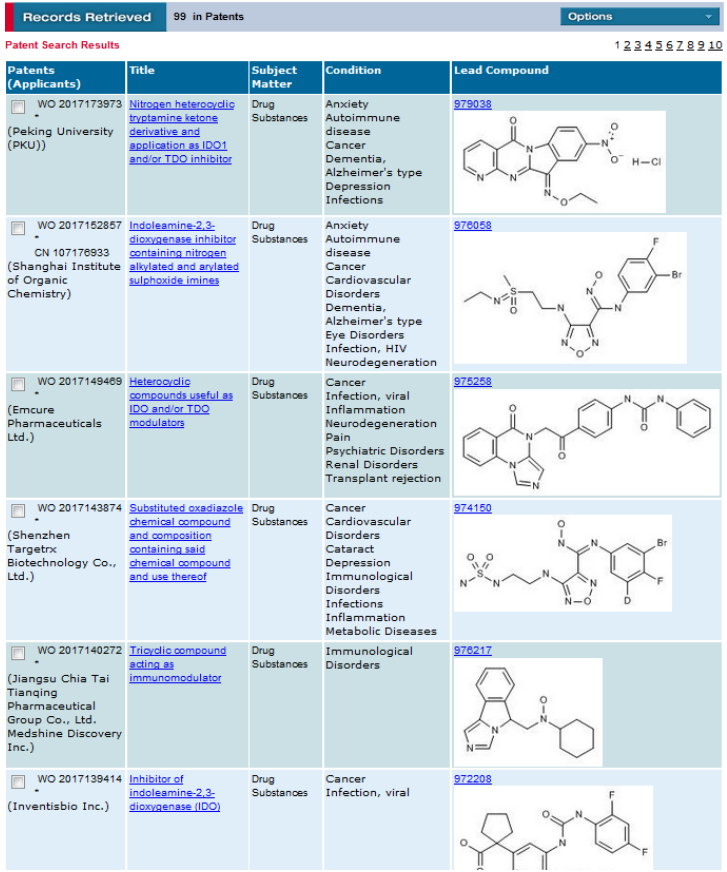
Records Retrieved 99 in Patents Options

Patent Search Results 1 2 3 4 5 6 7 8 9 10

Patents (Applicants)	Title	Subject Matter	Condition	Lead Compound
WO 2017173973 * (Peking University (PKU))	Nitrogen heterocyclic tryptamine ketone derivative and application as IDO1 and/or TDO inhibitor	Drug Substances	Anxiety Autoimmune disease Cancer Dementia, Alzheimer's type Depression Infections	979038
WO 2017152857 * CN 107176933 (Shanghai Institute of Organic Chemistry)	Indoleamine-2,3-dioxygenase inhibitor containing nitrogen alkylated and arylated sulphoxide imines	Drug Substances	Anxiety Autoimmune disease Cancer Cardiovascular Disorders Dementia, Alzheimer's type Eye Disorders Infection, HIV Neurodegeneration	976058
WO 2017149469 * (Emcure Pharmaceuticals Ltd.)	Heterocyclic compounds useful as IDO and/or TDO modulators	Drug Substances	Cancer Infection, viral Inflammation Neurodegeneration Pain Psychiatric Disorders Renal Disorders Transplant rejection	976268
WO 2017143874 * (Shenzhen Targetrx Biotechnology Co., Ltd.)	Substituted oxadiazole chemical compound and composition containing said chemical compound and use thereof	Drug Substances	Cancer Cardiovascular Disorders Cataract Depression Immunological Disorders Infections Inflammation Metabolic Diseases	974150
WO 2017140272 * (Jiangsu Chia Tai Tianqing Pharmaceutical Group Co., Ltd. Medshine Discovery Inc.)	Tricyclic compound acting as immunomodulator	Drug Substances	Immunological Disorders	976217
WO 2017139414 * (Inventisbio Inc.)	Inhibitor of indoleamine-2,3-dioxygenase (IDO)	Drug Substances	Cancer Infection, viral	972208

- 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

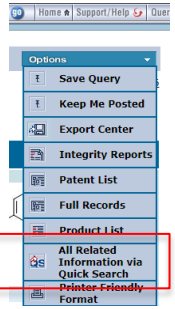
参考化合物的选择：由专利获取药物和活性数据



Records Retrieved 99 in Patents Options

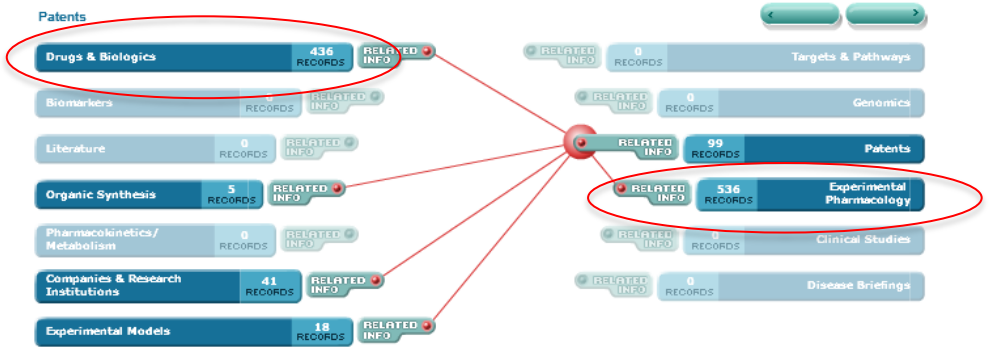
Patent Search Results 1 2 3 4 5 6 7 8 9 10

Patents (Applicants)	Title	Subject Matter	Condition	Lead Compound
WO 2017173973 (Peking University (PKU))	Nitrogen heterocyclic tryptamine ketone derivative and application as IDO1 and/or TDO inhibitor	Drug Substances	Anxiety Autoimmune disease Cancer Dementia, Alzheimer's type Depression Infections	979038
WO 2017152857 CN 107176933 (Shanghai Institute of Organic Chemistry)	Indoleamine-2,3-dioxygenase inhibitor containing nitrogen alkylated and arylated sulphoxide imines	Drug Substances	Anxiety Autoimmune disease Cancer Cardiovascular Disorders Dementia, Alzheimer's type Eye Disorders Infection, HIV Neurodegeneration	976058
WO 2017149469 (Emcure Pharmaceuticals Ltd.)	Heterocyclic compounds useful as IDO and/or TDO modulators	Drug Substances	Cancer Infection, viral Inflammation Neurodegeneration Pain Psychiatric Disorders Renal Disorders Transplant rejection	975258
WO 2017143874 (Shenzhen Targetrx Biotechnology Co., Ltd.)	Substituted oxadiazole chemical compound and composition containing said chemical compound and use thereof	Drug Substances	Cancer Cardiovascular Disorders Cataract Depression Immunological Disorders Infections Inflammation Metabolic Diseases	974150
WO 2017140272 (Jiangsu Chia Tai Tianqing Pharmaceutical Group Co., Ltd. Medshine Discovery Inc.)	Tricyclic compound acting as immunomodulator	Drug Substances	Immunological Disorders	976217
WO 2017139414 (Inventisbio Inc.)	Inhibitor of indoleamine-2,3-dioxygenase (IDO)	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



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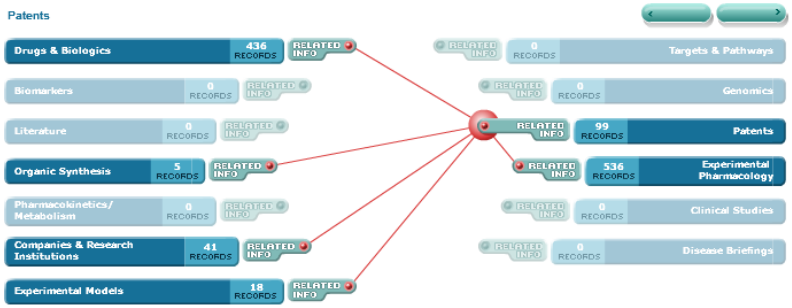
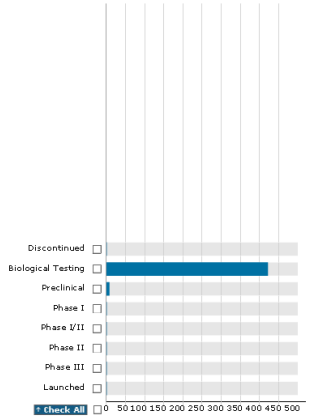
参考化合物的选择：1.从研发状态出发筛选



- 从专利获取相关早期活性分子及管线药物信息



Source: Thomson Reuters Integrity

Drugs & Biologics

Entry Number	Highest Phase	Code Name	Generic Name	Brand Name	Product Category	Therapeutic Group	Mechanism of Action	Organization
168220	Launched-1992	FI-7045 (free base)	Sertaconazole nitrate (Rec INNM)	Dermofix Dermoseptic Ertaczo Extens Fisderm Ginedermofix Onabet Zalain	Imidazoles, Antifungal Agents	Antifungal Agents	Immune Checkpoint Inhibitors Tryptophan 2,3-Dioxygenase (TDO) Inhibitors Indoleamine 2,3-dioxygenase 1 (IDO1; IDO) Inhibitors	Ferrer (Originator) Valeant 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 ArQule Dana-Farber Cancer Institute (Originator) KT&G Life Sciences
686486	Phase III	INCB-024360 INCB-24360 71596A9R13 (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 iTeos Therapeutics (Originator)

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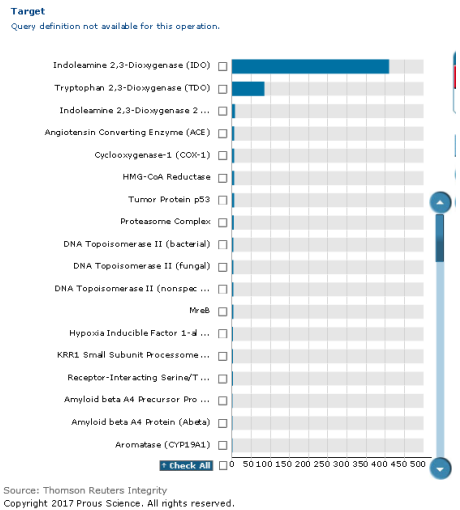
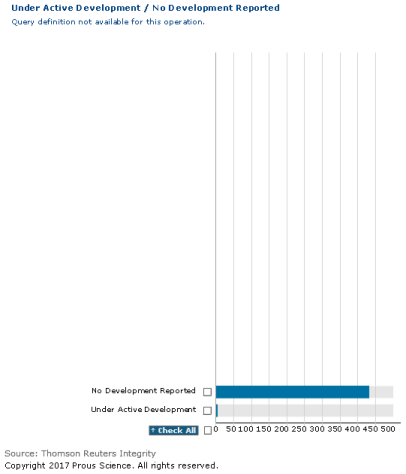
参考化合物的选择：1.从研发状态出发筛选

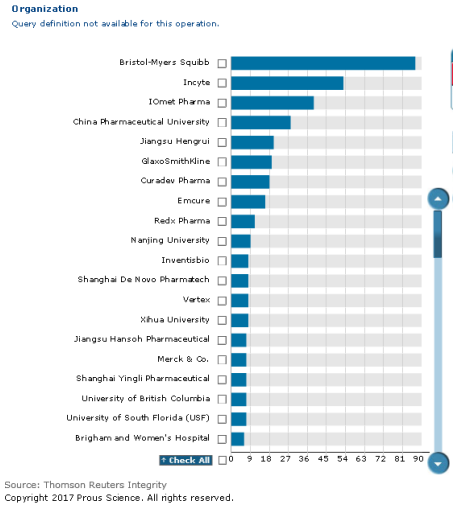
Drugs & Biologics



靶点覆盖范围
（化合物的选择性）



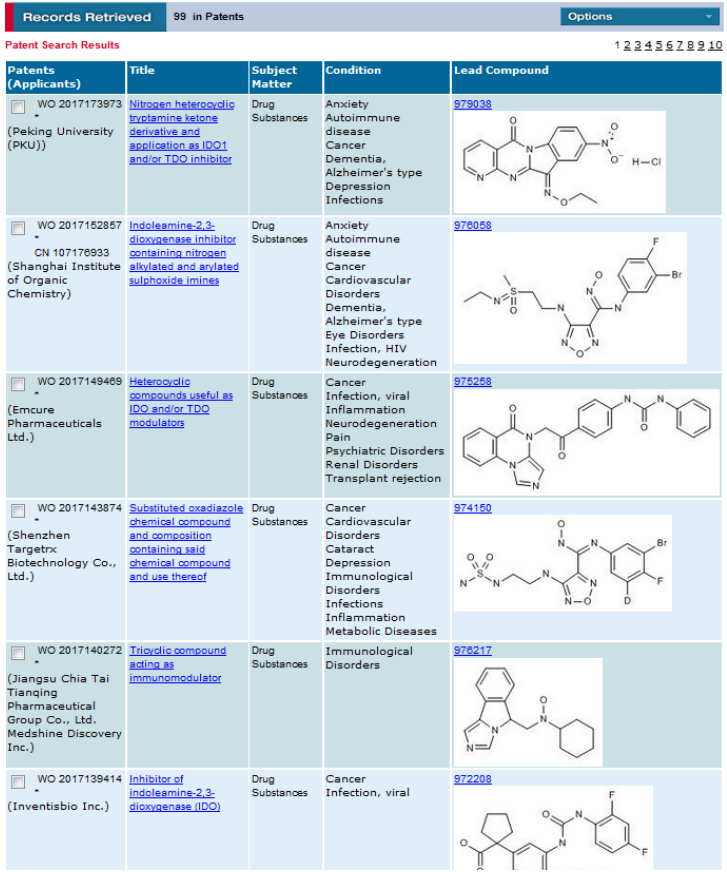
研发活跃度

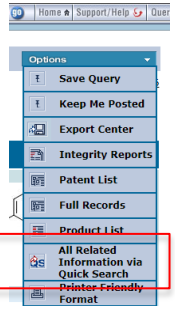


研发公司

Clarivate Analytics

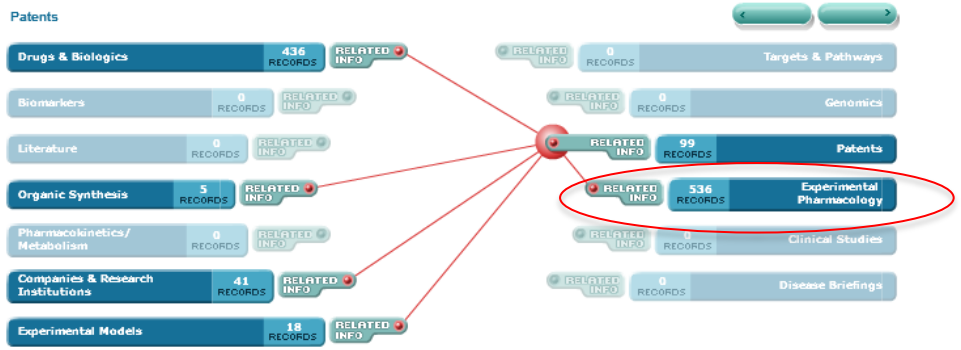
参考化合物的选择：2.由活性数据出发





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



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参考化合物的选择：2.从活性数据出发

Experimental Pharmacology

- 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

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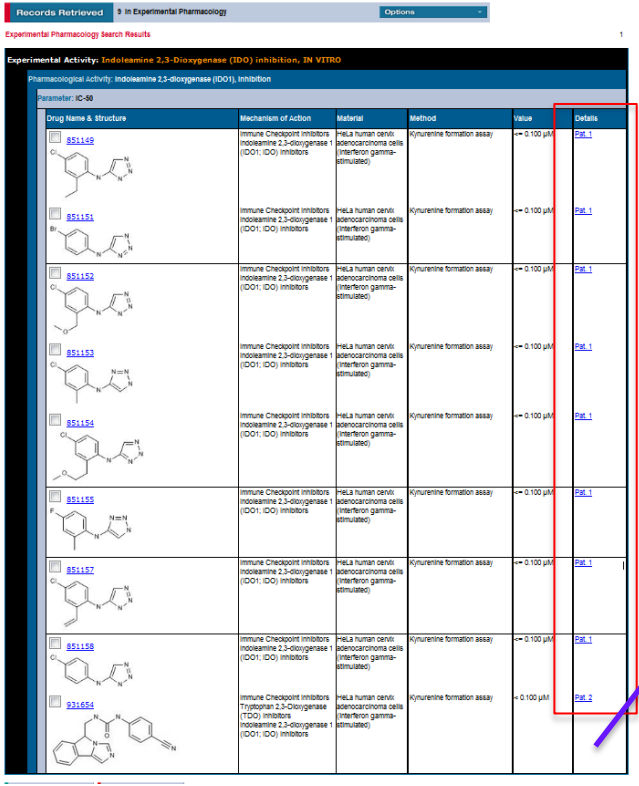
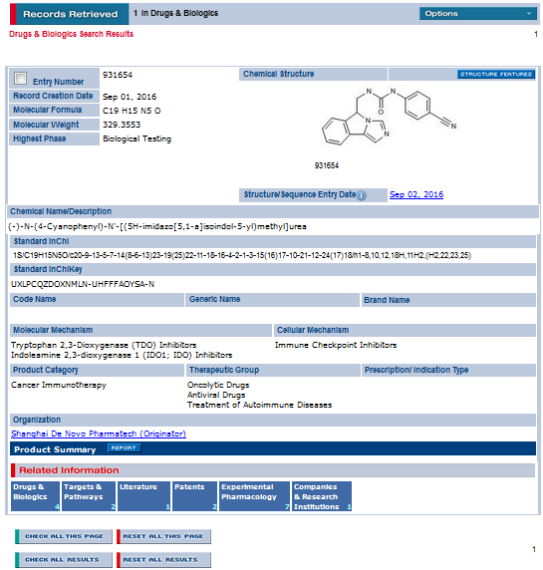
参考化合物：候选参考化合物

Options:选则 structure activity





- 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

Clarivate Analytics

参考化合物：公司信息

Companies & Research Institutions

Companies & Research Institutions Search Results 1

Organization

Vertex www.vrtx.com

Main Activity	Headquarters	Fiscal Year Ends
Biotechnology Genomics	Cambridge, MA (US)	Dec 31

Therapeutic Areas	Fiscal Year 2013 MORE	
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

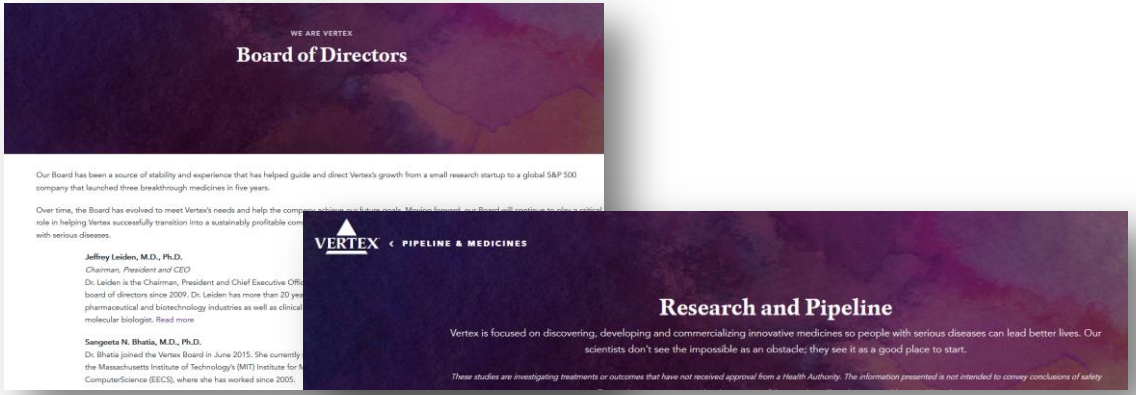
Marketed Products			
Fosamprenavir calcium	Lexiva (BN)	Launched - 2003	Infection, HIV
Ivacaftor	Kalydeco (BN)	Launched - 2012	Fibrosis, cystic SALES
Lumacaftor/ivacaftor	Orkambi (BN)	Launched - 2015	Fibrosis, cystic
Telaprevir	Incivek (BN)	Launched - 2011	Hepatitis C (HCV) SALES

Clinical Trials and Preclinical Research MORE		
BA-210	Phase II/III	Injury, spinal cord
Ivacaftor	Pre-Registered - 2015	Fibrosis, cystic
Ivacaftor	Registered - 2015	Fibrosis, cystic
Ivacaftor	Phase III	Fibrosis, cystic
Lumacaftor	Phase III	Fibrosis, cystic
Lumacaftor/ivacaftor	Pre-Registered	Fibrosis, cystic
Lumacaftor/ivacaftor	Phase III	Fibrosis, cystic
Tezacaftor	Phase III	Fibrosis, cystic
Tezacaftor/ivacaftor	Phase III	Fibrosis, cystic
Tezacaftor/ivacaftor	Pre-Registered	Fibrosis, cystic

Recent Patents	
DNA-PK inhibitors	Cancer
Mannose derivatives for treating bacterial infections	Inflammatory bowel disease Infection, urinary tract
Modulators of cystic fibrosis transmembrane conductance regulator	
Pyrrolopyrazine-spirocyclic piperidine amides as modulators of ion channels	Pain
Pharmaceutical composition and administrations thereof	Fibrosis, cystic Chronic obstructive pulmonary disease (COPD) Osteoporosis Dry eye
Method for treating cancer using a combination of DNA damaging agents and ATR inhibitors	Cancer
Pyridone amides as modulators of sodium channels	Pain
Prodrugs of pyridone amides useful as modulators of sodium channels	Pain
DNA-PK inhibitors	Cancer
Heteroaryl derivatives as CFTR modulators	Fibrosis, cystic

Related Information

Drugs & Biologics 2686 | Patents 675 | Literature 85



- 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

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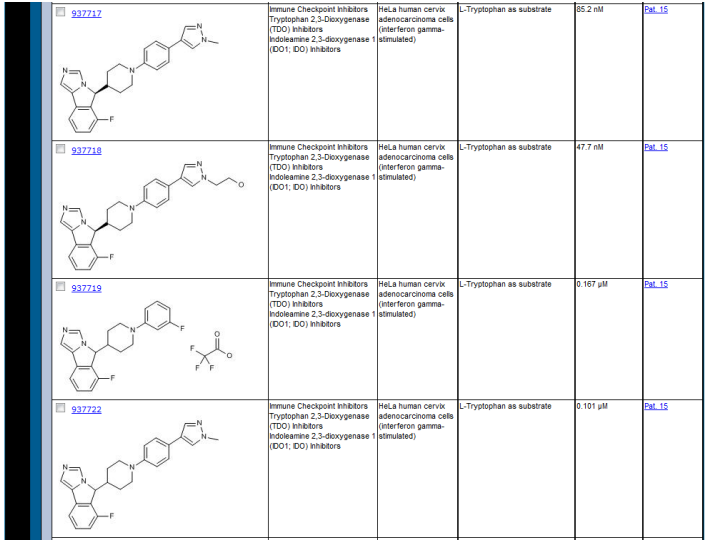
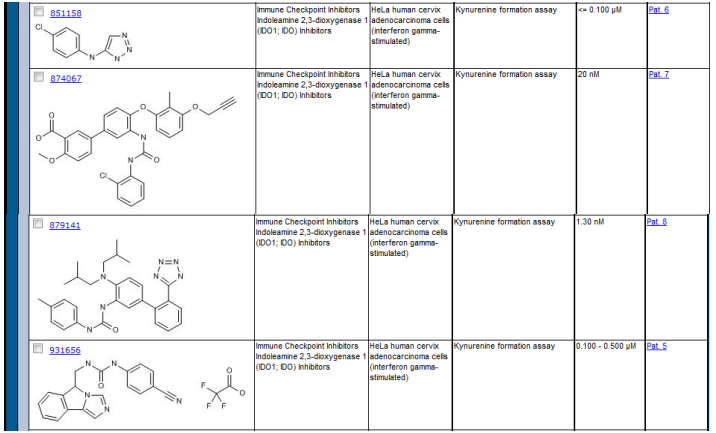
参考化合物：专利典型分子的SAR分析

- 如果不限制活性范围：即可进行SAR分析



937717	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	Pat. 15
937718	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	Pat. 15
937719	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	Pat. 15
937722	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	Pat. 15

- 同一专利内：
比较不同取代的影响



851158	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	Pat. 6
874067	Immune Checkpoint Inhibitors Indoleamine 2,3-dioxygenase 1 (IDO1; IDO) Inhibitors	HeLa human cervix adenocarcinoma cells (interferon gamma-stimulated)	Kynurenine formation assay	20 nM	Pat. 7
879141	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	Pat. 8
931656	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	Pat. 5

- 不同专利之间：
比较不同母核结构的修饰空间

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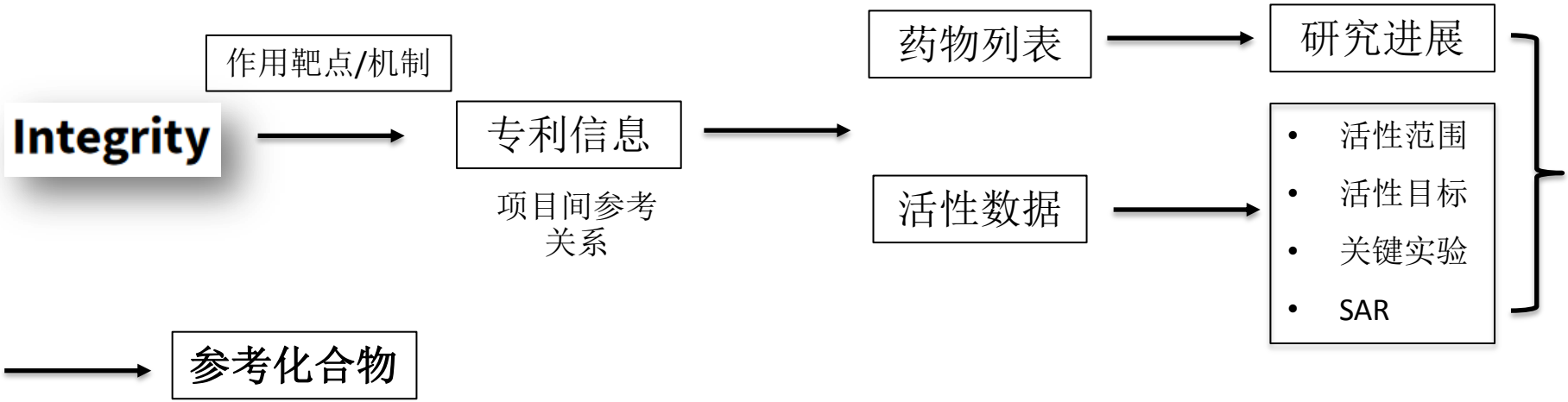
用Integrity选择候选参考化合物



- 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

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总结

疾病

- 通过生物标志物来了解疾病，患者
- 探索临床治疗需求

Integrity

Drug Research Advisor

- 从专利出发探索靶点要求
- 发掘高潜力分子，选择合适参考化合物

化合物 ⟷ 靶点

- 依据关键靶点信息来挑选，评估靶点
- 综合挖掘靶点信息，支持实验开展

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常见问题1

Drugs & Biologics

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
070003	Methylprednisolone		Vilnius University	Leukemia, chronic lymphocytic	Phase II			
070005 *	Metronidazole	Cytochrome P450 CYP1A2 Inhibitors	Institute for Drug Research	Conjunctivitis, infective	Phase II	United States		
070005 *	Metronidazole	Cytochrome P450 CYP1A2 Inhibitors	National Institute Allergy Infect Dis	Tuberculosis, multidrug resistant (MDR-TB)	Phase II	Korea, Republic of		

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常见问题2

Drugs & Biologics

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

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常见问题3

Drugs & Biologics

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 t marketing, but the drug is not yet available on the m
Launched	The drug is being marketed.
Discontinued	Development of the product has stopped before a re
Suspended	The product is stopped when undergoing regulatory
Withdrawn	The product is withdrawn from the market after laun
Undetermined	Development status is unknown.
Not Applicable	A preparation or extract that is under study as a drug already available on the market as an unregulated h

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。

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- **在线培训：**我们会为客户组织俱乐部活动，定期在线解答大家的疑问，提供最新的检索技巧，分享检索经验
- **数据库使用培训课程：**
- **可访问科睿唯安在线学院：** **http://clarivate.com.cn/e-Clarivate/**
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  TS技术支持团队：400 8822 031 ；ts.support.china@Clarivate.com

- **官方微信 扫描二维码** 或搜索“科睿唯安生命科学与制药”

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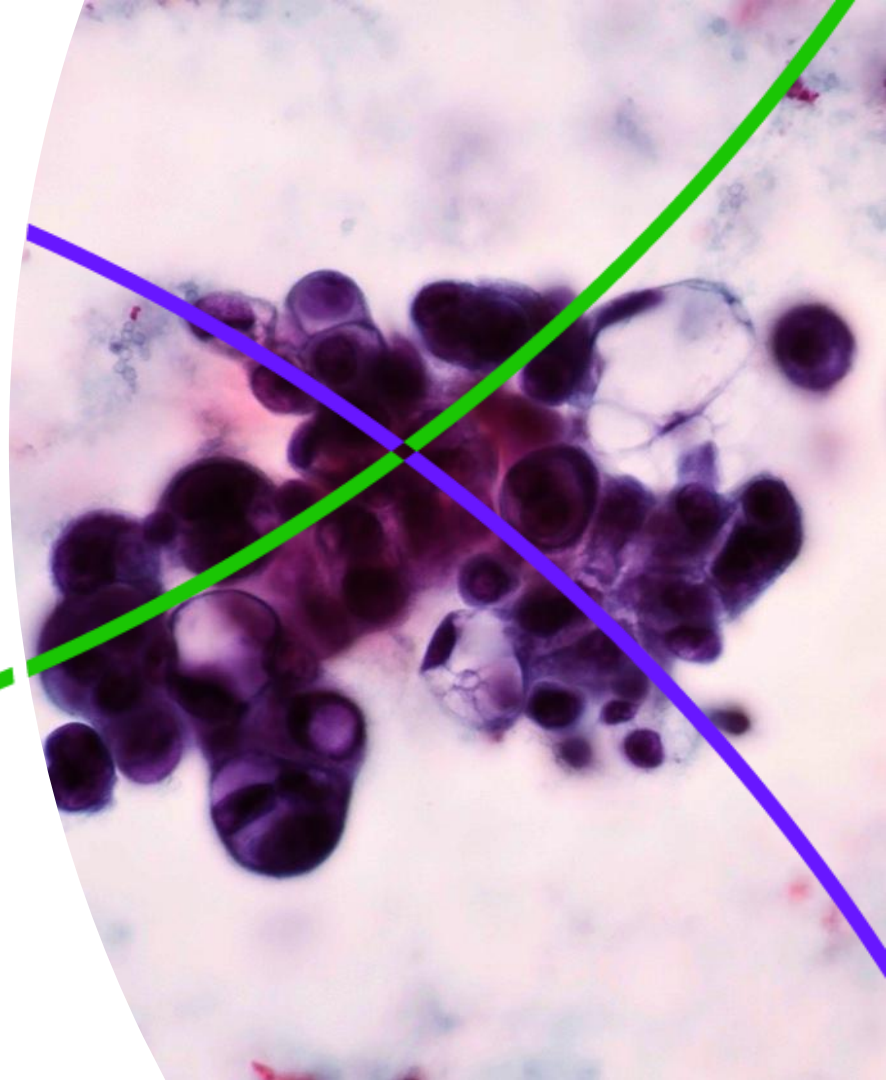
感谢参加本次会议！



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