临床试验中生物标志物的应用

Application Of Biomarkers Within Clinical Development

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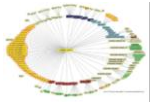

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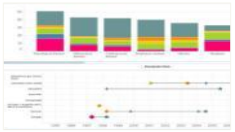

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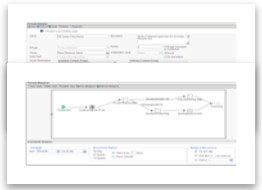

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Dr. Richard K. Harrison

Chief Scientific Officer
Clarivate Analytics

- Over 30 years of experience in the life sciences industry
- Career has focused on all aspects of pre-clinical drug discovery
- Has held positions of increasing responsibility at Aventis, Merck, DuPont and Wyeth Pharmaceuticals

Gavin Coney

Head of Clinical Products
Clarivate Analytics

- Supports decision making by professionals within Life Science organizations who are interested in gaining intelligence relating to:
  - Clinical Development
  - Clinical Operations
  - Competitive Intelligence
- Has worked within informatics for 17 years and within the Life Sciences for the last 8 years

Dr. Lee Lancashire

Principal Research Scientist
Clarivate Analytics

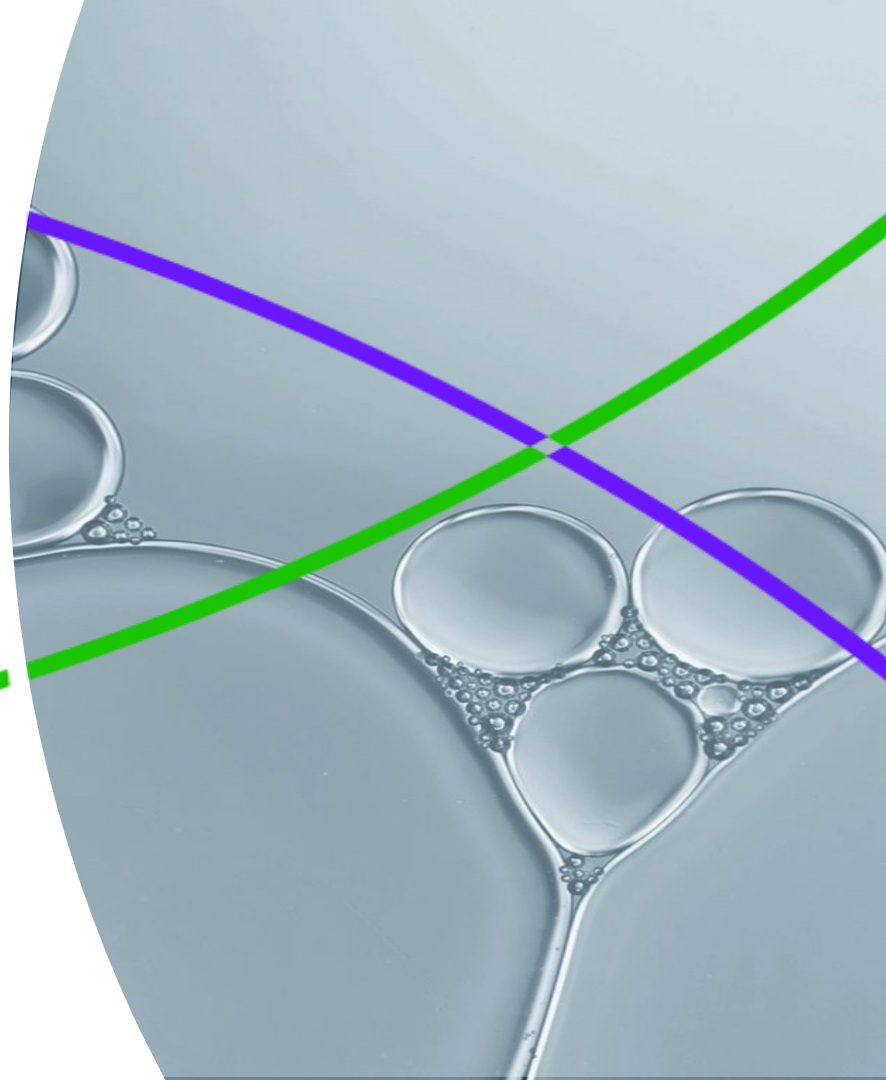
- Responsible for the development of machine learning based predictive modelling strategies
- Holds a Ph.D in machine learning
- His work leads the discovery of discriminatory biomarker signatures that will facilitate the design of molecularly targeted clinical trials

报告提纲

- 创新药领域在失败中求变
- 生物标志物在临床中的角色
- 通过基于网络的分析发现新生物标志物
- 数据库（CTI，INTEGRITY）在临床与生物标志物上的应用

失败率与“求变”

FAILURE RATES AND REASON FOR CHANGE



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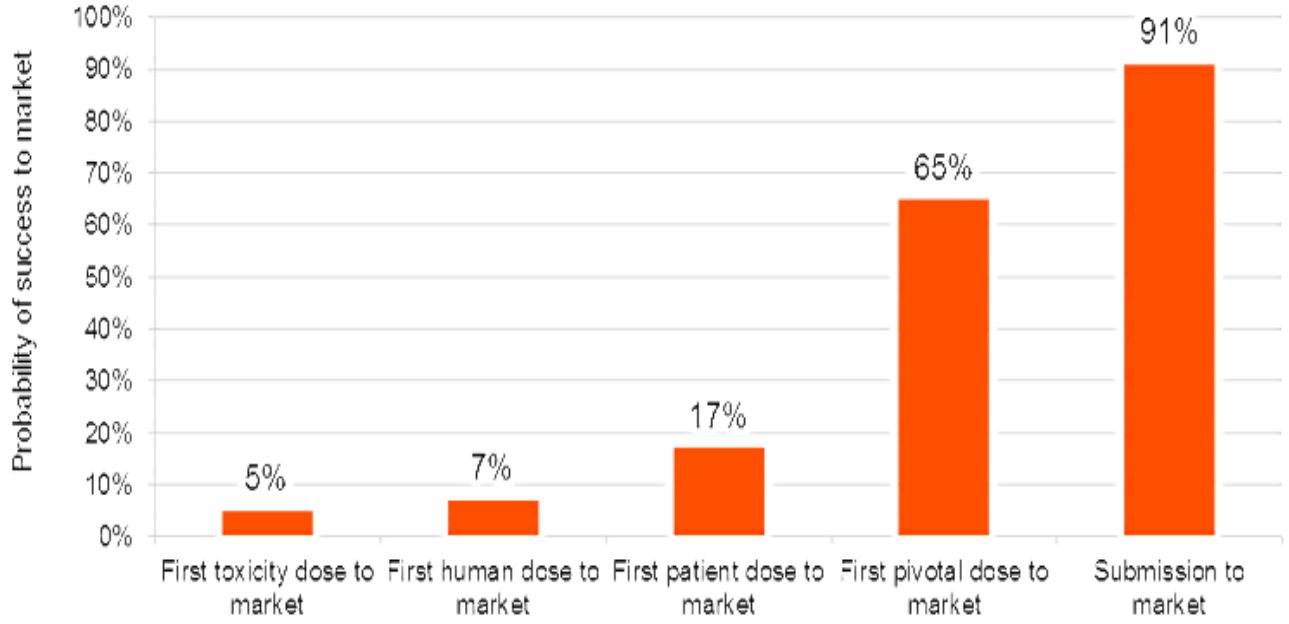
临床失败率与失败的原因

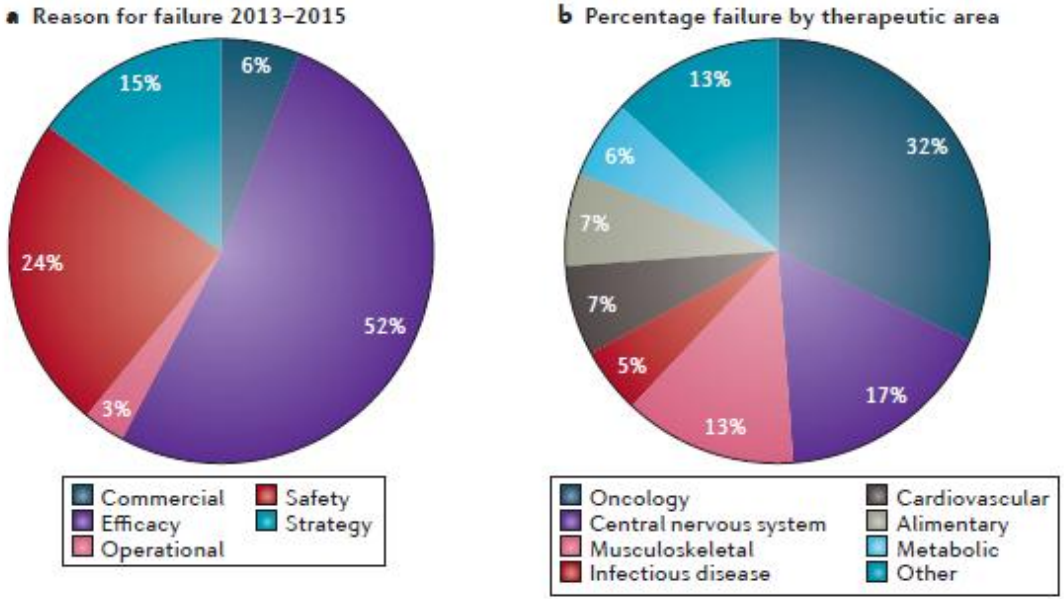
- 根据CMR Centers for Medical Research数据，在2015年从一期临床到上市的成功率小于10%（所有治疗领域的平均数据）



Nature Reviews Drug Discovery 13, 419–431 (2014) | doi:10.1038/nrd4309
Published online 16 May 2014

临床失败率及其原因

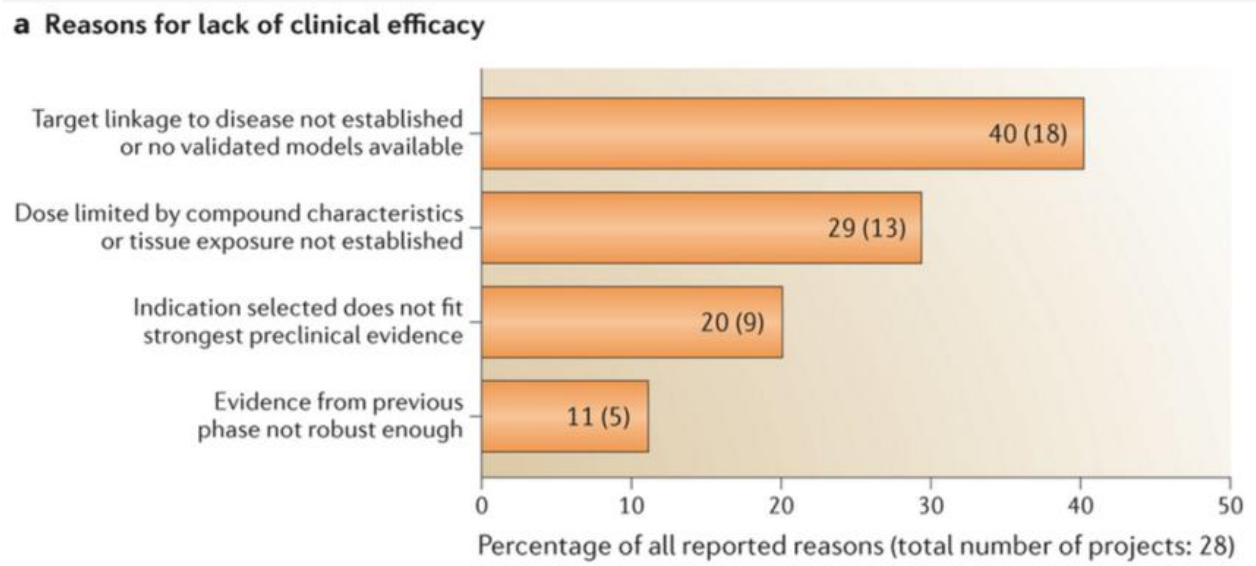
- Phase II and Phase III临床试验的失败有超过一半原因归咎于“缺乏有效性”
- 临床试验的失败广泛存在于所有的治疗领域中，但抗癌领域是最高的



Nature Reviews Drug Discovery 15, 817–818 (2016)

临床失败率及其原因

- 根据在AZ阿斯利康制药公司的一项研究，40%的临床项目是由于靶点作用机制和疾病的关联性没有被清晰的揭示出来而造成的
- 另29%的失败是由于化合物的物化性质不对或未能抵达靶组织



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我们为什么需要生物标志物

- 根据CMR Centers for Medical Research数据，在2015年从一期临床到上市的成功率小于10%
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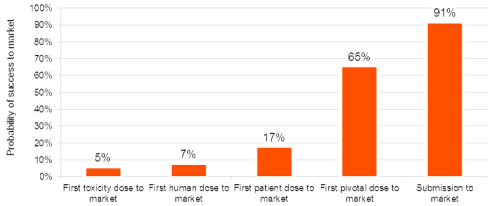

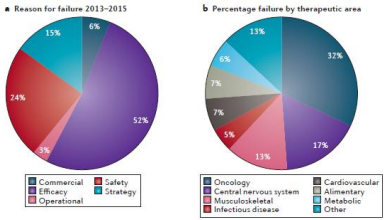

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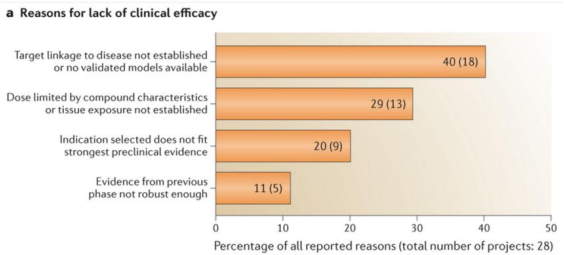

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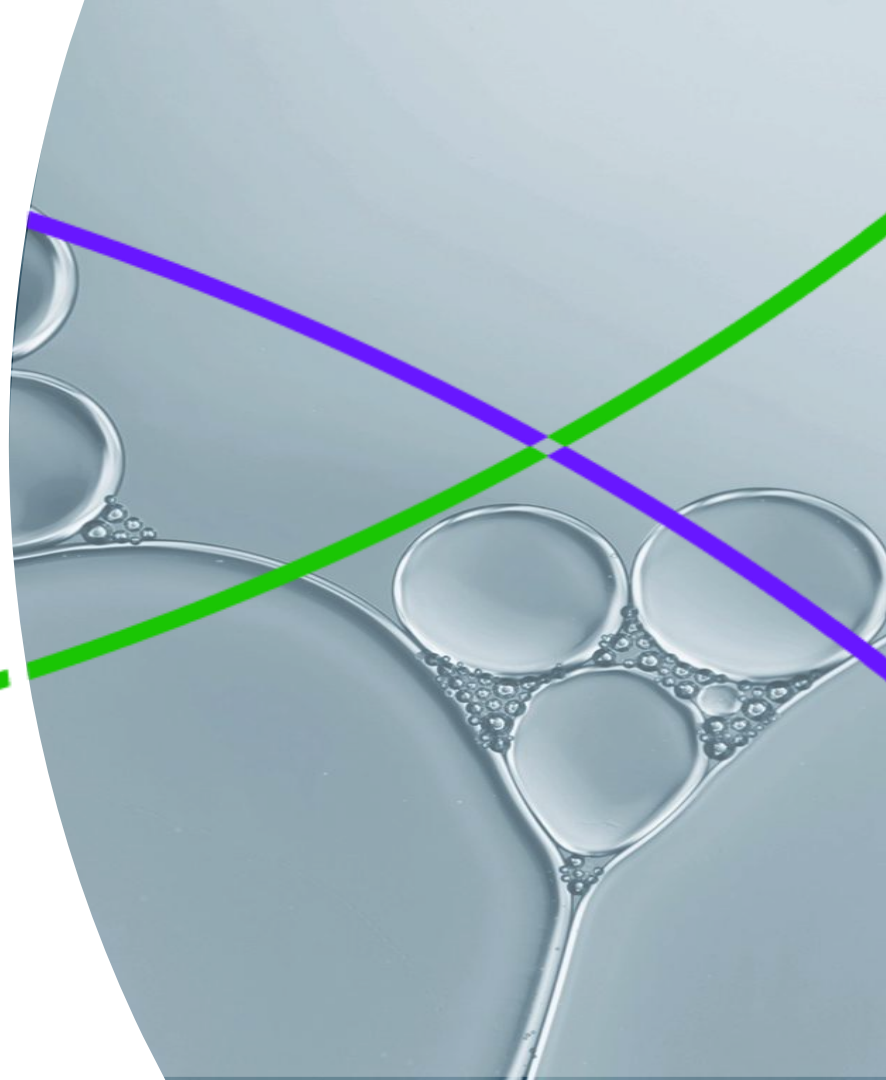
生物标志物在临床开发中的角色

BIOMARKER ROLES WITHIN CLINICAL DEVELOPMENT



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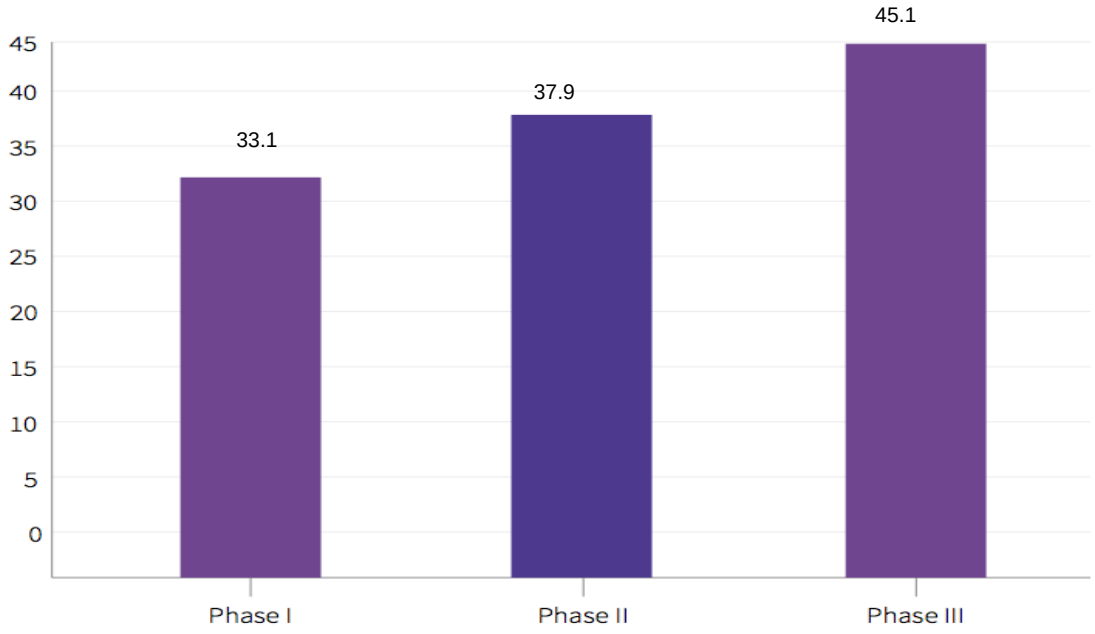
临床试验的平均周期 (Months)

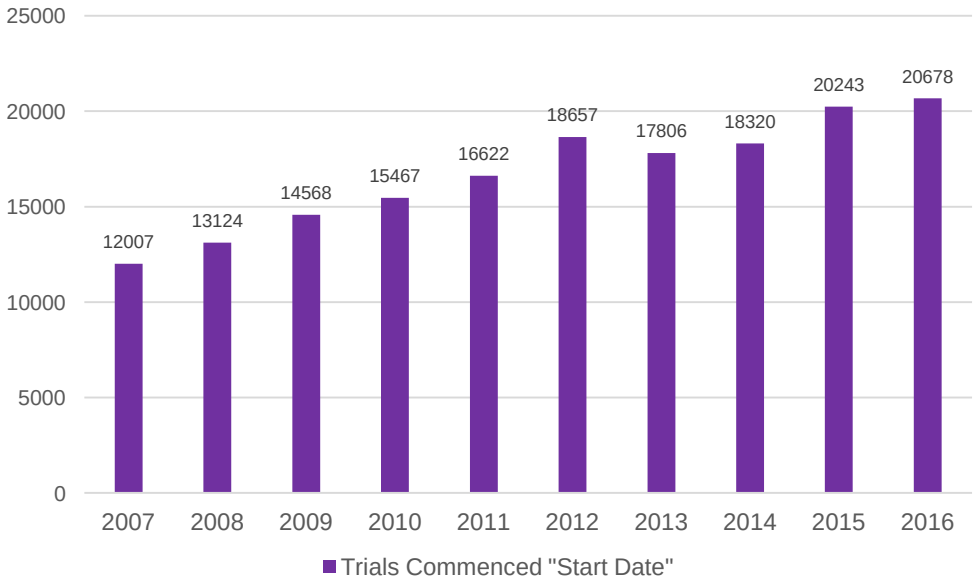


- 试验时间增加
- 临床期别之间的差别变小
- 药物研发费用增长，上市风险增加
- 尽量避免在启动试验之后，为了进一步证明疗效而对于试验方案设计的修改

（Graph includes all trials, sponsor-led and investigator led）

Journal of Health Economics, DiMasi, Joseph A, Grabowski Henry G & Hansen, Ronald W. "Innovation in the Pharmaceutical Industry: New estimates of R&D cost." 47 (2016) 20-33.

2007-2016 临床试验启动情况

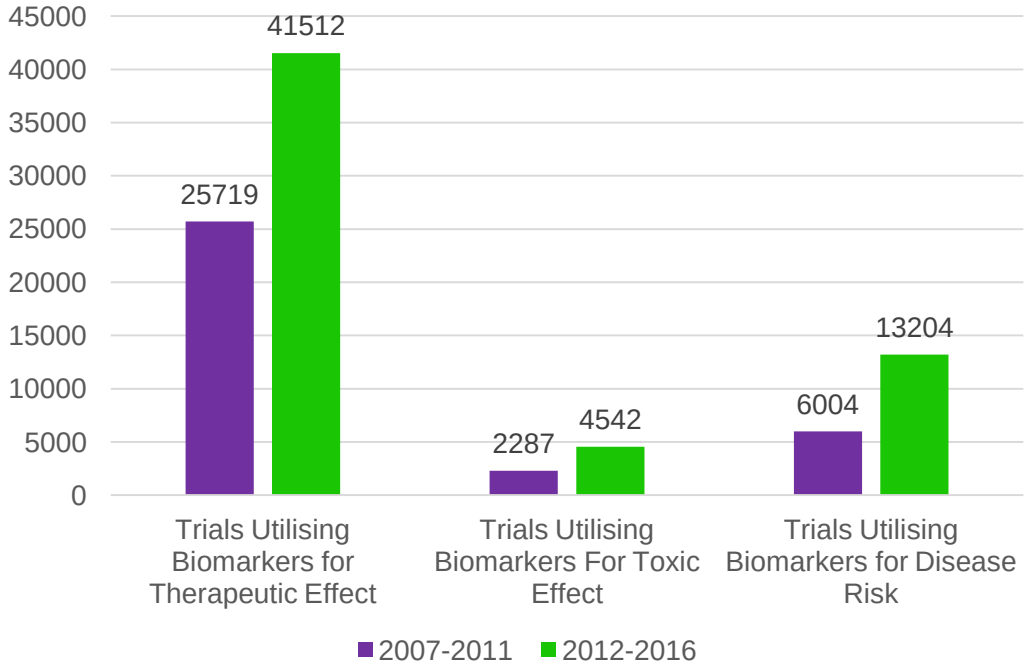


Cortellis Clinical Trials Intelligence, Clarivate Analytics, March 15, 2017.c

- 分析临床试验启动时间介于 2007-2016 年的试验
- 通过时间切片分析：
  2007-2011 vs 2012-2016,
  临床试验的数量增长了33 %
- 时间和费用的增长，意味着“病人招募”和“临床资源”竞争的加剧
- 更意味着临床试验需要一个清晰有效的战略，而且是在最佳情报支持基础上的战略：疾病机制，靶点作用，病源分层等等。
- 生物标志物的作用逐渐凸显

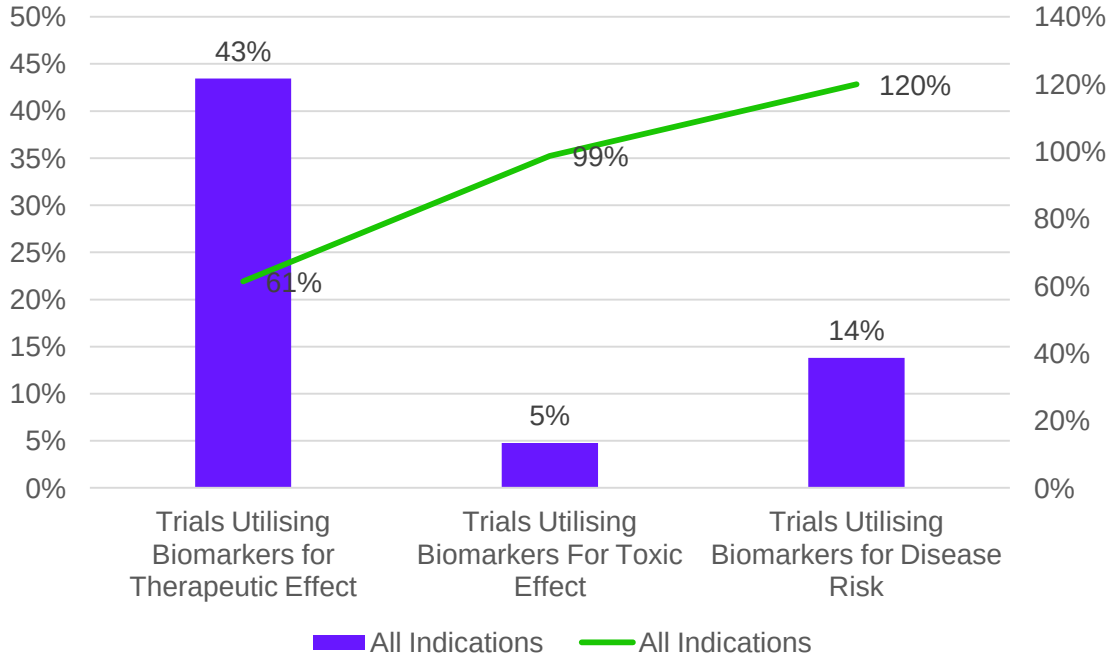
近十年来，生物标记物的应用对比 2007-2011 v.s. 2012-2016

- 对比时间段：
  - 2007 – 2011
  - 2012 – 2016
- 临床试验数量增长: 33%
- 使用生物标志物：>70%
- 在生物标记物的应用领域中，以下应用增长最为迅速：
  - 疾病相关 Disease: 120%
  - 毒理Toxic Effect: 99%
  - 治疗效果Therapeutic Effect: 61%

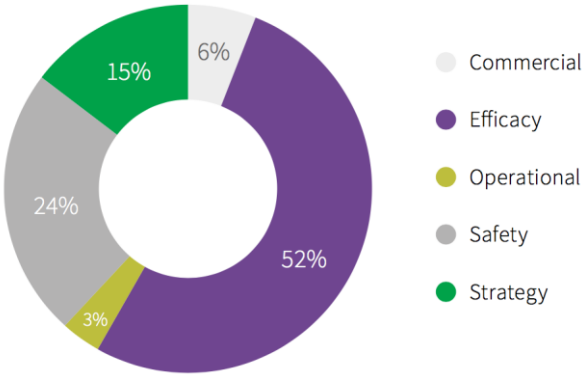


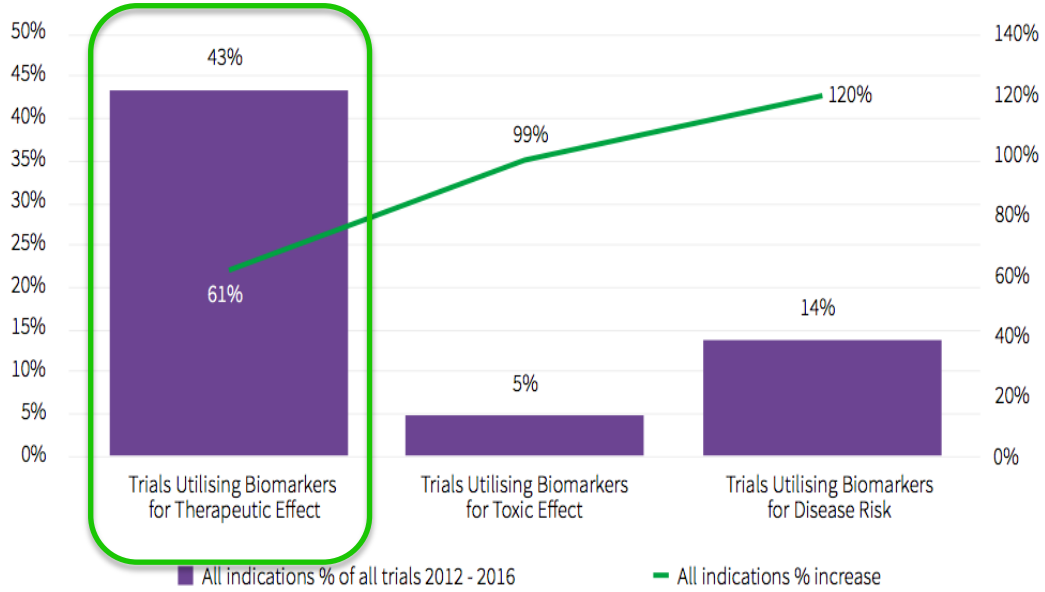
各种生物标记物“用途”在临床试验中的增长情况

- 治疗效果类
  Therapeutic Effect Biomarkers
  - Baseline: 43%
  - Growth: 51%
- 毒理类
  Toxic Effect Biomarkers
  - Baseline: 5%
  - Growth: 99%
- 疾病诊断类
  Disease Biomarkers
  - Baseline: 14%
  - Growth: 120%

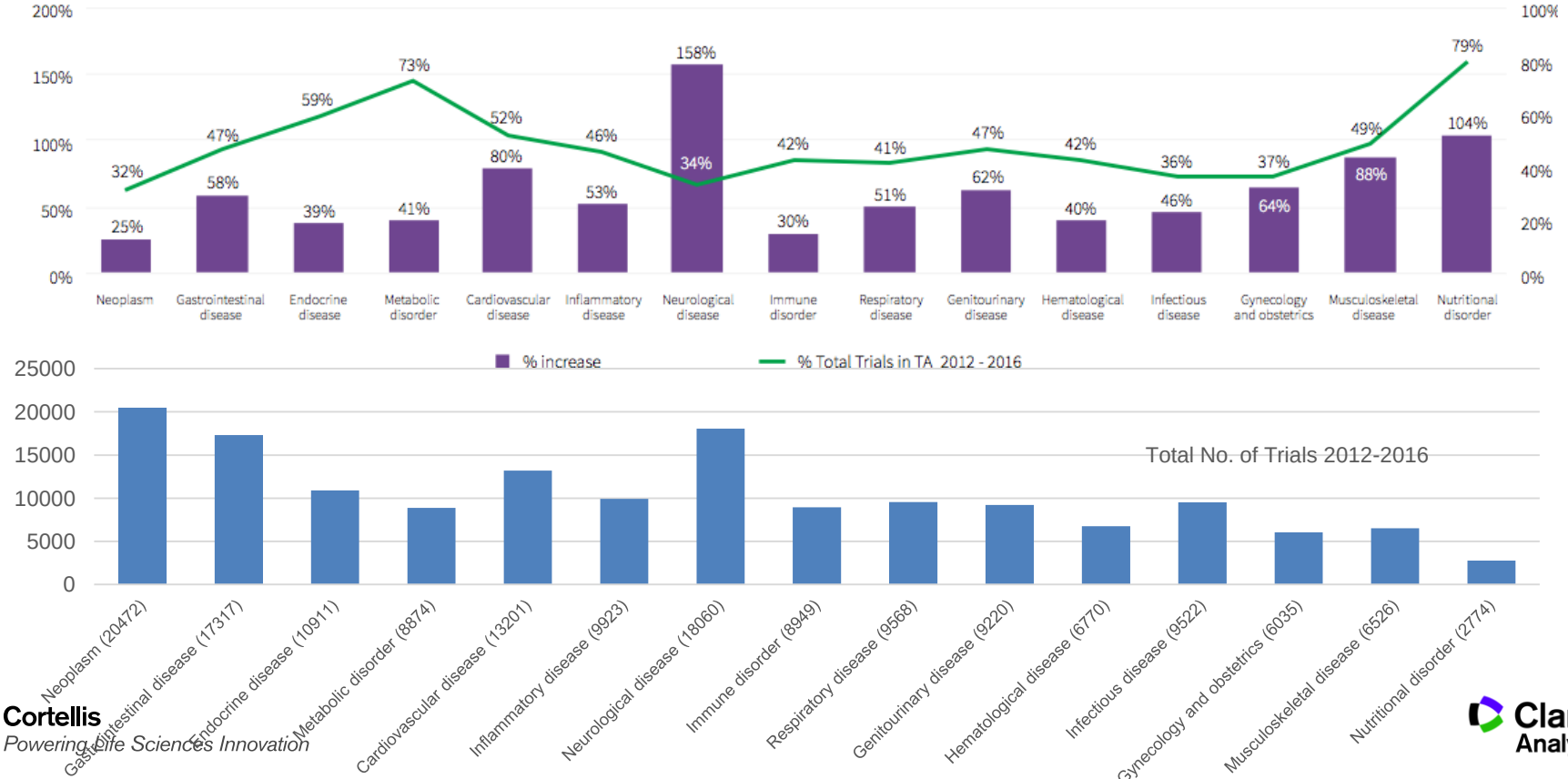


未来“疗效”类生物标志物的开发前景看好





治疗效果标记物在不同治疗领域中的变化
Therapeutic Effect Markers

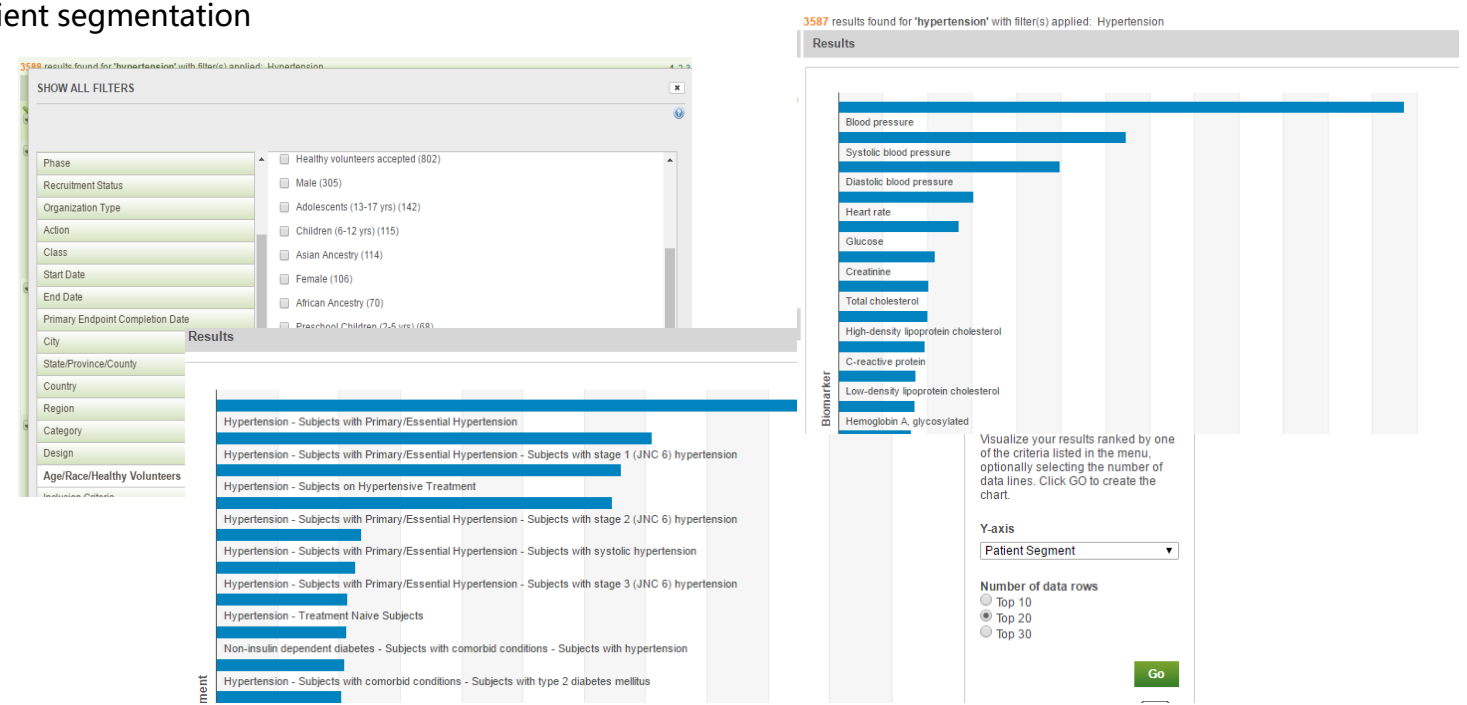


生物标记物在不同治疗领域中的变化比例分析

Cortellis Clinical Trials Intelligence, Clarivate Analytics, March 2017.c

CTI临床竞争情报: 病患分层 Patient Selection

- Cortellis has indexing for Age/Sex/Race and Healthy Volunteers
- There is also indexing on biomarkers being measured within trials, and specific gene variant indexing within the patient segmentation



CTI临床竞争情报：“生物标志物”的竞争情报

- 竞品使用的什么生物标记物?
- 为上市申报用关键临床中的基准生物标志物是什么?
- 在这个靶点机制中，有哪些生物标志物被应用与预测疗效并进一步加速临床试验进程?
- 竞品有没有伴随诊断，这对于我们的影响是什么?
- 哪个生物标记物可以展示我们药物的安全性优势？
- 竞品的生物标记物策略是什么？这如何影响竞争格局?
- 在这个靶点机制中，有没有可以进行病源分层的预测类标志物？

新生物标志物的发现

---基于网络通路，从高通量试验数据（组学数据）分析入手

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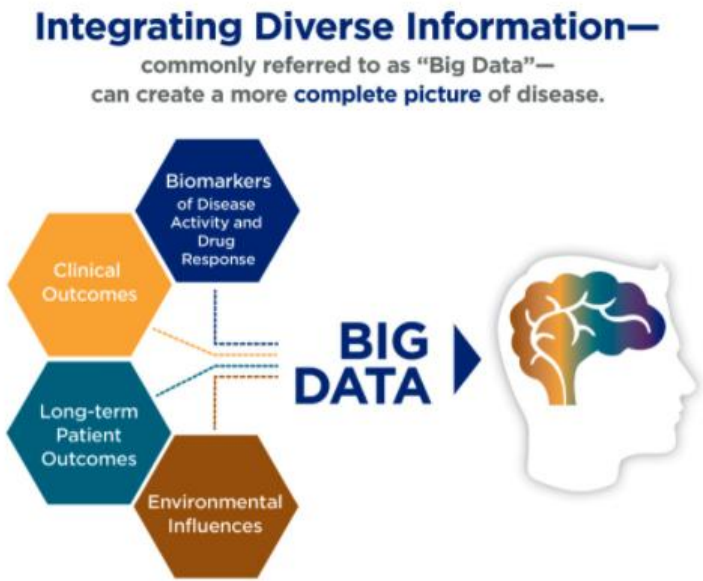
通过大数据系统建模的方式来探索疾病机理
Systems Modelling Approach to Understanding Disease



目前面临的挑战：“重复性” 低

Essay

Why Most Published Research Findings Are False

John P. A. Ioannidis

PlosMedicine, 2005

COMMENT

NIH plans to enhance reproducibility

Francis S. Collins and Lawrence A. Tabak discuss initiatives that the US National Institutes of Health is exploring to restore the self-correcting nature of preclinical research.

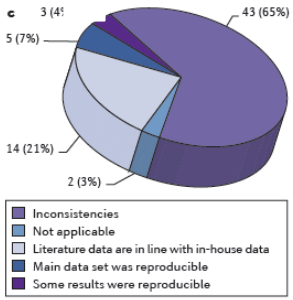
A growing chorus of concern, from scientists and laypeople, contends that the complex system for ensuring the reproducibility of biomedical research is failing and is in need of restructuring[1–3]. As leaders of the US National Institutes of Health (NIH), we share this concern and here explore some of the significant interventions that we are planning.

Science has long been regarded as 'self-correcting', given that it is founded on the replication of prior work. Over the long term, that principle remains true. In the shorter term, however, the checks and balances that once ensured scientific fidelity have been hobbled. This has compromised the ability of today's researchers to reproduce others' findings.

Let's be clear: with rare exceptions, we have no evidence to suggest that irreproducibility is about scientific misconduct. In 2011, the Office of Research Integrity of the US Department of Health and Human Services pursued only 12 such cases[4]. Even if this represents only a fraction of the actual problem, such papers are vastly

研究成果推进科学发展，但必须做到：

- **显著有效（significant），**
- **数据可靠（reliable），**
- **重复性（reproducible）.**



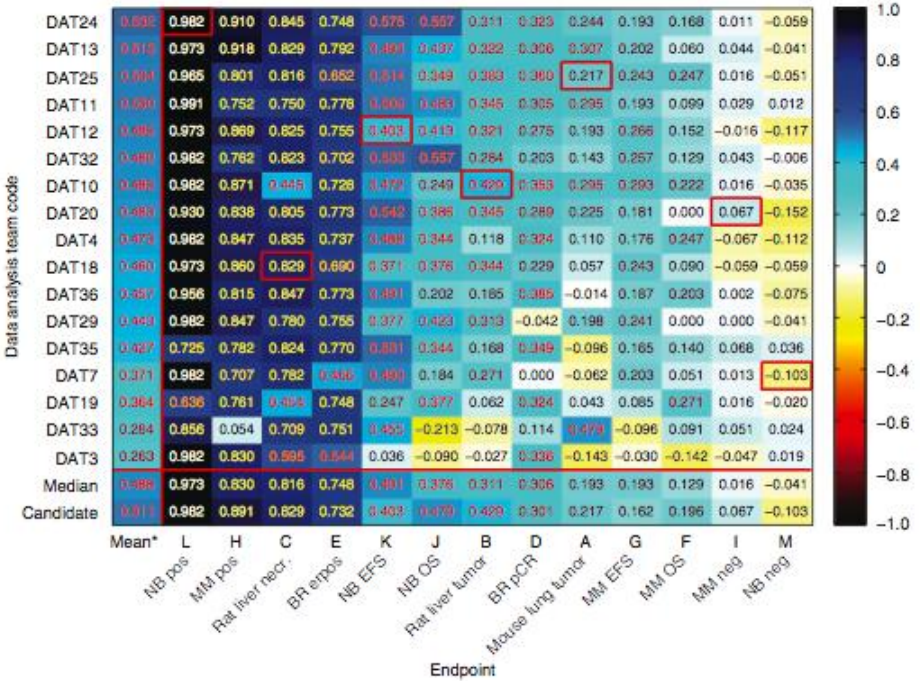
% Studies in in-house projects reproduced at Bayer (Oncology, Women's Health, Cardiovascular)

Prinz etal, Nat Rev Drug Dis, 2011

高假阳性率的可能风险因素：
Risk factors for high false-positive rates:

- 低统计功效研究 Underpowered studies;
- 有效群体小 Small effect sizes;
- Low pre-study odds;
- 研究设计/分析 Study design/analyses;
- 利益冲突 Biases and conflicts of interest;
- Bandwagon patterns;
- 缺乏合作 Lack of collaboration.

生物学机制是关注的重点



目的：检验mRNA作为生物标志物的可能性

试验：利用mRNA数据对于生物学功能（意义）进行数学建模

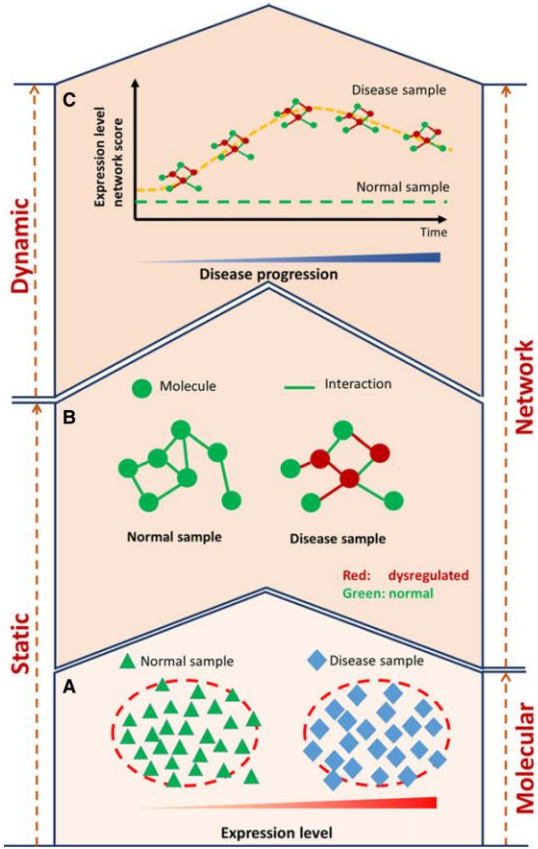
结果：

- 预测效果很不稳定
- 当模型用于“测试集”数据时，没有稳定的结果
- 不同算法产生不同的“基因指纹特征”
- 不同模型基因指纹图谱重合度低

指纹特征在信号通路层面更加一致

Leming Shi et al. MAQC-II study of common practices for the development and validation of microarray-based predictive models. Nat. Biotech., 2010

生物标志物的概念正在演进



(A) 传统分子生物标志物

- Single or a group of several markers that are static indicators on the disease state;

(B) 子网生物标志物
Subnetwork biomarkers

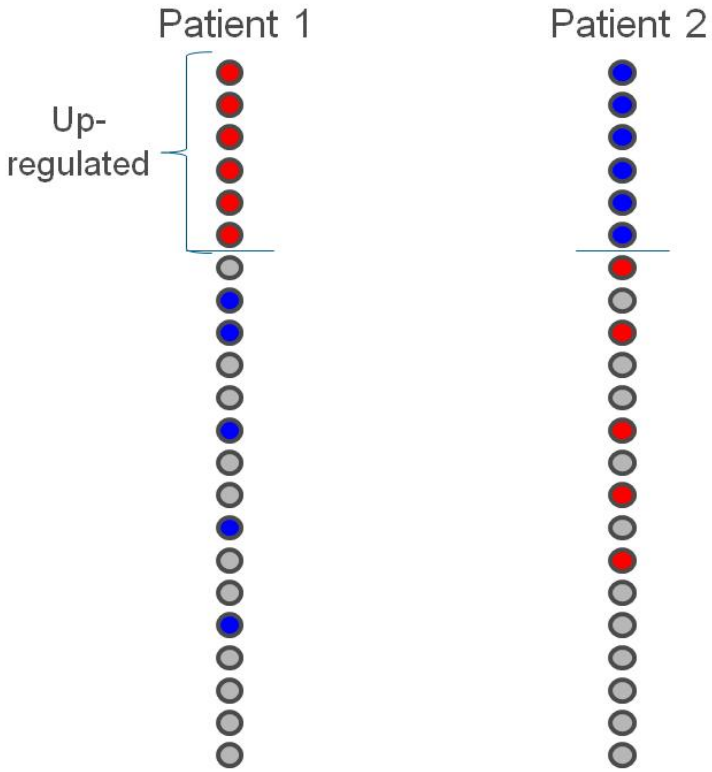
- Integration of knowledge on protein annotations, interactions, and signaling pathways, are static measurements on the disease state;

(C)动态网络生物标记物
Dynamic network biomarkers

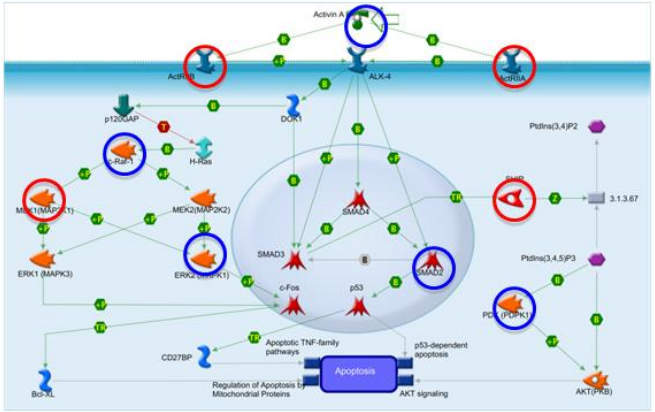
- Providing dynamic measurements on the disease state within a systems biology framework.

Chen *et al*, Journal of cellular and molecular medicine. 2015

基于网络及信号通路的方法

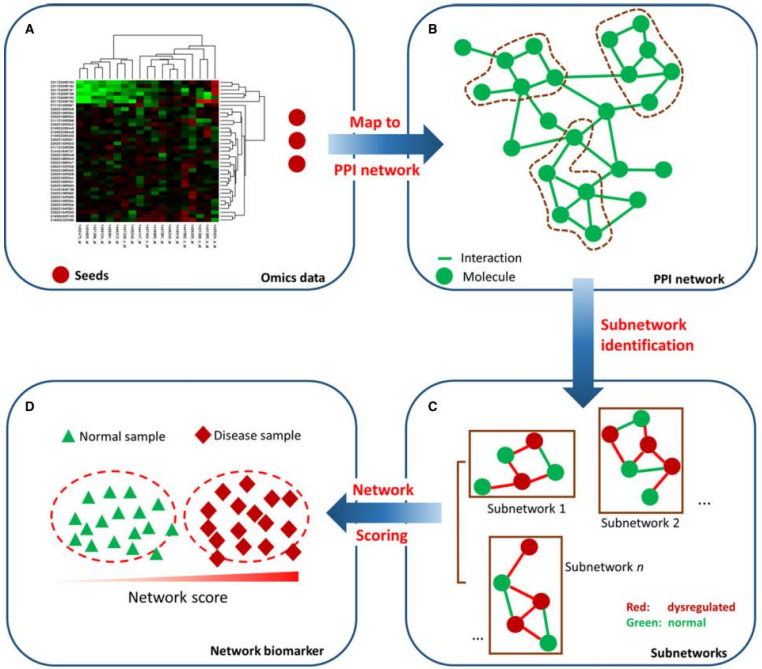


没有共同的上调基因，
但具有共同的上调通路



通过利用网络通路分析来发现新的生物标志物

表达谱（组学）数据
Expression profiles （‘omics’）of a disease phenotype (time to relapse) are obtained as ‘seeds’ of the disease module;



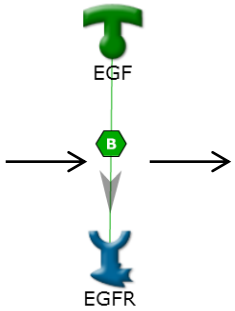
将“种子”基因整合到蛋白质网路中
Seeds integrated into the constructed protein network;

通过对于通路或子网的分析确认生物标志物
Disease pathways or modules and subnetwork biomarkers associated with time to relapse are identified.

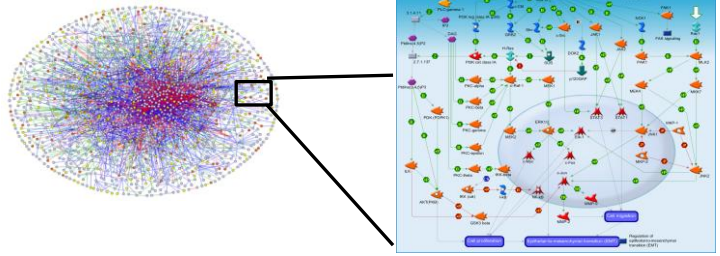
表型相关子网生物标记物将被打分排序并识别出来
Phenotype-associated subnetworks and/or pathways are then scored, ranked and identified;

数据库：Metabase 是通路信息的最佳来源

文献
PUBLICATIONS
(146 for EGF-EGFR interaction)



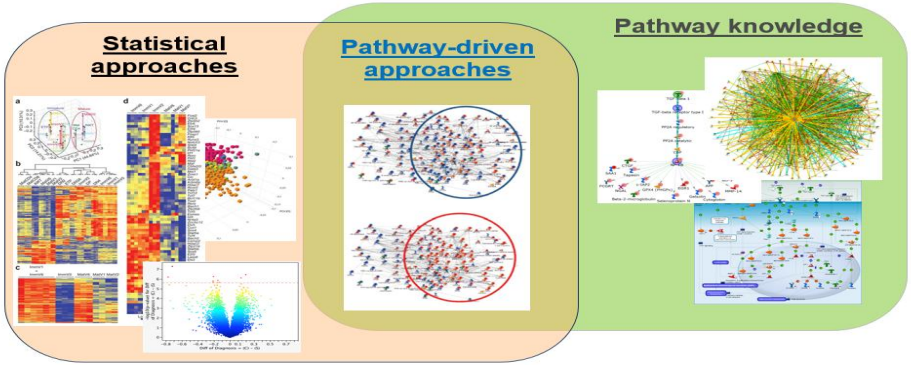
分子相互作用
MOLECULAR INTERACTION



网络 NETWORK
~ 1,500,000 molecular interactions

通路 PATHWAY
~ 3,000 pathways

- Manual annotation from publications
- Team of PhDs, MDs
- More than 10 years



分子亚型分析案例 Molecular Subtypes

挑战与目标 CHALLENGE & AIM

- **Challenge**: Multiple Sclerosis is a heterogeneous disease
- **Aim**: Identify disease subtypes and biomarkers for the subtypes

解决方案 SOLUTION

- Statistical and Pathway analysis of OMICs data
- **Input OMICs data**: CLIMB longitudinal study - gene expression profiles from ~200 multiple sclerosis patients

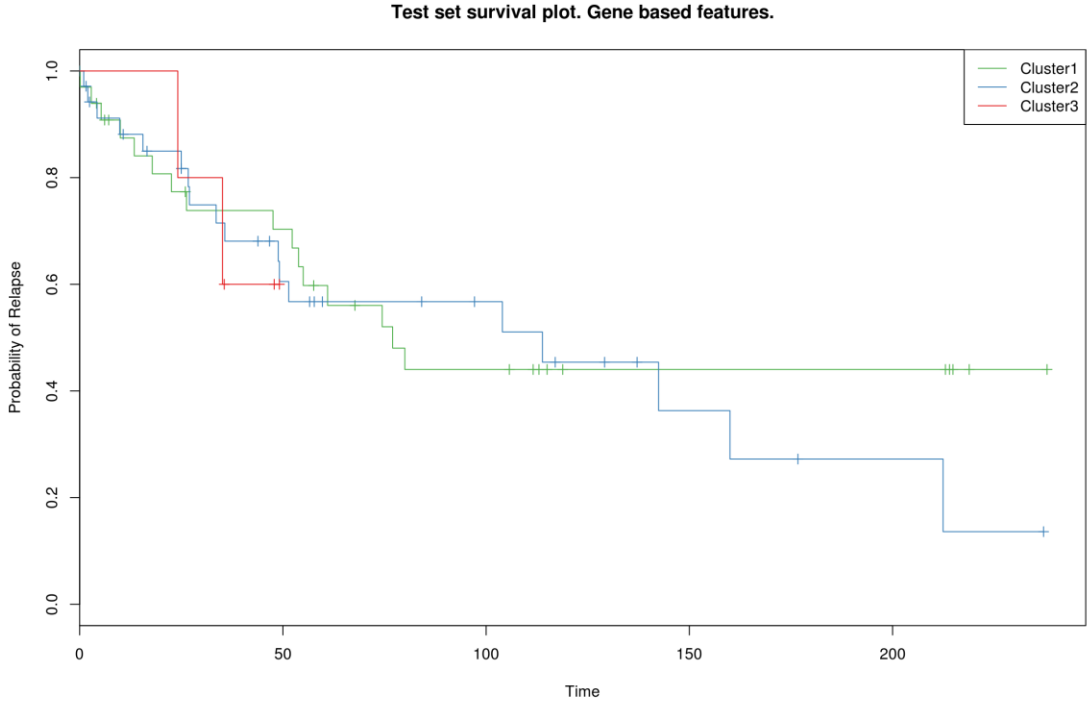
结果 RESULTS

- 3 molecular **subtypes of patients** significantly associated with disease prognosis
- Disease prognosis **biomarkers**
- **Validated on Independent Cohort**

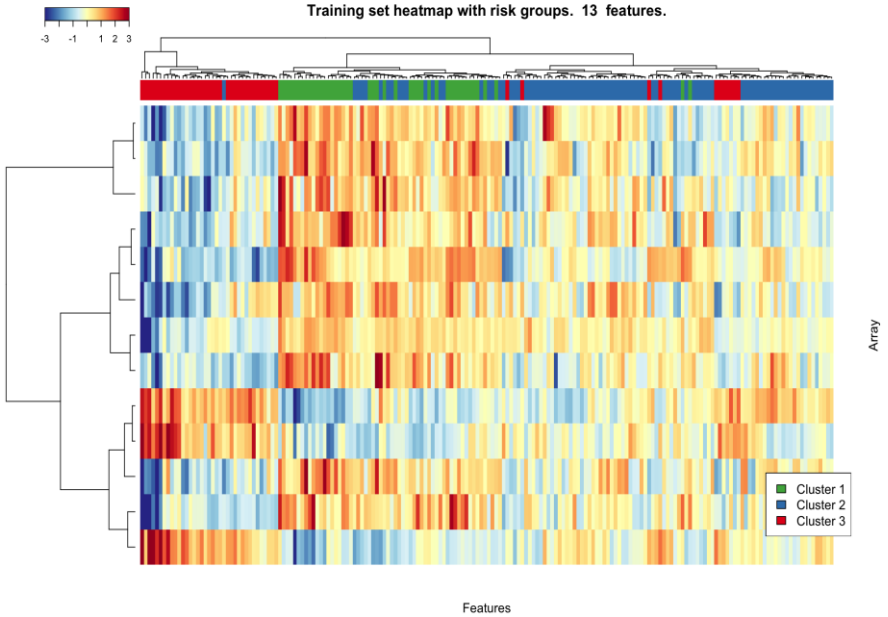
基因指纹图谱

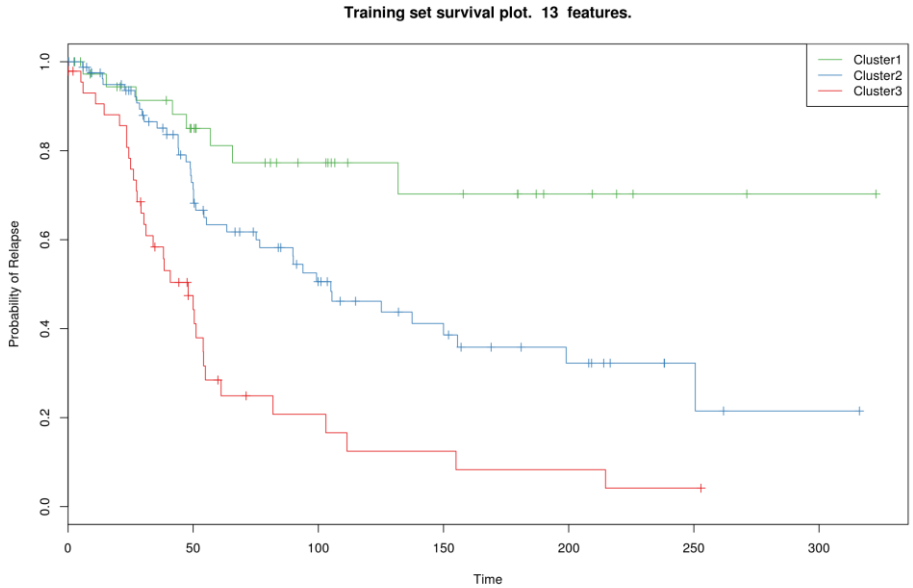
- 基因指纹图谱无法建立有效的预测模型

  Robust signature using expression data alone could not predict relapse

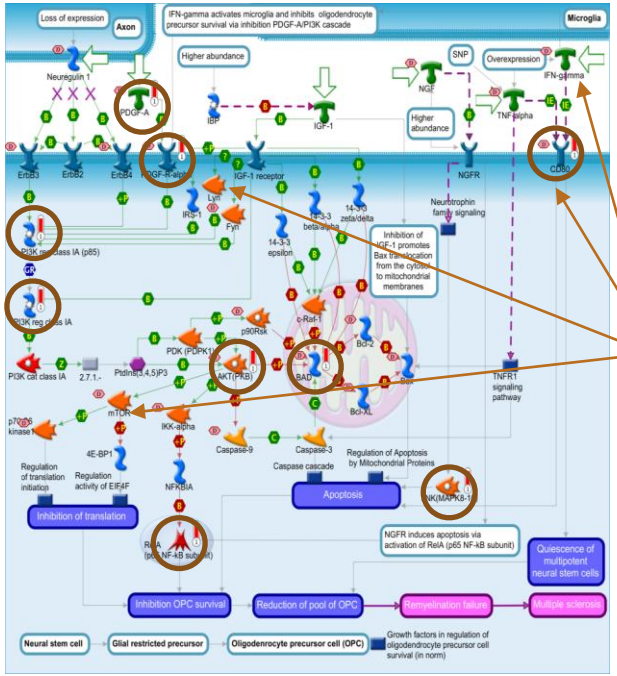


通路（子网）指纹图谱分析结果

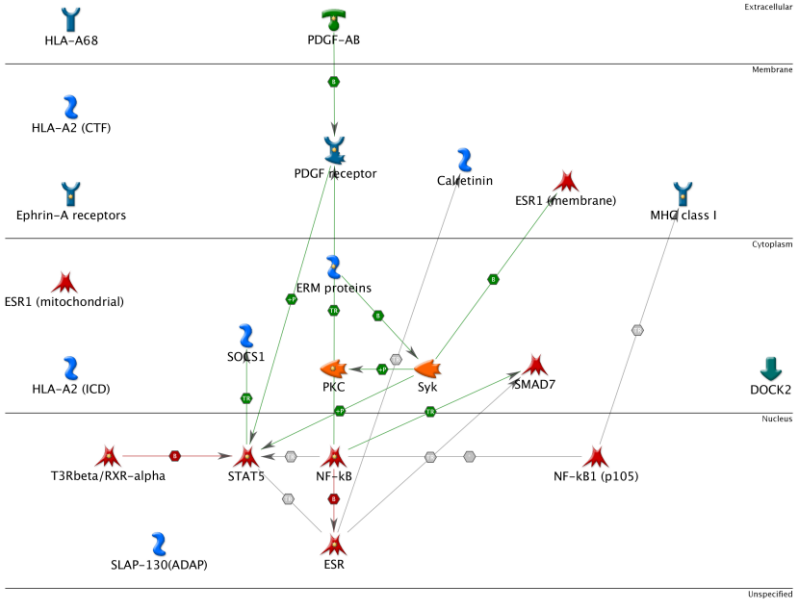




MS 疾病通路图的确认



Targets for MS drugs



临床前生物标记物的分析支持临床试验设计

目的 AIM

- Build an analytical pipeline for identification of drug response biomarkers from cell line data for further clinical trial design.

结果 RESULTS

- **A PLSR-based analytical workflow**
  - **输入数据：基线基因表达数据以及给药后细胞系IC50数据**
    Input: baseline gene **expression and post-treatment IC50 data for cell lines**
  - **输出：药物相应生物标志物**
    Output: drug response biomarkers

- **验证： Validation of the pipeline (Li et al, 2015)**
  - Identified drug response biomarkers for Erlotinib starting from gene expression and IC50 data for 240 cell lines (OncoPanel)
  - Validated the biomarkers on patient data from BATTLE clinical trial (84% accuracy).

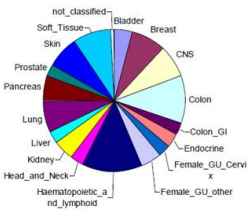
分析结果

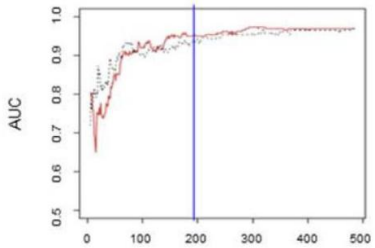
厄洛替尼的训练集

Trained Erlotinib sensitivity model on cell line data

- Built a PLSR model with 94% accuracy, 191 genes
- Signature was filtered using pathway information
- Functionally connected signatures genes retained in the model

Ricerca Oncopanel cell based assay:

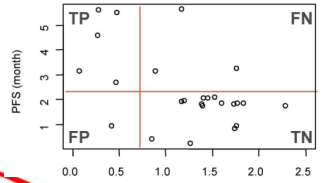


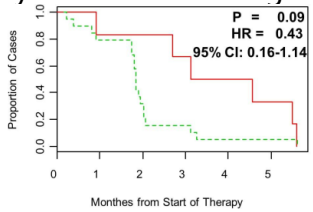


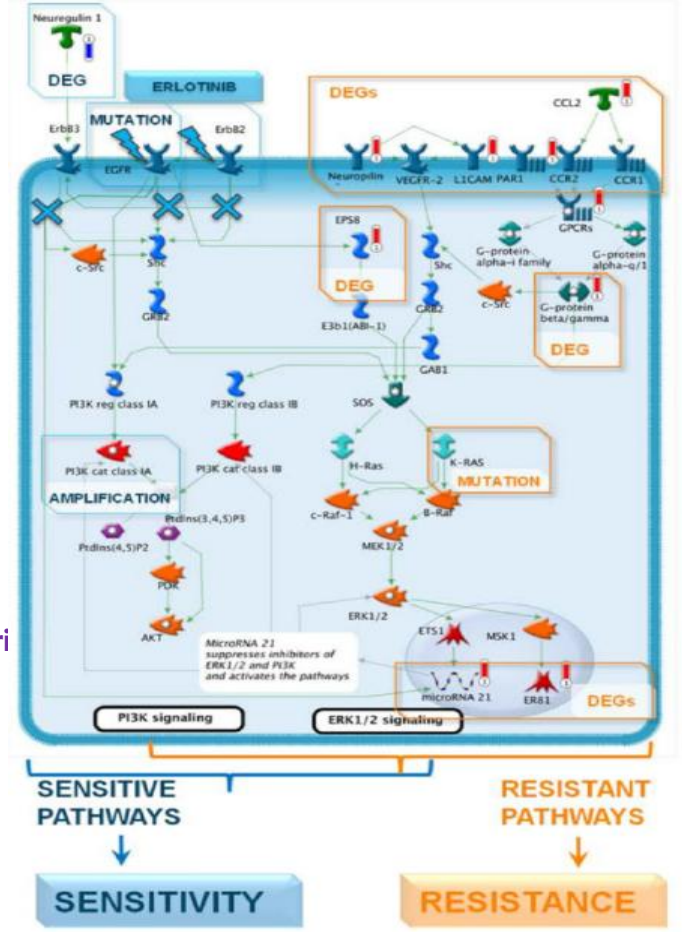
通过BATTLE临床试验检验模型的准确率

Tested Erlotinib sensitivity model on patient data from BATTLE clinical tri

- 84% accuracy and separating sensitivity and resistant subgroups







厄洛替尼与索拉芬尼的敏感性预测（GEO公开数据）

Results- Predicted percentage of Erlotinib and Sorafenib sensitive samples for some cancer indications from Gene Expression Omnibus datasets.

Cancer Type	Number of samples	Pred. Erlotinib Sen. percentage	Pred. Sorafenib Sen. percentage
***FDA approved Erlotinib or Sorafenib indications*:**			
Lung Cancer	329	15.81	0.61
Liver Cancer	85	0.00	31.76
Kidney Cancer	218	0.46	24.77
***Additional indications*:**			
Head and Neck Cancer	168	94.05	12.50
Bladder Cancer	102	41.18	3.92
Acute lymphoblastic leukemia	516	4.26	64.73
Diffuse Large B-Cell Lymphoma	816	2.45	30.51
Acute myeloid leukemia	1118	0.45	15.74
Multiple myeloma	596	0	27.01
Bone Cancer	88	0.00	29.55
Breast Cancer	1668	5.64	6.47
Colorectal Cancer	948	0.11	0.21
Pancreatic Cancer	75	0.00	1.33

The predictive models were derived from cell line Oncopanel expression data. Patient data normalization is described in the result section.

doi:10.1371/journal.pone.0130700.t001

Li B, Shin H, Gulbekyan G, Pustovalova O, Nikolsky Y, et al. (2015) Development of a Drug-Response Modeling Framework to Identify Cell Line Derived Translational Biomarkers That Can Predict Treatment Outcome to Erlotinib or Sorafenib. PLoS ONE 10(6): e0130700. doi:10.1371/journal.pone.0130700
http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0130700

Cortellis Clinical Trials Intelligence

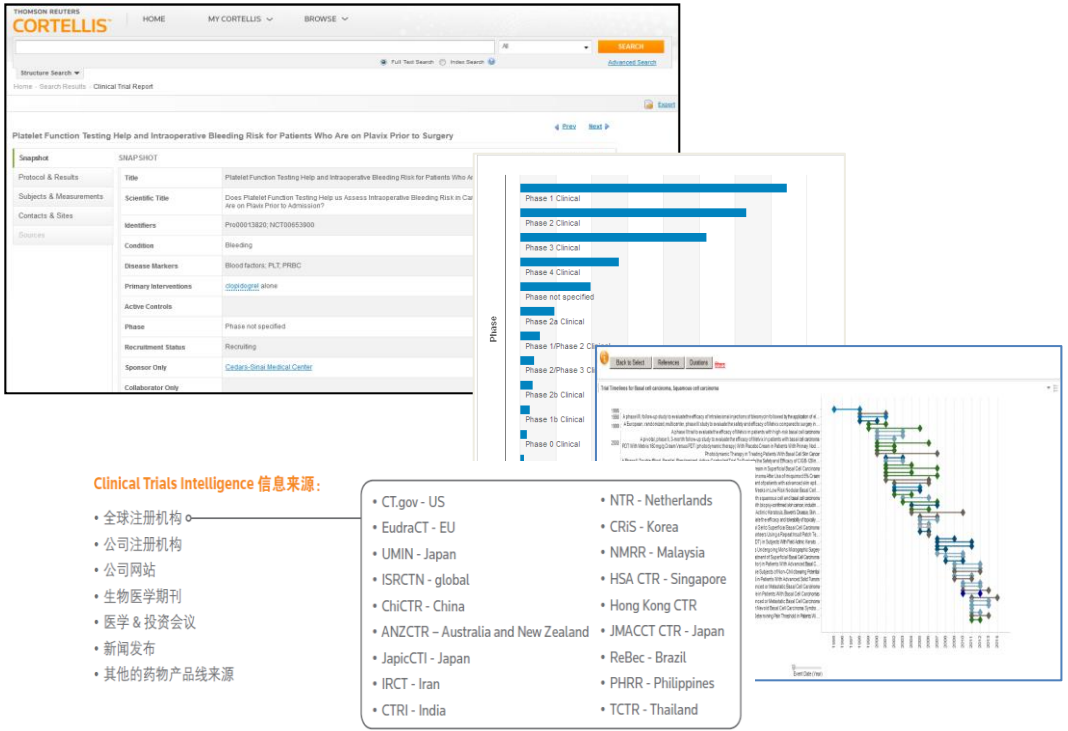
临床试验竞争情报数据库

Clarivate Analytics

CTI可以解决的问题

通过应用临床试验数据的降低临床试验风险

---Cortellis CTI 临床试验数据库



Clinical Trials Intelligence 信息来源：

- 全球注册机构
- 公司注册机构
- 公司网站
- 生物医学期刊
- 医学 & 投资会议
- 新闻发布
- 其他的药物产品线来源

- CT.gov - US
- EudraCT - EU
- UMIN - Japan
- ISRCTN - global
- ChiCTR - China
- ANZCTR – Australia and New Zealand
- JapicCTI - Japan
- IRCT - Iran
- CTRI - India
- NTR - Netherlands
- CRiS - Korea
- NMRR - Malaysia
- HSA CTR - Singapore
- Hong Kong CTR
- JMACCT CTR - Japan
- ReBec - Brazil
- PHRR - Philippines
- TCTR - Thailand

- 260,000多的美国及全球的临床试验记录（报告）
- 20,000多个信息来源
- 覆盖化药、生物药、医疗器械、生物标记物等
- 314,000多个新闻公告
- 240,000 临床文献全文索引临床试验结果
- 2,250,000 临床论文
- 53,000 临床会议综述

临床试验数据的来源

- Clinicaltrials.gov (US registry)
- Clinicastudyresults.org (PhRMA outcomes)
- UK registry
- Australia/NZ registry
- Chinese registry
- Indian registry
- EudraCT (EMA's registry)
- ISRCTN (pan European registry)
- Japanese registries (three)
- Netherlands registry
- Brazilian registry
- Korean registry
- Iranian registry
- Abbott registry
- Almirall registry
- Amgen registry
- Astellas registry
- AstraZeneca registry
- Bayer AG registry
- Boehringer Ingelheim registry
- Bristol-Myers Squibb registry
- Eli Lilly registry
- GlaxoSmithKline registry
- Hoffmann-La Roche registry
- J & J registry
- Lundbeck registry
- Menarini registry
- Merck registry
- Novartis registry
- Pfizer registry
- Sanofi registry
- Takeda registry

PubMed/Medline Literature

CCR Literature

Biosis Literature

Other Literature (DDF/Integrity)

Medical meetings (300+ covered)

Press releases (multiple sources)

African registry

Cuban registry

Sri Lankan registry

Malaysian registry

South African registry

Tanzanian registry

Canadian registry

Estonian registry

Czech registry

Peruvian registry

Italian registry

Russian registry

German registry

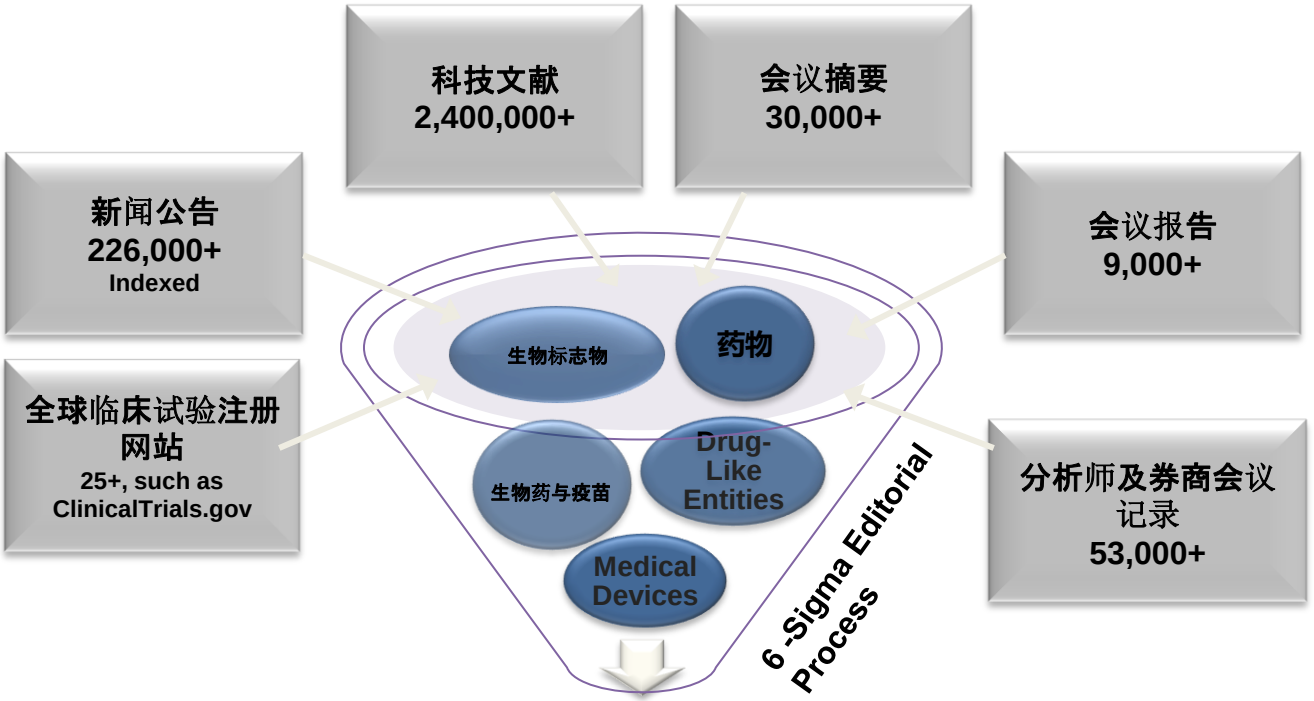
Expanded indication coverage

Backfile expansion for literature & news

Foreign language literature

Event Transcripts (Investor Meetings)

Cortellis Clinical Trials Intelligence 信息来源



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索引项目（可检索、过滤、分析、解读、跟踪）

试验概况	竞争状态	临床开发	临床运营
◦ 适应症 ◦ 干预药物 ◦ 期别 ◦ 入组状态 ◦ 作用机制 ◦ 类别 ◦ 种类 ◦ 设计 ◦ 先锋适应症 ◦ 独立用药 ◦ 联合用药 ◦ 活性对照 ◦ 注册来源 ◦ 跟新日期	◦ 申办方、合作方 ◦ 机构类别 ◦ 申办方 ◦ 合作方 ◦ 商业用途 ◦ 开始日期 ◦ 结束日期 ◦ 主要终点 ◦ 终点完成日期	◦ 病患分层 ◦ 生物标记物 ◦ 生物标记物类型 ◦ 生物标记物作用 ◦ 年龄/种族/健康受试者 ◦ 入组标准 ◦ 排除标准 ◦ 终点类型 ◦ 试验终点 ◦ 结果公布 ◦ 达到重点与否 ◦ 不良反应	◦ 中心名称 ◦ 联系人/PI名称 ◦ 城市 ◦ 省、州、县 ◦ 国家 ◦ 入组结束日期 ◦ 入组人数 ◦ 入组率

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Top 10 Use Cases

- 临床方案设计
  - 哪些生物标记物正用于病患分层，我该选用哪一种？
  - 哪一种阳性对照可以获得全球的认可？
  - 哪种入组条件可以让试验更简单，减小花费，增加招募，进而得到全球的批准？
  - 如何有效追踪我的竞争对手的临床方案设计？
- 临床科学数据
  - 竞争I期和II期的试验结果验证了我们关于作用机制的想法吗？
  - 为什么竞争对手会选择在这样一个特定的病患分层进行试验？
  - 生物标记物的临床有效性如何?

Top 10 Use Cases (续)

- 竞争情报
  - 在我的领域，谁还在做着临床研究？他们有可能与我形成竞争吗？他们以后会进入什么适应症？病患分层？
  - 我的竞争对手以后会到达什么临床终点？我需要拿出怎样的临床试验结果去迎战？我该做怎样的定位？
  - 竞争试验的时间轴如何？竞争对手的产品预计何时进入市场？对于相同的病人群体，至少有哪些竞争产品？
  - 我的竞争试验进展如何？我该如何运行我的试验以减小竞争产品对病人的影响？

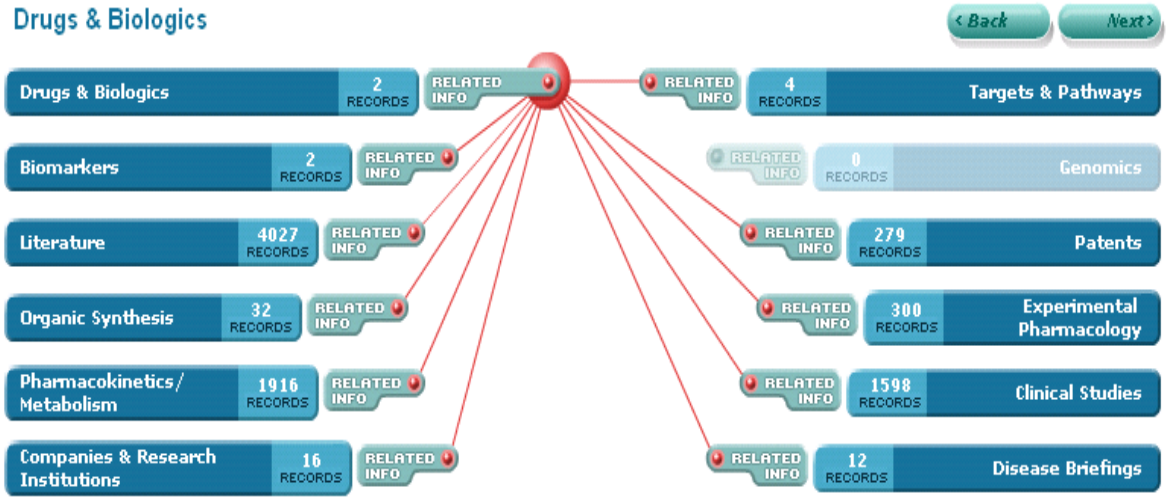
科瑞唯安的“CTI临床试验数据库”对于客户的价值

- 全面：
  - 250,000（CTI）vs 150,000（ct.gov）
  - 非英语区域（日本）：20,310（CTI）vs 4380（ct.gov）
  - 新兴市场（中国）：12,747 vs 8,964
- 及时：
  - 每天更新，包括结果
- 准确：
  - 有数据来源，经过信息核查，数据QAQC
- 整合：
  - 整合了最完善的管线竞争情报平台CCI，包含药物描述，竞品研发历程，市场信息
- 先进：
  - Biomarker信息的整合，帮助客户进行病源分层
- 可视化：
  - 最新的可视化内容

INTEGRITY 和 METACORE

INTEGRITY面向新药早期开发的深度的研发平台

- 早期研发药物产品管线
- 疾病、靶点评估
- 实验设计的参考与评价
- 药物研发的药理药代数据
- 临床、疾病、文献、专利等



数据：

药物 （化药与生物药）	>438,309 （>401,585结构式）
药物靶标	>2,556
基因组	>33,613
化学全合成途径	>26,702
生物标志物	>28,925
药理/毒理试验数据	>1,633,146
药代/药动试验数据	>647,939
试验模型	>27,263
临床试验	>234, 665
疾病综述	152
研发单位	>14,974
文献期刊及会议	>1,823,336
专利文献	>272,025

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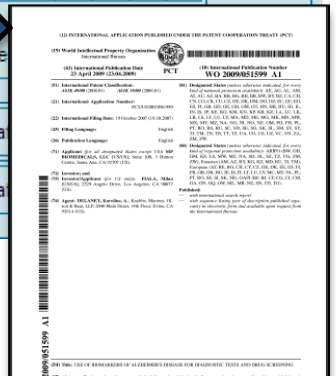
阿尔兹海默相关生物标志物列表及相关文献

- Have any competitors already thought of using CD44 as a marker for Alzheimer’s Disease?

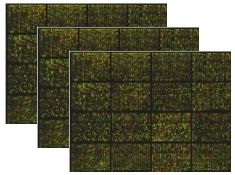
CD44 antigen — Show References — Show Patents

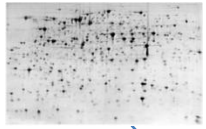
Dementia, Alzheimer's type

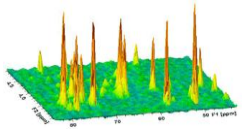
Population	Role	Technique (Substrate)	Parameter	Validity (Authority)	Sources	+	+/-	-	All	
All	Diagnosis	Confocal microscopy (PBMC)	NA	Emerging	Pat	1	0	0	1	View Use
All	Diagnosis	IHC (Tissue)	NA	Experimental	Ref	1	0	0	1	View Use
All	Diagnosis	Real Time PCR (RNA)	NA	Emerging	Ref	1	0	0	1	View Use
					Pat	1	0	0	1	
All	Disease Profiling	Oligonucleotide array analysis (RNA)	NA	Experim		1	0	0	1	View Use
All	Disease Profiling	Oligonucleotide array analysis (mRNA)	NA	Experimental	Re					
All	Risk Factor	ELISA (Plasma)	NA	Emerging	Pa					
All	Risk Factor	Oligonucleotide array analysis (mRNA)	NA	Emerging	Pa					



METACORE：系统生物学（机制研究）数据库

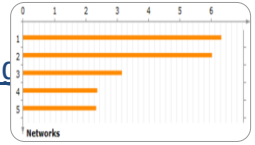




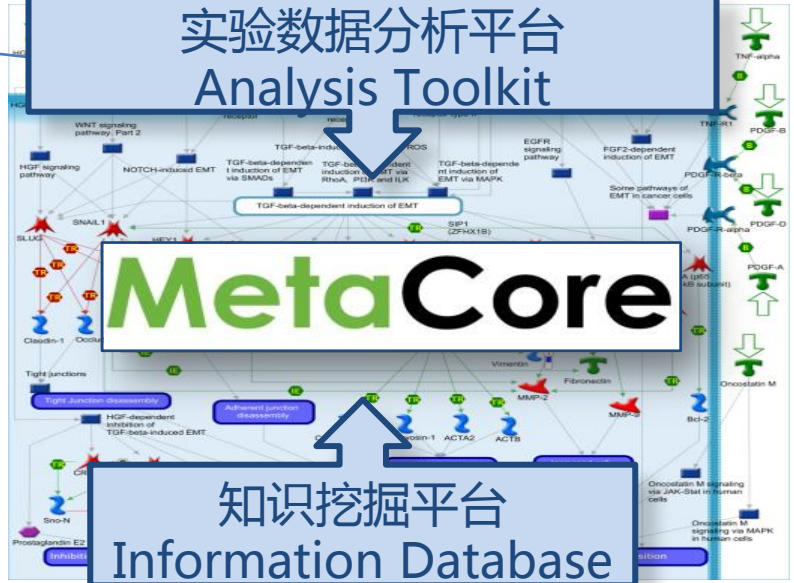


Experiment Data

Knowledge Mining Data



实验数据分析平台
Analysis Toolkit



知识挖掘平台
Information Database

Original Publications

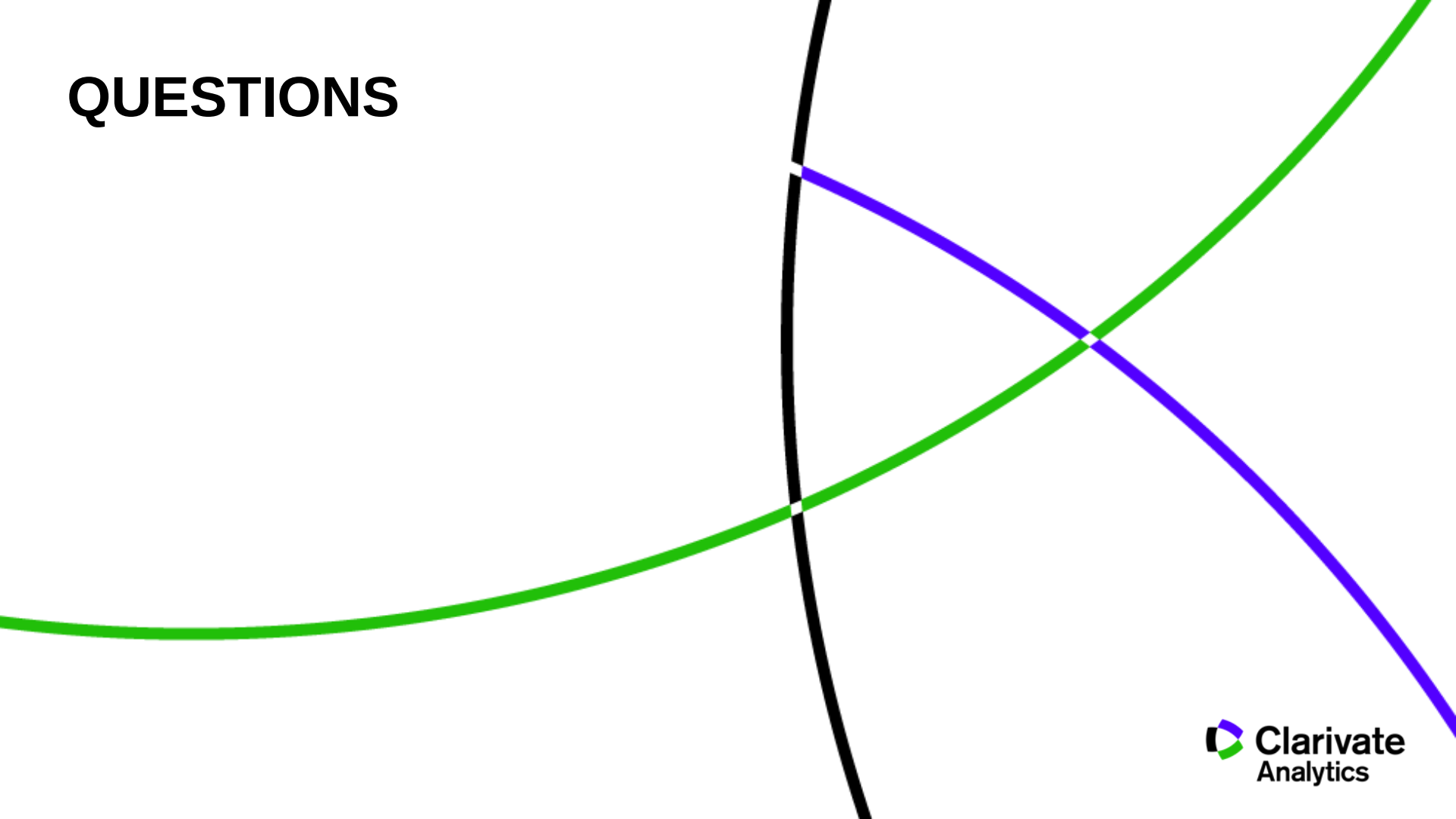
~3000 Scientific Journals 20+ YEARS

Annotated by PHD and MD level Scientists

Cortellis
Powering Life Sciences Innovation

Clarivate Analytics

QUESTIONS



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2016年药物靶点的机会和挑战
哮喘及慢性阻塞性肺病全球品牌药市场格局及趋势分析
《癌症研究》75周年：高被引论文精选
Simon Reed教授访谈：寻找癌症治疗之路
美国总统大选结果揭晓，生物制药和医疗器械行业的一些悬念解除
推进精准医疗，加强精准用药——基因变异的解读是关键瓶颈
肿瘤免疫在希望之光中前行：当前药物研发的机制、策略及方法（上）
肿瘤免疫在希望之光中前行：当前药物研发的机制、策略及方法（下）

非常感谢！

Clarivate Analytics

李寅

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