

AI助力科研选题

--从灵感到行动的全流程支持

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2025年1月



- ➔ 1. 科研中选题的重点
- 2. AI在医学科研中的作用和好处
- 3. 使用思路和案例
- 4. 附录

1.科研中选题的重点

要选好题需做好文献综述

研究价值和创新性

- (临床)需求为导向, 如未满足的诊疗需求、治疗空白
- 避免重复研究, 注重原创性和差异化
- 跨学科

可行性和资金

- 资源限制、伦理、风险
- 基金申请

文献和数据调研

- 充分的查询文献, 了解现状, 发现差距



1. 科研中选题的重点

选题是研究成败的关键，文献综述是克服选题难度的重要工具

- 识别学术空白(治疗机制研究薄弱)
- 前沿趋势分析(最新有影响力的文献)
- 识别不足与争议
- 明确技术和方法需求，提升可行性
- 增强选题的说服力，扩宽参考框架
- 加速学习和积累



文献综述贯穿于科研的整个生命周期

时间和文献上的挑战

60% 的科研人员时间用在科技资料上
(美国科学基金会)

3 年的时间让一个医生完成选题到发表

低 研究结论的可复现性
10% ~ 25% 临床前研究
40% ~ 60% 生物和医学

1.科研中选题的重点

案例1 —— 学术信任危机

53篇具有里程碑意义的研究中，仅11%结果得到确认

Over the past decade, before pursuing a particular line of research, scientists (including C.G.B.) in the haematology and oncology department at the biotechnology firm Amgen in Thousand Oaks, California, tried to confirm published findings related to that work. Fifty-three papers were deemed 'landmark' studies (see ['Reproducibility of research findings'](#)). It was acknowledged from the outset that some of the data might not hold up, because papers were deliberately selected that described something completely new, such as fresh approaches to targeting cancers or alternative clinical uses for existing therapeutics. Nevertheless, scientific findings were confirmed in only 6 (11%) cases. Even knowing the limitations of preclinical research, this was a shocking result.

nature

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nature > comment > article

Comment | Published: 28 March 2012

Drug development

Raise standards for preclinical cancer research

C. Glenn Begley & Lee M. Ellis

Nature 483, 531–533 (2012) | [Cite this article](#)

254k Accesses | 2438 Altmetric | [Metrics](#)

nature > letters > article

Letter | Published: 16 March 2006

RETRACTED ARTICLE: A specific amyloid- β protein assembly in the brain impairs memory

Sylvain Lesné, Ming Teng Koh, Linda Kotilinek, Rakez Kaye, Charles G. Glabe, Austin Yang, Michela Gallagher & Karen H. Ashe

Nature 440, 352–357 (2006) | [Cite this article](#)

72k Accesses | 2362 Citations | 1784 Altmetric | [Metrics](#)

This article was [retracted](#) on 24 June 2024

This article has been [updated](#)

案例2 —— 高被引文章被撤回

2006/3/16发表，2024/6/24被撤回. 图像过度操作，无法从记录中验证数据

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Editorial Summary

Early Warning Of Alzheimer's

Poor memory function has been noted in individuals that developed Alzheimer's disease up to 15 years before the eventual diagnosis of the condition. Experiments in a mouse model for the disease have now tracked down a possible cause for this early

[show all](#)

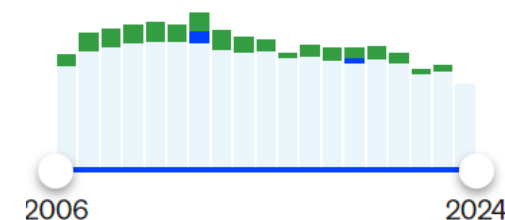
scite_

2,638
109
2,393
5
1

[hide](#)

Contrasting 5
 Unclassified 15

Year Published



1. 科研中选题的重点
- ➔ 2. AI在医学科研中的作用和好处
3. 使用思路和案例
4. 附录

2.AI在医学科研中的作用和好处

协同创新、效率提升、个性化服务



文本

- 医学文献分析
- 电子病历分析
- 新药研发(如药物与靶点潜在关联)



音频

- 语音转录与记录
- 医学助理功能(如预诊)
- 康复与治疗辅助



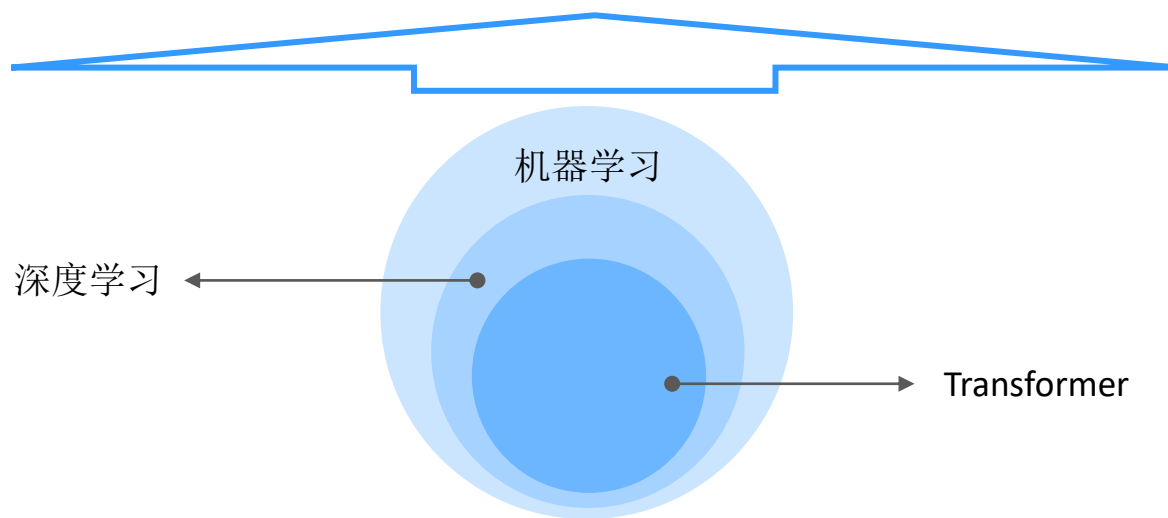
图像

- 医学影像诊断 (DeepMind)
- 病理切片分析
- 个性化手术计划



视频

- 手术视频辅助
- 医学教育
- 患者行为监测



2.AI在文本中应用--独一无二的Citation Statements

制作步骤

第1步
与各出版社签订协议，
获取全文访问的许可

第2步
使用深度学习模型提取引
文上下文

第3步
继续用AI模型
对引用做分类

制作结果

- 3类citation statement: **supporting/支持**, **mentioning/提及**, **contrasting/反对**
- 提供evidence，而不是情感分析
- 带有上下文内内容的引文，最具价值
- 其它信息也会提供 (如引用在文中的位置、出版年份、各引用类别的合计数量)

例子

“...Use of b-blockers in ascitic patients had not shown increased mortality in our study **as contrary to** previous study by Sersté et al **41**. Reasons for this difference are: (1) most patients in our study were in the middle stages of cirrhosis when portal hypertension was significant and medium-to-large varices and ascites developed but systemic hemodynamic were still preserved. (2) Patients with refractory ascites were negligible in our study...”

Section: Discussion ? **contrasting** confidence: 99%

“...Finally, our results are also **in accordance with** those published in a very recent paper by Serste et al **[17]** who showed in a cohort of 151 patients with refractory ascites that MELD score is not a predictive factor of mortality. MELDNa score, computed as previously described **[18]**, was not found to improve that result...”

Section: Discussion ✓ **supporting** confidence: 93%

2.AI在文本中应用--独一无二的Citation Statements

citation statements突破传统的引文数量和IF，揭示了文献何时、何处、为何、如何被引用，用户因此可更好地搜寻、理解和评价文献。

单篇

- 单个观点的真实性、可靠性
- 整篇文献的质量 (参考书评、谷歌PageRank)
- 影响力评价 (如用引用链)

主题

- 了解圈内1个主题是如何讨论争论的，或直接寻找问题的答案
- 发现更多的专家和意见领袖
- 作为补充指标来比较不同期刊

用户

- 更好探索、选择最相关、最靠谱的文献来细读 (精读与泛读)
- 激励批判性思维
- 节省时间

机构

- 评价和比较机构的学术成绩
- 为组织成员增效，帮助他们更好的做研究工作

引文上下文 vs 全文

The Citation Statements often mention claims or findings of papers as stated by other researchers, and by limiting our search within it, we are getting an extremely focused search which at times is even better than an unlimited Google Scholar full-text search. Often it may even immediately give you the answer you are looking for.




Aaron Tay
Head, Data Services
SMU Libraries

源头:


“Using Large language models to generate and extract direct answers - More academic search systems - Scite Assistant , Scispace, Zeta Alpha”,
posted on 7 July 2023,
<https://musingsaboutlibrarianship.blogspot.com/2023/07/using-large-language-models-to-generate.html>

2.AI在文本中应用—基于大语言模型的聊天助手

用AI进行对话式的探索、获取信息已是趋势

 采用自然语言，无需构筑复杂的搜索表达式

- 更好的个性化、交互式体验
- AI也能更灵活的适应用户需求

 用自己的大语言模型 或 用现成的最好的



首要考虑

垂直领域的AI应用，仍需模型具备强的通用能力



最好的LLM优势

- 优秀生，理解力、推理能力等强
- 通用知识多
- 自律



最好的LLM劣势

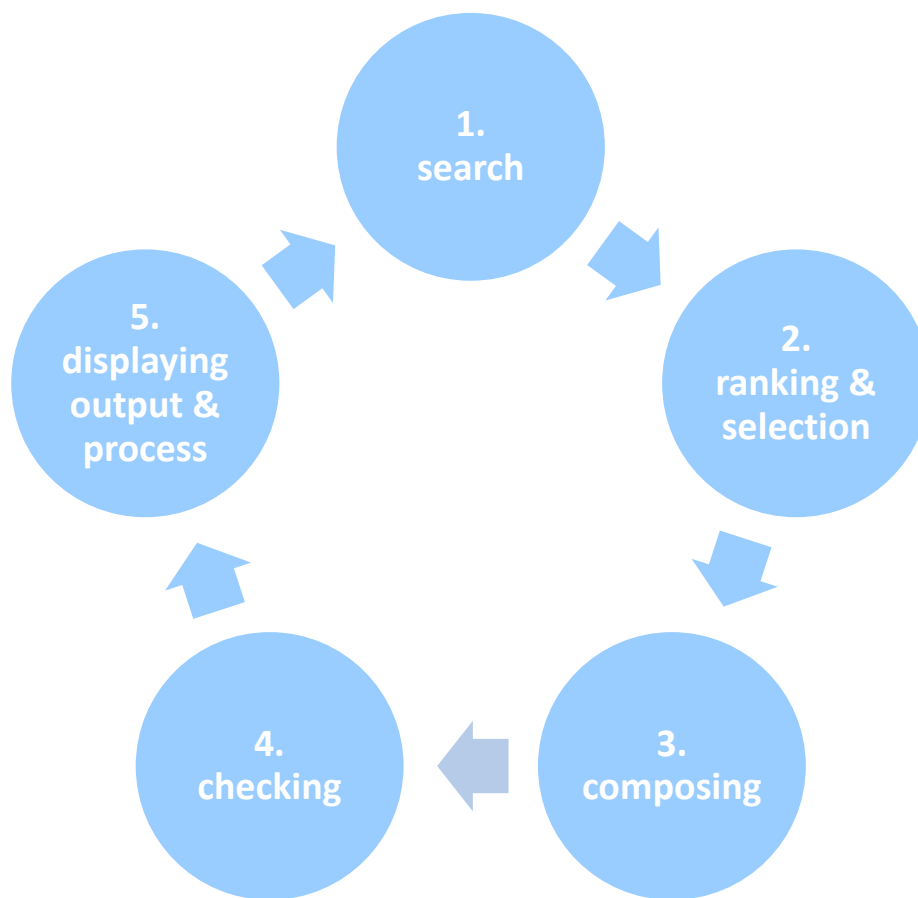
- 专业知识贫乏
- 先天性幻觉—不知真假
- 思考时间有限，只做task不做job

2.AI在文本中应用—基于大语言模型的聊天助手

- 精心设计的流程，力求生成可靠的、可定制的、可循证的答案
- 给用户成分控制权，把答案如何生成的过程信息呈现给用户
- 帮助用户获取信息、辅助读写

Scite 负责的部分

- 解读用户的需求
- 如何有效找到相关文献、如何挑选搜索出来的文献、如何读取相关内容喂给LLM
- 如何确保AI生成的答案是基于文献的
- 如何提供信息保持透明度，使用户方便验证和优化答案



用户负责的部分

- 人作为主导，做AI不擅长的部分
- 分解复杂大任务、分步给出提示词/prompts; 借鉴网上提示词的写法
- 使用Assistant Settings, 同时验证AI的答案

1. 科研中选题的重点
2. AI在医学科研中的作用和好处
- ➔ 3. 使用思路和案例
4. 附录

3.使用思路和案例

何时用

类别	场景	搜索 & 报表	Scite Assistant (AI聊天)
教学类活动	授课、学习、写作	•	•
研究类活动	选择课题	•	•
	文献综合调研	•	•
	研究设计	•	•
	写作	•	•
	选择投稿期刊	•	•
	同行评审	•	•

如何用

无固定模式,以下并非完整的使用方式。

Type 1: 先用Assistant获取基本的、框架的知识,再进入搜索模块获取全面的信息

Type 2: 先搜出相关文献,再用Assistant聚焦这些文献,提炼信息

Type 3: 上传文档,用Assistant辅助阅读

Type 4: 用Assistant辅助写作,比如需申请项目基金时,但Assistant更多是帮助头脑风暴、提供初步内容,而非替代人写作(请密切留意AI生成式内容用于写作的要求)

3.使用思路和案例

使用Scite Assistant(AI聊天工具), 输入提示语, 助力选题

1. 识别学术空白 (治疗机制研究薄弱)

- 当前关于**阿尔茨海默病**的治疗机制研究有哪些薄弱点或未被充分研究的领域?
- 有哪些关键治疗机制的研究尚未在高影响力期刊中讨论过? 例如, **帕金森病**中的线粒体功能障碍机制。

2. 前沿趋势分析 (最新有影响力的文献)

- 过去三年关于**癌症免疫治疗**的高被引文献主要聚焦在哪些研究方向?
- 最新发表的综述文章中, 哪些领域被认为是研究的前沿热点? 例如, **CRISPR基因编辑**在遗传病治疗中的应用。

3. 识别不足与争议

- 关于**抑郁症**的治疗方法, 现有研究中存在哪些争议或研究结论不一致的地方?
- 有哪些临床试验结果存在不一致或不足之处值得进一步研究? 例如, **干细胞治疗**在心脏病中的应用。

4. 明确技术和方法需求, 提升可行性

- 在**神经科学**研究中, 最常用的研究方法是什么? 是否有技术改进的需求? *What are the most commonly used research methods in neuroscience? Is there a need for technical improvements?*
- 进行**基因组学**研究时, 有哪些技术难点和已被提出的改进方向? *What are the technical challenges and proposed directions for improvement in genomics research?*

5. 增强选题的说服力, 扩宽参考框架

- 有哪些跨学科研究或新兴技术可以为**糖尿病**的研究提供参考或应用?
- 是否有类似疾病的研究成功经验可以借鉴到**自身免疫性疾病**的研究中? 例如, **类风湿性关节炎**的治疗经验。

注意:

- 英文的提示语往往提供更多的文献信息(可用浏览器插件的英翻中功能辅助阅读)
- 以上举例不代表为最佳提示语, 问题是宽泛好还是很细节好, 视具体情况

3.使用思路和案例 - AI助手Scite Assistant

Assistant Settings修改的参数，会改变AI的答案；用户可以检查答案的生成过程和最终内容

The screenshot displays the Scite Assistant interface. On the left, the 'Assistant Settings' panel includes controls for 'Reference year range' (From/To), 'Publication Types', 'Citation Style' (set to APA), 'Model' (GPT-4o-mini), 'Response Length' (set to Long), '# Publications to consult' (set to 50), 'Reference Ranking' (set to Relevance), 'Journals', 'Dashboards', and 'Analyzed Documents'. An orange arrow points from the 'Assistant Settings' header to the question input field.

The main question input field contains: "How does the structure of a protein affect its function?".

The AI-generated answer is displayed in the center, starting with: "The relationship between protein structure and function is a fundamental concept in biochemistry and molecular biology. Proteins are composed of amino acids that fold into specific three-dimensional structures, which are crucial for their biological activities. The structure of a protein can significantly influence its function through several mechanisms, including conformational dynamics, post-translational modifications, and interactions with other molecules." A yellow dashed box highlights a specific sentence in the answer: "...The holy grail is the physical principle that explains how the structure of a protein determines its function. The route to this principle starts with recognizing that most protein functions, such as ligand binding, allostery, and effects of mutations, involve significant conformational dynamics because a protein has". An orange arrow points from this highlighted sentence to the 'Searches Used' section on the right.

On the right side, the 'Searches Used' section lists three search terms: "how protein structure affects function", "structure function paradigm in proteins", and "protein structure function relationship". Below this, the 'Publications Consulted' section lists several relevant publications, including "A Rigorous Method for Identifying a One-Dimensional Reaction Coordinate in Complex Molecules" by Wu¹, Li², Ma³ (2022).

At the bottom of the interface, there are buttons for 'Clear All', 'Apply', and a question input field with the placeholder text "Ask a question... (type '/' for menu)".

3.使用思路和案例 - AI助手Scite Assistant

- 使用prompts分多步获取想要的信息。下方用了3次prompt，在AI初始答案里作比较，并使用结构化方式展现结果

Conductive hearing loss refers to a type of hearing loss that occurs when sound is unable to pass efficiently through the outer or middle ear. There are several methods available for the treatment of conductive hearing loss, each with its own advantages and considerations.

One effective treatment option for conductive hearing loss is the use of bone conduction systems. These systems bypass the outer and middle ear and directly stimulate the cochlea with sound vibrations (Georgescu et al., 2018). This approach offers a natural sound quality for recipients and can be particularly beneficial for individuals with conductive or mixed hearing loss (Georgescu et al., 2018). The Bonebridge bone conduction hearing implant is an example of an active bone conduction system that has been shown to provide stable audiological outcomes (Sprinzl & Wolf-Magele, 2016).

Another method for treating conductive hearing loss is through surgical interventions. Stapes surgery, for example, can be performed to improve hearing in individuals with conductive or mixed hearing loss due to otosclerosis (Sakamoto et al., 2010). This procedure involves manipulating the footplate of the stapes bone to restore its mobility and improve sound transmission to the inner ear. The use of potassium titanyl phosphate laser-assisted stapes surgery has also been investigated as a potential alternative to conventional techniques, with comparable hearing results and fewer complications (Sakamoto et al., 2010).

In cases where conductive hearing loss is caused by trauma or ossicular disruption, surgical repair may be necessary. Ossicular reconstruction can be performed to repair ossicular disruption and restore hearing (Patel & Groppo, 2010). However, it is important to note that ossicular reconstruction may not always result in complete hearing recovery and may require further surgery (Patel & Groppo, 2010).

Non-surgical options are also available for the treatment of conductive hearing loss. Adhesive bone conduction devices, such as the Bonebridge, can be used to bypass the middle ear and provide direct stimulation to the cochlea. These devices are particularly effective in improving hearing in individuals with conductive hearing loss in children who cannot undergo surgical treatment (Muzzi et al., 2021). Studies have shown that these devices can be effective in improving hearing in individuals with conductive hearing loss (Muzzi et al., 2021).

In summary, there are several methods available for the treatment of conductive hearing loss. These include surgical options such as stapes surgery and ossicular reconstruction, and non-surgical options such as adhesive bone conduction devices. The choice of treatment depends on the individual's hearing loss, the underlying cause, and the expertise of the healthcare provider.

what are methods to cure Conductive Hearing Loss

please make a comparison between Non-surgical options and surgical options, based on the above outcome. and please don't search citations or literatures.

could you rephrase the above paragraphs in bullet points, and separte them into pros and cons respectively, without searching citations or literatures.

Pros of Non-surgical Options for Conductive Hearing Loss:

- Non-invasive approach
- Adhesive bone conduction devices have been shown to improve hearing in individuals with conductive hearing loss

Cons of Non-surgical Options for Conductive Hearing Loss:

- Limitations in the degree of hearing improvement that can be achieved
- Some individuals may experience skin irritation or discomfort with adhesive bone conduction devices

Pros of Surgical Options for Conductive Hearing Loss:

- Can provide significant hearing improvement in individuals with conductive or mixed hearing loss
- Stapes surgery has been shown to be effective in improving hearing in individuals with conductive or mixed hearing loss due to otosclerosis
- Surgical repair can address trauma or ossicular disruption

Cons of Surgical Options for Conductive Hearing Loss:

- Invasive procedure with potential risks associated with anesthesia, infection, and damage to surrounding structures
- Surgery is typically not recommended earlier than three months after trauma to allow for proper healing of tissues

View searches run to ground this response

3.使用思路和案例 – 经典搜索

Citation Statements: 仅查询引文上下文

Papers: 仅查询元数据

All: 以上二种都查

Search by title, author, keywords or DOI

Search **All** Citation Statements Papers scite Assistant

高级搜索通过复杂的表达式，帮助发现最需要的文献信息

Add terms to the query box

All fields | Search all fields AND | Add Term

Query box

Search Clear

筛选

有各种筛选条件来缩小查询范围

系统已全面获取最新的Editorial notice

Editorial Notice ^ MeSH v More

<input type="checkbox"/>	Retracted	62,890
<input type="checkbox"/>	Has Expression Of Concern	2,506
<input type="checkbox"/>	Has Correction	164,840
<input type="checkbox"/>	Has Erratum	228,157
<input type="checkbox"/>	Withdrawn	17,751

排序

各种排序条件

Sort by: Relevance v

Sort by: Relevance

Sort by: Date published (recent)

Sort by: Date published (oldest)

Sort by: Most cited

Sort by: Least cited

Sort by: Most supported

Sort by: Least

Authors v Year v Sections v Types v Citations v Journal v Affiliation v Pub Type v Topics v Editorial Notice ^ MeSH v More

3.使用思路和案例 – 经典搜索



左侧二处按钮分别是“Analyze Search Results”(分析查询结果)和“Create Search Alerts”(创建搜索提醒)

分析报告的结构

Introduction

- the publication count on this topic
- the most highly cited publication discussing this topic
- the most supported paper
- the distribution of citation statements along a timeline

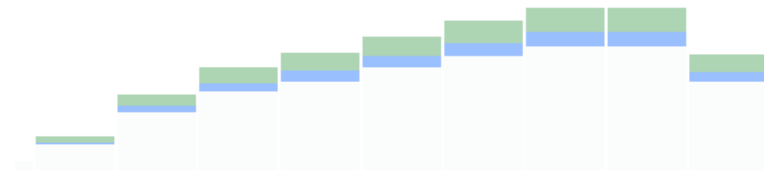
Who is publishing reliable research in this area

- Researchers that have published the most work related to these search parameters
- Researchers that have published highly supported work
- The institutions with the most supported papers in this area

What are researchers saying about this topic

- Insights from the most relevant papers (based on your search parameters)
- Insights from the most recently published papers
- Insights from supporting statements
- Insights from contrasting statements
- Insights from the most supported papers
- Insights from the most contrasted papers

publications, with a breakdown of what percent of them support, mention,



Insights from supporting statements.

“...To confirm CXCR5 expression patterns on HRS cells by both protein and RNA le immunohistochemistry (IHC) and reanalyzed published Affymetrix gene expressi of primary HL samples. **20** These analyses confirmed that variable CXCR5 surfa expression and CXCR5 was highly expressed in a subset of CHL tumors (Fig 2B, D with expression levels found in CD77 + germinal center B cells (Fig 2C). Interestir together with other CXCR5+ HRS cells forming cell clusters as an architectural fei

Section: Results supporting confidence: 78%

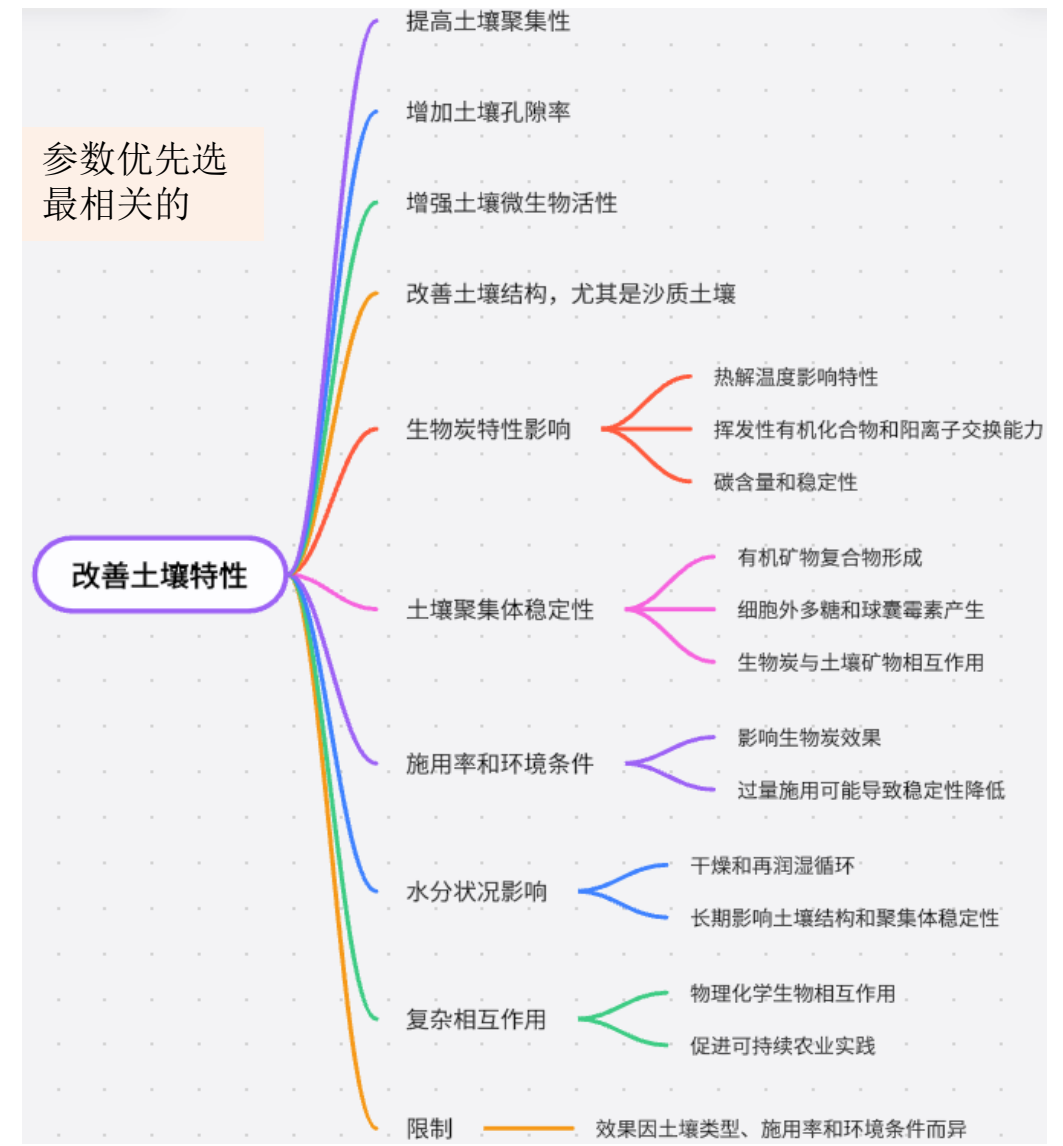
Spatially Resolved Tumor Microenvironment Predicts Treatment Out
Tomohiro Aoki 2024 *JCO*

3.使用思路和案例 – 重要拓展功能

功能	描述	作用
可视化交互图	用交互的图表来展现出版物之间的引用关系	直观看到文献的影响力，也便于追踪特定领域理论的演变
引用检查	检查上传文档的文献引用质量	在向期刊提交文稿前使用，或为一篇文章评估其参考文献的质量
仪表盘/面板	相关文献的集合，系统也有针对面板的报表 (可通过查询结果、Zotero/Mendeley插件、指定一串DOI、上传CSV文件来创建)	深入了解集合内的信息，限制Assistant的来源搜索范围
Explore Journals, Explore Organizations, Explore Funders	报表内可做搜索, 分别在期刊、研究机构、资助机构的层面提供见解信息和汇总信息	从Scite视角和度量来分析，帮助评估期刊和机构

3.使用思路和案例 – 最佳实践

在Assistant里尝试不同的设置，比较AI对应生成的不同答案，看哪一种更符合自己的特定需求，或综合得出最佳答案(下图结合第3方工具呈现结果)



3.使用思路和案例 – 最佳实践

- 使用Dashboard，把相关主题文献归纳在一起。1) 便于后继跟踪领域内最新发展， 2) 也可在Assistant里限定搜索范围，避免某些时候问题或范围过于宽泛

图1

Create Dashboard From Search Results

Name*

"organic fertilizer" AND soil AND sustainability

Search term: "organic fertilizer" AND soil AND sustainability, Sorted by: total_supported (desc)

Save search query?



Enable email alerts for newly detected Smart Citations?



Cancel

Save

图3

Dashboard - 2023/12/6 18:21:09 Set alert |

Last Updated: 2024-06-15

Ask a question... (type '/' for menu)

Settings Sources

Using: Dashboard: Dashboard - 2023/12/6 18:21:09

图2

Import your or library

Name*

What should we call your dashboard?

Description

(Optional) Tell us a little bit about the dashboard; what is it describing?

DOIs*

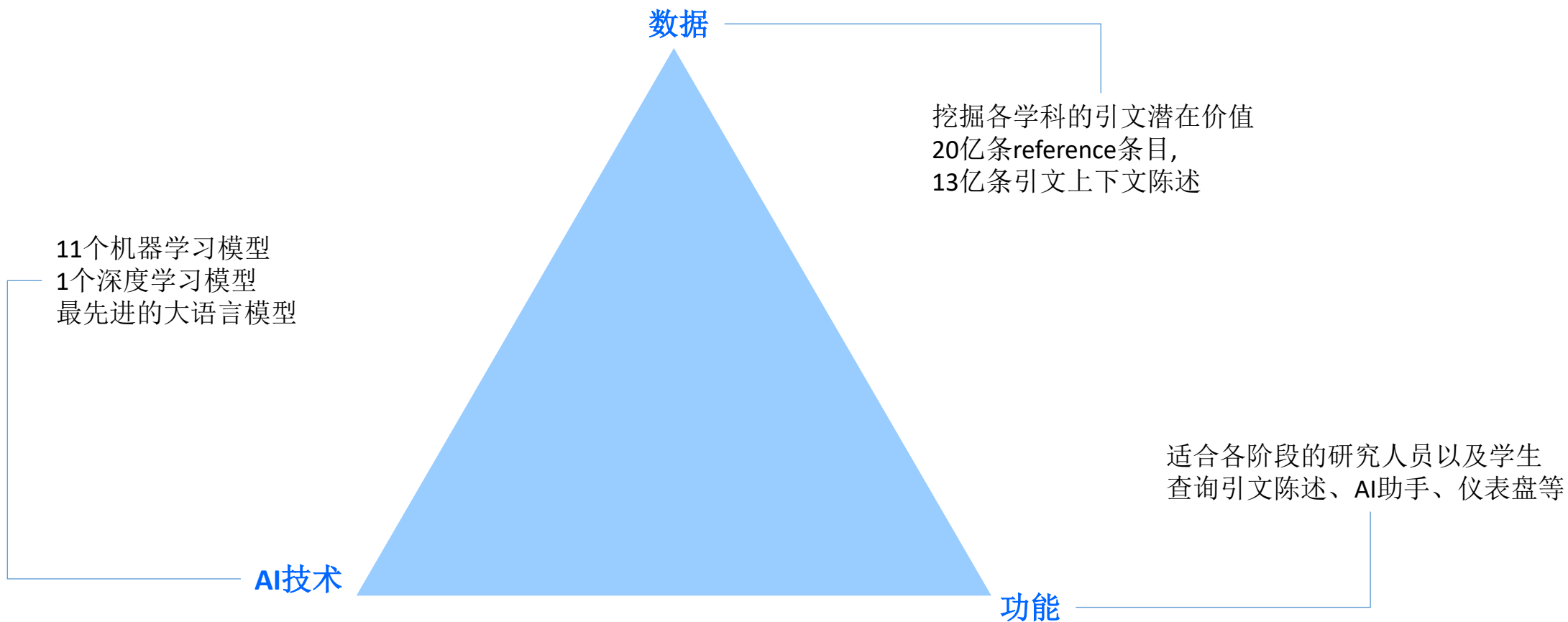
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3. 使用思路和案例
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duplication cycle [Holland and Cleveland, 2009; Thompson and Compton, 2010].

Studies carried out primarily in yeast and mammalian cell lines have shown that aneuploidy comes with a fitness cost. Aneuploid cells typically grow slower [McCoy et al., 1974; Torres et al., 2007; Williams et al., 2008; Tang et al., 2011; Siegel and Amon, 2012; Stinge et al., 2012] and suffer from replication stress that leads to DNA damage and gene mutation [Janssen et al., 2011; Crasta et al., 2012; Santaguida and Amon, 2015a; Passerini et al., 2016; Ly and Cleveland, 2017]. Also, both in vitro engineered aneuploid cells and chromosomally unstable cancer cells display gene expression patterns [Sheltzer, 2013] reminiscent of stress responses first described in yeast [Gasch, 2007]. Accordingly, aneuploid cells were found to show increased sensitivity toward compounds inducing energy stress and proteotoxic stress [Tang et al., 2011]. In nontransformed cells, chromosome missegregation generally leads to p53-dependent cell cycle arrest and, ultimately, cell death [Li et al., 2010; Thompson and Compton, 2010; Uetake and Sluder, 2010; Janssen et al., 2011; Lambrus et al., 2014]. Yet, despite this fitness cost, severe aneuploidy and CIN are hallmarks of human cancers [Hanahan and Weinberg, 2011; Holland and Cleveland, 2012; Funk et al., 2016; De Braekeleer et al., 2017]. They contribute to increased transformative potential [Paulsson and Johansson, 2007; Weaver et al., 2007] and correlate with poor prognosis [McGranahan et al., 2012]. To resolve this apparent conundrum, it is generally argued that aneuploidy and CIN result in deregulated gene expression, which then confers a selective advantage during the evolution of a tumor in a changing microenvironment [Baek et al., 2009; Pavelka et al., 2010; Kwon-Chung and Chang, 2012; Yona et al., 2012]. As one example supporting this notion, DLD-1 cells engineered to carry single-chromosome aneuploidies were found to have a selective advantage over diploid control cells when cultured under non-standard conditions, such as serum starvation, drug treatment, or hypoxia [Kutledge et al., 2016]. Such observations, as well as data obtained in tumor models, strongly support the hypothesis that aneuploidy is not a by-product of cell transformation but, when present at appropriate levels, contributes to tumor development [Hanks et al., 2004; Holland and Cleveland, 2012; Davoli et al., 2013].

Aneuploidy in cancer cells may arise when diploid progenitors gain or lose individual chromosomes. However, chromosome loss is not well tolerated in diploid cells [Alvaro et al., 2006; Anders et al., 2009]. Moreover, cancer cells often carry near-tetraploid chromosome numbers, indicative of whole genome duplication events [Zack et al., 2013]. This suggests that aneuploid cancer cells often derive from tetraploid intermediates [Cowell and Wigley, 1980; Mayer and Aguilera, 1990; Storchova and Pellman, 2004; Storchova and Kuffer, 2008; Holland and Cleveland, 2012]. Considering that tetraploidization creates redundancy in chromosome content, it is expected to protect descendant aneuploid cells from the negative effects of haploinsufficiency [Shackney et al., 1989; Storchova and Pellman, 2004; Ganem and Pellman, 2007; Thompson and Compton, 2010; Dewhurst et al., 2014].

Aneuploidy has traditionally been ascribed to defects in mitotic spindle organization and/or dysfunction of the spindle assembly checkpoint [Wang et al., 2007; Kops et al., 2005]. However, although mutations in spindle checkpoint genes can indeed cause aneuploidy [Hanks et al., 2004; Yost et al., 2017], such mutations have not been commonly observed in cancers [Cahill et al., 1999; Haruki et al., 2001]. Deregulated expression of essential regulators of chromosome segregation and cell division has been observed in cancers with high degrees of aneuploidy and, accordingly, a CIN marker signature (CIN70) was proposed [Carter et al., 2006]. However,

subsequent studies argued that this CIN signature reflects altered proliferation rate rather than chromosome missegregation [Vene et al., 2011; Sheltzer, 2013; Buccitelli et al., 2017]. Thus, a specific cellular response to CIN has not yet been identified.

Here we established a set of transformed cancer cell lines of isogenic origin but differing in chromosome content and propensity to chromosome missegregation. To determine the effects of gains in chromosome mass versus CIN on protein expression and phosphorylation, we subjected the different cell lines to extensive proteomic and phosphoproteomic analyses. We found that proteomic changes in response to CIN are similar to those observed in response to tetraploidy and are more readily detectable at the level of protein phosphorylation than at the level of protein expression. Furthermore, our results indicate that large gains in chromosome number, as caused by tetraploidization, trigger widespread responses in protein expression and phosphorylation patterns, lending support to the notion that an initial genome doubling event can set the stage for survival and propagation of descendant aneuploid tumor cells.

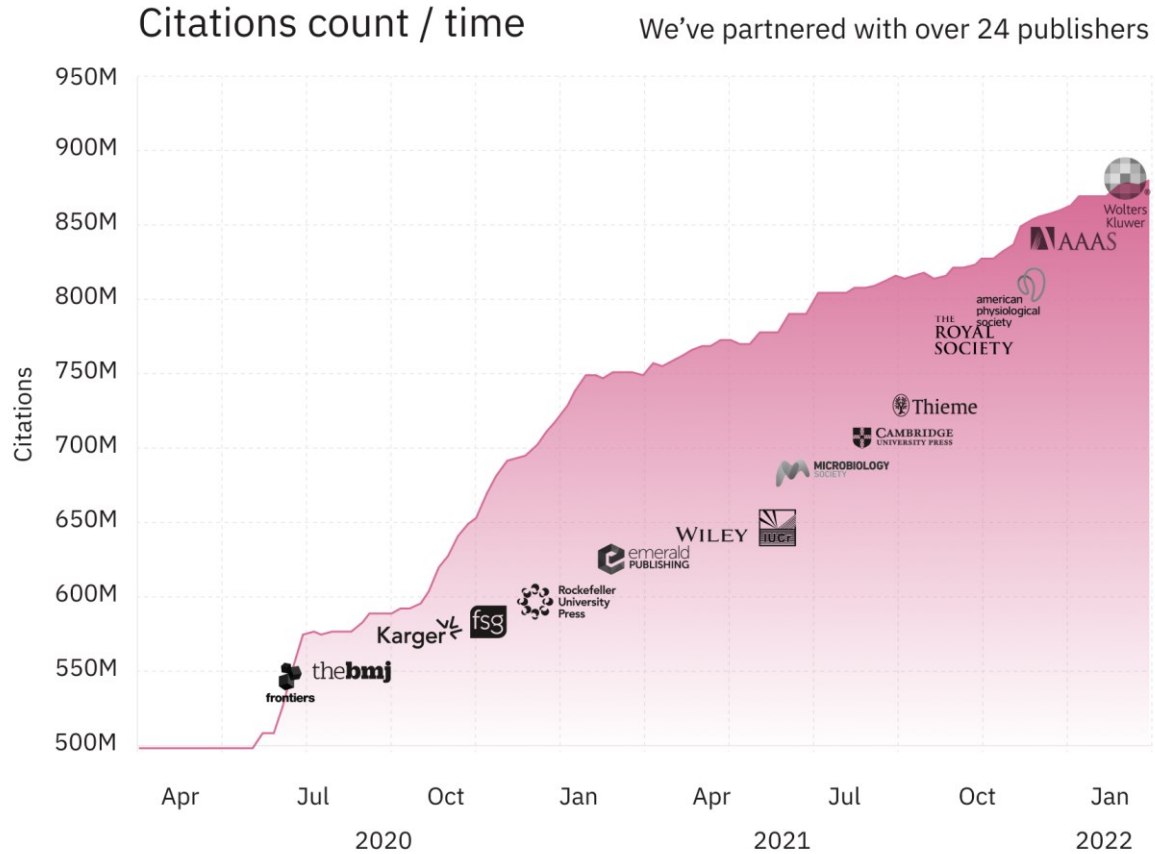
RESULTS

Establishment of DLD-1-derived cell lines differing in ploidy and aneuploidy

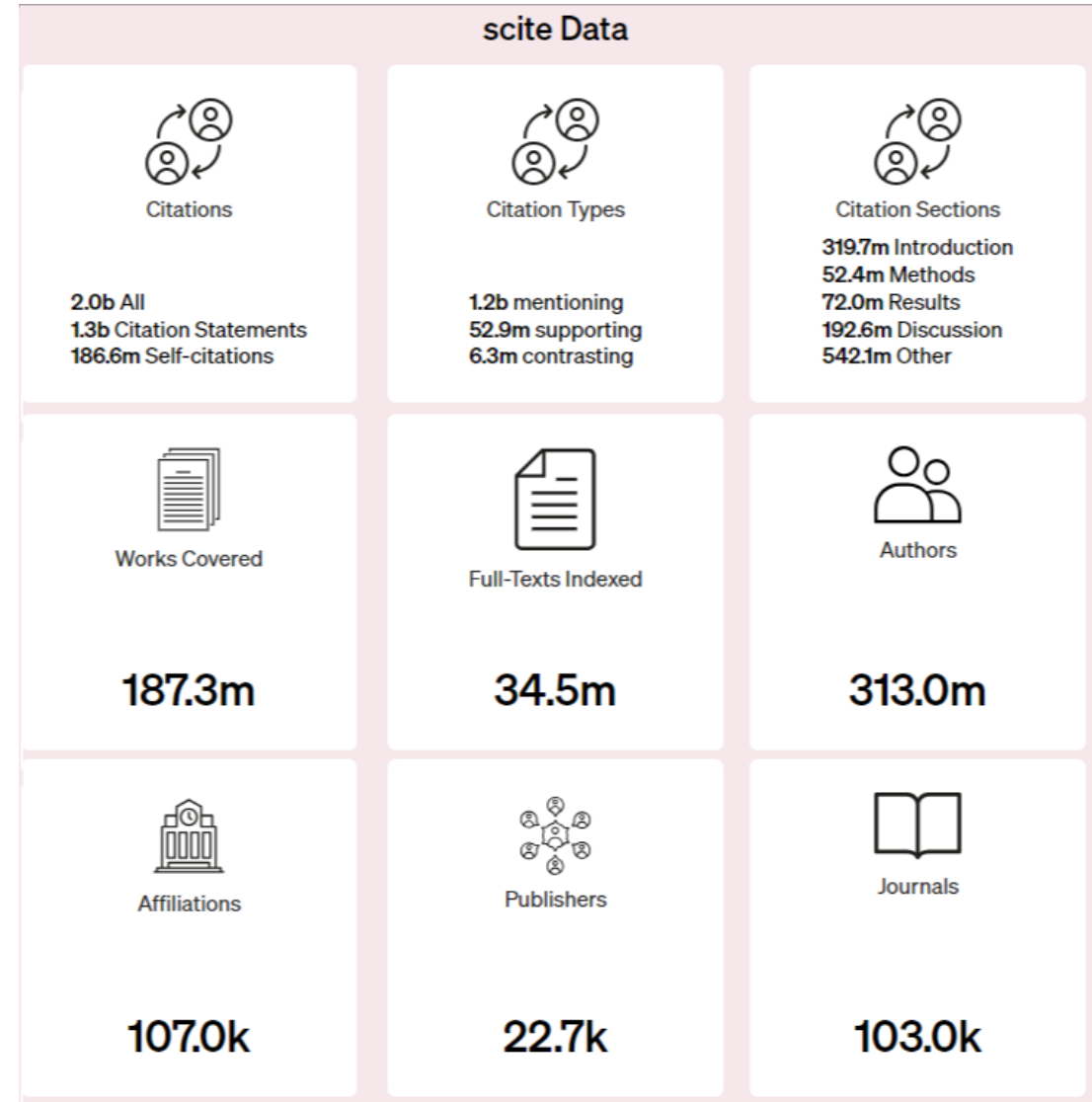
Chromosome gains or losses result in massive changes in gene expression [Lye et al., 2004; Jpender et al., 2004; Stinge et al., 2012], and protein expression patterns in cancer cell lines are known to reflect tissue origin, a priori making it difficult to identify a proteomic signature attributable to CIN. This notwithstanding, we subjected a panel of human cell lines to a proteomic quantification based on multiplexed tandem mass tag (TMT) labeling, a method of choice for achieving high proteome coverage in multiple samples and within a reasonable time frame [Thompson et al., 2003; Ahm et al., 2016] (Supplemental Figure S1A and Supplemental Table S1). This panel included seven karyotypically stable (nonCIN) and unstable (CIN) cancer cell lines originating from different tumor tissues [Gascoigne and Taylor, 2008] and the immortalized retinal cell line hTERT. In line with previous data [Gascoigne and Taylor, 2008], we found that differences in global protein expression patterns were too profound to allow a distinction between CIN and karyotypically stable (nonCIN) cell lines through hierarchical cluster analysis (Supplemental Figure S1B). Nevertheless, this pilot study showed that our proteomics approach allowed for reliable quantification of thousands of proteins in each cell line.

To reduce interline variation due to tissue origin, we next used the diploid colon cancer cell line DLD-1 to generate descendant lines differing in karyotype. DLD-1 cells show microsatellite instability (MIN) but proliferate in a near-diploid state [Lengauer et al., 1997]. As DLD-1 cells are deficient in p53, tetraploid derivatives can readily be established through inhibition of cytokinesis [Drosopoulos et al., 2014]. This afforded a syngeneic pair of stable diploid and tetraploid cells (Figure 1A). Starting with a culture of tetraploid DLD-1 cells, we then used single cell fluorescence-activated sorting (FACS) to isolate spontaneously arising aneuploid descendants. This provided us with four different PTA clones, specifically three near-triploid lines and one near-tetraploid line (Figure 1B). Finally, we applied microcell-mediated chromosome transfer [Stinge et al., 2012] to the parental diploid DLD-1 culture and obtained two viable trisomic clones carrying three copies of chromosome 7 (Tr 7) (Figure 1B). For all cell lines, DNA content was confirmed by chromosome counting (Figure 1C) and chromosome painting (Supplemental Figure S2A). This collection of isogenic cell lines set the stage for analyzing chromosomally stable diploid,

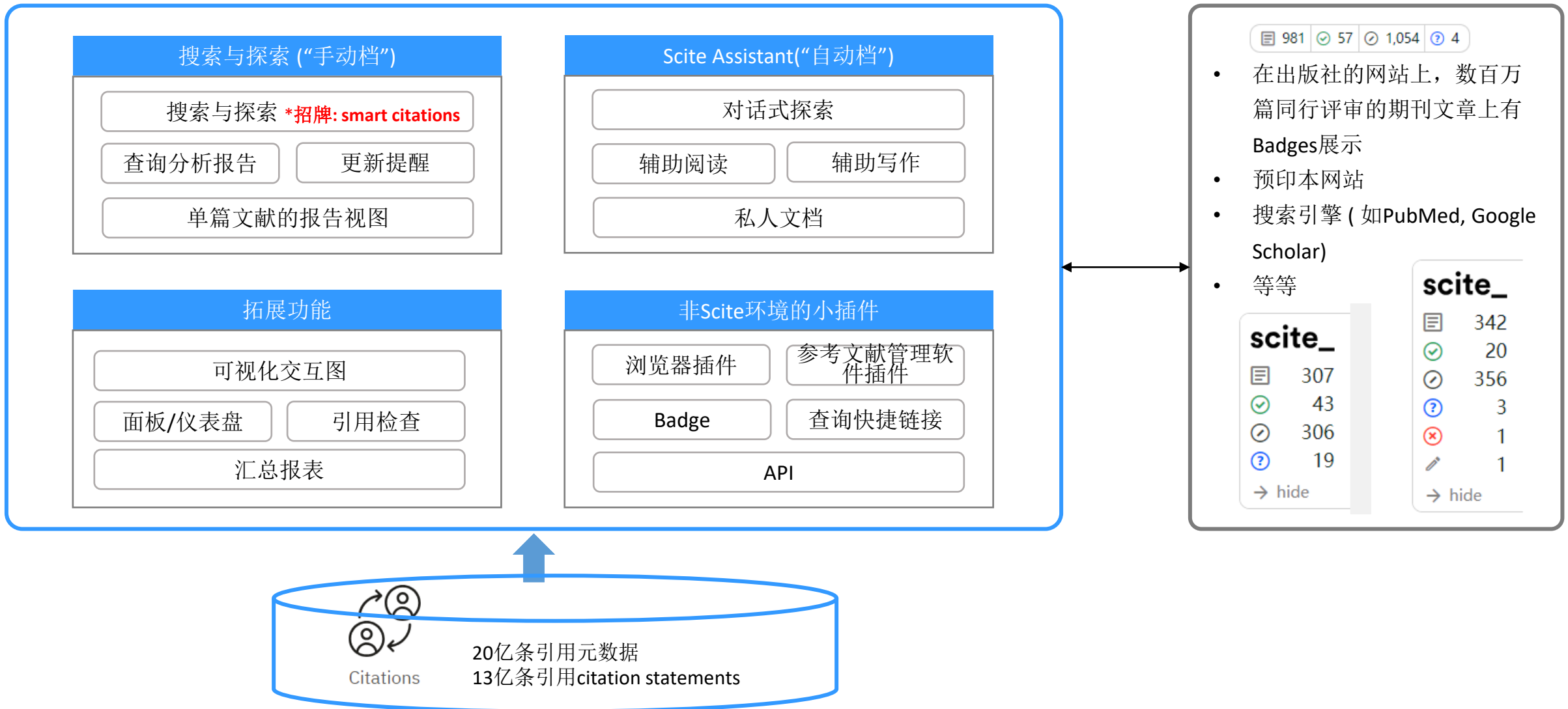
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