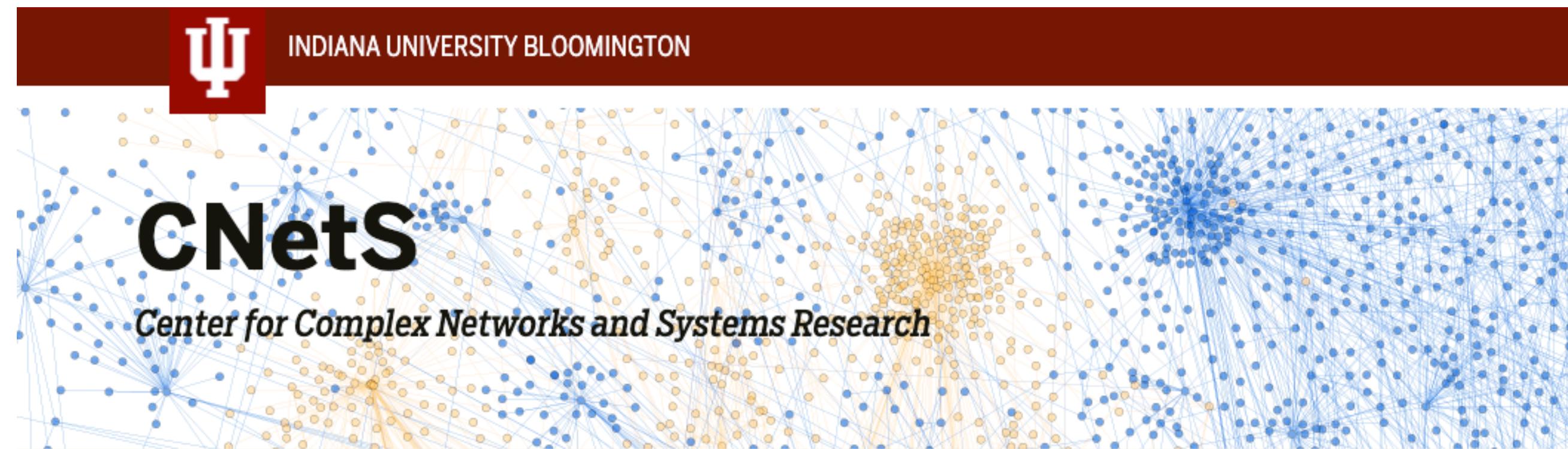


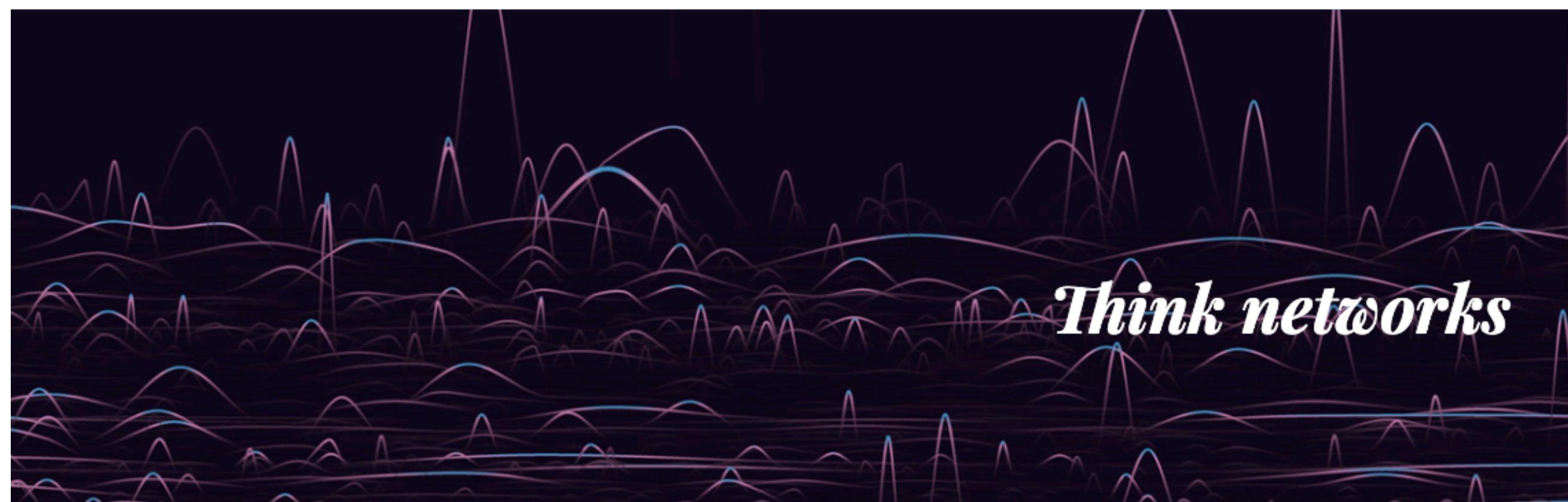
Basic and clinical research: Operationalization, impact, and knowledge flow

**Qing Ke
Northeastern University**



Barabási Lab

PUBLICATIONS PEOPLE PROJECTS JOBS COURSE COMMENTARY NETWORK SCIENCE

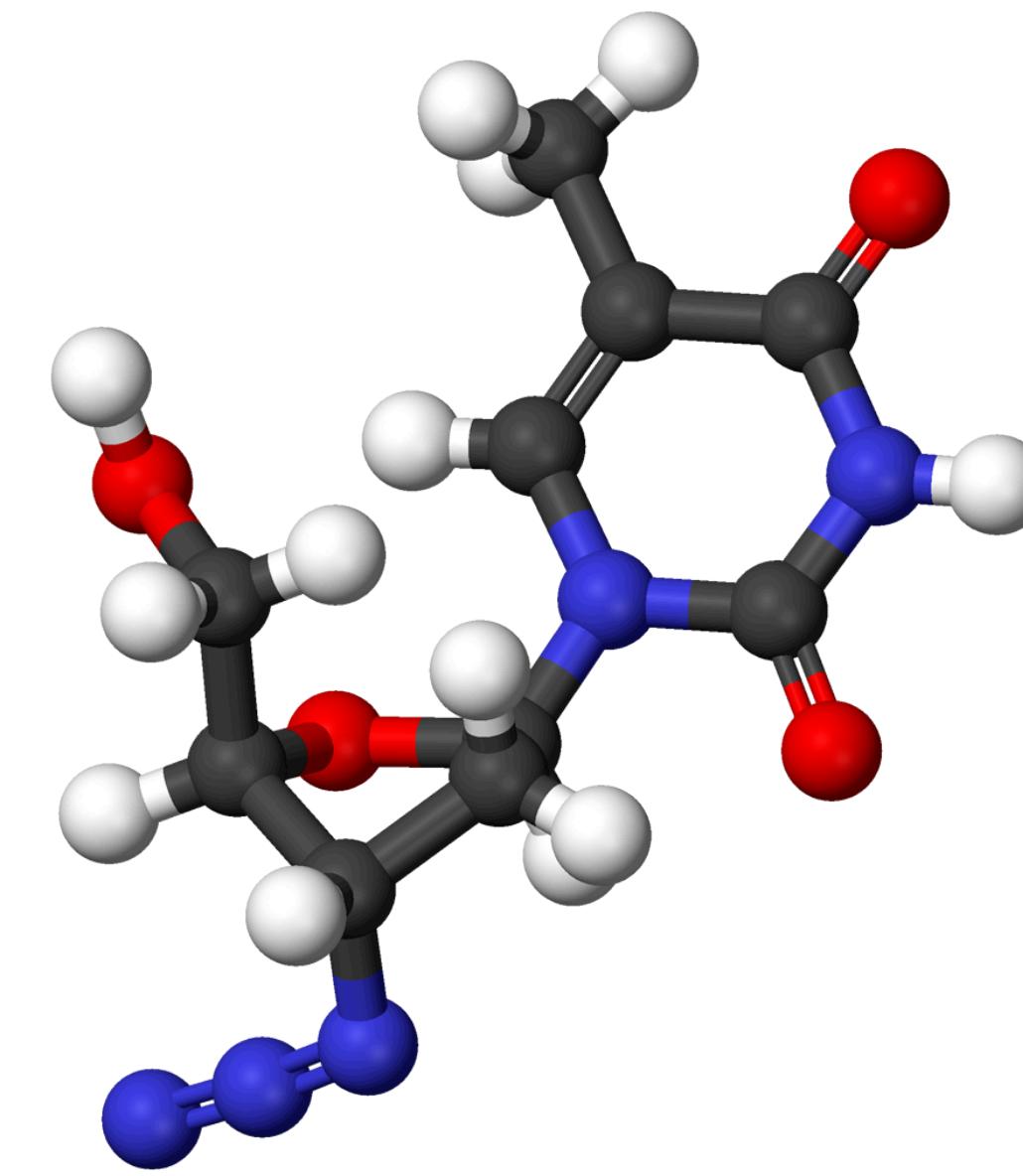


Center for Complex Networks and Systems Research

Zidovudine (AZT)

Zidovudine (AZT)

- The first treatment for HIV/AIDS
- WHO's List of Essential Medicines (“the safest and most effective medicines needed in a health system”)



$C_{10}H_{13}N_5O_4$

Zidovudine (AZT)

1964: First synthesized (*J Org Chem* 29, 2076), not active in mice for cancer treatment

1983: French researchers identified **retrovirus** HIV as the cause of AIDS

1985: Screening of anti-retrovirus chemicals, AZT showed efficacy *in vitro*

1986: First human use (Phase I clinical trial)

1987: Randomized controlled trial

1987: FDA approval

(*Science* 220, 868)

Isolation of a T-Lymphotropic Retrovirus from a Patient at Risk for Acquired Immune Deficiency Syndrome (AIDS)

(*PNAS* 82, 7096)

Proc. Natl. Acad. Sci. USA
Vol. 82, pp. 7096-7100, October 1985
Medical Sciences

3'-Azido-3'-deoxythymidine (BW A509U): An antiviral agent that inhibits the infectivity and cytopathic effect of human T-lymphotropic virus type III/lymphadenopathy-associated virus *in vitro*

(Inhibition of human T-lymphotropic virus type III/thymidine analogue/acquired immune deficiency syndrome/retrovirus)

**ADMINISTRATION OF
3'-AZIDO-3'-DEOXYTHYMIDINE, AN INHIBITOR
OF HTLV-III/LAV REPLICATION, TO PATIENTS
WITH AIDS OR AIDS-RELATED COMPLEX**

ROBERT YARCHOAN* RAYMOND W. KLECKER*
KENT J. WEINHOLD† PHILLIP D. MARKHAM*
H. KIM LYERLY† DAVID T. DURACK†
EDWARD GELMANN* S. NUSINOFF LEHRMAN‡
ROBERT M. BLUM‡ DAVID W. BARRY‡
GENE M. SHEARER* MARGARET A. FISCHL§
HIROAKI MITSUYA* ROBERT C. GALLO*
JERRY M. COLLINS* DANI P. BOLOGNESI†
CHARLES E. MYERS* SAMUEL BRODER*

(*Lancet* 327, P575)

The New England
Journal of Medicine

©Copyright, 1987, by the Massachusetts Medical Society

Volume 317

JULY 23, 1987

Number 4

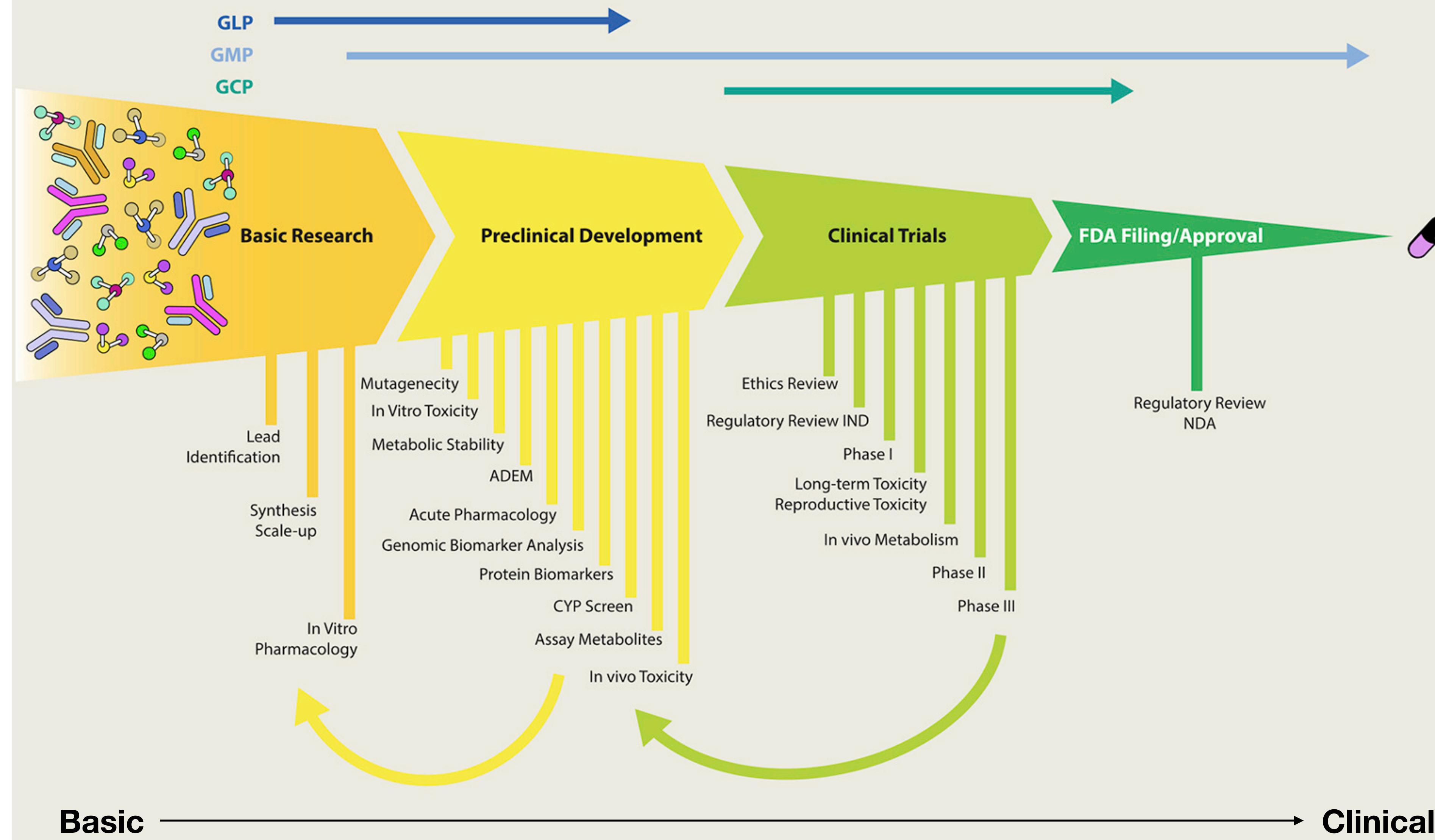
THE EFFICACY OF AZIDOTHYMIDINE (AZT) IN THE TREATMENT OF PATIENTS WITH

AIDS AND AIDS-RELATED COMPLEX

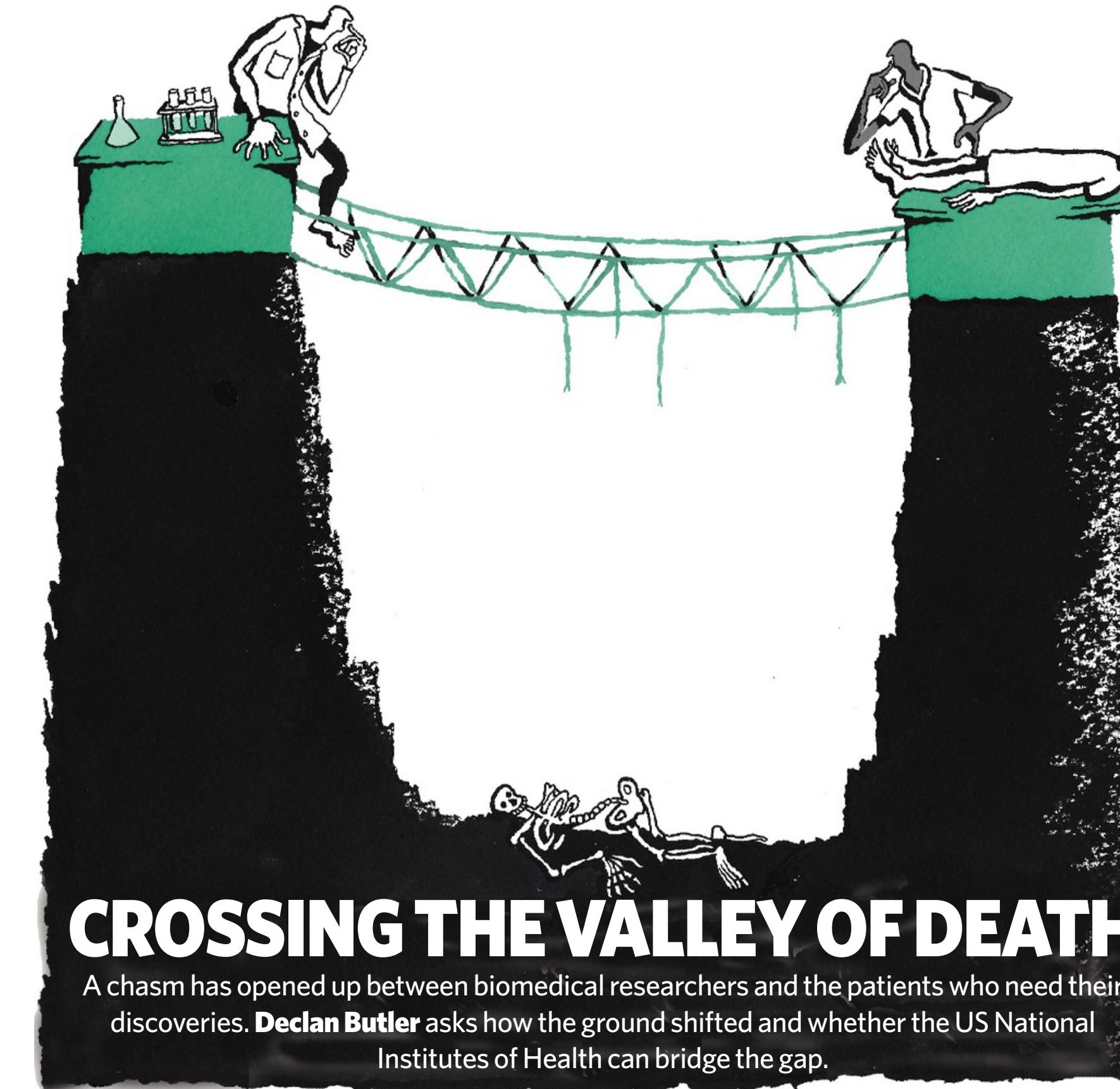
A Double-Blind, Placebo-Controlled Trial

(*NEJM* 317, 185)

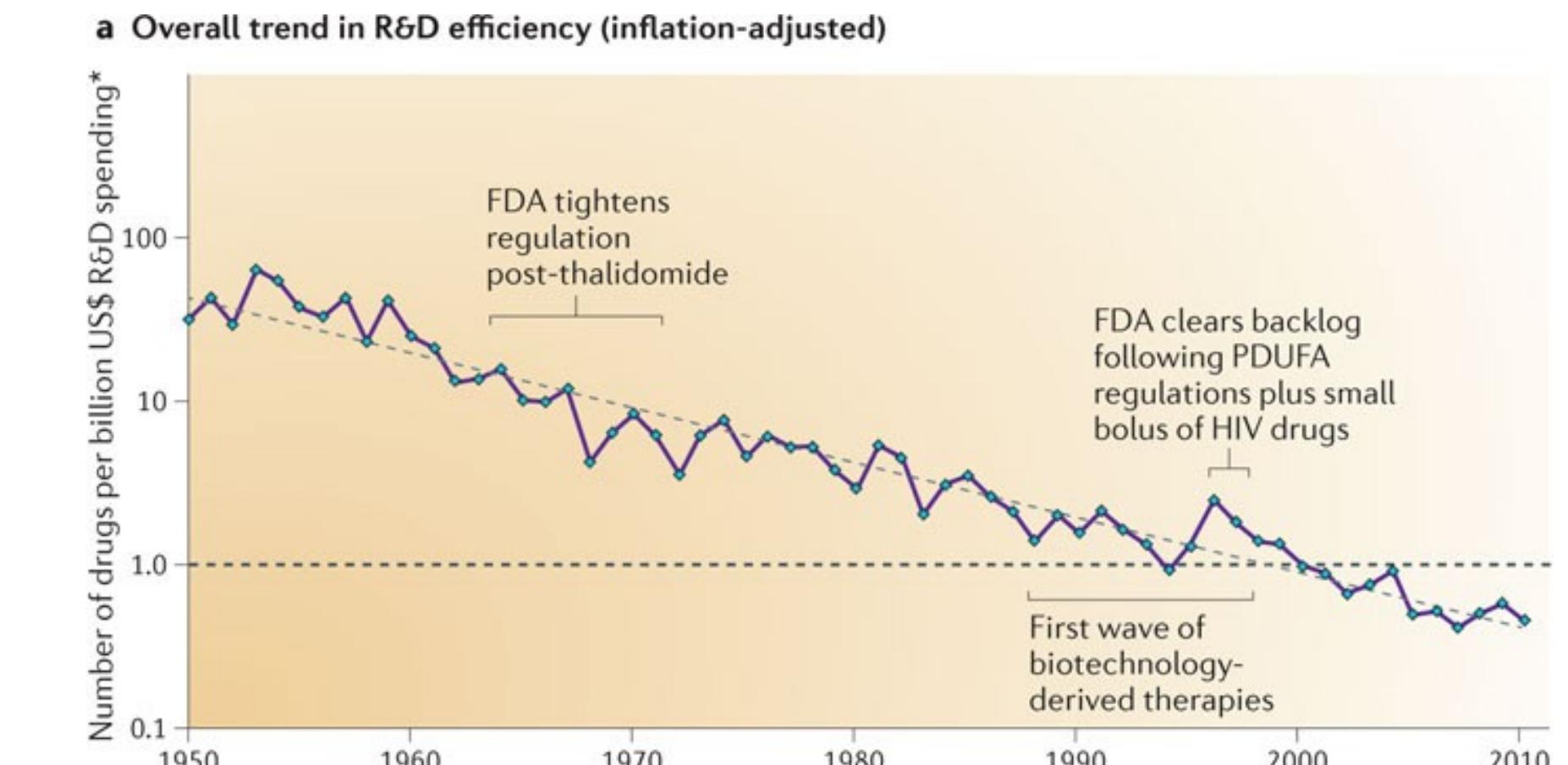
Drug Discovery and Development Activities



The gap between basic and clinical research



“the ecosystems of basic and clinical research have diverged ... The abyss left behind is sometimes labelled the '**valley of death**' – and neither basic researchers, busy with discoveries, nor physicians, busy with patients, are keen to venture there.”



Nature Reviews Drug Discovery 11, 191 (2012)

Translational research: Crossing the valley of death. Nature 2008

Ongoing efforts to bridge the gap

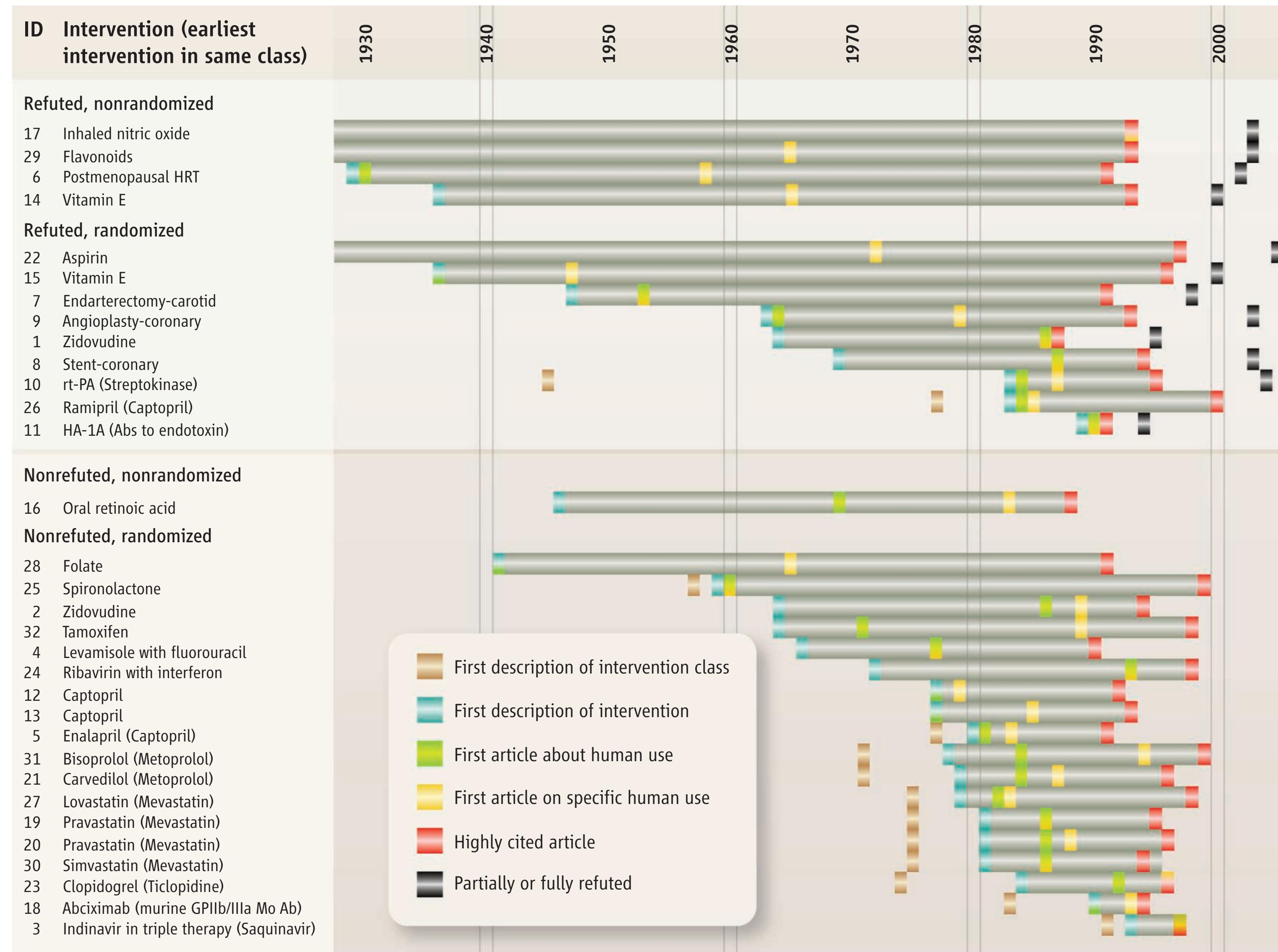
Policy interventions to promote translational research

- Clinical and Translational Science Awards;
- Translational centers in medical schools;
- New journals (e.g., *Science Translational Medicine*)

Evaluation of policy interventions requires identification of translational research

**But, we have a limited understanding of how
knowledge flows from basic into clinical research**

Life cycle of 32 interventions



How about other thousands of successful drugs?

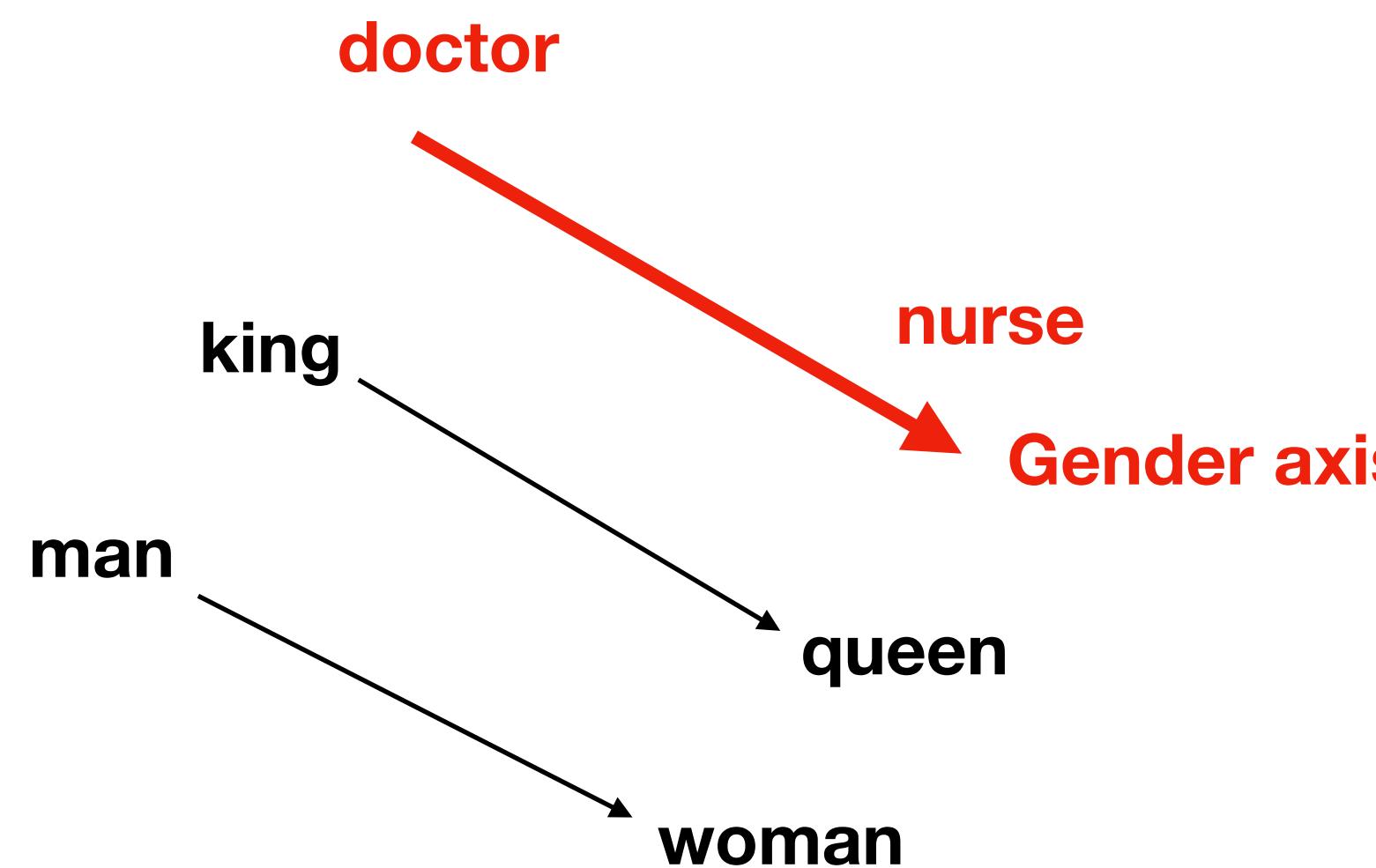
How about the vast majority, those **failed** drugs?

Where is the bottle-neck of the translation?

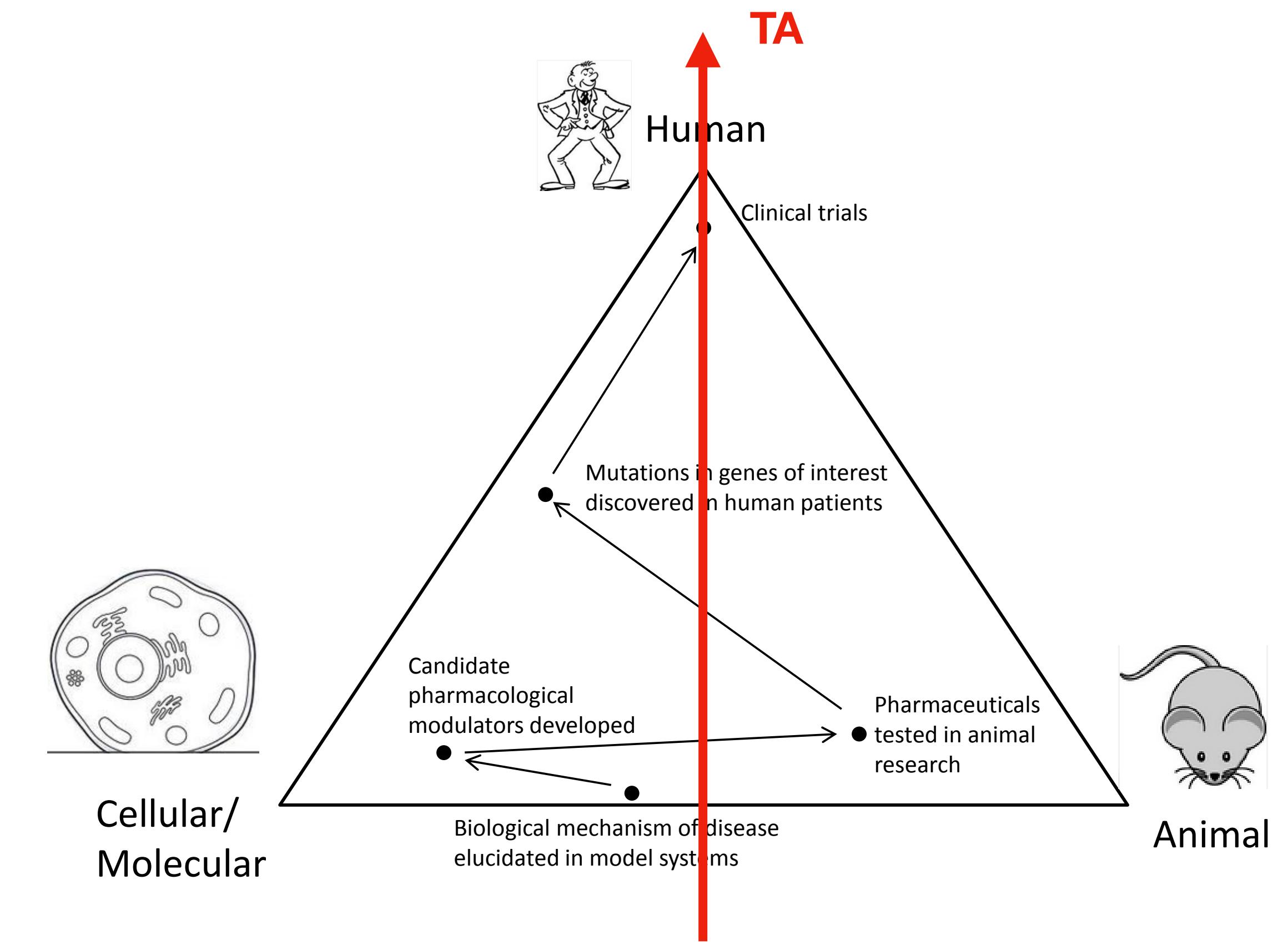
Operationalization of basic and clinical research

Gender axis

$$v(\text{king}) - v(\text{man}) + v(\text{woman}) \approx v(\text{queen})$$

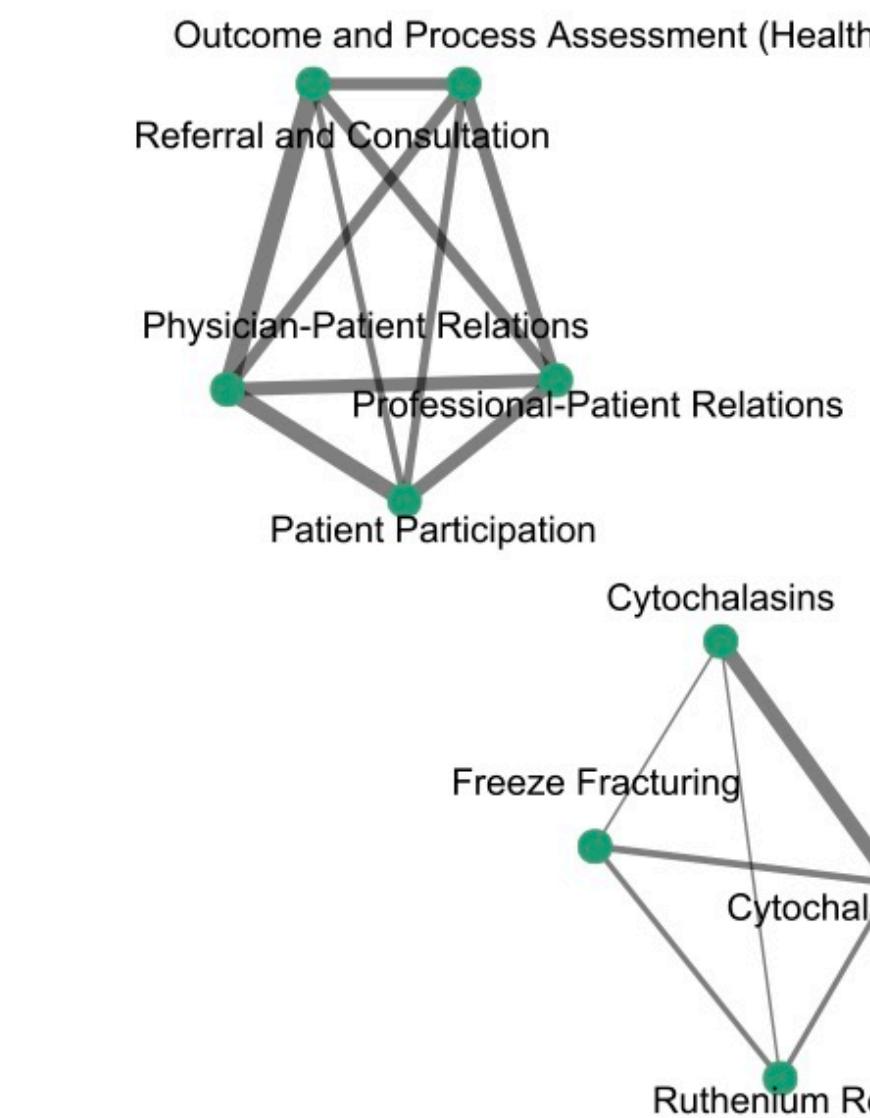


Translational axis



PMID	Year	MeSH terms
7449775	1980	Cell Membrane; Fixatives; Freeze Fracturing; Intracellular Membranes; Microscopy, Electron; Physarum
7404429	1980	Referral and Consultation; Physician-Patient Relations
...
2391304	2013	Arabidopsis; Arabidopsis Proteins; Plant Roots; Protoplasts

Cooccurrence network



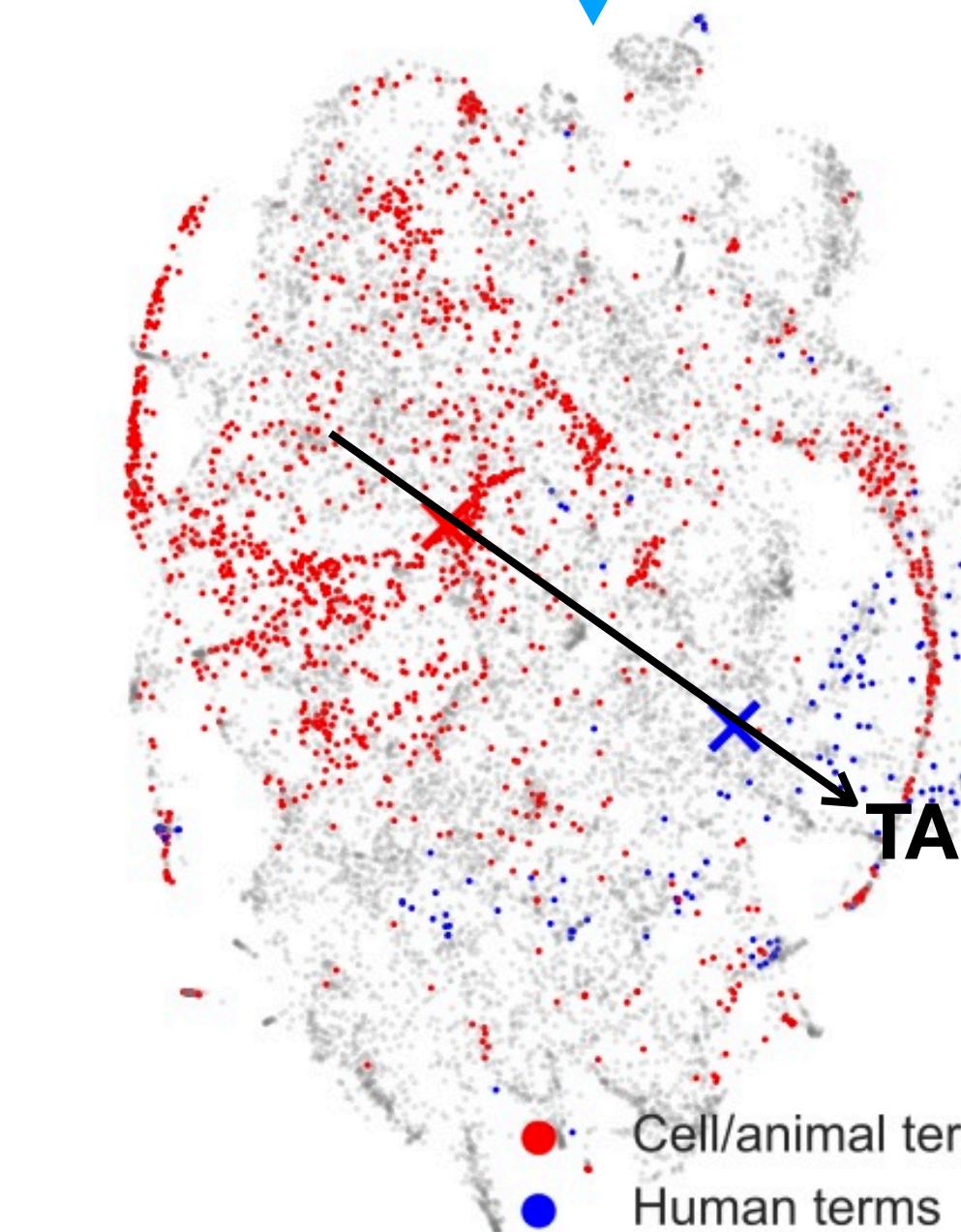
Network embedding
(LINE, GloVe)

MeSH term	Score
Freeze Fracturing	-0.640
Cytochalasins	-0.637
Cytochalasin B	-0.628
...	...
Referral and Consultation	0.873
Professional-Patient Relations	0.875
Patient Participation	0.876

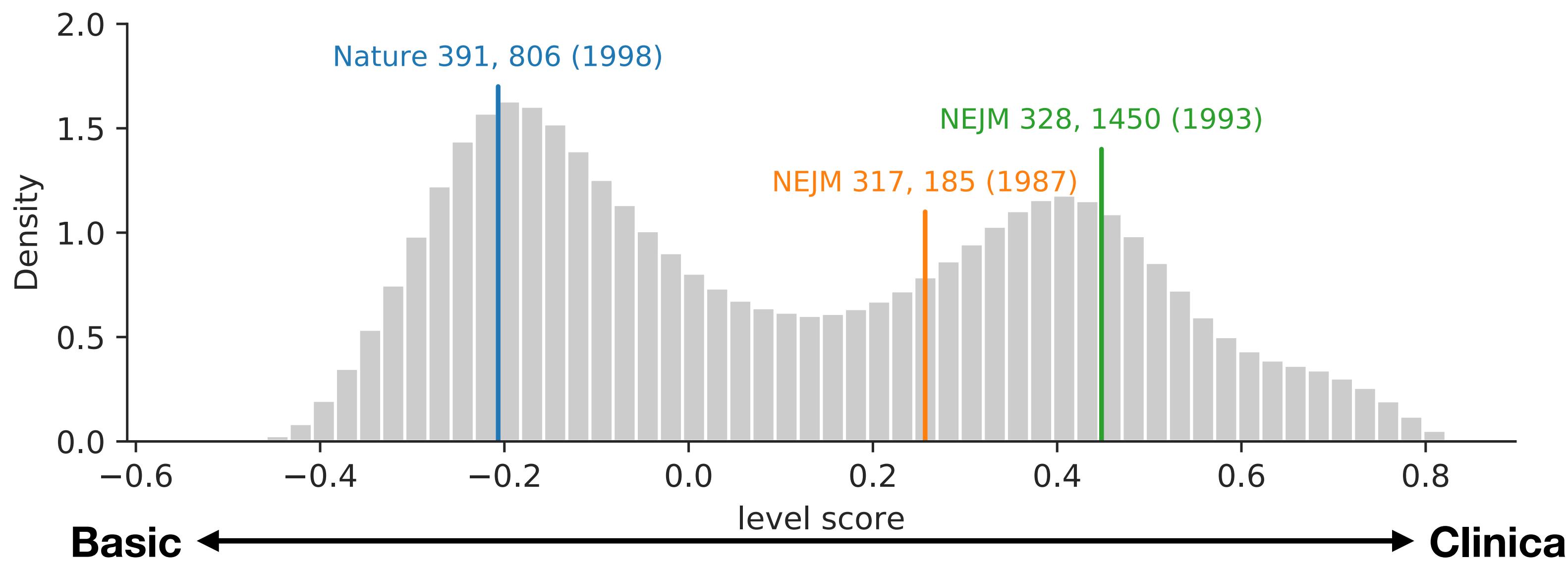
Projection



PMID	Score
6893735	-0.588
7449775	-0.543
7432463	-0.543
...	...
7425760	0.873
7404429	0.873
7241421	0.874

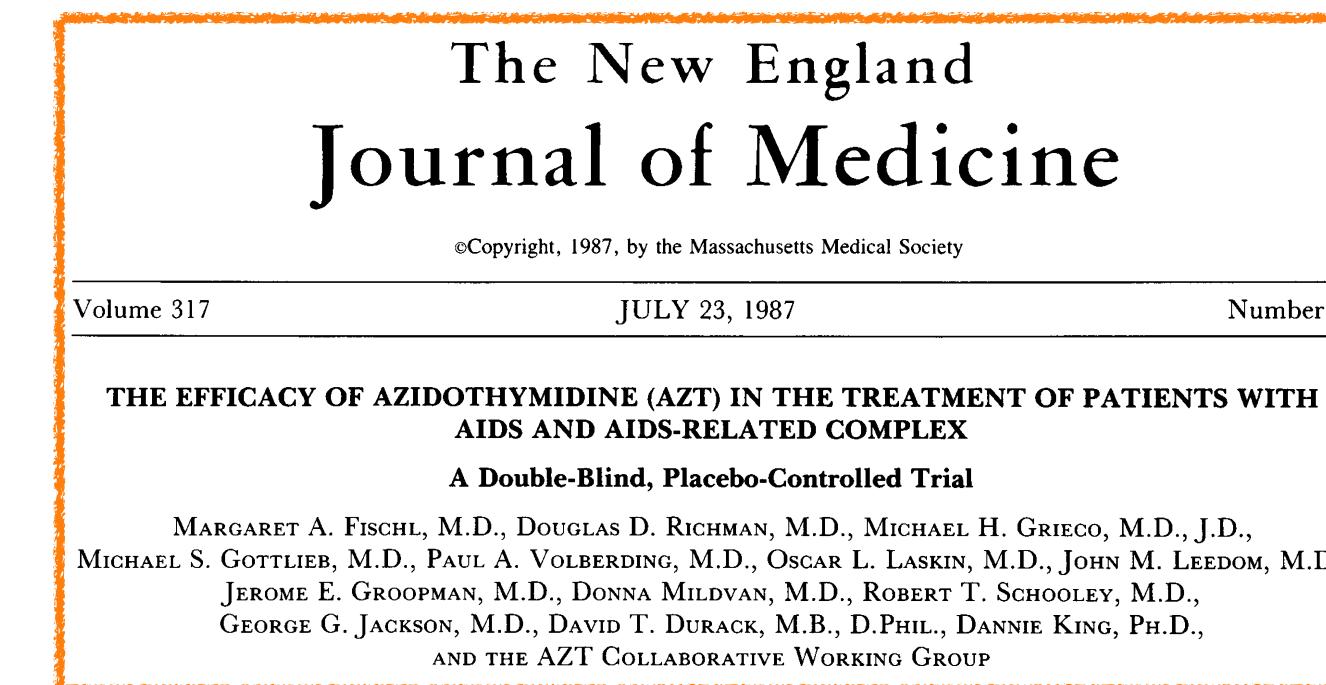


Validation - case studies

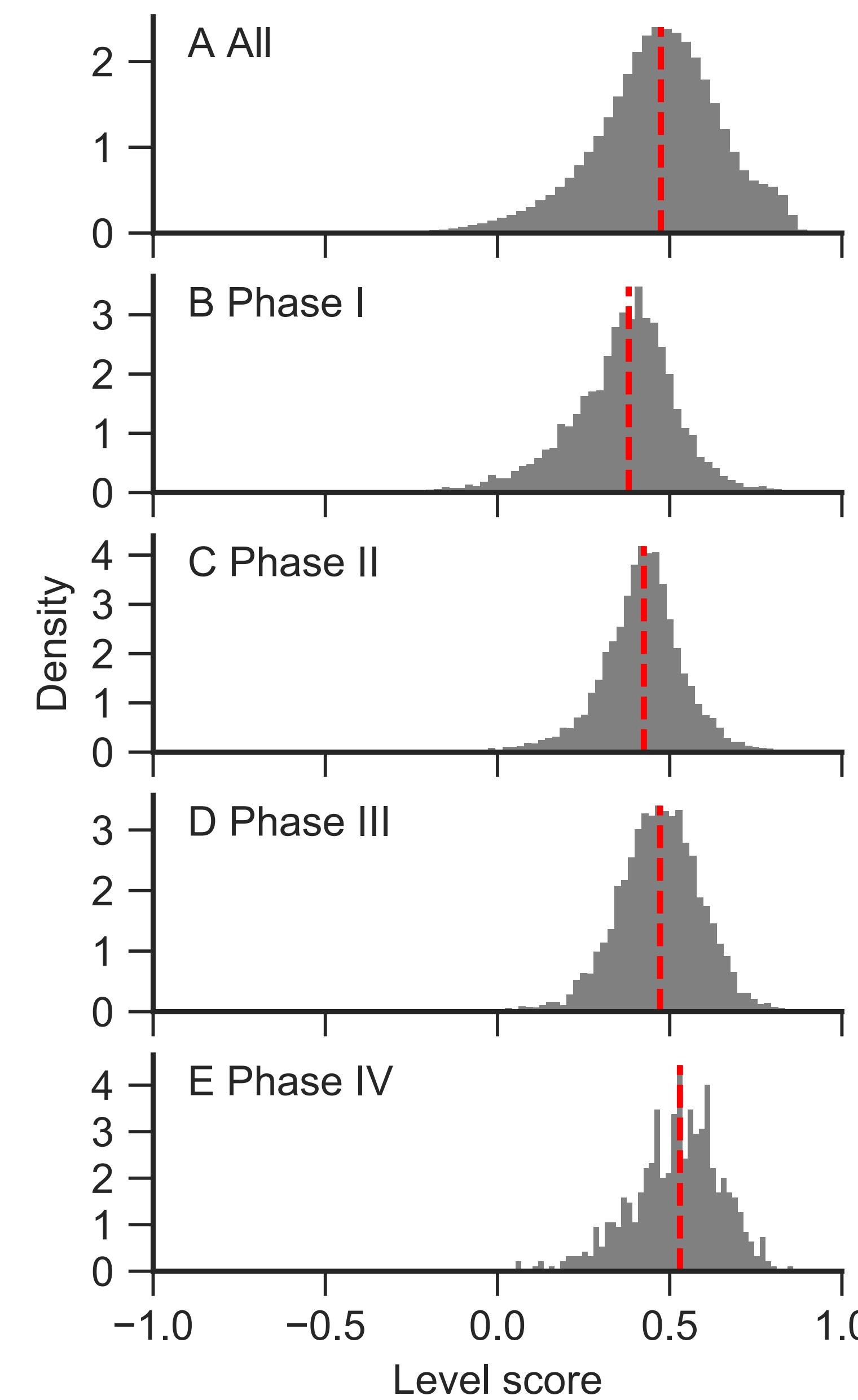


Potent and specific genetic interference by double-stranded RNA in *Caenorhabditis elegans*

Andrew Fire*, SiQun Xu*, Mary K. Montgomery*, Steven A. Kostas*†, Samuel E. Driver‡ & Craig C. Mello‡



Validation - clinical trials



Structure of the Biomedical Literature*

The structure and interrelations of the biomedical journal literature are investigated as a preparatory step for studies of biomedical research activity. Using newly developed methods of bibliographic citation analysis, approximately 900 biomedical journals are classified into approximately 50 separate fields and into four research levels. The research-level scale indicates research orientation ranging from clinical observation to basic research. Measures of influence are then obtained for individual journals, for biomedical fields and for research

levels. The fields of biochemistry and physiology are shown to have the highest citation influence.

A hierarchical influence diagram is presented to display the influence of 42 fields within biomedicine. Hierarchical influence diagrams are also presented for several individual fields showing the influence structure and citation relationships among their component journals. The combination of a subject, a level and an influence measure provides a unified framework for planned research activity analysis.

JASIST, 1976

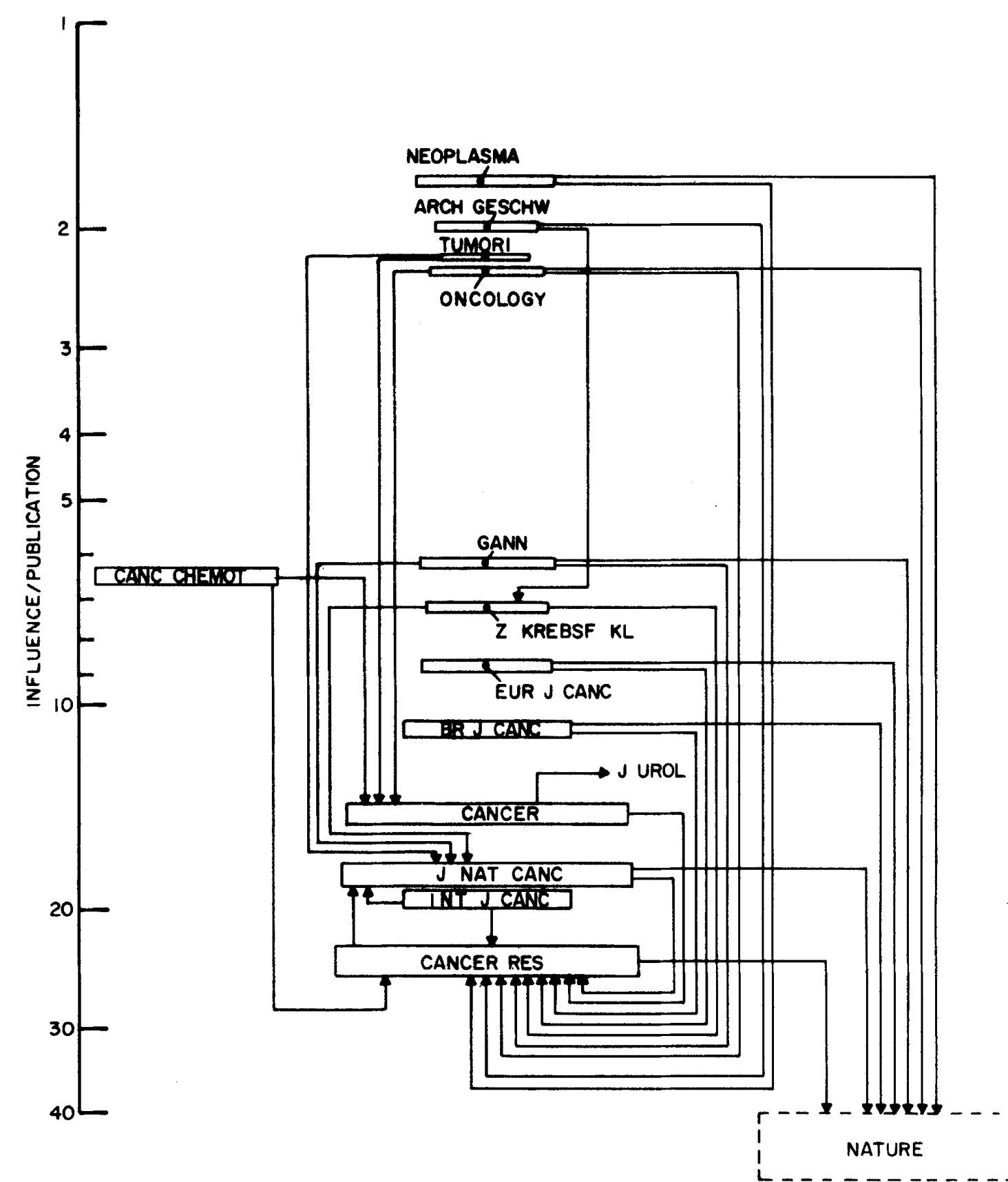


Fig. 5. Influence Map for Cancer Journals

Basic Research (e.g., *J. Biol. Chem*)

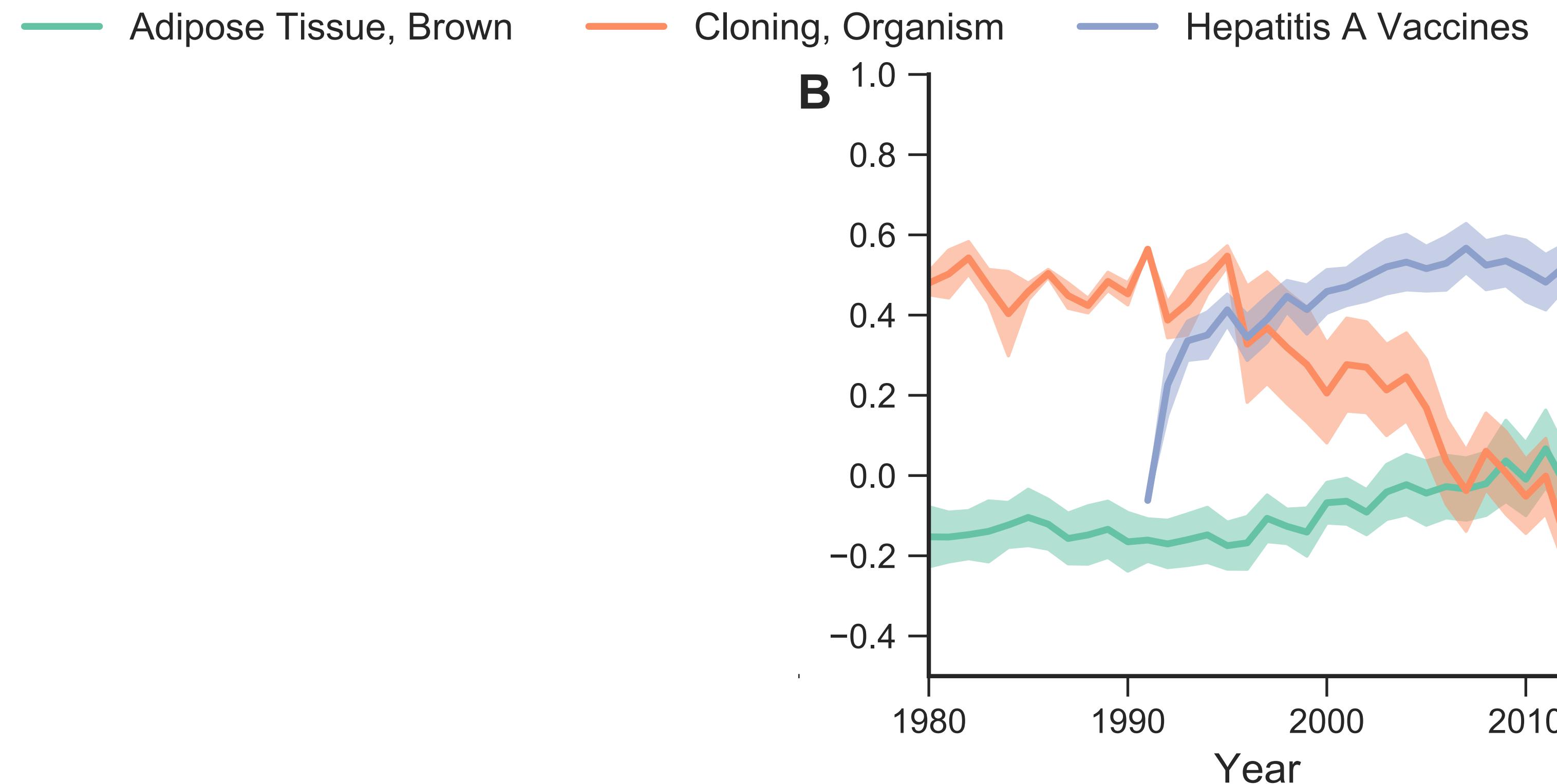
Clinical Mix (e.g., *NEJM*)

Clinical Observation (e.g., *JAMA*)

B

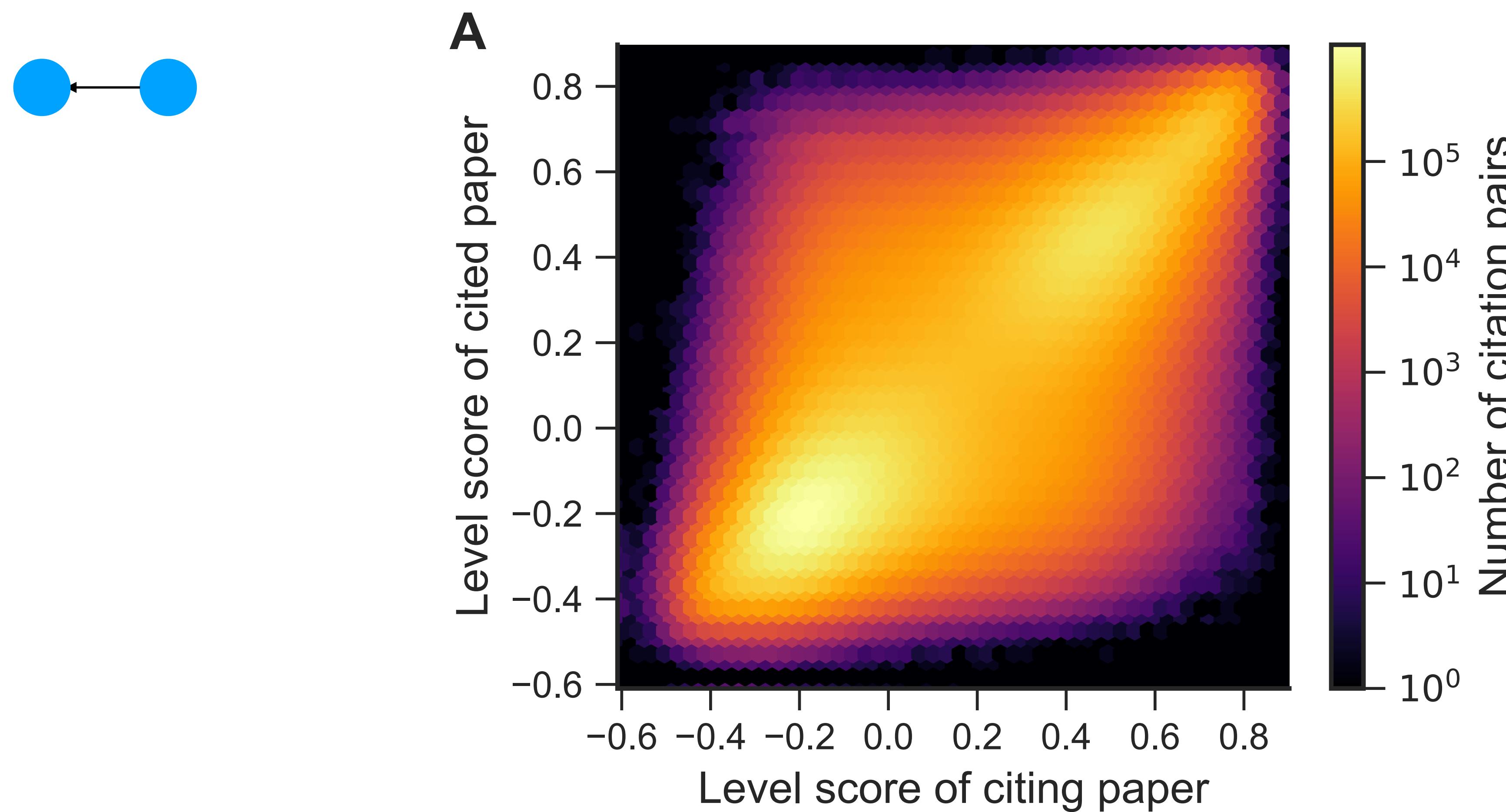
Panel B displays density plots for various journals, ordered from top to bottom by their level score. The x-axis is 'Level score' ranging from -1.0 to 1.0, and the y-axis is 'Density'. Each plot has a red vertical dashed line indicating the mean level score. The journals shown are: JBC (level ~-0.2), Cell (level ~-0.1), PNAS (level ~0.0), JCI (level ~0.1), Cancer Cell (level ~0.2), Nature (level ~0.3), Science (level ~0.4), Nature Medicine (level ~0.4), Neuropsychopharmacology (level ~0.4), Nat. Rev. Drug Discov. (level ~0.5), NEJM (level ~0.5), Lancet (level ~0.5), and JAMA (level ~0.6).

Changes over time

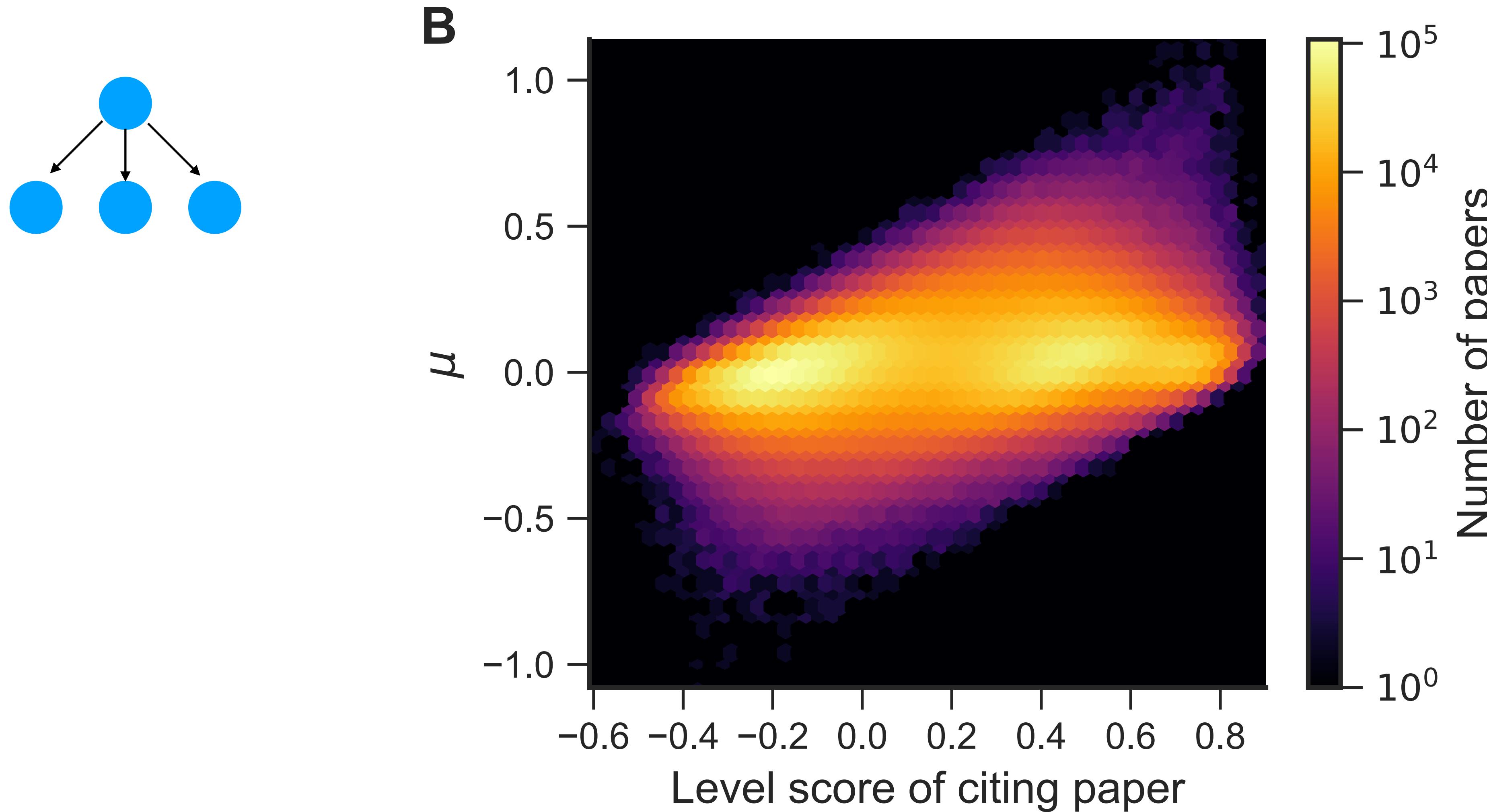


One-step knowledge flow

Do clinical papers cite basic or clinical papers?

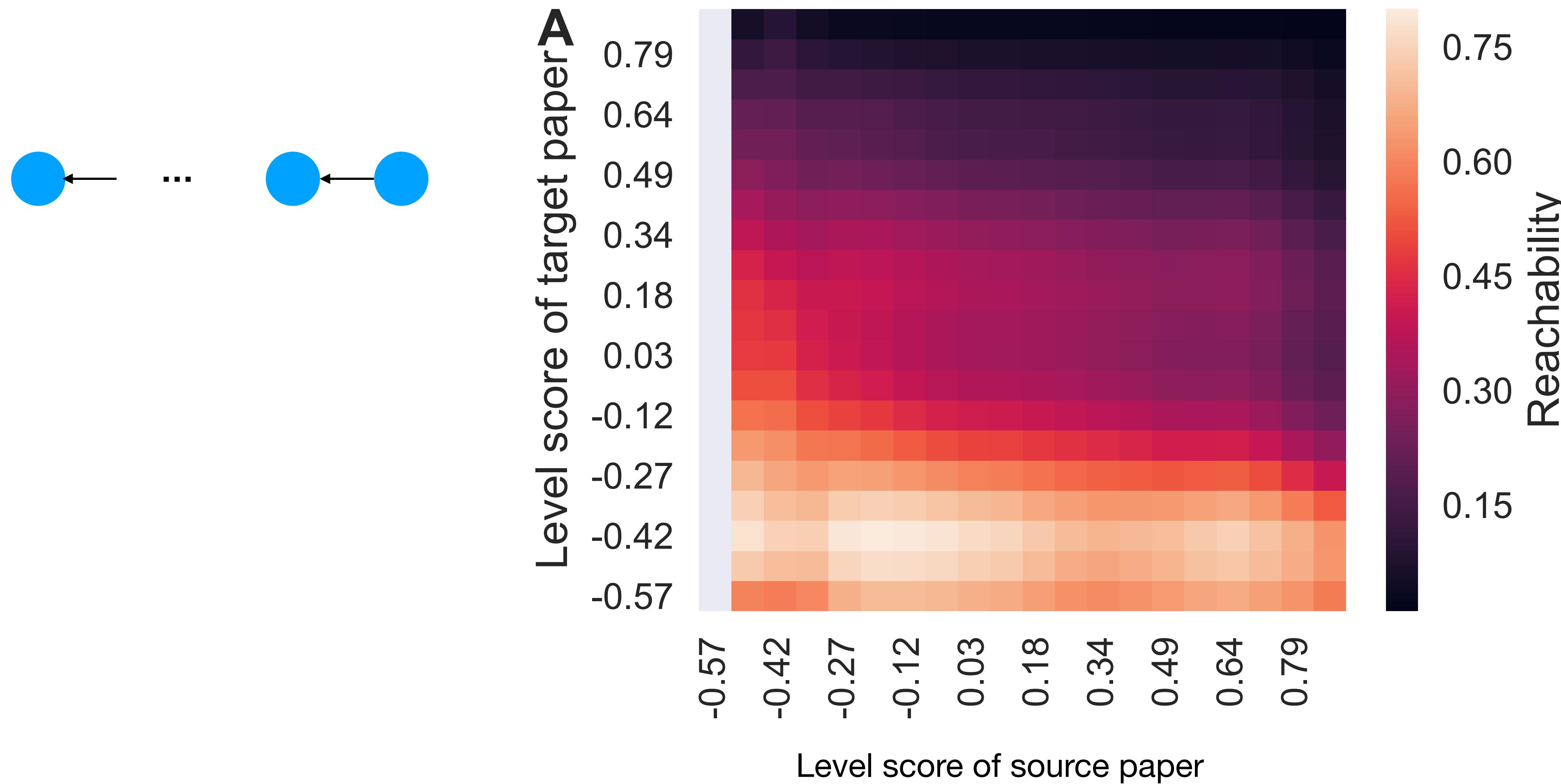


One-step knowledge flow



Multi-step knowledge flow

Do basic and clinical research operate in separated spheres?

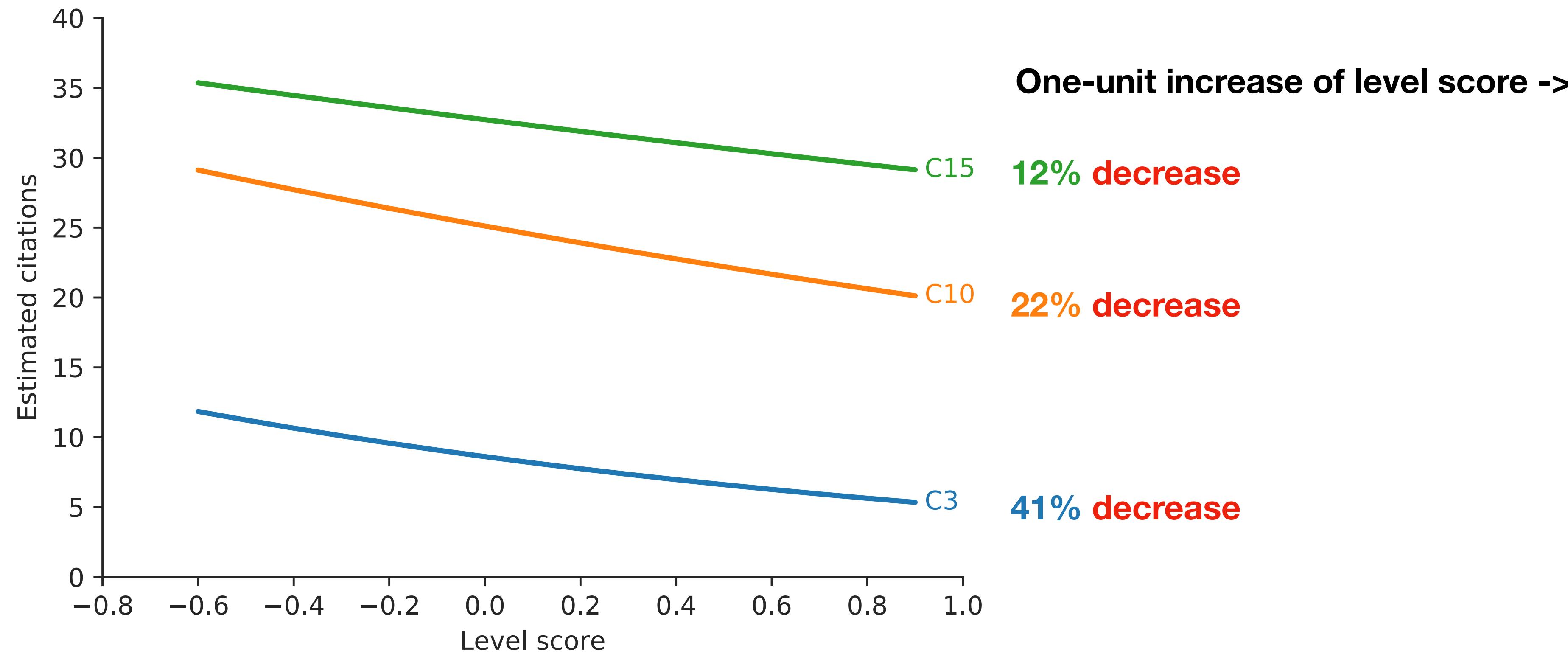


**Do basic and clinical research
get different citations?**

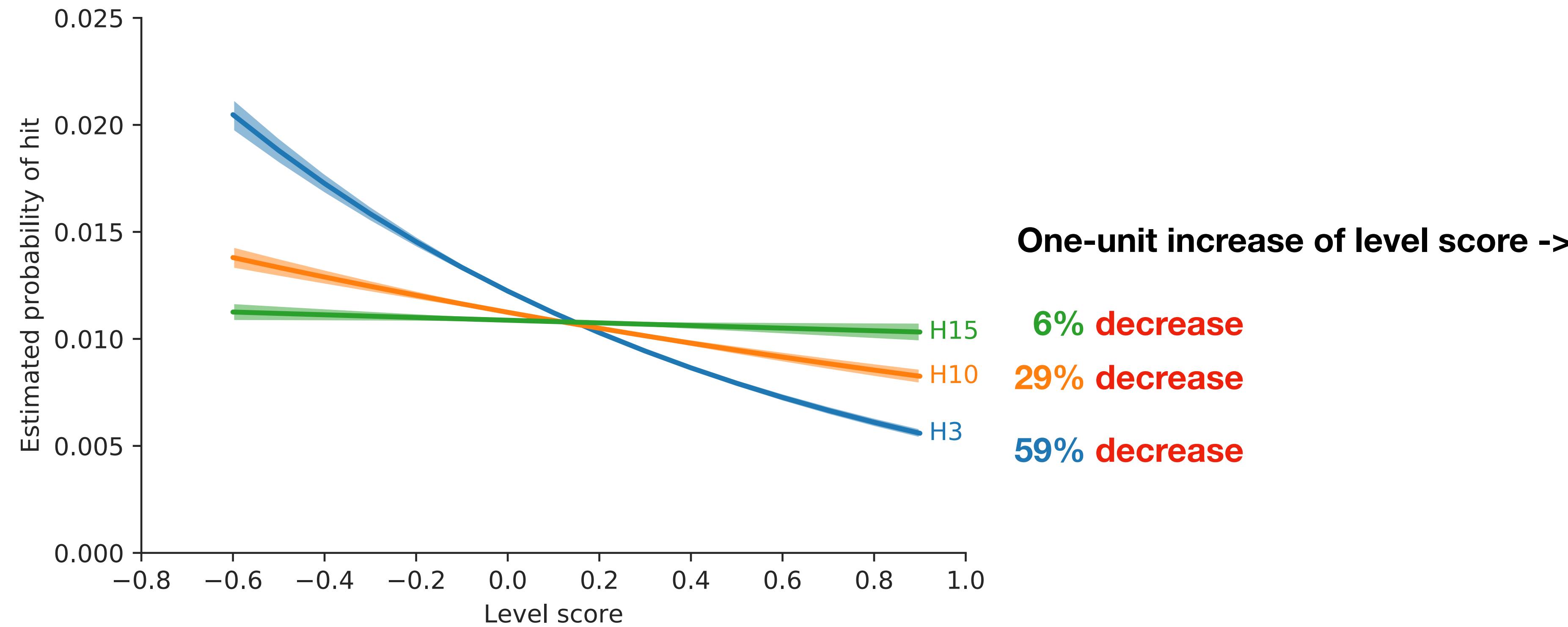
Clinical-oriented papers get less cited

Level score range	<i>c3</i>		<i>c10</i>		<i>c15</i>	
	Mean	Std. Dev.	Mean	Std. Dev.	Mean	Std. Dev.
< -0.308	13.691	24.619	34.425	66.751	41.522	84.190
< -0.007	10.766	20.601	29.606	69.053	37.723	98.234
< 0.295	6.706	13.976	20.015	48.280	26.372	80.252
< 0.596	5.049	11.702	16.736	39.610	22.859	58.260
≥ 0.596	4.445	10.034	17.241	39.490	25.199	67.556

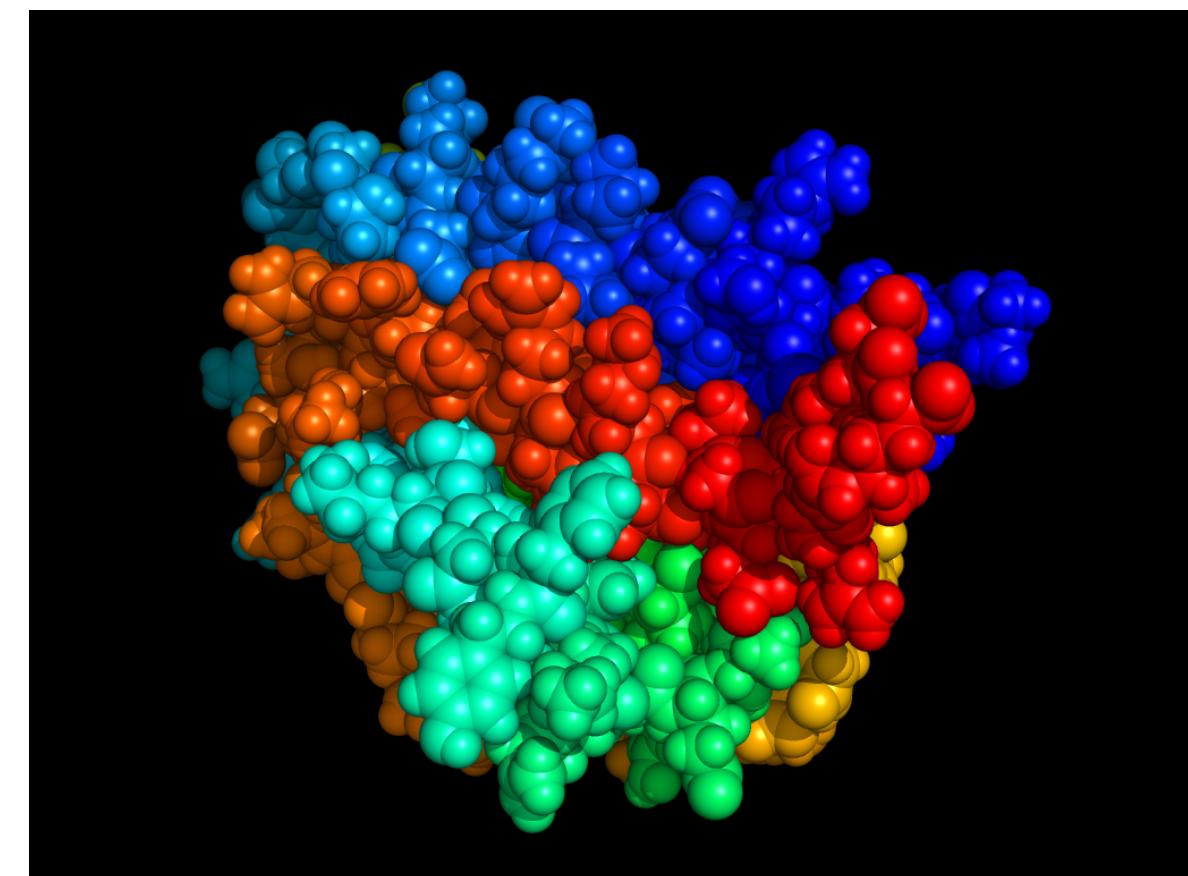
Clinical-oriented papers get less cited



Clinical-oriented papers are less likely to be hits

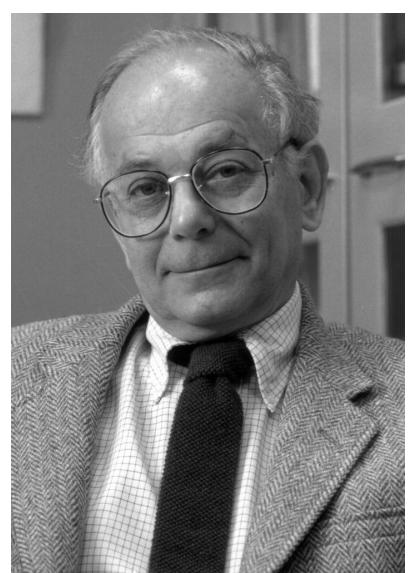


**How science and technology
are interacted?**

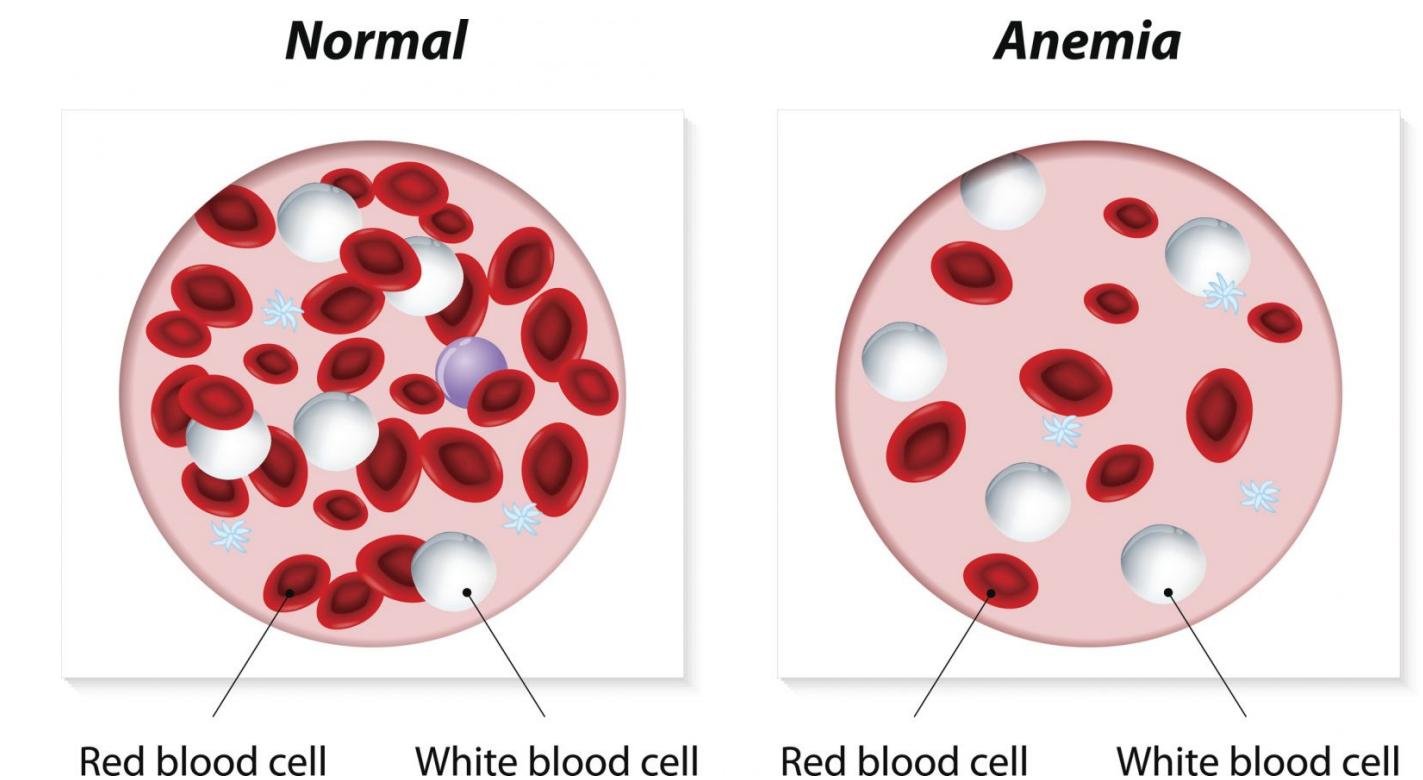
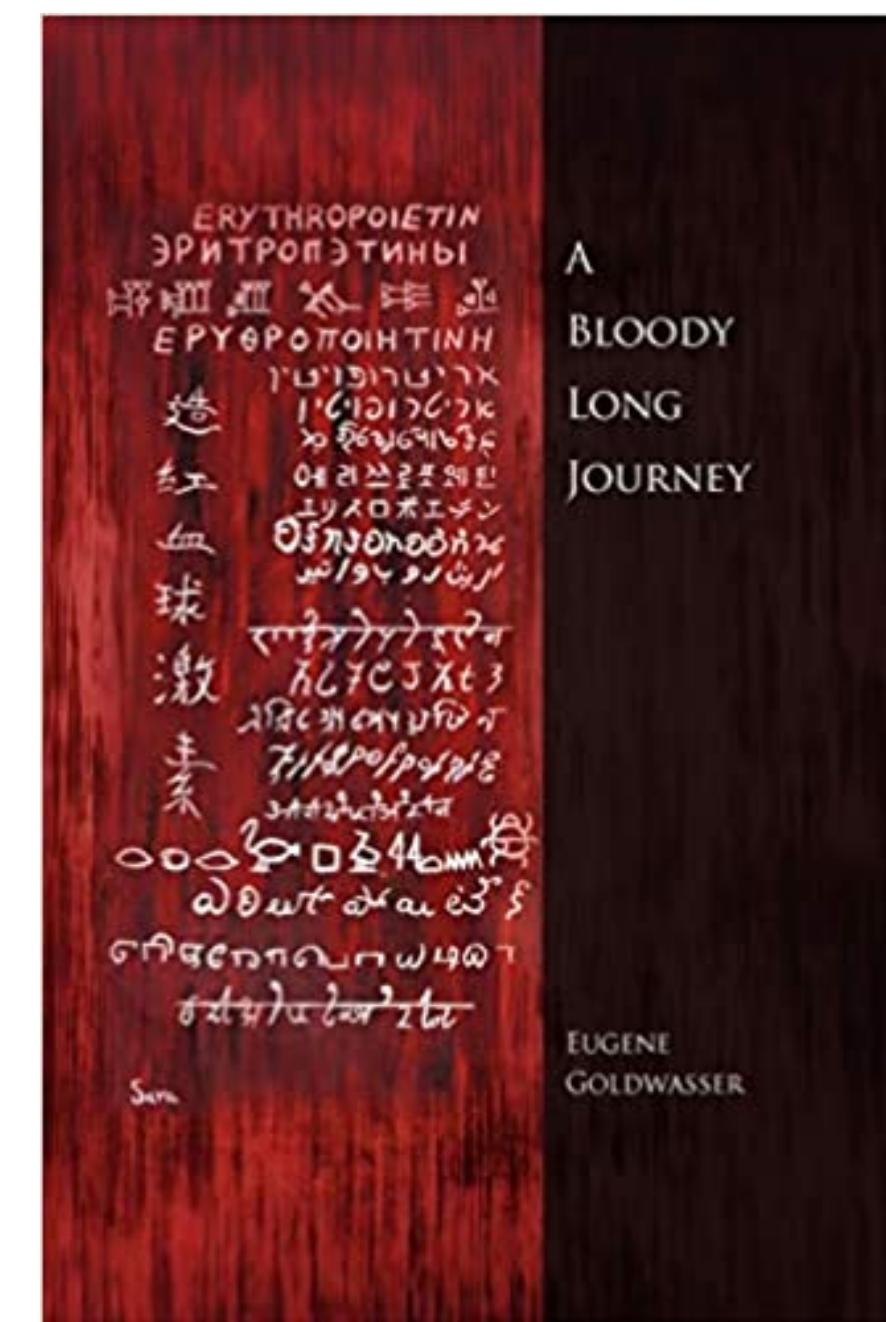


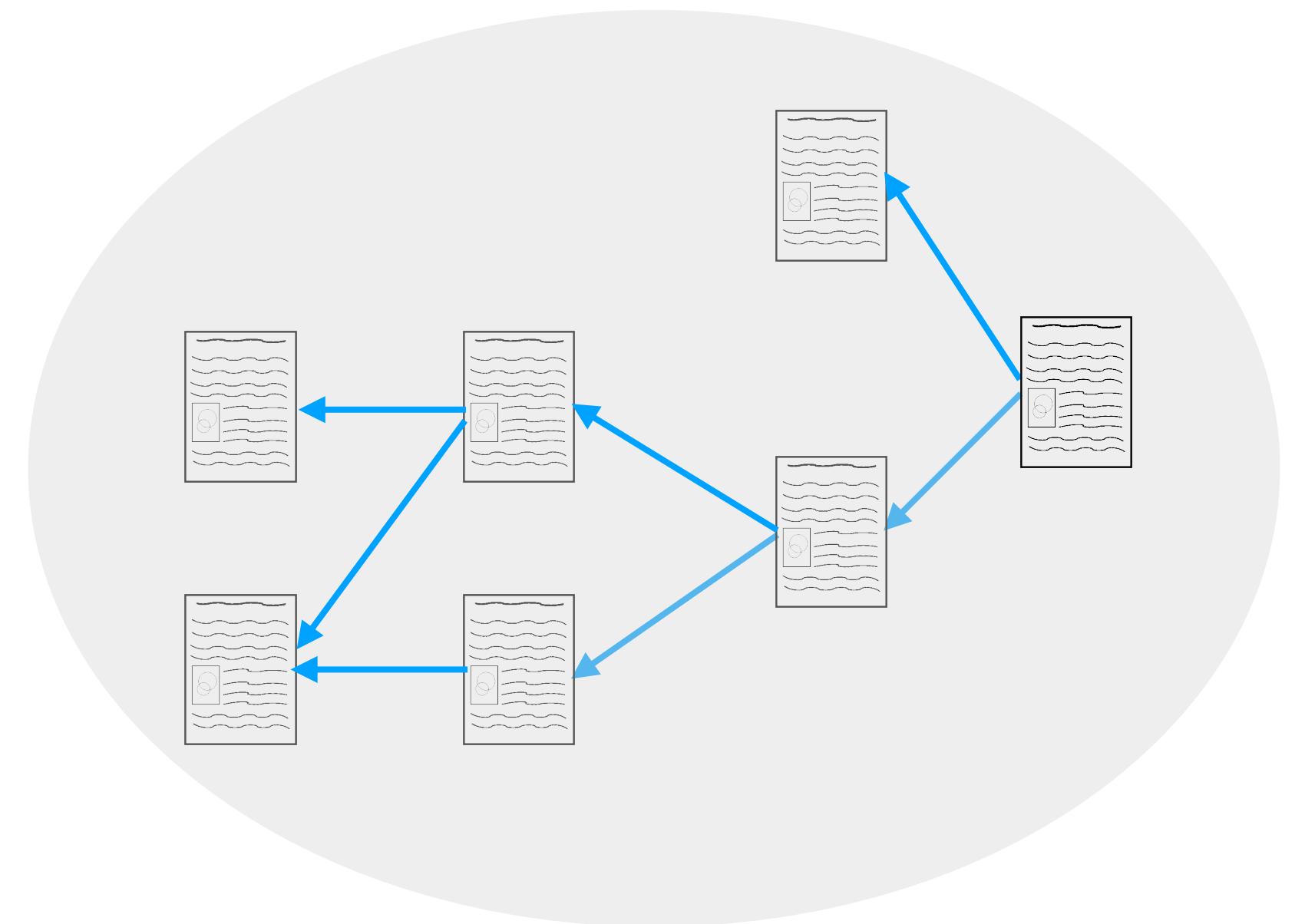
AMGEN

Erythropoietin (EPO)

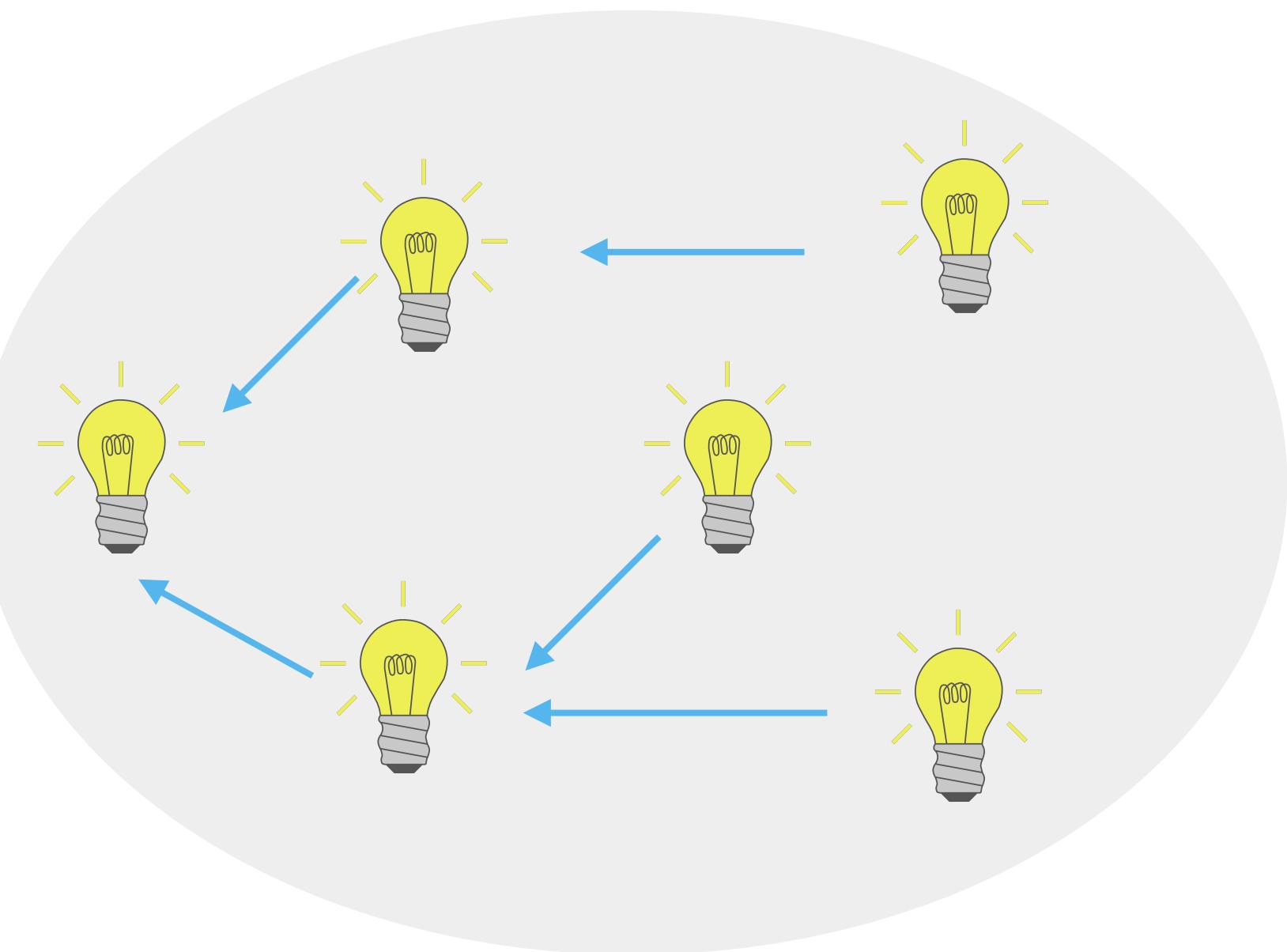


Eugene Goldwasser





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US007495103B2

(12) **United States Patent**
Hadida-Ruah et al.

(10) **Patent No.:** US 7,495,103 B2
(45) **Date of Patent:** Feb. 24, 2009

(54) **MODULATORS OF ATP-BINDING CASSETTE TRANSPORTERS**

(75) Inventors: **Sara Hadida-Ruah**, La Jolla, CA (US); **Anna Hazelwood**, San Diego, CA (US); **Peter Grootenhuis**, San Diego, CA (US); **Fred Van Goor**, San Diego, CA (US); **Ashvani Singh**, San Diego, CA (US); **Jinglan Zhou**, San Diego, CA (US); **Jason McCartney**, Cardiff-by-the-Sea, CA (US)

(73) Assignee: **Vertex Pharmaceuticals Incorporated**, Cambridge, MA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 450 days.

(21) Appl. No.: **11/165,818**

(22) Filed: **Jun. 24, 2005**

(65) **Prior Publication Data**

US 2006/0074075 A1 Apr. 6, 2006

Related U.S. Application Data

(60) Provisional application No. 60/582,676, filed on Jun. 24, 2004, provisional application No. 60/630,127, filed on Nov. 22, 2004, provisional application No. 60/635,674, filed on Dec. 13, 2004, provisional application No. 60/658,219, filed on Mar. 3, 2005, provisional application No. 60/661,311, filed on Mar. 11, 2005.

(51) **Int. Cl.**

C07D 215/38 (2006.01)
A61K 31/44 (2006.01)

(52) **U.S. Cl.** **546/156; 514/312**

(58) **Field of Classification Search** **546/153, 546/159, 167, 156; 514/312**

See application file for complete search history.

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Int J Pharm. 2004 Sep 10;282(1-2):87-94.

Pharmacokinetics of a cephalone (CQ-M-EPCA) in rats after oral, intraduodenal and intravenous administration.

Pérez-Guillé B¹, Sumanó LH, Villegas-Alvarez F, Soriano-Rosales R, González-Zamora JF, Jiménez-Bravo-Luna M, Carmona-Mancilla A, Ocampo CL.

Author information**Abstract**

As part of the development of a new series of antibacterial agents derived from coupling a beta-lactamic precursor with a fluoroquinolone and named cephalones, the pharmacokinetics of one derivate: CQ-M-EPCA in rats after intravenous, intragastric and intraduodenal routes, was carried out. After the IV injection of 20 mg/kg or 40 mg/kg of this cephalone, plasma concentrations at the time zero (Cp0) were 3.1 and 11.26 microg/ml, respectively. Plasma concentrations decreased rapidly to almost disappear in both instances. Forty-five minutes later, a surge in concentrations, in the 40 mg/kg group, with a maximal plasma concentration (Cpmax) of 2.97 microg/ml was observed. An elimination half-life (T1/2el) of 2.36 +/- 0.33 h. was calculated. The drug was undetected by the ninth hour. Intragastric administration of the drug resulted in Cpmax of 3.78 +/- 0.26 microg/ml with a time to reach Cpmax (Tmax) of 25 min and T1/2el = 3.22 h. Same variables after intraduodenal administration were Cpmax 4.71 microg/ml; Tmax 1h, and T1/2el 3.41 h. Outstandingly high bioavailabilities after intragastric and intraduodenal administration (169 and 246%, respectively), together with the shape of the concentration versus time profiles after IV administration suggest that the drug undergoes a complex redistribution phenomenon, while showing high tissue diffusion with an apparent volume of distribution of 3.33 l/kg.

PMID: 15336384 DOI: [10.1016/j.ijpharm.2004.06.001](https://doi.org/10.1016/j.ijpharm.2004.06.001)

[Indexed for MEDLINE]

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(Continued)

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Perez-Guille, International J of Pharm, vol. 282(1-2), pp. 87-94, 2004.*

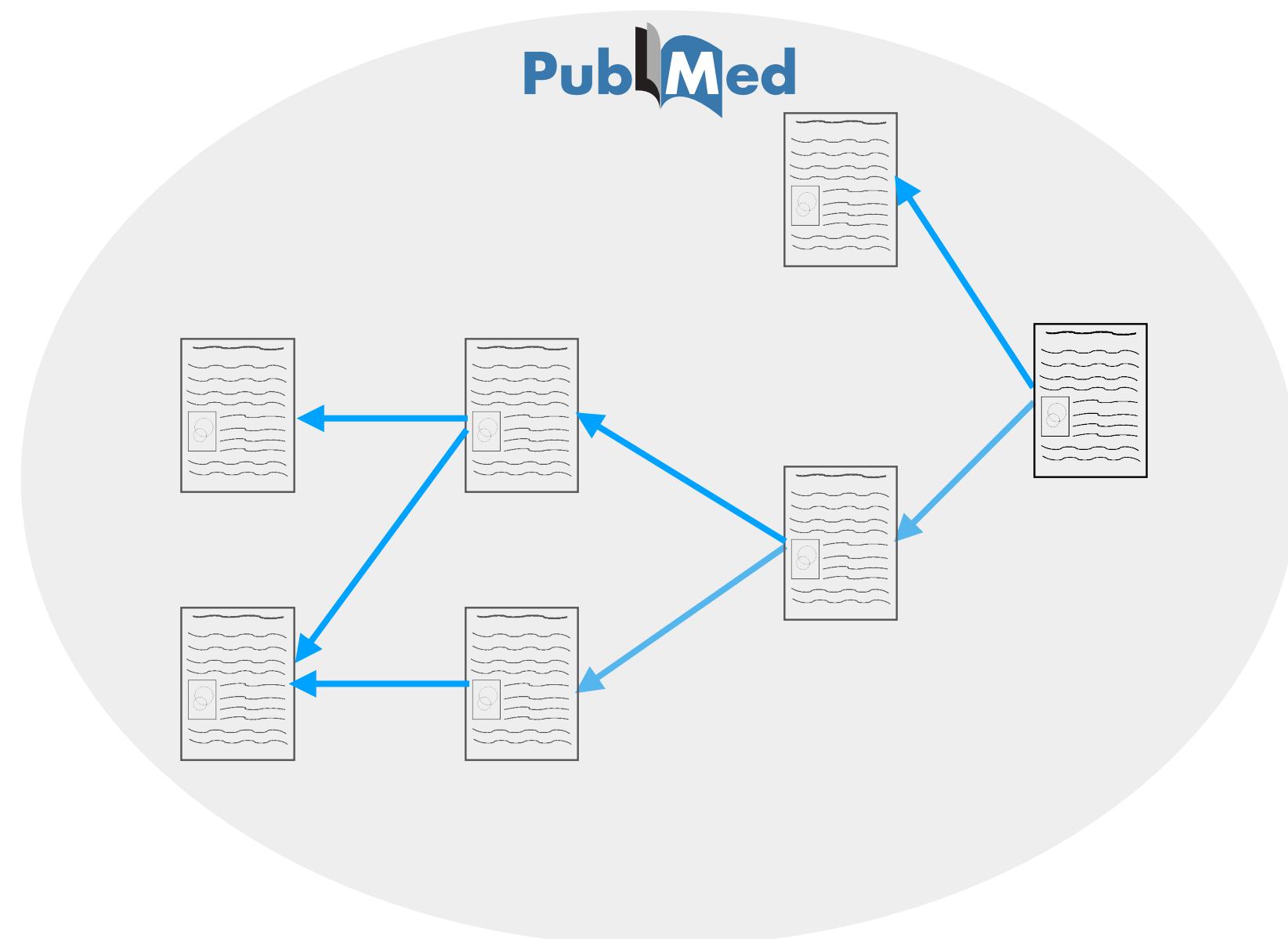
(Continued)

Primary Examiner—D. Margaret Seaman
(74) Attorney, Agent, or Firm—Nandakumar Govindaswamy; Nancy K. Brennan

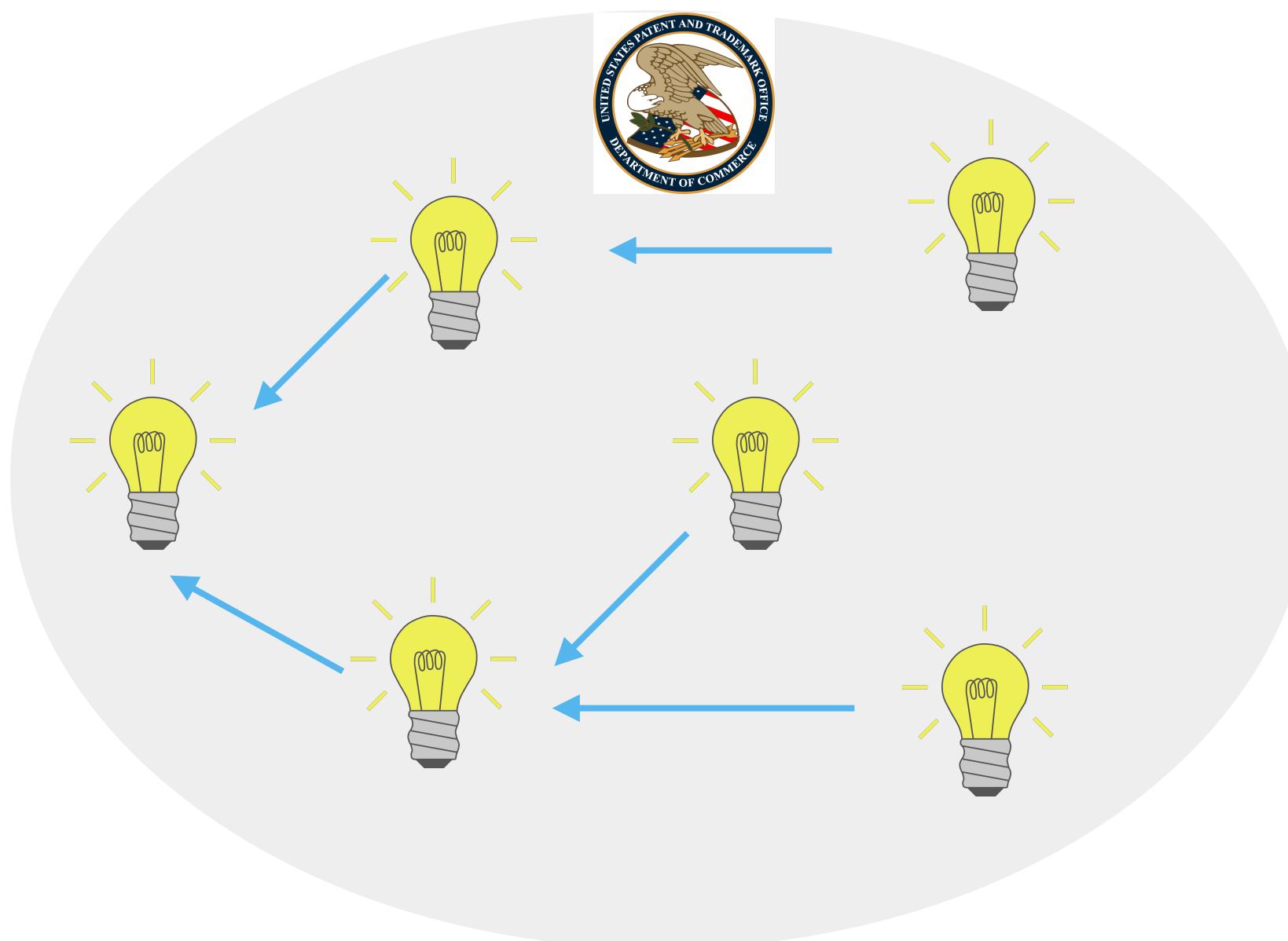
(57) **ABSTRACT**

The present invention relates to modulators of ATP-Binding Cassette ("ABC") transporters or fragments thereof, including Cystic Fibrosis Transmembrane Conductance Regulator, compositions thereof, and methods therewith. The present invention also relates to methods of treating ABC transporter mediated diseases using such modulators.

26M papers



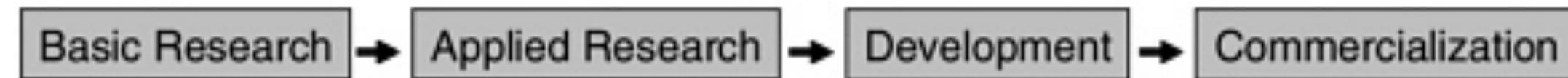
4.8M patents



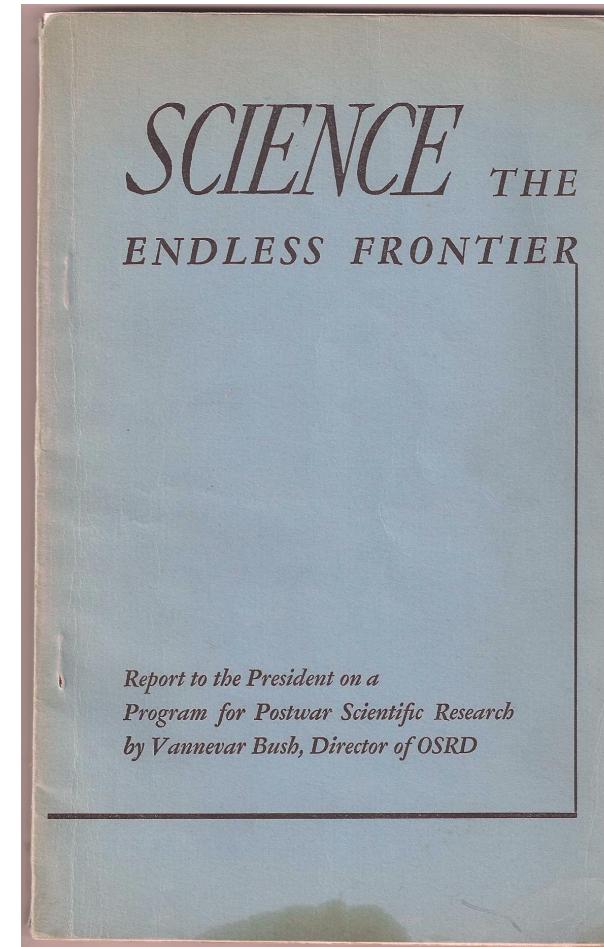
**Which characteristics of papers
make them more likely to have
patent citations?**

Basicness: Are basic or clinical papers more likely to be cited by patents?

Vannevar Bush's "Linear Model" (1945)



Provide a basis for funding basic research



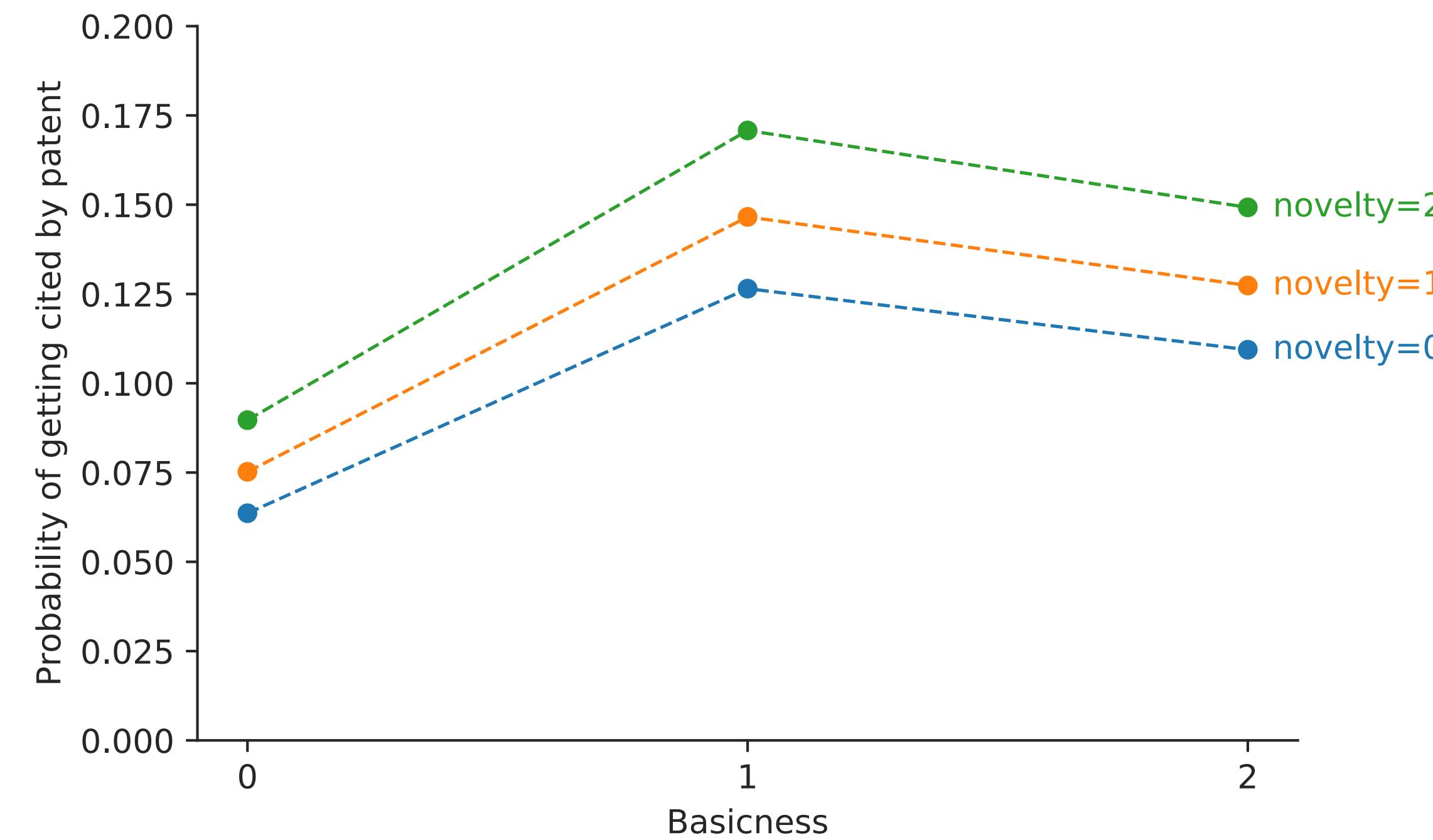
Novelty: Is novel research more likely to be cited by patents?

High risk and high return; face delayed recognition in the scientific community

Researchers tend to adopt conservative research; funders tend to favor safe project proposals

Provide a basis for promoting novel research

	Overall	Basicness			NoveltyCat		
		0	1	2	0	1	2
# papers	5 611 286	2 177 939	1 121 093	2 312 254	2 352 488	2 969 692	289 106
% cited by patents	11.19	4.54	18.76	13.80	7.94	13.50	13.96
% cited by US patents	8.84	3.64	15.04	10.75	6.20	10.71	11.21
% cited by US company patents	5.66	2.38	9.52	6.87	3.94	6.85	7.44



Summary

- Science of science study of biomedicine and beyond
- “Level score” provides a intuitive quantification of the degree of “basicness” of a biomedical paper
- Clinical papers have citation disadvantage
- Basic papers and novel paper are more likely to be cited by patents

Thanks & QA