

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/6397622>

The Increasing Dominance of Teams in Production of Knowledge

Article in *Science* · June 2007

DOI: 10.1126/science.1136099 · Source: PubMed

CITATIONS

1,464

READS

2,921

3 authors:



Stefan Wuchty

University of Miami

149 PUBLICATIONS 5,154 CITATIONS

[SEE PROFILE](#)



Benjamin Jones

Northwestern University

31 PUBLICATIONS 4,618 CITATIONS

[SEE PROFILE](#)



Brian Uzzi

Northwestern University

90 PUBLICATIONS 19,728 CITATIONS

[SEE PROFILE](#)

Some of the authors of this publication are also working on these related projects:



Ecological Networks [View project](#)

This copy is for your personal, non-commercial use only.

If you wish to distribute this article to others, you can order high-quality copies for your colleagues, clients, or customers by [clicking here](#).

Permission to republish or repurpose articles or portions of articles can be obtained by following the guidelines [here](#).

The following resources related to this article are available online at www.sciencemag.org (this information is current as of October 2, 2010):

Updated information and services, including high-resolution figures, can be found in the online version of this article at:

<http://www.sciencemag.org/cgi/content/full/316/5827/1036>

Supporting Online Material can be found at:

<http://www.sciencemag.org/cgi/content/full/1136099/DC1>

A list of selected additional articles on the Science Web sites **related to this article** can be found at:

<http://www.sciencemag.org/cgi/content/full/316/5827/1036#related-content>

This article **cites 14 articles**, 3 of which can be accessed for free:

<http://www.sciencemag.org/cgi/content/full/316/5827/1036#otherarticles>

This article has been **cited by** 70 article(s) on the ISI Web of Science.

This article has been **cited by** 13 articles hosted by HighWire Press; see:

<http://www.sciencemag.org/cgi/content/full/316/5827/1036#otherarticles>

This article appears in the following **subject collections**:

Sociology

<http://www.sciencemag.org/cgi/collection/sociology>

References and Notes

1. G. G. Simpson, C. Dean, *Science* **296**, 285 (2002).
2. L. Corbesier, G. Coupland, *Plant Cell Environ.* **28**, 54 (2005).
3. T. Imaizumi, S. A. Kay, *Trends Plant Sci.* **11**, 550 (2006).
4. B. Thomas, D. Vince-prue, *Photoperiodism in Plants* (Academic Press, London, 1997).
5. Y. Kobayashi, H. Kaya, K. Goto, M. Iwabuchi, T. Araki, *Science* **286**, 1960 (1999).
6. I. Kardailsky *et al.*, *Science* **286**, 1962 (1999).
7. S. Takada, K. Goto, *Plant Cell* **15**, 2856 (2003).
8. H. An *et al.*, *Development* **131**, 3615 (2004).
9. M. Abe *et al.*, *Science* **309**, 1052 (2005).
10. P. A. Wigge *et al.*, *Science* **309**, 1056 (2005).
11. J. A. D. Zeevaert, *Plant Cell* **18**, 1783 (2006).
12. E. Lifschitz *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **103**, 6398 (2006).
13. H. Böhlenius, S. Eriksson, F. Parcy, O. Nilsson, *Science* **316**, 367 (2007).
14. T. Izawa *et al.*, *Genes Dev.* **16**, 2006 (2002).
15. S. Kojima *et al.*, *Plant Cell Physiol.* **43**, 1096 (2002).
16. R. Hayama, S. Yokoi, S. Tamaki, M. Yano, K. Shimamoto, *Nature* **422**, 719 (2003).
17. R. Ishikawa *et al.*, *Plant Cell* **17**, 3326 (2005).
18. A. Guivarc'h, A. Spena, M. Noin, C. Besnard, D. Chriqui, *Transgen. Res.* **5**, 3 (1996).
19. T. Asano *et al.*, *Plant Cell Physiol.* **43**, 668 (2002).
20. R. Ando, H. Hama, M. Yamamoto-Hino, H. Mizuno, A. Miyawaki, *Proc. Natl. Acad. Sci. U.S.A.* **99**, 12651 (2002).
21. S. Arimura, J. Yamamoto, G. P. Aida, M. Nakazono, N. Tsutsumi, *Proc. Natl. Acad. Sci. U.S.A.* **101**, 7805 (2004).
22. P. Gialalisco, K. Kapitza, A. Kolasa, A. Buhtz, J. Kehr, *Proteomics* **6**, 896 (2006).
23. M. K. Chailakhyan, *C. R. Acad. Sci. URSS* **13**, 79 (1936).
24. A. Lang, in *Encyclopedia of Plant Physiology*, W. Ruhland, Ed. (Springer, Berlin, 1965), vol. 15, pp. 1380–1536.
25. J. A. D. Zeevaert, *Annu. Rev. Plant Physiol.* **27**, 321 (1976).
26. M. G. Muszynski *et al.*, *Plant Physiol.* **142**, 1523 (2006).
27. P. Teper-Bamnlöcker, A. Samach, *Plant Cell* **17**, 2661 (2005).
28. H. Böhlenius *et al.*, *Science* **312**, 1040 (2006).
29. We thank J. Kyojuka (University of Tokyo) for advice on the experiments and comments on the manuscript, K. Kadowaki (NIAS, Tsukuba) for the *RPP16* promoter, H. Uchimiya (University of Tokyo) for the *rolC* promoter, and members of the Laboratory of Plant Molecular Genetics at NAIST for discussions. This research was supported by Grants-in-Aid for Scientific Research on Priority Areas of the Ministry of Education, Culture, Sports, Science, and Technology of Japan (to K.S.).

Supporting Online Material

www.sciencemag.org/cgi/content/full/1141753/DC1
Materials and Methods
Figs. S1 to S3
References

26 February 2007; accepted 6 April 2007
Published online 19 April 2007;
10.1126/science.1141753
Include this information when citing this paper.

The Increasing Dominance of Teams in Production of Knowledge

Stefan Wuchty,^{1*} Benjamin F. Jones,^{2*} Brian Uzzi^{1,2,*†}

We have used 19.9 million papers over 5 decades and 2.1 million patents to demonstrate that teams increasingly dominate solo authors in the production of knowledge. Research is increasingly done in teams across nearly all fields. Teams typically produce more frequently cited research than individuals do, and this advantage has been increasing over time. Teams now also produce the exceptionally high-impact research, even where that distinction was once the domain of solo authors. These results are detailed for sciences and engineering, social sciences, arts and humanities, and patents, suggesting that the process of knowledge creation has fundamentally changed.

An acclaimed tradition in the history and sociology of science emphasizes the role of the individual genius in scientific discovery (1, 2). This tradition focuses on guiding contributions of solitary authors, such as Newton and Einstein, and can be seen broadly in the tendency to equate great ideas with particular names, such as the Heisenberg uncertainty principle, Euclidean geometry, Nash equilibrium, and Kantian ethics. The role of individual contributions is also celebrated through science's award-granting institutions, like the Nobel Prize Foundation (3).

Several studies, however, have explored an apparent shift in science from this individual-based model of scientific advance to a teamwork model. Building on classic work by Zuckerman and Merton, many authors have established a rising propensity for teamwork in samples of research fields, with some studies going back a century (4–7). For example, de Solla Price examined the change in team size in chemistry from 1910 to 1960, forecasting that in 1980 zero percent of the papers would be written by solo au-

thors (8). Recently, Adams *et al.* established that over time, teamwork had increased across broader sets of fields among elite U.S. research universities (9). Nevertheless, the breadth and depth of this projected shift in manpower remains indefinite, particularly in fields where the size of experiments and capital investments remain small, raising the question as to whether the projected growth in teams is universal or clustered in specialized fields.

A shift toward teams also raises new questions of whether teams produce better science. Teams may bring greater collective knowledge and effort, but they are known to experience social network and coordination losses that make

them underperform individuals even in highly complex tasks (10–12), as F. Scott Fitzgerald concisely observed when he stated that “no grand idea was ever born in a conference” (13). From this viewpoint, a shift to teamwork may be a costly phenomenon or one that promotes low-impact science, whereas the highest-impact ideas remain the domain of great minds working alone.

We studied 19.9 million research articles in the Institute for Scientific Information (ISI) Web of Science database and an additional 2.1 million patent records. The Web of Science data covers research publications in science and engineering since 1955, social sciences since 1956, and arts and humanities since 1975. The patent data cover all U.S. registered patents since 1975 (14). A team was defined as having more than one listed author (publications) or inventor (patents). Following the ISI classification system, the universe of scientific publications is divided into three main branches and their constituent subfields: science and engineering (with 171 subfields), social sciences (with 54 subfields), and arts and humanities (with 27 subfields). The universe of U.S. patents was treated as a separate category (with 36 subfields). See the Supporting Online Material (SOM) text for details on these classifications.

For science and engineering, social sciences, and patents, there has been a substantial shift toward collective research. In the sciences, team size has grown steadily each year and nearly

Table 1. Patterns by subfield. For the three broad ISI categories and for patents, we counted the number (*N*) and percentage (%) of subfields that show (i) larger team sizes in the last 5 years compared to the first 5 years and (ii) RTI measures larger than 1 in the last 5 years. We show RTI measures both with and without self-citations removed in calculating the citations received. Dash entries indicate data not applicable.

	Increasing team size			RTI > 1 (with self-citations)		RTI > 1 (no self-citations)	
	<i>N</i> _{fields}	<i>N</i> _{fields}	%	<i>N</i> _{fields}	%	<i>N</i> _{fields}	%
Science and engineering	171	170	99.4	167	97.7	159	92.4
Social sciences	54	54	100.0	54	100.0	51	94.4
Arts and humanities	27	24	88.9	23	85.2	18	66.7
Patents	36	36	100.0	32	88.9	–	–

¹Northwestern Institute on Complexity (NICO), Northwestern University, Evanston, IL 60208, USA. ²Kellogg School of Management, Northwestern University, Evanston, IL 60208, USA.

*These authors contributed equally to this work.

†To whom correspondence should be addressed. E-mail: uzzi@northwestern.edu

doubled, from 1.9 to 3.5 authors per paper, over 45 years.

Shifts toward teamwork in science and engineering have been suggested to follow from the increasing scale, complexity, and costs of big science. Surprisingly then, we find an equally strong trend toward teamwork in the social sciences, where these drivers are much less notable. Although social scientists in 1955 wrote 17.5% of their papers in teams, by 2000 they wrote 51.5% of their papers in teams, an increase similar to that in sciences and engineering. Mean team size has also grown each year. On average, today's social sciences papers are written in pairs, with a continuing, positive trend toward larger teams. Unlike the other areas of research, single authors still produce over 90% of the papers in the arts and humanities. Nevertheless, there is a positive trend toward teams in arts and humanities ($P < 0.001$). Lastly, patents also show a rising dominance of teams. Although these data are on a shorter time scale (1975–2000), there was a similar annualized increase in the propensity for teamwork. Average team size has risen from 1.7 to 2.3 inventors per patent, with the positive trend toward larger teams continuing.

The generality of the shift to teamwork is captured in Table 1. In sciences and engineering, 99.4% of the 171 subfields have seen increased teamwork. Meanwhile, 100% of the 54 subfields in the social sciences, 88.9% of the 27 subfields in the humanities, and 100% of the 36 subfields in patenting have seen increased teamwork.

Trends for individual fields are presented in table S1. In the sciences, areas like medicine, biology, and physics have seen at least a doubling in mean team size over the 45-year period. Surprisingly, even mathematics, long thought the domain of the loner scientist and least dependent of the hard sciences on lab scale and capital-intensive equipment, showed a marked increase in the fraction of work done in teams, from 19% to 57%, with mean team size rising from 1.22 to 1.84. In the social sciences, psychology, economics, and political science show enormous shifts toward teamwork, sometimes doubling or tripling the propensity for teamwork. With regard to average team size, psychology, the closest of the social sciences to a lab science, has the highest growth

(75.1%), whereas political science has the lowest (16.6%). As reflected in Fig. 1A, the humanities show lower growth rates in the fraction of publications done in teams, yet a tendency toward increased teamwork is still observed. All areas of patents showed a positive change in both the fraction of papers done by teams and the team size, with only small variations across the areas of patenting, suggesting that the conditions favoring teamwork in patenting are largely similar across subfields.

Our measure of impact was the number of citations each paper and patent receives, which has been shown to correlate with research quality (15–17) and is frequently used in promotion and funding reviews (18). Highly cited work was defined as receiving more than the mean number of citations for a given field and year (19). Teams produced more highly cited work in each broad area of research and at each point in time.

To explore the relationship between teamwork and impact in more detail, we defined the relative team impact (RTI) for a given time period and field. RTI is the mean number of citations received by team-authored work divided by the mean number of citations received by solo-authored work. A RTI greater than 1 indicates that teams produce more highly cited papers than solo authors and vice versa for RTI less than 1. When RTI is equal to 1, there is no difference in citation rates for team- and solo-authored papers. In our data set, the average RTI was greater than 1 at all points in time and in all broad research areas: sciences and engineering, social sciences, humanities, and patents. In other words, there is a broad tendency for teams to produce more highly cited work than individual authors. Further, RTI is rising with time. For example, in sciences and engineering, team-authored papers received 1.7 times as many citations as solo-authored papers in 1955 but 2.1 times the citations by 2000. Similar upward trends in relative team impact appear in sciences and engineering, social science, and arts and humanities and more weakly in patents, although the trend is still upward (20). During the early periods, solo authors received substantially more citations on average than teams in many subfields, especially within sciences and engineering (Fig. 2E) and social sciences (Fig. 2F).

By the end of the period, however, there are almost no subfields in sciences and engineering and social sciences in which solo authors typically receive more citations than teams. Table S1 details RTIs for major individual research areas, indicating that teams currently have a nearly universal impact advantage. In a minority of cases, RTIs declined with time (e.g., –34.4% in mathematics and –25.7% in education), although even here teams currently have a large advantage in citations received (e.g., 67% more average citations in mathematics and 105% in education).

The citation advantage of teams has also been increasing with time when teams of fixed size are compared with solo authors. In science and engineering, for example, papers with two authors received 1.30 times more citations than solo authors in the 1950s but 1.74 times more citations in the 1990s. In general, this pattern prevails for comparisons between teams of any fixed size versus solo authors (table S4).

A possible challenge to the validity of these observations is the presence of self-citations, given that teams have opportunities to self-cite their work more frequently than a single author. To address this, we reran the analysis with all self-citations removed from the data set (21). We found that removing self-citations can produce modest decreases in the RTI measure in some fields; for example, RTIs fell from 3.10 to 2.87 in medicine and 2.30 to 2.13 in biology (table S1). Thus, removing self-citations can reduce the RTI by 5 to 10%, but the relative citation advantage of teams remains essentially intact.

Because the progress of knowledge may be driven by a small number of key insights (22), we further test whether the most extraordinary concepts, results, and technologies are the province of solitary scientists or teams. Pooling all papers and patents within the four research areas, we calculated the frequency distribution of citations to solo-authored and team-authored work, comparing the first 5 years and last 5 years of our data. If these distributions overlap in their right-hand tails, then a solo-authored paper or patent is just as likely as a team-authored paper or patent to be extraordinarily highly cited.

Our results show that teams now dominate the top of the citation distribution in all four research domains (Fig. 3, A to D). In the early years, a solo author in science and engineering or the social sciences was more likely than a team to receive no citations, but a solo author was also more likely to garner the highest number of citations, that is, to have a paper that was singularly influential. However, by the most recent period, a team-authored paper has a higher probability of being extremely highly cited. For example, a team-authored paper in science and engineering is currently 6.3 times more likely than a solo-authored paper to receive at least 1000 citations. Lastly, in arts and humanities and in patents, individuals were never more likely than teams to produce more-influential work. These patterns also hold when self-citations are removed (fig. S5).

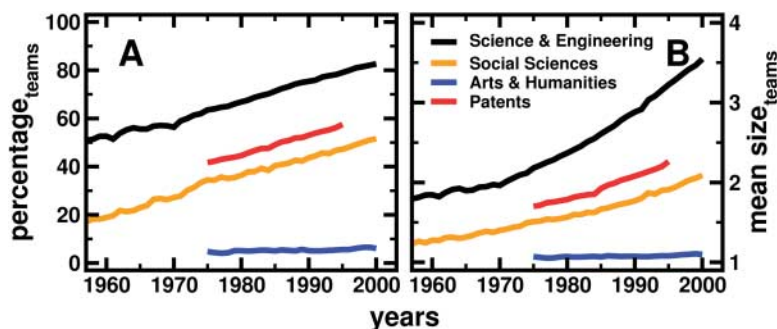


Fig. 1. The growth of teams. These plots present changes over time in the fraction of papers and patents written in teams (A) and in mean team size (B). Each line represents the arithmetic average taken over all subfields in each year.

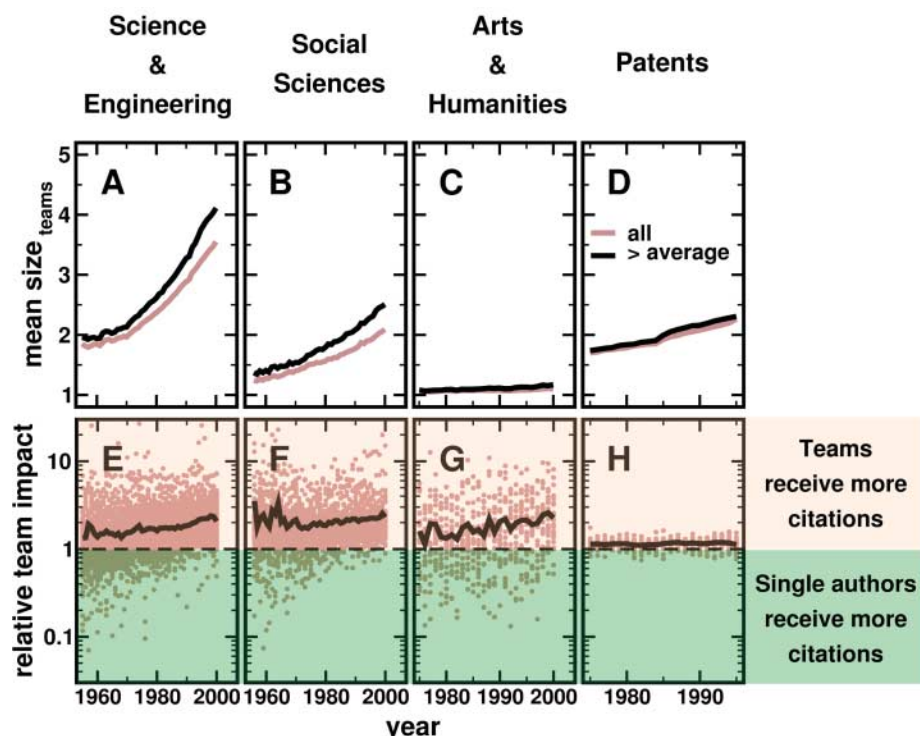


Fig. 2. The relative impact of teams. (A to D) Mean team size comparing all papers and patents with those that received more citations than average in the relevant subfield. (E to H) The RTI, which is the mean number of citations received by team-authored work divided by the mean number of citations received by solo-authored work. A ratio of 1 indicates that team- and solo-authored work have equivalent impact on average. Each point represents the RTI for a given subfield and year, whereas the black lines present the arithmetic average in a given year.

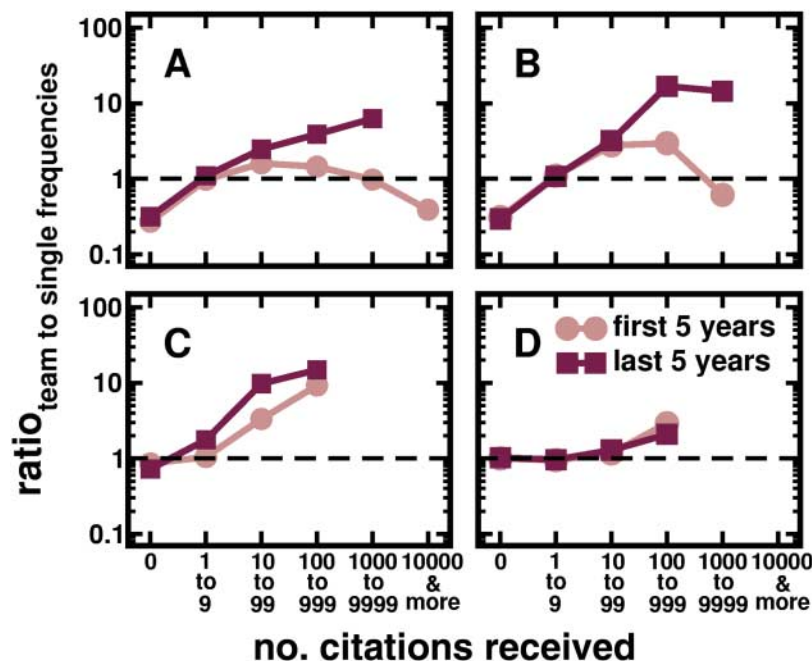


Fig. 3. Exceptional research. Pooling all publications and patents within the four research categories, we calculated frequency distributions of citations received. Separate distributions are calculated for single authors and for teams, and the ratio is plotted. A ratio greater than 1 indicates that a team-authored paper had a higher probability of producing the given range of citations than a solo-authored paper. Ratios are compared for the early period (first 5 years of available data) and late period (last 5 years of available data) for each research category, sciences and engineering (A), social sciences (B), arts and humanities (C), and patents (D).

Taken together, these results suggest two important facts about preeminent work in our observational periods. First, it never appeared to be the domain of solo authors in arts and humanities and in patents. Second, solo authors did produce the papers of singular distinction in science and engineering and social science in the 1950s, but the mantle of extraordinarily cited work has passed to teams by 2000.

Over our 5-decade sample period, the increasing capital intensity of research may have been a key force in laboratory sciences where the growth in teamwork has been intensive (8), but it is unlikely to explain similar patterns in mathematics, economics, and sociology, where we found that growth rates in team size have been nearly as large. Since the 1950s, the number of researchers has grown as well, which could promote finer divisions of labor and more collaboration. Similarly, steady growth in knowledge may have driven scholars toward more specialization, prompting larger and more diverse teams (7, 10). However, we found that teamwork is growing nearly as fast in fields where the number of researchers has grown relatively slowly (see Supporting Online Material). Declines in communication costs could make teamwork less costly as well (9, 23). Shifting authorship norms may have influenced co-authorship trends in fields with extremely large teams, such as biomedicine and high-energy physics (24, 25), and yet our results hold across diverse fields in which norms for order of authorship, existence of postdoctorates, and prevalence of grant-based research differ substantially.

References and Notes

1. R. K. Merton, *Science* **159**, 56 (1968).
2. P. J. Bowler, I. R. Morus, *Making Modern Science: A Historical Survey* (Univ. of Chicago Press, Chicago, 2005).
3. J. F. English, *The Economy of Prestige: Prizes, Awards, and the Circulation of Cultural Value* (Harvard Univ. Press, Cambridge, MA, 2005).
4. R. Collins, *The Sociology of Philosophies: A Global Theory of Intellectual Change* (Harvard Univ. Press, Cambridge, MA, 1998).
5. D. Cronin, D. Shaw, K. La Barre, *J. Am. Soc. Inf. Sci. Technol.* **54**, 855 (2003).
6. H. Zuckerman, R. K. Merton, in *The Sociology of Science*, R. K. Merton, N. Storer, Eds. (Univ. of Chicago Press, Chicago, 1973), pp. 545–550.
7. B. F. Jones, *Nat. Bur. Econ. Res. Work. Pap. Ser.*, no. 11360 (2005).
8. D. J. de Solla Price, *Little Science, Big Science* (Columbia Univ. Press, New York, 1963).
9. J. J. Adams, G. Black, R. Clemmons, P. E. Stephan, *Res. Policy* **34**, 259 (2005).
10. R. Guimerà, B. Uzzi, J. Spiro, L. Amaral, *Science* **308**, 697 (2005).
11. N. Babchuk, K. Bruce, P. George, *Am. Sociol.* **30**, 5 (1999).
12. K. Y. Williams, C. A. O'Reilly, in *Research in Organizational Behavior*, B. Staw, R. Sutton, Eds. (JAI Press, Greenwich, CT, 1998), vol. 20, pp. 77–140.
13. F. S. Fitzgerald, in *The Crack Up*, E. Wilson, Ed. (New Directions, New York, 1993), p. 122.
14. B. H. Hall, A. B. Jaffe, M. Trajtenberg, *Natl. Bur. Econ. Res. Work. Pap. Ser.*, no. 8498 (2001).
15. M. Trajtenberg, *Rand J. Econ.* **21**, 172 (1990).
16. B. H. Hall, A. B. Jaffe, M. Trajtenberg, *Rand J. Econ.* **36**, 16 (2005).

17. D. W. Aksnes, *J. Am. Soc. Inf. Sci. Technol.* **57**, 169 (2006).
18. N. S. Ali, H. C. Young, N. M. Ali, *Libr. Rev.* **45**, 39 (1996).
19. Citations received were counted from publication year to 2006. Recent publications have smaller citation counts because they have had less time to be cited, but this effect is standardized when comparing team versus solo publications within a given year.
20. In patenting, we may observe weaker trends because (i) citing earlier work can limit a patent's scope, so that applicants may avoid citations, and (ii) patent examiners typically add the majority of citations, which makes patent citations different from paper citations (26, 27).
21. A self-citation is defined as any citation where a common name exists in the authorship of both the cited and the citing papers. All citations were removed in which a citing and cited author's first initial and last name matched. This method can also eliminate citations where the authors are different people but share the same name. However, performing Monte Carlo simulations on the data, we find that such errors occur in less than 1 of every 2000 citations. Thus, any errors introduced by this method appear negligible. We did not remove self-citations from patents because citations to previous work in the patent literature are primarily assigned by the patent examiner (27), who independently assigns citations to earlier work based on the relevance of previous patents' content.
22. T. S. Kuhn, *The Structure of Scientific Revolutions* (Univ. of Chicago Press, Chicago, 1970).
23. G. Becker, K. Murphy, *Q. J. Econ.* **107**, 1137 (1992).
24. J. Drenth, *JAMA* **280**, 219 (1998).
25. B. Cronin, *J. Am. Soc. Inf. Sci. Technol.* **52**, 558 (2001).
26. B. Sampat, "Determinants of patent quality: An empirical analysis" (Columbia Univ., New York, 2005).
27. J. Alcacer, M. Gittelman, *Rev. Econ. Stat.* **88**, 774 (2006).
28. We thank R. Guimera, S. Stern, K. Murnighan, K. Williams Phillips, and two anonymous referees for their helpful comments. The Northwestern Institute on Complex Systems provided financial support.

Supporting Online Material

www.sciencemag.org/cgi/content/full/1136099/DC1
SOM Text
Figs. S1 to S5
Tables S1 to S5
References

10 October 2006; accepted 3 April 2007
Published online 12 April 2007;
10.1126/science.1136099
Include this information when citing this paper.

MET Amplification Leads to Gefitinib Resistance in Lung Cancer by Activating ERBB3 Signaling

Jeffrey A. Engelman,^{1,2,3} Kreshnik Zejnnullahu,^{4,5} Tetsuya Mitsudomi,⁶ Youngchul Song,^{2,3} Courtney Hyland,⁷ Joon Oh Park,^{4,5} Neal Lindeman,⁷ Christopher-Michael Gale,³ Xiaojun Zhao,⁵ James Christensen,⁸ Takayuki Kosaka,⁶ Alison J. Holmes,^{4,5} Andrew M. Rogers,⁵ Federico Cappuzzo,⁹ Tony Mok,¹⁰ Charles Lee,⁷ Bruce E. Johnson,^{4,5} Lewis C. Cantley,^{2,3} Pasi A. Jänne^{4,5*}

The epidermal growth factor receptor (EGFR) kinase inhibitors gefitinib and erlotinib are effective treatments for lung cancers with *EGFR* activating mutations, but these tumors invariably develop drug resistance. Here, we describe a gefitinib-sensitive lung cancer cell line that developed resistance to gefitinib as a result of focal amplification of the *MET* proto-oncogene. Inhibition of *MET* signaling in these cells restored their sensitivity to gefitinib. *MET* amplification was detected in 4 of 18 (22%) lung cancer specimens that had developed resistance to gefitinib or erlotinib. We find that amplification of *MET* causes gefitinib resistance by driving ERBB3 (HER3)—dependent activation of PI3K, a pathway thought to be specific to EGFR/ERBB family receptors. Thus, we propose that *MET* amplification may promote drug resistance in other ERBB-driven cancers as well.

Tyrosine kinase inhibitors (TKIs) are an emerging class of anticancer therapies that have shown promising clinical activity. Gefitinib (Iressa) and erlotinib (Tarceva) inhibit the epidermal growth factor receptor (EGFR) kinase and are used to treat non-small cell lung cancers (NSCLCs) that have activating mutations

in the *EGFR* gene (1–4). Although most *EGFR* mutant NSCLCs initially respond to EGFR inhibitors, the vast majority of these tumors ultimately become resistant to the drug treatment. In about 50% of these cases, resistance is due to the occurrence of a secondary mutation in *EGFR* (T790M) (5, 6). The mechanisms that contribute to resistance in the remaining tumors are unknown.

To explore additional mechanisms of gefitinib resistance, we generated resistant clones of the gefitinib hypersensitive *EGFR* exon 19 mutant NSCLC cell line, HCC827, by exposing these cells to increasing concentrations of gefitinib for 6 months. The resultant cell line, HCC827 GR (gefitinib resistant), and six clones isolated from single cells were resistant to gefitinib in vitro ($IC_{50} > 10 \mu M$) (Fig. 1A). Unlike in the parental HCC827 cells, phosphorylation of ERBB3 and Akt in the HCC827 GR cells was maintained in the presence of gefitinib (Fig. 1B).

We previously observed that *EGFR* mutant tumors activate phosphoinositide 3-kinase (PI3K)/Akt signaling through ERBB3 and that

down-regulation of the ERBB3/PI3K/Akt signaling pathway is required for gefitinib to induce apoptosis in *EGFR* mutant cells (7, 8). In addition, persistent ERBB3 phosphorylation has also been associated with gefitinib resistance in ERBB2-amplified breast cancer cells (9). We therefore hypothesized that gefitinib resistance in *EGFR* mutant NSCLCs might involve sustained signaling via ERBB3. After excluding the presence of a secondary resistance mutation in *EGFR* (10), we investigated whether aberrant activation of another receptor might be mediating the resistance. We used a phospho-receptor tyrosine kinase (phospho-RTK) array to compare the effects of gefitinib on 42 phosphorylated RTKs in HCC827 and HCC827 GR5 cells (Fig. 1C). In the parental cell line, EGFR, ERBB3, ERBB2, and MET were all phosphorylated, and this phosphorylation was either completely or markedly reduced upon gefitinib treatment. In contrast, in the resistant cells, phosphorylation of MET, ERBB3, and EGFR persisted at higher levels in the presence of gefitinib (Fig. 1C).

We next performed genome-wide copy number analyses and mRNA expression profiling of the HCC827 GR cell lines and compared them with the parental HCC827 cells (fig. S1 and table S1). The resistant but not parental cell lines showed a marked focal amplification within chromosome 7q31.1 to 7q33.3, which contains the *MET* proto-oncogene (Fig. 1D). *MET* encodes a transmembrane tyrosine kinase receptor for the hepatocyte growth factor (scatter factor), and *MET* amplification has been detected in gastric and esophageal cancers (11, 12). Analysis by quantitative polymerase chain reaction (PCR) confirmed that *MET* was amplified by a factor of 5 to 10 in the resistant cells (fig. S2), and sequence analysis provided no evidence of mutations in *MET*.

To determine whether increased MET signaling underlies the acquired resistance to gefitinib, we examined whether MET inhibition suppressed growth of the resistant cells. HCC827 GR cells were exposed to PHA-665752, a MET tyrosine kinase inhibitor, alone or in combination with gefitinib (13). Although the HCC827 GR5 cells were resistant to both gefitinib alone and PHA-665752 alone, combined treatment resulted

¹Massachusetts General Hospital Cancer Center, Boston, MA 02114, USA. ²Department of Systems Biology, Harvard Medical School, Boston, MA 02115, USA. ³Department of Signal Transduction, Beth Israel Deaconess Medical Center, Boston, MA 02115, USA. ⁴Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Boston, MA 02115, USA. ⁵Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA 02115, USA. ⁶Department of Thoracic Surgery, Aichi Cancer Center Hospital, Nagoya 464-8681, Japan. ⁷Department of Pathology, Brigham and Women's Hospital, Boston, MA 02115, USA. ⁸Pfizer Global Research and Development, Department of Research Pharmacology, La Jolla Laboratories, La Jolla, CA 92021, USA. ⁹Istituto Clinico Humanitas, Department on Hematology-Oncology, Rozzano 20089, Italy. ¹⁰Department of Clinical Oncology, Chinese University of Hong Kong, Shatin, New Territories, Hong Kong, China.

*To whom correspondence should be addressed. E-mail: pjanne@partners.org