Organization Science

Publication details, including instructions for authors and subscription information:
http://pubsonline.informs.org

Near Misses in the Breakthrough Discovery Process

Sen Chai

To cite this article:
Sen Chai (2017) Near Misses in the Breakthrough Discovery Process. Organization Science 28(3):411-428. https://doi.org/10.1287/orsc.2017.1134

http://pubsonline.informs.org/journal/orsc/

ORGANIZATION SCIENCE
Vol. 28, No. 3, May–June 2017, pp. 411–428
ISSN 1047-7039 (print), ISSN 1526-5455 (online)

Near Misses in the Breakthrough Discovery Process

Sen Chai[a]

[a] Management Department, ESSEC Business School, Cergy Pontoise CEDEX 95021, France
Contact: chai@essec.edu, http://orcid.org/0000-0003-1243-3404 (SC)

Received: June 2, 2014
Revised: April 27, 2015; March 12, 2016; November 25, 2016; January 16, 2017
Accepted: January 25, 2017
Published Online in Articles in Advance: May 1, 2017

https://doi.org/10.1287/orsc.2017.1134

Abstract. Why do researchers on the verge of breakthrough sometimes miss the discovery? While extensive literatures have modeled the course of successful discovery and pinpointed factors associated with groundbreaking discoveries, I focus on understanding why near misses occur by interviewing scientists who were very close to discovering the ribonucleic acid (RNA) interference breakthrough in biology but ultimately missed out. I identify three mechanisms rooted in paradigmatic rigidity that led to the seminal discovery being missed several times: not noticing or recognizing anomalies, actively resisting solutions, and failing to make the link between communities. These findings shed light on the process of breakthrough by clarifying that a better understanding of the mechanism behind near misses is crucial to mitigating them, saving time, and, consequently, boosting productivity and impact. They also have implications for boosting creative breakthrough performance in academic institutions and science-based firms, as well as for designing organizational research environments and guiding innovation strategy.

Keywords: near miss • breakthrough • individual cognition • creativity

Introduction

Starting with Schumpeter's (1942) notion of creative destruction and Kuhn's (1962) concept of paradigm shift, technological and scientific breakthroughs have long intrigued scholars and practitioners alike. There is good reason for this continuous interest, as such breakthroughs are the result of a creative discovery process and have proven to be important foundations of advancements that lead to wealth creation and economic growth for organizations and society (Rosenberg 1974). While most research has focused on understanding how breakthrough discoveries successfully arise, either by studying sources of breakthrough (Amabile 1983, Jones 2009, Kaplan and Vakili 2015, Simonton 1999, Singh and Fleming 2010, Weisberg 1988) or the process of breakthrough discovery from cognitive (Thagard 1992) and philosophical (Kuhn 1962) perspectives, much less attention has been paid to the opposite question of why breakthrough near misses occur. Instead of purely sampling on rare successes, I focus on near misses (Dosi 1982), defined as the failure to achieve a breakthrough after being on the verge of finding it, as they provide cases of nonbreakthrough that are consequential because of their proximity to success.

Following Kuhn (1962), I define a breakthrough as an advance that disturbs the previous understanding of a particular phenomenon. The breakthrough discovery fundamentally and irreversibly alters or replaces the existing paradigm, widely shared by the research community, upon which that understanding rests. Empirically, I conceptualize the process of breakthrough discovery as being marked by multiple near misses along the path before the eventual arrival at a final successful discovery. Because near misses are an integral part of the breakthrough process, it is important to gain a complete understanding of the full process. Moreover, specifically focusing on their mechanisms unpacks underlying obstacles that may not necessarily be the opposite or the lack of factors that enhance breakthrough successes. Various phenomena exhibit this kind of asymmetry, such as how rewards and punishments affect individuals and organizations differently, or how good versus bad leadership differ rather than one being the inverse of the other (Hackman 2009).

Though most studies on breakthrough emergence have not explicitly treated near misses or elaborated on how these mechanisms impede the path to discovery, many have alluded to factors that constrain thinking and eventually may lead to nonbreakthrough. For instance, Kuhn's (1962) notion of paradigm implies that researchers often are blinded or cognitively limited by habits of mind (Margolis 1993) to think within the confines of recognized views, models, and theories. The long periods of "normal science" that science undergoes once a paradigm has been established are aimed at extending the dominant theories through incremental improvement and are times when scientists may fail to imagine breakthrough solutions (Berson 1992). Even when divergences from the paradigm occur, ad hoc modifications to the theory are made to remove discrepancies (Kuhn 1962). Additionally, overly narrow

and deep knowledge can hinder creativity and trigger competence traps that result in difficulty breaking away from prevailing theories (Simonton 1999). The result is likely to be incremental progress and the potential neglect of path-breaking advances because search is confined locally instead of including more distant sources (Hargadon and Sutton 1997).

This work brings new insights to the literature by unpacking near misses in the breakthrough discovery process. It refines and expands Kuhn's (1962) concept of paradigm by specifying three underlying mechanisms of how rigidity stemming from paradigms prevented breakthrough and led to near misses on the path to discovery. I extend the setting into life science and qualitatively examine near misses and the final success throughout the discovery process of the ribonucleic acid (RNA) interference (RNAi) gene silencing phenomenon in biology. RNAi is an appropriate setting to examine the mechanisms behind near misses because not only was it a recognized Nobel Prize–winning breakthrough, but it was also characterized by multiple near misses in different scientific communities prior to the breakthrough discovery. I interviewed scientists who were on the verge of breakthrough, identified as those with high citations and those who were prominent enough to present at the first academic conferences on the topic, and show that the seminal discovery was missed because they either (1) did not notice or recognize anomalies appearing outside predictions of the established paradigm, (2) actively resisted trying possible solutions that were significantly different from those dictated by the paradigm, or (3) failed to make the link between communities thought to be operating under different paradigms. The findings suggest that, on the path to discovery, not being able to cognitively perceive beyond paradigmatic rigidity can lead to near misses at various stages. They also have implications for boosting creative breakthrough performance in the management of research projects in academic institutions and science-based firms, as well as for designing organizational research environments and guiding innovation strategy.

Near Misses and Breakthrough Discovery

Scientific breakthrough discovery has been a recurrent subject of inquiry within several research traditions. Various, sometimes conflicting, drivers have been tested within the debate between depth and breadth of knowledge as sources of breakthrough (Weisberg 1999). For instance, collaboration improves search diversity and idea selection efficiency (Singh and Fleming 2010, Wuchty et al. 2007), though working alone can benefit from reduced idea suppression and social loafing (Girotra et al. 2010). Depending on the circumstance, social brokers—group members who bring together disparate views—have shown to be more creative (Burt 2004) or less creative (Obstfeld 2005, Uzzi 1997). Individuals at the periphery of a community are not constrained by prevailing assumptions and theories (Jeppesen and Lakhani 2010), while those at the core enjoy enhanced information and resource access from social ties (Collins 1998, Gieryn and Hirsh 1983), but are also contingent on more distant partners (Whittington et al. 2009). Generalists can bring together disparate components, while specialists with deep technical knowledge are better equipped to see beyond the frontier and make more accurate predictions (Leonard-Barton and Swap 1999). Some individuals realize breakthroughs earlier in their careers because they are unconstrained by the thinking of their field (Simonton 1989), while others do so later in their careers because they must work through the accumulation of knowledge (Jones 2009). Finally, mobility across multiple affiliations increases exposure to a greater diversity of ideas, but staying in one location affords better use of resources and avoids high moving costs (McEvily and Zaheer 1999).

While these works have mainly focused on identifying factors that enhance breakthrough success, others have concentrated on characterizing successful breakthrough discovery as a creative process (Kuhn 1962, Margolis 1993). Scientific progress is seen as episodic (Kuhn 1962). Once a paradigm has been established, science undergoes long periods of normal science marked by incremental improvement aimed at extending the dominant paradigm's theories, and from time to time is marked by breakthrough upheaval. The process underlying a breakthrough starts when researchers become aware of anomalies that accumulate into a crisis that, once resolved, ultimately results in the acceptance and establishment of a new paradigm.

Although paradigms are unprecedented enough to attract a group of supporters away from competing models, they also are sufficiently open ended to leave room during periods of normal science for adherents to further refine them. These refinement activities are aimed at extending the paradigm's theories to different settings and demonstrating that empirical results are in agreement with the theories (Kuhn 1962). Search is local, as scientists are guided by established theory to reinforce the current paradigm rather than refute it. Researchers will vary experiments and try out alternatives until they find a solution that fits the paradigm (Knorr-Cetina 1999) by logically decreasing the number of possibilities (Latour and Woolgar 1986) in a variation-and-selection approach (Campbell and Overman 1988). Thus, the established paradigm draws bounds within which ideas can be tested and extended.

While most experimental observations are consistent with the paradigm-induced expectations that govern

normal science, anomalies may still occur (Kuhn 1962). The presence of these anomalies suggests that something novel and unexplained is present. A deep grasp of the paradigm's predictions and expectations allows scientists to expose anomalies by assessing whether an observation fits current theories (Kaplan and Vakili 2015, Taylor and Greve 2006). If the discovery process was logical (Popper 1959), scientists would abandon the established theory once anomalies were observed. However, even if deviations are detected, they may still be ignored, especially in earlier manifestations where restrictions posed by the paradigm remain rigid. To remove these observed divergences, ad hoc modifications of the theory are made (Kuhn 1962).

More observations of the same anomaly help ensure that it is not an artefact. However, breaking away from the paradigm also requires creativity and imagination, as recognizing an anomaly as such implies in part that researchers have started to doubt the current paradigm (Locke et al. 2008) and are imagining the anomaly to be something other than a bothersome deviation to the norm. An important vehicle for imagination is abductive reasoning. Whereas "deduction proves that something must be [and] induction shows that something actually is operative, abduction merely suggests that something may be" (Peirce 1931–1958, p. 171). This mere suggestion that something could happen originates numerous conjectures and explanations. Thus, abductive reasoning is a conjectural mode of inquiry that involves generating multiple ideas, hunches, and propositions to make sense of puzzling facts (Locke et al. 2008) and that form the basis of new concepts and patterns (Weick 2005). Propelled by doubt, abduction helps loosen paradigmatic rigidity and opens the possibility that a puzzling observation is indeed distinctive and anomalous, enabling its eventual recognition (Czarniawska 1999) and the start of a potential discovery of a new breakthrough.

When scientists finally recognize an anomaly as such, they will continue to acknowledge it and begin to relax paradigmatic constraints. This exposure to multiple occurrences of anomalies accumulates to a point of crisis, where the current paradigm becomes blurred. The rules and standards of normal science are loosened to transition into "extraordinary science," where researchers propose speculative theories and debate competing articulations of the fundamentals of the existing paradigm (Kuhn 1962). During this period of extraordinary science, prevailing paradigms may still limit proposals of speculative solutions and theories that explain the anomalies. For instance, Berson (1992) blames two breakthrough misses in chemistry on failures of the imagination. Moreover, too much depth of knowledge may also be damaging, as it constrains the search for solutions and idea sources to a narrow domain (Simonton 1999) and limits the recombination of more distant and diverse knowledge into potentially groundbreaking ideas (Hargadon and Sutton 1997). To come to a solution, the ability to think beyond cognitive habits reinforced by paradigms (Margolis 1993) is critical for conceptual revolutions (Thagard 1992). Instead of locally searching for known options that best fit existing facts, the process of abductive reasoning, of conjecturing and playing with various patterns and concepts, allows for the possibility of broader views, distant search, and the recombination of further and more diverse ideas (Weick 2005).

Contact between scientific communities also drives the distance of search. Managing knowledge boundaries is crucial, as researchers from different communities may study the same phenomenon from different vantage points, producing knowledge that can be complementary and useful (Dyson 1972). But when researchers are separated by the boundaries set by their respective communities, lack of communication restricts search distance and potentially hinders the connection and recombination of complementary ideas across communities. For instance, Dyson (1972) hints that progress in mathematics has been hampered by the field's disconnect from physics. Moreover, science's priority-based reward system (Merton 1957) pressures researchers to publish before their peers. This creates a divided, competitive, and secretive environment where researchers are reticent about sharing knowledge to avoid giving others an advantage (Knorr-Cetina 1999), thereby limiting search distance and recombination.

Finally, if and when a novel competing candidate theory does emerge during the extraordinary science phase, paradigmatic forces may still bring some to resist the presence of competing paradigms. The old paradigm is incommensurable (Kuhn 1962) with the new one, and proponents of each will talk past one another, heading off meaningful conversations between the conflicting schools of thought. Eventually, when new views and theories do become accepted, they replace the old paradigm and lead to a breakthrough. By altering the expectations, rules, and procedures of normal science, this change of paradigm causes scientists to completely alter the worldview of their research engagement (Kuhn 1962).

Most of the research reviewed above either highlights the successful emergence of breakthroughs or hints at elements that lead to nonbreakthrough but lack either empirical evidence (Margolis 1993) or contemporaneous in-depth analysis (Berson 1992, Kuhn 1962). None, however, have specifically focused on elaborating the mechanisms behind how near misses hinder the path to discovery. One reason the literature has not explored near misses as extensively as successes is that, methodologically, successes are more easily observable than near misses, which tend to be forgotten by history. Though for many of today's organizations that

rely on innovation to remain Competitive, unpacking the entire process of discovery is needed. Exploring why near misses occur sheds light on actions that can be avoided to mitigate them at different stages of the discovery process, while the study of successes provides a separate set of levers that could be enhanced to improve the odds of breakthrough.

Methods

To identify the underlying mechanism of near misses occurring on the path to breakthrough, I looked for a setting that featured (1) a recent, clear, and recognized measure of breakthrough success; (2) near misses throughout the discovery process; and (3) more than one identifiable community that was studying it. I chose RNAi as an example that fits these criteria to show near miss mechanisms at different stages of the discovery process. RNAi was discovered recently enough to enable first-hand interviews with the actors involved in it, and archival data were readily accessible to map progress toward the breakthrough. The discovery, one of the biggest in the field, opened up many research avenues and resulted in a measurable breakthrough success recognized with a Nobel Prize. Having two communities studying the phenomenon enabled me to see whether they communicated with one another and engaged in distant search. Finally, the period of search was long enough and the process intricate enough that several near misses occurred, making RNAi particularly attractive.

RNA Interference

RNA interference is a mechanism that can turn genes off. A process of gene silencing that occurs naturally within the organism, it can be triggered when double strands of RNA (dsRNA) are introduced in the cell. Andrew Fire and Craig Mello identified this potent trigger (Fire et al. 1998) and coined the term "RNA interference" for the mechanism. For the discovery, they were awarded the Nobel Prize in Physiology or Medicine in 2006.

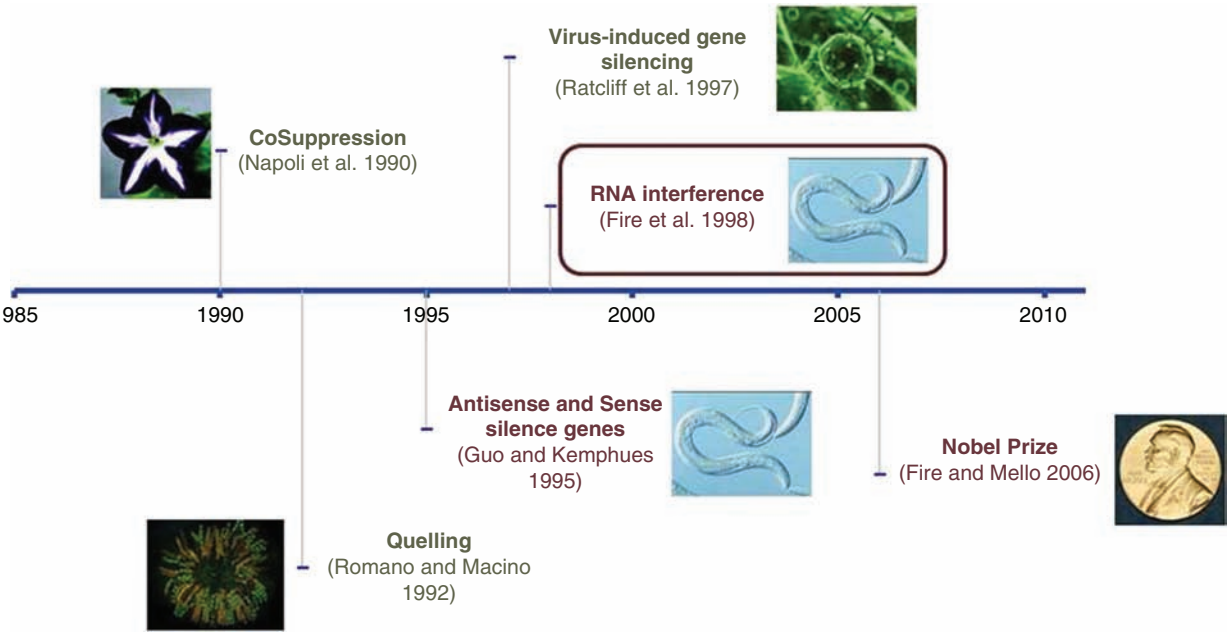
The prevalent paradigm before this seminal discovery followed from the central dogma of biology, where genetic information encoded in double strands of deoxyribonucleic acid (DNA) unzips, transcribes into a single strand of messenger RNA, and, using that as template, translates into protein. In this view, RNA is a passive transducer of information, whereas DNA and protein have more active roles. DNA contains the genetic encoding that protein ultimately expresses for proper functioning of the cell. The discovery of dsRNA as the trigger of RNAi provided evidence for a different paradigm in which RNA would play an active role in regulating genetic expression. The mechanism starts with dsRNA first unzipping into two single RNA strands, sense and antisense RNA. The resulting antisense RNA subsequently binds onto the messenger RNA and cuts it, thus effectively destroying its message and preventing translation into protein and subsequent gene expression.

The discovery of RNAi is a story of how several seemingly unrelated and unexpected phenomena observed in various organisms were finally connected after discovery of the trigger, as illustrated in Figure 1. Its modern-day discovery started in the late 1980s and early 1990s, when various odd observations of gene silencing were first made in plants and animals. Although they were not immediately recognized as related, both communities—plant and animal scientists—were independently aware of the phenomenon prior to the discovery of its trigger.

In the plant community, biologists attempted at that time to alter petunia color by introducing a transgene into petunias—a segment of DNA containing a gene sequence that encodes pigmentation isolated from other flowers. The expectation was to observe gene overexpression manifested through darker colors. Instead, to everyone's surprise, the petunias became *less* pigmented than their natural form, producing fully or partially white flowers (Krol et al. 1990, Napoli et al. 1990). This indicated that as opposed to the intended overexpression, activity of the introduced transgene had significantly decreased expression to the point of deactivating the gene responsible for regulating color pigmentation. This phenomenon was named cosuppression. In *Neurospora crassa* fungi, a similar phenomenon was independently observed and named quelling (Romano and Macino 1992). Both the underlying mechanism and trigger remained unknown, but the European plant community at the beginning of the 1990s had already started its own network of laboratories with the aim of collaboratively studying it. A few years later, plant virologists also found a similar unexpected gene silencing phenomenon when attempting to improve plant resistance to viral infections that they labeled virus-induced gene silencing (Ratcliff et al. 1997).

Concurrently, in experiments on animal organisms, many researchers had come across the phenomenon while also being unaware of the intricacies of the underlying mechanism. Researchers were using the precursor technology to RNAi, single-stranded antisense RNA, as a tool to study the function of specific genes by turning them on and off, even though they were not always obtaining reproducible results. A few years later, another close finding to the breakthrough discovery of the trigger to RNAi was observed in the *Caenorhabditis elegans* (*C. elegans*) worm. Scientists attempting to understand the purpose of particular genes in embryos surprisingly found that not only did single-stranded antisense RNA silence the gene under

Figure 1. (Color online) Timeline of Major Events in the Discovery of RNA Interference



study, but so did its complementary single strand of sense RNA, which was designed as a negative control and expected to be inert (Guo and Kemphues 1995). However, the silencing was not consistent when using the sense or antisense RNA strands. It was not until Fire and Mello's 1998 insight (Fire et al. 1998) into the potential of contamination between the sense and antisense RNA, which annealed into dsRNA during sample preparations, that the precise, stable, and potent trigger was found.

Data Sampling and Collection

To unearth the nuances of multiple trials along the path of discovery, irrespective of whether they were near misses or successes, I used a case history methodology. Many historical case studies of breakthroughs exist, but most explore the success of a breakthrough discovery without qualitatively delving into the process of near misses. Instead, to gain a perspective from this different vantage point, I concentrated my interviews on those who were extremely close to the discovery but ultimately did not achieve the breakthrough.

Identification of Near Misses. Because scientists who experienced a near miss were on the verge of discovering the actual breakthrough, I identified them by finding scientists who had a high potential of uncovering the breakthrough. To find those who were highly likely to discover the RNAi breakthrough, the gene expression and gene silencing communities needed to be identified. However, defining such communities is challenging, as their boundaries are unclear in the period immediately before a breakthrough has emerged. Thus, the goal was to find a set of researchers who shared the same research interests and who were at the forefront of their domain, thereby making them closer to discovering the breakthrough. Scientists with similar research interests write publications on related topics and attend the same conferences. My sampling strategy, which defines the research community studying gene expression and gene silencing up to the 1998 RNAi discovery, mirrors these scientific activities. It consists of a functional definition, using publication content encoded in the title, abstract, and keywords, as well as a conference definition with attendance lists. There are limitations to each method; therefore, I used a combination of the two to mitigate their drawbacks. Functional identification yields a noisy sample because other communities share keywords used to identify RNAi researchers. Moreover, given its dynamic nature, the identified community may also omit researchers who shifted their interest onto gene silencing around the time of the breakthrough. Conference sampling omits those in the community who did not attend.

From this community, I narrowed the interviewees to those who were on the verge of breakthrough—the near misses. Near misses are contributions that are significant, but not the ultimate breakthrough discovery, and that come from scientists with findings important enough to be highly cited. Therefore, I found researchers working in gene silencing and gene expression whose publications in the few years up to 1998 were highly cited but ultimately did not make the RNAi breakthrough. Just as the breakthrough is retrospectively recognized, near misses also tend to be recognized ex post. Had scientists known ex ante that their findings were very close to a breakthrough, they

might have changed their research direction or way of looking at or solving problems and actually made the breakthrough. I narrowed the conference list to attendees of the first two conferences on gene silencing. Choosing these first conferences ensures a time closest to the breakthrough discovery that therefore includes the fewest number of individuals who switched into the field after the discovery. Finally, I also used snowball identification by asking respondents whom among their colleagues I should interview. Snowball sampling is a suitable triangulation and validation technique of the initially identified sample, but solely using snowball identification may yield biases on a smaller clique within the community.

I used a content search of titles, abstracts, and medical subject headings (MeSH) keywords to functionally define the RNAi community. Because this study was centered on the period prior to breakthrough, where a distinct community of RNAi researchers had yet to emerge, RNAi-centric keywords such as "RNA, Interference" in animals, "cosuppression" in plants, and "quelling" in fungi did not enter the MeSH lexicon until 2002. To bypass this issue, I reviewed archival documents on the history of RNAi, including the Nobel lectures, and found that scientists sought to explain gene expression regulation or gene silencing by experimenting with both dsRNA and antisense RNA as causal agents. Consequently, I defined the community of researchers with the potential to discover the breakthrough from their published peer-reviewed articles using these MeSH search terms in PubMed.[1] I augmented the MeSH search with title and abstract searches to include scientists who initially observed the RNAi phenomenon in plants and fungi. I incorporated papers published until 1999, as researchers whose publications quickly followed the 1998 seminal paper also had the potential of discovering the breakthrough. By extracting authors from the set of papers, I identified a community of pre-RNAi-breakthrough scientists that included 1,551 papers and 3,959 unique authors. All scientists who had at least one publication found with the search criteria above were included in the sample.

To extract the near misses, I found researchers working in this community whose 1990 to 1998 publications were highly cited but who ultimately did not make the RNAi breakthrough. The year 1990 marks the first observation of the silencing phenomenon in petunias, while the discovery of dsRNA as trigger occurred in 1998. Because no interviewee was part of the Nobel-winning team for RNAi, the sampling provided accounts from those who had the potential to make the groundbreaking discovery and who were extremely close but ultimately missed it. This subsample of researchers was identified using publications with forward citations in the top 1% of the distribution who were actively studying gene expression and silencing. I identified a total of 23 interviewees, 15 of whom agreed to be interviewed.

There are three reasons the number of interviewees from the initial large sample of authors was so small. First, because I was studying a nascent field that expanded only after the breakthrough occurred, the number of scientists represented at the beginning was limited. According to a respondent, the field was initially very small and only grew significantly to further understand the mechanism after the seminal 1998 publication. Second, my technique of selection dropped the vast majority of the initial sample because I identified extreme cases of individuals whose citations for publications were highly cited. Finally, the community definition is noisy and broad, given that fields studying other biological phenomena, such as the interferon community, also employed the same MeSH keywords I used. Thus, since the sample of interviewees identified from this community is sensitive to its definition, it yielded false positives that had to be excluded.

On top of the false positives discussed above, the other limitation of such a functional definition is the presence of false negatives because the dynamic nature of the community may miss scientists who shifted their research interest to gene silencing around the period of the discovery. I used attendees of the two earliest conferences on gene silencing and RNAi—the 1997 Gordon Research Conference on Epigenetics and the 2002 Keystone Symposia on RNA Interference, Cosuppression and Related Phenomena—to find those who were omitted. The scientists were prominent enough to present a paper at the earliest conferences on gene silencing and would have also had the potential to discover the breakthrough. I chose these two conferences because each was the first in the respective conference series to feature gene silencing. The 1997 Gordon Research Conference had a small session on gene silencing with only plant scientists presenting. The Keystone Symposia marked the first time the entire gene silencing community of both plant and animal researchers met. Out of those identified using the functional method, 3 attended the Gordon Research Conference, while 10 (7 interviewed) attended the Keystone Symposia. Additionally, I identified four individuals, three of whom agreed to be interviewed, who were not already in the functional subsamples of interviewees.

Together, the subsamples yielded 27 scientists from whom I requested interviews; 18 responded positively. There were no significant differences between those who declined and those who accepted based on observable data such as age, prior productivity and eminence, and prestige of affiliation. See Table 1 for individual details of all identified interviewees and respondents and their sampling sources. Respondents spanned those studying model organisms, including

plants, worms, and mammals, as well as geneticists, developmental biologists, molecular biologists, and biochemists who contributed to RNAi research conceptually and technologically. They also included one Nobel Prize winner (not awarded for RNAi) and three winners of the Lasker Award, which is widely considered the second-most prestigious award in the life sciences after the Nobel Prize. Although the final sample of interviews was built using different subsamples, interviewees all missed the RNAi breakthrough discovery. Variation found in the data was along the community divide between plant and animal scientists rather than the subsamples.

Finally, to validate the above sampling approach, I asked the respondents which other individuals they recommended I meet who were within the gene silencing community at its inception. This substantiation is essentially a snowball sampling approach. Other than one individual who had left academia and was hard to find, the respondents' suggestions of individuals with breakthrough potential were all among the sample of 27 interviewees I identified with the selection methods described above. The overlap between the respondents' suggestions and those found using the functional and conference samplings was a reassuring indication that the final sample of interviewees would be useful in understanding near misses in the RNAi breakthrough discovery process.

Interviews. To develop an interview guide, I spoke with two individuals who were knowledgeable about RNAi and its history but did not do research in the area. Our discussions centered on how to define the community of scientists focusing on RNAi as well as the discovery trajectory. For instance, both brought my attention to observations of the phenomenon in plants and fungi. These conversations fine-tuned my existing interview protocol and triggered new questions for the final version shown in the appendix. For the 18 informants, interview questions were semistructured; I asked open-ended questions first, followed by more specific and probing ones. I started by inquiring about the line of research each respondent was undertaking during the period shortly before 1998. I covered several other topics, from understanding circumstances around and factors leading to breakthrough discovery to defining and characterizing the community of scientists prior to the field's evolution. Each interview lasted 60 to 120 minutes and averaged 75 minutes. All interviews were recorded with consent and transcribed verbatim.

Archival Data. Because I studied the breakthrough ex post, understanding the circumstances scientists faced ex ante was critical. Although interviews potentially suffer from hindsight bias, they were useful in identifying causes of near misses that were hard to obtain using purely archival methods. To minimize retrospective sensemaking, I triangulated my findings with quotes extracted from RNAi research articles (Golden 1992). For each interviewee, I selected all articles the individual published before 1998 with the same MeSH keywords as well as title and abstract search terms that I used to determine the community of pre-RNAi scientists. This amounted to a total of 49 publications. I also traced citation patterns of these publications and conference attendance lists prior to 1998 to verify whether the animal and plant communities were indeed in their own silos before the seminal discovery. Moreover, I consulted the Nobel lectures and Nobel interviews. Evidence of this triangulation can be found in the data tables presented with the main findings.

Data Analysis

To reveal the reasons underlying resistance to breakthroughs, I sought to capture instances in which scientists nearly missed a potential breakthrough discovery in the data analysis. Another aim was to uncover broader patterns to explain what kept breakthroughs from emerging. To fulfill these goals, I iterated between data analysis and literature. The analysis of each interview was conducted in line with coding principles set out by qualitative/inductive scholars (Corbin and Strauss 2008, Miles and Huberman 1984). Using QSR NVivo, I first open coded instances in the data where scientists referred to the research activities they or the community performed in the period prior to the discovery of RNAi. This exercise yielded codes such as "used antisense RNA to silence a gene," "studied functions of particular genes," "chose to pursue one research question over another," "heard about antisense tool at conference," and so on. Scientists recounted activities that led them to take a particular direction. I further refined the coding of these activities and found that the descriptions not only included positive instances where successful discoveries of novel findings were made, but also activities that hindered pattern recognition or solution proposal that ultimately would have led to finding the trigger to RNAi. Relating the data to the existing literatures on achieving breakthroughs, I found that near misses were undertheorized compared to successful emergence. Consequently, I concentrated on this latter set of near miss activities.

As I brought the category of near misses into my analysis and refined my coding, I noticed that interviewees were describing instances and reasons that resulted in missed breakthroughs. This refined axial coding of my data yielded codes such as "did not think of RNA," "did not think of double strands," "ignored weird result," and "did not look in other organisms." I then focused on constructing detailed accounts of instances that led scientists to miss breakthroughs.

Table 1. Identified Interviewee Research Focus, Positions, and Background

Respondents	Model organism	Field	Main research focus before 1998	Position in 1997–1998	Sub-sample
1	*C. elegans*	Developmental biology	Regulation of chromatin structure and developmental function	Assistant professor	2, 4
2	*C. elegans*	Developmental biology	Gene regulatory mechanisms controlling the timing of animal development	Professor	1, 2, 4
3	*Drosophila*, multiple	Biochemistry	Ribozyme function as a RNA-dependent RNA polymerase	Assistant professor	1, 4
4	Plants	Plant genetics	Specificity determinant in RNA-mediated gene silencing in plants and plant viruses	Associate professor	1, 2, 3, 4
5	*C. elegans*	Biochemistry	RNA splicing in gene regulation mechanisms	Postdoctoral fellow	1, 4
6	*Drosophila*	Molecular biology	Mechanisms and functions of RNA-based gene regulation	Associate professor	1, 2, 4
7	*C. elegans*	Molecular biology	Host cell response to virus infections	Associate professor	1
8	*C. elegans*	Molecular biology	Establishment of cell polarity and asymmetric cell divisions during embryonic development	Doctoral candidate	1, 4
9	Mammals	Epigenetics	Epigenetics of cell proliferation/differentiation and cancer	Assistant professor	1, 4
10	*C. elegans*	Molecular biology	Asymmetric cell divisions during embryonic development	Professor	1, 4
11	Mammals	Molecular biology	Inhibition and activation of serine protease enzymes	Director of molecular biology at biotech co.	2, 4
12	*C. elegans*	Molecular biology	Regulation by microRNA genes and other small RNA	Professor	1, 2, 4
13	*Drosophila*, multiple	Biochemistry	Gene expression in human cells and RNA splicing	Professor	1, 2, 4
14	Plant tobacco	Molecular genetics	Structure and function of nitrate reductase genes	Research scientist	2, 4
15	*Escherichia coli*	Molecular biology	Regulation by antisense RNAs in bacteria and RNA structure/function relationships	Associate professor	1, 4
16	*Drosophila*	Biochemistry and molecular biology	Role of RNA-binding proteins in *Drosophila* development	Assistant professor	1, 2, 4
17	Plant petunia	Plant genetics	Relationship between cosuppression and epigenetics	Associate professor	1, 3, 4
18	Plant tobacco	Molecular genetics	Epigenetic regulation of gene expression and interphase chromosome organization	Professor	1, 2, 3, 4
19	Mammals	Biochemistry and molecular biology	Protein regulation by RNA	Professor	1, 4
20	Plant tobacco	Plant virology and genetics	Virus resistance and gene silencing in plants	Research program leader	1, 2, 4
21	*C. elegans*	Molecular genetics	Evolution of animal development	Postdoctoral fellow	1, 4
22	Mammals	Molecular biology	Role of antisense RNA in methylation of RNA	Associate professor	1
23	*Tetrahymena thermophila*	Biochemistry and chemistry	Process of transcription in the nucleus of cells	Professor	1, 4
24	Fungus *N. crassa*	Molecular biology	Gene expression regulation and silencing in *N. crassa*	Professor	1, 4
25	*T. thermophila*	Molecular and cell biology	RNA structure and folding, RNA catalysis	Associate professor	1, 2
26	*Drosophila*	Biochemistry and molecular biology	RNA cleavage and RNA catalysis	Postdoctoral fellow	2, 4
27	Mammals, multiple	Biochemistry and molecular biology	Mechanisms and functions of RNA-based gene regulation	Associate professor	1, 2, 4

Notes. Respondents 1–18 are respondents who were interviewed; 19–27 are interviewees who were identified but declined or ignored interview requests. Subsample 1 includes those with a near miss between 1990 and 1998, Subsample 2 includes those who attended the 2002 Keystone Symposia on RNA Interface, Cosuppression and Related Phenomena, Subsample 3 includes those who attended the 1997 Gordon Research Conference on Epigenetics, and Subsample 4 includes respondents identified by snowball identification.

These included narratives detailing how the historical context of the RNAi discovery impacted research trajectories and the thought process behind why a particular solution was not plausible. Three salient categories emerged: (1) not noticing or recognizing anomalies, (2) actively resisting solutions, and (3) failing to make the link between communities. Asking why scientists were unable to recognize anomalies and actively resisted solutions, and making further comparisons between the literature and data, led me to conceptualize the reasons for missed breakthroughs as paradigmatic pressures. I iterated once again through the literature to analyze how paradigmatic rigidity affected behavior during the discovery process and found that paradigms stifled abductive reasoning and limited search distance.

I then classified my sample of interviewees into communities using two dimensions. I separated the plant and animal scientists to compare across the two communities. I also split the sample of interviewees into communities dictated by life science fields, such as biochemistry, molecular biology, genetics, etc. Within the plant and animal communities, some scientists spanned multiple fields, and the boundaries blurred. But between the plant and animal communities, no scientist spanned both communities at the same time; thus, a real boundary existed. Contrasting between the animal and plant communities, I noticed that within each community, research across scientists progressed at a similar pace, and understanding of the phenomenon progressed in comparable phases. However, across communities, the stage where the plant and animal communities respectively broke down differed. Moreover, there was little communication between the communities. By asking why the two communities failed to make the link and iterating through the literature, I found that the belief of being in different paradigms kept them apart, constrained their thinking, and limited their search space.

As confirmatory analysis, I triangulated across interviews and archival data sources. I coded abstracts and texts of the interviewees' 49 publications that I identified. To substantiate the category of not noticing and recognizing anomalies, I coded for how and where antisense RNA was described in the papers. For actively resisting solutions, I coded for mentions in line with the existing paradigm versus the new one—for instance, antisense RNA versus double-stranded RNA in publications from the animal community, and DNA versus RNA in publications from the plant community. For failing to make the link between communities, I mapped citation patterns between publications to see whether the plant and animal communities were citing each other's work before the seminal discovery. I concluded data collection and analysis once it captured the patterns within my data and when I felt it had reached theoretical saturation.

Findings

Scientists on the verge of breakthrough missed the seminal discovery for three reasons: (1) they did not notice or recognize the anomaly because they were blinded by the pursuit of normal science, (2) they actively resisted suggesting solutions that drastically diverged from accepted theory, and (3) they were unable to make the link between the animal and plant communities because each believed that they operated under a different paradigm. The first two mechanisms illustrate how paradigms constrain thinking and their effect on near misses at different stages of the research process: the former occurs when researchers are limited within the confines of normal science, while the latter occurs when researchers cannot come to a resolution despite having recognized and identified the anomaly. The third mechanism illustrates how paradigms may also prevent researchers from looking outside of their communities, thereby hindering similar anomalous patterns from being connected and further constraining their thinking. Tables 2 and 4 illustrate each reason with sample interview quotations, while Tables 3 and 5, respectively, provide publication quotes and citation patterns for confirmatory support.

Not Noticing or Recognizing Anomalies

Because most scientists working with animal models came in contact with the precursor phenomenon to RNAi as a technique to silence genes that was used when pursuing their initial research questions, their view of the phenomenon was predisposed toward seeing it as a tool rather than as a topic of inquiry worthy of scientific merit. This path dependence from prior techniques led researchers to not notice or recognize inconsistencies in the gene inhibition effects of antisense RNA. The pursuit of normal science and the pressure to publish blinded researchers in their quest to test their original hypotheses. Thus, except for Fire and Mello, the abductive reasoning of most researchers in the animal community was inhibited, as few doubted that something unexpected might be happening, and most ignored the anomaly that RNA could actually trigger gene silencing since it was believed to be passive. They did not challenge the existing paradigm despite empirically observing contradictory evidence, as described below:

> When people tried [antisense RNA] and it worked, it was like, okay, let's work with it. Very few people thought it was worth studying, but everybody wanted to use it. So then you'd go to the worm meetings and everybody was using it. (Respondent 12, animal researcher)

> My sense from [others] was that they just looked at this like a bizarre tool, they couldn't explain it but it was fabulous for what they wanted to do. They could silence genes. . . . They were focused on the thing at hand

> and ignoring this elephant in the room, which was far more important and interesting. (Respondent 6, animal researcher)

Most researchers valued the phenomenon's ability to inhibit specific genes without having to rely on mutations, which stemmed from the historical context of antecedent technologies. In the late 1980s, large commercial groups cornered the market with their ability to produce so-called "knock-out mice" and made it prohibitively costly for small laboratories to obtain such samples for research purposes. Therefore, many researchers viewed antisense RNA technology as the solution to this problem because it would allow them to do experiments faster and cheaper than by mutation. The technology was a means to an end rather than the end itself. This behavior is in line with the prediction that scientific research is extremely productive at expanding the central paradigm but also self-reinforcing during periods of normal science. As a case in point, the two scientists who were just shy of finding dsRNA as the trigger solution chose explicitly not to study why the anomalous gene silencing phenomenon occurred. They were the first to document the anomaly that both the treatment (antisense RNA) and the negative control (sense RNA) in the experimental design, which put together would form dsRNA, could silence genes (Guo and Kemphues 1995). "Once we knew it was a gene-specific effect," one of them explained, "we didn't really care how it worked. All we cared about was that we could use it" (Respondent 10, animal researcher).

When unexpected results appeared in tangential elements not affecting the research project's core hypotheses, either manifested in the tool or the experimental results, researchers' decisions about whether to follow and inquire deeper into a strange but intriguing observation or to stay with the experiment at hand was difficult. In particular, time and resource constraints, together with the low probability that the peculiarity would actually turn out to be influential, made it an especially hard decision, as such oddities often turn out to be mere artefacts. Consequently, in pursuit of normal science, most ignored the observed anomalies and carried on.

Confirmatory analysis in Table 3 of the interviewees' publications in the animal community prior to the 1998 seminal discovery corroborates interview findings. Antisense RNA was consistently mentioned as a technique rather than a research question to be explored and/or included in the methods section.

Actively Resisting Solutions

Researchers in the animal community did not consider the gene silencing phenomenon as an interesting scientific problem to pursue because using antisense RNA as a tool enabled them to accomplish their original research goal of understanding gene function. However, although the tool worked, its inhibitory effects were inconsistent and not always potent. Despite not seeing the problem as scientific, researchers still could have tried to improve the tool to make it more reproducible and effective. They could have experimented with dsRNA especially since both the sense and antisense RNA strands were shown to have inhibitory properties. While working to improve the tool, the trigger mechanism for RNAi could have emerged, as had happened with many other chance discoveries, such as penicillin.

Here again, the inaction was driven by paradigmatic rigidity. For most researchers, although the silencing tool was inconsistent, it was good enough. But even if they had tried to improve the tool, no one believed that dsRNA would be more efficient than single-stranded antisense RNA. They believed that if antisense were injected, it would have immediately found its target, whereas dsRNA would have had to perform an extra step of first unzipping. Moreover, according to the central dogma of biology, dsRNA was considered unnatural and passive because RNA was thought to naturally exist only in single-stranded form. Thus, scientists had to get past being restricted by the doctrine that challenged the ability for dsRNA to perform equally as well as antisense RNA in silencing genes. Reinforced by the paradigm, scientists did not speculate or search beyond the limits of single-stranded RNA. Given the state of knowledge at the time, respondents illustrated how implausible the idea of dsRNA being the trigger to RNAi was:

> Nobody would ever inject the sense strand [be]cause psychologically you could imagine how the antisense strand could work with the base pairing but the sense [strand] didn't make sense even though they showed they both worked equally well. No one ever did the sense strand [be]cause they just thought that just can't be right. They just kind of ignored it and thought it's antisense. (Respondent 1, animal researcher)

> Why should dsRNA work better than antisense? Because if you had stuck in an antisense providing it doesn't get degraded, it should find its target and take it out. When you put in preannealed dsRNA we thought it had to unzip, it's actually a weakness, because nobody realized that there is a machinery that does that. (Respondent 7, animal researcher)

The plant community, on the other hand, did notice the anomalies and recognized the phenomenon of gene silencing as a scientific endeavor worthy of pursuit, as two plant scientists described:

> I was intrigued by this phenomenon of silencing that I could not explain. I could just document them and observe that silencing was occurring but I wanted to go further and determine what was the mechanism on which this phenomenon was relying. (Respondent 14, plant researcher)

Table 2. Interview Quotes from Respondents Illustrating Two Mechanisms in the Research Process—*Not Noticing or Recognizing Anomalies* and *Actively Resisting Solutions*—That Led to Near Miss of Breakthrough

Organism	Not noticing or recognizing anomalies	Actively resisting solutions
Animals	"Scientifically you know that this is working and these people were just using this as a tool. Then you have to decide. On the one hand, this is just a tool and the reason you're using this tool is because you want to study the biology of these genes and you're really focused on that biology and so you're convinced that using this antisense method is teaching about the function of those genes and you go on and you focus on the function of those genes. And you don't get distracted by this oddity that the sense is also working." "[Be]cause it's a tool that everybody wants to use like recombinant DNA, many people who wanted to use it don't care how it works it just becomes a tool that they use." "We were obviously intrigued by it, but we could use to probe some biology that we were interested in it. And you want to do in science, it's almost like you see something and you want to harvest it. So we could harvest RNAi in a way by using it as a novel method, it allows you to leverage some biology. You didn't have to get mutations and you could get some information and learn something about it. The community started to adopt it as a method, because they knew it was specific."	*Most of the animal community broke down at the not noticing or recognizing anomalies stage. Only Fire and Mello attained the stage of explicitly looking for a solution.*
Plants	*Most of the plant community had identified cosuppression as an interesting topic of scientific research. Therefore, they were able to notice the anomaly, as illustrated by the quotes in the right column:*	"So there are these different mindsets that are so ingrained that you don't even appreciate that there is another way to look at this. And I think that's why we were really locked into that. It traced back to the discovery of DNA and the genetic material and the structure of DNA. We were introducing constructs that it turns out in retrospect did make dsRNA. We were thinking in terms of RNA being produced and then what happens to it? Well, it gets degraded, and I always thought it gets turned over so who cares what the degradation products look like. We were manipulating DNA not RNA. That was the one missing piece, had we gone into introducing RNA directly we could have done things like Fire and Mello did and we could have done it years before them." "We knew that silencing was what we were studying now and we designed our experiments and modified our constructs and our transgenes to the plant we were using to be able to really understand how silencing is going on."

> We were trying to do something different, this gene replacement, but in the process of doing those experiments we stumbled upon this gene silencing and at that point it was so interesting. It seemed so new and not explainable by anything that we had known before that we had started focusing on that phenomenon. (Respondent 18, plant researcher)

But they, too, were constrained by the established paradigm when called upon to think of solutions that often did not fit within its confines. The difficulty of explaining the observed silencing phenomenon and identifying the trigger was caused by the disparity in causal pathways between the silencing mechanism and the passive role of RNA stemming from the central dogma of biology. DNA was thought to be the active agent that encodes into protein, while RNA only passes information along. Again, abductive reasoning was hampered by the established paradigm, since plant researchers were cognitively impaired from speculating and conjecturing about possible solutions beyond DNA because the dogma dictated that gene expression is controlled at the DNA level since it contains the genetic information. This limited their search to DNA-based triggers and prevented them from proposing RNA-level triggers to gene silencing, as illustrated below:

> Why didn't the plant people get to where Fire and Mello did? My main insight is that we were so focused on transgenes to manipulate DNA expression. We never got to introducing RNA. It was regarded as unstable—that was never going to work. . . . There are these different mindsets that are so ingrained that you don't

Table 3. Quotes from Respondents' Publications Illustrating Two Mechanisms in the Research Process—*Not Noticing or Recognizing Anomalies* and *Actively Resisting Solutions*—That Led to Near Miss of Breakthrough

Organism	Not noticing or recognizing anomalies	Actively resisting solutions
Animals	—"Progress in identifying additional components could occur quite rapidly because of the recent development of a simple application of antisense RNA technology to *C. elegans*. . . . Using this technique, candidate genes identified by a variety of means can be assayed rapidly for important roles in cell polarity" (Guo and Kemphues 1995). —"Unless otherwise noted, fem-3 was detected using an antisense RNA . . . " (Ahringer et al. 1992). —"[T]ranslational control of gene expression by small antisense RNAs may be a particularly effective strategy for providing a developmental switch of very high specificity" (Lee et al. 1993). —"*In situ* hybridization to whole-mount eye imaginal discs was performed using a non-radioactive antisense RNA probe . . . " (Zheng et al. 1995).	*Most of the animal community broke down at the not noticing or recognizing anomalies stage. Only Fire and Mello attained the stage of explicitly looking for a solution.*
Plants	*Most of the plant community had identified cosuppression as an interesting topic of scientific research. Therefore, they were able to notice the anomaly.*	—"The nature of the trans-interaction between homologous sequences leading to gene inactivation is not clear. . . . The final outcome of the scanning can be either a modification of the chromatin structure or DNA methylation, both of which lead to gene inactivation" (Romano and Macino 1992). —"Unexpectedly, the introduced gene created a block in anthocyanin biosynthesis. . . . The mechanism responsible for the reversible co-suppression of homologous genes in trans is unclear, but the erratic and reversible nature of this phenomenon suggests the possible involvement of methylation" (Napoli et al. 1990). —"Cosupression results in the degradation of RNA from host genes and homologous transgenes after transcription in the nucleus. . . . Our results indicate that the presence of a 35S-Nia2 transgene is dispensable for the RNA degradation step of posttranscriptional silencing when host Nia mRNA over-accumulate above the level of wild-type plants" (Palauqui and Vaucheret 1998).

> even appreciate that there is another way to look at this. And I think that's why we were really locked into that. (Respondent 17, plant researcher)

Quotes from interviewees' publications in Table 3 corroborate interview findings. In the animal community, researchers were silent about sense RNA and dsRNA, while only antisense RNA was mentioned as a tool. In the plant community, only DNA-based transgenes and DNA methylation were studied.

Failing to Make the Link Between Communities

The history of RNAi's discovery was punctuated by several documented observations of the bizarre phenomenon, first in plants (Napoli et al. 1990), then in fungi (Romano and Macino 1992), worms (Guo and Kemphues 1995), and plant viruses (Ratcliff et al. 1997), and perhaps in even more undocumented observations before the underlying trigger agent was finally found. However, most respondents who worked with animal model organisms were unaware of the research done by plant scientists, and vice versa. Prior to Fire and Mello's discovery, collaborations and mixed conferences between plant and animal scientists working on gene expression and inhibition were scarce to none, as each community mainly published in its own organism-specific journals. A natural boundary separated the two communities, and communication was nearly nonexistent across them, even though they observed the same phenomenon of gene silencing. One scientist from each community describe this divide:

> The paper . . . on petunias was published in . . . the journal *Plant Cell*. Really nobody followed that. Nobody! (Respondent 10, animal researcher)

> During the initial years when we were working on [understanding gene silencing] we weren't talking with animal people very much. It was more just a small group of plant scientists who were first trying to figure out what was going on. (Respondent 18, plant researcher)

Researchers believed that the anomalies they observed would be unique to their own organism of

study—in other words, not evolutionarily conserved. This belief depended on the researcher's view of how a fundamental phenomenon such as gene silencing traces back to a common ancestor, in this case between animals and plants. As a respondent explained,

> We know that plants evolved as a multicellular life form independently from animals, so the last common ancestor of plants and animals was a single cell organism. . . . Thus, when you're talking about very fundamental processes that were there in the last ancestor, last single cell ancestor, those operate across kingdoms. In general, it just depends on whether you think it's an ancestral process or whether you think it's more derived. (Respondent 3, animal researcher)

For gene silencing, the bizarre and anomalous phenomenon that researchers observed in their experiments was thought to be unique rather than fundamental across kingdoms. As the following quotes illustrate,

> As far as we knew at the time, it was a very specific phenomenon for *C. elegans*. It was pretty much just thought of as a *C. elegans* phenomenon at the time. (Respondent 10, animal researcher)

> And at the time, I don't think we were thinking too much about necessarily the animal work. (Respondent 18, plant researcher)

No one actively communicated and no links were made because each community thought that it was in a different paradigm from the other. Each stayed within its own boundaries, which limited thinking and prevented anomalous observations from various fields to be linked.

Scientists in the animal community were unable to recognize a repeated pattern of anomalies because of their failure to link with the plant community. Skepticism and a lack of critical mass, caused by the perception that anomalies occurred only in animals, contributed to an inaccurate assessment of the impact of the phenomenon. Therefore, the mechanism that triggers gene silencing was not identified as an open scientific question in the animal community. While the plant community saw the scientific merit of pursuing research on gene silencing, it too believed that its observed gene silencing phenomenon was unique to plants and thus was dictated by a different paradigm than that in animal organisms. These scientists failed to link to the animal community, thereby locking themselves into the same paradigmatic mindset, bounding their views and search spaces to be local. When proposing solutions, they were unable to gain more confidence from similar results in other settings and were thus more deterred from proposing atypical groundbreaking solutions.

As it turns out, each community had one piece of the final puzzle. Animal scientists were fixated on single-stranded RNA, while the plant community was absorbed by DNA-based transgenes that were double stranded. Ultimately, had scientists been able to recombine the RNA component in animals with the double-stranded feature used in plants, they could have found dsRNA as the trigger to RNAi much earlier.

Tracing through citations of interviewee publications shown in Table 5, I found a clear dichotomy between plant and animal scientists that corroborates findings from the interviews. The two communities only cited within their own publications before the seminal 1998 paper. After the breakthrough paper, each community still cited within itself more but acknowledged research on gene silencing in the other community. Furthermore, none of the major scientific conferences series—Gordon Research Conferences, Cold Spring Harbor Meetings, and Keystone Symposia—held cross-organismic meetings in gene expression prior to 1998.

Fire and Mello's Breakthrough Success

One way to demonstrate that studying near misses is qualitatively different from studying breakthroughs and, therefore, important is to explore Fire and Mello's successful discovery. Had I solely taken this successful view in my analysis, I would have been unable to unpack near misses into the three mechanisms described above.

Although I did not obtain interviews with the two scientists, archival documents, including their Nobel lectures, were quite telling. Like most in the *C. elegans* community, Fire and Mello first came in contact with the phenomenon as a tool while trying to inactivate genes using antisense RNA technology. Unlike others, however, they realized that the phenomenon itself was interesting and important. "Andy and I knew that RNA interference was something incredible when we started working with it," said Mello in his Nobel lecture (Mello 2007, p. 247). Instead of dismissing the phenomenon as just a useful tool or a mere worm oddity, they noticed the anomaly and believed that it was important to study.

As they tested for the trigger agent, the central dogma of biology was a potential constraint, Fire explains in the following quote: "arguing strongly against dsRNA as a potential effector was the fact that native dsRNA would have no free base pairs to interact with matching molecules in the cell" (Fire 2007, p. 204). However, instead of actively resisting dsRNA as a solution, Fire's graduate work opened them to "test somewhat far-fetched hypotheses (like the involvement of dsRNA)," as he further explains below:

> From my graduate work with RNA polymerases, I was certainly also very familiar with the sometimes annoying ability of RNA polymerases to start in vitro at ends and other fortuitous sites. Thus, the concept that

Table 4. Interview Quotes from Respondents Illustrating that the Mechanism of *Failure to Make the Link Between Communities* Led to Near Miss of Breakthrough

	Animals—Not noticing or recognizing anomalies	Plants—Actively resisting solutions
Failure to make the link between communities	"At this time, I had never followed what was going on in plants. Preconception that whatever perhaps happens in plants is different in animals even in mammals, that there wasn't much attention paid to them, even within the community." "No one at that time, no one I had talked to was even thinking that it was related to the plant things. No one before '98. I had ever heard anyone mention anything to do with plants." "We were trying to penetrate what we thought what we thought was a novel phenomenon. We didn't believed that it really represented anything general." "I didn't know that the plant phenomenon would be related to the worm phenomenon. Obviously the people working in plants, were in fact trying to explain the same phenomenon but we didn't know any of those details."	"I don't think there were really conferences that brought the animal and plant fields together until probably as late as 2001." "There wasn't a lot of dialogue then between the plant and animal community. . . . And at the time I don't think we were thinking too much about necessarily the animal work. But during the initial years when we were working on it I think we weren't talking with animal people very much. It was more just a small group of plant scientists who were first trying to figure out what was going on." "We were publishing in different journals then a lot of the animal folks that yeast folks wouldn't see if they were at the wrong kind of institution, and that created an artificial barrier that doesn't exist now but was an important one then."

Table 5. Average Citations Between Animal and Plant Communities Before and After the 1998 Fire and Mello Paper

	Citing publications			Citing publications	
Before Fire et al. (1998)	Animals	Plants	After Fire et al. (1998)	Animals	Plants
Cited publications			Cited publications		
Animals	39.9	0	Animals	27.4	3.6
Plants	0	25.1	Plants	2.4	30.9

Source. Fire et al. (1998).

> double-stranded RNA might be a component of the injected material was hardly a leap of logic. (Fire 2007, p. 204)

Moreover, citations in the Nobel paper made reference to articles on both plants and *C. elegans*, suggesting that Fire and Mello were well aware of the work done by scientists in various communities and were able to connect the dots. The 1999 Gordon Research Conference on Epigenetics also featured Andrew Fire as the only animal researcher in the Gene Silencing Session.

Although the plant community was further along than most of the animal community in the discovery of the trigger to RNAi, it was still confined by DNA-level constructs. This evidence suggests that Fire and Mello's path to discovery was not marked by the setbacks that confronted their colleagues. Moreover, Fire's conference attendance shows that he interacted with plant scientists and was in a brokerage position to recombine information. These reasons explain why, despite being animal scientists, the two were able to leapfrog plant scientists and make the discovery.

Discussion

Implications to Literature

Most extant research on scientific discovery highlights the successful emergence of breakthroughs, and some alludes to elements that constrain thinking and lead to nonbreakthroughs. The present investigation contributes to this research by qualitatively examining mechanisms behind near misses throughout the breakthrough process. By interviewing scientists on the verge of the RNAi breakthrough and analyzing the animal and plant communities separately, I identify three mechanisms rooted in pressures from existing paradigms. These qualitative interviews add direct empirical evidence on how constrained thinking led to near misses and complement proxy measures such as age (Simonton 1989) and core (Collins 1998, Gieryn and Hirsh 1983) versus periphery (Jeppesen and Lakhani 2010) used in existing studies.

Kuhn (1962) proposed a mechanism of breakthrough deterrence during normal science in which researchers attempt to force fit anomalies by making ad hoc modifications to the paradigm to make it compatible with puzzling observations. From the case of RNAi, I also find that researchers will simply not notice or recognize anomalies if they appear to be secondary to the main experimental path, as researchers in the animal community were preoccupied with confirming and extending the established paradigm, where the search process is mainly incremental. This near miss hindered the process of discovery to proceed from the stage of normal science into the stage of anomaly and crisis, as

the lack of doubt in the puzzling observations inhibited researchers from noticing the anomalies that arose.

Even when an anomaly is recognized as such, the search for solutions that explain the anomaly may still be clouded by existing theories that automatically rule out far-fetched possibilities. Sometimes this constraint is unconscious, but it can be more deliberate, as researchers often talk themselves out of doing experiments. They will not try an experiment because the result can be predicted from existing theories. This near miss prevented the process of discovery from advancing from the stage of extraordinary science into resolution, where the established paradigm constrains thinking and search space.

Finally, structural boundaries between communities led to the belief in both communities that the puzzling observations occurred only in their own model organisms and that each were operating under a different paradigm. This cognitive bias constrained thinking and led each community to search locally without connecting with the other. It both reinforced the near misses of not noticing or recognizing anomalies and deterred the proposal of unconventional solutions, thereby leading to the active resistance of radical solutions.

Mapping the near misses onto Kuhn's (1962) model of breakthrough emergence suggests that paradigmatic rigidity may have cognitively confined the thinking of researchers by limiting the creativity and span of proposed solutions not only during problem solving, but also earlier in the process, when they failed to recognize arising anomalies. Throughout the discovery process, paradigms act as cognitive filters to determine the relevance of knowledge produced. Both when having to notice anomalies during normal science and when suggesting solutions during extraordinary science, beliefs and knowledge rooted in existing paradigms lead to oversight (Garud et al. 1997) and hinder creativity, especially when the outcome is radically different. These two mechanisms also suggest that searching and reasoning along the existing paradigm deter abductive reasoning, which ultimately leads to the near misses and prevents breakthrough discovery. The cognitive biases resulting from paradigmatic rigidity prevent scientists from doubting the established theories (Locke et al. 2008) and recognizing anomalies. Moreover, thinking dictated by the paradigm hampers the proposal of broader conjectures and speculations outside its confines (Weick 2005), and renders search to be local instead of more distant.

Taken together, these findings from near misses suggest that researchers can enhance their likelihood of achieving a breakthrough not only by possessing the driving characteristics and factors, but also by overcoming cognitive biases and barriers that limit thinking. Researchers should be cognizant that even when supporting evidence is available and observed, the discovery process is not likely to follow Popper's (1959) logical path. Instead, falsification of a theory through the incidence of anomaly is not fully rational, as cognitive impairments stemming from the rigidity of paradigmatic forces can hold back their recognition of the anomaly and ultimately prevent breakthrough. However, when such an abnormal and unexpected observation does occur, it has the potential to be novel and important. It is often because of these breaches that breakthroughs are discovered, as a Nobel laureate described below:

> When you have a well-defined system and it's telling you something you don't understand, it isn't consistent with the way you've designed the system then something is new in the system. It's paying attention to that [bizarre phenomenon] and not pushing it out of the way as you went towards your more conventional hypothesis-driven science. There is a new science there. (Respondent 13, animal researcher)

These mechanisms also speak to the ongoing debate between depth and breadth of knowledge as sources of breakthrough (Weisberg 1999). Since paradigmatic rigidity can lead to near misses, they provide evidence supporting the view that breakthroughs are more likely to originate from broader and less restricted knowledge sources (Simonton 1999). The animal and plant communities each having one piece of the puzzle also suggests that scientific discoveries and breakthroughs are becoming more and more complex. It complements existing works that show evidence of increased collaboration in the production of knowledge, which implies that it is due to the frontier of science moving further and becoming more complex, thereby making it harder for individual scientists to contribute at the frontier (Jones 2009, Wuchty et al. 2007).

Finally, while this paper solely focuses on cognitive breakdowns to breakthrough, incentive pressures also play a role. The funding of research grants and academic tenure evaluations significantly determine scientists' research paths and the experiments they run. Science's priority reward system (Merton 1957) and constant publication pressures may lead researchers to choose more incremental and less risky research directions unless they benefit from institutional settings that tolerate early failure, reward long-term success, and provide greater freedom to experiment (Azoulay et al. 2011). However, unlike the biases studied herein, these incentive pressures lead to more deliberate behavior.

Implications for Practice

This work also has practice implications for researchers involved in scientific discovery as well as management or administrators of organizations and institutions that partake in scientific discovery, including science-based

firms. It demonstrates that even when researchers are fully capable, rigidity of paradigms forces them into narrow mindsets. Thus, by elucidating the reasons why near misses occur, my findings imply that innovators can attempt to avoid these pitfalls and potentially intervene. For instance, expanding research scope by exploring at the fringe rather than always focusing on the mainstream can help researchers reach broader views and avoid being blinded by normal science; exploiting social ties as a mechanism of substantiation can overcome the problem of being constrained by the current paradigm and not thinking of creative solutions; and broadening exposure and awareness of work across multiple communities can mitigate the inability to connect the dots. Researchers can also expand themselves intellectually by reading outside of their immediate research area, collaborating with coauthors with complementary research specialties and skills, and paying even more attention to researchers who have expertise in other fields at conferences.

For science-based firms, the potential interventions speak to the design of research environments by providing structural characteristics and policies. To prevent innovators from being restricted by the existing paradigm, organizations can foster the production of groundbreaking discoveries by facilitating cross-boundary research teams. Internally, firms could institute organizational structures that enable for temporary research teams to be formed based on the expertise required by project or establish rotational programs where researchers could change teams after a certain time period. Externally, supporting the attendance of seminars and conferences for researchers enables the exchange of ideas and can also help establish collaborative links with academic laboratories or other firms with complementary know-how. Furthermore, hiring some researchers with a diverse range of backgrounds and expertise can also foster the diversity and breadth of ideas generated. Firms can also provide incentive structures that promote more experimentation in side projects at the fringe by leaving researchers more flexibility and freedom to allocate funding, as well as by establishing evaluation procedures that are more tolerant of early misses.

Generalizability

In-depth inductive-qualitative case studies afford us much richness of description, but they reduce the degree to which findings may generalize to other settings. This challenge may be exacerbated when studying idiosyncratic rare events, such as breakthroughs. However, the near misses at various stages proposed herein can be abstracted to a broader set of circumstances and settings in creative work. As evidenced by simultaneous discoveries (Bikard 2015), situations of two or more communities working independently on a similar phenomenon and potentially building on one another's work occur often. The recognition of anomalies as the starting point for eventual breakthrough discovery is also common:

> Steve McKnight has a story very similar in a process where he is looking at the association of proteins with a microcrystal-forming material. He didn't anticipate it at all. . . . It's the exact phenomenon: I don't understand what's going on, it's very likely to be important, and I can study this because it's happening in front of me in a controlled experiment. (Respondent 13, animal researcher)

Finally, problem solving is a process present in most creative work, and breakthrough is no exception.

Moreover, drawing from more diverse and distant knowledge sources to improve and accelerate the chances of breakthrough discovery can be generalized to other settings. This quote illustrates how the fields of evolutionary biology and microbiology could have benefitted from one another had there been more exchanges between them:

> Darwin might have found . . . marvelous experimental material for the study of evolution in populations of microbes—where generation time is measured in minutes, and where natural (or artificial) selection can be applied to tens of hundreds of billions of unicellular organisms at small cost and less ethical compunction. Pasteur and his successors in microbiology might have avoided decades of muddled thinking about variation in bacteria. (Lederberg 1988, p. 345)

The purpose of this work was to generate new theory and enhance the current limited understanding of why breakthroughs are missed. Further research could replicate the study in more settings, such as on a list of Nobel discoveries, and verify whether the identified mechanisms are comprehensive. These studies could use improved methods to identify those who missed breakthroughs by using content analysis rather than mere keywords to lessen noise in the definition. They could also benefit from several iterations of community definition, adding tangential fields as they arise onto the core and using more stringent sample cutoffs to reduce noise associated with the broader definition. Another research avenue could quantitatively test the constructs that I proposed to further improve the scope. This study will hopefully incite others to better understand the entire mechanism of invention and discovery.

Acknowledgments

The author would like to thank the Harvard Business School (HBS) Department of Research and Doctoral Program for supporting her work. She is also grateful to Lee Fleming, Vicki Sato, Sujin Jang, Luciana Silvestri, Melissa Valentine, Anil Doshi, Leslie Perlow, Anca Metiu, Hila Lifshitz, Anoop Menon, Tiona Zuzul, Richard Freeman, Fiona Murray, and

members of the HBS CRAFT course for their insightful comments and feedback. Finally, the author would like to thank the editor, Sarah Kaplan, and the three anonymous reviewers at *Organization Science* for their feedback and suggestions throughout the publication process. All errors remain the author's.

Appendix. Interview Question Guide

Open-Ended Questions

Describe your work leading to 1997, in 1998, and after 1998.

Probing Questions on Breakthrough

In the period of 1997–1998, were you and your peers aware that a breakthrough was about to be discovered? Was there excitement due to a potential impactful discovery?

Were scientists trying to solve a specific puzzling mechanism or did they just happen to stumble on the RNAi mechanism by chance while looking for something else?

Were there many teams working toward solving the same problem? Was there racing?

Do you feel like the breakthrough could have been made earlier? Why? What was the missing link that prevented it?

Was the discovery and its results a surprise? In terms of simplicity or complexity of the solution, in terms of who made the discovery?

Before you chose your research direction, how do you evaluate the potential impact of your research? How?

What papers or findings spurred your interest in RNAi research? What works had a decisive influence on your research interests?

What experiments, field or prior breakthroughs do you believe paved the road to the discovery? What inventions (tools), environment fostered the discovery?

Were you aware of the similar cosuppression and quelling results obtained in plants and fungi? As a plant scientist, did you think that cosuppression and quelling would be present in animals?

Probing Questions on the Community

Was there a defined community of RNAi scientists prior to breakthrough?

How would you define the community of RNAi scientists prior to breakthrough? Which subfields of biology came together to form such a community?

How would you characterize this community? Social, open, or collective?

How open was the community of scientists working toward solving this discovery? Was there an informal group established that frequently communicated and shared their ideas? Or were results withheld?

What kind of conference/research seminars did you attend at the time? Were they phenomenon-based, organism-based or something else?

How do you think about conferences? What role do conferences play in your research?

In your opinion, did the breakthrough come from within the community or from outside?

In your opinion, who were the big contenders in the community to discover the mechanism to RNAi? Why?

Given this list of scientists I am interviewing or will interview, who else do you think I should talk to?

Endnote

[1] The exact search string used in the PubMed query extracted on October 26, 2011, was as follows: ((((gene silencing[MeSH Terms] OR gene expression regulation[MeSH Terms]) AND (RNA, double-stranded[MeSH Terms] OR rna, antisense[MeSH Terms] OR rna, catalytic[MeSH Terms])) AND "1980"[Publication Date]: "1999"[Publication Date]) AND English[Language]) NOT interferon[MeSH Terms], augmented with ((((cosuppression[title/abstract] OR co-suppression[title/abstract] OR quelling[title/abstract] OR RNAi[title/abstract] OR RNA interference[title/abstract])) NOT interferons[MeSH Terms]) AND "1980"[Publication Date]: "1999"[Publication Date]) AND English[Language]. I also found that dsRNA generated a lot of noise, as it was heavily used by immunologists studying interferon responses. To minimize this, I included in the MeSH search the "NOT interferon[MeSH Terms]" term.

References

Ahringer J, Rosenquist TA, Lawson DN, Kimble J (1992) The *Caenorhabditis elegans* sex determining gene fem-3 is regulated post-transcriptionally. *Euro. Molecular Biol. Organ. J.* 11(6): 2303–2310.

Amabile TM (1983) The social psychology of creativity: A componential conceptualization. *J. Personality Soc. Psych.* 45(2):357–376.

Azoulay P, Graff Zivin JS, Manso G (2011) Incentives and creativity: Evidence from the academic life sciences. *RAND J. Econom.* 42(3):527–554.

Berson JA (1992) Discoveries missed, discoveries made: Creativity, influence, and fame in chemistry. *Tetrahedron* 48(1):3–17.

Bikard M (2015) Peer-based knowledge validation: A hurdle to the flow of academic science to inventors. Working paper, London Business School, London.

Burt RS (2004) Structural holes and good ideas. *Amer. J. Sociol.* 110(2):349–399.

Campbell DT, Overman ES (1988) *Methodology and Epistemology for Social Science: Selected Papers* (University of Chicago Press, Chicago).

Collins R (1998) *The Sociology of Philosophies: A Global Theory of Intellectual Change* (Belknap Press, Cambridge, MA).

Corbin JM, Strauss AL (2008) *Basics of Qualitative Research: Techniques and Procedures for Developing Grounded Theory*, 3rd ed. (Sage Publications, Los Angeles).

Czarniawska B (1999) *Writing Management: Organization Theory as a Literary Genre* (Oxford University Press, Oxford, UK).

Dosi G (1982) Technological paradigms and technological trajectories: A suggested interpretation of the determinants and directions of technical change. *Res. Policy* 11(3):147–162.

Dyson FJ (1972) Missed opportunities. *Bull. Amer. Math. Soc.* 78(5):635–652.

Fire A (2007) Gene silencing by double stranded RNA. Grandin K, ed. *Les Prix Nobel* (Nobel Foundation, Stockholm), 198–233.

Fire A, Xu S, Montgomery MK, Kostas SA, Driver SE, Mello CC (1998) Potent and specific genetic interference by double-stranded RNA in *Caenorhabditis elegans*. *Nature* 391(6669):806–811.

Garud R, Nayyar PR, Shapira Z, eds. (1997) Technological choices and the inevitability of errors. *Technological Innovation: Oversights and Foresights* (Cambridge University Press, Cambridge, UK), 20–40.

Gieryn TF, Hirsh RF (1983) Marginality and innovation in science. *Soc. Stud. Sci.* 13(1):87–106.

Girotra K, Terwiesch C, Ulrich KT (2010) Idea generation and the quality of the best idea. *Management Sci.* 56(4):591–605.

Golden BR (1992) The past is the past—Or is it? The use of retrospective accounts as indicators of past strategy. *Acad. Management J.* 35(4):848–860.

Guo S, Kemphues KJ (1995) par-1, a gene required for establishing polarity in *C. elegans* embryos, encodes a putative Ser/Thr kinase that is asymmetrically distributed. *Cell* 81(4):611–620.

Hackman JR (2009) The perils of positivity. *J. Organ. Behav.* 30(2): 309–319.

Hargadon A, Sutton RI (1997) Technology brokering and innovation in a product development firm. *Admin. Sci. Quart.* 42(4):716–749.
Jeppesen LB, Lakhani KR (2010) Marginality and problem-solving effectiveness in broadcast search. *Organ. Sci.* 21(5):1016–1033.
Jones BF (2009) The burden of knowledge and the "death of the Renaissance man": Is innovation getting harder? *Rev. Econom. Stud.* 76(1):283–317.
Kaplan S, Vakili K (2015) The double-edged sword of recombination in breakthrough innovation. *Strategic Management J.* 36(10): 1435–1457.
Knorr-Cetina K (1999) *Epistemic Cultures: How the Sciences Make Knowledge* (Harvard University Press, Cambridge, MA).
Krol ARvd, Leon AM, Beld M, Mol JNM, Stuitje AR (1990) Flavonoid genes in petunia: Addition of a limited number of gene copies may lead to a suppression of gene expression. *Plant Cell* 2(4): 291–299.
Kuhn TS (1962) *The Structure of Scientific Revolutions* (University of Chicago Press, Chicago).
Latour B, Woolgar S (1986) *Laboratory Life: The Construction of Scientific Facts* (Princeton University Press, Princeton, NJ).
Lederberg J (1988) Pandemic as a natural evolutionary phenomenon. *Soc. Res.* 5(3):343–359.
Lee RC, Feinbaum RL, Ambros V (1993) The *C. elegans* heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. *Cell* 75(5):843–854.
Leonard-Barton D, Swap WC (1999) *When Sparks Fly: Igniting Creativity in Groups* (Harvard Business School Press, Boston).
Locke K, Golden-Biddle K, Feldman MS (2008) Perspective—Making doubt generative: Rethinking the role of doubt in the research process. *Organ. Sci.* 19(6):907–918.
Margolis H (1993) *Paradigms and Barriers: How Habits of Mind Govern Scientific Belief* (University of Chicago Press, Chicago).
McEvily B, Zaheer A (1999) Bridging ties: A source of firm heterogeneity in competitive capabilities. *Strategic Management J.* 20(12):1133–1156.
Mello C (2007) Return to the RNAi world: Rethinking gene expression and evolution. Grandin K, ed. *Les Prix Nobel* (Nobel Foundation, Stockholm), 242–258.
Merton RK (1957) Priorities in scientific discovery: A chapter in the sociology of science. *Amer. Soc. Rev.* 22(6):635–659.
Miles MB, Huberman AM (1984) *Qualitative Data Analysis: A Sourcebook of New Methods* (Sage Publications, Thousand Oaks, CA).
Napoli C, Lemieux C, Jorgensen R (1990) Introduction of a chimeric chalcone synthase gene into petunia results in reversible cosuppression of homologous genes in trans. *Plant Cell* 2(4): 279–289.
Obstfeld D (2005) Social networks, the tertius iungens orientation, and involvement in innovation. *Admin. Sci. Quart.* 50(1):100–130.
Palauqui J-C, Vaucheret H (1998) Transgenes are dispensable for the RNA degradation step of cosuppression. *Proc. National Acad. Sci. USA* 95(16):9675–9680.
Peirce CS (1931–1958) *Collected Papers of Charles Sanders Peirce*, Vols. 1–8 (Harvard University Press, Cambridge, MA).
Popper KR (1959) *The Logic of Scientific Discovery* (Basic Books, New York).
Ratcliff F, Harrison BD, Baulcombe DC (1997) A similarity between viral defense and gene silencing in plants. *Science* 276(5318):1558–1560.
Romano N, Macino G (1992) Quelling: Transient inactivation of gene expression in *Neurospora crassa* by transformation with homologous sequences. *Molecular Microbiology* 6(22):3343–3353.
Rosenberg N (1974) Science, invention and economic growth. *Econom. J.* 84(333):90–108.
Schumpeter JA (1942) *Capitalism, Socialism, and Democracy* (Harper Perennial, New York).
Simonton DK (1989) Age and creative productivity: Nonlinear estimation of an information-processing model. *Internat. J. Aging Human Development* 29(1):23–37.
Simonton DK (1999) *Origins of Genius: Darwinian Perspectives on Creativity* (Oxford University Press, Oxford, UK).
Singh J, Fleming L (2010) Lone inventors as sources of breakthroughs: Myth or reality? *Management Sci.* 56(1):41–56.
Taylor A, Greve HR (2006) Superman or the fantastic four? Knowledge combination and experience in innovative teams. *Acad. Management J.* 49(4):723–740.
Thagard P (1992) *Conceptual Revolutions* (Princeton University Press, Princeton, NJ).
Uzzi B (1997) Social structure and competition in interfirm networks: The paradox of embeddedness. *Admin. Sci. Quart.* 42(1):35–67.
Weick KE (2005) Organizing and failures of imagination. *Inernat. Public Management J.* 8(3):425–438.
Weisberg R (1988) Problem solving and creativity. Sternberg RJ, ed. *The Nature of Creativity: Contemporary Psychological Perspectives* (Cambridge University Press, Cambridge, UK), 148–176.
Weisberg R (1999) Creativity and knowledge: A challenge to theories. Sternberg R, ed. *Handbook of Creativity* (Cambridge University Press, Cambridge, UK), 226–250.
Whittington KB, Owen-Smith J, Powell WW (2009) Networks, propinquity, and innovation in knowledge-intensive industries. *Admin. Sci. Quart.* 54(1):90–122.
Wuchty S, Jones BF, Uzzi B (2007) The increasing dominance of teams in production of knowledge. *Science* 316(5827):1036–1039.
Zheng L, Zhang J, Carthew RW (1995) Frizzled regulates mirror-symmetric pattern formation in the *Drosophila* eye. *Development* 121(9):3045–3055.

Sen Chai is assistant professor of management at ESSEC Business School. She received her DBA from Harvard Business School. Her research examines the entire developmental course of creative innovations from idea conception to commercialization, with the goal of helping managers and policy makers better support innovation and increase organizations' chances of creating commercially successful ideas.