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Resilience in Scientific Research: Understanding How Natural Product Research Rebounded in an Adverse Situation

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ABSTRACT *The recent declining rate in the discovery of new drugs has made natural product (NP) research—the traditional method of using living organisms to acquire drug candidates—regain its importance, despite the fact that it was once regarded as an obsolete method in the face of the exalted expectations about emerging new approaches since the 1990s. The concept of 'resilience' in scientific research provides a clue for understanding the dynamism of this rebound in research. Four elements may be highlighted in the context of microbial NP research in Japan: first, 'institutional precondition' is essential in the sense that the research must be rooted in an institutional complex involving academia, drug companies, and national policies. Second, the dual nature of the 'attack from rival innovations' including semiotic labeling and technical advances is examined. Third, four approaches to NP research are observed as responses to such challenges: (1) reevaluating the naturalness of NPs; (2) adopting various technical elements from their rivals; (3) shifting the emphasis from the practical pursuit of drug candidates to biological research using bioprobes; and (4) examining the uneven degree of resilience between academia and industry. Fourth and finally, NPs are viewed as an icon of cultural practice. This view may eventually open the door to questions about the meaning of 'tradition' in the context of general contemporary scientific research.*

KEY WORDS: resilience, obduracy, drug discovery, natural products, expectation, tradition

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Introduction

In 2012, Japanese media reports were filled with the auspicious news that Akira Endo, an ex-researcher from Sankyo Pharmaceuticals, was inducted into the National Inventors Hall of Fame in the USA, along with Steve Jobs and others (Tokyo University of Agriculture and Technology, 2012). This event was concurrent with increasing attention to his academic feats in the form of Endo's previously published books (2006a, 2006b, cf Yamauchi, 2006). Endo's achievement is the discovery of 'mevastatin, the first statin, pioneering research into a new class of molecules that are now a hugely successful class of drugs targeting the lowering of cholesterol' (National Inventors Hall of Fame, 2012). He discovered MK-236, an inhibitor of HMG-CoA reductase from *Penicillium citrinum*, when he was a researcher in the company. This substance later became a set of drugs collectively called 'statins' including Endo's initial mevastatin, Merck's lovastatin (Mevacor), and Phizer's atorvastatin (Liptor) (Endo, 2006a, 2006b; Shook, 2007). Sales of statins represent the largest global commercial success for years, reaching a sum of 24 billion dollars in 2005, until their very recent replacement by generics (Yamauchi, 2006, p. 8; cf. Baba and Walsh, 2010).

The research on statins was situated within the long tradition of research on natural products (henceforth, NPs) in general and that of antibiotics in particular—namely, the research on secondary metabolites produced from a biological source. NPs have generally been associated with both traditional healing and modern drug discovery; some argue that their earliest records go back to ancient Mesopotamia when there are descriptions of the use of oils for treating illness (Dias *et al.,* 2012). In terms of scientific research, developments in organic chemistry contributed to the formation of its modern phase, which has long concerned itself with the complex structure of secondary metabolites produced by a biological source (Hirota, 2013).

Conventionally, 'natural' products have been defined as such because of their natural sources, in contrast to those that are artificially synthesized. Some argue that recent developments in biological research demand a closer examination of what 'natural' means in NP research in the shifting scientific context (Editorial, 2007). In modern times, NPs in such research have been treated as invaluable sources for drug candidates, one of the most famous examples being Alexander Fleming's discovery of penicillin from fungus in 1929, followed by research into and production of the whole set of antibiotics (Bickel, 1973; MacFarlane, 1984; cf. Demain and Sanchez, 2009).

In 2007, I visited the Antibiotic Laboratory in RIKEN, a national research institute and one of the major flagships for Japanese science policy (RIKEN, 2005), for the purpose of initiating my ethnographic study of laboratory practices. This laboratory is headed by Hiroyuki Osada, one of the leading figures representing Japanese research into traditional microbial NPs and the newly emerging field of chemical biology.

To my surprise, Osada displayed a mixed sense of crisis and hope about the current state of research. Despite the successful lineage of antibiotics research at the institute, he had already decided to change the course of research from the original methods that Endo and others had pursued (Interview, 8 August 2007). In short, despite media hype, the research on this topic had come to be regarded as a declining discipline, a research subject for the losing side. It seemed proved both by the decline in its productivity in terms of providing drug candidates and by a sequence of emerging trends, accompanied by much fanfare, which seemed to herald revolutionary changes in the drug pipeline itself (Zucker and Darby, 1997; Ratti and Trist, 2001).

The fancy discourse, however, began to crumble when the sour fact emerged that the development of new drugs to be approved by government agencies, such as the US Food and Drug Administration, was stagnant or even declining (Bartfai and Lees, 2006, p. 68; Rydzewski, 2008, p. 18). Scholars were too busy to argue over possible causes, such as excessive drug regulations (Daemmrich, 2004; Epstein, 2006; cf. Angell, 2004, for an opposing stance), the rising costs of drug research (Rydzewski, 2008; cf. Goozner, 2004 for criticism of this argument), and even the closed nature of biomedical research to medical reality (Horrobin, 2003). Thus, by the time of our interview, Osada summarized this general trend with an enigmatic remark about the changing research situation: he felt, he said, that he was 'becoming a top runner who once was one lap behind'.

The central question of this paper, therefore, is as follows: how can any scientific research—collectively, as a topic or field—bounce back after being challenged and even dubbed as obsolete by new rival research? My attempt to answer this question focuses specifically on microbial NP research in Japan, which seems to be gaining new momentum after a period of stagnation and the loss of hope because of challenges from rival technology and research.

To answer this question, this article proposes the concept of 'resilience' in scientific research, borrowed from psychological studies in the 1970s on children who survived adverse situations and who grew healthily thereafter (Werner and Smith, 1982; Masten, *et al*., 1990). In the specific context of microbial NP research in Japan, four aspects for such resilience will be discussed as components pivotal for understanding this rebounding phenomenon: (1) the institutional background that supports the rootedness of such research, (2) the dual nature of the rival's attack in the shape of its embodied practices and its discursive onslaught on the old, (3) strategic reworking of the resourceful complexity of the research tradition, and (4) the 'cultural-icon status' of the research as an object of attachment for practitioners. These aspects demonstrate that behind the resilient process of scientific research lies the complex entanglement of culture, nature, and the artificial, which can also be summarized as the dynamics of research practice as a cultural legacy from the past.

Analytical Perspectives

In the history of technology studies, the emergence of a particular type of technology has been focused on its social construction (Pinch and Bijker, 1987; Bijker, 1995), within such layers as niche, technological regime, and landscape (Rip and Kemp, 1998; Geels and Smit, 2000) wherein the transitory dynamics of technology have been closely tracked (Geels, 2002; Geels and Schot, 2007). Similar attention has been paid to the expansion of mainstream scientific research themes: their laboratory settings (Latour and Woolgar, 1979; Collins, 1985; Lynch, 1985), inter-laboratory collectivity in terms of the research bandwagon (Fujimura, 1996), and the larger formation of such cases as biomedical platforms (Keating and Cambrosio, 2003).

Notwithstanding their pivotal importance, these can easily fall into a quasi-Whiggish historiography unless caution is taken to go beyond a narrow focus on what is new and emerging, to pay adequate attention to everything that might be affected by such processes of innovation. Geels and Smit's (2000) analysis of the predicted impact of information and communication technology on traffic and transportation can be such a caution. They reveal that analysts' pitfall has been in their tendency to understand new technology in existing technological contexts (e.g. the telephone may be seen as a new form of telegram or of radio), which has produced mistaken predictions that new technologies would always replace old ones in a straightforward manner.

Among researchers into these previous trends thus far, Edgerton is notable for his unrelenting attack on the existing predilection for what he calls 'technology-in-innovation', the emerging phase of technology, at the expense of attending to 'technology-in-use', which is widely spread and used everywhere but often considered 'as out-of-date, obsolete, and merely persisting' (1999, p. 112). His '10 eclectic theses on the predilection of innovation over use' addresses such pivotal topics as the neglect of the diffusion phase, disregard of maintenance and repair, and the reappraisal of technology determinism as a matter of technology-in-use (Edgerton, 1999).

Thus, Bijker is criticized for his limited attention to the diffusion stage of his preferred objects (Edgerton 1999, p. 115) and Hughes for generally identifying technology with innovation (p. 114; also n. 11). Edgerton (2006) subsequently explores the alternative version of the history of technology-in-use, enumerating various items from condoms to horse use to slaughter houses and covering a wide range of cases, including some from the third world.

A cognate attempt can be seen in Hommels' (2005a, 2005b) elaboration of the concept of 'obduracy', which is the resistance of urban technology to sociotechnical change. Her approach differs from Edgerton's in emphasizing the various, if distributed, concerns with obduracy already existing in STS, classifying them into three types of understanding: mentalist freeze of 'frame', 'embeddedness'

within the larger sociotechnical network, and 'persisting tradition' that involves wider elements like culture.

Thus, there has been a growing concern with the 'shadowy side' of technology that is old and inconspicuous, yet widespread and embedded in our everyday landscape. A problem emerges when we try to translate this concern to the realms of scientific research addressed in this article. One obvious difference between these two realms is that whereas the very embeddedness of these technological objects in our life legitimizes the claims of these scholars, scientific research demands constant production of new data and new understanding so that Edgerton's emphasis on the 'old' may appear simply inadequate. In fact, despite his attempt to expand his approach to the realm of research, his criticism is limited to 'the distinct silence on employment in other forms of work, such as teaching, routine testing, management, maintenance and so on' (1999, p. 125); he fails to demonstrate how his contrast of two types of technologies can be convincingly translated into the research process. Meanwhile, Hommels' (2005a, n. 1) concern is confined to technology studies without reference to the research process at all.

This difficulty in translation is further illuminated when we examine Rheinberger's (1997) ingenious description of research processes in terms of experimental systems, wherein research is described as a continuously transient process where the subject—epistemic things—oscillates between presence and absence, likened to Derrida's concept of *trace*, which shows the transient nature of signs. Such a formulation of research process may seem to preclude any possibility of theoretical dialog between the two different concerns discussed above.

However, Rheinberger's formulation is not without problems: his focus is too confined to the level of practices in a single laboratory level without attending to the dynamism of the wider collectivity regarding both research themes and institutional background. In fact, if the concept of epistemic thing is extended to wider research themes and practices, one segment of such a topic may wither as others are vitalized to keep the topic alive as a whole. Even Rheinberger (1997) himself admits that there is a dynamic interaction between epistemic things and research technology (cf. Clarke and Fujimura, 1992; Joerges and Shinn, 2001), meaning that research objects may become particular tools for further research, and vice versa (cf. Miettinen, 1998).

This consideration demonstrates that even the most radical formulation of innovation-oriented scientific research still has some room to dialog with the preceding authors' arguments: once the research process is defined at the level of research themes and institutions, the dynamism of a particular research line should be scrutinized at that level. For instance, a certain line of research in the topic may shift from epistemic things to providing research tools, whereas others may adopt such new tools to cultivate new epistemic things, and the research dynamism as a whole may be reconstituted. Considering this enlarged definition of the research process, arguments concerning the neglected side of technological development may have counterparts relating to the research process.

Hence, I propose a new concept: 'resilience' in scientific research. Resilience, rebounding, or springing back, derives from the Latin verb *resilire*, to recoil (Oxford English Dictionary online). Academically speaking, this term was used in a longitudinal study in the Kauai Islands in Hawaii in the 1970s in child psychology, concerning how high risk events in life—such as poverty, parents' mental problems, and divorce—may affect children's mentality (Werner and Smith, 1982; Nihei, 2014). Despite such hardships, this study revealed that some children can overcome such adverse situations and grow healthily; 'resilience' was the term used to describe the source of this toughness. For analyzing the causes of such development, Masten *et al*. (1990) summarize four main factors affecting resilience in a child: a positive relationship with a competent adult, being good learners and problem-solvers, engagement with others, and having areas of competence and perceived efficacy from which they derive their value.

At present, the concept has been applied to many venues, such as psychotherapy (Short *et al*., 2005), ecology (Zolli and Healy, 2013), management (Cooper and Flint-Taylor, 2013), and sociotechnical systems (Reason, 2008; Hommels *et al*., 2014). The shared concern among them is how a complex system, whatever it may be, deals with the challenges of its environment and recovers from damage. Thus, Zolli and Healy (2013, p. 13) argue that resilience is different from robustness, redundancy, and recovery because resilience focuses upon the dynamic process of reconstruction in a system; 'resilience also does not always equate with the *recovery* of a system to its initial state' (p. 13; italic in original). In other words, a resilient system has both fragility vis-à-vis its environment and tenacity in its core value and purpose (Zolli and Healy, 2013, chap. 9). Resilience should also be distinguished from obduracy or the resistance of urban technology to sociocultural change (Hommels, 2005a, 2005b), as the former implies the dynamic of transforming and bouncing back, whereas the latter does not.

This delineation of resilience applies to its definition in scientific research. In this article, resilience is applied to the capacity of a particular research topic to bounce back from an adverse situation—definable as an ensemble of mutually related elements, such as a loss of credibility; an inability to produce (industrial) results, with the ensuing difficulty of institutional reproduction; or challenges from rival technoscientific advancement.

Though resilience is familiar as a concept, sub-frameworks must still be developed for analysis because resilience is applicable to extremely diverse fields, from child psychology to environmental studies. Through an empirical analysis of microbial NP research in Japan, four major elements have emerged as pivotal sub-frameworks.

The first element is institutional preconditions. Resilience in research is less concerned with individual tenacity than with a certain level of institutional establishment in terms of research topics, disciplines, society, or even departments in higher education (Cambrosio & Keating, 1983; Lenoir, 1997; cf. Bourdieu and

Passeron, 1970). Without such a base, rebounding is not definable because of the lack of established parameters; thus, this notion applies more to the dynamism of an established topic than to its early stages through maturation (cf. Geels and Schot, 2007).

The second element is the nature of challenges from adversaries. Unlike famine or abuse in child psychology, it is emerging rival practices in research that challenge the *raison d'etre* of an existing research topic. Here, the challenge can be divided into dual phases: namely, the actual emerging of embodied practices and apparatus, and its discursive aspects which are studied according to the sociology of expectation (Van Lente, 1993; Brown *et al*., 2000; Berube, 2006; Borup *et al*., 2006; Milne, 2012), here as the semiotic labeling of the traditional way as 'old and obsolete', emphasizing the sharp discontinuity between them.

The third element is re-workable resourcefulness against an adverse situation. As resilience is not the mere restoration of the initial condition but the process of constant reconstruction (Zolli & Healy, 2013), rebounding should be enabled by the resourceful complexity afforded by various layers of effort. First, the original value of the research topic is symbolically reevaluated vis-à-vis the attack from its rivals. Technical elements are also adapted from the rivals, corresponding with the dual phases of the rivals' challenges.

Rebranding and/or shifts in emphasis of its content may also occur: for example, in nanotechnology, where traditional technosciences not exactly headed for nano-scale, the terminology is still applied to various phenomena in order to join the research-policy bandwagon (Mody, 2011; Gelfert, 2012). This rebranding strategy may be accompanied with a subtle shift in emphasis from research objects to research tools, as discussed above (Clarke and Fujimura, 1992; Rheinberger, 1997; Joerges and Shinn, 2001). This shift is intended to generate a new niche for the original research to survive. It may result in uneven resilience, implied by its theoretical connotation as constant reconstruction. In the case presented here, the diversity of institutional support for the research has resulted in different levels of resilience because of variances in institutional time and resources afforded to the research.

The fourth element is attachment to core values. This concept includes two aspects: (1) the inherited character of the actual research practices accompanied by the form of organizations from the past and (2) its symbolic/discursive aspects represented by the researchers' *emic* view of their practices. 'Cultural-icon status' is a factor because practitioners emphasize distinctive aspects in their practice, making them into a cultural icon, accompanied by a heightened sense of 'tradition'. Tradition itself is sometimes controversial—between its inherited, dialogical character (Eliot, 1950; Gadamer, 1975) and its invented, even politically manipulated, nature by particular social groups (Hobsbawm and Ranger, 1983; Clifford, 1988); in this article, both aspects are equally beneficial for understanding how certain research practices can be elevated as icons through resilience processes.

Though these four elements are drawn from an empirical examination of the following case, these criteria may be applied to wider cases beyond the present concern, a possibility briefly examined at the end of the paper.

Research Method

This project began with my ethnographic research into RIKEN's antibiotic laboratory, starting in 2007, wherein I intended to observe the relationship between intra-laboratory activities and extra-laboratory practices in one of the most influential national research institutes. However, a new issue emerged to become the topic of this article: In the face of a difficult situation, how do researchers make the effort to revitalize their traditional line of research by adopting new methods but keeping its original identity? My research, then, was extended both to the historical and institutional dynamism of this topic, and to the wider disciplinary background that involves agrotechnical chemistry. Additional retrospective interviews were conducted involving NP researchers, various types of biologists and chemists, employees of pharmaceutical companies, and various other officials from approximately 2009 through 2014. In sum, 36 open interviews, including those from the earlier phase, revealed how these practitioners viewed the situation, leading to my formulation of the various aspects of resilience.

In addition, examination of archival materials from journal articles, especially journals from the *Japanese Society of Agrotechnical-Chemistry*, among others, conference reports, and bibliometrical surveys, were helpful in clarifying the historical situations mentioned in the interviews and in highlighting the repeated emphases on the cultural significance of this topic of research, leading to the condition which I call cultural-icon status. These frameworks were then integrated into the concept of resilience, inspired by my decades' long concern with psychotherapy, in which this concept has been taken seriously for a long time.

NP Research: General Outline

Before offering details concerning the four aspects of resilience in NP research, a brief description of NP research methodology is needed. In Japanese slang, both the steps and the researchers are traditionally identified as *mono-tori*—substance (*mono*), taking or taker (*tori*)—symbolizing the rather unsophisticated nuances of the work. The first step involves the search for living sources—such as plants, microbes (mostly *Streptomyces*), fungi, marine organisms, and so forth—and acquiring bioactive secondary metabolites, through either collection or cultivation. The differences in such sources are important for understanding the rather special status of *microbial* NP research in Japan—the main subject of this paper—as each subdivision hinges upon rather different academic genealogies as well as different patterns of institutionalization.

Proven to be bioactive, their chemical structures are determined and often passed on to synthetic chemists eager to synthesize their unique structure. For synthetic chemists, NPs provide a unique and complex chemical structure from nature whose synthesis serves to invent new synthetic methods and mass production of lead compounds. Such synthesis is also useful for NP researchers because of the minuscular quantity of their original samples: the synthetic process provides a new understanding of the details of their favorite samples as well as future commercial exploration.

Institutional Precondition

NP research in general has been rooted in the Japanese university and industry complex, if showing different distributions and strengths among different subdivisions of the research. Research into plants has been conducted by researchers on traditional herbal medicines, often in the department of pharmacology (cf. Kim, 2007, similar to those in Japan). According to microbial researchers, their own method has been more progressive as microbes are easily propagated. Research on marine organisms, gaining currency in recent years, has also been limited mostly to those in basic science departments, partly because the more lucrative microbial research is dominated by other departments as well as industries (Interview, NP researcher 1, 31 July 2008; NP researcher 2, 5 June 2012).

In contrast, microbial NP research has had far stronger underpinnings in both academia and industry, as it has been intentionally supported by government industrial policy. Within academia, departments of agriculture have been the basis for this line of research. Unlike the traditional university system in Europe, in Japan both agricultural science and engineering have had a legitimate status within the emerging university system of the 1880s. The high status granted to engineering and agricultural science even made it possible for presidents of imperial universities to be from these areas (Okamoto, 2011).

In departments of agriculture, a core discipline is the so-called agrotechnical chemistry (*nôgei-kagaku*), a unique discipline without a precise counterpart in the west. German *Agrikulturalchemie*, following the tradition of Justus von Liebig, was first introduced as early as the 1880s, largely for the purpose of analyzing fertilizers and the chemical aspects of soil. However, when Umetaro Suzuki, the discoverer of orizanin—later identified as vitamin B1—established its society in 1924, the subject of research had already been rapidly expanded beyond the constraints of German agricultural chemistry to such areas as agrochemicals, nutrition, food, fermentation, and later antibiotics, where microbial NP research was also situated (Sakaguchi, 1974; JSBBA, 1987). At present the society boasts more than 10,000 members, close to the size of the molecular biology society.[1]

Since its early days, agrotechnical chemistry has promoted the fusion of chemistry and biology. This background would later provide powerful resources for

microbial NP researchers in redefining their identity in the global context of emerging chemical biology. This fusion also facilitated the deep rooting of its graduates in the Japanese drug industry, on par with those from departments of pharmacology (Interview, NP researcher 2, 23 June 2009). Akira Endo, mentioned above as the discoverer of statin, is a typical case as one of these graduates at a leading pharma in Japan. Suzuki, founder of its society, was also the founding figure of microbial NP research in RIKEN, whose genealogy up to the present laboratory (Antibiotic Laboratory, 2014) will be discussed later.

In addition, industrial policy elevated the very status of microbial NP research in this academia–industry complex vis-à-vis other branches of NP research. Soon after Florey and Chain succeeded in purifying penicillin in 1942, the Japanese government quickly mobilized their own research, and Japan became the first country to produce antibiotics on its own outside of the west (Umezawa, 1987). This policy momentum encouraged the development of microbial NP research in both academia and industry, unlike in the USA where applied microbiology research has been largely confined to industry (Interview, NP researcher 2, 21 April 2012.)

Thus by the 1960s, there were four powerful centers of such microbial NP research, all in Tokyo: The Institute of Applied Microbiology at the University of Tokyo, established in 1953; The Institute of Microbial Chemistry, established in 1958 and funded by patent revenue from the drug Kanamycin as discovered by Dr Hamao Umesawa; The Kitasato Institute, established in 1914;[2] and RIKEN, which is the fourth generation of a powerful antibiotic laboratory (Interview, NP researcher 2, 2 December 2008; Antibiotic Laboratory, 2014). These centers are eloquent witnesses to the powerful entanglement of research, industry, and national policy with regard to microbial NP research, though less visible in other branches of NP research.

The Two Faces of Rivals

The institutional background of microbial NP research, however, does not mean that its status was guaranteed. In summarizing how it has waxed and waned over time, researchers point to a decisive moment that the direction changed. It was the third international conference of NP chemistry in Kyoto in 1964—part of the International Union of Pure and Applied Chemistry (IUPAC)—that represented their zenith of attainment in this field (Takahashi, 1984; Suzuki, 1987). However, it was also a time for growing concern about the coming crisis of the existing method, as the advent of new instruments, such as high-performance liquid chromatography and nuclear magnetic resonance spectroscopy, might make the older way of structural determination, pivotal in the 1960s, obsolete. (Suzuki, 1987, p. 81; Morris, 2002). A similar concern was expressed about the possible exhaustion of antibiotics (Arima *et al.*, 1965). The issue of a similar or already known substance—*zoro* in Japanese pharmaceutical slang,

from *zoro-zoro*, an onomatopoeic expression showing movement in succession—was becoming worrisome.

Two points should be made about this period. First, the emphasis shifted from the race for structural determination—such as that of *tetrodotoxin*, the poison of swell-fish, which was one of the highlights of the conference mentioned above—to a trend toward a more fine-tuned concern about the relation between the structure of the metabolites and their actual biological function. Actually, this trend was positively promoted by the new instruments mentioned above, which enabled a minute examination of the biological dynamics, impossible in the 1960s (Takahashi, 1984; Suzuki, 1987).

Second, the realm of antibiotics was extended to new fields like cancer, as represented by Hamao Umezawa's successful career. He discovered the first Japanese antibiotic, Kanamycin, in 1956, and the powerful anti-cancer antibiotic, Bleomycin, in 1963, both from Streptomyces. He later collaborated with the National Cancer Institute (NCI) in their global search for anti-cancer substances in the 1970s (Maruyama, 1978; Umezawa, 1987; Parry, 2004; Keating and Cambrosio, 2012). His success prompted the International Society of Chemotherapy to found the Hamao Umezawa Memorial Award, its highest prize, commemorating his achievement in 1986.[3]

Compared to this early transitional phase, the challenges in the 1990s were more fundamental, for several reasons. One such challenge was presented when combinatorial chemistry, or *combichem*, was proposed as a radical new way of rapid synthesis by combining elementary chemical structures to produce large amounts of new and varied compounds. This method was accompanied with high-throughput screening technology to discover appropriate drug candidates (Patel and Gordon, 1996; Maehr, 1997).

Huge expectations were raised for the coming revolution in the drug discovery pipeline: 'numerous emerging new drug targets with huge numbers of potential ligands should increase the rate at which new leads are found and ultimately promote the efficiency of drug discovery' (Patel and Gordon, 1996, p. 143). Parry (2004) conveys an atmosphere of its early days when she says that the method could synthesize the existing chemical structures of '*all possible* combinations' (2004, p. 161; my emphasis). Barry (2005), in sketching a medium-sized drug company, ArQule, adds theoretical paraphernalia such as 'chemical space', the distribution of types of various molecules, and 'library', a collection of mass-synthesized molecules.

In contrast, NP research had the lingering problem of difficulty in making theoretical predictions, the opposite of what Fujimura (1996) calls 'doable' research based upon 'the standardized package of theory and method' in cancer research—the theory of proto-oncogene and the recombinant gene technology—which facilitated predictability for researchers in doing their jobs. In fact, NP research is somewhat serendipity based—very much *undoable*—so that

researchers often complain that it is not suitable for graduate students because they might not finish their work by graduation (Interview, NP researcher 2, 21 April 2012).

Combichem also 'promised' to provide a solution to the problem of *zoros*, the already known substances referred to above. A senior informant from a drug company noted that the new substances reported by researchers in academic meetings often turned out to be simply *zoros* in the 1980s (Interview, 6 June 2012). In fact, despite the long perceived problem of *zoros*, there had not been any alternatives until combichem emerged as a radical solution. In addition, biologics, based on proteins and peptides in the form of antibodies, was also a threat, having shown increasing success, from insulin for diabetes to the rise of cancer drugs, such as herceptin and rituximab (Goozner, 2004; Shook, 2007). These were expected to be on a fast track for approval by regulatory agencies because of their improved effectiveness (Bartfai and Lees, 2006; Rydzewski, 2008).

Thus, the challenges take two forms: (1) the actual technologies and (2) the semiotic construction of the binary opposition between the new and the obsolete: combichem contrasted the rational, mass-produced, more scientific method with the undoable, unsystematic, and largely hit-and-miss kind of NP research. Biologics boasted its target specificity compared to the side-effects produced by the conventional chemical molecules, including NP-based drugs.

The effect of such an adverse environment on microbial NP research was first observed in the reaction of drug companies. Starting in the mid-1980s, a number of leading pharmaceutical companies in and out of Japan made collective moves to abolish their departments of fermentation to redistribute staff to other sections (Interview, drug company staff 2, 2 March 2012; staff 3, 15 March 2012).[4] According to a senior NP researcher, the magnitude of the issue became evident when Bristol-Myers, an American drug company famous for successfully deriving drug candidates from microbes, decided to close its research center in Tokyo and fired more than 100 researchers in the early 1990s (Interview, NP researcher 2, 2 December 2008).[5]

The impact spread to academia. Among the four centers of microbial NP research, the Institute of Applied Microbiology at the University of Tokyo changed its name to the Institute of Molecular and Cellular Biosciences in 1992, eliminating its microbial orientation, while Kitasato Institute also changed its direction from traditional microbial research in 2001. In RIKEN, in the fourth generation of an antibiotic laboratory, Osada himself considered abolishing the concept of antibiotics from his laboratory established in 1994, following world trends; he then reduced the original *mono-tori* (collecting substances) practice and searched for a new direction in cancer research (Interview, 8 August 2007).

Showing Resilience through Resourceful Complexity

Despite such adversity, the challenges being visible both in terms of devaluating arguments concerning the research and the resulting institutional reorganization in both academia and industry, microbial NP researchers have shown resilience in using various strategies to deal with these challenges. As noted earlier, this resilience can be analyzed in four aspects, which are explored in the following sections.

Symbolic Reinterpretation of NPs' Value

Just as the sociology of expectation exhibits the examples of the bursting hypes (cf. van Lente, 1993; Berube, 2006; Borup *et al*., 2006), the first trigger for reaffirming the value of NP research was recognition of drawbacks in the combinatorial method (Drews, 2000). Despite the expectation of synthesizing '*all possible*' combinations (Parry, 2004, p. 161, emphasis mine), in reality the products showed poor structural diversity, demonstrated by the limited distribution in the chemical space, in contrast with the larger diversities of both NPs and real drugs (Ortholand and Ganesan, 2004). A recent study of the way statins combine with target proteins corroborates this point: it is less a direct binding than a subtle control over the target, thanks to their exquisitely complex structure (Istvan and Deisenhofer, 2001). A biographer of Endo records a comment of a researcher with a sense of awe: 'If Dr. Endo had not discovered statin, it would have been the realm of God!' (Yamauchi, 2006, p. 229). In fact, no synthesized drug candidates but Endo's MK-236 could combine with the HMG-Co enzyme (Yamauchi, 2006, pp. 229–230).

Barry's (2005) description of ArQule also attests to the failure of this company to produce effective drug candidates, forcing them to change their direction to testing other materials and computer simulations. The sense of disillusion was obvious in a blunt comment from a leading synthetic chemist in RIKEN—that combichem was dead for the purpose of drug discovery (Interview, synthetic chemist by Akira Ueno, 17 December 2008).

This situation prompted the symbolic reframing of the 'naturalness' of NP research. The capacity of combichem for producing an infinite variation of chemical structures by 'artificial' methods had been advocated as an advantage. However, the defenders of NP research now regard this artificiality as more a defect than an advantage, because their 'natural' products appear to be embedded in the evolutionary process (Bérdy, 2012) if their real meaning is still being argued (Davies, 2013). Thus, the complex structure of NPs, once considered an obstacle for more rationalized mass production, is now re-framed as a valuable source for druggability in its structural diversity (Interview, NP researcher 3, 8 March 2012).

In contrast with the shrinking hype on combichem, biologics have remained viable, still appearing to offer various promises. Yet, some critical voices

comment on its possible drawbacks. First, because they cannot be administered orally, they may be inconvenient for patients. Second, their targets are rather limited, like various types of cancer, as their molecular sizes are too big (Rydzewski, 2008). Third, their high price compared to their limited use may pose a serious threat to the world's existing health systems (Angell, 2004; Goozner, 2004). Thus, despite the ongoing momentum of biologics, some NP researchers tend to think that there still are some advantages in renewing the pursuit of traditional methods (Ortholand and Ganesan, 2004; Newman and Cragg, 2007; Bhuwan *et al*., 2011) (Interview, Hiroyuki Osada, 18 August 2009).

However, symbolic reframing is not enough for achieving true resilience, as the earlier weaknesses are not fully overcome at this point, and resilience involves constant re-adaptation to keep its identity (Zolli and Healy, 2013).

Technical Adaptation/Appropriation

Thus, assimilating the advantages of rivals is essential for true resilience in NP research. I will focus mostly on two cases of such technical appropriation though some other means were mentioned in the interviews, such as extending the global search for the new NPs. In searching for new plants and marine substances, such a global hunt by researchers, drug companies, and national institutes (like the NP Depository in NCI) is active and well-documented (cf. Hayden, 2003; Parry, 2004; McChesney *et al*., 2007).

However, the microbial NP researchers that I interviewed showed less concern about this method. Researchers indicated that unfamiliar microbes collected in exotic circumstances do not necessarily guarantee production of new bioactive metabolites, like their predecessors' efforts in China and elsewhere (Antibiotic Laboratory, 2014); besides, increasing problems involve biopiracy and indigenous patent rights (Brush and Stabinsky, 1996; Hayden, 2003) (interview, NP researcher 2, 2 December 2008; NP researcher 3, 13 January 2009). Of the 1,530 presentations given in the Annual Symposium of NP Chemistry over the past 10 years, only 24 were related to research abroad—none involving microbes.[6] As one NP researcher observed, 'In short, streptomyces are streptomyces, even if they originate from jungles or the deep sea' (Interview, NP researcher 3, 8 March 2012).

A related topic that emerged in the interviews is the so-called metagenomic research on microbes. Microbiologists in general are aware that the number of culturable microbes may be less than 1% of those existing in the soil, because the majority of them cannot survive without the support of the microbial network. Thus, the idea is to culture those unculturables by collecting and even synthesizing the fragments of genetic information found in soil (Handelsman *et al*., 1998; Chen and Pachter, 2005).

A report by the American National Academy on the bright prospects of this direction of research (Committee on Metagenomics, 2007) demonstrates the

momentum of such comprehensive microbial research, as well as the launch of the Earth Microbiome Project in 2010, for making the genetic atlas of microbiomes in the whole planet (Gerwin, 2012). However, among the mainstream NP researchers that I have observed, adoption of this approach is largely confined to those related to marine organisms where the microbes—cohabiting with these organisms—are hard to culture (Uemura, 2008 *inter alia*) (Interview, NP researcher 4, 3 November 2009; NP researcher 3, 8 March 2012). In fact, only two presentations on the metagenomic approach, both on marine organisms, out of 52 presentations on biosynthesis have been offered over the past 10 years in the abovementioned Annual Symposium. Aside from the underdevelopment of Japanese bioinformatics related to this topic (CRDS, 2013, pp. 274–278), NP researchers' concern is more directed to the actual metabolites of these microbes, rather than simply mapping their genetic codes and reclassifying their genealogy.

Thus, the more attended program has been biosynthesis, the molecular process of producing metabolites in a particular microbe, as observable in such organizations as The Fermentation and Metabolism Study Group of Japan Bioindustry Association (JBA) in Tokyo in 2013, where five out of six presentations were concerned with manipulating the genes of Streptomyces (fieldnote, 11 September 2013). In fact, drug specialists emphasize the malleability of bioactivity in accordance with the slightest change in its partial structure. The idea of research on biosynthesis is for the purpose of letting microbes produce more metabolites by activating dormant genes (NP researcher 5, 21 December 2007). The Osada Laboratory, among others, has taken the initiative in this line of research, focusing on a type of Streptomyces that produces growth inhibitors of osteoporosis.

This effort is not without obstacles. The older generation of NP researchers must be retrained to master the bioengineering technique. Some of them were actually sent to other labs specializing in those techniques (Interview, NP researcher 1 by Akira Ueno, 30 October 2007). In addition, such microbes as Streptomyces are far less standardized than the ordinary model animals such as *E. coli.* and even inserting a segment of genes can be very difficult—another case of an *undoable* job (Fujimura, 1996)—as the initial procedure took more than a year in the laboratory. These obstacles are one of the sources of the differing degrees of resilience between academic laboratories and those in industry.

Another case of technical adaptation is the use of a public NP library, accompanied by a high-throughput screening system, drawn from combichem to recycle already known substances. This move has corresponded with policy gestures for encouraging academia to participate in the drug discovery pipeline (Dalrymple *et al*., 2006; Fukushima, 2013), despite the fact that the Japanese pharmas preferred in-house drug discovery in the early 2000s (Kneller, 2003). The situation has been radically changing in a collective move to 'open innovation' and outsourcing at present (Iwaki, 2008; Fujita, 2013).

The Osada Laboratory has been directed to establish a Natural Products Depository (NPDepo), largely for academic use (Fukushima, 2013), while the Institute of

Advanced Science and Technology (AIST) has also developed the largest NP library in Japan, though confined to corporate members (Interview, NP researcher 3, 8 March 2012). The library efforts are accompanied by new technologies, such as a compound's array of high-throughput examinations of ligand–protein interaction, as well as various assay systems to speed up the examination of the bioactivity of the mass of candidate compounds, the majority of which are NPs.

Rebranding: Shifting Emphasis

Efforts to appropriate rivals' technologies are not merely for producing more drug candidates, however. The other dimension of their strategy is similarly important for understanding resilience in research, namely, rebranding original research by shifting the emphasis from research objects to research tools; here emerging chemical biology is the target of such a move, initially advocated by Stuart Schreiber, a graduate from synthetic chemist R.B. Woodward's laboratory in Harvard (Schreiber, 2004). Schreiber became known by determining pathways from the cell surface to the nucleus in relation to the powerful immunosuppressant FK506 (Schreiber and Crabtree, 1992), which was discovered by Japanese microbial NP researcher Toshio Goto (Yamashita, 2013), now the leader of RIKEN's drug discovery scheme. Since then, Schreiber and his colleagues were actively advocating this new trend of biology (Hopkin, 2004). Various communities of Japanese researchers, in and out of the NP circles, have boarded this bandwagon by re-contextualizing their own research. The outcome of this co-optation is manifest in the Japanese Society of Chemical Biology, established in 2007 as a global pioneer (Fukushima, 2013).

In this renewed context, NP molecules are redefined also as new biological tools: bioprobes (Osada, 2000). Interestingly, such ambivalence—NP compounds as both research objects and research tools—can be seen in chemical biology itself, in the dispute on whether it is headed for basic research or drug discovery (Hopkin, 2004). In any case, this shift of emphasis is essential if NP research is to be resilient, to create room for searching for new possibilities, and in the face of practical difficulty in coping with declining productivity in finding drug candidates.

Uneven Distribution of Resilience

This variety of strategies, however, has not been employed evenly within the academic and industrial complex that has supported this topic of research. Such differences were visibly demonstrated in the meeting of the Bioindustry Association mentioned earlier. After presentations of cutting-edge research from academic researchers, the last presenter from a leading Japanese pharma ironically explained why his company had finally decided to close its fermentation department while admitting the renewed possibility of NP-based drug discovery. The

presenter concluded that the prolonged times and increasing costs of this line of pursuit would not allow the company to continue (fieldnote, 11 September 2013). In short, industry cannot afford the two-front academic strategy—that is, shifting the focus to basic research while simultaneously pursuing the possibility of new drug candidates by new methods in the *longer* term. This difference allows academic researchers to be more resilient than their industry counterparts.

Attachment: Cultural-icon Status

Behind the efforts described above, wider claims have been also made on the very values of NP research itself, which I term 'cultural-icon status' in its crystallized form. Cultural-icon status can manifest in various forms, such as inter-cultural comparison of NP research practices and the very cultural meaning of microbial NP research or even chemical biology. Regarding the former aspect, a young researcher who spent three years in the NP Depository in the NCI in the USA reported on the various differences that impressed him between the USA and Japan, such as the NCI's systematic effort to collect NP samples on a global scale (cf. Parry, 2004) and the rigid division of labor in the USA. He narrated his shock, however, upon observing the rough-and-ready way researchers in the Depository dealt with NP samples, which he believes quite inadequate, considering the miniscule quantity of such extracts.

> We isolate the elements [by using HPLC] to put fractions into test-tubes, and transfer it to vials to weigh, then check density to examine the bioactivity. The way the American researchers put them in volumetric flasks to coordinate density was so rough: after using it, they put methanol or something to wash them and throw away what is left there. This is unbelievable for us, because then we'll surely lose what we are looking for. What we ordinarily do is after washing the flask meticulously, then take the content to the vial by using a Pasteur pipette very carefully, then wash the flask again to avoid any remainder . . . . (Interview, 29 January 2009)

An emphasis on the cultural differences concerning meticulousness in NP research is also seen in Endo's (2007) re-appraisal of NP research, wherein he expresses his own cultural theory of research. He describes the undoable character of NP research as *dorokusai* (unrefined: literally 'muddy' from *doro*, mud), underscoring his observation that such random search is not appreciated in Western science, wherein he believes theoretical projection and systematic research are more respected.

However, exactly because of this contrast, he claims that Japanese scholars should adhere to this *dorokusai* method—by which they may yet prevail against systematic exploration accompanied by high-throughput research technology—because it is exactly such an unrefined effort that led to his discovery of the

blockbuster statin.[7] Osada's recent emphasis on the limits of the high-throughput method, which he now believes may risk distracting researchers' attention from the detail of individual samples, can be interpreted as a call for returning to the traditional *dorokusai* method (Interview, 28 August 2014).

Another element—namely, the institutional embeddedness of microbial research in academia, industry, and national policy—is worth scrutinizing in terms of cultural-icon status. We may note first that microbial NP research has been embedded in departments of agriculture and agrotechnical chemistry. The latter's own history of institutional resilience cannot be detailed here; it suffices to note that the hybrid character of research pursued in this background facilitated the identification of chemical biology with its own research tradition, exemplified by the *Kagaku To Seibutsu* [Chemistry and Biology] journal published since the 1980s (Yoshida, 1994). In addition, the idea of studying life by using small molecules in chemical biology was nothing new as some NP researchers in Japan had already advocated a similar idea in the 1980s in books like *Dynamic Natural Products Research* (Goto, 1983). Hence, a historical figure like Umetaro Suzuki is even identified as one of the founding fathers of 'chemical biology' itself in Japan (Osada, 2006) long before the term was coined in the USA, in a manner not unlike 'the invention of tradition' (Hobsbawm and Ranger, 1983).

An echo of nationalism can even be observed in a reference to NP research as one of the 'fortes' in the Japanese history of both science and industry (Inamura *et al*., 2007), which should be understood in light of the historical entanglement of this research with both industry and national policy. In fact, iconic discourses are often observed from eminent leaders—like Endo or Osada above—who can influence industry and even bureaucracy to a certain degree. Hence the political nuance of the term *dentô* (tradition) is more visible, than, say, Hommels' reference to the persisting 'tradition' in urban technology (Hommels, 2005a, 2005b).

However, the political nuances of cultural-icon status should not be overemphasized, as the phenomenon has grassroots resources—namely, researchers' experiences of actual cultural differences in scientific practice, usually between the two sides of the Pacific Ocean—which may serve as a hotbed for fostering such discourse. The excerpt from the interview above is a concrete example but is only the tip of the iceberg in terms of existing discourse about cultural differences in research, not confined to NP research. Thus, while manifest cultural-icon status may partially originate from the leaders' level, it is likely enabled by a vaguely shared recognition of cultural distinctiveness among researchers in general.

Conclusion

The central question of this paper has been how scientific research can bounce back after challenges from emerging rival research, examined in the specific context of microbial NP research in Japan. For a better understanding of this process, I have proposed the concept of resilience in scientific research to describe

the system's dynamics in responding to the challenges of the environment. Four elements were tentatively highlighted for analyzing the dynamism of NP research. First is the institutional precondition of this resilience, rising from the deep rootedness of microbial NP research in an institutional complex that includes academia, drug companies, and national policies related to antibiotics and drug discovery at large. Second, despite such rootedness, an attack from rival innovations from both combichem and biologics has posed serious challenges because they provided alternatives to the intrinsic weaknesses of NP research, accompanied by the coming of age of a more rationalized drug pipeline. Third, NP research has responded by showing resilience in the following ways: (1) by reevaluating the meaning of the naturalness of NP as legitimized by evolution as opposed to artificial compounds; (2) by adopting various technical elements from its rivals, such as the genetic engineering of microbes in biosynthetic research and a library of NP compounds with a high-throughput system; (3) by re-contextualizing itself in emerging chemical biology, shifting its emphasis from a practical pursuit of drug candidates to biological research using bioprobes; and (4) which resulted in an uneven degree of resilience between academia and industry. These strategies are backed up by the fourth element, namely the cultural-icon status of research, manifest in the research traditions in Japan and often contrasted with traditions on the other side of the Pacific Ocean.

These four elements for analyzing the itinerary of microbial NP research do not exclude the possibility of extending the resilience concept to other cases. A number of studies on similar dynamics in the life sciences present intriguing cases for comparison. For instance, Shostak (2005) discusses the case of traditional toxicology as confronted by molecular biology, resulting in producing toxicogenomics, a hybrid discipline characterized by pragmatic theoretical translation between these two. Hine (2008) analyzes how traditional biological systematics has been redefined as a sort of cyber science in the face of emerging computer science, with all the difficulties and contractions within. Sommerlund's (2006) case of the molecularization of microbial ecology is a dramatic example wherein resilience may take the form of the odd co-existence of the traditional naturalist paradigm and that of molecular biology.

In these case studies, two of the elements, institutional precondition and technical appropriation, can be clearly detected as close parallels. In terms of the academic versus industrial aspect, as well as that of cultural-icon status, some differences may arise. For example, because microbial NP research has manifested in both academia and industry, a 'rebranding and shifting of emphasis' from the industrial pursuit of drug candidates to a more research-oriented definition of their practices has been able to buy time and space for its survival. The other cases noted above, however, are more confined to academia, which may decrease their capacity for resilience because of limited options for reconstruction.

Another point is the issue of cultural-icon status. In fact, although researchers may be deeply attached to their pet research subjects in these cases above, the general cultural conclusions drawn here may not apply. I have discussed the influence of the complex covering academia, industry, and national policy, further afforded by the grassroots perception of cultural differences of scientific practices. Future comparisons would need to be done to see if cultural-icon status is a factor in these specific cases, which may not have such a background.

Nonetheless, in conclusion, the concept of resilience in scientific research has further advantages. First, it allows for comparability between the dynamics of the shadowy part of technology, namely technology-in-use (Edgerton) or obduracy (Hommels), with the dynamics in scientific research at large, while admitting the latter's transient character in requiring constant innovation. This comparability is also expected to prompt a reexamination of the assumptions in the earlier discussion of technology here.

The second advantage is that this concept enables us to situate the issue in a wider field involving subjects from ecology to management to address the general question about the way how any system—whatever its definition is—may bounce back against adverse situations by changing its structure and keeping its sense of identity. This will surely provide a renewed perspective about technoscientific dynamics at large for re-interpretation from the wider perspective beyond its conventional confines.

Finally, this concept prompts renewed dialog between science and technology studies and the humanities in terms of 'tradition' if we acknowledge the lasting disputes on its nature as inherited or invented (Eliot, 1950; Gadamer, 1975; Hobsbawm and Ranger, 1983; Clifford, 1988). The visible difference between the scientific and the humanities focus is that the former is not confined to text, language, or ritual, but is extended to nonhuman entities—here, microbes, funges, and *Streptomyces*—which admirably produce useful metabolites for us that occasionally save our lives; these provide the occasion for a conversation between past and present, similar to great literary works or solemn religious practices.

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Notes

[1]Available at http://www.jsbba.or.jp/about/about_name.html (accessed, 14 December 2009).
[2]The Institute of Applied Microbiology at http://www.iam.u-tokyo.ac.jp/index.html. The Institute of Microbial Chemistry at http://www.bikaken.or.jp/english/. The Kitasato Institute at http://www.kitasato-u.ac.jp/lisci/life/ (all accessed, 14 December 2009).
[3]Available at http://www.ischemo.org/index.php/awards/hamao (accessed, 14 December 2009).
[4]A leading NP chemist suggested that this hasty move was accelerated by their ignorance of the big pharmas in the west sustaining in-house companies for NP research (interview by Akira Ueno, 26 December 2007).
[5]Available at www.raqualia.co.jp/userfiles/report_20110720.pdf (accessed, 11 September 2014).
[6]Archival data of the Annual Symposium of the NP Chemistry is available at http://www.tennenyuuki.ne.jp/index.php (Accessed, 11 September 2014).
[7]Interestingly, the very term *dorokusai* has been repeatedly used not only for discussing NP chemistry (Fukami, 1976) but also for agrotechnical chemistry at large (Matsuda, 1976) from the viewpoint not much differing from that of Endo's.

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