

## Chronic Disease, New Thinking, and Outlaw Innovation: Patients on the Edge in the Knowledge Commons

*Stephen Flowers*

### INTRODUCTION

The gap between the innovations some people really want and the innovations that can be supplied by the standard practices of mainstream innovators can sometimes be extreme. This gap may result from a variety of factors, including regulation, lack of scientific knowledge, the inflexibility of suppliers, and inadequate market size. Whatever the reasons for its existence, such a gap creates a demand that will not be met within normal channels, creating a space for new thinking and innovative activity outside the mainstream. One documented response to needs that are unmet by market innovators, is “user innovation,” in which users, often banding together in user communities, create their own innovative solutions to their needs. Innovation by users of all types (including patients) is a widespread phenomenon within modern economies (e.g., de Jong and von Hippel 2009; Flowers et al. 2010a; Schaan and Urbach 2009).

Chronic disease is one context in which market innovation fails to meet the needs of users. In this context the unmet demand of patients for a cure, or simply for effective symptom relief, meets a slow and inflexible medical industry that is unable to adequately respond. While industry in all fields often fails to meet the needs of some consumers, the medical context is particularly problematic because of the urgency of patients’ unmet needs along with the fact that innovation is highly regulated. Medical innovations must go through a series of large-scale trials and tests to make sure that they are “safe” to offer for sale. For reasons of public safety, new drugs and therapies are subject to a series of trials, tests, and approvals that often last for many years with the result that the relatively fast diffusion of innovations from users to the mainstream cannot take place.

Stephen Flowers is Professor of Management (Innovation), Kent Business School, University of Kent, Canterbury, Kent, UK.

This regulatory environment, though intended for consumer protection, often creates tensions between the patient – the user of the treatment – and the medical professional, who may be discouraged or forbidden from offering promising experimental therapies that have not gone through the full regulatory process. This tension may be particularly serious in the context of chronic diseases, in which therapies may require a decade or more of research before they can begin the process of regulatory approval, which may itself take many more years.

Confronted with this situation, some patients decide that they simply cannot afford to wait. They determine to sidestep regulated processes, draw on published scientific research, and attempt to create their own therapies. These activist patients engage in what we term “outlaw innovation,” which differs from much of the user innovation studied in prior research in its relationship to mainstream innovation. Newly created knowledge obtained by outlaw innovation is widely shared with other patients, but mainstream medical research is unable to draw upon it. The picture that emerges from our analysis is of a medical research system whose inflexibility means that it is unable to draw on vibrant sources of new knowledge that are being created by activist patients – the users of medical therapies – who have taken their treatment into their own hands.

This chapter explores the implications of outlaw innovation in the context of Crohn’s disease, a chronic form of inflammatory bowel disease, a type of autoimmune disorder. Autoimmune diseases present a particular challenge to medicine as their causes are not fully understood, no cures are currently available, and they are very hard to treat. To explore the rich and complex territory of patient activism, medical innovation, and chronic disease, this chapter draws on a diverse range of medical practitioner, medical research, and innovation literatures.

It begins by exploring existing literature about patient innovation, before going on to examine how innovation in mainstream medical therapy typically proceeds. The chapter goes on to explore some of the scientific research that provides a backdrop for patient innovation for Crohn’s disease: the use of helminths (a form of intestinal parasite) in treating autoimmune diseases. At the core of this chapter is the examination of the research and knowledge creation activities of a small group of activist patients as they work together, forming a knowledge commons, to try to develop an effective treatment for their Crohn’s disease. The part played by such patients in adding to the medical knowledge commons in this area, and the challenge their outlaw innovation poses to the mainstream, is explored in the final part of this chapter.

#### 14.1 PERSPECTIVES ON PATIENTS AS INNOVATORS

The contributions made by patients (as users) in the treatment of disease have been explored across a range of literatures, each with its own preoccupations and framing. The development of the broad discussion has tended to be driven by emergent empirical phenomena, as those afflicted with (often serious) medical conditions

mobilize and deploy a range of resources to improve their diagnosis, treatment, and prognosis. The role of the Internet, and of social media in particular, emerges as an important theme in this literature. The Internet both enables the development of online communities, which create and govern knowledge commons to pool resources and advance the treatment of chronic conditions, and also makes these efforts highly visible.

The first part of this review will draw on conceptual approaches in the innovation studies (IS) and science and technology studies (STS) literatures to better understand the challenges faced by users who wish to innovate on their own account, rather than act as partners to mainstream professional actors. It argues that the conceptual approaches developed within the IS and STS literatures are complementary and throw new light on the evolving phenomenon of patient involvement in health care. To provide a wider context, the review will also draw on the health care practice literature to outline the growing importance of online user communities in the treatment of medical conditions.

#### 14.1.1 *Patient Innovation: Insights from Innovation Studies*

An important thread of innovation studies examines the processes, motivations, and outcomes of “user innovators,” who benefit directly from using the novel things they create and distribute, rather than from selling them. Innovation by users is prevalent when it is aimed at satisfying a local niche, rather than a broader market need (von Hippel 1986). The phenomenon was first noted in the field of scientific instruments by von Hippel (1976) and has since been observed in many other contexts, including medical devices (e.g., Oliveira et al. 2014) and surgical instruments (e.g., Lettl 2007). This large body of work is reviewed by von Hippel (2005) and shows the significant proportions of users who innovate in many diverse fields. The literature also has explored a series of features of user innovation, including horizontal networks (von Hippel 2007), how firms make use of open source (Dahlander and Magnusson 2005) and hacker communities (Flowers 2008), and the role of users as co-developers (Jeppesen and Molin 2003). The observation that many users will freely reveal their innovations has also been explored (von Hippel and von Krogh 2003), as have the voluntary information spillovers that emerge (Harhoff et al. 2003), and the social welfare gains that result from user innovation (Henkel and von Hippel 2004).

User innovation often occurs when users have needs that are not satisfied by the products and services available to them from the market and are able to mobilize the resources required to meet those needs (von Hippel 1986). Users possess extensive local (sticky) information concerning their specific needs, something that is often hard for producers to access (von Hippel 1994). Users who innovate are often “lead users,” whose use is at the leading edge in a given arena and whose innovations thus point the way to the shape of a future market and are a valuable source of ideas for commercial firms (von Hippel 1986). The literature on lead users has been

elaborated over a series of contributions that have refined our understanding of how they may be defined (e.g., von Hippel 1986), their motivations (e.g., Urban and von Hippel 1988), and how the mainstream may seek to collaborate with them (e.g., Lilien et al. 2002). Lead users are of interest to producers because they experience their needs in advance of the typical user and can act as “a need-forecasting laboratory for marketing research” (von Hippel 1986), such that their innovative activity can point the way to future market demand, a key producer concern. User innovation thus is often depicted as synergistic with innovation by mainstream firms. A key assumption of this framing is that producers should be in a position to benefit from the work of lead users, for example, by developing relevant in-house capabilities (e.g., Berthon et al. 2007).

While much user innovation, including much patient innovation (see, e.g., Chapter 13, this volume) is complementary to mainstream commercial innovation, some user innovators, including the patient innovators described in this chapter, consciously set aside mainstream practices, including formal rules and regulations, to free themselves to engage in certain types of innovation (Flowers 2008). These “outlaw users,” whether working alone or in groups, actively oppose or ignore the limitations imposed on them by mainstream practices, setting up parallel, user-led innovation systems that are in tension with the mainstream system. They will generate outlaw innovations differing from those produced by mainstream practices (Flowers 2008). Because the mainstream is either unwilling or unable to work with outlaw users, they are a kind of doppelgänger lead user, with a different kind of relationship to mainstream commercial players than the symbiotic relationship envisioned in much of the user innovation literature. While there is now a considerable literature concerning the interactions between lead users and commercial producers, we understand far less about how producers deal (or could deal) with the challenges of absorbing the outlaw innovations that are developed by outlaw users.

#### 14.1.2 *Patient Knowledge: Insights from Science and Technology Studies*

The science and technology studies literature also offers a series of insights that will be useful in understanding the outlaw innovation explored here. The importance of patient knowledge and experience has been emphasized in this literature and active and informed patient associations (e.g., Barbot 2006) and “concerned groups” (Callon and Rabeharisoa 2003) are viewed as important innovation actors. The role of nonscientists in medical science – be they concerned citizens, patients, caregivers or (in the broadest terms) “users” – is also an important theme in this literature (e.g., Epstein 1996; Wynne 1996). Experimentation with the incorporation (or co-option) of these groups into professional scientific endeavors has led to the emergence of a new form of hybrid science, termed research “in the wild” (Callon and Rabeharisoa 2003). This form of research has been widely explored in the

context of patient organizations focused on chronic disease, and their importance as partners in seeking improved outcomes has been clearly established. This STS literature focuses primarily on ways in which patient knowledge and experience can be drawn upon and valued within the more traditional (and mainstream) system of science involving laboratory and clinical trials. A few STS studies also document that patient groups may move beyond standard approaches and construct new forms of scientific community based on patient experiments and a broader palate of scientific approaches (Barbot 2006). However, there are few accounts of such (potentially outlaw innovation) activity and this form of innovative patient behavior remains largely unexplored.

#### 14.1.3 *Patient Activism: Insights from Practice*

Complementary insights into the phenomenon of medical innovation by patients (as users) may be obtained by drawing on the practice literature in health care. This literature tends to be concerned with reporting and debating developments in medicine and is aimed at (and often written by) medical professionals. One feature that has been widely documented in this literature is the growing importance of online information sources. The practice literature contains many accounts of patients who benefited from advice and guidance found in online patient communities (e.g., deBronkart 2013) or who helped others by creating their own online communities (e.g., Seres 2013). Research has shown that the use of social media within health care is now widespread (e.g., Pew Internet 2010), and a wide range of approaches are employed, including discussion forums, blogs, and social networking (e.g., Hamm et al. 2013). This phenomenon continues to evolve and new forms of “crowd-sourced” clinical research have begun to emerge based on patient involvement in social media (e.g., Swan 2012a, 2012b).

This practice literature has long recognized that the core of this activity is the often detailed and in-depth knowledge that patients can possess: “[Patients] will typically know only about their one disease, but since they can devote a great deal of time to it, their knowledge within that single narrow niche can be impressive” (Ferguson 2000: 1130). The growing recognition within the practice literature of the valuable knowledge, experience, and expertise that are possessed and shared by some patients has also led to an exploration for new labels for these empowered groups. Terms that have been employed include “medical end user” (Ferguson 2002) and “e-patient” (Ferguson 2004; deBronkart 2013), but the term “patient” is still mainstream in discussions concerning the impact of social media on health care (e.g., Richards et al. 2013). Although within this literature is a recognition that the relationship between clinical professional and some patients is changing, the contribution of such groups is clearly positioned as an adjunct to mainstream medical practice and the issue of outlaw innovation remains mostly unexplored.

#### 14.2 THE DRIVERS OF PATIENT INNOVATION FOR CHRONIC DISEASE TREATMENT

Chronic disease presents a particular set of circumstances within which the role of user innovators may be explored. User innovation theory proposes that when possessed by a need not met by the market, users with the resources to do so will innovate (von Hippel 1986), although the nature of the need and the level of resources required for innovation to occur are left unspecified. The theory also suggests that users will innovate based on their sticky local knowledge of their particular circumstances. Individuals suffering from a chronic condition, especially one that is relatively rare, are likely to have a strong need to obtain something that the market is unable to provide (a cure, remission, reduction in symptom burden). They also are likely to possess extensive and detailed experience-based knowledge concerning the “local” circumstances and the impact the disease has upon them. Individuals with chronic medical conditions thus are likely to possess many of the common characteristics of user innovators. It might be anticipated that, as a group, they could be a strong source of innovation relating to their specific afflictions.

Patients with chronic medical conditions differ from user innovators in other fields in a number of important respects, however, which may dampen their ability to innovate. To begin with, it is important to recognize that patients who suffer from a chronic medical condition are ill and may lack those most valuable of resources required to innovate – time and energy. The high rate of innovation reported in the surveys of rare disease patients and their caregivers discussed by Oliveira et al. (Chapter 13, this volume) suggest, however, that urgent and persistent need can overcome these barriers, at least in some disease contexts.

Some types of medical innovation, particularly those involving drug-based treatments, seem particularly unlikely to result from patient innovation, since patients might be expected to lack the scientific expertise and other specialized resources required both to develop such treatments and to assess their safety and efficacy. Indeed, barriers to patient innovation in this arena arise not only from lack of scientific expertise but also from the regulatory systems that were designed with the goal of ensuring that patients receive safe and efficacious treatments.

The regulated nature of the medical innovation system, with its rigorous standards for safety and efficacy means, however, that it can take a long time for a new treatment to be approved, and still longer for it to become widely available to patients. From the point of view of a patient diagnosed with a serious chronic disease, the future in the interim may appear bleak, potentially filled with ongoing periods of illness, and a series of more or less unpleasant holding strategies, including drugs and surgery with unpleasant side effects and no long-term relief. The sufferer is largely excluded from the standard medical innovation system and is expected simply to wait for new and better treatments to emerge. In this situation, extreme need may provide motivation for patients to seek solutions that lie outside

the control of the regulated medical system, through a process of outlaw innovation. The next section explores one such case: the commons-based user innovation of helminthic therapy for Crohn's disease.

### 14.3 OUTLAW INNOVATION AND THE COMMONS-BASED PATIENT INNOVATION OF HELMINTHIC THERAPY FOR CROHN'S DISEASE

This section describes in detail how a small group of patients who suffer from Crohn's disease – a chronic disease for which there is no cure and no satisfactory long-term treatment for many patients – worked together to try and develop an effective therapy to treat the disease outside of mainstream medical processes of innovation and regulation. The case throws new light on what may drive users (in this case, patients with a chronic condition) to take a knowledge commons approach to pooling their knowledge and ideas. It illustrates how sufficiently strong user need, coupled with dissatisfaction with the pace of strongly regulated medical innovation, can facilitate the emergence of outlaw user communities (Flowers 2008) willing to innovate outside regulated processes. It also illuminates how this outlaw innovation process interacts with the standard scientific and medical research paradigms.

The case study involves the user-led development of helminthic therapy for Crohn's disease. In helminthic therapy, users ingest tiny worm larvae to develop the viable community of parasitic worms that will act to reduce the impact of their immune condition. The therapy is based on the firm foundation of mainstream scientific and medical research that suggests its potential safety and efficacy as a means of relieving serious and chronic symptoms of the disease, but it has been largely developed by a group of patients experimenting on themselves and pooling their knowledge and experiences in a form of outlaw innovation.

#### 14.3.1 *Prologue: Crohn's Disease, Treatment, and Emerging Research Directions*

To set the scene, a brief overview of Crohn's disease and the scientific research into autoimmune disease is provided as background for the application of helminths in a therapeutic context.

##### 14.3.1.1 Crohn's Disease and Its Treatment

Crohn's disease is a chronic condition whose cause is not fully understood and for which no cure is currently available (Van Assche et al. 2010a). The disease affects around 690,000 people in Europe (90,000 in the UK) (Cummings et al. 2008) and 1.4 million people in the United States (CCFA 2011). Crohn's tends to occur in the second or third decade of life and, although the precise cause remains unclear, it is

currently believed to result from an inappropriately vigorous immune response in the intestinal lumen (Weinstock and Elliott 2009).

Crohn's disease was first described in 1932 (Crohn et al. 1932) and is named after Dr. Burrill Crohn, a gastroenterologist who encountered patients with inflammation in the part of their gut that lies between the small and large intestine (the terminal ileum). The science around the development of helminthic therapy draws on a series of different aspects of the disease that point to a causal relationship between its prevalence and the presence (or absence) of intestinal parasites. The research in this area provides evidence on five main aspects of the disease: the incidence and distribution (epidemiology) of autoimmune diseases such as Crohn's, the role of pathogens in developing the immune system, the role of microorganisms such as intestinal worms in moderating immune reactions, specific chemical and biological mechanisms that moderate the disease, and safety.

The chronic nature of Crohn's disease means that many patients with this condition have to live their lives with ongoing symptoms that may include weight loss, abdominal pain, diarrhea, anemia, and fatigue (Van Assche et al. 2010a). Given that there is no cure for Crohn's, mainstream treatments focus on inducing and maintaining remission or dealing with the complications of earlier interventions (Dignass et al. 2010). The main treatment regimens are corticosteroids, immunosuppressants, and antibiotics (Dignass et al. 2010). The need for surgery to resection intestines to eliminate blockages arising from internal scarring is historically very high, with around 80 percent of patients undergoing surgery at some point (Van Assche et al. 2010b). Medical treatment has advanced significantly in recent years, but Crohn's remains a deeply unpleasant chronic disease.

#### 14.3.1.2 The Research Foundations of User-Led Helminth Therapy

The epidemiology of Crohn's disease displays what has become termed a North-South gradient in that, in common with many autoimmune diseases, prevalence is higher in North America and Europe than in more southerly, often developing, countries (Hutt 1979; Shivananda et al. 1996). Related evidence concerns the role of pathogens (i.e., a bacterium, virus, or other microorganism that can cause disease) in assisting in the development of the human immune system. This evidence, which led to the development of what came to be termed the Hygiene Hypothesis, proposed a link between exposure to pathogens while young and the development of allergic diseases (Strachan 1989). This hypothesis proposes that some of the increased prevalence of allergic and other autoimmune diseases is the result of poor regulation of the immune system as a result of reduced exposure to pathogens during childhood (Rook 2008). This hypothesis is linked to the Old Friends Hypothesis that suggests a mutually beneficial (symbiotic) relationship between ourselves and the fauna (e.g., intestinal parasites such as helminths) that have coevolved to inhabit the human gastrointestinal tract (Rook and Brunet 2005).



In addition to this contextual work, helminthic therapy also draws on extensive research that has explored the link between intestinal worms and immune responses. Animal trials have shown links between helminths and the prevention or treatment of intestinal infection (e.g., Elliott et al. 2000, 2003; Khan et al. 2002). Research has also examined the efficacy of different types of helminth, focusing on the pig whipworm (*Trichuris suis*) and the human hookworm (*Necator americanus*). As these helminths inhabit different parts of the gastrointestinal tract, their use in treatments is targeted at different forms of an autoimmune disease and, it is hypothesized, will have different effects according to the condition of the user, the scale of infection, and a host of other factors. To date, mainstream scientific research has explored the effects of both human and porcine (pig) helminths and their impact on immune responses in people.

Small-scale, experimental trials to study the safety and effectiveness of the pig whipworm *Trichuris suis* demonstrated that they were safe and were able to reduce the symptoms of Crohn's and also help with remission, with no side effects or complications (Summers et al. 2003, 2005a, 2005b). Since it has evolved to inhabit a different organism, *Trichuris suis* does not cause human disease and can only persist within humans for a relatively short period of time (Beer 1976). As a result, the application of these particular worms as "treatment" requires regular reinfection to maintain the required immune response, a feature that makes it potentially attractive from a commercial perspective.

In the context of human helminths, research on the application of human hookworm *Necator americanus* has also explored clinical responses to low doses of the helminths (Maxwell et al. 1987) and what appropriate levels of infection might be (Scrivener et al. 2001). This work revealed that small populations of helminths were supportable and examined the role of helminths in the suppression of asthma symptoms. Other research also found evidence to suggest that individuals who have previously been infected with human helminths have reduced immune responses (Borkow et al. 2000; Elliott et al. 2000) and that this effect may persist after infection has ceased (e.g., Bentwich et al. 1996).<sup>1</sup> In the context of autoimmune diseases such as Crohn's and colitis, this finding is encouraging and may suggest that the human autoimmune system can be "trained" to react in a more moderate fashion.

Thus a significant body of mainstream scientific research now points to the presence of a possible therapeutic link between helminths and Crohn's disease. This evidence has led to the question of whether the systematic elimination of all human helminths in modern developing countries may be responsible for the subsequent increased prevalence of Crohn's (Elliott et al. 2000) and the proposal of the IBD Hygiene Hypothesis (Weinstock and Elliott 2009) in which the absence

<sup>1</sup> A large body of research has also examined the problems caused by the heavy infestation with intestinal parasites (such as helminths) in developing countries and work is underway to develop a hookworm vaccine (e.g., Diemert et al. 2008).

of intestinal parasites in the human gut may be a contributing factor in the rise in the incidence of autoimmune diseases like Crohn's and colitis. However, despite the large body of careful scientific research that has examined a wide range of issues associated with helminths, and the promising results obtained from small-scale experimental trials, at the time of writing no large-scale clinical trials to examine their therapeutic effect are underway, with the first such trial being cancelled in 2013.

### 14.3.2 *User-Led Development of Helminthic Therapy*

The foundation for the application of human helminths as a therapy for a range of autoimmune diseases was laid down by the results of the mainstream scientific research outlined earlier. However, the translation of this research into an unlicensed therapy based on human hookworm, *Necator americanus*, has been primarily driven by patients, who have created an online community to pool their knowledge and efforts to develop a workable helminthic therapy for Crohn's disease. This section explores the way in which the online patient community formed and governs itself in working toward the goal of a safe and effective helminthic therapy for Crohn's disease.

The primary action arena for the helminth therapy community's innovative activity are the blogs on which community members post their activities, results, and comments, which are the personal accounts of patients who have made the decision to explore the use of helminths to seek remission from Crohn's and colitis. Analyzing this material provides detailed insights into the activities of these users and the governance of this highly specialized knowledge commons.

#### 14.3.2.1 *The Helminthic Therapy User Community: Formation and Membership*

This setting is an entirely open community in which experiences are published on blogs and "membership" is achieved by a shared need, an openness to experiment with helminths, and the willingness to share the results of one's activities. In common with many open source groups, this is a self-organizing community in which membership is open to all, but one's place is earned by the hard "work" of contribution. In general, users are all driven by the strong need to find relief from the often extreme symptoms that arise both from autoimmune afflictions such as Crohn's, colitis, multiple sclerosis, asthma, and psoriasis and from the side effects of the standard treatments they have receive. The blogs offer an insight into the shape and nature of unmet need that drives this form of user to participate. The overwhelming and extreme desire for a cure for Crohn's or colitis or for a means to obtain remission is a recurrent theme within the blogs, as is the loss of, and need for, hope that an end is in sight for their suffering. The following is a typical example:

My symptoms present as abdominal pain, rectal pain, diarrhea, fecal incontinence and malabsorption. And that's on a good day.

Orin Twist: May 7, 2013

The membership and narrative of the community are also strongly influenced by its “outlaw” approach. Members label themselves as “citizen scientists,” “experimental subjects,” or “pioneers” in the field and recognize that they are operating outside the regulated health care environment. A blog post that captures this position follows:

I can't see this ever being a mainstream . . . treatment that a doctor could prescribe. As a living organism, it's not something any drug company could ever patent, so it's unlikely to get all of the trials and testing it would need to get to that stage. But I've seen enough from the few trials that have taken place, and the anecdotal evidence I've read, for me to be certain that it's worth giving it a go. And whilst it may be experimental and therefore inherently risky, the types of risks we're talking about pale in to insignificance compared to the risks associated with the conventional treatments my consultant was proposing.

Hookworm for Crohn's: September 22, 2010

#### 14.3.2.2 Resources Shared and Created by the Community

The commons-based development of helminth therapy draws heavily on the current scientific understanding of the role and impact of human intestinal parasites on immune responses of people with an autoimmune condition. Infecting oneself involves swallowing parasite larvae with the intention of creating a viable, if small, colony to produce the required reduction in symptoms. However, although there is clear evidence for the therapeutic use of human helminths, there is little knowledge on how the treatment may be optimized. As a result, the treatment depends on the creation and sharing of a variety of knowledge resources, including relevant information from the mainstream scientific literature, the personal accounts of trial and error “experiments” conducted by members in treating their own disease, and collective discussion and critique of both. It also depends on the availability of hookworms, which are obtained from a small network of commercial suppliers or by “harvesting” them from those with viable helminth communities.

##### 14.3.2.2.1 MAINSTREAM MEDICAL RESEARCH PUBLICATIONS

Despite the fact that this is an outlaw user innovator community, in the sense that participants are content to accept the risks associated with stepping outside the regulated health care system and experimenting with their own treatment, it is also a well-informed community that draws on the results of research published by the mainstream scientific community in this area, as well as on a wide range of additional scientific sources. This patient innovator community relies heavily on publicly available knowledge obtained from formal scientific studies to provide insights into the mechanisms and effects of helminths in regulating autoimmune

diseases. As a result, the helminth therapy patient community is not fully outlaw in the sense of rejecting the results of mainstream medical research, and the main body of underpinning science is clearly outlined and the “case” for the therapeutic application of helminths is explored. For example:

More specifically, this blog is about the pursuit of a new, relatively untested treatment for UC: helminthic therapy. Also known as whipworm parasite, I’m planning to introduce 1,000 ova of these little fellas to my system in January in hopes they will be a game changer in my ongoing slog against this stupid disease. I’ll be using this space to document my progress on this treatment for other folks who are thinking of pursuing this course of action. Please note that under “For your information” I’ve included some links to what I think are some really good resources on the topic of IBD, including a couple of folks who are also keeping blogs about their experiences with helminthic therapy.

The UC Chronicles: December 17, 2010

Moreover, members of this community help one another stay abreast of the ongoing work of the mainstream researchers active in the field and routinely share (and critique) findings from the latest published helminth studies and discuss and evaluate the results of associated research, for example:

A new “biological fingerprint” – the bacterial enterotype – has recently been discovered which may eventually become as important as blood types and tissue types are today, with many implications for understanding and improving health . . . I suspect that this line of research will produce many more fascinating developments, and perhaps a few more surprises, along the way. This is definitely one to watch!

gut\_buddies: April 27, 2011

The helminth therapy community thus provides an example of a user innovator community that assimilates and shares specialized knowledge derived from scientific research and combines it with members’ local experience and personal evidence. Indeed, to be fully effective and make informed decisions, these users must make substantial investments to obtain and understand this specialized scientific knowledge.

#### 14.3.2.2.2 SHARING USER ACCOUNTS WITHIN THE COMMUNITY

At the heart of the development of the creation of experimental helminth therapy is users’ willingness to engage in informed trial-and-error experimentation with their own treatments and to share personal accounts of their experiences with the group. To that end, members of this group shared detailed information concerning their own symptoms, treatments, dosages, test results, adverse reactions, side effects, and any interactions with mainstream medicine. Evidence of the experimental therapy’s effects is examined in great detail through postings on the website and extensive debates among community members.

#### 14.3.2.2.3 SOURCING HUMAN HELMINTHS

The user-created therapy is based on the application of human helminths, which can be obtained from commercial organizations. Such firms supply both the human hookworm (*Necator americanus*) and the human whipworm (*Trichuris trichuria*) and offer guidance on how these helminths may be applied therapeutically. Access to these human helminths is a vital part of engaging with this therapeutic approach, and although these firms are important sources of supply some users have taken a do-it-yourself (DIY) approach.

The DIY approach to sourcing human helminths is at the more extreme end of user activity and involves harvesting human helminths and incubating them so that they are viable for ingestion. The DIY approach also provides information on helminth egg counts (to obtain evidence of hookworm infection in a human host) and explanations on culturing different types of helminth. The information that is shared is both published scientific research and straightforward instructions written by users that combine scientific knowledge and personal experiences. Groups like Incubating Hookworm and the Helminthic Therapy Open Source Wiki are excellent examples of this aspect of the wider DIY phenomenon.

#### 14.3.3 Norms and Governance

Though the helminthic therapy patient innovator community is not part of the mainstream medical research system, it has adopted norms aimed at importing the standards of scientific rigor into the process of patient innovation to the extent possible. For example, the website is designed such that each member has an opportunity to comment on each post made by another member. Though the detailed systematic review found within mainstream medical research is not observed, blog reports were subject to a form of “peer” review and vigorous debate was common. Moreover, blog comments were used not only for substantive discussion about the disease and the experimental therapy but also to emphasize and enforce norms of good user “science,” as illustrated in the following extract:

One note: as bloggers writing about an experimental therapy, we all have a responsibility to be careful about what we write . . . Also, please be clear about the details of your therapy – how many helminths or ova you took, what date(s), which provider, etc., always useful. I get emails every week from interested readers, and am nearing 10,000 hits, so I do take my responsibility seriously with this blog.

Colon Comrades: June 4, 2011

However, in the context of the scale of those suffering with autoimmune diseases, this is a small self-organizing community of individuals who decided to take action to try and find some form of remission for their conditions. This loose group coalesced around a shared commitment to experimenting with human helminths and sharing their results. What catalyzed the emergence of this community was press

coverage exploring the role of helminths in alleviating autoimmune conditions (something that is still ongoing, e.g., Kohn 2016) and the ability to access these organisms from the commercial suppliers. These commercial suppliers were two of the nodes in the information network that emerged around this treatment. The information network that developed was more organic, respectful, and challenging with the most prominent sites reflecting the effort, knowledge sharing, and value provided by the individual involved.

#### 14.3.4 *Relationship to Mainstream Medical Researchers*

Though the helminth therapy community draws heavily on the output of mainstream medical research, its outlaw character is reflected in the way it is perceived by mainstream researchers. Thus, the creation of such a user-led therapy has been controversial and has attracted negative reactions from researchers in the field who view their work as having been “bootlegged” (Weinstock 2009), and the therapy as “too risky” (Hotez 2008). In contrast, the following provides an alternative perspective concerning the negative reactions of mainstream researchers to the use of human helminths as an experimental therapy:

I would like these researchers to think about this deeply. How many years away is your medicine that mimics the worms’ effects? . . . If research could just move a little faster . . . Please don’t be so dismissive. We are suffering horribly. And you are taking far too long.

Waiting for the Cure: September 2009

#### 14.4 USERS, CHRONIC DISEASE, INNOVATION, AND OUTLAW KNOWLEDGE

The application and development of helminths within a therapeutic context has largely taken place within the user-led outlaw innovation system that produced and shared outlaw knowledge (Flowers 2008). Because of its outlaw status, this small community consciously operated outside normal channels and avoided hostile jurisdictions. As a patient-led community to which mainstream resources and processes were unavailable, it developed and required different forms of evidence and recognized different forms of legitimation (e.g., Ferguson 2000). The outlaw status of this effort distinguishes it from previously studied user innovator communities in several interesting ways.

First, patients facing chronic needs that are unlikely to be met by the market may engage in significant, long-term efforts to try to innovate to improve their lives. Chronic disease is a context in which need is likely to persist for a long period of time. Patients are driven to engage in their own outlaw innovation because of the

slow pace at which medical discoveries are translated into available treatments under current regulatory paradigms.

Second, the great need experienced by these patients drove them to make extensive efforts to acquire specialized knowledge that is not of the local experiential sort usually associated with user innovation. Their ongoing, persistent, and possibly urgent need stretching over many years provides a powerful platform for the development of the knowledge and network resources required both to innovate and to assess the merits of proposed innovations. Knowledge resources – the capability to understand medical mechanisms, the appreciation of breadth and depth of current research in the area, observations concerning clinical trials, knowledge of the benefits and limitations of the drugs available (including side effects), and understanding of the wider discourse over treatment options – may form an important part of the resources needed for innovation. Such knowledge is likely to be developed over many years and, as the case has shown, will be diffused through a network of blogs, fora, patient groups, and associations that are created around chronic diseases and may themselves act as focusing devices for the efforts of innovative users. Crucially, the mainstream medical knowledge on which the patient innovation here was based was publicly available in published form. The knowledge resources pooled and deployed by the patient innovator community thus included both the results of mainstream scientific investigation and the results of the patients' user experiences, permitting them to draw on both sets of resources in developing the experimental helminthic therapy.

Third, the outlaw status of this innovator community had significant effects on the potential for producer adoption and dissemination of the results of this user innovation. Within much of the user innovation literature, producers are observed to benefit from the activities of innovative users, with knowledge spillovers traveling from user to producer. As producers adopt lead user innovations and make them available on the market, a wider group of users also benefits. Such producers will also either appropriate lead user ideas or typically contribute to the innovation's dissemination to a wider body of users by using their expertise in areas such as quality control, user-friendly design, distribution chains, and so forth.

In contrast, the development of Helminthic therapy provides an example whereby the knowledge spillovers have flowed, in the first instance, from producers to users. The findings from the basic research undertaken within universities and other public bodies provided the initial hypothesis, proof-of-concept, and evidence of effect and risk that formed the basis for the experimental helminthic therapy developed by users. The synergy emphasized in lead user innovation studies, in which producers adopt and disseminate user innovations to a wider group of users, has not occurred in this context. Arguably, it is likely that such synergies can never take place in such contexts.

The regulated nature of health care innovation, along with the strict standards for demonstrating safety and efficacy, preclude the direction of knowledge spillovers

found elsewhere in the user innovation literature – knowledge created by users spilling over to producer firms (e.g., Jeppesen and Molin 2003) – to be appropriated by the mainstream. The nature of the human helminth therapy experimentation conducted within the user community is such that it is not recognized as an authoritative data source for the mainstream medical innovation system. Within the patient community, legitimation flows from the personal accounts of those who have taken the helminths and from other users' discussion of their reports. The questions that drive this activity are not “Do we fully understand how this works?” but more simply “Does it work at all?” and “How do we make it work better?” These users freely reveal their experiences, and, much like users of poorly understood technologies in past times (e.g., Allen 1983; Nuvolari 2004), the community shares outlaw knowledge and experience as it attempts to optimize its activities. While this knowledge is not in the form demanded for mainstream adoption, it is unquestionably a potentially valuable trove of clinical data.

However, the mainstream medical innovation system has no mechanism for learning from this outlaw knowledge or incorporating it into the ongoing stream of research. As a result, while benefits may be obtained (or lessons about risks learned) by the small group of patient innovators participating in the community, potentially beneficial spillovers are blocked. Full understanding, optimization, and validation of these patient innovations would require detailed scientific enquiry, which would take time, expertise, and resources that a group of patients afflicted with a chronic disease does not have. Moreover, the lack of any mechanism for absorbing the lessons of outlaw innovation within mainstream medical innovation can create tensions between users and clinicians and between the regulated medical system and the informal user-driven system that discourage patients even from discussing these efforts with medical professionals. One result of this is that the scale, scope, and depth of user activity in this area are obscured, and a great deal of potentially informative clinical data – outlaw knowledge – is lost to science.

Even when producers are open to adopting promising user innovations, there is always some time lag between user innovation and mainstream appropriation of that innovation. Factors that will have an influence on the scale and nature of any time lag include regulation, investment cycles, capital intensity of the innovation context, structure of the business model employed, tractability of the technological context, type of user involved (business or consumer), and the part played by online communities. In some environments the physical nature of the product and the investment cycles associated with capital equipment may limit the ability of suppliers to quickly respond to user activity, with the result that there may be extensive time lags. In highly regulated environments (such as medicine), the lag would likely be even longer. Mainstream adoption may demand extensive scientific evidence and long-term programs of testing and require detailed certification processes for doctors and other medical professionals. The lack of any accepted mechanism for transferring knowledge for patient outlaw innovators to the mainstream makes the lag even



longer – to the extent that spillovers from patient innovators to medical professionals occur at all. Patients are in great need, however, and many will simply be unwilling to wait. As a result, there may be a large gulf between the outcomes of “official” innovation processes and what users are doing on the ground. This may result in a disconnect between official and user activity and the evolution of quite different, and potentially conflicting, innovation trajectories.

From a knowledge commons perspective, this case demonstrates not only the potential importance of public domain knowledge as a resource for commons-based innovation but also the potential need for mechanisms for disseminating socially beneficial knowledge beyond the innovative community. Innovation researchers have recently begun to recognize that user innovators may lack incentives or face barriers to diffusing their innovations to a socially desirable degree. This case demonstrates that user innovator communities may have similar difficulties and that social value may be lost unless mechanisms are in place to ensure the appropriate level and type of synergy between a knowledge commons and the wider society.

#### CONCLUSIONS

This chapter has explored the way in which a certain form of user – individuals with a chronic medical condition – has led the development and application of a novel experimental medical therapy based on human intestinal parasites. The case provided the basis for an exploration of the role of users in medical innovation, and the difficulties that organizations may face in appropriating the outlaw knowledge that emerges from user communities was also explored.

The users active in the development of helminthic therapy possessed four shared characteristics: absence of effective long-term solutions from the mainstream medical system for their particular problems, a strong need to ameliorate their medical condition, access to the resources required to develop the medical therapy, and freedom of action unconstrained by medical regulations surrounding the development of new therapies. These shared characteristics meant that user innovation in this area was likely to be far faster, more responsive to new scientific insights, and quicker to close down lines of enquiry that are apparently unpromising. However, mainstream appropriation of the knowledge generated and shared in this process – outlaw knowledge – is likely to be difficult or impossible.

#### REFERENCES

- Allen, R. C., 1983. Collective invention. *Journal of Economic Behaviour and Organization* 4:1.

- Barbot, J., 2006. How to build an “active” patient? The work of AIDS associations in France. *Social Science and Medicine* 62:538.
- Beer, R. J., 1976. The relationship between *Trichuris trichiura* (Linnaeus 1758) of man and *Trichuris suis* (Schrunk 1788) of the pig. *Research in Veterinary Science* 20:47.
- Bentwich, Z., Z. Weisman, C. Moroz, S. Bar-Yehuda, and A. Kalinkovich, 1996. Immune dysregulation in Ethiopian immigrants in Israel: Relevance to helminth infections? *Clinical & Experimental Immunology* 103:239.
- Berthon, P. R., L. F. Pitt, I. McCarthy, and S. M. Kates, 2007. When customers get clever: Managerial approaches to dealing with creative consumers. *Business Horizons* 50 (1):39.
- Borkow, G., Q. Leng, Z. Weisman, M. Stein, N. Galai, A. Kalinkovich, and Z. Bentwich, 2000. Chronic immune activation associated with intestinal helminth infections results in impaired signal transduction and energy. *Journal of Clinical Investigation* 106:1053.
- Callon, M., and V. Rabeharisoa, 2003. Research “in the wild” and the shaping of new social identities. *Technology in Society* 25:193.
- CCFA, 2011. Estimate published by Crohn’s and Colitis Foundation of America, [www.ccfa.org/info/about/crohns](http://www.ccfa.org/info/about/crohns).
- Crohn B. B., L. Ginzburg, and G. D. Oppenheimer, 1932. Regional ileitis: A pathologic and clinical entity. *Journal of the American Medical Association* 99 (16):1323.
- Cummings, J. R. F., S. Kehave, and S. P. L. Travis, 2008. Medical management of Crohn’s disease. *British Medical Journal* 336:May 10.
- Dahlender L., and M.G. Magnusson, 2005. Relationships between open source software companies and communities: Observations from Nordic firms. *Research Policy* 3(4):481.
- deBronkart, D., 2013. How the e-patient community helped save my life: An essay by Dave deBronkart. *British Medical Journal* 346:April 2.
- de Jong, J., and E. von Hippel, 2009. Transfers of user process innovations to process equipment producers: A study of Dutch high-tech firms. *Research Policy* 38(7):1181.
- Diemert D. J., J. M. Bethony and P. J. Hotez, 2008. Hookworm vaccines. *Clin. Infect. Dis.* 46(2):282.
- Dignass A., G. Van Assche, J. O. Lindsay, M. Lémann, J. Söderholm, J. F. Colombel, S. Danese, A. D’Hoore, M. Gassull, F. Gomollón, D. W. Hommes, P. Michetti, C. O’Morain, T. Öresland, A. Windsor, E. F. Stange, and S. P. L. Travis, 2010. The second European evidence-based consensus on the diagnosis and management of Crohn’s disease: Current management. *Journal of Crohn’s and Colitis* 4(1):28.
- Elliott, D. E., J. F. Urban Jr., C. K. Argo, and J. V. Weinstock, 2000. Does the failure to acquire helminthic parasites predispose to Crohn’s disease? *FASEB J.* 14:1848.
- Elliott, D. E., J. Li, A. Blum, A. Metwali, K. Qadir, J. F. Urban Jr., and J. V. Weinstock, 2003. Exposure to schistosome eggs protects mice from TNBS-induced colitis. *American Journal of Physiology – Gastrointestinal & Liver Physiology* 284:G385.

- Epstein, S., 1996. *Impure Science: AIDS, Activism and the Politics of Knowledge*. Berkeley: University of California Press.
- Ferguson, T., 2000. Online patient-helpers and physicians working together: A new partnership for high-quality health care. *British Medical Journal* 321:November.
- Ferguson, T., 2002. Quality online patient networks need more attention than quality of online health information. *British Medical Journal* 324:March 9.
- Ferguson, T., 2004. The first generation of e-patients. *British Medical Journal* 328: May 13.
- Flowers, S., 2008. Harnessing the hackers: The emergence and exploitation of Outlaw Innovation. *Research Policy* 37:177.
- Flowers, S., J. de Jong, T. Sinozic, and E. von Hippel, 2010a. *Measuring User Innovation in the UK*. London: NESTA.
- Hamm, M. P. et al. 2013. Social media use among patients and caregivers: A scoping review. *BMJ Open* 3:e002819.
- Harhoff D., Henkel J., and von Hippel E., 2003. Profiting from voluntary information spillover show users benefit by freely revealing their innovations. *Research Policy*. 32:1753.
- Hotez, P., 2008. Quoted in S. Svoboda, The worms crawl in. *New York Times*, July 1, [www.nytimes.com/2008/07/01/health/research/01prof.html](http://www.nytimes.com/2008/07/01/health/research/01prof.html).
- Hutt M. S., 1979. Epidemiology of chronic intestinal disease in middle Africa. *Isr. J. Med. Sci.* 15:314.
- Jeppesen, L. B., and M. J. Molin, 2003. Consumers as co-developers: Learning and innovation outside the firm. *Technology Analysis and Strategic Management* 15(3).
- Khan, W. I., P. A. Blennerhasset, A. K. Varghese, S. K. Chowdhury, P. Omsted, Y. Deng, and S. M. Collins, 2002. Intestinal nematode infection ameliorates experimental colitis in mice. *Infection & Immunity* 70(11):5931.
- Henkel, J., and E. von Hippel, 2004. Welfare implications of user innovation. *The Journal of Technology Transfer* 30:73.
- Kohn, D., 2016. Why a diet of worms could be good for you. *The Guardian*, Feb. 8, online edition, [www.theguardian.com/lifeandstyle/2016/feb/08/why-a-diet-of-worms-could-be-good-for-you](http://www.theguardian.com/lifeandstyle/2016/feb/08/why-a-diet-of-worms-could-be-good-for-you)
- Lettl, C., 2007. User involvement competence for radical innovation. *Journal of Engineering and Technology Management* 24(1–2):53.
- Lilien, G., P. D. Morrison, K., Searls, M. Sonnack, and E. von Hippel, 2002. Performance assessment of the lead user generation process for new product development. *Management Science* 48(8):1042.
- Maxwell, C., R. Hussain, T. B. Nutman, R. W. Poindexter, M. D. Little, G. A. Schad, and E. A. Ottesen, 1987. The clinical and immunological responses of normal human volunteers to low dose hookworm (*Necator americanus*) infection. *American Journal of Tropical Medicine and Hygiene* 37:126.
- Nuvolari, A., 2004. Collective invention during the British Industrial Revolution: The case of the Cornish pumping engine. *Cambridge Journal of Economics* 28 (3):347.

- Oliveira, P., L. Zejnilovic, H. Canhão, and E. von Hippel, 2014. Innovation by Patients with Rare Diseases and Chronic Needs. Available at SSRN, <http://ssrn.com/abstract=2456580>.
- Pew Internet, 2010. More than half of e-patients living with chronic disease consume user-generated health information, *Social Media and Health*, Pew Internet & American Life Project, [www.pewInternet.org/2010/03/24/social-media-and-health/](http://www.pewInternet.org/2010/03/24/social-media-and-health/)
- Richards, T. et al. 2013. Let the patient revolution begin. *BMJ* 346:f2614.
- Rook, G. A., 2008. Review series on helminths, immune modulation and the hygiene hypothesis: The broader implications of the hygiene hypothesis. *Immunology* 126(1):3.
- Rook, G. A., and L. R. Brunet, 2005. Old friends for breakfast. *Clin. Exp. Allergy* 35 (7):841.
- Schaan, S., and Urbach, M., 2009. Measuring User Innovation in Canadian Manufacturing 2007. Statistics Canada.
- Scrivener, S., H. Yemaneberhan, M. Zebenigus, D. Tilahun, S. Girma, S. Ali, P. McElroy, A. Custovic, A. Woodcock, D. I. Pritchard, A. Venn, and J. Britton, 2001. Independent effects of intestinal parasite infection and domestic allergen exposure on the risk of wheeze in Ethiopia. *Lancet* 358:1493.
- Seres, M. J., 2013. Re: Patient powered health. *British Medical Journal* 346:April 13.
- Shivananda S., J. Lennard-Jones, R. Logan, N. Fear, A. Price, and L. Carpenter, 1996. Incidence of inflammatory bowel disease across Europe: Is there a difference between the north and south? Results of the European Collaborative Study on Inflammatory Bowel Disease (EC-IBD). *Gut* 39:690.
- Strachan, D. P., 1989. Hay fever, hygiene, and household size. *British Journal of Medicine* 299:1259.
- Summers, R. W., D. E. Elliott, K. Qadir, J. F. J. Urban, R. Thompson, and J. V. Weinstock, 2003. *Trichuris suis* seems to be safe and possibly effective in the treatment of inflammatory bowel disease. *American Journal of Gastroenterology* 98:2034.
- Summers, R. W., D. E. Elliott, J. F. Urban Jr., R. Thompson, and J. V. Weinstock, 2005a. *Trichuris suis* therapy in Crohn's disease. *Gut* 54:87.
- Summers, R. W., D. E. Elliott, J. F. Urban Jr., R. A. Thompson, and J. V. Weinstock, 2005b. *Trichuris suis* therapy for active ulcerative colitis: A randomized controlled trial. *Gastroenterology* 128:825.
- Swan, M. 2012a. Health 2050: The Realization of Personalized Medicine through Crowdsourcing, the Quantified Self, and the Participatory Biocitizen. *J. Pers. Med.* 2:93.
- Swan, M. 2012b. Scaling Crowdsourced Health Studies: The Emergence of a New Form of Contract Research Organization. *Personalized Medicine* 9(2):223.
- Urban, G.L., and E. von Hippel, 1988. Lead user analyses for the development of new industrial products. *Management Science* 34(5):569.
- Van Assche, G., A. Dignass, J. Panes, L. Beaugerie, J. Karagiannis, M. Allez, T. Ochskenkühn, T. Orchard, G. Rogler, E. Louis, L. Kupcinskis, G. Mantzaris, S. Travis, and E. Stange, 2010a. The second European evidence-based Consensus on

- the diagnosis and management of Crohn's disease: Definitions and diagnosis. *Journal of Crohn's and Colitis* 4(1):7.
- Van Assche G., A. Dignass, W. Reinisch, J. C. van der Woude, A. Sturm, M. De Vos, M. Guslandi, B. Oldenburg, I. Dotan, P. Marteau, A. Ardzizzone, C. Daniel, D. C. Baumgart, G., D'Haens, P. Gionchetti, F. Portela, B. Vucelic, J. Söderholm, J. Escher, S. Koletzko, K. Kolho, M. Lukas, C. Mottet, H. Tilg, S. Vermeire, F. Carbonnel, A. Cole, G. Novacek, M. Reinshagen, E. Tsianos, K. Herrlinger, B. Oldenburg, Y. Bouhnik, R. Kiesslich, E. Stange, S. Travis, and J. Lindsay, 2010b. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Special situations. *Journal of Crohn's and Colitis* 4(1):63.
- von Hippel, E., 1976. The dominant role of users in the scientific instrument innovation process. *Research Policy* 5(3):212.
- von Hippel, E., 1986. Lead users: A source of novel product concepts. *Management Science* 32(7):791.
- von Hippel, E. 1994. "Sticky information" and the locus of problem solving: Implications for innovation. *Management Science* 40(4):429.
- von Hippel, E., and von Krogh, G., 2003. Open source software and the "private-collective" innovation model: Issues for organization science. *Organization Science* 14(2):208.
- von Hippel, E., 2005. *Democratizing Innovation*. Cambridge, MA: MIT Press.
- von Hippel, E., 2007. Horizontal innovation networks—By and for users. *Industrial and Corporate Change* 16(2):293.
- Weinstock, J. V., 2009, quoted in Cox, L., Allergy desperation: I'll take a parasite, please. *ABC News Medical Unit*, July 20, <http://abcnews.go.com/Health/AllergiesNews/story?id=8114307>
- Weinstock, J. V., and D. E. Elliott, 2009. Helminths and the IBD Hygiene Hypothesis. *Inflammatory Bowel Disease* 15(1):128.
- Wynne, B. 1996. SSK's Identity Parade: Signing-Up, Off-and-On. *Social Studies of Science* 26(2):357.

#### SUGGESTED ADDITIONAL READING

- Adams, T., 2010. Gut instinct: The miracle of the parasitic hookworm. *The Observer*, May 22, [www.theguardian.com/lifeandstyle/2010/may/23/parasitic-hookworm-jas-per-lawrence-tim-adams](http://www.theguardian.com/lifeandstyle/2010/may/23/parasitic-hookworm-jas-per-lawrence-tim-adams)
- Alvesson, M., and Skolddberg, K., 2000. *Reflexive Methodology*. London: SAGE Publications Inc.
- Braun, V., and Herstatt, C., 2009. *User Innovation: Barriers to Democratization and IP Licensing*. Routledge.
- Coronado, 2011. Filing for registration of securities, Amendment No. 1 to Form 10, Submission to United States Securities and Exchange Commission, July 2011.
- Duncan, D. F., White, J. B., and Nicholson, T., 2003. Using internet-based surveys to reach hidden populations: Case of non-abusive illicit drug users. *American Journal of Health Behavior* 27(3):208.

- Flowers, S., 2010b. User innovation: The developing Policy Research Agenda, in Flowers, S., and F. Henwood (eds.), *Perspectives on User Innovation*. London: Imperial College Press.
- Franke, N., and von Hippel, E., 2003. Satisfying heterogeneous User Needs via Innovation Toolkits: The Case of Apache Security Software. *Research Policy* 32 (7):1199.
- Klein S. J., and Rosenberg, N., 1986. An Overview of Innovation, in Landau, R., and Rosenberg, N. (eds.), *The Positive Sum Strategy: Harnessing technology for economic growth*. National Academy of Engineering.
- Lüthje, C., Herstatt C., and von Hippel E., 2002. *The Dominant Role of Local Information in User Innovation: The Case of Mountain Biking*. MIT Sloan School. Working Paper #4377-02.
- Lüthje, C., Herstatt C., and von Hippel E., 2005. User-innovators and local information: The case of mountain biking. *Research Policy* 34(6):951.
- Luthje, C., 2004. Characteristics of innovating users in a consumer goods field: An empirical study of sport-related product consumers. *Technovation* 24(9):683.
- Meyer, P. B., 2003. *Episodes of Collective Invention*, BLS Working Papers, Office of Productivity and Technology, US Department of Labor.
- Morrison, P. D., Roberts, J. H., and Von Hippel, E., 2000. Determinants of user innovation and innovation sharing in a local market. *Management Science* 46 (12):1513.
- NESTA, 2006. The Innovation Gap: Why policy needs to reflect the reality of innovation in the UK. Research Report, October.
- Sonnenberg A., McCarty D. J., and Jacobsen, S. J., 1991. Geographic variation of inflammatory bowel disease within the United States. *Gastroenterology* 100:143.
- von Hippel, E., and Katz, R., 2002. Shifting Innovation to Users via Toolkits. *Management Science* 48(7):821.
- von Hippel, E., DeMonaco, H., and Oliveira, P., 2011. *Patients as Health Care Innovators: The Case of Cystic Fibrosis*, Open and User Innovation Workshop, June 4-6, Vienna.