Evolving Concept of Openness in the Health Commons: Engaging Global Stakeholders in Technology Development for Malaria

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Abstract:

Used originally to describe the sharing of natural resources including the interactions that occur to manage such natural resources, the health commons refers to knowledge-based assets that are shared or owned in common by stakeholders found across the health value chain. This health commons offers several advantages including knowledge sharing, knowledge verification, joint and efficient knowledge creation. The Human Genome Project is perhaps a turning point in the creation of the health commons—with both varied resources such as information, biological materials, research-based tools and models, and even chemical compounds deposited into the commons; further, stakeholders from both the public as well as private sectors appear to be participating in its construction.

Beyond the nature of the resource and participant types associated with the health commons, of interest is the evolving nature of openness. In this paper, the notion of openness is applied first to the health commons and second, is extended to incorporate a dynamic element. The paper explores how openness in terms of resource deposit and participant entry into the commons varies as a function of phase of development. Moving from early biological research, to compound development and then clinical testing, this notion of openness changes. Specifically, a framework is created and used to understand the historical evolution of openness in the discovery and development of technology targeted to malaria. Malaria is a very important case given its devastating effects in many developing countries. It has been the focus of a number of relatively well-funded efforts for a number of years. For this reason, malaria drug development is relatively further advanced than drug development for many other tropical diseases, and there are "open" initiatives at all stages of drug development, from upstream research through regulatory approval. The anticipated outcome should be an improved understanding of the characteristics of resources managed both within and outside the health commons—in this case at the bottom of the pyramid.

Introduction:

Increased technological and market complexities associated with new drug development are drivers in the formation of a health commons. Used originally to describe the sharing of natural resources including the interactions that occur to manage such natural resources, in this paper, the health commons refers to knowledge-based assets that are shared or owned in common by stakeholders found across the health value chain. This health commons offers several advantages including knowledge sharing, knowledge verification, joint and efficient knowledge creation. The Human Genome Project is perhaps a turning point in the creation of the health commons—with both varied resources such as information, biological materials, research-based tools and models, and even chemical compounds deposited into the commons; further, stakeholders from both the public as well as private sectors appear to be participating in its construction. The need for verification in the post genome era given the uncertainty of knowledge associated with disease processes and hence value creation, has become paramount. Further, the scale and cost of research is no longer manageable by isolated laboratories or firms.

Beyond the nature of the resource and participant types associated with the health commons, of interest is the evolving nature of openness. Traditionally, openness of resources in any commons has referred to the possession and control of resources, with an underlying notion that users must interact with one another in order to extract and use such resources from the commons (Ostrom et. al., 1994; Madison et. al., 2010). Openness with respect to the participant community refers to the rules used to manage membership or participation in the commons (Ostrom et. al., 1994; Madison et al., 2010). In this paper, the notion of openness is applied first to the health commons and second, is extended to incorporate a dynamic element.

The paper explores how openness in terms of resource deposit and participant entry into the commons varies as a function of phase of development. Moving from early biological research, to compound development and then clinical testing, the notion of openness changes: beginning with open access to information, materials, tools, and compounds including public sector entities, private sector stakeholders, and uniquely, patients in the commons; evolving to dissemination of newly created resources via open licensing strategies including stakeholders functioning within and outside the health commons; and emerging as open collaboration between stakeholders acting on the periphery of the health commons. Worth noting is that upon approval and market entry, open access strategies may be used to distribute medical products to those at the bottom of the pyramid. This paper has the objective of proposing a modified framework of the commons to incorporate these three notions of openness including the interaction of stakeholders inside the health commons and on its periphery. The framework is used to understand the historical evolution of openness in the discovery and development of technology targeted to malaria. Malaria is obviously a very important case given its devastating effects in many developing countries. It has been the focus of a number of relatively well-funded efforts for a number of years. For this reason, malaria drug development is relatively further advanced than drug development for many other tropical diseases, and there are "open" initiatives at all stages of drug development, from upstream research through regulatory approval (Strandburg and Allarakhia, 2011). There also are enough different entities working on malaria drug development to make it feasible to compare different approaches at each stage (Strandburg and

Allarakhia, 2011). The anticipated outcome should be an improved understanding of the characteristics of resources managed both within and outside the health commons given the evolution of both the notion of openness as applied to resources and openness of community.

Characterizing Knowledge: Public Good vs. Quasi-Private Good:

Kenneth Arrow (1962) and Richard Nelson (1959) have long shaped the discussion about knowledge and its supply. Technological knowledge has traditionally been classified as a public good associated with the properties of non-rivalry, non-excludability hence non-appropriability, and indivisibility (Antonelli, 2003). (Table 1) Non-rivalry implies that there is a zero marginal cost from an additional individual using the knowledge (Foray, 2004). Even if one could exclude another user from using the knowledge, it would be undesirable to do so because there are no marginal costs to sharing the benefits associated with the knowledge. Non-subtractability also used in the literature, means that usage by one firm or individual does not reduce the availability of that information for use by others (Foray, 2004). Knowledge is not destroyed or altered by use. Often, increased usage of the knowledge can enhance its value and applicability, thereby exhibiting positive externalities (Antonelli, 2003). Knowledge is also indivisible as the utility of this good cannot be parceled out among different individuals. Instead, value may be created through the collective use of the knowledge with individuals jointly benefiting from the knowledge (Antonelli, 2003).

Free-rider problems are typically associated with the provision of public goods—as the producer of knowledge cannot easily exclude others from using the knowledge. Free-riders do not need to reveal their preferences concerning which public goods should be provided. These individuals will understate their true preferences in the hope that others will bear the burden of the cost of producing the good. However, with individuals acting in their own self-interest, resources may be under-allocated to the provision of such goods (Nicholson, 1985).

In the Arrowian tradition of classifying knowledge as a public good, markets are not able to provide appropriate levels of knowledge because of the lack of incentives associated with non-excludability and non-appropriability. The public provision of scientific knowledge became a long regarded basic remedy to the problem of under-provision of knowledge and under-allocation of resources to knowledge production. Accelerating the introduction of new technology stemming from scientific discoveries became the domain of large corporations that could fund new technical knowledge production. Ex-ante monopolistic market power based on barriers to entry in existing product markets would provide the financial resources to fund new knowledge production (Antonelli, 2003). Appropriability would then be ensured by barriers to entry based on cost rather than barriers to entry based on imitation (Antonelli, 2003). With the creation of intellectual property rights and the ability to trade knowledge, incentives to produce both scientific and technological knowledge could be ensured by the market (Scotchmer, 1991; 2004; Foray 2004).

The transformation of knowledge from a purely public good to a "quasi-private good" has highlighted the need for balance between incentives for the market provision of scientific and technological knowledge by a first innovator and incentives for the market provision of

incremental knowledge by a follow-on developer (Scotchmer, 1991; 2004). The possibilities for holdouts and high transaction costs associated with gaining the right to use knowledge in downstream activities, increase as a function of the complementarity, non-substitutability, and applicability of the knowledge. (Table 1) Holdouts occur when buyers need to acquire complementary assets from sellers and sellers raise their prices to capture some of the value the buyer attributes to collectively holding the assets (Merges, 1994). Holdouts can also occur when owners control blocking patents, requiring the follow-on developer to license the knowledge for downstream research or to sell a product that embodies the knowledge. In this case, the first innovator will try to garner as much of the value of improvements or of the downstream product as possible (Merges, 1994). Licensing can involve fixed-fees, royalties, and reach-through claims on future knowledge (Burk and Lemley, 2003). Hence, bargaining failures occur when the first innovator and follow-on developer are unable to reach an agreement regarding the license to knowledge and the rights to future developments.

Impacting the bargaining process is the structure of knowledge. Upstream complementarity occurs among research inputs during the generation of new knowledge while downstream complementarity occurs in the development phase during the application of new knowledge (Antonelli, 2003). Complementary knowledge can be used to generate new knowledge in the same specific context or in other adjacent ones. Knowledge will be pooled from the public domain or from owners of the knowledge willing to trade at a reasonable cost. Knowledge may also be lacking in direct substitutes. Others may not be able to substitute for or "invent around" the knowledge and may require varying degrees of access for new knowledge creation. Without the availability of substitute knowledge, owners can extract high rents from potential users. Finally, knowledge can be applied to a variety of new products and processes. Both owners and downstream users of knowledge will treat knowledge that applies to a narrow and specific range of activities differently than knowledge that has important applications to a great array of downstream activities.

Knowledge Property	Definition
Non-rival	Zero marginal cost from an additional individual using the knowledge.
Non-subtractable	Use of knowledge does not reduce the availability of that knowledge for use by others.
Non-excludable	One cannot easily exclude others from using the knowledge; Free riding occurs.
Indivisible	Utility of knowledge cannot be parceled out among different individuals; Value created through the collective use of knowledge.
Complementarity	New knowledge production is conditional on the identification and integration of diverse and dispersed units acting as inputs.
Non-substitutable	Knowledge may be lacking in direct substitutes; One may not be able to "invent around" the knowledge.
Applicability	Knowledge can vary in terms of applicability in downstream use—from narrow to wide-ranging application.
Embodiment	Knowledge may serve as inputs into downstream use

	or as part of final embodiment.

Table 1: The Properties of Knowledge

Characterizing Biological Knowledge:

Knowledge first begins as an idea or concept. Knowledge may therefore, serve as an input into further development and the creation of new knowledge or serve as components of the final embodiment of research and development activities. From purely public knowledge, to quasi-private knowledge, to private knowledge embodied in products or processes, knowledge moves into the market with varying degrees of power provided to the owner (Dalrymple, 2003).

Hess and Ostrom (2003) propose that given the complex nature of knowledge a three-fold distinction is necessary for knowledge based assets—namely, facilities, artifacts, and ideas. Facilities store artifacts in order to make them accessible. Traditional facilities have been libraries and archives containing books, journals, and papers. New technologies have made electronic, distributed information possible. Artifacts are discreet, observable, nameable representations of ideas, such as articles, research notes, books, databases, maps, computer files, and web pages (Foray, 2004; Hess and Ostrom 2006). Whereas traditional knowledge artifacts such as books and journals are rivalrous, digital artifacts can often be used concurrently by multiple users. Ideas are coherent thoughts, mental images, creative visions, and innovative information. Ideas are the intangible content and the nonphysical flow units contained in artifacts (Hess and Ostrom, 2006). In the context of the health commons, it will be essential to distinguish those resources that are inputs to (information, funding, human capital, equipment) and those that are outputs (information, materials, tools, technology) from the commons. As a consequence, the notion of facilities or repositories must incorporate those that will house data, materials, and tools. Furthermore, it is equally important to expand on the attributes of biological knowledge by considering the underlying characteristics (complementarity, complexity, and applicability), as well as form of knowledge (disembodied vs. embodied). The characteristics and form of knowledge will directly influence how knowledge outcomes are managed physically or disseminated to members and the public at large.

For example, intellectual property rights are increasingly being sought for gene families, target families, and biological pathways. By staking out claims to such families and pathways, if the claims in a patent cover more than the territory of innovation of a first innovator, subsequent innovations by other innovators, based on the first innovation, can be blocked (Scherer, 2000). If the first innovator cannot or chooses not to fully exploit all technological opportunities presented by the patent, high private costs exist for those follow-on innovators who cannot "get around" such patents (Scotchmer, 1991; Merges, 1994). In Figure 1, two different knowledge units with varied characteristics and impact on downstream product development are represented. Knowledge unit A is high in complementarity, high in applicability, but also high in substitutability. The products developed from knowledge unit A are represented by the inner circle. The outer circle encloses substitute products that are supplied by competitors (targeting the same market) using non-infringing knowledge, thereby constraining the profits earned by the owner of knowledge unit A. Knowledge unit B is high in complementarity, high in applicability, but low in substitutability. The products developed from knowledge unit B are represented by the

inner circle. In this case, a patent on knowledge unit B is a blocking patent. Other firms will have to acquire a license from the owner of knowledge unit B in order to develop products that embody this knowledge; these infringing products are represented by the outer circle. It is possible that firms may develop products that will target the same market. The decision therefore to license knowledge unit B will have to include a comparative assessment of the increase in revenue from licensing versus the loss in revenue from competitor products.

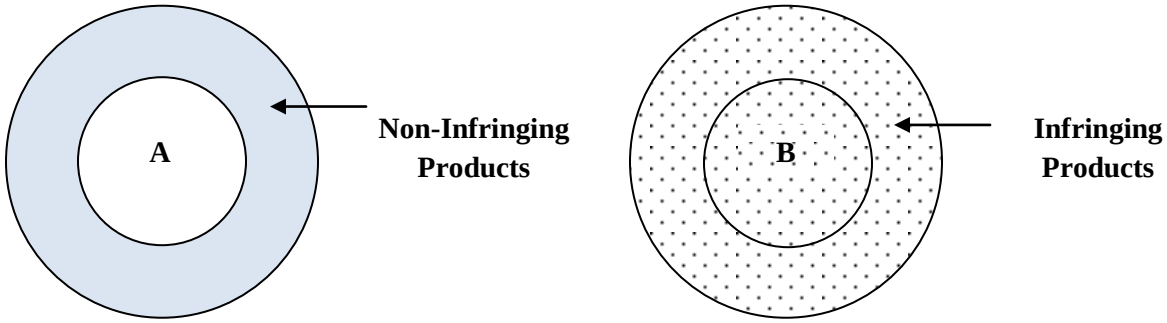

Figure 1: Comparing Knowledge Characteristics and the Impact on Downstream Development

As the degree of complementarity, non-substitutability, and applicability of upstream knowledge increases, excessive privatization will increase the transactions costs associated with procuring licenses to the required knowledge and the possibility of bargaining failures (Merges 1994; Antonelli, 2003). Differences in the ability to tolerate these transaction costs will complicate the bargaining process. Large corporations with substantial resources will be in a better position to negotiate licenses on a case-by-case basis than public sector institutions or small start-up firms. This asymmetry may make it difficult to develop mutually advantageous licensing agreements (Heller and Eisenberg, 1998).

Knowledge can then be valued as a good itself and sold in disembodied form in the market for technological knowledge or embodied into tools, diagnostics, or drugs (Antonelli, 2003; Foray 2004). The choice of exclusively licensing or non-exclusively licensing a patent is a function of the characteristics associated with the knowledge, the desire of the patent holder to maximize revenue from the disembodied versus embodied knowledge, and the desire to diffuse the knowledge versus develop the knowledge (Arora and Fosfuri, 2003; Foray, 2004). The decision to sell disembodied knowledge in the form of patents and licenses can complement or substitute for the sale of embodied knowledge in the form of products. Substitution may occur when the value attained from the sale of disembodied knowledge is greater than that from the sale of embodied knowledge (Antonelli, 2003; Arora and Fosfuri, 2003). When the costs of internal coordination of the knowledge are larger than the transaction costs associated with the market for technical knowledge, or when special assets are required to progress further downstream, the patent holder may pursue a licensing strategy, specifically an exclusive licensing strategy (Teece, 1986; Antonelli, 2003; Arora and Fosfuri, 2003).

Complementarity between the sale of disembodied knowledge and internal embodiment occurs when knowledge possesses high applicability and it is possible to operate in different, exploitable

markets from other licensees of the knowledge (Teece, 1986; Arora and Fosfuri, 2003; Foray, 2004; Scotchmer, 2004). In this case, a non-exclusive licensing strategy can ensure that multiple participants can pursue multiple streams of research. Finally, cross-licensing is a useful innovation management strategy when knowledge exhibits high levels of complementarity (Shapiro, 2001). With downstream activities dependent on the recombination of a variety of knowledge, the cost of the coordination including accumulation of the full range of required knowledge may be too high for one innovator (Antonelli, 2003; Burk and Lemley, 2003). Specifically, the capabilities of the one innovator may only cover a portion of the research domain. Innovators may therefore find it profitable to engage in cross-licensing for knowledge. However, the ability for each innovator to access knowledge depends on the amount and type of proprietary knowledge each one is able to contribute in any bargaining event (Antonelli, 2003).

A Response to IP Complexities—The Emergence of the Health Commons:

The ex-post view of intellectual property (IP) analyzes appropriation strategies and intellectual property rights transfer as a means of providing access to and then fostering downstream knowledge use in product development. In contrast, the ex-ante view analyzes other mechanisms available, either prior to patent assignment or during patent assignment, to ensure access to and use of knowledge for product development. For example, despite the accompanying issues, open source drug discovery is one solution that is increasingly being sought to manage product development complexities. Mirroring the efforts of the open source community that developed Linux, open knowledge networks and other cooperative strategies (classified as open source discovery initiatives) are enabling stakeholders to access knowledge-based resources critical to downstream drug development.

While the Human Genome Project catalyzed the open-source movement in genomics and proteomics based research, Allarakhia et al. (2010) discuss that increasingly open source based alliances seek to provide broad access to research based tools—including microarrays, assays, software, preclinical samples—including biological models and tissue samples, and downstream compounds. Interestingly, the emergence of open-source alliances appears to have shifted from the public sector to the private sector—in some cases, with private sector stakeholders such as Eli Lilly, Merck, Pfizer, and GSK unilaterally encouraging open source discovery. As evidence, Eli Lilly, Merck and Pfizer recently announced their commitment to launch a research group in Asia focusing on new therapies and diagnostics for Asia's most common cancer types. The Asian Cancer Research Group's (ACRG) formation represents an example of a growing trend in pre-competitive collaboration in which biopharmaceutical companies combine their resources and expertise to rapidly increase knowledge of disease and disease processes (Weigelt, 2009; Munos, 2010) The three pharmaceutical companies hope to create one of the most extensive pharmacogenomic cancer databases over the next two years using the open source approach.

Likewise, GlaxoSmithKline (GSK) announced that it would make 13,500 compounds that could lead to the development of new and innovative treatments for malaria, including the chemical structures and associated assay data, freely available to the public via leading scientific websites (Hunter and Stephen, 2010; GSK.com, 2010). The release of these data and creation of a

powerful public repository of knowledge are thought to parallel the scale of human genome data release (GSK.com, 2010).

Through the Eli Lilly Phenotypic Drug Discovery (PD2) Initiative, Lilly works with research universities, institutes, and biotechnology companies to uncover compounds that may become future medicines targeting cancer, neurological disorders, and metabolic diseases. Using the PD2 website, external investigators can access Lilly's phenotypic assays. As part of the PD2 business model, promising compounds can be further advanced through optimization. The goal of PD2 is not to promote a random, high-volume compound submission, but rather to stimulate the joint testing of compounds that represent novel chemical diversity and molecular hypotheses that are strategically considered in light of the biology associated with each assay (Hunter and Stephens, 2010; pd2.lilly.com, 2010).

Finally, keeping in mind the complexities associated with transferring technologies to underdeveloped markets, the Open Source Drug Discovery (OSDD) is a consortium that provides a global and open platform for collaborative discovery work into novel therapies for neglected tropical diseases including malaria, tuberculosis, and leishmaniasis (www.osdd.net, 2010). The OSDD provides an online platform for stakeholders with diverse expertise to participate in open drug discovery. Through this platform, the entire drug discovery process is divided into problems that are open for the community to contribute to and benefit from (Munos, 2010; www.osdd.net, 2010).

Such examples are only a handful of the ones that are rapidly emerging to construct the health commons. Critical then to understanding the nature of the health commons is the comprehension of the nature of openness in the commons—in terms of openness of resources and participants. Commons regimes are typically defined both by the degree of openness and control that they exhibit with respect to contributors, users, and resources, including the assignment of control and administration of resource access. The rules-in-use of a constructed commons will delineate its degree of openness including the sharing and use of resources, particularly with respect to use of the resources by members and those outside the commons who do not contribute to or maintain the commons (Madison et al., 2010). Likewise, openness of community is defined by the rules-in-use or criteria that define membership and participation in the community and the relations among participants including the degree to which participants in the commons collaborate with one another or otherwise share human capital as well as resources (Madison et. al., 2010).

In the health commons, an additional level of analysis of openness is necessary—one that evolves with the interactions that occur across the drug discovery value chain. From this perspective, it becomes apparent that openness with respect to resources evolves from open access during the discovery and possibly the preclinical stages to open licensing defining the legal rules associated with knowledge and technology diffusion and usage in product development, to open market access of products for those at the bottom of the pyramid. Openness of community equally refers to the rules-in-use that define membership in the health commons as well as to the open collaborations that occurs within the commons during the discovery and preclinical stages and on the periphery of the commons during the later stages of development including clinical development. Open licensing then involves the administration of

resources as members exit from the commons to interact on the periphery via the property regime where incentives management dictate the necessity for intellectual property and knowledge enclosure to recoup investments during the costly clinical stages.

Beyond the notion of openness, there is the need to consider the structure of the health commons. While the health commons traditionally includes the deposit of data, materials, tools, and patents—that is, upstream knowledge assets enabling the downstream development of drugs, devices and/or diagnostics, we must consider where and how final product based deposits are made given their market access (bottom of the pyramid) restrictions. The possibility of multiple commons exists with the associated interplay between commons consisting of varied levels and targets of openness, participants, and rules-in-use governing resources and participants. Knowledge and resources may be governed by the common pool regime as seen with upstream assets. Resources may be governed by the property based regime as occurs during the later clinical stages of development i.e. during open collaboration on the periphery of the health commons. Alternatively, final products may be governed by a hybrid strategy as seen with marketable product donations—that is, governed by a property based regime, but placed into a geographically restricted common pool governed by public agencies. I then stipulate that entry and exit from the health commons (movement from the common pool or the property based region) can dynamically occur with members entering and exiting and re-entering the commons as the understanding of knowledge progresses (including new knowledge discovery) from the preclinical to clinical stages. Movement however to and from the geographically restricted common pool will likely only occur from the open collaboration space on the periphery of the open access health commons.

Openness as a Function of Resource Type:

Openness can be better understood with the consideration of resource attributes—namely the underlying characteristics of the knowledge. The transition point model recently proposed by Allarakhia and Walsh (2011) is informative here. The transition point in discovery research is the moment when researchers come to believe that the unilateral gains from private management of knowledge through the enclosure of knowledge are greater than the shared gains from open or shared knowledge, via deposit into the health commons. If this transition point occurs too far upstream, holdouts and bargaining failures may preclude downstream development by making knowledge unavailable. The transition point model provides for many of the realities facing an industry under radical change including knowledge structures and the interactions that generate such resources. Shifts in the transition point are often critical to firms operating in similar research or product domains. Figure 2 illustrates the impact of knowledge form and knowledge characteristics on the placement of the transition point, as well as the applicable innovation management strategy. Available innovation management strategies include: deposit of knowledge into the health commons with knowledge open to contributors and non-contributors alike (open access); deposit of knowledge into a modified version of the health commons—open only to contributors (closed access); the use of property based regimes including non-exclusive licensing and exclusive licensing; and the internal use of knowledge assets by the creator(s). For example, when knowledge assets are high in complementarity and applicability but non-substitutable (top left quadrant) often the case for disembodied knowledge, firms can opt to share

knowledge via the health commons—either via the open or closed access commons, or can pursue a licensing or internal development strategy (both property based regimes as it is assumed that knowledge based assets not deposited into the health commons will be enclosed) depending on firm product development goals. I expect however, that the development of the health commons is an attempt to move the transition point further downstream toward development activities (i.e. further to the right in Figure 2).

Allarakhia and Walsh (2011) similarly discuss that as knowledge complementarity falls, or as it becomes less applicable regardless of substitutability (bottom left and right quadrants) or knowledge form, firms find it more effective to pursue exclusive licensing or internal development activities. This condition is intensified as the size of the market to which disembodied knowledge can be applied or embodied decreases (for example, in the case of orphan or rare diseases). Firms then will have to award exclusive licenses or pursue internal product development activities (property based regimes) in order for the licensee or firm to unilaterally capture as much of the market available respectively. It is also suggested that firms will tend to shift to licensing and internal development activities as knowledge becomes substitutable (top right quadrant). Here, protection of knowledge based assets is paramount for capture of downstream rents. This transition likely occurs with movement from discovery research to preclinical and clinical based research and the embodiment of knowledge as drugs and/or diagnostics. Alongside the transition may be the move from open access to open collaboration. During open collaboration the property based regime will dominate. Participants or clearinghouses can encourage for open licensing with the objective to permit broad diffusion of knowledge for product development (differential or humanitarian licensing may be used for example in the case of neglected disease technology). This is particularly salient where participants can operate in multiple adjacent product-based markets. In addition, participants may choose to re-enter the health commons with deposit of new knowledge-based resources generated during their open collaboration based interactions.

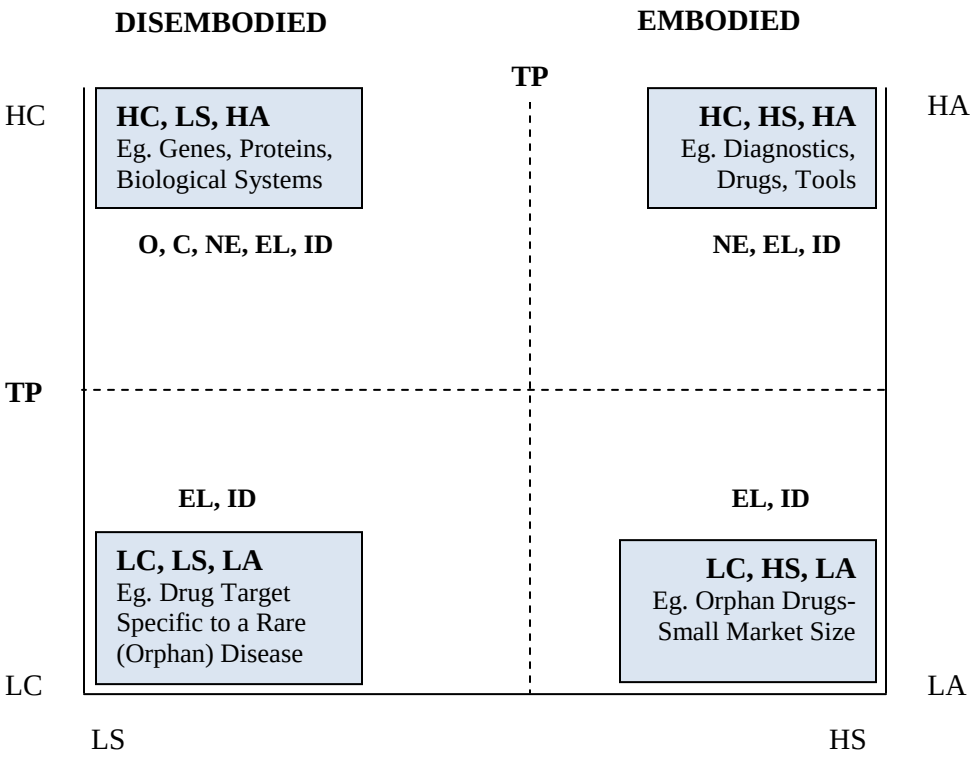

Figure 2: The Transition Point as a Function of Knowledge Form and Knowledge Characteristics

HC = High Complementarity; LC = Low Complementarity; S = Substitutable, NS = Nonsubstitutable; HA = High Applicability; LA = Low Applicability; O=Open Access i.e. Common Access; C=Closed/Exclusive Access for Members; NE=Non-exclusive licensing; EL=Exclusive licensing; ID=Internal Development

Openness as a Function of Participant:

Hess and Ostrom (2006) categorize participants as those that are providers, those that are users, and those that are policy-makers. I propose that participant type—public or private—can alternatively provide some indication of the underlying motivation for participation. Motives can include: the need to create general reciprocity obligations; the need to encourage the adoption of a technology as a standard; the improvement of industry productivity; the need to manage complex product development issues including bundled products with distinct regulatory issues; or the need to pre-empt rivals (Foray, 2004). Motivation for participation will subsequently impact the rules established to govern entry and exit from the consortium ensuring that the objectives regarding knowledge production and deposit levels are achieved and that knowledge appropriation does not occur prematurely (Ostrom et. al., 1994; Foray, 2004). Knowledge dissemination is distinctly associated with driving motivation for participation in the consortium. Of value then is the assessment of participant type, role in the catalyzation of the health commons and knowledge dissemination policy adopted. Allarakhia et al. (2010) provide evidence of this association. Grant agencies or other such government-based agencies tend to advocate knowledge exclusion and alienation rights that favour broad and unencumbered

dissemination[1]. While private sector catalyzed open source initiatives may also favour such broad and unencumbered dissemination—ensuring that downstream product development opportunities are left open for multiple stakeholders—the possibility exists that such private sector stakeholders could advocate more limited exclusion and alienation rights not typically encouraged by public sector agencies.

Rules-in-use Governing Openness:

Rules for participation should be understood at the outset such as the requirement to provide an upfront monetary or resource-based commitment to participate in and maintain the health commons. These commitments will have a differential impact as openness evolves. During the discovery phase, monetary commitments can ensure that supporting infrastructure is developed to ensure broad knowledge dissemination as well as grant policy creation rights for participants who offer such commitments. As openness evolves from open access to open licensing, we may see the commitment of patents via patent pools and monetary commitments to ensure the survival and governance of such pools by third party clearinghouses. Finally, as stakeholders move into open collaboration, monetary commitments enable product development and ensure equity in decision making. Such rules therefore, make certain that participation rights are not only a function of expertise, but also resource availability. In parallel, exit rules can determine when and how participants may move from the common pool regime where open access is paramount to a property based regime typically associated with open collaboration.

Rules must be clear as well for resource provision. Specifically, resource or knowledge control, access, and extraction must be determined in advance and communicated to participants in the health commons regardless of role as resource provider or user. Knowledge use and access can be governed by the following rules: sharing of information and materials with members of the health commons only (closed access); sharing of information and material with members internal to and external to the health commons (open access). In addition, I suggest that intellectual property rights on information and materials should not prevent or impede their future use in downstream activities such as enabled through the use copy-left licenses and royalty free, non-exclusive licensing respectively. Downstream product development rights will therefore, arise jointly with such dissemination policies (Ritala and Hurmelinna-Laukkanen, 2005; Hunter and Stephens, 2010).

Several possible actions may be prescribed to ensure openness. These actions can include: deposit of knowledge into a managed repository or deposit of knowledge within a certain timeframe of discovery. Deposit of knowledge can be to databases or materials and model repositories that are managed by participants within the health commons or managed by third-party organizations to make certain that deposits are validated and then available for usage (including access and extraction of resources) by others within the commons or outside the commons. Timely deposits can be for example, within 24 hours of discovery or creation as was mandated for the publicly funded laboratories engaged in the sequencing of the human genome

[1] Exclusion refers to the right to determine who will have access, contribution, extraction, and removal rights and how those rights may be transferred; and alienation refers to the right to sell or lease management and exclusion rights (Hess and Ostrom, 2006).

(NIH, 1999; Sanger 2011). The goal of the time based deposits is primarily to make sure that intellectual property rights are not filed on knowledge generated within the health commons. In support of this policy, the need may arise to monitor and sanction participants who do not adhere to the requirement for timely deposits. When participants can and do opt to appropriate knowledge, the need to secure broad licensing—namely open licensing, may require participants to either follow policies governing licensing and downstream usage rights crafted by the health commons participants or work jointly with a clearinghouse used by the health commons to manage such licensing and downstream usage rights. I contend that as participants move to the open collaboration space, where product development occurs typically between a limited number of partners, such partners will privately determine the most effective strategies to balance the need for openness of knowledge vs. protection of proprietary technology. During open collaboration, such a balance must seek to manage the positive spillover effect associated with collaboration whilst minimize any negative spillover effects that extend beyond the domain of the partnership (Cohen and Levinthal, 1990).

Multiple Interacting Commons:

I have considered that openness with respect to resources evolves from open access during the discovery and possibly the preclinical stages to open licensing defining the legal rules associated with knowledge and technology diffusion and usage in product development, to open market access of products for those at the bottom of the pyramid. I also discussed the open collaboration that occurs on the periphery of the commons during the later stages of development including clinical development. Open licensing then involves the administration of health commons based resources as members exit from the commons to interact on the periphery via the common property regime. However, once in the open collaboration space on the periphery, any knowledge generated on the periphery would be privately managed by the partners if not re-deposited into the open access health commons. It is important then to take into account the possibility of interactions between multiple commons—specifically, the open access health commons (based on the common pool regime) during the discovery phase and the open collaboration space (based on the property regime) to the open access commons that is based on product access rights. (Figure 3)

Governing movement first from the open access health commons to the property based regime associated with open collaboration during the clinical development phase, will be rules crafted to determine timing of exit, re-entry options, and appropriation rights—including exclusion and alienation rights. Here, on the boundary of these two commons may be third party clearinghouses used to encourage open licensing and downstream usage rights for knowledge assets contributed to and/or generated within the health commons. With respect to re-entry, participants may opt to move from the property based regime to the common pool regime as the understanding of knowledge increases—realizing for example, that knowledge assets once deemed to be of value as enclosed knowledge have more value as shared assets deposited within the open access health commons. Recent history is filled with examples of this movement particularly as knowledge of the genomic basis of disease is augmented. Specifically, we see the move from the property based regime to the common pool regime with genomic data increasingly re-deposited into the

open access health commons. Hence, discovery of new knowledge and changing knowledge structures will determine the movement between these two regimes.

In terms of the open access commons based on product access rights, movement may only be from the open collaboration space. The goal here is the provision of products, likely the donation of health products to those at the bottom of the pyramid. Product-based access is then managed with public agencies operating within this commons. Movement of knowledge from this space will be severely guarded, as participants balance economic (i.e. the need to appropriate rents) and social value creation (reputation effects from product donations for those at the bottom of the pyramid) from downstream product development. Hence, movement will be uni-directional and in only limited circumstances given the parameters of the target market for product development. I will discuss this movement as I now consider the saliency of openness for neglected diseases such as malaria.

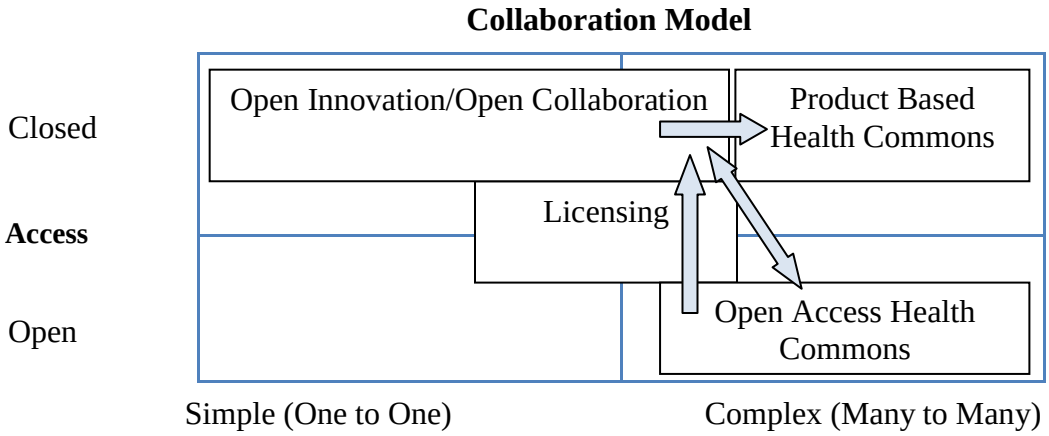

Figure 3: Interaction between the Commons

Open Access=Participation Open; Closed Access=Participation Closed or Limited; Simple=One to One Link between Partners; Complex=Many Links between Stakeholders. The location in the above grid determines the extent to which the collaboration is open or closed and between one, few or many partners; the arrows indicate the movement that is possible from each space.

Saliency of Openness for Neglected Disease Technology Development:

The incentive to engage in R&D targeting neglected diseases has typically been carefully managed through public-private partnerships (PPP). These partnerships have the objectives to encourage the creation of new technology and to ensure its availability to as many patients in disease-endemic countries. Taubman (2010) discusses that the World Health Organization has distinguished PPPs for product development for neglected diseases from PPPs focused on access to existing drugs (Merz, 1995). Product development PPPs are non-profit organizations that sponsor others to conduct R&D—be it discovery, preclinical, clinical, or manufacturing based activities. Access PPPs are instead non-profit organizations primarily concerned with expanding access to health-based technologies in existence, by collaborating with manufacturers and

funding agencies, as well as developing countries. Through such collaborations, access PPPs play a role in the purchase and distribution of existing drugs, vaccines and other medical technology in developing countries (Merz, 1995; Taubman, 2010).

Product development PPPs carefully craft out agreements pertaining to both the rights to and exercise of background intellectual property (that is, IP that both or either parties bring to the partnership from the outset) and research or project based IP (that is, IP generated from funded research and development). PPPs as such, must balance the need to encourage their private sector partners to engage in the necessary R&D including resource commitment where such R&D generally would not occur without sponsorship and the need to ensure broad access to the final products to patients in neglected markets. IP management in this case, may involve IP exercise rights segregated by market, with the private sector player maintaining ownership and/or exercise rights in developed markets while ceding rights for developing markets; access to IP beyond the scope of the sponsored research such as background technology required for final product development; march-in-rights that ensure that IP will be transferred to the non-profit organization in the event that the private sector partner fails to meet its commitment; and access to necessary IP (including to test data, background technology, manufacturing know-how) provided for third parties in the event that the original private sector partner fails to meet the agreed upon criteria for dissemination of the new product in neglected markets (Taubman, 2004; Taubman, 2010).

Access PPPs may alternatively consider the optimal downstream distribution of a finished product and not give priority to ownership of IP. As a consequence, IP ownership can be traded in exchange for meeting specified distribution targets. In this case, ownership rights to IP generated through funded research, access to background IP, and provisions pertaining to licensing new technology particularly for developed markets, can be used as part of the trade-off for fair and broad technology distribution to neglected markets. The trade-off will include distinct requirements for how the technology is to be distributed in target markets such as volume of distribution, preferential pricing, or access provided on the basis of non-market mechanisms (Merz, 1995; Taubman, 2004; Taubman, 2010; DNDi, 2011; IAVI, 2011).

While the literature is filled with discussions of PPP IP ownership and exercise rights provisions, further analysis reveals a multitude of other mechanisms employed by public sector and private sector stakeholders to promote openness including: the development of disease specific commons; open collaboration; humanitarian or preferential licensing; patent pools under a joint licensing scheme; patent commons with non-assertion pledges; and donation programs providing access to final products. I will now follow this evolution of openness and the associated strategies in the context of malaria. The attention surrounding malaria given its fatal impact in neglected markets will permit not only access to the necessary literature, but will reveal the usage of unexpected mechanisms promoting openness—moving beyond the sole consideration of IP ownership and exercise, to the openness of resources across the product value chain.

Evolution of Openness for Malaria:

Public-Private Partnerships: Open Collaboration, Licensing and IP Management

The discussion of strategies to develop technologies for the treatment of malaria typically begins with the Medicines for Malaria Venture (MMV) and Malaria Vaccines Initiative (MVI). MMV was launched in 1999. As a virtual organization, all of MMV's R&D, access and delivery activities are undertaken in collaboration with partner organizations across the world (MMV, 2011). MMV has worked in partnership with more than 130 research institutions and companies. Pharmaceutical and biotech partners bring expertise and facilities in drug discovery and development, including access to cutting-edge technologies to speed up discovery by compound screening, as well as manufacturing capability. In the public sector, academic research institutions bring scientific research expertise and facilities in areas ranging from basic biology to clinical medicine and field expertise (MMV, 2011).

When MMV enters into contractual relationships with its partners, its primary goal is to make certain that the malaria drugs it develops and launches will be accessible to those most in need in malaria-endemic countries. To facilitate this goal, MMV requires special treatment of the intellectual property (IP) that is brought to and developed under a research program. Specifically, MMV and its partners decide on an appropriate strategy for managing existing and newly generated IP. Such a strategy includes whether IP generated under the program should be the subject of a patent application or should be dedicated to the public domain. (Table 2) This requires MMV and its partners to determine whether the IP has value as an incentive for the partners or others in later-stage commercialization of the resulting products—providing evidence of the saliency of determining the correct transition point given the characteristics and structure of the associated knowledge. The decision is a matter of deposit then into the health commons or the decision to appropriate technology and move to the periphery of the health commons. If IP is generated during a given research program, it is not essential that MMV will take an ownership position in it to accomplish its mission. If, however, ownership of IP does not vest in MMV, MMV will insist on appropriate license rights to any compound(s) being developed under its portfolio (MMV and Intellectual Property Rights, 2011). Particularly in the event that partners cannot follow through with their original commitment, agreement provisions permit MMV to take ownership or appropriate licenses to both program and background intellectual property rights (IPR) to allow the project to be completed and the resultant drug to be launched in malaria-endemic countries. The provisions address exclusivity, royalties, and transferability rights (MMV and Intellectual Property Rights, 2011).

If MMV does not own the necessary IPR outright, it would insist on being granted an exclusive license to use the program IPR and any necessary background IPR. That license should be worldwide, to ensure maximum flexibility for later-stage activities such as manufacturing and distribution. Any such licenses are preferably royalty-free, at least in malaria-endemic countries, to help keep costs to a minimum and ensure that the drug will be sold at the lowest price possible in these countries (MMV and Intellectual Property Rights, 2011). The exclusive right enables MMV to control the broad dissemination of final products. Moreover, MMV does not conduct any R&D in-house or any manufacturing and, therefore, requires IPR that can be transferred to

other partners – especially manufacturing partners as necessary. With respect to final products, MMV will negotiate for delivery to the poor in developing countries to be on a "no profit, no loss" basis (MMV and Intellectual Property Rights, 2011).

The PATH Malaria Vaccine Initiative (MVI) also established in 1999 is a global program of the international non-profit organization PATH. MVI seeks to accelerate vaccine development through multiple approaches including partnering and the funding of promising projects. MVI has several partnerships in vaccine projects worldwide (Shotwell, 2007). The Initiative establishes product development partnerships around promising malaria vaccine approaches through the application of PATH's Guiding Principles for Private-Sector Collaboration. In openness with respect to participants or proposed private sector collaborations, PATH considers three issues: Availability, Accessibility and Affordability (PATH's Guiding Principles for Private-Sector Collaboration, 2011). In terms of availability, PATH ensures that the organization as well any associated collaborators can create a product-development program that will be sufficiently rigorous, funded, and prioritized to provide a reasonable opportunity for success. With respect to accessibility, PATH and any collaborators must develop a manufacturing and distribution plan that can lead to sufficient quantities of the product made available through appropriate channels to meet clearly defined public-sector demand in developing countries. Finally, affordability involves an open discussion and then agreement upon a product pricing approach that can result in widespread adoption in public-sector programs of developing countries over a reasonable time (PATH's Guiding Principles for Private-Sector Collaboration, 2011). The Initiative in parallel has outlined several rules-in-use for partner selection and management including assessment criteria, and the definition of roles, responsibilities and expectations respectively. Any agreement for example must include a clearly defined management, and decision-making structure for the collaboration and a clearly stated process for monitoring, evaluating, and terminating the collaboration (PATH's Guiding Principles for Private-Sector Collaboration, 2011).

As a publicly funded organization, PATH has an obligation to ensure dissemination of the results of its private-sector collaborations. PATH explores a variety of approaches, incentives, and mechanisms to fulfill both public and private sector goals (PATH's Guiding Principles for Private-Sector Collaboration, 2011). The management of intellectual property appears to be defined within the guidelines principally in terms of types of collaborations: technology transfer, product development support, and product introduction. The first two collaboration types are relevant to the discussion of technology and IP management. Transfer of a technology developed or owned by PATH may occur to a private sector collaborator including intellectual property for further development, manufacturing, and distribution. Ultimately then PATH supports collaborators by providing significant resources or expertise (such as funding, management, co-development, and assistance with clinical studies) to a private-sector collaborator. Once again we see interactions on the periphery of the open access health commons. In this case, IPR are utilized by PATH to ensure that a collaborator seeks to increase the availability, accessibility, and affordability of the technology in developing-country public health programs. PATH recognizes that commercial benefits are necessary in order to ensure a sustainable commitment to the collaboration (PATH's Guiding Principles for Private-Sector Collaboration, 2011). (Table 2)

The Drugs for Neglected Diseases Initiative (DNDi) is similarly, a not-for-profit product development partnership working to research and develop new treatments for neglected diseases, in particular human African trypanosomiasis, leishmaniasis, Chagas disease, malaria, paediatric HIV, and specific helminth-related infections. Since 2007, DNDi has delivered four products including a two fixed-dose anti-malarials (ASAQ developed with Sanofi and ASMQ) (DNDi, 2011). In the development of ASAQ with DNDi, Sanofi used differential pricing tailored to local conditions alongside discretionary IP enforcement. The company decided to forego its patent rights to the new formulation, while pricing was tailored for different distribution channels (Sanofi-aventis, 2007; Mansell, 2010). For example, in public sector markets, the new formulation is sold as ASAQ Winthrop at a no profit/no loss price, equivalent to less than $0.5 per day for children under five years of age and less than $1 per day for adults. A branded version, Coarsucam, is sold through private pharmacies at a regular price, and the combination product is also available under the Impact Malaria brand at a no profit/no loss price (Sanofi-aventis, 2007; Mansell, 2010).

As a move toward further open collaboration is the recent announcement by Sanofi and DNDi of a three-year research collaboration agreement for the research of new treatments for nine neglected tropical diseases (NTDs) to treat patients in endemic countries. The open collaboration will involve Sanofi bringing molecules from its libraries into the partnership, while DNDi and Sanofi will collaborate on research activities. Noteworthy is the agreed upon management of intellectual property generated through the collaboration (DNDi, 2011). The rights to results produced by this partnership will be co-owned by Sanofi and DNDi. Further, the partners will facilitate publication of the results (and hence deposit into the open access health commons) to ensure access to the wider community of researchers focusing on NTDs. The public sector will benefit from the drugs developed through this agreement with ease of access for patients in all endemic countries, irrespective of their level of economic development (DNDi, 2011). We see therefore, that the differential management of knowledge generated through the collaboration is a function of its form and structure. Technology generated through the partnership will be managed through the open collaboration partnership with research results deposited and managed through the health commons. (Table 2) The next sections discuss at greater length the governance of varied knowledge types such as sequencing information, chemical compounds, and other materials. The increased use and participation in the health commons to manage these knowledge types is likely a result of several factors namely: changing paradigms with an increased focus on the underlying and upstream biological processes of a disease; an increase in the knowledge of such biological processes with the completion of the Human Genome Project; and the increased complexities associated with technology development that require broad access to upstream knowledge from multiple sources and providers.

Initiative	Participation in the Health Commons	Participation in Open Collaboration
MMV	Possible IP donation to the Health Commons.	Technology based partnership; IP management and IP transfer as necessary.
MVI		Technology based partnership; IP transfer as necessary.
DNDi	Research results deposited into the Health Commons.	Technology based partnership; Co-ownership of resulting IP.

Table 2: PPP Participation in the Commons and on the Periphery of the Commons

Discovery Research—Balancing Open Access and IPR

The International Human Genome Project catalyzed the open-source movement in genomics-based research. Globally dispersed laboratories jointly collaborated to map and sequence the Human Genome (Senker and Sharp, 1997; Larsson et al., 1998; Davies 2001). The resulting data were rapidly deposited into the public domain to ensure an open and level playing field for all researchers (Davies, 2001). In this respect, we see the beginnings of the formation of the open access health commons. Allarakhia et al. (2010) recently analyzed 39 consortia focused on genomic, proteomic, and systems-based research. From their analysis of consortia, it was determined that many of the consortia themselves use rules and binding agreements to defer appropriation until the characteristics of knowledge warrant patenting to ensure that downstream products are developed. Consortia differentiated between disembodied knowledge in the form of raw data and embodied knowledge created by consortium members in the form of tools, biomaterials, and reagents. Although data that was high in complementarity and applicability, but low in substitutability was mandated in most cases for almost immediate release, tools, biomaterials, and reagents (in most cases, high in complementarity and applicability, as well as in substitutability) could be appropriated and licensed to consortium members and the public at large. In most cases, appropriation was also regulated by the provision of rules regarding licensing terms provided by the National Institutes of Health (NIH), the Wellcome Trust, the Creative Commons, and/or the Biological Innovation for Open Society (Allarakhia et. al., 2010).

For the purposes of this paper, an analysis of MalariaGEN, the ChEMBL—Neglected Tropical Disease archive, and the Malaria Research and Reference Reagent Resource Center (MR4) provides an understanding of the parameters of open access for upstream data, tools, materials, reagents, and compounds targeting malaria. In the first two cases, knowledge is deposited into the health commons with management of its dissemination ensured by a designated institution. In the latter case, MR4 enables material transfer and serves as a materials repository and clearinghouse. IPR associated with material and/or reagents deposited into the MR4 repository are however under the domain of the original depositor and must be respected in downstream commercial usage. MR4 therefore exists on the boundary between the open access health commons and the periphery where product development and open collaboration are common.

MalariaGen: MalariaGEN is the Malaria Genomic Epidemiology Network. MalariaGen was founded in 2005 and is a community of researchers in more than 20 countries. These researchers seek to understand the biology of both host and parasite as affecting disease progression and based on this knowledge have the objective to develop technology to control malaria. Supporting knowledge discovery and technology development, MalariaGen has established policies for data-sharing permitting large-scale collaborative projects to be conducted across multiple populations, bringing together clinical and epidemiological data with technologies for genome sequencing and web tools for data analysis (MalariaGen, 2011). The work of the network is coordinated by a resource centre whose members are based at Oxford University, the Wellcome Trust Sanger Institute, the London School of Hygiene and Tropical Medicine, and the Wellcome-Mahidol Unit in Bangkok (MalariaGen, 2011). The resource centre has responsibility for the stewardship of samples and data contributed to consortia-based and community-based projects.

MalariaGEN therefore aggregates the work of many different partner studies in malaria-endemic regions around the world, each of which is led by an independent investigator. MalariaGEN adds value to partner studies by providing access to genotyping and sequencing technologies and by providing a framework for sharing and integrating data in consortia-based projects and community-based projects (MalariaGen, 2011). In a consortia-based project, a group of investigators collaborate to address a scientific problem which requires standardized research methods. The main results are published collectively by all the investigators concerned, but individual investigators retain ownership of the samples that they have contributed, and can use the data for their own analyses and publications (MalariaGen, 2011). In a community-based project, there can be many partner studies which operate independently. Each partner study contributes specific items of data to an open-access database that is then available to the whole scientific community (MalariaGen, 2011). Multiple levels of participation—investigator, research participant, and research centre member are possible including the opportunity to collectively or unilaterally conduct research within the MalariaGen commons.

The MalariaGen 'Joint Policy on Data Sharing, Intellectual Property and Publications' addresses several key principles for knowledge management—defining both the openness and enclosure of knowledge. In addition, MalariaGen addresses the ethical issues associated with data release and sharing with the intention of protecting research participants and their communities (Parker et al., 2009). Issues addressed in the joint policy include: the sovereignty of physical samples and clinical data contributed as remaining with the contributing investigator; immediate access to genotyping data to contributing investigators generated on their samples; the availability of only phenotype data for consortium experiments; the need for consortium experiment results to made public unless they are being considered for IP protection as determined by the project management committee (part of the resource centre); and authorship issues related to consortium publications (MalariaGen Joint Policy, 2005). With respect to IPR, the joint policy further advocates that IPR will be deemed necessary only to enhance technology transfer to developing countries, that is, when the discovery is directly relevant to clinical application (with the clear identification of the appropriate transition point), likely to be immediately licensed out and needed as an incentive for further downstream development. In the event of royalties arising from IP licenses, mechanisms are sought to make certain that the resulting royalties are

distributed to the appropriate participating communities, and not to investigators. Finally, it is proposed that patents will be licensed to non-profit organizations unless private sector partners are able to dedicate significantly more resources to development. In this case, the necessary steps will be taken to ensure broad access to final products (MalariaGen Joint Policy, 2005). Hence, knowledge governance rights given to the project management committee determine the appropriate deposit of knowledge into the open access health commons versus knowledge development via open collaboration on the periphery. Once again, the project management committee functions on the boundary between the two regimes.

Key principles addressed for the ethical management of genome-wide association (GWA) studies involving research participants include: the need for managed open access by an independent data access committee to protect the identity of research participants; acceptable uses of the data i.e. for medical research only vs. anthropological studies; and timing of data with a policy that allows for a delay in data release for up to nine months after MalariaGEN investigators at the study site have access to their dataset. This latter measure combined with other capacity-building measures is designed to assist in balancing the significant differences in analytic capacity present in developed and developing countries (Parker et al., 2009). Where principal investigators from the study site concur, data may nevertheless be released immediately along with notification of areas of research the MalariaGEN network and individual principal investigators are undertaking with the dataset. Applicants accessing the data are asked to respect these areas of research and refrain from publishing analyses in them prior to the initial MalariaGEN publications on those topics (Parker et. al., 2009). Clearly then, use of managed open access is not only to protect research participants but to ensure equity with respect to capacity development in developing countries where the data may originate.

ChEMBL: In 2010, GlaxoSmithKline (GSK) teamed up with leading public-domain data providers European Bioinformatics Institute (EMBL-EBI), the US National Library of Medicine (NLM) and the US-based informatics service provider Collaborative Drug Discovery (CDD), to make openly available key scientific information on more than 13,500 compounds that could ultimately lead to new treatments for malaria. The release of this data apparently is the first time that a pharmaceutical company has made available the structures of so many compounds into the open access health commons. EMBL-EBI acts as the primary repository for the data on this compound set—serving to both host and manage the data. GSK anticipates depositing more information as it is generated (GSK, 2010).

The data contains the hits or results from a screening of the 2 million compounds in GSK's compound library to determine the effect of these compounds on the malaria parasite. The screening project identified approximately 13,500 compounds that showed strong inhibition on the parasite. Most of the compound structures identified have been classified as capable of being converted into leads. The current microbiological information for the compounds and the structures that have been deposited online can be easily and openly accessed by researchers. In terms of data access, users are permitted to download, copy, and redistribute data as needed. However, in the spirit of open collaboration and to enable rapid development of new therapeutics for neglected disease, when users annotate, add to, or modify these data in a way that adds significant value, these users are encouraged to release their work to the public domain, ideally

by re-contributing their findings to ChEMBL. Finally, users are required to correctly cite data used from the repository in papers or other scholarly work (www.ebi.ac.uk, 2011).

GSK has stated that it will not seek patents on any malaria drug that the compounds generate, and hopes other researchers will also donate their intellectual property to a patent pool for neglected diseases such as malaria. Alternatively, if the GSK donated compounds are used to develop a drug for other types of diseases, then the company would consider the associated intellectual-property issues. Stakeholders must therefore consider that any given compound could end up affecting more diseases than expected and have greater value than expected (Guth, 2010). GSK for instance, found that drugs that inhibited growth of the parasite that causes malaria were of a type marketed to treat cancer (Guth, 2010). As we have seen in the case of the compound donations—that is a movement from the property based regime to the common pool regime, we could equivalently see the movement from the open access health commons to the open collaboration space as new knowledge is discovered regarding the downstream applicability of the donated compounds.

MR4: The Malaria Research and Reference Reagent Resource Center (MR4) was established in 1998 to provide a central source of quality controlled malaria-related reagents and information to the international malaria research community. M4R is supported by the National Institute of Allergy and Infectious Diseases (NIAID) and now functions as part of the NIAID Biodefense and Emerging Infections Research Resources (BEI Resources). MR4 serves to provide improved access to malaria associated reagents; provide improved authentication of materials; standardization of materials and their subsequent usage; act as manager for the distribution and quality control for reagents deposited by investigators; serve as a knowledge resource for malaria research information and protocols; and generate new reagents and materials as knowledge advances (ATCC, 2011). Consequently, MR4 has the dual role of knowledge producer—depositing knowledge into the open access health commons and knowledge manager of deposits—in this case of materials.

MR4 is open to all scientists worldwide. Reagents are donated to the MR4 Center by malaria researchers and their institutions for distribution to other investigators. Special arrangements are possible for in-house reagent development or for the coordination of research collaborations. In addition to providing reagents, the MR4 also aims to promote technology transfer and to foster scientific exchange between new and established malaria researchers (Wu et al., 2001). In terms of intellectual property management, the MR4 preserves the intellectual property and ownership of the depositor materials as designated through the deposit process. Depositors must complete a distribution and ownership rights agreement. The agreement serves as a Material Exchange Agreement (MTA). The MTA governs the intellectual property and material rights for each reagent deposited with and distributed from repository. As a result, the commercial use of a reagent will require prior approval from the depositor and the affiliated institution (MR4, 2011). Hence, MR4 acts as a clearinghouse for reagents and materials, requiring adherence to the stated IPR and management in the MTA. Functioning within and on the boundary of the open access health commons and open collaboration space, the MTA manages the transition from the common pool regime to the property based regime.

In summary, while MalariaGen, ChEMBL, and MR4 all seek to increase the knowledge deposited into the open access health commons, these initiatives equivalently have the objective of fostering open collaborations where property based rights are paramount. In the case of MalariaGen, IPR is used to encourage technology transfer and downstream product development—with an active role assume by MalariaGen committees to manage the associated intellectual property rights. Discovery of any novel uses of ChEML deposited compounds i.e. beyond the scope of malaria could be subject to IPR. Finally, MR4 acquires, authenticates and distributes biological and molecular reagents, while preserving the IPR of depositors. MR4 does not take an active in the management of IPR—using instead the MTA to clarify the rights of both material depositors and users. (Table 3)

Initiative	Participation in the Health Commons	Participation in Open Collaboration
MalariaGen	Facilitates sharing and integration of data in consortia-based projects and community-based projects e.g. via the MalariaGen Commons.	IPR is used to encourage technology transfer and downstream product development.
ChEMBL	EMBL-EBI acts as host and manager of deposited data.	Discovery of any novel uses of ChEMBL deposited compounds subject to possible IPR.
MR4	Knowledge producer and manager of materials and reagents.	MTA clarifies IPR of depositor and affiliated institution; Facilitates collaboration between stakeholders.

Table 3: Malaria Discovery Research—Balancing Open Access and IPR

Moving Along the Value Chain—Openness during Product Development

The lessons of the past provide some indication of the use of open access further along the value chain—specifically, the Expression Project for Oncology (expO) established in 2004. The expO biospecimen repository was one of the first public repositories in the US for cancer biosamples, genomic data, and clinical outcome information. It is a resource that is available to assist non-profit and for-profit research worldwide. Associated with expO is the International Genomics Consortium (ICG). ICG performs many aspects of the project from collecting samples at hospitals, to ensuring quality control, performing analysis, obtaining clinical data and outcome information, creating the public database, and overseeing the redistribution of samples. The results of the expO project are openly available via the Genomic Expression Omnibus (GEO) database; all data is available free of intellectual property restrictions (www.intgen.org/expo, 2011). Contributing institutions play a key role in accelerating progress from discovery to translational or clinical application. As we move along the value chain, we also see the first role of patients in the open access health commons. In this case, patients permit the deposit of knowledge into the health commons via tissue sample donations. In parallel, institutions are encouraged to build upon the data generated through expO to design and perform studies with samples and acquire additional clinical data from donor patients (www.intgen.org/expo, 2011).

Evidence of the usage of this model of open access and collaboration for neglected disease product development is the Open Source Drug Discovery Project (OSDD). Open Source Drug Discovery (OSDD) is a Council of Scientific and Industrial Research (CSIR) Team India Consortium that provides a global platform for collaborative discovery work into novel therapies for neglected tropical diseases including malaria, tuberculosis, and leishmaniasis. OSDD enables the sharing of information, including but not limited to, ideas, articles, papers and other literary work, data, software, applications, notes, results of experiments, patented inventions, and other materials submitted by users. OSDD has more than 4500 registered participants and more than 150 projects on its initial endeavour-tuberculosis (TB) drug discovery. Participants formally register and agree to the terms outlined by the OSDD such as those referring to the management of knowledge assets and the associated intellectual property. These participants post innovative projects online, actively engage in ongoing scientific projects, share positive and negative results, as well as participate in the review process of other projects posted on the OSDD portal. The entire process of drug discovery is divided into problems that are open to the OSDD community.

Participants are required to partially assign their right(s) pertaining to the resources they contribute to CSIR, for the sole purpose of taking action against any potential infringement. Such an assignment is partial and only for the purpose of protecting the intellectual property generated by OSDD. This step seeks to prevent the IPR based on the information, ideas, and intellectual property generated by the OSDD users from being misappropriated. Thus OSDD/CSIR holds the intellectual property over the content generated as protected commons. Information available on the OSDD website in any form is confidential information and the proprietary right of the OSDD. Any appropriation of the information to acquire intellectual property rights, without an explicit license from OSDD, is considered misappropriation of the protected commons, and is liable to legal action under the applicable laws (sysborgtb.osdd.net). By submitting a patented invention for OSDD, donors agree not to place any encumbrances on products or processes arising out of the use of the patented contribution (sysborgtb.osdd.net). The OSDD serves to develop the open access health commons encouraging deposits and governing the associated IP (www.osdd.net, 2011).

In terms of translational research, two pharmaceutical companies recently expressed their desire to be a part of Council of Scientific and Industrial Research's (CSIR) open source drug discovery (OSDD) project for tuberculosis (TB). If the proposals are accepted, the bulk of the cost of the clinical trials will be borne by the government. In addition, if a drug is developed using the resources of OSDD, the parent organization will determine the pricing. Finally, the private company that develops the drug cannot apply for a patent. While stakeholders can engage OSDD via the open collaboration model, the interactions appear to be taking place within the open access health commons. As these downstream activities are unfolding, the early success of the tuberculosis project has provided the incentive to OSDD to target other diseases including malaria (www.osdd.net, 2011).

The expO and OSDD initiatives provide preliminary evidence of the deposit of once enclosed knowledge into the open access health commons. In the expO case, tissue samples donated by

patients are readily available from the commons for clinical research. OSDD is similarly hoping to encourage open collaboration for product development within the health commons rather than on its periphery. Time will tell whether others follow and encourage the broadening of the open access health commons (or the further downstream movement of the transition point). (Table 4)

Initiative	Participation in the Health Commons	Participation in Open Collaboration
expO	Clinical sample donation to the Health Commons.	
OSDD	Open Drug Discovery Process; Information and material deposits to the Health Commons.	IP control by CSIR/OSDD; Joint Product Development; Movement toward and engagement in the Open Access Health Commons.

Table 4: Moving Along the Value Chain—Openness during Product Development

Market Access-Donation Programs

With the launch of products onto the market, private sector stakeholders particularly in the case of neglected diseases may opt to donate drugs to patients in disease-afflicted countries. Public-private partnerships that have the goal of providing drug access play a role at this time. Stakeholders alongside patients will interact in this case via the product based open access commons. Differentiating this commons from the upstream open access health commons is the fact that only products are deposited or donated to the commons. Movement will be uni-directional (that is, from the open collaboration space to the product based open access commons) and in only limited circumstances given the parameters of the target market for product development. (Table 5)

Malarone Donation Programme: For example, in 1996 Glaxo Wellcome offered to donate up to a million treatment courses annually of Malarone, a new antimalarial. The Malarone Donation Programme (MDP) was established and eight pilot sites were selected in Kenya and Uganda to develop and evaluate the proposed donation strategy that ensured controlled and appropriate use of Malarone (Oyediran et al., 2002). Unfortunately the Malarone Donation Program encountered problems in implementation, and ended in September 2001 on completion of the pilot phase, which showed that the donation program was "not an efficient and effective use of resources to achieve the objective of reducing suffering and death from malaria" (Malarone Donation Program, 2001). The fact however that the program failed to meet its objectives, does not preclude the existence of the product based commons (Liese et. al., 2010). The Partnership for Disease Control Initiatives (PDCI) provides evidence of the continued need for this commons.

Partnership for Disease Control Initiatives (PDCI): PDCI is an alliance of pharmaceutical companies, non-government organizations (NGOs), WHO, donors, and other partners collaborating on drug donation programs for neglected tropical diseases (NTDs). The goal is to provide essential medicines free of charge for neglected tropical diseases. The PDCI supports communication, coordination, collaboration, and ensures commitment from stakeholders with assistance for field activities including program implementation, monitoring and surveillance

during the distribution of drugs (Mectizan, 2011). PDCI attests to participation in several donation programs with success attributable to partnerships that have emerged to address both disease control and elimination (Mectizan, 2011).

It appears that donation programs and the existence of a commons to facilitate such programs are not in themselves sufficient to ensure the successful distribution of treatments and reduction of disease burden. Governance and partnerships are equivalently necessary to manage the product based commons and the proposed outcomes of the market-based programs comprising this commons (Liese et al., 2010). Governance has become critical in light of the rise in donation programs and the particular concern among both drug companies and NGOs that the programs will start competing with each other and stretch the NGOs that do the field work. However, with drug companies proactively establishing donor coordination programs to address these concerns and outlining a joint set of objectives to maintain this commons, it is anticipated that these problems will be minimized (Wehrein, 1999).

Initiative	Participation in the Product Based Commons
Malarone Donation Program	One million treatment courses annually of Malarone-antimalarial drug; Eight treatment sites in Kenya and Uganda Chosen.
PDCI	PPP Drug Access Alliance; Governance of donation programs.

Table 5: Market Access-Donation Programs

Moving Forward—Taking Note of the Practical Lessons:

There are several lessons that emerge from this paper: that the changing notion of openness is likely a function of changing knowledge structures and increased discovery; that multiple stakeholders are required to solve the complex health problems facing patients—particularly those at the bottom of the pyramid; and as these stakeholders increasingly collaborate in the currently unfolding convergence paradigm—where multiple technologies such as drugs and diagnostics are used as part of the treatment process—the need for openness and management of IPR will be even more salient.

Health technology development has become associated with a much higher level of knowledge complexity as the sources of knowledge are diverse and derive from a wide variety of scientific fields and technological competencies. Generating new knowledge and embodying knowledge in products or processes are often conditional on the ability to access and then piece together a significant variety of complementary research inputs (Scotchmer, 1991; Foray, 2004; Grant and Baden-Fuller, 2004). In this case, knowledge will be pooled from the public domain or from owners of the knowledge willing to trade at a reasonable cost. The ability to invent around

knowledge will also determine whether or not new knowledge can be generated and then embodied by follow-on researchers that do not directly own the knowledge. The discovery of facts from nature, as is associated with many of the informational, upstream research inputs cannot be substituted (Kieff, 2003; Walsh et al. 2003). If follow-on inventors cannot develop or obtain substitute knowledge, first innovators can potentially extract high rents for rights to access and use the knowledge (Thumm, 2004). At the bottom of the pyramid, equitable capacity may not exist to exploit such knowledge assets. Equity must therefore be ensured for all relevant stakeholders. In the case of malaria drug development, beyond the special ex-post IP considerations used by public-private partnerships, stakeholder must look to ex-ante solutions including usage of the open access health commons. Finally, the reality is characterized by even higher appropriability risks. Research activities are characterized by high levels of risk and uncertainty in terms of both generating knowledge and then in terms of applying knowledge in downstream activities. As patent holders may not be aware ex-ante what knowledge will be key in disease development or drug intervention, patent holders should be willing to either provide access to this biological knowledge at a fair price or consider the transactional effectiveness of the open access health commons (Merges 1996; Heller and Eisenberg 1998; Scherer, 2002; Kieff, 2003).

The knowledge and technological complexities associated with new health technology development in the convergence paradigm (bridging together biotechnology, pharmaceuticals, nanotechnology, IT) create a commercialization space where few if any firms have the full scope to embrace the promise of product development. These factors have led many stakeholders—public or private, small or large, to explore open collaboration, merging together their knowledge and capital. With the convergence of disciplines to find solutions affecting those at the bottom of the pyramid, the issue of openness of new knowledge structures and technology must be considered carefully. As multiple disciplines are increasingly working together, it will be important to understand that each discipline will have its own priorities and conventions regarding knowledge dissemination and knowledge appropriation (Hilgartner, 1996). One discipline may signal its success during knowledge generation through the enclosure and the sale of disembodied knowledge (Hilgartner, 1996). Another discipline may measure its success exclusively by the embodiment of knowledge in products (Hilgartner, 1996). As collaborations cross institutional and national boundaries, the parceling out of intellectual property rights will be a daunting if not an impossible task. With the assignment of property rights, the role of the patent holder in providing broad versus narrow access to the knowledge will then depend on the original incentives for producing the knowledge and the differing countries' intellectual property rights legal systems (Kieff, 2003; Romig et al., 2007). No current intellectual rights model seeks to integrate these elements. Finding the correct transition point is paramount with the clear impact on the timing of and movement from the open access commons to the open collaboration space and vice versa.

The final lesson for stakeholders is the necessity for open-mindedness in interactions across the value chain. The results are of greater significance for those at the bottom of the pyramid who rely on developed countries to provide the health technology so critically needed for survival. Here, an analysis across neglected diseases should provide further insight into the construction of the open access health commons and novel forms of interactions in the open collaboration space,

or even downstream in the product-based health commons where donation programs have a role. (Figure 4)

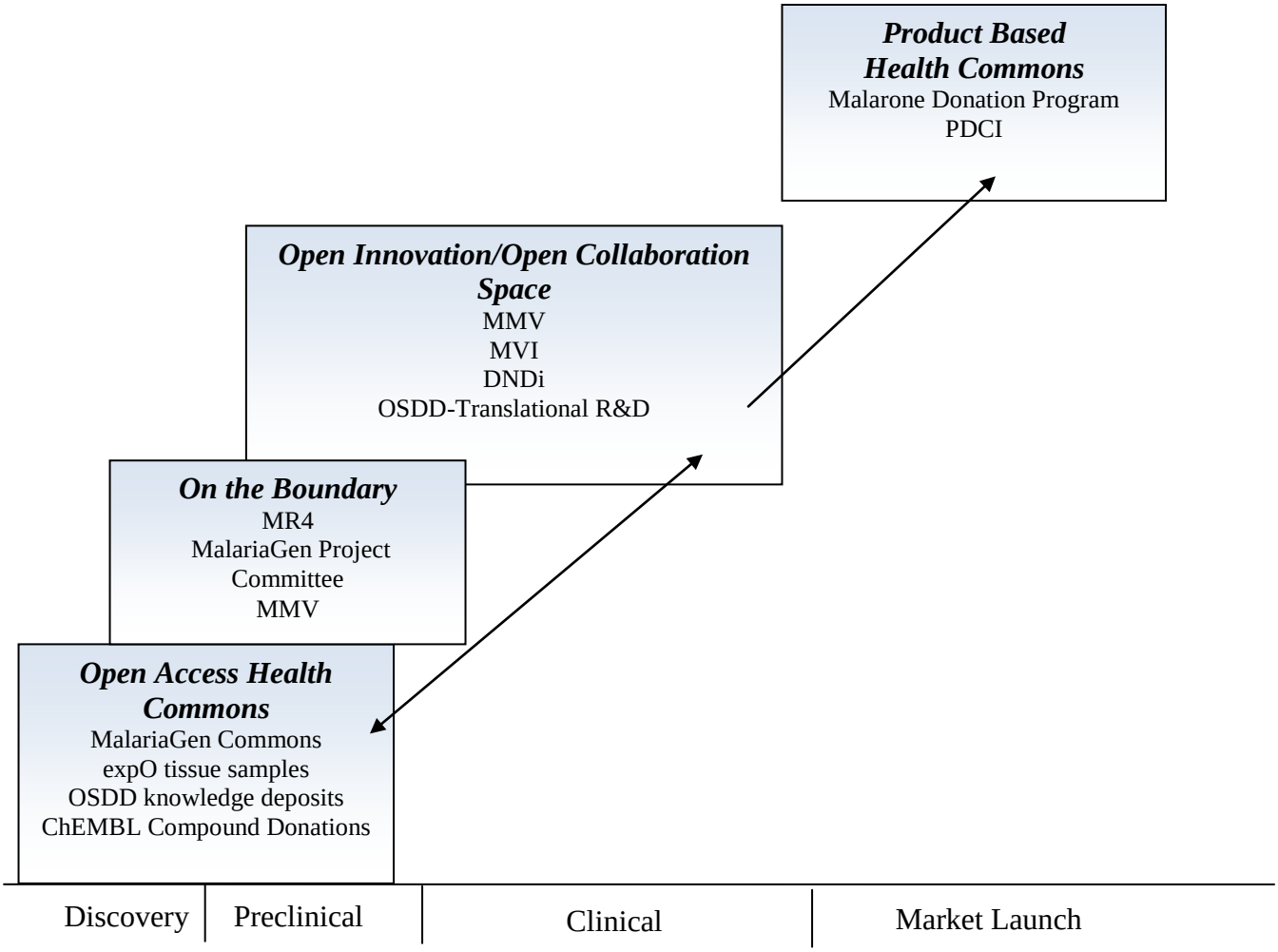

Figure 4: The Health Commons, Open Collaboration Space, and Product Access Commons for Malaria R&D

References:

Allarakhia, M., Kilgour, D.M., Fuller, D., 2010. Modeling the incentive to participate in open source biopharmaceutical innovation. R&D Management 40, 50-66.

Allarakhia, M., Strandburg, K., 2011. A Cultural Commons Study of New Approaches to Drug Development – Case Studies from the Fight Against Malaria, Convening Cultural Commons, Conference of the Engelberg Center on Innovation Law & Policy, September 2011.

Allarakhia, M., Walsh, S., 2011. Managing Knowledge Assets under Conditions of Radical Change: The Case of the Pharmaceutical Industry. Technovation 31, 105-117.

Antonelli, C., 2003. Knowledge complementarity and fungeability: Implications for regional strategy. Regional Studies 37, 595-606.

Arora, A., Fosfuri, A, 2003. Licensing the market for technology. Journal of Economic Behavior & Organization 52, 277-295.

Arrow, K., 1962. Economic welfare and the allocation of resources for invention, In The rate of and direction of inventive activity: Economic and social factors (A report of the National Bureau of Economic Research), Princeton University Press, Princeton NJ.

Burk, D.L., Lemley M.A., 2003. Biotechnology's Uncertainty Principle in Perspectives on Properties of the Human Genome Project, Elsevier Academic Press, San Diego CA.

Cohen, W.M., Levinthal, D.A., 1990. Absorptive Capacity: A New Perspective on Learning and Innovation. Administrative Science Quarterly 35, 128-152.

Dalrymple, D., 2003. Scientific Knowledge as a Global Public Good: Contributions to Innovation and the Economy, in The Role of Scientific and Technical Data and Information in the Public Domain, The National Academies Press, Washington, DC.

Davies, K., 2001. Cracking the Genome: Inside the Race to Unlock the Human DNA, The Free Press, New York NY.

Foray, D., 2004. The Economics of Knowledge, MIT Press, Cambridge MA.

Grant, R.M., Baden-Fuller, C., 2004. A knowledge accessing theory of strategic alliances. Journal of Management Studies 41(1), 61-84.

Guth, R.A., 2010. Glaxo Tries a Linux Approach, The Wall Street Journal, May 26 2010.

Heller, M.A., Eisenberg, R.S., 1998. Can patents deter innovation? The anticommons in biomedical research. Science 280, 698-701.

Hess, C., Ostrom E., 2006. Understanding Knowledge as a Commons: From Theory to Practice. MIT Press, Cambridge MA.

Hilgartner, S., 1996. Access to data and intellectual property: Scientific exchange in genome research, in: Intellectual Property Rights and Research Tools in Molecular Biology, National Academy Press, Washington DC, 28-39.

Hunter, J., Stephens, S., 2010. Is open innovation the way forward for big pharma? Nature Review Drug Discovery 9, 87-88.

Joint Policy on Data Sharing, Intellectual Property and Publications, MalariaGen, July 15 2005.

Kieff, S.F. (Ed.), 2003. Perspectives on Properties of the Human Genome Project, Elsevier Academic Press, San Diego CA.

Larsson, R., Bengtsson, L., Henriksson, K. and Sparks, J., 1998. The interorganizational learning dilemma: Collective knowledge development in strategic alliances. Organizational Science 9, 285-305.

Liese, B., Rosenberg, M., Schratz, A. Programmes, Partnerships, and governance for elimination and control of Neglected Tropical Diseases. The Lancet 375, 67-76.

Madison, M.J., Frischmann, B., Strandburg, K., 2010. Constructing Commons in the Cultural Environment. Cornell Law Review 95 657-710.

Malarone Donation Program, 2001. Malarone Donation Program to end on completion of the pilot phase, http://www.malaronedonation.org/malarone_text.html.

Mansell, P. Why patient access means market access, December 8 2010.
Merges, R., 1994. Intellectual property rights and bargaining breakdown: The case of blocking patents. Tennessee Law Review 62, 75-106.

Merges, R., 1996. Property rights theory and the commons: The case of scientific research. Scientific Innovation, Philosophy and Public Policy 13, 145-167.

Merz, F.J., 2005. Intellectual Property and Product Development Public/Private Partnerships Final Report. World Health Organization, Commission on Intellectual Property Rights, Innovation and Public Health.

MMV and Intellectual Property Rights, http://www.mmv.org/sites/default/files/uploads/docs/policy_documents/MMV_and_Intellectual_Property_Rights.pdf , accessed 9/2011.

Munos, B., 2010. Can open-source drug R&D repower pharmaceutical innovation? Clinical Pharmacology and Therapeutics 87(5), 534-6.

Nelson, R., 1959. The simple economics of basic scientific research. Journal of Political Economy 67, 297-306.

Nicholson, W., 1985. Microeconomic Theory, The Dryden Press, Chicago, IL.

Olukayode Oyediran, A.B.O., Ddumba, E.M., Ochola, S.A., Lucas, A.O., Koporc, K., Dowdle, W.R., 2002. A public-private partnership for malaria control: lessons from the Malarone Donation Programme. Bulletin World Health Organization 80, 817-821.

Ostrom, E., Gardner, R., Walker, J., 1994. Rules, Games and Common-Pool Resources, The University of Michigan Press, Ann Arbor MI.

Parker, M., Bull, S.J., de Vries, J., Agbenyega, T., Doumbo, O.K., et al., 2009. Ethical Data Release in Genome-Wide Association Studies in Developing Countries. PLoS Med 6.

PATH's Guiding Principles for Private-Sector Collaboration, http://www.path.org/files/ER_gp_collab.pdf, accessed 9/2011.

Principles and Guidelines for Sharing of Biomedical Research Resources, NIH, December 23 1999.

Ritala, P., Hurmelinna-Laukkanen, P., 2009. What's in it for me? Creating and appropriating value in innovation-related coopetition. Technovation 29, 819-828.

Romig, A., Baker, A., Johannes J., Zipperian, T., Eijkel, K., Kirchhoff, B. Mani, H.S., Rao, C.N.R., and Walsh, S., 2007. An introduction to nanotechnology policy: Opportunities and constraints for emerging and established economies. Technological Forecasting and Social Change 74, 1634-1642.

Sanofi and DNDi - Drugs for Neglected Diseases initiative - Sign an Innovative Agreement to Generate New Drugs for Neglected Tropical Diseases, May 30 2011.

Scherer, F.M., 2000. The economics of human gene patent. Academic Medicine 77, 1348-1367.

Scotchmer, S., 1991. Standing on the shoulders of giants: Cumulative research and the patent law. The Journal of Economic Perspectives 5, 29-41.

Scotchmer, S., 2004. Innovation and Incentives, MIT Press, Cambridge, MA.

Senker, J., Sharp, M., 1997. Organizational learning in cooperative alliances: Some case studies in biotechnology. Technology Analysis and Strategic Management 9, 35-51.

Shotwell S.L., 2007. Patent Consolidation and Equitable Access: PATH's Malaria Vaccines, Chapter 17.21 in IP Handbook of Best Practices, Concept Foundation.

Taubman, A., 2004. Public-Private Management of Intellectual Property for Public Health Outcomes in the Developing World: The Lessons of Access Conditions in Research and Development Agreements, Initiative on Public-Private Partnerships for Health Geneva.

Taubman, A., 2010. A Typology of Intellectual Property Management for Public Health Innovation and Access: Design Considerations for Policymakers, The Open AIDS Journal, 4, 4-24.

Teece, D.J., 1986. Profiting for technological innovation: Implications for integration, collaboration, licensing and public policy. Research Policy 15, 785-805.

Thumm, N., 2004. Patents for genetic inventions: a tool to promote technological advance or a limitation for upstream inventions? Technovation 25, 1410-1417.

Walsh, J.P., Arora, A., Cohen, W.M., 2003. Effects of research tool patents and licensing on biomedical innovation, in: Patents in the knowledge-based economy. The National Academies Press, Washington DC, 285-340.

Wehrwein, P., 1999. Pharmacophilanthropy. Harvard Public Health Review.

Weigelt J., 2009. The case for open-access chemical biology. EMBO Reports 10(1), 941-945.

Wu, Y., Fairfield, A.S., Oduola, A., Cypess, R.H., MR4 Scientific Advisory Committee, 2001. The Malaria Research and Reference Reagent Resource (MR4) Center--creating African opportunities. African Journal of Medicine and Medical Sciences 30, 52-54.

mectizan.org/pdci, accessed 9/2011.
pd2.lilly.com, accessed 9/2010.
www.atcc.org, accessed 9/2011.
www.dndi.org, accessed 9/2011.
www.ebi.ac.uk, accessed 9/2011.
www.gsk.com, accessed 9/2010.
www.iavi.org, accessed 9/2011.
www.intgen.org/expo, accessed 9/2011
www.malariagen.net, accessed 9/2011.
www.malariavaccine.org, accessed 9/2011.
www.mmv.org, accessed 9/2011.
www.mr4.org, accessed 9/2011.
www.osdd.net, accessed 9/2010.
www.sanger.ac.uk, accessed 9/2011.