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Consortia's critical role in developing medical countermeasures for re-emerging viral infections: a USA perspective

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Abstract

Viral infections, such as Ebola, severe acute respiratory syndrome/Middle East respiratory syndrome and West Nile virus have emerged as a serious health threat with no effective therapies. These infections have little commercial potential and are not a high priority for the pharmaceutical industry. However, the academic community has been active in this area for many years. The challenge is how to take this academic virology knowledge into a drug discovery and development domain. One approach is the use of consortia and public–private partnerships – this article highlights ongoing efforts in the USA. Public funds, such as those from government sources, can support research efforts that do not appear to have commercial value. The key to success is finding a way to combine the different cultural and operational values and reward systems into a productive collaboration to identify new antivirals.

Keywords

antivirals; collaboration; consortia; development; drug discovery; emerging infections; partnerships

Aim

Emerging & re-emerging viral infections

The past 15 years have witnessed the emergence and re-emergence of human viral infections that cause significant morbidity and mortality. These include SARS and MERS coronaviruses, highly pathogenic H5N1 influenza, the pandemic 2009 influenza, monkeypox, West Nile virus (WNV), chikungunya virus and dengue fever virus. Arguably,

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no efficacious therapies exist for most of these diseases and the development of resistance to existing drugs remains a constant concern. Significant effort has gone into identifying and developing vaccines and therapeutic agents for each one of these infections, but thus far success has been limited.

Perhaps one of the most alarming and certainly one of the most devastating recent examples of the re-emergence of an infectious disease is the 2014–2015 outbreak of Ebola Zaire in West Africa, the largest in recorded history. Although all prior outbreaks of Ebola Zaire had occurred in remote areas of Central Africa, this epidemic began in 2013 in the West African nation of Guinea [1]. It is believed that the epidemic started with a single introduction of the virus into the human population in December 2013 by a 2-year-old boy who died after presenting with fever, vomiting and black stools [2]. The outbreak subsequently spread by human-to-human transmission into highly populated areas in Liberia, Sierra Leone, Nigeria, Senegal and Mali. As of October 2015, approximately 28,000 probable, suspected and laboratory confirmed cases of Ebola had been reported, with 11,000 deaths [3]. These cases included 881 healthcare workers who were infected and of whom an estimated 60% died. The outbreak carried over into the USA and Europe via residents and healthcare workers who were exposed to the virus in West Africa (six cases). Two imported cases, including one that ended in death, and two acquired cases in healthcare workers occurred in the USA [4]. This outbreak clearly illustrates the limited ability of our current public health and medical research and development systems to respond to the rapid emergence of a rare, highly virulent infectious disease, particularly in densely populated urban centers. Although attempts were made to utilize vaccines and therapeutic agents in development (many with a primary indication for a different virus), no comprehensive report on how effective these interventions may have been has appeared to date.

To cite a few additional examples, about a decade ago, the total number of cases of SARS between November 2002 and August 2003 alone was 8422 with a mortality of 916 (10.9%). The majority of the cases occurred in Southeast Asia and Canada [5]. More recently, in 2012 a novel coronavirus was identified in the Middle East, causing a respiratory illness, dubbed the Middle East respiratory syndrome coronavirus (MERS-CoV). This virus is genetically and phenotypically distinct from the coronavirus that caused the SARS epidemic in 2003. However, like people infected with the SARS virus, people infected with MERS-CoV quickly developed severe respiratory illness. Approximately four out of every ten patients diagnosed with MERS died [6]. No existing therapies for patients with SARS or MERS, including ribavirin, corticosteroids and interferon were effective. There is clearly a need to develop therapeutics for these biologic threats.

Another emerging infection with pandemic potential is highly pathogenic H5N1 influenza. Since 2003, over 600 cases have been reported to the WHO with a mortality rate approaching 60% [7]. Treatment with neuraminidase inhibitors has shown some benefit; however, the emergence of resistance has occurred [8]. More recently, the engineering of highly pathogenic H5N1 has generated viruses that are readily transmissible in ferrets and has resulted in significant debate among scientists and ethicists as to the foundation for this research [9–13]. Inadvertent or intentional release of these engineered viruses into the general population could have devastating consequences. While no cases of either SARS or

H5N1 influenza have been detected in the USA, the probability of importation of these diseases by widespread global travel is not unreasonable.

The USA continues to experience multiple emerging infections. For example, introduction of WNV has caused clinical infections ranging in severity from totally asymptomatic and uncomplicated WNV fever, to fatal meningoencephalitis. As of December 2011, over 31,000 cases have been reported to the CDC in USA with 1263 deaths (~4.0%) [14]. In 2012, there was a resurgence of WNV disease with over 5300 cases and 243 deaths reported to the CDC. While there have been fluctuations in the number of reported cases, documented disease occurs annually in USA. No therapy, including the administration of high titer WNV immune globulin (Whitley *et al.*, personal experience) has proven efficacious. Furthermore, no small molecule drugs have been developed. Second, monkeypox, a member of the orthopox virus family, was inadvertently imported into USA in shipments of giant Gambian rats for the exotic pet trade. During quarantine, these animals transmitted the virus to pet prairie dogs, which are highly susceptible to infection. In May of 2003, monkeypox spread to approximately 70 individuals who had contact with these animals resulting in 11 clinical cases of disease, one of which was life threatening [15]. There were not and still are not any US FDA-approved drugs for the treatment of poxvirus infections. Third, the USA experienced pandemic 2009 H1N1 influenza that caused morbidity and mortality in select populations, particularly young adults and pregnant women. While the mortality was not as great as that associated with other pandemics, the need for improved antiviral therapies became apparent, especially against drug-resistant strains that circulate globally. Fourth, a decade ago, chikungunya was rarely detected in the USA, even in global travelers returning from areas where the disease was endemic. However, cases began to be identified in 2006, first in travelers returning from Asia, Africa or areas near the Indian Ocean, and subsequently, starting in 2013, in travelers returning from the Caribbean. Local transmission in Florida, Puerto Rico and the US Virgin Islands began to be identified in 2014, and starting this year the disease is a nationally notifiable condition, reporting to the CDC [16]. Fifth, dengue has been reported not only in Puerto Rico but also the continental USA [17,18]. Lastly, although not prevalent in the USA (yet), the most recent outbreak of the emerging infection with Zika virus in Brazil, resulting in microcephaly of babies born to infected mothers, is cause for concern and monitoring [19].

The role of drug discovery/development consortia

Very few emerging infectious diseases, including those cited above, appear to be high-priority targets for the pharmaceutical industry. This can be attributed to multiple factors including: the occurrence of these diseases is mostly in poor, developing countries, the incidence of disease is low and sporadic making it difficult to conduct clinical trials that meet US FDA standards, and the market size for these drugs is uncertain making it difficult to recoup direct development costs. Therefore, industry has focused its efforts on drugs for chronic diseases that are used regularly and consequently have substantially greater commercial potential. More generally, by out-sourcing basic discovery, pharma has the opportunity to save the initial research costs and be more confident in pursuing classic development as opposed to research. Nonetheless, an advantage for pharma in the development of drugs for emerging infections is the ability to apply for and secure from the

US FDA a voucher that can then be applied to expedited review of more traditional medications. However, for smaller biotechnology companies, it is still difficult to obtain early stage financing if the focus is on discovering and developing drugs for emerging/reemerging infections with marginal commercial potential.

Given the profound threat these diseases pose, it is fortunate that many academic drug discovery centers, most of them having started within the last decade, actually have a focus on infectious diseases [20–22]. This is perhaps due to the desire to meet unmet medical need, and the need to differentiate the academic efforts from commercial ones and thus not be in direct competition with entities with significantly greater financial resources. As will be discussed in more depth below, academic drug discovery efforts benefit from a depth of knowledge in biology and medicine, but often lack the infrastructure and expertise beyond target identification, hit identification and initial hit to lead efforts. By contrast, the strength of commercial enterprises resides in target validation, applied medicinal chemistry, preclinical toxicology, clinical trial design and execution, as well as the project management infrastructure necessary to navigate a novel chemical series from concept to investigational new drug (IND) and ultimately to a new drug application (NDA).

To establish a productive collaboration between academia and industry, and to recruit the strengths of both parties into a focused effort, sources of funding must be identified. These could include government sources, such as the Biomedical Advanced Research and Development Authority, whose mission is to advance development and procurement of medical countermeasures for pandemic influenza and other emerging infectious diseases. Additional sources include the advance development arm of the Department of Defense for biodefense-related agents, medical countermeasure systems and its parent entity joint program executive office, the NIH, the CDC, as well as private sources, such as the Gates Foundation and the Wellcome Trust. Early government funding can be used to establish programs and to advance them to the proof-of-concept stage, which can then facilitate securing private funds for commercial development. With adequate funding, academic industry consortia are well equipped to address unmet medical needs and to accelerate the development of medical countermeasures for these infections.

Drug discovery in academia

There has been a tremendous growth in recent years in the number of academic drug discovery centers [20,23]. This has been prompted, in part, by externalization of Research and Development (R&D) by pharmaceutical companies and an enhanced focus by the NIH on translational research (research specifically focused on developing a relevant innovation into a needed product). For example, the formation of the National Center for the Advancement of Translational Science, and its associated Centers for Translational Science Awards, is directed toward these efforts. Many of these academic drug discovery centers incorporate experts from the pharmaceutical industry into leadership positions. In addition, a collaborative network has been formed, the Academic Drug Discovery Consortium (ADDC) [21] to facilitate communication and coordination between these centers. ADDC facilitates matching interests from companies in specific targets and/or diseases with appropriate

academic partners. Their website [24] lists centers and their programs, events, job postings and partnership opportunities, all contributed by its active members.

As might be expected, many of the academic enterprises focus on early-stage projects. A survey by Frye *et al.* showed that as many as 60% of the projects are early stage, namely hit to lead identification, with only 2% of projects in clinical development under an IND [20,23]. The reasons may include practical ones, such as the lower cost and resources needed at earlier stages of discovery. However, it may be strategic as well, such that academic drug discovery has the flexibility of focusing on long-term, high-risk projects, since an immediate shareholder payout is not expected as would be the case for publicly traded pharmaceutical firms [20,25].

As noted above, the majority of funding for academic drug discovery centers tends to come from public sources [26], where the outcome is less rigorously tied to development deadlines, and generally not dependent on commercial expectations [27]. This is also illustrated by the aforementioned focus on noncommercial orphan diseases and ailments afflicting developing countries [20,27]. That is not to say that a desire for licensing revenues does not exist. The financial successes of Emory, Northwestern, the University of Minnesota and Princeton has undoubtedly contributed to the high-level support of novel drug discovery programs at various institutions [25].

However, with few exceptions, academic enterprises typically lack the infrastructure and expertise for later stage efforts to move from lead to clinical candidate. In Frye's overview of academic drug discovery in the USA, it was noted that only approximately half of the centers performed *in vivo* proof-of-concept testing or even basic distribution, metabolism and pharmacokinetic evaluations (DMPK) [20]. For centers that do have the capabilities of later stage projects, public funding from the NIH can be complemented by resources in kind, and/or milestone-based and licensing income from industry partners, if there is appropriate intellectual property (IP) protection for 'new composition of matter.'

Many academic institutions address IP matters inappropriately and focus on patenting targets and assays, which are invariably more difficult to protect and of less value. In addition, in some cases patents are filed too early, as the inventions have not been fully vetted. Another misconception is that once a patent is filed, an investigator is free to disclose the invention and it will be protected. Careful consideration must be given as to when an application will be published versus when the work is actually published in a peer reviewed journal or disclosed in a public forum. In some cases this would require delaying a publication. However, one of the main problems if one is working in a university environment is the academic promotion and tenure system, which rewards faculty for publications and extramural grants. This philosophy tends to be incompatible with the timelines associated with drug discovery and development [27]. In order to obtain protection for a chemical series, publications should be delayed until the patent is actually published, which typically is 18 months after the filing. Several academic groups have circumvented the publish versus patent issues on chemical matter by delaying publication of the lead series and publishing on compounds or series of less interest. Of course, the question remains as to

whether a university's research and teaching missions are compatible with delaying publications to establish an acceptable IP position [25].

Some academic institutions have overcome these sources of friction by creating two parallel tracks: one 'academic,' which is staffed with trainees, focuses on basic science and high-quality data to develop tool compounds and publications, and one 'commercial,' staffed with researchers with industry experience, with a focus on generating compounds with IP [26]. The academic track would follow the usual promotion and tenure guidelines, with the commercial one mimicking a promotion system that can be seen in pharmaceutical or biotechnology companies. Integration would be mediated by senior management, who would also decide which track is most appropriate for a particular project and individual [26].

With all the merits of drug discovery in an academic setting, there is consensus that using more rigorous project management and application of quality control and quality assurance principles as utilized in industry would be beneficial [23]. An example of the latter is that hits identified in high-throughput screens should be filtered to eliminate compounds with reactive groups. This is standard practice in commercial screening operations, but is often overlooked in academic efforts [23]. In a similar vein, the identity and activity of hit and lead molecules should be confirmed before proceeding with additional biological studies. Finally, more effort should be put into validation of targets, as only 18% of academic drug targets had any clinical evidence of validity in Frye's survey [20]. Partnering of academic enterprises with commercial entities that do these activities extremely well has thus immediate merit, since it would avoid duplication and wasting of resources.

Types of consortia & their advantages

There are at least two distinct types of consortia, sometimes also referred to as 'alliances':

- Academia with not-for-profit:
  - An example is the Alabama Drug Discovery Alliance, in which the University of Alabama at Birmingham is partnering with Southern Research, a not-for-profit research institute also located in Birmingham, AL, USA [28]. Other examples, although in the antimicrobial and not the antiviral space, include the opportunity of academic researchers to collaborate with the non-profit Global Alliance for TB Drug Development, whose own partners include industry, NGOs, governments and foundations to provide infrastructure, expertise and funding [29]. A similar structure is provided by the Tres Cantos Open Lab Foundation, which provides an opportunity for scientists around the world to collaborate with teams with pharma expertise from GSK, as well other participating partners in the area of drug discovery and development for malaria, tuberculosis, leishmaniasis and trypanosomiasis, among others [30].
- Academia with commercial partners:

- This category probably has the most examples, such as Janssen's alliance with Vanderbilt University and Eisai's collaboration with Johns Hopkins, both in the neuroscience space [21]. In the antiviral arena a prime example is Gilead Sciences' partnership with the Antiviral Drug Discovery and Development Center (AD3C), an NIAID-funded consortium coordinated out of the University of Alabama at Birmingham (see Box 1). Another earlier example that has yielded some success is the NIH-funded Southeast Regional Center of Excellence for Emerging Infections and Biodefense (SERCEB), which aided Chimerix in the early development of CMX001 (brincidofovir) for the potential prophylaxis and treatment of smallpox.

Box 1

Antiviral Drug Discovery and Development Center: a consortium example

An example of a consortium focused on the development of new antiviral therapeutics is the recently established Antiviral Drug Discovery and Development Center (AD3C), funded in 2014 via the U19 Centers of Excellence for Translational Research mechanism under the NIAID. The goal in the initial 5 years of funding allocated to AD3C is to identify clinical development candidates for one or more indications. AD3C is coordinated out of the University of Alabama at Birmingham ([UAB]; PI: Richard Whitley), and includes the following institutions in addition to UAB:

Academic partners

- Oregon Health and Science University (PIs: Jay A Nelson and Daniel N Streblow)
- Washington University (PI: Michael S Diamond)
- Vanderbilt University (PI: Mark R Denison)
- The University of North Carolina at Chapel Hill (PIs: Ralph Baric and Mark Heise)
- The University of Colorado, Denver (PI: Thomas Morrison)

Not-for-profit partner

- Southern Research (Core Director HTS: J Robert Bostwick; Core Director Medicinal Chemistry: Ashish K Pathak)

Pharmaceutical collaborator

- Gilead Sciences

AD3C focuses on developing new therapeutics for four virus families: influenza, flaviruses, coronaviruses and alphaviruses – all projects focus on inhibition of viral replication as the mechanism of action. The academic partners provide the virology knowledge and a deep understanding of the molecular biology of the various viruses

under investigation. The not-for-profit partner, Southern Research, provides expertise in drug discovery and development, in particular assay development, high-throughput screening and medicinal chemistry. Gilead is the commercial partner and contributes to the screening library and will provide additional chemistry expertise in the later stages of drug development. Since SR will screen the same library against all viruses, it will allow the identification of broad-spectrum compounds in addition to compounds active against only one type of virus.

As mentioned in this perspective, active management of the consortium is key, and is achieved via an administrative core, housed at UAB, which facilitated the reaching of a consortium agreement and ensures communication between partners with monthly conference calls, annual in-person meetings and additional *ad hoc* discussions. The administrative core has also established an external advisory board, which meets with the investigators at the annual in-person meeting and advises on the project portfolio and next steps. Importantly, most external advisory board members have a rich background in antiviral drug discovery, either in academia or the pharmaceutical industry, and have the ability to critically look at the compound progression pathways for the different projects.

In all cases, the strengths of partners' complement each other by combining in-depth understanding of the biology in the academic setting with the know-how of drug discovery and development in not-for-profit entities, such as Southern Research, the TB Alliance and Tres Cantos Open Lab or commercial pharmaceutical/biotechnology companies.

In addition to the two models described above, there are additional creative ways to capitalize on particular strengths of certain institutions that are unique to that particular environment and culture. An example of the latter is offered by Drug Innovation Ventures at Emory (DRIVE LLC). DRIVE was formed as a wholly owned subsidiary of Emory University and staffed with the expertise to finance and direct the development of drugs for emerging/reemerging diseases. It is allied to and under common management with the Emory Institute for Drug Development (EIDD). Taken together, DRIVE and the EIDD constitute a freestanding biotechnology company that has direct access to all of the intellectual and physical assets of Emory University and possess sufficient infrastructure to advance candidates through Phase IIa clinical trials by utilizing a combination of its own resources, external collaborations and outsourcing. Another unique dimension to DRIVE is that it can form for-profit spinouts to raise equity capital to further finance the development of promising drug candidates. Participation in academic consortia to leverage its discovery and development capacity is straightforward for DRIVE as the company already operates within an academic framework.

No matter the type of consortium, the ability to find the funding to support and sustain a consortium's activities remains a challenge. The most common sources include public funds, such as those provided by the NIH, and NIAID in particular. A prime example is the U19 mechanism through which the aforementioned AD3C is funded – a cooperative agreement research program that supports Centers for Excellence in Translational Research. Then, once an asset identified through these mechanisms has been carried through to the IND phase, for further clinical development, the consortium can tap into the funding available through

Biomedical Advanced Research and Development Authority, within the Office of the Assistant Secretary for Preparedness and Response in the US Department of Health and Human Services, as mentioned earlier.

Of note, in the development of antiviral therapeutics, compounds with broad activity are desired to inhibit both (re-)emerging infections and more common viral illnesses existent in developed nations. While this implies the lack of specificity of the target/drug, molecules with these attributes are beginning to emerge and have appropriate safety profiles. In those cases, government funds directed toward the development of the compound for the noncommercial indication can be leveraged to support the concurrent development of the compound for indications with a better commercial opportunity. Derisking the compound by demonstrating suitable pharmacokinetics and toxicity profiles would then make it very attractive for further development by commercial partners.

Factors important for consortium success

Collaborations between institutions with different cultures, both on value and operational levels have many challenges, and active management of the consortium is the key to success. First, the founding principal(s) behind the collaboration needs to be understood at all levels, from senior leadership to individuals working at the bench. This principle and associated mission and vision will also serve to guide the clarification and codification of goals of the consortium, and the definition of what constitutes success. Traditionally, in academia, publication of findings in high-impact journals and subsequent successful extramural grant applications would be considered appropriate metrics of productivity. This is often times incongruent with the metrics a commercial partner would typically pursue, such as meeting drug discovery and development milestones in a certain time frame, and the generation of IP. These two different sets of goals can often be achieved together, although the publication would typically be delayed until the IP position is secure, as mentioned earlier. Setting clear expectations at the outset of a project will be critical for mitigating conflict down the road, and allow the academic partner to go into the collaboration with a thorough understanding of the potential limitations and ramifications of delayed disclosure.

One of the frequent stumbling blocks in partnering negotiations is the ownership of the aforementioned IP. A general framework to consider is that ownership follows inventorship, but that future revenue distributions are more flexible and distributed (to a certain extent) among the consortium partners, regardless of actual contribution to one particular invention. This provides an incentive to participate in the consortium, especially when multiple projects are within the consortium's portfolio that all utilize expertise of a different subset of partnering institutions.

As alluded to above, one of the typical strengths of commercial partners in consortia is the project management capabilities put in place to monitor and enhance project performance. Already important in day-to-day operations of these institutions, it takes on an even more prominent role in consortia, where it needs to be completely clear about the responsibilities of each partner party, including the timelines for execution of these responsibilities. Project plans ensure that communications happen between the right individuals at the right time and that decisions are made with all the information that is available. One example highlighted

as best practice is Gilead's collaboration with Yale in the oncology space, in which there is a continuous communication and decision making loop in operation, in contrast to the more traditional 'quarterly updates' [30]. Ideally, there would be a project manager at each party, or at a minimum a point of contact who is included in all communications and has the charge and authority to follow-up on action items and decisions made.

Finally, it is of utmost importance that the leadership involved in these consortia has the expertise to guide the success of the enterprise. This includes a deep knowledge of biology and drug discovery, as well as what will be required for later-stage drug development activities. Typically, the former will be residing with the academic partner, who will provide the innovative energy to the project, where the latter resides with the commercial partner, who brings timeline and critical path management to the table. However, having consortia partners who understand both activities make the eventual transition and early decisions more productive. Toward the latter, it is highly advisable to generate a compound progression pathway, which delineates the parameters a compound needs to meet before moving on to the next phase in the drug discovery and development pipeline. This should include parameters associated with antiviral efficacy and safety, as well as drug-like properties. Importantly, this document needs to clarify the critical path, decision-making parameters versus 'nice to know' studies or data that are not absolutely critical for moving the compound forward as a potential therapeutic. For example, the exact mechanism of action at a molecular level needs to be determined as quickly as possible and is important to know for the academic virologist who wants to truly understand the biology of the target. However, arguably, it is not critical in the initial phases of identifying a chemical lead series. It would, therefore, not be in the critical path, but rather on a parallel path, the results of which would inform the project much later in the development stage.

It is extremely important to the success of the venture that the partners should respect each other's expertise and trust that decisions ranging from budget decisions to experimental design are made with the consortium's success in mind. Although a contract should be in place that specifies the exact contributions of the partners, potential gains, decision-making authorities and conflict resolution, it cannot substitute for the trust needed between individuals involved in the partnership to make the consortium a success. Furthermore, drug development almost never proceeds as initially planned. Consequently, the consortium must be able to accommodate change throughout its lifetime.

Conclusion & future perspective

Although it is too early to tell whether consortia will be successful in (rapidly) identifying and developing new therapies for emerging and re-emerging infections, logic dictates that they are the best option to achieve this goal. In fact, with the downsizing of in-house research and development departments in commercial operations, the use of consortia will likely expand into other therapeutic areas, well beyond infectious diseases. Lessons learned from the recently established consortia will need to be carefully recorded and applied to future collaborative infrastructures. This will help address the dichotomies between academic and commercial research cultures, and address issues, such as metrics of success, timing of publications and patent applications, collaborative decision making and project

management. As parties get educated about the processes and values at partner institutions, information will start to flow more quickly between individuals on project teams, thus streamlining the drug discovery and development process. Individuals who can manage this information appropriately and have the respect and trust of all parties involved will prove to be pivotal team members of these consortia, crucial for the ultimate success.

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EXECUTIVE SUMMARY

Emerging & re-emerging viral infections

- In recent years many viral infections emerged or re-emerged; examples include Ebola, SARS, MERS, pandemic influenza, West Nile, chikungunya and dengue, among others.
- There are no good medical countermeasures for these infections, limiting treatment to supportive care.

The role of drug discovery/development consortia & drug discovery in academia

- For commercial reasons, these infections are not a high-priority target for the pharmaceutical industry.
- Academic drug discovery has significantly grown in the last decade; however, the focus tends to be on early-stage discovery, lacking infrastructure, expertise and funding to go beyond hit to lead efforts.
- The strength of commercial enterprises in later stage discovery and drug development, along with project management principles to ensure, is a nice complement to academic efforts.
- Consortia between academic and experienced drug discovery and development organization are thus a natural solution, utilizing the strength of viral biology in academia and drug development know-how in industry.

Types of consortia & their advantages

- Consortia are typically between an academic partner and either a not-for-profit organization or a commercial pharmaceutical partner.
- Funding is most often obtained from the public sector, such as the NIH, Biomedical Advanced Research and Development Authority or other governmental health agencies around the world.
- Success depends on the clarity of vision and goals of the consortium, transparency and strong management of activities at each party in the collaboration, rapid, real-time sharing of information and leadership with drug discovery and development expertise.
- Finally, trust between parties on the institutional and individual level is key to a productive relationship.