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Viewpoint

Challenges and Opportunities for Drug Discovery in Developing Countries: The Example of Cutaneous Leishmaniasis

Abdrrahman S. Surur,* Abebaw Fekadu, Eyasu Makonnen, and Asrat Hailu

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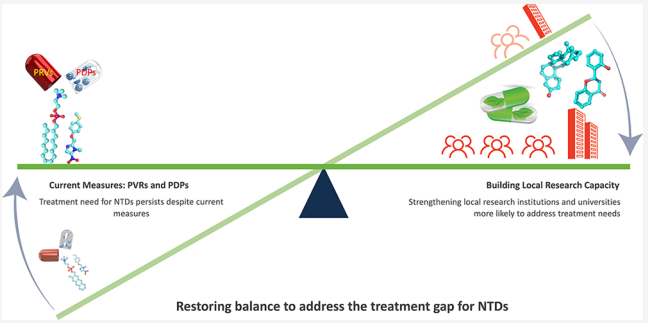
ABSTRACT: The current drug discovery paradigm has failed to address the treatment need for diseases of high priority to developing countries. Cutaneous leishmaniasis is a good example of such diseases with virtually no new effective drug developed in the past 70 years. The past two decades had witnessed relatively increased attention toward neglected diseases by stimulating pharmaceutical industries through introductions of Priority Review Vouchers (PRVs) and Product Development Partnerships (PDPs). However, the lion's share of resources allocated for research and development by PRVs and PDPs is directed toward research organizations and pharmaceutical industries in developed countries. This new approach has also not led to the development of drugs for most neglected diseases including cutaneous leishmaniasis. Improving the medical discovery capacity of countries where these diseases are prevalent and enabling exploration of the hitherto untapped natural resources are an effective and sustainable solution.



KEYWORDS: *Cutaneous Leishmaniasis, drug discovery, developing countries, natural products*

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Leishmaniasis is among the top ten neglected tropical diseases. It is caused by more than 20 protozoa species belonging to the genus *Leishmania* and is transmitted by the bite of infected female sand flies. The most common form of human leishmaniasis is Cutaneous Leishmaniasis (CL), which leads to 600,000 to 1 million new infections worldwide annually.[1] CL causes ulcers, leaving life-long scars and serious disabilities, and stigma. CL can be localized (LCL), or diffused (DCL), or mucocutaneous (MCL). MCL results in partial or total destruction of mucous membranes of nose, mouth, and throat. Unfortunately, the disease mainly affects the poorest countries. Over 90% of MCL occurs in Bolivia, Brazil, Ethiopia, and Peru.[1,2]

CL caused by *L. aethiopica* is endemic to Ethiopia, where around 30 million people are at risk. The increase in prevalence and recent outbreaks to new regions are creating a growing health threat. Lesions caused by *L. aethiopica* commonly occur on the face and tend to be more severe and chronic. Spontaneous healing, when it occurs, needs longer periods of treatment than CL caused by other leishmania species.[3,4]

TRENDS IN DRUG DISCOVERY AND THE TREATMENT IMBALANCE

To date, there is no safe and effective treatment for CL. Developing effective treatments for CL, however, may entail a lengthy and costly pharmaceutical innovation. According to a 2016 estimation, the cost may reach $2.87 billion.[5] A nonprofit consumers' right advocacy group had come up with an estimate of $1.4 billion, removing opportunity cost,[6,7] which remains substantial.

Pharmaceutical firms are for-profit organizations committed to not only good financial returns from approved drugs but also to cover costs of drug candidates failed during the regressive discovery and development processes. Accordingly, pharmaceutical firms have channeled innovations to diseases of high-income countries with potential access to a lucrative market for new treatments. This market-driven approach, however, has created a "fatal imbalance" against diseases of high importance to developing countries. Among the 1556 new molecular entities approved between 1975 and 2004, only 21 (1.3%) were developed for neglected diseases and tuberculosis.[8,9]

As no effective vaccine has yet been developed, chemotherapy has become the only effective and practical choice for

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CL. However, as the currently available treatments for CL are inadequate, there is a pressing need for the development of new and better drugs.[10−12] The gold-standard treatments that have been in use for over 70 years, mainly the antimonial compounds, such as sodium stibogluconate or meglumine antimonite, are associated with serious adverse effects and require prolonged treatment exposure with the emergence of rapidly increasing antimonial-resistant strains. Consequently, alternative treatments using amphotericin B as deoxycholate or the recent liposomal formulation or pentamidine have been recommended, though are again limited by severe toxicity and high treatment costs. The only orally active treatment, miltefosine (hexadecylphosphocholine), was originally developed as an anticancer agent and was approved in 2014 against infections caused by *L. braziliensis*, *L. panamensis*, and *L. guyanensis*. Data regarding the efficacy of miltefosine against Old World Leishmaniases is scarce and is extremely limited regarding complicated CLs caused by *L. aethiopica*.[13−16] Thus, the huge disease burden is unmatched by currently available treatments, complicated by the rapid surge in development of resistance. The strategies to address this need are failing to add new drugs, and hence the treatment gap in CL is expected to get even wider.

MEASURES FOR ADVANCEMENTS IN DRUGS FOR NEGLECTED DISEASES

The health budget of developing countries, including contributions from external partners, cannot support drug discovery programs tailored to endemic health threats. Considering the $2.6 billion estimated cost needed, the $13 billion 2016/2017 total annual budget of Ethiopia is equivalent to almost the discovery costs of 5 drugs only. Worse still, the budget for a health research in low income countries is negligible.[17−19] It is sobering that developing countries are unable to allocate resources for research against major health threats that claim millions of people each year.

The lack of financial and human resources has put developing countries entirely dependent on pharmaceutical firms in developed countries, which have little incentive to invest in developing drugs for neglected diseases. Local R & D models such as African Network for Drugs and Diagnostic Innovations (ANDI) are establishing platforms to assemble collaborative networks and partnerships to address the health needs of the African population.[20] Priority Review Vouchers (PRVs) and Product Development Partnerships (PDPs), on the other hand, are the major global measures taken to stimulate drug development against neglected diseases by pharmaceutical firms in developed countries. While these programs are very important, several limitations should encourage change in this paradigm: (1) the treatments produced so far have not been satisfactory; (2) the participation of discovery scientists from developing countries has been low; (3) endogenous knowledge and resources are neglected; (4) the paradigm is likely to lead to ongoing dependence of developing countries and persistence of the treatment gap. The authors here argue that promoting health research capacity of the affected countries is the better and sustainable solution.

Priority Review Vouchers. The Congress of the United States in 2007 approved a PRV program to encourage new drug developments for tropical diseases, rare pediatric diseases, and medical countermeasures. Compared to a standard review process, a PRV reduces time-to-market by 4 to 6 months creating competitive advantages, more sales, and greater financial return and helps patients access the treatment the earliest. The assumption is that the main impediment to developing new drugs for neglected diseases was lack of financial incentives for pharmaceutical companies rather than lack of scientific knowledge. The impact of a PRV for developing new drugs for neglected diseases is being questioned. The market value of a PRV has dropped from the peak value of $350 million in 2016 to $81 million in 2018. A PRV value below $100 million is no longer an incentive to drug discovery for neglected diseases. Moreover, a company granted a PRV is not obliged to avail the product at an affordable value, an underlying element of accessibility for antileishmanial drugs in low-income countries.[21,22]

Product Development Partnerships. Product Development Partnerships, a subcategory of Public Private Partnerships (PPPs), were established as global nonprofit alliances among the public, private, academic, and philanthropic sectors for funding development of drugs, vaccines, and diagnostics for neglected diseases. The delivery of some products was a testament for the potential of PDPs. Paromomycin for visceral leishmaniasis (VC) was developed by the Institute for One World Health in 2006, and in 2019, fexinidazole was developed for Human African Trypanosomiasis by Drugs for Neglected Diseases *initiative* (DND*i*).[23,24] Clinical trials to determine the efficacy of paromomycin plus miltefosine, imiquimod plus antimony immunochemotherapy, and topical amphotericin B for CLs are being conducted by DND*i*.[23,25,26]

Fourteen percent ($506 million) of the global R & D funding for neglected diseases was channeled through PDPs in 2017. From the traced PDPs expenditure of $145,630,751 on external R & D, 48.2% went to private sector organizations in developed countries—20.9% to Western Contract Research Organizations, 18.0% to small pharmaceutical industries, and 9.3% to big pharmaceutical industries. Academic and public research institutes in the industrialized countries received a further 22.1% of the external PDPs funding. Only 12.3% was allocated to research organizations in developing countries.[25] This allocation of R & D finances overlooks the contribution of research institutions of developing countries.

STRENGTHENING LOCAL HEALTH RESEARCH CAPACITY

International efforts aimed at correcting the health disparity worldwide should prioritize strengthening of the health research capacity of developing countries as the leading strategy. The inability to develop innovative solutions to endemic health challenges and reliance on foreign support is one of the primary reasons for the continuing health disparity and for diseases of poverty to continue unabated. Political instability, incoherent research initiatives, chronic underinvestment in universities and research institutions, restrictive rules and regulations, and impaired research dissemination and utilization are among the major predicaments.[27−29]

Very few capable research institutions are available in developing countries, which promoted brain drain to developed countries capable of offering more opportunities, and where most research organizations engaged in neglected diseases are primarily placed. Despite low wages and need of additional jobs to make ends meet, researchers in developing countries are highly driven to develop effective drugs for the society they live in. Furthermore, drug development in the developing countries is much more likely to be cost efficient

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and a sustainable solution. This will also open an opportunity for exploring the untapped biodiversity and biouniqueness in developing countries as part of the endeavor to finding solutions for global health problems such as cancer. We strongly believe investing in and empowering local researchers, universities, and research institutions as R & D actors or owners of research toward neglected diseases will have significant implications beyond addressing neglected diseases.

Competent research stakeholders, besides the primary scientists and research institutions, are needed for augmenting health research capacity. Sharpening of prohibitive rules and regulation in favor of promoting health research is to be expected from governmental institutions in order to amend some aspects of local health research capacity. Policy making is a complex, political process, but evidence-informed decision making is the best intervention toward closing the gap between research, policy, and implementation.[30,31] Unlike in developed countries, limited suppliers of instruments, equipment, and chemical reagents are present in low-income countries, thereby inaccessibility of the required research materials even supposing primary financial constraints is secured. Additional measures will be required to address this challenge.

NATURAL PRODUCTS AND CLINICAL TRIALS

The empty therapeutic niche in CL reflects the inability of the past and current drug discovery paradigms in targeting diseases that have affected developing countries persistently.[32] The capacity to respond to new threats and pandemics, such as the Coronavirus Disease 2019, is also extremely limited.[33] This disappointing trend calls for revised strategies in order to avail new, less toxic, and affordable treatments for neglected diseases of poverty. Treatments of natural origins are well regarded for low cost, safety, and novelty; hence, they are a perfect source for developing novel treatments capable of filling the unmet medical needs in CL.

Since antiquity, plant-derived therapeutic agents have supported the well-being of the human race. Recently, pharmaceutical companies have tended to adopt high-throughput synthesis and combinatorial chemistry in the quest to develop new drugs. However, natural products which have evolved over millions of years have diversities in biological activities and offer unique chemical structures difficult for synthetic medicinal chemists to envision.[34] Consequently, plant sources will continue to be an important source of drugs or lead compounds, and the current impact of natural products in the discovery of small drug molecules is still considered significant. For instance, of 175 approved anticancer small drug molecules between the 1940s and 2014, 85 (49%) were either natural products or their semisynthetic derivatives. However, of the 250,000−500,000 plant species in the world, only 6% are screened for their biological activities. It is worth noting that 25% of the world's biodiversity is found in Africa. Novel structures from natural sources may be important in addressing treatment resistance in that they offer a different mode of action that could tackle underlying mechanisms of resistance. Accompanying good efficacies of numerous plant extracts against antimonial-resistant leishmania parasites, the low incidence of adverse effects, and low cost suggests that plants are the ideal source of novel drugs for CLs.[35,36]

Most developing countries burdened by CL fortunately are equipped with the rich biodiversity of plants and other natural sources, highlighting the remarkable opportunities those countries have for developing new drugs capable of curbing CL and other diseases of poverty. Moreover, high costs related to the expensive antileishmanial drugs and the lengthy treatment needed are far beyond the means of poor patients typically affected by these diseases. The growing interest in natural products for treatment of leishmaniasis is welcome news.[36−38] The synergy created by the grand biodiversity and the high number of endemic plants in Africa and the tradition of using herbal medicine by 80% of the population is the colossal potential yet to be exploited.[39]

Insufficient clinical research has been the bottleneck for health innovations in developing countries. Limited investments, poor ethical and regulatory procedures, lack of research materials and infrastructures, and operational obstacles are the major barrier to clinical research in developing countries. Though underrepresented, Africa is emerging as an important destination for clinical trials. Diverse population, reduced cost, and time to recruit patients are among the arguments for this.[40,41] Promoting clinical trials in developing countries will raise research standards and bring the badly needed investments. Developing local capacity through education and training in diagnosis, clinical care, and data management has improved the clinical research practice in Africa.[42] Devoted to professional developments of clinical researchers in Africa, CDT-Africa (Centre of Excellence for Innovative Drug Development & Therapeutic Trials for Africa) is currently offering postgraduate studies in clinical trials and fellowships for African countries.

CONCLUSIONS AND RECOMMENDATIONS

The current paradigm of drug development for neglected diseases has failed miserably. A new model focusing on building partnerships and capacity in developing countries has to be prioritized. Strengthening research institutions and use of the rich biodiversity in developing countries are the more effective and sustainable solution.

AUTHOR INFORMATION

Corresponding Author

Abdrrahman S. Surur − *World Bank Center of Excellence for Innovative Drug Development and Therapeutic Trials for Africa (CDT-Africa), Addis Ababa University, Addis Ababa, Ethiopia;* orcid.org/0000-0002-4028-068X; Email: Abdrrahman.Surur@hotmail.com

Authors

Abebaw Fekadu − *World Bank Center of Excellence for Innovative Drug Development and Therapeutic Trials for Africa (CDT-Africa), Addis Ababa University, Addis Ababa, Ethiopia*

Eyasu Makonnen − *World Bank Center of Excellence for Innovative Drug Development and Therapeutic Trials for Africa (CDT-Africa), Addis Ababa University, Addis Ababa, Ethiopia*

Asrat Hailu − *World Bank Center of Excellence for Innovative Drug Development and Therapeutic Trials for Africa (CDT-Africa), Addis Ababa University, Addis Ababa, Ethiopia*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsmedchemlett.0c00446

Author Contributions

A.S.S. and A.F. designed the viewpoint. A.S.S. wrote the first draft. All authors critically revised the manuscript and approved submission of the final version of the manuscript.

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Notes

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■ ABBREVIATIONS

CL, Cutaneous Leishmaniasis; MCL, mucocutaneous leishmaniasis; PRVs, Priority Review Vouchers; PPPs, Public Private Partnerships; PDPs, Product Development Partnerships; R & D, Research and Development; CDT-Africa, Centre of Excellence for Innovative Drug Development & Therapeutic Trials for Africa

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