Consilience

SCHOLARLY ARTICLE

Biotechnology for Global Health:
Solutions for the Developing World

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Abstract:

Identifying and developing emerging biotechnologies is important in improving health in the poorest nations because current health products and practices are generally not suited for their developing economies, their inadequate transport and power infrastructures, their largely rural populace, and their rugged and often tropical environments. Advances in biotechnology will more likely be valued and adopted as innovations in developing countries if they are suited to these challenging conditions. These innovations in health will favor a shift away from a centralized, curative-based framework towards a decentralized, prevention-based paradigm. In this article, advances in microfluidics and in vaccine delivery and storage are highlighted within the context of disease diagnosis and prevention in the developing world.

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Introduction:

What is the link between scientific discovery, biotechnology, and innovation? Why is biotechnology particularly important for improving health in the world's poorest nations?

One can think of scientific discovery and innovation as being on two opposite sides of a continuum. *Scientific discovery* deals with acquiring new knowledge by correcting and integrating previous knowledge through the formulation of testable hypotheses, conducting experiments, collecting data, and interpreting results in order to form conclusions; it is largely carried out in universities and is often characterized by academic freedom and intellectualism. On the other end of that continuum lies *innovation*, which introduces a new product or process that is both *valuable* to adopters and *disruptive* to the status quo. Unlike scientific discovery, innovation is driven by economic and social pressures, which creates wealth or social welfare to a group of people, an organization, or a society by improving quality, efficiency, and productivity.

In the middle of the continuum lies *translational research*, where discoveries with potential value are identified and pursued; this is largely conducted by the private sector. In the context of health products and practices, this middle ground is the domain of *biotechnology*. Innovations in products such as vaccines, medical devices, and equipment start from scientific discoveries in genomics-related sciences and in applied sciences or engineering. Advances in biotechnology become innovations if they are considered valuable in demonstrating clinical efficacy, ease of administration and use, reducing costs, and so on; these are adopted by health workers, health ministries, companies, and organizations.

Unlike scientific discovery, which is a long-term investment associated with high-risks, advances in biotechnology may directly lead to innovation and therefore contribute value to health sooner rather than later. More importantly, however, developing countries cannot sustain the adoption of medical products that are conventional in developed countries. These products and practices are incompatible with their weak economies, their underdeveloped transport and power infrastructures, their largely poor and rural populations, and their rugged and often tropical environments.

Despite these challenges, developing countries are perhaps best positioned to adopt innovations in biotechnology. Not only do their circumstances pose significant challenges that demand creative and valuable solutions, but the significant gains over health products and practices currently inadequate or nonexistent in developing countries may also accentuate the value of an innovation. Specifically, this value can range from reducing early mortality and burden of disease with more effective recombinant vaccines, to preventing degradation of vaccines by creating and optimizing techniques for stable formulations that withstand large fluctuations in heat and humidity, to increasing portability and capability of diagnostic devices with miniaturized lab-on-a-chip technology.

In short, the impetus for innovation in health is vast. In fields other than those associated with healthcare, there has already been widespread adoption of relevant innovations. For example, the adoption of cell phones and wireless internet in Sub-Saharan Africa has replaced the historical precedent of developing landlines, thereby allowing for quick communication to places in rugged and remote regions,

without the need to develop significant infrastructure[2]. However, the mere adoption of technology may not be enough to develop appropriate health products; perfecting promising biotechnologies and even developing new ones may be necessary. In doing so, developing countries may be able to bypass medical technologies conventional to centralized health systems, such as hospitals for healthcare and labs for diagnostic results, and instead be able to develop innovative technology better-suited for decentralized health networks, such as point-of-care diagnosis and at-home healthcare, which emphasize cost-effective public health strategies such as disease prevention and epidemiological surveillance[3].

In identifying and developing promising biotechnologies, it is important to first understand the limitations of conventional health products in meeting the unique challenges in the developing world. These limitations can be divided into several major categories: (1) power (*e.g.* lack of ground electricity, lack of refrigeration), (2) ease of use/administration (*e.g.* lack of skilled workers), (3) efficacy (*e.g.* sensitivity and specificity for diagnostics, development of immunity for vaccines), (4) portability (*e.g.* potential for use at rural villages or at point-of-care), (5) cost (*e.g.* costs associated with the product itself versus those for peripherals), and (6) safety.

This paper focuses on identifying two active areas of biotechnology research relevant to health in developing countries: vaccines for building immunity against infectious diseases and microfluidics for point-of-care diagnostics. Each section highlights the limitations of current products in the settings of developing countries, and discusses the advantages and possible disadvantages emerging biotechnologies have in this setting.

Vaccines: Novel storage and delivery strategies

Vaccines for childhood illnesses—widely considered as essential in any strategy for disease prevention in developing and developed countries alike—have benefited greatly from recombinant DNA technologies. Not only are recombinant vaccines[4] already proving to be cheaper in testing and scale-up of production, as well as safer (particularly in immunocompromised individuals) than inactivated or attenuated vaccines[5], they may also address problems with vaccine storage and delivery. Normally, vaccines require refrigeration, needles, and multiple administrations to fortify or refresh immunity. In much of the developing world, however, refrigeration is unavailable, and when available, refrigeration can constitute up to 80 percent of the total cost of vaccine delivery[5]. Needles are often misused by inexperienced personnel in

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[2] UNDP, *Human Development Report 2001: Making New Technologies Work for Human Development*. 2001, United Nations Development Programme: New York.
and
Chin, C.D., V. Linder, and S.K. Sia, Lab-on-a-chip devices for global health: past studies and future opportunities. Lab Chip, 2007. **7**(1): p. 41-57.

[3] Alwan, A. and B. Modell, Recommendations for introducing genetics services in developing countries. Nat Rev Genet, 2003. **4**(1): p. 61-8.

[4] Recombinant vaccines are created by genetically modifying microorganisms such as bacteria and yeast and stimulating them to produce large quantities of immunogenic proteins.

[5] Daar, A.S., et al., Top ten biotechnologies for improving health in developing countries. Nat Genet, 2002. **32**(2): p. 229-32.

unsanitary conditions, leading to transmission of blood-borne pathogens such as HIV, HBV, and HCV[6]. Patient noncompliance is commonplace with poor rates of return visits, thereby making multiple vaccine administrations difficult.

These issues can be partially addressed by developing novel storage techniques or by optimizing established processes with new formulations in order to increase vaccine viability, and by researching different methods of vaccine administration to reduce the need for intravenous immunizations. For example, the Bacillus Calmette-Guérin vaccine[7] (BCG) is currently prepared commercially by freeze-drying[8], which is known to significantly reduce BCG viability after freezing. Researchers at Harvard University hypothesize that the presence of nonvolatile salts and cryoprotectants during the normal drying of droplets raised osmotic pressures high enough to damage bacterial membranes, which yield low vaccine viability and stability at room temperature[9]. They discovered that spray drying with a special protein matrix without salts and cryprotectants yielded improved viability and stability[9]. This is promising, given the potential of spray-dried vaccines to be inhaled rather than administered intravenously, and scaled-up in sterile conditions with lower operating costs as compared to freeze-drying methods[10,11]. Already, Medicine in Need[12] plans to develop stable cell dry powder vaccine formulations for efficient and noninvasive inhaled delivery. Furthermore, recent studies have demonstrated the effectiveness of porous particles and nanoparticles in efficiently delivering therapeutic aerosols, with the potential for larger dose delivery[13,14,15].

Besides pulmonary vaccine delivery, other needle-free methods of immunization in the developing world such as liquid-jet injection, epidermal powder immunization, topical application (through cutaneous routes), and oral and nasal immunizations (through mucosal routes) have been proposed as alternatives to intravenous immunizations[6]. Liquid-jet injections use the kinetic energy from a high velocity vaccine jet (typically up to 100 m/s, with a microneedle tip) to penetrate the skin and deliver the vaccine intradermally, subcutaneously, or intramuscularly. Targeting the skin promotes its contact with Langerhans cells, which initiate specific immune responses by processing and presenting antigen fragments to naïve T-cells in the lymph nodes. Vaccines delivered by liquid-jet usually spread over a larger tissue area than vaccines

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[6] Mitragotri, S., *Immunization without needles.* Nat Rev Immunol, 2005. **5**(12): p. 905-16.
[7] BCG vaccine is against tuberculosis which is prepared from a strain of the attenuated live bovine tuberculosis bacillus.
[8] Freeze-drying (also known as lyophilization) is a common dehydration process used to preserve a sensitive material and make transport convenient. Freeze-drying involves a two-step process: 1) freezing below the lowest temperature at which solid and liquid phases can coexist (eutectic point), and 2) sublimination of ice crystals to water vapor.
[9] Wong, Y.L., et al., *Drying a tuberculosis vaccine without freezing.* Proc Natl Acad Sci U S A, 2007. **104**(8): p. 2591-5.
[10] Millqvist-Fureby, A., M. Malmsten, and B. Bergenstahl, *An aqueous polymer two-phase system as carrier in the spray-drying of biological material.* Journal of Colloid and Interface Science, 2000. **225**(1): p. 54-61.
[11] Vanbever, R., et al., *Formulation and physical characterization of large porous particles for inhalation.* Pharm Res, 1999. **16**(11): p. 1735-42.
[12] Medicine in Need is a non-governmental organization founded by David Edwards, the principal investigator of the aforementioned study.
[13] Edwards, D.A., et al., *Large porous particles for pulmonary drug delivery.* Science, 1997. **276**(5320): p. 1868-71.
[14] Pulliam, B., J.C. Sung, and D.A. Edwards, *Design of nanoparticle-based dry powder pulmonary vaccines.* Expert Opin Drug Deliv, 2007. **4**(6): p. 651-663.
[15] Tsapis, N., et al., *Trojan particles: large porous carriers of nanoparticles for drug delivery.* Proc Natl Acad Sci U S A, 2002. **99**(19): p. 12001-5.

administered with needles, and may allow more contact with antigen-presenting cells before being degraded. While many vaccines (*e.g.* influenza and hepatitis B) have been successfully delivered using liquid-jets, cross-contamination and cost are major limitations. The development of disposable-cartridge jet injectors and single-use, pre-filled disposable devices have sought to alleviate concerns about contamination.

Epidermal powder immunizations facilitate storage of vaccine powders and there is strong clinical evidence for its applicability in DNA vaccines; however, non-DNA vaccines have enjoyed little commercial success. Topical vaccine application, like liquid-jet and epidermal powder immunizations, naturally target Langerhans cells and are cheaper and easier to use. However, simple topical delivery yields an inadequate immune response due to the low permeability of the stratum corenum, the outer layer of the skin. Current research includes using topically applied adjuvants[16], colloidal carriers[17], and physical methods such as microneedles, ultrasound, and electroporation with topical application[6,18].

Oral vaccine delivery has been used for live attenuated pathogens such as polio and typhoid, and is attractive because of its simplicity and ease of administration. However, vaccines are degraded and deactivated in the acidic gastrointestinal environment and high doses are required for adequate immune responses; improving response variability is an active area of research. Nasal delivery allows easier access to mucosal membranes than does oral delivery, but the short contact time and enzymatic activity, while less relative to that in gastrointestinal tract, poses considerable challenges which have yet to be overcome[6].

A subset of oral vaccine delivery is temperature-stable formulations of vaccines expressed in transgenic organisms such as plants or crops[19,20]. Edible vaccines are attractive because they are easy to administer; they are also theoretically cheap to produce because no protein purification steps are needed. Studies on edible plant vaccines have shown to stimulate immunogenic responses against the hepatitis B virus and Norwalk virus, which causes diarrhea. They also have protective capacity against pathogens causing bacterial diarrhea, such as cholera and enterotoxigenic *Escherichia coli*[21,22] , and tetanus toxin produced by bacterium *Clostridium tetani*[23]. The latter is a common childhood vaccination target along with diptheria and pertussis. Ongoing research aims to (1) understand variations in vaccine stability and immunogenicity in mucosal delivery, (2) express higher levels of antigen, (3) guard against degradation of protein components in the stomach and gut before they can elicit an immune response[22], and (4) understand the risks of genetic contamination of foodstuffs and the threats to biodiversity.

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[16] An adjuvant is an agent that is mixed with an antigen and increases the immune response to that antigen following immunization[6]

[17] A colloidal carrier is a stable system of small particles of lipds, polymers or any other material that encapsulate a vaccine[6]

[18] Guy, B., The perfect mix: recent progress in adjuvant research. Nat Rev Microbiol, 2007. **5**(7): p. 505

[19] Acharya, T., A.S. Daar, and P.A. Singer, *Biotechnology and the UN's Millennium Development Goals.* Nat Biotechnol, 2003. **21**(12): p. 1434-6.

[20] Acharya, T., et al., *Strengthening the role of genomics in global health.* PLoS Med, 2004. **1**(3): p. e40.

[21] Mason, H.S., et al., Edible plant vaccines: applications for prophylactic and therapeutic molecular medicine. Trends Mol Med, 2002. **8**(7): p. 324-9.

[22] Daniell, H., S,J. Streatfield, and K. Wycoff, Medical molecular farming: production of antibodies, biopharmaceuticals and edible vaccines in plants. Trends Plant Sci, 2001. **6**(5): p. 219-26.

[23] Tregoning, J.S., et al., *Protection against tetanus toxin using a plant-based vaccine.* Eur J Immunol, 2005. **35**(4): p. 1320-6.

Diagnostics: Microfluidic devices

Another promising biotechnology is microfluidics for development of portable and cheap health diagnostics[2,24]. Microfluidics deals with the behavior and precise manipulation of small volumes of liquids and gases moving through microchannels embedded in a chip. Also known as "lab-on-a-chip", microfluidic devices have the potential to automate complex laboratory tasks such as sample preparation, pre-concentration, and analyte detection (*i.e.* detection of desired biomarkers, such as antibodies against hepatitis B, conserved nucleic acid sequences in malaria parasites, T-cells for monitoring HIV/AIDS, etc.) on a chip. Usually, these laboratory tasks require bulky, mechanically complex, expensive, power-draining instruments, such as centrifuges (*e.g.* for sample preconcentration), vortexes and spinners (*e.g.* for mixing liquids), liquid-handling robots (*e.g.* for quantifying protein in benchtop immunoassays), thermocyclers (*e.g.* for amplifying nucleic acids), flow cytometers (*e.g.* for counting and sorting cells), and high-powered microscopes (*e.g.* for visualizing cells). A true "lab-on-a-chip" would allow health workers in developing countries to run common lab tests with greater accuracy and throughput without significant prior training (Figure 1).

Furthermore, miniaturizing onto a battery-powered or even solar-powered handheld device would allow health workers to diagnose at point-of-care, reducing time spent waiting for results and the number of patient visits to the clinic (Figure 1A). The time saved is on the order of days in situations where samples need to be sent to national and/or regional testing centers[25] for processing. Clinics with poor patient compliance in follow-up visits may particularly benefit because diagnosis and treatment prescriptions can be done on a single visit. Additionally, microfluidic diagnostic devices could be employed in a decentralized health care system where health workers travel to the village or rural home to deliver care.

Even in situations where the testing center has the capacity to run the desired assay, microfluidic diagnostics still save time by integrating multiple tasks and by processing microliter to nanoliter volumes. At these small volumes, reactions are rarely diffusion-limited, allowing for faster kinetics particularly when catalysts are involved, and thermal mass is minimized, allowing quicker responses to heat changes *e.g.* in thermocycling for PCR[26]. The ability to process small volumes also allows for less invasive patient sampling procedures such as fingerpricks as compared to more invasive techniques such as intravenous blood draws (Figure 1A).

Most studies to date have focused on particular microfluidic procedures such as fluid actuation, mixing, sample preparation, analyte detection, because each poses tremendous scientific and technical

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[24] Yager, P., et al., Microfluidic diagnostic technologies for global public health. Nature, 2006. **442**(7101): p. 412-8.

[25] The quality, conditions, and types of tests performed at health centers usually correlates with degree of urban development[2].

[26] PCR, or polymerase chain reaction, is a technique used for detection of nucleic acids (PCR for DNA, RT-PCR for RNA), typically for determining infection and pathogen strain or subtype identification. A section of target DNA is marked off with flanking DNA primers and amplified exponentially with repeated heating and cooling patterns (thermocycles).

challenges and depends on the physical, chemical, and biological makeup of the analyte[2]. With extensive work on new strategies and characterization, researchers are looking to integrate multiple procedures in order to be able to detect multiple analytes on a single chip (as illustrated in *Figure 1B*). Analytes are divided roughly into four classes: (1) cells, (2) metabolites, (3) nucleic acids, and (4) metabolites[27]. Each class of biomarker is described in terms of its importance in diagnosing infections and health conditions, and significant research advances relevant to the advancement of global health are identified.

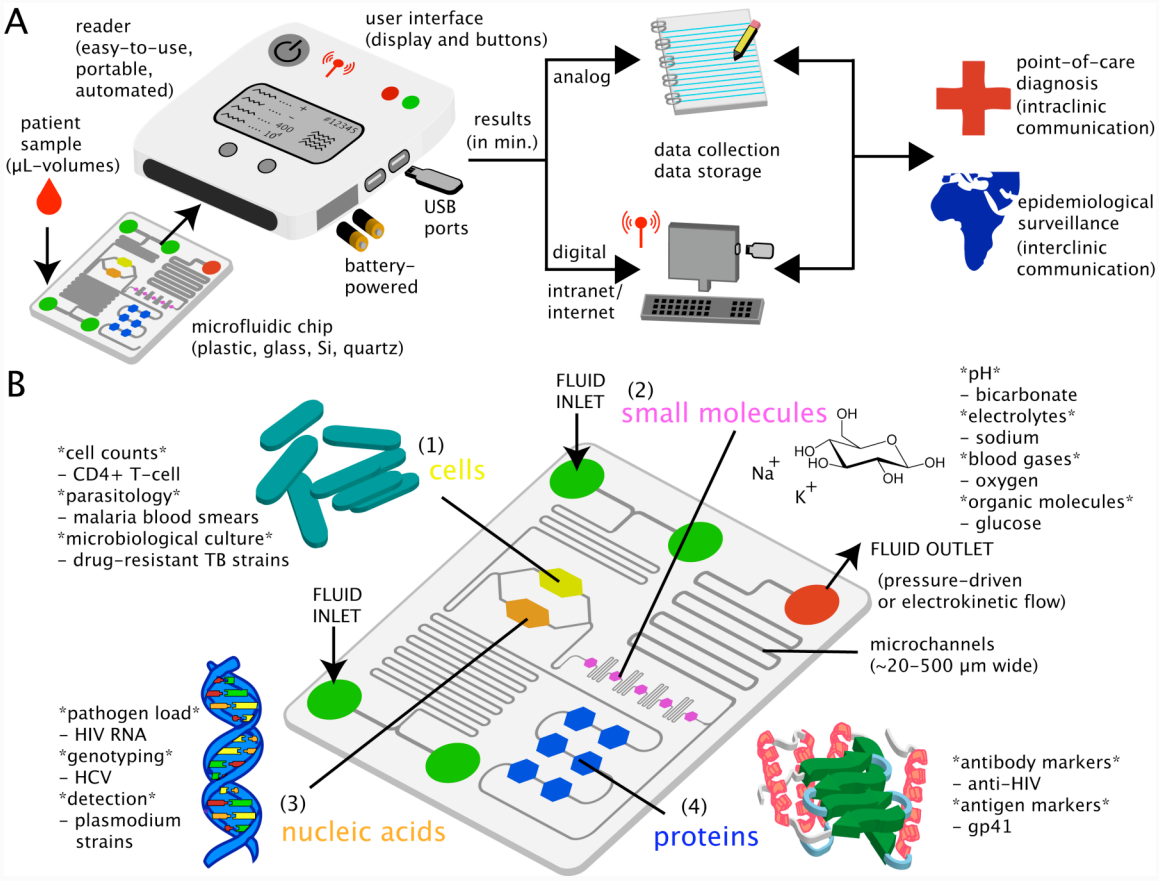

Figure 1*: Microfluidics: an emerging technology in portable, low-cost diagnostics. A: Proposed intervention of device in workflow. B: Ability of microfluidics to carry out multiple tests rapidly; cells, metabolites, nucleic acids, and proteins can all be analyzed for a complete diagnosis.*

Cells:

Cell counts are important measures in addressing anemia and hematology via red blood cell and complete blood counts, as well as in monitoring HIV-infected patients for structuring antiretroviral treatment regimens via $CD4^+$ T-cells. One study suggests that differential shear flows on antibody-functionalized surfaces can selectively capture $CD4^+$ T-cells without labeling in a simple microfluidic

[27] For a more detailed discussion on microfluidic diagnostic technologies for global health, see references 8 and 21.

format[28]. Cell analysis via microscopic examination is important for parasitology (*e.g.* blood smears for malaria). Additionally, microbiological culture is important for determining drug-resistant strains of bacteria (*e.g.* tuberculosis, Staph A), because culture is still considered the "gold standard" relative to newer molecular-based techniques detecting nucleic acids.

Small Molecules:

Detection of small molecules is important for monitoring blood chemistries. Common targets include bicarbonate for regulating pH, sodium and potassium for maintaining specific electrolyte levels in nerve and muscle function, oxygen and carbon dioxide for determining respiratory and/or metabolic problems, and glucose for metabolic disorders such as diabetes. Vitamins and minerals are also relevant targets for detection, as they allow for the diagnosis and monitoring of nutritional deficiencies. Popular techniques include electrochemical detection using thin-film patterned electrodes. iSTAT, a current commercial product produced by Abbot Diagnostics, employs this specific technique.

Nucleic Acids:

Conserved DNA or viral RNA sequences are often targets for detecting specific infectious diseases and for determining the stage of a disease (*e.g.* HIV RNA viral load). Genotyping is also common for distinguishing between pathogen strains (*e.g.* Hepatitis C). The most popular techniques are PCR and RT-PCR, due to their intrinsic specificity and signal amplification. Certain technical challenges include the need for sample pre-treatment of lysed cells and low-cost methods for portable signal amplification and detection. One study demonstrates that oligonucleotide-conjugated nanoparticle probes coupled with silver reduction amplification can yield a low-cost and sensitive system[29].

Proteins:

Antibody and antigen markers can indicate infections predominant in developing countries (such as anti-HIV antibodies, gp41 and gp120 antigens for HIV). One study uses a gold-silver sandwich immunoassay for detecting αHIV-1 antibodies in a microfluidic setup. The opacity of the solution due to silver reduction correlated with the amount of antibody in patient serum and was read by a simple, low-cost absorbance reader[30].

Cost-reduction is perhaps the most attractive quality of microfluidic diagnostic devices. Typically, one-time purchases of fixed instruments range from tens to hundreds of thousands of US dollars. For example, the cost of reagents is $5 for immunoassays and $50-300 for nucleic acid tests in a typical in-house hospital laboratory in the developed world[2]. In contrast, microfluidic devices in the developing world would need fixed instrument[31] costs at tens of dollars, and per-assay[32] costs on the order of pennies, which

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[28] Cheng, X., et al., A microfluidic device for practical label-free CD4(+) T cell counting of HIV-infected subjects. Lab Chip, 2007. **7**(2): p. 170-8.

[29] Taton, T.A., C.A. Mirkin, and R.L. Letsinger, *Scanometric DNA array detection with nanoparticle probes.* Science, 2000. **289**(5485): p. 1757-1760.

[30] Sia, S.K., et al., An integrated approach to a portable and low-cost immunoassay for resource-poor settings. Angew Chem Int Ed Engl, 2004. **43**(4): p. 498-502.

[31] Fixed instrument consists of hardware components for analyte detection, fluid actuation, power, and electronics for signal enhancement, user interfacing, and data tranmission.

would include both chips and reagents. By scaling down reagent volumes hundred- to thousand-fold and by using cheaper materials, such as injection-moulded plastics instead of glass, quartz, and silicon, and electrical components[2] (*Figure 1A*), the costs associated to fixed instrument and assay are reasonable for device deployment in limited-resource settings.

Implementing an appropriate intervention of microfluidic diagnostics, or of any new technology, in the health networks of developing countries is far from trivial. *Figure 1A* illustrates some of the considerations for a lab-on-a-chip both in and out of the clinic. For instance, it is necessary to minimize the number of moving parts needed on the chip and in the reader in order to design an easily operated device. Also, a minimal user interface consisting of a few buttons for powering and operation, and signal lights for showing status of test, on the reader itself may make the device easier for an untrained health worker to operate.

Considerations downstream of the microfluidic assay include recording, storing, and communicating results (*Figure 1A*). Typically, most centralized testing sites and practically all rural testing sites rely solely on written records, but digital records could improve quality of care (by assuring evidence-based medicine) and expedite communication, particularly in disease surveillance, where communication of results between clinics is vital[33]. Results that are typed, synced via USB storage key, or uploaded via wireless transmission to a computer can then be collected and stored locally on a clinic-level network database. Periodically, local networks of electronic records can communicate periodically with other clinics through syncing or internet upload.

D-Tree International, a non-governmental organization dedicated to improving medical records management in developing countries, plans to train and equip frontline providers with personal digital assistants, smart cards, and back up systems for sending data in real-time. This non-profit organization also develops evidence-based, standardized diagnostic and treatment protocols customized for local cultural conditions such as language, epidemiological patterns, and drug lists, also taking into account resources by calculating drug dosage based on patient statistics.

Technology is one part of the solution and must be designed appropriately to its settings (*Figure 2*). For example, backup batteries and dust covers (*Figure 2A*) are common in many regional and rural testing centers. This highlights performance and design considerations in alternative power, using backup batteries which may be rechargeable or even solar-powered, and dusty environments. Bench-top units are fine in centralized testing centers but cannot be transported to rural sites. Flow cytometers (*Figure 2B*) are bulky and expensive, complicated to use, and are often in English instead of native languages. It is also clear that many diagnostic tests require significant training and are inadequate due to their lack of specificity. For instance, malaria blood smears are widely performed, and yet are difficult to read due to the subtle differences in phenotype between erythrocytes infected with different *Plasmodium* species. One alternative to

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[32] Assay components include chips (which can be reused depending on the material and application) and reagents.
[33] Initiatives such as One Laptop Per Child (headed by John Negroponte, head of MIT's Media Lab) may also help close the digital divide.

microscopes and blood smears may be detecting differences in cell deformability, or electrical properties by using microfluidic setups[34],[35].

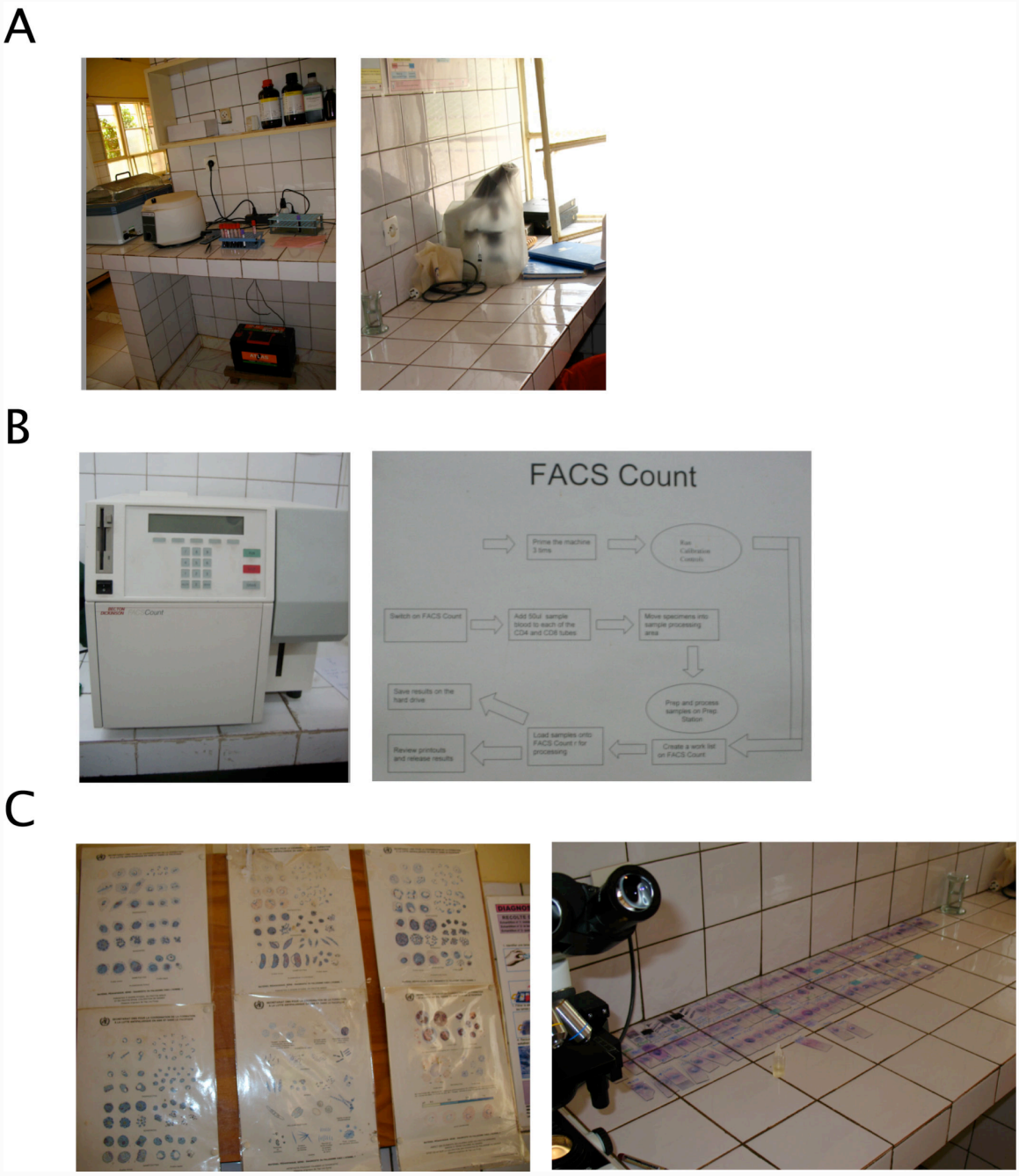

Figure 2: *Design constraints depend on circumstances in the developing world (pictures of labs). A: Lab at Kicukiro (outside Kigali, Rwanda) relies on backup batteries and dust covers. B: Flow cytometer at Gisenyi (regional test center in Rwanda) is*

[34] Shelby, J.P., et al., A microfluidic model for single-cell capillary obstruction by Plasmodium falciparum-infected erythrocytes. Proc Natl Acad Sci U S A, 2003. **100**(25): p. 14618-22.

[35] Gascoyne, P., J. Satayavivad, and M. Ruchirawat, *Microfluidic approaches to malaria detection.* Acta Tropica, 2004. **89**(3): p. 357-369.

bulky, expensive, difficult to use, and uses English instead of the local French or Kinyarwanda. C: Malaria blood smears are commonplace yet difficult to read, requiring trained personnel.

Conclusions:

There is a need for scientific innovation in global health, and the identification of key emerging technologies in diagnosis and prevention are the first steps. Technologies need to be relevant to local conditions, and developing countries have a unique set of challenges that advances in biotechnology need to address before they become valuable as innovations. The need for biotechnologies that can be compatible to a decentralized, prevention-based health paradigm is evident because a conventional health system is unsustainable and incompatible with a developing nation's budget, environment, and demographics.

Beyond identifying key biotechnologies, their development goes hand in hand with other efforts for improving health infrastructures. Training programs are critical for improving skills of health workers, particularly in rural areas, and new technologies intended to work in these circumstances need to be introduced and involved at an early stage. Faster and reliable communication and data storage systems will improve epidemiological surveillance and allow health workers to better customize diagnoses and treatments based on statistics pertinent to specific patients, as well as the local population as a whole. Health education and awareness programs are important cost-effective interventions for stressing disease prevention and healthy lifestyles, and new technologies need to be understood by the populations they serve, in terms of access, changes in healthcare, and the potential positive and negative health side effects. A multidisciplinary approach with biotechnology is important for sustained and comprehensive improvements in health infrastructures and quality of care in developing countries.

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