Local development of nanotechnology-based diagnostics

Sharing protocols with the end-users may allow their flexible implementation to produce nanotechnology solutions for global health challenges that better cater for local needs.

Jose Gomez-Marquez and Kimberly Hamad-Schifferli

The next-generation solutions for infectious diseases are ones that are self-propagating and leverage local resources and knowledge. Diagnostic middleware workers have tremendous potential to exploit nanotechnologies to design, test and implement new diagnostics that are usable in low resource settings. The potential for the most impact comes from deconstructing nanotechnology into toolboxes and protocols over conventional fully integrated devices.

Emerging viral outbreaks are a perpetual problem, and each one requires a unique rapid response for controlling epidemic spread. To continually meet this need, emergency preparedness needs to be drastically improved[1], as Bill Gates detailed in his article on lessons from the Ebola outbreak[2]. The COVID-19 pandemic has revealed that we as a society are woefully underprepared for the next big epidemic, as we are still predominantly responding to outbreaks instead of preparing for them.

Unfortunately, infectious diseases pose complex and multifaceted problems, even for diseases for which we already have vaccines and diagnostics. For example, the re-emergence of Ebola in the Democratic Republic of Congo in 2019 and 2020 in the midst of social unrest — three years after a vaccine and rapid diagnostic were announced — demonstrates the complexity of efficiently diffusing these innovations[3].

As we saw at the initial stages of COVID-19 and recently with the Middle East Respiratory Syndrome (MERS) and Ebola outbreaks, lack of the right diagnostic tools can lead to devastating effects for thousands, if not millions of people[4]. Diagnostics are needed for quarantining, surveillance and treatment. Over-prescription of antibiotics (Malaria), failure to segregate super-spreaders (Ebola), and saturation of limited hospital resources (COVID-19) can all be reduced with adequate, early diagnostic testing.

Nanotechnology, the study and application of nanoscale systems, has been a revolutionary and transformative force in science, stimulating major technological advances in electronics, photovoltaics and even consumer products such as clothing and displays. Disease diagnostics have benefited from nanotechnology primarily by exploiting the unique characteristics of nanomaterials such as their optical, fluorescent and magnetic properties to impart new device capabilities. However, applying nanotechnological solutions to infectious diseases is a delicate departure from its application to consumer goods, where the rules for success are met in a very different way. In fact, while the past ten years of global health diagnostic literature emphasized the promise of miniaturized point of care device innovation as a pathway for infectious disease monitoring[5], most of these devices have failed to make significant impact, largely because their wide diffusion beyond research labs has remained limited. Others have described the difficult odds of the bench-to-product journey[6]. Here, we argue for a different approach to diffusion, which is orthogonal to traditional commercialization. We suggest that nanotechnologies designed as a set of protocols, modular experiments and ready-to-run construction could be more easily integrated into the existent practice of low- and middle-income countries. It is therefore important to understand how such nanotechnology solutions can be effectively implemented in order to foster practical innovation in infectious disease diagnostics.

Adding agency for the end-user in the development process

To tackle the issue mentioned above, first we need to consider the engineering design process for global settings, and at what point it involves the local user. The traditional product development funnel involves a design lock before launching the diagnostic device. While diagnostic devices for global health should follow the ASSURED (affordable, sensitive, specific, user-friendly, rapid and robust, equipment-free and deliverable to end-user) criteria issued by the World Health Organization (WHO) to ensure their robustness in low resource settings, the approach has many shortcomings. As it is focused on a centralized model of scaling and delivery, it does not contemplate issues associated with local supply chains, or account for possibilities of local invention and fabrication. Chances of success can be much greater if one adds agency to the end-users, so they can tweak designs locally[7]. They can adapt protocols to the realities of local resources. They can mix and match ideas from other sources and generate homegrown approaches to a nanomaterial (Fig. 1). These allowances for design flexibility, or 'design trajectories', can occur post-launch. Design trajectories are intentional in their degrees of freedom and are not under the control of the original developer. However, they can only be enabled if we move away from the concept of a design lock, where the system remains a black box to the end-user and modifications can be implemented exclusively by the developing lab. For nanotechnology researchers, it means focusing on generating toolboxes instead of integrated products. It requires shipping the building blocks of nanomaterials, starting

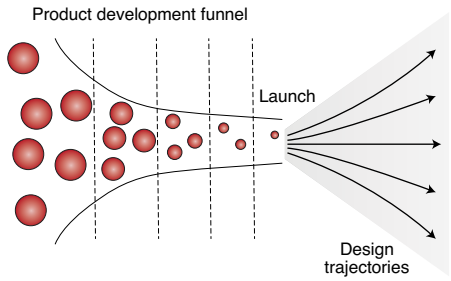

Fig. 1 | The product development funnel, and allowing for design trajectories post-launch. The classical product development funnel takes in multiple ideas for solutions and reduces them through iteration steps (vertical dashed lines), until it reaches a final singular solution with a design lock to be scaled. In contrast, the notion of Design for Hack and Reinvention, considers a set of reduced solutions and packages them into reconfigurable approaches that can then be rearranged into design trajectories by end-users.

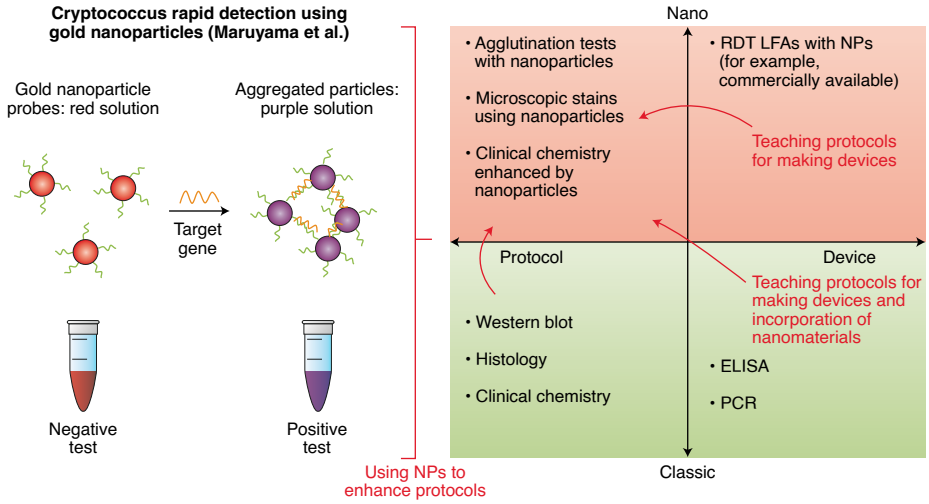

Fig. 2 | Using nanotechnology to improve diagnostic middleware. Example of using Au NPs to detect Cryptococcus, from Maruyama et al.[12] Diagnostic approaches include both protocols and devices, and can be a mix of classical and nanotechnology approaches. RDTs, rapid diagnostic tests; LFAs, lateral flow assays; ELISA, enzyme linked immunosorbent assay; PCR, polymerase chain reaction.

reagents, standards for calibration and stabilization agents so end-users can become collaborators and optimize the system on their own.

The rise of the diagnostic middleware worker

Who will perform these design trajectories? For this, we look to the widely distributed set of clinical laboratories in low-income settings that are equipped with essential tools such as spectrophotometers, microscopes, incubators and centrifuges for procedures such as clinical chemistry, histology, microscopy and other techniques. Collectively, they can be considered as a giant distributed lab, since they have the potential to operate under an umbrella that shares protocols, samples, specimens and working groups. Other fields, such as physics, astronomy, oceanography and climate science operate with the same ethos. They are the driving force behind the vast majority of proven diagnostic assays that are helping billions of patients around the world, playing a critical role in healthcare.

These labs are operated by 'diagnostic middleware' workers who have access to local reagents and local samples. They often lack good labelling and analysis technologies to create an integrated diagnostic tool, and still rely on methods that were often developed several decades ago, such as microscopy smears. Diagnostic middleware laboratories face their own challenges. The vertical strategy of the 'big three' diseases (human immunodeficiency virus (HIV), tuberculosis, malaria) has often left them sidelined from major lab system strengthening. Big centralized laboratories, with high-throughput automation, have generally been the major beneficiaries of expensive molecular diagnostics advancements. Moreover, due to their size, diagnostic middleware labs may be more susceptible to international supply chain interruptions for reagents they cannot produce locally (for an extensive review on the topic, see Jacobs et. al[8]).

The adoption of nanotechnology could be of great help to diagnostic middleware workers but for this to happen, we need to recognize that its use as a sensor platform spans both devices and protocols. Indeed, by classifying the diagnostic approaches into protocols and devices and separating what uses classical versus nanotechnology-based methods, one can identify many examples where nanotechnology can be implemented throughout the diagnostic process as opposed to embedding the nanotechnological innovation in a finished product. This might amplify nanotechnology's impact (Fig. 2).

To do so, the nanotechnological approach must be affordable and robust; ideally it will be self-propagating and capacity-building[7]. For example, one of the most widely used diagnostic methods in middleware labs are stains for microscopic or spectroscopic readout, which are decades-old techniques. Newer colorimetric labelling techniques such as small molecule fluorophores can be expensive and limited in local supply chains. Nanotechnology on the other hand offers numerous cost-effective nanoparticles as robust optical labelling, which diagnostic middleware workers can use to substitute stains[9,10]. In Brazil, for example, researchers developed a test for Cryptococcus using gold nanoparticles (Au NPs) offering an alternative to traditional kinyoun stains which can fade after 2 or 3 days[11,12].

Moreover, the presence of local companies for reagent production is also important. In 1989, when the term nanotechnology was mostly used to describe the study of the physical properties of semiconductor nanocrystals and carbon nanotubes, Katzin et al. used materials locally sourced in Argentina to develop a simple and straightforward non–invasive agglutination test to detect *T. cruzi* antigens in urine[13]. This was a time when Argentina was in an economic crisis due to hyperinflation and currency controls, presenting an enormous barrier for importing materials and reagents from abroad. More recently, nanoporous hydrogel particles produced by the Argentinian company Laboratory Lemos S.R.L. (Polychaco S.A.I.C.) were used to develop a novel urine test for congenital Chagas[14]. In another example, locally produced nanomaterials have been successfully applied for biosensors manufacturing in South Africa[15].

Achievements such as the ones described above are facilitated by the fact that low-income settings have adopted a focused approach to nanotechnology, as a broad attack would be impractical due to the costly infrastructure requirements for many nanotechnological methodologies[16]. Indeed, we find there are several successful examples of nanotechnology companies[17–19], where their home countries have identified particular areas with potential for economic and public impact[20,21]. Healthcare and medicine is one such sector[22], which includes using nanotechnology to develop low-cost diagnostic solutions. Successful working examples go beyond infectious disease diagnostics. For example, nano-enabled strategies can improve praziquantel delivery for treating schistosomiasis from hook-worm infection, a prevalent neglected tropical disease in sub-Saharan Africa[23]. Nanotechnology can also be used to increase nutrient delivery for crops[24] and for water treatment such as using nanoparticles for removing arsenic[25].

With desktop automation and digital protocols, local, small batch generation of innovative nanotechnologies is achievable. Possibilities for nanotechnology innovation range from local synthesis of nanoparticles and their surface modifications to the production of nano formulations for drugs, biosensors or agents for crop protection[26]. These aspects are critical for nanoparticle applications and yet, with ready-made nanoparticles, they offer little flexibility,

Box 1 | Summary of key concepts

- Best solutions for infectious disease are ones that are self-propagating and leverage local resources and knowledge.
- Diagnostic middleware workers have tremendous potential to exploit nanotechnologies to design, test and implement new diagnostics that are usable in low resource settings.
- COVID-19 has exposed biological reagent supply chain fragility, which underscores the importance of enabling local fabrication.

as they are often optimized with bespoke procedures.

Engaging local communities is key to technological advancement

Nanotechnologies for infectious diseases are much more than a label for lateral flow tests. They are the nanocellulose membranes that prevent water borne infectious diseases such as cholera, diarrhoea, guinea worm and river blindness[27]. They are the generation of protocols for sensing tuberculosis infection using glycan-coated magnetic nanoparticles without complex instrumentation[28]. They are the refractive measures to detect diagnostic patterns in otherwise unreliable rapid tests. They can be used for treatment, for sensing, as well as for tracking immunized populations[29]. How do we create more evenly distributed capacity so that Feynman's well-known notion includes plenty of room for populations in low income areas to participate in nanotechnology for infectious disease? Our science needs to engage local communities at the beginning of the engineering process, not at the end. We need to design protocols that make use of global and inclusive materials and instruments. We need to recognize that developing an infectious disease diagnostic solution requires much more than understanding the fundamental biological detection event.

Certainly, an important component for enhancing nanotechnology impact is the dissemination of protocols and training for making nanomaterials and their characterization in the field. As previously mentioned, one critical issue is tied to the importance of local fabrication. The massive demand for reagents, PPE supplies and medical devices created by the COVID-19 epidemic has exposed the fragility of the medical supply chain, creating dangerous bottlenecks. Things as commonplace as swabs became scarce leading to bottlenecks that prevented testing. Testing was held up when kits for DNA extraction were not available, which could have been circumvented by classic lab protocols for DNA extraction. We saw hints of this at the beginning of the pandemic in Seattle when there was a critical shortage of diagnostic tests, and scientists repurposed tests before US Food and Drug Administration approval[30]. This was an example of the power of sharing technical know-how about running tests. Thus, designing protocols that can be scaled as opposed to scaling the manufactured device can be more impactful. When combined with local fabrication, it can address supply chain issues by enabling end-users with ways to manufacture chemicals and biological reagents[31]. Understandably, protocols have to be followed and faithfully executed to deliver products that match good manufacturing practices. A connected community of practice, bolstered by shared analytical tools, and networks that can exchange specimens and samples will go a long way towards building rigorous external quality controls in the local manufacturing process. Exciting new opportunities for this exist with the trend towards open source chemistry for drugs[32]. Following this blueprint, we emphasize the power of scaling the nanotech protocols as opposed to employing self-contained manufactured systems.

Not heeding the needs and the capacity of the local population can undermine progress. Global health history has shown us that simply sending over sophisticated equipment, reagents and teams of people to operate them are often not sustainable solutions. It leads to a technological dependency sustained by a lack of transparency. Black box diagnostics prevent the local population from participating in the design process leaving them the most unable to become invested in the technology. Thus, partnering with endemic areas is crucial (Box 1).

It is critical to keep in mind that diagnostics are much more than sensors, and the broader context of their use must be accounted for in the design process. Ultimately, they are tools for decision-making, and each one is applied distinctly since each outbreak has its own unique challenges. As technologists, we often become comfortable controlling the technical aspects of a diagnostic — for example, sensitivities relative to biomarker levels across infection states. We should remember that the economic, social and human interaction elements of our nanotechnologies can be just as important as what we are able to pipette into a test tube. By committing to a transparent set of nanotechnologies that can enable those at the front lines to respond to this complexity, we can accelerate the impact and the latent promise of nanotech for the entire global community. ❐

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