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Hello and welcome to European Pharmaceutical Review Digital Newsletter!

In this issue we have the sixth instalment of Dr Sheraz Gul's Laboratory Automation Series, starting on page 3

Also in this issue we have a special qPCR article from Dr Jim Huggett and colleagues. This article looks at the challenges of qPCR in the developing world and talks about their own experiences of this in Tanzania and Zambia. You can read the article on page 11

Of course if you would like to be involved in a future European Pharmaceutical Review or European Pharmaceutical Review Digital News by providing news and press releases please get in touch with me.

Have a Happy Christmas and I look forward to you all joining us in 2010!

DIGITAL

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Vice President and Head of Biology, European ScreeningPort, Hamburg

Article 6: Lab Automation series

In this sixth part of the Drug Discovery Developments section of the European Pharmaceutical Review Digital a brief overview of the milestones in pre-clinical Drug Discovery will be covered. The pre-clinical stage of Drug Discovery, also known as the gene-to-Candidate phase can itself be subdivided into various stages. Each of these has defined milestones and criteria that need to be met for progression of the project. These stages are the gene-to-target, target-to-validated Hit and validated Hit-to-Lead and the criteria that are required to be met at each stage are overviewed in this article.

Drug Discovery is a high risk, expensive and lengthy process, typically lasting 10 years which can conveniently be dissected into various phases. The early stage of Drug Discovery, termed the pre-clinical stage, sometimes also referred to the gene-to-Candidate phase, can span a period of five years. During this stage in the Drug Discovery process, firstly a target deemed worthy of therapeutic intervention is identified and subsequently a biological reagent is prepared that contains the target of interest. This will complete the gene-to-target stage of the project. This biological reagent is utilised in developing an appropriate assay to monitor target activity, usually in microtitre plates of various densities (96, 384 and 1536 wells per microtitre plate). This assay often makes use of the target of interest in isolation (e.g. a relatively simple biochemical assay using the target protein in isolation in the form of a full length or truncate protein, preferably with no tag) or in a more complex cell based assay. Having developed an assay it is then used in a screening campaign against libraries of small molecules in order to identify those that modulate target activity in the desired manner. The small molecule libraries employed in the screening campaign contain large numbers (10,000 - 1,000,000) of compounds and the screening activity is termed high throughput screening (HTS). The primary HTS campaign is executed in a systematic manner where the compounds in the small molecule library are tested relatively rapidly. Each assay plate contains a number of low and high control wells and the data from test wells are usually normalised against the control samples and the final data are expressed as a percentage effect.

Having completed a primary HTS campaign, those compounds that give suitable activity are classified as Hit molecules. For illustrative purposes, a primary HTS campaign that makes use of 500,000 compounds with a Hit rate of 2% will yield 10,000 actives in the primary HTS. These primary Hit compounds are re-tested in a confirmation assay (usually in duplicate) to ascertain which of the primary Hits were real as all assays usually have a small but significant false positive Hit rate. In addition, these primary Hit compounds are also evaluated in a suitable counter assay to ensure that the activity in the primary HTS assay is not an assay artifact. This exercise will also allow frequent hitters to be identified and excluded from the pool of compounds for further study. A good assay will typically yield a reconfirmation rate >70% in the primary HTS assay and most of the compounds would also be inactive in the counter assay. Compounds that exhibit the desired profile are then assessed in dose-response experiments in the primary assay in order to allow the determination of the potencies of the compounds against the target of interest. This should be performed with compounds freshly prepared from solid samples that have met acceptable QC criteria (ensuring acceptable compound purity and integrity). From the typical HTS campaign as described above 7,000 dose-response experiments may be performed in the primary assay. The end result of these screening activities will be the identification of validated Hit molecules. This will also complete the target-to-validated Hit phase of the project and may take 9-12 months to complete.

In order to determine which compounds from amongst the validated Hits should be pursued for further study, they are annotated with additional data after which an informed decision can be made to select appropriate compounds for progression. The commonly employed method of annotating compounds

will include assigning them with regards to the Lipinski rule of five. The ideal properties for selecting compounds for further progression will include those that have (i) molecular weight less than 500, (ii) logP, a partition coefficient measuring hydrophobicity less than five, (iii) no more than five hydrogen bond donors and (iv) no more than 10 hydrogen bond acceptors. However, some compounds that violate the Lipinski rule of five but are deemed to be sufficiently novel should be retained for further study. From the initial list of validated Hit molecules, a relatively small number are usually considered for further exploration during the next phase of the project, termed the validated Hit-to-Lead (H2L) phase. There are also other additional factors that need to be taken into account when selecting which compounds to select for the H2L phase and these include clustering the validated Hits into classes of compounds and determining any preliminary structure-activity-relationships. Typically, optimisation of the potency at the target

Property	Criteria
activity	acceptable pharmacology against primary target
	significant biological activity in a cellular assay
	selectivity against other related targets
	search databases for activity against other targets
chemistry	show chemical tractability, synthesis route and ability to alter structure
	have a good drug-likeness (fulfills Lipinski's rule of five)
	free of Intellectual property and competitor activity
toxicology	does not interfere with the P450 enzymes, P-glycoproteins, hERG or exhibit gene-toxicity
	acceptable Absorption, Distribution, Metabolism and Excretion
physico-chemical properties	does not bind to human
	be soluble in water
	be chemically stable
	exhibit cell membrane permeability
	not metabolized rapidly
In vivo data	assessment of pharmacokinetics and the ability to reach target of interest
	elicit desired effect in animal models of the disease biological efficacy after oral administration
	acceptable bioavailability

Table 1

of interest is the priority during the H2L phase and it is commonplace to set a benchmark potency to be achieved (typically low nanomolar) as well as appropriate selectivity profiling. Additional data that will be required when selecting a Lead molecule will include target pharmacologic, Absorption, Distribution, Metabolism and Excretion (ADME) properties, toxicity, synthesis route and ability to alter structure, searching databases for the activities of the compounds against other targets, patentability, competitor activity, acceptable physico-chemical profile, solubility and stability in aqueous solution and human plasma. In addition, in vivo assays allowing the assessment of pharmacokinetics and the ability of compounds to reach the target of interest and thus elicit the desired effect in animal models of the disease is required. These animal models also provide information as to the likelihood of a compound meeting biological efficacy after oral administration and thus compound bioavailability. The criteria that are usually required to be fulfilled adequately for a compound to be considered to have reached the Lead criteria are listed in Table 1 and this phase can take one to two years to complete.

In summary, the aim of the gene-to-Lead phase in Drug Discovery is to initially identify and subsequently optimise compounds so that the most promising and thus those most likely to be successful enter the Lead-to-Candidate phase. Although this article documents a typical gene-to-Lead Drug Discovery program, there is always variability from project to project.

Dr Sheraz Gul

Dr Sheraz Gul is Vice President and Head of Biology at European ScreeningPort, Hamburg, Germany. He is responsible for the management and development of Medium and High Throughput Screening activities for academic partners across Europe. He has 12 years research and development experience in both academia (University of London) and industry (GlaxoSmithKline Pharmaceuticals). This has ranged from the detailed study of catalysis by biological catalysts (enzymes and catalytic antibodies) to the design and development of assays for High Throughput Screening for the major biological target classes. He is the co-author of numerous papers, chapters and the Enzyme Assays: Essential Data handbook.

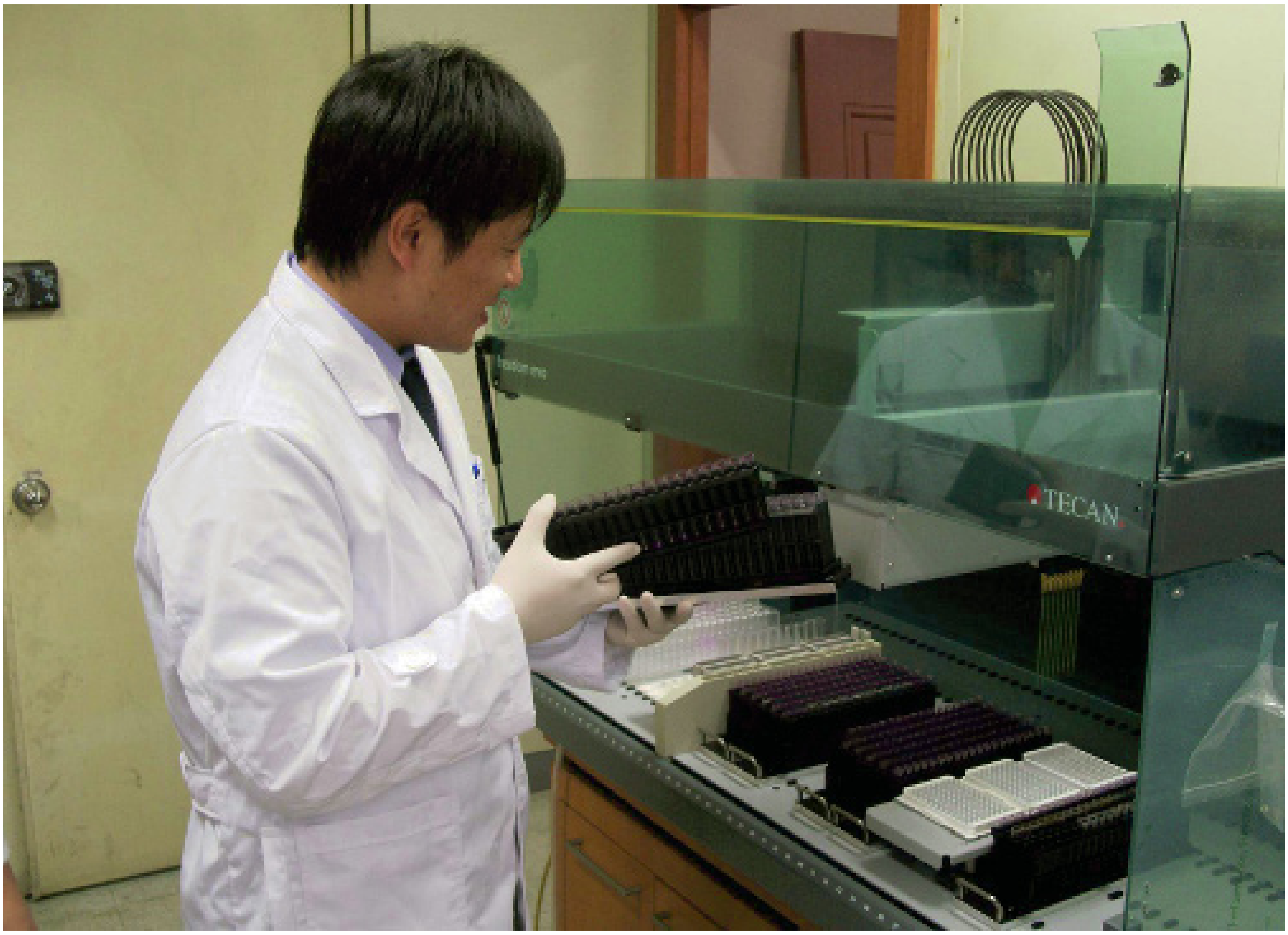
Freedom EVO® gives RIA workflows a boost

Shin Jin Medics, Inc. in Koyang-Si, South Korea, a manufacturer of in vitro immunodiagnostic products, has chosen Tecan's Freedom EVO® platform as a critical component in its automated radioimmunoassay (RIA) workflow solution, the RIA Automated Laboratory System (RALSystem).

Mr Seung-Jae Lee, manager of diagnostic instrument engineering at Shin Jin Medics, explained: "We developed the RALSystem, consisting of Tecan's Freedom EVO 150 liquid handling workstation integrated with our gamma counter, washer and shaker, to perform automated RIAs. We chose the Freedom EVO for the sample handling of the workflow because of its flexibility and compatibility with our own systems; our proprietary tube rack carries the total workflow through all four devices, minimising human error and saving labour and time. The Freedom EVO takes 10 minutes to distribute 100 samples into 500 reaction tubes, and the whole process from sample distribution to results takes about one or two hours, compared to several more hours it would take to do these assays manually."

"We received comprehensive training from Tecan for running and maintaining the instruments, as well as application and software support. We have been using the Freedom EVO routinely in the RALSystem since the beginning of 2008, and everything has worked smoothly, without a problem," concluded Mr Lee.

www.tecan.com/freedomevo



IDBS expands in Asia Pacific

IDBS, the leading worldwide provider of research data management and analytics solutions to R&D organisations, today announced that it has expanded its Asia Pacific presence with new centres in both China and Australia. From these new offices, IDBS is now providing customers with direct local support and training, as well as sales and business development across the entire portfolio of IDBS products; ActivityBase, E-WorkBook and InforSense Suites.

IDBS now has the largest presence in China of any life sciences software company.

IDBS' organisation in China is being run from Shanghai by David Hadfield and serves customers in mainland China, Hong Kong and Taiwan. Mr. Hadfield was formerly Senior Vice President and general manager at Spotfire and previously held senior executive roles at Molecular Devices Inc., and Oxford GlycoSciences, as well as senior management positions at Applied Biosystems.

IDBS has also expanded its existing Australian operations under the leadership of Conor Higgins. This organisation will serve customers in Australia, New Zealand and South East Asia. Mr Higgins, who has already developed a strong IDBS user base in Australia, has over 15 years experience in the IT field, specialising in data security, compliance and management. He has previously helped organisations such as Watchfire (IBM), Ironport (CSICO), and Acopia (F5Networks) expand their businesses in the region.

www.idbs.com

Copley Scientific introduces new inhaler product testing aid

The NGI cup coater is a new tool from Copley Scientific for use in semi-automated inhaler product testing.

The Next Generation Impactor (NGI) is used increasingly for aerodynamic particle size measurement, as prescribed by the regulators for all inhaled drug products. Applying a sticky layer to the cups of the impactor improves measurement accuracy, particularly for dry powder inhaler formulations, by reducing particle bounce and re-entrainment. Copley's NGI cup coater automates this process replacing conventional coating methods such as spraying, dipping or pipetting, that are often manual, messy and time-consuming.

Automating the coating process frees up analysts to perform other tasks, eliminates the variability associated with a manual procedure and reduces solvent wastage. The cup coater is easy to use and holds a full set of eight cups for simultaneous coating of all collection surfaces. The coating liquid, typically a solution of silicone oil, glycerol or PEG in a solvent such as hexane, is pumped into the rig to fill the cups and then the excess drawn out, the tray tilting to ensure the removal of all liquid. Fans assist in evaporating any remaining solvent leaving behind the sticky layer. The coating is dispensed in a fixed period of time, but the speed of the peristaltic pump used for filling and the drying time are variable, so the coating parameters can be adjusted in line with the viscosity of the solution.

www.copleyscientific.com

Life Sciences logistics provider expands into China

The Life Sciences logistics solutions provider, Biocair has recently expanded its operations into China. The opening ceremony, held on November 12th was attended by Carma Eliott, the British Consul General in Shanghai, who cut the ribbon together with Andy King, the Managing Director of Biocair. The British Consul general congratulated Biocair on the issue of their new Chinese Business Licence. She re-affirmed the British Government's support of the Life Sciences sector and acknowledged the vital logistics role for research materials and clinical trial samples that Biocair can now provide companies in China.

Biocair, established since 1987, is a proven international specialist in transporting temperature sensitive biological materials and drugs for clinical trials in and out of the main pharmaceutical and biopharmaceutical clusters in UK, Europe, USA, South America, Russia, Japan, and India. The new logistics operation in Shanghai has extended their Asia service offering. Andy King commented; *"This expansion into China is a key step in our international business development plan in response to growing customer demand in the region"*. He went on to say: *"We really appreciated all the encouragement and support we have had from customers, which helped us make this investment decision to enter the China market."*

Setting up a new operation in China is complicated and needs expert help to ensure it's done correctly, avoiding costly delays. Biocair used the consultancy company Asiasetup, who were able to gain 'Wholly Foreign Owned Enterprise' approval at Municipal level in just two weeks, which is a more difficult level for a foreign company to obtain in Shanghai; Biocair's business license was granted two weeks later. Chris Cooke, Biocair's CFO congratulated the Asiasetup team on achieving one of the fastest Chinese company registration's on record. It was achieved due to the detailed preparation and consultation with Government officials prior to submission, which Asiasetup is able to do very effectively, having built excellent relationships with the Government departments involved.

www.biocair.com

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The challenges, value and impact of conducting qPCR in the developing world

Molecular biological tools are at the forefront of biological and medical research worldwide. Currently, methods that employ nucleic acid amplification techniques (NAAT), like qPCR, are increasingly utilised to assess disease diagnosis, prognosis, incidence, prevalence and epidemiology. The development of NAATs for use in infectious disease research has historically been led by research institutes based in resource rich settings. Here we discuss the challenges posed when utilising NAATs for research in resource poor settings and assess the impact and value such an approach yields with reference to our own experiences in tuberculosis (TB) in Tanzania and Zambia.

TB is the most prevalent infective cause of death worldwide[1]. This disease, which has long been associated with the human race[2], can cause a range of presentations from a slow consumption of the patient leading to wasting and ultimately death, to rapid and aggressive infection of the brain leading to meningitis which generally has a poor prognosis. Today TB is at epidemic levels in much of the developing world[3] and certain forms are now threatening to increase in Europe (EASAC press release 24.03.09: http://www.easac.eu/news). Despite this, advances in TB diagnosis have barely advanced from the routine methods used over 100 years ago.

Where advances in TB diagnosis have occurred they are generally expensive, provide small benefit, when compared with existing methods, or are relegated to specialist areas where rapid turnaround is needed (e.g. drug resistance testing). NAATs have played an essential role in the latter, but could have arguably made a greater contribution to basic diagnosis than they have in the last 10 years. NAATs are generally not considered suitable in all but the most advanced diagnostic/research laboratories in countries like Zambia and Tanzania. However NAATs have the potential to provide a valuable contribution in combating TB as local infrastructure is improved and methodologies simplified.

Conducting research using NAATs by local scientists in the very countries suffering the highest disease burden ensures the development of molecular tools appropriate for that setting. Furthermore, this

Figure 1A: The University Teaching Hospital, Lusaka Zambia and B: The NIMR-MMRP, Mbeya, Tanzania.

promotes infrastructure development, and offers the opportunity to provide additional value as we discuss below. However, there are also considerable challenges to conducting such methodologies for both research and clinical assessment of TB.

Challenges

The challenges associated with NAAT based analysis of clinical samples in a developing world setting are many and varied. Operational challenges specific for the local infrastructure abound: incomplete cold chains, absence of trained laboratory personnel, under equipped laboratories, high cost of importing new equipment with the associated maintenance charges, delays and high cost of importing reagents and consumables[4]. In addition to the operational challenges, specific technical challenges exist when using NAATs in the developing world setting, such as quality assurance, troubleshooting and the correct interpretation of data. The operational and technical challenges of introducing any NAAT into such a setting are broadly similar, but we will illustrate these with reference to our experience of conducting qPCR for TB research in Zambia and Tanzania.

Perhaps the most testing operational challenge when conducting qPCR in resource poor settings at present is the incomplete and costly cold chain. When conducting qPCR at the University Teaching Hospital (UTH) (see Figure 1a) in Lusaka, Zambia's capital city, which has good air links the cold chain is less inhibitory. However for our research at NIMR-MMRP (see Figure 1b), in Mbeya, Tanzania, the established cold-chain requires intensive management. This CAP (College of American Pathologists) certified research laboratory is situated over 900km from the capital, Dar es Salaam. The transfer of cold items requires them being met at customs at Julius Nyerere International Airport, Dar es Salaam, with dry ice, transferred to suitable transportation containers and driven 13 hours by road to Mbeya. Increasingly lyophilised reagents[5] are being

Figure 2: Examples of leading developing world laboratory infrastructure to conduct microscopy (A) and microbiology (B).

developed for NAATs thus obviating the dependence on the cold-chain for reagent transfer. However, for the transfer of some research/diagnostic samples, essential for external quality control, there is no alternative at present to a complete cold-chain.

Both the UNZA-UTH, Zambia and NIMR-MMRP, Tanzania, have well equipped laboratories and the local infrastructure to provide uninterrupted constant electricity and water supplies (see Figure 2). Thus, many of the operational challenges encountered in the daily running of NAATs for research are not prohibitory. In an existing laboratory, the installation of qPCR technology requires little additional infrastructure improvements for example, no additional rooms, equipment (except the thermocycler) or biosafety considerations are required. The thermocyclers themselves benefit from a small footprint, so do not require extensive space, when compared to other advanced technologies, such as Fluorescence Activated Cell Sorting (FACS) machines[6]. As technologies become increasingly deployed, savings through establishing service contracts with fellow institutes in the same geographic region could be attained, though at present the low number of research centres in the developing world that use such technologies mean they do remain a high additional cost for qPCR. However, when presently choosing qPCR or other machinery, companies who offer the best support are frequently selected, despite an often increased cost.

The development of a robust, efficient and effective qPCR assay is a time-consuming and detailed process[7] and one technical challenge that needs to be met prior to deployment in any research setting. The ability to accurately control the quality of in-house PCR assays can be challenging in even the best equipped laboratory[8]. With this in mind, we have developed a simplified qPCR assay comprising three components:

1. The template
2. The DNA polymerase and buffer mastermix
3. An assay specific ADDMIX.

The ADDMIX, which is put together at University College London, contains everything else necessary to perform the qPCR. The three component approach provides several considerable advantages ranging from simplified standardisation, reduced resources due to shipping, purchasing and hands on time, and simplified quality control. We define the efficacy of every ADDMIX prior to shipping to partner sites and subsequently upon receipt to monitor safe transit. Additionally the use of centrally produced standards which are also shipped to all partners has the additional benefit of allowing easy exchange of data, which considerably eases troubleshooting and facilitates adherence to MIQE guidelines[9].

QPCR technology is a flexible platform for disease research; the thermocycler can be used to research any infectious disease with the appropriate assay and can be used for genotypic investigations. It is, however, important to note that without a useful product or continued research projects using similar platforms, it is unlikely that many of the challenges relating to supply of reagents, consumables and equipment will be sustainably addressed.

Figure 3: The European Union Framework Six funded TB trDNA consortium (project LSHP-CT-2006-037785) comprising seven partners from Europe and Africa.

Value

While the challenges associated with performing qPCR in Zambia and Tanzania are considerable, and require amongst other factors additional costs and human resources, we have demonstrated that such operational considerations do not preclude such research. But, the question of whether capacity building or capacity sharing is appropriate should be considered, and addressed at the very beginning developing the scientific hypothesis to be tested. Scientific researchers cannot ignore the moral obligation associated with conducting investigations in resource poor countries[10].

Rather than parachute research, we believe the development of local infrastructure should occur simultaneously with the research project. In our experience, conducting qPCR analysis *in situ*, where the clinical samples are collected, enables concurrent training of laboratory personnel and improvements in laboratory

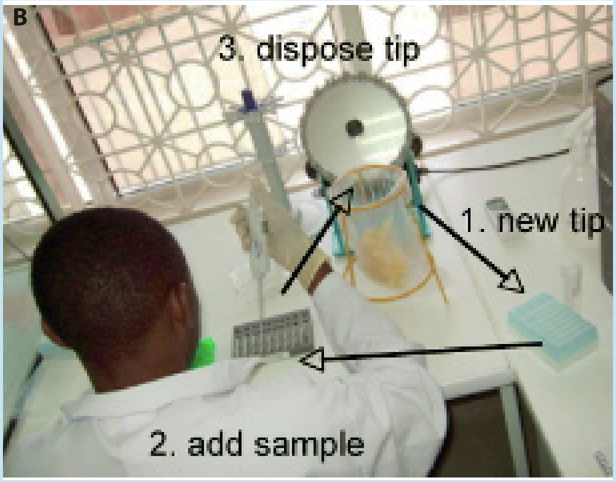

Figure 4: Examples of group and individual molecular biology training at UTH (A) and NIMR-MMRP (B).

equipment. The ability to "dove tail" such research into existing health care infrastructures and utilise local expertise will enable sustainable development. Such "out of the box" thinking as using mobile phones for disease diagnosis[11] and data capture or the development of mobile laboratories are prime examples of approaches to diagnosis relevant to the current situation in many resource poor settings.

With some rather high profile lapses in safe-guarding locally collected clinical samples (Sunday Times, SA, 15.02.09: "Bid to patent African DNA sparks outcry" www.sundaytimes.co.za/), Research Ethics Committees are increasing restrictions on moving samples from resource-poor to resource-rich countries. A secondary advantage of conducting research at the developing world site is the preservation of clinical samples which are considerably more valuable and unique than the reagents used to analyse them. It makes sense to transport the latter and not the former. An understanding of the need to increase local capacity to enable sustainable collaborations (see Figure 3) is evident in the grants provided by many funding bodies (eg EDCTP, EUROPAID). Stronger international collaborations are essential if the world is to meet the challenges posed by the dual pandemics of HIV and TB. As the demographics of diseases like TB change, sustainable high quality and cutting edge research in resource poor settings allows better monitoring of the development and distribution of drug resistance, a salient example being the first XDR outbreak in Africa reported from Kwa-Zulu Natal[12]. This capacity development can only be improved by increasing transfer of skills through providing training (see Figure 4), ranging from short courses to PhDs, thus empowering local scientists to lead the research.

Impact

While the challenges to conducting research in the developing world are clear and the associated value considerable, what is the actual and potential impact of NAATs like qPCR on disease like TB in the developing world?

Research

Scientific research has lead the way in installing the capacity to conduct molecular analysis in the developing world, and the area of TB research has been one of the leading fields. This has ranged from basic scientific research into the immunology[13, 14] and genetics[15, 16] associated with TB, to research into the development of newer[17] and investigating the potential of, existing diagnostic methods[18, 19], as well as drug sensitivity analysis. Such research, through collaboration with more established institutions or independently, has facilitated the infrastructure and training needed to conduct such techniques at a relatively small cost. While there are many examples of very successful research from the developing world, the greatest impact of these at the population level will be felt after translation of such findings into tools that can improve healthcare.

Clinical

While the actually clinical impact on developing world TB made by molecular approaches can be currently best described as minimal, we predict that the tide is about to turn. For a while now there have been a number of commercially available diagnostic methods for TB which have been limited to the more advanced molecular labs. However, over the past five years there has been considerable support from the groups like the World Health Organisation and the Gates Foundation to readdress this. NGOs like the Foundation for Innovative Diagnostics (FIND) have specifically encouraged industry to focus on the developing world when considering test development.

Methods like the PCR based line probe assay (LIPA) have considerably simplified both drug resistant assessment and pathogen speciation when investigating TB[20]. This method has been endorsed by the WHO TB STAG committee[21] for drug sensitivity testing and is becoming a key tool in developing world clinical trials. When the complexities of existing methods are considered, LIPA offers the potential for *Mycobacterium tuberculosis* (Mtb) drug sensitivity testing where none was available before. This is a particularly timely development with the increasing incidence of extensively resistant TB, which is resistant to the majority of available antibiotics[22].

While the LIPA offers tremendous advantages over established culture based tests they do still currently require the ability to perform Mtb culture prior to analysis. The loop mediated amplification method (LAMP) develop by Eichan and XPertTB real-time PCR machine, from Cepheid, offer arguably the first examples where simplified rapid molecular diagnosis of TB can actually leave the most advance laboratories and be performed at more regional clinics/laboratories at the microscopy level. This has tremendous potential because microscopy is the only investigative diagnostic technique available to much of the world.

While considerable efforts are currently underway to evaluate the efficacy of these methods and conduct the huge information campaign necessary to introduce these techniques, reagent supply and lack of expertise is likely to (at least initially) limit the real impact of these methods. Furthermore, for any NAAT for TB diagnosis to provide a valuable clinical input, the interpretation of the data produced should also be considered. Even the most facile rapid diagnostic test for *Plasmodium falciparum* malaria which have been shown to be highly efficacious[23] are sometimes ignored in the clinical setting[24]. Add to this the fact that we are no closer to an effective point of care test for TB than we were 10 years ago and it becomes clear that, despite many recently made advances, there is still a sizable gap in TB diagnosis in the developing world.

A possible solution would be a means where by a relatively small number of trained individuals could conduct the advanced molecular diagnoses on many different geographical populations. Such an approach requires mobility and we are considering using a mobile diagnostic and training centre (MDTC) to provide regional diagnosis and the associated training for TB and HIV diagnosis (see figure 5). The MDTC provides the first real opportunity to provide rural populations in the developing world with the fast accurate diagnosis of TB at the same time as it is being introduced in Europe. Trials are currently ongoing in Tanzania, and under development in Zambia, to establish if the MDTC approach really can fill the TB diagnostic gap, potentially providing major improvements to TB healthcare to hundreds of thousands of people in a relatively short period of time.

Conclusion

The potential advantages of using NAATs in the fight against TB in a developing world setting are manifold, including the ability to provide quantitative data relating to disease, to speciate and diagnose

Figure 5: External (A) and internal (B) photos of the MDTC visiting a rural site in Tanzania.

simultaneously and quickly, to provide data on drug resistance and to expand the use of the technology to other infectious diseases locally is important. It is important to develop confidence in new diagnostic assays and integrate them into the existing health care infrastructure ensuring ownership by the health care professionals and an expectation of level of care from the patients. The introduction of any new technology in a resource poor setting could be the beginning of a virtuous circle for both research and development; it is up to us all to ensure that this is the case.

Acknowledgements

We would like to thank the TB trDNA consortium and the European Commission Framework Programmes and EuropeAid for their ongoing support.

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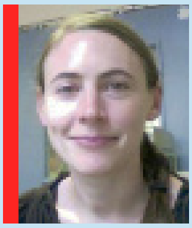
Jim Huggett

Jim Huggett obtained his PhD from Cardiff University investigating gene expression in bone disease. He then made a subject jump and moved to the Centre for Infectious Diseases at UCL where his principle interests focused on molecular analysis of respiratory tract infections. Recently he has moved to LGC to lead the diagnostics research at the Molecular and Cell Biology team. Here he is investigating the latest technologies for diagnosing a range of disease types including infection and cancer as well as foetal analysis. The mandate for this role focuses on defining both the technical and clinical utility of the various methodologies from a metrological point of view.

Jim's research philosophy is driven by the desire to ensure correct findings and frequently results in challenging established dogma when appropriate. Whether investigating RNA gene expression or molecular diagnosis using novel clinical samples, many dogmas exist that facilitate rapid findings enabling publication and/or commercialisation, but which are nevertheless partly or sometimes completely incorrect. This is a particular problem for molecular biological methodologies and a substantial amount of his work has specifically aimed at ensuring findings are accurate and that scientists are forewarned of the dangers of blind faith in these dogmas. His publication record reflects this and he has lectured on this subject, as an invited speaker, at a numerous conferences and workshops, including for EMBL.



Claire Green

Since graduating from Imperial College in 2004 with a Doctorate in molecular plant pathology, Clare's research focus has moved to human infectious disease diagnosis. Clare worked for two years at the MRC laboratories, Farafenni field station, The Gambia, between 2005 and 2007 for Durham University. Here she conducted the molecular research for two malaria intervention studies assessing large scale larviciding and house-screening in the local area. Her responsibilities here, besides the molecular identification of malaria vectors, encompassed managing and training the locally employed technical staff. Since joining UCL in 2007, Clare has been working on developing molecular diagnostic tools for TB, as part of the TB trDNA EU framework 6 (#037785) project. Clare has developed a number of diagnostic qPCR assays for tuberculosis and other infectious diseases, and has also investigated the fundamental aspects of the TB trDNA approach from the stability of DNA in urine under storage to the impact of inhibition on real-time PCR. Alongside which, she has travelled extensively to partner sites in Tanzania and Zambia to provide qPCR training to technical staff and implement the qPCR assays *in situ*.

Michael Hoelscher

Michael Hoelscher studied Medicine at Ludwig-Maximilians-Universität (LMU), Munich and since 1994 he has been employed at the Department of Infectious Diseases and Tropical Medicine at the LMU. In 2006 he became senior scientist.

His research interest is focused on the clinical development of tools to combat HIV and tuberculosis. His activities reach from basic research, searching for genetic or immunological factors that influence susceptibility to infection or disease progression to clinical trials of novel diagnostic tools, drugs and vaccines and operational research. The focus of his work is in Africa, where he established a large cooperative research centre, the Mbeya Medical Research Programme (MMRP).

Alimuddin Zumla

Alimuddin Zumla is internationally recognised for his high quality R&D work, outputs in infectious diseases (particularly TB, TB/HIV, respiratory infections and development of new diagnostics) and for his leadership in international health issues. Professor Zumla has led a number of projects that have taken qPCR into six African countries to conduct research ranging from TB diagnosis to immunology. Data from his health policy-relevant studies have been used by WHO and African governments for implementing and recommending policy change for TB management and management of childhood respiratory infections.