Impact Objectives

- Enable pain free skin biopsy and blood collection
- Utilise the microbiopsy device to provide rapid diagnosis of skin issues and blood testing, thus providing actionable diagnoses for faster treatment and recovery
- Use the new technology to move biopsy sampling out of medical centres and into the field, thus helping those in remote geographical areas by offering patients rapid diagnosis and treatment of not only skin conditions, but also infectious diseases

Revolutionising microsampling

__Professor Tarl Prow__ and __Dr Li Lin__ are Australian researchers that have developed a microbiopsy device. This sampling technology will not only minimise the need for painful sampling procedures in the diagnosis of skin disease, but will also decrease time to actionable diagnoses for both skin and blood testing. This new clinical and pathology approach will improve patient outcomes

Professor Tarl Prow

Dr Li Lin

Your current research is focused on skin sampling using microdevices. Can you explain more about how they work?

Our microbiopsy technology consists of a microbiopsy device and a modified spring-loaded blood lancet applicator. When applied, the microneedle captures a tiny sample of blood and skin. This sub-millimetre microbiopsy platform technology is less painful than a conventional blood lancet, so there is no need for local anaesthetics and has a safety profile similar to existing blood lancets.

What are the advantages of microsampling over traditional harvesting techniques?

Conventional methods of obtaining skin specimens involve invasive surgical techniques such as shave biopsy or Mohs surgery that require local anaesthetic injection, sutures and most result in scaring. Microsampling is quick and painless, which means physicians can sample many more areas than conventional biopsy approaches and repeat sampling over time. Conventional biopsy specimens are then preserved with formalin to maintain structural organisation and sent for histopathological analysis. Histopathological sections are rarely used for molecular fingerprinting in dermatology. Microsampling using our microbiopsy platform not only provides samples that are of higher quality than formalin fixed histopathological samples, but also have the capacity to target specific areas within a lesion. For blood sampling, patients have to undergo a phlebotomy procedure which requires a special room, trained healthcare workers, is painful and there are issues with needle stick injuries. Microsampling for blood removes all such barriers and risks.

Can you explain a little about absorbent microbiopsy techniques?

The absorbent microbiopsy is a simple approach where the microneedle that pierces the skin has an absorbent matrix. This device then captures a small amount of peripheral blood and lysed skin cell material within a porous matrix that will offer all the advantages that dried blood spot sampling is recognised for, but in miniature. This overcomes some issues associated with conventional blood spotting techniques. The blood sample can be dried or placed in buffer for single-step integration with molecular diagnostic kits. Current standard of care for blood testing involves collection of 20-60ml of blood using hypodermic needles and blood evacuation tubes, but only a tiny amount is needed for some tests. We believe that by combining the benefits of dried blood spotting and microneedles, defined quantities of blood can be extracted from the skin in a safe, painless and cost-effective manner that is biologically stable. This can then be used for blood tests that are sensitive and the technologies can be tailored for low resource regions.

How will this technology benefit other areas of dermatology research?

Surprisingly, one of the areas that is benefiting is the cosmetics field. Their only options have been cell culture research, non-invasive analysis and volunteers undergoing conventional biopsies. Now they are testing cosmetics in volunteers and taking microbiopsies to evaluate molecular changes in the treated skin. It is a very powerful tool for cosmeceutical development and testing. We are now working with groups around the globe who each have their own areas of investigative dermatology where microbiopsy is playing a large role. In Munich in Germany, we are working with a researchers learning about infant inflammatory disease; in Israel collaborators are using microbiopsy samples to detect leishmania in volunteers from Ghana and Ethiopia; in Brazil collaborators are applying microbiopsies to dogs to find signs of parasitic infection; and in New York, our collaborators are using microbiopsies to examine the molecular landscape of suspicious nevi in patients at risk for melanoma. Together we have done over 2200 microbiopsies on many different body sites including the face and neck. There are many uses for this technology that we never imagined. We look forward to seeing how we can help these creative people put our technology to work.

Novel microbiopsy tools for minimum invasive sampling

The increase in incidents of skin disorders are leading to a corresponding increase in biopsies to extract sufficient material for analysis and diagnosis. Exciting new research into sub-millimetre extraction tools is helping to remove the need for painful and invasive extraction techniques

Human skin is the largest organ of the integumentary system, comprising up to seven layers of ectodermal tissue, offering protection for the underlying muscles, bones, ligaments and internal organs. While similar to the skin of many other mammals, it has much lower hair follicle density, and generally exhibits a fine hair rather than the thick coats that some animals have. This can lead to problems with skin conditions and overexposure to the sun's rays and the complications that go with it. While the exposed parts of some mammals suffer from serious skin complaints, the relatively unprotected skin of humans is prone to a far greater incidence of lesions and potentially carcinogenic problems. Typically, an excisional biopsy is carried out when a melanoma is suspected or it is decided to remove a small tumour entirely for histopathological examination. A skin biopsy typically takes about 15 minutes, including preparation time, dressing the wound and detailed instructions for at-home care.

SAMPLING ISSUES

Biopsies of suspect areas are now a routine process, but remain one that is uncomfortable, risky and difficult to carry out in non-medical facilities. The collection of samples from the field is also of growing importance, but to do so with the current methods would be problematic. This has led to an interest in micro-dermatological sampling devices that are essentially non-invasive and allow sampling under difficult or extreme conditions.

Traditional skin biopsies can involve harvesting a section of skin using either a sharp-edged tool such as a razor blade or a circular punch, which can vary in size from around 1.5mm up to 8mm in diameter, depending on the size of the sample required. Both methods usually result in some bleeding and may require a stitch to close them. Local anesthetic may be required and pain relief is often administered post procedure. Following the healing process, there is likely to be a scar and that can become a major issue if several biopsies are required. Healing can take several weeks and the results can be unsightly. The other option is to investigate a means of obtaining smaller, less invasive samples that don't have such added complications, and that is the focus of the work of Professor Tarl Prow, Dr Li Lin and their team from The Future Industries Institute, University of South Australia and Dermatology Research Centre, The University of Queensland, Australia. Prow explains: 'We believe microbiopsy technology will be most useful to the public in the form of an inexpensive device sold at pharmacies and in general practice clinics for blood testing and skin disease testing. The device is targeted at those with many lesions, longitudinal testing, cosmetically sensitive areas and children.'

HARVESTING SMALL SAMPLES

The major issue with current biopsy techniques is the sheer size of the sampling tool. These large cutting devices are intended to harvest a substantial amount of the area under investigation in order to give a reasonable indication of the lesion's make-up. Prow and Lin's team however, consider that harvesting smaller amounts from specific areas may actually increase the accuracy of the result, remove the need for pre-procedure anesthetic, and avoid scarring. Furthermore, sampling of this nature could

take biopsies out of the medical centre and allow routine sample gathering in the field. Microsampling is carried out using a specially made lancet, laser-etched from surgical-grade stainless steel. The cutting head of the device is typically just 0.5mm wide and 0.15mm thick, making it pin-prick sized. Crucially, however, the actual cutting tip consists of an accurately formed twin-prong fork rather than a single point, and this allows a small sample of skin to be completely removed rather than just a cut made in the skin. The tiny piece of skin is sufficient to allow a physician to examine a specific skin complaint, but because it is possible to take a sample without substantial damage to the area, several samples can be harvested from specific areas, pinpointing any potential difference in the lesion or melanoma over its span.

SMALLER SAMPLES, BETTER RESULTS

While small, the samples can be used to determine the molecular fingerprint – such as genotyping and RNA sequencing – of the skin sample, providing accurate analysis. The practice offers the distinct advantage of targeting specific areas of a skin lesion and can therefore provide exacting results for different regions of the sample area. This is generally not the case with large traditional extractions. That approach can lead to the gathering of material, which may be key to determining if a sun spot is likely to become skin cancer with a simple and non-invasive technique.

Because microsampling can be carried out with relative ease, and leaves no lasting scar, it can be routinely used on patients who are at a higher risk of developing skin cancer before mutation has occurred, leading to a greater incidence of preventive medicine rather than playing catch-up with a tumour that has already taken hold. Furthermore, the micro-sampled site is generally so small that it is not evident when healed, even multiple gathering can be taken from cosmetically sensitive areas, as well as those sites that could be associated with poor healing, without fear of leaving permanent damage or unsightly scaring.

BEYOND SKIN CANCER

With the process proven, Prow and Lin have been keen to examine other areas of medical procedure where it may also be advantageous. One of the most obvious is that of dried blood spot sampling, used routinely for the mass screening of serious and infectious diseases

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in the rural areas of poor and Third World countries. Current practice calls for up to 60ml of blood to be taken from each subject, but a modified microsampling head with an inbuilt wick is capable of taking sufficient blood for analysis without needing to drain usual amounts via hypodermic needles. This has enormous benefits, not least the trauma that can be caused to younger patients, but also eliminates the need for a cold-chain to transport the blood samples to the analytical laboratory.

While microsampling was developed as a more efficient means of gathering material for the identification of skin complaints and the potential for dysplastic nevi to develop further, the sampling tools have also been taken up and employed by other groups of researchers for a variety of different methods. An Israeli team is using these microsampling tools and the process to determine instances of leishmania amongst volunteers from countries prone to the Sandfly disease.

THE FUTURE OF MICROSAMPLING

With the microsampling process now well-defined and proven, its use is likely to become increasingly widespread, not only in the field of skin disorders, but in an increasing number of medical applications too. The manufacturing processes for the micro-samplers are well-defined, and production of these and variations of the harvesting prongs are now routine, making samples easy to harvest and analyse.

Microsampling is quick, clean, painless and non-invasive, making it the process of choice. The current method of skin punches and the need for anaesthetic and post-procedure care are being rendered obsolete, and that will bring harvesting out of the medical centre and into the field, where it has the potential to make some real differences in many areas of early diagnosis.

Project Insights

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Professor Tarl Prow earned his PhD from the University of Texas, US in the field of Nanomedicine. He then completed his T32 funded post-doc at the Wilmer Eye Institute at Johns Hopkins Hospital, US and was faculty there until he relocated to the University of Queensland, Australia in 2007. In 2015, he was promoted to Associate Professor within the University of Queensland's School of Medicine and began his NHMRC CDF Level II Fellowship. He now focuses on translational outcomes from his micromedical device development team as a Research Professor in the Biomaterials Engineering and Nanomedicine Strand within the Future Industries Institute at The University of South Australia.

Dr Li Lin spent four years involved in skin-related research and the set-up of clinical-testing facilities at Procter & Gamble Singapore from 2005. She moved to Queensland, Australia in 2009 to pursue higher education and graduated with a PhD in biomedical engineering from The University of Queensland, Australia. She is currently a NHMRC Peter Doherty ECR Fellow at The University of Queensland whose research interest is to develop new technologies with a focus on drug delivery, diagnostics and imaging in the context of dermatology.

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