In with both feet

Until recently, research into chronic wound care was small scale, localised and largely uncoordinated. The Diabetic Foot Consortium (DFC) is looking to change that. With an initial focus on bringing more advanced biomarkers for predicting wound healing and recurrence into the clinic, the DFC is the first ever research network of its kind. Tim Gunn speaks to **Dr Teresa Jones**, the National Institute of Diabetes and Digestive and Kidney Diseases' project scientist for the group, and **Professor Chandan Sen**, the principal investigator for its first protocol.

Some questions need to be asked in a white coat. Before he discusses the work of the National Institute of Diabetes and Digestive and Kidney Diseases' (NIDDK) Diabetic Foot Consortium (DFC), Professor Chandan Sen slips off-screen to grab his from the hanger on the back of his office door. Now then: what does it mean for a wound to have healed?

Sen, associate vice-president of research at Indiana University (IU), is the principal investigator for the DFC's first protocol, a large-scale validation study into

whether transepidermal water loss (TEWL) could be a biomarker for the likely recurrence of diabetic foot ulcers. In his words, "It's pretty big". At present, the FDA defines a closed wound as one that has been entirely re-epithelialised and has no discernible exudate, drainage or need for dressing for two weeks. For one-third to half of all diabetic foot ulcer patients, however, that might be inaccurate. All skin is not recreated equal.

"Hundreds of millions of dollars of investigative trials are happening today," says Sen. "In any trial, the end point is critically important, and if the end point itself is faulty, the value of the trial dramatically drops. So, we need to define the right end point of wound closure, because today there is no way of separating the wound healing product that gives you functional skin [from one that gives you] faulty skin. That is not even a consideration."

First in pigs, and then in people, Sen and his team observed that a large proportion of chronic wounds are closed with defective skin that can't perform its full barrier function. DFC pilot studies suggest that these 'leaky' closures, which lose water at a much higher rate than normal skin, make it far more likely for wounds to recur. The ease with which we slip into thinking of skin as a purely superficial organ, apt for judging simply by appearance, might have made us blind to it.

"If I was having a heart transplant, and you put a heart in my body that didn't beat, people would be mad about it," says Sen. "But with the skin, whether it beats or not, meaning whether it performs its barrier function or not, we never bothered to take a look. Now we are saying that the skin must be functionally intact for the wound to be closed. So, we are basically redefining the clinical end point of wound closure, and the impact could be really large."

There's no better way for the DFC to announce itself. The first trial network of its kind – bringing together six leading US research universities under the aegis of the NIDDK, one of the National Institutes of Health – it was launched to advance basic science on biomarkers into the clinic while helping bring a bit more synergy to the research around diabetic wounds. Sen attributes any success it might have to the vision of endocrinologist and NIDDK programme director Teresa Jones, who felt studies into diabetic wound healing were too disconnected to really make a difference to the field. Should the consortium find that those studies had also been evaluating healing according to a misleading end point, she will have been validated many times over.

Merely the tip of the spear

But the DFC is about much more than a single study, however impactful it might prove. For one thing, the network is already running another biomarker trial. The second, led by the University of Miami, is testing whether levels of the cellular protein c-Myc in tissue samples from an ulcer can predict the likelihood of it healing within the next 12 weeks. As antibodies for silencing c-Myc expression are commercially available, it could open a new treatment pathway for hard-to-heal wounds.

Chandan Sen with Donnell Hayes, the DFC's first patient, at an IU hospital in Indianapolis.

Jones hadn't initially planned for the DFC to begin with this specific focus, but early consultations with experts and stakeholders convinced her that the meaningful clinical trials for wound-healing products she wanted to facilitate required a more robust set of biomarkers. At the time – just a few years ago – those barely existed in any practical sense. As she recalls, the only one in consistent use was a measurement of the proportion of a wound that was re-epithelialised in four weeks. "If you have 50% closure over four weeks, it's likely to heal eventually with standard care, and, if not, then it probably isn't," she says, almost apologetically. "It's kind of a stretch to call it a biomarker, but that's what was being used in the field."

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As with the TEWL study, the c-Myc trial will take place across all of the clinical research sites in the DFC – which also include the University of Michigan at Ann Arbor; the University of California, San Francisco; Stanford University; and the University of Pittsburgh. Each centre recruits up to 70 participants undergoing foot ulcer treatment or follow-up care per study.

Although similar models are well established in disciplines like oncology, where clinical trials for orphan drugs are often only possible because there exist research networks able to recruit a sufficient number of patients, chronic wounds are troublingly common, and the approach to treating them

$1.22bn

The wound dressings market in 2020, compared with $1.35bn in 2019.

GlobalData

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Covid-19's impact on wound care

The patchwork spread of the pandemic across the globe has led to a patchwork recovery. Smith+Nephew shared that elective procedures in China, Japan and Germany were back above 80% of expected levels in June, but that the UK was slower to recover, with procedures at only around 35% of expected levels. The US, with its quick reopening, had also briefly recovered to over 80% of expected levels, but the continued surge of Covid-19 cases in some states has again resulted in restrictions, a trend that is now being repeated across Europe.

The pandemic has also forced healthcare providers to explore alternative ways of continuing care. One promising method has been the use of telehealth, although there was some concern that it might be less effective in more specialised fields like wound care. Addressing this, a recent study by Wamsley and colleagues in the *Aesthetic Surgery Journal* found that a switch to telehealth for their plastic surgery and wound care practices improved appointment completion rates when compared to the in-person completion rate for the same month in 2019.

Of course, there remain concerns regarding inaccurate diagnoses, reimbursement and privacy when compared to an in-person visit for wound care patients. As these concerns are addressed in the coming months, telehealth may allow wound care patients to continue to receive care from home, especially for chronic wounds. This, in turn, could help lessen the market impact from Covid-19. For example, GlobalData currently expects the wound dressings market to drop from $1.35bn in 2019 to $1.22bn in 2020, but telehealth may accelerate recovery by allowing physicians to continue care remotely, even if elective procedures are halted again.

Source: GlobalData

unhelpfully diffuse. "Wound is not a medical specialisation really acknowledged in the US," explains Sen, who has pushed against that by setting up comprehensive wound centres at IU and the University of Ohio. "When you're a med student, you study very little about wounds – especially the care of chronic wounds. There is no mainstream residency programme, and the discipline itself is very mixed. You have infectious diseases, surgery, dermatology and a whole host of other specialisations."

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Dr Teresa Jones

A help and a hindrance

The rapid growth in the number of comprehensive and advanced wound care centres is an acknowledgement of the difficulty of fitting wound care into traditional medical practice. Still, Sen can't think of a dozen of them at academic institutions in the US. That might have something to do with what Jones notes is the often laborious and less-than-innovative work needed to move wound care research beyond basic science. Either way, it's a niche that has been filled primarily by commercial management companies, which are able to coordinate the range of specialists required to support wound healing to the best of our current ability, but can't do much to improve it.

In fact, the need for comprehensive chronic wound care for today's increasingly immunocompromised populations may well have stifled research into doing it better. As many as 34% of people with diabetes develop foot ulcers, so it's usually possible to recruit enough participants to trial a wound-healing product at only one or two sites, increasing the likelihood of unrepresentative, uninstructive patient samples. That's doubly the case because wound care products are almost exclusively devices, rather than drugs, which means they can be approved with less evidence and fewer subjects.

"One of the goals of this was to improve the research in the area," explains Jones. "When you have clinical trials that just take all comers with diabetic foot ulcers, then it's hard for a therapy in a phase-II or phase-III trial to show efficacy, as you have a lot of wounds that are going to heal already." A network, however, is able to recruit patients that meet more precise entry requirements – a particular c-Myc level, for instance – without jeopardising its ability to populate the study. By doing exactly that, the DFC is building up a database and a biorepository for future use, along with an infrastructure that can accelerate the launch of ancillary studies and provide a framework for researchers to investigate promising new leads without the frictions that kept biomarkers out of the clinic for so long.

The first of those, TEWL, comes out of work Sen was doing before the DFC was established, so it's perhaps not surprising that he's so passionate about its potential. ("It's human nature," as he says). But IU only became one of the founding members of the consortium after making it through an NIH competition, and Sen's study was chosen from among 12 others after another selection process. It's been rigorous.

"Because we're in this consortium, any finding we have is vetted and critically discussed," Sen explains. "When you have several other top minds in the field at the table, they tend to critically debate, and the key take-home message emerges from that." The data has its own home, too. The University of Michigan won another grant to set up a separate data coordination centre, where all of the information is stored and evaluated outside of the context in which it was collected, further minimising the potential for mishandling or bias. This is not the wound care research of even a few years ago. The DFC may be the best resourced group ever to work on chronic wound healing – and, as importantly as anything else, it might bring more researchers to the wound care cause.

"We have the leaders in the field, the best people in the country as clinical investigators, so that adds interest," reasons Jones. And a new research cycle, with opportunities for new entrants, starts in 2022. Grab your coat. ●