

## THE BYSTANDER EFFECT

Dr Lipi Shukla's research will help treatment for those who have cell damage from radiotherapy cancer treatments

Plastic and Reconstructive Surgery Trainee Dr Lipi Shukla has spent the past three years investigating the cellular and molecular causes, and progression of, the damage done to healthy nearby tissue by radiotherapy cancer treatments, a condition known as Radiation Induced Bystander Effect (RIBE).

Considered an inevitable side-effect of radiotherapy, RIBE is a progressive, late-onset soft-tissue injury that can expose vital underlying structures and is characterised by symptoms including pain, contracture, tissue breakdown, recurrent infection and lymphoedema.

With improvements in cancer treatments and the consequent cohort of cancer survivors growing year by year, RIBE is now presenting as both a significant quality of life issue for such patients and an increasing challenge to surgeons across all specialties.

It is now part of a growing list of ailments called "diseases of survivorship".

Dr Shukla said that RIBE-affected tissue had a restricted ability to redevelop a new blood supply and recover from injury, which restricts surgical treatments particularly in such specialties as Plastic and Reconstructive Surgery, ENT, General Surgery and Colon Surgery.

"Important implications of RIBE for surgeons are that surgical procedures – whether for functional restoration or cancer recurrence – in irradiated tissues are made more difficult," Dr Shukla said.

"Direct wound closure or local flaps are restricted by stiff, non-compliant tissue and even if wound edges are opposable, they are frequently subject to poor wound healing or breakdown.

"The ability of an irradiated wound bed to accept a skin graft is also diminished, which often necessitates more complex, potentially hazardous reconstructive procedures

such as free microvascular tissue transfer from distant sites, in which radiation is a chief contributing factor to poor patient outcomes.

"Methods to salvage irradiated tissues to a point at which soft-tissue quality permits simple wound or tissue repair is desperately needed by clinicians."

Dr Shukla undertook the research into RIBE as part of a PhD through the Australian Catholic University, St Vincent's Hospital in Melbourne and the O'Brien Institute of Tissue Engineering with financial support from the College as the first recipient of the Foundation for Surgery Tour de Cure Cancer Research Scholarship.

Not only did she set out to understand the effects of radiotherapy injury on cell function in-vitro and the role such alterations played in the development of lymphoedema and fibrosis but also to find out if there was scientific evidence to support anecdotal reports that fat grafts could ameliorate the effects of RIBE.

"For some time, Plastic and Reconstructive Surgeons, particularly those conducting breast reconstruction surgeries following mastectomy, were anecdotally reporting that irradiated tissue overlying the fat graft became more complaint and less lymphoedematous," Dr Shukla said.

"While these effects had been clinically validated in murine models, the scientific mechanisms behind the phenomenon remained poorly understood so I wanted to find out why this was happening.

"As part of this research, we broke down RIBE effected tissue to the cellular level to understand the molecular signalling changes that were taking place in damaged cells, while also trying to identify growth factors that may reverse the effects."

Dr Shukla said she investigated adipose derived stem cells, extracted from samples of excess fat and found that these cells secreted specific growth factors that were able to reverse the

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effects of radiotherapy injury on cells such as fibroblasts and lymphatic endothelial cells.

Another series of laboratory experiments investigating the effects of irradiation on normal human dermal fibroblasts, indicated that it resulted in a hyperactivity, rather than suppression of certain physiological functions

"This was a significant finding because it suggests that this hyper-active state represents cellular dysfunction resulting from sub-lethal radiotherapy injury and that it could be a contributing factor to the formation of fibrosis and the spread of RIBE rather than the more traditional hypotheses of large scale cell death," Dr Shukla said.

"We also found in our model of fat grafting that hyperactivity of irradiated normal human dermal fibroblasts was reduced and reversed in the presence of growth factors secreted by adipose derived stem cells.

"We now believe that these stem cells have great regenerative potential and aim to identify specific growth factors that can reduce the effects of radiotherapy injury in a cell-specific manner.

"It was very exciting to build up a scientific base which supports the anecdotal evidence that has been the subject of increasing interest in Plastic and Reconstructive Surgery literature for the last decade."

Dr Shukla conducted her research under the supervision of Professor Wayne Morrison, the former Director of the O'Brien

Institute, and Mr Ramin Shayan, the current Director of the Institute.

She is now back at work as a SET1 Plastic and Reconstruction Registrar at the Maroondah and Box Hill Hospitals in Melbourne.

Now in the process of writing up her thesis, Dr Shukla thanked the College and Tour de Cure Foundation for the generous support given to her to complete her research.

"It is always a difficult decision to take time away from training to dedicate to research, but this area of medicine is of great intellectual and clinical interest to me. It has given me the opportunity to develop a set of skills facilitating bedside to lab bench research, seeing the problems in clinic and trying to find a scientific solution to the problems faced by our patients," she said.

"This PhD has allowed me to acquire expertise in the rapidly evolving area of fat grafting and radiotherapy injury, with the hopes to discover novel and targeted ways to restore normality to the lives of patients who have already been through the pain and discomfort of cancer treatments.

"It was also rewarding to be able to contribute to a surgical specialty that I will be working in for the rest of my life and I hope to incorporate ongoing contributions to translational research, tissue engineering and regenerative surgery throughout my surgical career."

The Foundation for Surgery Tour de Cure Cancer Research Scholarship was established in 2014 and provides a stipend and departmental maintenance for Fellows, Trainees and International Medical Graduates wishing to undertake a cancer research project.

*With Karen Murphy*

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