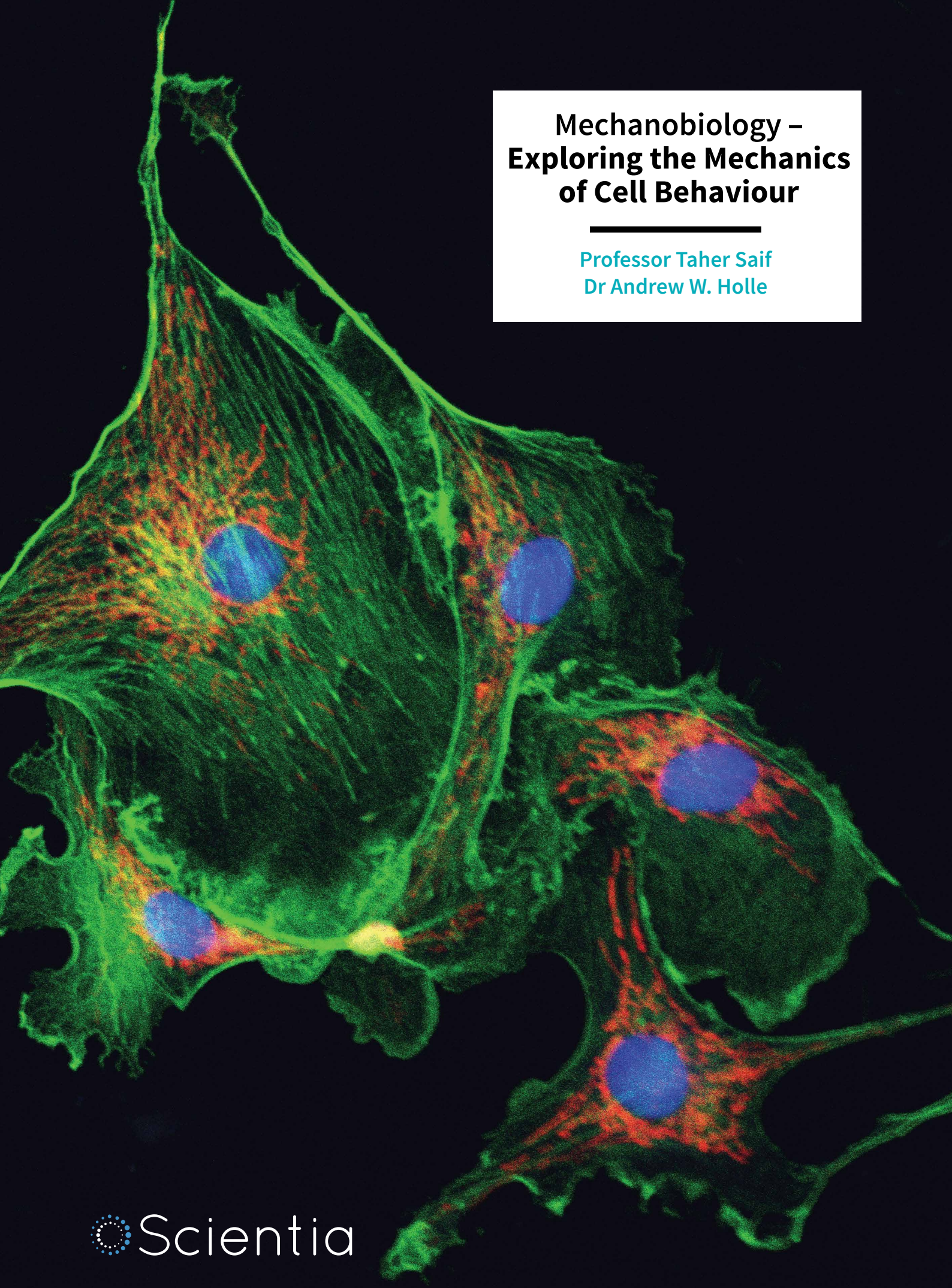


Mechanobiology – **Exploring the Mechanics of Cell Behaviour**

Professor Taher Saif
Dr Andrew W. Holle

Scientia

MECHANOBIOLOGY – EXPLORING THE MECHANICS OF CELL BEHAVIOUR

Understanding how cells interact with the physical world around them is at the core of mechanobiology, a growing subfield connecting the arenas of cell biology and bioengineering. Two leading researchers, **Professor Taher Saif and Dr Andrew Holle**, with the support of an international body of scientists, are spearheading work in this field that aims to uncover how cells are impacted by their mechanical microenvironment in a physiologically relevant context.

A Union of Biology and Engineering

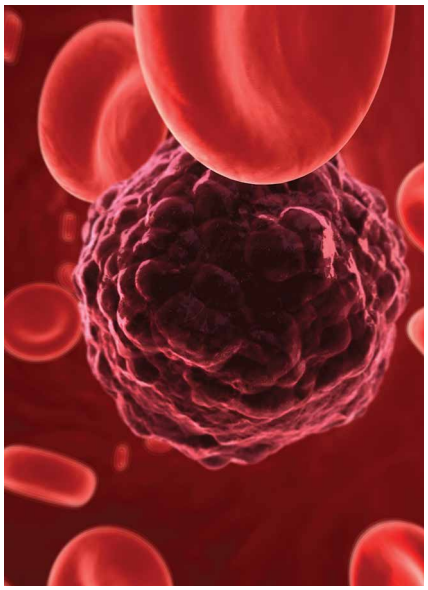
Like the humans in whom they reside, cells within our bodies are constantly seeking to make sense of the physical world around them. In the same way that we are compelled to feel and touch our surroundings in order to better understand them, cells also need to explore and interact with their environment in order to know how and when to function. Exactly how this happens is currently under investigation by researchers working in the emerging field of mechanobiology – a union of biology and engineering that focuses primarily on how physical forces and changes in the mechanical properties of cells and tissues contribute to development, physiology, and disease. Two innovators in this exciting arena are Professor Taher Saif from the Department of Mechanical Science and Engineering at the University of Illinois, USA, and Dr Andrew Holle from the Department of Cellular Biophysics at the Max Planck Institute for Medical Research in Heidelberg, Germany. Together, they are aiming to bring mechanobiology to the forefront of cell biology. 'This is a growing field, as almost every type of cell behaviour worth studying can be affected by the physical characteristics of the material around them,' says Dr Holle.

There is an increasing body of evidence that suggests that mechanical forces, both extracellular and intracellular, have a profound influence on a variety of cell functions, including cell division, cell death (apoptosis), proliferation, and differentiation. Understanding how cells interact with the physical world around them is core to determining their behaviour and function says Professor Saif: 'The focus of our research for the last ten years is to understand the effect of mechanical micro-environments on cell functionality. The ultimate goal is to explore the underlying mechanism of cellular mechanotransduction in a physiologically relevant context, particularly in human diseases.'

Mechanotransduction, a novel term being used with increasing frequency, refers to the various mechanisms by which cells sense their physical three-dimensional environment. This form of sensory transduction converts mechanical stimulus (or force) – exerted by properties of the extracellular matrix (ECM; a non-cellular scaffold-like component that is present within all tissues and organs, and capable of biochemical support), neighbouring cells and physical stress – into biochemical signals. In turn, these signals result in the adjustment of cellular and extracellular structures. This mechanosensitive feedback modulates a myriad of cellular functions and is vital for organ development and homeostasis.

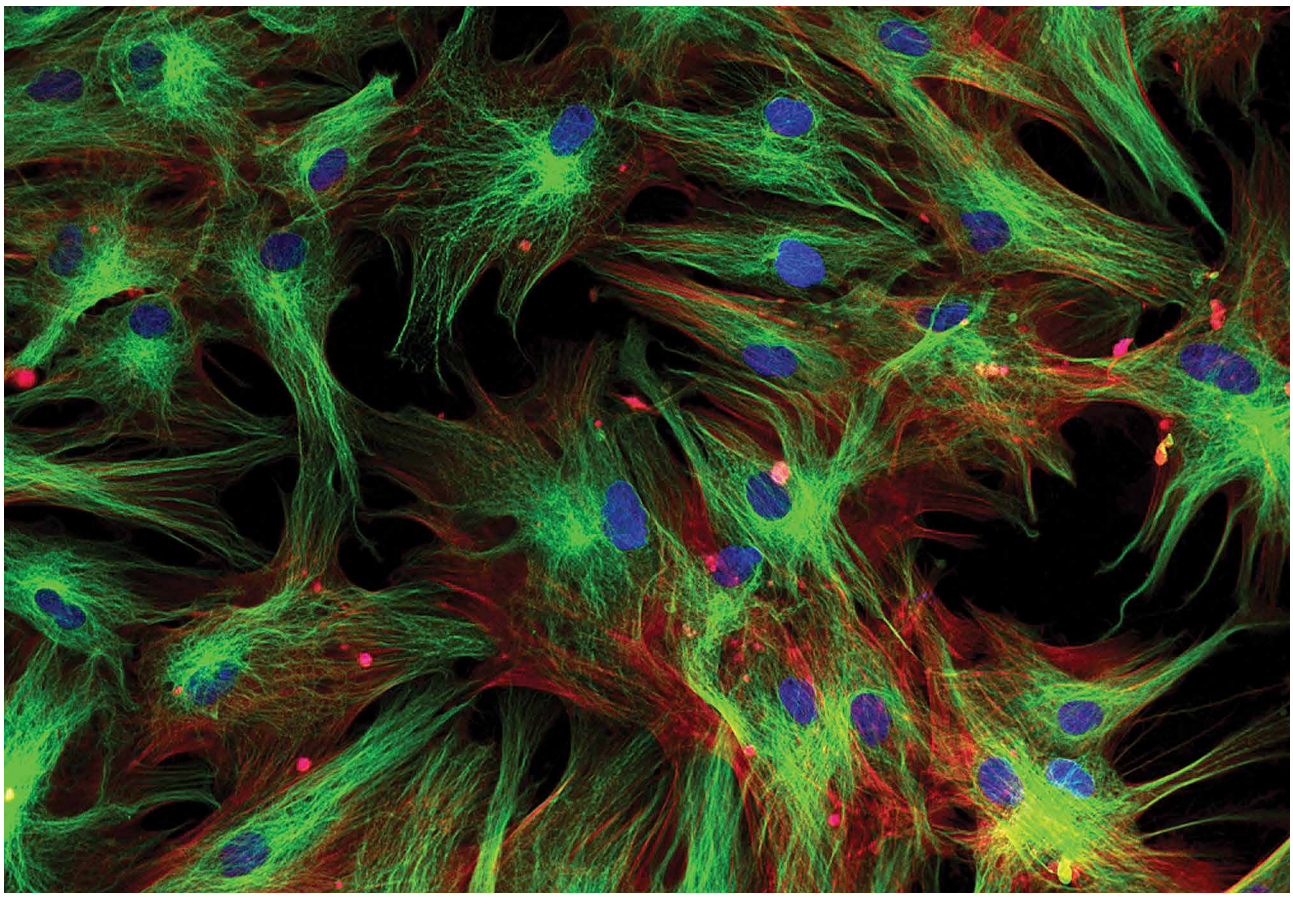
The Mechanobiology of Cancer Cells

The accomplishments of Professor Saif and Dr Holle have brought together a number of expert researchers, namely Professor Joachim Spatz and Dr Jennifer Young at the Max Planck Institute for Medical Research and the University of Heidelberg in Germany, Professor Ralf Kemkemer at the Max Planck Institute for Intelligent Systems and Reutlingen University in Germany, Professor Yu Suk Choi at the University of Western Australia, and a group of US-based researchers comprising Professor Adam



Engler at the University of California, San Diego, Professor Mark Kuhlenschmidt at the University of Illinois at Urbana-Champaign, Professor Paul Janmey at the University of Pennsylvania, and Post-doctoral Associate Xing Tang at Harvard University. This international collaboration, whose expertise spans the fields of stem cell biology, biophysics, bioengineering, and mechanical science, is currently focusing on the mechanobiologics of cancer cells, with the aim of identifying the mechanisms by which cancer cells navigate different types of extracellular environments.

Death from cancer is predominantly caused



by the development of secondary growths (metastases) and not by the parent tumour. During metastasis, malignant cells break away from the parent tumour and spread through the blood or lymph system to invade new tissues and organs. Consequently, one of the first steps in the spread of cancer is the invasion by malignant cells of normal tissue surrounding the tumour. This invasion is initiated and controlled by various mechanical interactions in the tissue, particularly through the ECM. These mechanical interactions can take two forms: the first involving remodelling of the ECM by nearby contractile cells on the tumour surface, and the second involving the alignment of fibres in the ECM and adjacent cytoskeleton – an active, complex and multifunctional network of interlinking tubules and actin filaments that extend throughout the cytoplasm in all cells. These actions enhance the tendency of cancer cells to follow alignment; thus, enhancing their invasion of neighbouring tissue via contact guidance.

Although great strides have been made in unearthing the underlying mechanics of cancer cell invasion, the physical-chemical mechanisms and parameters within the cellular microenvironment that initiate the onset of metastasis are, as yet, not fully understood. 'For cancer cells to escape from their primary tumour and metastasise, they have to poke around and feel their environment, then make changes to their cell programming,' explains Professor Saif. 'If we can figure out exactly how these cancer cells get this information, then we can prevent them from learning about their environment and hopefully stop them from metastasising.'

From Stem Cells to Cancer Cells

As a basis for his exploration into the mechanobiology of cancer cells, Dr Holle, who currently holds the post of American Association for Cancer Research Basic Research Fellow, as well as a Max Planck Institute Postdoctoral Fellowship, has conducted considerable research into mechanotransduction pathways in stem cells – unspecialised cells that can differentiate into many different cell types. It is well known that stem cells receive a myriad of chemical and mechanical cues from their microenvironment that must be translated into signals that dictate cell behaviour. More recently, however, light has been shed on the underlying mechanical forces that shape organismal development and direct disease response. In particular, Dr Holle's graduate research focused on the interaction between stem cells and the ECM.

Through building a platform that combines the application of analytical computational techniques (bioinformatics) with a small (or short) interfering RNA (siRNA) screen capable of identifying novel proteins and high content cell imaging and analysis, Dr Holle was able to study the influence of focal adhesion proteins – multi-protein structures that form mechanical links between the intracellular and extracellular environment – on stem cell differentiation. In doing so, they have identified new candidate focal adhesion proteins that play a significant role in cell differentiation. It is hoped that the development of interdisciplinary tools such as this can be applied to cancer mechanobiology, with target proteins and resultant cell behaviour assayed on a high content/throughput scale.

Dr Holle went on to investigate the interplay between cancer cell-ECM interactions and the reorganisation of intermediate filaments comprising the cytoskeleton. He found that by freeing the mechanically-active actin component of the cytoskeleton from the more 'dampening' intermediate filament cytoskeleton, cancer cells were able to

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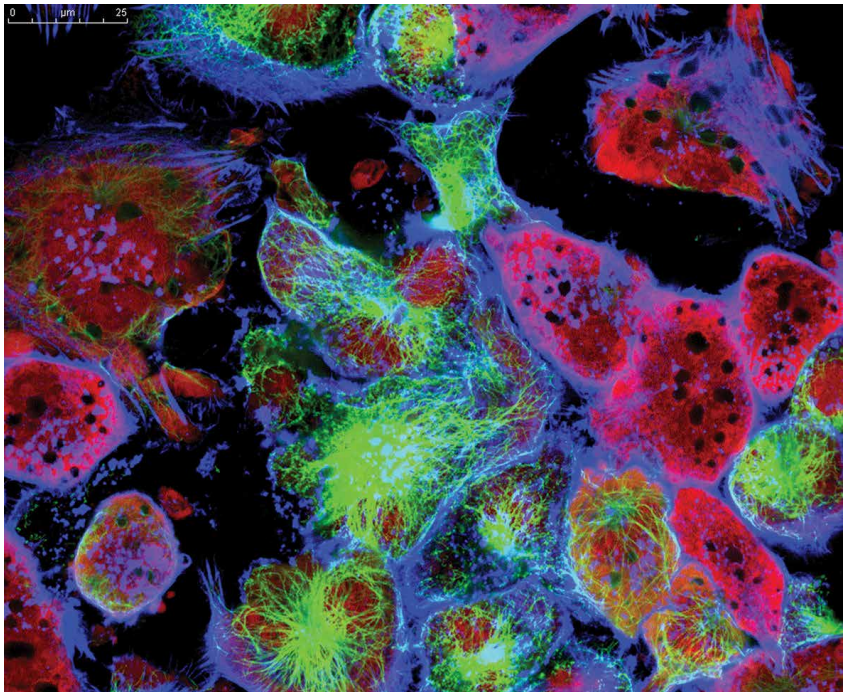

display enhanced contact guidance. As cancer cells are generally softer, faster, and more sensitive to nanoscale topography than normal cells, this vein of research presents an interesting possibility for future work in slowing cancer cells down by enhancing their intermediate filament cytoskeleton.

Dr Holle was also part of an international team that developed a new method for fabricating linear gradient stiffness in hydrogels – macromolecular gels constructed of a network of water-laden, cross-linked polymers. Using hydrogels of varying stiffness gradients spanning the entire *in vivo* physiological and pathological mechanical landscape, he and his fellow researchers were able to monitor different stiffness-dependent processes in stem cells and, thus, find optimal stiffness values for inducing desired cell behaviour, such as cell migration. These findings have significant relevance, in that some cancer cell lines are inversely sensitive to substrate stiffness and, consequently, show markedly different migration phenotypes. ‘Simple tools like these, which are straightforward to build, use, and analyse, will help make investigations into cancer cell mechanobiology more accessible and widespread,’ says Dr Holle.

Understanding Cancer Cell Mechanics

Similarly, Professor Saif, who has a background in mechanical science and engineering, is keen to understand the effect of a cell’s mechanical microenvironment on its functionality. Towards this goal, he and his team have developed a number of modalities for measuring cell forces, including new imaging methods that allow the visualisation of cells and their intracellular dynamics while they are under mechanical stress, and biophysical modelling of cellular microenvironment. To assist his research, Professor Saif utilises a variety of nanoscale quantitative tools, including very-high-resolution microscopes (atomic force microscopy and traction force microscopy), and computational and theoretical modelling. Notably, his lab at the University of Illinois (Saif Lab) has pioneered a number of methods and concepts, including microfluidics, nanofabrication, micro and nanotechnology, and novel stages for mechanical manipulation.

Professor Saif’s work involves both *in vitro* and *in vivo* models, and he has been conducting research into the behaviour and mechanics of cancer cells since 2007. Initially, he and his team investigated human cancer cell lines, discovering that tumour mechanical microenvoronment is a critical player in cancer cell metastatic transition. More recently, Professor Saif has been focused on the mechanobiology of primary human colon tumour cells and tissues. Findings from his studies have shown that human colon cancer cells with low metastatic potential exhibit a metastatic-like phenotype when cultured on appropriately soft substrates, whereby they dissociate from each other and become migratory. This behaviour led to the upregulation of several oncogenes playing important roles in cancer cell migration, invasion, proliferation, and the suppression of apoptotic genes – resulting in the cancer cells becoming much more tumorigenic compared to the parent tumour.

Currently, Professor Saif and his research group, in collaboration with Carle Foundation Hospital and Presence Hospital in Illinois, and the Mayo Clinic, are working to address the following questions: (i) what is the role of intra-cellular forces in transforming the parent HCT-8 cells to metastatic ones? (ii) Can cell forces be used as a marker for drug screening? And, (iii) is there a mechanical signature in metastatic colon cancer cells from human patients and can such signatures be used for cancer prognosis?

The Future of Mechanobiology

The next step in Professor Saif’s and Dr Holle’s research is to take what they have learned and attempt to alter it to facilitate their understanding of cancer cell mechanobiology. ‘If we know how cancer cells can squeeze through very tight passages, our goal is to treat those cells with a chemical or protein that stops them from doing so,’ they tell us. Their combined body of work provides fundamental insight into the critical role the tumour mechanical microenvironment may play in the metastatic transition of cancer cells, and hence cancer progression.

Meet the researchers

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Professor Taher Saif began his training in Civil Engineering at Bangladesh University of Engineering and Technology before moving to continue his studies at Washington State University, USA. He achieved his PhD in Theoretical and Applied Mechanics at Cornell University in 1993, going on to become a Research Associate in Cornell's National Nanofabrication Facility in 1996. He joined the faculty at the University of Illinois in 1997, where he is currently Gutgsell Professor in the Department of Mechanical Science and Engineering. He is a member of the Board of Directors for the Society of Engineering Science and a Fellow of the American Society of Mechanical Engineers. He is Associate Editor of the Journal of Applied Mechanics and on the editorial board of the International Journal of Applied Mechanics.

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Dr Andrew W. Holle received his BSE in Biomedical Engineering from Arizona State University, USA and went on to achieve his PhD at the University of California, San Diego with a thesis entitled 'Focal adhesion proteins are mechanosensitive and regulate stem cell differentiation'. From 2014 to 2017, he performed postdoctoral research on cancer invasion in synthetic microchannels in the Department of New Materials and Biosystems at the Max Planck Institute for Intelligent Systems in Stuttgart, Germany. He is currently continuing this research in the Department of Cellular Biophysics at the Max Planck Institute for Medical Research. He was awarded a Basic Cancer Research Fellowship from the American Association for Cancer Research from 2016 to 2017.

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