Smart and Noninvasive Combinational Therapies for Cancer

Cancer is the second-most-common cause of death in the world. This disease overall kills more than 8 million people each year. It is expected that this statistic will increase by about 50% in the next few decades. 'Cancer' is an umbrella term used for diseases characterized by uncontrolled, autonomous growth of cells in any tissue. Most often times, there is not a single factor that leads to this disease, but generally are either inherent (unavoidable genetic changes), or acquired (ionizing radiation, chemical carcinogens, lack of exercise, imbalance in nutrients, hormones, growth factors, etc.). Over the years, several therapies (including radiotherapy, which could lead to genetic alterations by itself) have been used to treat cancer, but few have succeeded, often temporarily. Immunotherapy for cancer has recently shown promise in therapy, by taking the brakes off the body's natural response towards tumour control, and help lead to a cure. The recent clinical success of immunotherapy highlighted by a 2018 Nobel-prize awarded to James Allison and Tasuku Honjo, who discovered immune checkpoints, and subsequently its therapeutic angle. Although revolutionary, this therapy, unfortunately, fails as a monotherapy (immunotherapy by itself as a therapy) in most cancer types and is quite expensive, and patients often suffer from side-effects. Local noninvasive therapies along with immunotherapy could help turn off the tumour's defences effectively, and render them defenceless, longer. This combinational attack strategy seems to also work well in cancers that are otherwise stubborn. Ultrasound-based high intensity focused ultrasound (HIFU) is an exciting and innovative technology that is noninvasive and nonionizing, and capable of killing tumour cells or breaking them apart with no need for an incision, and does not damage tissue between the tumour and skin (Fig. 3).

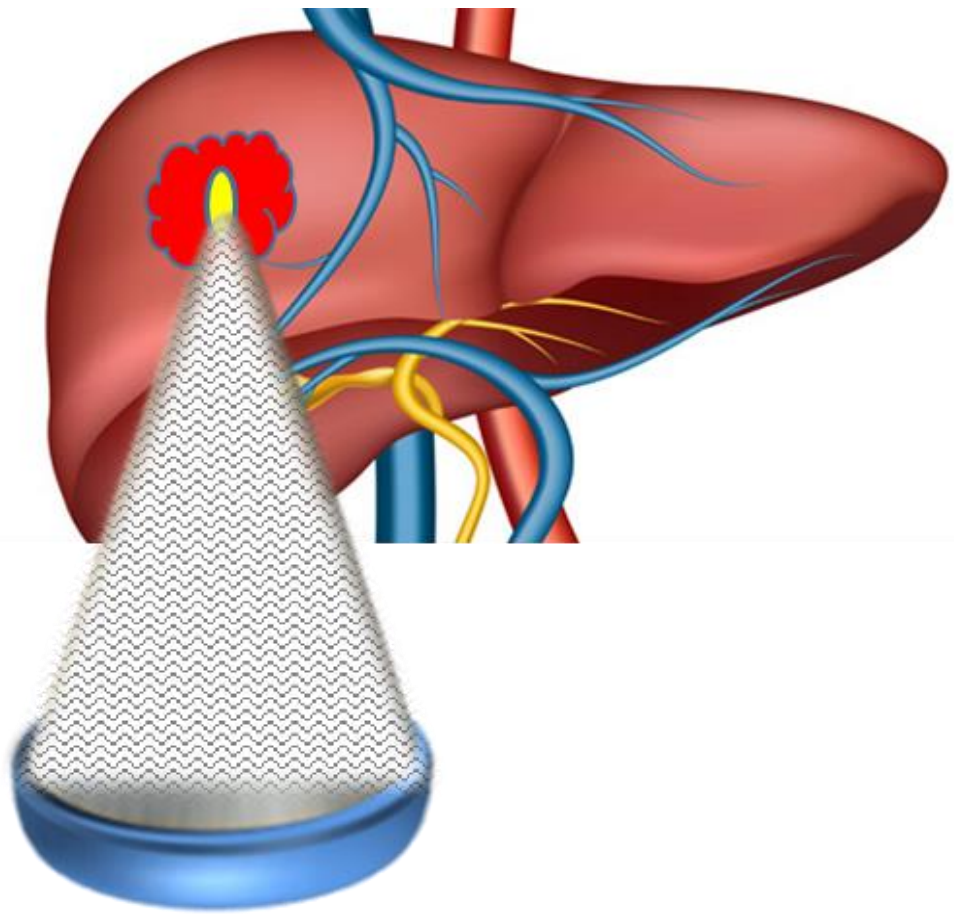

Figure 3: HIFU can noninvasively treat tumors inside the body using ultrasound energy (nonionizing radiation), and lead to tumor regression and cure.

HIFU is currently used to treat various other disorders like uterine fibroids, essential tremor, Parkinson's, prostate cancer, benign prostatic hyperplasia, and bone metastases. It is also being tested for other solid tumours such as soft tissue sarcomas, desmoid tumours, osteoid osteoma, and others. The great benefit of using HIFU to treat these patients is that most patients are generally considered as out-patient, and return home on the same day, after therapy. They also would not need to antibiotic administration after HIFU due to therapy's inherent noninvasive approach.

Continued…

Medical Ultrasound Research Laboratory (MURL) at Indian Institute of Technology, Hyderabad is currently working on newer HIFU methods that are more efficient in treating solid tumours. One of these methods of HIFU is termed 'Boiling Histotripsy (BH-HIFU)'. BH-HIFU physically breaks the tumours into smaller fragments and can do this with very sharp boundaries or high spatial resolution. BH-HIFU has demonstrated to cause the immune system to 'wake-up' and respond against tumours (Fig.4).

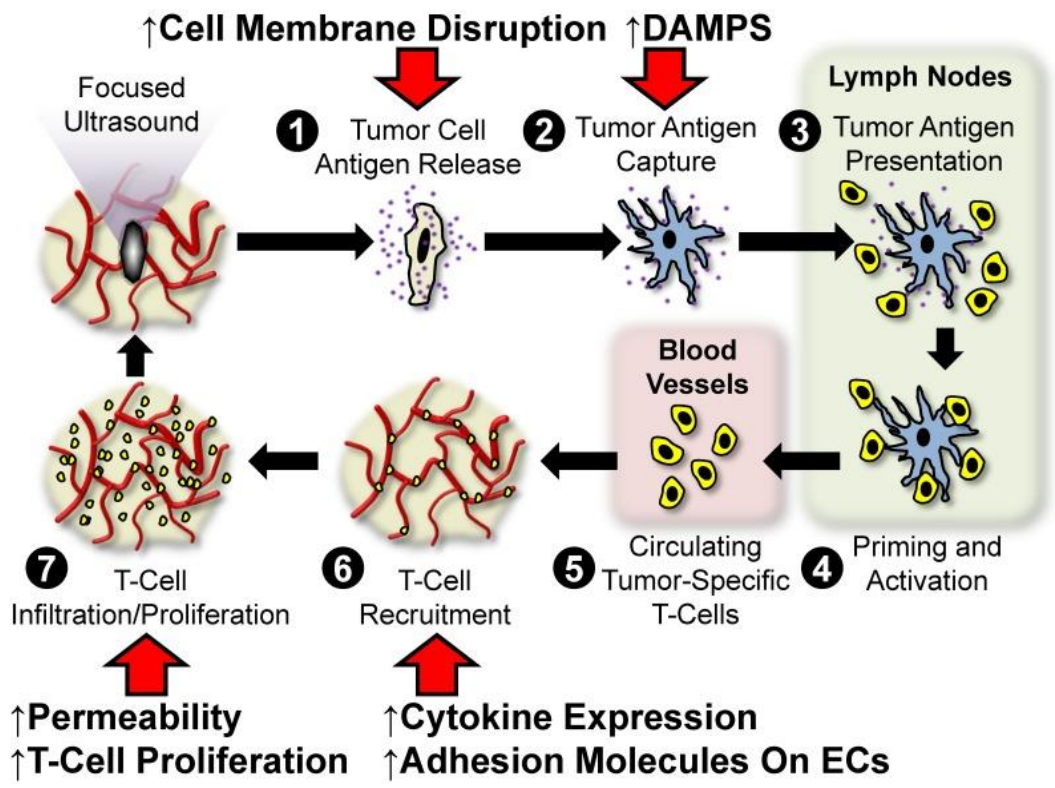

Figure 4: HIFU generates an immune response that could help the body fight the tumor. *From: Curley, Colleen T., et al. "Focused ultrasound immunotherapy for central nervous system pathologies: challenges and opportunities." Theranostics 7.15 (2017): 3608.*

In addition, it has also shown to make the tumour become detectable to the immune system, making them more vulnerable to an attack from the immune system. We also demonstrated that tumours tend to have multiple 'weapons' in their armoury, and protect themselves from additional attacks from the body's immune response (Fig.5). It is at this point where we are able to use immunotherapy or local delivery of encapsulated chemotherapy, to break these secondary defence mechanisms in tumours, which otherwise just monotherapy would not have worked against these tumours.

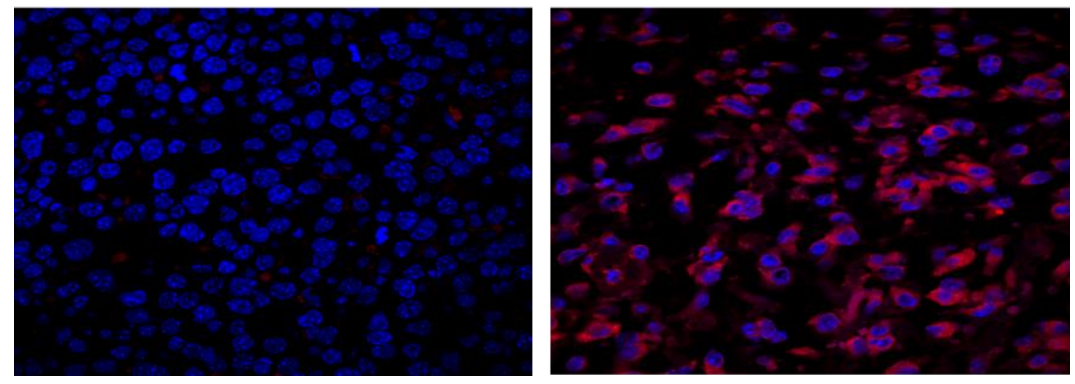

Figure 5: BH-HIFU forces the tumor to use its secondary defense mechanisms, and expose itself. It is at this point, that immunotherapy could be used to shut down the defense system(s), and kill the tumor cells. *From: Eranki, Avinash, et al. "High-Intensity Focused Ultrasound (HIFU) Triggers Immune Sensitization of Refractory Murine Neuroblastoma to Checkpoint Inhibitor Therapy." Clinical Cancer Research 26.5 (2020): 1152-1161.*

Tumours further become weaker and defenceless, and succumb to the body's immune attack, leading to local and metastatic tumour regression. Along with our collaborators at National Institutes of Health, University Medical Center Utrecht, University of Washington, and Children's National Medical Center we recently demonstrated the ability to create an 'abscopal effect' (treat a local tumour, and all metastatic tumours shrink) while treating locally large, refractory Neuroblastoma murine tumours. Monotherapy failed to treat these tumours, but the combination of BH-HIFU and immunotherapy worked well.

Continued…

More about this work can be found here:

Eranki, Avinash, et al. "High-Intensity Focused Ultrasound (HIFU) Triggers Immune Sensitization of Refractory Murine Neuroblastoma to Checkpoint Inhibitor Therapy." Clinical Cancer Research 26.5 (2020): 1152-1161. These results are very significant since it demonstrates the ability to convert a 'cold' tumour to a 'hot' tumour, and making the tumour defenceless to immunotherapy. Our group is also starting the world's first clinical trial using this BH-HIFU plus immunotherapy combination to treat patients suffering from triple-negative breast cancer (TBNC), and Neuroblastoma. These are patients who have unfortunately exhausted all other available options of therapy, and we hope this novel combinational therapy could give them more time in life to do what they have always loved to do.

Along with ultrasound-based technologies, other noninvasive technologies such as photothermal therapy (PTT) and photodynamic therapy (PDT) are also being tested as a monotherapy and combinational therapy to treat tumours such as melanoma. The technologies either use laser light to either accumulate a photosensitizer within the tumour (PDT) or use optical light (near-infrared wavelength) to generate heat and ablate (thermally kill) the tumour cells. These smart and noninvasive technologies are paradigm-shifting in terms of treating solid tumours, potentially leading to cure. There are several unanswered questions, and we have some ground to catch up to cure cancer. The time is now right for folks working on these technologies and similar areas to have a chat with each other and work together to tackle this devastating disease.

Dr. Avinash Eranki
Department of Biomedical Engineering