Defining the molecular mechanisms behind drug resistance in cancer

How could your research help fight cancer?

The goal of my research is to improve the long-term effects of currently approved therapies by identifying and inhibiting critical drug targets that drive multiple tumor-promoting pathways. I am currently investigating the effect of blocking regulators of chromatin in cetuximab- and cisplatin-resistant models of cancer.

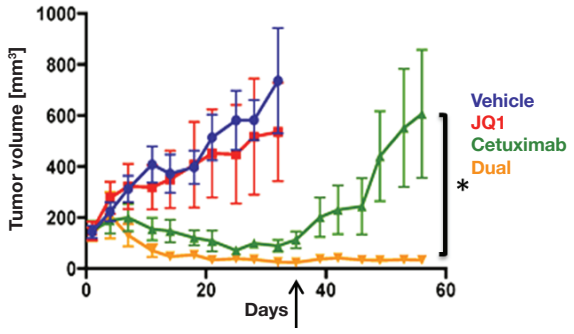
Neil Bhola

I am an Adjunct Assistant Professor in the Department of Otolaryngology and Head and Neck Surgery at the University of California San Francisco. I work with a group of scientists trying to discover novel druggable targets that can improve current therapies to eradicate head and neck squamous cell cancer (HNSCC). We take discoveries made on the laboratory bench and in animals to cancer patients enrolled in clinical trials. This is translational research.

Head and neck squamous cell cancer affects nearly 600,000 people worldwide and is associated with risk factors such as tobacco, alcohol and human papillomavirus infection. This type of cancer is defined by the overexpression of a cell receptor called Epidermal Growth Factor Receptor (EGFR), which makes it a promising therapeutic target. In 2006, a therapy designed to block EGFR called cetuximab (Erbitux) was approved by the FDA for treating HNSCC. However, over the last decade, the efficacy of cetuximab in the clinic has been underwhelming. This has led many investigators to identify biomarkers that can predict which patients will benefit from cetuximab therapy or to identify the molecular mechanisms employed by tumor cells that drive resistance to cetuximab.

I did post-doctoral research at Vanderbilt University and I gained an appreciation for the dynamic nature of breast cancer cells to develop resistance to various pharmacological agents. I observed that within a tumor, cells can switch their dependency on different tumor-promoting pathways, endowing them with a "chameleon-like" ability to elude the effect of various drugs.

Now I am trying to understand how a cancer cell adopts this "chameleon-like" behavior. I recently published a paper showing that a regulator of chromatin called Bromodomain-containing Protein 4 (BRD4) drives the expression of multiple cellular growth receptors. These growth receptors have been shown to mediate cetuximab resistance in HNSCC. This study highlights that HNSCC cells acquire resistance to cetuximab by altering the state of their chromatin resulting in a new gene expression pattern that, in turn, allows the cells to survive and evade cetuximab treatment (see figure). Chromatin is the compact state of our chromosomes harboring the genetic code, DNA, which is critical to the function of the cell. Chromatin can exist in two states, closed or open. If a certain chromatin region is open, it is accessible to other factors that can facilitate the expression of the gene encoded by that region of DNA. On the other hand, if the chromatin is closed, the DNA in that region is inaccessible and the genes that they encode are not expressed by that cell. Therefore, my goal is to understand the pathways triggered by drugs like cetuximab that result in the altered state of chromatin in cancer cells. By delineating these events, I can identify potential molecular targets that can be used to prevent cancer cells from acquiring drug resistance.



A tumor derived from a patient with head and neck cancer was divided and surgically implanted into mice who were then treated with placebo (vehicle), the FDA-approved EGFR inhibitor (cetuximab), an inhibitor against the chromatin regulator BRD4 (JQ1), or the combination of cetuximab and JQ1. The cetuximab treated tumors (green) were initially sensitive and then acquired resistance (arrow), as reflected by changes in tumor size. However, treatment with JQ1 prevented the acquisition of cetuximab resistance.

What sparked your interest in science?

In high school, I was very interested in Physics, particularly the subjects of fluid mechanics and telecommunications. Growing up with a strong athletic background, I was also very interested in understanding how the human body functions from a molecular standpoint so I pursued Biology. Merging both interests, I have dedicated my research to understanding the dynamic molecular pathways that make human cells resilient to any stress thrown at them.