OPTIMIZING A GAS AND LIQUID GRADIENT BIOREACTOR TO MIMIC TUMOR MICROENVIRONMENT

AN ADAPTATION FOR CANCER CLINICAL TRIALS: MEDIATING BIASED AND LIMITED ACCRUAL

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SOCIOTECHNICAL SYNTHESIS

Cancer continues to be one of the leading causes of death globally, with new cancer cases diagnosed every year. A significant factor to this continued trend is the high rates of failure associated with developing new cancer therapeutics, which commonly fail due to efficacy and toxicity concerns. New innovations are therefore needed to resolve these issues as traditional preclinical research methods are unreliable in modeling the dynamic tumor microenvironment and as a result fail to accurately characterize the activity of novel therapeutics. As developments continue to improve the accuracy and speed for preclinical research, a growing concern with cancer therapeutic development is the lack of demographic representation when verifying these novel drugs in clinical trials. Given the necessity for accelerating cancer drug development and the potential risks from the rapid expansion of cancer therapeutics in entering clinical trials, developments must be made to ensure the accuracy and safety of these potential therapeutics.

Preclinical drug development is often reliant on in vitro studies that are not reproducible and do not accurately model the tumor microenvironment. Furthermore, the development of novel therapeutics takes an average of approximately eight years to bring to patients. Traditional cell culturing techniques, such as petri dishes, are only capable of subjecting cells to static conditions that are unreflective of the various physical, chemically, and spatial organizations that natural tumor cells encounter yet are cheap and easy to analyze. 3D cell culturing techniques, such as spheroids and hydrogels, are often difficult to develop and challenging to replicate but more accurately captures the tumor microenvironment. Thus a solution that can more accurately mimic the in vivo tumor environment while maintaining comparable cost and accessibility advantages of 2D cell culturing should be developed to further improve preclinical cancer research. By developing such a device, preclinical research will be improved in regards to

reproducibility and accuracy to predict tumor cell behavior which will lead to major discoveries and developments in novel cancer therapeutics.

In order to address these concerns, the technical project sought to design a bioreactor capable of subjecting cancer cell cultures to simultaneous gradients of liquid and gas. Designs for microfluidic linear concentration gradient generators for gas and liquid were found through literature and adapted into two components to be printed through SLA printing and tested on. The liquid gradient component was based on a design found in literature and found to be capable of generating somewhat stable linear concentration gradients through colorimetric analysis of food dye solution pumped through . The gas gradient component was based on a design found in literature and found to be capable of generating linear concentration gradients ranging from 0% to 21%, or atmospheric, oxygen concentration through use of optical oxygen dot sensors. Unfortunately, the final assembly of the two components to generate an orthogonal linear concentration gradient plane at the cell culture stage failed due to pressure and liquid filling issues. Further design iterations to resolve these issues will likely resolve these issues and accomplish the intended goals of the device.

Given the rapid innovations in developing cancer therapeutics and the potential number of new therapeutics as a result of improvements in preclinical research, the STS project sought to examine the current issues with cancer clinical trials and their methodologies. In particular, the project sought to investigate the potential of adaptive clinical trials in addressing the low representation of racial and ethnic minorities in oncological clinical trials and investigate the risks and benefits such modifications can have on the clinical transformations of developing cancer drugs. Using Actor Network Theory, comparative analysis was performed to examine the differing relationships and actors between typical drug development clinical trials and adaptive

clinical trials. Based on the features of adaptive clinical trials to address demographic biases and safety risks present throughout the drug development process, adaptive clinical trials should be further explored within cancer drug development as a safer and more equitable clinical trial methodology.

In order to address the continued impact of cancer, innovations must be made to resolve the various difficulties with developing cancer therapeutics. Preclinical research of cancer therapeutics and clinical trials must be improved to resolve present problems in modeling the tumor microenvironment and demographic biases. Through developing new cell models and implementation of adaptive clinical trials, the growing necessity for innovative cancer therapeutics can be resolved to decrease the mortality of cancer.

TABLE OF CONTENTS