ELUCIDATING PLECTIN SPECIFIC PATHWAYS TO DEVELOP NOVEL PANCREATIC CANCER THERAPIES

IRESSA: WHAT A FAILED EGFR INHIBITOR CANCER THERAPY LOOKS LIKE

A Thesis Prospectus
In STS 4500
Presented to
The Faculty of the
School of Engineering and Applied Science
University of Virginia
In Partial Fulfillment of the Requirements for the Degree
Bachelor of Science in Biomedical Engineering

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December 13, 2024

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On my honor as a University student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments.

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Introduction

The challenge of developing effective therapies for pancreatic cancer is inherently sociotechnical, as it involves not only the scientific advancements in drug design but also the social dynamics of healthcare delivery and patient access. This challenge unites the interests of researchers, healthcare providers, patients, and policymakers, all of whom seek to improve outcomes for a disease that remains one of the deadliest cancers. To address this challenge, novel therapeutic strategies need to be developed that target specific molecular pathways involved in pancreatic cancer progression.

The technical project focuses on elucidating plectin-specific pathways to create new pancreatic cancer therapies that improve upon existing treatment options. By identifying and targeting the interactions that plectin has with signaling pathways, this project aims to enhance therapeutic efficacy and minimize side effects, ultimately delivering greater value to patients and healthcare providers. Simultaneously, the STS project will explore the role of social factors using Actor-Network Theory (ANT) to understand how various actors, such as patients, doctors, and healthcare systems, influence the implementation and effectiveness of Iressa, an epidermal growth factor receptor (EGFR) inhibitor made by AstraZeneca. By examining these interactions, insights into the sociotechnical landscape surrounding cancer treatment will be gained.

Ignoring the interactions among various factors that contribute to a project's success, and treating the proposed system as if it exists in isolation from its sociotechnical environment, risks creating a system unable to properly engage with those crucial elements. If this happens, the system's capacity to effectively develop pancreatic cancer therapies will be severely impaired, ultimately resulting in the project's failure. Therefore, because the challenge of developing effective pancreatic cancer therapies is sociotechnical in nature, it requires attending to both its

technical and social aspects to accomplish successfully. In what follows, I set out two related research proposals: a technical project proposal for elucidating plectin-specific pathways to develop novel pancreatic cancer therapies and an STS project proposal for exploring how social dynamics influence the effectiveness of cancer therapies in the case of Iressa in cancer targeted therapy.

Technical Project Proposal

According to the American Cancer Society, pancreatic ductal adenocarcinoma (PDAC) has the highest mortality rate of all major cancers: for all stages combined, the 5-year relative mortality rate is 87%. Despite decades of research and numerous clinical trials there have been no significant improvements in overall prognosis for PDAC patients in over 40 years. Therefore, novel therapies against primary and metastatic pancreatic cancer are desperately needed (*Cancer Facts & Figures 2024*, 2024). In 2008, Kelly et al. used a phage-display-based functional proteomic approach to identify novel cancer-specific targets (Perez, Brinton, et al., 2021). Among these was plectin, a 500 kDa protein known for its contribution to cytoskeletal structure and dynamics in normal homeostatic conditions. Studies performed by Kelly et al. showed plectin is a useful marker for distinguishing between normal and malignant patient specimens as cancer specific plectin (CSP) is displayed on the cell surface as opposed to internally in normal cells. Loss-of-function studies have implicated plectin as a pro-tumorigenic regulator of cancer cell proliferation, migration, and invasion (Perez, Brinton, et al., 2021; Perez, Dimastromatteo, et al., 2021). By delineating the signaling pathways and molecular mechanisms by which plectin influences pancreatic tumor progression, I aim to identify unique biomarkers and potential therapeutic targets that are more precise than current approaches. Accordingly, the primary goal

of this project is to understand the molecular mechanism of plectin and its role in tumorigenesis as well as potential resistance mechanisms to plectin targeted drugs.

My proposed solution provides multiple advantages over current pancreatic cancer therapies, which often rely on broad-spectrum chemotherapeutics and show limited effectiveness against this highly aggressive and treatment-resistant cancer type. Targeting plectin-specific pathways has the potential to deliver increased specificity, as this approach would affect cancer cells with minimal impact on healthy tissue, unlike traditional chemotherapies that harm both cancerous and non-cancerous cells. Additionally, focusing on plectin modulation could mitigate the common challenge of drug resistance in pancreatic cancer, potentially offering a more durable therapeutic outcome. Beyond therapy, this approach enhances prognostic and diagnostic capabilities, as plectin-related biomarkers could enable earlier detection and more accurate staging of pancreatic cancer, leading to better patient outcomes.

I propose that targeting plectin-specific pathways is a novel and promising strategy in pancreatic cancer treatment. This project's main objective is to identify plectin-mediated molecular interactions that can be disrupted for therapeutic gain, creating a new technical approach that could enhance treatment efficacy and quality of life for patients. By focusing on plectin, this research supports precision medicine by contributing unique biomarker identification; plectin's overexpression in pancreatic cancer, relative to healthy tissue, positions it as an ideal candidate for more personalized, targeted treatment. Additionally, a deeper understanding of plectin's role in cytoskeletal dynamics and downstream signaling pathways may reveal previously unrecognized mechanisms driving tumor invasiveness, thus guiding the development of targeted therapeutic strategies. Finally, mapping these plectin-specific pathways provides a foundation for developing new treatment pathways, including small molecules,

antibodies, or gene therapies that can precisely target the disease. This project uses advanced bioengineering and molecular biology techniques to investigate plectin's role in PDAC as a therapeutic target. For my first aim, I will explore plectin-specific signaling by comparing pathways between control and shRNA-mediated plectin knockdown (KD) in fast-growing L3.6 and slower-growing Panc1 PDAC cell lines. Western blotting will measure proteins like pERK, pAKT, p21, and cyclin-D1 to pinpoint proteins with which plectin interacts to drive cancer proliferation. For my second aim, I will use CRISPR/Cas9 to achieve inducible, complete knockout (KO) of plectin in PDAC cells, a more definitive approach than shRNA KD. This will allow for real-time monitoring of cell signaling changes, validated by western blotting of Cas9, plectin, and related cell cycle proteins. These methods will yield valuable data on how plectin influences PDAC cell behavior, guiding potential targeted therapies that may be more effective and specific than current options.

STS Project Proposal

This study investigates the efficacy of AstraZeneca's EGFR inhibitor, Iressa, as a targeted therapy in cancer treatment. EGFR inhibitors are designed to disrupt cancer cell growth by blocking the EGFR signaling pathway, which plays a critical role in cell proliferation (Sim et al., 2018). While these inhibitors have demonstrated potential, real-world results vary significantly, pointing to factors beyond simple drug-target interactions that impact therapeutic outcomes (Frantz, 2005). Understanding how various actors, such as patients, healthcare providers, regulatory agencies, and the drugs themselves, interact to influence these therapies' effectiveness is essential to improving cancer treatment.

Current literature on EGFR inhibitors primarily examines their efficacy from a pharmacological standpoint, focusing on biochemical and molecular interactions between the

drugs and cancer cells (Ayati et al., 2020). These studies highlight mechanisms of action, optimal dosages, and resistance patterns but often overlook external factors such as patient adherence, healthcare accessibility, and societal support for targeted therapies. Authors in this domain typically assume that efficacy depends primarily on optimizing drug design and administration, with limited consideration of the broader networks that affect treatment efficacy. By focusing narrowly on molecular efficacy, these perspectives risk overlooking how social and technical elements collectively shape the actual success of EGFR therapies.

This limited view presents significant shortcomings. While molecular and pharmacokinetic data provide valuable insights, they do not account for the full spectrum of actors and interactions that impact clinical outcomes. EGFR inhibitors may perform differently based on factors such as patient access to medications, adherence to prescribed regimens, and the broader healthcare ecosystem. By ignoring these dimensions, the current approach risks giving an incomplete picture of what truly influences therapeutic efficacy in real-world applications. Consequently, without a broader perspective, readers may miss the opportunity to understand and address the systemic challenges in delivering targeted therapies effectively.

This study proposes a more holistic approach, suggesting that the case of Iressa should be understood within the framework of Actor-Network Theory. Developed by STS scholars like Michel Callon, Bruno Latour, and John Law, this theory proposes that all technical projects can be understood as networks of human and non-human actors, organized by a network builder to achieve a specific goal. A key aspect of ANT is that the strength and success of the network depend on the connections and interactions among these actors (Cressman, 2009). Additionally, I will draw on Callon’s concept of "translation," which explains the process of network formation, to identify where AstraZeneca faltered in creating the Iressa project network and why certain

actors were not successfully integrated (Callon & Latour, 1981). ANT offers a unique perspective by emphasizing that both human and non-human actors—such as patients, doctors, regulatory policies, and drugs—are interdependent agents within a network, collectively influencing outcomes. This framework highlights how treatment success relies not only on drug efficacy but also on the broader network's structural and social dynamics, including patient compliance, healthcare accessibility, and regulatory oversight (Latour, 2005). By examining these complex interactions, this study aims to provide a comprehensive understanding of Iressa in cancer treatment, guiding readers toward a more integrated view of therapeutic efficacy.

To answer this research question, this study will gather corroborating evidence from a range of primary sources. Data on patient adherence, treatment outcomes from clinical trials, and regulatory records will be analyzed to understand how these variables interact with the efficacy of EGFR inhibitors. Where possible, this analysis will include patient outcome data segmented by access and adherence to treatment (Araki et al., 2012). This multifaceted approach will illuminate how both clinical and social factors contribute to the practical effectiveness of Iressa, ultimately offering a more actionable framework for improving cancer treatment.

Conclusion

In conclusion, the technical project on elucidating plectin-specific pathways aims to develop a novel, targeted therapy for pancreatic cancer, addressing limitations of current treatments by identifying molecular mechanisms that drive tumor growth. This approach provides stakeholders, including clinicians and patients, with an improved, more precise therapeutic option tailored to interrupt cancer-specific pathways, potentially reducing side effects and improving efficacy.

The STS project, using ANT to examine Iressa, provides a broader understanding of how different actors—such as patients, doctors, and regulatory policies—impact cancer therapies. Insights from the ANT framework, especially regarding the interplay of social and technical actors, can be applied to the plectin-focused project by highlighting the need to consider patient accessibility and healthcare infrastructure in therapy design. Together, these projects address the sociotechnical challenge of creating effective, accessible cancer therapies that are not only biologically optimized but also viable within complex healthcare networks.

Word Count: 1722

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