Dr Amy Tang has made it her lifetime mission and ultimate scientific goal to defeat late-stage metastatic cancer. Here, she talks about her latest efforts and how close she is to realising her ambition.

Could you detail the driving force of your research?

Finding a novel and effective way to control and eradicate metastatic cancer is of paramount importance. Targeting the oncogenic EGFR/HER2/K-Ras signalling pathway has always been an important strategy against metastatic cancer. In my latest work we have demonstrated a logical and innovative strategy to control and eradicate metastatic cancer by targeting the most downstream signalling module — a ‘gatekeeper’ component, required for proper oncogenic EGFR/HER2/K-Ras signal transduction that is prevalent in the vast majority of metastatic human cancers. Hyperactive K-Ras signalling is a menace that drives aggressive tumour growth and rapid metastasis in human pancreatic cancer. Currently, there are no effective ways to treat pancreatic cancers that have oncogenic K-Ras mutations combined with tumour suppressor losses. Therefore, finding improved mechanisms and effective molecular targets to inhibit oncogenic K-Ras is an urgent goal and the major challenge in pancreatic cancer therapy.

Why is your approach novel?

Hyperactive K-Ras protein acts like a car’s gas pedal that is permanently stuck in acceleration, propelling the pancreatic cancer cells to grow and metastasise uncontrollably without any brakes, namely tumour suppressors. This is detected in virtually all pancreatic cancer patients. Instead of targeting the upstream signalling modules, we are attempting to stop this runaway car by attacking the downstream transmission of pancreatic cancer cells — the Seven in absentia homologue (SIAH) E3 ligases — in the K-Ras signalling pathway. We find that an anti-SIAH-based anti-K-Ras strategy is amazingly effective in stopping pancreatic tumourigenesis and metastasis in our preclinical studies. Through our work, SIAH has emerged as a new, innovative and potent drug target against oncogenic K-Ras activation in pancreatic cancer.

What have your preclinical studies demonstrated so far?

We have seen that SIAH-dependent proteolysis is an Achilles’ heel for human pancreatic cancer cells. Albeit at a preclinical stage, knowledge gained from this study has great promise and generated therapeutic excitements with promising translational value. We are gathering evidence to show that SIAH is a beautiful biomarker and an effective and logical anti-K-Ras and anticancer drug target whose inhibition can block the K-Ras-fuelled tumourigenesis and metastasis in late-stage and extremely large pancreatic cancer in our animal models. Thus, targeting SIAH may represent an innovative way to inhibit K-Ras hyperactivation, halt tumour growth and metastasis, and provide novel strategies for therapeutic intervention in pancreatic cancer.

Is collaboration important to your research endeavours?

Scientific integrity, creativity, innovation, persistence, hard work and teamwork are all key ingredients in the successful implementation of our ongoing innovative projects at the Eastern Virginia Medical School (EVMS), Sentara Cancer Network and the Mayo Clinic, and in the future clinical translation to benefit our cancer patients with metastatic diseases.

I have been extremely fortunate to be given several opportunities to interact with the best, brightest and most innovative research scientists and physician scientists in the world. Without their unwavering support and generous encouragements, several of our highly original and innovative research projects may not have come to fruition.

How critical is raising public awareness to the major funding challenges facing the medical research field in the US?

The appropriate funding in support of many highly innovative, original and creative scientific projects has reached a real crisis point at the National Institutes of Health in the US. The negative impact on the education, training and job opportunities for our next generation of scientists and physicians will be felt for many years to come. It has significantly decreased our international competitiveness in the world. I sincerely hope that our leaders in science, medicine, finance and business will do something innovative to address these unprecedented funding challenges.

What are your plans for the future of your research?

Developing anti-SIAH-based therapy against oncogenic EGFR/HER2/K-Ras is an under-developed area in pancreatic and breast cancer. Inspired by the National Cancer Institute’s (NCI) new US $10 million mega-project targeting the oncogenic K-Ras gene in human cancer, we believe that developing anti-SIAH therapy can pay dividends for the collaborative effort underway at EVMS, Sentara, Virginia Oncology Associates and the Mayo Clinic to benefit our pancreatic and breast cancer patients in the near future. We are confident that by developing anti-SIAH-based cancer therapy, EVMS will be in a unique position to harness and support this new initiative.
Targeting the gatekeeper

Groundbreaking research into novel drug targets for the treatment of metastatic cancers by Eastern Virginia Medical School scientists is bringing fresh hope to sufferers of some of the most aggressive and deadliest forms of human cancer.

METASTATIC DISEASE – a cancer capable of spreading from a primary tumour to other body parts – is the most terminal form of cancer known to humankind, responsible for the vast majority (up to 90 per cent according to the American Cancer Society) of cancer-related deaths. Eager to reduce the burden, a team of researchers at the Eastern Virginia Medical School (EVMS), with support from the US National Institutes of Health (NIH), is attempting to target the evolutionarily highly conserved mechanism that controls the signal transmission of K-Ras proteins, a family of oncogenic proteins found inside tumour cells that are responsible for promoting unchecked cell proliferation, uncontrolled tumour growth and rapid cancer cell dissemination in 30 per cent of all human cancers. Seven in absentia homologue (SIAH) E3 ligase is a new and logical cancer target whose proper function is a clear and new vulnerability identified in the oncogenic ERBB/K-Ras pathway. Thus, developing anti-SIAH-targeted anti-K-Ras and anti-cancer therapy should hold great promise that can benefit cancer patients with metastatic diseases in the future.

The EVMS project, ‘SIAH2-Dependent Proteolysis in Cell Migration, Tumour Growth and Cancer Metastasis’, is particularly interested in K-Ras as it can become cancerous upon even a single amino acid substitution. The team headed by Dr Amy Tang, an Associate Professor of Cancer Biology in the EVMS Department of Microbiology and Molecular Cell Biology and the Leroy T Canoels Cancer Center, is assessing innovative ways in which hyperactive K-Ras signalling can be obstructed to impede and block malignant cancerous growth in nude mice models using some of the most aggressive human cancer types as reported in the scientific literature. As the project title would suggest, the SIAH2 gene plays a key role in regulating the cellular response of K-Ras and controlling cellular behaviours such as cancer cell dissemination, cell migration, invasion and metastasis. Without proper SIAH function, K-Ras cannot transmit its oncogenic signalling in human cancer cells. Acting as a critical signalling gatekeeper, SIAH2 function is crucial to the proper signal transduction of the oncogenic K-Ras signalling pathway that fuels the aggressive tumour growth and rapid metastasis in human cancer.

Through Tang and her team’s collective efforts, a clearer picture of SIAH2 mechanisms has started emerging, such as the ways in which SIAH2 operates downstream of K-Ras pathways to control focal adhesion, cell junctions and cell migration. Understanding these molecular-level changes will allow the scientists to identify new and druggable anticancer targets in focal adhesions and cell junction in the context of K-Ras and SIAH function, specifically target cancer-causing cells, improve drug efficacy and reduce negative side effects. Indeed, Tang believes that the very poor prognosis for metastatic cancer is not helped by the lack of effective therapies: “Currently, there are no effective ways to treat metastatic cancers that have oncogenic K-Ras mutations combined with tumour suppressor losses that confer drug resistance, aggressive tumour growth, systemic metastasis and poor clinical outcome”. She continues: “As the most downstream ‘gatekeeper’ and the new oncogenic K-Ras vulnerability identified in the oncogenic K-Ras signalling pathway, SIAH is ideally and logically positioned to become a great and effective anti-K-Ras drug target”.

MULTIPLE MODEL SYSTEMS

The research has benefited from a multipronged methodology. Namely, RAS signal transduction pathway was explored through model systems that including Drosophila fly eye development, transgenic mice as a proxy for human cancer, as well as human cancer cell lines and human cancer tissues for tumour biospecimens.

Tang points out that there are a few laboratories in the world that have such unique capacity, flexibility and access to such a diverse array of investigative tools across several species. “Our ability to utilise multiple and complementary systems to study molecular details of the RAS signalling transduction in normal development and cancer biology in our experimental designs and data validation is a great strength in our synergistic, complementary and cohesive approaches,” she notes.

A FLY ON THE WALL

In another innovative project to dissect the molecular mechaehnsims of innate immune activation and host-pathogen recognition, Tang and her colleagues are utilising the Drosophila model system to delineate how a host cell differentiates a pathogenic microbe from a nonpathogenic microorganism. This is because, whilst it has a simplistic adaptive immune system, fruitflies also share many important similarities to the complex immune surveillance pathways and host-pathogen interactions found in humans – a reason why it is so often the model species for genetic abnormalities in the absence of human samples. By using the Drosophila model, the researchers have uncovered how the altered structural integrity of sentinel receptors and sensors as a result of infection and inflammation will serve as an effective alarm system to warn the host cells about pathogen invasion, disease progression and pathogen-host warfare. “We hypothesise that protease release, which is common during pathogen-host antagonism, may provide an important cue for the host to distinguish a pathogenic versus a non-pathogenic microorganism,” explains Tang. In addition, the transgenic fly models highlight the ways in which host cells are alerted following tissue damage and invasion by pathogens. The research group would also like to understand how the host cells maintain
SIAH2-DEPENDENT PROTEOLYSIS IN CELL MIGRATION, TUMOUR GROWTH AND CANCER METASTASIS

OBJECTIVES

• To delineate SIAH2 function in cancer, through a proteomic approach, by identifying three focal adhesion and LIM domain proteins, TRIP6/FHL2/LPXN, as novel SIAH2-interacting proteins from three of the most aggressive human cancer cell lines with oncogenic K-Ras hyperactivation (human pancreatic cancer, lung cancer and breast cancer)

• To extend the observations made in nude mice to a more robust in vivo animal system to test the anti-tumour efficacy of anti-SIAH molecules in the mouse models of human cancer

KEY COLLABORATORS

Gloria M Petersen, PhD, Purvis and Roberta Tabor Professor of Cancer Research, Associate Director of Population Sciences at the Mayo Clinic Cancer Center (MCCC), Director of Mayo Clinic Specialized Program of Research Excellence (SPORE) in Pancreatic Cancer • Edward B Leef, PhD, Erivan K Haub Family Professor of Cancer Research, Associate Director of Basic Sciences for the Mayo Clinic Cancer Center (MCCC), Minnesota • Richard A Hoefer, DO, FACS, Medical Director for Development, Sentara Cancer Network, co-Director, Dorothy G Hoefer Comprehensive Breast Center, Surgical Oncologist • Roger R Perry, MD, FACS, Robert L Payne, Jr Professor of Surgery, Chief, Division of Surgical Oncology, Eastern Virginia Medical School • Stephen I Deutsch, MD, PhD, Ann Robinson Endowed Chair in Psychiatry and Chairman in the Department of Psychiatry and Behavioural Sciences, Eastern Virginia Medical School • Jeffrey L Platt, MD, Professor of Surgery and Microbiology and Immunology, University of Michigan, Ann Arbor • Richard V Homan, MD, President and Provost, Dean of the School of Medicine, Eastern Virginia Medical School, Virginia • Gerald M Rubin, PhD, Vice President and Director of Planning for the Janelia Farm Campus, Howard Hughes Medical Institute, Virginia • Ronald A DePinho, MD, President, The University of Texas MD Anderson Cancer Centre, Texas

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CONTACT

Amy H Tang, PhD
Principal Investigator

Department of Microbiology and Molecular Cell Biology
Leroy T Canoles Jr Cancer Research Center
Eastern Virginia Medical School
Harry T Lester Hall, Room 423
651 Colley Avenue
Norfolk, Virginia 23501, USA

T +1 757 446 5664
E tangah@evms.edu

INTelligence

Attacking a new vulnerability in the oncogenic ERBB/K-Ras signalling pathway to treat late-stage and well-established metastatic human cancer in mouse models.

ON THE RIGHT PATH

Preliminary data gathered from the nude mice models are also showing great promise; important as they more closely represent molecular function in humans. The results indicate that SIAH2-insufficiency blocks K-Ras-mediated lung tumour formation in mice. This has provided a robust research platform from which they can move on to determine the efficacy of anti-SIAH-based therapies against the oncogenic ERBB/K-Ras hyperactivation, malignant tumour growth and metastatic cancer in the multiple model systems. By extending their methodologies from the nude mice models to in vivo systems using patient-derived tumour samples, Tang and her team will be able to analyse the anti-tumour ability of anti-SIAH molecules in humans.

The study is currently at the preclinical trial stage but the substantive results will likely lead to an extension to human trials in the not-too-distant future to uncover the specific biomarker involved. In the meantime, the scientists at EVMS are working closely with clinicians to apply and combine anti-SIAH-pathway therapies with existing anti-cancer therapies: “By focusing on the SIAH proteolysis pathway and with the help and staunch support of our clinician colleagues and brilliant collaborators, we soon hope to control metastatic cancers by applying such approaches at the cancer clinics,” Tang concludes.