

Joseph Chao: good research is the search for the truth!

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Editor's note

“For a patient who is initially diagnosed with a gastrointestinal cancer and wondering what’s the next step to take, certainly there is a lot of anxiety and fear”, said Dr. Joseph Chao from City of Hope, Duarte, California in a self-introduction video, “so it’s very important that you are within a team approach—whether it’s a medical oncologist, surgeon, or radiation oncologist involved, and having the right dietician and nutrition support—Having physicians that talk to each other carries a big weight in terms of having a successful treatment outcome.”

As the saying goes—unity makes strength. It is always a common goal to improve the lives of people who are afflicted by illness, especially in the field of gastrointestinal oncology, which remains an area of considerable unmet medical need. As a world leader in the research and treatment of cancer, City of Hope is one of the 49 comprehensive cancer centers in the United States designated by the National Cancer Institute (NCI) to work as a robust team to create innovative treatment that provides medical care for people in need.

This time, *Journal of Gastrointestinal Oncology (JGO)* is honored to interview Dr. Chao, who currently serves as the Staff Physician and Assistant Clinical Professor at the Department of Medical Oncology & Therapeutics Research of City of Hope. In the following interview, he is going to share with us the ongoing research and clinical efforts of their team at City of Hope in the development of novel therapies for gastrointestinal cancers.

Expert's introduction

Joseph Chao, MD, currently serves as an Assistant Clinical Professor in the Department of Medical Oncology & Therapeutics Research at City of Hope in Duarte, California (Figure 1). After earning his medical degree in 2004 at the University of Illinois at Chicago, he received his residency training in Internal Medicine at Harbor-UCLA Medical Center in Torrance, California. He then joined City of Hope in 2007 in a joint program with Harbor-UCLA Medical Center as a fellow in medical oncology and hematology. He was subsequently recruited on faculty

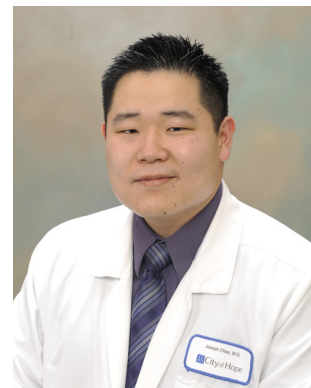


Figure 1 Dr. Joseph Chao.

at City of Hope in 2010 in his current position providing expertise on gastrointestinal malignancies with a particular focus on gastroesophageal cancers.

Dr. Chao is currently leading clinical trial efforts to develop novel therapies for gastroesophageal cancers. He is also conducting research to discover new blood biomarkers for this disease. In 2011, he is named one of the “top doctors” for oncology by *Pasadena* magazine. He received the Extramural Clinical Research LRP Award and Paul Calabresi Career Development Award in Clinical Oncology from National Institutes of Health in 2013 and 2014 respectively.

Interview

JGO: *Would you introduce us to the “City of Hope Clinical Oncology Career Research Development Program” that has been receiving funding support from NIH?*

Dr. Chao: The goal of the K12 Paul Calabresi Career Development Award for Clinical Oncology is to provide a structured multidisciplinary environment primarily to train translational clinical oncology investigators to: (I) perform clinical oncology therapeutic research that develops and tests scientific hypotheses based on fundamental and clinical research findings; (II) design and test hypothesis-based, clinical therapeutic protocols and adjunctive biological analyses and for

clinician candidates to administer all phases (i.e., pilot/phase I, phase II, and phase III) of cancer therapeutic clinical trials; and (III) conduct cancer therapeutic research in a team setting in which basic research and clinical scientists collaborate and interact to expedite the translation of basic science research discoveries into patient-oriented therapeutic cancer research. The principal investigator for our institution's K12 program is Dr. Joanne Mortimer, whose expertise in clinical research has been paramount to the ongoing program's success. I was fortunate to be a scholar within the K12 program as it required an internal competitive grant application process that was vigorously reviewed by an institutional committee among a selection of excellent candidates. Funding from this grant was critical to my development as a successful junior faculty member in both providing salary support for protected research time as well as seed funding for initial projects. This program also paired me with both a basic science and a clinical research mentor, as well as opportunity to garner ongoing review and feedback from an institutional internal K12 committee composed of successful senior researchers whom reviewed interval progress reports. I echo the statements of many in academic medicine that strong mentorship is critical to success and fulfillment for an individual early in his/her career in oncology research.

JGO: *The field of oncology contains a vast multitude of ongoing research efforts. How does your program differ from those of other centers?*

Dr. Chao: City of Hope is proud to be one of only two centers that have offered the K12 Paul Calabresi Career Development Award for Clinical Oncology Program since its inception in 1982. As such, we have a longstanding history of training successful academic career oncologists, and it was one of the deciding aspects of City of Hope that led me to train there for fellowship. In terms of research in gastroesophageal cancers, our center also leverages unique advantages in providing significant contributions to this field. With our institution residing in the Greater Los Angeles area, the patients we see undeniably represent the rich cultural diversity of Southern California. It is from these immigrant populations that we see a relatively high volume of patients which are affected by a high incidence of gastric cancer. Furthermore, we also have representation of the rising incidence of gastroesophageal junction cancers affecting Caucasian patients. As such, we contribute significantly in clinical trial efforts and tissue biomarker analyses. We are also starting to form collaborations internationally to better understand both differences and

similarities in Asian versus Western gastric patient populations that will improve novel therapies.

JGO: *Your center had conducted a pilot trial of CRLX101 in patients with advanced, chemotherapy-refractory gastroesophageal cancer. What were the results and major findings of this pilot trial?*

Dr. Chao: Novel drug delivery mechanisms including nanoparticle drug conjugates have been and remain an ongoing area of active research. CRLX101, formerly known as IT-101, is one such agent in which in preclinical models Camptothecin was able to be selectively delivered to tumor tissue versus normal tissue. As such this agent holds significant promise in improving the therapeutic index of cytotoxic agents which would otherwise be too toxic. City of Hope conducted the initial phase I trial which established the safety of this agent, and strong rationale existed to conduct a pilot phase II trial in treatment-refractory gastroesophageal cancers. In our pilot trial in which laboratory correlates were pursued on pre- and post-treatment biopsies of both primary tumors and adjacent normal tissue, we observed selective nanoparticle drug uptake in tumor versus normal tissue. However, clinical anti-tumor activity was still limited with lack of robust responses demonstrated in our trial. We concluded that CRLX101 should continue active investigation in the context of combinatorial approaches, including the possibility of leveraging immune responses when paired with immune checkpoint inhibitors.

JGO: *What is your team currently working on in the development of novel therapies for gastroesophageal cancers?*

Dr. Chao: Immuno-oncology, as in many solid tumors, has demonstrated tremendous potential for this disease. Combining immune checkpoint inhibitors with radiation therapy in attempts to promote immune cell infiltration in tumors otherwise devoid of immune cell recognition (so-called "immune deserts") is a very active area of research, and we are also uniquely conducting an institutional clinical trial for gastroesophageal cancers. Palliative radiation for stage IV disease is a common standard of practice, whether it be to palliate dysphagia or bleeding arising from a primary tumor, or to alleviate pain from a metastatic site. As such our study is a window-of-opportunity trial in the sense we are delivering the immune checkpoint inhibitor pembrolizumab concordant with a palliative course of radiotherapy. The trial is still ongoing,

but we have observed some interesting laboratory correlates in circulating immune markers which are exploratory objectives of the trial, and we are hoping to share some preliminary results at an upcoming national research conference.

JGO: *In your years of personal research experience, were there any difficult moments or times that you felt frustrated and did not know how to move forward?*

Dr. Chao: I think every researcher runs into moments where his/her original ideas and/or hypotheses do not pan out as anticipated. I also believe every good researcher understands he/she needs to understand to invariably “accept the null hypothesis” if that is what is yielded from the data. Ultimately, I believe good research is the search for the truth, and you need to follow where the research takes you and be flexible in reformulating ideas and hypotheses. The subsequent discovery and breakthroughs with rewarding of intellectual curiosity for me helps outweigh any disappointments and hurdles along the way.

JGO: *We are excited that you are going to lead a focused issue entitled “The study of intratumoral heterogeneity in gastric cancer and its challenges in therapeutic progress” in JGO. What was your initial thought of organizing this issue? Who will be involved in this issue?*

Dr. Chao: I was honored for the invitation to be a guest editor for a special issue on a topic of my choosing in the field of gastroesophageal cancer. With improvements in technology that permit high throughput mutational analyses all the way down to the single cell level, the data has been rapidly emerging of interpatient and most importantly intratumoral heterogeneity that appears to be inherent in gastroesophageal cancer. As such I felt the timing was right on dedicating an issue on this topic on where we currently stand and where we need to go to tackle this issue in improving therapeutic approaches. I have invited a colleague and frequent collaborator, Dr. Samuel Klemperer, Director of Precision Medicine for The Angeles Clinic/Cedars-Sinai, as a co-guest editor for the issue. We have invited leading researchers in the field to contribute review articles and perspectives on this topic, for which I am very excited.

JGO: *What led you down the path of gastrointestinal oncology?*

Dr. Chao: Gastrointestinal oncology, and especially

gastroesophageal cancers remain I believe an area of great unmet medical need. As such, it is an area in which I believe I can make a significant positive impact when I envision the end of my career. As such when I was recruited to stay on at City of Hope at the end of my fellowship it was an easy decision, with the additional benefit of serving a patient population in which I grew up, that being the San Gabriel Valley. Looking back, I believe it is quite amazing how treatment for gastroesophageal cancer has evolved over the last few years. Ten years ago, I never would have foreseen that I would be telling patients that we would be harnessing their immune system to successfully combat their cancer. This approach has been highly effective for some patients, but still not all, so we have continued work to do.

JGO: *In 2011, you were named one of the “top doctors” for oncology by Pasadena magazine. As a rising star in oncology, what was your aspiration of being a doctor?*

Dr. Chao: I believe it is very important for one to not lose sight that a major purpose in medicine is to always strive to improve the lives of those afflicted by illness. In my medical training and still to this day I am asked that oncology must be a very difficult field to be involved in. However, I entered this field with the understanding it is not static, that over the 30-year projected course of my career there will be many scientific and clinical advances which will revolutionize therapy dramatically. To envision that I can contribute to those advances and touch the lives of so many fills me with tremendous humility, optimism, and gratitude in being a physician.

Acknowledgements

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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