Interview with Dr. Lillian Siu

UTMJ Interview Team (Kathleen O'Brien and Alexandra Florescu)

Biography

Dr. Lillian Siu is a senior medical oncologist at Princess Margaret Cancer Centre since 1998 and has been a Professor of Medicine at the University of Toronto since 2009. She is the Director of the Phase I Program and Co-Director of the Bras and Family Drug Development Program at Princess Margaret Cancer Centre and holds the BMO Chair in Precision Genomics (2016-2026). She is also the Clinical Lead for the Tumor Immunotherapy Program at Princess Margaret Cancer Centre. Dr. Siu served on the Board of Directors for the American Society of Clinical Oncology (ASCO) for a four-year term (2012-2016). She also served as a member of the Nomination Committee for the American Association for Cancer Research (AACR) (2014-2016). She currently serves on the AACR Board of Directors for a three-year term (2017-2020).

Dr. Lillian Siu

Dr. Siu's major research focus is in the area of new anticancer drug development, particularly with respect to phase I trials and head and neck malignancies. She is the Principal Investigator of a phase I cooperative agreement UM1 award (2014-2019) sponsored by the United States National Cancer Institute. In addition to her active research in early phase clinical trials, she has been leading genomics initiatives and immuno-oncology trials at the Princess Margaret Cancer Centre. Together, the three programs of drug development, cancer genomics and tumor immunotherapy form a triad of synergy that supports the institution's core vision to deliver precision cancer medicine.

Internationally, Dr. Siu was the recipient of the US NCI Michaele C. Christian Award in Oncology Drug Development in 2010. Locally, she was awarded the University of Toronto Department of Medicine Eaton Scholar Researcher in 2016. She was the ASCO Conquer Cancer Foundation Grants Selection Committee Chair in 2009-10. She was Chairperson of the AACR Education Committee, Co-Chairperson of the Scientific Committee for the 2012 Annual Meeting and Co-Chairperson for the Clinical Trials Committee 2015-2017. Dr. Siu has published over 300 peer-reviewed manuscripts, and she is currently a scientific editor for Cancer Discovery and is on the editorial board for JAMA Oncology.

Interview

UTMJ: As an oncologist and researcher at Princess Margaret, can you describe what your research focuses on in the context of precision medicine?

LS: I have been a medical oncologist here since 1998, so 21 years. I focus mainly on solid tumors, so cancers that are not haematological malignancies. But, my main area of expertise is developing new drugs. In the last ten years or so, precision medicine has become a main part of cancer. I lead the Cancer Genomics Program, which tries to find molecular vulnerabilities in cancer that we can target to give more individualized treatment to our patients.

UTMJ: Would you be able to explain for our readers what precision medicine means in your research and in your work?

LS: [It is both] simple and difficult. We are trying to understand that every cancer is different, even though under the microscope they look similar. Colon cancer looks like colon cancer, but if you actually decipher it at the molecular level, they are quite different. For example, lung cancer used to just be divided by histology, small cell and non-small cell. Now, there are many subgroups of lung cancer that are being treated based on the molecular findings. These are somatic changes, changes in cancer cells, not hereditary or germline changes that are present in every cell in a patient's body. However, what we are trying to do is understand what is present in the genetic material of the cancer that could be used as a way to target the cancer. We are trying to find the Achilles heel, in simple terms.

[We use] different techniques such as next-generation sequencing, simple immunohistochemistry… [and] different technologies, such as transcriptomics, genomics, etc. to find things that we can then use as drug targets. Much of my research is really promoting this kind of molecular testing in patients with cancer—not just for my patients but across the institution to enable clinicians to find the right treatment for the patient that perhaps would be more individualized and provide a higher degree of benefit.

UTMJ: How did you end up getting into precision medicine?

LS: It's a logical next step from what we do in the Phase I program, which involves testing new drugs in humans after rigorous laboratory research. We are trying to find out if these drugs are safe to start a Phase I trial, but as more of this kind of molecular information becomes available, sometimes when you find these molecular mutations or aberrations, those are exactly the drugs we are testing in the Phase I program. So it is a really natural match. For example, if I am testing PI-3 kinase inhibitor, and I now have patients that have PI-3 kinase mutations, it becomes an opportunistic match for us to not just test for the safety of these new

drugs but perhaps we have the opportunity to benefit them as early as in a Phase I study. It was a natural match to take new drugs to patients but at the same time try to find out if, in addition to safety, certain patient populations will benefit from certain drugs. You can see that many of the scientists and investigators in the molecular profiling characterization space are drug developers and to some extent that is not coincidental, because that is where our interest lies.

UTMJ: At a clinical level, what changes have you been able to see in regard to precision medicine? You spoke a lot about the research side of it, but what is it like when you have a patient in front of you? What is the process of implementing precision medicine tools at a clinical level?

LS: We have several molecular testing programs in the hospital which bridge between research and clinic. These are approved clinical tests. For example for lung cancer, certain tests like EGFR mutations and ELK translocations are approved tests because there is a proven clinical utility - patients benefit and it has proven to make them live longer and do better. So those are clinical tests done in a clinical lab. The programs in the cancer genomics program that we are running are not yet necessarily proven to benefit patients yet, but we are allowing clinics to test patients that are at a stage of their cancer treatment where they are well enough to undergo molecular testing. The reason I say that is we don't really want to profile somebody's tumor when they are near terminal, because by the time you are finished testing, they won't be able to benefit. We have certain qualifications or eligibility criteria that enable people to be enrolled in these molecular programs. These programs are not Ministry of Health funded because they are not approved yet to the level of EGFR and ELK. We have studies like Ontario-wide Cancer TArgeted Nucleic acid Evaluation (OCTANE) which is allowing people in the clinic to say to a patient, "you have a cancer that we know a lot about in the pathology lab but we don't know a lot about it at a genetic level, so we are going to request a sample that we have previously removed and we are going to test it with Next Generation Sequencing technology." The results come back in a few weeks, during which time the patient may be on standard treatment or standard chemotherapy. When the results come back, we see after analysis from our genomic experts and bioinformatics experts whether we can identify certain genes that are druggable – whether we have drugs to match the gene mutations. If they do, we can enrol them in trials that get them on treatment.

If you look across history so far, many institutions have are doing [these trials] for the last ten years, we are not unique. I would say approximately 40% of patients have actionable DNA mutations. Only about 10-20% of patients get enrolled in these matching trials and even a smaller percentage benefit – not everybody that gets enrolled into these drug trials benefit. The field is at a point where people will question, is precision medicine an illusion? Is it helping a lot of patients or is it a lot of profiling and testing but not getting a big gain from such efforts? We are not going to be

able to settle that [right now]. If you look at certain areas where precision medicine really has helped, an example is EGFR mutations and lung cancer. There is also a recent class of drug called NTRAC inhibitors. When you treat patients with NTRAC fusion with this kind of drug, the response rate is 75% and is very durable. So clearly in patients that have this rare mutation, it is going to help you, there is no question. But I think the whole effort of precision medicine is not to just look at these rare abnormalities, we need to spend more time finding out what else beyond the genetic level can be looked at. A lot of efforts are being invested in the mRNA and protein level to see if there are other ways that we can understand the map within the cancer, that we are not just picking one city, we are actually looking at the country or the world of the cancer. Beyond that, there are epigenetic things that happen after the protein is transcribed. We can even look at the immune system - how can we personalize immunotherapy, so that we are not just looking at the cancer but also how we can personalize the patient's immune response to therapy? I think the field is actually quite young despite the fact that precision medicine is a term that has been around for probably a decade. We are just turning the leaf to the next era, so to think that [precision medicine] is a failure is a bit short-sighted. Nobody reads the first chapter of a book and says its a bad book. I think you need to read on before making a decision.

UTMJ: Thank you for that, I think that gives us a good idea of the work you do. In a slightly different vein, when you take patient samples, does it go to any sort of biobank?

LS: Yes. In OCTANE as an example, we test a patient's previous cancer sample that has been archived. We also store an extra set of samples, DNA and RNA because in those that don't have targetable mutations, we could do whole-genome sequencing, for example, to see if we can understand more. It may not benefit that patient but it will benefit [research]. The other thing that we are doing on a big scale is that Terry Fox Research Institute has successfully obtained a huge hundred and fifty million dollar grant from the federal government to create a comprehensive cancer network across the country where precision medicine initiatives such as the ones we are doing are also being run in British Columbia and Montreal. We will be able to pool our results and create a big cohort of patients' genomics and other 'omics that were mentioned. [There is a big opportunity] to learn from these big numbers. This is actually just taking off now, and [further shows] that the field is quite active.

UTMJ: Some people have criticized precision medicine simply because of the cost and feasibility of implementation. What are the barriers to implementation and how can we overcome them?

LS: I think most people have criticized [personalized medicine] because of the cost of sequencing, but sequencing has gone down in cost substantially. We can imagine in time it's not

going to cost a lot of money to do a whole genome. The harder part of sequencing is to know what to do with the results. Even if you understand the science, you then have to find an action to act on that result – finding new drugs and testing if these drugs are active based on the biomarker. Interpreting the results is far more limiting than the cost of sequencing… We have to try to keep finding ways to go beyond the simple Pi-3 kinase mutation, so we need to find a Pi-3 kinase inhibitor – cancer is much more complex than one gene, one mutation, one drug. If it was, my career would be done and I wouldn't have a job in two years. Another big shortcoming of the current mutation or precision medicine understanding is that most of the studies can only profile one sample. But we know that cancers change, so in time we need to learn how to do multiple sampling. However, this is expensive, so a lot of the field has moved to circulating DNA (liquid biopsies) to be able to follow with just blood rather than biopsying the tumour. We have a huge program called LIBERATE that is doing that kind of dynamic monitoring and using that to understand where the cancer is trying to head and stop it from going there before it even has a chance to grow. I think that is where the field is going and to say that cancer precision medicine based on its current iteration is unsuccessful, again I think it is not looking at it longer term.

UTMJ: I think you mentioned a couple specific mutations already, but we had wanted to ask about the BRCA gene because a lot of people know about it and its treatment. Are there other genes or conditions that have made similar strides in terms of personalized medicine?

LS: You know, the majority of cancers are not due to hereditary syndromes… however, because of the somatic testing, you have incidental germline findings. It is something that we have to anticipate in advance. In our molecular testing consent, we will ask "if we have an incidental finding of BRCA or any other kind of incidental hereditary gene, do you want to know about it?" If they do, we have a whole genetic team that would help educate them on what to do and if other family members need to be tested.

But to answer your question, in terms of breakthroughs. Many of the drugs that have been approved over the last few decades are really only approved because we understood that there are cancers being driven by that mutation. [For example,] we now know that certain lung cancers are epidermal growth factor receptor (EGFR) driven and we now actually have three or four generations of EGFR inhibitors, not just the first one. We can actually anticipate how they evolve and become resistant and we have drugs to target them as they become resistant.

We are even using that kind of information to help us use immunotherapy, a whole area of drugs that has very much been changing the whole field. So there are certain genomic testing markers like tumor mutational burden, where you count the number of mutations that are able to elicit an immune response, and try to use that marker to predict whether [a patient] would have a better response to immunotherapy. We are trying to add more of these kinds of winners to the list, but it takes time, and it takes studies to prove that they have clinical utility.

UTMJ: In the same vein, another one of our questions was about the use of personalized medicine in screening people, so the way that BRCA is used to screen people for potentially developing breast cancer. You make this distinction between somatic and germline mutations – is there a role for somatic mutation precision medicine in screening?

LS: Well, in my role I do not do that kind of testing, but there are people like [Dr.] Raymond Kim in our institution who is essentially using panels, for example, to do testing for patients who have enough characteristics from the clinical history to warrant testing. We also have one of our liquid biopsy studies, where one of the cohorts is actually looking at patients who have a high risk of developing cancer. So, for example, family members of people who have BRCA cancers, and trying to really develop a circulating tumor DNA panel that can be used in addition to augment the routine testing.…They have the routine testing for high risk patients and family members, but we are trying to develop tests that can allow us [to augment testing] in a cost effective way, because if you test the general public it becomes a bit cost ineffective, but I think there definitely is a role in the high risk individuals to augment their routine testing. And I think most of our testing these days is no longer single-plex (detecting one target sequence)–it's very ineffective to test serial single tests. It's much more cost effective to do a multiplex assay (detecting multiple target sequences). That's why we have these panels to try and do 200 genes [or] 600 genes at the same time, such that we can use one sample to test multiple things. Over time the cost is actually not [that] much different, and in time exome sequencing and genome sequencing will again be becoming much and much more prime time.

UTMJ: What makes someone high-risk aside from having a mutation like BRCA? Or is that the only time you consider someone high-risk?

LS: Well family history, obviously, is a big one for these kinds of hereditary syndromes. Generally, there is a whole genetic team that understands the pedigree of the patient's history. In lung cancer, for example, people who smoke cigarettes have a higher risk for lung cancer, for somatic cancers not for hereditary cancers, so we don't really do genetic testing for people who are smoking, it's really mainly family history that drives that kind of genetic testing. But as I said right now because we are doing this somatic testing for cancers, we have identified…some of these individuals who now need genetic testing because we have incidental germline findings. So even though I am not a medical geneticist we are linked to them because we have found [these] individuals [where] we need to have experts to handle the information and educate the patients. And I think it's a thought that is going to be important to clarify–that patients do not

come to me to look at [whether] they have any inherited risk, that's not my job. My job is to find [out if] I have treatment for their cancers that can be more tailored.

UTMJ: When we talk about genomic and technological advancements there is often moral or ethical issues that can present. Have any challenges like that presented themselves in precision medicine or not yet?

LS: Yes, I mean there is always that concern that if I put my genetic data out in the public, am I going to have a higher risk of not being approved for certain insurance? I think different countries have different sort of views on that. I think Canada at this point is still quite acceptive of these kinds of sharing initiatives and I think [the] U.S. is actually quite open that data sharing is important, and it would not bias you from having your insurance retracted or disapproved because people can look into your genomic information. Honestly, obviously I'm biased, [but] I think if we don't have all that kind of information shared and everybody keeps their own data, especially their cancer or genomic data to themselves, we'll probably not be able to move the field much, because how can we, right? And this is the whole reason for these journals requiring that if you do any sequencing studies you have to deposit your raw data into a control website that people can learn [from] and share together, like the CCPA, etc. I think that's the right thing to do and if we had not done this we would not have learned what we [know] now. I think it's really important to work with these individuals that have concerns about privacy and data sharing, etc. to make sure we put in the right safeguards such that we are not being careless about it, but at the same time we need to look at the bigger picture to enable people to learn and share.

UTMJ: In 20, 30, maybe 50 years from now, what is the end-goal or 'big picture' that you see?

LS: I sort of hinted where I think the field is going. I think every patient in 2030 should already by the time they are diagnosed probably have their cancer not just molecularly tested but other "-omics" as well, in addition to pathology which remains very important. Over time as things evolve they would allow us to use liquid biopsies to follow the cancer, or to pre-empt the cancer, and I think we would have enough artificial intelligence knowledge to really help us understand all that information, to recommend the best treatment. I think where we are lagging behind is really producing good drugs that actually can act on this new information. The field of drug development is not going as fast as the field of molecular testing. It takes time to develop new drugs, so I think hopefully we can catch up such that if you have the right algorithm that tells you [that] you need to have this drug, we have that easily available. And I think the other important thing is that we are doing this kind of testing in much earlier stages of cancer, such that we can actually stop cancers from relapsing, rather than 'they already relapsed let's try and slow it down', but we still cannot cure them.

We're trying to cure, [that] is our goal, and I think the field is moving this kind of testing much earlier in people who have, for example, molecular residual disease that we're trying to actually nick at this point so that it does not get to come back.

UTMJ: How do interested students get involved in precision medicine?

LS: For students, there are always electives [and such] that are open, and I think the field of oncology is so rewarding that it has become attractive for a lot of medical trainees. I think oncology is getting its way into the medical curriculum more. When I was doing medical school, I think I hardly actually studied much in terms of oncology, so I think now things have changed – that people get exposed to oncology much earlier in time. A lot of summer students come here, a lot of fellows and residents train, and obviously precision medicine is not something that you can just do over a summer and learn everything about. But it's a build up of that new kind of information in training that if that's an area you want to pursue there's a lot of opportunities.

UTMJ: A lot of students are also really excited about the use of artificial intelligence. When you're handling such big data sets like sequencing someone's entire genome, could you speak to the use of AI? Have you seen it implemented already? Can you see that happening?

LS: Oh, yes. I mean we're just beginning to do this, we've worked with scientists like [Dr.] Benjamin Haibe-Kains who is one of our bioinformatics AI experts. It's certainly something that we are all thinking of.... But AI is not just you putting your smart phone over the genomic information and seeing on the screen "use this drug" – I wish it was that easy, right, [but] this is not at that time point. I think the cancer field is moving but it is still a very complex area. I think it makes sense especially when you have millions of data sets, how can we make anything out of it in our brain? We don't have that computational power with just one or two brains. I think this is where using the [AI] computational capacity comes in, then you still need the human interpretation. I think together that would make it much more successful. So the answer is yes, there are tons of activities going on, including the Terry Fox initiative I mentioned to you – AI is big in the centre of it. And I think clearly in the next ten, twenty years it will help us do a lot of things that currently we are doing manually, and I think it will be quite interesting.