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A Golden Age of Drug Discovery in Cancer – A Chat With Yujiro Hata, CEO of IDEAYA Biosciences

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"We are entering into a golden age of drug discovery in cancer. Our understanding of disease, and what causes cancer, has really transformed. …If you want to create an extremely valuable company, I think a phenomenal model is to build a drug discovery engine targeting areas of big biology."

Biotech veteran Yujiro Hata has a keen interest in finding the possible in impossible, renaissance and zero-gravity thinkers, company building, disruptive ideas, emerging technologies, and business model innovation, to name a few. Hata, an entrepreneur at heart, has leveraged all of these to help drive several successful biotech companies. In his latest venture, the oncology veteran is leading IDEAYA Biosciences, a start-up that is developing breakthrough therapies for patients with cancer.

IDEAYA – which recently raised a $46 million Series A from 5AM Ventures, Canaan Partners, Celgene, WuXi Healthcare Ventures, Novartis Institute of Biomedical Research, and Alexandria Real Estate – plans to develop novel drugs to selectively kill cancers by targeting specific cancer mutations, such as BRCA, with an approach called "synthetic lethality." The company is also researching drugs to improve response to cancer immunotherapy. IDEAYA has already

assembled a world-class drug discovery team and Scientific Advisory Board that includes a Nobel Laureate and three members of the National Academy of Sciences.

Hata –who has more than two decades of experience in the life science sector – recently shared with me the drive behind IDEAYA's science and business model, as well as his perspectives on future of breakthroughs in the oncology space.

Hui Cai: Can you share with us the premise of creating IDEAYA?

Yujiro Hata: If you would have asked, what approach of personalized medicine can be pursued, I don't think you can find a better example than synthetic lethality. This concept applies to identifying synthetically lethal "pairs" of genes, where when both genes are inactivated the cells die. So our approach is to develop drugs that inhibit a target that has a synthetic lethal relationship with a specific mutation that resides in a cancer of interest. This paradigm has not been exploited to its full potential due to the lack of optimal tools to systematically identify and study synthetic lethality, particularly in mammals. Now, with the advent of tools like CRISPR, the ability to do gene knock-outs in a precise and clear and effective way becomes an extraordinarily powerful tool to determine and establish synthetic lethality driven relationships. You can imagine a situation where you have a cancer cell line for ovarian cancer that has a BRCA mutation, and then you do various knock-outs of genes that might have a synthetic lethal relationship and then you observe if there's a dropout or not. If there's a dropout, then that gives you more comfort that there's a bona-fide synthetic lethal relationship. So we think the time is right to build a company like this and to leverage technologies like CRISPR.

Hui Cai: Using ovarian cancer as an example, can you explain the benefit of the IDEAYA approach?

Yujiro Hata: Ovarian cancer historically has been a very difficult cancer to treat. A recent success was the approval in late 2013 of Lynparza (olaparib), which is a PARP inhibitor and a synthetic lethality agent for the treatment of resistant ovarian cancer in BRCA patients. At IDEAYA, we've made a strategic decision that we're not going to pursue another PARP inhibitor, and whatever profile we pick, we're going to pick a target that has a genetic signature that goes beyond BRCA. The goal here is to broaden the spectrum of patients that you can treat that extend beyond BRCA. There are many mutations that are prevalent in various cancer types that we're interested in, and that's the reason why we started this company. We believe that there are many unexploited synthetic lethal interactions that have yet to be pursued.

Hui Cai: What does IDEAYA's business model look like?

Yujiro Hata: Companies and start-ups have three general models. One is to in-license an asset, whether it's in Phase 1 or Phase 2, and then raise $30 million to $50 million, and advance it to a clinical readout. That has worked great for a lot of companies. The second model is to license a platform; CRISPR and CAR-T are a good example of this. There's a third model, which is focused on interesting biology hopefully in a therapeutic area that is important, and building a high performing drug discovery organization to pursue that biology. We fit into that third category. Our hope and intent with IDEAYA – not just in one year or five years, but hopefully a

decade and beyond – is what's going to really drive this organization's value is our ability to innovate and do drug discovery.. Having worked on building several start-ups, I have come to appreciate that the most critical piece to building a company of this profile is to ensure you are assembling the best scientific team possible.

Hui Cai: You are starting from the very earliest stage of drug discovery with an "idea". Is that where the name IDEAYA come from?

Yujiro Hata: Yes. It's derived from the word 'idea.' We were a very small company that was just forming, and wanted to pick a name that symbolized entrepreneurship. If you can generate truly innovative ideas, then it gives you the ability to compete. As a start-up you have to think about what advantage you have when competing against pharmaceutical companies because you can't out-resource the larger and more established companies. However if we have the right strategy and ideas, the right individuals in the company, especially the scientific staff and you empower the organization with the ability to make decisions quickly and execute quickly, then you have given yourself the opportunity to be competitive.

Hui Cai: And your early discovery model has endorsement from some of the most reputable investors out there.

Yujiro Hata: Yes. 5AM and Canaan are phenomenal investors because they support the growth of these types of early stage companies. We approached Celgene and Novartis because of their strengths and expertise in oncology. We're also very delighted to have WuXi Healthcare Ventures as part of that syndicate. We were very impressed by their speed and ability to go through diligence and make its investment decision. We appreciate the importance of China, both in the area of innovation and as a market presence in healthcare moving forward in the future. I think these organizations all have a similar commitment to basic research and early drug discovery. So from that aspect, our investor base really reflects the same commitment that our company has, and that's exactly what you want.

Hui Cai: It's really important to have such strong alignment of vision. Do you see any risks down the road?

Yujiro Hata: Our goal is to advance two of our small molecule programs in the clinic in the first half of 2019. We're starting from the beginning and rolling up our sleeves and doing drug discovery. We do appreciate there is risk in that type of proposition. I think what it does is it shifts the focus to having the best strategy, particularly on program selection, drug discovery execution, and recruiting the best talent possible, which will ensure the best chance for success. I'm a believer in not worrying about things you can't control, and instead to spend time on things you do have control over, and the strategic decisions you make and who you hire and the culture your build is something you have a lot of control over. I think we have to be smart about target selection and the type of chemical risk we're taking. We're doing it from day zero as a very objective and analytical assessment of both the biological and chemical risk of each of these programs that we're considering in making sure we have a diversified portfolio. I think we're being very thoughtful in making sure we have a diversified strategy.

Hui Cai: How is recruitment coming along?

Yujiro Hata: We are doing a lot of hiring now. We're thinking 10 plus chemists internally, and we will ramp that up over time. We're thinking the same in biology. We are looking for medicinal chemists, strong cancer biologists, and other discovery expertise. We're also looking for folks who are knowledgeable about CRISPR and use of modern biology tools. That is a sizable effort in terms of internal drug discovery. We are also collaborating with WuXi as our external partner, and launched our first CRISPR study last year. Our goal is to best leverage the capability and expertise of external groups like WuXi and complement that with our internal team.

Hui Cai: Let's talk about yourself a bit… You have worked with a lot of start-ups in cancer field. Is this a cognizant decision to pick oncology?

Yujiro Hata: For me personally, like many of us, have been in some way impacted by cancer. My initial desire to go into oncology was based on a personal desire to make some contribution to the field, and now when we think about it, we are really entering into a golden age of drug discovery in cancer. Our understanding of disease, and what causes cancer, has really transformed. Immunotherapy will be a very big cornerstone, and now if you look at how clinical trials are done and how patients are treated with genetic screening, I fundamentally believe that this decade will transform how people treat and think about cancer. My hope and ambition is that I can dedicate the rest of my career to the field of cancer.

Hui Cai: What transformations would you anticipate happening in oncology in the next three-to-five years?

Yujiro Hata: I think it's going to be three areas: One is around precision medicine which has already made a big impact on cancer. I think we're going to continue to see great progress on this front as we mature and improve our understanding of the genetic component of cancer. And that's one of the premises of why IDEAYA was created – to utilize the approach of synthetic lethality to target specific cancer mutations. Now when you think about clinical trials, there are companies and academic institutions that are taking the charge in this area of basket trials, in which you are no longer treating breast cancer patients, you're treating BRCA patients, and that can go across from colorectal cancer, breast cancer, and prostate cancer. The focus is around the mutation that you have, versus the classical characterization of cancer by organ. That would be an evolution of how we characterize and think about cancer, as well as how we do drug discovery and development.

The second is immunotherapy. The first wave of immunotherapy agents has come out and we know the predominance of the work has been on the checkpoint inhibitor side. There's also been ongoing interest in cell-based therapy, such as CAR-T. The observation that cancer is partly or even substantially driven by a faulty immune system is a remarkable finding. What's really exciting about immunotherapy is that these responses have the potential to be quite durable. The downside today, however, is that some patients aren't responding, so I think there's still much more research to do. If you look at the landscape of research being done in precision medicine

and immunotherapy, much of the innovation and substantial jumps in responses will likely come from these two areas.

And the third area, similar to what we saw with HCV, is going to be around combinations. It's unclear how many permutations and combinations can there really be, will it be 10 or 12 or will it be two or three mechanisms that you bring together that have a truly profound effect. I think the difference between cancer and HCV is that cancer is more heterogeneous. You have different mutational backgrounds and you have different cancer types, so there will likely be more sets of combinations, and we'll have to see how the data unfolds. Once you get into the combination area, we see some distinct advantages to having small molecules due to their potential in combinability, including potential future fixed dosed combinations. This is one of the reasons why IDEAYA is excited about the role small molecules can potentially play in the future of immunotherapy.

Hui Cai: Thanks very much Yujiro for your time. This is very insightful. I wish IDEAYA great success.

Yujiro Hata: My pleasure, and thank you.