Michael G. Kauffman – Founder & CEO, Karyopharm Therapeutics

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Karyopharm Therapeutics' Dr Michael G. Kauffman outlines the genesis of the company he co-founded with his wife, the approval journey of key product XPOVIO®, his ambitious internationalisation plans, and the challenges of being a biotech entrepreneur.

Michael, could you start by sharing a little about the genesis of Karyopharm?

I have a PhD from Johns Hopkins Medical School and trained in internal medicine and rheumatology at Beth Israel and Massachusetts General Hospitals. I moved to the biopharma industry after my fellowship because I realised that I wanted to leverage my training in science and medicine to develop and deliver new drugs to patients. I started my career with Biogen before joining Millennium Pharmaceuticals, where I led the Velcade® development program, and subsequently, I held leadership roles at a number of biotech companies including Predix Pharmaceuticals, Epix Pharmaceuticals, Onyx Pharmaceuticals, as well as Proteolix Inc, where I led the development of Kyprolis®.

Karyopharm is actually my fifth company and the one I am proudest of. Our first drug, XPOVIO®, was approved by the US FDA in July 2019, which is actually the third drug approval in which I have been heavily involved. All three of these drugs have been in the multiple myeloma field, though XPOVIO® has since also been approved in June 2020 for diffuse large B-cell lymphoma (DLBCL),

and is being evaluated for other cancer indications.

I co-founded Karyopharm with our current President and CSO – and, full disclosure, my wife – Dr Sharon Shacham in 2008. Sharon has a PhD in biophysical chemistry and computational biology, and a MBA from Tel Aviv University. Our company name comes from the word ‘karyo’, which means ‘nucleus’. As a pharma company, we are focused on modulating nuclear export, i.e. the conversation between the cell nucleus and the cell cytoplasm.

This idea actually came from Sharon. She had been working on neuropsychiatric drugs at her previous company but when she left, she decided to move into oncology. She wanted to work on a new type of drug that could be effective against many different types of cancer simultaneously. This went against the conventional wisdom of the time: many biotech and small pharma companies tended to focus on very specific mutations in different cancers, which resulted in drugs that were highly effective against patients with those specific mutations but did not work for the remaining, typically majority, of cancer patients without those mutations.

After perusing the literature extensively, she realised that every time she read a paper about a tumour suppressor protein that had stopped working, the explanation was that the protein had been removed from the nucleus by a single carrier, the Chromosomal Maintenance 1 (CRM1) protein, now called exportin 1 (XPO1). This was important because tumour suppressor proteins only work when they are present within the nucleus. That was when we began to explore this target.

How challenging was it to develop this new target and develop your first product, XPOVIO®?

There was certainly a huge amount of scepticism at the beginning. It was extremely scary, even for venture investors, so in the beginning, we invested about USD 500,000 of our own capital to start our investigations. Karyopharm’s initial patents were filed by Sharon and I! What helped us a lot was that Sharon reached out to Dr Ronald DePinho, who was then at the Dana-Farber Cancer Institute and later became President of the MD Anderson Cancer Center. He had also come up with some insights into this pathway and had, among other things, written a short review article published in *Science* in 2007 about the potential importance of restoring tumour suppressor proteins within the nucleus. When Sharon spoke to him about our company, he thought it was a great idea and he helped us establish Karyopharm.

From my experience, many great ideas actually come from people unconstrained by the conventions and cultural uniformities of large organisations. When I was working on Velcade®, which was the first proteasome inhibitor approved for cancer, people told us it was almost unethical to block such an important pathway. It was such a novel idea that Big Pharma companies would not go near it initially. Of course, Velcade® turned out to be a ‘mega’ blockbuster drug, reaching USD 2.5 billion in sales by the early-2000s, a huge figure back then, and was subsequently acquired by Takeda. Kyprolis®, a second-generation proteasome inhibitor, was acquired by Amgen. But just like in these two cases, the process of developing XPOVIO® – proving that the drug was safe and incredibly effective – required a lot of effort and a level of risk tolerance not found within Big Pharma companies.

Subsequently, we put together our pre-IND and IND packages and carried out Phase I studies in the US, Canada and Europe, with a broad program in both hematologic malignancies and solid tumours. This was important because we wanted to develop a cancer drug that was more broadly applicable to many different indications. The idea of restoring tumour suppressor proteins to inhibit cancer growth is applicable to any malignancy. If we draw a comparison to the immunotherapies and particularly the checkpoint inhibitors that are so prevalent today, these checkpoint inhibitors

take advantage of a fundamental mechanism of cancer that is external to the cell and focused on the immune system. We are working on a fundamental mechanism of cancer internal to the cell, nuclear export dysregulation, where tumour suppressor protein(s) have mutated or more typically, have been removed from the cell nucleus, which helps cancer cells evade detection from the body's own defence mechanisms.

With XPOVIO® already approved for two indications, could you outline your global commercialisation strategy for your first drug?

There are three components to our global strategy. Firstly, within the US, we have built our own commercial salesforce. We wanted to launch XPOVIO® ourselves instead of partnering with other companies. XPOVIO®'s first indication is for relapsed refractory multiple myeloma (RRMM), and I have extensive experience with multiple myeloma drugs and more generally, the US market. Having worked with a number of biotech companies and dealt with partnerships and collaboration agreements with Big Pharma companies, while Big Pharma companies do many things well, even in co-promotion agreements, I think there is never a true partnership. Any collaboration between a small company and a Big Pharma player will always be heavily weighted towards the latter since smaller companies cannot compete in terms of funding and resources. While a partnership with Big Pharma would be financially more stable, ultimately our Board and our leadership team made the decision that the best option for us in the US is to commercialise XPOVIO® ourselves. Another consideration was that XPOVIO® is a very innovative oral product with high potency and high differentiation from other multiple myeloma drugs. We wanted to work directly with patient groups and physicians to properly educate them on the drug. Commercialising the drug ourselves in the US would ensure that we retain the innovation and the nimbleness within the US organisation.

The second region we have defined is the Far East, specifically the markets of Greater China, South Korea, ASEAN countries, Australia and New Zealand. Here, we recognised that a small company like Karyopharm cannot commercialise a drug efficiently or expeditiously, which is why we are working with Chinese biopharma player Antengene. They have done a remarkable job of advancing XPOVIO® in terms of clinical and regulatory approvals, and we expect to file an NDA with the China NMPA very soon. We are very excited about the potential of XPOVIO® in a market like China because one of the key advantages of our drug is that it is an oral drug with no sterility or known stability issues, which means that it can be transported at room temperature and there is no need for IV units or needles. For a vast country like China where transportation is a challenge, these characteristics make XPOVIO® a very attractive product. Antengene's CEO Dr Jay Mei has extensive experience in the industry, and in particular, was heavily involved with the launch and commercialisation of Celgene's multiple myeloma drug, Revlimid®, in China, so they are a great partner to have.

Then finally we come to Europe, Japan, and of course, the rest of the world. We are speaking to many potential partners in Europe and Japan, and we will strike the best deal we can. We do not plan to establish a direct presence in these geographies for now, and in any case, COVID-19 has made that prospect even less feasible than previously evaluated, though Europe remains an important region for us, as most of the patients we have recruited in clinical trials are actually in Europe. There, we are speaking mostly to mid-caps and smaller companies. We did approach multinational companies but all of them wanted a piece of the US, which was not in line with our strategy. Fortunately, Europe does have many regional or local companies that have smaller portfolios and are Europe-focused. This fits very well with Karyopharm because we want to have a strong European partner who will see XPOVIO® as a very important and strategic asset within their portfolio.

What are your commercial expectations for XPOVIO® in the next year or two?

We have been pleased with XPOVIO®'s performance so far. Following our July 2019 approval, many industry observers actually thought our drug would struggle to perform and the analyst expectation for the first quarter was USD 2 million. Our actual sales were USD 12 million! In terms of COVID, we were negatively affected when the pandemic reached the US in late-February and through March because our salesforce was no longer able to speak to doctors face-to-face and we had not yet implemented video conferencing capabilities. As a result, our sales dipped a little in Q1 2020 though the actual number of prescriptions stayed flat. However, we adapted fairly quickly and implemented video conferencing systems for our salesforce, and by late-April, we had recovered while other companies were still struggling. Q2 2020 results were very good with sales of nearly USD 19 million, and we are very excited about the current quarter. Wall Street expectations for 2020 is USD 80 million and then more than double that – USD 170 million – for 2021.

In addition, we see a lot of potential in XPOVIO®. The first approved indication, RRMM, is a very tough indication to treat because patients are typically very sick by then. We have just announced positive Phase III data for second-line multiple myeloma, which is the real market for this drug. Later this year, we also believe that we will have very intriguing data for other solid tumours, including Phase III data for advanced unresectable dedifferentiated liposarcoma in what is the largest such study to date in the US and Europe, and next year, we hope to see positive Phase III data in uterine cancer and other indications. This, along with our geographic expansion, will see XPOVIO® reach revenues of around USD 300-600 million over the next couple of years.

Ultimately, as we have stated publicly, one of our financial goals as a company is to break even by 2022, and I believe we are well on track.

Karyopharm has also investigated XPOVIO® as a treatment for COVID-19. What was the rationale for this given that Karyopharm is at its core an oncology company?

To be honest, we actually found out about the potential of XPOVIO® as a treatment for COVID-19 because a number of laboratories – who we did not even know were testing our drug – reached out to us. In one week, we received two emails saying that our drug demonstrated remarkable *in vitro* activity against COVID-19, with low concentrations of the drug thought to block viral replication. It was a conundrum because we are a small company and we are very busy with our multiple cancer trials but within the context of a global pandemic, we thought we had a responsibility to pursue this avenue. Therefore, in April 2020, we began enrollment in a placebo-controlled, randomised Phase 2

study across the US, Europe and Israel to evaluate low doses of XPOVIO® in hospitalised patients. However, we ended the trial early because it seemed that the drug was unlikely to demonstrate a statistically significant efficacy benefit across the entire heterogeneous patient population studied *though* it did show statistically significant improvement in terms of hospital discharges and the conversion of PCR test results from positive to negative in around 75 percent of the patient population. However, the financial resources required for a confirmatory Phase III study are beyond our capabilities so we are working closely with other organisations and entities to figure out how best to conduct that study. We are all hoping for a vaccine to be approved soon but notwithstanding that, COVID-19 cases will persist globally for a while yet and even if this pandemic is resolved, there may be other viruses where this pathway could be relevant.

Having built and developed so many biotech companies in what can often be challenging journeys, what keeps you motivated?

Looking broadly, as a society, I think we are at a state of civilization where it is all about innovation. We have the choice of contributing to that innovation and creating novel products or being critics of innovation. One of the beauties of the biotech industry is that we have the ability to treat and maybe even cure diseases. Regardless of the differences between and even within societies, all of us will grow older and have various health concerns eventually. There are so many diseases out there that still require treatments and cures, so the work is not even close to being done, and I am always motivated by hearing patient stories.

I am also very inspired by Celgene as a company. They were developing Revlimid® when I was developing Velcade® and they were also a US-only company for many years before they expanded into Europe through an acquisition. They have since grown into one of the largest biotech companies globally. As a company, Karyopharm has great drugs and great technology with really no competition at the moment so we truly have the potential to become the next Celgene.

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