Karen Jagoda: Welcome to the empowerpatientpodcast.com show. I am Karen Jagoda, and my guest today is Isaac Israel. He's the CEO of Kitov Pharma, that's kitovpharma.com, and they're an innovative biopharmaceutical drug development company. And I'm delighted to get you on the show today, Isaac. It's a really interesting topic that we've got on the queue today so welcome.

Isaac Israel: Thank you very much, and thank you for having me online. I'm looking forward to discuss these topics with you.

Karen Jagoda: Thank you. I understand that Kitov has recently changed direction from looking at pain and arthritis, and now that you are focusing on oncology, and I'm wondering why oncology? What was the cause for the change in direction?

Isaac Israel: Yeah, of course. Well, after the approval, when we approved our first drug, Consensi, which is actually a painkiller, with the FDA last year... During this very long development and submission process, we established a very, I believe, unique and high-end infrastructure in the company, including a professional team that also has a strong background and track record bringing oncology drugs all the way to the market.

Isaac Israel: When we had to think about our long-term strategy, we realized that maybe the best usage and value-creating of this infrastructure would probably be in the oncology field.

Isaac Israel: In addition, there are so many unmet medical needs in the field, which makes it such a global effort that we feel we might contribute to and bring hope to many cancer patients. I'm personally familiar with those kind of patients and feel a real passion every morning to get up and to do something about it.

Karen Jagoda: Okay. And so what is the current challenge for most cancer therapies today?

Isaac Israel: Yeah, that's a good question because even in the... nowadays, in the era of revolutionary modern cancer therapies, still the incidence of relapse following treatments is still very high, especially due to drug resistance, also due to low targets, selectivity or just the inability to effectively address metastatic disease.

Isaac Israel: Today is the most promising cancer treatments today include modern immunotherapy. Still, single agents immune oncology therapies are not effective for all or for most cancer patients.
Isaac Israel: As an example, by 2018 only 48% of the U.S. cancer patients was or still are eligible for checkpoint inhibitor treatments and it was the same year, 2018 only about 12% of the patients responded to a single agent checkpoint inhibitor drugs across all tumor types.

Isaac Israel: Speaking about combination therapies, so combination therapy is targeting multiple components of the tumor development, has the potential to substantially enhance the efficacy, enhance the response rate and also the durability of the cancer treatments. Doing that by enhancing multiple anti-tumor responses.

Isaac Israel: Speaking also about combination therapy, we need to understand that this includes also checkpoint inhibitors such as anti-PD1, that has shown to be very effective actually in up to almost 70% of patients for some cancers.

Isaac Israel: The bottom line is, in my opinion, is that the major challenge in the field today is to identify the best new combinations and not only the best new combinations but also the best doses for, and to get an effective and long lasting, therapies.

Karen Jagoda: And we've talked a little bit on the show about this move towards a combination therapies and part of the challenge it seems is that a lot of these drugs are developed within silos and there's not a large community interested in sharing some of this intellectual property, too early on. Are you seeing this as really the direction that the pharmaceutical industry is going? That there's going to have to be more openness and sharing and collaboration to come up with these kinds of innovative combinations?

Isaac Israel: Yeah, I think that the answer is definitely yes. And I think that it's not only about being opened, but for example, in our case, both drugs that we are combining our drugs with are drugs that are already in the market and being already in the market, commercial drugs, so you actually ran combination trials without having the prior approval or consent from the owner of the drug.

Isaac Israel: For example, in CM-24, this is one of our two combination drugs, we are going or planning to combine CM-24 with Opdivo and this is something that we are doing together with Bristol Myers Squibb in a collaboration.

Isaac Israel: For example, I can tell you from firsthand that Bristol Myers is a great example of a big pharmaceutical company that is looking to many, many different combinations to enhance the efficacy of their current drug.
Karen Jagoda: And so it extends the life of their research because it doesn't require additional research on their part, I assume it's more research on your part?

Isaac Israel: This is true, this is true. And we know for a fact that companies like Merck and BMS have sometimes hundreds of different collaborations, some of them are cosponsored with the other companies, some of them are fully sponsored by the big Pharmas and some of them are sponsored by the biotech. But definitely there are hundreds of trials running out there, trying to find the next big combination to get a very good and very... better efficacy in the oncology field.

Karen Jagoda: Okay. This is really like playing multi-dimensional chess, just so many different variables there.

Karen Jagoda: Can you tell us a little bit more about the two oncology drugs that you're currently developing and a little bit more about how they work?

Isaac Israel: Sure. Kitov nowadays is advancing its drug candidates targeting novel resistant pathways. All of them known to modulate tumor survival, metastasis and also drug resistance.

Isaac Israel: I would start describing NT-219, this is a first in class small molecule, which is a dual inhibitor of STAT3 and IRS1/2. Both IRS1/2 and STAT3 are common pathways, what's it called? Parallel pathways involved in cancer drug resistance.

Isaac Israel: It's so important to emphasize that research has shown that blocking both pathways at the same time is necessary to prevent drug resistance by tumors, not good enough to block only one of them. In an experimental model of head and neck cancer that we have conducted, we found a very interesting finding that adding NT-219 to the approved drug Erbitux or cetuximab resulted in a strong efficacy in preventing resistance and also increased survival.

Isaac Israel: The second drug that we developed is CM-24. This is the only clinical stage therapeutic blocking of CEACAM1. As general note, CEACAM1 is a novel immune checkpoint which is expressed in both tumor and immune cells. The immune checkpoints are generally a new target being used for cancer treatment.

Isaac Israel: Cancer researchers all over the world are focusing on immune checkpoints as potential ways to stimulate a person's own immune system in order to respond to and fight off unwanted tumor cells. Maybe the most well- known immune checkpoint is a PD-1 or PDL-1, being the target for blockbuster cancer therapies as I mentioned before, like Keytruda by Merck and Opdivo, by BMS.
Developing Combination Therapies to Attack Cancer
With Isaac Israel Kitov Pharmaceuticals
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Isaac Israel: Now since binding between CEACAM1 in immune cells and other proteins in the tumor microenvironment, it allows the tumor cells to evade, to escape the immune attack and therefore we think this has an enormous potential.

Isaac Israel: We actually believe that we have potentially found the next PD-1, PDL-1 target in CEACAM1. To conclude, our pre-clinical studies have shown a very strong evidence that CM-24 enhances the immune activity at the tumor site through multiple pathways and in the phase one testing that was performed CM-24 was found to be safe and generally well tolerated when it was administrated as a single agent after dose of 10 mg in patients with a variety of tumor cells, tumor types.

Karen Jagoda: I'm listening to you explain what your work is all about and I'm wondering if what you're also learning about is the sort of underlying causes of drug resistance? Are you on the frontier of a larger challenge here?

Isaac Israel: Well, this is a great question and I think that there are many... There are known to be... There are many parallel drug resistance and evasion pathways. There are many of them.

Isaac Israel: The tumor is using these pathways to evade treatment and what you need to do is actually to attack them, as I described before, at the same time to effectively prevent or overcome resistance.

Isaac Israel: Basically you have the main therapy with the main pathway. Initially, it works and after a while the tumor in the biology is sophisticated enough to evade the main target and the main pathway of the drug. Almost any drug can be chemotherapy, targeted therapy or immunotherapy.

Isaac Israel: By blocking these resistance mechanisms, resistance pathways, we actually manage in a way to re-sensitize the tumor to the main drug. Giving or administrating the main drug, the primary drug, let's call it this way, with NT-219 or with CM-24, actually enhances the potential of the main drug to access it's efficacy.

Karen Jagoda: Okay. This seems like it's an ongoing struggle to stay one step ahead of the cancer. And so that sounds extremely strategic in the way that you're approaching this challenge.

Karen Jagoda: I'm just wondering, can you say a little bit about your own career path that that's led you to this position at Kitov? I'm suspecting it's quite an interesting path so can you just take a minute and tell us?
Isaac Israel: Of course, yeah. Well, I actually started my career doing software engineering and algorithm development. I found myself in just the beginning of 2000 founding my own company and that... For the communication and software company, it grew very fast.

Isaac Israel: Unfortunately, by 2008 I had to spend a few months in a hospital to treat myself for a disease that I had at the time. And it was a great opportunity for me to look around and see the physicians and the doctors that are around me and I said to myself, "Oh, this is much more interesting than what I do."

Isaac Israel: I took a personal decision to focus on, to move, to switch to the biotech industry. And I spent some time, I sold my previous company and I started to discover to learn this new world and eventually I found myself in a VC looking for investments, healthcare investments.

Isaac Israel: And eventually when I had the opportunity to actually jump through the water and manage a company by myself, I took it with two hands.

Karen Jagoda: And how old the company is Kitov?

Isaac Israel: Yeah. Kitov was actually founded at 2010. We started and I joined the company in 2013, and at 2013 we actually listed the company initially to Tel Aviv Stock Exchange and we ramped up the development efforts. Then we completed a Nasdaq IPO in 2015. Rode the first drug, Consensi, all the way to approval and to commercialization all around the world with a network of commercialization partners.

Isaac Israel: Then, as I described before, switching into the oncology, very exciting oncology field, and doing what you heard so far.


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