“Identifying Personalized Treatment Recommendations for Gastro-Intestinal Cancers“ (Laura Towart and Nahuel Villegas, PhD) [#131]

Brad Power
February 12, 2025

“We have our own variant-calling software, which identifies the genetic alterations that are driving that patient's unique cancer. We can select up to twenty genetic alterations. We engineer them in fruit flies. We use fruit flies as an avatar. We do this for many reasons, but one of the most important is that the flies are so malleable, and we’re able to engineer a significant number of alterations to make these truly complex tumors in an animal. Then we expand the fly population to hundreds of thousands of animals, and we use this, what we call an ‘avatar army’, for screening thousands of drugs and drug combinations. So, at the outset, we’ve screened everything that's ever been approved by the FDA alone, and then in combinations, and then we see combinations that will rescue the fly, and then we make a human treatment recommendation. Now we've generated this large dataset, and we incorporate machine learning algorithms and the dataset to be able to have rapid, personalized recommendations without the need for the modeling in the animal.” – Laura Towart

Meeting Summary

Cancer is extremely complex. It is driven by multiple genetic mutations. Current treatments often target only a single mutation, which can lead to resistance as cancer evolves. Personalized medicine is improving treatment effectiveness with tools like genomic profiling, but we still have a long way to go to fully tailor treatments to the genetic complexity of each patient. This is one of the reasons you see high failure rates and resistance to the "standard of care" therapies, and why it is essential to assess your tumor and identify your unique, complex tumor network. Each tumor signature may respond to a different therapy.

Laura Towart and Nahuel Villegas are uniquely qualified to lead a discussion about how you can more fully personalize your cancer treatment. Laura Towart is the founder and CEO of Vivan Therapeutics, a company with a ground breaking personalized approach to cancer and rare disease developed at Mt Sinai Medical Center. Laura became passionate about personalized medicine during her PhD studies at Weill Cornell Graduate School for Medical Sciences/Memorial Sloan Kettering Cancer Center. Since then she has been actively involved in translational advances in medicine. In 2008 she co-founded Celmatix, and helped build a next-generation women’s health company leveraging big-data and genomics. Laura has a strong personal link to colon cancer as it sadly claimed her mother and grandmother and affected other family members and friends. She is committed to the identification of new therapies that are tailored to each patient and advocates for patients and their access to these therapies.

Dr. Nahuel Villegas is the Chief Scientific Officer of Vivan Therapeutics. He has a background in genetics, stem cells, and cancer biology. He obtained his PhD in biological sciences from the University of La Plata (Argentina). Afterwards, he trained in embryonic stem cells and developmental biology at the MRC Centre for Regenerative Medicine (University of Edinburgh, UK), and in cancer research at the Institute for Neuroscience (CSIC-University Miguel Hernandez, Spain). Dr. Villegas has broad expertise modeling human tumorigenic processes in

the fruit fly Drosophila melanogaster to study druggable conserved oncogenic targets. His work bridges basic and translational science, combining cancer genetic analysis with in vivo high-throughput drug discovery strategies aimed at finding novel pharmacological anticancer cocktails for personalized therapy.

The mission of Vivan Therapeutics is to offer patients personalized cancer treatment options. They coordinate sequencing of your tumor biopsy and blood sample and their variant calling software identifies your unique constellation. They then use their TuMatch software, which leverages their proprietary data set and AI/machine learning, to enable rapid, personalized cancer treatment guidance. They assist you with treatment direction from identifying the most effective standard of care options, identifying potential clinical trial options, and providing novel options when standard of care is no longer effective.

Why might you want to pursue innovative tests, such as animal models, to personalize your cancer treatment?

- Identify unique drug combinations tailored to your specific tumor genetic profile
- Find potential treatments beyond standard care, including non-cancer drugs that might be effective
- Screen thousands of drug combinations to find the most promising therapies
- Reduce toxic side effects by finding more targeted, precise treatment approaches

How can you use data from animals and AI models to identify drugs for your unique cancer?

- A testing service based on an animal model of your cancer can replicate your tumor and test the effectiveness of different drugs in vivo. There are different animal models, we use fruit flies to model the patient tumor, which offer several advantages over mice, zebrafish and other animal models, creating a personalized, living representation (“twin”, “avatar”) of your disease. This “avatar” can allow systematic drug screening across thousands of drug combinations, especially novel drug combinations, including non-cancer drugs that might be effective.
- Since the platform collects and analyzes data from millions of animals and thousands of drugs and drug combinations, AI&ML techniques can be implemented to generate accurate predictions leading to more efficient personalized treatment recommendations.

What are the key challenges in accessing and integrating animal model services into your cancer care?

- **Time**: It takes six months to build an animal model. Many patients approach us when they have already run out of therapeutic alternatives and it is already too late to identify a personalized treatment on time, due to the time-consuming process of building and screening avatars.

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- **Cost**: It costs $20,000+ to generate the fully tailored therapies, even though much cheaper than other strategies, still could be a barrier for some patients.
- **Regulatory**: Conservative medical review boards make it difficult to approve personalized treatments from novel tests.
- **Clinical trial limitations**: Traditional clinical trial designs struggle with personalized, one-of-a-kind treatments, making it hard to validate efficacy.

Who should consider this approach of animal models and AI?

- You have GI cancer: colorectal, pancreatic, etc.
- You have a brain tumor
- You have a rare cancer with no standard treatment options.
- Standard of care, traditional treatments have been ineffective.
- You have been recently diagnosed, allowing time for modeling and screening.
- You are cancer free, but the rate of recurrence of your tumor type is high.
- Your cancer is not extremely aggressive, allowing time for modeling and screening.
- You are searching for novel drug combinations, including non-cancer drugs that might be effective.

How can you learn more about animal models and AI for personalizing your treatment?

- Attend patient-focused webinars and conferences discussing personalized cancer treatments using animal models and AI
- Explore the Vivan website, review their published case studies, particularly those from Mount Sinai Medical Center
- Contact Laura Towart (laura@vivantx.com) or Nahuel Villegas (nahuel@vivantx.com) to schedule a consultation and discuss the process for accessing Vivan Therapeutics' services
- See other discussions we have had on animal models (organoids) and personalizing your cancer treatments:
    - "Organoids Guide Treatment Decisions" (Payel Chatterjee, SEngine) [#13]
    - "Using Functional Profiling to Predict Drug Response" (Dr. Robert Nagourney) [#30]
    - “Identifying the Most Effective Treatment on the Tumor Rather than Trying It Out on the Patient” (Dr. Chris Apfel) [#84]
    - “Finding Personalized Cancer Treatments Beyond the Standard through a Unique Test” (Travera) [#77]

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Meeting Notes

KEYWORDS

Precision medicine, cancer treatment, personalized therapy, fruit flies, machine learning, tumor sequencing, genetic alterations, drug screening, oncology, patient care, clinical trials, AI models, genetic profiling, novel combinations, patient outcomes.

SPEAKERS

Laura Towart (48%), Nahuel Villegas (28%), Brad Power (14%), Bill Paseman (5%), Video (3%), Tony Magliocco (1%), Yara Alrokh (1%), Hilary Elkin (1%)

CHAT CONTRIBUTORS

Hilary Elkin, Allen Morris, David Plunkett, Yara Alrokh, Zakaria, Bill Paseman

SUMMARY

Brad Power introduced Laura Towart and Nahuel Villegas from Vivan Therapeutics, who discussed their precision medicine methodology for cancer treatment. Vivan Therapeutics uses machine learning and a large proprietary dataset of tumor signatures to identify personalized cancer treatments. They create fruit fly avatars to screen drug combinations, testing thousands of therapies. A case study highlighted a patient with colorectal cancer who responded well to a novel combination of trametinib and a bisphosphonate, extending life very significantly, with stable disease for 11 months. The service costs $25,000 for personalized drug screening and $5,859 for treatment recommendations. They have modeled 45 patients, mostly with colorectal and pancreatic cancers.
As a case report, a patient with nine genetic alterations responded well to a novel combination of a MEK inhibitor and a bisphosphonate. Target and nontarget lesions displayed a strong response and remained stable for 11 months.

OUTLINE

Introductions

- Laura Towart introduced herself as the founder and CEO of Vivan Therapeutics, which uses technology developed at Mount Sinai Medical Center.
- Their technology was licensed in partnership with Mount Sinai in 2019 and has been expanded upon for personalized medicine, particularly in cancer.
- Nahuel Villegas is an expert in cancer genomics, and he has developed models used for high-throughput screening.

Development of a Unique Data Set and Predictive Model

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- A video introduction was played, explaining the software's ability to provide personalized cancer treatment recommendations using machine learning and a large proprietary data set of tumor signatures.
- Nahuel Villegas explained the process of generating the unique data set, which involves working with patients and their oncologists to coordinate tumor and blood sequencing.
- The variant calling software identifies genetic alterations driving the patient's unique cancer, and up to 20 genetic alterations are engineered in fruit flies.
- Fruit flies are used as avatars to screen thousands of drugs and drug combinations, with the goal of identifying effective human treatment recommendations.
- The technology has been used at Mount Sinai, with published case studies showing remarkable success in patients with no remaining treatment options.

Case Studies and Personalized Treatment Recommendations

- A patient with nine genetic alterations responded well to a novel combination of a MEK inhibitor and a bisphosphonate. Target and nontarget lesions displayed a strong response and remained stable for 11 months.
- The TuMatch software provides oncologists and patients with a report containing treatment directions, potential clinical studies, and novel drug combinations.
- Identifying novel combinations of targeted agents and non-cancer drugs makes treatment more personalized, less toxic, and more effective.

Applications of this Approach

- Bill Paseman asked about the applicability of the technology to kidney cancer and the mechanism of failure when treatments do not work.
- Laura and Nahuel explained that the technology can be applied to solid tumors, including kidney cancer, but they have not yet modeled kidney cancer patients.

Challenges and Future Directions

- There are challenges of creating tumors in fruit flies and testing combinations that are not toxic to the flies.
- The process needs deep genomic sequencing.
- The cost of the personal discovery process is high.
- Many patients die before receiving treatment recommendations due to the time-consuming process of building and screening avatars.
- Laura mentions efforts to work with organizations like Cancer Commons to file decentralized IRB trials and provide concierge services to help patients access treatments.
- The discussion also covers the importance of validating predictions in larger data sets and the potential for collaboration with other companies in the space.

Final Remarks and Contact Information

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- Brad Power thanks Laura and Nahuel for their presentation and encourages participants to reach out if they are interested in learning more about the services offered by Vivan Therapeutics.
- Laura and Nahuel provide their contact information and express their willingness to spend time working through potential options for patients or their loved ones.

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TRANSCRIPT

[This transcript has been edited for clarity and flow. Repetitions and filler words have been removed, and technical terms have been clarified.]

Brad Power
This is the Cancer Patient Lab.

We’re honored to have with us Nahuel Villegas, who’s coming to us from Abu Dhabi, and Laura Towart from London. They’re with Vivan Therapeutics, and they’ll be describing the methodology they’ve developed for precision medicine.

Just a few housekeeping things before we get started. First of all, this is for information purposes only. This is not medical advice. We try to arm patients and caregivers with information they can take to their medical team.

We are a nonprofit patient-led organization, and so we welcome donations, which you can do through our website cancerpatientlab.org, where there's a Donate button.

Laura Towart 1:14
Thank you everyone for joining, and for your interest in learning more about what we do at Vivan Therapeutics.

I'm going to start off with a brief introduction of myself and the company. I'm Laura Towart. I'm the founder and CEO of Vivan Therapeutics. We've been working with technology originally developed at Mount Sinai Medical Center in New York. We licensed this technology in

partnership with Mount Sinai in 2019. Since then, we've been building and expanding upon this technology and its applications across personalized medicine – particularly cancer.

Villegas Nahuel is an expert in cancer genomics (*def: one of several omic branches of biological study, concentrates on the structure, function, and inheritance of an organism’s genome or its entire set of genetic material*). We are working with specific models used to model patients' cancers and for high throughput screening.

I'll play a short video introduction about the technology:

Video 2:24
Introducing TuMatch software: rapid, personalized cancer treatment recommendations. Tumors are complex, composed of unique genetic signatures or constellations. Each constellation may respond to a different therapy, and Vivan TuMatch software utilizes machine learning coupled with a large proprietary data set of tumor signatures matched with the treatment response to identify the most effective therapy for each. Vivan Therapeutics offers the most personalized cancer treatment direction service possible, using a genomics-based drug screening technology developed at and in partnership with Mount Sinai Medical Center. The process begins when an oncologist refers a patient and provides a biopsy and blood sample for sequencing. Vivan’s TuMatch software scans the tumor sequence and identifies the genetic variants that characterize the tumor. Utilizing artificial intelligence, machine learning, and data gathered from thousands of tumor profiles, we identify a personalized treatment recommendation based on your unique cancer profile. Unlike any other provider, we may identify novel combinations of targeted agents and also non-cancer drugs that make treatment highly personalized, less toxic and more effective. All therapeutic recommendations and dosing information will be provided in one TuMatch report shared with the patient and oncologist for review.

Laura Towart 3:53
I'd like to back up and share how we generated the unique data set we have, that we've been developing for some time.

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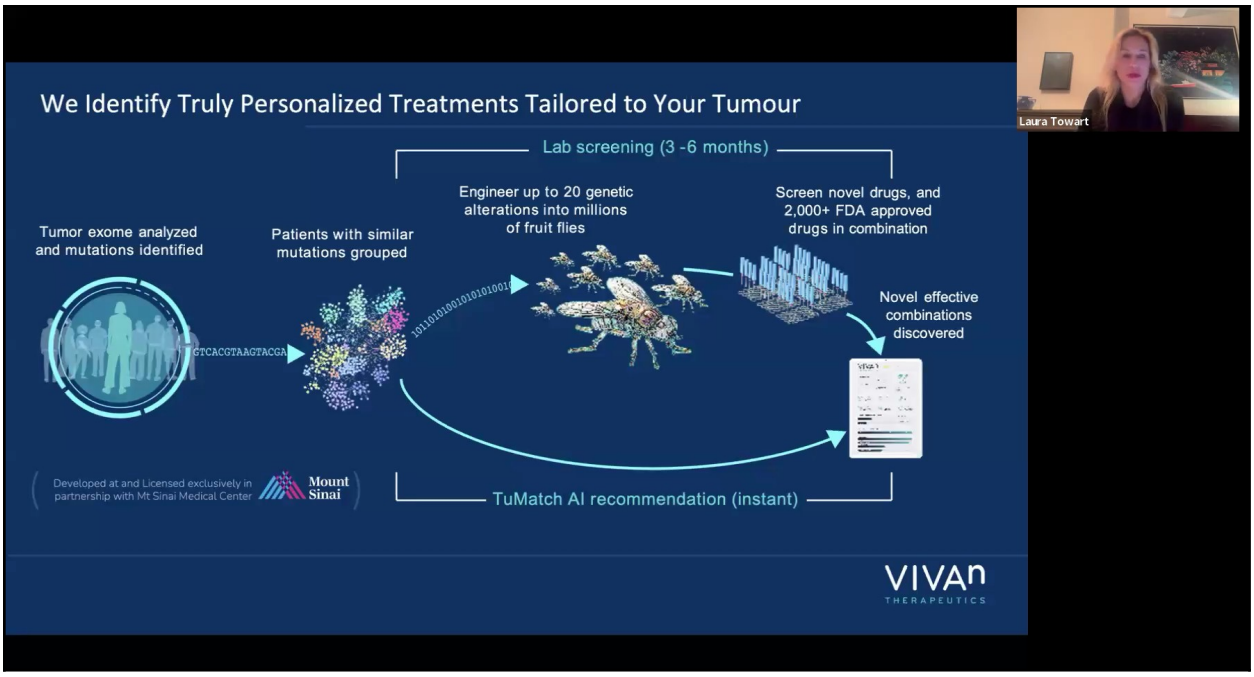

We work with patients and their oncologists. Patients usually have their tumor biopsy. If they haven't already had a biopsy sample, we coordinate the sequencing of the tumor and also of the patient's blood. Then, we have our own variant-calling software, which identifies the genetic alterations driving that patient's unique cancer. We can select up to twenty genetic alterations.

We engineer them in fruit flies and use them as an avatar. We do this for many reasons, but one of the most important is that the flies are so malleable, we’re able to engineer a significant number of alterations to make these truly complex tumors in an animal. Then we expand the fly population to hundreds of thousands of animals. We use an “avatar army”, for screening thousands of drugs and drug combinations. At the outset, we’ve screened everything that's ever been approved by the FDA alone, and in combinations. Then we see combinations that will rescue the fly, and make a human treatment recommendation.

We've generated this large data set, and we incorporate machine learning algorithms to have rapid, personalized recommendations without the need for the modeling in the animal. TuMatch also incorporates other omics (*def: any of area of biological study defined by the investigation of the entire complement of a specific type of biomolecule or the totality of a molecular process within an organism*) data sets, including human outcomes.

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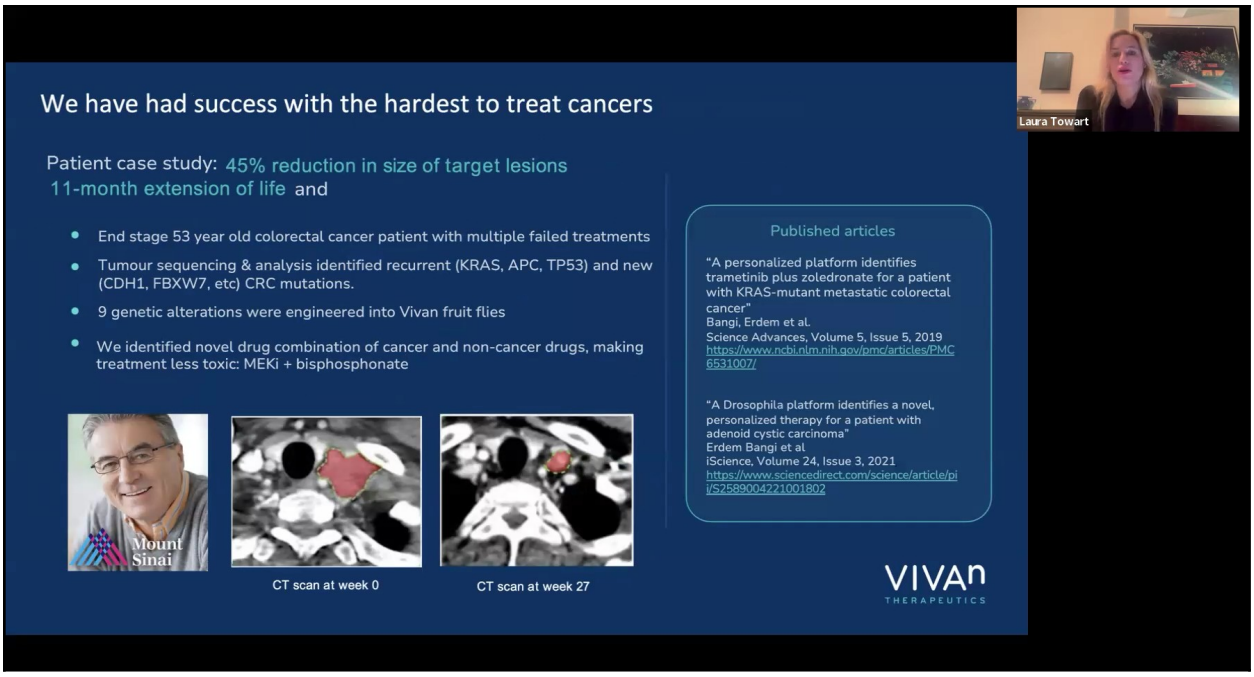

When the technology was used at Mount Sinai, they had a few published case studies of patients that had remarkable success using these novel drug combinations. As an example, one patient who had failed all of the standard of care options and had no remaining treatment options available, was enrolled in this study and had nine genetic alterations identified using the variant software. We were able to identify a novel combination. It was a MEK inhibitor and a bisphosphonate, a non-cancer drug, and this was the only combination that worked for the patient. He ended up having a 45% reduction in his target lesions and an eleven-month extension of life, which was considered remarkable given the stage of cancer the patient was at. All of these stories are published.

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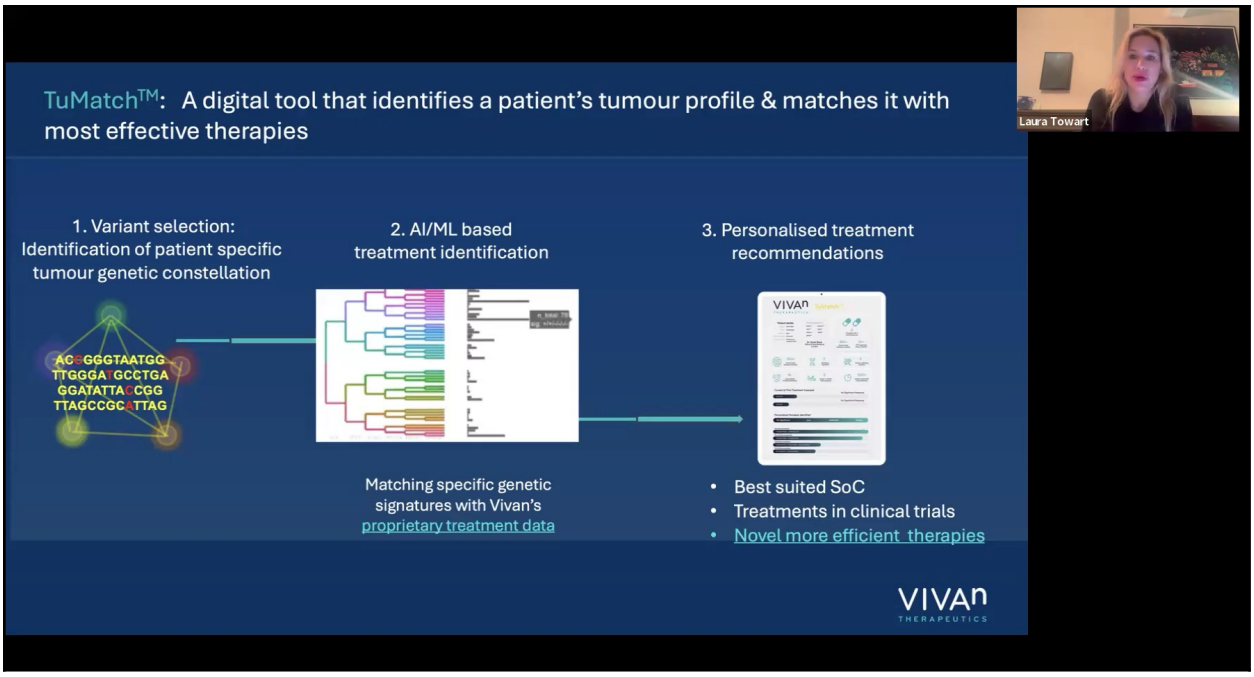

Through the TuMatch software, what we provide to the oncologist and the patient is really a report that contains treatment direction among the standard of care therapies. It also could potentially identify clinical studies that the patient would seemingly have success with. Lastly, we have these novel, more efficient and personalized drug combinations. Usually, they include non-cancer drugs, meaning oncologists would have to wait until the patient has failed other options before progressing to that line. But, as the world evolves towards personalized medicine, we're hoping patients will be able to access some of the combinations earlier.

Brad Power 8:17
This is from Bill Paseman: Does this work for kidney cancer? I think your headline, Laura and Nahuel, was something about gastrointestinal cancer, so you didn't really speak to that. But can you speak to the focus you have and why? What about kidney cancer?

Bill Paseman 8:39
One of the issues with kidney cancers, it's quite heterogeneous (*def: consisting of dissimilar or diverse ingredients or constituents*). Depending on exactly the way you shove the needle in, you wind up getting potentially different DNA out from just a single metastasis (*def: the spread of a disease-producing agency (such as cancer cells) from the initial or primary site of disease to another part of the body*). The second thing is this method isn't always 100% effective; when it does fail, how? What is the mechanism of failure?

Nahuel Villegas 9:00
We can do several solid tumours. We specialise in gastrointestinal cancer, because it’s a really good model to create tumours in the gastrointestinal tract of the fruit fly. But we can also create tumours in other tissues, as well as the epithelium in the fruit fly. We can create tumours similar to the kidney, but we haven’t taken any patients up until today.

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Bill Paseman 9:40
Especially in kidney cancer, if you have single therapies, the side effects are pretty awful. If you have combo therapies, they get even worse. If you're creating a drug cocktail for this stuff, how do you go in and handle the side effect issues?

Laura Towart 9:55
Most of the combinations we would identify wouldn’t be multiple cancer drugs. Let's say we could identify a therapy that's working for me or approved for melanoma, but we find it works in kidney cancer, but with an asthma medicine. The cocktails are quite unique and not a heavy burden. In terms of toxicity, all of these therapies we’ve tested in the fruit fly. In the same test tube, we put flies without cancer and flies that do. At the end, we want to see that flies without cancer haven't been negatively affected in their survival by the treatment.

Brad Power 10:44
Are you able to manage dosing? In your test, do you tend to test different levels of dosing?

Nahuel Villegas 10:51
Yes, I can get to that. But to complete what Laura was saying, in the assay, we tested drugs and the combination of drugs in flies with the tumors and in normal flies as well. From time to time, you find a combination that kills the tumor but is also toxic for the fly. We would not recommend that and we discard those therapies. We only recommend those not affecting the fruit fly at all (which is much more sensitive than humans). And for the dosing, we cannot extrapolate exactly the same dose, because they are different animals, but we can extrapolate the ratio of the doses. Once we identify a combination, we get one drug at the fixed dose. Then you change the other ones up and down to see what is the optimal ratio between drug A and drug B. This is what we recommend to the oncologist.

Brad Power 12:05
There are a couple of questions from Allen Morris about accessing your services, your fees, and also about how many patients you have studied so far.

Laura Towart 12:18
We have a few different services. We have what we call “the personal discovery process”. This is the process where we create the patient’s personalized fruit fly avatar, and do personalized drug screening. This service costs $25,000, including the sequencing of the tumor and the sequencing of blood. The sequencing of the tumor we do at a very deep depth, and how we can sort out the heterogeneity of the tumor, but if a patient has already had sequencing, we look to see if it's comprehensive enough to not warrant further sequencing. If the patient already has suitable sequencing, then we don't charge for that. That charge is built in at $2,500, so then we would subtract it. This also includes as many consultations as needed with the team and with our medical advisory board.

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For the TuMatch service, we were charging $15,000 for but we're now reducing the price, and it's $5,859 – that doesn't include sequencing. If sequencing is needed, that would be approximately another $2,500. We won't know if a patient is eligible for TuMatch until we see their tumor signature.

Brad Power 13:43
And then the question about patients you have studied so far, both in your full fruit fly service and in your AI service, which I gather is newer.

Nahuel Villegas 13:54
Yeah, we have created a model for approximately 45 patients. The vast majority are colorectal and pancreatic cancer patients, most of them with KRAS (*def: A gene that makes a protein that is involved in cell signaling pathways that control cell growth, cell maturation, and cell death.*) mutations. We have a lot of therapies for these types of patients, which are more urgent-need, but our models are not only based on patients but from databases. We have studied around 7,000 different tumors – colorectal tumors – to get the most frequent profiles that exist today. We have created several avatars as well for patients we actually haven’t seen yet, but we know these patients exist. When these patients eventually come to us, we have all the therapies ready to go.

Hilary Elkin 15:03
On slide number three, personalized treatment recommendations, do you have a larger view you can share? Where are the recommended therapeutics (*def: combined discipline of medical oncology, which may be defined as the non-surgical, non-radiotherapeutic management of patients with solid tumours and clinical pharmacology, based on classic cytotoxic chemotherapy and the new signal transduction inhibitors*)? Are these therapeutics available in the United States?

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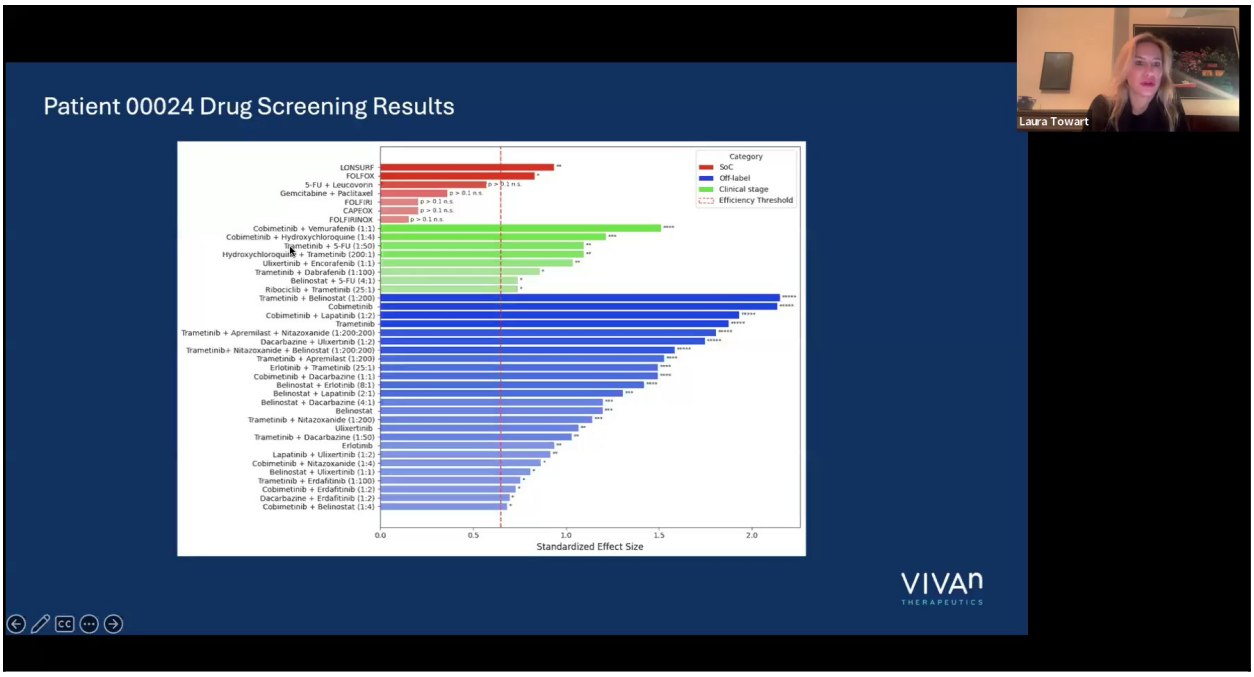

Laura Towart 15:22
Yes. This is just an example of the screening data we would share to the patient and the oncologist. First, it would have the standard of care therapies at the top, potential clinical trial therapies, and these would be the types of off-label. The ratio is the ratio of the dosing.

All of these drugs are available in the United States, but the combinations might be harder to obtain. This is something we've been working with when we went in discussion with Cancer Commons; I know they're looking to do some kind of decentralized IRB (Institutional Review Board) trial or protocol so patients can access these therapies. But we've had experience working with some of these therapies at Mount Sinai Medical Center, and we know of a number of centers in the United States where oncologists are comfortable with off-label therapies. It's something that would have to go through the review with the oncologist and the tumor board.

We also provide kind of at the end of the report, and I can share with anyone who's interested, but it's like a publication for a patient. It would also go into a breakdown of any place where similar or same combinations have been used in a patient case study around the world, or where there's further evidence for the use of this type of combination and in that patient's signature.

Nahuel Villegas 17:04
It also depends on the stage of a patient. The oncologist might want to use either standard of care or a new therapy. As you can see, the red ones here, the standard of care therapies, are less efficient. The best therapies we identify usually are novel combinations, but sometimes the oncologist doesn't have the flexibility to use these combinations as first line or second line. They can use these therapies more in advanced cases. But for the first line, they can choose between different standard of cares or investigational combos.

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Laura Towart 17:46
Nahuel, do you want to touch a bit more on the resistance mechanisms and how some of the novel combinations can evade these mechanisms?

Nahuel Villegas 17:57
Does your solution deal with resistance? Yes, because when we create the tumor, these tumors are already resistant because we consider all the complexity of the tumor. Resistance usually comes when you have a new genetic alteration in the tumor. You started with one tumor that gets treated, and some of the cells get resistance because they have different genetic alterations – probably acquired later on. When we create the tumors, these alterations are already there, so the therapies we identify are also attacking this resistance. Of course, the resistance can come later on with reoccurrence, etc.. What we do in those cases is to reanalyze the tumor, get the new sequencing of a tumor, and get new treatments for the resistant clones.

Laura Towart 18:56
As an aside, one of the patients in the Mount Sinai clinical study started off with one of the top ranked therapies. The patient had a marked response, a sustained response, and then when the patient started to become resistant to that therapy, they just went back to the original report and tried another therapy on the list that they could see was attacking the tumor from a different perspective. It is really useful that we identify a large number of combinations.

Nahuel Villegas 19:35
This one about false positives, how do we deal with that? That is a really good question, because false positives happen all the time when you use animal models, and this is if you consider the most classical experiments with mice or rats that you treat just a few numbers of animals. If you use the same treatment on five mice or five humans or five fruit flies, and each one of these animals are going to give you a slightly different answer, because we all respond differently. And many times you get a false positive, you see a response that actually is not real for the drug. You cannot deal with that rat or mice or whatever other model, but with fruit flies the advantage is that every treatment is being tested in 100 in 1000 of different animals, so the statistical outputs are really reliable. What we do is first to do what we call a primary screen in which we test every treatment in eight different replicas, each replica containing 40 different animals - we get the hits in there. This drug is a positive, we collect all the positives and then we re-screen them in a secondary validation screening using, in this case, 12 replicas with 40 animals in each of thess replicas. You really validate what is positive and you exclude what is negative. In this case, a false positive.

Bill Paseman 21:26
This seems like a really incredible piece of work. I want to congratulate you both on that. Laura, one of the things you mentioned was there's a test you go through to determine suitability. Did you go on and tell me a little bit more about that test?

Laura Towart 21:45

For most patients, it’s so we can model if they have solid tumors, but the suitability is more for TuMatch or not. TuMatch is really available, mainly for patients with gastrointestinal cancer, not all patients. We've built TuMatch based on the patients that have the most frequently seen genetic signatures, then patients that have used our service. We wouldn't know if we have a match until we see the patient's tumor sequence. If you have any type of genetic profiling on the tumor already, we can take a look and tell if it looks like we'll have a TuMatch.

Nahuel Villegas 22:35
Maybe that is linked with a new question: “What percentage of patients are colorectal and GI?” Most of our patients are colorectal and GI, including colorectal, esophageal, gastric and some pancreatic as well. For those types of patients, we can use TuMatch. For patients who do not have GI cancers, we might need to create a new model.

Bill Paseman 23:14
I guess I am confused. If it's genetic based, what difference does it make what kind of a cancer it is? What am I missing?

Nahuel Villegas 23:22
No, you're right. This is a big discussion because if a lung cancer patient has the same mutations like a KRAS and some of the typical ones, the question is: is this patient going to respond to the same therapies as the colorectal cancer patient with the same signature? The answer is probably yes, but we still don't know definitively.

Laura Towart 23:49
We have a lung cancer patient. We're in the process of building the avatar for them and we're modeling the lung and the lung cancer in the gut of the fly.

Bill Paseman 24:03
I remember Bucha G in a New York Times article talked about the fact that you can have two different genes that have similar genetic anomalies in two different people. It results in two different kinds of cancer, potentially, or no cancer at all. Looking at the combinations, doing the match, seems to me to make sense. It's a pretty complicated mess. As a result, I can see why you guys do this, but I wanted to hear from you as to exactly the reason. Thank you.

Brad Power 24:35
I understand you had your proprietary experience with the fruit flies and helping those patients. What was it like to then take that unique, proprietary data set and then build predictive models using AI? Is that a process where you needed to get a bioinformatician? Is that as easy as a consumer using ChatGPT? Can you speak a little bit to the skills required and the work required to migrate from your proprietary data set to more something more generalized, using AI and machine learning.

Nahuel Villegas 25:13

Yeah, we need a team not in the wet lab, but in the dry side of the things of bioinformaticians and data scientists, which is a continuously evolving field. We have too much in this big database already. We feed it too much, but at the same time, we are constantly generating more data that we use to feed it too much. With new data, you are able to make better predictions. So it's constantly evolving, but yes, it's not so heavy in the company. Now we have two sides, the proper lab – the wet lab – where we do all the experiments, and then the people using the computers to make predictions.

Brad Power 26:03
How do you measure statistical significance? How do you know you have enough proprietary data to train the model to give you statistically valid results?

Nahuel Villegas 26:20
The statistics coming from the experiments in the fruit flies are very robust. The statistics for the AI models, these are open questions, because you don't know how much is too much. How little is too little? We are dealing with millions of data points here. 10 million is better than 1 million, but 1 million is already enough to make the predictions. The more data we collect, the better our predictions.

Laura Towart 26:53
‘Too much data’ is also continually evolving in terms of the way we're modeling and as well as the data set is growing, but too much. Version one really didn't involve much machine learning. It was just a software tool for when a new patient came to say, “Okay, what is the tumor signature, what are the alterations we feel are really driving that patient's cancer? How did we model a similar patient before, or potentially the same patient? Was it just matching to the therapy?

TuMatch version two is able to make predictions beyond our proprietary data set and into other omics data sets. Then there's a kind of a simpler layer. You can go into making further predictions. The next step would be being able to make inferences on immunotherapy in combination with the proprietary drug combinations or small molecule therapies. We're still evolving too much, but we have excellent data science and bioinformatics teams. We're innovating the methods we're using to do this type of modeling and prediction.

Brad Power 28:13
There's a question from Allen Morris: “What percent of your patients are colorectal and GI and in general?”

Nahuel Villegas 28:23
Most of them, 80% of the patients.

Laura Towart 28:32
We've had some prostate, lung, uterine, we've had some head and neck. That's it. And pancreatic, colorectal, gastric.

“Identifying Personalized Treatment Recommendations for Gastro-Intestinal Cancers“ (Laura Towart and Nahuel Villegas, PhD) [#131]

Bill Paseman 28:48
How well did those work?

Laura Towart 28:51
Unfortunately, we haven't had the chance to treat a number of patients with therapy. A lot of the initial patients were what we call pioneer patients. They were patients that came to us when they were at a very late stage. Then, it was taking about six months to build and screen their avatars. By the time we got them the recommendation, a lot of the patients, unfortunately, had passed away.

We have a few patients now that have had the therapies. We sold a number of patients through leading medical centers in the UK, but some patients were blocked from getting the therapies by something called the Genome Board in the UK, even though the tumor board and the oncologist recommended the treatment. We have one of those patients now that we're helping to get the therapy through one of our partner centers and in Switzerland. We're hoping that we'll have a positive outcome with that patient, but it's been really limiting in the outcomes data that we've been able to generate. We're really trying to find new avenues to help the patients get access to the therapies.

Bill Paseman 29:58
What was the genome board's rationale for a rejection?

Laura Towart 30:02
The UK is a very conservative environment. One of the ways around it is to file a clinical trial protocol at one of the medical centers here, and then have it be very specific to say a patient has failed all other options. These are a list of potential combinations that can be used if a patient has this specific tumor signature. Once that's on file, the Genome Board might be able to refer to that protocol to be able to provide treatment. They're giving us very iffy information. They're hesitant to say exactly what will be needed: “if you have this, it would be more likely to be available.”

Bill Paseman 30:51
That seems to be the general problem for acceptance for personalized medicine anyway, which is, you can't go do a clinical trial if there's just one person that you've gone over and created this thing for. That's how do you handle that issue?

Laura Towart 31:08
We're now providing more of a concierge service for the patients. This is something we didn't set out to do, but because we're really committed to the patients being able to get access and we know patients at Mount Sinai are able to get access. The oncologists there have been very open, and because they had a clinical trial protocol filed with clinical trial.gov, this was for a fly to bedside clinical trial. It was already allowed that whatever combination identified in the fly, the oncologist would be able to treat the patient with. They had the hardest hurdle because they

were the first to be able to do that. They had two successful patients and they had enough data to do extensive case studies that were published. Now it would seem it's easier because we can refer to those successes. We're working with a number of oncologists that are able to provide those recommendations, and we're also looking to expand and work with groups like Cancer Commons and with Brad to be able to put on file some of these decentralized IRB submissions.

Bill Paseman 32:24
The personalization protocol is part of the clinical trial. That's how you're getting around it.

Nahuel Villegas 32:28
When you have a therapy that is very personalized to a patient, how do you compare that? You cannot treat the patient with two different therapies at the same time, standard of care and the new one, and if the second patient received a different therapy.

How do you make comparisons? There are two main ways we are working out. One of them is comparing the patient against themselves with the previous therapy, so this is not for first line treatment. The patient has been through several lines of therapy, usually, and we can compare our personalized therapy against the previous therapy that the patient went through. This is one of the ways to test to do an end of one clinical trial, the patient is their own control.

The other way is you split the patients into arms. In one arm, the patients take the personalized therapies. In the other arm, patients take the physician's choice, and you make a statistical comparison on the response.

Laura Towart 33:50
One of the things they're looking to do now is to make some predictions on standard of care therapies. For example, within the NHS (National Health Service) in the UK, and we've recently been admitted to an Innovate UK supported program for AI and Health. We're looking to see, using our algorithms, “Okay, if a patient had a specific tumor signature, what is the therapy we would recommend?” Then look at retrospective data in either genomics England or others like cBioportal, Memorial Sloan Kettering Cancer Center’s data set, to see if we can validate the predictions made.

It's still proven difficult because we're recommending these novel combinations, and it's not likely any of the patients have had those. We look to see, “okay, even in standard of care, have patients with certain tumor signatures been successful in a therapy which we also have said they would be unsuccessful with?” But the number of patients are limited, so we're still looking at geting access to larger data sets.

Brad Power 35:04
It seems like TuMatch would deliver results in a matter of hours or days. That would be really useful, relative to waiting three to six months for the fruit fly avatars, since people need to make decisions often quite urgently. Is there a way for you to assess confidence in your

recommendations? Is there a way like you had that table of different recommendations? Do you have confidence levels you can associate with those recommendations?

Nahuel Villegas 35:44
We provide the ranking where we say, “these therapies are much more efficient than these are in the avatar model.” That provides confidence. Then the response in humans needs to be tested.

Laura Towart 36:06
For example, we've gotten a lot of funding, particularly from the European Innovation Council for colon cancer, to take three of our novel drug combinations and validate them in patient derived organoids (*def: small, simplified, 3D copies of organs created outside of a living body*). This is done independently at the Vall d’Hebron Center in Spain.

We've just validated one of the novel combinations in organoids. Once we validate the others, the idea would be we'd have 60 patients, 20 get given one of each of these therapies, and then we would have some more outcomes data to publish on too much.

Brad Power 36:49
Zacharia asks, “Can you speak to drug metabolism variations in fruit flies versus humans? Surely, is there a significant difference?”

Nahuel Villegas 37:00
They're different, but not massively different. The fruit fly had a CYP system to metabolize the drug, similar to most animals, including humans. So even though it's not the same, the response, the expected metal you metabolize the drug is very similar, of course, it's not 100% perfect. And when all this starting being, when, when people are starting thinking about fruit flies to test drugs. One of the very first experiment was actually to drag the flies. And it was 15 years or 20 years ago you drag the fruit flies exactly the same, the same drugs that we human use. And it was demonstrated that several times that the drugs that the fruit flies responds to the exactly same chemotherapy drugs that's as we do so. It is a very strong empirical demonstration that the drugs do the same work if it flies and humans.

Yara Alorkh 38:23
If you envision too much being used on skin and on breast cancers, because mostly you're now using them for gastrointestinal, colorectal and Kidney and more, like internal organs. So what about breast and skin

Nahuel Villegas 38:45
so for breast, yes, definitely, yes. We envision TuMatch providing recommendation for breast as well. There are already some fly models of breast cancer. For skin cancer, to be honest, is probably on the bottom of the list is one of the last tumors that we we are going to start modeling, because that is much more difficult for us, because the the skin system is very

different in the in the fruit fly than in the in the humans. So we we prefer to start with other tumor types. Thank you,

Brad Power 39:24
Laura, just another question on access. Then can you just sort of go through the steps, if someone were interested in your services, what the steps are? You know, you have a website. You have some onboarding there. How do you How does someone access?

Laura Towart 39:38
Yes, sure. So. So you will, anyone can contact either laura@vivantx.com or Noel or patient care at or go to our website, vivantx.com. You can book a consultation immediately through calendar with Nahuel, and we can have an initial consultation. We usually like to see if the patient has had any tumor profiling before, just to share it with us before the consultation, so that we can already have some information as to what we envision the process would be for that particular patient. So it could be that, in some cases, one thing we didn't mention that it's not always a day or six months. Sometimes it could be where the process could only be a few months. And in these cases, we've already built the fly, but we just haven't done the drug screening. So you can imagine that the drug screening is one of the rate limiting steps, because it's it's so involved, because we're screening such a large number of animals and drugs and multiple rounds. And so a lot of times, we have the most frequently observed genetic signatures already engineered into the flies and just ready for expanding that population and doing the screening. So the first step would be sharing any profiling information. If you haven't had any profiling before, we're happy to coordinate it for you. Also happy to work with whatever type of sequencing or profiling might be covered by your insurance? So we're quite flexible about the input data.

Laura Towart 41:17
I can take you through an example of one of our patient cases. Yeah, sure. I shared the Mount Sinai case. This is one of our cases. So this patient had colorectal cancer and had sequencing that we coordinated. This patient had seven genetic alterations that we modeled, including K, Ras, G, 12, D and others. We in this case, we tested 1897 therapies and about 700,000 animals, and we've identified one known treatment and 13 novel treatment, and each treatment was tested in approximately 400 animals. And so this is an example of the screening. So some of these therapies are blinded because we haven't patented them. But the top ranked combination is tremetinib, which is a MEK inhibitor, and this is a kind of anti parasitic so this was the top ranked then trematinum also was here alone. These are most of the standard of care therapies. So here, a lot of them were not really significant, and it's not surprising, because the patient had a care SG 12 D mutation and and many others that were modeled and and so then we start to work backwards. What is the combination, and how is it? How is it working? And so we start doing some path, pathway modeling. I'll say this. I don't think this slide works very well. Sorry. So anyway, this novel, do you want to I don't have the other slide here with it.

Nahuel Villegas 42:55
Now. Is this? Okay? Very simple. So trametinib, it's not a surprise to be here because it's targeting part of the pathway. So this is a K RAS mutant patient, and trametinib is targeting one

step on the cascade using make inhibitor, but Ramet you can see down down there is efficient, but not as efficient as when you put it with empty set, what need of success in that that was a surprise, because in non cancer, drug that by its own is not doing anything, but together with Trametinib, increase the deficiency. Increasing deficiency here, it means increasing the survival of the of the animal, which is the readout that that, that we use. And then what is probably missing here is that then we found in the literature, a lot of works showing that knee toxic, even though people doesn't really know why or how, is having an effect in against colorectal cancer with KRAS mutations. And

Laura Towart 43:59
this is the, this is the combination that we went to do the further studies on in the patient derived organoids that were able to validate that data. And then actually we looked in, we tested that combination in a number of k rash driven avatars, and it also had the same effect where it was the top ranked combination. This

Nahuel Villegas 44:19
is one combination that looks very interesting for us, because, as Laura mentioned, is not working only for this molecular profile, but across different K grass molecular profile, usually when we do a screening, there are some combinations that works only in that molecular profile this unique for that. But as in this case, sometimes you find combinations that works in different molecular profile, and these are, of course, much more interesting because it means that you can use the same therapy in different patients.

Laura Towart 44:55
I see there's a question, how did the patient do? Oh, is this? The, oh, okay, patient treated which went into so we haven't treated any patients with a combination yet. So this is the, this is one of the combinations that will be used in the study at the valdebron. But it was also very effective in the patient-derived organoid.

Brad Power 45:19
I have a question about who this is best for. I'm particularly intrigued by something we also see in functional testing, where you can have serendipitous discoveries, as you said, maybe of a an asthma drug or a diabetes drug that's completely outside of any of the standard therapies that doctors would even consider and so that would be useful, in my mind, for diagnoses where there's no good treatment options, like maybe glioblastoma, or rare cancers where there's no easy answer, there's no stand, no, no, maybe no standard. So can you speak to which cancers and which profiles of which patients would this be most suited for?

Nahuel Villegas 46:10
This is specific therapies more suited for GI patients because they share the provisions sharing KRAS mutant profiles. This, this, this therapist, but for other types of patients, we have to build a model and do the screenings. And if I may, it is not by chance that we find the best treatment. So it's not a serendipitous way here, because it's not just that we find that by luck. We test

everything that has been approved by the FDA, and we test the same drug 100% of time until we find what is working and what is and what is not.

Bill Paseman 46:53
If projecting here a little bit, it seems like you basically have a very good knowledge of GI stuff, because you understand all the pathways involving in that particular disease. And as a result, if you wanted to have other diseases, you'd have to do equivalent study to figure out the pathways in those as well. Is that sort of what's happening here?

Laura Towart 47:14
We have a lot of expertise in different pathways. I think it's just that we wanted to be able to offer the TuMatch product across one cancer type has been the main objective, because we want to make sure that we have one tool for one cancer type that covers the majority of the population. So we've been very focused, but I'll just, I'll just share it. So we have modeled a patient that had a rare salivary gland tumor, and we were able to treat that patient, and the patient had a measured response, but we weren't able to collect enough data around that patient to publish. And the patient came to us very late in the game, so unfortunately, he had a response, but it wasn't sustained very long, and then it was too late to start to try something else, but the model is very suited for rare cancers, but rare cancers that are not extremely aggressive, so that we have time to do the modeling and the screening, we also use the same platform to model some rare diseases. And we recently modeled a rare metabolic disease on behalf of a group of children and their families and foundations, and we were able to identify a number of effective therapies.

We are really passionate about the rare space as well. It's just it does take some time to especially if we're generating a model that we haven't, you know, generated before, in a particular tissue type. And we are, we are also working in therapeutics discovery and development. So while for patients today, we want to offer novel combinations of approved drugs, we are actively developing new therapies, and we have an active collaboration with the Institute for Cancer Research in London, and it about in Spain, where we're developing new multi target therapeutics, which are for KRAS G, 12, D and EGFR, and we're working with Bart's Cancer Institute on the glioblastoma therapeutics discovery. And the platform has been used by Mount Sinai for many years, most significantly with AstraZeneca, where they use the platform to identify Vendetti, which is now the standard of care for metal a thyroid carcinoma. So we know that the platform is able to identify drugs that can go on to be FDA approved, and it's a really useful model for being able to identify these unique combinations.

Brad Power 49:41
I have another question on the modeling aside, so that you were calling the dry lab. The data side, you have, I guess, general purpose models like you can get whatever it is, llama from, from meta, and you can build on top. With that you haven't gotten spoken to that. But then also the modeling of the molecular pathways, as we've been talking about, which may be different by cancer type. And there are a number of companies working in that space. I gather you're developing your own, as opposed to collaborating with other people in that space. There's an

individual that we've had on our webinar series, Michael Castro, who's with personalized cancer medicine in the LA area, and he's got an AI based model for all cancers and all molecular pathways, it would seem like some collaboration like that would be useful to you. How are you thinking about collaboration with others developing similar models to yours?

Laura Towart 50:41
So actually, Michael Castro is on our Medical Advisory Board, and he's a close collaborator, but we're not collaborating with CellWorks. We're just working with Michael Castro. Now we are. We have explored a number of collaborations with different kinds of, I guess, other companies in the space. We've spoken with CureMatch. Today, I had a call with Tempus, and we've been discussing how we can access their unique data set for the validation of TuMatch, and possibly for the development of a later version of TuMatch, which would be based upon transcriptomic data. And so we're very interested in that we're generally interested in collaboration. We haven't yet forged an official partnership with anyone, but we are really interested in, of course, trying to identify the most effective therapies and to validate them in other models or data sets as well.

Brad Power 51:42
It sounds like a big opportunity for somebody to run a kind of an open source challenge. Pete. Kane, are you paying attention? Like this is something for you to take on. Pete does research to the people. But I could imagine an open source environment where all the models would be pooled, instead of being, you know, proprietary, and that might be good for evolving as some of these AI models are being open sourced,

Laura Towart 52:12
One of the things that our technology is unique in that we're able to identify these novel combinations, including non-cancer drugs, where a lot of the other models that we see are really only able to identify cancer therapies, traditional cancer therapy. So it does make it a bit difficult to collaborate when there's different treatment recommendations that makes

Tony Magliocco 52:40
Hi, Laura. It's Tony here. I heard you say that you're looking for data. I do have access to some data sources from clinical trials, messenger RNA, that have really good outcomes that'll be level 1A, 1b, type data and so on as well. So there are some opportunities there, with the cooperative groups and also some of the Canadian centers have centralized molecular data with a link to outcomes and so on. And many could be open to sort of academic type collaborations, where that data could be shared if it was going to lead to publications and things like that as well. So, you know, you can follow up with me on those things, if there's any interest on that, on provisioning that data.

Bill Paseman 53:40
This looks like great work, and I really appreciate you taking the time to go on and show it to us. There's a lot of people that are interested in this area that could go on and use your product, and I'm glad you guys have taken the time and the effort to put together something.

“Identifying Personalized Treatment Recommendations for Gastro-Intestinal Cancers“ (Laura Towart and Nahuel Villegas, PhD) [#131]

Laura Towart 53:57
Oh, thank you so much. I really appreciate it.

And if anyone is interested in chatting, just please send us an email. We're happy to spend the time and work through what might be possible for you or your loved one.

“Identifying Personalized Treatment Recommendations for Gastro-Intestinal Cancers“ (Laura Towart and Nahuel Villegas, PhD) [#131]

CHAT DISCUSSION

00:11:45 Hilary Elkin: Hilary Elkin - UCSF, endometrial IIIC1, mesonephric-like adenocarcinoma.
00:13:43 Allen Morris: How much is Vivan's consultative fee?
00:17:58 Allen Morris: How many patients in total have you studied so far?
00:19:18 Bill Paseman: Does this work for kidney cancer?
00:19:28 Bill Paseman: When it fails, what is the issue?
00:23:07 Roger Royse: Does your solution deal with resistance? Can it predict resistance and suggest changes ?
00:24:34 Zakaria: How do you account for false positives? Any major learnings thus far?
00:32:53 Allen Morris: What percent of your patients are colorectal and GI in general?
00:38:40 Zakaria: Can you speak to drug metabolism variations in fruit flies vs humans? Surely, there is a (significant?) difference.
00:43:30 Yara Alrokh: Do you envision TuMatch being used for breast and skin cancers?
00:51:16 David Plunkett: Seeing a slide with "Patient Case" title, but no other content.
00:55:57 Allen Morris: So, how did the Trametinib with NTZtreated patients do and against what control?