“The Potential of Personalized Cancer Vaccines, Starting with Brain Cancer” (Saskia Biskup, MD, PhD) [#141]

Brad Power and Rhea Burjanroppa
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“The larger steps will come from the multiomics approach. We frequently see that genes are not everything. You need the transcriptome, the proteome, the spatial information, metabolomic information, metabolites, and the microbiome.” – Saskia Biskup

“I would rather combine strategies than pretend that there's a magic bullet. We have one platform technology, which is the neoantigen platform, but it can be easily combined.” – Saskia Biskup

“My vision is that every person, even the healthy ones, are getting fully personalized, anti-cancer vaccines. The reason why I believe this is so relevant is because we need to have immune responses before we get sick. I built a prophylactic cancer vaccine for my husband, Dirk, and myself. I tested the peptides. I noticed that I already have T-cell responses. I see for many patients that they do not have a pre-existing T-cell response against their driver mutations, so that there must be a time where the immune system is failing, or maybe some patients do not build up these relevant immune responses. I believe that everyone should have access to a fully personalized anti-cancer vaccine during their lifetime.” – Saskia Biskup

Meeting Summary

Many cancers are aggressive and have few good treatment options, like pancreatic cancer and glioblastoma, which is an aggressive brain cancer. Getting a diagnosis of one of these cancers is devastating. They are often diagnosed very late, and are usually fatal. There are few good treatment options. Patients who are diagnosed with these cancers are confronted with difficult decisions that must be made urgently. Immunotherapies provide lots of promise. But for glioblastoma, brain treatments must pass the blood-brain barrier. Immunotherapies have been very successful in blood cancers, but less so in solid tumors. Personalized cancer vaccines have promise across many cancers, and much research is being done.

Saskia Biskup, MD, PhD, co-founder and managing director at the Center for Genomics and Transcriptomics (CeGaT GmbH) in Tuebingen, Germany, is uniquely qualified to lead a discussion on the potential of personalized cancer vaccines, especially in brain cancer. She received her medical degree and her PhD at the University of Wuerzburg, Germany. She started her professional training in human genetics at the Technical University in Munich, Germany. She co-founded CeGaT with her husband, Dirk, in 2009. CeGaT is a leader in genetics testing. Dirk and Saskia founded Cecava with the aim to launch a clinical trial for a personalized cancer vaccine for glioblastoma. Other clinical trials will follow. They are notable for connecting test results to your personalized care context.

Why do you need to know about personalized cancer vaccines?

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Compared to traditional treatments like surgery, chemotherapy, and targeted therapies, a personalized vaccine potentially offers several advantages:

- **Durable response**: The vaccine can potentially induce T-cell responses that last for years, unlike shorter-term effects from some other treatments.
- **Fewer side effects**: Unlike chemotherapy, which damages healthy cells, the vaccine aims to stimulate the immune system to target cancer cells.
- **Personalization**: Unlike standard treatments, the vaccine is tailored to the individual patient's specific tumor mutations.
- **New treatment options** (especially for patients who have exhausted standard treatment options)

How can a personalized cancer vaccine fight your cancer?

Your immune system fights cancer through your white blood cells (T cells) that can recognize and target the unique mutations (neoantigens) specific to your cancer cells. You can identify your unique mutations by comparing the DNA from your normal cells and cancer cells, then design a personalized vaccine that helps T cells recognize and attack your cancer cells more effectively. The goal is to train the immune system to specifically target cancer cells while minimizing damage to healthy cells. Your personalized vaccine can be combined with other drugs (“adjuvants”) to enhance the immune response. The goal is to help your T cells build a strong, long-lasting response against your unique mutations.

Are you a good candidate for a personalized cancer vaccine?

- If you have a cancer with limited treatment options
- If your tumor has identifiable unique mutations (high “tumor mutational burden”)
- If your immune system is capable of mounting a strong response (which can depend on your overall health and prior treatments, e.g., chemotherapy and radiation)
- If you can afford the treatment
- If it can be combined with other treatments like checkpoint inhibitors or targeted therapies
- If you can get a comprehensive genetic analysis

What do you need to do to access a personalized cancer vaccine?

- **Exhaust standard treatment options**
- **Provide recent high quality tumor tissue and a blood sample**: to identify unique mutations in your cancer cells through genome and transcriptome sequencing, mutation analysis, and review by an interdisciplinary tumor board).
- **Have time**: the complex analysis of multiple tests takes about 4-6 weeks, and the complex manufacturing process takes 3-4 months
- **Be able to pay**: the diagnosis costs $10,000 to $20,000 and the manufacturing, treatment, and monitoring costs up to $60,000.

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- **Be able to travel to the treatment center**

What are innovations that might expand access to personalized cancer vaccines?

- Run clinical trials to reduce costs, prove efficacy, and increase insurance coverage
- Get public funding and investor support
- Develop a phased approach to make the technology more scalable
- Create off-the-shelf peptide options for common cancer types
- Combine personalized vaccines with other treatment modalities, like checkpoint inhibitors or targeted therapies

How can you learn more?

- See the meeting summary or video recordings:
    - Personalized Cancer Vaccines (Willy Hoos) [#29]
    - "Cancer Vaccines” (Lisa Butterfield) [#50]
    - “Unlock the Potential of Your Immune System” (Simo Arredouani, PhD) [#135]
    - “A Unique Personalized Killer T-cell Treatment for Glioblastoma" (Wayne Carter, DVM, PhD) [#110]
    - “A Novel Immunotherapy Approach for 'Cold' Cancers” (Gary Onik, MD) [#86]
    - “Growing Your White Blood Cells to Treat Your Cancer” (Matthew Dons) [#79]
- Review the CeGaT website for diagnostics services and the Cecava website for the clinical trial.
- Contact Saskia Biskup at saskia.biskup@humangenetik-tuebingen.de

For the video, please see here.

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Meeting Notes

KEYWORDS

Personalized cancer vaccine, neoantigens, Glioblastoma, Tumor sequencing, Immune therapy, Clinical trial, Tumor mutational burden, Peptide vaccine, Immune response, Diagnostic pillar, Tumor board, Treatment cost, Multi-omics approach, Adjuvants, Patient accessibility.

SPEAKERS

Saskia Biskup (67%), Roger Royse (7%), Darren Rhea (7%), Chris Apfel (6%), Cindy Ness (5%), Elliot Davis (3%), Jason Binder (1%), Richard Anders (1%), Rick Bartram (1%), Karen Sachs (1%), Brad Power (<1%)

SUMMARY

Saskia Biskup, co-founder of CeGaT, discussed their personalized cancer vaccine for glioblastoma. The process involves genome sequencing of tumor tissue and normal tissue, isolating DNA and RNA, and identifying unique mutations (neoantigens). The vaccine, consisting of 20 peptides, costs $60,000 and includes 14 doses. Early detection and treatment is ideal, as is a multimodal (multiple therapies) approach. Success rates are challenging to quantify due to late-stage patient presentations. (This is often only available as a last ditch treatment.) The vaccine's efficacy is influenced by tumor mutational burden and the need for multiple tests (“multiomics”). Challenges include accessibility, affordability, and the need for clinical trials.

OUTLINE

Overview of Personalized Cancer Vaccines

- Saskia Biskup, MD, PhD, is co-founder and managing director of CeGaT, a leader in genetics testing.
- The diagnostic process ideally needs recent tumor tissue and blood sample collection and analysis for comparative sequencing.
- The process involves isolating DNA and RNA from tumor and blood samples, followed by whole exome and whole transcriptome sequencing.
- The analysis identifies unique mutations, driver mutations, and passenger mutations, and neoantigens.
- The manufacturing involves prioritizing the neoantigens and creating the unique combination of peptides (protein fragments).

Success Rate

- The success rate is hard to measure in exact numbers due to the unique clinical situations of patients.
- A publication in Nature Communications showing evidence of longer overall survival in patients with immune responses.
- More clinical trials are needed. Funding is difficult.
- Accessibility is limited.

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Comparison with mRNA Vaccines

- The difference between CeGaT's neoantigen peptide vaccine and mRNA vaccines is the direct presentation of peptides in the skin compared to the more complex process of mRNA vaccines.
- The immune response of peptide vaccines may be longer.
- It is difficult to compare different modalities.
- CureVac's mRNA glioblastoma vaccine must overcome the heterogeneity of GBM.

Accessibility and Affordability

- Jason Binder asked about the accessibility and affordability of CeGaT's treatment for glioblastoma patients in the US.
- The process, including sequencing, clinical data collection, and interdisciplinary tumor board recommendations, is complex and expensive.

Treatment Protocol and Patient Experience

- The typical protocol for patients includes three pillars of personalized medicine: diagnostic, interdisciplinary tumor board, and treatment.
- Immune system monitoring is important.

Multi-omics Approach and Future Directions

- A multiomics approach, including single-cell transcriptome sequencing with spatial resolution, is important.
- Using off-the-shelf peptides is challenging.

Adjuvants and Side Effects

- The adjuvants used in CeGaT's vaccine are GM-CSF and imiquimod to enhance the immune response.
- There is a potential for allergic reactions and monitoring the skin for side effects is important.

Collaboration and Data Sharing

- To move the field forward, there is a need for collaboration between different groups and countries in personalized medicine.

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TRANSCRIPT

Roger Royse
Welcome to this week's webinar of the Cancer Patient Lab.

This week we have Saskia Biskup. She's an MD, PhD, and co-founder and managing director of CeGaT in Germany. If any of you have ever thought about a personalized cancer vaccine, CeGaT is probably one of the first names that has ever come up, so she is uniquely qualified to lead this discussion about personalized cancer vaccines. She received a medical degree and PhD at the University of Wurzburg, Germany, and she did her training in human genetics at Technical University in Munich, and co-founded CeGaT with her husband in 2009. CeGaT is a leader in genetics testing, and they have recently launched a clinical trial for a personalized cancer vaccine for glioblastoma.

Saskia Biskup
I'm a geneticist, that's my background. I'm a medical doctor, but specialized in genetics.

When a patient approaches us, the first thing we do is to try to understand the clinical situation of each individual patient. For example, if a patient approaches us with glioblastoma, which is a very malignant brain cancer, we hear about the clinical history and then we ask when the surgery took place, or the biopsy, because for our diagnostic step, we need tumor tissue, and it's crucial to have the most recent tumor tissue. For some patients, a biopsy is a while ago. But especially when you design personalized treatments, you need to have very recent tissue. Then we get a blood sample from each patient, because what we are doing in the end is a comparative sequencing. We compare the normal genome of each patient with the tumor genome. Then, most importantly, we need the informed consent of a patient and coverage of costs.

From a technical perspective, we isolate the DNA from the leukocytes from the blood and from the tumor, and also we isolate the RNA from the tumor. Then we use a very comprehensive sequencing approach, which we call whole exome and whole transcriptome. “What are the unique mutations that we find in the tumor?” Because every human carries mutations. We are different in about 3 to 4 million positions in our genome. But what we need to understand is what is unique to the tumor. We need to understand what is driving the tumor to grow and the mutations. These are the ones that we are interested in.

We have two different groups of mutations. One group we classify as “driver mutations” – they are driving the growth of the tumor – and the other class we call “passenger mutations” – they are riding on the surface of tumor cells. They are presented through HLA. We try to find out the number of what we call “neoantigens”. The mutations that are unique to the tumor are presented through HLA, because these mutations can theoretically be recognized by T cells, and these are the cells that we are interested in when we are talking about the immune system and about personalized immunotherapy. Our approach of sequencing the tumor genome in comparison to blood, identifying the neoantigens, is what we do in a very first step, which usually takes about four weeks.

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How do we define the list of neoantigens that is unique for each individual patient? This is the recipe that we can use in order to manufacture a personalized vaccine.

How do we prioritize these neoantigens? If you think about the number of a mutation load in a tumor, you have large differences. For example, if you take a malignant melanoma or a lung cancer from a smoker, you have hundreds and thousands of mutations. If you, for example, take a brain cancer sample from a child, you have a very small number of mutations, and then you have a very large spectrum. The number that we use in order to define the tumor mutational burden is called “TMB”. This is the number of mutations per megabase, per 1 million positions in the tumor genome. Depending on this number, we have a larger or a smaller set of in the end, neoantigens. The neoantigen is defined as being unique as presented through HLA. We need to know the likelihood that this mutation is on the surface of the tumor and can therefore be used for a personalized immunotherapy strategy. Here, lots of algorithms are used. They are either published and developed in house. Then we have a large database of immune data. Once we do a personalized vaccine in a patient, we can after a certain time, usually about three months after the first vaccine, measure the T cell response that is specific towards a neoantigen. Here we also have a large database. Using databases, using different algorithms, we can come up with a list of neoantigens that we prioritize for each individual patient. Here we also filed several patents, because it's not only about the list of neoantigens, but it's also about the knowledge you need to have on the solubility of peptides, on the likelihood they all go in solution. They are stable in solution, they are then basically presented by antigen-presenting cells, and the likelihood you induce an immune response. This number, the likelihood of inducing an immune response for our approach, is nearly 90%.

Roger Royse 9:30
You've been doing this for a long time at CeGaT. Can you talk a little bit about what the success rate is? Do we have any data on how well this has worked outside of glioblastoma?

Saskia Biskup 9:45
That's an important question, and it's difficult to answer, because when a patient approaches us, it's always a unique situation. The majority of patients approaching us are late stage IV. They have been running out of standard options. They have been running out of guideline therapies, even off-label therapy. They are, by definition, in a “not so good” situation. It's hard to tell you an exact number, because there's a broad spectrum of different tumor entities. The majority of our patients have glioblastoma, and this is what we just published last August in Nature Communication. Yet there, we provide evidence for the finding that if a patient develops an immune response, that they have longer overall survival compared to patients without immune response, but there's nothing standardized. It's not a clinical trial. It's a real world observation which makes it so difficult. I'm not pretending that we are really having a causal effect here, but what we see is an observation, and this is now tested in the clinical trial that was mentioned in the introduction.

Roger Royse 11:03

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We've been reading a lot in the papers over the last year or so about the mRNA vaccine, which I think is similar. But how does your neoantigen peptide vaccine differ from that?

Saskia Biskup 11:18
If you think about the process of presentation: if you go from DNA to RNA and translation into protein and then presentation through HLA, you might notice that the peptide vaccine approach is more direct, because when you synthesize peptides, inject peptides in the skin, where you find antigen presenting cells that basically take up peptides and present to the immune system. This is much more direct compared to bringing in the coding information through an mRNA vaccine that needs to be translated within a cell, that needs to be processed in the cell, presented in this through the cell. This is much more complicated, so our process in general is more direct.

Then the question is about immunogenicity, and there's no data of comparison. Ideally, you would have the same patient who has the same tumor and the same mutation, and you immediately see this is not possible. We have to rely on what is published by other groups, and then we can especially see how the long-term effect compares from a peptide vaccine. It's known that you can induce a long-term immune response even for years, up to 10 years. An immune response could be measured. We have to see whether this is true for mRNA. We actually know from COVID that this doesn't look so great. So we will see.

Darren Rhea 12:55
I talked to CureVac, which I understand is your neighbor. You work directly next to CureVac, Myriam Mendila and Markus Bergmann were talking to me. It sounds like they have an mRNA GBM vaccine based on antigens that are common to pretty much all patients. They found like nine epitopes that are pretty typical of glioblastoma, and so would not be based upon sequencing anything. You would just have an off-the-shelf vaccine that works for all patients, because suppose, like Survivin (also known as BIRC5), as an example, occurs in quite a lot of cancers and quite a lot of glioblastoma.

I didn't know whether you use these kinds of antigens that are not neoantigens, but just tend to be found on glioblastoma in general, whether that's effective or not. Of course, they are also doing mRNA as the modality rather than peptides. But do you think that those are worth targeting?

Saskia Biskup 14:17
I can look at it from different angles, but I can at least tell you my personal view, and from my genetics perspective, GBM is a very heterogeneous disease, meaning that you have different tumor cell populations with different types of mutations. In the end, I'm convinced that you need a multi-modal approach. There's no magic bullet in GBM. This has been shown in the past.

The question is how to intelligently combine different treatment approaches. It makes a lot of sense to combine neoantigens with tumor-associated antigens, like Survivin, or other targets. The reason for that is that if you induce an immune response, and if you have specific results,

you might need some more recognizing additional targets, and you might need to combine even with checkpoint antibodies, viva situma (?), or even some inhibitors that are targeting specific pathways in these tumor cells.

To answer your question, I don't have a definitive answer. It's maybe not possible. Otherwise we would cure this disease. But in the future, we will have multi-omic diagnostic approaches to understand the disease better, and then we have a very intelligent combination of therapies at the right time point.

Jason Binder 16:07
I'm a caregiver, and my wife has had glioblastoma for about 39 months post diagnosis, and had a recurrence last September, when I was evaluating your treatment. One of the blockers was accessibility and affordability. Are there any plans to make it more accessible and affordable for those in the US?

Saskia Biskup 16:32
These are obstacles we have to overcome. A fully personalized approach is difficult to implement, especially when you want to bring this into a clinical trial. It took me a really long time to get funding. When you do a clinical trial, and we are doing this in the US, you need so much money to get approval that in the end, the therapy will be much more expensive compared to what we have right now.

The first thing is accessibility. Ideally, patients would get much, much earlier access to clinical trials. We need many more clinical trials, and then they need to be financed in a very efficient way, so that in the end, the vaccine is affordable. At the moment, it's very challenging.

For example, in Germany, we have a very strict process. We have to have a deadly disease with running out of options from the conventional side. With evidence of success, we have to go through the process of sequencing, of collecting all the clinical data, going through an interdisciplinary tumor board, making a treatment recommendation through the team, and then manufacturing a fully individualized vaccine and then applying it in a patient which is highly complicated and timely. I wish we could do this much faster and much cheaper, but at this point, this is as good as we can do it, but it's far from being good.

Roger Royse 18:20
Do you handle all of those steps at CeGaT, both the design of the vaccine testing for the antigens, the neoantigens, the administration, the treatment? Or do you have to farm that out to other labs?

Saskia Biskup 18:38
This personalized medicine stands on three pillars. The first pillar is the diagnostic pillar. The second one is the interdisciplinary board, and the third pillar is the therapy. CeGaT is a diagnostic company, so CeGaT is doing the tumor normal control sequencing from genome, transcriptome. CeGaT is doing the neoantigen prediction and is providing these reports. This

goes into the interdisciplinary board, and then we have a treatment center which is actually providing the treatment. According to German law, I'm the only responsible person, so I have to overlook all processes, and it's independent of any entity. So from the legal perspective, I'm responsible as a medical doctor. I have to supervise all these steps. So, yes, this is all happening here. But only the first part is actually associated with CeGaT.

Elliot Davis 19:55
I am a long time prostate cancer sufferer, which is now in remission, and I also do research on neoantigens. How would you define a neoantigen?

Saskia Biskup 20:17
A neoantigen, according to my definition, is a variant that is unique to the tumor, and was highlighted to present it on the surface of the tumor cell.

Elliot Davis 20:31
When you say “unique to the tumor”, and the literature is just chock full of those claims, do you mean overexpressed or really unique?

Saskia Biskup 20:44
Both. This is not exclusive. If you have a mutation that is important to the tumor, it's frequently also over-expressed. But we distinguish between tumor-specific mutations, tumor-associated antigens, for example, over-expression of genes by definition, is not new, for example, EGFR or HER-2, TROP-2, these are targets that are normal cells, but they are over-expressed in the tumor. If you have a particular mutation that's crucial to a tumor, this mutation can be overexpressed, and you see this in the transcriptome data,

Elliot Davis 21:24
Given the potential to harm normal cells or antigens that are overexpressed, do you have much experience? Have you ever really found any surface antigens that are really found only, either on a particular person's cancer cells or even as a general related to glioblastoma, something that's really unique, not something that's also expressed in the same way on normal cells?

Saskia Biskup 22:11
That's an interesting question, because you can have cells that have mutations that are not malignant, and we know that because when I do what I call immune monitoring, measure my T cell response, for example, in my blood, and I don't have cancer, I find T cells that recognize x3, a mutations, KRAS even, or other hot Spot, typically, cancer mutations, although I don't have cancer. Every human has cancer-specific neoantigens that come and go. Potentially, the immune system is able to eradicate these malignant cells, or potentially malignant cells. This is not something that's really unique to cancer, but these mutations, they should not be there. And if they are there, the immune system should be able to recognize them. Those are the ones I would call neoantigens. I'm pretty sure that they exist, because I can measure T-cell responses specifically recognizing hotspot cancer mutations.

Elliot Davis 23:28
How do you get rid of it? I assume that the body is not recognizing it because of the checkpoint effect? Is that the case, or is there some other reason?

Saskia Biskup 23:40
This is a spectrum. There could be an initial time where the body is indeed recognizing the mutations, but later on, the tumor, when it's growing, is building mechanisms to protect itself, and then you get upregulation of checkpoints, for example. There could be different stages. It's not black and white. It's a spectrum, in my view.

Roger Royse 24:13
Do you use checkpoint inhibitors along with the vaccine? Typically or not often?

Saskia Biskup 24:23
It's not me personally. We call it a molecular and immunological tumor board, which consists of all different kinds of people, oncologists, radiologists, surgeons, pathologists, geneticists, immunologists, if they think that when it comes to determining the right combination for each individual patient, a combination of a vaccine with a checkpoint, any body makes sense, and also all side effects considered in comparison to other options, then yes. This is indeed suggestive and a thumbnail.

Cindy Ness 25:10
The work that you're doing is important. I ask this question in trying to piggyback on a couple of things that have been raised. The cost of this personalized vaccine, very understandably, has to be high for all the reasons that you pointed out. It's very unfortunate, and it's very hard for a patient who is looking for an answer, and has really tried everything to think that, “Hey, there's something here which might be able to help me, if I only had you know that X amount of dollars.” It's a tough situation. What I'm wondering is, you had said that people come to you stage four cancer, so it's really hard to treat them when they're presenting at that point. So the success rate doesn't necessarily reflect what perhaps the personalized vaccine might do for someone at stage two or stage three, but it's stage four. It's going to be much harder. That makes sense. It goes without saying.

What stage of development is this vaccine? In other words, is it reasonable at this point for someone who's stage 4 to think if they could come up with all the money that's required? How helpful? How advanced is it? What are you seeing? I don't know if you can give percentages. But do we know enough to really operationalize this? Someone has at least a 50% chance, 30% chance that at stage 4, or perhaps at stage 3 or stage 2, whatever, that this vaccine will be something that gives them more than just about six months or eight months? What is the stage of development? Is this ready for patients? I ask that because I work with patients, and that's something that they'd want to know and something that I would want to know before I would say, “Saskia has a holy grail.”

Saskia Biskup 28:01

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I don't have to do this, don't get me wrong, because I'm already working day and night.

My vision is that every person, even the healthy ones, are getting fully personalized, anti-cancer vaccines. The reason why I believe this is so relevant is because we need to have immune responses before we get sick. I built a prophylactic cancer vaccine for my husband, Dirk, and myself. I tested the peptides. I noticed that I already have T-cell responses. I see for many patients that they do not have a pre-existing T-cell response against their driver mutations, so that there must be a time where the immune system is failing, or maybe some patients do not build up these relevant immune responses. I believe that everyone should have access to a fully personalized anti-cancer vaccine during their lifetime.

This is what drives me, but this is impossible to implement.

To come to your point, if you have a late stage disease, you have usually gone through heavy chemo and your immune system is down. You get surgery, you get radiation, so it makes it challenging to build an immune response. Still, in these patients, we see that we can make a difference. We published on a patient with pancreatic cancer. We published on a patient with ovarian cancer. We published on a patient with prostate cancer. We published on glioblastoma patients, on breast cancer patients. We have a lot of evidence that it is possible to induce a T-cell response in each patient, even heavily pretreated patients. Is this sufficient to help this patient in a particular situation? I don't know. I personally believe the earlier you do this, the better it is. It's impossible to have a clinical trial funded, because then for me, for example, to prove that my prophylactic vaccine is helping me not to get cancer, we might know, hopefully in maybe 20 or 30 years. So no, no one is going to finance that. This is the spectrum.

Now we come back to your patient in an individual situation, not being able to potentially afford treatment. The peptide vaccine is expensive, but inhibitors are sometimes 345 times more expensive monthly. They are approved, but insurance has to cover it, and these are really high costs. What we have to think about is not only what is most efficient to kill the tumor, but what is actually accessible. Because some treatments, even when they are off-label, are not accessible to patients, and then they need to be affordable in the combination.

In the beginning, I said we need to combine a vaccine, potentially with an inhibitor, potentially with a checkpoint antibody, potentially with an angiogenic treatment. This, if you add this up, plus the diagnostics, it's not affordable at all. I cannot answer your question. We need to go towards early detection of cancer, towards early treatment with immunotherapies. We have to get away from chemo, from therapies that are more destructive. The peptide vaccine has lots of advantages, but also lots of disadvantages. It takes time to manufacture a vaccine. It takes time to induce an immune response. You can never compare it to an antibody that you take out from the freezer and fridge and apply immediately. You have, on the other hand, the CAR-T cell therapies that have an immediate effect that doesn't really last that long. You have to combine the treatment that works efficiently immediately. You have to combine as a treatment that potentially gives you a long-term perspective. You need to have a treatment with no side effects. And this is a big advantage of a peptide vaccine.

Cindy Ness 32:22
In the success cases that you've published on, was there anything that became apparent in terms of a pattern of what might have worked in these various types of cancers?

Saskia Biskup 32:40
I wish I knew. I don't have a pattern. The only principle that comes over and over again is that it's a numbers game. If you start out with millions of tumor cells, you will always run behind. Then you can maybe control the disease for a certain time, but you will never get control. If I assume that one T cell can potentially kill four or five cancer cells, you can calculate how many T cells you need to detect or recognize cancer mutations in order to get rid of a tumor that is a size of millions of tumor cells. The number is crucial, and the timing of when you come in with the approach.

Rick Bartram 33:30
Could you walk us through a typical protocol for a patient, newly diagnosed and then recurrent, understanding that each patient is unique and that might vary, but for those of us who are a little bit less familiar with the therapy, I think that would be helpful to understand how it works and plays out.

Saskia Biskup 33:58
I mentioned the three pillars, the diagnostic pillar, the tumor board, and then the treatment. In the diagnostic pillar, we not only do the genome, transcriptome sequencing, we also do a lot of protein analysis. We do multiplex immunofluorescence. We look at imaging. We look at the clinical data, the lab parameters. We bring in all this data into the molecular tumor board, which is very interdisciplinary, and then the tumor board makes a recommendation. And when, for example, a peptide vaccine is recommended by the board, then the patient comes back to us, asking for a cost offer, and then we issue a cost offer, and then patients can discuss this with their insurances, or they say they did, or they have private funding, or did a GoFundMe project, or found money to afford this treatment, we can actually start manufacturing.

Manufacturing takes about three to four months, and then we have a fully personalized vaccine that, on average, consists of 20 peptides that are all different and formulated into the vaccine. Then, once the treatment starts, the patient has to travel to us to achieve. In Germany, they come and see the team. They get four vaccines in one week. We call it an induction, and then they get monthly booster shots every four to six weeks. After three months, we measure the immune response, and repeat the immune monitoring every three months. Then we have interdisciplinary meetings where we look at the immune response, and then we make a suggestion on how frequently we would do a booster. We have 14 doses in total. On average after 10 vaccine shots, we get a plateau, so we come to a point where the immune response can't get much better, and then from there on, we recommend doing immune monitoring on a regular basis, or ideally having booster shots every six months, or sometimes even only once per year.

Chris Apfel 36:34
Your spouse sent me your publication. That's really very impressive with the outcomes that you had in terms of glioblastoma patients.

On one hand, you do the DNA sequencing and then the RNA sequencing as well. You also mentioned that you're doing proteomics. In general, the transcriptomics is closer to the biology that is effective, than the DNA genomics. Do you then need the DNA genomic testing, if you already have RNA or proteomic analysis?

Saskia Biskup 37:44
We need a multiomics approach. We go very much in the direction of single cell transcriptome sequencing with spatial resolution. We really want to understand where the tumor cells are located, how they are and in which microenvironment they are embedded. We are not only looking at the transcriptome of tumor cells, but also look at the transcriptome of neighboring cells, and so the transcriptome profile helps us to classify cells, and then we get a spatial resolution, and then we can see the strategy of tumor cells on the way to escape from treatment. The transcriptome gives us a lot of information. The bulk transcriptome sequencing is something that we use for the neoantigen prediction, but this in the single cell transcriptome analysis with the subsequent spatial resolution will give us much more insight in the future. We are already doing this. This is horribly expensive, because you sequence the transcriptome of 1000s of cells individually, and you need a lot of algorithms and bioinformaticians and experts to get some biological sense out of this data. But this is giving us a great promise for the future, and we understand much more how tumors are organized, how they protect themselves against the immune attack and against treatment. More omics, even metabolomics, microbiome sequencing. So we are extending our omics platforms, and when it comes to transcriptome, we go from bulk to single cell transcript on the spatial resolution.

Chris Apfel 39:38
How do we get from there to know what the sequence of the new antigens are, and then how difficult is it to synthesize them, on a moment's notice for the individual patients? I would also assume that there are some new antigens for certain tumor types that are more common than others.

My question would be, could we shelve them and therefore have a more cost effective approach to apply vaccinations?

Saskia Biskup 40:10
Absolutely, and a very good point. This is nothing we do. We are only specialized on the fully individual neoantigens, but other groups have off-the-shelf peptides that they can use to determine the neoantigens. You can bridge time by shelf peptides. Like I said in the beginning, I would rather combine strategies than pretending that there's a magic bullet. We have one platform technology, which is the neoantigen platform, but it can be easily combined. It's just a question of money, and who is going to do this, the legal framework, and the design of clinical trials in order to show efficacy of a multimodal approach.

Chris Apfel 40:56
I had a conversation yesterday with a melanoma patient. The Sage Onco test showed that the tumor is basically multidrug resistance against chemotherapies, which is not surprising for melanoma, but also against the BRAF and MEK inhibitors as well. And so there is nothing in the targeted chemotherapy and targeted therapy that could work. We were very pleased to see that there are some off-label drugs, in this case, disulfiram, that had anti-proliferative effects, very strong anti-proliferative effects. I was excited to see that we at least found something that gives space and hope. But there's the next step. Will it be the normal PDL-1 inhibition for this patient? But I'm actually wondering if this patient would be interested in your neoantigen vaccine approach. How would this work? And the question is also, what would be the approximate cost for this patient?

Saskia Biskup 42:10
The first step when the patient is approaching us is just to generate the data, including the sequencing data for genome and transcriptome and to look at the neoantigen list. This is what CeGaT does. This takes about four to six weeks, and depending on what we include in terms of tumor boards and looking at imaging, and this is in the range of 10 to 20,000 euro in order to get to the point that we can access a tumor board that would be in a position to bring a personalized vaccine into a clinical context for this particular patient. Then when the tumor board recommends that neoantigen vaccine from our platform would make sense for this patient, then the cost is maximum an additional 60,000 Euros in order to manufacture 20 personalized peptides to have 14 applications in our center here in Tuebingen, and that also includes every subsequent tumor board, immune monitoring, multiplex immunofluorescence and other diagnostic tests that need to be done during the navigation of the patient through the vaccine journey.

Karen Sachs 43:50
I was intrigued that you said it was a numbers game. Could you comment? I would naively expect the relevant T cell to expand quickly. Out of curiosity, and also given that there is a numbers game, could you expand the T cells ex vivo?

Saskia Biskup 44:15
I wish we could calculate this a bit better. It has a lot to do with accessibility of T cells to cancer cells and the microenvironment, because we know also when T cells expand and they get a very unfriendly environment that contains a lot of lactate, for example, and a type of macrophages that we call them, they very fast exhaust. This is not only a number, but it's also about activity and exhaustion, and to see whether these T cells are, in the end, efficient. And yes, there are approaches to expand T cells. If you have the platform, you can, once a patient has developed a peripheral T cell response, you can do a leukapheresis. You can get the T cells. You can expand them by stimulating them ex vivo with an individual peptide, or even a peptide pool, and then you can activate them ex vivo, and then we infuse them. Technically, this is possible. I have been with a patient who has undergone such a procedure. It's nothing that I

would say is doable in an easy way, but technically, it's possible, and it's an interesting approach.

Roger Royse 45:48
I assume you're using an adjuvant with the vaccine. Is that right?

Saskia Biskup 45:57
Of course. Yes. Peptides per se are not very immunogenic, so we are using GM-CSF. It's called “Glucan” in the US. It's FDA approved, and we use imiquimod topically. So glucan subcutaneously, and imiquimod topically, and this is also described in our publications.

Roger Royse 46:19
Do you get strong side effects from that or not so much?

Saskia Biskup 46:24
Not at all. We sometimes have allergic reactions, and they can occur over time, and we have to closely monitor them. The skin is actually showing us very nicely how we can go from no reaction towards more redness and itchiness, more reaction towards the vaccine over time. Sometimes, when we do a vaccine on the right side, we see the bumps coming up on the left side. The skin is actually a very good organ to observe the work of the immune system.

Roger Royse 46:59
I ask because I did a neoantigen peptide vaccine, and I would get flu symptoms. Most days they were super mild. One day it was just really, it really knocked me out.

Darren Rhea 47:17
We've been working on access issues in America, and Vanessa Hugo and Jason Binder also. In here, there's a file, and you can file with the FDA a single patient IND. I've met a variety of neurosurgeons. They're willing to fill out this paperwork. It's essentially a single patient clinical trial for one, and the Jaime Leandro Foundation and others have worked on that paperwork. Willy Hoos in particular, on getting that paperwork to be easier to fill out.

Why not have some American file a single patient IND with their neuro-oncologist and with the FDA, and then essentially mail it back and forth? You could imagine a world where there's only so many advanced processing centers to do the target selection and then print out the peptides and stuff like that. Maybe we should be doing this by mailing back and forth?

Saskia Biskup 48:28
It's a legal problem that's not happening in the US, but in Germany, we have a specific framework, which is called an individual healing attempt that allows a medical doctor to do a treatment that's not approved, but you are not allowed to send it out. So the IND filing, the individual filing in the US, isn't helping me. Then you need to find a partner in the US, like the Jaime Leandro Foundation, but I cannot be a partner. What I'm trying to do is to run a clinical trial. We are very close to starting phase one for GBM. Very soon, we will have our publication

out on IDH mutated brain cancer. I want to start a clinical trial for those tumors, I'm seeing children with stage three mutated diffuse gliomas. We have BRAF-mutated brain cancers. We would like to do a phase one for pancreas, for colorectal and so on, so we can run through all the tumor entities once we have sufficient funding. We would do this in the US, but all patients have like you describe it in the US.

Jason Binder 50:00
What can I or the brain cancer community in the US be doing to help you, besides getting funds? I'm going to head to the Hill next week. I'm connected to a lot of folks in the US who are trying to destroy GBM like you. If you have a promising thing like this, what could I have in the back of my mind that could be helping your cause?

Saskia Biskup 50:30
Our plan is to start with private placements now. And then we will try to find investors for series A funding to really start to lay out the Phase Two for GBM, and then we want to go public. And at the moment, it's a difficult time in the US, but we hope that once we can go public, we can have many smaller contributions. At the moment, we need a few people believing in the technology helping us to do these initial steps. But once we get going, I think we will potentially have many more people helping us with smaller amounts of money in order to get approval. Once we have approval, I can assure you I'm not taking the money for myself. I will put it in the next clinical trial. This is the way that I'm trying to do this now. But the more you connect, and we have many friends and believers at the moment, and I think it feels a little bit like a tipping point. I've been working on this for so many years, frustrating, evenings, weekends, and so on, and now it feels like we have come to a point where many things are coming together, and maybe as a community and maybe as many partners, foundations. We speak to so many people at the moment, I hope we come to a point where we get this going faster.

Elliot Davis 53:04
Most of these vaccine type things focus on T cells. Has there been any investigation on the B cell response?

Saskia Biskup 53:20
Wonderful question. I wish I knew better. I think there will be some antibodies that we potentially will be able to detect in the future, but we do not have the technology at this point. But if I had to bet, I think B cells will have a role. When we do the multiplex immunofluorescence on those slides from tumor tissue, we very rarely see B cells in the immediate area of the tumor, but I think it can be a systemic response, and I think especially the communication between immune cells is crucial. We know this from infectious diseases, and I think it will be very similar, yet I don't have the data to answer this question at this point.

Roger Royse 54:06
You were talking about the tumor mutational burden.

“The Potential of Personalized Cancer Vaccines, Starting with Brain Cancer” (Saskia Biskup, MD, PhD) [#141]

Does the vaccine respond to cold tumors the same way as other immuno-oncology agents? How?

Saskia Biskup 54:26
We need to better understand what it means in your code. There are differences in how the tumor microenvironment is structured, and I mentioned the spatial transcriptome analysis. We need much, much more data, and this is also, again, individual. The puzzle becomes more clear when I have the spatial resolution of tumors, and then based on this information, we can make better suggestions, and potentially we might need some support by machine learning and other algorithms in order to understand better what will be the killer of this particular disease.

Darren Rhea 55:13
We have a number of groups in America and Mexico doing somewhat similar things with a certain software stack I just mentioned, the Pan American Cancer Institute, Matt Halpert at Immunocine in Cancun and MD Anderson, Roy de Souza and David H Hawk at BreakBio, Dilio Amigo (?) Montefiore Einstein at the Albert Einstein Medical College, doing GBM and the sort of peptide vaccine.

Is it possible that we might take the patient and not definitely do the medical care through the mail, but take the sequencing information and have everyone's software stack pick the targets, to compare on target selection to say that these different groups at Mayo Clinic and whatever, ran the sequencing through and decided these were the top targets that are most likely to cause a strong response, and then do that comparative analysis to say that for this one patient, the different groups found different target predictions in a different sort order of what was most likely to be effective. Is it possible there might be a cooperation of that, like on a data level, rather than on a treatment level, between the different groups and countries?

Saskia Biskup 56:34
First of all, we are sharing data. Each patient has the right to access his own data and can share with everyone. This is done daily and is important, but it will not move the field in large steps. It's only incremental.

The larger steps will come from the multiomics approach. We frequently see that genes are not everything. You need the transcriptome, the proteome, the spatial information, metabolomic information, metabolites, and the microbiome.” It's much more complex, and sharing DNA and transcriptome data is not moving us really fast where we need to go. So that's what I think, and I think as a geneticist, I can say that.

What's really moving the field is exchanging our knowledge, combining human intelligence. It was a pleasure to speak with you, and I hope we will be in contact.

“The Potential of Personalized Cancer Vaccines, Starting with Brain Cancer” (Saskia Biskup, MD, PhD) [#141]

CHAT CONVERSATION

00:15:47 David Plunkett: https://cegat.com/
00:27:36 Nancy: Are their any support supplements you suggest for those pursuing your vaccine, ie. Curcumin.
00:41:42 Dr. Chris Apfel: Dr. Biskup. What you do sounds very impressive. Also, congrats to your amazing publication. Perhaps it might be helpful for me and/our our group if you could address a few questions.
Given RNA transcriptomics is more relevant than the underlying DNA mutations, why do we still need the DNA analysis?
How do we get from there to understanding the neo-antigen length and structure? And are some neo-antigens "standard" for certain tumor types? If so, could some be a 'shelved product.'
How difficult is it to synthesize those neo-antigens for individual patients? Time, costs?
00:51:07 Dr. Elliot Davis: Is there any B cell response?
00:52:43 Mass Medical Angels: Do you use any adjuvants? If not, what are your thoughts on whether that might be useful?
00:53:22 Rick Davis: Has a patient cost been mentioned beyond $$$?
00:55:48 Mass Medical Angels: Are the tumor boards similar to IRBs in the US? If so, are they hospital tumor boards or for-profit tumor boards
00:56:29 PWE Kane: Tumor Board is not an IRB
00:56:46 PWE Kane: IRB is for protecting patients in research.
00:57:05 Mass Medical Angels: In the US I know they are not, but I am surprised that a tumor board by itself can authorize a treatment. I am not sure that can happen in the us
00:57:07 Jason Binder: Tumor board is interdisciplinary team of experts in the disease field
00:58:12 Mass Medical Angels: By treatment I mean an unapproved treatment, which I assume this is. I am not an expert on EU regulatory, but did serve for several years on an IRB at the Farber
01:04:52 Jason Binder: Question for those who listen…so much of GBM $s are diluted. How can we consolidate and prioritize to fund translational de-risked opps?
01:05:04 Rick Davis: Does your vaccine technology respond to 'cold' tumor the same way as other immuno-oncology agents?
01:08:10 Naomi: Thank you Dr. Biskup and the Cancer Patient Lab for such an informative session.
01:09:16 Jason Binder: Thank you!
01:09:36 Vanessa Hugo: Thank you, Dr. Biskup.
01:09:38 briankane: Thank you Dr. Biskup!
01:09:48 Roger Royse: Saskia Biskup <Saskia.Biskup@humangenetik-tuebingen.de>
01:09:54 Darren Rhea: darren.rhea@gmail.com