COMBINATION THERAPY DEVELOPMENT: EMERGING I-O THERAPEUTIC MODALITIES & PREDICTIVE TECHNOLOGIES

SPOTLIGHT

INTERVIEW

A career in cancer vaccines: exploring the promise of B cell epitopes

Roisin McGuigan, Editor, *Immuno-Oncology Insights*, speaks to **Pravin TP Kaumaya,** Professor and Director of Vaccine Research at The Ohio State University

PRAVIN KAUMAYA is Professor of Medicine in the Department of Ob/Gyn at the OSU Wexner Medical Center and the James Comprehensive Cancer Center. Dr Kaumaya is internationally recognized as an expert in the fields of vaccine research with emphasis on peptide vaccines for cancer. His work over three decades in developing B cell epitope-based cancer vaccines is a paradigm shift in the immune-oncology landscape. Dr Kaumaya is an elected fellow of the American Association for the Advancement of Science (AAAS), and he was elected as the treasurer of the American Peptide Society since 2009. He has lectured worldwide and has published over 130 peer-reviewed articles in major scientific journals. He conducts research in the areas of immune-oncology, tumor immunology, peptide design and immune mechanisms supported largely by NIH, Pelotonia and more recently by Imugene, Ltd. He is an inventor on several issued and pending patents for peptide cancer vaccines and immune-therapeutic technologies. Vaccines developed for HER-1, HER-3, IGF-1R and VEGF at the university has been licensed to IMUGENE Ltd. Dr Kaumaya has conducted two first man/woman NCI funded and FDA approved Phase 1 Trial in Cancer Patients (Stage four) with solid tumors in several indications (Breast, Ovarian, GIST) at the OSU James Cancer Hospital has recently been completed successfully demonstrating the safety and efficacy of the vaccine. Dr Kaumaya's laboratory has recently developed a PD-1-Vaxx (programmed cell death) B cell peptide cancer vaccine that induces the body to produce polyclonal antibodies that block PD-1 signaling and produce an anticancer effect similar to the marketed immunotherapy drugs Keytruda® and Opdivo®.

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Cancer vaccines hold potential in the immuno-oncology space as an alternative to monoclonal antibodies or other approaches – but why have they not yet gained more traction in the immuno-oncology space? Professor and director of vaccine research at The Ohio State University, Pravin Kaumaya, once described B cell epitope cancer vaccines as a "new paradigm for combination immunotherapies". Here, he speaks about their untapped potential.

Q Can you tell us a bit about your own background and your current role?

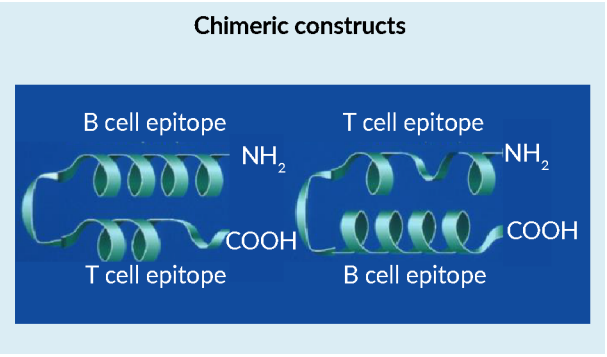
PK: I was born in Mauritius and completed my primary schooling there, and I then obtained my bachelor's degree in London, then spent four years at the University of Portsmouth to obtain my PhD in 1980. As soon as I graduated, I traveled to the US to do a post-doc at the University of Texas, Austin, School of Pharmacy. I then did a second post-doc at Northwestern University in Evanston, Illinois, where I became a research associate professor in 1987.

I was recruited at Ohio State University (OSU) in 1989, under a specialized program of protein engineering funded in perpetuity by the board of trustees. I was appointed assistant professor, became an associate professor with tenure in 1993, and a full professor in 1998. In 1995, I chaired the 14th American Peptide Symposium which attracted 1650 delegates from 33 different countries. I also served as Chairman, 1st International Symposium Peptide, Protein and Nucleic Acid Vaccine, held at Oxford University, England in 1998. I served as the treasurer of the American Peptide Society from 2009–2018. In 2006 I was elected Fellow of the American Association for the Advancement of Science (AAAS). I have 108 patents (issued and submitted) and I have served continuously on several National Institutes of Health Study Sections from 1997 to date, and am a permanent member of the National Cancer Institute (NCI) institutional training and education study section (T32, R25 and K12), July 1 2022–June 30 2026.

At Northwestern University, I started developing the idea of engineering secondary and tertiary B cell epitopes to be used as vaccines. I further developed chimeric B and T cell epitopes (Figure 1) incorporating 'promiscuous' T cell epitopes as a universal vaccine using human T-lymphotropic virus 1 (HTLV-I), the distant cousin of HIV, as the model antigen. In 1995, I began looking at cancer vaccines with the human epidermal growth factor receptor 2 (HER-2) oncogene

FIGURE 1

Chimeric B and T cell epitopes.



which is overexpressed in breast cancer (30%) as well as other cancers such gastrointestinal cancers, including colon cancer.

Q In your opinion, why have B cell epitope vaccines, and cancer vaccines in general, not yet gained more traction in the immuno-oncology space?

PK: There are a few cancer vaccines in existence, such as the range of available human papillomavirus (HPV) vaccines to treat cervical and anal cancers. There is also Provenge, a dendritic cell vaccine developed by Dendreon. Most cancer vaccines target the T cell component of the immune system, specifically cytotoxic T lymphocytes (CTLs). I would say 95 % of all research done to date has been on the activation of T cells, which is very important.

In the 1980s, crystallography showed the binding of peptides to major histocompatibility complex (MHC) class I and class II, and how they activate the T cell receptor. Most of those peptides are 8–10 amino acids in length. This discovery led to an explosion of CTL vaccines. Viral infection exposes multiple epitopes. We are unlikely to get a vaccine with just 8–10 amino acid peptides that bind MHC class I. We do not currently have a CTL vaccine approved by the FDA.

Our basic immunological knowledge has made great strides over the years, and we know that helper T cells are important, with helper T cell epitopes of between 10–30 amino acids that bind MHC class II. Vaccinologists and immunologists have started using those together. Even with this improvement, we do not yet have T cell vaccines.

We now know that checkpoint inhibitors are important. Scientists are using cytotoxic T cells together with the PD-L1 checkpoint inhibitor to put the brakes on T cell activation. Hopefully, that together with additional new discoveries might lead to a CTL vaccine.

In terms of B cell vaccines, there are several monoclonal antibodies (mAbs) that have been FDA-approved, such as Herceptin for HER-2 and Cetuximab for HER-1/EGFR. Cancer immunotherapy has recently been energized by the discovery of checkpoint inhibitor proteins. James P. Allison and Tasuku Honjo won the 2018 Nobel Prize in Physiology or Medicine for discovering immune checkpoints programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), demonstrated that they acted as a 'brake' role in immune function. More recently, we have seen mAbs to PD-1, PD-L1, and CTLA-4, which have all been FDA-approved.

If you can treat with mAbs, and they can prolong life or be effective for at least 20–30% of the adult population with cancer, why not have the immune system make those antibodies? That has been my driving force over the last 20–25 years. I started developing contraceptive vaccines first for LDH-C4, then for HTLV. HTLV is a viral oncogene – some cancers that are of viral origin have been caught early on with Provenge and HPV vaccines. The oncogenes that are over-expressed in tumors are considered self-protein. It is more difficult to develop a vaccine to a self-protein.

We have mapped B cell epitopes on protein antigens. The crystal structure (Figure 2) of the complex of lysozyme with its mAb was published in 1987. The large conformational interaction over 900 amino acids showed that short linear synthetic peptides of 10 amino acids would not mimic the surface-oriented secondary or tertiary structure. That is one of the major barriers to developing efficacious antibodies to B cell epitopes.

I embarked on engineering epitopes on protein antigens by mimicking the pertinent secondary attributes of the epitope by using our knowledge of protein folding and structure. In the 1990s, we published our findings that antibodies raised to those various secondary structures elicited high-affinity antibodies to the native protein and thus provide a potential strategy for developing an effective peptide vaccine. That was the first step to solving one of the problems with B cell vaccines, by designing peptides that are conformational in nature.

The second problem was that most vaccinologists used B cell epitopes and coupled them to a carrier protein, for example bovine serum albumin (BSA) or keyhole limpet hemocyanin (KLH). When you vaccinate with these small peptides coupled to a carrier protein, you have no control over the immunogenic epitope, because the resulting vaccine requires processing by the immune system in a way that cannot be predicted, thereby resulting in a less effective immunogen [1].

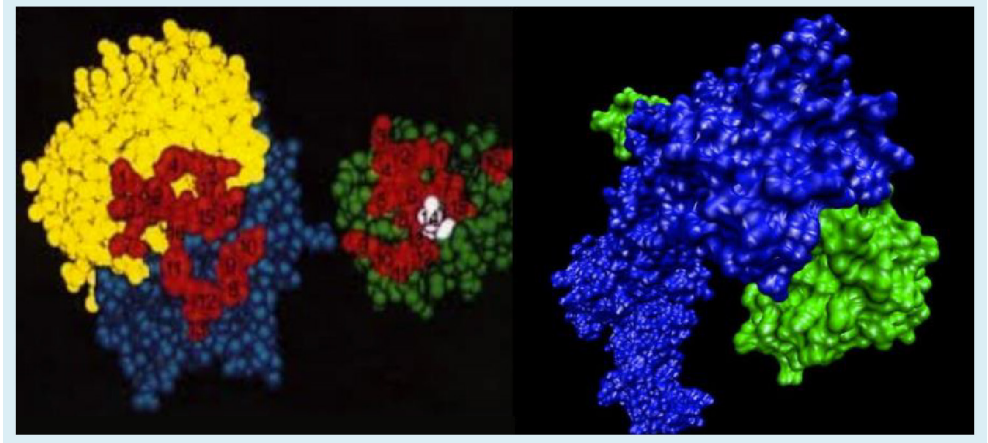
In the 1990s, the idea of 'promiscuous' T cell epitopes was published by a group in Switzerland and a group in Australia. They identified a number of 'promiscuous' T cell epitopes from measles virus or tetanus toxoid, that bind MHC molecules in a universal fashion.

I proposed the idea of using those T cell epitopes in combination with our B cell epitopes. At that time, we did not know whether they were going to be processed or not. Afterwards, we found out that those around 50 amino acid chimeric constructs are not processed *in vivo*, and therefore the immune response generally generates antibodies of high affinity to the native protein.

This was the start of my work at Northwestern and then at OSU in 1995, I started looking at HTLV as our model antigen to develop a vaccine for HTLV-I. I also started looking at cancer vaccines, using the HER-2 oncogene, which is overexpressed in breast cancer. We

FIGURE 2

Lysozyme (green) and mAb to lysozyme (blue/yellow) are shown to have a conformational interaction.



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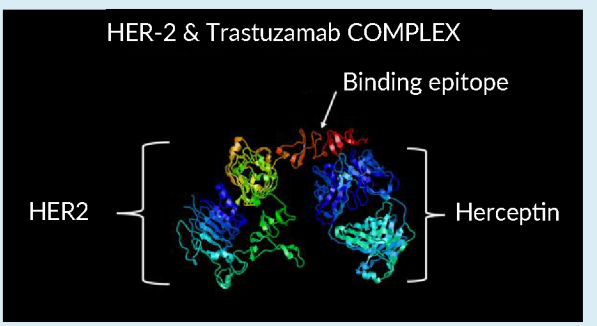
developed epitopes for HER-2 and translated those into a first-generation HER-2 vaccine. Then in 2000, the structure of trastuzumab (Herceptin®) in complex with HER-2 was published (Figure 3). Similarly, the complex of HER-2 with pertuzumab (Perjeta®) was published.

FIGURE 3

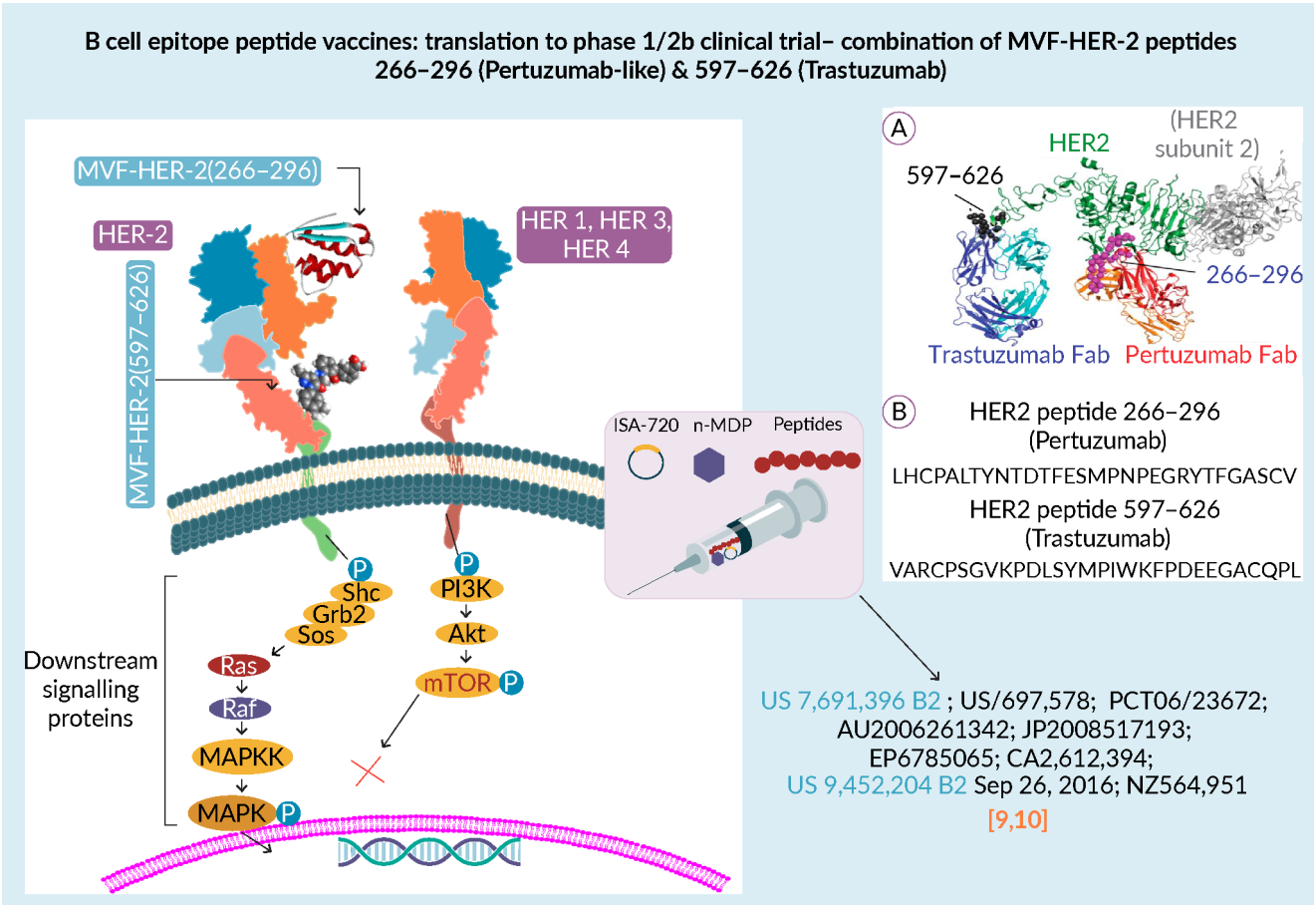
HER-2 and Herceptin binding molecular structure.



We developed several epitopes to mimic the binding region and discovered two novel epitopes that mimic Herceptin and Perjeta. We completed a combination immunotherapy vaccine of two epitopes MVF-HER-2 (266–296) (Perjeta-like) and MVF-HER-2 (597–626) (Herceptin-like) in animal models, then we translated the combined vaccines (B-Vaxx) to a Phase 1 clinical trial conducted at the James Cancer Hospital at OSU. We published the completion of a dose escalation Phase 1 trial in 2019. The combination vaccine was emulsified with ISA720 vehicle (water-oil-emulsion, Seppic INC, Fr) and

FIGURE 4

Combination HER-2 vaccine (B-Vaxx) in Phase 1 clinical trial.



[9,10]

amuramyl-dipeptide (nor-MDP) adjuvant to deliver our vaccine (Figure 4) intramuscularly [1].

Presently, we are conducting a Phase 1b trial, and have attained FDA approval to target HER-2-positive cancer patients. It has taken us 15 years to get here, but we are happy with where we are going with the HER-2 vaccine. The landscape for breast cancer has evolved from FDA-approved Herceptin, Perjeta, Kadcyla and now Enhertu and our HER-2 B cell vaccine should be competitive in the treatment of breast and other cancers overexpressing the HER-2 gene. We have also proposed how the vaccine works (Figure 5).

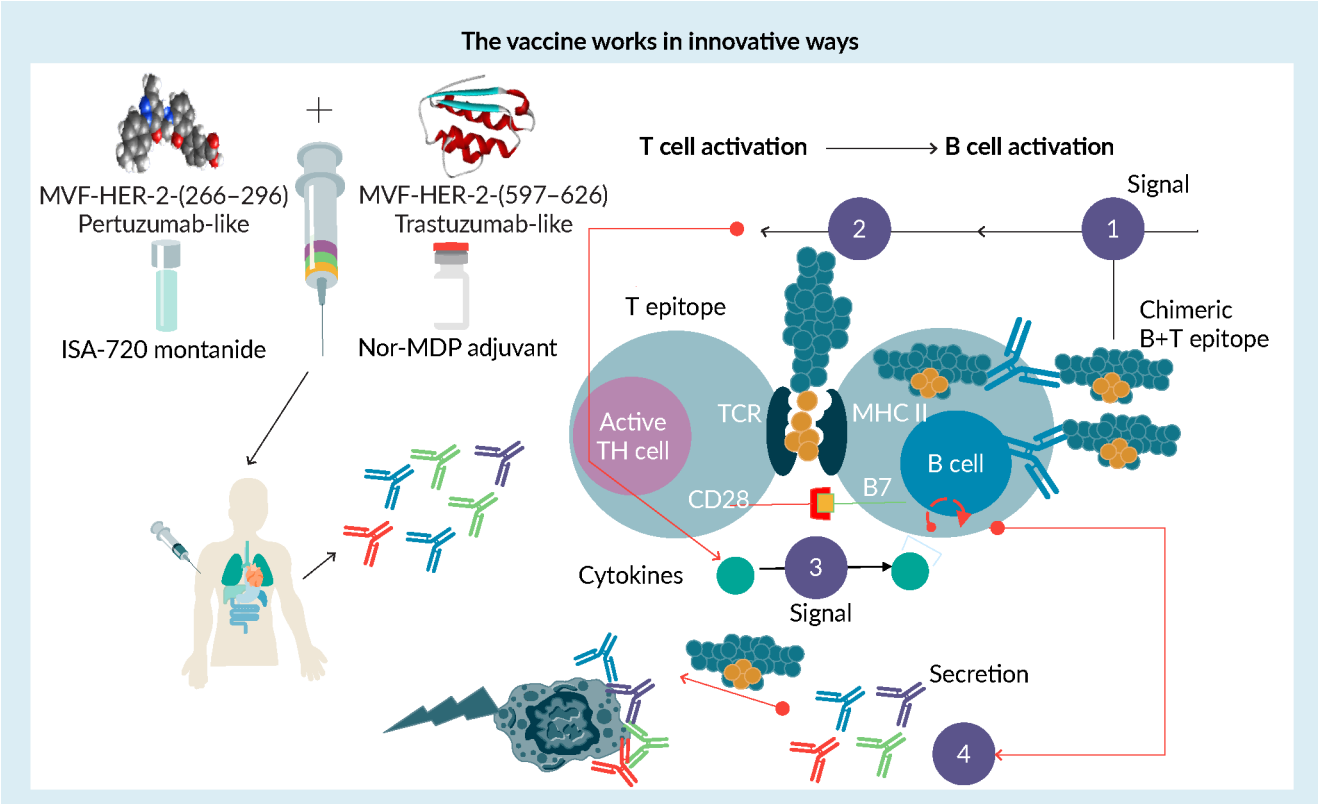
Q What are the key advantages that vaccine-based approaches offer, versus mAbs or other approaches?

PK: In general, mAbs are effective in about 20–30% of adults. The mAbs that have been used to treat breast cancer are Herceptin and Perjeta. As soon as patients were treated with these, they become refractive to treatment and stop responding. These antibodies are US $ 120000 per treatment, and they are not a cure.

Another set of FDA-approved mAbs such nivolumab (Opdivo) or pembrolizumab (Keytruda®) are monoclonal targeting PD-1 a protein on the surface of T and B cells that plays an important role in regulating the immune system's response. Ipililumab (Yervoy®) is a mAb targeting another checkpoint CTLA-4.There are also mAbs (e.g. Avelumab, Atezolizumab)

FIGURE 5

Proposed mechanism of how the vaccine works.



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to the PD-L1 located on tumor cells that play an important role in various malignancies through the PD-1/PD-L1 axis.

Nivolumab and pembrolizumab are also given together with a chemotherapeutic agent. However, many patients do not want chemotherapy. mAbs do have a place in our armamentarium of treatment for cancer, but they are also toxic. Our approach of using the immune system to generate vaccines is a paradigm shift. We are still having difficulty getting it generally accepted.

There are many advantages to peptide vaccines. They are safe, non-toxic, highly stable, can break tolerance, can elicit B and T cell memory response, and have no oncogenic material included. A multi-epitope approach could lead to broad antigen recognition and universal coverage.

Humanized mAbs have many disadvantages, such as full penetration, ineffective tumor targeting, a half-life of 12 days, and the requirement of weekly infusions of large quantities of humanized antibodies. Treatment is expensive and cardiotoxicity and gastrointestinal perforation can occur. The most important thing is that there is no immunological memory. This is a treatment, not a cure. A peptide vaccine could be used in both a prophylactic fashion, as well as in a therapeutic mode. There are many advantages to peptide vaccines over mAbs.

Q You mentioned you returned to cancer research in 1995. What inspired your work and made you pursue this particular area?

PK: My dad was diagnosed with leukemia in 1981. He was treated with vincristine, which at the time was an experimental drug. They have since worked out the right doses for vincristine, and it is now used often in leukemia. Within a month of being treated with this experimental drug, he passed away.

There were toxic events happening when my dad was treated with that drug. We know now that some similar drugs, such as axitinib, are highly toxic. You can extend life by a couple of months, but with extraordinary toxicity. This galvanized my passion for developing peptide vaccines because I knew these would be safe and non-toxic. Biological materials, including peptides, are well known to be very safe.

I also spent a lot of time studying how to make B cell vaccines immunogenic or antigenic, to provide high efficacy. In so doing, we developed our HER-2 vaccine. Signal transduction pathways involving the dimerization of HER-2 drive cancer metastasis. If this can be blocked, like with Herceptin, cetuximab, or pertuzumab, then you block cancer.

When patients are treated with mAbs, they develop resistance and stop responding. Over a span of 10 years, we hypothesized that one of the reasons for the resistance mechanism in those targeted therapies was the upregulation of the other oncogenes, such as HER-1, HER-3, HER-4, IGF-1R and VEGF. [1]. We developed a plethora of vaccines for all of those molecules, to use in combination. In 2010, with our combination of HER-2 with VEGF in animal models, we showed that we could increase the efficacy of those vaccines when used in combination. Cancer immunologists started to see the potential of using the immune system to try and conquer cancer.

The crystal structure of the checkpoint inhibitors enabled us to design a vaccine for PD-1 and PD-L1. We looked at the entire structure of PD-1 and PD-L1 and developed all those various antibodies. We studied them in multiple animal models. The epitope 92–110, which we now call PD1-Vaxx, is a chimeric construct with a measles virus promiscuous epitope linked to the B cell epitope. We published this in 2020 in *OncoImmunology* [2]; showing in syngeneic models that this particular epitope was quite effective in preventing tumors. We used a syngeneic model of colon cancer where the mice were treated with CT26, a carcinoma cell line, and we showed that we could duplicate the efficacy together with the mouse mAb to PD-1. Then, when we used those in combination with our HER-2 vaccine, we obliterated cancer growth in that CT26/ HER-2 model.

We have developed PD1-Vaxx (Figure 6). Imugene contacted me to enquire about our PD-1 vaccine, and within a few months we licensed not only the PD1-Vaxx but my entire portfolio to Imugene. We then developed protocols to conduct a Phase 1 trial in humans to apply for an IND and get FDA approvals. A study in dogs was published this year, where we defined how to deliver those peptides. Imugene contracted Charles River to conduct a non-human primate study in Ashland, Ohio, and raised money to do a clinical trial with three cohorts both in the US and in Australia [3].

The Phase 1 trial in advanced/metastatic non-small cell lung cancer (NSCLC) completed a dose escalation to determine the safety and Optimal Biological Dose (OBD) monotherapy of the vaccine. The results show the vaccine was safe and one patient had no observable recurrence for 20 months [4–7].

Now, Imugene and Roche have formed a collaboration in which Roche are going to provide their mAb to PD-L1, atezolizumab, and Imugene will conduct a combined treatment with PD1-Vaxx and atezolizumab. This Phase 1b trial in advanced/metastatic NSCLC dose escalation: NSCLC checkpoint inhibitor naïve or have progressed on/after checkpoint inhibitors will start in the next few months, and we are looking forward to what this study will teach us [7].

We have developed a PD-L1 B cell epitope vaccine (Figure 7). One of the epitopes, 130–147 (PDL1-Vaxx), has turned out to be one of the most effective epitope in several different syngeneic (BALB/c; C57BL/6)J models and carcinoma cell lines (CT26WT, CT26/

FIGURE 6

Molecular structure of human PD1-Vaxx.

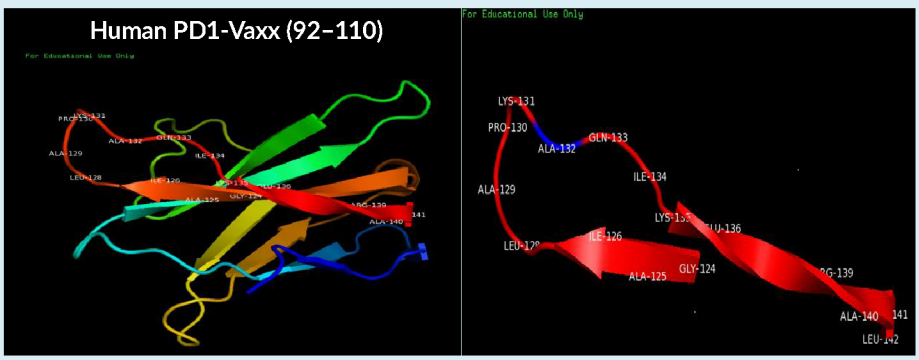

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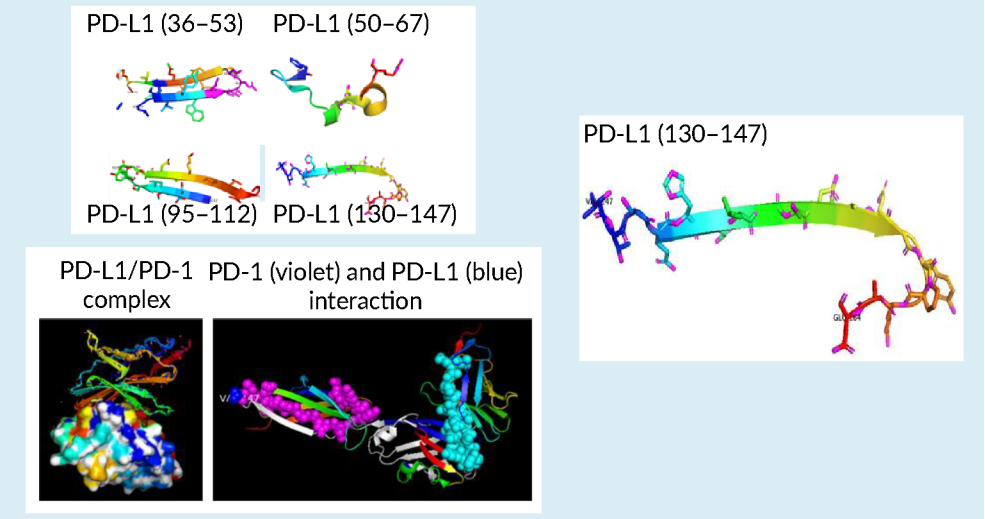
FIGURE 7

PD-L1 epitopes.



HER-2, 4T1, D2F2,D2F2/E2,MC38, MC38/HER-2 and B16.F10 in colon, breast cancers, triple-negative breast cancer, and melanoma). This work was recently published in *OncoImmunology* [8].

We have already completed PD-1 and PD-L1 combination immunotherapy in animal models which showed synergistic inhibition in several different cancer models. We have shown the efficacy of using both vaccines together, and in a triple version together with our HER-2 vaccine. These ongoing studies will expand to Phase 1 clinical trial in the near future.

Q What have been the most significant milestones of your work to date, and what's next?

PK: We have established the template of how to design B cell vaccines by using chimeric constructs, delivering them, and studying them in multiple syngeneic models. Next, we can translate this to human clinical trials.

However, one of the main important things going forward is regarding our CTLA-4 peptide vaccine (CTLA-4-Vaxx), which is similar to ipilimumab. We have completed a CTLA-4 and PD-L1 combination immunotherapy in a syngeneic mouse model, which is not yet published. This combination is going to be important.

We have also designed peptide B cell epitope vaccines to all the various checkpoint inhibitors. We have vaccines for PD-1, PD-L1, LAG-3, and TIGIT. Now, we are using all those in combination to explore how we are going to design combination immunotherapy. I think the PD-1 and PD-L1, or the PD-1 and CTLA-4 may gain FDA approval. I believe this is the future of cancer vaccines using peptides.

Q Could you tell us a bit more about the CTLA-4, LAG-3 and TIGIT vaccines that you are developing?

PK: Some of our work has not yet been published, but we have a large cancer vaccine project pipeline (Figure 8).

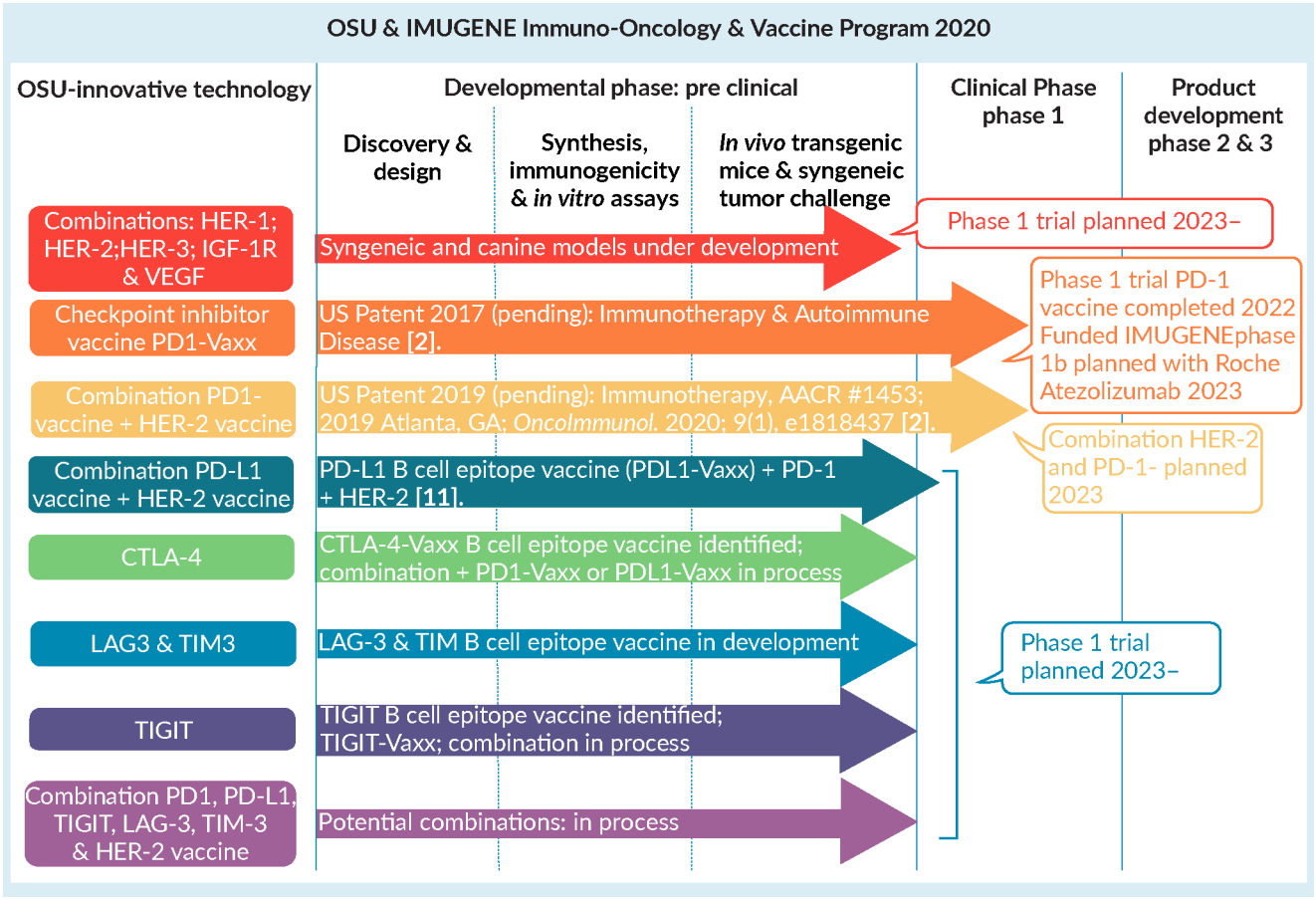
We looked at immunogenicity and antigenicity of the CTLA-4 peptides, first in rabbits, then in mice, and then at all four epitopes. Now, we are looking at several syngeneic models. They are highly immunogenic and recognize a native protein. However, we have also identified CTLA-4(130) as a good epitope to be used for vaccination.

Our second model, 4T1 breast cancer, showed that the results for the mAb were not very good. Our vaccine was much better. We saw similar results in the D2F2 model, a mammary tumor model. Based on that, we know now that the CTLA-4 epitope is good.

Now, we are looking at peptide mimics instead of vaccination. We are currently conducting a duplicate experiment to see if we can use only a peptide to prevent mammary tumors. We have identified 2 LAG-3 peptides and completed the study in a tumor model. We have an epitope that is acceptable. We also have 8 TIGIT peptides, and we are conducting studies in rabbits and C57BL/6 mice.

FIGURE 8

OSU and Imungene cancer vaccine project pipeline 2019–2022.



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Q You have previously described B cell epitope peptide cancer vaccines as "a new paradigm for combination immunotherapies". What unmet needs can novel combinations incorporating cancer vaccines potentially address?

PK: There is a multitude of checkpoint inhibitors and mAbs. All the big companies are now looking at combining those mAbs together. The problem there is that each mAbs has a toxicity profile, and when you add them together the toxicity is going to be elevated.

We can treat those and play with the amount of mAb or combine them with radiotherapy or chemotherapy. The goal now is to reduce toxicity. We know which checkpoint inhibitor can be used, and how you can reduce toxicity by decreasing the number of antibodies infused in the patient.

Biomarkers are going to be an important factor in finding which cancer to target, and in doing so, developing methods to reduce toxicity. Yervoy and Atezolizumab are now being used in combination.

But although these are good ways of treating cancer, we will prove that our vaccine platform is also a great method to treat cancer patients, with very little toxicity. We want to figure out how to deliver the peptides in combination. It is well known that combination immunotherapies with mAbs exhibit toxicity, and both Roche and Imugene were interested in finding out how the PD-1 vaccine when combined with Roche's PD-L1 mAb (atezolizumab) could have less toxicity. This could move the field forward. If we can have patients being treated by the proposed combination that could expand our platform of vaccines to checkpoint inhibitors together with targeted mAb therapy.

In the meantime, we still nee to figure out vaccines to CTLA-4, to TIGIT, to LAG-3, and how to combine those together. Once the scientists and the doctors that treat cancer patients find out that those vaccines are a plausible approach, then we will get recognition for the work that we have done on how to move our science forward.

Q What will be your own chief goals and priorities in the coming years?

PK: The chief goal is to see which combinations will be effective by looking at multiple syngeneic models.

We are in academia, not in big pharma where they have much more funding. Imugene is funding all the research for those combinations. From starting the combination to figuring out the efficacy, it takes between 6–9 months. Thus, Imugene must take the first step by developing those vaccines in GMP conditions and be ready off-the-shelf to go into clinical trials within 18 months.

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AUTHORSHIP & CONFLICT OF INTEREST

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