Cancer Prevention INITIATIVE
For a World Without Cancer

Frontiers in Cancer Prevention: Interview with Eduardo Vilar Sanchez, MD PhD

Dr. Eduardo Vilar Sanchez is a physician-scientist and a medical oncologist with expertise in gastrointestinal cancers such as colorectal cancer and inherited cancer syndromes such as **Lynch syndrome (LS)**[1] and **familial adenomatous polyposis (FAP)**[2] that carry a high risk for the development of colorectal cancer. His research interests include study of the genomic and immune landscape of inherited colorectal cancer and chemo- and immune-strategies to prevent them. In addition to leading a successful research lab, he remains an active clinician and regularly cares for patients. Dr. Vilar currently holds professorships in the Department of Clinical Cancer Prevention, in the Division of Cancer Prevention and Population Sciences, and the Department of Gastrointestinal (GI) Medical Oncology at the MD Anderson Cancer Center in Houston.

We sat down with Dr. Vilar to learn about his remarkable journey from Spain to the US and from cancer treatment to cancer prevention. He also discusses his efforts towards developing a vaccine for Lynch syndrome.

Tell us a little about your path into medicine and science.

I was born and raised in Spain. My dad was a physician-scientist—a gynecologist who also conducted clinical work and research in gynecological cancers. He was department chair, and the department felt like an extension of our family, with fellows often stopping by our house. That was the environment I grew up in—medicine and research were always in my blood.

I completed both my MD and PhD at Miguel Hernández University in Alicante before being recruited to Vall d'Hebron Institute of Oncology in Barcelona for my residency. At the time, Jose Baselga was the Chair of the Department, and the institute was a powerhouse in breast cancer and phase I clinical trials. But I had already identified GI cancers as my field of interest. Luckily, Josep Tabernero, now director of Vall d'Hebron Institute of Oncology, was working on colorectal cancer, and he became my mentor.

Vall d'Hebron was, and still is, a major hub for clinical trials, and I gained a great deal of clinical experience there. By the end of my residency, I wanted to spend some time at the bench. I connected with Stephen Gruber at the University of Michigan, a physician-scientist who worked on colorectal cancer and cancer genetics. From early on, it was clear that Steve was going to be a phenomenal mentor. I applied for and received a scholarship from Spain to spend two years in his lab. That's how I landed in the U.S.

How did you become interested in the cancer prevention space?

This was the height of targeted therapies[3] and in Steve's lab I started working on identifying new targeted therapies for microsatellite instable colorectal[4] cancer. Steve was also the Director of the genetics clinic at Michigan, and he saw patients with inherited cancers. That opened up an opportunity to work on Lynch syndrome.

I was completing my fellowship, and Steve and I had this conversation where he encouraged me to be a little flexible in my thinking and consider reshaping the research I had been doing toward prevention—develop the next wave of chemopreventives (drugs for prevention) for high-risk populations. With that he connected me to Powel Brown at MD Anderson. He opened my eyes to the incredible opportunities in the cancer prevention space. MD Anderson has a strong cancer genetics registry going back many

years, Patrick Lynch - son of Henry Lynch who discovered Lynch syndrome was on the faculty. They made a great case for me to come to MD Anderson and set up shop.

In hindsight I wonder how they thought it was going to work. I think MD Anderson has that Texas "can do" spirit, boldness, and entrepreneurship. Here, they were bold enough to think that a junior faculty who had been working on established cancers and targeted therapy will be able to switch to prevention. Some other places I interviewed wanted me to work under senior faculty first. I was bold enough and stubborn enough to think "I want my own shop for better or for worse, I want that little sign that says 'Vilar Lab.'" My path to prevention is unconventional, which I think is true for many people in the field.

What were some of the early major discoveries from your lab?

I thought that instead of looking at full blown cancers I can study the transition between normal colorectal epithelium and precancer (adenoma). In one of the first papers from my lab that I am very proud of, we showed that several mutations found in adenomas were already present in the at-risk tissue of FAP patients[5].

Another big impact factor paper was based on an NCI-sponsored clinical trial that established the common non-steroidal anti-inflammatory drug (NSAID) naproxen as a promising strategy for preventing colorectal cancer in LS patients[6-7].

With Jim Allison winning the Nobel Prize in 2018 for his work on immune checkpoints[8], the focus really shifted to immunotherapy in my lab. His work showed that by activating immune checkpoints, cancer cells can evade the immune system and avoid being identified and destroyed. We showed that LS precancers already express immune checkpoints, meaning they start evading the immune system at an early stage[9].

How does your work in the high-risk hereditary cancer populations relate to the general population?

This is an important question. In my opinion, **risk stratification** is necessary to successfully implement prevention in the general population. We need to identify subgroups of the general population who are more prone to developing cancers for genetic, environmental, or some other reasons. Then target and encourage those higher-risk individuals to take preventive measures.

I don't think people are motivated to take preventive measures without a better understanding of their individual risk. Colonoscopy is a good example. The population risk for colon cancer is around 5%. The risk seems low and people are not motivated; less than 50% of the people eligible for screening do it. There may be other barriers, like insurance and inconvenience, but I think lack of risk stratification is a reason colonoscopy is not more widely adopted. If we can provide a specific piece of data— tell them, you should have a colonoscopy because you have a higher-than-average risk for XYZ reasons— that would convince people. High-risk populations like LS patients and BRCA mutation carriers are different. A BRCA1 mutation carrier will have their ovaries removed. Same thing with FAP patients who have an almost 100% life-time risk for developing colorectal cancer and remove their colon because they don't have any other way to avoid cancer.

What do you think the main challenge is for risk stratification beyond inherited genetic markers?

My opinion is that oncology researchers think that we still don't have good biomarkers and risk assessment tools to measure risk. They don't want to use the imperfect tools we currently have. I don't think we should let perfection get in the way— **imperfect biomarkers are better than no biomarkers.** Cardiovascular researchers have done a much better job than cancer researchers in convincing an entire

population that "risk biomarkers" such as hypertension and cholesterol levels are good indicators, even though the thresholds change every so often. These tests are not perfect, but they motivate people to take preventive measures.

The anecdote of our lives in cancer prevention is that people will take aspirin for cardiovascular disease prevention but not for prevention of colon cancer. If a cardiologist runs one of their models and tells the patient that they have a high risk for cardiovascular disease, they will willingly take 100 milligrams of aspirin or 300 milligrams of aspirin because they are convinced that if they don't, they will die from a heart attack. You tell a patient to take 100 milligrams of aspirin to prevent colon cancer, they say "no, no, that will give me an ulcer." But if we have a risk assessment test that we can run to show elevated risk, they will be willing to take up preventative measures.

I think cancer prevention goes hand in hand with risk stratification. We can work in cancer interception- develop vaccines, pills, etc. but we will never get them implemented or engage the public without risk stratification. This is the reality.

In your experience, do patients find the concept of risk hard to understand?

Yes, it is difficult. You must be careful how you communicate the information because it is easy to misinform. In one way, you can amplify the perceived risk. If you just tell an *MLH1* gene mutation carrier (*MLH1* is a gene commonly mutated in LS) that their risk for colon cancer is 80%, they will leave the clinic completely terrified. You need to explain that 80% is cumulative risk over their lifetime. I show graphs from a large population study done in Europe called Prospective Lynch Syndromes Database (PLSD)[10] to explain how cancer risk changes by age, cancer type, etc.

You recently completed a prevention trial that tested a cancer vaccine with the potential to prevent colorectal cancer in LS carriers. Tell us about that.

Yes, I was the principal investigator in a clinical trial[11-12] that showed the Nous-209 vaccine is safe and well tolerated in LS carriers and stimulates a robust immune response. Following these positive results, it will move to the next phases to test whether it can prevent cancer in LS carriers.

This vaccine was initially developed as a therapeutic/treatment vaccine for mismatch repair deficient (dMMR)[4] cancers by the Swiss company Nouscom. I convinced them to run a prevention trial in LS carriers as well, because almost all LS tumors are dMMR. In general, early disease onset and high cancer frequency make high risk populations like LS carriers an ideal setting to test prevention. Nouscom provided the vaccine and the trial was funded by the National Cancer Institute (NCI).

With the support of CPI, we are also developing an independent vaccine for LS at MD Anderson. Both vaccines target neoantigens—abnormal/mutant protein fragments produced by tumor cells and recognized by the immune system. Due to the specific deficiency in DNA repair, dMMR tumors generate hundreds of neoantigens, most of them that are shared among dMMR tumors. The Nous-209 vaccine targets neoantigens expressed in established dMMR tumors, identified from publicly available database run by NCI and NIH. The neoantigens used in our vaccine were identified from our LS patients with stage 1 cancers and precancers.

What are your thoughts on the limited enthusiasm for cancer prevention trials that treat individuals who are not yet sick? Are biopharmas uncertain about a market for prevention vaccines?

Yes, when giving anything, a shot or a pill, to the healthy general population it has to be considered very carefully because of side effects. The bar for safety and tolerability is very high. And as I mentioned

before, without knowledge of individual risk, individuals would be less motivated to take part in prevention. However, in this prevention trial, the participants were LS carriers who are at high risk and therefore willing to tolerate some side effects; the trade-offs are different for someone with high risk. Recruiting the 45 participants for the trial happened very fast. There were weeks when I got like 10 emails asking about the trial. **There are an estimated one million Lynch syndrome carriers in the US which is a substantial number when talking about a "market."**

Is this a one-and-done vaccine?

This vaccine had a prime and a boost – so two shots, two months apart. Because this was a phase 1/2 trial, the interest was to verify that the vaccine was safe and well tolerated. It was a bonus that a robust immune reaction was seen. In future trials, the number of shots necessary will be considered. Even in the fields of immunology and vaccinology it is not known how many vaccinations are necessary for a sustained immune response. You may recall that this was a big question when we were all getting vaccine boosts for COVID. There are theories that the number of vaccinations doesn't matter or that it may depend on the vaccine. Recently, it was reported that one shot of the Human Papillomavirus (HPV) vaccine was sufficient to prevent cancers caused by this virus.

It is even argued that a sustained immune response may not be necessary for the vaccine to be effective. The immune response may drop, but it is okay because having a very tiny group of memory T cells may be sufficient. The idea is that this cell population will expand when they re-encounter the neoantigens of the (pre)cancer cells and eliminate them.

I also think that many more vaccines will become available in the future, and the answer might be multiple immunizations with different types of vaccines rather than multiple doses of the same vaccine. We will have to wait and see.

In addition to treating cancer and preventing it in high-risk individuals, could cancer vaccines also help prevent relapse?

Yes, there is a lot of push now in oncology to use vaccines for treating minimal residual disease— the presence of a small number of cancer cells that remain after initial treatment and potentially drive relapse. When the tumor-derived DNA can be detected in the blood, it is called "molecular relapse." This is considered to be a good stage to intervene to reduce the chance of clinical relapse, because the disease burden is low. However, immune tolerance can be a challenge; this is a patient who has already had cancer and the immune system has started to ignore it. To "reawaken" the immune system, the vaccine may need to be combined with checkpoint inhibitors. This is not true prevention, but treatment in an adjuvant setting.

You come across as someone very positive. How about times when things were tough? What motivates you day in and day out?

I have definitely had difficult times—the life of a researcher trying to make a living in science is not easy. Through all of it I realized my greatest strength is as a medical oncologist and a translational researcher.

This is what I always wanted to do. For me, it is the patients, the lab, the people, and the research. It is genuinely fun. To be honest, despite the rejections, harsh grant reviews, and the moments of internal strife and self-doubt, I can't see myself doing anything else.

It sounds like your mentors, starting from your parents, have had a huge impact on your career.

Yes, absolutely. In my opinion, your parents are your first mentors. Beyond them, three individuals played key roles in shaping my career. Josep Tabernero had the time and bandwidth to meet and coach me at a time when I needed that guidance. Stephen Gruber who encouraged me to think beyond being a clinician and consider a career as a physician–scientist. He also shaped my research interest in prevention along the way. And Powel Brown, who took a chance on me, hired me to MD Andeson when I was still a young researcher without a track record in cancer prevention. I am deeply grateful to all of them for their influence on my career.

Anything else you would like to add?

It is hard to get grants funded in prevention as there are only a few individuals and organizations interested in funding cancer prevention research. So, I am very glad that CPI exists, and I am grateful for the support CPI has given me.

References and glossary

1. Lynch syndrome (LS): LS is one of the most common, if not the most common, inherited cancer syndromes, affecting about 1 in 300 people (or roughly 1 million people in the US). LS is caused by germline pathogenic variants in DNA mismatch repair (MMR) genes (MLH1, MSH2, MSH6, and PMS2) and EPCAM. Affected individuals have an elevated risk of developing colorectal cancer as well as certain other cancers from a young age.

2. Familial adenomatous polyposis (FAP): FAP is a type of hereditary colorectal cancer, caused by pathogenic mutations in the APC gene. Many polyps (abnormal growths) form in the colon and the rectum and these may develop into cancer. Without intervention, FAP patients have a 100% life-time risk for developing colorectal cancer.

3. Targeted therapy: Targeted therapy is a precision cancer treatment that uses drugs to attack specific molecules (like proteins or genes) driving cancer growth. Unlike chemotherapy, which uses drugs that kill fast-growing cells generally, thereby also causing damage to healthy cells, targeted therapies are more selective to cancer cells and cause fewer side effects. Trastuzumab (Herceptin) for HER2 positive breast cancer and Imatinib (Gleevec) for chronic myelogenous leukemia (CML) are examples.

4. Mismatch repair (MMR) and microsatellite instability: Mismatch repair (MMR) is a type of DNA repair pathway. MMR pathway components are encoded by genes such as (MLH1, MSH2, MSH6, and PMS2). MMR-deficient (dMMR) tumors have mutations in MMR genes and are therefore unable to correct certain errors, resulting in tumors with high microsatellite instability and high mutational burden.

5. Borras, et al., 2016. Genomic landscape of colorectal mucosa and adenomas. Cancer Prevention Research. PMID: 27221540

6. Naproxen in Preventing DNA Mismatch Repair Deficient Colorectal Cancer in Patients with Lynch Syndrome. Clinical trial NCT02052908. https://clinicaltrials.gov/study/NCT02052908

7. Reyes-Uribe et al., 2021. Naproxen chemoprevention promotes immune activation in Lynch syndrome colorectal mucosa. Gut. PMID: 32641470

8. Immune checkpoints: They are natural “brakes” expressed by cells in the body to stop the immune system from attaching them. Cancer cells hijack this system and activate checkpoints like PD-1 and CTLS-4, to evade detection and destruction by the immune system.

9. Chang, et al., 2018. Immune Profiling of Premalignant Lesions in Patients with Lynch Syndrome. JAMA Oncology. PMID: 29710228

10. Prospective Lynch Syndromes Database (PLSD) https://plsd.eu/

11. Cancer Preventive Vaccine Nous-209 for Lynch Syndrome Patients. Clinical trial NCT05078866. https://clinicaltrials.gov/study/NCT05078866

12. D’Alise, et al., 2026. Nous-209 neoantigen vaccine for cancer prevention in Lynch Syndrome carriers: a phase 1b/2 trial. Nat Med. PMID: 41545594