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News and Views

# Expert's views and perspectives: an interview with distinguished investigator Dr. Ira Pastan at the National Cancer Institute at NIH

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**Statement of Significance: The FDA-approved Lumoxiti, a first-in-class medicine for hairy cell leukemia, is based on a remarkable translational research led by Dr Ira Pastan, a pioneer in immunotoxins. As a new class of anti-cancer drug, the immunotoxins have demonstrated clinical benefits for patients with cancers.**

**KEYWORDS: immunotoxin; moxetumomab pasudotox; CD22; *Pseudomonas* exotoxin A; cancer immunotherapy**

As an honoree of Paul A. Volcker Career Achievement Medal, 2020 and one of Samuel J. Heyman Service to America Medal (Sammies) finalists, Ira Pastan, MD, Co-Chief of the Laboratory of Molecular Biology (LMB), discovered a new class of drugs that can successfully treat a rare form of leukemia and hold promise to be effective therapies for pancreatic and lung cancer as well as mesothelioma. This US Food and Drug Administration (FDA)-approved drug, Lumoxiti [moxetumomab pasudotox (Moxe)] for the treatment of patients with relapsed or refractory hairy cell leukemia (HCL), is the result of decades of research led by Dr Pastan at the National Cancer Institute at National Institutes of Health (NIH). In 2018, shortly after the Lumoxiti was approved by FDA for marketing, the Chinese Antibody Society ("the Society") was honored to interview Dr Pastan who shared his insights on the opportunities and challenges for immunotoxin-based cancer therapy, his past experience to be a physician and then a scientist and his valuable suggestions for the Society and the Society's peer-reviewed journal, *Antibody Therapeutics*. Below is the transcript of the interview with Dr Pastan by the Society's volunteers Peng Lin, PhD, JD and Cong Yao, PhD., JD.

**Interviewers:** This is Peng Lin and Cong Yao from the Chinese Antibody Society. Thank you so much for agreeing to do an interview with us. Cong and I are both volunteers for the Chinese Antibody Society. Before the interview, we would like to briefly introduce our society. Our society is a non-profit organization, established in 2017 and serves as a platform fostering communication and collaboration among its members worldwide. The mission of Chinese Antibody Society is to bring together industry leaders, healthcare providers, researchers, academics, and investors to connect and collaborate on the discovery, development, manufacturing and marketing of therapeutic antibodies.

**Interviewers:** We had many successful events in the past, including our annual conference, webinar series and PharmaConnect. This interview is part of our new program experts' perspective. As part of this program, we plan to interview renowned experts in the therapeutic antibody field, and we will publish the interview transcripts on the Society's website and social media channels. We feel much honored to have you as our first expert in this program.

**Interviewers:** Today's interview will include three parts. The first part centers on your background, research and

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your current role in the NIH. For the second part, we hope to have your insights on the challenges and opportunities of immunotoxin-based immunotherapy. For the third part, we will seek your suggestions on our society, especially on our society's peer-reviewed journal *Antibody Therapeutics*.

**Interviewers:** We understand that you are the founder of the LMB in the National Cancer Institute, and you are also the expert of immunotoxin therapies. Could you please briefly talk about your past experience, what made you decide to become a physician and then a scientist, and what your experience was like at the LMB of the NIH?

**Dr Pastan:** I was born in Winthrop Massachusetts. I grew up in a working-class community.

When I was a kid, I was very good in science. At that time, being a doctor was a good career track for kids who were good at science, so I thought I probably would become a physician. I went to the Tufts College and majored in biology, and then to Tufts Medical School. In my first year of medical school, I talked to my advisor and told him that I wanted to do something related to medicine as a summer job and asked him if he could give me some advice. My advisor was a clinician but also had some space in a lab that was headed by Dr Ted Astwood. Ted was a professor of medicine and very famous endocrinologist. He had discovered anti-thyroid drugs that were used to treat hyperthyroidism. And he was also the editor of *Endocrinology*, the major endocrine journal at that time. So, the summer after my first year in medical school I worked in an endocrine lab for my advisor Bill Vanderlaan. He later moved to California and I was able to work directly with Dr Astwood. I worked in his lab all summers and was also able to do research during the school year. That was when I fell in love with research and actually published my first paper in *Endocrinology*, when I was a medical student. Remarkably, I was the sole author. Imagine what a generous person my boss was.

**Dr Pastan:** Then I went to Yale in New Haven to do my residency training in medicine. At the end of my 2-year residency training, I was drafted for military service and needed to go into the Army or the Navy or do some other form of military service. At that time, if you were a doctor and did well in the medical school, you could apply to the NIH and become an officer in the Commissioned Corps of the Public Health Service, which would fulfill the military obligation. So many young physicians applied to the NIH and became officers in the US Public Health Service. This led to the rapid expansion of NIH.

**Dr Pastan:** I joined the NIH in 1959. In the first 2 years, I worked in the clinical endocrinology branch of what was then called the National Institute of Arthritis and Metabolic Diseases. It is now called National Institute of Diabetes and Kidney Disease. I spent about 20% of my time seeing patients with endocrine disorders and thyroid disorders, and 80% of my time working in the lab. I discovered I liked working in a lab more than seeing the patients. I began to work on polypeptide hormones, e.g., thyroid stimulating hormone (TSH), and tried to figure out how TSH worked to stimulate thyroid growth and function. After doing that for 2 years, I realized that I did not have enough knowledge of biochemistry to do the research. Remember, molecular biology did not yet exist at that time. So, I went to work with a well-known biochemist Earl Stadtman, who is known for his pioneering work on glutamine synthetase. He was also the president of the American Society of Biological Chemistry. Earl was a great biochemist and also a great mentor. I worked with him for 2 years. At the end of the 2 years (around 1963), I was offered a full-time job back in the endocrinology branch doing research and seeing patients.

**Dr Pastan:** My early research focused on how thyroid stimulating hormone controls thyroid function and my research interest later expanded into insulin and cyclic AMP (cAMP). One big question at that time was how peptide hormones outside the cells can regulate something inside the cells. We provided some of the first evidences that the receptors for polypeptide hormones were located on the outside of the cells. Polypeptide hormones do not enter cells to carry out their function, but they bind to the receptors on the outside of cells and somehow activate signals inside the cells. I also became interested in the function of cAMP in cells, and I began to collaborate with Bob Perlman. Together, we showed cAMP plays a very important role in regulating gene expression in *Escherichia coli*. Receptors and cAMP were my two early research areas of interest.

**Dr Pastan:** Within a few years, I was asked to move to the National Cancer Institute and received additional resources to do my research. In the National Cancer Institute, I began to think about cancer. I realized that receptors probably have an important role in controlling cancer cell growth and that the overexpression of some receptors could actually cause cancer. In one of my early projects, we showed that Epidermal Growth Factor (EGF) receptors were overexpressed in many cancers. We further showed working with Doug Lowy that introducing an EGF receptor gene into normal cells and activating it with EGF can transform normal cells to cancer cells.

**Dr Pastan:** Later on, Dave Fitzgerald joined my lab as a postdoctoral fellow. He came to my lab because he was interested in how toxins enter cells, and we had developed methods to study this. David was interested in *Pseudomonas* exotoxin A, and after a few months' work, we showed that it enters the cell by a common endocytic pathway. While doing these studies, we were impressed with how effective *Pseudomonas* toxin was in killing cells and thought that it might be a good idea to attach it to a monoclonal antibody to target and kill the cancer cells. Around that time, there was a lot of interest in using monoclonal antibodies to deliver radioisotopes, cytotoxic drugs and toxins to kill cancer cells.

**Dr Pastan:** Our initial efforts focused on figuring out the functions of different domains of *Pseudomonas* exotoxin A [1]. We determined that one region of the toxin binds to the cell, and another region can kill the cell. Thus, we could get rid of the cell binding region and replace it with an antibody or a piece of an antibody. Originally, we used a chemical cross-linker to couple a modified toxin to an antibody. But then we became more sophisticated, and one of my fellows, Vijay Chaudhary, constructed a fusion protein composed of the Fv portion of an antibody directly fused to the toxin. We called these fusion proteins recombinant immunotoxins (RITs). That was really a great breakthrough. We did this for several different immunotoxin targets. We initially made an immunotoxin targeting CD25 named LMB-2. It has been in clinical trials and has produced responses in

patients with T cell leukemia. But the number of leukemias expressing CD25 is relatively low, so we decided to focus on CD22, because CD22 is expressed on many lymphomas and other B cell malignancies. We identified a monoclonal antibody that bound to CD22, cloned the Fv portion and attached it to PE38 to make a RIT named BL22 [2]. We carried out clinical trials with BL22 and showed it produced complete remissions in some patients with drug-resistant HCL, but it unfortunately also produced hemolytic uremic syndrome (HUS) in a few patients [3].

To overcome this side effect, we altered the binding region of BL22 to increase its affinity, making it about 10-fold more active. This change also reduced the frequency and severity of HUS in patients. This new protein was named HA22 and was eventually licensed to Medimmune for clinical development. Medimmune named the agent Moxe and sponsored several clinical trials in which Moxe was shown to be safe and effective. These findings led to a world-wide multi-center clinical trial that was completed in 2018 in which 80% of patients achieved hematologic remission, and 41% achieved complete durable remissions [4]. On the basis of these results FDA approval was granted in September 2018, and the agent is now marketed as Lumoxiti. Although approved for refractory HCL, Lumoxiti has shown anti-cancer activity in other B cell malignancies, and clinical trials in other diseases are underway.

**Interviewers:** This is really a great story. Thank you for sharing the story with us. What is your current research interest? Are you still working in this particular area?

**Dr Pastan:** Yes. Because targeting CD22 for B cell malignancies works really well, I decided to work on multiple myeloma. Multiple myeloma is another B cell malignancy, but the cells are more mature. One of my new projects is to develop an immunotoxin targeting B-Cell Maturation Antigen (BCMA). We have published a few articles, and we have shown that anti-BCMA immunotoxins are really effective in many models. A company is now working on it for clinical trials. I think one of the articles on targeting BCMA was published in your Society's new journal, *Antibody Therapeutics* [5].

**Dr Pastan:** We also have evidence showing that there is a synergy between immunomodulator therapies (e.g., checkpoint inhibitors) and immunotoxins. We have evidence that immunotoxins produce immunogenic cell death. We are now doing clinical trials combining an immunotoxin targeting mesothelioma with a checkpoint inhibitor [6].

**Interviewers:** That is really impressive. So in your opinion, what will be the future of immunotoxin-based immunotherapies? What will be the biggest challenge in immunotoxin in the next 5–10 years?

**Dr Pastan:** I will try and give you a big picture. There is a lot of progress in this field, but if a patient has a metastatic cancer, except for melanoma, it is very likely that the patient is still going to die because of the metastatic cancer. I believe we need different kinds of agents that can kill the cancer by different mechanisms, because the cancer cell evolves very quickly and becomes drug-resistant, e.g., resistant to taxane, taxane analoges and doxorubicin. Anyway, cancer cells become resistant to chemotherapies very quickly. Inhibiting protein synthesis that toxins do is a novel mechanism to kill the cancer cells. I think we need to purse using that in addition to everything else.

One of the main barriers to immunotoxin therapy is that in patients with normal immune system, anti-drug antibodies appear after 1 or 2 two cycles, or 3 to 6 doses [7]. So I have been working in various ways to remove B and T cell epitopes on the protein so that the patient will have less or delayed formation of Anti-Drug Antibodies (ADAs) [8]. In summary, the most important advantage of immunotoxins is that they can kill cancer cells by a novel mechanism. The biggest barrier is the development of anti-drug antibodies.

**Interviewers:** For those immunotoxins, are you also looking for novel targets or novel cancer antigens?

**Dr Pastan:** I think you are asking me what would be a good target for immunotoxins? The answer is an antigen that is frequently expressed on tumors and not expressed on essential normal tissues. Lineage restricted differentiation antigens are good targets such as GPC3, CD19, CD20, CD22, CD25 and mesothelin. We spent a lot of time looking for novel targets for immunotoxins on solid tumors, and this led to the discovery of mesothelin, which is expressed on about 30% of solid tumors. Mesothelin is now a very popular target for antibody and Chimeric Antigen Receptor (CAR)-T cell based therapies.

The problem is that even if a normal tissue expresses a small amount of target antigen there will be toxicity. One major factor that contributes to this toxicity is blood flow, because normal tissues have very good blood flow and solid tumors do not. For example, as soon as an immunotoxin is injected into a patient, the immunotoxin goes to normal tissues, whereas it takes many hours to enter solid tumors. So the normal tissues are damaged even before the tumor responds. Some people may think that if the target is not expressed at high level in normal tissues, it might be okay. But I do not think so. I think that we need a target that is not expressed in normal cells, e.g., lineage restricted differentiation antigens, or carcinoembryonic antigens.

**Interviewers**: This is very interesting. For the third part of our interview, do you have any suggestions for our society, in particular our society's official journal, *Antibody Therapeutics*?

**Dr Pastan:** So clearly the field of antibody-based therapies is still rapidly expanding. There is a need for good journals to publish good solid research papers in this field. The journal should not try to compete with the cell or nature, as I do not think that should be the function of the Society's journal. I think the journal should ensure that the Society's members would have a place to publish quickly and obtain wide publicity. Being able to publish quickly would be very helpful.

**Interviewers:** So your point is that one primary function of this journal is to provide a platform so that the members of the Society can publish their work very quickly.

**Dr Pastan:** Yes, that is important. However, you should also be careful. All articles should be given a careful peer review.

**Interviewers**: As you may be aware of, Mitchell Ho is the Editor-In-Chief of the journal.

**Dr Pastan:** Yes. Mitchell works very closely with me. He is a very remarkable man. I think he will do a very good job.

**Interviewers:** We also notice that you have agreed to speak at our annual conference, which will be held on 7 April,

2019 in Cambridge, MA. We are very curious what you will talk about at our annual conference.

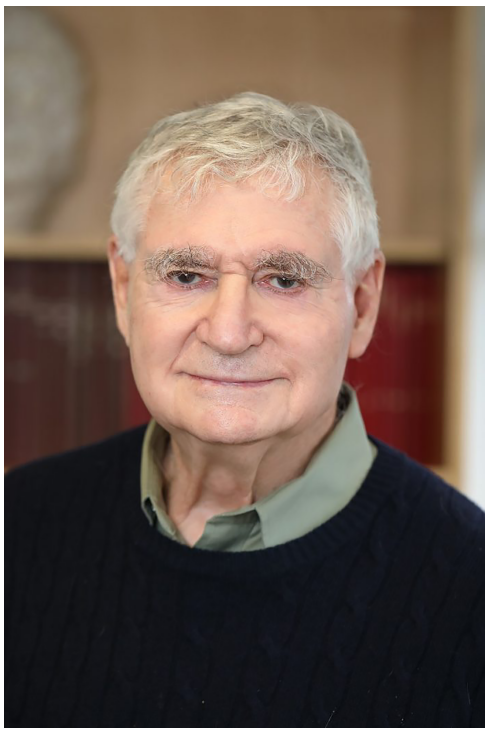
**Dr Pastan:** It is likely that my topic would be Immunotoxins: From Conception to FDA Approval.

**Interviewers:** We are also curious about your experience as a physician scientist. When we were doing the research, we had the impression that a lot of research are relatively basic and may not be perceived as closely related to immediate clinic use. Do you think that as researchers, we should focus more on something that is more clinically relevant?

**Dr Pastan:** I think we have to be very careful about that. I spent most of my life doing basic research on receptors, gene regulation and endocytosis. And then I did some work in multidrug-resistant cancer and immunotoxins, which are more clinically relevant. But as you know, the most important advancement in cancer therapy right now is checkpoint inhibitors. These agents came out of basic research in immunology. If we did not have research trying to understand what controls inflammation, we would not have checkpoint inhibitors. Both the basic research and translational research are very important. I think we must support both.

**Interviewers:** After the basic research, how do you think we can facilitate the transition from the basic research to translational medicine?

**Dr Pastan:** We need many different players. We need people doing basic research. We also need companies who have people with the right skills to get the drug to the market. This is a very complicated process.



Dr. Ira Pastan (Co-Chief, Laboratory of Molecular Biology; Head, Molecular Biology Section, National Cancer Institute).

**Interviewers:** One mission of the Chinese Antibody Society is to build up a platform that can bring everybody together.

**Dr Pastan:** Yes, during my career making immunotoxins, I found speaking at meetings where companies were present was very important, because that provided me some context that helped me with the drug development. I do think it is very important to create an environment where everyone can get together and talk to each other.

**Interviewers:** Great! Hopefully, we can talk to you again at our annual meeting.

**Dr Pastan:** OK. See you guys during the meeting!

**Interviewers:** We look forward to meeting you this April in Cambridge, MA! Thank you for your time.

**Dr Pastan:** You are very welcome!

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