

Thank you, Sarah for kind introduction. Thank you, Craig and the member of the board. Thank you everyone. Thank you so much for this great honor.

I am so honored to receive this award. This is a high mark of my research career.

I was born in a family of medical tradition and actually graduated from a medical school to be a gynecologist. Some luck and support by mentors and family brought me to this country, and this country nurtured me as a basic cell and developmental biologist. While basic biology gives me excitement which I have been enjoying for a long time, I have had a feeling that I have not met the expectations of my family, friends, and mentor, who probably expected that all the basic training I had received in this country would eventually contribute to clinical medicine back home in Japan. However, this recognition by the MHE Research Foundation gives me a relief for this long-standing remorse of mine, especially because it is related to a human disease. That is why this award from the Foundation has even more special meaning to me.

Before continuing, I must remind you that there are many scientists who have studied this disease for long time and made much greater contribution than mine, For example, Dominique Stickens, who just received the REACH Award, and Maurizio Pacifici here in the audience. Compared with their contribution, my contribution on the disease itself is small.

I have been studying heparan sulfate and heparan sulfate proteoglycans in my entire scientific career. And since I became an independent principal investigator in early 1990's, I focused on the brain and nerves. Like other heparan sulfate researchers, I knew nothing about MHE until 1999 when the Ext1 gene was demonstrated to be a critical enzyme for heparin sulfate production. That was literally eye-popping news. But for some time, I did not pay much attention to MHE until 2003 when my office phone rang out of blue, which was of course from Sarah.

One of the reasons why I had not paid much attention to MHE before 2003 was that textbooks in the orthopedics and pediatrics seldom mentioned MHE symptoms outside the skeletal system. It was very puzzling to me. All researchers working on heparan sulfate knew that

heparan sulfate is expressed in all organs and tissues in the human body. For my part, I knew that heparan sulfate is highly concentrated in nerve cell synapses, which are the junctions between individual nerve cells and where nerve cells communicate each other. So why MHE manifests only as a bone disease? Honestly, this notion was not only puzzling but also disappointing for most of the heparan sulfate researchers, because it suggested that the molecule they believed to have essential functions in many organs and tissues might be important only in bones.

But, Sarah's call and subsequent help from the MHE patient community hardened my belief that the deficiency of heparan sulfate can affect tissues and cells other than bone. And our analysis of brain-specific Ext1 knockout mice has shown that it is indeed the case. Now we are in the position to directly address whether deficiency in heparan sulfate can cause dysfunction of nerve cells and muscle cells. Using our mouse model, other researchers are studying the effect of heparan sulfate deficiency in other cells, such as blood vessels, and skin. These studies are expected to shed light to neglected symptoms of MHE.

Having said that, I was initially reluctant to speak up that MHE symptoms may not be limited to bones. After all, patients already suffer from bone tumors. What is the benefit of telling them that they can have yet other problems? But quite unexpectedly, I was thanked and encouraged by Sarah and MHE families, so that we continue this line of research. I also got a few phone calls from patients asking what they can do for my research on neurological symptoms. I was impressed by the courage of patients and families to commit to understand this.

Scientifically, the notion that MHE is not a simple bone disease but a multifaceted syndrome is perfectly consistent with the idea that heparan sulfate researchers have about the molecule. In a way, the name of the disease "multiple hereditary exostosis" is a kind of misnomer. And I am afraid that this name may put it a little disadvantageous position in terms of public attention and federal research funding.

With these words, now I would like to move on to the last thing I really need to say on behalf of researchers working on MHE and heparan sulfate. We need more federal funding to study this

disease and to eventually find a cure. Although supports from the Foundation mean a lot to researchers, but federal funding is the key to bring it to the next level. I hope that the Foundation will intensify the effort toward this direction, and I will do everything I can do for this cause.

Of course, senators and congressmen have probably heard million times such a plea from scientist. So I present just one sales pitch for MHE. MHE is unique in that the research on this disease could have very broad implication, because, as I said, heparan sulfate is present and functions in many organs and tissues. For instance, our study on Ext1 conditional knockout mice can help understand developmental mental problems in children, such as autism and attention deficit disorders. So I believe funding MHE research is a very good investment for the country's biomedical research and public health.

When Sarah told me the other day that I was supposed to give a speech at this gathering, I replied that I was not particularly comfortable making a speech in a formal setting and was going to give a really short one. It turned out now that my speech is not very short. I apologize for that. I would appreciate your understanding that it is because my gratitude of receiving this award has deepened since then. I just wanted to express my appreciation to this recognition. Although I cannot promise a cure for the disease, I promise to continue my utmost effort to study the function of heparan sulfate and Ext genes, and thereby contribute the research on MHE. Thank you for your attention. And thank you for your recognition and encouragement to my research.

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