William S. Blaner: successful researchers ought to be exceptionally motivated towards generating new knowledge

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Editor's note

Over the century, our understanding of retinoids has been evolving and there remains a lot of unanswered questions to their significance in human body. Retinoids, in fact, are a class of chemical compounds that are vitamers of vitamin A or are chemically related to it. They are commonly used in medicine that works to regulate epithelial cell growth. Retinoids have been found to play essential roles in vision, energy metabolism, immune function, growth of bone tissue, treatment of skin lesions, and even maintenance of the normal endocrine activities of pancreas.

Prof. William S. Blaner is the Professor of Nutritional Medicine in Columbia University, New York, USA. Over the years, he has been conducting researches that strive to understand the metabolism and actions of retinoids, with focuses on the essential biological processes mediated by retinol-binding protein (RBP), the processes through which provitamin A carotenoids are converted to retinoids, establishing actions for retinoids that are independent of their roles as transcriptional regulators, and developing new methodologies for assessing retinoid status in infants who are at risk of vitamin A deficiency.

Hepatobiliary Surgery and Nutrition (*HBSN*) is happy to interview Prof. Blaner this time, who will share with us the current understandings about retinoid actions and metabolism, the mechanism by which retinoid helps prevent or slow pancreatic disease progression, the significance of retinoid-dependent actions in cancer prevention and embryologic development, and some interesting behind-the-scene stories in his research.

Expert's introduction

William S. Blaner, PhD, currently serves as the Professor of Nutritional Medicine in Columbia University, New York, USA (*Figure 1*). He obtained his PhD in Biochemistry from University of Tennessee in 1979, and was then trained as a post-doctoral fellow in the laboratory of Dr. Dewitt S. Goodman in Columbia University from 1980 to 1982. Prof. Blaner's research is focused on understanding the metabolism and actions of retinoids. His recent work has employed genetic manipulations of mice to study these processes. He has published over 200 original research articles, reviews and book chapters. He also serves as editorial board member for multiple distinguished journals including *HBSN*.

Figure 1 Prof. William S. Blaner.

Interview

HBSN: What are the current understandings about retinoid actions and metabolism?

Prof. Blaner: Retinoids (vitamin A and its natural and synthetic analogs) are potent transcriptional regulators. Retinoic acid, the most transcriptionally active naturally occurring retinoid species, acts through three distinct ligand-dependent transcription factors referred to as retinoic acid receptors (RARs; specifically, RARα, RARβ, and RARγ). Retinoic acid and the RARs have been established to regulate directly the transcription of literally hundreds of genes. In addition, retinoic acid and some of its metabolites are potent agonists for the three distinct retinoid X receptors (RXRs; specifically, RXRα, RXRβ, and

RXRγ), but it is still a matter of controversy whether these retinoids are the sole natural ligands for the RXRs.

Although mostly lost in contemporary considerations of retinoids, one must also note that the work of Wald and others nearly a century ago establishing that 11-cis-retinaldehyde, another vitamin A metabolite, is the visual chromophore responsible for photoreception in the retina, and hence vision. There is also growing evidence that retinoic acid and other retinoids may have actions within cells that are independent of their direct transcriptional regulatory effects. This notion though is not universally accepted by all investigators working in the retinoid area.

The genes that have been shown to be transcriptionally responsive to retinoic acid do not fit easily into a few physiological categories. However, many are important for regulating cell proliferation and differentiation. Owing to this, retinoids act critically in embryogenesis, the immune response, maintaining barrier functions, spermatogenesis and oogenesis, and the replenishment of somatic cells upon tissue injury. The early clinical interest in using retinoids for preventing or treating disease came primarily from oncologists and dermatologist. More recent clinical interest in retinoid actions has come from those focused on metabolic disease development and prevention.

HBSN: You proposed that retinoid may be useful for preventing or slowing pancreatic stellate cell (PSC) activation and pancreatic disease progression. Can you explain the mechanism behind?

Prof. Blaner: My proposal for PSCs simply extends ideas that have been proposed regarding retinoid and retinoic acid metabolism and actions in hepatic stellate cells (HSCs) and hepatic disease. It is well known that both HSCs and PSCs share many morphological and biochemical characteristics, including great capacity for the storage of retinoids. Since HSCs store more than half to the total retinoid present in the body of a healthy individual, there has long been research interest in HSC retinoids and how their loss during HSC activation may affect hepatic disease development. Recent independent work from Gudas and colleagues at Weill Cornell in New York and del Río Hernández and colleagues at Imperial College London has established that all-trans-retinoic acid and synthetic retinoic acid agonists that specifically recognize RARβ can mitigate HSC activation and nonalcoholic fatty liver disease development. This work, which was carried out in mouse models and rodent and human HSCs in culture, will need to be extended to the clinical setting. Given the similarities between HSCs and PSC, one would suspect that treatments with RARβ agonists would likely be effective in blocking PSC activation.

HBSN: Are you aware of any clinical trials going on right now that support the validity of your proposal?

Prof. Blaner: No, not for PSC activation or pancreatic disease. I am aware of investigators who are proposing to investigate the use of retinoids in trials to block HSC activation and hepatic disease. But I am not aware of where these plans currently stand. If these planned trials are undertaken and meet with some success for blocking HSC activation, these will undoubtedly be extended to PSC activation.

Albeit somewhat different, I am also aware of planned trials to use RARβ agonists to restore pancreatic islet β-cell function.

HBSN: Your team has been using animal model to study the essential biological processes mediated by RBP. What is the significance of retinoid-dependent actions in cancer prevention and embryologic development?

Prof. Blaner: Yes, we have been studying RBP actions for a considerable number of years. However, these studies are focused on the role of RBP in the development of metabolic diseases including obesity, glucose intolerance, insulin resistance, hepatic steatosis and vessel wall disease and not on cancer prevention or embryologic development. As noted above in my response to question #1, retinoids are potent transcriptional regulators that act through many genes important to cell proliferation, differentiation and death. This accounts for the research interest in cancer prevention and embryologic development. However, the actions of retinoids on cells also have limited the usage of retinoids in clinical medicine owing to their potential adverse effects on cell proliferation and differentiation (resulting in a high degree of teratogenicity associated with retinoid usage) and the possibility of off target toxic effects.

HBSN: Your laboratory has been developing new methodologies to assess retinoid status in infants having vitamin A deficiency. What is the current status and future direction of this study?

Prof. Blaner: We have shown that blood RBP levels

are as effective for predicting vitamin A deficiency in infants as blood retinol levels. Moreover, RBP levels can be measured cheaply and effectively using immunologic approaches, whereas retinol measures require sophisticated instrumentation. This idea was picked up and carried forward by a number of governmental and non-governmental agencies. We are no longer actively involved in this research.

HBSN: Would you introduce us to some of your current funded research?

Prof. Blaner: My research is supported by the National Institutes of Health (NIH), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). I am the principal investigator on two NIH R01 grants. One of them is called "Postprandial Vitamin A" (R01DK068437). The goal of the project is to identify the mechanistic basis for why RBP4 synthesized in adipocytes gives rise to impaired glucose clearance from the circulation and the development of fatty liver. These investigations involve the use of novel transgenic mice that express RBP4 specifically in adipocytes. Another one is called "Vitamin A Homeostasis: Retinyl Ester Stores" (R01DK101251). One goal of this project is to identify at the molecular level the enzymes responsible for the hydrolysis of chylomicron remnant retinyl esters that are taken up by hepatocytes. The second goal of this project is to identify at the molecular level the enzymes responsible for the hydrolysis of stored retinyl esters within the lipid droplets of HSCs.

HBSN: What are the constant challenges/difficulties encountered in research?

Prof. Blaner: The administrative burdens that are imposed on investigators and research groups are ever increasing. These burdens have progressively increased over the past twenty years. I now spend approximately half of my time dealing with administrative matters associated with research. This includes taking required courses, online and in person, completing required research protocols for human and animal research, dealing with personnel issues, and dealing with issues internally and externally associated with chemical usage, drug usage, and radiation usage. Possibly, my experiences are unique to my University but they drain enthusiasm for doing research. Half of my professional activities are now directed at responding to various administrators' demands that I address their concerns. If I had encountered these sorts of administrative demands earlier in my career, I may have left academic research.

HBSN: What led you to study retinoid metabolism and actions?

Prof. Blaner: Since the time of my graduate education, I have been interested in understanding the actions in the body of small bioactive lipids like the retinoids. Early on, I became attracted to the retinoids and have worked in this area for most of my career. I have colleagues who have used an analogy to the Star Wars movies to explain this. They maintain that research involving retinoids is like "the dark side of the force" that continually draws one in deeper and never allows one to leave.

Although I have worked primarily with retinoids throughout my career, I have also work with other bioactive lipids exploring their metabolism and actions. I am presently excited about a project that is ongoing in my lab exploring the metabolism and actions of N-acylethanolamides and 2-acylmonoglycerols. The research questions we are addressing here are intellectually similar to those we have addressed in our retinoid work.

HBSN: You have been actively involved in research throughout your career. In your opinion, what are the most enticing aspects of research?

Prof. Blaner: I derive considerable satisfaction from posing a scientific question in need of being addressed, undertaking the research activities needed to answer the question, and obtaining an answer to the question. Often this process can take many years, but I do find this to be very satisfying intellectually.

At the more personal level, I enjoy traveling abroad and meeting with other scientists who similarly enjoy and are committed to doing research. There is a certain pleasure in meeting with others who share the same intellectual excitement and satisfaction for research. I have enjoyed my experiences in meeting with biomedical scientists in China, elsewhere in Asia, and in Europe and South America and in sharing our enthusiasm for undertaking research.

HBSN: What are the key qualities a successful researcher must possess/cultivate?

Prof. Blaner: This is a very difficult question for me to address, but one I have often thought about. Over

the course of my career, especially in my early career, I came to know many who were pursuing a career as an independent researcher, but who were not successful. I saw many needed abilities and characteristics in these individuals, ones that I judged to be superior to my own. Some were exceptionally bright or remarkably insightful thinkers, some had great skill in the laboratory, others had exceptional communication skills, still others possessed great management and interpersonal skills, but for some reason these considerable skills were insufficient to bring success as a scientific researcher. Certainly, to be successful one needs to possess strong skills in each of these areas. However, I suspect that, above all, one needs to be exceptionally motivated towards generating new knowledge and exceptionally driven to this end.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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