Article:
Julia Weber, et al.
Sandwich Immunoassay for Bioactive Plasma Adrenomedullin.
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Guest: Dr. Andrea Sparwasser, head of the Research and Development Laboratory and the Intellectual Property Manager of Sphingotec GmbH in Berlin, Germany.

Randye Kaye: Hello, and welcome to this edition of "JALM Talk" from *The Journal of Applied Laboratory Medicine*, a publication of the American Association for Clinical Chemistry. I'm your host, Randye Kaye.

In the early '90s, a group of scientists were screening peptides from a pheochromocytoma for biological activity. They purified a protein that they named adrenomedullin as it raised platelet cyclic AMP concentrations and found that it is a 52 amino acid protein hormone that shares homology with calcitonin gene-related peptide. It is expressed in a wide range of issues, with the highest expression in endothelial tissues, reflecting its role in maintaining the vascular endothelium.

Further, plasma adrenomedullin concentrations are elevated in the cardiovascular disorders, suggesting a role for this hormone in the homeostasis of blood pressure. The highest concentration increases are found in septic shock and it therefore, may play a role in the hypotension observed in these patients. Due to these clinical applications, an article titled "Sandwich Immunoassay for Bioactive Plasma Adrenomedullin," published in the September 2017 issue of JALM discusses the steps involved in the development of an assay suitable for routine use to measure bioactive adrenomedullin, including testing for a common interference, compliment factor H.

One of the authors of this article is Dr. Andrea Sparwasser, head of the Research and Development Laboratory and the Intellectual Property Manager of Sphingotec GmbH in Berlin, Germany, and she is our guest for today's podcast. Welcome, Dr. Sparwasser. You developed a rapid sandwich immunoassay for the detection of bioactive adrenomedullin. Can you describe to us what bioactive adrenomedullin is?

Andrea Sparwasser: Yeah, sure. Bio-ADM or bioactive adrenomedullin is a circulating peptide that is produced from its precursor molecule for adrenomedullin via two-stage enzymatic process. First, the precursor is converted into an inactive C-terminal glycine-extend peptide intermediate which is then subsequently converted into the mature form with 52 amino

acids through enzymatic amidation. It plays a highly relevant role in the pathophysiology of acute clinical settings.

Randye Kaye: Okay, thank you. In what pathological space would this bioactive adrenomedullin be relevant to measure?

Andrea Sparwasser: Well, bio-ADM is a biomarker for vascular integrity, including vasodilatory activity and has a function as stabilizator of vascular leakage. There are two major clinical situations where these properties are highly relevant. One is sepsis and the other one is acute heart failure. The sepsis patients are likely to develop a shock situation where every hour to the treatment counts. Due to its vasodilatory activity, high plasma levels of bio-ADM predict the development of shock in septic patients up to two days before the onset of shock, giving the physician the time he needs for intervention. In acute heart failure patients, the major cause of mortality and pre-hospitalization is due to incomplete decongestion. The physiological background behind this is the vascular leakage that leads to edema. In these patients, bio-ADM concentrations will increase as bio-ADM has the property to stabilize this leakage.

The physiological background helps the physician to detect residual congestion in patients where the congestion status is unclear. Bio-ADM is in both pathophysiologic situations, a unique biomarker.

Randye Kaye: Since bio-ADM is relevant in critically ill patients who are mainly treated in the ED and ICU, what technical requirements need to be fulfilled before this can be a routinely used biomarker?

Andrea Sparwasser: Here, we should distinguish two things, one is the requirement of the biomarker and the other, the assay itself. First of all, a biomarker needs to meet an unmet medical need. It needs to give information on top of standard of care to become a biomarker of relevance. Useful biomarker in acute settings needs to be measurable so the analyte has to be stable. Secondly, you need to have a clear cutoff, meaning that it should be independent from any comorbidities, so the threshold is applicable in all clinical settings.

In addition, it is essential to have a biomarker that is changing dynamically; that is of importance if that allows the physician to act timely on the patient's condition. It is also valuable to have a sample matrix that is easily accessible. Bioactive adrenomedullin fulfills all the mentioned criteria as validated in almost 20,000 patients.

Now, getting to the requirements of the methods to deliver the patient's result. An assay suitable for laboratory routine needs to have a short incubation time, needs to be easy to perform, has to have a sufficient assay sensitivity, and should be able to distinguish normal and pathological elevated bio-ADM concentration. The Sphingotech bio-ADM assay meets all the requirements and has properties beyond that that can be found in more detail in the publication.

Randye Kaye: Besides the active hormone bio-ADM, other peptides derived from the precursor peptide pro-adrenomedullin. Why is bioactive adrenomedullin unique, and what's the difference between bio-ADM and other molecules derived from this precursor?

Andrea Sparwasser: Well, besides bio-ADM, the well known biomarker of prognosis is the mid-regional pro-ADM, which is shortly termed MR-proADM. Both bio-ADM and MR-pro-ADM are deduced from the same precursor molecule, but only bio-ADM has an active function in the body's physiology. To enable an early prediction and the timely monitoring for clinical routine, a good biomarker needs to be stable but also needs to change accordingly to the patient's condition. So only bio-ADM, as the name says, is able to detect the bioactive adrenomedullin that is of relevance for prediction, diagnosis, and monitoring of critically ill patients.

Randye Kaye: Thank you. And just one more, is there anything else that I haven't asked you that you would like to add to what you've said or is this good?

Andrea Sparwasser: No. I guess that's it. That's the story about bio-ADM.

Randye Kaye: Okay. Thank you so much for joining us today.

Andrea Sparwasser: Okay. Thank you. That was great.

Randye Kaye: That was Dr. Andrea Sparwasser from Sphingotec GmbH talking about the JALM article, "Sandwich Immunoassay for Bioactive Plasma Adrenomedullin" for this podcast. Thanks for tuning in for "JALM Talk." See you next time and don't forget to submit something for us to talk about.