AUTHOR COMMENTARIES - From Special Topics

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Bo Ahrén
From the Special Topic of Diabetes

In our Special Topics analysis of diabetes research over the past decade, the paper "Inhibition of dipeptidyl peptidase IV improves metabolic control over a 4 week study period in type 2 diabetes," (Ahrén B, et al., Diabetes Care *25:869-875 [2002]) is the #1 paper in the Research Front Map Dipeptidyl Peptidase-4 Inhibition Treatment of Type 2 Diabetes. It had 218 cites at the time of the analysis, and according to* Essential Science Indicators℠ *from Thomson Reuters, it now has 224 cites.*

Lead author Dr. Bo Ahrén's record in Essential Science Indicators *includes 222 papers, the majority of which are classified in the fields of Clinical Medicine and Biology & Biochemistry, cited a total of 5,030 times between January 1, 1999 and February 28, 2009. Three more of these papers are also key papers in the same Research Front Map. Dr. Ahrén is the Dean of the Faculty of Medicine at Lund University in Sweden.*

In the interview below, ScienceWatch.com *talks with Dr. Ahrén about this paper and its impact on the research community.*

SW: Would you please describe the significance of your paper and why it is highly cited?

The paper published in 20021 was the first clinical study in which an inhibitor of dipeptidyl peptidase-4 (DPP-4) was examined in subjects with type 2 diabetes. The study was the proof-of-concept of the strategy to inhibit DPP-4 as a therapy in type 2 diabetes. The study was performed at five different research centers in Sweden. It had a four-week duration and showed that a DPP-4 inhibitor reduced fasting and 24-hour glucose levels as well as HbA1c levels. Furthermore, the paper also showed that DPP-4 inhibition is safe and tolerable.

This paper initiated a huge interest in this concept of treating subjects with type 2 diabetes and has since been followed by a number of studies and also development of several DPP-4 inhibitors. Some of these DPP-4 inhibitors (vildagliptin and sitagliptin) have now reached the market, whereas others are in late phase III and/or have been filed2.

SW: How did you become involved in this research, and were there any particular successes or obstacles that stand out?

DPP-4 inhibition as a therapy is based on the characteristic of this enzyme to inactivate the incretin hormone glucagon-like peptide-1 (GLP-1). GLP-1 is an incretin

hormone which has islet effects of potential interest to perturb in type 2 diabetes, such as stimulation of insulin secretion, inhibition of glucagon secretion, and also, at least in rodents, an increase in ß-cell mass. I had been working on this gut hormone since the mid 1980s and on DPP-4 inhibition ten years before this publication. In 1992, GLP-1 had already been suggested as a potential novel therapy of type 2 diabetes in a study which was performed together with Suad Efendic and Mark Gutniak in Stockholm3. A problem in this development was that GLP-1 was rapidly inactivated, which made native GLP-1 unrealistic as a therapy. This was overcome by acknowledging that the inactivation of GLP-1 is executed by DPP-4, and therefore DPP-4-resistant GLP-1 receptor agonists or DPP-4 inhibitors are therefore possibilities for GLP-1-based therapy in the clinic.

"The rapid and extensive development of DPP-4 inhibition as a therapy of type 2 diabetes, which is now used clinically worldwide, therefore had its clinical start in this publication."

SW: Where do you see your research and the broader field leading in the future? What are the implications of your work for this field?

After the establishment that it was DPP-4 which was responsible for the rapid inactivation of GLP-1, it was suggested that DPP-4 inhibition would be an alternative approach to use the therapeutic promises of GLP-1 without using native GLP-14. Therefore, since the late 1990s, DPP-4 inhibition has been explored, and we showed that this was feasible in animals5. Thereafter, it was natural to examine this in subjects with type 2 diabetes, which was the study initiated by Novartis Pharma, which resulted in the 2002 publication1. The rapid and extensive development of DPP-4 inhibition as a therapy of type 2 diabetes, which is now used clinically worldwide, therefore had its clinical start in this publication.

1 Ahrén B, Simonsson E, Larsson H, Landin-Olsson M, Torgeirsson H, Jansson PA, Sandqvist M, Båvenholm P, Efendic S, Eriksson JW, Dickinson S, Holmes D, "Inhibition of dipeptidyl peptidase IV improves metabolic control over a 4 week study period in type 2 diabetes," *Diabetes Care* 25:869-75, 2002.

2 Ahrén B, "Dipeptidyl peptidase-4 inhibitors—clinical data and clinical implications," *Diabetes Care* 30:1344-50, 2007.

3 Gutniak M, Ørskov C, Holst J, Ahrén B, Efendic S, "Antidiabetogenic effect of glucagon-like peptide-1 (7-36)amide in normal subjects and patients with diabetes mellitus," *N. Engl. J. Med.* 326:1316-22, 1992.

4 Holst JJ, Deacon CF, "Inhibition of the activity of dipeptidyl-peptidase IV as a treatment for type 2 diabetes," *Diabetes* 47:1663-70, 1998.

5 Ahrén B, Holst JJ, Mårtensson H, Balkan B, "Improved glucose tolerance and insulin secretion by inhibition of dipeptidyl peptidase IV in mice," *Eur. J. Pharmacol.* 404:239-45, 2000.

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Bo Ahrén's current most-cited papers:

- In *Essential Science Indicators*, with 300 cites: Wallenius V, *et al.*, "Interleukin-6-deficient mice develop mature-onset obesity," *Nature Med.* 8(1): 75-9, January 2002.
- In the Research Front Map (Drug Treatment for Type 2 Diabetes), with 224 cites: Ahrén B, *et al.*, "Inhibition of dipeptidyl peptidase IV improves metabolic control over a 4-week study period in type 2 diabetes," *Diabetes Care* 25(5): 869-75, May 2002. 224 cites.

Source: *Essential Science Indicators* from Thomson Reuters.

KEYWORDS: DIPEPTIDYL PEPTIDASE 4 INHIBITOR, DDP-4, TYPE 2 DIABETES, THERAPY, MULTICENTER TRIAL, FASTING GLUCOSE, 24-HOUR GLUCOSE, HBA1C, VILDAGLIPTIN, SITAGLIPTIN, GLUCAGON-LIKE PEPTIDE-1, GLP-1, INSULIN SECRETION, GLUCAGON SECRETION, BETA-CELL MASS.

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