Why Discovery of PSA was not Granted a Nobel Prize?

Author: Oktay Özman

Affiliation: Urology Department, The Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands

Oktay Özman, **Corresponding author**
The Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital,
Plesmanlaan 121, 1066 CX Amsterdam,
Mobile: +31 6 23 03 54 02,
e-mail: ozmanoktay@hotmail.com

Keywords: Prostate-specific antigen, prostate cancer, Nobel Prize

At the time, I was composing my thesis concerning prostate-specific antigen (PSA) on diagnosis of prostate cancer (PCa) and realized that PSA, a unique biomarker ever affecting clinical practice of a commonly seen cancer comprehensively and radically, has took for granted for decades. Yet, although being considered a groundbreaking discovery, PSA was not awarded a Nobel Prize. I aimed to draw attention to PSA discovery's lack of Nobel Prize acknowledgement despite its significance for PCa clinical practice. The committee has some reasons for not considering discovery of PSA for the prize. Instead of therapeutic applications, the Nobel Prize is often given for advances that have a substantial influence on basic science. But still, in 2003, they rewarded the developments concerning magnetic resonance imaging[1]. This imaging modality may be seen as a sound clinical application that is also altering PCa care nowadays.

Discoveries regarding micro-organisms, especially viruses like hepatitis-C virus (HCV), human papilloma virus, human immunodeficiency virus, which stand as underlying causes of cancers have been always a popular topic and researchers who involved in the topic dominated the prize[2]. Discovery of HCV nearly coincided with the same time period of early PSA studies. It is interesting to note that during the long duration of the award, not just PSA but the whole PCa research area has been disregarded. Charles Brent Huggins received the lone PCa research prize for his work on the hormonal treatment of the disease[3]. He shared the prize with another researcher who -again- investigates the association of cancers and viruses.

Another committee policy-related reason for the omission of PSA from being rewarded may be abundance of pioneers contributing the topic. Based on widely spoken acknowledgement, PSA was discovered by Richard Ablin in 1979[4]. But this presumption conceals a more contentious issue than the ongoing discussion about the widespread use of PSA in PCa screening. For instance, a group of scientists led by T. Ming Chu, who carried out research into the topic concurrently with Ablin patented

the molecule rather than Ablin himself[5]. The backstory of the discovery is way more extensive. Earliest studies reporting about a prostate-specific molecule is dating back the 60s. In terms of chronology, Rubin Hyman Flocks may be the first person to discover the protein known as PSA today, despite realizing only later that the protein he discovered was prostate-specific[6]. Flocks set out with the intention of obtaining a prostate-specific protein during the planning phase of his studies. And he arrived precise deductions that are still valid today. One of the author's conclusions was that it is hard to isolate an antigen particularly for cancer because PSA is the same in benign and malignant cells. Despite the passage of over fifty years, no one is in a position to claim that Flocks was wrong. The author also stated that semen agglutination is brought on by antibodies against certain prostatic tissues. Today, we acknowledged that PSA's sole function is liquefaction of semen. So, it is deemed necessary to claim that Flocks is the researcher who comes closest to discovering PSA by observing its existence and function, and foreseeing its largest flaw which continues to be the main frame of the most heated discussions in urology today. Personally, I would cast my vote for him. As a result, no one received the biggest credit for discovering PSA. Instead, the generosity of cancer rather than the efforts of researchers was credited. Another prostate-specific molecule (membrane antigen, PSMA) that PCa cells overexpress and which has a game-changing impact on the management of the cancer, was such kind of prove of this generous disease originated from a troublesome organ.

As living individuals, Ablin and Chu still can be candidates of the prize. But there is a final reason that makes prize committee carefull against advancements over PSA molecule. After approving by FDA, PSA has been widespreadly used to screen PCa. Millions of patients diagnosed in early stages of the disease and had a cure chance. Overuse of PSA brought along with the terms insignificant cancer, active surveillance of cancer, overdiagnosis and overtreatment. In 2012, the United States Preventive Services Task Force (USPSTF) recommended against the routine use of PSA for mass screening, citing the aforementioned harms outweighing the benefits of screening. The recommendation quickly resulted in more advanced disease and more PCa-related mortality[7]. USPSTF loosened its recommendation against the use of PSA in 2018 but even Ablin, one of the pioneers, opposes PSA as a screening tool. Probably, Nobel Prize also heard of these contradictory voices arose from the side of PSA. We must concur that the factors contributing to PSA's underappreciation include the lack of a clear pioneer in its discovery and the contradictory opinions around its use. It looks like PSA will wait to be rewarded till we come up with a far better application of it.

References

1. Wehrli FW. On the 2003 Nobel Prize in medicine or physiology awarded to Paul C. Lauterbur and Sir Peter Mansfield. Magn. Reson. Med. 51, 1-3 (2004).
2. Lipsick J. A History of Cancer Research: Tumor Viruses. Cold Spring Harb. Perspect. Biol. 13, a035774 (2021).

3. Huggins C. How Charles Huggins made his Nobel prize winning discovery--in his own words: an historic audio recording. Interviewed by Willard Goodwin and Elmer Bell. Prostate. 72, 1718 (2012).
4. Rao AR, Motiwala HG, Karim OM. The discovery of prostate-specific antigen. BJU Int. 101, 5-10 (2008).
5. Research Corporation. Purified human prostate antigen. https://patents.justia.com/patent/4446122 (1981).
6. Özman O, Talat Z, Erözenci A. Prostat Spesifik Antijen'in Tarihi. Lokman Hekim Dergisi. 9, 184-188 (2019) [In Turkish].
7. Fleshner K, Carlsson SV, Roobol MJ. The effect of the USPSTF PSA screening recommendation on prostate cancer incidence patterns in the USA. Nat. Rev. Urol. 14, 26-37 (2017).