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PERSPECTIVE

# History of the discovery and clinical translation of prostate-specific antigen

**William J. Catalona**

*Department of Urology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA*

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## 1. Introduction

In recent years, there has been considerable controversy concerning the discovery and translation into clinical practice of the prostate-specific antigen (PSA) [1–4]. In this brief review, I offer the relevant historical facts as I believe them to be true.

Before the development of the PSA blood test, prostatic acid phosphatase was the most important blood test for prostate cancer, but it was of no value for the early detection of prostate cancer, because serum acid phosphatase levels became elevated mainly in men who already had bone metastases [5].

## 2. Early discovery of prostate-specific antigen

In the 1960s and 1970s, many researchers were searching for tumor-specific antigens that might be useful as biomarkers or targets for immunotherapy of cancer. Typical experiments involved injecting an extract of a human tissue or body fluid, such as a prostate tissue or seminal fluid, into rabbits and testing the rabbit serum for antibodies against the antigens present in the extract or fluid.

The earliest report on the properties of antigens in the prostate was by the American urologist, Rubin Flocks, in 1960 [6,7]. In 1966, Mitsuwo Hara, a Japanese forensic scientist, reported on and partially characterized a protein, which he called "gamma-seminoprotein". He suggested its possible value as forensic evidence in rape cases [8]. In 1970, Tien Shun Li and Carl Beling [9,10], conducting research on male infertility, reported on antigens in human semen, one of which was later shown to have the same amino acid sequence of PSA. That same year, Richard Ablin and coworkers reported finding two antigens that were specific to the human prostate, one of which was distinct from acid phosphatase [11–13]. Ablin then moved on to pursue clinical studies attempting to induce an anti-tumor immune response through cryoablation of the prostate gland. In 1978, forensic scientist George Sensabaugh also identified a protein in semen that was similar to one of Li's antigens and was later shown to have the same amino acid sequence as PSA [14,15].

## 3. Purification, characterization, and development of PSA as a biomarker blood test for prostate cancer

In my opinion, the real credit for the discovery of PSA as a clinically useful biomarker for prostate cancer and for translating it into clinical use belongs to T. Ming Chu and his research group, most notably Ming C. Wang, who conducted a remarkable focused series of studies over several years at the Roswell Park Memorial Institute [1,2]. In a landmark study in 1979, Wang and coworkers purified and characterized PSA and suggested potential clinical applications as a biomarker for prostate cancer [16]. This set the stage for the development of a PSA blood test, which was subsequently achieved in steps by Lawrence D. Papsidero [17] and Manabu Kuriyama [18], Wang and their coworkers in Chu's research group. They developed a sensitive ELISA

*E-mail address:* wcatalona@nmff.org.

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immunoassay that could be used for blood testing, and performed early studies exploring the potential clinical uses of PSA as a biomarker in prostatic diseases. Ultimately, T. Ming Chu and Roswell Park Memorial Institute received the patent for the discovery of "purified human prostate antigen" in 1984, and Chu has been honored on many occasions as the discoverer of PSA [19].

What emerged from the early clinical studies by Chu's group, and was further validated by Thomas A. Stamey [20] and others, was that PSA was clinically useful for monitoring the course of patients already known to have prostate cancer. However, because there was overlap of serum PSA levels between patients with prostate cancer, benign prostatic hyperplasia, and prostatitis, and PSA levels were sometimes "normal" or low in patients with prostate cancer, it was not believed that PSA could be used as a first-line screening test for prostate cancer. Rather, physicians and researchers were focused on finding a marker that functioned like a pregnancy test, i.e., always positive when cancer was present and always negative when cancer was absent. Therefore, until the 1990s, PSA was largely used for monitoring the response of prostate cancer patients to treatment.

In the early 1990s, it was first demonstrated that the PSA blood test could be used as a first-line screening test for prostate cancer [21], which led to the approval of the PSA test by the United States Food and Drug Administration (FDA) as an aid to the early detection of prostate cancer [22]. PSA derivatives, such as PSA velocity [23], PSA density [24,25], and the free-to-total PSA ratio [26] (also FDA approved) served to improve the accuracy of PSA testing. More recently, other PSA isoforms, such as the [-2]proPSA, have been found to be a more cancer-specific biomarker for prostate cancer, which has led to FDA approval of the Prostate Health Index (PHI) in 2013 [27].

## 4. PSA testing reduces prostate cancer-specific mortality

During the "PSA era" in the United States, the proportion of patients having advanced disease at diagnosis has decreased by 80%, and the age-adjusted prostate cancer mortality rate has decreased by more than 42% [28]. Statistical modeling studies have estimated that 45%—70% of this mortality decrease is attributed directly to PSA screening [29,30]. Similar trends have been observed in countries that have adopted widespread PSA screening but not in those that have not adopted PSA screening [31]. Two large prospective, randomized clinical trials in Europe have demonstrated a 21% and 44%, respectively, decrease in prostate cancer-specific mortality associated with PSA screening [32,33].

## 5. Concerns about overdiagnosis and overtreatment

Although in recent years, population-based PSA screening has been called into question because of concerns that the benefits of screening may not justify the risks of overdiagnosis and overtreatment of possibly harmless prostate cancers [34], I believe that PSA-based testing (including PHI) is the best cancer blood test in all branches of medicine, and certainly the best test currently available for early prostate cancer detection. Although PSA-based testing has limited specificity, I am convinced that the intelligent use of PSA-based testing, careful selection of patients for screening and treatment, combined with high quality, effective treatment, could reduce the overall prostate cancer death rate by more than half.

## Conflicts of interest

The author declares no conflict of interest.

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