

### Uromodulin and its two discoverers: Igor Tamm and Frank Lappin Horsfall, Jr.



Anna Bednarek-Skublewska<sup>1,2</sup>, Andrzej Woliński<sup>2</sup>

<sup>1</sup> Department of Nephrology, Medical University in Lublin, Poland

<sup>2</sup> Diaverum Lublin Chodźki Dialysis Clinic, Poland

**Corresponding Author:** Prof. Anna Bednarek-Skublewska  
Diaverum Lublin Chodźki Dialysis Clinic 6 Prof. Gębali Street, Lublin 20-093, Poland  
Tel: 048 81 740 46 59, fax: 048 81 742 73 03; e-mail: anna.bednarek@diaverum.com

#### ABSTRACT

In 1985 a glycoprotein was isolated from urine of pregnant women and called uromodulin. This protein is the most abundant one in human urine and it is a potential immunoregulatory molecule associated with nephrolithiasis and urinary host defence. Thanks to demonstration by the amino acid sequencing, it turned out the protein backbone of uromodulin and another “urinary mucoprotein”, discovered about 35 years before by Igor Tamm and Frank Lappin Horsfall, Jr., are identical. Dr Tamm and Dr Horsfall, Jr. did not take interest in nephrology but their names, by coincidence, are found in each nephrological manual. The most important data from the lives of these scientists are worth reminding.

Dr Igor Tamm (1922-1995) was born in Estonia and died in the USA. He was a physician and a pioneer in the Rockefeller Institute studies on virus replication and its chemical inhibition. In 1959 he became the head of the Virology Laboratory, succeeding his mentor Dr Horsfall, Jr., who left the Rockefeller Institute. Dr Frank Lappin Horsfall, Jr. (1906- 1971) was born and died in the USA. He was a clinician and a virologist, whose influential leadership came primarily through his scientific experimentation, both in the laboratory and the clinic. He worked in the Rockefeller Hospital from 1934 to 1960, then he became the Director of the Sloan-Kettering Institute. Together with Dr Tamm, he initiated a series of chemotherapeutical experiments with the benzimidazoles and their derivatives on influenza virus infection. He authorized over 200 publications and received several honorary degrees.

**KEYWORDS:** Igor Tamm, Frank Lappin Horsfall, Tamm–Horsfall protein (THP), uromodulin

#### Background

Uromodulin, a 616-amino acid, 85-kilodalton immunosuppressive glycoprotein, is the most abundant in normal human urine. Its location is in nephrons and limited to the thick ascending limb and the early distal convoluted tube (1). This protein was isolated from urine of pregnant women by lectin adherence. On the basis of its tissue source and *in vitro* activity, the name “uromodulin” was given by Muchmore et al. in 1985 (2). Uromodulin has the same structure as another glycoprotein, named Tamm-Horsfall protein (THP). This one was discovered and characterized by Dr Igor Tamm and Dr Frank Horsfall, Jr. in the 1950s (3). They isolated this factor from urine and found it to be the substance responsible for urinary inhibition of myxovirus induced hemagglutination.

Evidence that these glycoproteins are the same is based on amino acid sequence identity, immunologic cross-reactivity, and tissue location (4, 5). Thus, uromodulin (THP) may act as a unique renal regulatory glycoprotein that specifically binds to and regulates the circulating activity of a number of potent cytokines, including interleukin 1 and tumor necrotic factor  $\alpha$  (4). This protein together with uropontin and nephrocalcin are the three known urinary glycoproteins that affect the formation of calcium-containing kidney stones.

In fact today, even if THP function is still not clear, the mutations in the gene UMOD encoding this protein are also associated with the following disorders: rare autosomal dominant diseases, urinary tract infections, hyperuricemia, ion transport, and kidney innate immunity. Some results to define its role in nephrology are reported by the study of urine spectrometry mass.

Dr Tamm and Dr Horsfall, Jr. did not take interest in nephrology but their names, by coincidence, are found in each medical manual devoted to nephrology. It should be highlighted that they dedicated their scientific life mainly to virology, studying the inhibition of virus multiplication by chemical means. By chance, during performing numerous studies, these scientists discovered a glycoprotein mentioned above. They were searching for a natural inhibitor of virus replication and they chose urine as a possible source. For this reason this protein was given their names. Taking into consideration these scientists’ input in nephrology, the most important data from their biographies and professional careers is worth reminding. Here are the most important facts about these famous physicians.

#### Igor Tamm (1922 – 1995) (Figure 1)

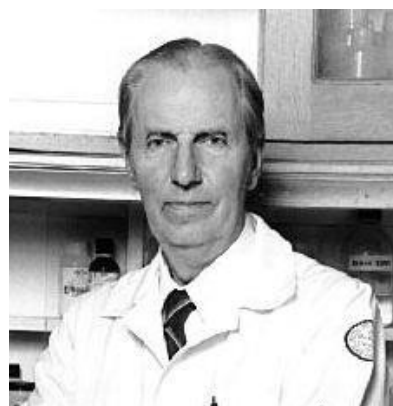


Figure 1 - Igor Tamm.

Dr Igor Tamm, a scientist and pioneer in studies of the virus composition and replication in the body cells, was an American professor and physician. He was born in Tapa, Estonia in 1922 (6). At the beginning of his professional life

he achieved a high level of education. He attended the State English College in Tallinn, and then from 1942 to 1943 the Tartu University Medical Faculty also in Estonia. In 1943, after the word went out that Estonian teenagers were to be taken into the German army and sent to the Russian front, he and his fellow medical student escaped in a small boat, which they sailed late at night through the German blockade to Finland. This country was at that time occupied, so they stowed away in the coal storage area of a freighter for several days until it arrived in Sweden. Soon after emerging from the ship, he developed the first symptoms of the disease from which he would suffer for the rest of his life. In Stockholm he entered the medical school at the Karolinska Institute. He had long been interested in going to the United States, and at the Karolinska Institute he met an American diplomat, who encouraged him to apply to the Yale Medical School. After two years of house-staff training in internal medicine at the Yale-New Haven Hospital, Tamm transferred to the Yale Medical School, receiving his M.D. with honors in 1947.

Following his educational great achievements at Yale, he became associated with the Rockefeller Institute for Medical Research in New York, which remained his beloved scientific home. This unit was the first institution in the United States devoted solely to understanding the causes of different diseases. Today, renamed The Rockefeller University, it is one of the foremost research centers in the world. Dr Tamm was also deeply involved in the work of the Rockefeller Hospital. He was nominated to an associate professor in 1956, and a physician in 1958, then a professor and senior physician in 1964. Finally, Dr Tamm was named Abby Rockefeller Mauze Professor in 1986. It is worth mentioning that Dr Tamm also joined the Rockefeller Hospital Laboratory of Virology in 1949. This was a period of time when he closely collaborated with Dr Horsfall. They began their work with isolation, purification, and extensive biochemical characterization of that glycoprotein, which is known as the Tamm-Horsfall protein, named for him and his mentor.

The work with this glycoprotein was the start of a long career in the study of the inhibition of viral multiplication by both natural products and chemicals. Achieving the great knowledge in this field, they published several articles. Later, in 1959, Dr Tamm became the head of the Laboratory of Virology, succeeding his mentor Dr Frank Lapin Horsfall, Jr., who had been appointed to the director of the Sloan-Kettering Institute for Cancer Research. Dr Tamm was in effect acting as the head of the laboratory and primary mentor of the younger people there. He was also interested in studying inhibitors to elucidate the biochemical and cell biological mechanisms of virus replication. There were many important contributions of the Virology Laboratory at the Rockefeller University under Dr Tamm's leadership.

Dr Tamm was an editor or member of the editorial board of several journals, including: *'Journal of Immunology'*, *'Proceedings of the Society for Experimental Biology and Medicine'*, *'Journal of Experimental Medicine'*, *'Biochemical Pharmacology'*, and *'Journal of Interferon Research'*. He served on many advisory boards and study sections for government agencies and private organizations concerned with research, including the National Institute of Health, the American Cancer Society, and the Sloan-Kettering Institute for Cancer Research.

The most outstanding achievements and some details from the biography of the second discoverer of THP, Dr Frank Horsfall, are also worth presenting.

**Frank Lappin Horsfall, Jr. (1906-1971) (Figure 2)**



**Figure 2 - Frank Lappin Horsfall, Jr.**

Dr Frank Lappin Horsfall, Jr., a clinician and a virologist, was born in Seattle in the USA (7). He attended medical school at McGill University in Montreal, Canada, graduating in 1932 at which time he received the Holmes Gold Medal for having attained the highest scholastic record in his class. Trained as a surgeon, he spent his first year after medical school at the Peter Bent Brigham Hospital in Boston as a pathologist. But, he developed a severe hypersensitivity to

formaldehyde, which forced him to leave his pathology studies, and ultimately, surgery. Dr Horsfall spent another resident year at the Montreal's Royal Victoria Hospital and Montreal General Hospital, but realized he could not work in any environment where formaldehyde was present. Thus, in 1934, he joined the pneumonia service of the Rockefeller Institute for Medical Research, starting his career in microbiology and infectious diseases. At the beginning of this work at the Rockefeller Hospital, he focused on immunological reactions between pneumococcal capsular polysaccharides and the antibodies to them produced by immunization of various animals. His studies resulted in the use of rabbit antisera over that of horse serum as standard pneumonia treatment. In 1937 Dr Horsfall began a four-year term with the International Health Division of the Rockefeller Foundation. Here he began his work on the human influenza virus and the pneumonia virus of mice, the two most significant highlights of his laboratory research career.

Dr Horsfall returned to the Rockefeller Hospital in 1941, becoming the Vice President for Clinical Studies. He began the main period in his scientific life, which was to last about twenty years. During World War II, he served in the Naval reserves as a part of the Naval Medical Research Unit at the Rockefeller Hospital, concentrating on respiratory tract diseases. In 1950s he initiated a further series of chemotherapeutic experiments with the benzimidazoles and their derivatives on influenza virus infection, and thereafter the series was carried on by Dr Tamm and others.

Dr Horsfall's second career from 1960 as the Director of the Sloan-Kettering Cancer Research Center was also very important. His work centered around carcinogens, especially the role of viruses as oncogenic agents. Additionally, Dr Horsfall studied the concept of interdependency between viruses and chemicals marking an important shift in cancer etiology and achieving some results in rapid advances in cancer research. Thanks to his great scientific effort, Dr Horsfall became a member of the American Academy of Arts and Sciences in 1967. He authored over 200 publications and received several honorary degrees. In addition, he had a very important influence in the organization and development of the Health Research Council of New York City, which for many years played a very important role in public health research. He had decided to retire just before it was discovered that he had cancer, of which he died in 1971.

## Summary

Taking into consideration the fact that there is rather poor knowledge about the biography of Dr Igor Tamm and Dr Frank Lippin Horsfall, Jr., it is worth reminding the most important data from their lives and professional careers. It is also a possibility to present the genesis of the THP discovery. Those two American doctors had important input not only into some nephrological diseases but also into the development of virology.

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