

MEMORANDUM REGARDING THE DISCOVERY OF THE FIRST WATER CHANNEL PROTEIN BY GHEORGHE BENGA IN ROMANIA, A FEW YEARS BEFORE PETER AGRE (2003 NOBEL PRIZE IN CHEMISTRY)

In 1985, after a decade of systematic studies on water channels in human red blood cells (RBC) performed at "Iuliu Hatieganu" University of Medicine and Pharmacy in Cluj-Napoca, Romania, Gheorghe Benga and coworkers discovered the presence and location of the first water channel protein in the human (RBC) membrane among polypeptides migrating in the region of 35-60 kDa on the electroforetogram of RBC membranes (Benga Gh, Popescu O, Pop IV, Holmes R, *Biochemistry*, 25, 1535-1538, 1986). In this landmark publication Benga also indicated the way to further studies, by protein purification and reconstitution in lipid vesicles (liposomes). This work was extended (Benga Gh, Popescu O, Borza Victoria, Pop VI, Mureşan A, Mocsy I, Brain A, Wrigglesworth JM, *Eur J Cell Biol* 41: 252-262, 1986) and reviewed by Benga in several articles including a chapter in a book published in the USA (Benga Gh, (Ed) 1989. *Water transport in biological membranes*. CRC Press, Boca Raton).

In 1988, Peter Agre and coworkers (Denker BM, Smith BL, Kuhaida FP, Agre P, *J. Biol. Chem.* 1988, 263:15634-15642), while working on the rhesus blood group antigen at Johns Hopkins University in Baltimore, USA, serendipitously isolated a new 28 kDa membrane protein from human red blood cells, called, CHIP28 ("channel forming integral membrane protein of 28 kDaltons"); in addition to the 28 kDa component, this protein had a 35-60 kDa glycosylated component, the one detected in 1986 by the Benga's group. Agre and coworkers suggested that "this new protein may play a role in linkage of the membrane skeleton to the lipid bilayer" (Smith BL, Agre P., *J. Biol. Chem.* 1991, 266:6407-6415).

Only in 1992, the Agre's group suggested that "it is likely that CHIP28 is a functional unit of membrane water channels" (Preston G.M, Carroll TP, Guggino WB, Agre P, *Science*, 1992, 256:385-387). In this paper, they cited a paper of Benga and coworkers from 1983 (Benga Gh, Popescu O, Pop VI. 1983, *Cell Biol Int Rep*, 7: 807-818), without mentioning their landmark 1986 papers or any of the reviews. In 1993 CHIP28 was renamed aquaporin 1 (the first water channel protein).

It is obvious and overwhelmingly documented from the facts presented above that the first water channel protein (aquaporin 1) was first discovered by the Romanian scientist Gheorghe Benga and his group in 1985 and reported in publications in 1986. They detected the glycosylated form of the protein (subsequently worked on by Agre's group), which they correctly identified as playing the key role in water transport across RBC membrane.

In October 2003, Peter Agre was awarded the Nobel Prize in Chemistry, "for the discovery of water channels". An invited review of the history of the discovery of water channels proteins was published by Benga in September 2003, one month before the Nobel Prize for Chemistry was awarded (Benga Gh, *Cell Biol. Int.* 2003, 27:701-709). The seminal contributions from 1986 of the Benga's group, also mentioned in this review, were completely overlooked by the Nobel Prize Committee.

After the announcement of the 2003 Nobel Prize in Chemistry was released by Nobel Foundation Gheorghe Benga received a multitude of spontaneous messages (phone calls, E-mailed messages and faxed letters) from all over the world. The scientists who sent messages to Gheorghe Benga considered that in fact he discovered the first water channel protein in the red blood cell membranes (the protein later called aquaporin1) several years before Peter Agre and the chemical definition of this channel protein by Peter Agre has no more value than the first demonstration and labeling of the site in the red blood cell membrane where the water channel protein is located. As a result Gheorghe Benga wrote a PETITION, presented on October 18th at the 6th International Symposium of Molecular Medicine (Hersonissos, Crete, Greece) that is now available at www.ad-astra.ro/benga, where a full background to the controversy can be seen..

The priority of Gheorghe Benga's group in the discovery of the first water channel protein has been mentioned in comments on the 2003 Nobel Prize in Chemistry (Bradley D. *Spotlight*, www.psigate.ac/uk/spotlight/issue13b/chemistry/html; Bradley D., *The Alchemist*, 13 October 2003; Vandenberg IJ, Kuchel P., *Medical Journal Australia*, 179: 611-613, 2003; Rogerund K. Kemipriset vållar ny Nobelstrid, *Dagens Nyheter*, 10 Decembrie 2003; Strid kring medicinpriset...och kring kemipriset, *Sydsvenska Dagbladet*, December 11, 2003; Nobel mystery. *Newsletter of King's College*, January 2004).

More than 2000 supporters from dozens of countries, including a Nobel Laureate, have signed at www.ad-astra.ro/benga. By now, many academic institutions, faculties, universities, scientific organizations and associations, research institutes, have recognized Gheorghe Benga as a discoverer of the first water channel protein before Peter Agre.

Considering the facts presented above, we agree to recognize Gheorghe Benga as a discoverer of the first water channel protein a few years before Peter Agre (2003 Nobel Prize in Chemistry).