Professor Claudiu Supuran, a Highly Cited Chemist and Biochemist

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The Hirsch index h measures scientific achievement or research output based on the numbers of publications and citations. The present author's index h has been considerably exceeded by the h index of one of his Ph. D. students, Claudiu Supuran, who is at present Professor at the Universita degli Studi, Florence, Italy. Professor Supuran's research activity is centered on selective inhibitors and activators of carbonic anhydrase isoforms, with various applications in the fight against various diseases such as glaucoma, epilepsy, gastric and duodenal ulcers, migraine, and cancer.

A saying of Confucius reads as follows: "if you think in terms of a year, plant a seed; if in terms of ten years, plant trees; if in terms of a hundred years, teach people". For someone who teaches, a sign of success is to see a disciple outshine the teacher; or, citing from Leonardo da Vinci's *Thoughts on Art and Life*, "He is a poor disciple who does not surpass his master." This sign has happened to the author of these lines, thanks to Claudiu Supuran.

As a professor of organic chemistry at the Polytechnic Institute (now "Politehnica" University) in Bucharest, Romania, I responded favorably to Claudiu Supuran's request to be admitted as a Ph. D. student, after he graduated in 1987, when he was 25 years old. The fall of communism in Romania at the end of the year 1989 and the involvement of many young people in what they believed to be a revolution (but was rather a well-planned coup) slowed down for several months Claudiu's research, but in October 1991 he defended his Thesis "Design of inhibitors and activators of carbonic anhydrase". This topic was, and is, the leit-motif of Claudiu's research. At present he is the "world's authority on carbonic anhydrase".

Carbonic anhydrases (abbreviated as CAs) are zinc-containing enzymes (proteins) that are widespread in all living organisms for speeding up the slow reaction between two molecules in condensed phase (carbon dioxide and water) resulting in the formation of bicarbonate anions and protons (actually, hydronium cations): $CO_2 + H_2O \leftrightarrows HCO_3^- + H^+$. These CA enzymes rival in importance with rubisco (1,5-ribulose-bisphosphate carboxylase/oxygenase), the most abundant enzymes in the biosphere, which initiates the formation of organic molecules from sunlight and a dozen of the same molecules in gas phase: $6CO_2 + 6H_2O \rightarrow (CH_2O)_6 + 6O_2$ (glucose $C_6H_{12}O_6$ is the first carbohydrate formed by this photoassimilation; its chain of six carbon atoms is formed stepwise either as 3+3 carbon atoms for most plants, bacteria and algae, or as 4+2 carbon atoms for plants growing under hot climates,). All the oxygen in the Earth's atmosphere has been generated by photoassimilation.

Till now in all life families (archaea, prokaryotes and eukaryotes), five distinct genetic families have been identified. Cellular organisms with a nucleus in each of their cells (eukaryotes) including vertebrates and green plants contain several isoforms of α-CAs. Thus, in mammals including humans there are 16 α-CA isoforms localized in the cell plasma, membranes, mitochondria, or secretions. Some isoforms of these enzymes accelerate the hydration of CO_2 and the dehydration of carbonic acid up to as million times. Human carbonic anhydrases (hCAs) regulate the pH and fluid balance in various organs, and thus are involved in maintaining the acidity needed for digestion in the saliva, stomach and bowels, or in regulating the fluid transport in our kidneys, brain, or eyes; hCAs are also responsible for converting the byproducts of oxidative energy generation into carbon dioxide which is conveyed to the lungs are exhaled. Whereas hCA inhibitors have been used since 1950 for treating glaucoma, newer uses for hCA inhibitors are being developed at present for treating epilepsy, gastric and duodenal ulcers, migraine, and cancer.

Claudiu Supuran merged in his Thesis his early interest about carbonic anhydrase with my favorite class of aromatic heterocycles, pyrylium salts (six-membered rings in which one CH group of benzene is replaced by a positively-charged oxygen atom). After his graduation as a chemical engineer, he worked for two years as researcher in the Center for Gastroenterology Research, directed by Dr. I. Puşcaş at the Hospital Şimleul Silvaniei, Claudiu's birthplace. In a collaboration with a young and promising inorganic chemist Marius Andruh (at present academician and professor at the Bucharest University), and I. Puşcaş, Claudiu Supuran had published in 1987 his first paper in a long series about carbonic anhydrase inhibitors [1]. Starting with 1990, Claudiu moved to Bucharest and embarked in an academic career as assistant professor of organic chemistry and biochemistry at the Bucharest University (1990-1991), and associate professor of bio-organic chemistry at the same University (1992-1994). Results of his diligent work were published with me and other coauthors in 1990-1994 [2–13]. It is fitting to mention here several of these coworkers, some of whom emigrated to USA or France: Dr. G. Manole, physician specialized in cardiology, living in Bucharest; Academician Mircea D. Banciu, Professor at the Bucharest Polytechnic University, deceased; Dr. Ovidiu Maior, Professor at the Bucharest University, deceased; Dr. Mircea D. Gheorghiu, Professor at the Bucharest Poytechnic, then Director of Undergraduate Studies at MIT, USA, and at present Adjunct Professor at St. Mary College of California, USA; Dr. Antonie Dinculescu, research chemist in USA, at present interested in cosmogony and physics; Professor Mihai Barboiu, University of Montpellier, France. One should also mention Drs. Jose Elguero and his wife, Rosa Claramunt, Madrid, Spain. Among Claudiu's early findings published with me, Drs. Banciu and Andruh, the most significant is the discovery of selective membrane-impermeable hCA inhibitors obtained by synthesizing pyridinium salts from pyrylium salts combined with aromatic sulfonamides; these initial promising results were developed after 2009 with coworkers from Turkey and Italy [14,15].

After post-doctoral fellowships in USA during 1994 (University of Florida in Gainesville and University of Washington in Seattle), Claudiu Supuran has found a stable position in Florence, Italy: as research fellow (1995-2000), then contract

professor (2000-2006), and now professor at the Universita degli Studi, Firenze, Italy, with two "intermezzos" of visiting professorships at the universities in Brisbane, Australia and La Plata, Argentina.

Among Claudiu's numerous other findings about CAs, a brief survey is summarized in the following.

(i) Another confluence of common interests resulted when trying to find quantitative structure-activity correlations (QSARs) for classes of substances acting as carbonic anhydrase inhibitors. One has to take into account that chemical structures are represented by molecular graphs, which are discrete entities, whereas biological activities are measured on continuous numerical scales. A simple tool for such QSAR studies is the use of topological indices based on graph-theoretical invariants [16]. With colleagues from India we published in 2004-2006 several papers on QSAR studies using topological indices for inhibition for carbonic anhydrase-I, -II, -IV and -VII [17-20]; in one of these papers [18] we used a topological index that is known as the Balaban index.

(ii) The mechanism of action for CA inhibition involves interfering with the coordination of water oxygen by the zinc atom. X-Ray diffraction of CA before and after the addition of inhibitor molecules shows how amino acids are surrounding the zinc atom leaving a channel that can be blocked by the inhibitor, usually a sulfonamido group or an anion [21-23]. Claudiu's work led to the discovery of a large number of inhibitors belonging to the sulfonamide, sulfamide or sulfamate classes, which showed not only very good affinity for these enzymes, but also selectivity for the numerous isozymes of the human CAs (hCAs).

(iii) He has discovered several completely new classes of CA inhibitors, as well as their mechanism of action: (i) the coumarins, which act as "prodrug" inhibitors, being hydrolyzed within the enzyme active site to 2-hydroxy-cinnamic acid derivatives, which afterwards occlude the entrance of the active site cavity; (ii) the polyamines (spermine, spermidine, etc) which anchor to the zinc-coordinated water molecule; (iii) the dithiocarbamates, which coordinate to the metal ion within the CA active site; and (iv) the xanthates, which bind in a similar manner to the dithiocarbamates.

(iv) Claudiu has elucidated the mechanism of action of the CA activators, by using X-ray crystallography and spectroscopic techniques. The activators bind at the entrance of the active site cavity and participate to the proton shuttling processes between the active site and the medium, favoring the rate-determining step of the catalytic process. They may possess pharmacologic applications for the management of Alzheimer's disease or for memory therapy.

(v) He has published the proof-of-concept studies regarding the involvement of some CA isoforms in tumorigenesis (CA IX and XII), of others in lipogenesis (CA VA and VB, and from here to the development of anti-obesity agents), whereas for some bacterial/fungal/protozoan CAs, he has showed that they are essential for the life cycle of the pathogen and thus may lead to antibacterials, antifungals or antiprotozoan agents with a new mechanism of action.

(vi) He has discovered many CA enzymes from various organisms, starting with bacteria, cyanobacteria, archaea, protozoa, plants, corals, fungi, etc. The cloning, characterization, inhibition and activation studies of these new enzymes were also published by his group.

In 2005, the physicist Jorge Hirsch proposed a measure of scientific achievement or research output based on the numbers of publications and citations, known nowadays as the Hirsch index *h*. According to his definition, a scientist has index *h* if *h* of his/her *N* papers have at least *h* citations each, and the other (*N* - *h*) papers have no more than *h* citations each. In other words, if one lists all relevant publications in the order of decreasing number of citations on the abscissa, then *h* (the number of papers each of which has been cited in other papers at least *h* times) is found at the intersection of the bisector of the Cartesian coordinates with the concave curve of the citation numbers. At present, one can find easily the *h* index for scientists on the Internet by accessing citation databases. For manual calculation of the *h* index one can use the subscription-based databases such as Scopus and the Thomson-Reuters Web of Knowledge databases which provide automated calculators. The Google Gadget database and Harzing's *Publish or Perish* program calculate the *h*-index based on Google Scholar entries. Various databases can produce different *h* indices for the same scholar because of different coverage: Google Scholar citations include journals, books, and conferences, whereas Web of Knowledge has strong coverage of journal publications, but poor coverage of conferences. Scopus has better coverage of conferences, but poor coverage of older publications.

The *h* index of established researchers with comparable impact varies according to the research field: life sciences lead to higher indices than chemistry followed by physics, whereas mathematics leads to lower indices. Hirsch estimated that for physicists after 20 years a "successful scientist" will have an *h*-index of 20, an "outstanding scientist" an *h*-index of 40, and a "unique individual" an *h*-index of 60. The researcher's advancing age also contributes to increasing *h*-index values. In time, various proposals have been advanced for offering improved estimation of the impact of individuals, and by extension, of institutions, universities, or countries.

In the following years several attempts were published in the hope to improve the *h*-index for multiple authorship or other factors. In 2006 Dr. Tibor Braun assembled in two volumes such papers published in *Scientometrics* [25] and in 2008 he edited another volume about the uses and misuses of the *h*-index.

Claudiu's citations and Hirsch index are outstanding: at the beginning of the year 2014, he has over 31,600 citations for his papers and a Hirsch index $h = 85$; his papers [21] and [22] have 860 and 780 citations, respectively. I do not know any living scientist of Romanian descent with such outstanding figures; for comparison, my Hirsch index is 62, my most cited paper has 842 citations, and I have a total of over 13,000 citations. Therefore I am happy to fulfil the success achievement described in the first paragraph of this paper.

As a fitting conclusion of this personal account, I would like to reproduce a few intimate thoughts of Claudiu Supuran from a recent message: «The "imprinting" I had (for research, publishing, ethics, etc.) was from you. The *model* as a scientist (a *great* scientist) was you – and I dare say, will always be. Sorry if it sounds as a confession but my admiration and esteem for you is now as it was 24 years ago, when I started to work on my Ph. D. (and it was/is extremely important for me as a kind of model for my own research and relationship with collaborators/students). As this is something very intimate, I leave it to your option whether to publish it or not, but it is something I wanted you to know. I hope I am not too daring, but I also feel that I am like your son (scientifically speaking, of course).»

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