The gasotransmitters hydrogen sulfide (H\textsubscript{2}S), nitric oxide (NO), and carbon monoxide (CO) exhibit different pharmacological effects at low and high concentrations. The role of the three gasotransmitters on cancer cell proliferation has not yet been studied simultaneously. First, we quantified the expression of NO, CO and H\textsubscript{2}S-generating enzymes in primary colon cancer tissues and in HCT116 colon cancer cells. There was an increased expression of the NO synthases eNOS, iNOS, and nNOS in colon cancer tissue (compared to surrounding normal tissue) and in HCT116 tumor cells (compared to the non-transformed cell line NCM356). Moreover, there was an increase in the H\textsubscript{2}S-producing enzymes CBS and CSE as well as an upregulation of HO-1. Next, we evaluated the effect of donation or inhibition of the biosynthesis of each of the three gasotransmitters on the proliferation of HCT116 cells. DETA and SNAP were used for NO donation, CORM3 for CO donation and AP39 for H\textsubscript{2}S donation; L-NMA was used to inhibit NO biosynthesis, zinc protoporphyrin to inhibit CO biosynthesis and aminooxyacetic acid to inhibit H\textsubscript{2}S biosynthesis. All donors produced a bell-shaped response: enhancement of HCT116 proliferation at low concentrations and inhibition at higher concentrations. Inhibition of NO, CO or H\textsubscript{2}S biosynthesis all suppressed cell proliferation. Combination of different donors or combination of different inhibitors did not produce marked additive or synergistic effects. We conclude that each of the three gasotransmitters exert bell-shaped pharmacological effects in the control of tumor cell proliferation and their effects converge on similar or overlapping effector pathways.
BIOGRAPHY

My graduate and postgraduate education gave me a broad and deep background in clinical medicine, physiology and pharmacology. My subsequent 20 years in Academia and Industry gave me a broad and deep set of skills and knowledge ranging from basic research in pharmacology to applied/translational pharmacology including drug discovery and preclinical/clinical drug development. On the academic track, as postdoctoral fellow at the William Harvey Research Institute, my work, under the supervision of Nobel Laureate Sir John Vane, focused on basic research on the pharmacology of NO and NO synthases, with special reference to the experimental therapy of critical illness. As Research Director of the Division of Critical Care at Children’s Hospital Medical Center in Cincinnati, and later as Professor at UMDNJ/Newark (now: part of Rutgers), I expanded my scope to apply methods of classical and molecular pharmacology to study pathways of cell death during oxidative and nitrosative stress, with special reference to the experimental therapy of circulatory shock, acute lung injury, neuroinjury and neurotrauma, vascular dysfunction and inflammation. Over the last decade, I became a leading authority in H2S pharmacology and pathobiology and have completed in--depth studies on the role of H2S in vascular and bioenergetic regulation in health and disease;; I have also advanced the pharmacology of H2S donors and H2S biosynthesis inhibitors.

Currently, at the University of Texas Medical Branch my laboratory integrates contemporary methods of classical and molecular pharmacology, approaches of physiology, cell biology and molecular biology, methods of cell--based high--throughput screening approaches and in vivo models of disease in rodents and large animals. As PI or co--Investigator on multiple grants funded by the NIH and other agencies, I have discovered multiple novel pathophysiological pathways and processes, some of which became targets for subsequent drug development. This work involved diverse targets, including key checkpoints in intracellular signaling and cell death pathways (e.g. PARP1, SHIP1), free radical/oxidant processes, cell membrane receptors (e.g. adenosine receptors) and gaseous transmitters (NO, H2S); I have led the pharmacological characterization of these agents and in many cases I have led their translation from preclinical tools into clinical drug development candidates. The latter translational efforts included efforts that I have conducted in parallel with my academic work, on the industry track, as Chief Scientific Officer of several successive biotech companies. In these roles I led multiple project teams focused on target identification, creation and pharmacological characterization of first--in--class drug development candidates, and their progression through preclinical development into proof--of--concept clinical trials. The therapeutic applications of these pathways include inflammation, vascular disease, cancer, lung diseases, ophthalmologic indications, and various forms of critical illness. These activities have led to several hundred--million+ dollar deals and resulted in three publicly traded companies (Inotek [ITK], Aquinox [AQXP] and Bellerophon [BLPH]). From an administrative standpoint, I have successfully led R&D groups of various size, including complex, multidisciplinary research projects, often involving multiple geographical locations. I have had continuous NIH funding for the last 20 years and have received over $15M cumulative grant funding. I have published extensively (over 500 papers); I have acted on the Editorial Board of several leading pharmacology journals;; I have received numerous awards in pharmacology (including the Novartis Award of the British Pharmacological Society and the Pharmacia Award for Experimental Therapeutics of the American Society of Pharmacology and Experimental Therapeutics). My work is highly cited in the literature (H--Index of 118). For the last decade I have been consistently listed as one of the top 10 most highly cited scientists in the field of Pharmacology and I was listed among the top 400 highest cited biomedical scientists in the world alive (all disciplines considered).
PERSONAL DATA:

Born: July 12, 1967, Gyor, Hungary
Citizenship: US and Hungarian dual citizen
Spouse: Anita Marton, M.D.
Children: Lili Szabo (age 17), Marcell Szabo (age 15)
Spoken languages: Hungarian (native), English (national examination, highest level), German (national examination, highest level)

POSITIONS AND HONORS

Education, Degrees:
1991: M.D. Semmelweis University Medical School, Budapest, Hungary ("Summa Cum Laude" Diploma)
1994: Ph.D. (Physiology) Role of local factors in the regulation of cerebrovascular tone; Dept. of Physiology, Semmelweis University Medical School, Budapest, Hungary and the Hungarian Academy of Sciences, Budapest, Hungary
1995: Ph.D. (Pharmacology) Role of nitric oxide in circulatory shock; University of London, United Kingdom
2012: F.B.P.S. -- Elected Fellow of the British Pharmacological Society

Academic Positions and Employment:
1994-1999 Assistant/Associate Professor, Division of Crit. Care, Children's Hospital Medical Center, Cincinnati, OH
1999-2008 Professor, Department of Surgery, MDNJ, Newark, NJ
2008-present Professor, Department of Anesthesiology and Department of Pharmacology University of Texas Medical Branch at Galveston, Galveston, TX

Industry Positions and Employment:
1998-2005 Chief Scientific Officer, Inotek Pharmaceuticals, Beverly, MA
2006-2010 Chief Scientific Officer, Ikaria, Seattle, WA / Clinton, NJ
2010-2012 Chief Scientific Officer, Aquinox, Vancouver, BC
2013-present Chief Executive Officer, CBS Therapeutics Inc., Galveston, TX

Career Highlights:
- Multidisciplinary education and comprehensive scientific training.
- Graduate and postgraduate training in medicine and physiology in premier institutes in Europe.
- Postdoctoral training in pharmacology with Nobel Laureate Sir John Vane.
- Proven academic track record from basic pharmacology research to technology transfer and commercialization.
- My research has opened up several new fields of biology in nitric oxide, peroxynitrite, poly(ADP-ribose) polymerase, adenosine receptors, H2S and cystathionine-beta-synthetase. This work identified novel drug development targets in inflammation, reperfusion, diabetic complications and cancer.
- Proven track record and significant management experience with the drug development process from target identification to proof-of-concept clinical trials.
- 2010-2012: Chief Scientific Officer of Aquinox, a biopharmaceutical company involved the development of small molecule activators of the leukocytic phosphatase
SHIP1. I led the research group, which identified a development candidate and progressed it into Phase Ia development.

- 2006--2010: Chief Scientific Officer of Ikaria, a Seattle, WA/Clinton, NJ fully integrated private pharmaceutical company. I was responsible for the preclinical research group, which identified several drug development candidates. One of these compounds progressed into Phase II trials.
- 1999--2005: Co-founder of Inotek, a biopharmaceutical company. As its Chief Scientific Officer, acted as a key player in its progression into a mid-size, venture-funded company. I led the research group, which identified several first-in-class drug development candidates and progressed them into clinical trials.
- Expertise in multiple fields including inflammation, cardiovascular disease, immunology and critical care.
- Established track record in raising R&D financing (private and public).
- Recipient of several academic and commercialization awards.

**Fields of Scientific Expertise:**
- Cellular mechanisms of circulatory shock, inflammation and reperfusion injury
- Pathophysiological roles of free radicals, oxidants, cytokines and chemokines
- Pathophysiological roles of DNA damage and poly (ADP-ribose) polymerase activation
- Modulation of the inflammatory response by adenosine and adrenoceptors
- Pathomechanisms of diabetes and diabetic cardiovascular complications
- Pathomechanisms and experimental therapy of various forms of inflammation
- Role of pro-inflammatory bacterial components (LPS, LTA, flagellin) in the pathogenesis of shock
- Intracellular effector pathways of cell death
- Pathomechanisms of mitochondrial dysfunction
- Vascular regulation (including mechanisms of angiogenesis and pathogenesis of endothelial dysfunction)
- Regulation and pharmacotherapy of pulmonary inflammatory/atopic diseases
- Biological roles of hydrogen sulfide, with particular emphasis on bioenergetics and vascular regulation
- Pathogenetic role of hydrogen sulfide in critical illness, diabetic complications, vascular dysfunction, cancer
- Bioenergetic/metabolic aspects of colon cancer

**Drug Discovery / Drug Development Experience:**
- Nitric oxide synthase inhibitors (research, preclinical efficacy, safety, IND, Phase I)
- PARP inhibitors (research, preclinical efficacy, safety, IND, Phase I, Phase II)
- Xanthine oxidase inhibitor (research, preclinical efficacy, safety, IND)
- Modified purine molecules (research, preclinical efficacy, safety, IND, Phase I)
- Catalytic antioxidants (research, preclinical efficacy, safety, IND, Phase I)
- Adenosine receptor agonists (research, preclinical efficacy, safety)
- Flagellin neutralizing antibodies (research, preclinical efficacy)
- Nitric oxide donors (research, preclinical efficacy)
- Inhaled nitric oxide (preclinical support to on-market drug)
- Hydrogen sulfide donors (research, preclinical efficacy/safety, IND, Phase I--II)
- Hydrogen sulfide prodrugs (research, preclinical efficacy)
- Carbon monoxide as a therapeutic agent (preclinical support to Phase II stage program)
- SHIP1 activator compound (preclinical, early clinical development, IND, Phase I--II)
• Cell-based high-throughput screening; identification of novel drug targets from mechanism-agnostic screening in diverse models (kidney ischemia, neuronal injury, hyperglycemic endothelial cell injury, myocardial reperfusion)
• Whole-organism-based molecule/pathway screening (in C. Elegans)
• Identification of new inhibitors of H2S-producing enzymes through HTS and medicinal chemistry

Professional Memberships:
1993-- British Pharmacological Society
1994-- The Shock Society
1999-- ASPET
2012-- American Diabetes Association

Editorial Boards:
• Shock, 1996 -- present
• British Journal of Pharmacology, 1998--2002 and 2015--present
• International Journal of Molecular Medicine, 1998--present
• Journal of Pharmacology and Experimental Therapeutics, 2001--2005
• Molecular Medicine, 2002--2005 and Contributing Editor, 2013--present
• Current Vascular Pharmacology, 2004--present
• International Journal of Clinical and Experimental Medicine, 2008--present
• F1000Research, 2014--present
• Nitric Oxide, 2015--present

Honors:
1989: “Pro Scientia” Award of the Hungarian Academy of Sciences (Budapest, Hungary)
1992: Lloyd’s of London Tercentenary Foundation Award (London, UK)
1992: Young Investigator Award, 2nd International Symposium on Endothelium-Derived Vasoactive Factors (Basel, Switzerland)
1994: Travel Grant, “Vascular Endothelium: Response to Injury” Meeting (Crete, Greece)
1994: Young Investigator Award, Novel Therapeutic Targets in Circulatory Shock Congress (London, UK)
1997: Travel Grant, First International Symposium on Peroxynitrite (Ascona, Italy)
1997: Hans Selye Award of the First International Stress Conference (Budapest, Hungary)
1997: Young Investigator Travel Award, Fifth International Meeting on Nitric Oxide (Kyoto, Japan)
1997: Scientific Faculty, International Symposium on Intensive Care Medicine (Brussels, Belgium)
1999: Peroxynitrite Award, Second International Meeting on Peroxynitrite (Crete, Greece)
1999: D. Sc. (Doctor of Sciences, Hungarian Academy of Sciences (Budapest, Hungary)
2001: Scientific Faculty, Novel Mechanisms of Critical Illness Round Table (Brussels, Belgium)
2002: Scientific Faculty, International Symposium on Intensive Care Medicine, (Brussels, Belgium)
2003: Novartis Prize of the British Pharmacological Society (London, UK)
2004: Dennis Gabor Innovation Award (Budapest, Hungary)
2006: Officer's Cross -- Order of Merit Award of the Hungarian Republic (Budapest, Hungary)
2006: Marie Curie Chair of Excellence, European Community (Brussels, Belgium) [declined]
2008,9: Scientific Faculty, International Symposium on Intensive Care Medicine, (Brussels, Belgium)
2009: Texas Star Award -- University of Texas System (Austin, TX)
2012: F.B.P.S. -- Elected Fellow or the British Pharmacological Society (London, UK)
2013: Faculty of 1000, Member (Critical Care and Emergency Medicine)
2013: Listed amongst the top 400 "highly influential biomedical researchers, 1996--2011"
2014: Elected Member of the ASCI (American Society for Clinical Investigation)
2016: Du Vigneaud Keynote Lecture
2016: ASPET--Pharmacia Award for Experimental Therapeutics

Scientometric Data

**Cumulative citations:** 53,000 (since 2011: 19,000)
**Cumulative Impact Factor:** over 3,000
**Hirsch Index:** 118 (since 2011: 65)
**110 Index:** 540 (since 2011: 374)
**Annual top 10 rankings among the most highly cited pharmacologists** (ISI--Thomson, Philadelphia):

Publication record: >500 full papers, impact factor >3,000, >55,000 citations, H--Index: 118.

Since 2005, listed in the top 10 most frequently cited pharmacologists in the world. In 2013, I was listed as one of the top 400 most influential biomedical scientists in the world.

**LIST OF PUBLICATIONS**

**Original Papers:**


List of 5 The Most Important Contributions:


