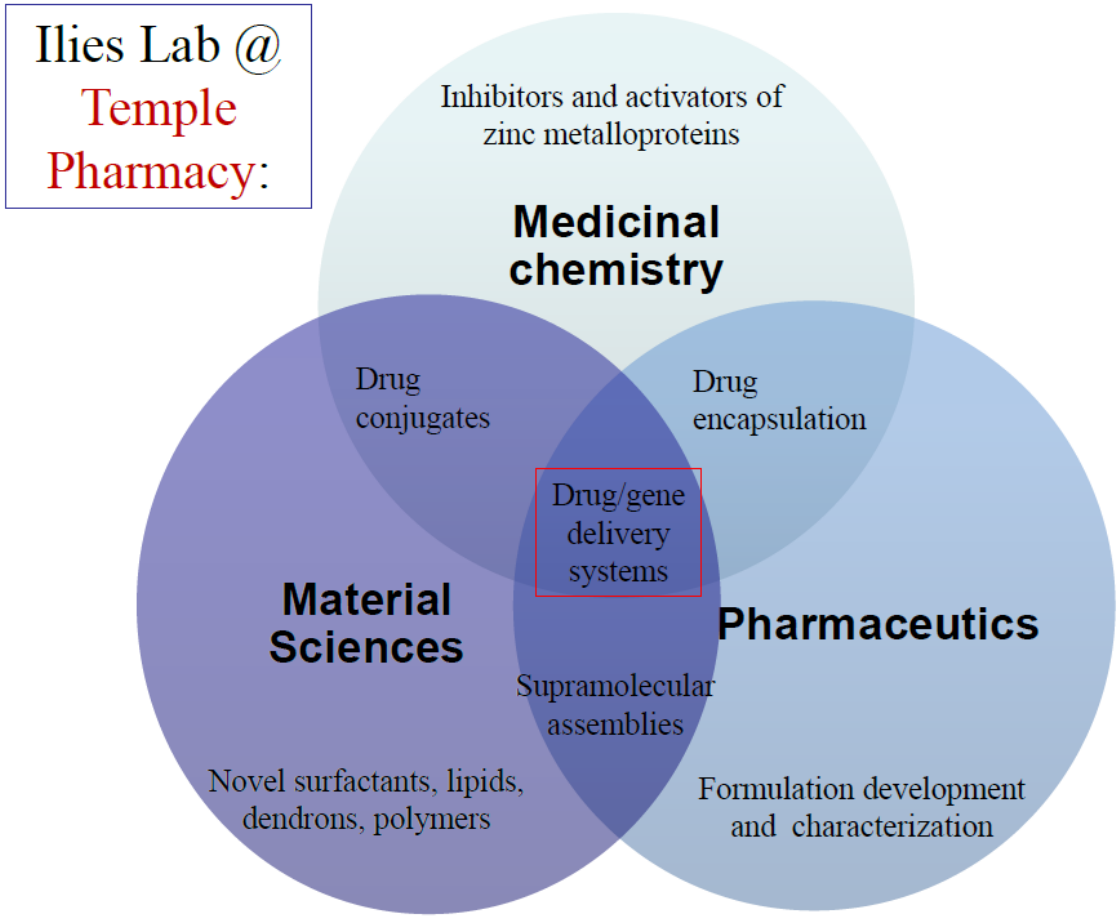
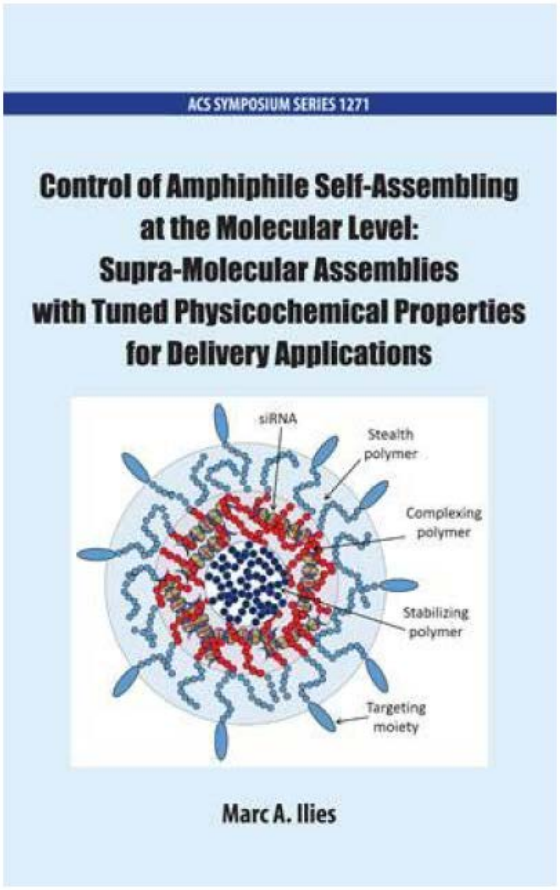
Research in Ilies Lab

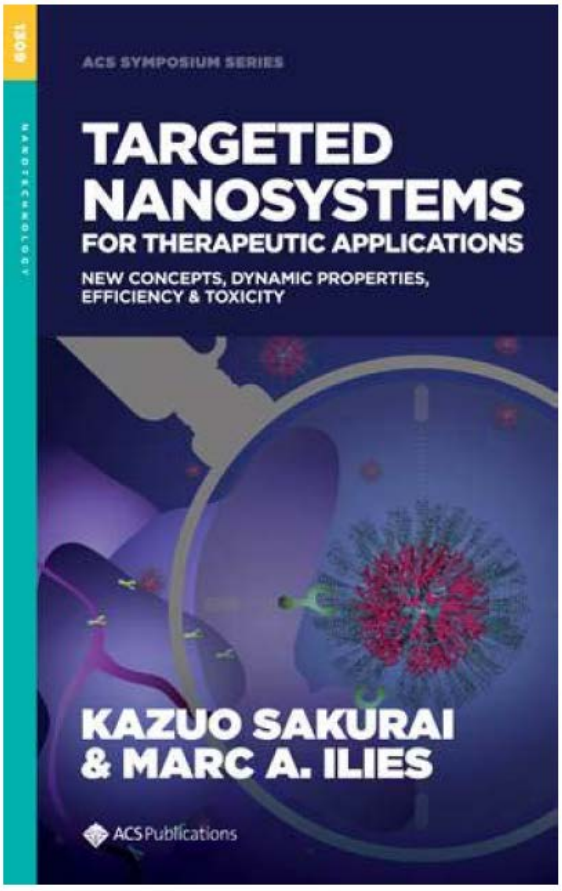
The work in our lab combines medicinal chemistry, material sciences and pharmaceutics/pharmaceutical sciences to provide synthetic solutions to delivery problems. We are active in all these individual concentrations of pharmaceutical sciences, with specific projects for each areas, but especially in inter-disciplinary projects that combine elements of each concentration to create new drug and nucleic acid delivery systems.



Please see below a brief overview of our research activities. Need one of our papers? Send me an email!

Edited books:





M. A. Ilies, Editor: “Control of Amphiphile Self-Assembling at the Molecular Level: Supra-Molecular Assemblies with Tuned Physicochemical Properties for Delivery Applications”, ACS Books & Oxford University Press, ACS Symposium Series 1271, American Chemical Society: Washington, DC, 2017, 331 pp, ISBN 9780841232747, web: https://pubs.acs.org/isbn/9780841232747.

K. Sakurai, M. A. Ilies, Editors: “Targeted Nanosystems for Therapeutic Applications: New Concepts, Dynamic Properties, Efficiency, and Toxicity”, ACS Books & Oxford University Press, American Chemical Society: Washington, DC, 2019, 348 pp, published online 03/20/19 (https://pubs.acs.org/isbn/9780841233836).

Self-assembled synthetic amphiphiles, supramolecular assemblies, encapsulation and delivery of drugs and nucleic acids

A. Development of synthetic nucleic acid delivery systems

We are involved in the design, synthesis and characterization of synthetic amphiphiles with different packing parameters, molecular weights and self-assembling properties. A particular focus of our research is represented by pyridinium cationic amphiphiles designed for delivery of nucleic acids (pDNA, siRNA, mRNA). We have synthesized pyridinium amphiphiles belonging to the classes of simple surfactants, gemini surfactants, pseudo-gemini surfactants, lipids, lipophilic polycations. We assessed their synthesis, self-assembling properties, physicochemical characteristics of supramolecular assemblies, either alone or in combination with different co-lipids. We have studied the association of the pyridinium supramolecular assemblies with nucleic acids and the amphiphiles/nucleic acid complex formation, structure, physicochemical and biological properties (efficiency of delivery, associated toxicity. Efforts were made towards elucidation of mechanism of internalization, ability to overcome delivery barriers and to efficiently unload the nucleic acid cargo. We have shown that different classes of pyridinium amphiphiles can be combined to enhance nucleic acid delivery in a synergistic manner, with simultaneous reduction of the amount of cationic amphiphile needed to fully compact and protect the nucleic acid. We also introduced pyridinium amphiphiles designed to be able to associate with gold nanoparticles and we have shown that gold nanoparticles decorated with these pyridinium amphiphiles can mimic the supramolecular properties of self-assembled pyridinium amphiphiles and can deliver pDNA, alone or in combination with co-lipids, in a similar manner with traditional amphiphiles. We periodically reviewed the field and we are actively pursuing translational work towards efficient in vivo delivery of different types of nucleic acids for treatment of cancer and genetic disorders.

Selected publications

M. A Ilies, U. Satyal, V. D. Sharma "Synthetic Delivery Systems for DNA, siRNA, and mRNA Based on Pyridinium Amphiphiles", in "Control of Amphiphile Self-Assembling at the Molecular Level: Supra-Molecular Assemblies with Tuned Physicochemical Properties for Delivery Applications", M. A. Ilies Ed., *ACS Books & Oxford University Press*, Washington, DC, 2017, 1-34.

M. A. Ilies, T. V. Sommers, L. C. He, A. Kizewski, V. D. Sharma "Pyridinium Amphiphiles in Gene Delivery - Present and Perspectives" in "Amphiphiles: Molecular Assembly and Applications", R. Nagarajan Ed., *ACS Books & Oxford University Press*, 2011, 23-38.

U. Satyal, B. Draghici, L. L. Dragic, Q. Zhang, K. W. Norris, M. Madesh, E. Brailoiu, M. A. Ilies "Interfacially-engineered pyridinium pseudo-gemini surfactants as versatile and efficient supramolecular delivery systems for DNA, siRNA and mRNA", *ACS Appl. Mater. Interfaces*, 9 (35), 29481–29495 (2017).

A. Kizewski, M. A. Ilies "Efficient and synergetic DNA delivery with pyridinium amphiphiles–gold nanoparticle composite systems having different packing parameters" *Chem. Commun*. 52, 60-63 (2016).

B. Draghici, M. A. Ilies “Synthetic nucleic acid delivery systems - present and perspectives”, *J. Med. Chem*., 58(10), 4091-4130 (2015).

V. D. Sharma, J. Lees, N. E. Hoffman, E. Brailoiu, M. Muniswamy, S. L. Wunder, and M. A. Ilies “Modulation of pyridinium cationic lipid-DNA complex properties by pyridinium gemini surfactants and its impact on lipoplex transfection properties”, *Mol. Pharm*., 11 (2), 545–559 (2014).

S. Savarala, E. Brailoiu, S. L. Wunder, and M. A. Ilies, “Tuning the self-assembling of pyridinium cationic lipids for efficient gene delivery into neuronal cells”, *Biomacromolecules*, 14, 2750-2764 (2013).

V. D. Sharma, E. O. Aifuwa, P. A. Heiney, M. A. Ilies, “Interfacial engineering of pyridinium gemini surfactants for the generation of synthetic transfection systems”, *Biomaterials*, 34, 6906-6921 (2013).

V. D. Sharma, M. A. Ilies, "Heterocyclic Cationic Gemini Surfactants: A Comparative Overview of their Synthesis, Self-assembling, Physicochemical and Biological Properties", *Medicinal Research Reviews*, 2014, 34, 1-44 (published online August 20, 2012 doi: 10.1002/med.21272).

A. T. Balaban, M. A. Ilies, A. Eichhofer, T. S. Balaban, “Molecular and crystal structure of a self-assembling pyridinium cationic lipid”, *J. Mol. Struct*., 984, 228-231 (2010).

M.A. Ilies, W.A. Seitz, B.H. Johnson, E.L. Ezell, A.L. Miller, E.B. Thompson, A.T. Balaban, “Lipophilic Pyrylium Salts in the Synthesis of Efficient Pyridinium-Based Cationic Lipids, Gemini Surfactants, and Lipophilic Oligomers for Gene Delivery”, *J. Med. Chem*., 49, 3872-3887 (2006).

M.A. Ilies, B.H. Johnson, F. Makori, A. Miller, W.A. Seitz, E.B. Thompson, A.T. Balaban, “Pyridinium cationic lipids in gene delivery: An in vitro and in vivo comparison of transfection efficiency versus a tetraalkylammonium congener”, *Arch. Biochem. Biophys.*, 435, 217-226 (2005).

M.A. Ilies, W.A. Seitz, I. Ghiviriga, B.H. Johnson, A. Miller, E.B. Thompson, A.T. Balaban, “Pyridinium cationic lipids in gene delivery: a structure-activity correlation study”, *J. Med. Chem*., 47, 3744-3754 (2004).

M.A. Ilies, W.A. Seitz, M.T. Caproiu, M. Wentz, R.E. Garfield and A.T. Balaban, “Pyridinium-Based Cationic Lipids as Gene Transfer Agents”, *Eur. J. Org. Chem*., 14, 2645-2655 (2003).

M.A. Ilies, W.A. Seitz and A.T. Balaban, “Cationic lipids in gene delivery: principles, vector design and therapeutical applications”, *Curr. Pharm. Des*., 8 (27), 2441-2473 (2002).

M.A. Ilies and A.T. Balaban, “Recent developments in cationic lipid-mediated gene delivery and gene therapy”, *Expert Opin. Ther. Patents*, 11 (11), 1729-1752 (2001).

B. Drug delivery, formulation development, nanomedicine

Our team is actively developing several platforms for drug delivery based on self-assembled amphiphiles and/or different biocompatible/biodegradable nanoparticles (gold, palladium, silica, and soft materials). We are extensively using liposomes generated from natural and synthetic lipids and polymeric micelles made out of amphiphilic diblock and triblock copolymers to encapsulate and deliver hydrophilic, amphiphilic and hydrophobic drugs with the goal of improving the early detection and treatment of various types of cancers. We also study the interaction of these supramolecular assemblies with nanoparticles for generating composite systems as well as for understanding the interaction of nanoparticles with biological membranes, nanoparticle (de)stabilization and internalization within different cells. A particular interest is to develop targeted delivery systems towards epitopes overexpressed by different tumors and delivery systems with tuned stability circulation vs. tumor site. We pursue formulation development and optimization, and we study the self-assembling of synthetic amphiphiles (lipids, polymers), the physicochemical characteristics of the self-assemblies, drug loading and encapsulation efficiency, stability of the assemblies, drug release profile and associated biological effect, in vitro and in vivo.

Selected publications

K. Sakurai, M. A. Ilies, Editors: "Targeted Nanosystems for Therapeutic Applications: New Concepts, Dynamic Properties, Efficiency, and Toxicity", *ACS Books & Oxford University Press*, American Chemical Society: Washington, DC, 2019, 348 pp, published online 03/20/19, https://pubs.acs.org/isbn/9780841233836).

M. A. Ilies, Editor: "Control of Amphiphile Self-Assembling at the Molecular Level: Supra-Molecular Assemblies with Tuned Physicochemical Properties for Delivery Applications", *ACS Books & Oxford University Press*, ACS Symposium Series 1271, American Chemical Society: Washington, DC, 2017, 331 pp, ISBN 9780841232747, web: https://pubs.acs.org/isbn/9780841232747.

A. M. Shabana, M. A. Ilies "Drug delivery to hypoxic tumors targeting carbonic anhydrase IX", in "Targeted Nanosystems for Therapeutic Applications: New Concepts, Dynamic Properties, Efficiency, and Toxicity", K. Sakurai, M. A. Ilies Eds., *ACS Books & Oxford University Press*, Washington, DC, 2019, pp. 223-252.

A. M. Shabana, U. K. Mondal, Md. R. Alam, T. Spoon, C. A. Ross, M. Madesh, C. T. Supuran, M. A. Ilies, "pH-Sensitive Multi-ligand Gold Nanoplatform Targeting Carbonic Anhydrase IX Enhances the Delivery of Doxorubicin to Hypoxic Tumor Spheroids and Overcomes the Hypoxia-Induced Chemoresistance", *ACS Appl. Mater. Interfaces*, 10 (21), 17792–17808 (2018).

U. Satyal, V. D. Sharma, J. A. Shif, M. A. Ilies "Interface-Engineered Amphiphilic Block Copolymers with Tuned Enzymatic Resistance for Controlled Delivery of Chemotherapeutic Drugs", in "Control of Amphiphile Self-Assembling at the Molecular Level: Supra-Molecular Assemblies with Tuned Physicochemical Properties for Delivery Applications", M. A. Ilies Ed., *ACS Books & Oxford University Press*, Washington, DC, 2017, 211-229.

Z. Lu, Y. Yang, R. A. Covington, Y. Bi, T. Dürig, M. A. Ilies, Reza Fassihi, “Supersaturated controlled release matrix using amorphous dispersions of glipizide”, *Int. J. Pharm*., 511, 957–968 (2016).

V. D. Sharma, S. Akocak, M. A. Ilies, R. Fassihi “Solid state interactions at the core-coat interface: Physicochemical characterization of enteric-coated omeprazole pellets without a protective sub-coat”, *AAPS PharmSciTech*., 16, 934-943 (2015).

X. Zhu, V. D. Sharma, M. Fryd, M. A. Ilies, B.B. Wayland, “Lipase Catalyzed Degradation of Amphiphilic Block Copolymer Micelles: Interfacial Activation Model”, *Polymer*, 54, 2879-2886 (2013).

B. Tangeysh, M. Fryd, M. A. Ilies, B. B. Wayland, “Palladium Metal Nanoparticle Size Control through Ion Paired Structures of [PdCl4]-2 with Protonated PDMAEMA”, *Chem. Comm*. 48, 8955-8957 (2012).

X. Zhu, M. Fryd, B. D. Tran, M. A. Ilies, B. Wayland, “Modifying the Hydrophilic-Hydrophobic Interface of PEG-b-PCL to Increase Micelle Stability: Preparation of PEG-b-PBO-b-PCL Triblock Copolymers, Micelle Formation and Hydrolysis Kinetics”, *Macromolecules*, 45, 660-665 (2012).

V. V. Shuvaev, M. A. Ilies, E. Simone, S. Zaitsev, Y. Kim, S. Cai, A. Mahmud, T. Dziubla, S. Muro, D. E. Discher, V. R. Muzykantov “Endothelial targeting of antibody-decorated polymeric filomicelles”, *ACS Nano*, 5, 6991-6999 (2011).

S. Savarala, F. Monson, M. A. Ilies, S. L. Wunder, “Supported Lipid Bilayer Systems Stabilization by Undulatory-Protrusion Forces, and Destabilization by Lipid Bridging”, *Langmuir*, 27, 5850-5861 (2011).

S. Savarala, S. Ahmed, M. A. Ilies, S. L. Wunder “Stabilization of soft lipid colloids: competing effects of nanoparticle decoration and supported lipid bilayer formation”, *ACS Nano*, 5, 2619-2628 (2011).

S. Savarala, S. Ahmed, M. A. Ilies, S. L. Wunder, “Formation and Colloidal Stability of DMPC Supported Lipid Bilayers on SiO2 Nanobeads”, *Langmuir*, 26, 12081-12088 (2010).

Collaborators: **Drs. Reza Fassihi** (TUSP), **Stephanie Wunder**, **Bradford Wayland** (CST), **Eugen Brailoiu** (TUSM), Drs. Margie Clapper, Harvey Hensley (Temple Fox Chase Cancer Center), (intramural), **Dr. Kazuo Sakurai** (University of Kitakyushu, Japan) (extramural)

Medicinal chemistry and drug design

We are focused on the investigation of zinc metalloproteins, especially carbonic anhydrases and matrix metalloproteinases, with more than 20 years of experience in the inhibition and activation of these enzymes. Through their isozymes, these metalloproteins are involved in respiration and CO_2 excretion, pH homeostasis, electrolytes secretion in different environments, gluconeogenesis, lipogenesis and ureagenesis, tissue and bone remodeling and cancer. We designed and synthesized both activators and inhibitors, some with significant isozyme selectivity, useful as antiglaucoma, antiobesity, anticancer agents, as well as potential nootropics, and anti-dementia agents.

Selected publications:

M. A. Ilies, J.-Y. Winum, "Carbonic anhydrase inhibitors for the treatment of tumors: therapeutic, immunologic, and diagnostic tools targeting isoforms IX and XII." in "*Carbonic Anhydrases*", C. T. Supuran, A. Nocentini Eds, *Elsevier*, 2019, pp. 331-365.

S. Zamanova, A. M. Shabana, U. K. Mondal, M. A. Ilies, "Carbonic anhydrases as disease markers", Expert Opin. Ther. Patents, 2019, 29(7), 509-533.

R. K. K. Sanku, J. S. John, M. Salkovitz, M. A. Ilies, E. A. Walker, "Potential learning and memory disruptors and enhancers in a simple, one-day autoshaping-operant task in mice", *Behavioural Pharmacology*, 29(6), 482-492 (2018).

A. Bhatt, U. K. Mondal, C. T. Supuran, M. A. Ilies, R. McKenna, "Crystal Structure of Carbonic Anhydrase II in Complex with an Activating Ligand: Implications in Neuronal Function", *Mol. Neurobiology*, 55(9), 7431-7437 (2018).

S. Akocak, Md. R. Alam, A. M. Shabana, R. K. K. Sanku, D. Vullo, H. Thompson, E. R. Swenson, C. T. Supuran, M. A. Ilies "PEGylated Bis-Sulfonamide Carbonic Anhydrase Inhibitors Can Efficiently Control the Growth of Several Carbonic Anhydrase IX-Expressing Carcinomas", *J. Med. Chem.*, 59, 5077-88 (2016).

B. Draghici, D. Vullo, S. Akocak, E. A. Walker, C. T. Supuran, M. A. Ilies "Ethylene bis-imidazoles are highly potent and selective activators for isozymes VA and VII of carbonic anhydrase, with potential nootropic effect", *Chem. Comm.*, 50, 5980-5983 (2014).

S. Akocak, M. A. Ilies "Next-generation primary sulfonamide CA inhibitors" in "*Targeting Carbonic Anhydrases*", C. T. Supuran, C. Capasso Eds., *Future Science*, London, 2014, 35-51.

K. Dave, A. Scozzafava, D. Vullo, C. T. Supuran and M. A. Ilies "Pyridinium derivatives of histamine are potent activators of cytosolic carbonic anhydrase isoforms I, II and VII: solution and crystallographic studies", *Org. Biomol. Chem.*, 9, 2790-2800 (2011).

K. Dave, M. A. Ilies, A. Scozzafava, C. Temperini, D. Vullo, C. T. Supuran "An inhibitor-like binding mode of a carbonic anhydrase activator within the active site of isoform II", *Bioorg. Med. Chem. Lett., 21, 2764-2768* (2011). (**Cover article, revealing the fine boundary between CA activation and inhibition**)

M. A. Ilies "Metal complexes as dual carbonic anhydrase inhibitors" in "*Drug Design of Zinc-Enzyme Inhibitors: Functional, Structural, and Disease Applications*" (Binghe Wang Series in Drug Discovery and Development), C. T. Supuran, J. Y. Winum Eds., *Wiley*, 2009, 439-472.

M. A. Ilies and M.D. Banciu, "Non-sulfonamide carbonic anhydrase inhibitors" in "*Carbonic Anhydrase, Its Inhibitors and Activators*", C.T. Supuran, A. Scozzafava, J. Conway Eds., *CRC Press*, Boca Raton, 2004, pp. 207-239.

M.A. Ilies, D. Vullo, J. Pastorek, A. Scozzafava, M. Ilies, M.T. Caproiu, S. Pastorekova and C.T. Supuran, "Carbonic anhydrase inhibitors. Inhibition of tumor-associated isozyme IX by halogenosulfanilamide and halogeno-aminobenzolamide derivatives", *J. Med. Chem*., 46, 2187-2196 (2003). (**First CA IX inhibition study with synthetic inhibitors**)

M. Ilies, M.D. Banciu, A. Scozzafava, M.A. Ilies, M.T. Caproiu, and C.T. Supuran, "Protease inhibitors: Synthesis of bacterial collagenase and matrix metalloproteinase inhibitors incorporating arylsulfonylureido and 5-dibenzo-suberenyl/suberyl moieties", *Bioorg. Med. Chem*., 11, 2227-2239 (2003).

M. Ilies, M.D. Banciu, M.A. Ilies, A. Scozzafava, M.T. Caproiu and C.T. Supuran, "Carbonic anhydrase activators: Design of high affinity isozymes I, II and IV activators, incorporating tri-/tetrasubstituted-pyridinium-azole moieties", *J. Med. Chem*., 45 (2), 504-510 (2002).

A. Casini, A. Scozzafava, F. Mincione, L. Menabuoni, M.A. Ilies, C.T. Supuran, "Carbonic Anhydrase Inhibitors: Water-Soluble 4-Sulfamoylphenylthioureas as Topical Intraocular Pressure-Lowering Agents with Long-Lasting Effects", *J. Med. Chem*., 43 (25), 4884-4892 (2000).

A. Scozzafava, M.A. Ilies, G. Manole, C.T. Supuran, "Protease inhibitors. Part 12. Synthesis of potent matrix metalloproteinase and bacterial collagenase inhibitors incorporating sulfonylated N-4-nitrobenzyl-□-alanine hydroxamate moieties", *Eur. J. Pharm. Sci*., 11(1), 69-79 (2000).

A. Scozzafava, F. Briganti, M.A. Ilies, C.T. Supuran, "Carbonic anhydrase inhibitors: Synthesis of membrane-impermeant low molecular weight sulfonamides possessing in vivo selectivity for the membrane-bound versus the cytosolic isozymes", *J. Med. Chem*, 43, 292-300 (2000).

C.T. Supuran, A. Scozzafava, M.A. Ilies, B. Iorga, T. Cristea, F. Briganti, F. Chiraleu, M.D. Banciu, "Carbonic Anhydrase Inhibitors. Part 53. Synthesis of Substituted-Pyridinium Derivatives of Aromatic Sulfonamides: The First Non-Polymeric Membrane-Impermeable Inhibitors with Selectivity for Isozyme IV", *Eur. J. Med. Chem*., 33, 577-594 (1998).

C.T. Supuran, F. Mincione, A. Scozzafava, F. Briganti, G. Mincione, M.A. Ilies, “Carbonic Anhydrase Inhibitors. Part 52. Metal Complexes of Heterocyclic Sulfonamides: A New Class of Strong Topical Intraocular Pressure-lowering Agents With Potential Use as Antiglaucoma Drugs”, *Eur. J. Med. Chem*., 33, 247-254 (1998).

C.T. Supuran, A. Scozzafava, B.C. Jurca, M.A. Ilies, “Carbonic Anhydrase Inhibitors. Part 49. Synthesis of Substituted- Ureido and Thioureido Derivatives of Aromatic/ Heterocyclic Sulfonamides with Increased Affinities for Isozyme I”, *Eur. J. Med. Chem*., 33, 83-93 (1998). (**the paper introduced ureido-sulfanilamides as potent CA inhibitors, later evolved into ureidosulfonamide SLC-0111, currently in clinical trials for treatment of solid tumors**)

C.T. Supuran, M.A. Ilies, A. Scozzafava, “Carbonic anhydrase inhibitors. Part 29. Interaction of isozymes I, II and IV with benzolamide-like derivatives, possible precursors of inhibitors with applications in positron emission tomography imaging”, *Eur. J. Med. Chem*., 33, 739-751 (1998).

M.A. Ilies, M.D. Banciu, M. Ilies, F. Chiraleu, F. Briganti, A. Scozzafava, C.T. Supuran, “Carbonic Anhydrase Activators. Part 17. Synthesis and activation study of 1-(1,2,4- triazole- (1H)-3- yl)-2,4,6- trisubstituted-pyridinium salts against isozymes I, II, IV”, *Eur. J. Med. Chem.*, 32 (11), 911-918 (1997) (**one of the first activation study of CA with azoles**)

Collaborators: Drs. **Ellen A. Walker** (TUSP), **Silvia Fossati** (TUSM) (intramural), Drs. **Claudiu T. Supuran** (University of Florence), **Robert McKenna** (University of Florida) (extramural)