BIOGRAPHICAL SKETCH

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NAME: Stefano Toldo

eRA COMMONS USER NAME (credential, e.g., agency login): STEFANOTOLDO

POSITION TITLE: Associate Professor of Medicine

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University 'La Sapienza', Rome, Italy	BS	1997-2004	Biological Sciences
University 'La Sapienza' and National Research Council (CNR), Rome, Italy	MS	2004-2006	Molecular Biology-Neuroscience
Catholic University of the Sacred Heart, Rome, Italy	PhD	2006-2010	Cellular and Molecular Cardiology
Virginia Commonwealth University, Richmond, VA	Postdoctoral	2010-2015	Molecular Cardiology and Physiology

A. Personal Statement

My research is oriented toward understanding the mechanism by which stress signals and myocardial injury lead to the activation of the local and systemic inflammatory response. The presence of high inflammatory markers increases the risk of developing heart failure and correlates with adverse prognosis. In recent years, I devoted my effort to understanding the way the inflammatory response is activated as a consequence of the injury that follows ischemic injury to the heart. Specifically, I studied the mechanisms that regulate the inflammatory response and myocardial remodeling acutely and chronically. A major focus of our research has been the characterization of the role of the NLRP3 inflammasome and related cytokines, Interleukin-1β and Interleukin-18) as mediators of myocardial damage and dysfunction. I have successfully completed investigator-initiated projects in collaboration with pharmaceutical companies and have successfully competed for NIH support. In 2020, part of my research effort has been devoted to COVID-19 research.

Ongoing, recent, and pending projects

R01HL150115, NHLBI — Abbate, Antonio; Toldo, Stefano (M-PI)
02/01/2020 –01/31/2025 — Role: Principal Investigator
Unconventional Interleukin-1 signaling in heart failure.

R01HL174999, NHLBI — Abbate, Antonio; Saucerman, Jeffrey; Toldo, Stefano. (M-PI)
08/12/2024 –08/11/2028 — Role: Principal Investigator
Modeling of cell-specific LRP1 signaling in acute myocardial infarction.

1R35HL161237, NHLBI — Gourdie, Robert (PI)
01/01/2020 –12/31/2024 — Role: Co-Investigator
Connexin-based Signaling in the Heart: Cellular and Exosomal.

Completed Research Support in the last three years

Investigator initiated study-Cardiol — Toldo, Stefano (PI)
01/01/2022 – 12/31/2022 — Role: Principal Investigator

Investigator initiated study-Kamada — Toldo, Stefano (PI)

05/01/2021 – 10/31/2022 Role: Principal Investigator
Human recombinant AAT in acute myocardial infarction: a pilot pre-clinical study

Investigator initiated study-Kiniksa Toldo, Stefano (PI)
01/01/2019 – 12/31/2021 Role: Principal Investigator
IL-1 blockade in acute pericarditis.

Citations

a. Mauro AG, Bonaventura A, Vecchié A, Mezzaroma E, Carbone S, Narayan P, Potere N, Cannatà A, Paolini JF, Bussani R, Montecucco F, Sinagra G, Van Tassel BW, Abbate A, **Toldo S**. The Role of NLRP3 Inflammasome in Pericarditis: Potential for Therapeutic Approaches. **JACC Basic Transl Sci**. 2021;6:137-150.
b. **Toldo S**, Kannan H, Bussani R, Anzini M, Sonnino C, Sinagra G, Merlo M, Mezzaroma E, De-Giorgio F, Silvestri F, Van Tassell BW, Baldi A, Abbate A. Formation of the inflammasome in acute myocarditis. **Int J Cardiol**. 2014;17:e119-21.
c. **Toldo S,** Bussani R, Nuzzi V, Bonaventura A, Mauro AG, Cannatà A, Pillappa R, Sinagra G, Nana-Sinkam P, Sime P, Abbate A. Inflammasome formation in the lungs of patients with fatal COVID-19. Inflamm Res. 2021 Jan;70(1):7-10.
d. Mezzaroma E, Mauro A, **Toldo S.** Identifying Inflammasome Activation in Human Tissues. **Methods Mol Biol**. 2023;2641:101-113.

Peer-reviewed Publications: 128 *Scopus Citations: 11,185* *Scopus H-index: 44*

B. Positions and Honors

Positions and Employment

Sep 2007-Apr 2009	Doctoral Student, Cardiology Division, Catholic University of the Sacred Heart, Rome, Italy.
Apr 2009-Mar 2010	Research Associate, Department of Internal Medicine, VCU Pauley Heart Center Virginia Commonwealth University, Richmond, VA.
Mar 2010-Aug 2015	Post-doctoral fellowship, Department of Internal Medicine, VCU Pauley Heart Center Virginia Commonwealth University, Richmond, VA.
Sep 2015-Jun 2021	Assistant Professor of Medicine, VCU Pauley Heart Center, Department of Internal Medicine and Department of Surgery, Virginia Commonwealth University, Richmond, VA.
Jul 2021-Nov 2022	Associate Professor of Medicine, VCU Pauley Heart Center, Department of Internal Medicine and Department of Surgery, Virginia Commonwealth University, Richmond, VA.
Dec 2022-Present	Associate Professor of Medicine, Robert M. Berne Cardiovascular Research Center, Department of Medicine, University of Virginia, Charlottesville, Virginia.

Other Experience & Professional Memberships

2011-present	American Heart Association *Basic Science Council.*
2013-2021	Italian Society of Cardiology.

Review Committees

2022-2023	Ad-hoc Member, Integrative Myocardial Physiology/Pathophysiology A (MPPA), NHLBI, NIH
2017-2023	Reviewer for the British Heart Foundation
2017-2023	Reviewer for the European Science Foundation
2020	Ad-hoc Member, Cardiac Contractility and Heart Failure (CCHF), NHLBI, NIH
2020	Study Section Member-American Heart Association-Transformational Basic Cardiac Science
2019-2020	Study Section Member-American Heart Association-Immunology BSc Fellowship

Honors and Awards

2020, 2022	Reviewer NHLBI, NIH
2020	Virginia Commonwealth University Department of Internal Medicine "Excellence in Scholarship and Research" award.
2013	Virginia Commonwealth University, *Travel grant*
2013	American Heart Association, *Post-Doctoral Training Grant*
2012	Italian Society of Cardiology, *Young Investigator Award, 2nd place*
2011	International Cytokine Society- *Travel Grant*

2010 European Society of Cardiology *Young Investigator Award - Finalist*
2009 Italian Society of Cardiology *Training Grant*

Lectures and Seminars

2024 Invited speaker, session title: “Recent Advances in NLRP3 Inflammasome Signaling in Cardiovascular Diseases.” Presentation Title: “Interleukin-1 beta in heart remodeling and dysfunction”. ASPET Annual Meeting 2024 in Arlington, VA.

2023 19th World Congress of Basic & Clinical Pharmacology 2023. Invited Speaker, Session Title:"Emerging role of NLRP3 inflammasome as a therapeutic target in cardiovascular and infectious diseases”. Lecture Title "Inflammasome activation and COVID-19 patients".

2022 European Society of Cardiology Workgroup on Myocardial and Pericardial Disease 2022 (MPD2022). Invited Speaker, Session: "The Inflammasome and Myopericardial Diseases”. Lecture Title: "What is the inflammasome and why it’s important for cardiologists".

2019 Heart Failure Society of America (HFSA) Annual Scientific Meeting. Invited Speaker, Session Title: "Diet, Nutrition, and Cardiac Functions: From Bedside to Bench and Back Again”. Title of the Lecture "NLRP3 Inflammation and Diet-Induced Cardiac Dysfunction: A Novel Therapeutic Target".

2019 Invited Lecture, Noll Seminar, Pennsylvania State University. Title: “IL-1 and the Inflammasome in Acute Myocardial Infarction & Heart Failure”.

2018 American Heart Association Scientific Session. Invited Speaker, Session Title: “Molecular and Cellular Regulation of Cardiac Inflammation”.

2017 American Heart Association Scientific Session. Invited Speaker, Session Title: “Immunometabolism, Inflammation, and Cardiovascular Disease”. Presentation title: “Interleukin-18 blockade as a strategy to reduce contractile dysfunction in heart failure”.

2016 The ASIP 2016 Annual Meeting at Experimental Biology. Presentation Title “NLRP3 in Inflammasome Inhibition in Acute Myocardial Injury”.

2015 American Heart Association Scientific Session. Invited Speaker, Session Title: The Inflammasome in Heart Disease. Presentation title: “Inflammasome-targeted therapies”.

2014 Research highlights from young investigators, Italian Society of Cardiology annual meeting, Rome, Italy. Title of the Lecture: “Induction of MicroRNA-21 with Exogenous Hydrogen Sulfide Attenuates Myocardial Ischemic and Inflammatory Injury in Mice”.

2013 Research highlights from young investigators, Italian Society of Cardiology annual meeting, Rome, Italy. Title of the Lecture: “Targeting Interleukin-1 in heart disease”.

2012 Invited lecture at the University of East Anglia, Norwich, United Kingdom. Title of the lecture: “The inflammasome and the heart”.
“Inhibition of early inflammatory injury during acute myocardial ischemia reperfusion.”
“IL-1 and the inflammasome in acute myocardial infarction and heart failure”.

Editorial activities

2010-present Peer reviewer for the international journals: Nature Medicine, JACC BTS*International Journal of Cardiology, Public Library of Science (PLOSONE), Journal of Biochemical Chemistry, Antioxidants and Redox Signaling, Journal of the American Heart Association, Journal of clinical investigation, Journal of Cellular Physiology, Critical Care, Molecular Immunology,* etc.

2017-present Guest Editor-O*xidative* M*edicine and Cellular* L*ongevity, Frontiers in Cardiovascular Medicine*

C. Contribution to Science

1. Interleukin-18 and heart failure

I investigated the effects of a second cytokine produced by the inflammasome, interleukin-18 (IL-18). This cytokine was first described in 1989 for its ability to induce the production of interferon gamma (IFN-γ). By others, exogenous IL-18 has been associated with myocardial fibrosis and diastolic dysfunction. We are now focusing on the effects of endogenous IL-18 produced in response to cardiac injury.

Selected publications in this area:

- Quader M, Mezzaroma E, Kenning K, **Toldo S**. Modulation of Interleukin-1 and -18 Mediated Injury in Donation after Circulatory Death Mice Heart. J Surg Res. 2020;257:468-476.

- Carbone S, Lee PH, Mauro AG, Mezzaroma E, Buzzetti R, Van Tassell BW, Abbate A, **Toldo S.** Interleukin 18 Mediates Cardiac Dysfunction Induced by Western Diet Independent of Obesity and Hyperglycemia in the Mouse. **Nutrition & Diabetes 2017**. 2017;7:e258
- **Toldo S***, Mezzaroma E, O'Brien L, Marchetti C, Seropian IM, Voelkel NF, Van Tassell BW, Dinarello CA, Abbate A. Interleukin-18 mediates interleukin-1-induced cardiac dysfunction**. Am J Physiol Heart Circ Physiol**. 2014;306:H1025-31. ***Corresponding author**
- O'Brien LC, Mezzaroma E, Van Tassell BW, Marchetti C, Carbone S, Abbate A, **Toldo S**. Interleukin-18 as a therapeutic target in acute myocardial infarction and heart failure. **Mol Med**. 2014;20:221-9 PMCID: PMC4069269.

2. The role of the inflammasome in myocardial diseases.

My research interest on the inflammatory mechanisms activated during AMI started when I was hosted for three months in Dr. Abbate's laboratory in 2008 for a summer internship. During that time, I was exposed to his work on using the interleukin-1 (IL-1) receptor antagonist (IL-1ra) in AMI. During the last year of my Ph.D. course, I permanently joined Dr. Abbate's lab in Richmond, VA, and became a post-doctoral fellow in 2010. Since then, we better deciphered the effects of IL-1 in the acute and chronic phases of post-AMI heart remodeling and tested the impact and safety profile of IL-1 blockade. Moreover, we investigated the mechanisms leading to the production of IL-1 in the heart and described the inflammasome pathway as a source of inflammation and cell death in the ischemic heart. In recent years, we then investigated the mechanisms of the inflammasome formation and its involvement in other types of cardiac injury.

Selected publication in this area:

- **Toldo S**, Abbate A. The NLRP3 inflammasome in acute myocardial infarction. **Nat Rev Cardiol**. 2018;15:203-214.
- **Toldo S***, Mezzaroma E, McGeough MD, Peña CA, Marchetti C, Sonnino C, Van Tassell BW, Salloum FN, Voelkel NF, Hoffman HM, Abbate A. Independent roles of the priming and the triggering of the NLRP3 inflammasome in the heart. Cardiovasc Res. 2015;105:203-12. ***Corresponding Author; Editor's Choice**
- **Toldo S**, Das A, Mezzaroma E, Chau VQ, Marchetti C, Durrant D, Samidurai A, Van Tassell BW, Yin C, Ockaili RA, Vigneshwar N, Mukhopadhyay ND, Kukreja RC, Abbate A, Salloum FN. Induction of MicroRNA-21 with Exogenous Hydrogen Sulfide Attenuates Myocardial Ischemic and Inflammatory Injury in Mice. **Circ Cardiovasc Genet**. 2014,7:311-20. PMCID:PMC4090021
- Mezzaroma E, **Toldo S**[#], Farkas D, Seropian IM, Van Tassell BW, Salloum FN, Kannan HR, Menna AC, Voelkel NF, Abbate A. The inflammasome promotes adverse cardiac remodeling following acute myocardial infarction in the mouse. **Proc Natl Acad Sci U S A**. 2011;108:19725-30. PMCID: PMC3241791 #**contributed equally to the work.**

3. *IL-1 inhibition in AMI*.

My research interest on the inflammatory mechanisms activated during AMI started when in 2008, I was hosted in the VCU Pauley Heart Center for a summer internship. During that time, I was exposed to ongoing research on AMI's interleukin-1 (IL-1) receptor antagonist (IL-1ra). Since then, we better deciphered the effects of IL-1 in the acute and chronic phases of post-AMI heart remodeling and tested the effects and safety profile of IL-1 blockade. Moreover, we investigated the mechanisms leading to the production of IL-1 in the heart and described the inflammasome pathway in inflammation and cell death in the ischemic heart.

Selected publication in this area:

- **Toldo S**, Mezzaroma E, Bressi E, Marchetti C, Carbone S, Sonnino C, Van Tassell BW, Abbate A. Interleukin-1β blockade improves left ventricular systolic/diastolic function and restores contractility reserve in severe ischemic cardiomyopathy in the mouse. **J Cardiovasc Pharmacol**. 2014;64:1-6.
- Van Tassell BW, **Toldo S**, Mezzaroma E, Abbate A. Targeting interleukin-1 in heart disease. **Circulation**. 2013;128:1910-23.
- **Toldo S**, Schatz AM, Mezzaroma E, Chawla R, Stallard TW, Stallard WC, Jahangiri A, Van Tassell BW, Abbate A. Recombinant human interleukin-1 receptor antagonist provides cardioprotection during myocardial ischemia-reperfusion in the mouse. **Cardiovasc Drugs Ther.** 2012;26:273-6.
- **Toldo S**, Mezzaroma E, Van Tassell BW, Farkas D, Marchetti C, Voelkel NF, Abbate A. Interleukin-1β blockade improves cardiac remodeling after myocardial infarction without interrupting the inflammasome in the mouse. **Exp Physiol**. 2013;98:734-45.

4. **Study of anti-inflammatory therapies to reduce the activation of caspase-1 and the inflammasome**
   In recent years the inflammasome has emerged as a central node connecting damage sensing to initiation of the inflammatory response. However, the inflammasome activation in the heart leads to further damage by activating caspase-1, the effector enzyme responsible for the maturation of cytokines of the IL-1 family and induction of cell death. Currently, there are no therapies to prevent inflammasome activation following AM. We, therefore, attempted to identify novel therapies that could block the activation of the inflammasome in a preclinical, experimental setting.

Selected publication in this area:

- **Toldo S**, Seropian IM, Mezzaroma E, Van Tassell BW, Salloum FN, Lewis EC, Voelkel N, Dinarello CA, Abbate A. Alpha-1 antitrypsin inhibits caspase-1 and protects from acute myocardial ischemia-reperfusion injury. **J Mol Cell Cardiol**. 2011;51:244-51.
- Marchetti C, Chojnacki J, **Toldo S**, Mezzaroma E, Tranchida N, Rose SW, Federici M, Van Tassell BW, Zhang S, Abbate A. A novel pharmacologic inhibitor of the NLRP3 inflammasome limits myocardial injury following ischemia-reperfusion in the mouse. ***J Cardiovasc Pharmacol***. 2014;63:316-322. PMCID: PMC3980088.
- **Toldo S**, Zhong H, Mezzaroma E, Van Tassell BW, Kannan H, Zeng D, Belardinelli L, Voelkel NF, Abbate A. GS-6201, a selective blocker of the A2B adenosine receptor, attenuates cardiac remodeling after acute myocardial infarction in the mouse. **J Pharmacol Exp Ther**. 2012;343:587-95.
- **Toldo S**, Austin D, Mauro AG, Mezzaroma E, Van Tassell BW, Marchetti C, Carbone S, Mogelsvang S, Gelber C, Abbate A. Low-Density Lipoprotein Receptor–Related Protein-1 Is a Therapeutic Target in Acute Myocardial Infarction. JACC BTS 2017;2:561-574.

5. **Apoptosis and myocardial damage**
   Cardiomyocyte apoptosis is one of the mechanisms activated following injury. Secondary to inflammatory signals or the production of non-functional mitochondria or anti-oxidant enzymes or the accumulation of non-functional protein or DNA damage, the apoptotic pathway is a cellular clearance mechanism that reduces toxic effects to the rest of the healthy tissue. However, loss of cardiomyocytes reduces due to apoptosis reduces the contractile capacity of the cells and promotes changes in the fine architecture of the myocardial tissue (increase in interstitial collage in cell-cell interaction. We have studied therapies to limit cardiomyocyte apoptosis following myocardial damage.

Selected publication in this area:

- Abbate A, Sinagra G, Bussani R, Hoke NN, Merlo M, Varma A, **Toldo S**, Salloum FN, Biondi-Zoccai GG, Vetrovec GW, Crea F, Silvestri F, Baldi A. Apoptosis in patients with acute myocarditis. **Am J Cardiol**. 2009;104:995-1000.
- **Toldo S**, Mezzaroma E, Van Tassell BW, Farkas D, Marchetti C, Voelkel NF, Abbate A. Interleukin-1β blockade improves cardiac remodeling after myocardial infarction without interrupting the inflammasome in the mouse. **Exp Physiol**. 2013;98:734-45.
- **Toldo S**, Breckenridge DG, Mezzaroma E, Van Tassell BW, Shryock J, Kannan H, Phan D, Budas G, Farkas D, Lesnefsky E, Voelkel N, Abbate A. Inhibition of apoptosis signal-regulating kinase 1 reduces myocardial ischemia-reperfusion injury in the mouse. **J Am Heart Assoc**. 2012;1:e002360.
- **Toldo S**, Goehe RW, Lotrionte M, Mezzaroma E, Sumner ET, Biondi-Zoccai GG, Seropian IM, Van Tassell BW, Loperfido F, Palazzoni G, Voelkel NF, Abbate A, Gewirtz DA. Comparative cardiac toxicity of anthracyclines in vitro and in vivo in the mouse. **PLoS One**. 2013;8:e58421.