VANDERBILT
School *of* Medicine Basic Sciences

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Biosketch

Walter J. Chazin is the Chancellor's Chair in Medicine in the Departments of Biochemistry and Chemistry Departments. He serves as Director of the Chemical and Physical Biology Ph.D. Program and the Molecular Biophysics Training Program, and Founding Director of the Center for Structural Biology.

He received a B.Sc. (Chemistry, 1975) from McGill University and a Ph.D. (Chemistry, 1983) from Concordia University (Montreal), and went on to postdoc in the lab of 2002 Nobel Laureate Kurt Wüthrich (E.T.H. Switzerland).

After 13 years at the Scripps Research Institute, he moved to Vanderbilt in 1999.

Key Publications

"Molecular basis for manganese sequestration by calprotectin and roles in the innate immune response to invading bacterial pathogens," *Proc. Natl. Acad. Sci.*, USA 110, 3841-3846 (2013).

"The [4Fe4S] Cluster of Human DNA Primase functions as a Redox Switch using DNA Charge Transport," *Science* 355, 218 & eaag1789 (2017).

"XPA tumor variants lead to defects in NER that sensitize cells to cisplatin," *bioRxiv*: 2023.06.29.547124 (2023).

"Integrative structural biology in genome maintenance and innate immunity"

Our laboratory uses a 'whatever it takes' structural biology approach integrated with small molecule discovery, in vitro and cell-based biochemistry, and wide ranging collaborations to solve fundamental questions in medicine and biology.

One program involves elucidating how proteins act together as molecular machinery to perform the major processes in a cell. We determine molecular mechanisms of human DNA replication and nucleotide excision repair machines, currently focused on the human DNA polymerase alpha-primase complex and the XPA/RPA/TFIIH complex, respectively. To translate of our knowledge into potential new therapeutic strategies we use fragment-based discovery of inhibitors, e.g., targeting the XPA-RPA interaction interface with the goal of increasing the efficacy of Pt-based cancer chemotherapeutics.

A second program involves discerning the molecular mechanisms of S100 proteins and their inflammatory receptors in innate immunity. Working with >30 collaborators around the world, we have shown that S100 proteins can suppress infections by starving invading pathogens of essential transition metals needed for survival and growth, but are also used by pathogens to evade the immune response. We are also determining the structural basis of S100 protein activation of inflammation and the development of small molecule inhibitors to suppress hyper-inflammation that arises from aberrant stimulation of immune responses.