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Simon's research interests center around biomedical imaging. His major accomplishments have been in developing systems for positron emission tomography, for example as co-leader of the EXPLORER consortium which developed the world's first total-body PET scanner. He also has contributed to detector technology innovations for PET, conducted early biomedical studies using Cerenkov luminescence, and developed the first proof-of-concept hybrid PET/MRI (magnetic resonance imaging) systems.

Simon is an elected fellow of six professional societies and a Member of the National Academy of Engineering and National Academy of Inventors. He has received several international awards including the Society of Nuclear Medicine and Molecular Imaging Cassen Prize in 2022. He served as Editor-in-Chief of the journal *Physics in Medicine and Biology* from 2011-2020. Simon is the author of more than 300 peer-reviewed journal articles, review articles and book chapters in the field of biomedical imaging. He is also lead author of the widely-used textbook "Physics in Nuclear Medicine".