BIOGRAPHICAL SKETCH

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NAME: IZARD, Tina

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

POSITION TITLE: Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Basel, Biocenter, Switzerland	B.Sc.	06/1989	Biochemistry
University of Basel, Biocenter, Switzerland	M.Sc.	06/1990	Biophysics/Crystallography
University of Melbourne, Australia	Ph.D.	12/1994	Physics/Crystallography
University of Washington, Seattle, WA, USA	Post-doc	08/1996	Biochemistry/Crystallography

A. Personal Statement

Dr. Tina Izard, Principal Investigator (PI) is an expert in macromolecular X-ray crystallography, with over 25 years of experience in the field. She received outstanding training in the laboratories of Drs. Hans Jansonius (Basel, Switzerland), Peter Colman (Melbourne, Australia), and Wim Hol (Seattle, USA). In 1996, the PI began her academic career as a Lecturer at the University of Leicester and in 2000 she joined the faculty of St. Jude Children's Research Hospital as an Assistant Professor. She was promoted to Associate Professor in 2005 and was recruited to The Scripps Research Institute (TSRI) in 2007 as an Associate Professor with Tenure and promoted to full Professor in 2017. At TSRI FL, her duties also include those as Director of the Scripps Florida Macromolecular X-ray Crystallography and management of the Scripps SER-CAT beamline share at the Advanced Photon Source at Argonne National Laboratory. The PI serves on NIH Study Sections and is a reviewer for several journals, including *The Journal of Cell Biology, EMBO Journal, Nature, Nature Structural & Molecular Biology*, *Proceedings of the National Academy of Sciences of the USA,* and *Science Advances*.

As a daughter of a primary school teacher at her own K-12 school, the PI often spent time in her mother's classroom at the German School in Barcelona (Spain). While in middle school, the PI tutored students in various subjects, which continued throughout high school. In graduate school (1991-1994), she tutored a class in Physics at Melbourne University (Australia) as part of their curriculum. During her Lectureship appointment at Leicester University in England (1997-1998), the PI taught undergraduates in Chemistry and provided tutorials as part of their curriculum and she also privately tutored several middle and high school students. After joining the faculty of St. Jude Children's Research Hospital (SJCRH) in Memphis (2000-2007), the PI obtained an adjunct appointment at The University of Tennessee where she taught 'Physical Chemistry and Applications' in the Structural Biology Graduate Course. During her tenure at SJCRH, she was also a lecturer of the Graduate Student Journal Club. Further, the PI was an active mentor in the SJCRH Pediatric Oncology Education (POE) Program that provides research training and education to top-tier undergraduate students to promote careers in biomedical research. She trained several POE students and was also a member of the Rhodes College/St. Jude Summer Plus Undergraduate Research Program, which provides training to outstanding young undergraduates at Rhodes College (Memphis, TN). Finally, the PI was often approached to serve as a role model to female students, whom she enjoyed mentoring, including under-represented minorities. These students included a female African American undergraduate student from LeMoyne Owen College (a minority college located in Memphis, TN) as part of the McNair Program, as well as a black female graduate student from Paris (France). In addition, during her lectureship at Leicester University, the PI trained and hosted a female graduate student from the laboratory of her collaborator Professor Sygusch (University of Montreal) in the preparation of seleno-methionine substituted proteins. In addition to mentoring many undergraduate and graduate students, the PI mentored many post-doctoral fellows. More recently, the PI

participated in the TSRI Florida outreach program and organized DNA extraction and drug discovery hands-on workshops in middle schools and participates in the High School Student Summer Internship Program made possible by a generous grant from the William R. Kenan, Jr. Charitable Trust where she mentored a student entering his senior year at Suncoast High School in Palm Beach County for six weeks in the Summer and provided hands-on research experience. The PI also mentors High School students from Oxbridge Academy for academic credit. Finally, besides her appointment as a Graduate Program faculty member at TSRI, the PI is heavily involved with a middle school, where she recently served as the Chair of the science fair and where she uses the TSRI demonstration laboratory to bring in middle school students for hands-on research experience.

B. Positions and Honors

Positions and Employment

1987 - 1988	Apprenticeship, Department of Vitamin Research, Hoffmann-La Roche, Basel, Switzerland
1990 - 1991	Research Assistant, Structural Biology, Biocenter, University of Basel, Switzerland
1995 - 1996	Research Associate, HHMI, Biological Structure, University of Washington, Seattle, WA
1996 - 1999	Lecturer, Department of Biochemistry, University of Leicester, Leicester, England
2000 - 2005	Assistant Faculty Member, St. Jude Children's Research Hospital, Memphis, TN
2000 - 2007	Adjunct Assistant Professor, Department of Molecular Sciences, University of Tennessee Health Science Center, Memphis, TN
2005 - 2007	Associate Faculty Member, Department of Oncology, St. Jude Children's Research Hospital, Memphis, TN
2007 - 2017	Associate Professor with Tenure, The Scripps Research Institute (TSRI, Florida)
2015 - 2017	Adjunct Associate Professor with Tenure, Department of Immunology and Microbiology, TSRI
2016 - present	The Scripps Research Institute Graduate Program Faculty Member
2017 – present	Professor, Department of Integrative Structural and Computational Biology, TSRI
2017 - present	Adjunct Professor, Department of Immunology and Microbiology, TSRI

Other Experience and Professional Membership

1985 - 1990	The Educational Department Bellinzona, Switzerland, scholarship
1991, 1993-4	Dr. Max Husmann Foundation, Zurich, Switzerland
1991 - 1994	Melbourne University Postgraduate Scholarship, Australia
1991	Swiss National Science Foundation
1992,1994	International Union of Crystallography Young Scientist Award
1993	Scholarship from the Society of Crystallography in Australia
1997, 1998	The Wellcome Trust Travel Grant
1997 - present	*Ad hoc* Reviewer for: Acta Crystallographica D, Acta Crystallographica F, Biochemistry, Cell Communication and Adhesion, Cell Motility and the Cytoskeleton, FEBS Letters, FEBS Journal, Journal of Structural Biology, Nature, Nature Communications, Nature Structural & Molecular Biology, Proceedings of the National Academy of Sciences of the USA, Protein Science, Scientific Reports, Structure, The EMBO Journal, The Journal of Cell Biology, The Journal of Biological Chemistry, The Journal of Molecular Biology, Trends in Biochemical Sciences
2006	*Ad hoc* Reviewer, Macromolecular Structure & Function B (MSFB) Study Section
2009 - present	Reviewer, Macromolecular Crystallography Proposals, Advanced Photon Source
2009 - present	Reviewer, The Wellcome Trust (England, UK) project grant applications
2012 - present	Reviewer, Biotechnology and Biological Science Research Council (England, UK) project grant applications
2014	Reviewer, Special Emphasis Panel, Macromolecular Structure & Function E (MSFE) Study Section
2015	Reviewer, Special Emphasis Panel, Biological Chemistry & Macromolecular Biophysics (BCMB) Study Section
2017 - 2022	Editorial Board Member, The Journal of Biological Chemistry
2017	*Ad hoc* Reviewer, Intercellular Interactions (ICI) Study Section
2017 - present	The Scripps Research Institute faculty search committee member
2019	The Scripps Research Institute faculty promotion committee member

C. Contributions to Science

1. I started my academic career with a 3-year Lectureship appointment at Leicester University in England (1997-1998) where my laboratory, comprised of me only, made major contributions to the understanding of several bacterial enzymes and how these could be exploited as novel antibacterial drug targets.
   (i) We determined the first crystal structure of phosphopantetheine adenylyltransferase (PPAT) from *Escherichia coli* and *Mycobacterium tuberculosis* in its apo form and in complex with several ligands that we published in 6 papers which were cited 183 times. PPAT catalyzes the penultimate step of coenzyme A (CoA) biosynthesis, the major acyl carrier for all organisms. Our results were the foundation for a pharmaceutical startup company (PanTherix Ltd).
   (ii) We determined the crystal structure of chloramphenicol phosphotransferase, an enzyme that inactivates chloramphenicol, which inhibits ribosomal peptidyl transferase activity, from *Streptomyces venezuelae* alone and in complex with ligands that we published in 3 papers which were cited 52 times.
   (iii) We determined the crystal structure of the metal dependent 2-dehydro-3-deoxy-galactarate aldolase from *Escherichia coli* and proposed a novel mechanism that we published in 2 papers with 42 citations.

   a. **T Izard*** & A Geerlof (1999)
   The crystal structure of a novel bacterial adenylyltransferase reveals half of sites reactivity
   EMBO J 18:2021-2030, PMCID = 1171286

   b. **T Izard*** & J Ellis (2000)
   The crystal structures of chloramphenicol phosphotransferase reveal a novel inactivation mechanism
   EMBO J 19:2690-2700, PMCID = 212772

   c. **T Izard*** & NC Blackwell (2000)
   Crystal structures of the metal-dependent 2-dehydro-3-deoxy-galactarate aldolase suggest a novel reaction mechanism
   EMBO J 19:3849-3856, PMCID = 306599

   d. **T Izard*** (2003)
   A novel adenylate binding site confers phosphopantetheine adenylyltransferase interactions with coenzyme A
   J Bacteriol 185:4074-4080

2. Upon being appointed as junior faculty at St. Jude Children's Research Hospital in 2000, I set up a cell adhesion laboratory to study key cell adhesion proteins both structurally and functionally. Initially, our studies on the vinculin interactions with talin were supported by an NIGMS R01 award (2004-2012), which scored a 5% and a 1% in the renewal. These studies redefined the understanding of vinculin structure and function where we showed that the talin binding site on the vinculin head domain VH does not overlap with that of the vinculin tail domain Vt, implying that the binding of talin occurs first, then triggers VH-Vt dissociation. We established that talin and α-actinin are physiological activators of vinculin, and that they do so by provoking an entirely new mechanism of α-helix/helix bundle interactions termed helix bundle conversion. We further established that activation of focal adhesions involves a relay of structural alterations, whereby unfurling of helix bundles in talin or α-actininn exposes their vinculin binding sites (VBSs) that then bind to and alter the structure of vinculin. More recently, we established how the phospholipid PIP_2 induces oligomerization of vinculin to promote adhesion turnover and cell migration. These key contributions significantly contributed to the rapid maturing of the field. We also solved the crystal structures of vinculin in complex with the ribonucleoportein raver1 that shuttles between the nucleus and cytoplasm and contains three RNA recognition motif (RRM) domains. Our studies showed that the raver1-vinculin interaction is distinct from known RRM-protein interactions and that only activated vinculin binds to raver1. Furthermore, we determined key residues responsible for the co-localization of raver1 and vinculin in cells and, notably, that *vinculin* mRNA binds to raver1, suggesting that the raver1/vinculin complex could promote translation of components of adhesion complexes at the site of focal adhesions.

   a. RA Borgon, C Vonrhein, G Bricogne, PRJ Bois & **T Izard*** (2004)
   Crystal structure of human vinculin

Structure 12:1189-1197

b. **T Izard***, G Evans, RA Borgon, CL Rush, G Bricogne & PRJ Bois (2004)
Vinculin activation by talin through helical bundle conversion
Nature 427:171-175
Commentaries: ***Nature*** 430:513-514 (2004); ***Advanced Photon Source Annual Report*** (2004)
Nature Struc Mol Biol 20:188-193

c. JH Lee, ES Rangarajan, SD Yogesha & **T Izard*** (2009)
Raver1 interactions with vinculin and RNA suggest a feed-forward pathway in directing mRNA to focal adhesions
Structure 17:833-842 PMCID = 2811071
Commentaries**:** ***Structure*** 17**:**781-783 (2009)

d. K Chinthalapudi, ES Rangarajan, DN Patil, EM George, DT Brown & **T Izard*** (2014)
Lipid binding promotes oligomerization and focal adhesion activity of vinculin
J Cell Biol 207:643-656, PMCID = 4259812
Highlighted "*In This Issue"* of ***J Cell Biol*** 207:572 (2014)

3. In collaboration with Drs. Marie-France Carlier (CNRS), Guy Tran Van Nhieu (Pasteur Institute), and Philippe Sansonetti (Pasteur Institute) we have also made very significant inroads into our understanding of how key cytoskeletal proteins such as vinculin and talin are co-opted for the nefarious purposes of pathogens such as *Shigella flexneri*, the principle pathogen of bacillary dysentery, and a major cause of morbidity and mortality in the human population. Our work on vinculin interactions with the *Shigella* IpaA was supported by an NIAID R01 award (2006-2010), which scored a 4%. We showed that the *C*-terminal domain of IpaA harbors two high-affinity VBSs, which bind to and activate vinculin in a novel fashion and which disrupt vinculin's contacts with talin and α-actinin and revealed that *Shigella* subverts vinculin's function by molecular mimicry of talin. We showed that this interaction is necessary for efficient entry of *Shigella* into the host cell.

a. **T Izard***, G Tran Van Nhieu & PR Bois (2006)
Shigella applies molecular mimicry to subvert vinculin and invade host cells
J Cell Biol 175:465-475, PMCID = 2064523

b. G Tran Van Nhieu & **T Izard*** (2007)
Vinculin binding in its closed conformation by a helix addition mechanism
EMBO J 26:44588-4596, PMCID = 2063484

c. H Park, C Valencia-Gallardo, A Sharff, G Tran Van Nhieu & **T Izard*** (2011)
Novel vinculin binding site of the IpaA invasin of *Shigella*
Paper of the week in ***J Biol Chem*** 286:23214-23221

d. H Park, JH Lee, E Gouin, P Cossart & **T Izard*** (2011)
The rickettsia surface cell antigen 4 applies mimicry to bind to and activate vinculin
J Biol Chem 286:35096-35103

4. We also defined the structure and regulation of specialized cytoskeletal proteins that regulate the formation and function essential for the coordinated functions of specialized cells in tissues such as cardiac muscle and how mutations in these proteins lead to defects in development and to myopathies, in particular to inherited dilated idiopathic cardiomyopathies (DCM), the most common form of cardiomyopathy and a disease that manifests high morbidity and mortality. Mutations have been described in cardiomyopathies and notably these include mutations in *metavinculin*, an alternatively spliced, muscle-specific isoform of vinculin. We solved the structures of human full-length wildtype metavinculin (a polypeptide chain of 1,134 residues with two molecules in the asymmetric unit) and the cardiomyopathy-associated metavinculin (MV) deletion mutant. Our structures revealed that the vinculin tail domain (Vt) α-helix H1 and its preceding extended coil are replaced in MV by similar residues from the MV specific insert. We showed that the α-helix H1 of Vt is responsible for vinculin to oligomerize in the presence of PIP_2 while MV does not. Our

studies unravel the unique properties of metavinculin in interacting with its partners, regulating the actin cytoskeleton, and in establishing tight cell junctions, and how these regulatory circuits are disrupted in myopathies. It is also hoped that these studies will suggest new avenues for therapeutic intervention for this deadly disease.

a. ES Rangarajan, JH Lee, SD Yogesha & **T Izard*** (2010)
A helix replacement mechanism directs metavinculin functions
PLoS ONE 5:e10679, PMCID = 2873289

b. JH Lee, ES Rangarajan, C Vonrhein, G Bricogne & **T Izard*** (2012)
The metavinculin tail domain directs constitutive interactions with raver1 and vinculin RNA
J Mol Biol 422:697-704

c. K Chinthalapudi, DN Patil, ES Rangarajan, C Rader & **T Izard*** (2015)
Lipid-directed vinculin dimerization
Biochemistry 54:2758-2768

d. K Chinthalapudi, ES Rangarajan, D Brown & **T Izard*** (2016)
Differential lipid binding of vinculin isoforms promotes quasi-equivalent dimerization
Proceeding of the National Academy of Sciences USA 113:9539-9544

5. The formation of cell-cell junctions is critical for the development and maintenance of multi-cellular organisms and a loss of cell-cell junctions is associated with several disease states. We determined the crystal structure of dimeric full-length human α-catenin, a structure long-thought to be 'not suitable for crystallization studies' which was a major advance for the field, and of vinculin-bound α-catenin, and these structures and our biochemical and biological studies defined the roles of the vinculin-α-catenin interaction in the formation and stabilization of adherens junctions. We established that α-catenin unfurls upon binding to vinculin and solved a long-standing conundrum by showing how α-catenin cannot bind to F-actin and β-catenin simultaneously. We also made major contributions to another cell-cell junctions protein, neurofibromin 2, which is responsible for NF2.

a. ES Rangarajan & **T Izard*** (2012)
The cytoskeletal protein α-catenin unfurls upon binding to vinculin
J Biol Chem 287:18492-18499, PMCID = 3365723

b. ES Rangarajan & **T Izard*** (2013)
Dimer asymmetry defines α-catenin interactions
Nature Struc Mol Biol 20:188-193, PMCID = 3805043

c. K Chinthalapudi, V Mandati, J Zheng, AJ Sharff, G Bricogne, PR Griffin, J Kissil & **T Izard*** (2018)
Lipid binding promotes the open conformation and tumor-suppressive activity of neurofibromin 2
Nature Communications 9:1338

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/40480084/?sort=date&direction=descending

D. Additional Information: Research Support and/or Scholastic Performance

ACTIVE

NIH, NIGMS, 5 R01 GM094483 IZARD (PI) 07/15/2010 - 04/30/2020
Mechanisms Directing Adherens Junctions and Actin Network Interactions
(1) Role of dimeric α-catenin binding directly to the membrane
(2) Analysis of the mechanisms by which α-catenin binds the actin cytoskeleton