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 cell adhesion structure-function studies with decades 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 of leadership of the macromolecular crystallography and cryo-electron microscopy and the management of the TSRI 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*, and *Proceedings of the National Academy of Sciences of the USA*.

Significant service to the scientific community that are beyond mentoring and committee duties: The PI never had any teaching responsibilities as part of an appointment and all her teaching is voluntary. 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). As a middle and high schooler, the PI tutored students in various subjects. In graduate school, she tutored a class for the Physics Department at Melbourne University (Australia). During her Lectureship appointment at Leicester University (England), the PI taught an undergraduate Chemistry tutorials 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, 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). 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. The PI participates in the TSRI FL 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. 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 or travels to Bak Middle School of the Arts for lectures related to their science curriculum. Notably, the PI recently set up cryo-electron microscopy at TSRI FL and provides training in negative stain data collection and 2D classifications (as well as

sample freezing) to pre-screen samples for their suitability for cryo-electron microscopy. In 2019, NIGMS recognized her leadership by awarding administrative supplementary funds for her purchase of a plunge freezer, glow discharger, and computer for cryo-electron microscopy structure determination. This proposal will allow the PI to further train students and post-doctoral fellows in cryo-electron microscopy, an incredible asset that she will bring to a very large scientific community that does not have cryo-electron microscopy expertise.

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, **S**t. **J**ude **C**hildren's **R**esearch **H**ospital (SJCRH), 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, SJCRH, Memphis, TN
2007 - 2017	Associate Professor with Tenure, **T**he **S**cripps **R**esearch **I**nstitute (TSRI)
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, eLife, 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 for the National Institutes of Health
2015	Reviewer, Special Emphasis Panel, Biological Chemistry & Macromolecular Biophysics (BCMB) Study Section for the National Institutes of Health
2017 - 2022	Editorial Board Member, The Journal of Biological Chemistry
2017	*Ad hoc* Reviewer, Intercellular Interactions (ICI) Study Section for the NIH
2017 - present	The Scripps Research Institute faculty search committee member
2019	The Scripps Research Institute faculty promotion *Ad hoc* committee member
2019	Reviewer, Special Emphasis Panel for the National Institutes of Health
2019	PPG Reviewer for the National Heart, Lung, and Blood Institute, National Institutes of Health
2019 - present	Board Member, South East Regional Collaborative Access Team, Argonne National Lab
2019 - present	Mentor of The Scripps Research Institute fellow Dr. Raktim Roy

C. Contributions to Science

C.1. Bacterial enzymes as novel drug targets

I started my academic career with a 3-year Lectureship appointment at Leicester University in England (1997-1999) 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. 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.

(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.

In collaboration with Drs. Marie-France Carlier (CNRS), Guy Tran Van Nhieu (Pasteur Institute), and Philippe Sansonetti (Pasteur Institute) we have also made significant inroads into our understanding of how key cytoskeletal proteins 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 the *Shigella* invasion 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 binding sites, which bind to and activate vinculin in a novel fashion and which disrupt the contacts of vinculin with talin and α-actinin and revealed that *Shigella* subverts the function of vinculin by molecular mimicry of talin. We showed that this interaction is necessary for efficient entry of *Shigella* into the host cell.

c.1.1. **T Izard*** & A Geerlof (1999)
"The crystal structure of a novel bacterial adenylyltransferase reveals half of sites reactivity" ***EMBO J*** 18:2021-2030

c.1.2. **T Izard*** & J Ellis (2000)
"The crystal structures of chloramphenicol phosphotransferase reveal a novel inactivation mechanism" ***EMBO J*** 19:2690-2700

c.1.3. **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

c.1.4. G Tran Van Nhieu & **T Izard*** (2007)
"Vinculin binding in its closed conformation by a helix addition mechanism" ***EMBO J*** 26:44588-4596

C.2. Cell-matrix interactions in normal and malignant cells

Upon being appointed as junior faculty member 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. Our persistence in structural studies of key linkers of cell-substrate and cell-cell junctions that control transmission of and responses to force paid off as they have had a major fundamental impact such as our studies on how lipid binding to vinculin regulates focal adhesion turnover. Our seminal paper in *Nature*, showed how a talin-derived vinculin binding site could activate talin. Our laboratory had previously shown that vinculin was auto-inhibited through an intramolecular interaction, thereby preventing vinculin from binding to the actin cytoskeleton. We discovered a new helix bundle conversion mechanism that we first observed in talin activation of vinculin. Although the field initially wondered whether the talin-derived vinculin binding sites used in our studies were physiologically relevant given that the folded full-length talin failed to activate vinculin, the field concurred with our findings as it was then discovered that talin must be partially unfolded, usually by traction forces, to bind and activate vinculin. Thus, our work provided the molecular basis of a central event in mechanotransduction. 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.

c.2.1. RA Borgon, C Vonrhein, G Bricogne, PRJ Bois & **T Izard*** (2004)
"Crystal structure of human vinculin" ***Structure*** 12:1189-1197

c.2.2. **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.2.3. 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; Highlighted "*In This Issue"* of ***J Cell Biol*** 207:572 (2014)

c.2.4. K Chinthalapudi, ES Rangarajan & **T Izard*** (2018)
"The interaction of Talin with the cell membrane is essential for integrin activation and focal adhesion formation"
Proceedings of the National Academy of Sciences USA 115:10339-10344

C.3. Specialized cell junctions of the heart and their role in cardiomyopathies

Our work has also had a major fundamental impact by providing clues as to the mechanisms of some forms of dilated cardiomyopathy. 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 **d**ilated idiopathic **c**ardio**m**yopathies (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 **m**eta**v**inculin (MV) deletion mutant. Our structures revealed that the **v**inculin **t**ail 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.

c.3.1. ES Rangarajan, JH Lee, SD Yogesha & **T Izard*** (2010)
"A helix replacement mechanism directs metavinculin functions" ***PLoS ONE*** 5:e10679

c.3.2. 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.3.3. K Chinthalapudi, DN Patil, ES Rangarajan, C Rader & **T Izard*** (2015)
"Lipid-directed vinculin dimerization" ***Biochemistry*** 54:2758-2768

c.3.4. K Chinthalapudi, ES Rangarajan, D Brown & **T Izard*** (2016)
"Differential lipid binding of vinculin isoforms promotes quasi-equivalent dimerization"
Proceedings of the National Academy of Sciences USA 113:9539-9544

C.4. Cell-cell interactions in normal and malignant cells

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. The epithelial, endothelial, and neuronal tissues of multicellular organisms are held together by specialized cell-cell junctions called adherens junctions. These are required for several biological processes including wound healing, embryonic morphogenesis, development, differentiation, as well as tissue integrity, homeostasis, and organization. The disassembly of these junctions causes loss of cell polarity and contact inhibition as well as epithelial-to-mesenchymal transitions. Thus, adherens junctions need to be regulated dynamically to allow cells to migrate and engage and disengage continuously in adhesive interactions with neighboring cells. Dysregulation of these highly coordinated interactions can lead to the development of cancer and vascular diseases. Changes in cell-cell adhesion reinitiate cell migration during cell turnover or wound healing or allow metastatic cells to scatter to distant organs. At adhesion complexes, the β-catenin-cadherin receptor complex binds to the cytoskeletal protein α-catenin, which is essential for both the formation and stabilization of cell-cell junctions. Loss of α-catenin or E-cadherin promotes unrestricted growth of cells and facilitates transformation, tumorigenesis, and metastasis. Thus, understanding the molecular mechanisms that control proper assembly and stabilization of these junctions is a fundamental process in cell biology that also goes awry in important pathological scenarios, especially cancer.

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 neurofibromatosis type II.

c.4.1. ES Rangarajan & **T Izard*** (2012)
"The cytoskeletal protein α-catenin unfurls upon binding to vinculin" ***J Biol Chem*** 287:18492-18499

c.4.2. ES Rangarajan & **T Izard*** (2013)
"Dimer asymmetry defines α-catenin interactions" ***Nature Struc Mol Biol*** 20:188-193;
Commentaries: ***Nature Reviews Mol Cell Biol*** 14:66 (2013)

c.4.3. 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

c.4.4. M Janiszewska, MC Primi & **T Izard** (2020)
"Cell adhesion in cancer: Beyond the migration of single cells" ***J Biol Chem*** [Epub ahead of print]

C.5. Collaborations on structure-functions studies relevant to diseases

In 2019, the PI built the cryo-electron microscopy facility for TSRI in Florida and provided hands-on leadership in the purchase of the first JEOL CryoARM300 in the United States. The PI also set up the neighboring Max Planck Florida Institute for Neuroscience for automatic data collection of negative stained protein samples and ensures the training in cryo-electron microscopy, in negative stain data collection, and 2D classifications (including sample freezing) to pre-screen samples for their suitability for cryo-electron microscopy. NIGMS recognized her leadership by awarding administrative supplementary funds for her purchase of a plunge freezer, glow discharger, and computer for cryo-electron microscopy structure determination. This facility that the PI set up at TSRI in Florida will be particularly important in her already established in-house collaborations studying the structure-function of membrane and membrane binding proteins.

c.5.1. DN Patil DN, ES Rangarajan, SJ Novick, BD Pascal, DJ Kojetin, PR Griffin, **T Izard***, KA Martemyanov* (2018)
"Structural organization of a major neuronal G protein regulator, the RGS7-Gβ5-R7BP complex" ***eLife*** 7

c.5.2. W Cao, H Kayama, ML Chen, A Delmas, A Sun, SY Kim, ES Rangarajan, K McKevitt, AP Beck, CB Jackson, G Crynen, A Oikonomopoulos, PN Lacey, GJ Martinez, **T Izard**, RG Lorenz, A Rodriguez-Palacios, F Cominelli, MT Abreu, DW Hommes, SB Koralov, K Takeda, MS Sundrud (2017)
"The Xenobiotic Transporter Mdr1 Enforces T Cell Homeostasis in the Presence of Intestinal Bile Acids" ***Immunity*** 47:1182-1196.e10

c.5.3. JD Stender, JC Nwachukwu, I Kastrati, Y Kim, T Strid, M Yakir, S Srinivasan, J Nowak, **T Izard**, ES Rangarajan, KE Carlson, JA Katzenellenbogen, XQ Yao, BJ Grant, HS Leong, CY Lin, J Frasor, KW Nettles & CK Glass (2017)
"Structural and molecular mechanisms of cytokine-mediated endocrine resistance in human breast cancer cells" ***Molecular CELL*** 65:1122-1135

c.5.4. JC Nwachukwu, S Srinivasan, NE Bruno, J Nowak, NJ Wright, F Minutolo, ES Rangarajan ES, **T Izard**, XQ Yao, BJ Grant, DJ Kojetin, O Elemento, JA Katzenellenbogen & KW Nettles (2017)
"Systems structural biology analysis of ligand effects on ERα predicts cellular response to environmental estrogen and anti-hormone therapies" ***CELL Chem Biol*** 24:35-45

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

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

NIH, NIGMS, 5 R01 GM094483 IZARD (PI) 07/15/2010 - 04/30/2021
Mechanisms Directing Adherens Junctions and Actin Network Interactions