Name	SHARON TOOZE
Position	Senior Group leader
Year joined *(Crick or founder institute)*	1994

Career History

1981- 1982: Graduate PhD student, Yale University New Haven, Connecticut USA
1982- 1986: Graduate PhD Student, European Molecular Biology Laboratory, Heidelberg, Germany
1987- 1990: Post-doctoral Fellow, European Molecular Biology Laboratory, Heidelberg, Germany
1990- 1993: Staff Scientist, European Molecular Biology Laboratory, Heidelberg, Germany
1994- 2002: Junior Group leader, Imperial Cancer Research Fund, London, England
2002- 2015: Senior Scientist Cancer Research UK, London Research Institute

Major Awards, Honours and Prizes

Elected:
EMBO member in 2010
AcademiaNet fellow in 2014
Fellow of the Academy of Medicine in 2018
Fellow of the European Academy of Sciences 2020
Awards:
Georgina Sweet Travel Award for Women in Quantitative Biological Science in 2019

Membership of external committees, editorial boards, review panels, SABs etc

Review panels, external committees etc
2015 Research Council of Norway (RCN), review panel member
2016 Tenure panel member, University of Dundee
2016 Research Council of Norway (RCN), Panel Chair
2018 ERC Synergy 2018, LS panel member
2018 Institut Pasteur Review Panel member Cell Biology Department
2019 Review Panel member DFG CRC1177
2019 Scientific advisory board SMICH – Vienna
2019 ERC Synergy 2020 LS Panel Chair
Editorial boards
Traffic, Editor, January 2015-present
Faculty of 1000, Cell Biology Faculty, Biology Reports Ltd., March 2001-Dec 2016
Autophagy, Associate Editor, September 2009-2016
EMBO Journal, Editorial Board, January 2011-present
Molecular Cell Biology, Editorial Board, August 2013-present
Journal of Cell Science, Editorial advisory board, November 2015-present
Cell Logistics Editorial Board Jan 2017-present
Current Biology, Advisory Board, Jan 2019-present
PLOS Biology, Editorial Board, Jan 2019-present

Lab Name	*Molecular Cell Biology of Autophagy Laboratory*

Research programme and achievements

Autophagy is a highly conserved intracellular degradation process which acts both as an intracellular recycling pathway and a surveillance mechanism to ensure cell homeostasis and survival. As a highly regulated process, autophagy enables the cell to respond to prevent or negate external and internal damage, proteostasis or metabolic dysfunction, and even pathogen invasion by sequestering the damaging agent within autophagosomes. Formation of the double membrane autophagosome membrane is controlled by both protein and lipid kinase signalling, and these concerted activities are key to the formation of the autophagosome and the selection of cargo incorporated into the autophagosome for delivery to the lysosome and degradation.

My main research interest is to understand at a molecular level how autophagosomes are formed in mammalian cells. My lab has identified and continues to delineate the function of dedicated core autophagy proteins (ATG proteins) and novel regulators, the latter largely those involved in vesicular trafficking. My research programme addresses the role of the ATG proteins required for autophagosome initiation including ATG9A, a multi-spanning membrane protein, ULK1, a serine-threonine protein kinase found in the ULK complex, and WIPI2, the phosphoinositide effector required for lipidation of the ATG8 cargo receptor family. The study of these three proteins is my mainstream activity, as the function and regulation of all three during autophagy remains incompletely understood.

Building upon this core activity my lab has investigated trafficking proteins identified by the lab including TBC1D14, TRAPPIII, and less well understood proteins, WAC, SCOC and FEZ1. We also investigated the selectivity of the LIR (LC3 interacting region) motif in the interaction with autophagy regulators or cargo, in particular PCM1, a centriolar satellite protein. Cargo (ubiquitinated, misfolded or damaged proteins) binds directly to, or through autophagy cargo receptors to, lipidated ATG8 family members (LC3A, B and C, GABARAP, GABARAPL1, and GABARAPL2) via LIR motifs. This allows the recruitment of regulators or delivery of cargo to the autophagosome for degradation in the lysosome.

Using my expertise in molecular cell biology and organelle biogenesis, my work has and will continue to address the fundamental question of how autophagy is initiated. A complete understanding of this complex membrane-mediated process will provide a knowledge base and tools to address the role of autophagy in human disease, infection and ageing. My research is discovery science which by elucidating function and mechanism of proteins and lipids required for autophagy, in both a temporal and spatial context in mammalian cells, underpins the translational work needed to address the treatment of human disease and infection, and mitigate the impact of ageing.

Through a rigorous investigation of the core machinery, the effectors, and trafficking regulators, I aim to obtain a fuller understanding of the autophagosome formation process. My goal is to reach a near atomic level of understanding of the function of the proteins, and protein complexes involved in the formation process by combining cell and biochemical analyses, high resolution microscopy techniques, temporally and spatially defined analysis and in vitro reconstitution. This will be done using two approaches, a targeted analysis based on understanding i) substrates of the ULK complex, ii), the specific function and regulation of the function of WIPI2 and iii) ATG9A, and secondly a

reconstitution approach focusing on i) membrane templates, ii) lipids and iii) cargo recruitment.

Research outputs

Judith, D., Jefferies, H. B. J., Boeing, S., Frith, D., Snijders, A. P., & Tooze, S. A. (2019). *ATG9A shapes the forming autophagosome through Arfaptin 2 and phosphatidylinositol 4-kinase IIIβ*. Journal of Cell Biology, *218*(5), 1634-1652. DOI:10.1083/jcb.201901115
This paper represents an important step forward in our understanding of ATG9, the only multi-spanning autophagy protein and a major focus of my lab's current work. Here we discovered the composition of the ATG9 vesicle and uncovered an important role for a protein which can induce membrane curvature and a lipid kinase. I chose this work as it has provided us with important insights into the function of ATG9A.

Wirth, M., Zhang, W., Razi, M., Nyoni, L., Joshi, D., O'Reilly, N., Johansen, T., Tooze, S.A., Mouilleron, S. (2019). *Molecular determinants regulating selective binding of autophagy adapters and receptors to ATG8 proteins*. Nature Communications, 10(1). DOI:10.1038/s41467-019-10059-6
This paper follows on from our work on WAC and the role of centrosomes in autophagy. We discovered an important centriolar protein has a specific motif (LIR motif) enabling its binding to a key autophagy protein. In collaborative work, we determined the structure and the important features of the LIR motif, and extended the findings to a group of autophagy proteins to provide an important advance on our understanding of selective autophagy. I chose this work because it is a tour de force of structure and biochemistry and a very substantial collaboration between Structural Biology and Peptide Chemistry STPs.

New, M., Van Acker, T., Sakamaki, J. -I., Jiang, M., Saunders, R. E., Long, J., Wang, V.M.Y., Behrens, A., Cerveira, J., Korcsmaros, T., Jefferies, H.B.J., Ryan, K.M., Howell, M., Tooze, S. A. (2019). *MDH1 and MPP7 regulate autophagy in pancreatic ductal adenocarcinoma*. Cancer Research, 79(8), 1884-1898. DOI:10.1158/0008-5472.Can-18-2553
This work represents findings from a collaborative effort between my lab, Astellas Pharmaceuticals and the Ryan lab at the Beatson Institute. Using a differential siGenome screening pipeline we identified candidates which are important for autophagy-dependent survival of pancreatic ductal adenocarcinoma cells. I chose this paper because the work was funded by and done in a joint collaborations with a pharmaceutical company, and together we identified novel targets which may have a therapeutic benefit in future work.

Lamb, C. A., Nühlen, S., Judith, D., Frith, D., Snijders, A. P., Behrends, C., & Tooze, S. A. (2016). *TBC1D14 regulates autophagy via the TRAPP complex and ATG9 traffic*. EMBO Journal, 35(3), 281-301. DOI:10.15252/embj.201592695
This work uncovered a role for the RabGAP TBC1D14 in vesicle traffic between the endosome and the Golgi complex. Importantly, it highlighted the crucial role of the recycling endosome in formation of the autophagosome. I chose this paper because it identified for the first time the mammalian TRAPPIII complex and showed that, in contrast to yeast, TRAPPIII functions to control ATG9A positioning in the cell, a crucial aspect to allow an immediate response to starvation signals.

Joachim, J., Jefferies, H. B. J., Razi, M., Frith, D., Snijders, A. P., Chakravarty, P., Judith, D., Tooze, S. A. (2015). *Activation of ULK kinase and autophagy by*

***GABARAP trafficking from the centrosome is regulated by WAC and GM130*.**
Molecular Cell, 60(6), 899-913. DOI:10.1016/j.molcel.2015.11.018
This paper uncovered the function of WAC, which we identified in a siGenome screen, as a positive regulator of autophagy. Furthermore, it provided data to understand how in a non-hierarchical mechanism the ULK1 kinase activation can be maintained during the expansion of the phagophore. Finally, it revealed a role for the centrosome and centriolar satellites in controlling autophagosome formation. I chose this paper because the starting point was the identification of an uncharacterised protein in a siGenome screen which through our study revealed its function and an unexpected link between the Golgi complex, centrosomes, and formation of autophagosomes.