BIOGRAPHICAL SKETCH

NAME	POSITION TITLE
Charles J. Weitz eRA COMMONS USER NAME: CHARLES_WEITZ	Robert Henry Pfeiffer Professor of Neurobiology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Harvard College, Cambridge, MA	A.B.	1978	Philosophy
Stanford University School of Medicine, Stanford, CA	M.D.	1983	Medicine
Stanford University Medical Center, Stanford, CA	Internship	1983-4	Surgery/Neurosurgery
Stanford University School of Medicine, Stanford, CA	Ph.D.	1988	Neuroscience
Johns Hopkins School of Medicine, Baltimore, MD	Postdoctoral	1988-93	Molecular Biol. & Genetics

A. Personal Statement

Since its inception in 1993, my laboratory has studied the molecular biology and genetics of circadian clocks. Our work has primarily focused on dissecting the mechanism of the mammalian clock by means of identification and characterization of its molecular components and determining the physiological functions of clocks in vivo by means of conditional mouse genetics. In recent years we have been developing biochemical and structural biology strategies to study the circadian clock in mechanistic detail.

I have been deeply involved in training the next generation of biomedical scientists. For 17 years I directed Neurobiology 221, "Molecular Neurobiology," a core course in the Ph.D. Program in Neuroscience, Harvard University. To date, seven graduate students in two Ph.D. programs have been awarded doctorates for work performed under my direction. For the past twenty years, I have given lectures in Molecular and Cellular Biology 186, "Circadian Biology: from cellular oscillators to sleep regulation" at Harvard College.

B. Positions and Honors. List in chronological order previous positions, concluding with your present position.

Positions

1993-98 Assistant Professor, Department of Neurobiology, Harvard Medical School, Boston, MA
1998-03 Associate Professor, Department of Neurobiology, Harvard Medical School, Boston, MA
2003- Robert Henry Pfeiffer Professor of Neurobiology, Harvard Medical School, Boston, MA

Honors & Awards

1972 Governor's Scholar, State of California
1977 Goethe Institute Scholar, Prien, Federal Republic of Germany
1983 J. W. Hanbery Clinical Neuroscience Scholar, Stanford University School of Medicine
1985 Research Foundation Fellow, American Association of Neurological Surgeons
1988-93 Physician Scientist Award, National Eye Institute
1994-6 Young Investigator Award, National Alliance for Research on Schizophrenia and Depression
1994-8 Scholar Award, McKnight Endowment Fund for Neuroscience
1997-00 Fellowship Award in the Neurosciences, Esther A. and Joseph Klingenstein Fund
1998-00 Research Award, Giovanni Armenise-Harvard Foundation for Advanced Scientific Research
1999-01 Investigator Award, National Alliance for Research on Schizophrenia and Depression
2002-03 Jesse Siegelman, M.D. Award for Innovation in Neurobiology
2003 Gulf Oil Outstanding Achievement in Biomedical Science Award
2007-10 Neuroscience of Brain Disorders Award, McKnight Endowment Fund for Neuroscience
2008-17 G. Harold & Leila Y. Mathers Charitable Foundation Award
2018-20 Dean's Innovation Award, Harvard Medical School

C. Contribution to Science

Circadian clocks are endogenous oscillators that drive daily (24-hour) rhythms in behavior, physiology, and metabolism. Such clocks are widespread across phylogeny, found in cyanobacteria, fungi, plants, and animals. In 1993, when I established my laboratory and decided to work on the molecular basis of circadian rhythms in mammals, the mechanism of the circadian clock was unknown in any organism. Two clock genes had been identified not long before in landmark genetic screens, *Period* (*Per*) from flies and *Frequency* (*Frq*) from fungi, but nothing was known about the biochemical activities of their protein products. A few published results, at odds with much opinion in the circadian field at the time, suggested that the clock mechanism in animals was likely to be cell-autonomous and perhaps transcriptional in nature.

Using molecular biological and genetic tools, my laboratory, along with a number of others, identified and characterized core components of the mammalian circadian clock, providing central support for the notion that circadian rhythms are built on a negative transcriptional feedback loop:

Gekakis N, Staknis D, Nguyen HB, Davis FC, Wilsbacher LD, King DP, Takahashi JS, Weitz CJ. Role of the CLOCK protein in the mammalian circadian mechanism. *Science* 1998; 280:1564-69, PMID: 9616112.

Griffin EA, Staknis D, Weitz CJ. Light-independent role for CRY1 and CRY2 in the mammalian circadian clock. *Science* 1999; 286: 768-71, PMID: 10531061

Zhao W-N, Malinin N, Yang F-C, Staknis, D Gekakis N, Maier B, Reischl S, Kramer A, Weitz. CJ. CIPC is a mammalian circadian clock protein without invertebrate homologs. *Nature Cell Biology* 2007; 3: 268-275.

Robles MS, Boyault C, Knutti D, Padmanabhan K, Weitz CJ. Identification of RACK1 and Protein Kinase Cα as integral components of the mammalian circadian clock. *Science* 2010; 327: 463-6, PMID: 20093473. (PMC N/A)

In parallel work, we contributed to the identification and characterization of molecular components of the *Drosophila* circadian clock. This clock and the mammalian clock are clearly conserved, but the Drosophila clock has some differences in molecular organization. We also developed a novel cDNA subtraction method to identify transcripts induced in the hypothalamus in vivo by light as a strategy for molecular analysis of circadian clock is phase-shifting by light:

Gekakis N, Saez L, Delahaye-Brown A-M, Myers MP, Sehgal A, Young MW, Weitz CJ. Isolation of *timeless* by PER protein interaction: Defective interaction of *timeless* protein with long-period mutant PER^{L}. *Science* 1995; 270: 811-15, PMID: 7481773.

Darlington TK, Wager-Smith K, Ceriani MF, Staknis D, Gekakis N, Steeves TDL, Weitz CJ, Takahashi JS, Kay SA. Closing the circadian loop: CLOCK induced transcription of its own inhibitors, *period* and *timeless. Science* 1998; 280: 1599-1603. PMID: 9616122.

Ceriani F, Darlington TK, Staknis D, Mas P, Petti AA, Weitz CJ, Kay SA. Light-dependent sequestration of TIMELESS by CRYPTOCHROME. *Science* 1999; 285: 553-56. PMID: 10417378.

Morris ME, Viswanathan N, Kuhlman S, Davis FC, Weitz CJ. A screen for genes induced in the suprachiasmatic nucleus by light. *Science* 1998; 279: 1544-1547. PMID: 9488654

Ingenious neural transplant studies by others in the 1990's suggested that the circadian clock in the suprachiasmatic nucleus (SCN) of the brain drives daily cycles of rest and activity by rhythmically releasing diffusible factors onto an adjacent target area that controls locomotor activity. To identify such putative factors, my laboratory developed a molecular biological screen for peptides or proteins secreted from the SCN and a real-time behavioral assay to monitor the potential effects of any identified factors on locomotor activity. This

work led to the discovery of SCN secreted factors that rhythmically regulate locomotor behavior (an additional factor was identified in a different way by another group):

Kramer A, Yang F-C, Snodgrass P, Li X, Scammell TE, Davis FC, Weitz CJ. Regulation of daily locomotor activity and sleep by hypothalamic EGF receptor signaling. *Science* 2001; 294: 2511-15, PMID: 11752569.

Kraves S & Weitz CJ. A role for cardiotrophin-like cytokine in the circadian control of mammalian locomotor activity. *Nature Neuroscience* 2006; 9: 212-19, PMID: 16429135.

In the years 1998-2001, work from other laboratories indicated that circadian clocks in mammals are present in most tissues, not just the suprachiasmatic nucleus (SCN) of the brain and the retina, as had been generally believed. These observations, surprising at the time, raised important new questions regarding the circadian control of physiology. Are circadian clocks other than that of the SCN important for mammalian physiology? Do peripheral clocks regulate tissue-specific physiological processes, and if so, how? To address these questions, we established two lines of investigation. We adopted newly-available microarray technology and developed algorithms to monitor circadian rhythms of gene expression on a large scale, and we constructed conditional alleles in mice that would allow for the first time tissue-specific genetic ablation of circadian clock function. In microarray studies, we found, as did several other laboratories at about the same time, that roughly 500-1000 genes are regulated in a circadian fashion in a given tissue; different tissues have very different sets of clock-regulated genes, pointing to a broad transcriptional basis for local circadian regulation of tissue physiology. In conditional genetic studies, we demonstrated that circadian clock function within particular tissues is essential for the rhythmic physiological functions of the tissue in question, indicating that rhythmic physiology in mammals is essentially a composite of the independent actions of many autonomous, local circadian oscillators set to a common time. (The mouse conditional genetic tools we constructed have been used widely in the field to investigate tissue-specific circadian clock function):

Storch K-F, Lipan O, Leykin I, Viswanathan N, Davis FC, Wong WH, Weitz CJ. Extensive and divergent circadian gene expression in liver and heart. *Nature* 2002; 417: 78-83, PMID: 11967526.

Storch K-F, Paz C, Signorovitch J, Raviola E, Pawlyk B, Li T, Weitz CJ. Intrinsic circadian clock of the mammalian retina: importance for retinal processing of visual information. *Cell* 2007; 130:730-41, PMCID: PMC2040024.

Lamia K, Storch K-F, Weitz CJ. Physiological significance of a peripheral tissue circadian clock. *Proc Natl Acad Sci USA* 2008; 105: 15172-7. PMCID: PMC2532700.

Work from my laboratory and others in the late 1990's and early 2000's established the general outline of the mechanism underlying the mammalian circadian clock. The clock is built on a cell-autonomous transcriptional feedback loop in which PERIOD (PER) and CRYPTOCHROME (CRY) proteins accumulate, enter the cell nucleus, and inhibit the activity of CLOCK-BMAL1, the transcription factor that activates *Per* and *Cry* gene expression. The molecular basis of this negative feedback, arguably the defining feature of the circadian clock as an oscillator, had to general frustration remained mysterious. Early (and naïve) experiments from my laboratory and others, based on a few known examples of transcriptional inhibition in other contexts, failed to reveal the biochemical actions of PERs and CRYs. After finding in 2005 that PER and CRY proteins are present together in a nuclear complex of >1 megaDaltons in mass (PER complex; also observed independently by another group), sufficient for perhaps 15 or more constituent proteins, my laboratory embarked on a long-term project to purify the PER complex from mouse tissues and comprehensively identify its protein constituents. I did not understand why such a large complex would be necessary to inhibit a single transcription factor, but I reasoned that knowledge of the composition of the protein complex would likely reveal the mechanism of circadian clock negative feedback and confront us with the true richness and complexity of the molecular timekeeping machinery. To achieve this goal, we invested 5 years in constructing and validating mouse lines in which one or another PER protein was replaced by a functionally-equivalent epitope-tagged version, allowing use of high-affinity monoclonal antibodies to purify the PER complexes from mouse tissues.

From this ongoing work we have developed a clearer picture of the clock mechanism and the actions of the PER complex, which we now know is ~2 megaDaltons in mass and comprised of ~30 constituent proteins, a macromolecular machine of ribosome-like size and complexity. Two fundamental properties are essential to its role in circadian negative feedback. First, upon assembly in the nucleus, the PER complex incorporates several pre-existing, widely-acting transcriptional repressor complexes that serve as effectors. This cargo includes chromatin-modifying machinery that inhibits transcriptional initiation and factors that inhibit transcriptional termination and possibly transcriptional elongation, indirectly suppressing initiation. Second, the PER complex directly interacts with DNA-bound CLOCK-BMAL1, thereby delivering the repressor cargo to chromatin at the regulatory regions of *Per* genes and other circadian target genes. In addition, the project has revealed unanticipated mechanisms for specificity built into the circadian feedback loop, especially interesting in the light of its generic effectors. Our present efforts are aimed at obtaining high-resolution cryo-EM structures of the nuclear PER complex and its cytoplasmic precursor complexes (see Aryal et al. below for our initial low-resolution structural views), as well as the CLOCK-BMAL1 transcriptional activator complex:

Duong HA, Robles MS, Knutti K, Weitz CJ. A molecular mechanism for circadian clock negative feedback. *Science* 2011; 332: 1436-9, PMCID: 3859310.

Padmanabhan K, Robles MS, Westerling T, Weitz CJ. Feedback regulation of transcriptional termination by the mammalian circadian clock PERIOD complex. *Science* 2012; 337: 599-602. PMID: 22767893. (PMC N/A).

Kim JY, Kwak PB, Weitz CJ. Specificity in circadian clock feedback from targeted reconstitution of the NuRD co-repressor. *Molecular Cell* 2014; 56: 738-748. PMID 25453762. (PMC N/A).

Aryal RA, Kwak PB, Tamayo AG, Gebert M, Chiu PL, Walz T, Weitz CJ. Macromolecular assemblies of the mammalian circadian clock. *Molecular Cell* 2017; 67: 770-782. PMCID: PMC5679067.

In closely related work, we identified unexpected chromatin-modifying properties of circadian clock complexes:

Duong HA, Weitz CJ. Temporal orchestration of repressive chromatin modifiers by circadian clock Period complexes. *Nature Struct Mol Biol* 2014; 21: 126-32. PMCID: PMC4227600.

Tamayo AG, Duong HA, Robles MS, Mann M, Weitz CJ. Histone mono-ubiquitination by a Clock–Bmal1 complex marks *Per1* and *Per2* genes for circadian feedback. *Nature Struct Mol Biol* 2015; 22: 759-766. PMCID: PMC4600324.

Published work (as principal investigator): http://www.ncbi.nlm.nih.gov/pubmed/?term=Weitz+CJ+circadian

D. Research Support. List selected ongoing or completed (during the last three years) research projects (federal and non-federal support). Begin with the projects that are most relevant to the research proposed in this application. Briefly indicate the overall goals of the projects and responsibilities of principal investigator identified above.

ONGOING:

Project: R01 NS095977 (P.I.: Charles J. Weitz) Sept.1, 2016 – Aug. 31, 2021
Agency: National Institute of Neurological Disorders and Stroke
Title: Mammalian circadian clock: genetics of PERIOD complex composition and structure

Biochemical and analysis of circadian clock nuclear transcriptional regulatory complex. The project initiates studies into the structure and function 2-megaDalton nuclear PER complex as an integrated macromolecular machine.

Project: A34689 (P.I.- Charles J. Weitz) Feb. 16, 2018 – Mar. 1, 2020
Agency: F-Prime Biomedical Research Institute
Title: Circadian clock protein complexes in the brain: a source of novel therapeutic targets for neurodegeneration?

Biochemical analysis to identify components or modifications of circadian clock protein complexes that are specific to the brain.

COMPLETED:

Project: Mathers Foundation Award (P.I.: Charles J. Weitz) Jan. 1, 2015 - Dec. 31, 2017
Foundation: G. Harold & Leila Y. Mathers Charitable Foundation
Title: PERIOD protein complexes of the mammalian circadian clock

Identification and characterization of unknown proteins physically associated in the cell nucleus with PERIOD-1 and/or PERIOD-2, core components of the mammalian circadian clock mechanism.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Alan Brown

eRA COMMONS USER NAME (credential, e.g., agency login): ALANBROWN1

POSITION TITLE: Assistant 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 Warwick, UK	B.Sc.	06/2005	Biochemistry
University of Cambridge, UK	Ph.D.	01/2010	Biochemistry
University of Cambridge, UK	Postdoc	06/09-10/12	Structural biology
Medical Research Council - Laboratory of Molecular Biology (MRC-LMB), UK	Postdoc	11/12-08/15	Structural biology

A. Personal Statement

My laboratory visualizes biologically important macromolecular complexes at the atomic level. We are interested in understanding cilium-specific signal-transduction pathways. In particular how molecular trafficking achieves the spatial organization necessary for visual phototransduction in photoreceptor neurons. To do this, we combine biochemical, biophysical, and structural approaches with an emphasis on high-resolution electron cryomicroscopy (cryo-EM). Many of the approaches that we use are influenced from my postdoctoral research with Nobel-laureate Venki Ramakrishnan on the structure and function of ribosomes. In late 2013, I solved the structure of the large subunit of the yeast mitochondrial ribosome. This was the first asymmetric particle to be solved to near-atomic resolution by cryo-EM and remains one of the most complex structures ever solved. This structure heralded the beginning of the so-called “resolution revolution” in cryo-EM and was described as “one of the most exciting results in structural biology in recent years” and one that “completely changes structural biology”. I have been at the forefront of this revolution, developing techniques to interpret cryo-EM data that have been widely adopted by the field. The ability to purify endogenous complexes from native sources, reprogram them with factors, and visualize them using cryo-EM has led to high-impact publications in Science (5), Nature (2), Cell (2) and eLife (1) among others. The eLife publication was the first reported use of cryo-EM to determine the binding site and mechanism of action of a small inhibitory molecule: proof of principle for an emerging role of cryo-EM in drug discovery.

B. Positions and Honors

Positions and Employment

2002 - 2003 Laboratory Technician, Unilever, Lowestoft, UK
2004 - 2004 Wellcome Trust Vacation Scholar, University of East Anglia, Norwich, UK
2005 - 2009 BBSRC Doctoral Training Fellow, University of Cambridge, Cambridge, UK
2009 - 2012 Postdoctoral Associate, University of Cambridge, Cambridge, UK
2012 - 2015 Career Development Fellow, Medical Research Council, Cambridge, UK
2015 - 2017 Senior Investigator Scientist, Medical Research Council, Cambridge, UK

09/2017 - Assistant Professor, Department of Biological Chemistry & Molecular Pharmacology, Harvard Medical School, Boston, MA

Other Experience and Professional Memberships

2009 Guest Editor, International Journal of Molecular Sciences (IJMS)

Honors

2002 Norfolk County Scholar
2002 Institute of Petroleum Exporters Scholar
2002 - 2005 University of Warwick Graduates' Association Scholarship
2004 Biochemistry Class Award, University of Warwick
2006 John Rose Prize, King's College, University of Cambridge

C. Contributions to Science

1. Structures of mitochondrial ribosomes. Mitochondria have specialized ribosomes (mitoribosomes) that synthesize the few proteins encoded by mitochondrial DNA, typically the essential transmembrane subunits of the respiratory chain complexes. To understand how mitoribosomes have adapted to the translational needs of mitochondria, we solved the structures of mitoribosomes from yeast and human cells using cryo-EM. The first of these structures, the large subunit of the yeast mitoribosome, was a milestone in structural biology. Together, our structures have improved our understanding of mitochondrial translation and revealed the incredible diversity of mitoribosomes. For example, the human mitoribosome has half of the length of ribosomal RNA and 36 additional proteins compared to the bacterial ribosome with which it shares a common ancestor.

   a. Amunts A*, Brown A*, Bai XC*, Llácer JL*, Hussain T, Emsley P, Long F, Murshudov G, Scheres SH, Ramakrishnan V. (2014). Structure of the yeast mitochondrial large ribosomal subunit. **Science**, 343(6178):1485-9. PMCID: PMC4046073.
   b. Brown A*, Amunts A*, Bai XC, Sugimoto Y, Edwards PC, Murshudov G, Scheres SH, Ramakrishnan V. (2014). Structure of the large ribosomal subunit from human mitochondria. **Science**, 346(6210):718-22. PMCID: PMC4246062.
   c. Amunts A*, Brown A*, Toots J, Scheres SH, Ramakrishnan V. (2015). Ribosome. The structure of the human mitochondrial ribosome. **Science**, 348(6230):95-8. PMCID: PMC4501431.
   d. Desai N, Brown A, Amunts A, Ramakrishnan V. (2017). The structure of the yeast mitochondrial ribosome. **Science**, 355(6324):528-531. PMCID: PMC5295643.

2. How protein synthesis terminates with and without a stop codon. Translation terminates when a ribosome reaches one of three nucleotide sequences (UAA, UAG, or UGA) on the mRNA. These stop codons are universal to all kingdoms of life and are recognized by protein release factors that evolved independently in prokaryotes and eukaryotes. Using cryo-EM we solved the first high-resolution structures of the eukaryotic release factor (eRF1) engaged with each of the three stop codons (Nature, 524:493-496). These structures revealed how eRF1 is able to accurately decode stop codons and discriminate against all other nucleotide combinations including the highly similar UGG, which codes for the amino acid tryptophan. How a single release factor could do this had been a long-standing unanswered question in molecular biology. We were able to contrast this with the situation in bacteria, in which two separate protein release factors (RF1 and RF2) are required. We subsequently solved the complete termination pathway in mammals that includes delivery of eRF1 to the ribosome by the GTPase eRF3 and post-termination recycling of the ribosome by the ATPase ABCE1 (Cell, 167:1229-1240). These structures provide a framework for the development of novel therapeutics that may be useful to treat the ~11% of hereditary diseases caused by premature termination.

Occasionally, defective mRNAs lack a stop codon that causes ribosomes to stall. As the accumulation of stalled ribosomes is toxic to cells, both bacteria and eukaryotes have evolved rescue mechanisms. We have solved structures of eukaryotic (Cell, 167:1229-1240) and bacterial (Science, 354:1437-1440) rescue complexes.

a. Brown A*, Shao S*, Murray J, Hegde RS, Ramakrishnan V. (2015). Structural basis for stop codon recognition in eukaryotes. **Nature**, 524(7566):493-6. PMCID: PMC4591471.
b. Shao S*, Murray J*, Brown A*, Taunton J, Ramakrishnan V, Hegde RS. (2016). Decoding mammalian ribosome-mRNA states by translational GTPase complexes. **Cell**, 167(5):1229-1240. PMCID: PMC5119991.
c. James NR, Brown A, Gordiyenko Y, Ramakrishnan V. (2016). Translational termination without a stop codon. **Science**, 354(6318):1437-1440. PMCID: PMC5351859.

3. The role of the ribosome in the activation of stringent control. Stringent control represents the central adaptive response to nutrient starvation in bacteria. It is implicated in the induction of bacterial virulence, persistent bacterial infections and antibiotic tolerance. Bacteria sense nutrient starvation through the depletion of aminoacylated tRNAs, which result in accumulation of ribosomes stalled with uncharged tRNA. A protein, RelA, is recruited to these stalled ribosomes and activated to synthesize a second messenger, (p)ppGpp, that causes a comprehensive reprogramming of transcriptional and metabolic patterns. Although stringent control was first identified in 1952, and linked to RelA a decade later, very little was known about how RelA worked. Using cryo-EM, we solved the structure of RelA bound to the *E. coli* ribosome. The structure revealed how RelA binds to stalled ribosomes, how it discriminates against aminoacylated tRNAs, and that activation of ppGpp catalysis is indirect, resulting from the ribosome-induced suppression of RelA auto-inhibition. Given the importance of stringent control in clinically relevant aspects of bacterial physiology and that inactivation of stringent control can re-sensitize tolerant bacteria to antibiotics, this structure has potential to help the development of novel antibiotics.

a. Brown A*, Fernández IS*, Gordiyenko Y, Ramakrishnan V. (2016) Ribosome-dependent activation of stringent control. **Nature**, 534(7606):277-80. PMCID: PMC4900451.

Complete List of Published Work:

1. Brown A. (2009). Analysis of cooperativity by Isothermal Titration Calorimetry. **IJMS**, 10(8):3457-77. PMCID: PMC2812830.
2. Lee S*, Brown A*, Pitt WR*, Higueruelo A, Bickerton GR, Gong S, Schreyer A, Tanramluk D, Blundell TL. (2009). Structural interactomics: informatics approaches to aid the interpretation of genetic variation and the development of novel therapeutics. **Mol. Biosyst**., 5(12):1456-72. PMID: 19763326.
3. Brown A, Higgins MK. (2010). Carbohydrate binding molecules in malaria pathology. **Curr. Opin. Struct. Biol.**, 20(5):560-6. PMID: 20655195.
4. Bengtsson A, Joergensen L, Rask TS, Olsen RW, Andersen MA, Turner L, Theander TG, Hviid L, Higgins MK, Craig A, Brown A, Jensen AT. (2013). A novel domain cassette identifies Plasmodium falciparum PfEMP1 proteins binding ICAM-1 and is a target of cross-reactive, adhesion-inhibitory antibodies. **J. Immunol.**, 190(1):240-9. PMCID: PMC3539686.
5. Higgins MK, Tkachenko O, Brown A, Reed J, Carrington M. (2013). Structure of the trypanosome haptoglobin-hemoglobin receptor and implications for nutrient uptake and innate immunity. **Proc. Natl. Acad. Sci. USA**, 110(5):1905-10. PMCID: PMC3562850.
6. Brown A, Turner L, Christoffersen S, Zhao Y, Szestak T, Craig AG, Higgins MK. (2013). Molecular architecture of a complex between an adhesion protein from the malaria parasite and intracellular adhesion molecule 1. **J. Biol. Chem.**, 288(8):5992-6003. PMCID: PMC3581401.
7. Brown A, Robinson CJ, Gallagher JT, Blundell TL. Cooperative heparin-mediated oligomerization of fibroblast growth factor-1 (FGF1) precedes recruitment of FGFR2 to ternary complexes. (2013). **Biophys. J**., 104(8):1720-1730. PMCID: PMC3628569.

8. Herbert C, Schieborr U, Saxena K, Juraszek J, de Smet F, Alcouffe C, Bianciotto M, Saladino G, Sibrac D, Kudlinzki D, Sreeramulu S, Brown A, Rigon P, Herault J-P, Lassalle G, Blundell TL, Rousseau F, Gils A, Schymkowitz J, Tompa P, Herbert JM, Carmeliet P, Gervasio FL, Schwalbe H, Bono F. (2013). Molecular mechanism of SSR128129E, an extracellularly acting, small-molecule, allosteric inhibitor of FGF receptor signalling. **Cancer Cell**, 23(4):489-501. PMID: 23597563.
9. Gemma S, Brogi S, Patil PR, Giovani S, Lamponi S, Cappelli A, Novellino E, Brown A, Higgins MK, Mustafa K, Szestak T, Craig AG, Campiani G, Butini S, Brindisi M. (2014). From (+)-epigallocatechin gallate to a simplified synthetic analogue as a cytoadherence inhibitor for P. falciparum. **RCS Advances**, 4, 4769-4781.
10. Brown A, Adam LE, Blundell TL. (2014). The crystal structure of fibroblast growth factor 18. **Protein Cell**, 5(5):343-7. PMCID: PMC3996155.
11. Amunts A*, Brown A*, Bai X-C*, Llacer JL*, Hussain T, Emsley P, Long F, Murshudov G, Scheres SHW, Ramakrishnan V. (2014). Structure of the yeast mitochondrial large ribosomal subunit. **Science**, 343(6178):1485-1489. PMCID: PMC4046073.
12. Wong W*, Bai X-C*, Brown A*, Fernández IS, Hanssen E, Condron M, Tan YH, Baum J, Scheres SHW. (2014). Structure of the malaria parasite 80S ribosome bound to the anti-protozoan drug emetine. **eLife**, 3:e03080. PMCID: PMC4086275.
13. Brown A*, Amunts A*, Bai X-C, Sugimoto Y, Edwards PC, Murshudov G, Scheres SHW, Ramakrishnan V. (2014). Structure of the large ribosomal subunit from human mitochondria. **Science**, 346(6210):718-722. PMCID: PMC4246062.
14. Brown A, Long F, Nicholls RA, Toots J, Emsley P, Murshudov G. (2015). Tools for macromolecular model building and refinement into electron cryo-microscopy reconstructions. **Acta Cryst. D**71:136-153. PMCID: PMC4304694.
15. Shao S, Brown A, Santhanam B, Hegde RS. (2015). Structure and assembly pathway of the ribosome quality control complex. Mol. Cell, 57(3):433-444. PMCID: PMC4321881.
16. Amunts A*, Brown A*, Toots J, Scheres SHW, Ramakrishnan V. (2015). The structure of the human mitochondrial ribosome. **Science**, 348(6230):95-98. PMCID: PMC4501431.
17. Zhang R, Alushin GM, Brown A, Nogales E. (2015). Mechanistic origin of microtubule dynamic instability and its modulation by EB proteins. **Cell**, 162(4):849-859. PMCID: PMC4537847.
18. Brown A*, Shao S*, Murray J, Hegde RS, Ramakrishnan V. (2015). Structural basis for stop codon recognition in eukaryotes. **Nature**, 524(7566):493-496. PMCID: PMC4591471.
19. Lennartz F, Bengtsson A, Olsen RW, Joergensen L, Brown A, Remy L, Man P, Forest E, Barfod LK, Adams Y, Higgins MK, Jensen ATR. (2015). Mapping the binding site of a cross-reactive Plasmodium falciparum PfEMP1 monoclonal antibody inhibitory of ICAM-1 binding. **J. Immunol.**, 195(7):3273-3283. PMCID: PMC4574524.
20. Ott M, Amunts A, Brown A. (2016). Organisation and regulation of mitochondrial protein synthesis. **Annu. Rev. Biochem.**, 85:77-101. PMID: 26789594.
21. Brown A*, Fernández IS*, Gordiyenko Y, Ramakrishnan V. (2016). Ribosome-dependent activation of stringent control. **Nature**, 534(7606):277-80. PMCID: PMC4900451.
22. Shao S*, Murray J*, Brown A*, Taunton J, Ramakrishnan V, Hegde RS. (2016). Decoding mammalian ribosome-mRNA states by translational GTPase complexes. **Cell**, 167(5):1229-1240. PMCID: PMC5119991.
23. James NR, Brown A, Gordiyenko Y, Ramakrishnan V. (2016). Translational termination without a stop codon. **Science**, 354(6318):1437-1440. PMCID: PMC5351859.
24. Desai N, Brown A, Amunts A, Ramakrishnan V. (2017). The structure of the yeast mitochondrial ribosome. **Science**, 355(6324):528-531. PMCID: PMC5295643.
25. Wong W, Bai X-C, Sleebs BE, Triglia T, Brown A, Thompson JK, Jackson KE, Hanssen E, Marapana DS, Fernández IS, Ralph SA, Cowman AF, Scheres SHW, Baum J. (2017). Mefloquine targets the Plasmodium falciparum 80S ribosome to inhibit protein synthesis. **Nat. Microbiol**., 2:17031. PMCID: PMC5439513.

26. Brown A, Rathore S, Kimanius D, Aibara S, Bai XC, Rorbach J, Amunts A, Ramakrishnan V. (2017). Structures of the human mitochondrial ribosome in native states of assembly. **Nat. Struct. Mol. Biol.**, 24:866-869. PMCID: PMC5633077.

27. Brown A and Shao S. (2018). Ribosomes and cryo-EM: a duet. **Curr. Opin. Struct. Biol.**, 52:1-7. PMID: 30015201.

28. Brown A, Baird MR, Yipp MCJ, Murray J, Shao S. (2018). Structures of translationally inactive ribosomes. **eLife**, 7:e40486. PMCID: PMC6226290.

29. Brown A, Clardy J. (2018). Tiny crystals have big potential for determining structures of small molecules. **Nature**, 564:348-349. PMID: 30559356.

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Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/labs/bibliography/1fq3ktw3_Fj/bibliography/public/

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

Ongoing Research Support

Research Grant, International Retinal Research Foundation 10/01/17–09/30/19
Structural basis of opsin trafficking
The goal of this project is to dissect the role of the BBSome in trafficking ciliary opsins to the outer segments of photoreceptor cells in the retina.
Role: PI

Research Grant, E. Matilda Ziegler Foundation for the Blind 01/01/18–12/31/20
Visualizing rhodopsin trafficking by cryo-EM
The goal of this proposal is to visualize rhodopsin as it is trafficked in rod cells.
Role: PI

Richard and Susan Smith Family Foundation 03/01/19–02/28/22
Structural basis of intraflagellar transport
The goal of this proposal is to use cryo-EM to solve structures of the IFT-A and IFT-B complexes from the model organism, *Chlamydomonas reinhardtii*.
Role: PI

Pending Research Support

Searle Scholars Program 07/01/19–06/30/22
Mechanisms of ciliary transport
The goal of this proposal is to reconstitute intraflagellar transport in vitro to build a testable platform to study the detailed mechanisms of ciliary transport.
Role: PI

Pew Scholars Program 08/01/19–07/31/23
Organization of visual phototransduction by ciliary trafficking.
The aim of the proposal is to elucidate the role of the mammalian BBSome and IFT complexes in establishing the spatial organization necessary for visual transduction in photoreceptor neurons.
Role: PI