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STIFTUNG PROFESSOR DR. MAX CLOËTTA

Heft Nr. 43

Prof. Dr. Dominique Soldati-Favre

«The Ins and Outs of Apicomplexa Invasion and Egress from Infected Cells»

Prof. Dr. Fritjof Helmchen

«Watching Brain Cells in Action: Two-Photon Calcium Imaging of Neural Circuit Dynamics»

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PROFESSOR DR. MAX CLOËTTA

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VORWORT

Professor Adriano Fontana
Präsident des Stiftungsrates

Alljährlich verleiht die Stiftung Professor Dr. Max Cloetta einen Preis an Persönlichkeiten, welche im Bereiche der medizinisch-biologischen Forschung hervorragend tätig sind. Die Auswahl der Kandidaten fällt dem Stiftungsrat angesichts der hohen Innovationskraft der Wissenschaften in der Schweiz meist schwer. Nebst den herangezogenen Indikatoren zur Messung der Qualität der Forschungs- respektive Publikationsleistung (Impact factor, Zitationsindex etc.) geben in zunehmendem Masse auch erfolgreiche Patentanmeldungen einen Hinweis, wie innovativ die Forschungsleistung ist. Die wirtschaftliche Umsetzung von Forschungsergebnissen der Universität baut unter anderem auch auf den von Forschern eingereichten Patenten auf. Gemäss einer Mitteilung des Europäischen Patentamtes (EPA) wurden aus der Schweiz im Jahr 2014 auf eine Million Einwohner 848 Patente angemeldet. Damit ist die Schweiz nicht nur in Europa, sondern weltweit das patentaktivste Land. In absoluten Zahlen gesehen nimmt die Schweiz weltweit den 8. Platz ein und steht in Europa auf dem 4. Platz. Welch bemerkenswerte Leistung! Der grösste Patentanmelder aus der Schweiz war wie schon 2013 der Elektrotechnikkonzern ABB mit 450 Anmeldungen. Dahinter folgen der Lebensmittelkonzern Nestlé mit 442 Patentanmeldungen sowie die Pharmakonzerne Roche und Novartis mit 357 respektive 323 Anträgen. Unter den Top 25 der Schweiz sind mit den ETH Zürich und Lausanne sowie der Universität Zürich auch drei Hochschulen zu finden. Insgesamt gingen aus der Schweiz beim EPA 7900 Anmeldungen ein (Handelszeitung, 26.2.2015).

Der diesjährige Preis der Professor Dr. Max Cloetta Stiftung geht an die folgenden zwei hochrangigen Wissenschaftler: *Prof. Dr. Dominique Soldati-Favre,* Professorin in der Abteilung für Mikrobiologie und Molekulare Medizin und Vize-Dekanin für Grundlagenforschung an der Medizinischen Fakultät der Universität Genf, und *Prof. Dr. Fritjof Helmchen,* Professor für Neurowissenschaften und Co-Direktor des Institutes für Hirnforschung an der Universität Zürich.

Dominique Soldati-Favre untersucht die molekularen Vorgänge, welche es Apicomplexa ermöglichen, in das Gewebe von mit diesen Parasiten befallenen Menschen einzudringen und Malaria- und Toxoplasmen-Erkrankungen hervorzurufen.

Seit der ersten Preisverleihung 1974 zählen wir 76 Preisträger und davon waren 6 Frauen, eine Quote von 8 %. Hoffnungsvoll ist die Anmerkung, dass seit der Jahrtausendwende 5 von 23 Preisträgern Professorinnen sind. Diese Zahl vergleicht sich mit 1 Professorin unter 53 Preisträgern in den Jahren 1976–1999. Hoffnungsvoll ist aber auch, dass der Anteil der Professorinnen an Schweizer Universitäten in den letzten Jahren stetig gestiegen ist. Lag der Frauenanteil bei Professuren an der Universität Zürich im Jahr 2003 bei 13 % (51 Frauen), beträgt er im Jahr 2014 21 % (129 Frauen). Der Frauenanteil bei den ordentlichen Professuren an Universitäten liegt in den EU-Mitgliedstaaten zwischen 5 % in den Niederlanden und 18 % in Finnland.

Prof. Dr. Fritjof Helmchen gelang es, eine Methode zu entwickeln – die in-vivo 2-Photonenmikroskopie – mit welcher sich bei Säugetieren die Signalübertragung und Aktivität nicht nur wie bis anhin von einem einzigen Neuron oder von Hirnarealen bestimmen lässt, sondern von Nervenzellverbänden. Um die Grundregeln der Informationsverarbeitung neuronaler Netzwerke besser zu verstehen, nutzt Fritjof Helmchen gentechnisch induzierte Aktivitätsmarker und minimal-invasive optische Verfahren. Wie lernt das Gehirn, auf einen bestimmten Sinnesreiz sinnvoll zu reagieren und die entsprechenden Bewegungen auszulösen? Mit der Preisverleihung von Fritjof Helmchen erhöht sich die Zahl der seit 1974 ausgezeichneten Neurobiologen auf 17 (22 %). Dies wiederspiegelt auch das enorm hohe internationale Ansehen der Neurowissenschaften in der Schweiz.

Ich möchte hier meinen Kolleginnen und Kollegen im wissenschaftlichen Ausschuss, den weiteren Mitgliedern des Stiftungsrates und der Geschäftsstelle der Prof. Dr. Max Cloetta Stiftung für Ihren Einsatz während des vergangenen Jahres herzlich danken.

Prof. Dr. med. Adriano Fontana

Brigitt Küttel
Geschäftsführerin

Stiftungsrat

«Vernetzungen und Brückenbildungen sind wichtig: wie können wir die Grundlagenforschung besser mit der klinischen Forschung und diese wiederum mit der Praxis, also der Versorgungsforschung, verbinden – und umgekehrt? Dieser interdisziplinäre Ansatz, diese Interaktionen, diese Aspekte einer translationalen Forschung interessieren mich.» Dieses Zitat aus einem Interview mit Prof. Peter Meier-Abt, erschienen 2012 in der Schweizerischen Ärztezeitung, ist bezeichnend für den Internisten, Klinischen Pharmakologen und Präsidenten der Schweizerischen Akademie der Medizinischen Wissenschaften. Während seiner fünf Jahre im Stiftungsrat der Stiftung Prof. Dr. Max Cloëtta hinterfragte er immer wieder den Nutzen von Forschungsprojekten für die Klinik – und damit letztlich für den Menschen. Auf Ende 2014 ist Prof. Meier-Abt aus dem Stiftungsrat zurückgetreten. Wir danken ihm sehr herzlich für sein grosses Engagement und seine immer profunden Überlegungen. Das wichtige Thema des Verhältnisses von Grundlagenforschung zu klinischer Forschung wird dem Stiftungsrat auch in Zukunft präsent und wichtig sein.

An dieser Stelle möchten wir wie jedes Jahr danken – den Mitgliedern des Stiftungsrates, die ihr Fachwissen einbringen, sei es im wissenschaftlichen Bereich oder zu den Themen Finanzen und Recht, aber auch den Expertinnen und Experten, die uns mit ihren Gutachten bei der Entscheidungsfindung in verschiedenen Gebieten unterstützen. Ohne diese breit abgestützte Erfahrung könnte die Stiftung ihren Zweck nicht so wirkungsvoll umsetzen.

Cloëtta-Preis

Auch dieses Jahr wird der hoch angesehene Preis der Stiftung Prof. Dr. Max Cloëtta wie im Vorjahr an zwei Preisträger verliehen. Die beiden Preisträger stammen aus verschiedenen Landesteilen, Prof. Dr. Domi-

nique Soldati-Favre aus Genf und Prof. Dr. Fritjof Helmchen aus Zürich. Wir freuen uns, nach 2011 das zweite Mal in Genf zu Gast sein zu dürfen, und danken den Verantwortlichen der Université de Genève und ihrem Vertreter in unserem Stiftungsrat, Prof. Dr. Walter Reith, herzlich für ihre Unterstützung.

Schriftenreihe als e-Papers

Seit ihrer Errichtung publiziert die Stiftung Prof. Dr. Max Cloëtta jedes Jahr anlässlich der Preisverleihung eine Broschüre mit Beiträgen der Preisträger. In mehr als 40 Jahren ist so eine spannende Sammlung von Forschungsberichten entstanden, die auch medizinhistorisch von Bedeutung ist. Seit ein paar Jahren wurden die Publikationen auf der Website aufgeschaltet, 2015 erfolgte ein weiterer wichtiger Schritt: Alle Ausgaben der Cloëtta-Schriftenreihe seit 1974 wurden digitalisiert und stehen auf der Website nun auch einem breiteren Publikum zur Verfügung.

Forschungsstellen

Das Forschungsstellenprogramm der Stiftung Prof. Dr. Max Cloëtta ist für den akademischen Mittelbau in der Schweiz von grosser Bedeutung. Finanziert werden Stellen an schweizerischen Hochschulen, Kliniken oder Instituten für bereits ausgebildete und selbständig arbeitende Forscherinnen und Forscher bis max. 40 Jahre. Mit diesem Programm will die Stiftung einem Mangel an Forschernachwuchs in der Schweiz entgegenwirken und den Stelleninhabern helfen, die manchmal nicht einfache Phase bis zur Berufung auf eine ordentliche Professur zu überbrücken. Die Stipendien werden alle zwei Jahre vergeben, das nächste Mal wieder 2016.

2015 finanzierte die Stiftung Prof. Dr. Max Cloëtta folgende Forscher an Schweizer Universitäten mit fünfjährigen Grants:
Dr. Rajesh Jayachandran, 1977, Biozentrum der Universität Basel. Projekt: Role for Coronin 1 signaling in the development of autoimmunity and T cell mediated disorders. Unterstützungsdauer 1.7.2011–30.6.2016.

Dr. Mathias Hauri-Hohl, 1975, Universitäts-Kinderspital Zürich, Abteilung Stammzellentransplantation. Projekt: Improving T-Cell Reconstitution and Enhancing Central Tolerance Mechanism in Hematopoietic Stem Cell Transplantation. Unterstützungsdauer: 1.1.2016–31.12.2020
Dr. Alexandre Theocharides, 1975, Universitätsspital Zürich, Klinik für Hämatologie. Projekt: The Role of Cell-Extrinsic Factors in Hematopoietic Stem Cell Malignancies. Unterstützungsdauer: 1.6.2015–31.5.2020
Dr. Wei Lynn Wong, 1976, Universität Zürich, Institut für experimentelle Immunologie. Projekt: The Role of IAPs and RIPKs in Hematopoiesis and Disease, Specifically in Tumor Formation and Metastasis. Unterstützungsdauer: 1.1.2016–31.12.2020

Klinische Medizin Plus

Seit 2010 vergibt die Stiftung Prof. Dr. Max Cloëtta in Zusammenarbeit mit der Uniscientia Stiftung, Vaduz, Stipendien «Klinische Medizin Plus». Medizinerinnen und Medizinern werden während oder unmittelbar nach Abschluss der Facharztausbildung Stipendien von drei bis maximal zwölf Monaten für die Absolvierung einer Spezialausbildung an einer renommierten, vornehmlich ausländischen Institution ausgerichtet. Die Uniscientia Stiftung finanziert das Programm, die Stiftung Prof. Dr. Max Cloëtta ist verantwortlich für den wissenschaftlichen Teil.

2015 kommen folgende Medizinerinnen und Mediziner in den Genuss eines Stipendiums (Unterstützung läuft oder wurde 2015 zugesprochen):

Dr. med. Alexia Anagnostopoulos, 1978, Fellow Infectious Diseases and Hospital Epidemiology, Zurich University Hospital. Research training program in HIV/AIDS research (Barriers to Treatment in HIV/HCV Co-Infected Intravenous Drug Users: A Collaborative Analysis from Switzerland & USA). Guest Institution: Johns Hopkins Bloomberg School of Public Health, Department of Epidemiology, Baltimore, Maryland USA, 1.7.2015–31.12.2015
Dr. med. Baharak Babouee Flury, 1977, Research Fellow Department of Infectious Diseases and Hospital Epidemiology University Hospital Basel. Topic: Emerging Carbapenem-Resistance in Enterobacter spp:

what is the threat we face? Guest Institution: Antimicrobial Resistance and Healthcare Associated, Infections Reference Unit (AMRHAI) of the Health and Protection Agency UK, Colindale/London, 1.10.2014–30.9.2015

Dr. med. Frederique Hovaguimian, 1981, Anaesthesiology resident, Department of Anaesthesiology, Zurich University Hospital. Master of Clinical Research Methods and Clinical Research Project. Guest Institution: Department of Epidemiology, Monash University, Melbourne, AU and Department of Anaesthesiology, Alfred Hospital, Melbourne, AU, 1.3.2014–28.2.2015

Dr. med. Florence Hoogewoud, 1986, Resident in ophthalmology, Geneva University Hospital. Intensive training in the uveitis subspecialty and in medical retina. Guest Institution: Hôpital Cochin-Uvéites and Hôpital Lariboisière-Rétine, Paris, FR, 1.6.2015–31.5.2016

Dr. med. Christian Schürch, 1983, Resident, Institute of Pathology, University of Berne, Associate Postdoc, Tumour Immunology, Department of Clinical Research. 1) Special training in hematopathology and Research Project. Guest Institution: Eberhard-Karl's University, Institute of Pathology, Tübingen, DE, 1.8.2015–31.7.2016

Dr. med. Petra Sabine, Zimmermann, 1982, Fellow in Paediatric Infectious Disease, University Children's Hospital Berne. Training in Paediatric Infectious Diseases. Guest Institution: Royal Children's Hospital Melbourne, AU, 1.9.2015–30.10.2016

Zusammen mit dem Team der Geschäftsstelle freue ich mich, die Stiftung Prof. Dr. Max Cloëtta auch weiterhin in eine aktive Zukunft für die Förderung der medizinischen Forschung in der Schweiz begleiten zu dürfen. Dem Stiftungsrat, unseren Stipendiatinnen und Stipendiaten und den medizinischen Fakultäten danken wir herzlich für die jederzeit sehr angenehme Zusammenarbeit.

THE CLOËTTA PRIZE 2015
IS AWARDED TO

PROFESSOR

DOMINIQUE SOLDATI-FAVRE

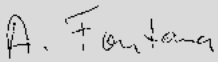
BORN IN 1962 IN CHENIT (VD), SWITZERLAND
PROFESSOR IN THE DEPARTMENT OF MICROBIOLOGY
AND MOLECULAR MEDICINE AND VICE-DEAN OF THE
FACULTY OF MEDICINE AT THE UNIVERSITY
OF GENEVA

MEMBER OF THE SWISS ACADEMY OF MEDICAL SCIENCES
FOR HER OUTSTANDING WORK IN THE DOMAIN OF
MOLECULAR PARASITOLOGY

GENEVA, 13 NOVEMBER 2015

IN THE NAME OF THE FOUNDATION BOARD:

THE PRESIDENT



THE VICE PRESIDENT

MEMBER

Prof. Dr. Dominique Soldati-Favre

BIOGRAPHY

Family name, First name: **Soldati-Favre, Dominique**
Nationality: Swiss
Status: married, four children
Date of birth: June 26th 1962, Switzerland
URL for web site:http://www.unige.ch/medecine/mimo/fr/groupes/773soldati-favre/

Education
1995–2000: Private-Docent in Cell Biology, University of Heidelberg, Germany. 1987–1990: PhD in Molecular biology University of Zurich, Switzerland. 1986 Master in Biochemistry, University of Geneva, Switzerland.

Current Position
2010–: Full Professor Faculty of Medicine, Department of Microbiology and Molecular Medicine, University of Geneva, Switzerland.

Previous Positions
2004–2010: Associate Professor Faculty of Medicine University of Geneva, Switzerland. 2001–2004: Senior Lecturer and Reader Imperial College London, United Kingdom. 1995–2001: Assistant Professor at the ZMBH University of Heidelberg, Germany. 1991–1995: Post-doctoral fellow University of Stanford, Medical School, USA.

Fellowships and Awards
2015: Cloëtta Foundation Award. 2014: Member of the Swiss Academy of the Medical Sciences. 2013: Member of the European Academy of Microbiology. 2012–2017: HHMI Senior International Research Scholar. 2012: Prix Pfizer for basic Research in infection 2012. Laureate: Joana Santos. 2011: EMBO Member. 2009: Prix Pfizer for basic Research in infection 2009. Laureate: Fabienne Plattner. 2009: Prix de la Fondation Gertrude von Meissner together with Dr. Paco Pino. 2000–2005: HHMI International Scholar in infectious diseases. 2005–2010: HHMI Interna-

tional Scholar in infectious diseases. 2001: Rodolfi Medal Deutsche Gesellschaft für Parasitologie. 1993–1994: EMBO long-term fellowship. 1994: Förderungspreis der Schweizerischen Gesellschaft für Mikrobiologie. 1991–1992: SNSF post-doctoral fellowship.

Supervision of Graduate Students and Postdoctoral Fellows
1995–2015: 15 Postdoctoral fellows/25 PhD students/13 Master students.

Selected Mentoring Activities
2014–: Member of the Swiss-French network for mentoring Women careers. 2008–: Member of the Educational board of SystemX.ch. 2012: Cell Biology workshop Bamako Mali. 2011–2013: Instructor at MBL summer course on the Biology of Parasitism Woods Hole. 2010–2014: Coordinator of the SNSF ProDoc training program on Infection & Immunity. 2009–2011: Swiss-German Mentoring Program for Women careers' development. 2008–2012: Helmholtz International Research School for Infection Biology Germany.

Institutional Responsibilities
2011–: Vice-dean for research at the Faculty of Medicine, University of Geneva. 2008–: President of the Graduate School Biology-Medicine, Faculty of Medicine.

Editorial Activities
2011–: Editor at Molecular Microbiology. 2006–: Associate Editor PLoS Pathogens. 2006–: Contributor for F1000 «the Faculty of 1000». 2007–2010: Deputy Editor International Journal for Parasitology.
Editorial board member: eLife, Cell Host & Microbe, Cellular Microbiology, Traffic, Current Opinion in Microbiology, BMC Microbiology
Reviewer for grants: National Science Foundation (USA), DFG (D). ANR, ATIPs (F), BBSRC (UK) NSERC, EMBO fellowships.

Commissions of Trust
2010–: Member of the Swiss National Research Council, Div. III Biology-Medicine. 2012–: Member of the Wellcome Trust's Peer Review College. 2008–: Member of the Friedrich Miescher Award committee. 2008–2015: Expert for the European Research Council.

Member of evaluation committee Helmholtz Research-Programme.
Member of the SAB Sanger Institute Malaria Programme, Wellcome Trust.
Member of the Working Group Malaria Host-Pathogen Interaction Center NIAID & Emory.

Selected Invitations to International Conferences
Molecular Approaches to Malaria Lorne, Australia MAM 2004, 2008, 2012.
Gordon Research Conference on Host-Parasite Interactions GRC 2008, 2010, 2012.
G8 Summit in Sapporo on Women career Development 2008.
10th Anniversary Hunter Cellular Biology Meeting 2009.
36th FEBS Congress, Torino 2011.
International Congress of Parasitology, Australia 2010, Mexico 2014.
The Human Genome Organization, Singapore 2013.
11th International Coccidiosis meeting, Dresden 2014.

Organiser of International Conferences
Gordon Research Conference on Host-Parasite Interactions 2014.
EMBO conference «Subversion of host cellular functions by pathogens» 2010, 2012.
Molecular Parasitology meeting, Woods Hole 2007, 2008, 2009.

Selected Funding
2015–2017: Sinergia-SNSF co-applicant with A Hehl and D. Bumann. 2014–2017: SystemsX.ch-IPhD co-applicant with A. Hehl and V. Hatzimanikatis. 2013–2016: Project grant Division III-SNSF. 2012–2016: HHMI International Senior Scholar. 2009–2015: EVIMalaR-FP7 FP7 Network of Excellence.

Publications
Total number of publications: 129 (84 research articles, 39 reviews, 6 book chapters)
H-index 46

SELECTED PUBLICATIONS

1. Hammoudi PM, Jacot D, Mueller C, Di Cristina M, Dogga SK, Marq JB, Romano J, Tosetti N, Dubrot J, Emre Y, Lunghi M, Coppens I, Yamamoto Y, Sojka D, Pino P and Soldati-Favre D. Fundamental roles of the Golgi-associated Toxoplasma aspartyl protease, ASP5, at the host-parasite interface. PloS Pathog. 2015. ***In press.***

2. Oppenheim RD, Creek DJ, Macrae JI, Modrzynska KK, Pino P, Limenitakis J, Polonais V, Seeber F, Barrett MP, Billker O, McConville MJ, Soldati-Favre D. BCKDH: the missing link in apicomplexan mitochondrial metabolism is required for full virulence of ***Toxoplasma gondii*** and ***Plasmodium berghei.*** PLoS Pathog. 2014 Jul 17;10(7):e1004263.

3. Frénal K, Marq JB, Jacot D, Polonais V, Soldati-Favre D. Plasticity between MyoC- and MyoA-glideosomes: an example of functional compensation in ***Toxoplasma gondii*** invasion. PLoS Pathog. 2014 Nov 13;10(10):e1004504

4. Jacot D, Daher W, Soldati-Favre D. ***Toxoplasma gondii*** myosin F, an essential motor for centrosomes positioning and apicoplast inheritance. EMBO J. 2013 Jun 12;32(12):1702–16.

5. Mueller C, Klages N, Jacot D, Santos JM, Cabrera A, Gilberger TW, Dubremetz JF, Soldati-Favre D. The Toxoplasma protein ARO mediates the apical positioning of rhoptry organelles, a prerequisite for host cell invasion. Cell Host Microbe. 2013 Mar 13;13(3):289–301.

6. Pino P, Sebastian S, Kim EA, Bush E, Brochet M, Volkmann K, Kozlowski E, Llinás M, Billker O, Soldati-Favre D. A tetracycline-repressible transactivator system to study essential genes in malaria parasites. Cell Host Microbe. 2012 Dec 13;12(6):824–34.

7. Frénal K, Polonais V, Marq JB, Stratmann R, Limenitakis J, Soldati-Favre D. Functional dissection of the apicomplexan glideosome molecular architecture. Cell Host Microbe. 2010 Oct 21;8(4):343–57

8. Daher W, Plattner F, Carlier MF, Soldati-Favre D. Concerted action of two formins in gliding motility and host cell invasion by ***Toxoplasma gondii.*** PLoS Pathog. 2010 Oct 7;6(10):e1001132.

9. Plattner F, Yarovinsky F, Romero S, Didry D, Carlier MF, Sher A, Soldati-Favre D. Toxoplasma profilin is essential for host cell invasion and TLR11-dependent induction of an interleukin-12 response. Cell Host Microbe. 2008 Feb 14; 3(2):77–87.

10. Foth BJ, Goedecke MC, Soldati. New insights into myosin evolution and classification. Proc Natl Acad Sci U S A. 2006 Mar 7;103(10):3681–6.

THE INS AND OUTS OF HOST CELL INVASION BY TOXOPLASMA GONDII

Dominique Soldati-Favre

«It is not the most intellectual or the strongest of species that survives; but the species that survives is the one that is able to adapt to and adjust best to the changing environment in which it finds itself»
Charles Darwin

Summary

One of the fundamental challenges in parasitology is to study and understand how a eukaryotic cell can penetrate survive and replicate within another eukaryotic cell. Pathogens have evolved a great variety of mechanisms to evade the host immune system. One of the efficient strategies is to adopt an intracellular life style. While bacterial pathogens can easily enter non-professional phagocytes by induced-phagocytosis, such a task is more complicated for the significantly larger protozoan parasites. *Leishmania* species rely on the host phagocytosis activity to invade the host but its range of host cell types is limited to macrophages and dendritic cells and consequently, this parasite needs to cope with the hostile environment of the phagolysosomes/lysososmes. In contrast, *Trypanosoma* cruzi penetrates host cells by a more active process, involving the recruitment of the lysosomal compartment at the periphery of the host cell[1]. Soon after penetration, the parasite escapes into the cytosol where it replicates safely. Most Apicomplexa have evolved a unique, fast and active mode of host cell entry. This parasite driven process presents numerous advantages i) the parasite can enter almost any cell types including red blood cells as it is the case for *Plasmodium* species ii) this smooth mode of penetration does not trigger the host cell defense mechanisms iii) the process leads to the formation of a parasitopho-

rous vacuole, a membrane bound compartment that is segregated from most cellular trafficking pathways[2]. This compartment is largely devoid of host cell proteins and completely refractory to acidification and lysosomal fusion, enabling the parasite to survive in almost any cell type including macrophages.

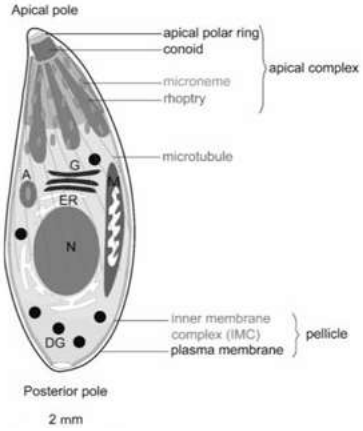
Toxoplasma gondii is an ideal parasite to address some aspects of the vast and fascinating question of host cell entry. This obligate intracellular parasite is one of the most successful invaders, with a remarkable ability to actively penetrate almost any nucleated cells from virtually all warm-blooded animals. This genetically tractable parasite is amenable to biochemical studies and its convenient size combined with its excellent preservation after fixation makes it best suited for high-resolution light and electron microscopy analyses.

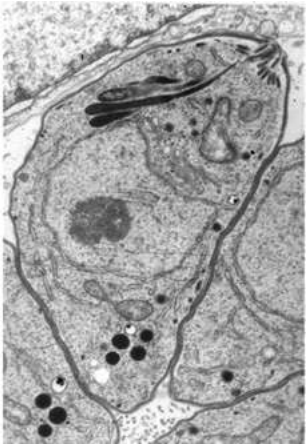
Over the last 25 years, many laboratories including ours have investigated the invasion process in the hope to resolve it in detail at the molecular level. This journey led us to study myosin motors, actin dynamics, adhesins, proteases and more recently lipid signaling mediators. A prerequisite to this work was the establishment of a robust inducible system to dissect the function of essential genes and a better understanding of protein trafficking and organelle biogenesis in this parasite.

Toxoplasma gondii is a member of the Apicomplexa phylum

Protozoan parasites belonging to the phylum of Apicomplexa are of enormous medical and veterinary significance, being responsible for a wide variety of diseases in human and animals, including malaria, toxoplasmosis, coccidiosis and cryptosporidiosis. The life cycle if these of these parasite is complex, alternating between sexual and asexual stages as well as intermediate and definitive hosts[3]. *Toxoplasma T. gondii* is a zoonotic, apicomplexan parasite that belongs to the subclass of coccidians. This protozoan is an important cause for abortion in sheep and responsible for important economic loss. In humans, the global prevalence for *T. gondii* infections is estimated to be approximately 30 %. Infection during pregnancy can lead to congenital toxoplasmosis, which may have serious consequences for the new born or cause abortion. For the majority of in-

fected people, the disease is asymptomatic. Although clinical symptoms can occur in healthy individuals, in particular manifesting as ocular toxoplasmosis and abortion or birth defects, mostly immunosuppressed people are severely affected. The natural life cycle of *T. gondii* takes place in the definitive felid host that sheds up to 10^8 environmentally resistant oocysts. Humans are infected either by ingestion of oocysts shed by felids or by bradyzoites in tissue cysts form infected meat. The high prevalence of latent toxoplasmosis in intermediate hosts such as sheep, pigs, and free-range poultry is responsible for the direct introduction of infectious *T. gondii* tissue cysts into the human food chain. Early during infection, dendritic cells are recruited for rapid dissemination of the fast-replicating tachyzoites[4]. These infected cells are believed to serve as *Trojan horse* for the parasite to cross biological barriers, i.e. into the extravascular space of the brain[5] or across the placenta into the foetus[6] where further dissemination occurs.



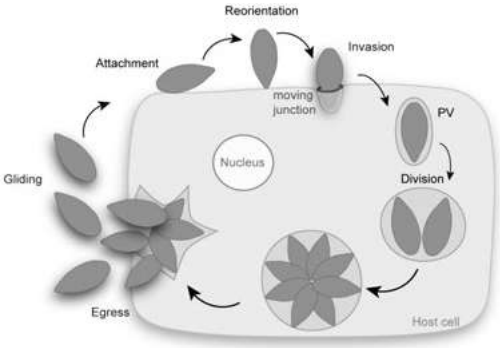


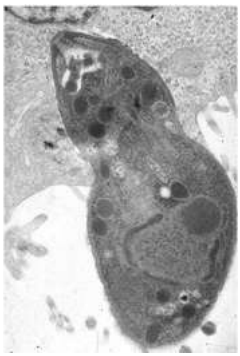
JF Dubremetz

Members of the Apicomplexa are morphologically unified by a common set of apical structures suggesting that invasion is to a large extent mechanistically conserved across the phylum. The apical complex is composed of *rhoptry* and *microneme* organelles that secrete their contents in a regulated fashion during motility and invasion. The coccidian subgroup of

Apicomplexa possesses a dynamic organelle termed the *conoid*. This organelle composed microtubule fibers arranged into a spiral, protrudes in motile and invading parasites.

The actin cytoskeleton has previously been reported to play an essential role in host cell invasion by *T. gondii*[7] *Eimeria* and *Plasmodium*. However, unexpectedly, the parasite actin appears to form short and unstable filaments. As members of the *genus* Alveolata, the Apicomplexa possess a pellicle composed of three membrane layers composed of the plasma membrane and an *inner membrane complex (*IMC) formed by juxtaposed flattened vesicles underneath the plasma membrane and covering a basket of sub-pellicular microtubules[8,9]. The IMC is interconnected with the parasite cytoskeleton and plays a fundamental role in motility and cytokinesis.





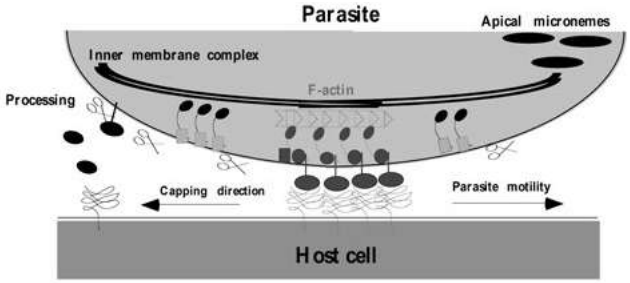
JF Dubremetz

The lytic cycle of *T. gondii* can be divided into several distinct steps that include i) apical attachment to the host cell, ii) parasite apical reorientation, ii) formation of a circular junction (CJ) also referred to as the moving a moving, iii) penetration, iv) sealing of the *parasitophorous vacuolar membrane* (PVM) and host cell plasma membrane. Immediately following invasion, the parasite comes to rest within the PV and vi) at once initiates a program of cell division to produce new daughter cells equipped to egress[10]. Two daughter cells are produced per replication cycle by a mechanism called endodyogeny. Parasites undergo several rounds of rep-

lication prior to vii) egress that causes lysis of the host cell. Finally, viii) the parasites glide and rapidly invade neighboring cells, to initiate new lytic cycles.

Motility and host cell invasion: The «capping model»

In the absence of locomotive organelles such as cilia or flagella, the invasive tachyzoites of *T. gondii* exhibit an unusual form of substrate-dependent motility that is essential for host cell invasion[9]. According to the *«capping model»*[11] gliding motility is driven by the redistribution of adhesins associated to host cell receptors, towards the posterior pole of the parasites. This translocation is powered by the parasite actomyosin system, which is anchored in the inner membrane complex and linked to the cytoplamic tail of the microneme proteins bound to host receptors or extracellular matrix[12]. The model implied the existence of a connector able to couple surface adhesins to the actomyosin system underneath the plasma membrane as well as the action of proteases to release the host-parasite interactions.



Taken together, *T. gondii* utilizes a substrate-dependent motion to propel into host cells and to spread throughout the host organism. The molecular machinery that powers parasite locomotion involves multiple classes of proteins, which are to great extent conserved across the members of the phylum and constitutes the «*glideosome*». To define how structural proteins of the cytoskeleton, the cytoskeletal dynamics and motor proteins are harnessed to generate movement, we have investigated i) regulated exocytosis of apical adhesins, ii) actin polymerization underneath the plasma membrane, iii) recruitment of a connector to link adhesins to

the actomyosin system. iv) myosins implicated in the translocation of adhesins to the rear of the parasite, v) proteolytic processing of the adhesins. Prior to the identification and functional characterization of these various classes of invasion factors, we first established an inducible system to study the function of essential genes in *T. gondiii.*

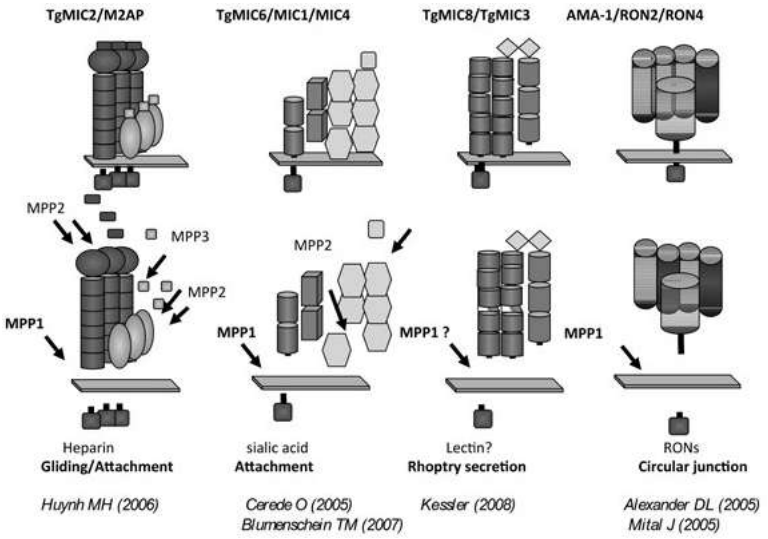
Development of Toxoplasma gondii as a genetically tractable system

Among the Apicomplexa, *T. gondii* was the most attractive model organism with great potentials for genetic tractability. Initially, we developed a transient transfection system[13] and soon after established stable selection protocols for this parasite[14]. We were able to disrupt the first gene in an apicomplexan parasite and also to rescue it[15]. This technology offered the opportunity to study the elements involved in the regulation of gene expression in this primitive eukaryote[16]. Genetic manipulation coupled to expression of green fluorescent protein helped understanding the biogenesis and sorting of secretory proteins[17,18]. We then invested considerable efforts toward the establishment of an inducible control system for gene expression and notably explored the use of Cre recombinase[19]. We first established an inducible gene expression system based on the tetracycline repressor (tetR) of *Escherichia coli*[20]. This system is suitable to conditionally express toxic genes and dominant negative mutants but not appropriate to generate conditional knockouts. In consequence, we developped a genetic screen based on random integration in order to identify a parasite specific transactivator. This approach led us to the establishment of a robust inducible system suitable for the study of essential genes[21].

Regulated secretion of adhesins by the micronemes

The information obtained from *T. gondii* expression sequence tags prior to the era of genome sequencing, uncovered the existence of proteins harboring protein-protein interaction domains and adhesive domains including EGF-like, integrin-like, thrombospondin, and apple domains containing proteins. A comprehensive investigation of these proteins revealed that they corresponded to microneme proteins (MICs), assembled as complexes and contributing to invasion with non-overlapping functions. We established that some transmembrane MICs could act as escorters for targeting of multi-protein complexes to the micronemes[22]. We first charac-

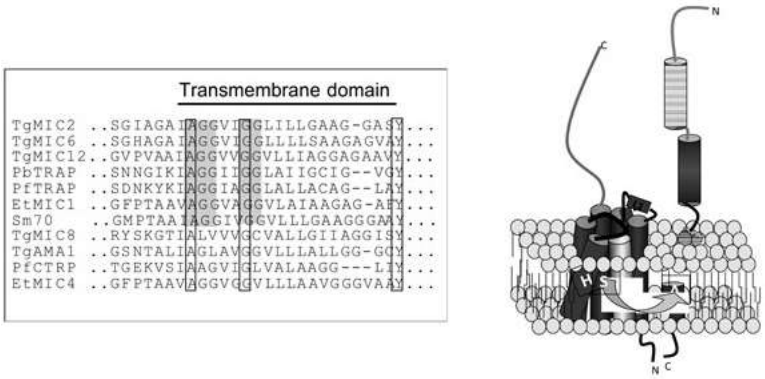
terized the complex composed of TgMIC1, TgMIC4 and TgMIC6[23,24]. MIC6 serves as escorter, is processed within the transmembrane domain during invasion, and contains the conserved C-terminal acidic residues and a tryptophan residue presumed to connect with the actomyosin system. MIC6 contains EGF-like domains, MIC4 contains six apple domains and MIC1 contains two thrombospondin-like domains. Both MIC1 and MIC4 exhibit adhesive properties and bind to host cells. We have built on a fruitful interdisciplinary approach to study the structure/function relationships of the TgMIC1-4-6 complex in collaboration with Dr. S. Matthews at Imperial College. This led to the demonstration that carbohydrate structures on cell surfaces are finely exploited by *T. gondii* for invasion. TgMIC1 is an important adhesin, exhibiting a new structural module termed Microneme Adhesive Repeat (MAR) that recognizes terminally sialylated oligosaccharides on the host cell surface[25,26]. We have elucidated the domains responsible for the interaction between TgMIC1 and its escorter protein TgMIC6, providing new information on the stoichiometry of the complex[27]. Analysis of TgMIC4 led us to postulate that galactose recognition by TgMIC4 may compromise host protection from galectin-mediated activation of the host immune system[28]. Finally, we described the family of MAR containing protein including TgMIC13, which displays distinct preferences to sialylated oligosaccharides on glycoarrays compared to TgMIC1[29]. Importantly, sialic acids that are ubiquitously found on the surface of all vertebrate cells at the extremities of glycan chains were known to be widely exploited by viruses and bacteria to enter host cells and now recognized to critically contribute to selective host cell recognition by the Apicomplexa[30]. We reported an interaction between TgMIC3 and TgMIC8[31] and TgMIC8 was subsequently demonstrated to play a key critical for invasion by contributing to rhoptry secretion[32]. TgAMA1 is an atypical microneme protein that also plays a fundamental role during invasion[33] but forms a large complex with parasite proteins secreted by the rhoptries. This complex uniquely localizes to the circular junction[34] and contains the rhoptry proteins TgRON2, TgRON4, TgRON5 and TgRON8[35] and the TM-MIC TgAMA1, which anchors the complex to the parasite plasma membrane. Others have shown that TgMIC2 forms a multimeric complex with the soluble partner TgM2AP[36,37]. Parasites depleted in TgMIC2 are markedly deficient in host-cell attachment and motility[38].



Proteolytic processing of the microneme proteins by rhomboids

Remarkably, most MICs are proteolytically cleaved during their biogenesis and/or post-exocytosis. We showed that TgAMA1, TgMIC2, TgMIC6, MIC8 and TgMIC12, are all cleaved during invasion within their transmembrane domain (TMD) at the cleavage site IA*GG[39,40] by a protease activity termed microneme protein protease 1 (MPP1) previously described[41]. This shedding was proved to critical for MIC2 function during invasion[42]. Studies have indicated that MPP1 is a member of the rhomboid protease family, a group of broad substrate-specificity serine proteases that recognize helix-destabilizing residues within the TMD of their substrates[43] Among the six rhomboid-like proteins encoded in the *Toxoplasma* genome[44] prime candidates for this shedding activity are TgROM4 and TgROM5[45,46]. ROM4 was recently shown to be responsible for the cleavages of MIC2, AMA1 and most likely MIC8, and to have an important but not essential function during invasion[47,48]. Taken together these results indicate that MPP1 activity primarily contributes to parasite reorientation during invasion by generating a gradient of adhesins that concentrates toward to apical pole rather than causing a disrup-

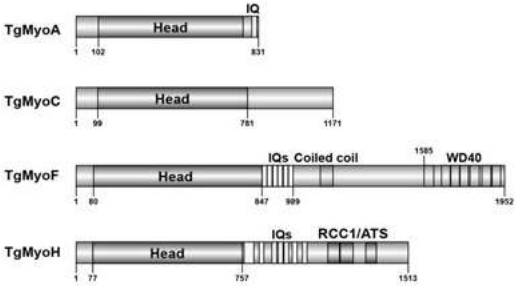
tion of the tight interaction between host cell and parasite at the end of the invasion process. We showed that in addition to TgROM4, TgROM5 is responsible for the processing of a small population of TgAMA1 that is not routing via the micronemes[48]. The significance of that residual cleavage especially in the context of the block in replication observed with a dominant negative catalytically dead mutant of TgROM4 complemented with TgAMA1tail[49] still await further investigations.



The actin-based motors of class XIV in Apicomplexa

The basic engine for this unique type of gliding locomotion is the actin cytoskeleton[7] and involves myosin(s) to generate the mechanochemical force along the actin filaments. In *T. gondii,* gliding is characterized by three distinct forms of motility: circular gliding, upright twirling, and helical rotation. All three forms of motility were disrupted by inhibitors of actin filaments (cytochalasin D) and myosin ATPase (butanedione monoxime), indicating that they rely on the parasite actomyosin system[50]. *T. gondii* possesses eleven myosins that we have been able to assign to various novel classes of myosins based on a comprehensive phylogenic analysis of their conserved heads[51]. The biochemical and biophysical properties of TgMyoA, heroically purified from the parasites, demonstrated that this motor is capable of hydrolysing ATP to track along actin filaments. Motility and microneedle/laser trap assays established that TgMyoA moves in unitary steps of 5.3 nm with a velocity of 5.2 mm/s and toward the plus (barbed) end of actin filaments. TgMyoA is thus likely

powered by novel structural and mechanical element, and is the first example of a fast, single-headed myosin[52]. The inducible system developed from *T. gondii* was exploited to generate a conditional knockout for *TgMyoA,* providing compelling evidence for the critical role of this motor in gliding motility, host cell invasion and egress, and pathogenicity *in vivo*[21]. Demonstration that TgMyoA propels the parasite into host cells validated the capping model[53]. TgMyoB and TgMyoC are encoded by two alternatively spliced mRNA variants and differ only in their C-terminal tails[54]. TgMyoC was demonstrated to play a key role in compensating for the absence of MyoA[55,56]. More recently, we have dissected the function of TgMyoH. This motor possesses 3 alpha tubulin suppressor domains, localizes to the conoid and is associated to microtubules. Despite the presence of MyoA, conditional disruption of TgMyoH revealed the essential nature of this motor for parasite motility, invasion and egress. The detailed phenotypic analyses established that TgMyoH in triggering the first step of the parasite helical motion along the conoid (Graindorge A et al, unpublished). In parallel we have investigated the role of MyoF, which is like MyoA broadly conserved across the phylum. MyoF is a non-dispensable motor implicated in apicoplast inheritance and in the apical positioning of the rhoptries[57]. Importantly, this motor acts in concert with an acylated armadillo repeats containing protein anchored at the surface of the rhoptries[58].

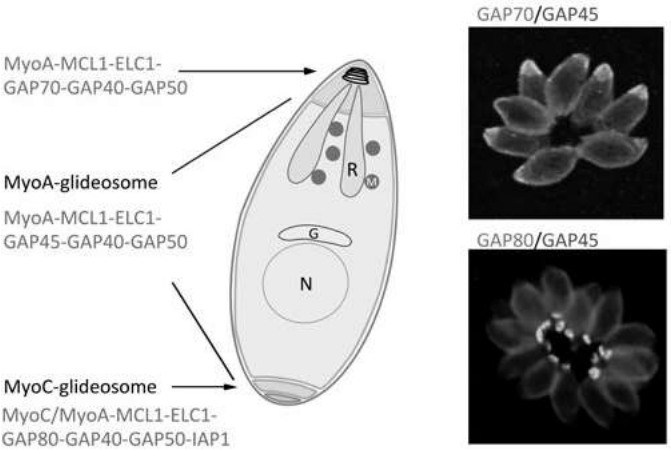


The myosin motor crucial for parasite motility and invasion (MyoA, MyoC and MyoH) and for organelles inheritance (MyoF)

The Components of the glideosome

T. gondii possesses 22 subpellicular microtubules that are covered by an elaborate matrix of articulin-like proteins connected to flattened membranous cisternae composing the IMC, which lies underneath the plasma

membrane. The rigid cytoskeleton formed by these elements is important for maintaining cell shape during parasite motility and invasion and for morphogenesis during cell division. Two gliding associated proteins, TgGAP45 and TgGAP50, have been shown to anchor TgMyoA and its associated light chain TgMLC1 to the IMC[59]. A detailed investigation of GAP45 lead us to establish that the protein is spanning between the plasma membrane and the IMC and plays a key role in preserving the pellicle integrity during invasion. Moreover, GAP70, a coccidian GAP45 homolog GAP70 specifically recruits the glideosome to the apical cap of the parasite[60]. Recently a third member of this family GAP80 was demonstrated to anchor TgMyoC at the posterior pole of the parasite[56].



Actin dynamics

F-actin has been difficult to detect in Apicomplexa with the majority of the actin pool is maintained under its globular form. However, the susceptibility of the parasite to actin-polymerizing and -depolymerizing drugs as well as molecular genetic studies confirmed that actin nucleation and polymerization is critical for motility. Unexpectedly, the Apicomplexans lack a canonical Arp 2/3 complex, which is otherwise widespread among eukaryotes to orchestrate actin assembly by nucleating filaments from the pointed end[61]. Instead these parasites rely on profilin (PRF)[62], two

conserved formins acting as potent actin nucleators[63,64] and a abundantly expressed actin-depolymerizing factor (ADF)[65] to control actin dynamics. We showed that TgPRF is not required for intracellular growth but is indispensable for gliding motility, host cell invasion, active egress from host cells and for virulence in mice[62]. Most interestingly, TgPRF has a separate role as ligand for TLR-11 and the conditional knockout was instrumental in confirming its role in the modulation of the immune response[66]. A study in Plasmodium provided evidence that formin 1 (PfFRM1) is capable of polymerizing actin and guilty by localization, suggestive of a role in motility and invasion[63]. *In T. gondii,* functional analyses of the two formins established that they both play an important role in gliding motility and work in concert during invasion as well as during egress TgFRM1 and TgFRM2 relocalize during invasion to the tip and periphery of the parasite, respectively. Furthermore, the FH2 domains of these fomins have been expressed and shown to exhibit a very potent activity in actin nucleation[64].

Discharge of apical secretory organelles

By successive regulated exocytosis, rhoptries and micronemes release their contents as part of the invasion process. Calcium-mediated signalling is critical for a microneme secretion and invasion[67] and an essential role of TgCDPK1 in the transduction of this calcium signalling was firmly demonstrated[68]. Indeed parasites depleted in CDPK-1 are defective in motility, invasion and egress and treatment with a specific inhibitor of TgCDPK1 recapitulates the phenotype[68]. Recently, TgDOC2.1 was identified as the target gene responsible for a *T. gondii* conditional mutant impaired in host cell invasion and egress[69]. TgDOC2 and other related proteins conserved in Apicomplexa resemble the ferlin/synaptotagmin that trigger many forms of exocytosis by acting on membrane fusion events, in diverse eukaryotic cells. TgDOC2 is the first calcium dependent vesicle fusion mediator implicated in microneme secretion.

The natural triggering factor(s) and the signaling cascade involved are still poorly understood. Changes in extracellular potassium levels and other stimuli trigger a signaling cascade leading to parasite phosphoinositide-phospholipase *C (*PI-PLC) activation, generation of diacylglycerol

(DAG) and inositol triphosphate, and ultimately to microneme secretion. We have recently shown that a delicate balance between DAG and phosphatidic acid (PA) is essential for controlling microneme discharge. Governing this balance is the conserved, apicomplexan-specific DAG-kinase-1, conditional depletion of which leads to parasite death via loss of plasma membrane integrity. Importantly, an acylated pleckstrin homology (PH) domain containing protein (TgAPH) present on the microneme surface, acts as a sensor of PA during microneme secretion. TgAPH is uniquely conserved in Apicomplexa and is critical for microneme secretion, invasion and egress. Overall, this work identifies a key lipid mediator underpinning microneme exocytosis in Apicomplexa (Bullen et al, unpublished). TgAPH presumably contributes to docking of vesicles to the plasma membrane by fostering the close apposition of TgDOC2 and other ferlins to trigger membrane fusion during exocytosis in a Ca2+ dependent manner.

Rhoptry organelles are also viewed as an unusual secretion system, injecting membranous materials to form the PVM as well as effector proteins that contribute to virulence and successful infection by interfering with host cellular functions[70]. Identification of TgARO, an acylated protein implicated in the apical positioning of the rhoptries[58], constitutes a first element to fish the machinery implicated in the discharge of these organelles at the tip of the parasite. The point of discharge might correspond to the *porosome,* a supramolecular lipoprotein structure where the organelle can dock and release its content without substantial fusion[71].

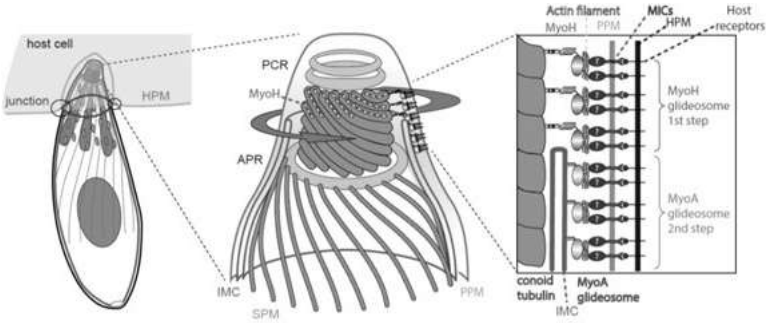
The connector between the actomyosin system and the adhesins

During invasion, transmembrane adhesins discharged by the micronemes on the parasite surface bridge with the targeted host cell. Their reward translocation by the glideosome anchored to the inner membrane complex, propels the parasite inside the host cell. For the last decade, the connection between the adhesins complexes and the glideosome was thought to be established by the glycolytic enzyme *T. gondii* aldolase (TgALD) [72]. However, a recent study demonstrated that depletion of TgALD does not impair motility and invasion but causes the accumulation of toxic me-

tabolites[73]. In consequence, the connection between micronemal adhesins and the glideosome remained an open question. We have identified a glideosome-adhesins connector (TgGAC), which is uniquely conserved across the Apicomplexa phylum. TgGAC binds to rabbit filamentous actin in *in vitro* pull-down assay and predominantly accumulates at the apical pole of intracellular parasites while it progressively re-localizes to the basal end of extracellular gliding parasites. Depletion of TgGAC impairs motility, invasion and egress without affecting microneme or rhoptry secretion. Importantly, *T. gondii* myosin H, a microtubule associated motor confined to the conoid acts as the first translocator of the circular junction complex composed of TgRONs-AMA1 and TgGAC. At the level of the apical polar ring, *T. gondii* myosin. TgMyoA takes the relay and translocates the complex to the posterior pole. This translocation of GAC is necessary for gliding motility, host cell entry and egress from infected cells (Jacot et al, unpublished).

Conclusion

Motion is an intrinsic property of all living organisms and each cell displays a variety of shapes and modes of locomotion. Apicomplexans have



invading/gliding parasite | *protruded parasite* | *MyoH and MyoA glideosomes*

superbly harnessed cytoskeletal structural proteins and molecular motors to generate polarized motion that ensure their survival and infectivity. This closes our current view (opened to future changes) on the molecular composition and mode of action of the glideosome.

Open questions and Future directions

Over the years, the concept of gliding motility and invasion has been consolidated by the identification and characterization of the major actors (regulators of actin dynamics, myosins, microneme adhesins, rhoptry neck proteins, rhomboid proteases, and signalling molecules). Although the critical components of the glideosome have been identified and in large part characterized, the mechanisms allowing its concerted action in a timely controlled fashion remain largely uncharacterized. We have reached a point at which the components of the process have been set on the stage, and reconstructing their interactions is possible. The future challenge will be to understand the mechanistic details of their contributions and how they are orchestrated in time and space. In the next few years, our specific objectives will be to i) *Increase our understanding of the architecture of the glideosome.* If successful, the 3D reconstitution of the glideosome is anticipated to make a seminal contribution to the molecular understanding of a unique cellular mode of motion. Today and despite extensive investigations, its remains a mystery how myosin A, one of the smallest myosin motor, manages to propel the apicomplexan parasites at 5 mm/s. ii) *Elucidate the processes of rhoptry organelle biogenesis and discharge.* This unique club-shaped organelle is at the centre of parasitism by Apicomplexa, contributing to invasion, PVM formation and subversion of host cellular functions. iii) *Assess the function of conoid protrusion.* In intracellular replicating parasites, the conoid remains confined inside the basket of the subpellicular microtubules, which then protrudes in extracellular freshly egressed, gliding or invading parasites. The conoid extends and retracts repeatedly as the parasite moves along the host cell surface but the function if this mysterious, motile organelle is unknown.

The findings that will emerge from our work and others are anticipated to be of significant interest to the fields embracing basic cell biology, microbiology and parasitology. Ultimately, they can lead to the identification of new targets or strategies for intervention against these important human and animal pathogens.

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I wish to express my deepest gratitude to the Cloëtta Foundation and its committee for honoring our work with this prize and by doing it positioning parasitic diseases under the spotlight. This expedition into the fascinating world of Parasitology started for me in 1991. I wish to thank those who introduced me to the field and shared their expertise and talents and communicated their passion. These guides were Dr. Walter Schaffner and Daniel Schuemperli at the University of Zuerich and Bern, Dr. Kami Kim and Dr. John Boothroyd at Stanford University, Dr. Jean Francois Dubremetz (University of Montpellier) and Dr. David Ferguson (University of Oxford) among others. I have also benefited of the unconditional help from colleagues who allowed me to launch an independent career in research. These supporters and wise advisers were Dr. Christine Clayton and Dr. Herman Bujard at the Center for Molecular Biology at the University of Heidelberg and Dr. Robert Sinden at Imperial College London.

I wish to dedicate this Cloetta prize to the memory of Dr. Dirk Dobbelaere and Dr. Klaus Lingelbach. Both were great parasitologists and wonderful colleagues who left us too early. The lab members are the magic players at the center of research. It has been an immense privilege to work with absolutely terrific lab teams over the years. All the past and present lab members have been instrumental to the research presented here and they deserve immense credit and my deepest gratitude.

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REFERENCES

1. Sibley LD and Andrews NW (2000) Cell invasion by un-palatable parasites. Traffic **1**:100–6. doi: tra010202 [pii]

2. Joiner KA, Fuhrman SA, Miettinen HM, Kasper LH and Mellman I (1990) *Toxoplasma gondi*i: fusion competence of parasitophorous vacuoles in Fc receptor-transfected fibroblasts. Science **249**:641–6.

3. Plattner F and Soldati-Favre D (2008) Hijacking of host cellular functions by the Apicomplexa. Annu Rev Microbiol **62**:471–87. doi: 10.1146/annurev.micro.62.081307.162802

4. Fuks JM, Arrighi RB, Weidner JM, Kumar Mendu S, Jin Z, Wallin RP, Rethi B, Birnir B and Barragan A (2012) GABAergic signaling is linked to a hypermigratory phenotype in dendritic cells infected by *Toxoplasma gondii*. PLoS pathogens **8**:e1003051. doi: 10.1371/journal.ppat.1003051

5. Dellacasa-Lindberg I, Fuks JM, Arrighi RB, Lambert H, Wallin RP, Chambers BJ and Barragan A (2011) Migratory activation of primary cortical microglia upon infection with *Toxoplasma gondii*. Infection and immunity **79**:3046–52. doi: 10.1128/IAI.01042-10

6. Wujcicka W, Wilczynski J and Nowakowska D (2014) Do the placental barrier, parasite genotype and Toll-like receptor polymorphisms contribute to the course of primary infection with various *Toxoplasma gondii* genotypes in pregnant women? European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology **33**:703–9. doi: 10.1007/s10096-013-2017-3

7. Dobrowolski JM and Sibley LD (1996) Toxoplasma invasion of mammalian cells is powered by the actin cytoskeleton of the parasite. Cell **84**:933–9. doi: S0092-8674(00)81071–5 [pii]

8. Anderson-White B, Beck JR, Chen CT, Meissner M, Bradley PJ and Gubbels MJ (2012) Cytoskeleton assembly in *Toxoplasma gondii* cell division. Int Rev Cell Mol Biol **298**:1–31. doi: 10.1016/B978-0-12-394309-5.00001-8

9. Morrissette NS and Sibley LD (2002) Cytoskeleton of apicomplexan parasites. Microbiol Mol Biol Rev **66**:21–38; table of contents.

10. Black MW and Boothroyd JC (2000) Lytic cycle of *Toxoplasma gondii.* Microbiology and molecular biology reviews: MMBR **64**:607–23.

11. Russell DG (1983) Host cell invasion by Apicomplexa: an expression of the parasite's contractile system? Parasitology **87 (Pt 2)**:199–209.

12. Opitz C and Soldati D (2002) ‹The glideosome›: a dynamic complex powering gliding motion and host cell invasion by *Toxoplasma gondii*. Molecular microbiology **45**:597–604.

13. Soldati D and Boothroyd JC (1993) Transient transfection and expression in the obligate intracellular parasite *Toxoplasma gondii.* Science **260**:349–52.

14. Kim K, Soldati D and Boothroyd JC (1993) Gene replacement in *Toxoplasma gondii* with chloramphenicol acetyltransferase as selectable marker. Science **262**:911–4.

15. Soldati D, Kim K, Kampmeier J, Dubremetz JF and Boothroyd JC (1995) Complementation of a *Toxoplasma gondii* ROP1 knock-out mutant using phleomycin selection. Molecular and biochemical parasitology **74**:87–97.

16. Soldati D and Boothroyd JC (1995) A selector of transcription initiation in the protozoan parasite *Toxoplasma gondii.* Molecular and cellular biology **15**:87–93.

17. Soldati D, Lassen A, Dubremetz JF and Boothroyd JC (1998) Processing of Toxoplasma ROP1 protein in nascent rhoptries. Molecular and biochemical parasitology **96**:37–48.

18. Striepen B, He CY, Matrajt M, Soldati D and Roos DS (1998) Expression, selection, and organellar targeting of the green fluorescent protein in *Toxoplasma gondii.* Mol Biochem Parasitol **92**:325–38. doi: S0166685198000115 [pii]

19. Brecht S, Erdhart H, Soete M and Soldati D (1999) Genome engineering of *Toxoplasma gondii* using the site-specific recombinase Cre. Gene **234**:239–47.

20. Meissner M, Brecht S, Bujard H and Soldati D (2001) Modulation of myosin A expression by a newly established tetracycline repressor-based inducible system in *Toxoplasma gondii*. Nucleic acids research **29**:E115.

21. Meissner M, Schluter D and Soldati D (2002) Role of *Toxoplasma gondii* myosin A in powering parasite gliding and host cell invasion. Science **298**:837–40. doi: 10.1126/science.1074553

22. Di Cristina M, Spaccapelo R, Soldati D, Bistoni F and Crisanti A (2000) Two conserved amino acid motifs mediate protein targeting to the micronemes of the apicomplexan parasite *Toxoplasma gondii.* Molecular and cellular biology **20**:7332–41.

23. Reiss M, Viebig N, Brecht S, Fourmaux MN, Soete M, Di Cristina M, Dubremetz JF and Soldati D (2001) Identification and characterization of an escorter for two secretory adhesins in *Toxoplasma gondii*. The Journal of cell biology **152**:563–78.

24. Brecht S, Carruthers VB, Ferguson DJ, Giddings OK, Wang G, Jakle U, Harper JM, Sibley LD and Soldati D (2001) The toxoplasma micronemal protein MIC4 is an adhesin composed of six conserved apple domains. J Biol Chem **276**:4119–27. doi: 10.1074/jbc.M008294200

25. Saouros S, Edwards-Jones B, Reiss M, Sawmynaden K, Cota E, Simpson P, Dowse TJ, Jakle U, Ramboarina S, Shivarattan T, Matthews S and Soldati-Favre D (2005) A novel galectin-like domain from *Toxoplasma gondii* micronemal protein 1 assists the folding, assembly, and transport of a cell adhesion complex. The Journal of biological chemistry **280**:38583–91. doi: 10.1074/jbc.C500365200

26. Blumenschein TM, Friedrich N, Childs RA, Saouros S, Carpenter EP, Campanero-Rhodes MA, Simpson P, Chai W, Koutroukides T, Blackman MJ, Feizi T, Soldati-Favre D and Matthews S (2007) Atomic resolution insight into host cell recognition by *Toxoplasma gondii.* The EMBO journal **26**:2808–20. doi: 10.1038/sj.emboj.7601704

27. Sawmynaden K, Saouros S, Friedrich N, Marchant J, Simpson P, Bleijlevens B, Blackman MJ, Soldati-Favre D and Matthews S (2008) Structural insights into microneme protein assembly reveal a new mode of EGF domain recognition. EMBO Rep **9**:1149–55. doi: 10.1038/embor.2008.179

28. Marchant J, Cowper B, Liu Y, Lai L, Pinzan C, Marq JB, Friedrich N, Sawmynaden K, Liew L, Chai W, Childs RA, Saouros S, Simpson P, Roque Barreira MC, Feizi T, Soldati-Favre D and Matthews S (2012) Galactose recognition by the apicomplexan parasite *Toxoplasma gondii*. The Journal of biological chemistry **287**:16720–33. doi: 10.1074/jbc.M111.325928

29. Friedrich N, Santos JM, Liu Y, Palma AS, Leon E, Saouros S, Kiso M, Blackman MJ, Matthews S, Feizi T and Soldati-Favre D (2010) Members of a novel protein family containing microneme adhesive repeat domains act as sialic acid-binding lectins during host cell invasion by apicomplexan parasites. J Biol Chem **285**:2064–76. doi: 10.1074/jbc.M109.060988

30. Friedrich N, Matthews S and Soldati-Favre D (2010) Sialic acids: key determinants for invasion by the Apicomplexa. Int J Parasitol **40**:1145–54. doi: 10.1016/j.ijpara.2010.04.007

31. Meissner M, Reiss M, Viebig N, Carruthers VB, Toursel C, Tomavo S, Ajioka JW and Soldati D (2002) A family of transmembrane microneme proteins of *Toxoplasma gondi*i contain EGF-like domains and function as escorters. Journal of cell science **115**:563–74.

32. Kessler H, Herm-Gotz A, Hegge S, Rauch M, Soldati-Favre D, Frischknecht F and Meissner M (2008) Microneme protein 8--a new essential invasion factor in *Toxoplasma gondii.* Journal of cell science **121**:947–56. doi: 10.1242/jcs.022350

33. Mital J, Meissner M, Soldati D and Ward GE (2005) Conditional expression of *Toxoplasma gondii* apical membrane antigen-1 (TgAMA1) demonstrates that TgAMA1 plays

a critical role in host cell invasion. Molecular biology of the cell **16**:4341–9. doi: 10.1091/mbc.E05-04-0281

34. Alexander DL, Mital J, Ward GE, Bradley P and Boothroyd JC (2005) Identification of the moving junction complex of *Toxoplasma gondii*: a collaboration between distinct secretory organelles. PLoS pathogens **1**:e17. doi: 10.1371/journal.ppat.0010017

35. Besteiro S, Michelin A, Poncet J, Dubremetz JF and Lebrun M (2009) Export of a *Toxoplasma gondii* rhoptry neck protein complex at the host cell membrane to form the moving junction during invasion. PLoS Pathog **5**:e1000309. doi: 10.1371/journal.ppat.1000309

36. Rabenau KE, Sohrabi A, Tripathy A, Reitter C, Ajioka JW, Tomley FM and Carruthers VB (2001) TgM2AP participates in *Toxoplasma gondii* invasion of host cells and is tightly associated with the adhesive protein TgMIC2. Molecular microbiology **41**:537–47.

37. Jewett TJ and Sibley LD (2004) The toxoplasma proteins MIC2 and M2AP form a hexameric complex necessary for intracellular survival. J Biol Chem **279**:9362–9. doi: 10.1074/jbc.M312590200 M312590200 [pii]

38. Huynh MH, Rabenau KE, Harper JM, Beatty WL, Sibley LD and Carruthers VB (2003) Rapid invasion of host cells by Toxoplasma requires secretion of the MIC2-M2AP adhesive protein complex. The EMBO journal **22**:2082–90. doi: 10.1093/emboj/cdg217

39. Opitz C, Di Cristina M, Reiss M, Ruppert T, Crisanti A and Soldati D (2002) Intramembrane cleavage of microneme proteins at the surface of the apicomplexan parasite *Toxoplasma gondii.* The EMBO journal **21**:1577–85. doi: 10.1093/emboj/21.7.1577

40. Sheiner L, Santos JM, Klages N, Parussini F, Jemmely N, Friedrich N, Ward GE and Soldati-Favre D (2010) *Toxoplasma gondii* transmembrane microneme proteins and their modular design. Molecular microbiology. doi: 10.1111/j.1365-2958.2010.07255.x

41. Carruthers VB, Sherman GD and Sibley LD (2000) The Toxoplasma adhesive protein MIC2 is proteolytically processed at multiple sites by two parasite-derived proteases. The Journal of biological chemistry **275**:14346–53.

42. Brossier F, Jewett TJ, Lovett JL and Sibley LD (2003) C-terminal processing of the toxoplasma protein MIC2 is essential for invasion into host cells. J Biol Chem **278**:6229–34. doi: 10.1074/jbc.M209837200

43. Urban S and Freeman M (2003) Substrate specificity of rhomboid intramembrane proteases is governed by helix-breaking residues in the substrate transmembrane domain. Mol Cell **11**:1425–34. doi: S1097276503001813 [pii]

44. Dowse TJ and Soldati D (2005) Rhomboid-like proteins in Apicomplexa: phylogeny and nomenclature. Trends Parasitol **21**:254–8. doi: S1471–4922(05)00102–9 [pii]

45. Brossier F, Jewett TJ, Sibley LD and Urban S (2005) A spatially localized rhomboid protease cleaves cell surface adhesins essential for invasion by Toxoplasma. Proc Natl Acad Sci U S A **102**:4146–51. doi: 0407918102 [pii]

46. Dowse TJ, Pascall JC, Brown KD and Soldati D (2005) Apicomplexan rhomboids have a potential role in microneme protein cleavage during host cell invasion. Int J Parasitol **35**:747–56. doi: S0020-7519(05)00126-8 [pii]

47. Buguliskis JS, Brossier F, Shuman J and Sibley LD (2010) Rhomboid 4 (ROM4) affects the processing of surface adhesins and facilitates host cell invasion by *Toxoplasma gondii*. PLoS Pathog **6**:e1000858. doi: 10.1371/journal.ppat.1000858

48. Rugarabamu G, Marq JB, Guerin A, Lebrun M and Soldati-Favre D (2015) Distinct contribution of *Toxoplasma gondii* rhomboid proteases 4 and 5 to micronemal protein protease 1 activity during invasion. Mol Microbiol **97**:244–62. doi: 10.1111/mmi.13021

49. Santos JM, Ferguson DJ, Blackman MJ and Soldati-Favre D (2011) Intramembrane cleavage of AMA1 triggers Toxoplasma to switch from an invasive to a replicative mode. Science **331**:473–7. doi: 10.1126/science.1199284

50. Hakansson S, Morisaki H, Heuser J and Sibley LD (1999) Time-lapse video microscopy of gliding motility in *Toxoplasma gondii* reveals a novel, biphasic mechanism of cell locomotion. Mol Biol Cell **10**:3539–47.

51. Foth BJ, Goedecke MC and Soldati D (2006) New insights into myosin evolution and classification. Proc Natl Acad Sci U S A **103**:3681–6. doi: 0506307103 [pii]

52. Herm-Gotz A, Weiss S, Stratmann R, Fujita-Becker S, Ruff C, Meyhofer E, Soldati T, Manstein DJ, Geeves MA and Soldati D (2002) *Toxoplasma gondii* myosin A and its light chain: a fast, single-headed, plus-end-directed motor. The EMBO journal **21**:2149–58. doi: 10.1093/emboj/21.9.2149

53. Keeley A and Soldati D (2004) The glideosome: a molecular machine powering motility and host-cell invasion by Apicomplexa. Trends Cell Biol **14**:528–32. doi: 10.1016/j.tcb.2004.08.002

54. Delbac F, Sanger A, Neuhaus EM, Stratmann R, Ajioka JW, Toursel C, Herm-Gotz A, Tomavo S, Soldati T and Soldati D (2001) *Toxoplasma gondii* myosins B/C: one gene, two tails, two localizations, and a role in parasite division. The Journal of cell biology **155**:613–23. doi: 10.1083/jcb.200012116

55. Egarter S, Andenmatten N, Jackson AJ, Whitelaw JA, Pall G, Black JA, Ferguson DJ, Tardieux I, Mogilner A and Meissner M (2014) The toxoplasma Acto-MyoA motor complex is important but not essential for gliding motility and host cell invasion. PloS one **9**:e91819. doi: 10.1371/journal.pone.0091819

56. Frenal K, Marq JB, Jacot D, Polonais V and Soldati-Favre D (2014) Plasticity between MyoC- and MyoA-glideosomes: an example of functional compensation in *Toxoplasma gondii* invasion. PLoS pathogens **10**:e1004504. doi: 10.1371/journal.ppat.1004504

57. Jacot D, Daher W and Soldati-Favre D (2013) *Toxoplasma gondii* myosin F, an essential motor for centrosomes positioning and apicoplast inheritance. The EMBO journal **32**:1702–16. doi: 10.1038/emboj.2013.113

58. Mueller C, Klages N, Jacot D, Santos JM, Cabrera A, Gilberger TW, Dubremetz JF and Soldati-Favre D (2013) The Toxoplasma protein ARO mediates the apical positioning of rhoptry organelles, a prerequisite for host cell invasion. Cell host & microbe **13**:289–301. doi: 10.1016/j.chom.2013.02.001

59. Gaskins E, Gilk S, DeVore N, Mann T, Ward G and Beckers C (2004) Identification of the membrane receptor of a class XIV myosin in *Toxoplasma gondii*. J Cell Biol **165**:383–93. doi: 10.1083/jcb.200311137

60. Frenal K, Polonais V, Marq JB, Stratmann R, Limenitakis J and Soldati-Favre D (2010) Functional dissection of the apicomplexan glideosome molecular architecture. Cell host & microbe **8**:343–57. doi: 10.1016/j.chom.2010.09.002

61. Soldati D and Meissner M (2004) Toxoplasma as a novel system for motility. Current opinion in cell biology **16**:32–40. doi: 10.1016/j.ceb.2003.11.013

62. Plattner F, Yarovinsky F, Romero S, Didry D, Carlier MF, Sher A and Soldati-Favre D (2008) Toxoplasma profilin is essential for host cell invasion and TLR11-dependent induction of an interleukin-12 response. Cell host & microbe **3**:77–87. doi: 10.1016/j.chom.2008.01.001

63. Baum J, Tonkin CJ, Paul AS, Rug M, Smith BJ, Gould SB, Richard D, Pollard TD and Cowman AF (2008) A malaria parasite formin regulates actin polymerization and localizes to the parasite-erythrocyte moving junction during invasion. Cell Host Microbe **3**:188–98. doi: 10.1016/j.chom.2008.02.006

64. Daher W, Plattner F, Carlier MF and Soldati-Favre D (2010) Concerted action of two formins in gliding motility and host cell invasion by *Toxoplasma gondii*. PLoS pathogens **6**:e1001132. doi: 10.1371/journal.ppat.1001132

65. Mehta S and Sibley LD (2011) Actin depolymerizing factor controls actin turnover and gliding motility in *Toxoplasma gondii*. Molecular biology of the cell **22**:1290–9. doi: 10.1091/mbc.E10-12-0939

66. Yarovinsky F, Zhang D, Andersen JF, Bannenberg GL, Serhan CN, Hayden MS, Hieny S, Sutterwala FS, Flavell RA, Ghosh S and Sher A (2005) TLR11 activation of dendritic cells by a protozoan profilin-like protein. Science **308**:1626–9. doi: 1109893 [pii]

67. Nagamune K, Moreno SN, Chini EN and Sibley LD (2008) Calcium regulation and signaling in apicomplexan parasites. Subcell Biochem **47**:70–81.

68. Lourido S, Shuman J, Zhang C, Shokat KM, Hui R and Sibley LD (2010) Calcium-dependent protein kinase 1 is an essential regulator of exocytosis in Toxoplasma. Nature **465**:359–62. doi: 10.1038/nature09022

69. Farrell A, Thirugnanam S, Lorestani A, Dvorin JD, Eidell KP, Ferguson DJ, Anderson-White BR, Duraisingh MT, Marth GT and Gubbels MJ (2012) A DOC2 protein identified by mutational profiling is essential for apicomplexan parasite exocytosis. Science **335**:218–21. doi: 10.1126/science.1210829

70. Kemp LE, Yamamoto M and Soldati-Favre D (2013) Subversion of host cellular functions by the apicomplexan parasites. FEMS microbiology reviews **37**:607–31. doi: 10.1111/1574-6976.12013

71. Jena BP (2009) Porosome: the secretory portal in cells. Biochemistry **48**:4009–18. doi: 10.1021/bi9002698

72. Starnes GL, Coincon M, Sygusch J and Sibley LD (2009) Aldolase is essential for energy production and bridging adhesin-actin cytoskeletal interactions during parasite invasion of host cells. Cell Host Microbe **5**:353–64. doi: 10.1016/j.chom.2009.03.005

73. Shen B and Sibley LD (2014) Toxoplasma aldolase is required for metabolism but dispensable for host-cell invasion. Proc Natl Acad Sci U S A **111**:3567–72. doi: 10.1073/pnas.1315156111

THE CLOËTTA PRIZE 2015
IS AWARDED TO

PROFESSOR

FRITJOF HELMCHEN

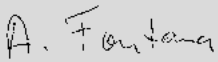
BORN IN 1966 IN TÜBINGEN, GERMANY
PROFESSOR OF NEUROSCIENCES AND
CO-DIRECTOR OF THE BRAIN RESEARCH INSTITUTE
OF THE UNIVERSITY OF ZURICH

FOR HIS OUTSTANDING WORK
IN THE DOMAIN OF NEURONAL NETWORKS

GENEVA, 13 NOVEMBER 2015

IN THE NAME OF THE FOUNDATION BOARD:

THE PRESIDENT



THE VICE PRESIDENT

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Prof. Dr. Fritjof Helmchen

BIOGRAPHY

Fritjof Helmchen is Professor of Neuroscience and Co-Director of the Brain Research Institute at the University of Zurich. He was born in 1966 in Tübingen, Germany. He studied physics and the non-clinical part of medicine and received his PhD from the University of Göttingen in 1996 for research that he performed in the department of Bert Sakmann at the Max-Planck Institute for Medical Research in Heidelberg. He then went for 3 years to the Bell Laboratories at Lucent Technologies, New Jersey, where he started to apply two-photon microscopy for in vivo brain imaging as a postdoc with Winfried Denk and David Tank. In 2000 he returned to Heidelberg, where he became a junior group leader at the Max-Planck Institute for Medical Research, further expanding in vivo applications of two-photon calcium imaging. In 2005 he was appointed associate professor at the Medical Faculty of the University of Zurich and in 2013 he was promoted to full professor. Fritjof Helmchen has received several awards, including the Otto-Hahn Medal of the Max-Planck Society, the Emil Du Bois-Reymond Prize of the German Physiological Society in 2003, the Pfizer Research Prize 2011 (with B. Grewe), and most recently an ERC Advanced Grant. His research group is one of very few European labs that so far have received an NIH research grant within the US BRAIN Initiative. He is currently member of the Scientific Advisory Board of the Centre for Integrative Neuroscience, Tübingen, and acts as President of the Betty and David Koetser Foundation of Brain Research, Zurich.

Fritjof Helmchen's research is focused on the advancement and application of optical methods – in particular two-photon microscopy – to study neural activity on the subcellular, cellular, and circuit level. His scientific interest is to understand principles of neural circuit operation and thereby build a bridge in our understanding of brain function from the small scale to the larger scale of brain-wide signal flow. Resolving the healthy brain's working principles he also sees as the basis for examining what goes wrong in various brain diseases. His group has pioneered several microscopy techniques, including 3D two-photon imaging, high-

speed calcium imaging, two-photon microscope miniaturization, and most recently a two-area microscope for the simultaneous measurement of activity in two communicating brain regions. Currently, in most of the ongoing research projects his group studies behaving mice, employing imaging techniques to directly visualize neural activity patterns under relevant behavioral conditions.

SELECTED PUBLICATIONS

1. Chen JL, Margolis DJ, Stankov A, Sumanovski LT, Schneider BL, ***Helmchen F*** (2015) Pathway-specific reorganization of projection neurons in somatosensory cortex during learning. ***Nature Neuroscience,*** 18(8):1101–1108.

2. Chen JL, Carta S, Soldado-Magraner J, Schneider BL, ***Helmchen F*** (2013) Behavior-dependent recruitment of long-range projection neurons in somatosensory cortex. ***Nature,*** 499:336–340.

3. Margolis DJ*, Lütcke H*, Schulz K, Haiss F, Weber B, Kügler S, Hasan MT, ***Helmchen F*** (2012) Reorganization of cortical population activity imaged throughout long-term sensory deprivation. ***Nature Neuroscience,*** 15(11):1539–1546. *equal contribution

4. Schulz K, Sydekum E, Krueppel R, Engelbrecht CJ, Schlegel F, Schröter A, Rudin M, ***Helmchen F*** (2012) Simultaneous BOLD fMRI and fiber-optic calcium recording in rat neocortex. ***Nature Methods,*** 9:597–602.

5. ***Imaging in Neuroscience:*** A Laboratory Manual. ***Helmchen F,*** Konnerth A eds. Cold Spring Harbor Laboratory Press, Cold Spring Harbor. 92 Chapters, 1084 pp. (2011) (Edited book)

6. Grewe B, Langer D, Kasper H, Kampa BM, ***Helmchen F*** (2010) High-speed in vivo calcium imaging reveals spike trains in neuronal networks with near-millisecond precision. ***Nature Methods*** 7(5): 399–405.

7. Kerr JND, de Kock, CPJ, Greenberg, DS, Bruno, RM, Sakmann B, ***Helmchen F*** (2007) Spatial organization of neuronal population responses in layer 2/3 of rat barrel cortex. ***Journal of Neuroscience*** 27(48):13316–13328.

8. Göbel W, Kampa BM, ***Helmchen F*** (2007) Imaging cellular network dynamics in three dimensions using fast 3D laser scanning. ***Nature Methods*** 4: 73–79.

9. Kerr, JND, Greenberg, D, ***Helmchen F*** (2005) Imaging input and output of neocortical networks in vivo. ***Proc. Natl. Acad. Sci. USA*** 102: 14063–14068.

10. ***Helmchen F,*** Denk W (2005) Deep tissue two-photon microscopy. ***Nature Methods*** 2(12):932–940. (Review)

11. Nimmerjahn A, Kirchhoff F, ***Helmchen F*** (2005) Resting microglial cells are highly dynamic surveillants of brain parenchyma in vivo. ***Science*** 308:1314–1318.

12. Nimmerjahn A, Kirchhoff F, Kerr NDJ, ***Helmchen F*** (2004) Sulforhodamine 101 as a specific marker of astroglia in the neocortex in vivo. ***Nature Methods*** 1(1): 31–37.

13. ***Helmchen F,*** Fee MS, Tank DW, Denk W (2001) A miniature head-mounted two-photon microscope: high-resolution brain imaging in freely moving animals. ***Neuron*** 31:903–912.

14. ***Helmchen F,*** Svoboda K, Denk, W, Tank DW (1999) In vivo dendritic calcium dynamics in deep-layer cortical pyramidal neurons. ***Nature Neuroscience*** 2(11):989–996.

15. ***Helmchen F,*** Imoto K, Sakmann B (1996) Ca^{2+} buffering and action potential-evoked Ca^{2+} signaling in dendrites of pyramidal neurons. ***Biophysical Journal*** 70:1069–1081.

WATCHING BRAIN CELLS IN ACTION: TWO-PHOTON CALCIUM IMAGING OF NEURAL CIRCUIT DYNAMICS

by Fritjof Helmchen

Summary

Brain cells act together to generate the myriad of complex behaviors shown by all creatures while they constantly react and adapt to the challenges in the environment. The networks of excitable neurons in the brain continually generate activity patterns that maintain body functions, process the various sensory inputs, take into account memorized previous experiences, and dynamically coordinate and control muscle activity as needed for specific behaviors. The principles of sensorimotor representations and information processing in neural circuits are still poorly understood, however, largely because in the past methods were scarce for measuring neuronal population activity during behavior. Over the last decade, new opportunities have emerged to investigate neuronal networks in action, most prominently utilizing 2-photon microscopy. Many «activity sensors» are now available, especially fluorescent proteins that have been designed to change their fluorescence emission depending on cell activity. For example, so called «genetically encoded calcium indicators» are now in widespread use. These protein indicators report neuronal activity based on action potential-evoked calcium influx. Long-term expression of genetically-encoded indicators in neuronal populations allows for repeated monitoring of the same cells over weeks and months. In this way both stability and plasticity of functional properties can be investigated longitudinally. Most notably, high-resolution imaging with cellular resolution can be performed in the brain of awake, behaving animals, enabling neuroscientists to «watch» ongoing neuronal network activity while the brain performs a task and to relate network activity patterns to behavioral aspects. In addition, it has become possible to track changes in activity patterns throughout task learning. These advances promise to help reveal principles of neural circuit dynamics underlying sensorimotor processing and learning. In the following, I will summarize our own recent contributions to this rapidly expanding field of neural network imaging, exemplifying the new research opportunities with experimental findings from the mouse brain.

Introduction

The functional organization of the brain is hierarchical, ranging from the molecular and cellular level, to the intermediate level of local neuronal circuits, to the brain-wide communication network of different brain regions established by long-range projection pathways. Local neuronal circuits are highly complex, densely connected networks of excitatory and inhibitory neurons, for instance in a region of neocortex or in a particular deep brain nucleus. Their function cannot be understood in isolation as they typically have numerous short- and long-range connections with other brain regions, for receiving input signals and for transmitting output, respectively. A central idea is that specific computational operations are carried out while signals flow through such local networks. Therefore, uncovering the underlying cellular and molecular mechanisms will be crucial for understanding of information processing in the brain (Harris and Mrsic-Flogel, 2013). However, the complexity of neuronal networks – with regard to both anatomy and physiology – cannot be underestimated. The greatness of the research challenge is illustrated by just considering the very different dynamic brain states under anesthetized and awake conditions.

A first, supposedly simple step is the measurement of neuronal network activity under relevant conditions, i.e., in situations, in which the brain is performing a task, when it is «in action». However, the experimental possibilities for such a phenomenological, descriptive approach have been limited in the past. On the macroscopic level, functional magnetic resonance imaging (fMRI) provides a means to infer activity of particular regions of the human brain in various situations but it is lacking cellular resolution. On the microscopic level, basic properties of individual cell types and molecular events underlying the communication between neurons have been characterized over the past decades with electrophysiology and high-resolution microscopy. However, these experiments were typically carried out in isolated brain tissue slices or under anesthesia. Electrophysiological recordings, although used for long time to study brain cell activity during wakefulness, only can take limited sample measurements of the activity of a few but not all neurons within a local network. Strikingly, in the past it was hardly possible to measure the activity of the

same neurons repeatedly over a long time period to examine functional changes of network dynamics, e.g., during learning. Such direct measurement of activity patterns in local neuronal circuits, in particular in the living brain («in vivo») and over long time periods, would also be of high significance to improve our understanding of malfunctions of neuronal networks during brain diseases.

Monitoring neuronal activity with calcium indicators

Since several decades, neuroscientists have utilized the combination of activity-dependent fluorescent indicators and high-resolution microscopy techniques to visualize dynamic excitation patterns of neuronal cell populations. Until the end of last century most indicators were small organic molecules that change their fluorescence properties in response to membrane potential changes or binding to calcium ions (Grienberger and Konnerth, 2012). Fluorescent calcium indicators are particularly attractive because of the extremely high calcium concentration gradient between extracellular and intracellular space that guarantees a large fluorescence change with high signal-to-background ratio each time an action potential elicits a brief calcium influx. Following the development of 2-photon-microscopy around 1990 (Denk et al., 1990) these sophisticated small molecule indicators enabled high-resolution calcium imaging of neurons in the intact brain (Svoboda et al., 1997). The key advantage of 2-photon microscopy is that it is relatively insensitive to light scattering and therefore allows imaging several hundred microns deep in tissue (Helmchen and Denk, 2005). Staining procedures with these synthetic indicators remained challenging, however, and repeated measurements over several days or longer time periods were nearly impossible.

Shortly after of the cloning and widespread distribution of the green fluorescent protein (GFP) (Tsien, 1998) several groups started to develop activity indicators based on GFP variants. The first genetically-encoded calcium indicator «Cameleon» was reported in 1997 (Miyawaki et al., 1997). It is built from two fluorescent proteins (FPs), linked via a calcium-binding protein domain (calmodulin). Binding of calcium to calmodulin triggers a conformational rearrangement that alters the distance and the orientation of the FPs, which in turn leads to an optically detectable

change of the «Förster resonance energy transfer» (FRET) between the FPs (Figure 1). FRET-based calcium indicators have been varied and improved ever since (Mank et al., 2008a; Horikawa et al., 2010). They form

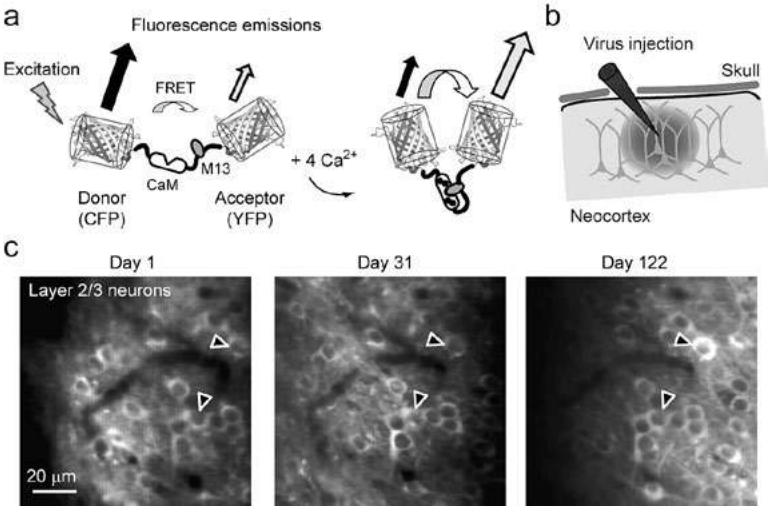

Figure 1: *Expression of genetically encoded calcium indicator in neuronal populations of the mouse neocortex.* ***a:*** *One important class of indicators is based on a distance-dependent energy transfer (so called «Förster resonance energy transfer», FRET) between two coupled fluorescent proteins (here cyan fluorescent protein, CFP, and yellow fluorescent protein, YFP). Binding of calcium ions to the linker-protein calmodulin (CaM) causes interaction with the CaM-binding protein M13, inducing a conformational change that brings the fluorescent proteins closer together. As a consequence, energy transfer from the donor to the acceptor protein increases and the ratio of the fluorescence emission signals at two respective wavelengths changes, indicating calcium influx.* ***b:*** *Virus-mediated expression of genetically encoded calcium indicators. Virus-containing solution (some ten to hundreds nanoliter) are injected into the mouse neocortex through a thin glass pipette. Typically, adeno-associated viruses (AAV) are used, which lead to sufficient expression levels within 2–3 weeks.* ***c:*** *Two-photon microscopic images of neurons in neocortical layer 2/3 of the mouse brain, taken through a chronic cranial glass window at different time points. The exact same neurons were observed in repeated experiments in anesthetized animals over several months (two examples cells marked). Neurons expressed the calcium indicator YC3.60. Modified from Margolis et al., 2012.*

one important class of protein sensors today. Another class consists of single fluorescent proteins with a built-in calcium-binding domain, so that their fluorescence intensity is modulated depending on the intracel-

lular calcium concentration. The most important members of this group are the so-called GCaMP-proteins, of which a large palette is now available (Nagai et al., 2004; Ohkura et al., 2012; Chen et al., 2013b). The most important features of genetically encoded calcium indicators are their calcium-binding affinity (with typical dissociation constants in the nanomolar range), the dynamic range of attainable fluorescence changes, and their kinetic properties that influence the time course of fluorescence change following calcium influx. For more details, I refer to recent reviews (Grienberger and Konnerth, 2012; Knöpfel, 2012).

Unlike classic small-molecule calcium indicators, genetically encoded indicators can be expressed in neurons by various genetic means. The respective genes can be introduced into the organism either by direct gene transfer (e.g. by in utero electroporation in mice), by creating transgenic animals or by using viral vectors. For viral delivery, adeno-associated viruses (AAV) have found widespread application (Dombeck et al., 2007; Lutcke et al., 2010). Appropriate promoters permit neuron-specific expression of indicator genes and selected neuronal subtypes can be targeted using conditional expression methods. Protein concentrations typically increase during the first weeks after virus injection, ideally reaching an expression level that remains stable over several months (Figure 1). As nuclei usually are devoid of indicator protein, cells appear as fluorescent circles in the microscope images. In fact, nuclear fluorescence should remain low as it is an indication of beginning impairment of cell physiology and possibly toxicity, shortening the time window for the experiment.

A critical parameter of genetically encoded calcium indicators is their sensitivity to action-potential evoked calcium signals. Ideally, they should be sensitive enough to report single action potentials in vivo and display little saturation during bursts of action potentials. The sensitivity can be tested in calibration experiments by simultaneous electrical recordings from individual test neurons (Kerr et al., 2005; Grewe et al., 2010; Chen et al., 2013b). Meanwhile, the newest generation of genetically-encoded calcium indicators has reached a sensitivity that is comparable to the best synthetic indicators (Chen et al., 2013b) (Chen et al., 2013a). The combination of high sensitivity and long-term expression makes genetically

encoded calcium indicator the tool of choice for observing and studying neuronal activity patterns in local circuits under various conditions.

Long-term calcium imaging of the same neurons

Repeated monitoring of the activity of individual neurons in local microcircuits over long time periods (weeks to month) is now possible with 2-photon-microscopy. In this approach, often termed «chronic imaging», a small piece of the skull is surgically removed and replaced by a permanent glass window (Holtmaat et al., 2009). The virus injection can also be made during this procedure. Additionally, a small head-post is usually secured to the skull, to enable fixation of the animal's head under the 2-photon microscope (Lütcke et al., 2010). Typically, water-immersion objectives with 16x- to 40x-magnification and a high numerical aperture are used, allowing simultaneous imaging of ten to hundreds of cells within 100-500 µm field-of view. The vasculature system provides ideal landmarks for repeatedly finding the same cells during chronic experiments with the same animal.

Long-term chronic imaging was first used to study morphological changes in vivo, for example changes of synaptic structures following plasticity protocols (Grutzendler et al., 2002; Trachtenberg et al., 2002). Genetically encoded calcium indicators now in addition enable long-term tracking of functional properties of neurons. Of special interest are the study of stability and plasticity of responses to sensory stimuli (such as visual or tactile stimuli) as well as the correlation of cellular activity with processing of sensory stimuli or with movement patterns during behavior.

In a first chronic 2-photon imaging study using a genetically encoded calcium indicator, the same neurons in mouse visual cortex neurons were imaged repeatedly during anesthesia (Mank et al., 2008b). Orientation turning of the same neurons was found to remain stable over the entire experiment period (2–3 weeks), showing for the first time directly that fundamental properties of receptive fields of cortical neurons remain stable over longer time periods. In our own study, we measured neuronal responses in the primary somatosensory cortex (S1) of mouse – in the area corresponding to the facial whiskers, the so-called «barrel cortex»

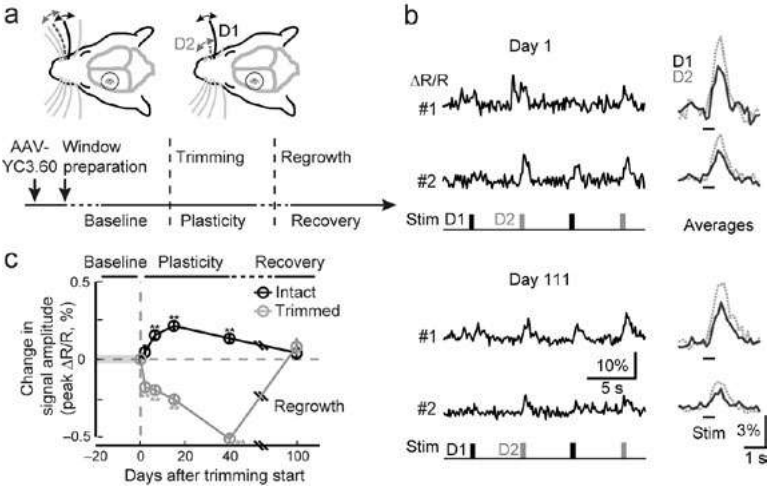

Figure 2: *Chronic imaging of sensory-evoked neuronal activity and reorganization of neuronal activity following sensory deprivation.* ***a:*** *Experimental protocol for studying plasticity of neuronal network activity induced by unilateral trimming of all but one whisker in primary somatosensory cortex of the mouse using YC3.60.* ***b:*** *Example calcium transients of two cortical neurons (those indicated in Fig. 1), evoked by mechanical deflection of the D1 and D2 whisker, respectively (left, raw signals; right, averaged traces). The same cells were measured before, during, and after whisker trimming. Calcium signals shown were measured on day 1 (top) and day 111 (bottom).* ***c:*** *Changes in signal amplitude (mean of all neurons) for the spared (non-trimmed) and the neighboring trimmed whisker over the entire time course of the experiment. Modified from Margolis et al., 2012.*

(Petersen, 2007) – and used tactile stimulation by mechanically moving the whiskers (Margolis et al., 2012). In these experiments, we applied the FRET-indicator Yellow Cameleon 3.60 (YC3.60). Through an implanted cranial window, sensory-evoked activities of S1 neurons in cortical layer 2/3 were repeatedly measured under anesthesia, first during a baseline period with all whiskers intact, then after all whiskers except for one were trimmed (and re-trimmed over a few weeks), and finally following regrowth of the whiskers (Figure 2). During baseline, activity levels in the neuronal population were quite heterogeneous but the activity distribution across the population remained stable over time (Figure 2). Following trimming, we compared stimulus-evoked calcium signals for the trimmed whiskers and the non-trimmed (spared) whisker. Whisker trimming is a

classical, so-called deprivation protocol that reduces sensory input and thereby induces plastic changes in the brain, especially in the affected neocortical regions. The responses of S1 neurons to stimulation of the spared whisker versus the neighboring trimmed whiskers were monitored for several weeks, which was the first time individual neurons could be followed over long time after induction of plasticity. The results showed that responses evoked by stimulation of the trimmed whisker were generally reduced, whereas stimulation of the spared whisker on average evoked stronger responses, indicating an enhanced representation of this whisker in the cortex (Figure 2). However, changes in responsiveness for the spared whisker were not homogenous across the cell population. While initially low-responsive cells became more active, the activity of formerly high-responders tended to decrease. Further analysis of such redistribution of neuronal population activity, e.g., following changes in sensory inputs or in mouse models of brain diseases like Alzheimer's disease or stroke, may help to reveal principles of functional reorganization of neuronal networks during adaptation and regeneration (Lütcke et al., 2013a; Margolis et al., 2014).

Activity of neocortical projection pathways during behavior

Activity patterns in neuronal networks eventually need to be interpreted within a relevant behavioral context. For experiments in awake, behaving animals, genetically encoded calcium indicators are especially beneficial, not least because they enable repeated calcium-imaging experiments to be performed following the time-consuming habituation of an animal to the experimental setup and the behavioral task training. A prime experimental approach is to habituate mice to tolerate head restraining by fixation of the head with the implanted head-post so that stable imaging can be performed with a 2-photon microscope. The animal can either sit snuggly in a card board tube or can even run on a treadmill, constructed for example from an air-supported free-floating Styrofoam ball (Dombeck et al., 2007). In this setting, the animal can be trained to perform in various sensory detection or discrimination tasks as well as to engage in locomotion behavior. From our and others experience, calcium imaging of individual neurons is still possible even when the animal is running fast on a treadmill, albeit clearly motion artifacts sometimes need to be corrected for.

In our own work, we have established a texture discrimination task, in which the mouse has to discriminate with its whiskers the perceived coarseness of sandpaper panels presented to its whiskers in the dark (Chen et al., 2013a). Using a classic «go/nogo» paradigm, the mouse has to learn to report the detection of a target texture (e.g. the roughest sandpaper) by licking at a water spout, from which it receives a water drop as reward (Figure 3). Mice are motivated to perform this task by keeping them thirsty before they enter the experimental session and they can learn this task within a few days to a week. We first aimed to study in well-trained, expert mice the relationship between neuronal activity in layer 2/3 of S1 cortex and the whisker touches of the sandpaper textures. We were particularly interested in disentangling different subpopulations within layer 2/3, since this area is known to give rise to very different long-range projections, in particular to the secondary somatosensory area (S2) and the primary motor cortex area (M1) (Aronoff et al., 2010). We therefore used retrograde tracing techniques to label S2-projecting and M1-projecting neurons in S1, respectively, which turn out to represent fairly separate, non-overlapping, but spatially mingled neuronal pools (Figure 3).

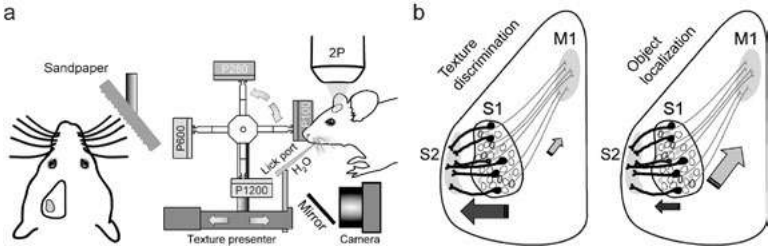

Figure 3: *Calcium imaging of in defined neocortical populations in awake, behaving mice.* ***a:*** *Setup for two-photon (2P) imaging of S1 layer 2/3 neurons in head-fixed mice performing in a texture discrimination task, in which they had to judge the roughness of sandpapers presented to their facial whiskers. Mice were trained to lick when presented with a target texture (the coarse sandpaper, P100), receiving a water reward for correct «hit» trials) and to withhold licking when presented with one of three non-rewarded, «non-target» textures of increasingly smoother grades (P280, P600, P1200; «correct rejections»). Misses on go trials were not rewarded, and false alarms on no-go trials were punished with a time-out period.* ***b:*** *We discriminated neuronal pools in S1 with different projection targets (either S2 or M1) using retrograde staining techniques. Our results demonstrated that the S1-to-S2 projections were prominently involved in the texture discrimination task, whereas S1-to-M1 projection neurons were better in a different, object localization task. Thus, signal flow across neocortical regions is dependent on the specific learned behavior. Modified from Chen et al., 2013a.*

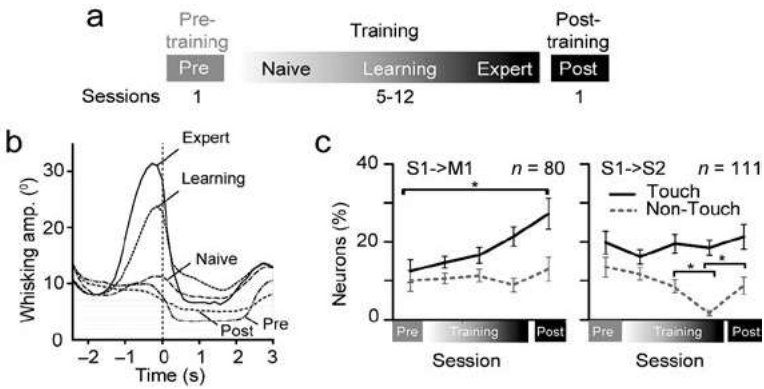

Figure 4: *Learning-related changes in behavior and neuronal activity.* ***a:*** *Experimental time course for chronic imaging during learning of the texture discrimination task. As control layer 2/3 neuronal activity was measured before and after training with passive texture presentations («Pre» and «Post»). The training period was divided into «Naïve», «Learning», and «Expert» phases according to the animal's performance.* ***b:*** *Time course of whisking amplitude aligned to first touch across different training periods. Mice developed a characteristic anticipatory whisking during training. c: Distribution of active neurons across sessions for M1- and S2-projecting neurons (n=7 mice). The number of touch-related S1-to-M1 projecting neurons increased during learning. Although the mean fraction of S1-to-S2 projecting neurons remained constant, further experiments analysis showed that this pool underwent large reorganization. Moreover, neurons that displayed activity not related to touch were suppressed specifically in expert sessions. Modified from Chen et al., 2015.*

Using 2-photon calcium imaging in S1 while the mouse performed the task, we found that S1-to-S2 neurons are particularly involved in the texture discrimination task, displaying a high fraction of neurons that are activated during touch and possess higher discrimination power compared to S1-to-M1 neurons (Chen et al., 2013a). Notably, a different picture emerged when mice were trained in a different task, where they had to judge the localization (rather than the textural quality) of an object with their whiskers. Here, S1-to-M1 neurons apparently were more prominently involved and encoded object location to a comparably higher degree, in line with other studies (Huber et al., 2012) (Xu et al., 2012). We concluded from this study that the information flow between cortical regions, the strength and content conveyed along distinct cortico-cortical pathways, depends on the particular behavior (Figure 3), presumably adjusting according to the computational needs to solve the task.

Learning-related changes in neuronal pathway activity

The findings described in the previous section indicate that neuronal network activity largely depends on the environmental situation and the behavioral circumstances. This means that neocortical signal flow will need to adjust when an animal encounters a new situation, when it learns how to solve a new problem, in order to adequately process sensory information. Chronic 2-photon calcium imaging is perfectly suited to study such modifications in neural circuit dynamics that are associated with learning. In a follow-up study we therefore investigated how the activity patterns in the two distinct S1-to-S2 and S1-to-M1 pathways adapt during learning of the texture discrimination task (Chen et al., 2015). First of all, we found that mice typically develop a behavioral strategy that apparently helps them to solve the task: over time they showed increased «active whisking» (back-and-forth movements of whiskers) in anticipation of the arriving sandpaper panel (auditory cues indicated the arrival time) (Figure 4). We could show that this active whisking strategy enhances texture-related whisker bending features and thereby improves performance in the task.

When comparing the activity of identified S1-to-S2 and S1-to-M1 projection neurons in S1, we found different alterations during the learning phase (Chen et al., 2015). We observed an increase in the mean fraction of touch-related active M1-projecting neurons (Figure 4), as a result of recruitment of further neurons. This result indicates a robust representation of touch events in the S1-to-M1 neuronal pool and a strengthening of transmission of this sensory representation to frontal motor areas. In contrast, the mean fraction of S2-projecting neurons remained constant but a more detailed analysis of the distribution of active neurons revealed that a larger reorganization happened in this S1-to-S2 pool, with some neurons becoming silent and others being newly recruited (Figure 4). In addition, the ability to discriminate between the behaviorally relevant trial types («Hit» for the target texture, «Correct reject» for the non-target texture) increased during the learning phase particularly strongly in neurons of the S1-to-S2 pool. Moreover, in this pool we observed a suppression of non-touch related active neurons only when mice were engaged in performing the task (Figure 4). In conclusion, we propose that these changes in neu-

ronal pathway activity relate to procedural learning, in which a percept becomes linked to an action (here licking). The modifications in S1 presumably serve to both route specific information to downstream areas and refine sensory representations in specific pathways that are relevant for executing behavior. Apart from elucidating signal processing in the sensory cortex, these experiments highlight the most significant potential of genetically encoded calcium indicators, namely the possibility to reveal changes in neuronal dynamics over long time periods during learning.

Conclusions and outlook

The development of genetically encoded calcium indicators and their combination with 2-photon microscopy have opened many new possibilities to study neuronal network activity, especially under behaviorally relevant conditions when the examined networks are in action. These new experimental opportunities may provide fundamental insights into the operation of local microcircuits and they can also help to bridge the levels of single-cell integration and of macroscopic network activity in connected brain regions. Further development of protein-based indicators is currently ongoing and additional improved indicators, not only for calcium but also for membrane potential can be expected soon. Besides virus injections, other means of inducing calcium indicator expression are emerging. For example, new transgenic mouse lines have been generated, which allow to induce expression of the best available genetically encoded calcium indicator, if needed only during adulthood and in a cell-type specific manner (Madisen et al., 2015). In addition to discriminating distinct pools of neurons with different projection patterns, as in our studies, further dissection of the different neuronal subtypes is an important goal. In this respect, functional characterization of the diverse subtypes of inhibitory interneurons, which presumably are highly relevant for local signal processing, is of particular importance (Kepecs and Fishell, 2014). Finally, calcium indicators are also suitable for studying the activity of non-neuronal cells, e.g., astrocytes and microglial cells, for which it is still poorly understood how they interact with their neighboring neurons.

Imaging methods also experience continual further development. One major goal is to improve the temporal resolution of fluorescence mea-

surements, in order to infer action potential patterns in neuronal network with even higher temporal precision (Grewe et al., 2010; Lütcke et al., 2013b). Minimization or compensation of motion artifacts, especially in awake, behaving animals, will be crucial to achieve this goal. Moreover, imaging of ever-larger neuronal populations (and at greater imaging depths) is desirable to obtain an as-complete-as-possible view of neuronal network dynamics. Currently, the modest state of research allows functional imaging of a few hundred neurons, which is obviously a tiny fraction of the total number of neurons presumably involved in a particular behavior (in one cubic millimeter there are on the order of 100 000 neurons). Within the next few years, it seems feasible to achieve in vivo imaging of several thousand cells, albeit probably at relatively low acquisition rates. Such experiments should give us further insights into the principle features of network activity patterns. Furthermore, recently developed methods for visualizing deeper brain structures with miniaturized endoscopic optics, even in freely behaving animals, will be further optimized.

Finally, in future studies we plan to move beyond purely descriptive studies in order to attain a deeper understanding of neuronal circuit function. New anatomical methods promise to reveal further and further structural details of the connectivity in neuronal networks (Denk et al., 2012; Oh et al., 2014), which should allow us to correlate structural aspects of neuronal wiring with functional microcircuit operation. Combining functional imaging with novel optogenetic (Fenno et al., 2011) or chemogenetic (Sternson and Roth, 2014) methods that allow for specific manipulations such as activating or silencing a particular neuronal pathway using light or specially-designed drugs, should help to move beyond a purely correlative description and elucidate causal relations between network activity and behavior.

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REFERENCES

Aronoff R, Matyas F, Mateo C, Ciron C, Schneider B, Petersen CC (2010) Long-range connectivity of mouse primary somatosensory barrel cortex. *Eur J Neurosci* **31**:2221–2233.

Chen JL, Carta S, Soldado-Magraner J, Schneider BL, Helmchen F (2013a) Behaviour-dependent recruitment of long-range projection neurons in somatosensory cortex. *Nature* **499**:336–340.

Chen JL, Margolis DJ, Stankov A, Sumanovski LT, Schneider BL, Helmchen F (2015) Pathway-specific reorganization of projection neurons in somatosensory cortex during learning. *Nature Neuroscience* **18**:1101–1108.

Chen TW, Wardill TJ, Sun Y, Pulver SR, Renninger SL, Baohan A, Schreiter ER, Kerr RA, Orger MB, Jayaraman V, Looger LL, Svoboda K, Kim DS (2013b) Ultrasensitive fluorescent proteins for imaging neuronal activity. *Nature* **499**:295–300.

Denk W, Briggman KL, Helmstaedter M (2012) Structural neurobiology: missing link to a mechanistic understanding of neural computation. *Nature Reviews Neuroscience* **13**:351–358.

Denk W, Strickler JH, Webb WW (1990) Two-photon laser scanning fluorescence microscopy. *Science* **248**:73–76.

Dombeck DA, Khabbaz AN, Collman F, Adelman TL, Tank DW (2007) Imaging large-scale neural activity with cellular resolution in awake, mobile mice. *Neuron* **56**:43–57.

Fenno L, Yizhar O, Deisseroth K (2011) The development and application of optogenetics. *Annual Review of Neuroscience* **34**:389–412.

Grewe BF, Langer D, Kasper H, Kampa BM, Helmchen F (2010) High-speed in vivo calcium imaging reveals neuronal network activity with near-millisecond precision. *Nature Methods* **7**:399–405.

Grienberger C, Konnerth A (2012) Imaging calcium in neurons. *Neuron* **73**:862–885.

Grutzendler J, Kasthuri N, Gan WB (2002) Long-term dendritic spine stability in the adult cortex. *Nature* **420**:812–816.

Harris KD, Mrsic-Flogel TD (2013) Cortical connectivity and sensory coding. *Nature* **503**:51–58.

Helmchen F, Denk W (2005) Deep tissue two-photon microscopy. *Nature Methods* **2**:932–940.

Holtmaat A, Bonhoeffer T, Chow DK, Chuckowree J, De Paola V, Hofer SB, Hubener M, Keck T, Knott G, Lee WC, Mostany R, Mrsic-Flogel TD, Nedivi E, Portera-Cailliau C, Svoboda K, Trachtenberg JT, Wilbrecht L (2009) Long-term, high-resolution imaging in the mouse neocortex through a chronic cranial window. *Nature Protocols* **4**:1128–1144.

Horikawa K, Yamada Y, Matsuda T, Kobayashi K, Hashimoto M, Matsu-ura T, Miyawaki A, Michikawa T, Mikoshiba K, Nagai T (2010) Spontaneous network activity visualized by ultrasensitive Ca^{2+} indicators, yellow Cameleon-Nano. *Nature Methods* **7**:729–732.

Huber D, Gutnisky DA, Peron S, O'Connor DH, Wiegert JS, Tian L, Oertner TG, Looger LL, Svoboda K (2012) Multiple dynamic representations in the motor cortex during sensorimotor learning. *Nature* **484**:473–478.

Kepecs A, Fishell G (2014) Interneuron cell types are fit to function. *Nature* **505**:318–326.

Kerr JND, Greenberg D, Helmchen F (2005) Imaging input and output of neocortical networks in vivo. *Proc Natl Acad Sci USA* **102**:14063–14068.

Knöpfel T (2012) Genetically encoded optical indicators for the analysis of neuronal circuits. *Nature Reviews Neuroscience* **13**:687–700.

Lütcke H, Gerhard F, Zenke F, Gerstner W, Helmchen F (2013b) Inference of neuronal network spike dynamics and topology from calcium imaging data. *Frontiers in Neural Circuits* **7**:201.

Lütcke H, Margolis DJ, Helmchen F (2013a) Steady or changing? Long-term monitoring of neuronal population activity. *Trends in Neurosciences* **36**:375–384.

Lütcke H, Murayama M, Hahn T, Margolis DJ, Astori S, Zum Alten Borgloh SM, Gobel W, Yang Y, Tang W, Kugler S, Sprengel R, Nagai T, Miyawaki A, Larkum ME, Helmchen F, Hasan MT (2010) Optical recording of neuronal activity with a genetically-encoded calcium indicator in anesthetized and freely moving mice. *Frontiers in Neural Circuits* **4**:9.

Madisen L et al. (2015) Transgenic mice for intersectional targeting of neural sensors and effectors with high specificity and performance. *Neuron* **85**:942–958.

Mank M, Santos AF, Direnberger S, Mrsic-Flogel TD, Hofer SB, Stein V, Hendel T, Reiff DF, Levelt C, Borst A, Bonhoeffer T, Hubener M, Griesbeck O (2008) A genetically encoded calcium indicator for chronic in vivo two-photon imaging. *Nature Methods* **5**:805–811.

Margolis DJ, Lütcke H, Helmchen F (2014) Microcircuit dynamics of map plasticity in barrel cortex. *Current Opinion in Neurobiology* **24**:76–81.

Margolis DJ, Lütcke H, Schulz K, Haiss F, Weber B, Kügler S, Hasan MT, Helmchen F (2012) Reorganization of cortical population activity imaged throughout long-term sensory deprivation. *Nature Neuroscience* **15**:1539–1546.

Miyawaki A, Llopis J, Heim R, McCaffery JM, Adams JA, Ikura M, Tsien RY (1997) Fluorescent indicators for Ca^{2+} based on green fluorescent proteins and calmodulin. *Nature* **388**:882–887.

Nagai T, Yamada S, Tominaga T, Ichikawa M, Miyawaki A (2004) Expanded dynamic range of fluorescent indicators for Ca^{2+} by circularly permuted yellow fluorescent proteins. *Proc Natl Acad Sci USA* **101**:10554–10559.

Oh SW et al. (2014) A mesoscale connectome of the mouse brain. *Nature* **508**:207.

Ohkura M, Sasaki T, Sadakari J, Gengyo-Ando K, Kagawa-Nagamura Y, Kobayashi C, Ikegaya Y, Nakai J (2012) Genetically encoded green fluorescent Ca^{2+} indicators with improved detectability for neuronal Ca^{2+} signals. *PLoS One* **7**:e51286.

Petersen CC (2007) The functional organization of the barrel cortex. *Neuron* **56**:339–355.

Sternson SM, Roth BL (2014) Chemogenetic tools to interrogate brain functions. *Annual Review of Neuroscience* **37**:387–407.

Svoboda K, Denk W, Kleinfeld D, Tank DW (1997) In vivo dendritic calcium dynamics in neocortical pyramidal neurons. *Nature* **385**:161–165.

Trachtenberg JT, Chen BE, Knott GW, Feng G, Sanes JR, Welker E, Svoboda K (2002) Long-term in vivo imaging of experience-dependent synaptic plasticity in adult cortex. *Nature* **420**:788–794.

Tsien RY (1998) The green fluorescent protein. *Annual Review in Biochemistry* **67**:509–544.

Xu NL, Harnett MT, Williams SR, Huber D, O'Connor DH, Svoboda K, Magee JC (2012) Nonlinear dendritic integration of sensory and motor input during an active sensing task. *Nature* **492**:247–251.

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