BIOGRAPHICAL SKETCH

NAME: Marc-Jan Gubbels

POSITION TITLE: Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
Agricultural University Wageningen, The Netherlands	BS	08/1991	Molecular Sciences
Agricultural University Wageningen, The Netherlands	MS	08/1994	Molecular Sciences
University of Utrecht, The Netherlands	PhD	06/2000	Parasitology
University of Georgia, USA	Post-doc	08/2005	Parasitology, Cell Biology

Positions and Honors

Positions

1995 – 1996 Community Service, Utrecht University (The Netherlands), Lab. for Physiological Chemistry.
2000 Post-Doc University Utrecht (the Netherlands) and Co-organizer of a laboratory workshop at the University of Pretoria, (South Africa). With Drs. Frans Jongejan and Albert W.C.A. Cornelissen.
2001 - 2005 Post-Doc/Assistant Research Scientist at the Center for Tropical and Emerging Global Diseases, University of Georgia (USA). With Dr. Boris Striepen
2005 - 2011 Assistant Professor at the Department of Biology, Boston College (USA)
2011 - 2012 Sabbatical: Visiting Scientist at the Max Planck Institute for Infection Biology, Berlin, Germany (Humboldt fellowship; host: Dr. Kai Matuschewski).
2011 - 2015 Associate Professor at the Department of Biology, Boston College (USA)
2015 - date Professor at the Department of Biology, Boston College (USA)

Professional Activities

Journal reviewer

PLoS Pathogens, Cytoskeleton, PLoS Biology, Journal of Biological Chemistry, International Journal for Parasitology, Cellular Microbiology, Molecular Microbiology, Microscopy and Microanalysis, BMC Veterinary Research, Applied Microbiology and Biotechnology, Trends in Parasitology, Molecular and Biochemical Parasitology, Infection and Immunity, Traffic, FASEB J

Grant reviewer

NIH Special Emphasis Panels ZRG1 IDM-M (02) M, PAR-14-080, ZGM1 RCB-7 (SC), ZRG1 IDM-P (02) M K-awards-MID-B, ZRG1 IDM-P (02), ZRG1 AARR-K(04), ZRG1 IDM-M (03), ZRG1 IDM-B (03), ZRG1 AARR-E (02), ZRG1 AARR-K (02) ZRG1 IDM-M (03) M, the American Heart Association (Microbiology section), National Science Foundation (Molecular and Cell Biology section), Wellcome Trust (UK), Canada Foundation for Innovation, and the European Research Council (EU).

Editorial boards

2010 - 2018 Editorial Board member on the journal Infection and Immunity
2010 - 2015 Editorial Board member on the journal Experimental Parasitology
2014 - 2016 Editorial Board member on the journal Eukaryotic Cell
2014 - 2017 Reviews Editor for the journal PLoS Pathogens

Other professional Service

2009 - 2011 Advisory committee member for the *Toxoplasma gondii* genome website portal, ToxoDB.org
2010 - 2012 Vice President, New England Association for Parasitologists (NEAP)
2013 - 2015 President, New England Association for Parasitologists (NEAP)
2013 - 2014 Chair-Elect of Division AA (free-living, symbiotic, and parasitic protists) of the American Society for Microbiology
2014 - 2015 Chair of Division AA (free-living, symbiotic, and parasitic protists) of the American Society for Microbiology

2017 - Scientific Working Group (SWG) member for the Eukaryotic Pathogen Genomics Resource, EuPathDB.org

Honors and Awards

2002, 2005 Speaker Award at the XIII[th] Molecular Parasitology Meeting, Marine Biology Laboratory, Woods Hole, MA, September 2002 and 2005
2006 New Investigator Award from the Smith Family Foundation
2008 March of Dimes Basil O'Connor Starter Award
2011 American Cancer Society Research Scholar Award
2011 Humboldt Foundation Fellowship Award for Experienced Researchers

Contribution to Science *(in chronological order)*

1. Development of a Reverse Line Blot (RLB) assay to simultaneously diagnose *Theileria* spp. and *Babesia* spp. infection. My PhD research revolved around *Theileria annulata*, a tick-borne apicomplexan parasite causing tropical theileriosis in cattle and spanned a variety of aspects [1-4]. By way of background, besides *T. annulata* several other benign and pathogenic tick-transmitted *Theileria* and *Babesia* spp. infect cattle, causing a lot of confusion. I generated a RLB assay to simultaneously diagnose and identify these apicomplexan parasites [1]. A variable region of the 18S rRNA gene was amplified using conserved primers and subsequently hybridized perpendicular on a blot with species-specific probes with a line blotter (**Fig A**). This sensitive and versatile assay revealed many missed- and mis-diagnosis made in the past. RLB has since been widely applied in the field to a wide variety of studies, (e.g. goat & sheep [4], dogs and to measure parasitemia). After my PhD I co-organized a RLB workshop in South Africa to train a group of African researchers, a course that continued in later years under the EMBO banner. The number of citations of the original publication [1] is still sharply rising, underscoring its high impact.

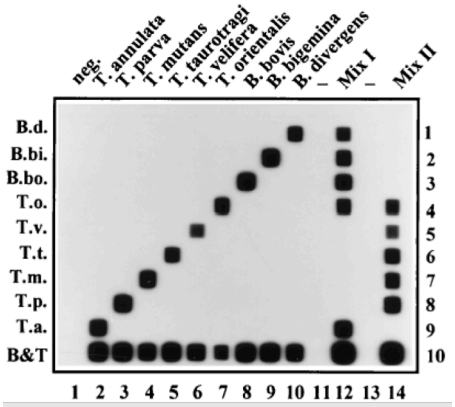

Fig A. RLB assay on 18S rRNA gene of *Theileria* spp. and *Babesia* spp. Probes horizontal; PCR products vertical. From Gubbels *et al* 1999 *J. Clin. Microbiol.*

1. **Gubbels, J.M.,** A.P. de Vos, M. van der Weide, J. Viseras, E. de Vries, L.M. Schouls and F. Jongejan. 1999. Simultaneous detection of bovine *Theileria* and *Babesia* species using reverse line blot hybridization. *J. Clin. Microbiol*. 37: 1782-1789.
2. **Gubbels, M.-J.,** H. Yin, M. van der Weide, Q. Bai, I.J. Nijman, G. Liu and F. Jongejan. 2000. Molecular and biological characterization of the *Theileria buffeli/orientalis* group. *Int. J. Parasitol.* 30: 943-952.
3. **Gubbels, M.-J.,** F. Katzer, B.R. Shiels and F. Jongejan. 2001. Study of *Theileria annulata* population structure during bovine infection and following transmission to ticks. *Parasitology* 123: 553-561.
4. Schnittger, L.,H. Yin, B. Qi, **M.-J. Gubbels,** D. Beyer, S. Niemann, F. Jongejan and J. S. Ahmed. 2004. Simultaneous detection and differentiation of *Theileria* and *Babesia* parasites infecting small ruminants by reverse line blotting. *Parastiol. Res.* 92: 189-196.

2. Development of forward genetics for *Toxoplasma gondii.* Over 50% of the predicted genes in *Toxoplasma* have no homology with any gene outside the Apicomplexa. Especially processes unique to the parasite are expected to employ unique genes, which will be hard to discover by comparative biology. To identify genes based on their function rather than on their identity, the goal of my post-doc in Boris Striepen's lab was to develop forward genetics for *Toxoplasma*. Although chemical mutagenesis had been established in the 1970s, identifying the mutated gene was impossible by classical genetic crosses (cat infections are unproductive with *in vitro* adapted strains). To overcome this challenge we developed different genetic complementation approaches using cDNA and genomic DNA libraries. High efficiency genomic complementation was achieved with a cosmid library with 35+ kb inserts [1]. Hence, this approach was a major breakthrough and identified the causative mutations and genes in >2 dozen growth mutants [1]. Furthermore I pioneered whole-genome re-sequencing by Illumina short reads in collaboration with the bioinformatics expertise of Dr. Gabor Marth [2]. Raising the impact of this breakthrough was the novelty of the causative gene in this invasion/egress mutant, underscoring the power of forward genetics. Lately we have evaluated and optimized chemical mutagenesis protocols and analyzed the nature of the DNA damage [3]. Finally, our forward genetic tools have been successfully adopted by other labs applied to other questions (e.g. [4]).

1. **Gubbels, M.-J.,** C.F. Brooks, M. Muthalagi, T. Szatanek, J. Flynn, B. Parrot, B. Striepen and M.W. White. 2008. Forward Genetic Analysis of the Apicomplexan cell and division cycle in *Toxoplasma gondii*. *PLoS Pathogens*. 4(2): e36 (0001-0015). *(Editor's Pick).* PMC2242837
2. Farrell, A. S. Thirugnanam, A. Lorestani, J.D. Dvorin, K.P. Eidell, B.R. Anderson-White, D.J.P. Ferguson, Duraisingh, G.T. Marth, and **M.-J. Gubbels.** 2012. A DOC2 protein identified by mutational profiling is essential for apicomplexan parasite exocytosis. *Science*. 335:218-221. (*Editor's choice).* PMC3354045
3. Brown, K.M., E. Suvorova, **A. Farrell,** A. McLain, A. Dittmar, G.B. Wiley, G.T. Marth, P.M. Gaffney, **M.-J. Gubbels,** M. White, and I.J. Blader. 2014. Forward genetic screening identifies a small molecule that blocks *Toxoplasma* growth by inhibiting both host- and parasite-encoded kinases. *PLoS Path.* 10(6): e1004180. PMC4055737
4. Farrell, A., B.I. Coleman, B. Benenati, K.M. Brown, I. Blader, G.T. Marth, and **M.-J. Gubbels.** 2014. Whole genome profiling of spontaneous and chemical mutagenesis induced mutations in *Toxoplasma gondii*. *BMC Genomics.* 15: 354. PMC4035079

3. Dissection of *Toxoplasma gondii* cell division by endodyogeny. In humans *Toxoplasma* divides asexually through endodyogeny, wherein two daughter cells bud inside a mother (**Fig B**). We study this unique process to identify new drug targets. We have demonstrated that the daughter cytoskeletons initiate around the duplicated centrosomes [4] and subsequently elongate to serve as the scaffold for organelle partitioning. Furthermore, we have shown that a family of intermediate filament-like IMC proteins is sequentially assembled in the daughter bud [3]. This work resolved developmental steps at an unprecedented level, which has since been applied in the analysis of division mutants (e.g. [2, 4]). A big open question we are pursuing is how the cytoskeleton tapers toward the end. We have shown that a contractile force assembles on the basal end of the buds [1]. This basal complex is the functional ortholog of the mammalian contractile ring, but its constriction is independent of actin/myosin. In fact, it is our goal to reveal its identity. In addition, we still lack mechanism on how the various steps are controlled and coordinated. To this end my lab has started addressing kinases operating on endodyogeny [4]. Overall, our work has deciphered key events at in daughter budding, which has filled a widely applied toolbox that is being applied to dissect both endodyogeny as well as other apicomplexan division modes such as schizogony in the malaria parasite.

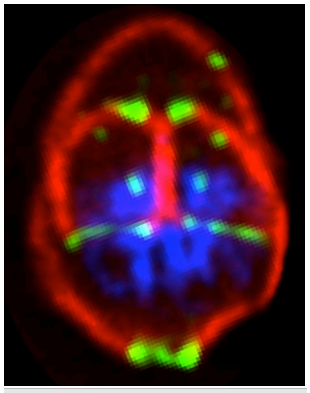

Fig B. Dividing parasite. **IMC1 – MORN1 – DNA.** Gubbels *et al* 2006 *JCS*

1. Anderson-White, B.R., F.D. Ivey, K, K. Cheng, T. Szatanek, A. Lorestani, C.J. Beckers, D.J.P. Ferguson, N. Sahoo, and **M.-J. Gubbels.** 2011. A family of intermediate filament-like proteins is sequentially assembled into the cytoskeletal scaffold of *Toxoplasma gondii*. *Cell. Microbiol.* 13:18-31. PMC3005026
2. Chen, C.-T. and **M.-J. Gubbels.** 2013. The *Toxoplasma gondii* centrosome is the platform for internal daughter budding as revealed by a Nek1 kinase mutant. *J. Cell Sci.* 126:3344-3355. PMC3730244
3. Chen, C.-T., M. Farrell, J. de Leon, B. Nwagbara, P. Ebbert, D.J.P. Ferguson, L.A. Lowery, N. Morrissette*, and **M.-J. Gubbels***. 2015. Compartmentalized *Toxoplasma* EB1 bundles spindle microtubules to secure accurate chromosome segregation. *MBoC.* 26:4562-4576. *co-corresponding author. PMCID: PMC4678015
4. Engelberg, K., F.D. Ivey, A. Lin, M. Kono, A. Lorestani, D. Faugno-Fusci, T.W. Gilberger, M. White, and **M.-J. Gubbels.** 2016. A MORN1-assocatiated HAD phosphatase in the basal complex is essential for *Toxoplasma gondii* daughter budding. *Cell Micro*. 18:1153-1171. PMCID: PMC4961593

4. Dissection of *Toxoplasma gondii* host cell invasion and egress. Invasion and egress are inherently part of the parasitic life style and are essential steps in completing the lytic cycle. Host cell egress and invasion are completely controlled by the parasite and therefore these processes are viable drug targets. Egress and invasion are closely related and rely on shared processes such as secretion of micronemes, activation of actin-myosin based motility and conoid extrusion, all of which are controlled by the release of Ca^{2+} in the cytoplasm. Using our forward genetic mutant system we identified a new protein, TgDOC2, which we demonstrated to control Ca^{2+}-dependent microneme secretion and is essential for egress and invasion [3]. Our collaborator Dr. Manoj Duraisingh at Harvard demonstrated DOC2 functions orthologous in the malaria-causing parasite [3]. In addition, we have used this mutant to design a forward genetic phenotypic screen to isolate more mutants with same phenotype [1]. Furthermore, we published this approach as an instructional video in the Journal of Visualized Experiments (JoVE), which covers a variety of the forward genetic techniques we developed [2]. In the first three years since its publication the corresponding JoVE page has been visited 7887 times, illustrating

its impact. Furthermore, we are following up on the DOC2 gene itself as well as other genes with multiple C2 domains in the genome. This exciting work has started to uncover the inner workings of Ca^{2+}-mediated microneme secretion and turns out to be unconventional in many ways, which highlights novel biology as raises its potential as a specific drug target. Lastly we have started to look into other aspects of control of microneme secretion (e.g. calcineurin [4]). We correlate this work with Dr. Duraisingh in the malaria parasite as the controls are largely conserved across parasites, yet their biological role caters to their specific host cells.

1. Eidell, K., T. Burke, and **M.-J. Gubbels.** 2010. Development of a screen to dissect *Toxoplasma gondii* egress. *Mol. Biochem. Parasitol.* 171:97-103
2. Coleman, B.I., and **M.-J. Gubbels.** 2012. A genetic screen to isolate *Toxoplasma gondii* host cell egress mutants. *J. Vis. Exp.* 60:e3807. PMC3350636
3. Farrell, A. S. Thirugnanam, A. Lorestani, J.D. Dvorin, K.P. Eidell, B.R. Anderson-White, D.J.P. Ferguson, Duraisingh, G.T. Marth, and **M.-J. Gubbels.** 2012. A DOC2 protein identified by mutational profiling is essential for apicomplexan parasite exocytosis. *Science*. 335:218-221. (*Editor's choice).* PMC3354045
4. Paul, A.S., S., Saha, K. Engelberg, R.Y. Jiang, B.I. Coleman, A.L. Kosber, C.-T. Chen, M. Ganter, N. Espy, T.-W. Gilberger, **M.-J. Gubbels*,** and M.T. Duraisingh*. 2015. Apicomplexan calcineurin regulates specific attachment of free parasites to host cells for infection. *Cell Host Microbe.* 18, 1–12. *co-corresponding author. PMC4506782

A complete list of my 60+ peer-reviewed publications can be found in the following link:
http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/40720124/?sort=date&direction=descending

Research support

Ongoing Research Support

R21AI117241 (Gubbels) 04/10/2015 – 03/31/2017* 0.75 Ac / 0.00 Su
National Institutes of Health $ 275,000
Experimental evolution of *Toxoplasma gondii* virulence
The major goals of this project are the lab adaptation of GT1 through specific phenotypic screens representing *in vivo* virulence and identification of epigenetic gene interactions by whole genome and transcriptional profiling
*The project has an approved no-cost extension with an amended end date of 03/31/2018

R01AI110638 (Samuelson; sub-contract Gubbels) 08/01/2015 – 01/31/2020 0.20 Ac / 0.30 Su
National Institutes of Health $ 150,000
Structure and Development of Oocyst and Sporocyst Walls
The major goals of this sub-contract project are the dissection of the meiotic and sporogony development of *Toxoplasma gondii* by developing specfic reagents for these events.

R56AI110690 (Gubbels) 09/01/2015 – 08/31/2016* 0.75 Ac / 0.85 Su
National Institutes of Health $ 317,645
Dissecting the mechanism and regulation of *Toxoplasma* cytokinesis
The major goals of this project are to understand how the kinases and phosphatases organize cell division, and how the basal complex contracts in the cell division process.
*The project has an approved no-cost extension with an amended end date of 08/31/2017

R03AI122042-01 (Gubbels, Weerapana) 02/18/2016 – 01/31/2018 0.10 Ac / 0.00 Su
National Institutes of Health $ 100,000
Proteomic mapping of differential secretion in *Toxoplasma gondii*
The major goals of this project are to use different *Toxoplasma* microneme secretion mutants to map the excreted and secreted antigens of tachyzoites in general, and in particular potential differential secretion of microneme sub-sets

R01AI122923-01 (Gubbels) 06/01/2016 – 05/31/2021 0.75 Ac / 1.85 Su
National Institutes of Health $ 1,250,000

The Ca^{2+}-sensing machinery operating on exocytosis in *Toxoplasma*
The major goals of this project are to understand how the Ferlin proteins operate and control *Toxoplasma* secretion of micronemes and rhoptries.

R21AI128136-01 (Gubbels) 07/01/2017 – 06/30/2019 0.00 Ac / 1.00 Su
National Institutes of Health $ 275,000
Mapping the protein landscape of the *Toxoplasma* basal complex
The major goal of this project is to identify the protein composition of the basal complex.

Recently Completed Research Support (last 3 years)

National Institutes of Health, R03 Research Grant (R03AI107475) – P.I.
"Organization of *Toxoplasma* invasion and cell division by EF-hand proteins"
Runtime: 05/01/2013 – 04/30/2015
Goal: Dissect the repertoire of small, multiple EF-hand containing proteins by determining their sub-cellular localization dynamics through the lytic cycle and generate knock-outs for a limited sub-set

National Institutes of Health, R21 Research Grant (R21AI099658) – P.I.
"The role of the DOC2.1 protein in *Toxoplasma gondii* Ca^{2+}- dependent exocytosis"
Runtime: 08/09/2013 – 07/31/2015
Goal: Assign specific functions to conserved domains and residues and identify the proteins through which DOC2.1 exerts its function

American Cancer Society (ACS), Research Scholar Grant – P.I.
"Genetic dissection of *Toxoplasma gondii* host cell invasion and egress"
Runtime: 07/01/2012 – 06/30/2016
Goal: Identify essential genes in host cell egress and invasion