

## Tropical Medicine at the University of Tübingen

In 1956 the Institute of Tropical Medicine of the University of Tübingen was founded. Created as a small institute in post-war Germany, it has become a leading institution in its field in the German speaking countries and beyond within the last decade. After a long time of local separation of the institute's clinical department and the research laboratories, the institute was recently reunified in one building in the centre of Tübingen.

The institute has the mandate to cover research, clinical duties in treatment and prophylaxis as well as training and education for students and postgraduates in the areas of tropical medicine, human parasitology and travel medicine.

The main and most longstanding collaborations within Europe exist with the Division of Infectious Diseases and Tropical Medicine at the University Clinics in Vienna, the Division of Infectious Diseases at the St. George's Medical School in London and the Department of Parasitology at the University of Leiden. In Africa the main partner is the Albert Schweitzer Hospital in Lambaréné [1] and additionally, the University of Libreville, Gabon [2] and the Regional Hospital in Sokode, Togo [3].

In the following lines I would like to highlight a few scientific achievements of our institute in the last years in the field of malaria research, mainly in interventional studies and parasites and allergy.

Our group developed quinine-clindamycin as an *ad-hoc* combination therapy for *Plasmodium falciparum* malaria [4–6]. It is used today in several European countries as a therapy of choice for inpatient malaria.

The key studies in the clinical development of atovaquone-proguanil for therapy [7, 8] and prophylaxis [9, 10] were performed by our group. By us tafenoquine was first shown to be a very potent chemoprophylaxis against malaria [11]. The development of tafenoquine as a chemoprophylactic drug was temporarily stopped by the company due to safety concerns from preclinical trials, however, the clinical studies with this promising drug have been taken up again.

We also coordinated the phase III WHO sponsored trial for the development of amodiaquine-artesunate, the first artemisinin based antimalarial combination for Africa [12], which became the recommended therapy for malaria in children in most African countries subsequently. We highlighted at the same time the safety issues surrounding malaria therapy with chlorproguanil-dapsone [13, 14].

Fosmidomycin-Clindamycin have been developed clinically, successfully by us throughout from the beginning to the end of phase II clinical trials, where we stand today [15–19].

Our groups in Tübingen and Lambaréné were leading a Bill and Melinda Gates funded consortium together with other academic centres over many years for testing the safety and efficacy of intermittent preventive treatment with sulfadoxine-pyrimethamine in infants against malaria and anaemia [20–22].

Different malaria vaccines are currently tested and we are actively looking into a few of them [23–25].

We have been initiators and co-leaders of the consortium for severe malaria in African children [26], which conducted the biggest trials on severe malaria ever, including more than 26,000 children with severe malaria. There we investigated different prognostic markers for death [27] and finally developed via a simplified organ dysfunction score [28], the very simple and highly predictive Lambaréné organ dysfunction score consisting of prostration, coma and deep breathing [29].

In a study called 1/95C we enrolled 100 children with severe malaria and 100 matched controls with mild malaria and investigated them closely over a period of seven years with two visits monthly [30]. Malaria severity and frequency of malarial attacks in individual cases were analysed in relation to immunological and genetic host and parasitic factors as well as environmental factors.

Among others polymorphisms in the genes of nitric oxide synthase 2 [31, 32], mannose binding lectin [33, 34], NADPH oxidase [35] and in several genes relevant for erythrocytes [36–38] were found to be associated with protection against malaria. In addition, oxygen radical production and interferon gamma production were also shown to be beneficial against malaria [39, 40].

In a series of studies in Gabon we were able to demonstrate the inhibitory influence of parasitic infections on the development of atopic reactions and allergy [41–45] as well as on the immunogenicity of vaccines [46].

This supplement appears for the reunification of our institute. Scientific group leaders present their work in a short report each.

Akim Adegnika is being appointed as one of my codirectors of our research centre in Lambaréné and he is starting a junior group in Tübingen. His research focusses on immunological aspects of parasitic infections [47, 48].

Meral Esen heads a group mainly dealing with clinical vaccine trials [24].

Matthias Frank is continuing our research on var genes of *Plasmodium falciparum* [49–51].

Wolfgang Hoffmann is starting a group looking into immunological and pathological variables of coinfections in animal experiments [52].

Saadou Issifou is my codirector in Lambaréné and leading a series of clinical trials there [53, 54].

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Carsten Köhler is my vice-director caring for project management and heading our Baden-Württemberg centre of competence for tropical medicine.

Andrea Kreidenweiss is currently establishing her own group in our institute [55].

Jürgen Kun, my vice-director is leading a group looking into genetic factors of men and parasites influencing the outcome of infectious diseases [32, 56–58].

Bertrand Lell is my longstanding codirector in Lambaréné and has formed the research centre there, as it is today, a world class unit for clinical and basic research in Central Africa [9, 11, 25, 59].

Benjamin Mordmüller is a group leader successfully conducting research both in Tübingen as well as Lambaréné from basic to clinical research [60, 61].

Francine Ntoumi is leading a group in Tübingen and additionally heading the Multilateral Initiative for Malaria as well as the Central African Network of Tuberculosis, AIDS and Malaria [62, 63].

Peter Soboslay is leading a group in Tübingen and heading the research group in Sokode looking into immunological aspects of worm infections [3, 64].

Philipp Zanger is heading a recently created group mainly looking into staphylococcal infections in travellers and in the tropics [65].

Peter Gottfried Kremsner

### Conflict of interest

The author declares that there is no conflict of interest.

### References

- Ramharter M, Adegnika AA, Agnandji ST, Matsiegui BP, Grobusch MP, Winkler S, et al (2007) History and perspectives of medical research at the Albert Schweitzer Hospital in Lambaréné, Gabon. *Wien Klin Wochenschr* 119[Suppl 3]: 8–12
- Bouyou-Akotet MK, Mawili-Mboumba DP, Kendjo E, Mabika-Mamfoumbi M, Nguongou EB, Dzeing-Ella A, et al (2009) Evidence of decline of malaria in the general hospital of Libreville, Gabon from 2000 to 2008. *Malaria J* 8: 300
- Hamm DM, Agossou A, Gantin RG, Kocherscheidt L, Banla M, Dietz K, et al (2009) Coinfections with *Schistosoma haematobium*, *Necator americanus*, and *Entamoeba histolytica/Entamoeba dispar* in children: chemokine and cytokine responses and changes after antiparasite treatment. *J Infect Dis* 199: 1583–91
- Kremsner PG, Winkler S, Brandts C, Neifer S, Bienzle U, Graninger W (1994) Clindamycin in combination with Chloroquine or Quinine is an effective therapy for uncomplicated *Plasmodium-falciparum* malaria in children from Gabon. *J Infect Dis* 169: 467–70
- Kremsner PG, Radloff P, Metzger W, Wildling E, Mordmüller B, Philipps J, et al (1995) Quinine plus Clindamycin improves chemotherapy of severe malaria in children. *Antimicrob Agents Chemother* 39: 1603–5
- Ramharter M, Oyakhrome S, Klein Klouwenberg P, Adegnika AA, Agnandji ST, Missinou MA, et al (2005) Artesunate-clindamycin versus quinine-clindamycin in the treatment of *Plasmodium falciparum* malaria: a randomized controlled trial. *Clin Infect Dis* 40: 1777–84
- Radloff PD, Philipps J, Nkeyi M, Hutchinson D, Kremsner PG (1996) Atovaquone and proguanil for *Plasmodium falciparum* malaria. *Lancet* 347: 1511–4
- Borrmann S, Faucher JF, Bagaphou T, Missinou MA, Binder RK, Pabisch S, et al (2003) Atovaquone and proguanil versus amodiaquine for the treatment of *Plasmodium falciparum* malaria in African infants and young children. *Clin Infect Dis* 37: 1441–7
- Lell B, Luckner D, Ndjavé M, Scott T, Kremsner PG (1998) Randomised placebo-controlled study of atovaquone plus proguanil for malaria prophylaxis in children. *Lancet* 351: 709–13
- Faucher JF, Binder R, Missinou MA, Matsiegui PB, Gruss H, Neubauer R, et al (2002) Efficacy of atovaquone/proguanil for malaria prophylaxis in children and its effect on the immunogenicity of live oral typhoid and cholera vaccines. *Clin Infect Dis* 35: 1147–54
- Lell B, Faucher JF, Missinou MA, Borrmann S, Dangelmaier O, Horton J, et al (2000) Malaria chemoprophylaxis with tafenoquine: a randomised study. *Lancet* 355: 2041–5
- Adjuik M, Agnamey P, Babiker A, Borrmann S, Brasseur P, Cisse M, et al (2002) Amodiaquine-artesunate versus amodiaquine for uncomplicated *Plasmodium falciparum* malaria in African children: a randomised, multicentre trial. *Lancet* 359: 1365–72
- Allouche A, Bailey W, Barton S, Bwika J, Chimpeni P, Falade CO, et al (2004) Comparison of chlorproguanil-dapsone with sulfadoxine-pyrimethamine for the treatment of uncomplicated falciparum malaria in young African children: double-blind randomised controlled trial. *Lancet* 363: 1843–8
- Kremsner PG, Krishna S (2004) Antimalarial combinations. *Lancet* 364: 285–94
- Missinou MA, Borrmann S, Schindler A, Issifou S, Adegnika AA, Matsiegui PB, et al (2002) Fosmidomycin for malaria. *Lancet* 360: 1941–2
- Borrmann S, Adegnika AA, Matsiegui PB, Issifou S, Schindler A, Mawili-Mboumba DP, et al (2004) Fosmidomycin-clindamycin for *Plasmodium falciparum* infections in African children. *J Infect Dis* 189: 901–8
- Borrmann S, Issifou S, Esser G, Adegnika AA, Ramharter M, Matsiegui PB, et al (2004) Fosmidomycin-clindamycin for the treatment of *Plasmodium falciparum* malaria. *J Infect Dis* 190: 1534–40
- Borrmann S, Lundgren I, Oyakhrome S, Impouma B, Matsiegui PB, Adegnika AA, et al (2006) Fosmidomycin plus clindamycin for treatment of pediatric patients aged 1 to 14 years with *Plasmodium falciparum* malaria. *Antimicrob Agents Chemother* 50: 2713–8
- Oyakhrome S, Issifou S, Pongratz P, Barondi F, Ramharter M, Kun JF, et al (2007) Randomized controlled trial of fosmidomycin-clindamycin versus sulfadoxine-pyrimethamine in the treatment of *Plasmodium falciparum* malaria. *Antimicrob Agents Chemother* 51: 1869–71
- Grobusch MP, Lell B, Schwarz NG, Gabor J, Dornemann J, Potschke M, et al (2007) Intermittent preventive treatment against malaria in infants in Gabon – a randomized, double-blind, placebo-controlled trial. *J Infect Dis* 196: 1595–602
- Grobusch MP, Gabor JJ, Aponte JJ, Schwarz NG, Poetschke M, Doernemann J, et al (2009) No rebound of morbidity following intermittent preventive sulfadoxine-pyrimethamine treatment of malaria in infants in Gabon. *J Infect Dis* 200: 1658–61
- Aponte JJ, Schellenberg D, Egan A, Breckenridge A, Carneiro I, Critchley J, et al (2009) Efficacy and safety of intermittent preventive treatment with sulfadoxine-pyrimethamine for malaria in African infants: a pooled analysis of six randomised, placebo-controlled trials. *Lancet* 374: 1533–42
- Oliveira GA, Wetzel K, Calvo-Calle JM, Nussenzeig R, Schmidt A, Birkett A, et al (2005) Safety and enhanced immunogenicity of a hepatitis B core particle *Plasmodium falciparum* malaria vaccine formulated in adjuvant Montanide ISA 720 in a phase I trial. *Infect Immun* 73: 3587–97
- Esen M, Kremsner PG, Schleucher R, Gässler M, Imoukhuede EB, Imbault N, et al (2009) Safety and immunogenicity of GMZ2 – a MSP3-GLURP fusion protein malaria vaccine candidate. *Vaccine* 27: 6862–8
- Lell B, Agnandji S, von Glasenapp I, Haertle S, Oyakhrome S, Issifou S, et al (2009) A randomized trial assessing the safety and immunogenicity of AS01 and AS02 adjuvanted RTS,S malaria vaccine candidates in children in Gabon. *PLoS One* 4: e7611
- Taylor T, Olola C, Valim C, Agbenyega T, Kremsner P, Krishna S, et al (2006) Standardized data collection for multi-center clinical studies of severe malaria in African children: establishing the SMAC network. *Trans R Soc Trop Med Hyg* 100: 615–22
- Kremsner PG, Valim C, Missinou MA, Olola C, Krishna S, Issifou S, et al (2009) Prognostic value of circulating pigmented cells in African children with malaria. *J Infect Dis* 199: 142–50
- Helbok R, Issifou S, Matsiegui PB, Lackner P, Missinou MA, Kombila D, et al (2006) Simplified multi-organ dysfunction score predicts disability in African children with *Plasmodium falciparum* malaria. *Am J Trop Med Hyg* 2006: 443–7

29. Helbok R, Kendjo E, Issifou S, Lackner P, Newton CR, Kombila M, et al (2009) The Lambaréné Organ Dysfunction Score (LODS) is a simple clinical predictor of fatal malaria in African children. *J Infect Dis* 200: 1834–41
30. Kun JF, Schmidt-Ott RJ, Lehman LG, Lell B, Luckner D, Greve B, et al (1998) Merozoite surface antigen 1 and 2 genotypes and rosetting of *Plasmodium falciparum* in severe and mild malaria in Lambaréné, Gabon. *Trans R Soc Trop Med Hyg* 92: 110–4
31. Kun JF, Mordmüller B, Lell B, Lehman LG, Luckner D, Kreamsner PG (1998) Polymorphism in promoter region of inducible nitric oxide synthase gene and protection against malaria. *Lancet* 351: 265–6
32. Kun JF, Mordmüller B, Perkins DJ, May J, Mercereau-Puijalon O, Alpers M, et al (2001) Nitric oxide synthase 2(Lambaréné) (G-954C), increased nitric oxide production, and protection against malaria. *J Infect Dis* 184: 330–6
33. Luty AJ, Kun JF, Kreamsner PG (1998) Mannose-binding lectin plasma levels and gene polymorphisms in *Plasmodium falciparum* malaria. *J Infect Dis* 178: 1221–4
34. Boldt AB, Luty A, Grobusch MP, Dietz K, Dzeing A, Kombila M, et al (2006) Association of a new mannose-binding lectin variant with severe malaria in Gabonese children. *Genes Immun* 7: 393–400
35. Uhlemann AC, Szlezák NA, Vonthein R, Tomiuk J, Emmer SA, Lell B, et al (2004) DNA phasing by TA dinucleotide microsatellite length determines in vitro and in vivo expression of the gp91phox subunit of NADPH oxidase and mediates protection against severe malaria. *J Infect Dis* 189: 2227–34
36. Lell B, May J, Schmidt-Ott RJ, Lehman LG, Luckner D, Greve B, et al (1999) The role of red blood cell polymorphisms in resistance and susceptibility to malaria. *Clin Infect Dis* 28: 794–9
37. Barragan A, Kreamsner PG, Wahlgren M, Carlson J (2000) Blood group a antigen is a coreceptor in *Plasmodium falciparum* resetting. *Infect Immun* 68: 2971–5
38. Missinou MA, Lell B, Kreamsner PG (2003) Uncommon asymptomatic *Plasmodium falciparum* infections in Gabonese children. *Clin Infect Dis* 36: 1198–202
39. Greve B, Lehman LG, Lell B, Luckner D, Schmidt-Ott R, Kreamsner PG (1999) High oxygen radical production is associated with fast parasite clearance in children with *Plasmodium falciparum* malaria. *J Infect Dis* 179:1584–6
40. Luty AJ, Lell B, Schmidt-Ott R, Lehman LG, Luckner D, Greve B, et al (1999) Interferon-gamma responses are associated with resistance to reinfection with *Plasmodium falciparum* in young African children. *J Infect Dis* 179: 980–8
41. van den Biggelaar AH, van Ree R, Rodrigues LC, Lell B, Deelder AM, Kreamsner PG, et al (2000) Decreased atopy in children infected with *Schistosoma haematobium*: a role for parasite-induced interleukin-10. *Lancet* 356: 1723–7
42. van den Biggelaar AH, Lopuhaa C, van Ree R, van der Zee JS, Jans J, Hoek A, et al (2001) The prevalence of parasite infestation and house dust mite sensitization in Gabonese schoolchildren. *Int Arch Allergy Immunol* 126: 231–8
43. van den Biggelaar AH, Rodrigues LC, van Ree R, van der Zee JS, Hoeksma-Kruize YC, Souverijn JH, et al (2004) Long-term treatment of intestinal helminths increases mite skin-test reactivity in Gabonese school children. *J Infect Dis* 189: 892–900
44. Lell B, Borrmann S, Yazdanbakhsh M, Kreamsner PG (2001) Atopy and malaria. *Wien Klin Wochenschr* 113: 927–9
45. Yazdanbakhsh M, Kreamsner PG, van Ree R (2002) Allergy, parasites, and the hygiene hypothesis. *Science* 296: 490–4
46. van Riet E, Adegnik AA, Retra K, Vieira R, Tielens AG, Lell B, et al (2007) Cellular and humoral responses to influenza in Gabonese children living in rural and semi-urban areas. *J Infect Dis* 196: 1671–8
47. Adegnik AA, Köhler C, Agnandji ST, Chai SK, Labuda L, Breiting LP, et al (2008) Pregnancy-associated malaria affects toll-like receptor ligand-induced cytokine responses in cord blood. *J Infect Dis* 198: 928–36
48. Köhler C, Adegnik AA, Van der Linden R, Agnandji ST, Chai SK, Luty AJ, et al (2008) Comparison of immunological status of African and European cord blood mononuclear cells. *Pediatr Res* 64: 631–6
49. Khattab A, Kun J, Deloron P, Kreamsner PG, Klinkert MQ (2001) Variants of *Plasmodium falciparum* erythrocyte membrane protein 1 expressed by different placental parasites are closely related and adhere to chondroitin sulfate A. *J Infect Dis* 183: 1165–9
50. Winter G, Chen Q, Flick K, Kreamsner P, Fernandez V, Wahlgren M (2003) The 3D7var5.2 (var COMMON) type var gene family is commonly expressed in non-placental *Plasmodium falciparum* malaria. *Mol Biochem Parasitol* 127: 179–91
51. Frank M, Kirkman L, Costantini D, Sanyal S, Lavazec C, Templeton TJ, et al (2008) Frequent recombination events generate diversity within the multi-copy variant antigen gene families of *Plasmodium falciparum*. *Int J Parasitol* 38: 1099–109
52. Hübner MP, Pasche B, Kalaydjiev S, Soboslay PT, Lengeling A, Schulz-Key H, et al (2008) Microfilariae of the filarial nematode *Litomosoides sigmodontis* exacerbate the course of lipopolysaccharide-induced sepsis in mice. *Infect Immun* 76: 1668–77
53. Issifou S, Kendjo E, Missinou MA, Matsiegui PB, Dzeing-Ella A, Dissanami FA, et al (2007) Differences in presentation of severe malaria in urban and rural Gabon. *Am J Trop Med Hyg* 77: 1015–19
54. Schwarz NG, Oyakhrome S, Pötschke M, Gläser B, Klein Klouwenberg P, Altun H, et al (2005) 5-day nonobserved artesunate monotherapy for treating uncomplicated *Falciparum* malaria in young Gabonese children. *Am J Trop Med Hyg* 73: 705–9
55. Kreidenweiss A, Kreamsner PG, Mordmüller B (2008) Comprehensive study of proteasome inhibitors against *Plasmodium falciparum* laboratory strains and field isolates from Gabon. *Malar J* 7: 187
56. de Messias-Reason I, Kreamsner PG, Kun JF (2009) Functional haplotypes that produce normal ficolin-2 levels protect against clinical leprosy. *J Infect Dis* 199: 801–4
57. Song le H, Xuan NT, Toan NL, Binh VQ, Boldt AB, Kreamsner PG, et al (2008) Association of two variants of the interferon-alpha receptor-1 gene with the presentation of hepatitis B virus infection. *Eur Cytokine Netw* 19: 204–10
58. Tena-Tomás C, Pedrosa ML, de Messias-Reason IJ, Kreamsner PG, Kun JF (2007) Polymorphisms in the IFNAR1 gene in patients with chronic hepatitis C: outcome of combined IFN-alpha therapy. *Eur Cytokine Netw* 18: 136–41
59. Lell B, Ruangweayut R, Wiesner J, Missinou MA, Schindler A, Baranek T, et al (2003) Fosmidomycin, a novel chemotherapeutic agent for malaria. *Antimicrob Agents Chemother* 47: 735–8
60. Mordmüller B, Kreamsner PG (1998) Hyperparasitemia and blood exchange transfusion for treatment of children with *falciparum* malaria. *Clin Infect Dis* 26: 850–2
61. Mordmüller B, Fendel R, Kreidenweiss A, Gille C, Hurwitz R, Metzger WG, et al (2006) *Plasmodia* express two threonine-peptidase complexes during asexual development. *Mol Biochem Parasitol* 148: 79–85
62. Ntoumi F, Flori L, Mayengue PI, Matondo Maya DW, Issifou S, Deloron P, et al (2005) Influence of carriage of hemoglobin AS and the Fc gamma receptor IIa-R131 allele on levels of immunoglobulin G2 antibodies to *Plasmodium falciparum* merozoite antigens in Gabonese children. *J Infect Dis* 192: 1975–80
63. Mayengue PI, Luty AJ, Rogier C, Baragatti M, Kreamsner PG, Ntoumi F (2009) The multiplicity of *Plasmodium falciparum* infections is associated with acquired immunity to asexual blood stage antigens. *Microbes Infect* 11: 108–14
64. Kocherscheidt L, Flakowski AK, Grüner B, Hamm DM, Dietz K, Kern P, et al (2008) *Echinococcus multilocularis*: inflammatory and regulatory chemokine responses in patients with progressive, stable and cured alveolar echinococcosis. *Exp Parasitol* 119: 467–74
65. Zanger P, Holzer J, Schleucher R, Steffen H, Schitteck B, Gabrysich S (2009) Constitutive expression of the antimicrobial peptide RNase 7 is associated with *Staphylococcus aureus* infection of the skin. *J Infect Dis* 200:1907–15