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Institute of Clinical Pharmacology
RWTH University Hospital

The value of EU-AU collaboration in PM research

Global Health Clinical Pharmacology: collaborative research with African partners

Prof. Dr. Julia C. Stingl

Our collaboration…..

Supported by:

Federal Ministry of Health

GHP Programme

on the basis of a decision
by the German Bundestag

Global Health Protection Programme

Infectious disease outbreaks occur on a regular basis and respect no borders as they take their toll. Epidemics threaten population health, creating enormous human suffering and potentially causing devastating economic losses. It is therefore crucial for societies – in Germany and across the world – to be able to rely on resilient health systems that can respond effectively to population needs, both under normal circumstances and in the event of outbreaks.

In 2016, the German Federal Ministry of Health established the Global Health Protection Programme (GHPP). Since then, a number of German institutions operating in the field of health have been supporting partners across the world in preventing and fighting disease outbreaks. In doing so, the GHPP contributes to achieving the United Nations Sustainable Development Goal 3, which aims to "Ensure healthy lives and promote well-being for all at all ages".

All of the institutions involved with the GHPP contribute valuable expertise in the area of Global Health to the realisation of international projects. These projects are complementary to the development cooperation activities of the Federal Ministry of Economic Cooperation and Development, the humanitarian aid projects of the Federal Foreign Office and research promotion by the Federal Ministry of Education and Research. The thematic focus of the GHPP with particular importance to global health protection is presented below:

Research project

GHP Programme

Combating Resistance in the Treatment of Infectious Diseases by Promoting Judicious/Rational Use of Anti-infective Drugs

CPA

Scientific Training and Collaborative Research on Optimal Use of Anti-Infectives

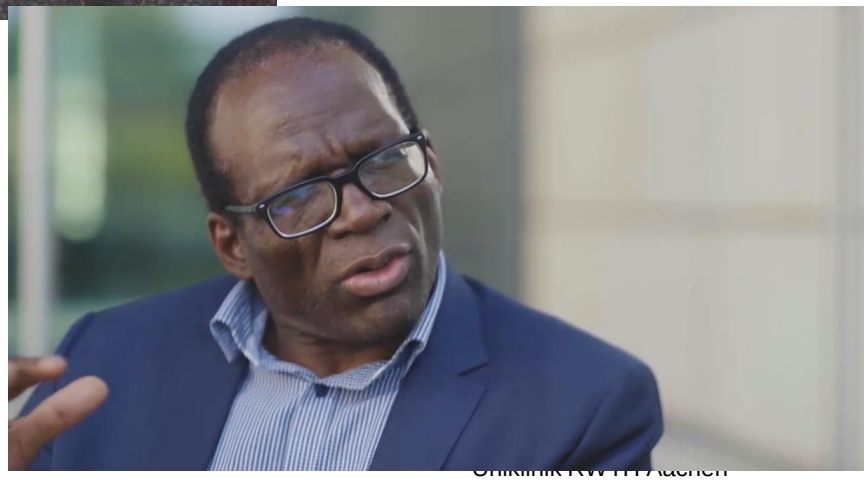
- Rational drug prescribing
- Pharmacogenetic profiles
- Drug drug interaction profiles
- Healthcare professionals‘ knowledge and attitude towards personalized medicine

Video: Interview on common research questions

Prof. Julia Stingl
Federal Institute for Drugs and Medical Devices/BfArM,
Bonn, Germany

in dialogue with

Prof. Collen Masimirembwa
African Institute of Biomedical Science and Technology/AiBST,
Harare, Zimbabwe



https://ghpp.de/en/projects/cpa-and-cpa-plus/

Collaborative activities

- Common supervision of PhD students
- Comparative research
- Teaching and eLearning

Collaborative activities

- Common supervision of PhD students
  - 3 PhD from Sambia, Malawi and Zimbabwe
  - Enroled to the University of Zimbabwe
  - Teaching via Zoom, common regular progress reports
  - Summerschool in Germany, Conference on Personalized Medicine in Harare, Zimbabwe

Participants at the Symposium on Personalized Medicine for Global Health, Zimbabwe, 2019

Collaborative activities

- Common supervision of PhD students
- **Comparative research**
- Teaching and eLearning

Comparative research

- Differences between African and European patients
  - Pharmacogenetic profiles
  - Drug Drug Interactions
  - Dosing/vulnerability
  - Accessability: Drug availability and quality
  - Indications for drug treatment

Publications:

CYP2B6 Functional Variability in Drug Metabolism and Exposure Across Populations—Implication for Drug Safety, Dosing, and Individualized Therapy

*Immaculate M. Langmia[1], Katja S. Just[1], Sabrina Yamoune[1], Jürgen Brockmöller[2], Collen Masimirembwa[3] and Julia C. Stingl[1]**

[1] Institute of Clinical Pharmacology, University Hospital of Rheinisch-Westfälische Technische Hochschule Aachen, Aachen, Germany, [2] Department of Clinical Pharmacology, University Medical Center Göttingen, Georg-August University, Göttingen, Germany, [3] African Institute of Biomedical Science and Technology (AiBST), Harare, Zimbabwe

TABLE 2 | Selected studies revealing variability in allele frequency of CYP2B6 alleles in different ethnicities.

Country/region/population	*N*	CYP2B6*2	CYP2B6*4	CYP2B6*6	CYP2B6*9	References
Europe						
German	430	5.3	4	32.1	28.6	Giardina et al., 2018; Patel and Patel, 2018
Spaniard	360	-	6.2	21.5	1.4	Agency, 2017
Swiss	226		3.9	24.8	26	Giardina et al., 2018; Schurig et al., 2018
British	270	3.7	2.2	28.15	28.6	Stingl et al., 2013
Ukraine	102	-	-	-	25	Weinshilboum, 2003
Turkish	344	-	6.4	25.3	2	Giardina et al., 2018
Africa		-		-	-	
West Africa	153	4	42	-	50	Evans and Relling, 2004
Congo	418	-	-	-	55[¥]	Lynch and Price, 2007
Ghana	800	-	-	-	48	Zanger and Schwab, 2013
Botswana	570	-	-	22		Nebert et al., 2013
Mozambique	360	5.7	41	-	42.6[¥]	Lonsdale et al., 2013
Nigeria (Hausa)	100	-	-	42	-	Thorn et al., 2010
Nigeria (Igbo)	100	-	-	38	-	Thorn et al., 2010
Nigeria (Yoruba)	100	-	-	42	-	Thorn et al., 2010
Tanzania	256	-	-	-	36[¥]	Desta et al., 2021
Ethiopia	285	-	-	-	31.4[¥]	Rendic, 2002
Kenya (Kikuyu)	102	-	-	34	-	Thorn et al., 2010
Kenya (Luo)	100	-	-	37	-	Thorn et al., 2010
Kenya (Maasai)	152	-	-	35	-	Thorn et al., 2010
Zimbabwe (San)	64	-	-	40	-	Thorn et al., 2010
Zimbabwe (Shona)	100	-	-	38	-	Thorn et al., 2010
Cameroon	75	-	-	-	37[¥]	Hanna et al., 2000
South Africa	163	-	-	-	36[¥]	Hanna et al., 2000
South Africa (Venda)	81	-	-	36		Thorn et al., 2010
South Africa (Xhosa)	109	-	-	-	20[¥]	Zanger et al., 2008
South Africa (MA)	67	-	-	-	23[¥]	Zanger et al., 2008
Uganda Bantus	58	-	-	25.9	-	Sarfo et al., 2014
Asia		-	-	-		

TABLE 3 | CYP2B6 polymorphisms and adverse drug reactions reported amongst patients in various ethnicities.

Substrate	Subjects	*N*	CYP2B6 genotype	Predicted functional effect on CYP2B6 enzyme activity	Patient exposure to the drug	Frequency of allelic variants (%)	Population	Adverse drug reaction	References
Efavirenz	HIV/TB	185	CYP2B6*6/*6	↓ Activity	Higher exposure	45	Zimbabwe	Central nervous system adverse events(CNS) including insomnia, severe headaches, vivid nightmares, drowsiness, ataxia, dystonia and dizziness.	Patel and Patel, 2018
	HIV, TB-HIV co-infected patient	353	CYP2B6 516TT	↓ Activity	Higher exposure	31.6	Ethiopians	Anti-retroviral and anti-tuberculosis drug induced liver injury in TB-HIV co-infected patients.	Agency, 2017; Giardina et al., 2018
	HIV	285	CYP2B6 516TT	↓ Activity	Higher exposure	31	Ethiopians	Higher risk of drug induced liver injury (DILI)	Agency, 2017; Schurig et al., 2018
	HIV	800	CYP2B6 516TT	↓ Activity	Higher exposure	48	Ghanaian	Neuropsychiatric toxicity	Stingl et al., 2013
	HIV	134	CYP2B6*6/*6	↓ Activity	Higher exposure	8.2	Thai	Increase risk of hepatotoxicity	Weinshilboum, 2003; Evans and Relling, 2004; Lynch and Price, 2007
	HIV/AIDS	1,147	CYP2B6 G516TT	↓ Activity	Higher exposure	38, 21.9	Mixed population European American, African American, Hispanics	Central nervous system toxicity	Zanger and Schwab, 2013
	HIV/AIDS	373	CYP2B6 516TT	↓ Activity	Higher exposure	30, 37	Mixed population (Black & White)	Central nervous system related effects and 131 patients withdrew from therapy within the first 3 months	Nebert et al., 2013
	HIV	197	CYP2B6 516TT	↓ Activity	Higher exposure	30	Ugandans	Neuropsychiatric symptoms. High incidence of vivid dream, sleepwalking, insomnia and tactile hallucination	Thorn et al., 2010; Lonsdale et al., 2013
	HIV/TB patients	473	CYP2B6 516GT CYP2B6 516TT	↓ Activity	Higher exposure	35.5	Tanzanians	Development of efavirenz based HAART liver injury	Agency, 2017; Desta et al., 2021
	HIV adults	142	CYP2B6 516GT CYP2B6 516TT	↓ Activity	Higher exposure	32	South Africans	High efavirenz level associated with severed sleep disturbance	Rendic, 2002

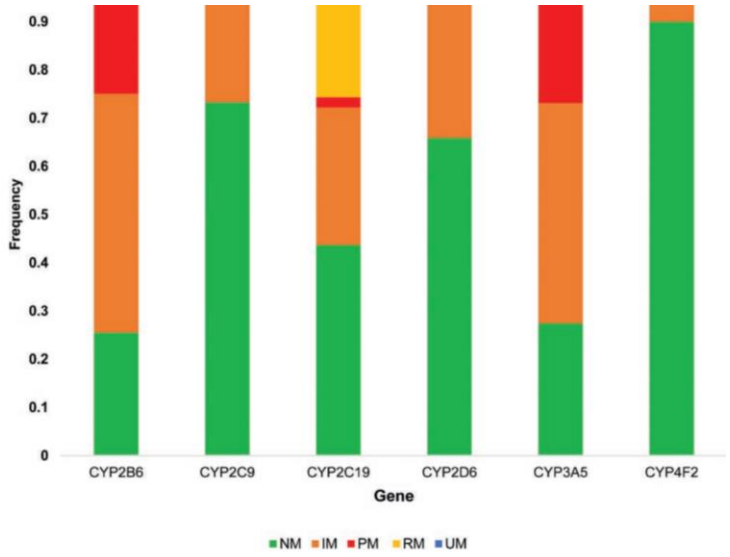
Publications

Population genetic polymorphisms of pharmacogenes in Zimbabwe, a potential guide for the safe and efficacious use of medicines in people of African ancestry

Bianza T. Mbavha[a*], Comfort R. Kanji[a*], Nadina Stadler[b], Julia Stingl[c], Andrea Stanglmair[b], Catharina Scholl[b], William Wekwete[d] and Collen Masimirembwa[a]

Table 3 Population allele frequencies for CYP450 genes, comparison between frequencies obtained in this study and those for other Africans, Eastern Asians, South Asians, Europeans and Americans

Gene	Allele	This study	Africans	Eastern Asians	South Asians	Europeans	Americans
CYP2B6	*4[a,b,c,e]	0.0201	0.3553	0.2655	0.3775		0.3327
	*5	0.0067	0.0113	0.003	0.089	0.1123	0.072
	*6	0.3774	0.3744	0.2153	0.3814	0.2356	0.3732
	*7	0.0038	NA	NA	NA	NA	NA
	*18[e]	0.1054	0.0825	0	0	0	0.0101
CYP2D6	*2	0.1850	0.1557	0.12	0.29	0.2765	0.2208
	*2A	0.0173	0.0063	0.0195	0.0819	0.0908	0.0859
	*5[a–e]	0.1156	0.0539	0.0486	0.0459	0.0295	0.0159
	*10	0.0318	0.1127	0.5714	0.1646	0.2018	0.1484
	*17[b–e]	0.1503	0.2179	0	0	0.002	0.0086
	*29[b–e]	0.0954	0.1074	0	0	0	0.0029
	*41	0.0087	0.0182	0.0377	0.1217	0.0934	0.062
CYP2C9	*2	0.0010	0.0083	0.0010	0.0348	0.1243	0.0994
	*3	0.0029	0.0023	0.0337	0.1094	0.0726	0.0375
	*4	0.0010	0.0000	0.0000	0.0000	0.0000	0.0000
	*5[b–e]	0.0153	0.0166	0	0	0	0.0014
	*6[b–e]	0.0048	0.0109	0	0	0	0.001
	*8[b–e]	0.0977	0.053	0	0.001	0.002	0.0014
	*11[b–e]	0.0307	0.0242	0	0.001	0.002	0.0014
CYP2C19	*2[b,c]	0.1609	0.1702	0.3125	0.3579	0.1451	0.1052
	*3	0.0019	0.0023	0.0556	0.0123	0.0000	0.0000
	*10	0.0010	0.0015	0	0	0	0.0014
	*17	0.1667	0.2352	0.0149	0.136	0.2237	0.1196
CYP3A5	*3[b–e]	0.1775	0.18	0.7133	0.6677	0.9433	0.7968
	*6[b–e]	0.1833	0.1543	0	0	0.003	0.0231
	*7[b–e]	0.1363	0.118	0	0	0	0.0029
CYP3A4	*1B[b–e]	0.7682	0.7655	0.004	0.0399	0.0278	0.1052
CYP4F2	*3[b–e]	0.0517	0.0825	0.2143	0.4131	0.2003	0.2778



notype frequencies for CYP450 pharmacogenes in Black Zimbabwean population.

Differences in drug-drug interactions

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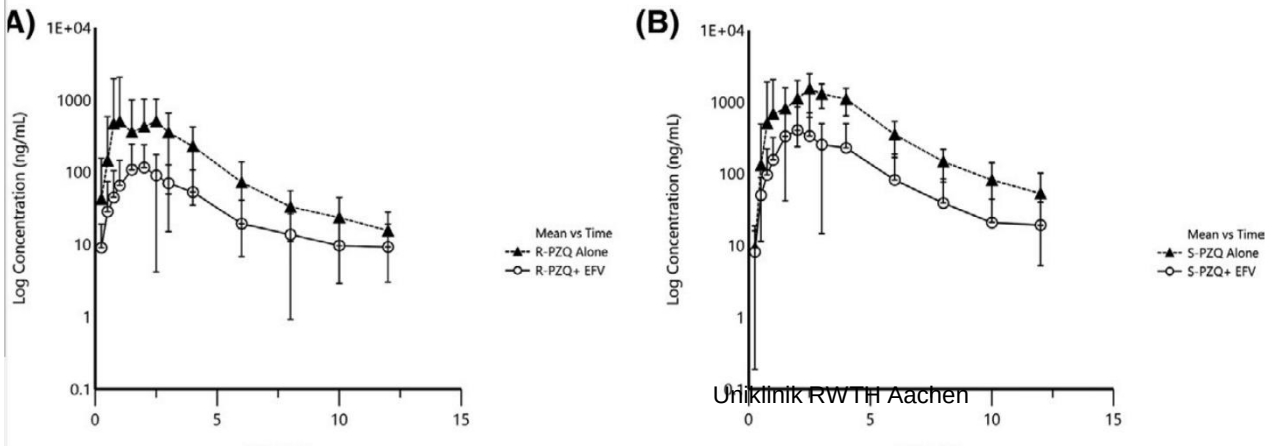
ORIGINAL ARTICLE

Clinically relevant enantiomer specific R- and S-praziquantel pharmacokinetic drug-drug interactions with efavirenz and ritonavir

Chenai Sheilla Mutiti[1,2] | Nyasha Nicole Kapungu[1,2] | Comfort Ropafadzo Kanji[1,2] | Nadina Stadler[3] | Julia Stingl[4] | Charles Nhachi[2] | James Hakim[5] | Collen Masimirembwa[1] | Roslyn Stella Thelingwani[1]



Differences

- In Drug Availability and Usage

Availability and Accessibility of Medication

According to our findings, HAART combination therapy that includes EFV or NVP is mostly used in LMICs despite the high frequency of CYP2B6 loss of function alleles in these populations. Thus, pharmacovigilance is urgently needed in these populations for the detection and subsequent prevention of ADRs. Contrary to LMICs, in HICs more potent, less toxic and novel antiretroviral drugs are used quite often. Higher donor dependency and cost of medication has been highlighted as barriers to the accessibility of quality and less toxic drugs in LMICs. Donor funding has saved many lives in LMICs for the past decades. The help from richer countries is provided in the form of finance or medication via Government officials or private agencies in health sectors. With the growing population in LMICs, it is evident that donor funding can no longer benefit every individual. Therefore, in this era, donors should focus more on human capacity building and establishment of infrastructures that will help LMICs become independent or self-sponsored (Pillai et al., 2018). For example, antiretroviral drugs are manufactured and sold at a cheaper rate in India compared to

Pharmacogenetic collaboration in Europe

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A 12-gene pharmacogenetic panel to prevent adverse drug reactions: an open-label, multicentre, controlled, cluster-randomised crossover implementation study

Prof Jesse J Swen, PharmD • Cathelijne H van der Wouden, PhD * • Lisanne EN Manson, PharmD * • Heshu Abdullah-Koolmees, PhD • Kathrin Blagec, MD • Tanja Blagus, BSc • et al. Show all authors • Show footnotes

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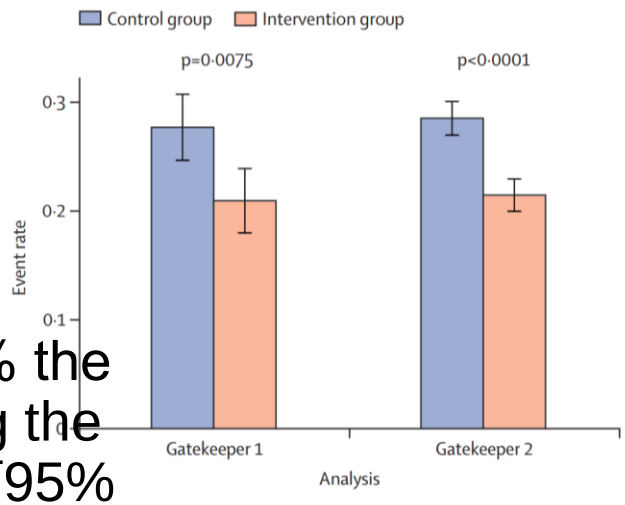

…, the prevalence of the development of a causal clinically relevant adverse drug reaction was …21% the study group and 29% in the control group, reducing the risk of an adverse drug reaction by 30% (OR 0·70 [95% CI 0·61–0·79]; p <0·0001; figure 2).

Collaborative research

- The need for **research on patient differences**:
- Capacity building for drug manufacturing
- Pharmacogenetic diagnostics
- Clinical data on therapy outcomes
- Pharmacovigilance
- Data Science

Collaborative activities

- Common supervision of PhD students
- Comparative research
- **Teaching and eLearning**

Publications

Healthcare Professionals' Knowledge of Pharmacogenetics and Attitudes Towards Antimicrobial Utilization in Zambia: Implications for a Precision Medicine Approach to Reducing Antimicrobial Resistance

Webrod Mufwambi[1,2,3], Julia Stingl[4], Collen Masimirembwa[2], Justen Manasa[2,3], Charles Nhachi[3], Nadina Stadler[5], Chiluba Mwila[1], Aubrey Chichonyi Kalungia[1], Moses Mukosha[1], Chenai S. Mutiti[2,3], Alfred Kamoto[2,3], Patrick Kaonga[6,7], Brian Godman[8,9,10] and Derick Munkombwe[1]*

TABLE 4 | Knowledge of pharmacogenetics among healthcare professionals about antimicrobial resistance, Lusaka Zambia 2019.

Pharmacogenetics questions	Total (*n* = 304)	Nurses (*n* = 100)	Physicians (*n* = 65)	Pharmacists (*n* = 58)	Biomedical personnel (*n* = 80)	*p*-value
1. Are you aware of individual variation in the way antibiotics work and in the way different individuals experience adverse drug reactions and/or toxicity to antibiotics?	240 (81.1)	67 (69.1)	59 (92.2)	49 (85.9)	65 (83.3)	0.001
2. Have you heard of the term pharmacogenetics and know what it means?	225 (76.0)	54 (55.7)	52 (82.5)	53 (91.4)	66 (84.6)	<0.001
3. Is genetic testing important in the use of medicines for reducing cost of treatment?	100 (33.4)	34 (35.1)	12 (18.8)	25 (43.1)	29 (36.3)	0.029
4. Is genetic testing important in the use of medicines for understanding drug action?	102 (34.1)	32 (32.9)	17 (26.6)	23 (39.7)	30 (37.5)	0.411
5. Is genetic testing important in the use of medicines for reducing adverse drug reactions?	125 (42.1)	25 (26.0)	27 (42.2)	37 (63.8)	36 (45.6)	<0.001
6. Is genetic testing important in the use of medicines for improving efficacy?	104 (35.0)	24 (25.0)	14 (21.9)	31 (53.5)	35 (44.5)	<0.001
7. Is the knowledge of genetic testing in drug use likely to decrease the number of adverse drug reactions?	88 (29.8)	18 (18.9)	12 (18.8)	28 (49.1)	30 (37.9)	<0.001
8. Is the knowledge of patient genetic make-up likely to decrease the cost of developing drugs?	15 (15.6)	8 (12.5)	14 (24.1)	28 (49.1)	20 (25.3)	0.141
Overall score (mean ± SD)[a]	3.04 ± 1.1	2.5 ± 0.8	2.7 ± 0.9	3.8 ± 1.1	3.4 ± 1.2	<0.001

[a]*All values are mean and Standard Deviation (SD) and p-value from One Way Analysis of Variance (ANOVA). Otherwise, Chi-square tests were used.*

Projects

Development of Master of Science in Pharmacogenomics (MScPGx) in Zambia

The University of Zambia, together with GHPP CPA project partners in Zimbabwe and Germany, has initiated the development and introduction of a master's program in pha

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As an effective approach, CPA has recognized the need to increase knowledge of PGx among healthcare professionals in Zambia. The country is a signatory to the charters laid out by the United Nations and the World Health Organization (WHO) in the Sustainable Development Goals (SDGs) and envisions to achieve Goal # 3 concerned with good health and wellbeing by 2030. To have relevant skills in the Zambian health value chain, there is a need to train personnel in specialized areas such as PGx.

Research collaborations in personalized medicine

To understand patient differences in drug therapy outcome: Personalized drug prescription and dosing

To overcome issues in drug accessibility and usage: capacity building, pharmacovigilance

Teaching collaborations: supervision of PhD, curricula, sommerschools, etc.