Westfälische Wilhelms-Universität Münster

wwu.usp

PROGRAM & BOOK OF ABSTRACTS

II WORKSHOP AND SUMMER SCHOOL

NEGLECTED DISEASES

11.09.16 - 15.09.17

University of São Paulo

Westfälische Wilhelms-Universität Münster

DAAD Deutscher Akademischer Austausch Dienst German Academic Exchange Service

CENTRO BRASILEIRO Universidade de Münster

Centro Alemão de Ciência e Inovação – São Paulo
Alemanha País de Ideias

Deutsches Wissenschafts- und Innovationshaus – São Paulo
Deutschland Land der Ideen

PROGRAM

Local Organizing Committee
- Karina M. Stefani - FCFRP International Office (CRInt)
- Fernando B. da Costa - Brazilian coordinator
- Carla Menegatti, Felipe Calil and Gisele Bulhões – Support

Monday, 11 September

09:30 – 10:30, Opening ceremony
Prof. Vahan Agopyan (USP Vice-president)
Prof. Maria Vitória L.B. Bentley (FCFRP Dean)
Dr. Ricardo Schuch (Executive Director of the Brazil Center from WWU, Münster)
Anja G. Lorenz (Director of the Brazil Center from WWU, São Paulo)
Prof. Fernando B. Costa (Brazilian coordinator of the thematic focus "neglected diseases")
Prof. Thomas J. Schmidt (German coordinator of the thematic focus "neglected diseases")
Prof. Maurício S. Baptista (USP International Cooperation Office, AUCANI)
Rudolf Schallenmüller (Honorary consul of the Federal Republic of Germany, Ribeirão Preto)
Prof. Renata F.V. Lopez (Coordinator of the Pharmaceutical Sciences Graduate Program)
Prof. Alessandro Hirata (President of the USP International Relations Committee at the Campus of Ribeirão Preto – GCARI-RP, Ribeirão Preto)
Anna Barkhausen (German Academic Exchange Service – DAAD, São Paulo)
Dr. Kathrin Winkler (Director of the German Research Foundation – DFG Office Latin America)
Prof. Luiz N. Oliveira (FAPESP Adjunct Panel, Special Programs and Collaboration in Research)
Alexandre Roccatto (FAPESP)
Prof. Hans-Ulrich Humpf (WWU)
Prof. Joachim Jose (WWU)
Prof. Stephan Ludwig (WWU)
Prof. Ariel Silber (USP)
Prof. Fabiani G. Frantz (USP)
Prof. Gustavo H.G. Trossini (USP)
Prof. Ivone Carvalho (USP)
Prof. Maria C. Nonato (USP)
Prof. Mônica T. Pupo (USP)
Prof. Norberto P. Lopes (USP)
Prof. Sérgio Albuquerque (USP)

10:30, Coffee break

11:00 – 11:30, Short talk
Anna Barkhausen (DAAD)

12:00 – 14:00
Lunchtime

14:00 – 14:20
Thomas Schmidt (WWU.USP Thematic Focus "Neglected Diseases")

14:20 – 15:00
Luiz N. Oliveira (FAPESP)
Alexandre Rocatto (FAPESP)

15:00 – 16:00
Kathrin Winkler (DFG)

16:00, Coffee break

16:30 – 17:00
Discussion

18:30 – 21:00
Poster session and welcome reception in a pub*
Meeting point: in front of the pub (full address available at the end of this document)

Posters: P01 – P23

*non-registered participants or accompanying persons can obtain extra tickets (R$ 60,00 per person).

Tuesday, 12 September

2nd WWU.USP Summer School on Neglected Diseases - Science beyond the borders: actions against neglected diseases

Chairperson: Fernando B. Costa
09:00, Plenary lecture 1 (PL1)
Thomas Schmidt (WWU): Pitfalls, detours, dead ends and ways out to new perspectives: lessons from 15 years of research on natural products against neglected diseases

10:00, Coffee break

10:15, Short talks
ST01: H.L. Greve – Search for new antiplasmodial leads in the oleo-gum-resin of *Boswellia serrata*
ST02: L.O. Bortot – Identifying potential leads for the inhibition of the dengue virus infection using molecular modeling and computational structure-based drug discovery methods
ST03: I. Lengers –
ST04: C. Menegatti – Bacterial symbionts of social insects as sources of antiparasitic compounds

11:15, Short lecture 1 (SL1)
Fabiani G. Frantz (FCFRP): Epigenetic markers and immune response against Tb

12:00 – 14:00
Lunchtime

14:00 – 17:30, 2nd WWU.USP Workshop on Neglected Diseases
IRTG Proposal (researchers only)

14:00 – 17:30, Pharma tour
Guided tour at eight selected FCFRP research laboratories (20' in each lab)
Meeting point: hall at the main FCFRP entrance (building A, yellow)
Guides: Carla Menegatti, Felipe Calil and Gisele Bulhões

1) Laboratory of Pharmacognosy, Prof. Fernando B. Costa, building G (green)

Host: Jolindo A. Freitas

2) Organic Synthesis, Prof. Ivone Carvalho, building M (1st floor)
Host: Peterson de Andrade

3) Laboratory of Microbial Chemistry (LQMo), Prof. Mônica T. Pupo, building M (1st floor)
Host: Carla Menegatti

4) Protein Crystallography Lab (LCP-RP), Prof. Cristina Nonato, building M (3rd floor)
Host: Felipe Calil

5) Research Support Center in Natural and Synthetic Products (NPPNS), Prof. Norberto Lopes, building J
Host: Anelize Bauermeister

6) Laboratory of Molecular Parasitology, Prof. Ana P. Yatsuda-Natsu, building S (1st floor)
Host: Luiz Miguel Pereira

7) Laboratory of Parasitology, Prof. Sérgio Albuquerque, building S (3rd floor)
Host: Gisele Bulhões

8) Laboratory of Immunology, Prof. Fabiani G. Frantz, building S (3rd floor)
Host: Fabiana A. Zambuzi

Wednesday, 13 September

2nd WWU.USP Summer School on Neglected Diseases - Science beyond the borders: actions against neglected diseases

Chairperson: Thomas Schmidt
09:00, Plenary lecture 2 (PL2)
Stephan Ludwig (WWU): Persuing new avenues in antiviral therapy

10:00, Coffee break

10:15, Short talks
ST05: A. Bauermeister – Molecular networking accelerating the identification of new molecules candidates for neglected diseases treatment
ST06: N.M. Kimani – Antiprotozoal sesquiterpene lactones and other constituents from *Tarchonanthus camphoratus*, *Schkuhria pinnata* and *Vernonia lasiopus*
ST07: F. Calil – Design of selective inhibitors for *Schistosoma mansoni* dihydroorotate dehydrogenase
ST08: A. Mayers – A high-throughput-compatible method to determine the optical density of bacterial cell cultures in microplates without sample dilution

11:15, Short lecture 2 (SL2)
Gustavo H.G. Trossini (FCF-SP): Exploring epigenetic targets in drug discovery using *in silico* strategies

12:00 – 14:00
Lunchtime

14:00 – 17:30, 2nd WWU.USP Workshop on Neglected Diseases
IRTG Proposal (researchers only)

14:00 – 17:30, Campus tour
Guided tour in the USP Campus
Meeting point: hall at the main FCFRP entrance (building A, yellow)
Guide: Fernanda H. Bartolomeu (USP International Relations Committee at the Campus of Ribeirão Preto – GCARI-RP)

19:30 – Dinner
Dinner* in a typical Brazilian "churrascaria" (steak house) / vegetarian meals available
Meeting point: in front of the restaurant (full address available at the end of this document)

*R$ 45,00 per person (to be paid in the restaurant), drinks and deserts not included.

Thursday, 14 September

2nd WWU.USP Summer School on Neglected Diseases - Science beyond the borders: actions against neglected diseases

Chairperson: Mônica T. Pupo
09.00, Plenary lecture 3 (PL3)
Joachim Jose (WWU): Protein interactions as a target in drug discovery: from assay development to potent small molecule inhibitors

10:00, Coffee break

10:15, Short talks
ST09: A. Jagels – Isolation of secondary metabolites from *Stachybotrys* species and their exploration concerning human health risk
ST10: L. Chibli – Natural products as inhibitors of *Leishmania major* dihydroorotate dehydrogenase
ST11: J.-F. Uth – Natural product inspired development of novel anti-malarial drugs
ST12: I.A. Cardoso – Structural and biochemical characterization of *Schistosoma mansoni* fumarate hydratase

11:15, Short lecture 3 (SL3)
Ivone Carvalho (FCFRP): Synthesis of heterocycle derivatives with potential anti-trypanosomal activity

12:00 – 14:00
Lunchtime

14:00 – 17:30, 2nd WWU.USP Workshop on Neglected Diseases
IRTG Proposal (researchers only)

14:00 – 17:30, City tour
Guided tour in the city of Ribeirão Preto
Meeting point: main FCFRP entrance (building A, yellow)
Guides: Carla Menegatti, Felipe Calil and Gisele Bulhões

Friday, 15 September

09:00 – 12:00, Brain storming

Final discussion about the IRTG proposal (all participants)

12:00 – 14:00
Lunchtime

14:00
Closing remarks

15:00 – 18:00, Beer tour
A guided tour* to two local craft breweries (Colorado and Pratinha)
Meeting point: main FCFRP entrance (building A, yellow)
Guide: beer sommelier Carla Valentim

*value per person: R$ 100,00 (minimum 10 people)

Important information

Venue
School of Pharmaceutical Sciences of Ribeirão Preto, USP Campus
Av. do Café, s/n – Campus Universitário, Ribeirão Preto, SP
All scientific activities, including the opening ceremony, will take place at the Building R (auditorium)

Accommodation for researchers and guests
Hotel Pousada Santa Rita
Av. do Café, 2295 – Vila Amélia – Ribeirão Preto, SP
Phones: (16) 3966-5404 | 3966-6409
http://hotelpousadasantarita.com.br

Accommodation for foreign students
House for Foreign Guests
House #7, R. Pedreira de Freitas – USP Campus, Ribeirão Preto, SP
Phones: (16) 3515-4469 | 3515-8541
http://www.prefeiturarp.usp.br/page.asp?url=hospestrang

Poster session and welcome reception
Biergarten Chope & Comida
R. São José, 1483, Jardim Sumaré, Ribeirão Preto, SP

Dinner at "churrascaria" (steak house)
Estância Churrascaria
Av. Presidente Vargas, 1100 - Alto da Boa Vista, Ribeirão Preto, SP

Drinking and smoking regulations
It is prohibited to consume alcoholic beverage under 18 years of age. Smoking is forbidden at any closed area by federal law. In the State of SP, this also includes open areas under a roof. In most places there are designated smoking zones.

Electricity
The electric current in São Paulo state is 110 V. In most places a type N (three prongs round pins) plug is used and usually sockets which fit the standard European 2 round pin prongs can also be used. Adapters are available in airport shops.

Money exchange
The currency in Brazil is the Brazilian Real (R$). Banking hours are typically 10:00 to 16:00 from Monday to Friday. Foreign currency and traveller checks can be exchanged in banks and exchange offices (available in the four shopping malls in the city). ATMs for cash withdrawal are widespread, including in the USP Campus. Major credit cards are widely accepted anywhere.

Taxis
Taxis can be hired from taxi stands, booked by phone, smartphone apps, or sometimes hailed on streets. The cars have a meter indicating the fare but it is normal to round up the final price.

Time in Brazil
Brazilian Standard Time is 3 hours earlier than G.M.T.

Tipping

In most restaurants and bars a 10% service fee is automatically added to the bill. Cab drivers do not expect a tip.

Weather in Ribeirão Preto

The month of September is characterized by essentially constant daily high temperatures with daily highs around 31 °C, while daily low temperatures are usually from 16 to 20 °C. The season is dry, but sometimes rainfall can occur.

Lectures

Plenary Lecture 1 (PL1)

Pitfalls, detours, dead ends and ways out to new perspectives: Lessons from 15 years of research on natural products against neglected diseases

Thomas J. Schmidt[1]

[1] *Institute for Pharmaceutical Biology and Phytochemistry (IPBP), University of Münster, Münster, Germany*

"How many drugs have you brought to the patient?", I was recently asked by a student after a presentation on the potential of natural products (NPs) against neglected diseases (NDs) at a conference. She looked somewhat disappointed by my answer "Not a single one". Of course, this question might appear naïve to an experienced scientist in the field of drug research. But of course is is a well justified quesion. "Not so many colleagues from my field have managed that", I said, "because it is a long and difficult way." But, of course, the question inspired me once again to think about it more deeply....

Fifteen years have passed since we first found that certain representatives of the class of sesquiterpene lactones (STLs) are extremely potent antitrypanosomal agents killing African trypanosomes (*Trypanosoma brucei*), casative pathogens of the most deadly protozoan parasite disease on this planet, at nanomolar concentrations, much lower than cytotoxic concentrations to mammalian cells. It was this finding, among other things, that initiated and inspired much of our further research over the following years. Yet we could not exploit this potential properly until now.

Many further natural products were since disovered in my group to have interesting anti-protozoal activity. As the many STLs tested over the years, most of them were obtained in quantities too low to warrant *in vivo* tests or, if this was possible, failed to show *in vivo* activity or displayed toxicity *in vivo* that precluded further development. Another problem frequently encountered is that sometimes, extracts show a very promising *in vitro/ex vivo* activity but the isolation of any single active principle is just not possible. Unfortunately, sometimes what you expect is not what you get. Sometimes you find unexpected very unexpected new perspectives by chance. That is science. Thus, NP vs. ND research along many different lines is still going on in my group, to find other new active natural products, to solve the riddle why some promising compounds do not work *in vivo*, to solve the mechanism of action of such candidates to gain deeper insight into the way they work so that this knowledge may help to find possibilities to finally exploit their potential as drug leads. "It is a long and stony road to this goal…", I said to the student. And then I went on and told her why I do not stop to follow this goal. I will try to explain it to the students of this Summer School in this lecture.

Short Talk 1 (ST1)

Search for new antiplasmodial leads in the oleo-gum-resin of *Boswellia serrata*

Hippolyt L. Greve[1], Marcel Kaiser[2], Reto Brun[2], Thomas J. Schmidt[1*]

[1] *Institute for Pharmaceutical Biology and Phytochemistry (IPBP), University of Münster, Münster, Germany*
[2] *Swiss Tropical and Public Health Institute (Swiss TPH) and University of Basel, Basel, Switzerland*

Keywords: *Boswellia serrata*, Burseraceae, *Plasmodium falciparum*, terpenoids

Abstract

Malaria is a vector-borne disease caused by pathogens of the genus *Plasmodium* that are transmitted by the bite of infected female *Anopheles* mosquitoes. Worldwide this infectious disease caused almost 430,000 deaths in 2015 [1]. Despite some improvements in prevention and therapy, especially increasing drug resistances remain a big problem [2]. As part of our continued search for natural products with antiprotozoal activity, Indian frankincense, the oleo-gum-resin of *Boswellia serrata* (Burseraceae) showed activity against *Plasmodium falciparum* (NF54 strain) *in vitro*. Successive extraction with solvents of increasing polarity showed best results for the dichloromethane extract (IC_{50} = 2.6 µg/ml). Bioactivity-guided fractionation led to the isolation of 22 compounds that were characterized by spectroscopic measurements. 17 compounds could be identified by comparison with literature data, three of which were obtained as natural products for the first time. The five remaining constituents were identified as *rel*-(1*S*,3*R*,7*E*,11*S*,12*R*)-1,12-epoxy-4-methylenecembr-7-ene-3,11-diol, 3-epi-neoilexonol, isoflindissol lactone, *rel*-(8*R*,9*S*,20*R*)-tirucall-24-ene-3β,20-diol and *rel*-(3α,8*R*,9*S*,20*R*,24*S*)-20,24-epoxytirucalla-3,25-diol. To the best of our knowledge, these compounds are not described in literature so far. All substances were tested for anti-plasmodial activity *in vitro* using established protocols [3]. Isoflindissone lactone showed the best activity with an IC_{50} value of 2.2 µM [4].

References

[1] WHO (2017), Fact sheet: Malaria, www.who.int/mediacentre/factsheets/fs094/en/
[2] Schmidt TJ *et al.* (2012), Curr Med Chem, 19: 2128-2175
[3] Nour AMM *et al.* (2009), Planta Med, 75: 1363-1368
[4] Greve HL *et al.* (2017), Planta Med, epub ahead of print, DOI: 10.1055/s-0043-116943

[*] **Corresponding author: thomschm@uni-muenster.de**

Short Talk 2 (ST2)

Identifying potential leads for Dengue Virus infection inhibition using molecular modeling and computational structure-based drug discovery methods

Leandro Oliveira Bortot[1], **Antonio Caliri**[1*]

[1] *Laboratório de Física Biológica, Faculdade de Ciências Farmacêuticas de Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto, São Paulo, Brazil.*

Abstract

Dengue is the world's fastest spreading mosquito-borne disease that currently threatens half the global population. It is caused by any of the four existing viral serotypes and has symptoms that ranges from mild and nonspecific to a lethal syndrome. Despite advances towards a safe and effective vaccine, the development of antivirals has received little attention. The quick emergence of Zika Virus, which is closely related to Dengue Virus, as a potential global threat reinforces the general need for developing strategies that enable us to find molecules that can be readily tested as leads. It was demonstrated that the envelope glycoprotein of Dengue Virus is recognized by the cellular C-type lectins DC-SIGN, Mannose Receptor and CLEC5A and that these interactions are promising targets for the development of new antiviral therapies. We report the combined use of molecular dynamics simulations, virtual screening assays, a ligand selection approach which is independent of the docking scoring function, and free energy calculations to identify molecules with high potential to be leads for the inhibition of the Dengue Virus infection.

Short Talk 3 (ST3)

Human Hyal-1 – from *in silico* pharmacophore modeling to *in vitro* inhibitor screening

Lengers I[1*], Hermann F[2], Haidar S[1] and Jose J[1]

[1] Institute of Pharmaceutical and Medicinal Chemistry, and [2] Institute of Pharmaceutical Biology and Phytochemie, PharmaCampus, Westfälische Wilhelms-Universität, Corrensstraße 48, 48149 Münster, Germany

Keywords: Hyaluronan, Hyaluronidase, cancer, natural compounds.

Abstract

The endoglycosidase hydrolase Hyaluronidase 1 (Hyal-1) is one of five hyaluronidases in human body. Degradation of high molecular weight hyaluronan (HA) is mainly catalyzed by Hyal-1 into smaller fragments. These fragments have inflammatory and angiogenic effects.[1] The role of Hyal-1 in cancer progression, e. g prostate or bladder cancer, has been discussed for a long time. In several cancer types, the expression level of Hyal-1 was elevated in comparison to not malignant cells, resulting in higher Hyal-1 activity and tumor progression.[2,3] Although Hyal-1 is an interesting target for pharmaceutical purposes, no potent inhibitors have been found so far. The enzyme source seems to be the bottleneck in investigation of potent inhibitors. Production of active Hyal-1 is one of the most challenging tasks. Eukaryotic extraction and purification is very time consuming and expensive. Recombinant expression in bacteria leads to inactive Hyal-1 forming inclusion bodies. Therefore, potent Hyal-1 inhibitors, like chemical compounds or plant extracts, are routinely screened against bovine testis hyaluronidase, which has an amino acid sequence identity of approx. 40 % compared to human Hyal-1. This again causes problems in interpretation of the obtained data, development of a pharmacophore model or searching for leader compounds inhibiting human Hyal-1. Using Autodisplay technology, we are able to express human Hyal-1 on the surface of *Escherichia coli* in an active form.[4] With this system, it is possible to screen compounds, directly using the desired target. A combination of pharmacophore modeling followed by docking studies using a virtual system and Hyal-1 crystal structure, helped us to get first impressions about binding of the substances to Hyal-1. Next, screening the best hits with whole-cells displaying Hyal-1 seems to be a promising way to find the needle in the haystack.

References

[1] Stern (2008), Semin Cancer Biol., 18, 275-280, [2] Lokeshwar *et al*. (2000) J Urol, 163, 348-356., [3] Lokeshwar *et al*. (2001) J Biol Chem, 276, 11922-11932., [4] Orlando Z. *et al.* (2015) J. Molecules, 20, 15449-15498.

[*]**Corresponding author: isabelle.lengers@uni-muenster.de**

Short Talk 4 (ST4)

Bacterial symbionts of social insects as sources of antiparasitic compounds

Carla Menegatti[1], Weilan G. da P. Melo[1], Bárbara M. do Prado[1], Fábio S. do Nascimento[2], Cameron R. Currie[3], Adriano D. Andricopulo[4], Jon Clardy[5], and Mônica T. Pupo[1]

[1] *School of Pharmaceutical Sciences of Ribeirão Preto, University of São Paulo, Ribeirão Preto, Brazil*
[2] *School of Philosophy, Sciences and Letters of Ribeirão Preto – University of São Paulo, Ribeirão Preto, Brazil*
[3] *Department of Bacteriology, University of Wisconsin, Madison, USA*
[4] *Physics Institute of São Carlos, University of São Paulo, São Carlos, Brazil*
[5] *Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School, Boston, USA*

Keywords: microorganisms, social insects, symbiosis, antiparasitic compounds.

Abstract

Microorganisms play an important role in natural products discovery since they produce compounds with highly complex chemical structures and diverse biological activities. Microorganisms and insects are involved in complex relationships, ranging from parasitism to obligate mutualisms and biologically active natural products act as signaling molecules in such interspecies interactions. It is known that social insects are subjected to climate and population conditions that increase their susceptibility to parasites. Therefore, these insects have developed an evolutionary defense mechanism consisting in symbiotic association with bacteria that biosynthesize antimicrobial products against pathogens. One of the best-known symbiotic associations was established over 50 million years between Attini ants and fungi cultivated by them for food. Bees are also associated with microorganisms however this relationship is still unclear. Based on these ecological evidences, this work aims to identify natural products biosynthesized by symbiotic microorganisms associated with social insects: *Acromyrmex* leaf-cutter ants and the stingless bee *Melipona scutellaris*. The ethyl acetate extract of MP15013-2, an actinobacteria isolated from *Acromyrmex* ants, displayed antiprotozoal activity against *T. cruzi* (63% inhibition) and *L. donovani* (83% inhibition). The bioguided fractionation of ethyl acetate extract by SPE and HPLC led to the isolation of four analogous glycosylated polyketides known as chromomycins. The bacterium *Paenibacillus polymyxa* ALLI-03-01, a symbiont of the stingless bee *Melipona scutellaris,* produced nine cyclolipodepsipeptides known as fusaricidins identified in mixture using MALDI-TOF-MS/MS. The different mixtures of fusaricidins displayed IC_{50} values of 0.46, 0.63, 1.03, 1.09 and 2.25 µg/mL against the parasite *L. donovani.* The compounds were also very active against other Trypanosomatidae parasites such as *T. brucei* and *T. rhodesiense*.

[*]**Corresponding author: mtpupo@fcfrp.usp.br**

Plenary Lecture 2 (PL2)

Pursuing New Avenues in Antiviral Therapy

Stephan Ludwig[1]

[1] *Institute of Virology (IVM), Centre for Molecular Biology of Inflammation (ZMBE), Münster, Germany*

Influenza is still one of the major plagues worldwide with the threatening potential to cause pandemics. We are currently limited to two groups of licensed anti-influenza drugs: the neuraminidase inhibitors oseltamivir and zanamivir, and the M2 ion-channel inhibitors amantadine and rimantadine. In recent years, there is an increasing incidence of resistance to these FDA-approved anti-influenza drugs. This underlines the urgent need for novel antivirals in preparation for future influenza epidemics or pandemics. Because we cannot predict the strain of influenza virus that will cause the next epidemic or pandemic, it is important that we develop novel anti-influenza drugs with broad reactivity against all strains, and subtypes that would not show the tendency to induce viral resistance.

Influenza virus infection results in the activation of a variety of intracellular signaling responses. It is a common view that most of these signaling events are initiated as an innate cellular response to defend the invading pathogen. While influenza viruses have evolved strategies to keep these responses in a tolerable limit, the virus also has acquired the capability to exploit some of these activities to support efficient replication. This dependence of influenza virus propagation on cellular signaling factors provides opportunities for a novel mode of antiviral interventions that targets essential host factors instead of viral components. In the last couple of years we have identified several cell signaling targets that are suitable for antiviral strategies, including the classical mitogenic MAPK cascade, that regulates active viral RNP export, or the NF-kappaB pathway, that interferes with the apoptotic response. Inhibition of these pathways efficiently blocked virus replication in cells and animals without toxicity or the tendency to induce resistant virus variants. The future perspectives of these novel antiviral attempts will be discussed.

Short Talk 5 (ST5)

Molecular networking accelerating the identification of new molecules candidates for neglected diseases treatment

Anelize Bauermeister,[1*] Luisa P. Gimenes,[1] João Luis C. Lopes,[1] Norberto P. Lopes[1]

[1]*Research Nucleus of Natural and Synthetic Products, Faculty of Pharmaceutical Sciences of Ribeirão Preto, University of São Paulo, São Paulo-SP, 14040-903, Brazil.*

Keywords: molecular networking; mass spectrometry; natural products; trypanosomatids.

Abstract

Studies of chemical content of natural sources have increased in last years mainly due to the development of technologies, as mass spectrometry approaches, that have allowed the analysis of a large amount of sample generating a great amount of data. Molecular Networking is an online molecular tool available in GNPS (Global Natural Products Social Molecular Networking) that has been widely employed in natural products to accelerate the identification of known and unknown molecules. This approach uses data obtained from mass spectrometry, more specifically fragmentation data, to cluster chemical compounds by structural similarity,[1] once similar structures show similar fragmentation pattern. In this work, we applied molecular network to investigate the chemical content of many species from different genera from the subtribe Lychnophorienae (Asteraceae), a plant endemic in the Brazilian Cerrado and traditionally used for medicinal purposes. Compounds isolated from this subtribe, such as sesquiterpene lactones (STL) and flavonoids, present biological activity against neglected diseases. For instance, the STLs lychnopholide, centratherin, goyazensolide and 15-desoxygoyazensolide, and the flavonoids luteolin and vicenin-2, isolated from *Lychnophora* species, were shown to be active against *Trypanosoma cruzi*, the etiological agent of Chagas' disease (American trypanosomiasis).[2] The obtained extracts were analyzed by HPLC ESI-IT-MS/MS using an untargeted method, in both positive and negative ionization mode. The data was converted in mzXML format and upload at GNPS using the online workflow. The molecular network was visualized as clusters and nodes in Cytoscape software. This strategy allowed the identification of chlorogenic acids, lactones and flavonoids (aglycone and C and/or O glycosylated), besides many new structures, including poly-glycosylated flavonoids, detected for the first time in Lychnophorineae subtribe. Here, the molecular network highlighted new structures with potential to be active against *T. cruzi*, and other trypanosomatids, directing their isolation and also assisting the structure characterization. To conclude, molecular network is a potential tool to be used in the search for new molecules with potential biological activity. Additionally, this approach has been widely applied to answer many kinds of questions, employing different strategies, in many different research areas.

References

[1] Wang et al. Sharing and community curation of mass spectrometry data with Global Natural Products Social Molecular Networking. Nature Biotechnology, v. 34, 2016.

[2] Grael, CFF; Albuquerque, S; Lopes, JLC. Chemical constituents of *Lychnophora pohlii* and trypanocidal activity of crude plant extracts and of isolated compounds. Fitoterapia, v. 76, 2005.

[*]**Corresponding author: ane.meister@usp.br**

Short Talk 6 (ST6)

Antiprotozoal sesquiterpene lactones and other constituents from *Tarchonanthus camphoratus, Schkuhria pinnata* and *Vernonia lasiopus*

Njogu M. Kimani [1], Josphat Matasyoh [2], Marcel Kaiser [3,4], Reto Brun [3,4] and Thomas J. Schmidt [1]

[1] Institute of Pharmaceutical Biology and Phytochemistry (IPBP), University of Münster, PharmaCampus Corrensstraße 48, Münster D-48149, Germany
[2] Department of Chemistry, Egerton University, P.O. Box 536, Egerton 20115, Kenya
[3] Swiss Tropical and Public Health Institute (Swiss TPH), Socinstr. 57, Basel CH-4051, Switzerland
[4] University of Basel, Petersplatz 1, Basel CH-4003, Switzerland

Keywords: Asteraceae, Sesquiterpene lactones, antiprotozoal activity.

Abstract

Through our sustained search for antiprotozoal agents in plants of the family Asteraceae, we have reported interestingly potent natural products particularly sesquiterpene lactones (STLs) (1). Here, we have investigated *Schkuhria pinnata, Tarchonanthus camphoratus* and *Vernonia lasiopus* collected from Kenya. Bioactivity guided isolation of secondary metabolites from dichloromethane extracts of the three plants have yielded 29 STLs; 3 new and 19 known from *S. pinnata*, 6 elemanolide type from *V. lasiopus* and two more from *T. camphoratus*. Additionally, pectolinarigenin and a benzenepropanol derivative were isolated. These compounds were identified through analysis of their HR-MS and 1D and 2D NMR data in comparison with literature data (2,3). All these compounds were tested for *in vitro* antiprotozoal activity and for cytotoxicity against mammalian cells (L6 cell line). Santhemoidin A was the most active from *S. pinnata* with an IC_{50} value of 0.10 µM against *Trypanosoma brucei rhodesiense* (Tbr) trypomastigotes and a selectivity index (SI) of 21.5. From *T. camphoratus*, 3-oxo-1,2-dehydrocostic acid displayed interesting activity with IC_{50} values of 2.8 µM and 0.18 µM against Tbr and axenic grown *L.donovani* amastigotes and SI values of 6.2 and 95.4 respectively. Vernolepin, from *V. lasiopus*, displayed an IC_{50} value of 0.19 µM against Tbr and an SI value of 14.5. These bioactivity data complement previous data obtained in our group and give more insights into structure- anti-trypanosomal activity relationships of STLs (1).

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***Corresponding author: mark.njogu@gmail.com**

Short Talk 7 (ST7)

Design of selective inhibitors for *Schistosoma mansoni* dihydroorotate dehydrogenase

Felipe A. Calil[1], Juliana S. David[1], Fernando Fumagalli[1], Flávio S. Emery[1], Marcelo S. Castilho[2], Franco H. Leite[2], Micah Maetani[3], Stuart L. Schreiber[3], M. Cristina Nonato[1*]

[1] *School of Pharmaceutical Sciences of Ribeirão Preto, University of São Paulo, 14040-903, Ribeirão Preto, SP, Brazil*

[2] *School of Pharmacy, Federal University of Bahia, 40170-115, Salvador, BA, Brazil*

[3] *Broad Institute of MIT and Harvard, 415 Main Street, Cambridge, MA 02142, USA*

Keywords: dihydroorotate dehydrogenase, schistosomiasis, drug repositioning, inhibition studies.

Abstract

Drug repositioning consists in evaluating or using existing drugs for the treatment of diseases other than those for which they were originally developed.[1] Schistosomiasis, also known as snail fever, is a parasitic disease caused by blood flukes of the genus Schistosoma. In terms of impact, this disease is second only to malaria as the most devastating parasitic disease and up to this moment, only one medication is known and applied: Praziquantel. Although this drug has been widely and effectively used for many years, some studies have already shown resistant organisms towards it.[2] That is the reason we chose this disease as focus of study to repurpose drugs. One of the approaches to the development of new drugs is through the inhibition of enzymes present in important biochemical pathways. *S. mansoni* possesses all six enzymes in the *de novo* biosynthesis of pyrimidine, including the enzyme dihydroorotate dehydrogenase, DHODH, a flavoenzyme that contains FMN as a cofactor. The reaction catalyzed by DHODHs is the fourth and the only redox reaction in this biochemical pathway. Due to the importance of pyrimidine biosynthesis pathway, the fact that the DHODHs from *S. mansoni* and *Plasmodium falciparum* share high similarities and the latter already has known inhibitors which are already in clinical studies and/or in the market, we decided to evaluate the repurposing of malarial DHODH inhibitors against *Sm*DHODH. In our studies inhibitors were identified with great inhibitory potential (low micro molar scale). A number of derivatives from one in-market antimalarial drug were synthetized. Those derivatives with better potential (low nanomolar scale) had their inhibition mechanisms performed, in which, competitive, non-competitive and mixed inhibition mechanisms were found. Pharmacophore model was also performed, giving important insights on how to improve such molecules for obtaining lead compounds.

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[*]**Corresponding author: cristy@fcfrp.usp.br**

Short Talk 8 (ST8)

A high-throughput-compatible method to determine the optical density of bacterial cell cultures in microplates without sample dilution

Meyers A*, Furtmann C and Jose J

Institute of Pharmaceutical and Medicinal Chemistry, PharmaCampus, Westfälische Wilhelms-Universität, Münster, Germany

Keywords: optical density, bacteria, microplate reader, conversion formula.

Abstract

A convenient method to determine the growth state of a bacterial cell culture is to determine the optical density (OD) spectrophotometrically. Incident light of similar wavelength to the size of a particle is scattered in suspensions like bacterial cell cultures,[1] but if a beam of light is scattered through contact with more than one cell, the attenuation of light measured spectrophotometrically will not be proportional to the number of particles.[2] This results in an apparently lower OD.[3] Therefore, monitoring the OD of a bacterial culture directly in a microtiter plate without dilution, for example during cell growth or as a control in advance of enzymatic assays, is inaccurate and a dilution of the samples is necessary to measure within the linear range of a spectrophotometer. This process is time-consuming, prone to errors and not compatible with high-throughput applications. Here we present a direct method to estimate the OD at 578 nm (OD_{578}) of bacterial cultures in microplates without the need for removing aliquots and additional dilution of the samples. To establish this method, cell cultures of *Pseudomonas putida* KT2440 were used. A data set of 343 OD_{578} values which have been determined in parallel directly in the microplate without dilution and measured conventionally in a spectrophotometer after dilution, was generated. The software Origin 9 was used to identify an exponential function, which allowed the reliable transformation of one dataset into the other. The formula derived thereof enabled the direct conversion of OD measurements of undiluted microplate reader-measured samples into OD values anticipated for diluted samples measured with a conventional spectrophotometer. Moreover, the applicability of an exponential fit for OD conversion was verified by a serial dilution of a formazine suspension of defined turbidity, which is usually used in water quality measurements.[4] Although our method was established with cultures of *P. putida* KT2440, it can be easily transferred to any other bacterial strain.

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***Corresponding author: annika.meyers@uni-muenster.de**

Plenary Lecture 3 (PL3)

Protein interactions as a target in drug discovery: from assay development to potent small molecule inhibitors

Joachim Jose[*1]

Institute of Pharmaceutical and Medicinal Chemistry, PharmaCampus, Wesfalian Wilhelms-University Münster, Germany

Abstract

To address selected protein-protein interactions (PPIs) by small – or rather small – molecules that bind and interfere with them appears to be a promising and emerging target for drug discovery. In contrast to the active site of an enzyme or the ligand binding site of a receptor, the PPI interface in general does not represent a cavity, but rather a surface exposed domain or area of the protein. Hydrophobic patches are important in such interfaces, but the number and role of hydrogen bonds and water molecules can be rather different from classical cavities. Furthermore, the influence of protein flexibility and induced fitting is more difficult to predict, than it is for an enzyme or a receptor.
Based on bacterial surface display, we have developed a flow cytometry based screening assays to identify small molecule PPI inhibitors for human cancer target proteins. The assays developed could be used to identify inhibitors of heterologous PPI, as in the case of human protein kinase CK2 [1] and transcription factor Myb [2,3], as well as inhibitors of homologous PPI as in the case of human HSP90 [4]. KD values of the new compounds identified with the corresponding targets were determined by microscale thermophoresis (MST). This strategy led to new potent small molecule PPI inhibitors that turned out to be active in a mouse model as well as in primary human leukemia cells.
In conclusion, the strategy as applied here, in particular combining bacterial surface display and flow cytometry for the rapid screening for PPIs and IC_{50} value determination, followed by MST for K_D measurement of the best candidates appears to be a practical and valuable way to identify novel small molecule inhibitors of PPIs.

Acknowledgments:
I am grateful for the valuable contributions of my colleagues Karsten Niefind, Karl-Heinz Klempnauer, Holger Gohlke, Julia Hauer and their groups, as well as to my co-workers involved in this work.

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[*]**Corresponding author: joachim.jose@uni-muenster.de**

Short Talk 9 (ST9)

Isolation of secondary metabolites from *Stachybotrys* species and their exploration concerning human health risk

Annika Jagels[1*], Svetlana Kalinina[1], Yannick Hövelmann[1], Florian Hübner[1], Benedikt Cramer[1], Hans-Ulrich Humpf[1*]

[1] *Institute of Food Chemistry, Westfälische-Wilhelmsuniversität, Münster, Germany*

Keywords: *Stachybotrys*, isolation, phenylspirodrimanes, structure elucidation, bioactivity.

The occurrence of fungi of the genus *Stachybotrys*, also known as the "toxic black mould", in the indoor environment has been reported frequently, particularly in water-damaged buildings. Approximately 140 bioactive compounds from *Stachybotrys* species are known and may be responsible for adverse health effects in humans. Important representatives are macrocyclic trichothecenes, atranones, and the phenylspirodrimanes, the most dominant group of secondary metabolites among the genus *Stachybotrys*. Recent investigations showed there is still a great potential for the identification and isolation of new phenylspirodrimane derivatives. Furthermore, little attention has been paid to this class of compounds. Although these compounds are known to derive from polyketide as well as terpenoid metabolism, the exact biosynthetic pathway is yet unclear. They show a variety of biological activities such as disruption of the complement system, inhibition of enzymes and TNF-α release, neurotoxicity, cytotoxicity, fibrinolysis and plasminogen activation, as well as antiviral and antiplasmodial activity[1,2,3].

In the course of our study, our objective is to investigate the relationship between human health and fungal contamination in indoor environments. After isolation and characterisation of *Stachybotrys* metabolites from fungal cultures, the potential human exposure will be investigated by screening different mouldy building materials as well as physiological samples for the occurrence of *Stachybotrys* exposure biomarkers. Regarding these facts, the focus is on the isolation and structure elucidation of known and new bioactive phenylspirodrimane derivatives from fungal cultures of *Stachybotrys* species using HRMS, NMR, and LC-MS/MS techniques. Cytotoxicity experiments are conducted to give first insights into bioactivity. Considering that the chemical diversity is often dependent on environmental factors, metabolites are analysed, particularly in view of profile changes, to identify new secondary metabolites and to develop new strategies for isolation by using the one strain-many compounds (OSMAC) approach.

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[*]**Corresponding author: a_jage01@wwu.de; humpf@wwu.de**

Short Talk 10 (ST10)

Natural products as inhibitors of *Leishmania major* dihydroorotate dehydrogenase

Lucas A. Chibli[1], Maria Cristina Nonato[2], Thomas J. Schmidt[3] and Fernando B. da Costa[1*]

[1]AsterBioChem Research Team, School of Pharmaceutical Sciences of Ribeirão Preto, University of São Paulo, Ribeirão Preto, Brazil. [2]Laboratory of Protein Crystallography, School of Pharmaceutical Sciences of Ribeirão Preto, University of São Paulo, Ribeirão Preto, Brazil. [3]Institute of Pharmaceutical Biology and Phytochemistry (IPBP), University of Münster, Germany.

Keywords: Dihydroorotate Dehydrogenase, *Leishmania major*, Natural Products, Quantitative Structure-Activity Relationship.

The flavoenzyme dihydroorotate dehydrogenase (DHODH) stands out as a key molecular target for parasites causing Neglected Diseases (NDs), since it catalyzes the fourth reaction of the *de novo* pyrimidine biosynthetic pathway[1]. Trypanosomatids survival and growth in mammalian hosts depends on this rote, since pyrimidine nucleotides exerts vital functions in the cells, especially within DNA and RNA biosynthesis[2]. There are no relevant results up to now in the literature for the inhibition of *Leishmania major* DHODH (*Lm*DHODH). Thus, this study screened 57 natural products, most of them isolated from Asteraceae, for *in vitro* inhibition of *Lm*DHODH, including a set of 21 sesquiterpene lactones (STLs). Classical QSAR (Quantitative Structure-Activity Relationship) studies, using 2D and internal 3D descriptors, was performed with the STLs to establish reliable models capable to provide mechanistic interpretation, regarding which and how the structural features influence their inhibitory activity and also predict the activity of untested STLs[3]. The IC_{50} values varied from 27 to 1200 µM, with 2 STLs, 1 diterpene and 1 flavonoid showing values below 50 µM. A reliable QSAR model was obtained (R^2: 0.83; Q^2: 0.69 and P^2: 0.66) composed by one 2D and two 3D descriptors, indicating that higher inhibition of *Lm*DHODH require balanced distribution of the hydrophobic regions across the molecular surface (vsurf_ID8); higher width (std_dim2); lower hydrophobicity and protonation state (GCUT_SLOGP_2). This outcome indicates that natural products can actually inhibit *Lm*DHODH, which is a quite relevant discovery since an infinity of antileishmanial secondary metabolites active against promastigotes and amastigotes have been reported[4], yet for most of them the mechanism of action remains unknown. The unprecedented and promising data obtained highlighted some of those 57 natural products as promising lead compounds for the discovery of new antiparasitc drugs, aiming new and effective therapeutic alternatives for NDs caused by trypanosomatids, especially leishmaniasis.

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***Corresponding author: febcosta@fcfrp.usp.br**

Short Talk 11 (ST11)

Natural product inspired development of novel anti-malarial drugs

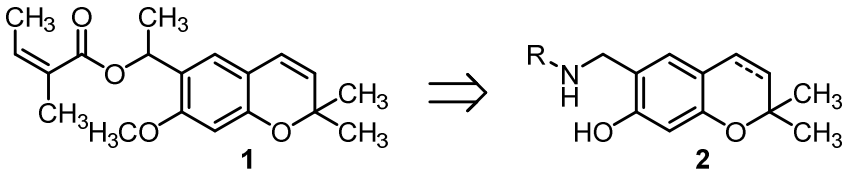
Jan-Frederik Uth[1*], Marcel Kaiser[2], Thomas J. Schmidt[3], Bernhard Wünsch[1]

[1] *Institute of Pharmaceutical and Medicinal Chemistry, Corrensstraße 48, WWU, Münster, Germany*
[2] *Swiss Tropical and Public Health Institute, Socinstrasse 57, Basel, Switzerland*
[3] *Institute of Pharmaceutical Biology and Phytochemistry, Corrensstraße 48, WWU, Münster, Germany*

Keywords: malaria, chromanes, plasmodium, encecalol angelate

Abstract

Nature has been a constant source of inspiration for organic chemists all over the world. Plants used in folk medicine have been investigated for novel lead compounds for a long time. In 2011, Schmidt *et al*. published a study about the anti-protozoal activity of the dichloromethane extract of *Ageratum conyzoides L.*, a medicinal plant widespread in tropical and subtropical regions.[1] Encecalol angelate (**1**), a chromene isolated from this extract, served as lead structure for the development of several anti-protozoal compounds by Wünsch *et al.*.[2] Two 7-hydroxychromene derivatives in this study exhibited remarkable anti-malarial activity. Based on these results, we started to develop novel chromane- and chromene-based compounds with high anti-malarial activity, good biopharmaceutical profile and metabolic stability, while maintaining a short and efficient synthetic route (**2**). Efficient organic reactions were used to create the chromane- and chromene-scaffolds. The anti-malarial activity of a first set of achiral compounds was tested in vitro, showing moderate to high activity.



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[*]**Corresponding author: jan.uth@uni-muenster.de**

Short Talk 12 (ST12)

Structural and biochemical characterization of recombinant *Schistosoma mansoni* fumarate hydratase

Iara Aimê Cardoso[1], Aline Kusumota Luiz de Souza[1], Maria Cristina Nonato[1]

[1]*Department of Physics and Chemistry, School of Pharmaceutical Sciences of Ribeirão Preto, University of São Paulo, Ribeirão Preto, SP, Brazil*

Keywords: Fumarate hydratase, *Schistosoma mansoni*, thermal shift assay, enzymatic kinetic, crystallization.

Abstract

Schistosomiasis is a parasitic neglected disease caused by the parasite *Schistosoma*, which has been reported from 78 countries, and is responsible for 200 thousands of deaths per year[1]. In the search for new targets against schistosomiasis, an important strategy consists in the identification and characterization of essential enzymes from *Schistosoma*. The class II fumarate hydratase of *Schistosoma mansoni* (*Sm*FH) catalyzes the reversible hydration of fumarate to L-malate. It's known that the accumulation of fumarate may result in protein succination[2], that can lead a metabolic toxicity. Thus, the inhibiton of SmFH could be a interesting strategy against schistosomiasis. In this present work, we establish a protocol for *Sm*FH expression in *E. coli* BL21(DE3), and we obtained soluble protein with a good yield. The gel filtration chromatography showed that the enzyme is tetrameric, compatible with enzymes of the same class. We determine the optimal pH for SmFH activity, and the results indicates that the maximum activity is reached at pH 7 and 7.5 using fumarate as substrate, and pH 8 using malate. The enzymatic kinetics using both substrates (malate and fumarate) were performed in 50mM Tris pH 7.5 and 150mM KCl, and the results reveal a K_m of 0.47mM and 0.13mM for malate and fumarate, respectively. For *Sm*FH crystallization experiments we used the vapor diffusion technique, by sitting-drop method. Crystals were obtained with *Sm*FH at 10mg/mL in 50mM Tris pH 8, 100mM sodium malonate pH 4 and 12% polyethylene glycol 3350, and the dataset collected using x-ray diffraction are currently being processed and refined. The results obtained so far are just a part of a major characterization of *Schistosoma mansoni* fumarate hydratase, which will provide the framework for the validation of *Sm*FH as a macromolecular target for the design of new antischistosomiasis drugs.

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[*]**Corresponding author: iara.cardoso@fcfrp.usp.br**

Poster Session

(in alphabetical order of last names)

P01. Anelize Bauermeister (USP)
Molecular networking accelerating the identification of new molecules candidates for neglected diseases treatment

P02. Freddy Bernal (WWU)
Synthesis and docking studies of dihydrobenzofuran neolignan analogues as antileishmanial agents

P03. Leandro O. Bortot (USP)
Identifying potential leads for the inhibition of the Dengue Virus infection using molecular modeling and computational structure-based drug discovery methods

P04. Gisele Bulhões (USP)
In vitro trypanocidal activity of indolizines analogues in suspension and encapsulated in nanostructured lipid carriers

P05. Felipe A. Calil (USP)
Design of selective inhibitors for *Schistosoma mansoni* dihydroorotate dehydrogenase

P06. Iara A. Cardoso (USP)
Structural and biochemical characterization of *Schistosoma mansoni* fumarate hydratase

P07. Ricardo C. Castro (USP)
Notch signaling pathway activation in response to *Mycobacterium tuberculosis*

P08. Lucas A. Chibli (USP)
Natural products as inhibitors of *Leishmania major* dihydroorotate dehydrogenase

P09. Marília L. Cirqueira (USP)
Assessing structural stability of *Trypanosoma cruzi* nitroreductase enzyme by differential scanning fluorimetry

P010. Dagmar Flittner (WWU)
Antitrypanosomal alkaloids from *Pachysandra terminalis*

P011. Hippolyt L. Greve (WWU)
Antiplasmodial leads in oleo-gum-resins from Burseraceae: bioactivity-guided fractionation of myrrh

P012. Diego Hernandez (USP)
Bacterioma associated with stingless bee *Melipona scutellaris*: studies of their chromatographic profiles

P013. Annika Jagels (WWU)
Isolation of secondary metabolites from *Stachybotrys* species and their exploration concerning human health risk

P014. Njogu M. Kimani (WWU)
Antiprotozoal sesquiterpene lactones and other constituents from *Tarchonanthus camphoratus*, *Schkuhria pinnata* and *Vernonia lasiopus*

P015. Isabelle Lengers (WWU)
Human Hyal 1 – from *in silico* pharmacophore modeling to *in vitro* inhibitor screening

P016. Mairin Lenz (WWU)
4,15-Isoatriplicolide tiglate: irreversible inhibitor of trypanothione reductase

P017. **Veronica Lippi (USP)**
Development of real time RT-PCR for the differential diagnosis of chikungunya, dengue and Zika

P018. Pedro H. Luccas (USP)
Trypanosoma cruzi nitroreductase: kinetics with new substrates

P019. Maristela B. Martins-Teixeira (USP)
Targeting trypanosomal DNA topoisomerase: anthracyclines against *Trypanosoma cruzi*

P020. Carla Menegatti (USP)
Bacterial symbionts of social insects as sources of antiparasitic compounds

P021. Annika Meyers (WWU)
A high-throughput-compatible method to determine the optical density of bacterial cell cultures in microplates without sample dilution

P022. Jan-Frederick Uth (WWU)
Natural product inspired development of novel anti-malarial drugs

P023. Fabiana A. Zambuzi (USP)
Antitrypanosomal global DNA methylation may impair monocyte function in *M. tuberculosis* infection accounting to disease progression