



Platforms and Technologies to discover Novel Antibiotics: HIPS & the international IRAADD network

Marcus Miethke

Helmholtz Institute for Pharmaceutical Research Saarland (HIPS)

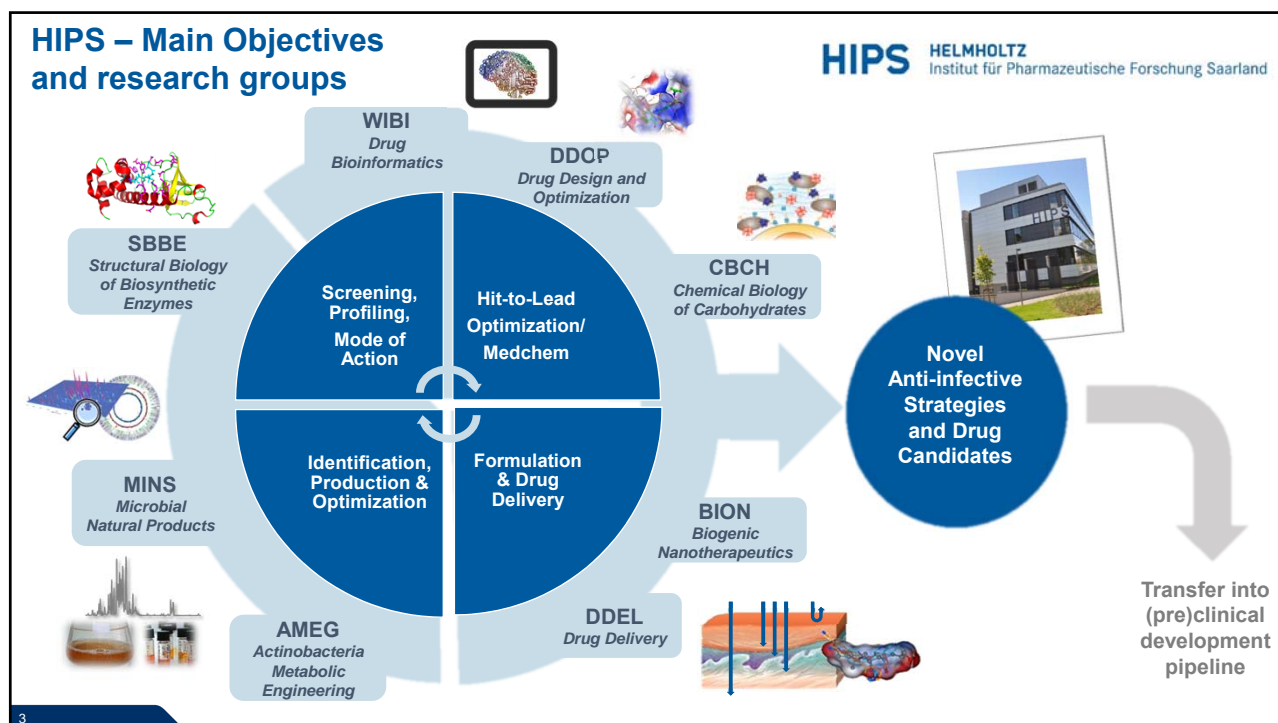
Dept. of Microbial Natural Products (MINS)

Amsterdam, 05 June 2019

HIPS HELMHOLTZ
Institut für Pharmazeutische Forschung Saarland

HIPS – Helmholtz Institute for Pharmaceutical Research Saarland



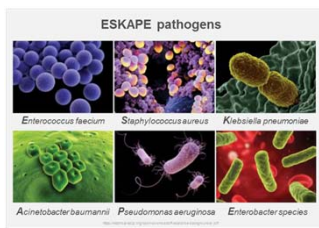


DZIF – The German Centre for Infection Research

Mission: From discovery to therapeutic application



- **Virtual Centre for Translational Infection Research**
- Established in 2011 by BMBF
- Multidisciplinary research at 7 main partner sites
- 35 German research institutions affiliated since 2015
- DZIF Head Office at HZI
- **Aim: Bridging the "Translational Gap"**



HZI HELMHOLTZ
Centre for Infection Research

MHH
Medizinische Hochschule
Hannover



Technische Universität Braunschweig

TWINCORE

TTU „Novel Antibiotics“
Coordinated by HIPS

HIPS HELMHOLTZ
Institut für Pharmazeutische Forschung Saarland

5

German Centre for Infection Research

DZIF, road to translation



Core research structure of DZIF:
9 Thematic Translational Units (TTUs)

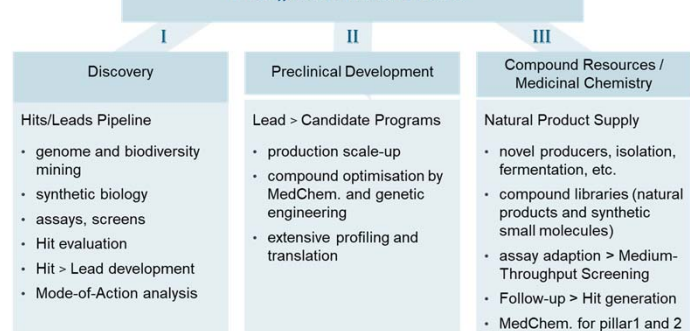
- Emerging Infections
- HIV
- Hepatitis
- Malaria
- Tuberculosis
- Gastrointestinal Infections
- Infections of the Immunocompromised Host
- Healthcare-associated and Antibiotic-resistant bacterial Infections

- Novel Antibiotics (incl. Natural Compound Library)

HZI HELMHOLTZ
Centre for Infection Research

HIPS HELMHOLTZ
Institute for Pharmaceutical Research Saarland

TTU „Novel Antibiotics“



6

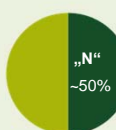
Our Strategy: Natural Products Research & Therapeutic Development

- “Natural products possess **enormous structural and chemical diversity** that cannot be matched by any synthetic libraries of small molecules and continue to inspire novel discoveries in chemistry, biology, and medicine.”
- “They are **evolutionarily optimized** as drug-like molecules and remain the best sources of drugs and drug leads.”

Newman DJ, Cragg GM. *J. Nat. Prod.* **2012**
Shen B, *Cell* **2015**

Role of **Natural Products** in Drug Discovery 1940-2010:

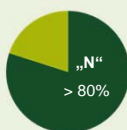
Anticancer



„N“: Natural Products (NPs) or NP-derived Small Molecules

Newman & Cragg, *JNP* 2012

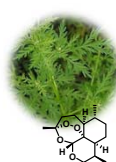
Antibacterial



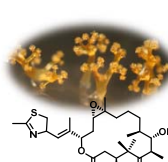
Selected examples of NPs used for therapy



anti-bacterial



anti-malarial



anti-cancer

Our approach

- Natural products as promising source for novel anti-infectives
- Genome/Metabolome Mining combined with Bioinformatics/ Database analyses to identify novel drug candidates addressing new molecular targets and/or novel modes of action

7

Our Strategy: Natural Products Research & Therapeutic Development

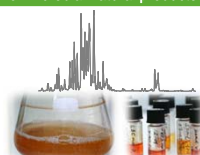
- “Natural products possess **enormous structural and chemical diversity** that cannot be matched by any synthetic libraries of small molecules and continue to inspire novel discoveries in chemistry, biology, and medicine.”
- “They are **evolutionarily optimized** as drug-like molecules and remain the best sources of drugs and drug leads.”

Newman DJ, Cragg GM. *J. Nat. Prod.* **2012**
Shen B, *Cell* **2015**

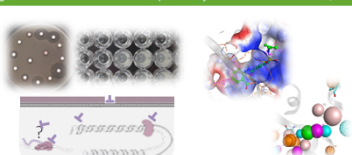
HIPS is the first public research institute in Germany explicitly devoted to the pharmaceutical sciences



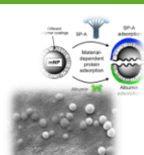
Identification & Production of microbial natural products



Screening, Profiling, Hit-to-Lead Optimisation
Target ID/ Mode of Action (Semisynthesis/MedChem, PK/PD,...)

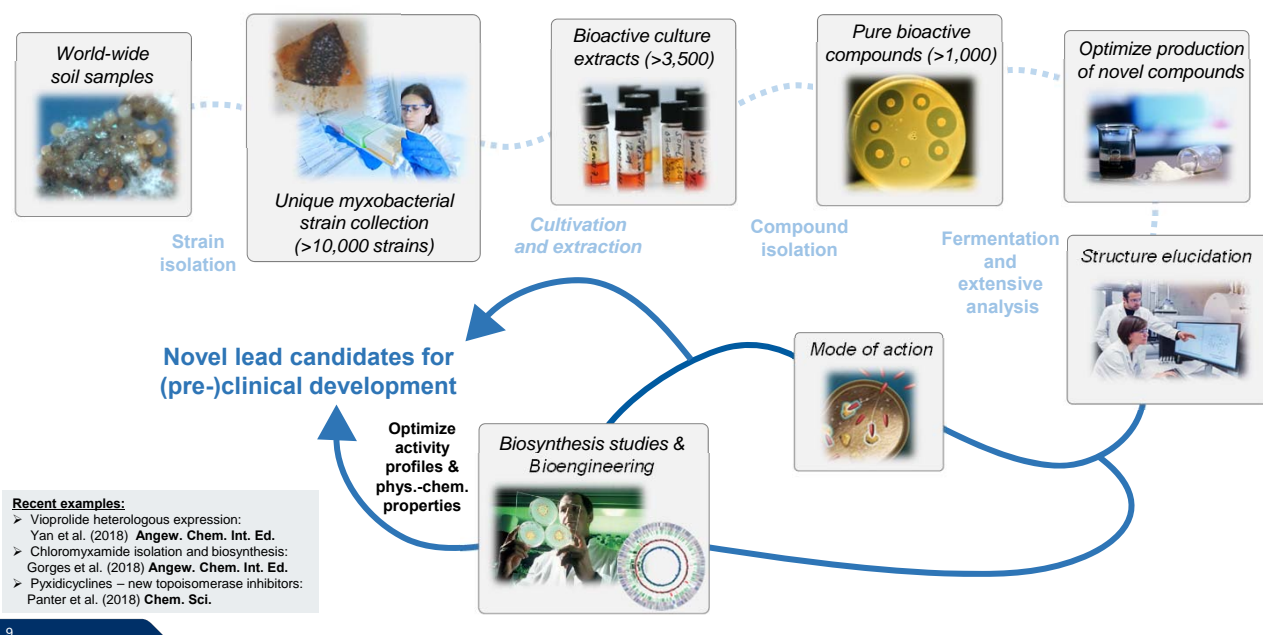


Formulation & Drug delivery



8

Dept. of Microbial Natural Products (MINS): From Soil Samples to Drug Candidates



9

Microbial Biodiversity and Synthetic Biotechnology – Potential to find, modify and produce novel natural products

Myxobacteria

Rod-shaped soil bacteria

Collective swarming behavior

Multicellular fruiting bodies

Predatory lifestyle ('wolfpack bacteria')

Well-known and underexplored secondary metabolite producers!

Cytotoxic

Disorazol

Argyirin

Myxopyronin

Antibacterial

Antiviral

Epothilone

Aetheramide

Tatrolon

Ajudazole

Ambruticin

Antifungal

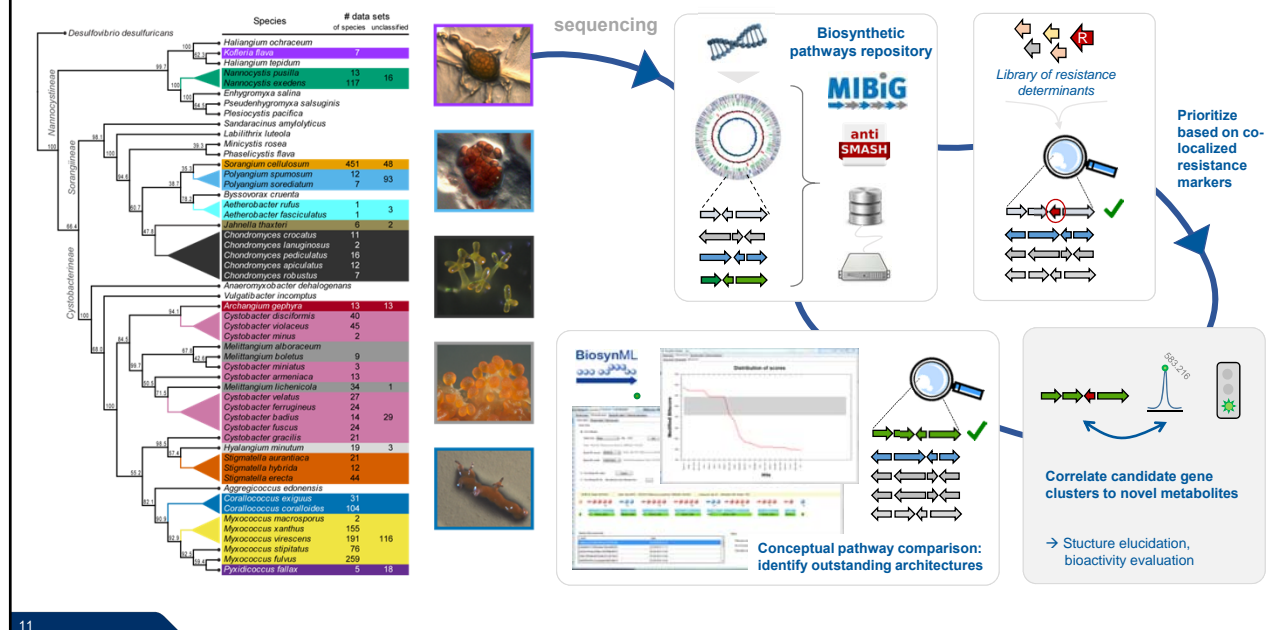
Myxobacteria

Cystobactamid

Herrmann et al. (2015) *Nat. Prod. Rep.*
Hoffmann et al. (2018) *Nature Commun.*

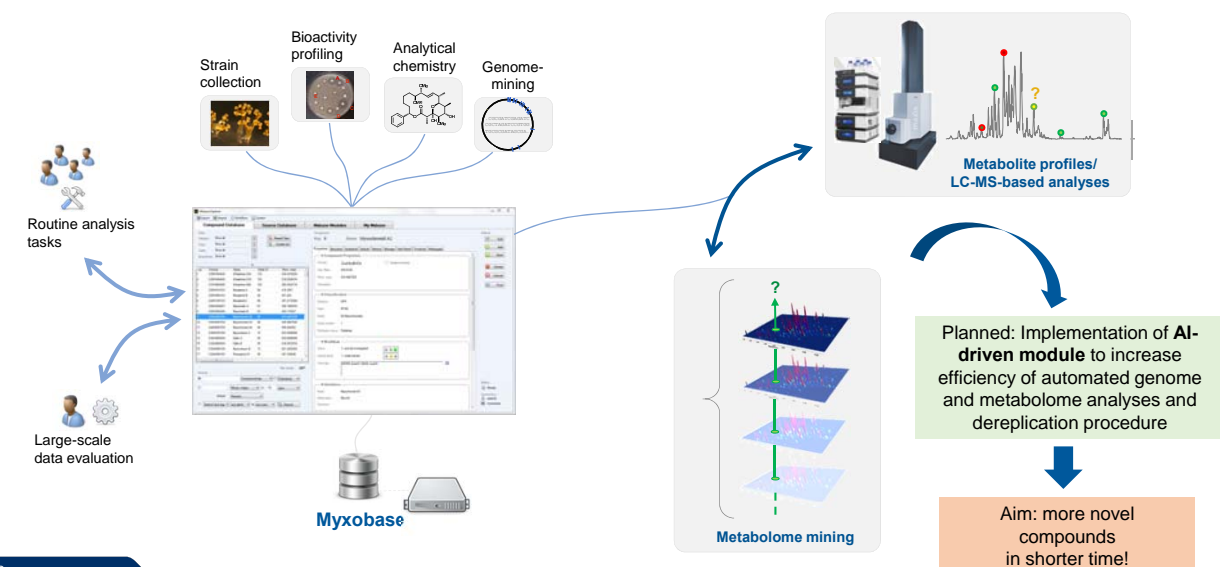
10

Myxobacterial genome mining for compound discovery



Myxobase

NP information hub & LC-MS-based **discovery & dereplication** platform for novel drug candidates



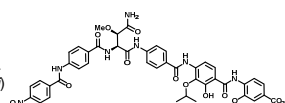
Recently discovered novel natural products from Myxobacteria and Actinobacteria with promising anti-infective activities (published/patented by HIPS/HZI groups)

Biodiversity mining:
Isolation of novel strains,
genera & families of
bacteria and fungi

Genome mining:
biosynthetic pathway
analysis / engineering

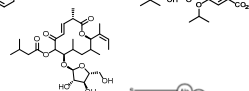
Metabolome mining:
target compounds &
producer strains

- **Cystobactamids**
(broad-spectrum activity incl. ESKAPE, e.g. *A. baumannii*)



Baumann et al. (2014) *Angew. Chem. Int. Ed.*
Hüttel et al. (2017) *Angew. Chem. Int. Ed.*
Pat.: WO2015003816A3, EP13003539

- **Disciformycins**
(anti-MRSA, anti-VRSA)



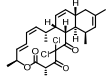
Surup et al. (2014) *Angew. Chem. Int. Ed.*

- **Pinensins**
(antifungal)



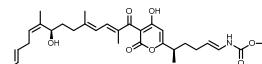
Mohr et al. (2015) *Angew. Chem. Int. Ed.*

- **Chlorotonil**
(antimalarial)



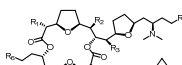
Held et al. (2014) *Antimicrob. Agents Chemother.*
Abou-Fayad et al. (2017) Pat.: EP 17200445.9

- **Corallopyronin A**
(anti-Wolbachia/anti-filarial)



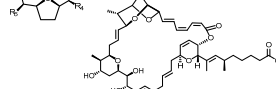
Sucipto et al. (2015) *Chem. Sci.*
Sucipto et al. (2017) *Metab. Eng.*
Pat.: WO 2014181000 A1; EP 2994535 A1

- **New Pamamycins**
(anti-TB)



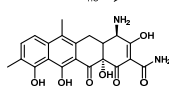
Rebets et al. (2015) *Angew. Chem. Int. Ed.*

- **Neosorangins**
(broad spectrum anti-Gram-positives)



Pat.: EP 16002083.0 (filed in 2016)

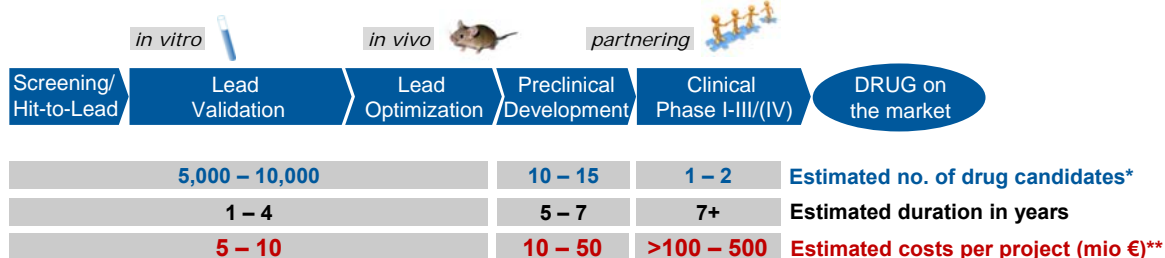
- **Amidochelocardin**
(broad-spectrum activity incl. ESKAPE)



Lesnik et al. (2015) *Angew. Chem. Int. Ed.*
Pat.: US8361777B2 (2013)
Pat.: EP17210536.3 (filed in 2017)

13

Challenge: Create research synergies for new antibiotic development programs



TTU „Novel Antibiotics“



Coordinating Institution: HIPS

recently
established
JPIAMR-VRI
network:
IRAADD

International Research Alliance for
Antibiotic Discovery and Development



<https://www.jpiamr.eu/iraadd/>

14

jpiamr **IRAADD – Network partners and expertise** **IRAADD**

Current status: 36 scientific representatives from organisations of 14 different countries

<u>Natural Products Discovery & Biosynthetic Engineering</u>	<u>Target-based drug design/ Medicinal Chemistry</u>	<u>Drug/Target Bioinformatics & Chemical Biology/Genetics</u>	<u>Medical and Environmental Microbiology/Parasitology & Biotechnology</u>
Rolf Müller HIPS, Germany	Marco Pieroni University of Parma, Italy	Barrie Wilkinson John Innes Centre, UK	Atanas G. Atanasov INPST, Poland
Youming Zhang Shandong University, China	Yves L. Janin CNRS/Institut Pasteur, France	Heike Broetz-Oesterhelt University of Tübingen, Germany	Philippe Glaser Institut Pasteur, France
Tilman Weber Technical University, Denmark	Mark Brönstrup HZI, Germany	Gilles P. van Wezel Leiden University, Netherlands	Achim Hoerauf Univ. Medical Center Bonn, Germany
Yanyan Li CNRS-MNHN, France	Jean-Louis Reymond University of Bern, Switzerland	Bertrand Aigle University of Lorraine, France	Valerie Mizrahi Univ. of Cape Town, South Africa
Helge B. Bode University Frankfurt, Germany	Violetta Cecchetti University of Perugia, Italy	Eriko Takano University of Manchester, UK	Jörn Kalinowski Bielefeld University, Germany
Stefano Donadio NAICON, Italy	Rui Moreira University of Lisbon, Portugal	Marnix Medema Wageningen University, Netherlands	Jean-Luc Pernodet University Paris-Saclay, France
Andriy Luzhetskyy Saarland University, Germany	Anders Karlén Uppsala University, Sweden	Philippe Chaignon University of Strasbourg, France	Wolfgang Wohlleben University of Tübingen, Germany
Olga Genilloud Fundación MEDINA, Spain	Ian Gilbert University of Dundee, UK	Tanja Schneider Bonn University, Germany	Hrvoje Petković University of Ljubljana, Slovenia
Jörn Piel ETH Zurich, Switzerland		Kira J. Weissman University of Lorraine, France	Ingo B. Autenrieth Univ. Hospital Tübingen, Germany
		Maarten van Dongen AMR Insights, Netherlands	

15

jpiamr **IRAADD** **IRAADD – Mission and Goals**

- Unite **internationally renowned groups** with excellent track records in **AMR research** (Focus: **early stages of antibiotic discovery and development**)
- Implement a **global cooperative platform** to exchange scientific data, translational knowledge and interdisciplinary expert advice
- Develop **sustainable long-term concepts** for **project funding** together with international stakeholders

↓

Joint Antibiotics Research in Europe and Globally

- Take **collaborative AMR research** to a new level by creating synergies on the international level
- Define and tackle **innovative antibiotic development projects** to refill the pipeline with new drug candidates
- Address the demands of the **EU „One Health Action Plan“** and the **WHO program** to fight priority pathogens
- Establish an **International Center for Translational Antimicrobial Drug Research** (Focus on Europe)
- Foster **development and visibility of JPIAMR-VRI**

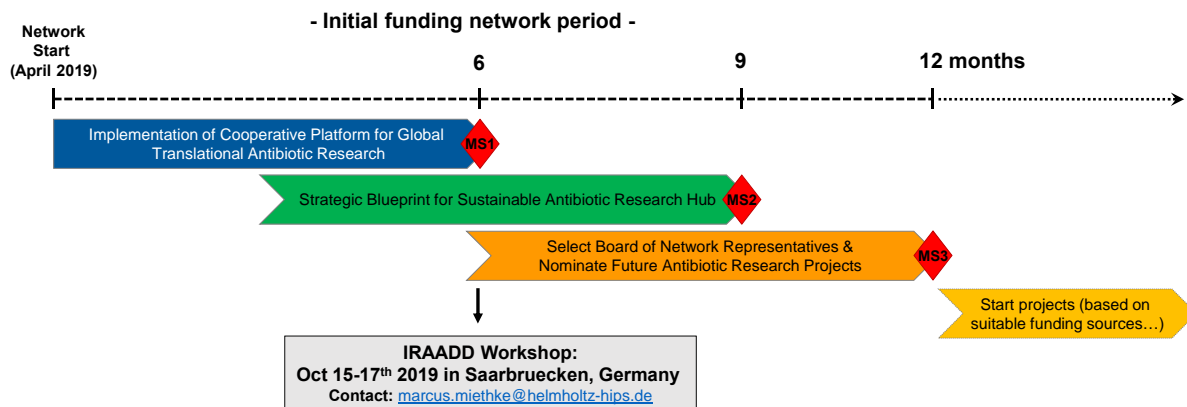
Build partnerships with

- **Industry/SME**
- **Global Health Organizations**
-

16



IRAADD – Plans and Milestones for 2019/20 and beyond



Further mid-to-longterm goals:

- Integration of additional partners (especially industry/SME)
- Close collaboration with key international stakeholders (e.g. Global Health Foundations, EU policy etc.)
- Generation and protection of IP ownership for initiated projects within the network

17

Helmholtz Institute for Pharmaceutical Research Saarland



Many thanks
for
your attention!

HIPS HELMHOLTZ
Institute for Pharmaceutical Research Saarland

