Notes, links and information in: https://bit.ly/3IMpY4e

Agenda:

- Introductions, Icebreaker
- Survey of participant background (anonymous)
- Ersilia Model Hub: short introduction
- BreakOut Rooms around sustainability, contributor guidelines and ethics, community building
- Wrap-up

Ersilia

Software Sustainability Institute

Open Source AI/ML for infectious disease research

Collaborations Workshop 2022, Software Sustainability Institute
05.04.2022

Gemma Turon, gemma@ersilia.io
Ersilia Open Source Initiative
https://ersilia.io

Ersilia

Software Sustainability Institute

Ersilia

Miquel Duran-Frigola, PhD

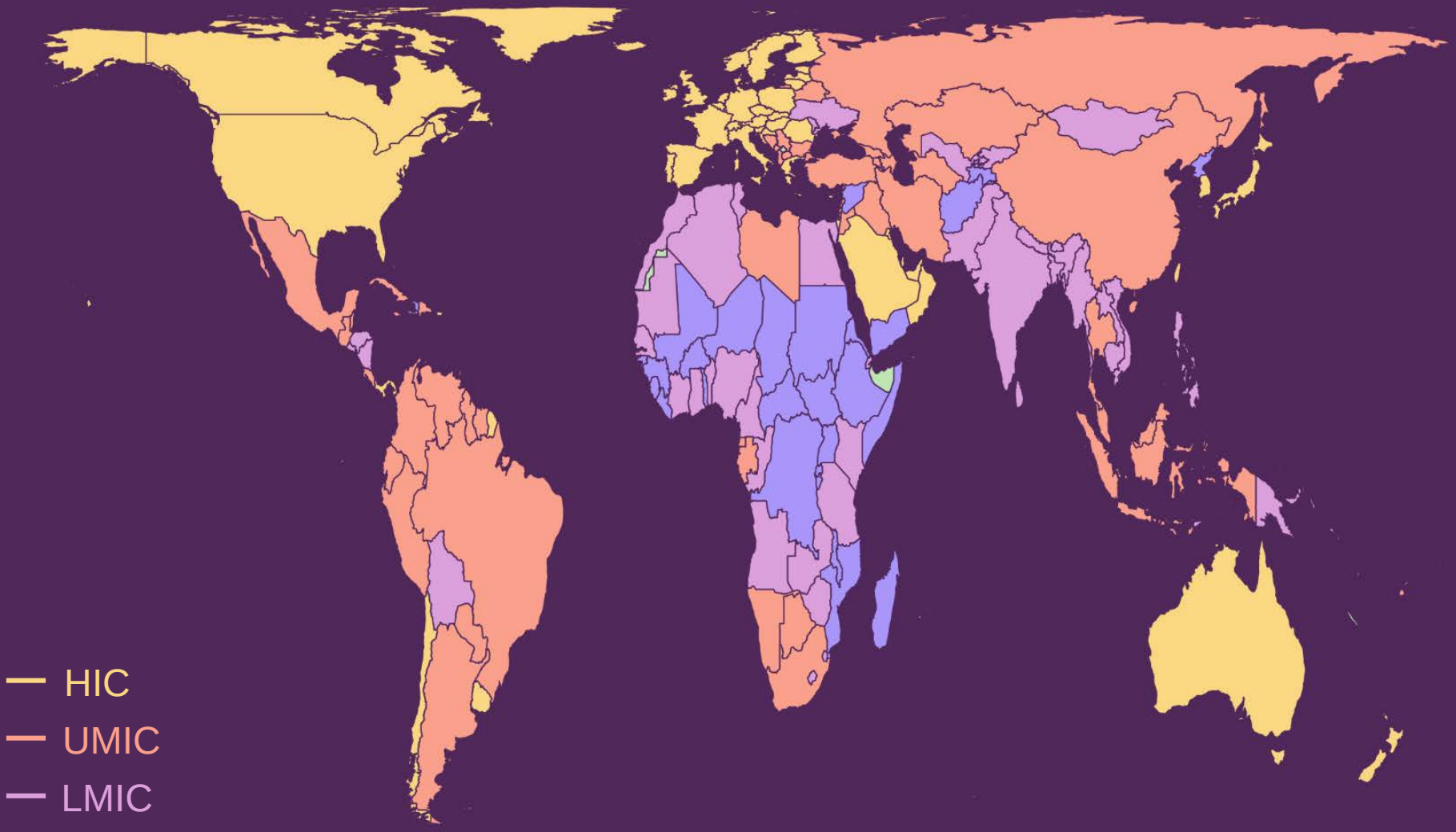
Co-founder & CSO
Trained as a computational chemist at IRB Barcelona, Spain

Gemma Turon, PhD

Co-founder & CEO
Trained as molecular biologist at IRB Barcelona, Spain

Software Sustainability Fellow 2022

Land area

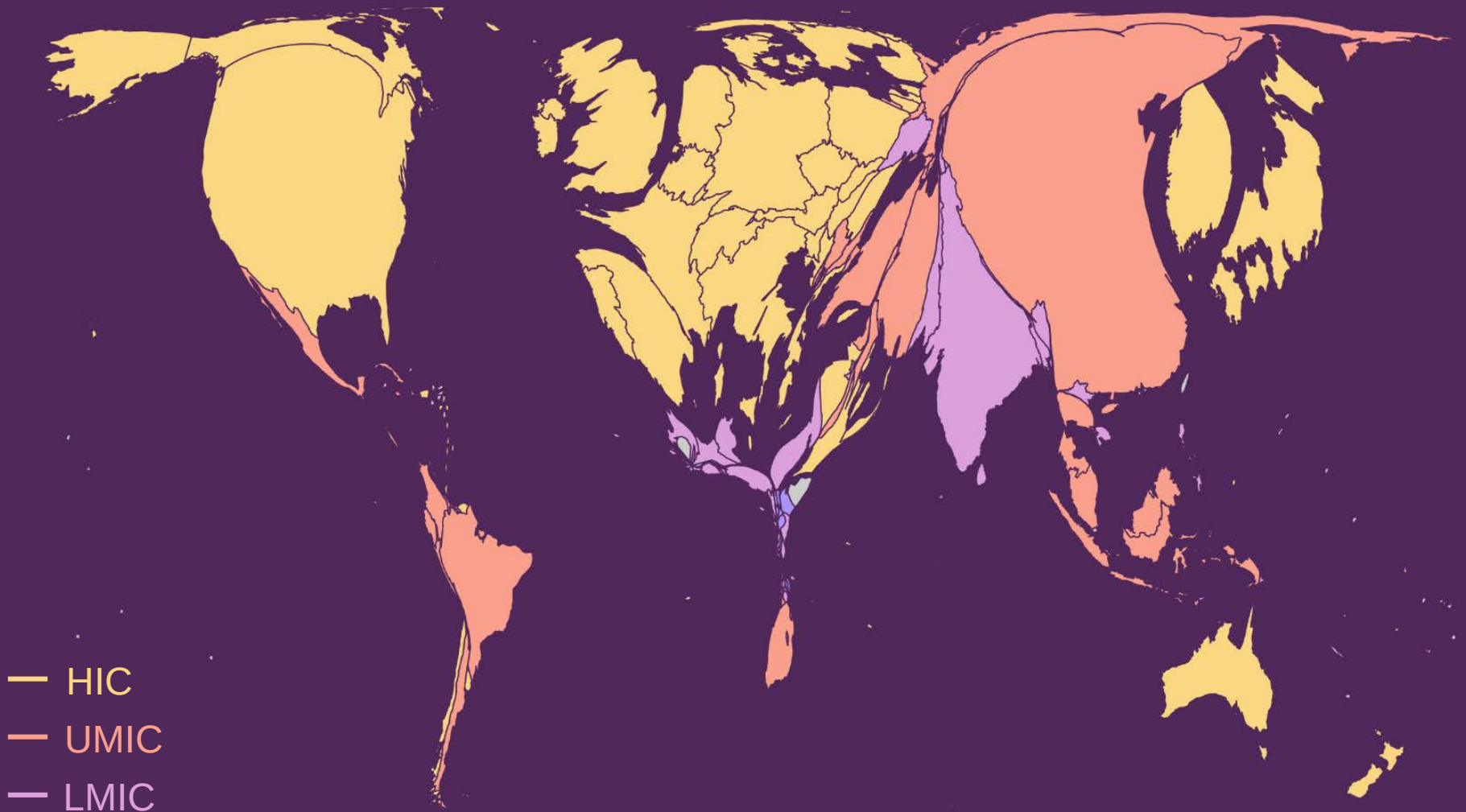


Data from WHO Reports 2019

DALY – Communicable Diseases

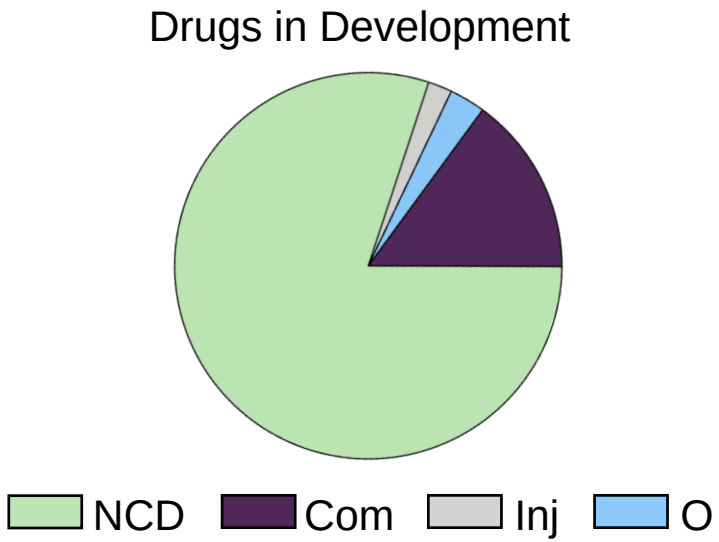
Data from WHO Reports 2019

Scientific Publications



Data from WHO Reports 2019

Imbalance in the research ecosystem



- Pharma industry does not focus on diseases affecting LMICs
- LMIC researchers lack resources to tackle their countries needs:
  - Infrastructure (including digital)
  - Training opportunities

Strengthen the research capacity around neglected communicable diseases in low and middle income countries by lowering the barrier to access computational tools

Free & Open Source

Real-time code sharing

Permissive licenses

No patents

Reproducibility

In-Country Research

Avoid “helicopter research”

Science led by local institutes

Implementation *in situ*

Sustainable Collaborations

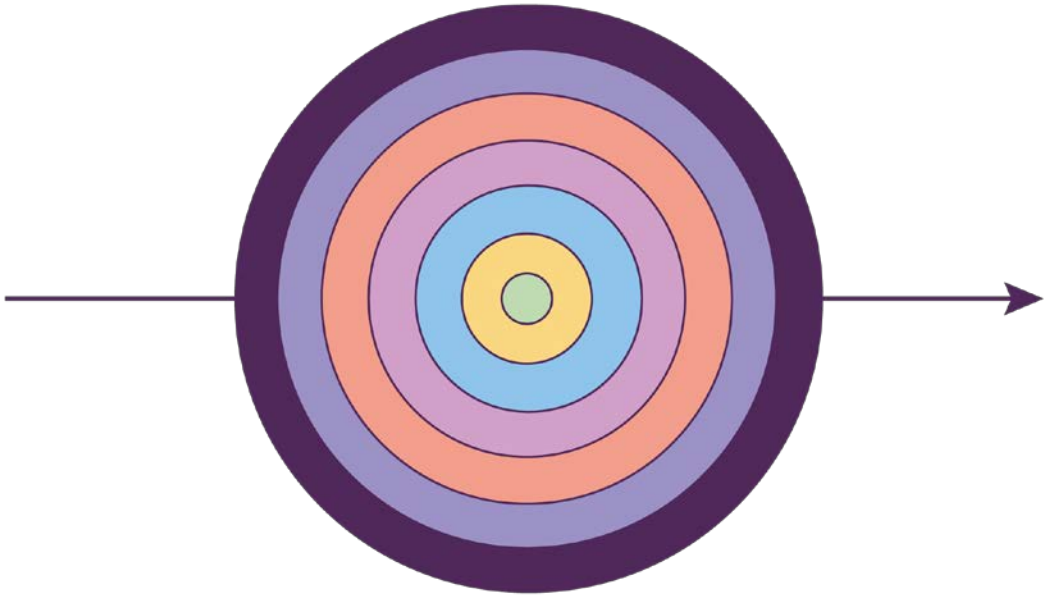
Capacity building activities

Identify & train local champions

AI/ML with low resources

The Ersilia Model Hub: ready to use AI for biomedical researchers

Input:
e.g natural products



Output:
e.g activity against a pathogen

AI/ML from the literature

- Ersilia "bundles" a model developed by others

Cell

Article

A Deep Learning Approach to Antibiotic Discovery

Jonathan M. Stokes,[1,2,3] Kevin Yang,[3,4,10] Kyle Swanson,[3,4,10] Wengong Jin,[3,4] Andres Cubillos-Ruiz,[1,2,5] Nina M. Donghia,[1,5] Craig R. MacNair,[6] Shawn French,[5] Lindsey A. Carfrae,[7] Zohar Bloom-Ackerman,[2,7] Victoria M. Tran,[2] Anush Chiappino-Pepe,[3,7] Ahmed H. Badran,[2] Ian W. Andrews,[1,2,5] Emma J. Chory,[1,2] George M. Church,[3,7,8] Eric D. Brown,[6] Tommi S. Jaakkola,[3,4] Regina Barzilay,[3,4,9,*] and James J. Collins[1,2,5,8,9,11,*]

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https://doi.org/10.1016/j.cell.2020.01.021

SUMMARY

Due to the rapid emergence of antibiotic-resistant bacteria, there is a growing need to discover new antibiotics. To address this challenge, we trained a deep neural network capable of predicting molecules with antibacterial activity. We performed predictions on multiple chemical libraries and discovered a molecule from the Drug Repurposing Hub—halicin—that is structurally divergent from conventional antibiotics and displays bactericidal activity against a wide phylogenetic spectrum of pathogens including *Mycobacterium tuberculosis* and carbapenem-resistant Enterobacteriaceae. Halicin also effectively treated *Clostridioides difficile* and pan-resistant *Acinetobacter baumannii* infections in murine models. Additionally, from a discrete set of 23 empirically tested predictions from >107 million molecules curated from the ZINC15 database, our model identified eight antibacterial compounds that are structurally distant from known antibiotics. This work highlights the utility of deep learning approaches to expand our antibiotic arsenal through the discovery of structurally distinct antibacterial molecules.

INTRODUCTION

Since the discovery of penicillin, antibiotics have become the cornerstone of modern medicine. However, the continued efficacy of these essential drugs is uncertain due to the global dissemination of antibiotic-resistance determinants. Moreover, the decreasing development of new antibiotics in the private sector that has resulted from a lack of economic incentives is exacerbating this already dire problem (Brown and Wright, 2016; PEW Trusts, 2019). Indeed, without immediate action to discover and develop new antibiotics, it is projected that deaths attributable to resistant infections will reach 10 million per year by 2050 (O'Neill, 2014).

Historically, antibiotics were discovered largely through screening soil-dwelling microbes for secondary metabolites that prevented the growth of pathogenic bacteria (Clardy et al., 2006; Wright, 2017). This approach resulted in the majority of clinically used classes of antibiotics, including β-lactams, aminoglycosides, polymyxins, and glycopeptides, among others. Semi-synthetic derivatives of these scaffolds have maintained a viable clinical arsenal of antibiotics by increasing potency, decreasing toxicity, and sidestepping resistance determinants. Entirely synthetic antibiotics of the pyrimidine, quinolone, oxazolidinone, and sulfa classes have also found prolonged clinical utility, and continue to be optimized for the same properties.

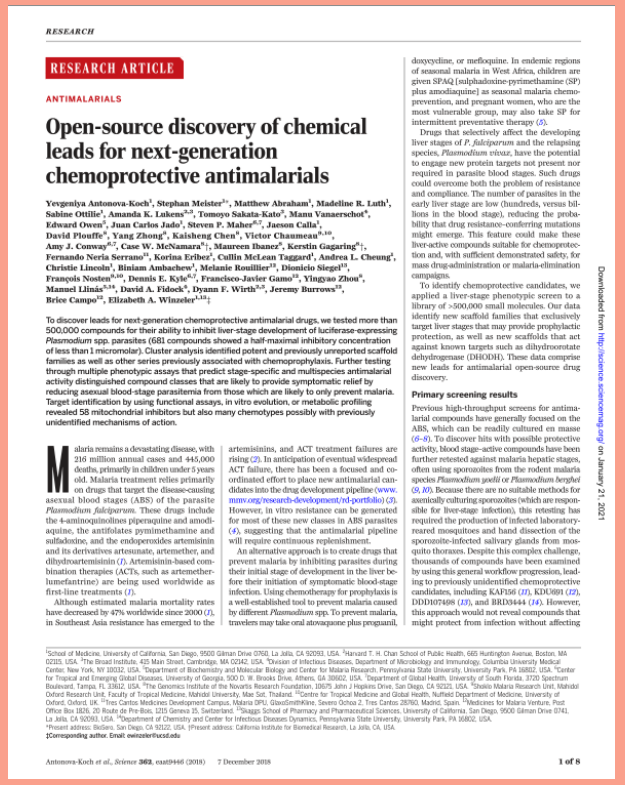
Unfortunately, the discovery of new antibiotics is becoming increasingly difficult. Natural product discovery is now plagued by the dereplication problem, wherein the same molecules are being repeatedly discovered (Cox et al., 2017). Moreover, given the rapid expansion of chemical spaces that are accessible by the derivatization of complex scaffolds (Ortholand and Ganesan, 2004), engineering next-generation versions of existing antibiotics results in substantially more failures than leads. Therefore, many antibiotic discovery programs have turned to screening large synthetic chemical libraries (Tommasi et al., 2015). However, these libraries, which can contain hundreds of thousands

Antibiotic activity *E.coli*
Stokes et al, 2020

Halicin — Active

In-House AI/ML

- Ersilia trains an AI/ML model based on data



RESEARCH

RESEARCH ARTICLE

ANTIMALARIALS

Open-source discovery of chemical leads for next-generation chemoprotective antimalarials

Yevgeniya Antonova-Koch[1], Stephan Meister[2†], Matthew Abraham[1], Madeline R. Luth[1], Sabine Ottilie[1], Amanda K. Lukens[2,3], Tomoyo Sakata-Kato[2], Manu Vanaerschot[4], Edward Owen[2], Juan Carlos Jado[2], Steven P. Maher[6,7], Jaeson Calla[1], David Plouffe[2], Yang Zhong[2], Kaisheng Chen[2], Victor Chaumeau[8,10], Amy J. Conway[6,7], Case W. McNamara[2‡], Maureen Ibanez[2], Kerstin Gagaring[2‡], Fernando Neria Serrano[2‡], Korina Eribez[2], Caitlin McLean Taggard[1], Andrea L. Cheung[1], Christie Lincoln[1], Biniam Ambachew[1], Melanie Rouillier[10], Dionicio Siegel[10], François Nosten[8,10], Dennis E. Kyle[6,7], Francisco-Javier Gamo[12], Yingyao Zhou[2], Manuel Llinás[3,5], David A. Fidock[4], Dyann F. Wirth[2,3], Jeremy Burrows[2‡], Brice Campo[12], Elizabeth A. Winzeler[1,13]‡

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To discover leads for next-generation chemoprotective antimalarial drugs, we tested more than 500,000 compounds for their ability to inhibit liver-stage development of luciferase-expressing *Plasmodium* spp. parasites (681 compounds showed a half-maximal inhibitory concentration of less than 1 micromolar). Cluster analysis identified potent and previously unreported scaffold families as well as other series previously associated with chemoprophylaxis. Further testing through multiple phenotypic assays that predict stage-specific and multispecies antimalarial activity distinguished compound classes that are likely to provide symptomatic relief by reducing asexual blood-stage parasitemia from those which are likely to only prevent malaria. Target identification by using functional assays, in vitro evolution, or metabolic profiling revealed SB mitochondrial inhibitors but also many chemotypes possibly with previously unidentified mechanisms of action.

Malaria remains a devastating disease, with 216 million annual cases and 445,000 deaths, primarily in children under 5 years old. Malaria treatment relies primarily on drugs that target the disease-causing asexual blood stages (ABS) of the parasite *Plasmodium falciparum*. These drugs include the 4-aminoquinolines piperaquine and amodiaquine, the antifolates pyrimethamine and sulfadoxine, and the endoperoxides artemisinin and its derivatives artesunate, artemether, and dihydroartemisinin (*1*). Artemisinin-based combination therapies (ACTs, such as artemether-lumefantrine) are being used worldwide as first-line treatments (*1*).

Although estimated malaria mortality rates have decreased by 47% worldwide since 2000 (*1*), in Southeast Asia resistance has emerged to the artemisinins, and ACT treatment failures are rising (*2*). In anticipation of eventual widespread ACT failure, there has been a focused and coordinated effort to place new antimalarial candidates into the drug development pipeline (www.mmv.org/research-development/rd-portfolio) (*3*). However, in vitro resistance can be generated for most of these new classes in ABS parasites (*4*), suggesting that the antimalarial pipeline will require continuous replenishment.

An alternative approach is to create drugs that prevent malaria by inhibiting parasites during their initial stage of development in the liver before their initiation of symptomatic blood-stage infection. Using chemotherapy for prophylaxis is a well-established tool to prevent malaria caused by different *Plasmodium* spp. To prevent malaria, travelers may take oral atovaquone plus proguanil, doxycycline, or mefloquine. In endemic regions of seasonal malaria in West Africa, children are given SPAQ (sulphadoxine-pyrimethamine (SP) plus amodiaquine) as seasonal malaria chemoprevention, and pregnant women, who are the most vulnerable group, may also take SP for intermittent preventative therapy (*5*).

Drugs that selectively affect the developing liver stages of *P. falciparum* and the relapsing species, *Plasmodium vivax*, have the potential to engage new protein targets not present nor required in parasite blood stages. Such drugs could overcome both the problem of resistance and compliance. The number of parasites in the early liver stage are low (hundreds, versus billions in the blood stage), reducing the probability that drug resistance–conferring mutations might emerge. This feature could make these liver-active compounds suitable for chemoprotection and, with sufficient demonstrated safety, for mass drug-administration or malaria-elimination campaigns.

To identify chemoprotective candidates, we applied a liver-stage phenotypic screen to a library of >500,000 small molecules. Our data identify new scaffold families that exclusively target liver stages that may provide prophylactic protection, as well as new scaffolds that act against known targets such as dihydroorotate dehydrogenase (DHODH). These data comprise new leads for antimalarial open-source drug discovery.

Primary screening results

Previous high-throughput screens for antimalarial compounds have generally focused on the ABS, which can be readily cultured en masse (*6–8*). To discover hits with possible protective activity, blood stage–active compounds have been further retested against malaria hepatic stages, often using sporozoites from the rodent malaria species *Plasmodium yoelii* or *Plasmodium berghei* (*9, 10*). Because there are no suitable methods for asexually culturing sporozoites (which are responsible for liver-stage infection), this retesting has required the production of infected laboratory-reared mosquitoes and hand dissection of the sporozoite-infected salivary glands from mosquito thoraxes. Despite this complex challenge, thousands of compounds have been examined by using this general workflow progression, leading to previously unidentified chemoprotective candidates, including KAF156 (*11*), KDU691 (*12*), DDD107498 (*13*), and BRD3444 (*14*). However, this approach would not reveal compounds that might protect from infection without affecting

Chemoprotective antimalarials
Antonova-Koch et al, 2018

Atovaquone analog — Active

AI/ML in collaboration

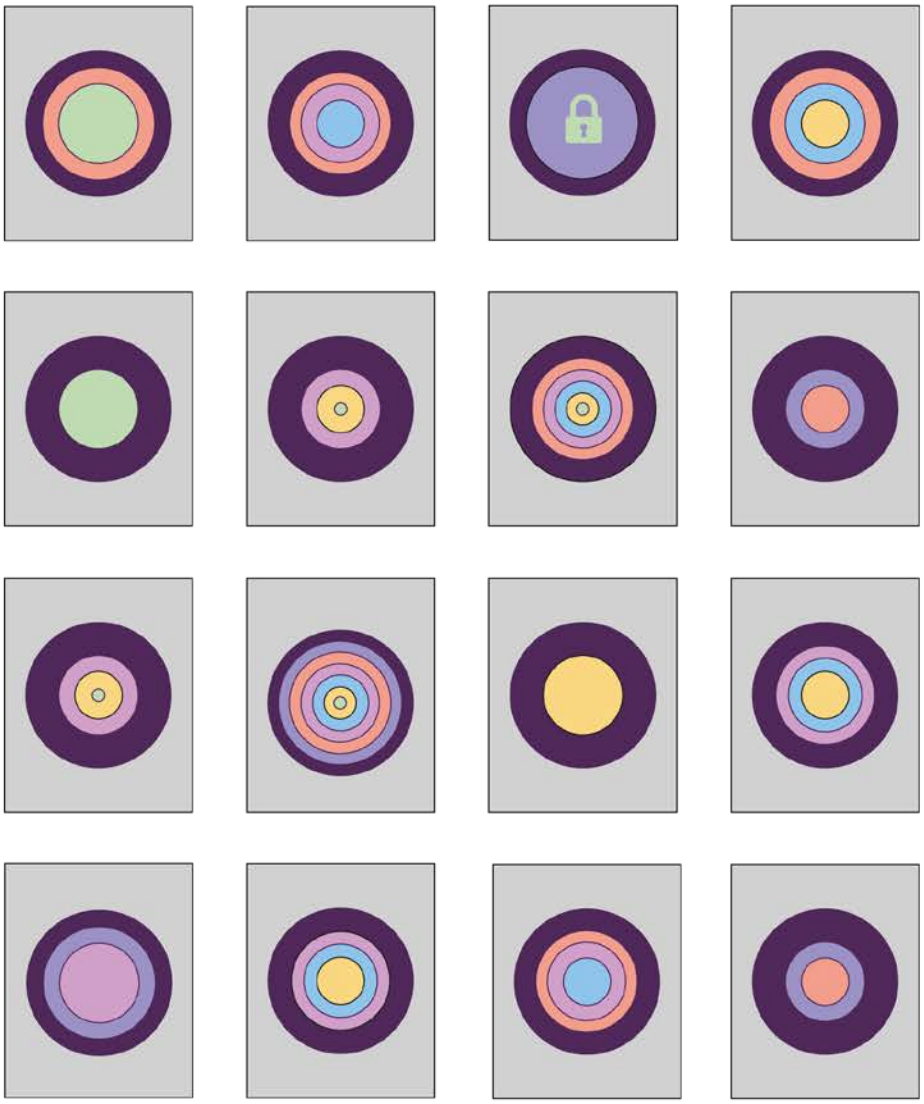
- Ersilia trains an AI/ML model based on partner's data

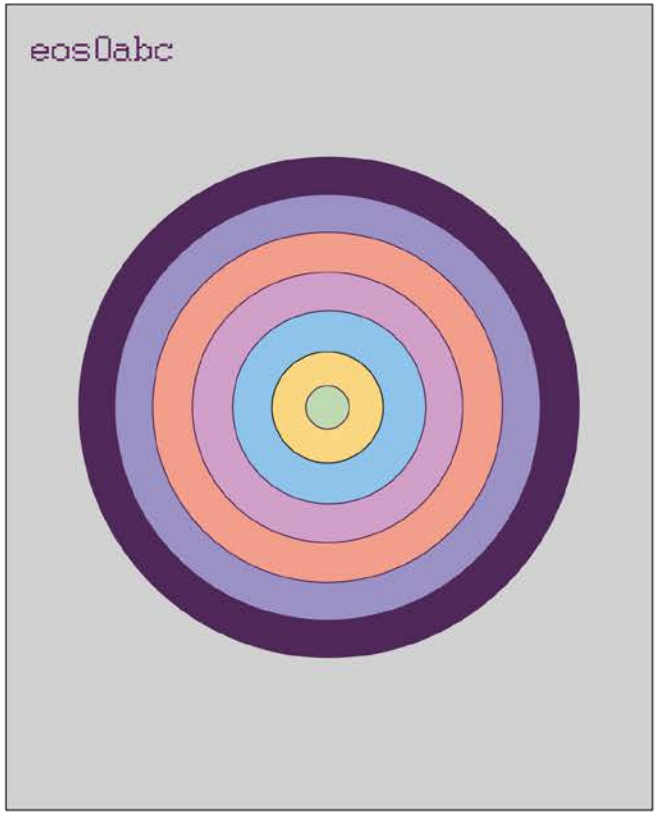
Your awesome project
You and Ersilia, 202

Your question | Our answer

The Ersilia Model Hub

Software Sustainability Institute





User Query

Active

Author

GitHub repository

Summary / Applicability

The Ersilia Model Hub – How to

https://github.com/ersilia-os/ersilia

1. Ersilia installation in local computer
2. Selection of model of interest:

   40 publicly available models – browsable catalog
3. Use a command line interface to download model from our repository
4. Select the model api (predict, calculate…) and input the molecule (or list of molecules) of interest
5. Close model

```
ersilia fetch chemprop-antibiotic
ersilia api predict -i "C1=C(SC(=N1)SC2=NN=C(S2)N)[N+](=O)[O-]"
ersilia close
```

**Disclaimer: the EMH is in testing mode*

The Ersilia Model Hub – How to

Credit: Outreachy Contributor Applicant

```
(ersilia) dauinh:ersilia dauinh$ ersilia fetch chemprop-antibiotic
⬇️ Fetching model eos4e40: chemprop-antibiotic
👍 Model eos4e40 fetched successfully!
(ersilia) dauinh:ersilia dauinh$ ersilia delete molecular-weight
Deleting model eos3b5e
💥 Model eos3b5e deleted successfully!
(ersilia) dauinh:ersilia dauinh$ ersilia serve chemprop-antibiotic
🚀 Serving model eos4e40: chemprop-antibiotic

   URL: http://127.0.0.1:51074/
   PID: 50487
   SRV: conda

👉 Available APIs:
   - predict
(ersilia) dauinh:ersilia dauinh$ ersilia api predict -i "C1=C(SC(=N1)SC2=NN=C(S2)
N)[N+](=O)[O-]"
{
    "input": {
        "key": "NQQBNZBOOHHVQP-UHFFFAOYSA-N",
        "input": "C1=C(SC(=N1)SC2=NN=C(S2)N)[N+](=O)[O-]",
        "text": "C1=C(SC(=N1)SC2=NN=C(S2)N)[N+](=O)[O-]"
    },
    "output": {}
}
(ersilia) dauinh:ersilia dauinh$
```

Collaborations Workshop 2022

- Providing research software engineers and computational biologists with an infrastructure for model deployment:
  - Incentives for third party model contribution: metrics of interest, scientific credit and others – not everyone can afford to volunteer?
  - Requirements for new model incorporation: for example, models that have not been published in a peer reviewed journal
  - Incorporation of software checking tools (codecheck?)
  - Ethics: development of ethical guidelines: both in accepting new models and for contributor recognition, including data providers
- Making research software more accessible to non-experts:
  - Channels to reach out to these communities
  - Creating a community with closer ties between RSE and end users
  - Should we prioritize accuracy of the tools or ease of use? i.e use smaller, simpler models deployed in the cloud
  - Strategies to deliver training together with the platform
  - Technical features required for adoption: CLI X

Collaborations Workshop 2022

10 Minutes BreakOut Rooms – Use drive document to write down ideas

5 Minutes Wrap Up – One person from each group to provide feedback