Deliverable reports

Deliverable 15. Report on biomarker and receptor-based assays in ecotoxicology. M24 (WG4).

(Action Deliverables are distinct, expected, and tangible outputs of an Action which are meaningful in terms of the Action's overall Objectives, such as reports, documents, technical diagrams, software, etc.)

Challenge of reference:

Challenge 2. The impact of pharmaceutics and their R&D process on the environment is high and it is responsible of huge loss due to contaminated water that affects human and animal health, generate drug resistance problems. *Integrated multidisciplinary efforts (design, synthesis/extraction, in vitro and in vivo biological/animal studies, delivery) should be developed to reduce the drugs impact on the environment at every step of the drug research and development process. This requires the coordinated action of researchers and stakeholders (governmental bodies, patients' organizations, industries and SME***.**

Objective of reference (Research Coordination Objective)

Objective 3. **Coordination of the translation from *in vitro*-to-*in vivo* activities to obtain high quality leads and candidates**. Actions: Introduction of omics technologies (genomic, proteomics and transcriptomics) and imaging for a limited number of validated leads. Drug delivery of biodegradable nanotechnology and drug targeting tools applications for both H&A R&D, pharmacology (pharmacokinetics and pharmacodynamics) on animal models by changing drug regimen and study of the effects of the different drug bioavailability tools. This can be acquired through European RTD organization and allow the achievement of high-quality leads with associated biological properties tailored for the H&A VB parasitic infections drug research program. **KPI**: 3 metrics adopted to measure objective 3 to be reviewed once a year. 2.1 Number of successful examples of biodegradable nanotechnology formulation on dose regimen for each infection. 2.2 Number of projects developed in collaboration with the RTD platform and other stakeholders. 2.3 Number of animal studies including the degradable formulation and targeting vectorization.

Working group of reference:

WG3. Coordination of *in vitro*-to-*in vivo* translation *of One Health* leads and candidates. (Challenge 3**) Objectives.** Promoting and strengthening of innovative technologies required in the translation of leads and candidates from animal to humans and vice versa to ensure the progression of qualified leads and candidates to the end of the pre-clinical phase and de-risk studies in clinical phase 1. This is restricted to advanced leads and candidate.

T3.3 *Coordination and integration of omics studies (PROTEOMICS, Genomics, TRANSCRITTOMICS) and validation technologies*, to better qualify the mechanism of action and drug resistance. All data will be deposited in the FARIDOM database. Protein targets and biological pathways from the omics studies will be validated through the evaluation of differential expression of proteins and their functional studies in cells models. (D3.3). **T3.5** *Ecotoxicology assays to detect the expected effect of the advanced candidate on animals and environment*. (D3.5)

And

WG4. Integration of R&D process-environmental studies for the translation in informed white paper. (Challenge 4) Objectives: Coordination of the R&D programs innovative strategies and compliance with the overall environmental impact to provide a sharable guideline-like document. This may inform the compounds probability of exposure, an

information derived from a more detailed understanding on the substances environmental fate. The validation against the ecological interpretation of selected indicators (see below) is important to properly inform drug designer and managers of environmental risks compared to societal benefits. T4.1 Identify the most relevant ecotox aspects emerged from WG1-WG3 activities, identify the life cycle principles included in the whole discovery & development design for the responsible pharmaceutical use and disposal, improved environmental monitoring and risk assessment of the drugs (D4.1). T4.2 Critical assessment of the steps necessary to achieve the dual sustainable goals of improving health and protecting the environment. **T.4.2 addresses the challenges offered by ecotoxicology and identifies the various possibilities to assess the environmental effects of pharmaceuticals and their degradation products or metabolites following a tiered approach and foster their prevention (D4.2). T4.3 Concerted activity of receptor-based and biomarker assays to screen pharmaceuticals (preclinical and clinical) effects using small volumes of the drug or its degradation product. (D4.3)** T4.4 Strengthening of omics technologies as impressive possibility to identify potential molecular initiating events in organisms central to ecosystems and their functioning. Selection of test species for these ecotoxicology experiments (D4.4). The achievements from the above studies are important for the development, validation and use of adverse outcome pathways at early stages of the design of antiparasitic drugs. The validation against the ecological interpretation of such indicators is important to properly inform drug designer and risk managers which balance amongst those environmental risks with societal benefits.

Deliverable description

Report on biomarker and receptor-based assays in ecotoxicology

Vector-borne diseases pose global health challenges, requiring innovative drug discovery approaches. Target identification and mechanism of action (MoA) studies are essential to understand pathogen-host interactions and identify molecular targets crucial for pathogen survival, replication, or transmission. Compounds to be tested are selected properly during the early phase of drug discovery and lead development. Previous strategies and technologies are today implemented with recent discoveries. Therefore one of the main aim is to promote and strengthen innovative technologies required in the translation of leads and candidates from animal to humans and vice versa to ensure the progression of qualified leads and candidates to the end of the pre-clinical phase and de-risk studies in clinical phase 1. Ecotoxicology evaluation is essential therefore to this aim. Therefore established assays and receptor based assays are already existing and should be discussed and implemented. Marker/biomarker suggesting that in vivo the compounds is maintaining a risky or safe profile are required. Therefore the research work in the field is falling in the more general field of the identification of existing and novel assays including standardization procedures and problems.

Description of what we have done: the meetings, training schools, STSM workshop performed, the *reports, documents, technical diagrams, software etc. with reference – link to the website or other external document of interest*
The work performed inside the network to achieve the Deliverable related to "Report on biomarker and receptor-based assays in ecotoxicology **" T.4.2 addresses the challenges offered by ecotoxicology and identifies the various possibilities to assess the environmental effects of pharmaceuticals and their degradation products or metabolites following a tiered approach and foster their prevention (D4.2). T4.3 Concerted activity of receptor-based and biomarker assays to screen pharmaceuticals (preclinical and clinical) effects using small volumes of the drug or its degradation product" has been considered. Specific activities have been organized and are reported below:**

1.WG4-Workshop 2 - Date 20-21 September 2023 Giessen (DE) in presence meeting
Biomarkers, screening, standardized and non-standardized ecotoxicological testing in One Health drug discovery and development.
https://www.onehealthdrugs.com/events/scientific-meeting/biomarkers-screening-standardized-and-non-standardized-ecotoxicological-testing-in-drug-discovery-and-development/
2.Environmentally friendly systems to replace classical animal models in drug testing for VBD – IN PRESENCE MEETING. 14-15 May 2024 | i3S, Porto, Portugal Mini-Workshop: "Young Innovators" 15 May 2024 | i3S, Porto, Portugal

https://www.onehealthdrugs.com/events/scientific-meeting/environmentally-friendly-systems-to-replace-classical-animal-models-in-drug-testing-for-vbd/

3. Omics technologies as a new tool in ecotoxicology. Workshop 26/03/2024 3pm-5pm online
https://www.onehealthdrugs.com/events/scientific-meeting/omics-technologies-as-a-new-tool-in-ecotoxicology/

4. National Hellenic Research Foundation Athens, Greece. IN PRESENCE MEETING - Novel leads and drugs for vector borne diseases: Targets and off targets (toxicity and ecotoxicity) and mechanism of action. September 19-20 2024.
https://www.onehealthdrugs.com/events/scientific-meeting/novel-leads-and-drugs-for-vector-borne-diseases-targets-and-off-targets-toxicity-and-ecotoxicity-and-mechanism-of-action/

5. Environmental impact of pharmaceuticals and international organizations monitoring. WG4, Workshop 1 - 03/04/2023
https://www.onehealthdrugs.com/events/scientific-meeting/environmental-impact-of-pharmaceuticals-and-international-organizations-monitoring/

Scientific impact (from the MoU)

- a shared experience for researchers, industry stakeholders and national/international organizations opening the way to novel fruitful collaborations for transfer of knowledge/ new knowledge creation about targets, drug research strategies, hits and leads elaboration, assays for HTS approaches, nanotechnology for drug delivery and animal studies; ecotoxicology and environmental tools applied to the research process.
- new biological assays for HTS and HCS screening and for lab scale studies of the mechanism of action together with the reduction of parasite growth;
- ecotoxicology-based model organism selection for biomarkers and indicators assay;

The long-term benefits (from the MoU

- a long-lasting impact on antiparasitic drug development in Europe due to targeted training of Young Researchers and Innovators;
- a permanent on-line network of stakeholders in antiparasitic drug discovery and development to maintain a transfer of knowledge, new One Health knowledge creation and strengthen collaboration;
- engagement of RTD platforms active in the field;
- increased funding into antiparasitic drug development integrated with environmental scientists due to the improved multidisciplinary and multi-centre applications resulting from collaborations between participants in the Action and successful activity of contact and networking within this Action.
- reduction, recycle and reuse of waste material with consequent long term positive environmental impact in the long term.

Innovation

Cross-sectorial and interdisciplinary networking approach to advance the drug discovery and development field in VB parasitic diseases in H&A (because an effective cure of the human infections can be achieved if animals' infections are cured or eliminated). Integration of the innovative approaches with the environmental impact concepts, will involve also pharmaceuticals manufacturing and use.

The Action will facilitate such innovation through active promotion of the database (IP regulated) and search for collaborators in academia and industry. IP on new advanced candidates with promising or relevant pharmacological activity will be promoted.