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Tropical Diseases Conference 2019: Reverse Pharmacology for developing Novel Compounds for Malaria - Ivana Haluskova Balter - Consultant Research and Development Partnership for Health

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Malaria as VBD is of crucial medical importance within context of raising resistance and lack of new alternatives. There are challenges of R&D pharma for new drugs, potential to use reverse pharmacology for new compound evaluation. Reverse pharmacology is the science of integrating documented clinical/experiential hits, into leads by Tran's disciplinary exploratory studies and further developing these into drug candidates by experimental and clinical research. Many potential compounds seems to be used in traditional medicine in Asia and Africa which share many similarities and this effort seems to be confirmed by agreement between Malaysia and India to move forward this direction (only one of many examples) The scope of reverse pharmacology is to understand the mechanisms of action at multiple levels of biological organization and to optimize safety, efficacy and acceptability of the leads in natural products, based on relevant science. Latest anti-malarial drugs Artemisinin derivatives & ACTs are becoming ineffective in malaria endemic countries (Dr Charlie Woodrow et al. Lancet, Feb.2015, D L Saunders, The Infectious Diseases, Lancet, and June 2015). Accurate diagnostic and surveillance with better understanding of genetic and immunologic background of host specific response and pathogen evolution drives adapted research but also preventive interventions. As one of examples to illustrate it, global mapping of resistance to artemisinin (the KARMA study driven by Institute Pasteur in Paris and the Institute Pasteur in Cambodia and members of Institute Pasteur International Network) monitoring risk of spread of artemisine resistance from Asia to Africa using discovery of kelch (K13)??? In an observational cohort study, a herbal drug has been tried in 35 cases of Drug Resistant Malaria in children of 5 to 8 year??? age, during Feb 2014 to June 2016, in India. Only, patients showing resistance to Cholroquine & Artemether + Lumefantrine combination therapy (ACT) were included for study. Every patient was given 3 days??? Indoor treatment with herbal drug. Pulse Rate & Temperature was monitored 6 hourly. Blood smear for parasite was examined at 12 hours, 24 hours, 30 hours, Day-5, Day-30 & Day-60. Fever Clearance Time observed was 30 to 48 hours in 98% cases of P. falciparum & 94% cases of P. vivax. Parasite Clearance Time observed was 12 to 30 hours in about 98% cases of P. falciparum & about 94% cases of P. vivax. None of the successfully treated patients got recurrence in next 8 months??? Time. There was no intolerance / adverse reaction to the herbal drug. Concept of Immune-Modulation applied to herbal anti-malarial drug, can explore potential for discovery of novel herbal drug for Neglected Tropical Diseases also the last step was to identify active compounds which can be used as markers for standardization and quality control. This example of "reverse pharmacology" shows that a standardized phytomedicine can be developed faster and more cheaply than conventional drugs. There is already discussion about intermittent presumptive treatment of infants, children, pregnant women, and even mass drug administration in some settings it is important to maximize the lifespan of existing anti-malarias, and to consider all options for the development of new anti-malarias. Traditional medicinal plants have provided the source of the two major families of anti-malarial drugs still in use today, artemisinin and quinine, so many researchers are screening plants for novel chemical entities to develop as "lead compounds" for new anti-malarial drugs In contrast the parallel development of standardized phytomedicines can be done faster, more cheaply, and more sustainably for remote areas. They could then be proposed and tested as a complement to existing strategies where clinical evaluation was prioritized from the start. Isolation of compounds was done only at the end of the pathway, mainly for the purposes of quality control, agronomic selection and standardization, if justified by the clinical results yet conventional ethno botanical studies rarely involve clinicians. They could and should provide much more clinical information if the ultimate goal is to know which one, among numerous treatments for a given ailment, has the best effects. Although identification of the plants is usually of a good standard, definition of the diseases which they treat is not. There is rarely sufficient questioning about the observed patient status and progress, perceived efficacy and limitations of the remedies, and whether these are indeed the "treatment of choice Clinical information is collected retrospectively on the presentation and progress of a defined disease episode. Treatments and subsequent clinical outcomes are analysed to elicit statistically significant correlations between them. Such an approach requires a large sample if the number of different treatments is high. This method makes it possible to identify the remedy which has the highest statistical correlation with reported clinical recovery. The aim was to maximize the chances that the respondents were giving information about the disease of interest to researchers. For uncomplicated malaria, the definition was "fever with no other obvious cause during the rainy season. Mechanistic reasons for the poly-pharmacological effects of plants constitute increased bioavailability, interference with cellular transport processes, activation of pro-drugs/deactivation of active compounds to inactive metabolites and action of synergistic partners at

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different points of the same signalling cascade. These effects are known as the multi-target concept.