

## Tropical diseases research and antifungal research linked with cancer research

This correspondence refers to the similarities and differences between mammalian genomes and the genomes of parasites and fungi. It is indicated, that this may serve as a basis to discover and develop novel antifungal agents and novel antiparasitic agents, by linking these research areas with cancer drug discovery, and optimizing synergies within a suitable framework of intellectual property protection.

Tropical diseases have traditionally been considered under infectious diseases. Tropical diseases have the unique feature of being endemic and a high disease burden in countries with low or moderate per capita incomes, and insufficient coverage through health insurance, where the scope for recovering the investments in research and development for tropical diseases is quite low<sup>1,2</sup>. The option of recovering a portion of the costs and investments of preclinical research in tropical diseases, by adjusting the prices of medicines in Asia, Africa and Latin America by 0.5–1% or so, may be of interest for the relevant research organizations.

Several research and development organizations have been developed, involving public–private partnerships, including MMV (medicines for malaria venture), DNDi (drugs for neglected diseases initiative), TB Alliance, etc. with their portfolios of projects. Research and development organizations such as the CSIR (Council of Scientific and Industrial Research, India), are strengthening their research and development capabilities in tropical diseases, through public funding (CSIR, New Delhi, personal communications).

A potentially efficient approach for tropical diseases (parasites) remains underutilized and it may be worthwhile to examine this further. This approach is based on the similarities and differences between human and parasite genomes and proteomes<sup>3–9</sup>, and the scope to develop anti-cancer (or cytotoxic) agents

into selective and potent antiparasitic agents, by modifying the scaffold and pharmacophore of the anti-cancer agents, to achieve the desired efficacy, selectivity and safety. Inhibitors of human, parasite and bacterial dehydrofolate reductases may be mentioned as examples of this approach<sup>10,11</sup>. A significant number of natural products-based cytotoxic compounds have been described and the total syntheses of these have been reported.

Given the similarities and differences between the essential proteins of parasites and humans or other mammalian hosts, it is of some interest to enquire of the connection between anti-cancer drug discovery and tropical diseases drug discovery and the scope for synergies. Given the high importance of anti-cancer drug discovery, within the pharma industry, and the similarities and differences between human and parasite genomes, there is a large scope for developing these proprietary agents into antiparasitic agents. While there are a few examples of this approach being used at present, one may hope that this will develop further, through adequate funding.

Given the known QSAR (quantitative structure–activity relationships) for such anti-cancer compounds and the associated chemical libraries (analogs), the molecular models of the drug-binding site, with reference to activity and cytotoxicity, this would provide a pointer for developing antiparasitic agents that are efficacious and selective. It would be attractive for such research and development to be done in a suitable framework of intellectual property protection and confidentiality, given the proprietary nature of anticancer agents and the associated focused chemical libraries within pharmaceutical companies. As there is likely to be some similarities between the ensuing anti-parasitic agents and the parent anticancer compounds, and some overlap of the respective chemical libraries in the exploration of drug space, the essential-

ity of intellectual property protection and confidentiality may be mentioned.

Given the similarities between the essential proteins such as actin, tubulin of parasites of tropical diseases (including malaria, trypanosomiasis, leishmaniasis, schistosomiasis), and the differences between parasites and mammals, it would be possible to develop a set of antiparasitic agents for each of these diseases, in parallel projects, starting with a few anticancer compounds as starting points. This would generate synergies and economies, which may translate into a higher than usual degree of success in lead discovery and lead optimization. Importantly, this approach may also be valid for developing novel antifungal agents, for which there is a good option of recovering the investments in research and development.

1. Sachs, J. and Moloney, P., *Nature*, 2002, **415**, 680–685.
2. Ridley, R. G., *Nature*, 2002, **415**, 686–693.
3. Doerig, C., *Biophys. Biochem. Acta*, 2004, **1697**, 155–168.
4. Reguera, R. M. *et al.*, *Biophys. Biochem. Acta*, 2006, **1759**, 117–131.
5. Kappes, B. and Rohrbach, P., *Future Microbiol.*, 2007, **2**, 409–423.
6. McKerrow, J. H. *et al.*, *Curr. Opin. Infect. Dis.*, 2008, **21**, 668–672.
7. Lau, A. O., *Mol. Biochem. Parasitol.*, 2009, **164**, 1–8.
8. Carlton, J. M., Escalante, A. A., Neafsey, D. and Volkman, S. K., *Trends Parasitol.*, 2008, **24**, 545–550.
9. Callejas, S. and Melville, S., *SEB Exp. Biol. Ser.*, 2007, **58**, 1–24.
10. Silverstein, R. B., *The Organic Chemistry of Drug Design*, 2nd edn, 2004.
11. Nzila, A. *et al.*, *Trends Parasitol.*, 2005, **21**, 292–298.

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