Industry Sessions : Natural Product Research and IUPHAR

- IUPHAR can play a major role in bringing together two different worlds by creating synergies between them, rather than independent research :

• **Natural/traditional products (NPs)**	**New Molecular Chemical Entities (NMEs).**
• Plant, Microbial, Animal, Marine-based	Synthetic chemistry-based
• Sometimes Mixtures	Frequently multiple metabolites
• Chinese, Indian, African -based research	USA and European-based research
• Benefits from centuries of natural practice	Benefits from molecular research
• Biological Synthesis	Organic/Aqueous phase separation
• Novel ?	NPs Starting points for NMEs

Nobel prize for Artemesin, Youyou Tu.

Encourage mechanism of action studies and clear effects in clinical pharmacology.

Multiple compounds with small structural similarities are also found in classical medicinal chemistry.

Cross-over technologies, increase database access,
define mechanism of action?

Can we synthesise them in sufficient quantity? Eg Abolis technology

How do we get out of the mechanistic 'soup' of poorly defined redox, antinflammatory, immunological, antiaging effects claimed for some NPs

NDD article ?

IUPHAR
International Union of Basic and Clinical Pharmacology

Challenges of Natural Products in drug discovery programs: a future to reinvent ? 1

Plant and microbial biodiversity still represents a huge reservoir of chemically diversified and bioactive molecules, but the pharmaceutical industry and Natural Products seem divorced today : a stop or at least strong reduction in many companies.

- **Drawbacks of NP for a lot of companies:**
  - **The access to biodiversity and associated legal uncertainty adds risk, how to manage? Are WHO guidelines compatible?**
  - **Mixtures are problematic : dereplication and isolation steps, up to date technologies (profiling of new compounds)**
  - **Hits are easy to discover, leads and candidates more rare : are most NP druggable? (e.g. curcumin, Nelson et al, 2016) Recollection and scaling up are challenging. Is redox critical to many NPs? What are the best ways to prevent issues such as those raised about curcumin developability?**
  - **Many new chemical entities have been derived from natural products – have we taken the 'low hanging fruits' ?**

Theoretically, a very huge numbers of underexplored NP and large chemical diversity : let us be sure of it. How to conclude ?

- **New screening technologies, new targets?**
- **Phenotypic and uncommon assays ? in vivo (systemic effect)?**
- **Metabolomics?**
- **Rare samples/products ? Special attention to minor compounds?**
- **Virtual screening?**

Is the road for success comes with the evolution/progress of platforms and translational medicines strategies?

- **"omics" technologies?**
- **Repositioning of known compounds?**
- **Valorization of complex mixtures as herbal drugs?**

Challenges of Natural Products in drug discovery/development programs: a future to reinvent 2

- **Development of NPs and NCEs for use as medicines are well defined (and expensive), yet NPs are used everywhere – how can we navigate between the two worlds, Or do we just leave them separate ?**
- **There is an immunopharmacology revolution and reactivating the immune system, or suppressing it, can have immense impact. There thousands of papers about NPs affecting inflammation, but with little mechanistic or clinical follow-up.**
- **IUIS and IUPHAR have agreed to collaborate on delineating immunopharmacology drug targets and prepare common databases of validated targets. Furthermore, simple lists of human biomarkers are validated by IUIS/SITC and these could be rapidly applied to human NP research.**

So is it worth keeping searching ? Are we prepared to invest again in a new maturity of NP research in Pharma/Biotech/Academic drug discovery? If so we need clear recommendations.

This is the last meeting of a series of strategic events to propose recommendations.

Industry Sessions: IUPHAR and Natural Products

1. We encourage clear definition of the chemical substance and molecular targets
2. We already have a very good database tool to encourage worldwide access and establish guidelines
3. The clinical group are implicated in guidelines for registration cf FDA and EMEA.
4. Worldwide discussions, Africa (Phar*f*A), India, China, Brazil, US FDA centre.
5. Real recommendations from the IUPHAR Natural Products meeting at Aberdeen, with the possibility of a Nature Drug Discovery article.
6. Define differences and synergies between Food – Dietary Supplement – Drug. Must be Oral – if skin application then a cosmetic. A new category is 'New Dietary Ingredient' (DTI).
7. Chemical NP libraries for screening
8. Deep metabolomics for defining mixtures – centralised facilities.
9. Breakthroughs in biological synthesis.
10. Phenotypical screening.
11. Clear recommendations of testing NPs.
12. We recommend mixtures be tested for rare/orphan diseases (FDA route)
13. We propose protocols for worldwide screening, especially in immunology.
14. YOUR input is necessary.