Immunopharmacology
The new frontier
IUPHAR – IUIS Collaboration
The Guide to immunopharmacology

H-index 54, 11 drugs into the clinic, 100,000kms run

Just do it !

Michael Spedding, *H-index 60*

Secretary General, IUPHAR,

President, Spedding Research Solutions SAS,
Research company, for:
- Sports science
- 'Impossible diseases'
Motorneurone Disease,
(Glioblastoma).

IUPHAR

International Union of Basic and Clinical Pharmacology

IUPHAR is a registered charity based in Switzerland

IUPHAR is a WHO-recognised non-governmental organisation (NGO) with an official WHO collaboration for pharmacology education and for clinical pharmacology in the developing world. 37,000 pharmacologists.

IUPHAR Natural Product Section: MS since June: India, Singapore, UK, Italy, Brazil, China, Discussions FDA centre NIH.
Strategy : Expert driven databases, on drug targets, which are freely available to all. Edinburgh, Scotland. Central financing (e.g. Wellcome Trust grants), encouraging local finance, from Indian, African, Chinese, Brazilian sources etc, and links to scientists exchange. 125 publications, H-Index 80,

IUPHAR Immunopharmacology/Antibody Group formed

Francesca Levi-Schaffer is chair (>60 members)
Wellcome immunopharmacology kinase grant obtained (0.5M€)
www.guidetoimmunopharmacology.org Alliance with IUIS.

TARGET, inhibitors	WHICH IMMUNE DISEASES ?
• Akt	• Asthma
• Multiple chemokine receptors	• Rheumatoid arthritis
• INFα	• Multiple sclerosis (IL17+)
• IL1	• Aspects of schizophrenia
• IL6	• Juvenile diabetes
• IL17	• Cardiomyopathy
• Inflammasome	• Antiphospholipid syndrome
• IRAK4	• Guillain-Barré syndrome
• Jak/stat	• Crohn's disease
• Mtor	• Graves' disease
• PI3K δ /γ	• Sjogren's syndrome
• Syk	• Vitiligo
• TLR2/4/7/9	• Myasthenia gravis
• TNFα	• Systemic lupus erythematosus (SLE)
• ROR-γ	• Psoriasis

?

Immunopharmacology : Which target for which disease ?

III International Pharmacological Congress

Under the auspices of

The INTERNATIONAL UNION OF PHARMACOLOGY (IUPHAR)

and

The BRAZILIAN FEDERAL GOVERNMENT
Ministry of Education
National Research Council
CAPES

The GOVERNMENT OF THE STATE OF SÃO PAULO
FAPESP

The UNIVERSITY OF SÃO PAULO

July 24 - 30, 1966
SÃO PAULO, BRAZIL

8) Is man a unique mammal in response?
By B.B. BRODIE (U.S.A.)

12) Pharmacology of γ-hydroxybutyric acid
By V.V. ZAKUSOV (U.S.S.R.)

13) Neural control of the formation and actions of melatonin, a pineal gland hormone
By J. AXELROD and R.J. WURTMAN (U.S.A.)

Symposium

XI — **Immunopharmacology**

Chairman: H.O. SCHILD (England)

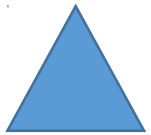
Vice-Chairmen: B. BENACERRAF (U.S.A.) and B.N. HALPERN (France)

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 :

Traditional Medicine, Biodiversity
Medicine in the developing world

Balance



Evidence-based Medicine, Safety.
Modern technology. Innovation.

Natural/traditional products (NPs)	**New Molecular Entities (NMEs).**
Plant, Microbial, Animal, Marine-based	Synthetic chemistry-based, or Antibodies
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, or Abs
Biological Synthesis	Organic/Aqueous phase separation
Novel ?	NPs Starting points for NMEs

Nobel prize for Artemesin, Youyou Tu.

Metabolomics: a breakthrough in ensuring substance validity and activity in mixtures?

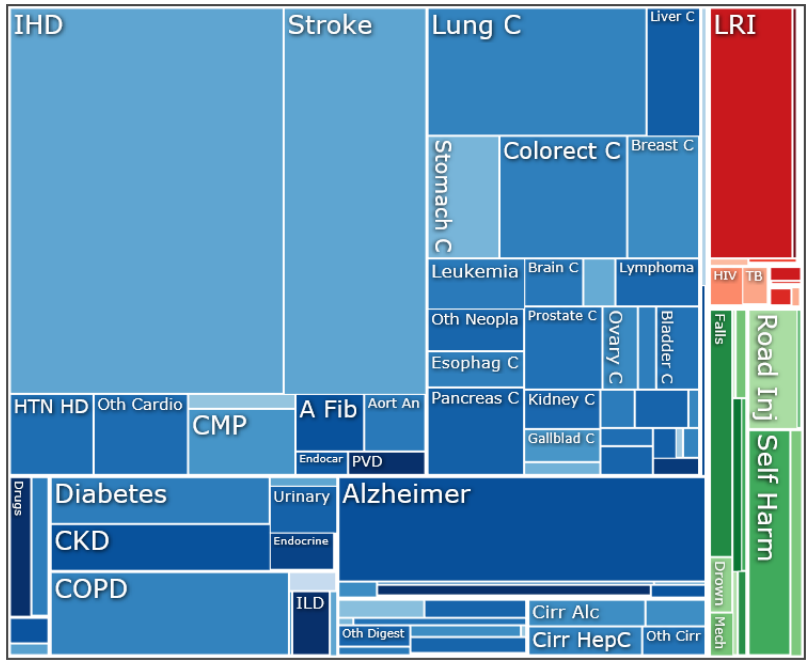
Can we synthesise them in sufficient quantity – **Biosynthesis** now on a >G scale

How do we get out of the mechanistic 'soup' of poorly defined redox, antinflammatory, immunological, antiaging effects claimed for some NPs: IUPHAR establishes MofU with IUIS.

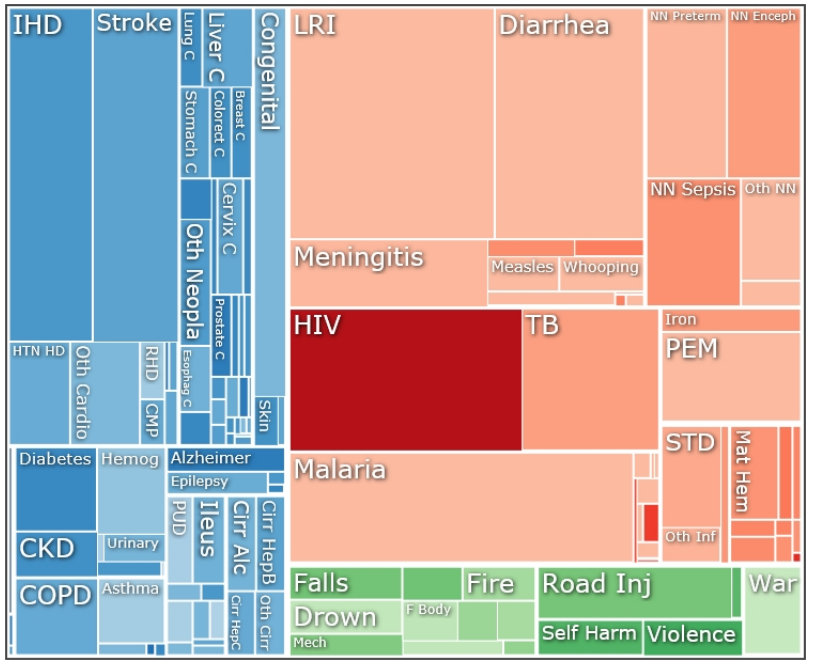
Recommendations being finalised for Nature Drug Discovery Article (Impact Factor 58)

Healthcare : two worlds

Global Deaths High Income



Global Deaths Low Income



Blue: non-communicable, Red: communicable, Green: Injuries

WHO:
>4800 million people live in developing countries
>2700 million people live on <2$/day.

Two worlds also in natural products versus NMEs

M Spedding, organised from http://vizhub.healthdata.org/gbd-compare/

Some relevant WHO Priorities where IUPHAR is active

- Promote Drug Discovery R&D, with open-source knowledge, databases, compound libraries,
- Support early-stage drug discovery and development, particularly in developing countries,
- Stimulate global cooperation in R&D
- Encourage research on mechanisms of action and PK of natural products and traditional medicines. Evidence-based medicine.
- Capacity building for clinical trials, particularly in developing countries,
- Encourage development of regulatory affairs in developing countries

IUPHAR is an official Non-Governmental Organisation (NGO) to WHO for preclinical and clinical pharmacology and education

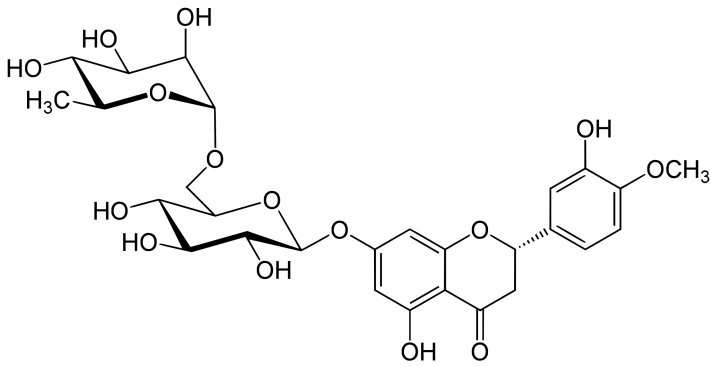
Polyphenol Natural Products

Flavonoids, **Anthocyanins**, **Chalcones**, **Dihydrochalcones**, **Dihydroflavonols**, **Flavanols**, **Flavanone**, **Flavones**, **Flavonols**, **Isoflavonoids**, **Phenolic acids**, **Hydroxybenzoic acids**, **Hydroxycinnamic acids**, **Hydroxyphenylacetic acids**, **Hydroxyphenylpropanoic acids**, **Stilbenes**, **Stilbenes**, **Lignans**, **Hydroxycinnamaldehydes**, **Alkylmethoxyphenols**,**hydroxycoumarins**, **Hydroxyphenylpropenes**, **Methoxyphenols**, **Naphtoquinones**, **Phenolicterpenes**, **Tyrosols**, **Alkylphenols**, **Curcuminoids**, **Furan ocoumarins**,**Hydroxybenzaldehydes**, **Hydroxybenzoketones**

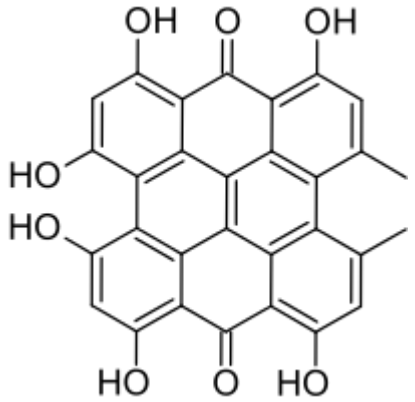
See www.phenol-explorer.eu

Polyphenol glycosides are normally absorbed as aglycones, and then reglycosylated.
However, glycosylation has remarkable recognition properties, which are underestimated.
We take in ~1.8 g of polyphenols/day, extensively metabolised by microbiome.

Hisperidine:



Hypericin is a naphthodianthrone, which, together with hyperforin, is one of the principal active constituents of *Hypericum* (Saint John's wort) On exposure to light (650-700nm.), hypericin undergoes type II photosensitization in which singlet oxygen and other reactive molecular species are produced : viricidal and anticancer



IUPHAR Natural Products meetings

- **Third IUPHAR NP World Congress IUPHAR Singapore 2015, (local organiser Eric Wong)**
- **Paris ICSU IUPHAR meeting May 2017 (M Spedding)**
- **Indian Pharmacology Society Meeting, July 2017, plus Ayush research centre**
- **Singapore, July 2017 (E Wong)**
- **Meeting with FDA-accredited research centre, Mississipi,**
- **Fourth IUPHAR NP World Congress IUPHAR Aberdeen (local organiser Cherry Wainwright), 2017**
- **Brazil Pharmacology Society, October 2017**
- **CNPHARS Lianyungang Meeting 2017 (Yongxiang Zhang, Guanhua Du)**
- **Paris ICSU IUPHAR meeting 2018 (M Spedding)**
- **CNPHARS Beijing 2018 (Yongxiang Zhang, Guanhua Du),**
- **IPS organise the 5th IUPHAR NP World Congress meeting in Hyderabad in December 2019.**

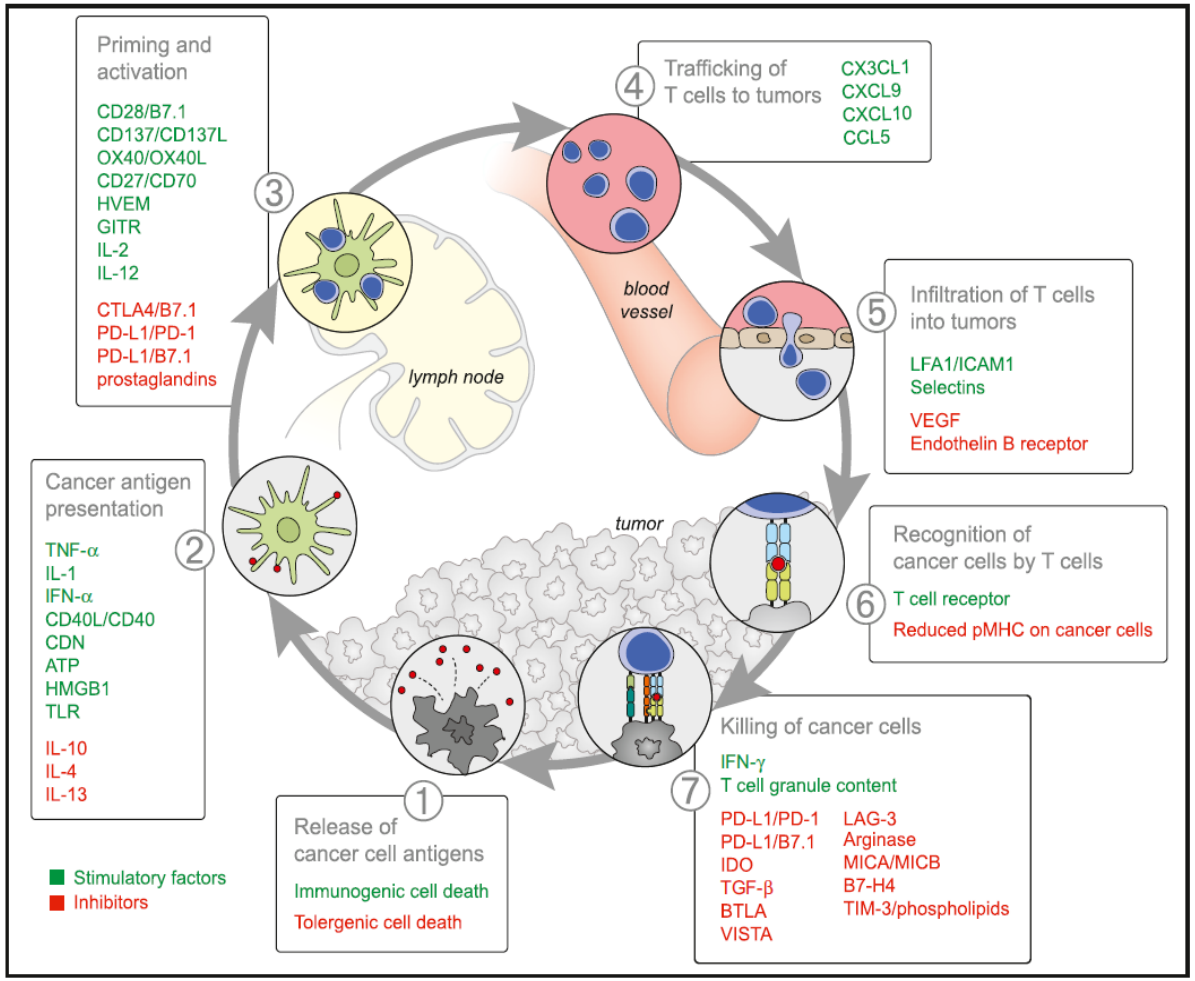
Natural Product research and immunopharmacology – resources wasted ? Or not?

Pubmed citations as of 28/9/2018

Natural Products	613,220	curcumin	12,206
Natural Products & antioxidant	45,275	curcumin	3,337
Natural Products & inflammation	21,354	curcumin	1,403
Natural Products & cytokine	37,813	curcumin	1,554
Natural Products & Freund's adjuvant	2,696	curcumin	20

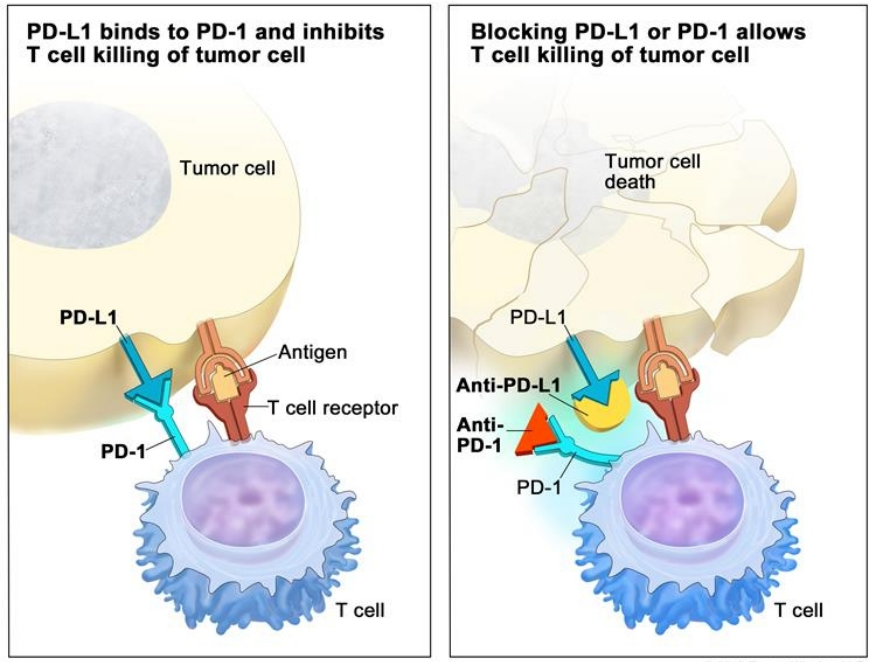
Clinicaltrials.gov

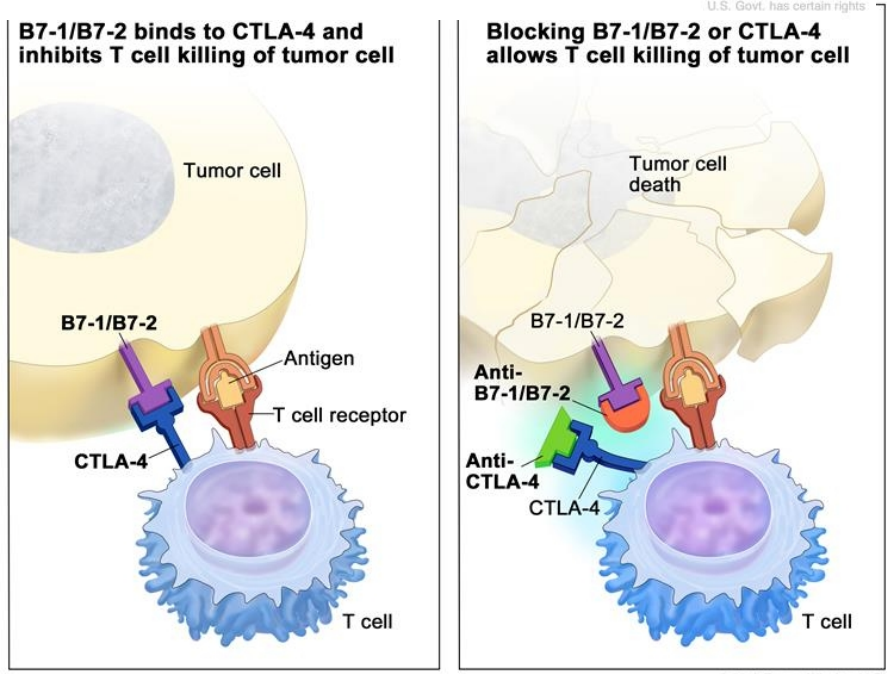
Various (including formulations)	NA	curcumin	160



Oncology Meets Immunology: The Cancer-Immunity Cycle

Daniel S. Chen[1,3] and Ira Mellman[2,3,*]





The website of the National Cancer Institute (https://www.cancer.gov)

Anti-PD-1 MAb combinations with small molecules

Source: EvaluatePharma® September 2015

	Combination drug	Pharmacology class	Indication	Sponsor
Keytruda – Merck & Co				
	RTA 408	NRF2 activator	Melanoma	AbbVie/Reata
	BBI608	STAT3, Nanog & β-catenin pathways inhibitor	Various	Boston Biomedical
	BBI503	Cancer cell stemness kinase inhibitor	General cancer indications	Boston Biomedical
	PLX3397	FMS, c-kit, CSF-1R & Flt-3 kinase inhibitor	Melanoma and multiple other solid tumours	Daiichi Sankyo
	SD-101	TLR9 agonist	Advanced melanoma	Dynavax Technologies
	Lenvatinib	VEGFr tyrosine kinase inhibitor	Solid tumours	Eisai
	Halaven	Microtubule/tubulin inhibitor	Metastatic triple-negative breast cancer	Eisai
	Pazopanib	Multi-kinase inhibitor	Renal cell carcinoma	GlaxoSmithKline
	GSK3174998	Not disclosed	General cancer indications	GlaxoSmithKline
	ACP-196	BTK inhibitor	Various	Merck
	Mekinist + Tafinlar	MEK inhibitor/B-Raf kinase inhibitor	Melanoma	Merck
	Pomalyst	Immunomodulator	Multiple myeloma	Merck
	CC-486 and/or romidepsin	DNMT inhibitor/HDAC inhibitor	Colorectal cancer	Merck & Celgene
	Ziv-Aflibercept	VEGFr kinase inhibitor	Advanced solid tumors	NCI (NIH)
	Axitinib	VEGFr 1-3 tyrosine kinase inhibitor	Renal cancer	Pfizer
	Xalkori	ALK & c-Met kinase inhibitor	ALK-positive advanced NSCLC	Pfizer
	Entinostat	HDAC inhibitor	NSCLC or melanoma	Syndax Pharmaceuticals
	Niraparib	PARP inhibitor	Triple-negative breast and ovarian cancers	Tesaro
	Birinapant	IAP antagonist	Relapsed or refractory solid tumours	TetraLogic Pharmaceuticals
	Gilotrif	EGFR & HER2 kinase inhibitor	NSCLC	University of California/ NCI (NIH)
	Defactinib + Gemzar	FAK inhibitor + pyrimidine analogue	Pancreatic cancer	Washington University School of Medicine
Opdivo – Bristol-Myers Squibb				
	Imbruvica	BTK inhibitor	Non-Hodgkin's lymphoma	AbbVie
	RTA 408	NRF2 activator	Melanoma	AbbVie/Reata
	BBI608	STAT3, Nanog & β-catenin pathways inhibitor	Various	Boston Biomedical
	BBI503	Cancer cell stemness kinase inhibitor	General cancer indications	Boston Biomedical
	Vidaza	DNMT inhibitor	Myeloid leukaemia	Bristol-Myers Squibb
	Tafinlar	B-Raf kinase inhibitor	Metastatic melanoma	Bristol-Myers Squibb
	Mekinist	MEK inhibitor	Metastatic melanoma	Bristol-Myers Squibb
	RRx-001	Radiation sensitizer	Solid tumours	EpicentRx
	Capmatinib	c-Met kinase inhibitor	NSCLC	Incyte
	Galunisertib	TGF-beta RI kinase inhibitor	Glioblastoma, hepatocellular	Lilly

Check-point inhibitors

The main cancer immunological breakthrough

More than 800 combination clinical trails ongoing.

Which synergies ?

Natural products ?

How can you define which may work?

Propose protocols for NP research world-wide

Natural Product research and immunopharmacology – more targeted research?

Pubmed citations as of 28/9/2018

Natural Products	**613,220**	**curcumin**	**12,206**
And:		**And:**	
PD-1	**331**		**0**
PD-L1	**168**		**3**
CTLA-4	**474**		**3**
FoxP3	**635**		**18**
CD40L	**476**		**5**
CD25	**881**		**20**
CD28	**433**		**15**
ICOS	**38**		**0**

BUT: **Clinical trials listed with PD-1 & combinations: 1112, PD-L1, 957, CTLA4, 363**

– none associated with NPs

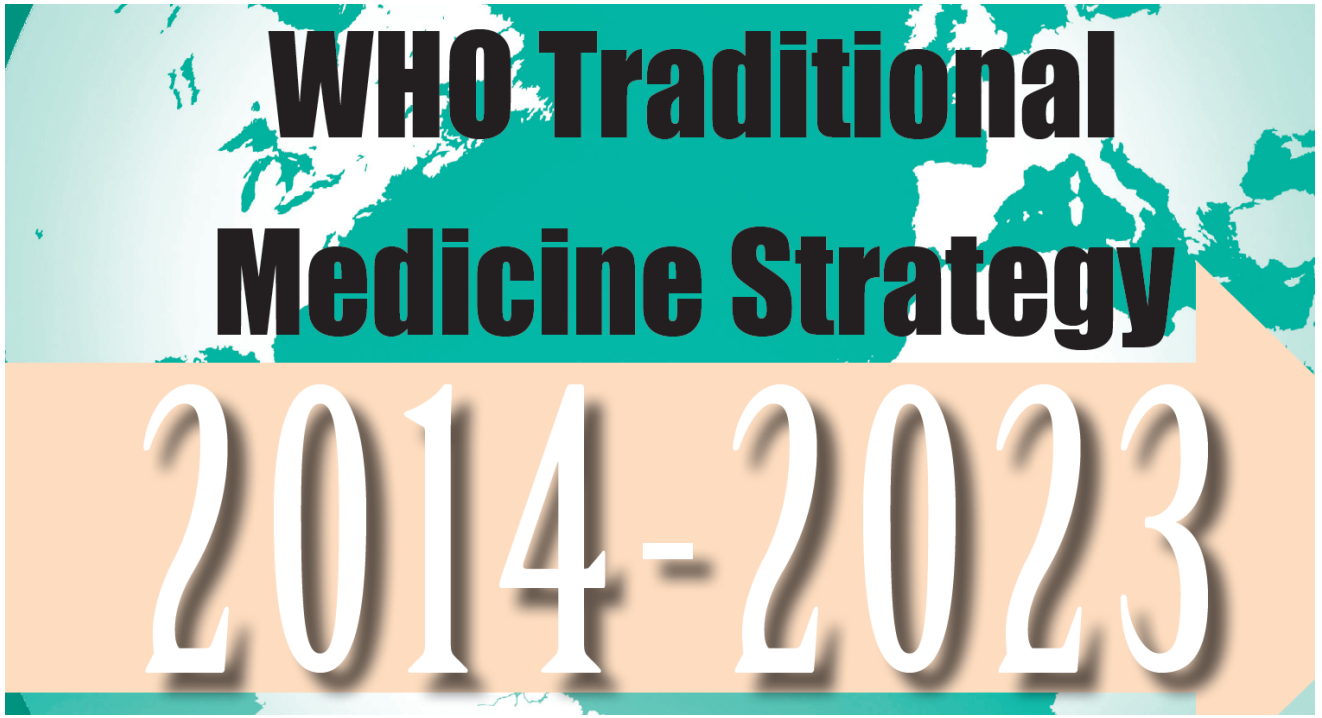


Table 1: Key performance indicators

Strategic objective		Strategic direction		Expected outcomes	Critical indicator
4.1	To build the knowledge base for active management of T&CM through appropriate national policies	4.1.1	Understand and recognize the role and potential of T&CM	▪ T&CM practices and practitioners identified and analysed by Member State and country profile devised for T&CM. ▪ T&CM policies and programmes established by government.	▪ Number of Member States reporting a national/ provincial/state T&CM policy. ▪ Number of Member States reporting increased governmental/public research funding for T&CM;
		4.1.2	Strengthen the knowledge base, build evidence and sustain resources	▪ Strengthened knowledge generation, collaboration and sustainable use of TM resources.	
4.2	To strengthen quality assurance, safety, proper use and effectiveness of T&CM by regulating products, practices and practitioners.	4.2.1	Recognize the role and importance of product regulation	▪ Established and implemented national regulation for T&CM products including registration. ▪ Strengthened safety monitoring of T&CM products and other T&CM therapies. ▪ Technical guidelines and methodology developed for evaluating safety, efficacy and quality of T&CM.	▪ Number of Member States reporting national regulation for T&CM products ▪ Number of Member States reporting national/ provincial/state regulation for T&CM practice ▪ Number of Member States reporting national/ provincial/state regulation/ registration for T&CM practitioners
		4.2.2	Recognize and develop practice and practitioner regulation for T&CM education and training, skills development, services and therapies	▪ Standards for T&CM products, practices and practitioners developed by government. ▪ Established education/training programme, benchmarks and implementation capacities for T&CM practitioners ▪ Improved safe and effective use of T&CM	
4.3	To promote universal health coverage by integrating T&CM services into health care service delivery and self-health care	4.3.1	Capitalize on the potential contribution of T&CM to improve health services and health outcomes.	▪ Integration of T&CM into the health system. ▪ Improved T&CM services and accessibility. ▪ Improved communication between conventional medicine practitioners, professional bodies and T&CM practitioners concerning the use of T&CM.	▪ Number of Member States reporting national plan/ programme/approaches for integrating T&CM service into the national health service delivery ▪ Number of Member States reporting consumer education project/ programme for self-health care using T&CM
		4.3.2	Ensure consumers of T&CM can make informed choices about self-health care.	▪ Better awareness of and access to information about the proper use of T&CM. ▪ Improved communication between conventional medicine practitioners and their patients about T&CM use.	

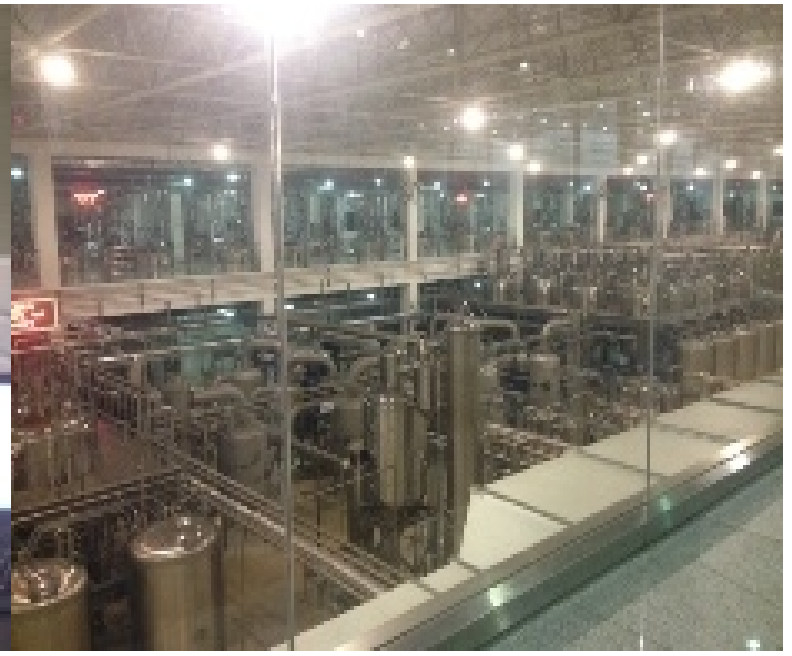
NEWS FEATURE · 26 SEPTEMBER 2018

Why Chinese medicine is heading for clinics around the world

For the first time, the World Health Organization will recognize traditional medicine in its influential global medical compendium.

David Cyranoski

CNPHARS, Innovation in Chi



The NCI Library of Traditional Chinese Medicinal (TCM) Plant Extracts

Traditional Chinese Medicine (TCM) has been practiced over thousands of years in China and other Asian countries for the treatment and symptom management of a wide range of medical conditions. The successful development of anti-malaria drug artemisinin, the discovery of which was inspired by a TCM practice, highlights the potential importance of this unique resource for drug discovery. A prototype TCM library has previously been established through joint efforts of US and Chinese scientists (funded by NCI and other foundations), consisting of more than 200 authenticated medicinal plant and fungal species that collectively represent the potential therapeutic content of commonly used TCM prescriptions.[1] The collection has duplicate or triplicate samples of each plant species that were collected at 2-3 sites with precise GPS documentation and have been authenticated visually and chemically, as well as tested for heavy metals and/or pesticides contamination.[2]

The **NCI Library of TCM Plant Extracts** is a processed library from a subset of this collection, containing both the organic solvent and aqueous extracts of 332 samples of 132 TCM plant species in 96- and 384-well plate formats. It is accessible by drug discovery researchers worldwide (academic and non-profit organizations) to investigate TCM plants as potential sources of agents for the treatment of human disease.

References

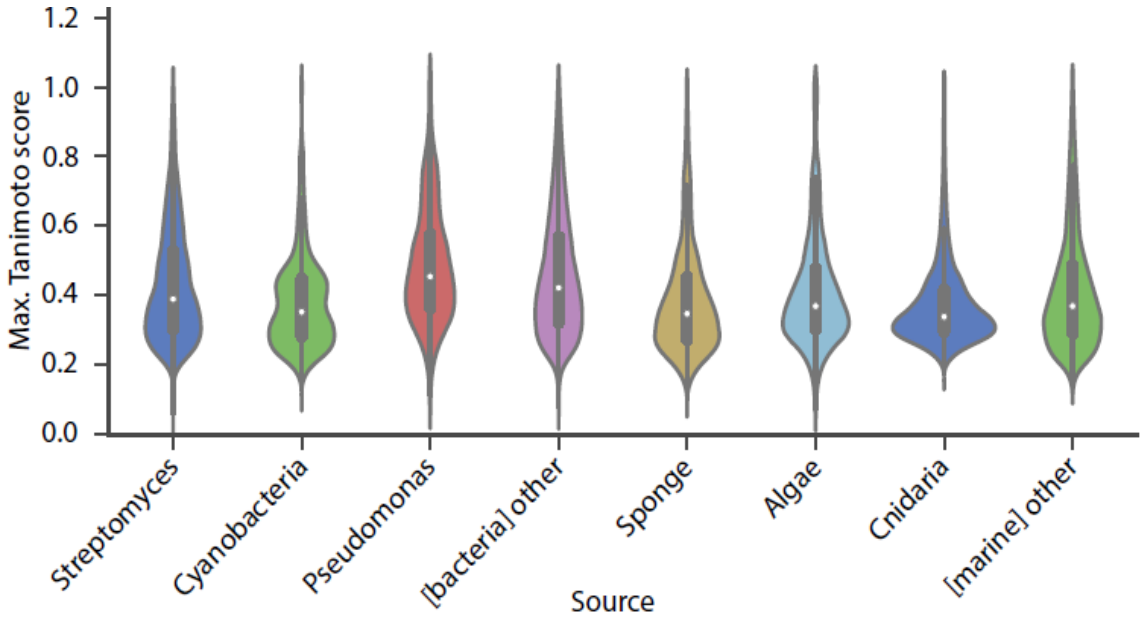
Eisenberg DM, Harris ES, Littlefield BA, Cao S, Craycroft JA, Scholten R, Bayliss P, Fu Y, Wang W, Qiao Y, Zhao Z, Chen H, Liu Y, Kaptchuk T, Hahn WC, Wang X, Roberts T, Shamu CE, Clardy J. Developing a library of authenticated Traditional Chinese Medicinal (TCM) plants for systematic biological evaluation-rationale, methods and preliminary results from a Sino-American collaboration. *Fitoterapia*. 2011; 82(1):17-33

Harris ES, Cao S, Littlefield BA, Craycroft JA, Scholten R, Kaptchuk T, Fu Y, Wang W, Liu Y, Chen H, Zhao Z, Clardy J, Woolf AD, Eisenberg DM. Heavy metal and pesticide content in commonly prescribed individual raw Chinese Herbal Medicines. *Sci Total Environ*. 2011; 409(20):4297-305. doi: 10.1016/j.scitotenv.2011.07.032.

How much chemical diversity in natural p
Currently about 1600 molecules/year pub

Retrospective analysis of natural products provides insights for future discovery trends

Cameron R. Pye[a], Matthew J. Bertin[b,c], R. Scott Lokey[a], William H. Gerwick[b,c,1], and Roger G. Linington[d,1]



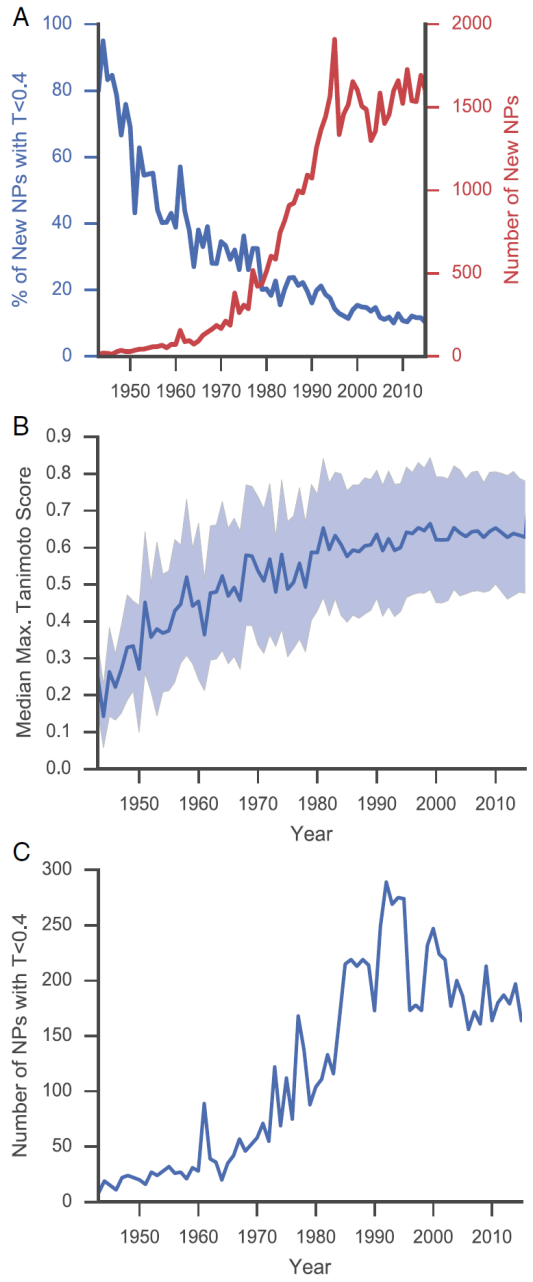
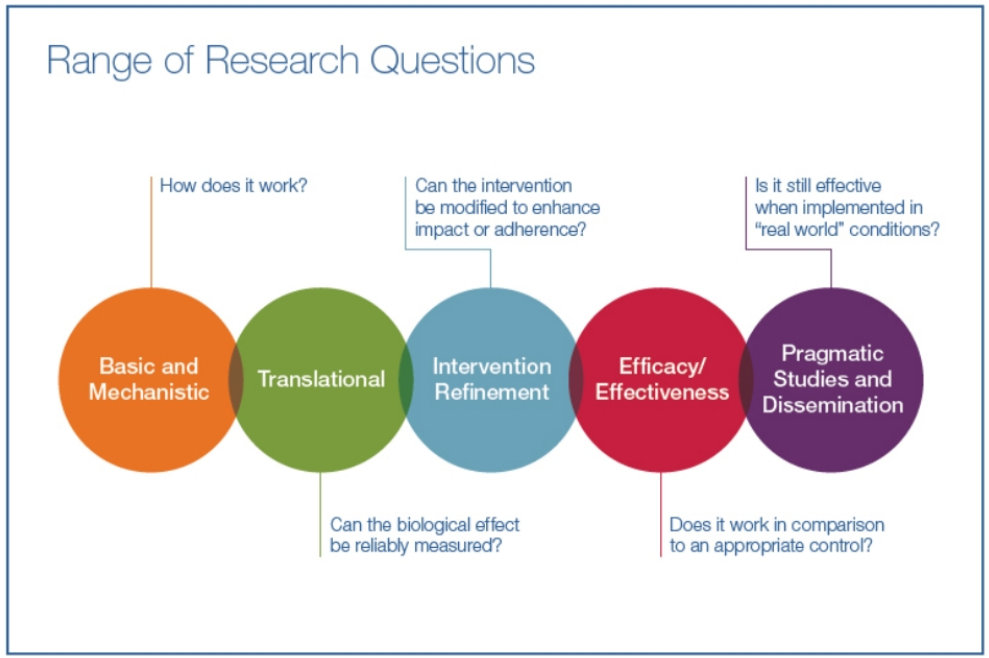
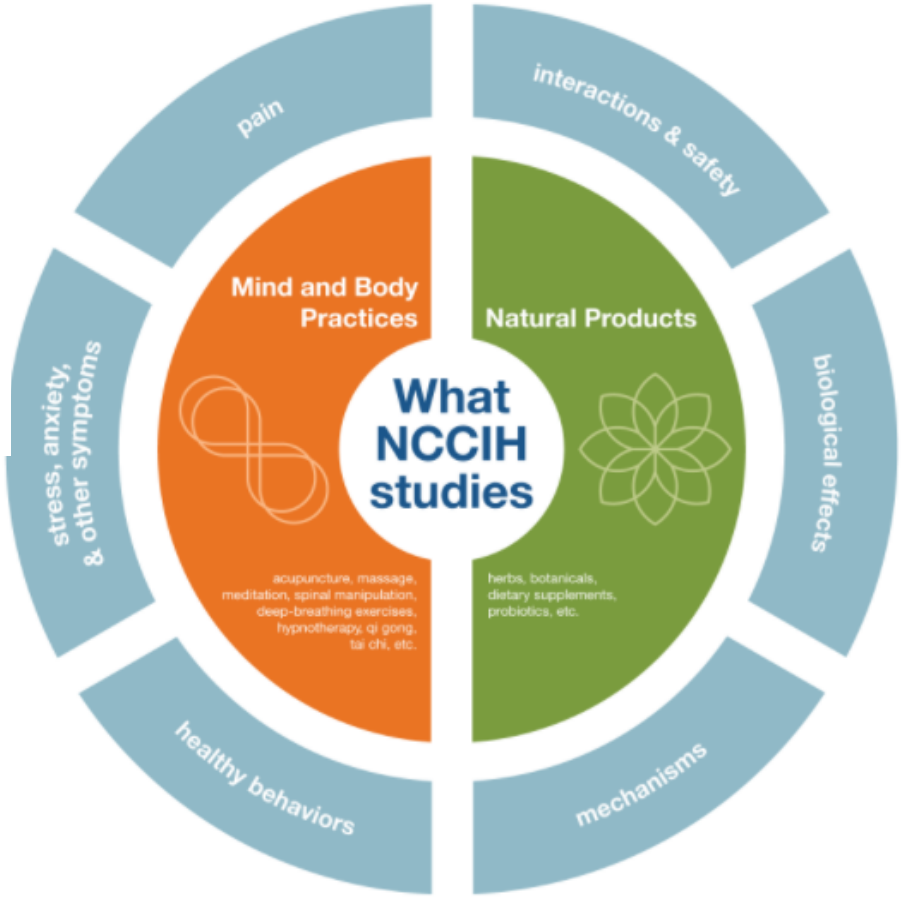


Fig. 1. Examining structural diversity. (*A*) Number of compounds published per year and rate of novel compound isolation as a percentage of total natural product isolation. (*B*) Median maximum Tanimoto scores as a function of time. Median average deviation shown as shaded blue region. (*C*) Absolute number of low similarity compounds (T < 0.4) per year. NP, natural product.

National Center for Complementary and Integrative Health

NIH…Turning Discovery Into Health





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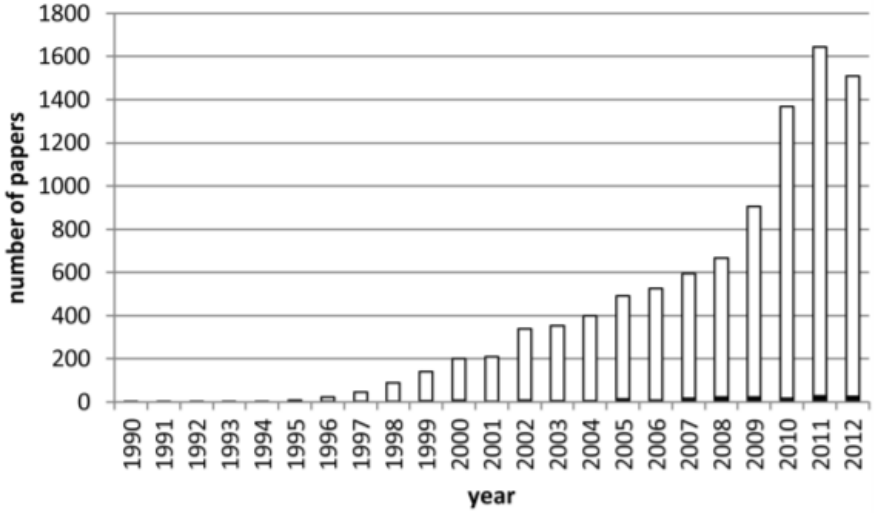


Heinrich & Beuler 2013,
NPs mentioned in HTS papers

NCI has a 'humanitarian patent system', where drugs are not patented in developing countries.

NIH, NCI

NP library, 230,000 collections at current time
Will announce screening resource of 1,000,000 in early 2019
150,000 preplated for assays.
Purification procedures on samples,
Subfractions in 96 well plates to screening centres

Traditional Medicines Libraries (Jeff White)

MTA includes agreement to enter into an amicable agreement with the host country if commercial applications

Collector number held by NCI, includes photos of collection with GPS.
Collector number is secret.
Extract number supplied by NCI to experimenter, only NCI can make the link.

Direct links with Ayush Centre, Delhi; Brazil

IUPHAR and NCNPR – Joint initiatives for Natural Product Research

Michael Spedding, Ikhlas Khan, Larry Walker

Agreed Actions

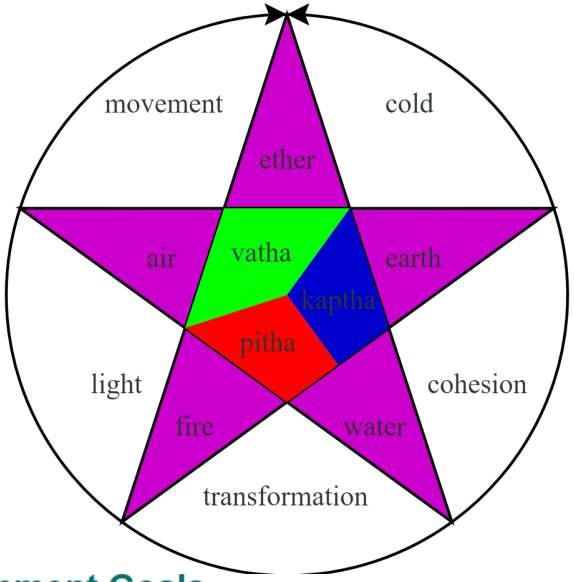
- Make a formal link (IK or LW corresponding member)
- Encourage education and ensure that much of current work is of a high standard
- Work on having a web site designated
- Protocols for immunological testing would be an excellent idea (eg IUIS)
- Define standards with world experts (identified)
- Engage pharma (multiple contacts)
- Search joint finance.

Define simply on such sites the difference between between Food – Dietary Supplement – Drug.

Aim for a Nature Drug Discovery article.

NITI Aayog

(National Institution for Transforming India),
Government of India



How to situate:

Ayurveda, Unani, Siddha, Sowa Rigpa and Yoga & Naturopathy

With:

- *New Chemical Entities,*
- *Evidence-Based Medicine*
- *Natural Product Research?*

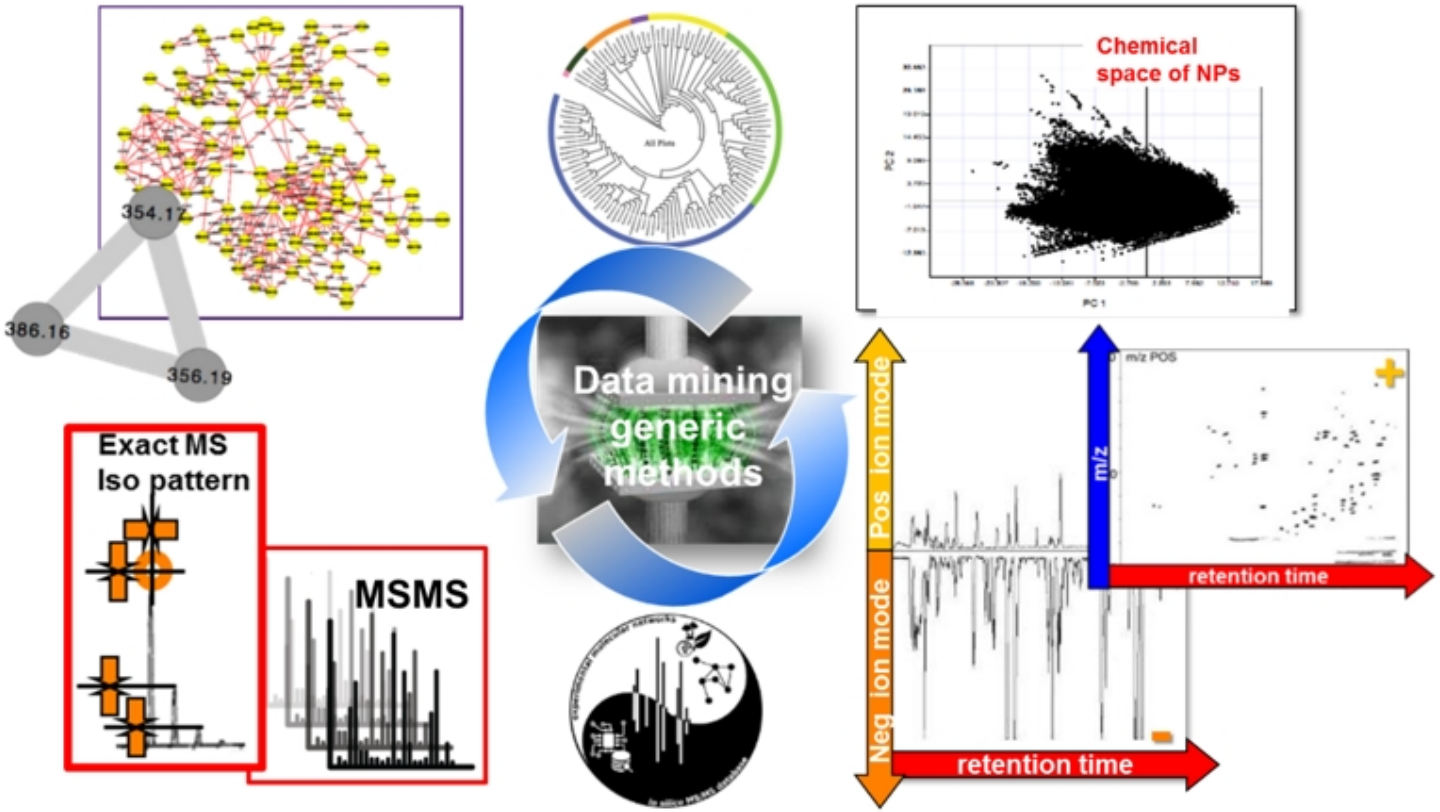
- *1. Address Philosophy*
- *2. Address Variables*
- *3. What we know and don't know*
- *4. Education*
- *5. Use world experts and web sites*
- *6. Define simple messages, propagate on web sites*
- *7. 'Syn'tegrate funding in Europe/US with Indian funding*
- *8. IUPHAR*

Quality Control, Definition of activity:

Metabolomics

Deconvolution of complex mixtures by metabolomics (Jean-Luc Wolfender).

High resolution mass spectrometry (HRMS) and converging feedback
from MS/MS analyses can define secondary metabolites for detailed metabolomic definition.[1]
Tens of thousands of metabolites can be tentatively analysed with 30sec machine time.
Molecular network (MN) approaches for the mining of such data in combination with spectral database generated in silico[2] allows evaluation of relationships
between metabolites[3].



Keywords: *Dereplication, metabolite profiling, metabolomics, MS-targeted isolation*
References: [1] Wolfender J-L *et al. J Chromatogr A* 2015 1382: 136-164. [2] Allard PM *et al. Anal. Chem.* 2016 88: 3317-23. [3] Allard P-M. *et al. Curr. Opin. Chem. Biol.* 2017 36: 40-49. Allard, P.-M. *et al. Curr. Opin. Biotechnol.* 2018, 54, 57-64.

Citation

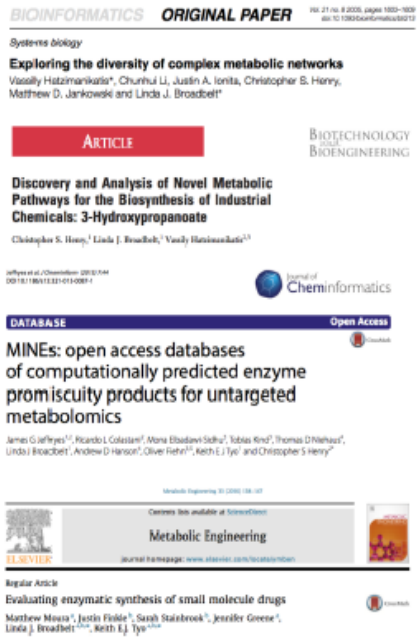
Wang, Mingxun, et al. "Sharing and community curation of mass spectrometry data with Global Natural Products Social Molecular Networking." Nature Biotechnology 34.8 (2016): 828-837. PMID: 27504778

Biosynthesis of Natural Products

Finding pathways between two pools of compounds: state-of-the-art

Metabolic engineering for Natural Products

Jean-Loup Faolon, Paris


BIOINFORMATICS ORIGINAL PAPER

Systems biology

Exploring the diversity of complex metabolic networks

Vassily Hatzimanikatis*, Chunhui Li, Justin A. Ionita, Christopher S. Henry, Matthew D. Jankowski and Linda J. Broadbelt*

ARTICLE

BIOTECHNOLOGY AND BIOENGINEERING

Discovery and Analysis of Novel Metabolic Pathways for the Biosynthesis of Industrial Chemicals: 3-Hydroxypropanoate

Christopher S. Henry,[1] Linda J. Broadbelt,[2] Vassily Hatzimanikatis[1,3]

Journal of Cheminformatics

DATABASE Open Access

MINEs: open access databases of computationally predicted enzyme promiscuity products for untargeted metabolomics

James G Jeffryes[1,2], Ricardo L Colastani[2], Mona Elbadawi-Sidhu[3], Tobias Kind[3], Thomas D Niehaus[4], Linda J Broadbelt[4], Andrew D Hanson[5], Oliver Fiehn[3,6], Keith E J Tyo[1] and Christopher S Henry[2*]

Metabolic Engineering

Regular Article

Evaluating enzymatic synthesis of small molecule drugs

Matthew Moura[a], Justin Finkle[b], Sarah Steinbrook[b], Jennifer Greene[a], Linda J. Broadbelt[a,c,*], Keith E.J. Tyo[a,b,c,*]

BNICE

~100 reaction rules manually curated


BMC Systems Biology

METHODOLOGY ARTICLE Open Access

Prediction of novel synthetic pathways for the production of desired chemicals

Ayoun Cho[1], Hongseok Yun[1,2], Jin Hwan Park[1,2], Sang Yup Lee[*1,2,3] and Sunwon Park[*4]

nature chemical biology

ARTICLE

Metabolic engineering of *Escherichia coli* for direct production of 1,4-butanediol

Harry Yim[1,2], Robert Haselbeck[1,3], Wei Niu[1,2], Catherine Pujol-Baxley[1,2], Anthony Burgard[1,2], Jeff Boldt[1], Julia Khandurina[1], John D Trawick[1], Robin E Osterhout[1], Rosary Stephen[1], Jasnil Estadilla[1], Sy Teisan[1], H Brett Schreyer[1], Stefan Andrade[1], Tae Hoon Yang[1], Sang Yup Lee[2], Mark J Burk[1] & Stephen Van Dien[1*]

Metabolic Engineering

Generation of an atlas for commodity chemical production in *Escherichia coli* and a novel pathway prediction algorithm, GEM-Path

Miguel A. Campodonico[1,2], Barbara A. Andrews[3], Juan A. Asenjo[3], Bernhard O. Palsson[1,*], Adam M. Feist[1,4,*]

SimPheny /GEM-Path

~50 reaction rules manually curated


METHODOLOGY ARTICLE Open Access

A retrosynthetic biology approach to metabolic pathway design for therapeutic production

Pablo Carbonell, Anne-Gaëlle Planson, Davide Fichera and Jean-Loup Faulon*

BMC Systems Biology

RESEARCH ARTICLE Open Access

Enumerating metabolic pathways for the production of heterologous target chemicals in chassis organisms

Leading Edge Select

Designer Genes and Engineered Circuits

Making Metabolites The XTMS interactive platform ranks promiscuous enzymatic steps, toxicities, and yields to facilitate exploration of prospective biosynthetic pathways. Courtesy of J.-L. Faulon.

ACS SyntheticBiology

Retropath: Automated Pipeline for Embedded Metabolic Circuits

Pablo Carbonell[1,2,*], Pierre Parutto[1,2], Claire Baudier[1], Christophe Junot[3] and Jean-Loup Faulon[1,2,*]

[1]Univ. Evry, ISSB, F-91000 Evry, France, [2]CNRS, ISSB, F-91000 Evry, France and [3]SEER Mohali, SAS Nagar, Manauli, PO 140306, Mohali, Punjab, India

Published online 03 May 2014

Nucleic Acids Research, 2014, Vol. 42

XTMS: pathway design in an eXTended metabolic space

Pablo Carbonell[1,2,*], Pierre Parutto[1,2], Joan Herisson[1,2], Shashi Bhushan Pandit[3] and Jean-Loup Faulon[1,2,*]

[1]University of Evry, ISSB, F-91000 Evry, France, [2]CNRS, ISSB, F-91000 Evry, France and [3]SEER Mohali, SAS Nagar, Manauli, PO 140306, Mohali, Punjab, India

Received January 31, 2014; Revised April 04, 2014; Accepted April 15, 2014

RetroPath

~14000 reaction rules automatically generated

Rules specific or promiscuous

Nagoya Protocol

The *Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization (ABS) to the Convention on Biological Diversity* is a supplementary agreement to the Convention on Biological Diversity and entered into force on 12 October 2014 - the fair and equitable sharing of benefits arising from the utilization of genetic resources, thereby contributing to the conservation and sustainable use of biodiversity.

A genetic resource is defined as:

- any resource produced naturally, made of DNA, RNA or biochemical compound produced by the genome: protein, lipids, carbohydrates ...
- obtained from any organism: animal, vegetable, fungal, bacterium, virus ... whether alive or dead
- at the molecular scale, cell, tissue, organ, org
- group of the same species or multi-species gr
- be taken or already removed, on site or in a c
- Genetic resources are the property of the stat or indigenous population of origin.

Visit the ABS Clearing-House:

ABSCH

The *Access and Benefit-sharing Clearing-House* (ABS Clearing-House) is a platform for exchanging information on access and benefit-sharing established by Article 14 of the Protocol, as part of the Clearing-House of the Convention established under Article 18, paragraph 3 of the Convention. The ABS Clearing-House is a key tool for facilitating the implementation of the Nagoya Protocol, by enhancing legal certainty and transparency on procedures for access and benefit-sharing, and for monitoring the utilization of genetic resources along the value chain, including through the internationally recognized certificate of compliance. By hosting relevant information regarding ABS, the ABS Clearing-House will offer opportunities for connecting users and providers of genetic resources and associated traditional knowledge.

Issues about Nagoya

- How to define a natural product which falls under Nagoya,
- How to deal with plants which go beyond country boundaries, and NPs which go beyond country boundaries,
- Who decides this as it is an international decision, and what ‘authoritative lists’ researchers and suppliers can use.
- How can this be accommodated with the date of signature of Nagoya,
- How can post hoc claims be managed by over-ambitious and organised nations.

Steve Trevenna

Department for Business, Energy & Industrial Strategy

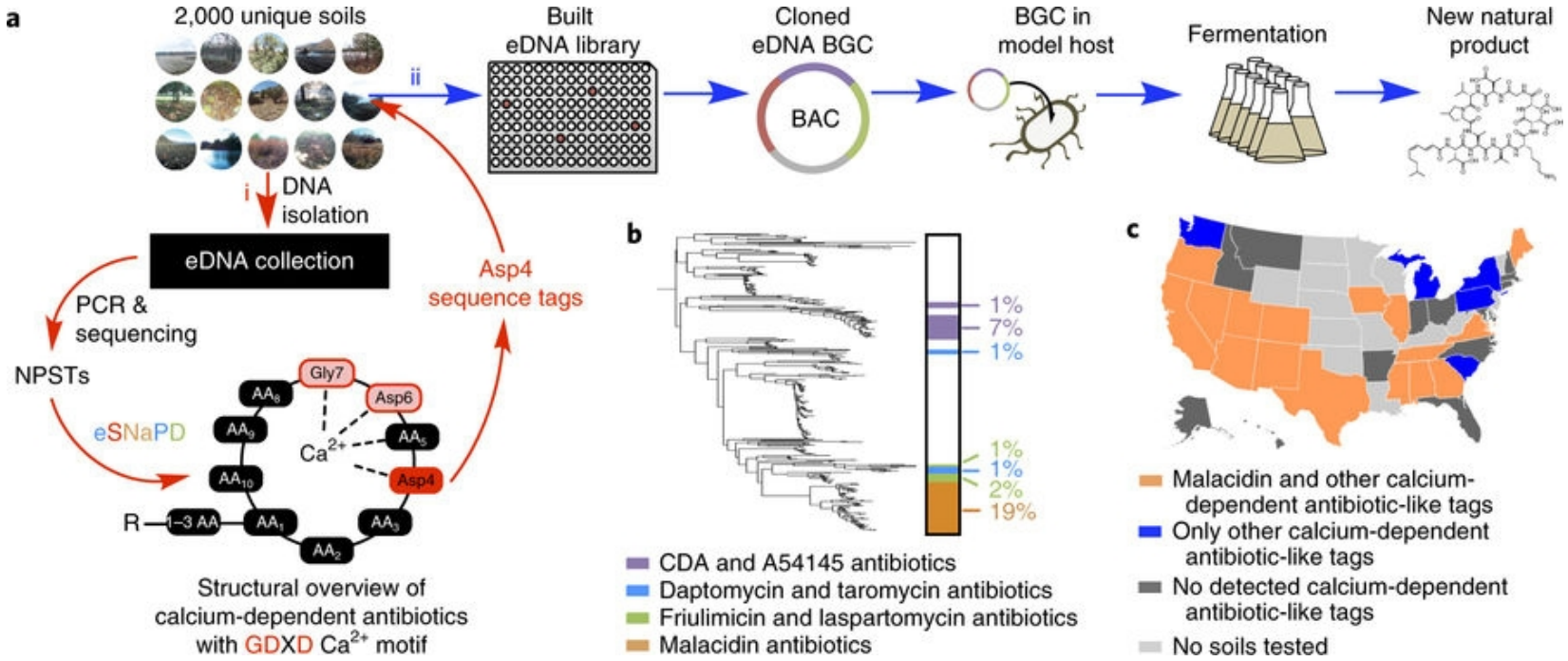
- **How to define a natural product which falls under Nagoya?** (as compared to foxglove, digoxin for example). Need to be clear that with the Protocol and discussing scope, there is always two elements – access legislation of the provider country and compliance regulation where you are taking the resource to. This comes down to the national access legislation of the provider. Foxglove is the genetic resource which would be covered under national legislation, Digoxin is isolated from the foxglove plant – therefore a derivative and less likely to be claimed. However it depends on what the provider dictates – for example if you were to access from the UK there would be no access requirements and it would fall out of the Protocol.
- **How to deal with plants which go beyond country boundaries, and NPs which go beyond country boundaries?** This issue is who you access the resource from – compliance will be with their National Legislation – it is possible for two nations to claim sovereignty of a resource. PIC and MAT are bilateral agreements for material being accessed from one Party by another. Easier to be able to identify one provider country and establish contract and permit from them. I am unsure yet of any conflict on this. From the Protocol:

Article 11. Transboundary Cooperation

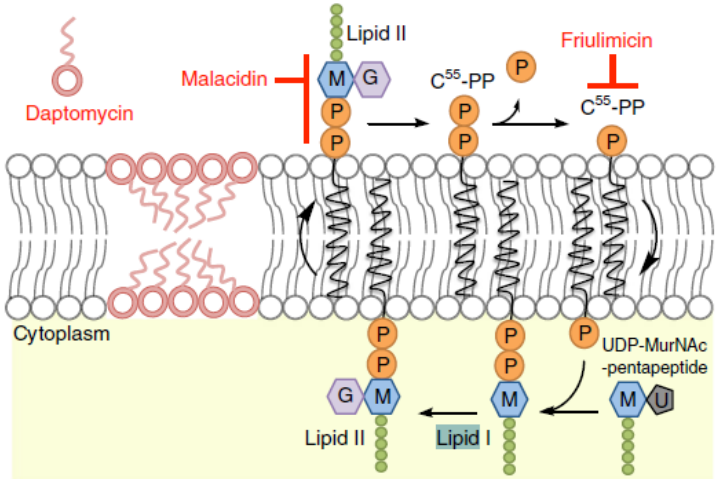
1. *In instances where the same genetic resources are found in situ within the territory of more than one Party, those Parties shall endeavour to cooperate, as appropriate, with the involvement of indigenous and local communities concerned, where applicable, with a view to implementing this Protocol.*

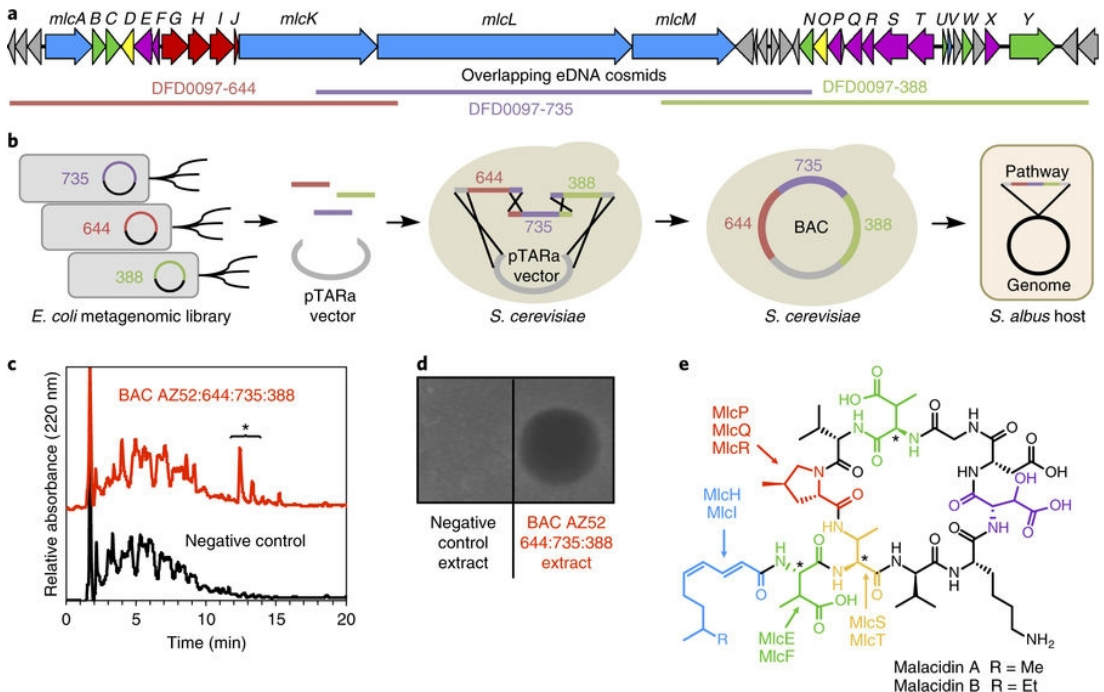
2. *Where the same traditional knowledge associated with genetic resources is shared by one or more indigenous and local communities in several Parties, those Parties shall endeavour to cooperate, as appropriate, with the involvement of the indigenous and local communities concerned, with a view to implementing the objective of this Protocol*

- **Who decides this as it is an international decision, and what 'authoritative lists' researchers and suppliers can use?** Not sure if there is an authoritative list for individual genetic resources at this point – Some individual countries have set up lists of those species considered indigenous. It is possible to determine what a given country claims sovereignty over through the ABS Clearing House and reviewing their legislation/ contacting the Focal Point.
- **The Nagoya Protocol is not retroactive and only covers resources accessed after 12 October 2014,**



Mechanism of action?





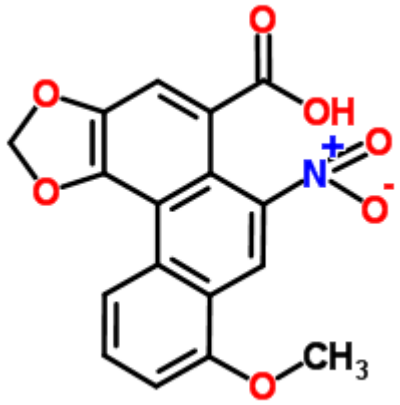
nature microbiology
LETTERS
https://doi.org/10.1038/s41564-018-0110-1
OPEN

Culture-independent discovery of the malacidins as calcium-dependent antibiotics with activity against multidrug-resistant Gram-positive pathogens

Bradley M. Hover[1], Seong-Hwan Kim[1], Micah Katz[1], Zachary Charlop-Powers[1], Jeremy G. Owen[1], Melinda A. Ternei[1], Jeffrey Maniko[1], Andreia B. Estrela[1], Henrik Molina[2], Steven Park[3], David S. Perlin[3] and Sean F. Brady[1]*

A break-through paper?
Lodo makes major deal with Genentech

Traps of Natural Products ?



1. Toxicity,
e.g. Aristolochic acid

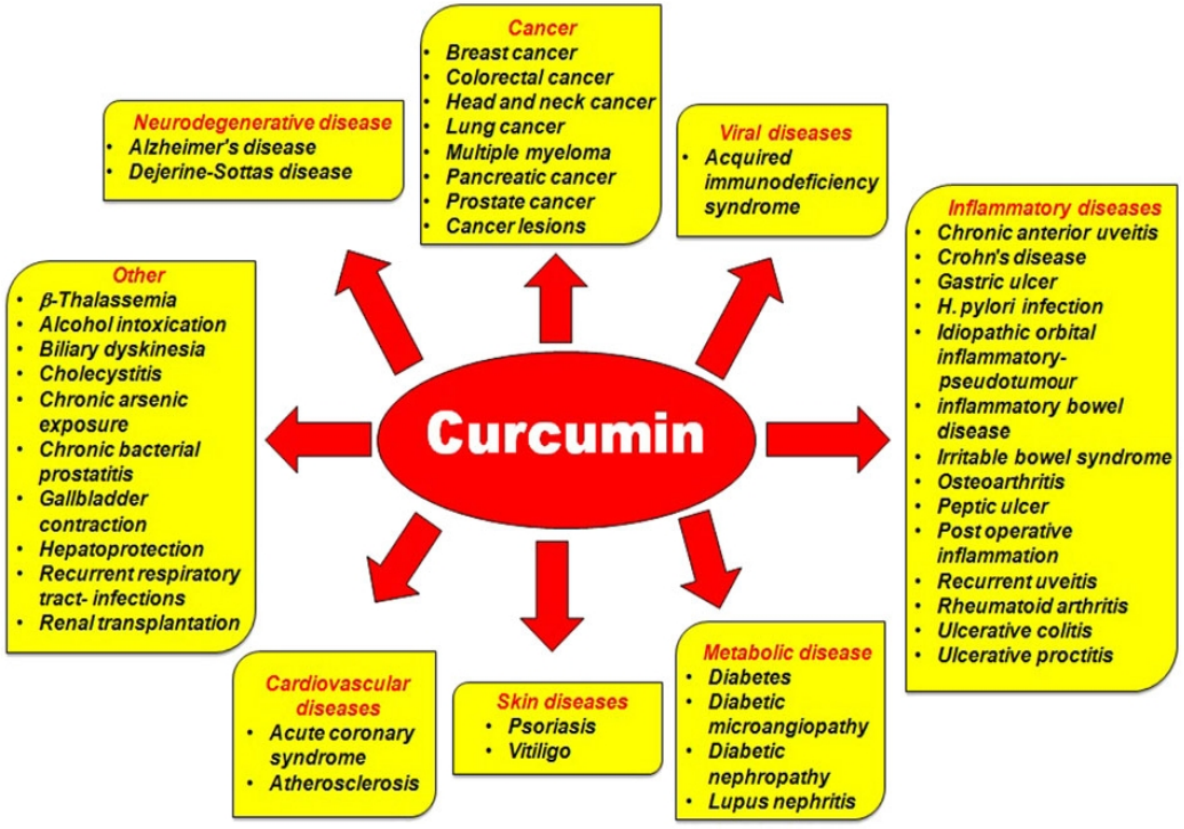
2. PAINS

3. Rapid metabolism

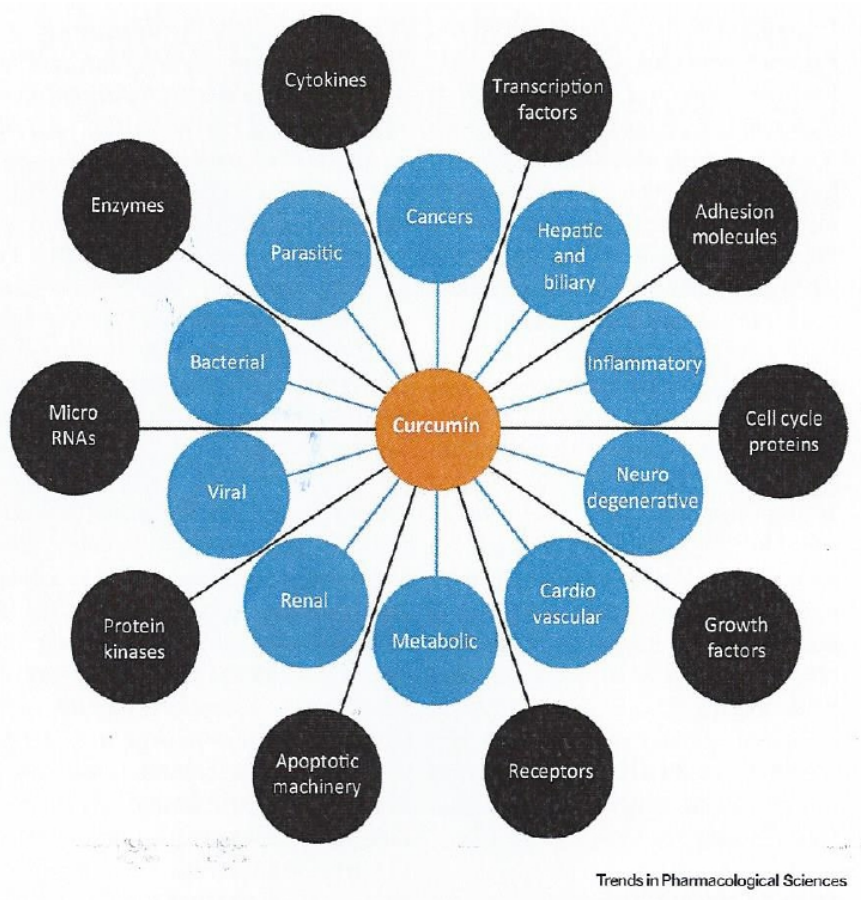
Curcumin, the golden nutraceutical: multitargeting for multiple chronic diseases

Ajaikumar B Kunnumakkara[1], Devivasha Bordoloi[1], Ganesan Padmavathi[1], Javadi Monisha[1], Nand Kishor Roy[1], Sahdeo Prasad[2] and Bharat B Aggarwal[3]

British Journal of Pharmacology (2017) **174** 1325–1348 1325



Curcumin as an adjunct drug for infectious diseases
G Padmenaban & PN Rangajaran
TiPS

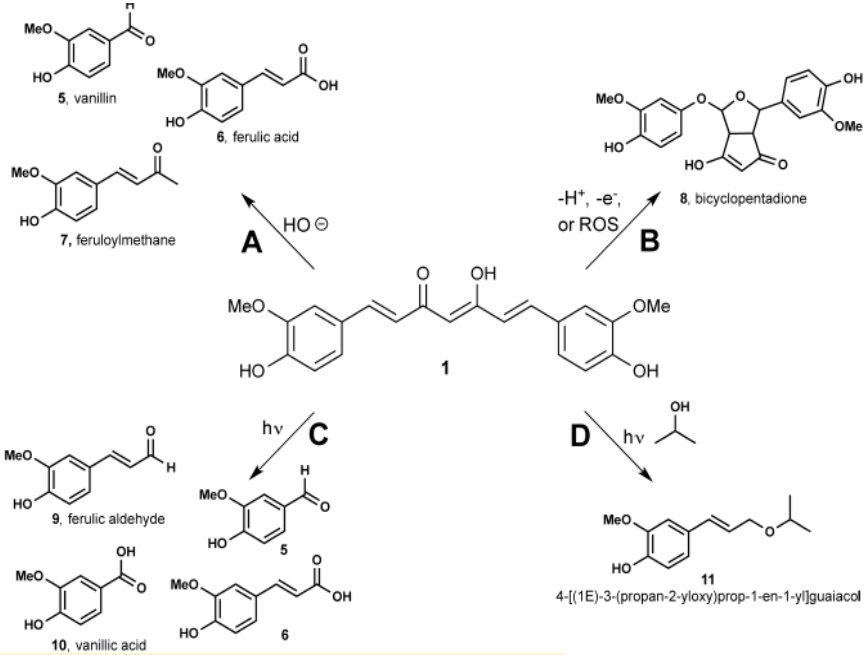


Journal of Medicinal Chemistry

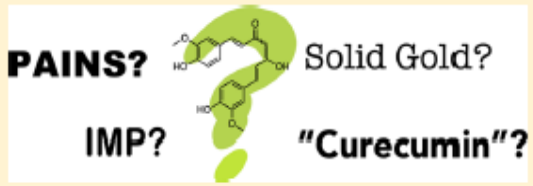
The Essential Medicinal Chemistry of Curcumin

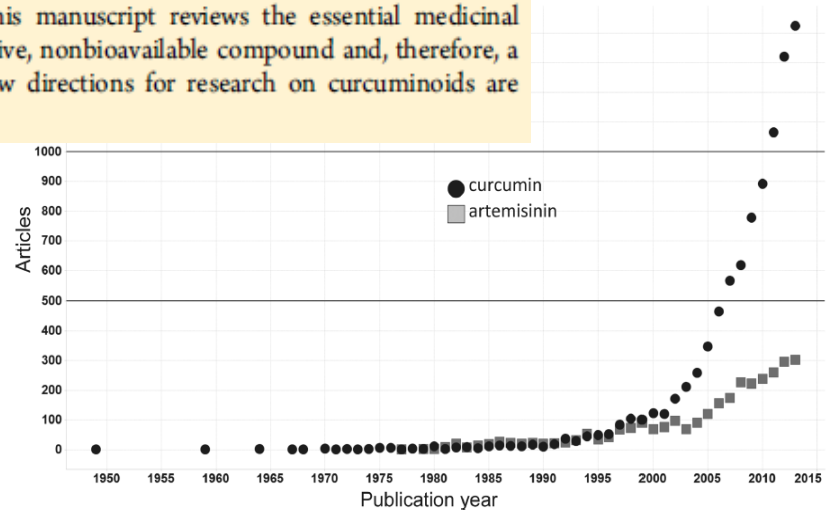
Miniperspective

Kathryn M. Nelson,[†] Jayme L. Dahlin,[‡] Jonathan Bisson,[§] James Graham,[§] Guido F. Pauli and Michael A. Walters*[,†]



ABSTRACT: Curcumin is a constituent (up to ~5%) of the traditional medicine known as turmeric. Interest in the therapeutic use of turmeric and the relative ease of isolation of curcuminoids has led to their extensive investigation. Curcumin has recently been classified as both a PAINS (pan-assay interference compounds) and an IMPS (invalid metabolic panaceas) candidate. The likely false activity of curcumin in vitro and in vivo has resulted in >120 clinical trials of curcuminoids against several diseases. No double-blinded, placebo controlled clinical trial of curcumin has been successful. This manuscript reviews the essential medicinal chemistry of curcumin and provides evidence that curcumin is an unstable, reactive, nonbioavailable compound and, therefore, a highly improbable lead. On the basis of this in-depth evaluation, potential new directions for research on curcuminoids are discussed.





1. Look for evidence of compound stability in assay buffer/media, including when molecular models are invoked as supporting evidence of target engagement.
2. Look for the presence of detergent and thiol-scavenging reagents in biochemical assays to mitigate the impact of chemical aggregation and nonspecific thiol reactivity. Are/were any additional counterscreens performed to rule out these phenomena?
3. Examine the selectivity data. What are the magnitudes of any observed selectivity? Are these significant? Can any selectivity be explained by differential target susceptibilities to nonspecific interference modalities like thiol reactivity? Can any apparent selectivity be explained by the assay conditions, such as target or total protein concentration?
4. Examine the potency of the compound. At those concentrations, would there be any expected aggregation or off-target effects? And if so, can one make *meaningful* conclusions about specific pathways and target engagement? Does the stoichiometry make sense?
5. Evaluate the methods to confirm target engagement. Look for biophysical orthogonal methods for support of target engagement (e.g., SPR, ITC, CETSA), not solely phenotypic assays.
6. Carefully examine the detection method for determining the concentration of **1** present in an assay. What biophysical method is/was used for detection? Can likely degradation products or metabolites have a similar response and/or explain the data/hypothesis?

Thousands of articles on NPs or extracts having poorly defined antinflammatory/immune effects in animals – what benefit?

IUPHAR international union of basic and clinical pharmacology
Better Medicines through Global Education and Research

ICSU

BBSCRC Grant applied for.

Alliance IUPHAR/IUIS.

Project Summary

Currently, 4800 million people live in developing countries; 2700 million live on less than US$2 a day. Much of the world's population has limited access to evidence-based clinical medicine based on studies with new chemical entities (NCEs) or antibodies, because of expense, or with either natural products/traditional medicine (NPs), where there is little clinical evidence for NP efficacy or if/how they work. NPs are often described to affect inflammation/immune system, but without a consensus on the standardisation of protocols. Immunopharmacological drug targets are crucial for new drug discovery, particularly in, and for, the developing world. For example, immunological therapy for cancer has revolutionised the field. **However, particularly, but not exclusively, in the developing world, immunological protocols are poorly defined and are inadequate to support competitive research. There is a major need for simple validated immunological protocols around drug targets, which can be performed in labs without major facilities.** IUIS and IUPHAR can meet this gap and supply scientific education to the developing (and developed) world via our publicly available web sites backed up by expert subcommittees (example: www.guidetopharmacology.org is supported by >90 subcommittees of scientists), and high quality publications, for which we have already shown our competence.

18 letters of support !
Letter from President of IUIS stating that we should have an alliance whether we get the grant or not.

Goals: Enabling Pharmacology throughout the world by supplying protocols and advice to make better experiments, and progressing NP research to allow real progress.

Immunopharmacology
The new frontier
IUPHAR – IUIS Collaboration
The Guide to immunopharmacology

Drug Screening, Key Issues

Chemical libraries of NPs for drug screening? Nagoya Protocol?

Virtual libraries of NP structures?

Screening for what?
My advice: - go for orphan diseases.

Dear Mr Spedding,

I am glad to inform you that on 19 April the COMP issued a positive opinion on the application for orphan drug designation of Ambroxol hydrochloride for treatment of amyotrophic lateral sclerosis.

The sponsor (SRS!) will, in due course, receive the opinion together with the summary report and subsequently the EMA Public Summary of Opinion for comments and finally the Decision from the European Commission.

Kind regards,
Agnieszka Wilk-Kachlicka
Orphan Medicines Office and PRIME Assistant
Product Development Scientific Support

European Medicines Agency
30 Churchill Place | Canary Wharf | London E14 5EU | United Kingdom
Tel. +44 (0)20 3660 8503
Agnieszka.Wilk@ema.europa.eu

Evolution, Man

Noakes and Spedding, 2012, Nature.

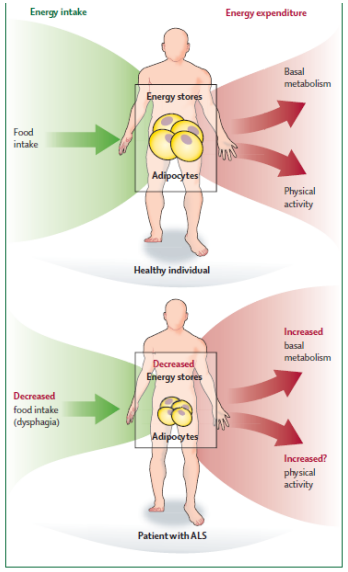
1. Metabolic evolution to triple VO2 max in ~1 Myears ~3M years ago
   AND prolong lifespan.
1. Evolution of brain size and circuits
2. Very recent evolution (100K years) to occupy all planetary niches (SNPs, epigenetics, bacteriome and virome) which « hides » #1.
4. Modern lifestyle and modern diseases.

Mitochondria & Lipid Metabolism (Khaitovic)

Servier lipidomics
3000 lipids

Energy metabolism in amyotrophic lateral sclerosis

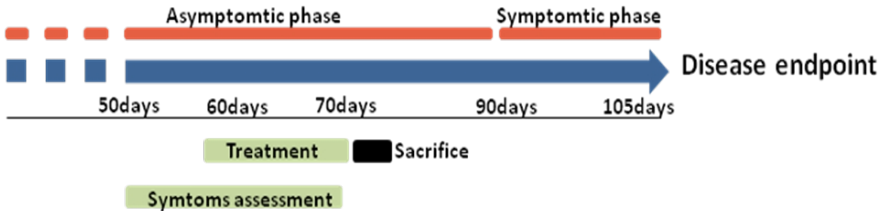
Luc Dupuis, Pierre-François Pradat, Albert C Ludolph, Jean-Philippe Loeffler



Superoxide dismutase (SOD1) Tg model
Metabolomic & transcriptomic analysis
Human patient tissue.

New enzymatic **target (GCase)**

Powerful phenotypical screens



Other Screens
CHMP2B
C9orf72
TDP43

New (Old) Drug
EMA Orphan Drug Designation
Phase II

IUPHAR Immunopharmacology/Antibody Group formed

Francesca Levi-Schaffer is chair (>60 members)
Wellcome immunopharmacology kinase grant obtained (0.5M€)
www.guidetoimmunopharmacology.org Alliance with IUIS.

TARGET, inhibitors	WHICH IMMUNE DISEASES ?
• Akt	• Asthma
• Multiple chemokine receptors	• Rheumatoid arthritis
• INFα	• Multiple sclerosis (IL17+)
• IL1	• Aspects of schizophrenia
• IL6	• Juvenile diabetes
• IL17	• Cardiomyopathy
• Inflammasome	• Antiphospholipid syndrome
• IRAK4	• Guillain-Barré syndrome
• Jak/stat	• Crohn's disease
• Mtor	• Graves' disease
• PI3K δ /γ	• Sjogren's syndrome
• Syk	• Vitiligo
• TLR2/4/7/9	• Myasthenia gravis
• TNFα	• Systemic lupus erythematosus (SLE)
• ROR-γ	• Psoriasis

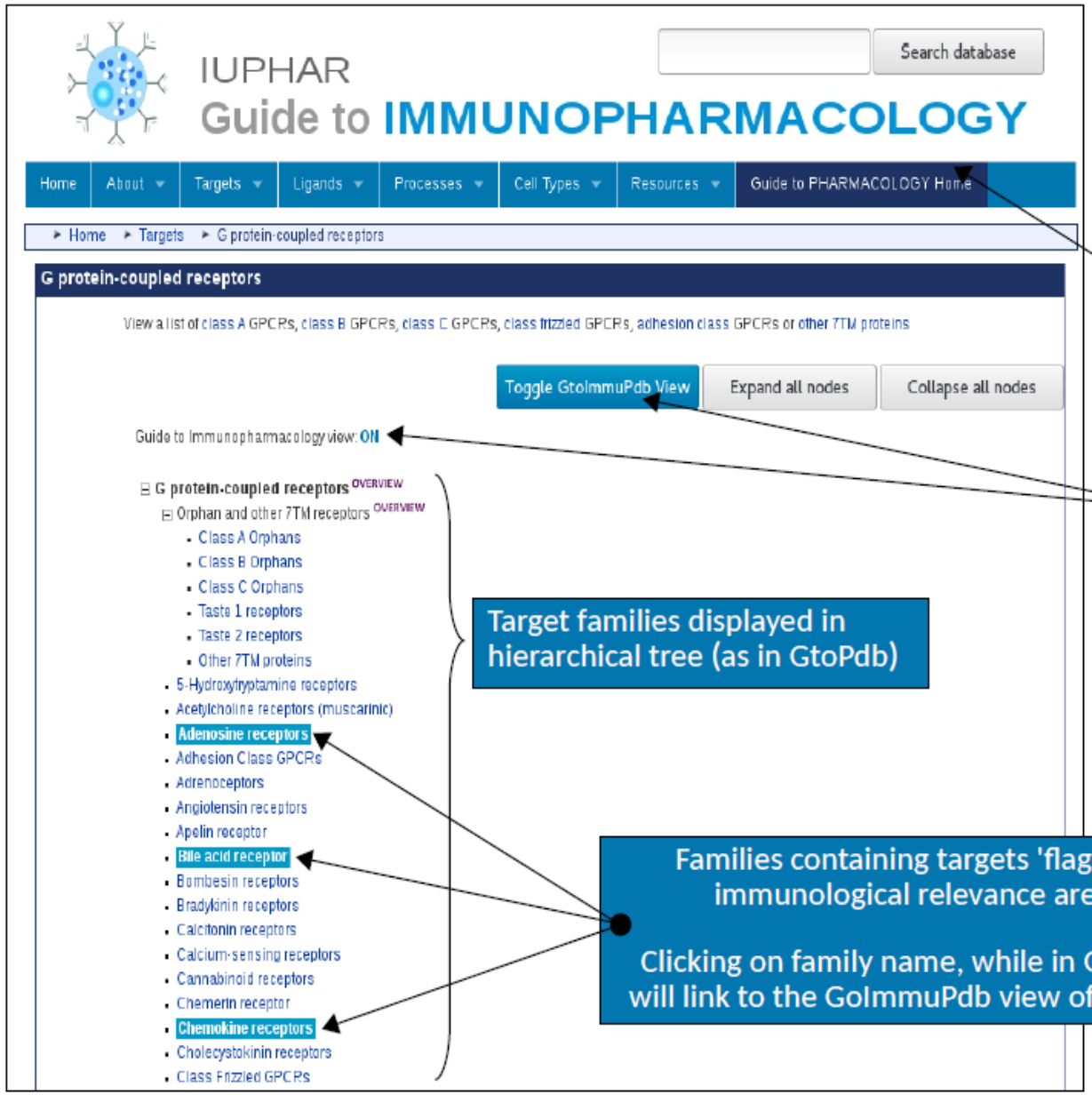
?

Immunopharmacology : Which target for which disease ?

GtoImmuPdb User Guide – Target Families Page

IUPHAR international union of basic and clinical pharmacology

Better Medicines through Global Education and Research



Uses same page as for GtoPdb, but has the GtoImmuPdb view switched on.

GtoImmuPdb view has it's own header and menu-bar.

Toggle button switches between GtoImmuPdb and GtoPdb view.

Target families displayed in hierarchical tree (as in GtoPdb)

Families containing targets 'flagged' as being of immunological relevance are highlighted.

Clicking on family name, while in GtoImmuPdb view, will link to the GoImmuPdb view of that family's page.

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.

Possibilities ?

- *Link to GNPS*
- *The same polyphenols are found across multiple species so I do not see how the notion of sovereignity exists <u>where</u> they are world-wide resources. If only one polyphenol is found in only one plant found in one country then this is an argument like TCMs, but worldwide resources should not be held to ransom by single nations. There is a case for a website showing providence, using metabolomics such as GNPS. Surely NPs such as quercetin are so widespread that it cannot be covered by Nagoya? So where is the dividing line, based on scientific evidence? Here IUPHAR could make clear recommendations.*
- *Propositions based on Metabolomics, Biosynthesis and orphan designations. Biosynthesis now offers the possibility of making single NPs or mixtures which are original. Metabolomics can now define these mixtures reasonably well. Furthermore, metabolomics coupled with in vitro drug screening can deconvolute mixtures to find active synergies. This presumably would not be covered by the Nagoya protocol?*

- IUPHAR could organise pharmacological societies world-wide to have a common voice but this would require substantial resources. We could also put up a database of common natural products which are ‘multinational’ and hence not restricted. IUPHAR has had sufficient influence in the past to make scientific recommendations which have withstood the test of time.

How to Progress Natural Products and clinical development ?

Ways Forward

Pharmacology Education, IUPHAR web sites, Practical training.
Proper Phenotypical screening
Metabolomic Analysis of complex mixtures
Rescreening and amelioration of mixtures
'Virtual' libraries of established NP structures
Improve immunological screening, with immunological revolution, IUPHAR/IUIS
Biological Synthesis of Single compounds or of Mixtures
I recommend clinical testing in orphan and 'impossible' diseases !

'Syn'tegrate funding in Europe/US central facilities with Chinese funding using our model.

We must avoid: including in TCM sensitive environmental issues:
Bear paws, sharks fins, rhinoceros horns which will discredit everything.
Proposed in Jiang et al, 2018, Clin J Pharm Tox, 32, 1

Pour information, une ressource biologique est définie comme étant :
- toute ressource produite naturellement, faite d'ADN, d'ARN ou de composé biochimique produit grâce au génome : protéine, lipides, glucides…
- obtenue à partir de n'importe quel organisme : animal, végétal, fongique, bactérie, virus… qu'il soit vivant ou mort
- à l'échelle de molécule, cellule, tissu, organe, organisme, groupe d'une même espèce ou groupe multi-espèce

- **à prélever ou déjà prélevée, sur place ou dans une collection**

- **Protocole de Nagoya.**

Scottish Natural Product Collections

Organisation	Location	Collection	Additional Information
Glycomar	European Marine Science Park, Oban	Glycobiological products from marine organisms: • Microalgae • Marine invertebrates]	• Commercial screening collection of purified compounds and extracts • Applied to in house drug discovery activities focused on novel anti-inflammatory agents.
Lallemand Aquapharm	Formerly Aquapharm, European Marine Science Park, Oban	8,750 marine microbial strains • Bacteria • Yeast • Fungi • Actinomycetes] Some extracts and 50-60 purified compounds may still exist.	• High quality source of organisms • Source of purified, structural elucidated compounds with some associated biological data
Marine Biodiversity Centre	Aberdeen University	• 400+ plant derived purified natural product compounds • 200+ marine microbial derived purified natural product compounds	• Significant source of purified, structural elucidated compounds with some associated biological data • 96 well plate formatted
Robert Gordon University Natural Products Library (Formerly Housed at Strathclyde University)	RGU, Aberdeen	• 5,000+ plant extracts • Plus 2,000 dried plant material • ~60 purified compounds	• Source of natural product extracts with some associated biological data • 96 well plate formatted

Organisation	Location	Collection	Additional Information
Agronomy Institute	Highlands and Islands University, Orkney	Collections of Scottish Native (Orkney) plants	• Source of plant material • Experience of working with Healthcare company (Boots)
Culture Collection for Algae and Protozoa (CCAP)	European Marine Science Park, Oban	• 2,500 strains of algae and protozoa • 300+ strains of multicellular seaweed	High quality source of organisms
National Collection of Industrial, Marine and Food Bacteria (NCIMB)	Aberdeen University	8,000+ strains of bacteria, actinomycetes, plasmids and bacteriophages	High quality source of organisms
SeaBioTech	Glasgow	Marine sourced natural product collection development	• Potential source of new novel organisms • Potential source of screening extracts and purified compounds
Royal Botanic Gardens of Edinburgh	Edinburgh	Large collection of plant species with taxonomy experts to aid in proper identification	• High quality source of raw material
Pharma-Sea Consortium	Aberdeen	Marine microbial sourced natural product collection development [from mud and sediment]	• Potential source of new novel organisms • Potential source of screening extracts and purified compounds
International Centre for Brewing and Distilling	Heriot Watt University, Edinburgh	Brewing products such as Hop related products	Potential source of raw materials