Gb Sciences' PhAROS™ Drug Discovery Platform

GbSciences

OTCQB:GBLX

DISCOVERY

PhAROS™ Drug Discovery Platform

Pre-validates efficacy of plant-inspired mixtures for disease-targeted therapies

PIPELINE

Top 2 programs advancing to First-in-Man

5 preclinical programs
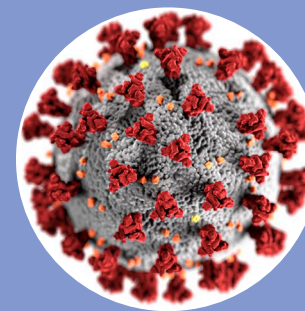
65+ discovery projects

IP PORTFOLIO

ISSUED PATENTS:

5 US & 3 PCT/WIPO

PATENT-PENDING:

19 US & 40 PCT/WIPO

CNS PROGRAM

Parkinson's disease formulas advancing to First-in-Man,

Positive PoC data

US Patent Issued

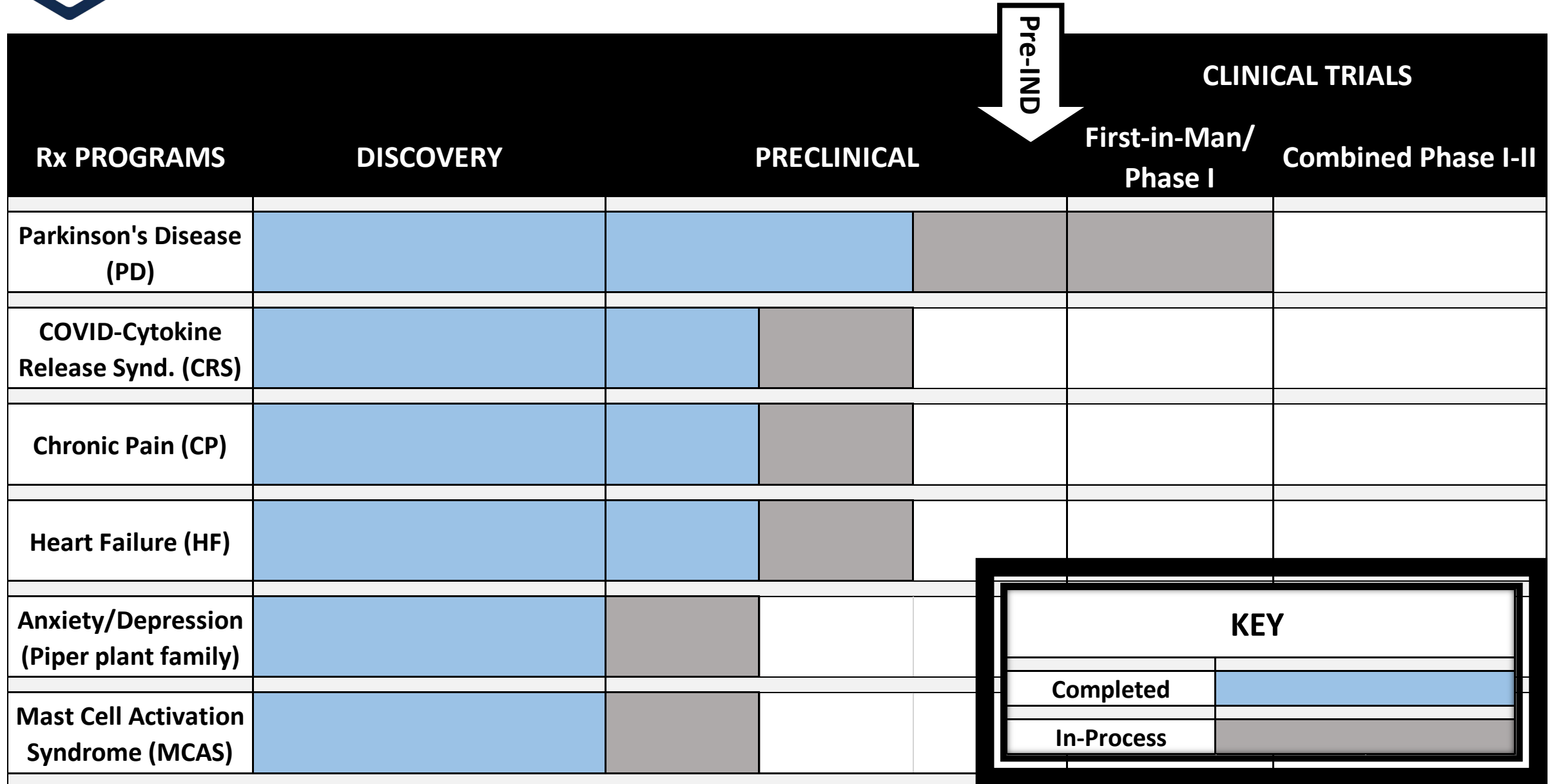## COVID-related Cytokine Release Syndrome

Positive PoC data

Patent-Pending

CHRONIC PAIN

Oral, time-released nanoparticles

Positive PoC data

US Patent Issued

Gb Sciences' Drug Development Pipeline

Rx PROGRAMS	DISCOVERY	PRECLINICAL	Pre-IND	First-in-Man/ Phase I	CLINICAL TRIALS Combined Phase I-II
Parkinson's Disease (PD)	▉ Completed	▉ Completed	▨ In-Process	▨ In-Process	
COVID-Cytokine Release Synd. (CRS)	▉ Completed	▉ Completed / ▨ In-Process			
Chronic Pain (CP)	▉ Completed	▉ Completed / ▨ In-Process			
Heart Failure (HF)	▉ Completed	▉ Completed / ▨ In-Process			
Anxiety/Depression (Piper plant family)	▉ Completed	▨ In-Process			
Mast Cell Activation Syndrome (MCAS)	▉ Completed	▨ In-Process			

KEY

Completed	▉
In-Process	▨

PhAROS™ Drug Discovery Platform

Phytomedical Analytics for Research Optimization at Scale

- Proprietary plant-based Rx therapies based on traditional medicine systems
- Minimum Essential Mixtures
- Pre-validates efficacy of drug-target-indication relationships
- "Transcultural Medicines" = ingredients not constrained by geography or culture
- De-risked as Rx therapies
- Multiple Uses: Novel Rx & Global Health Initiatives

Jansen C, Baker JD, Kodaira E, Ang L, Bacani AJ, Aldan JT, Shimoda LMN, Salameh M, Small-Howard AL, Stokes AJ, Turner H, Adra CN. Medicine in motion: Opportunities, challenges and data analytics-based solutions for traditional medicine integration into western medical practice. *J Ethnopharmacol*. 2021 Mar 1;267:113477. doi: 10.1016/j.jep.2020.113477. Epub 2020 Oct 21. PMID: 33098971; PMCID: PMC7577282.

TMS: Traditional Medical Systems

- Until ~1850, TMS = Medicine

- Even today, 65% of the global population rely on TMS

- Historical *and* Contemporary

- From shamanistic to formalized pharmacopeias

- Predominantly leverage plant/fungal secondary metabolomes as poly-pharmaceutical active ingredients

Jansen C, Baker JD, Kodaira E, Ang L, Bacani AJ, Aldan JT, Shimoda LMN, Salameh M, Small-Howard AL, Stokes AJ, Turner H, Adra CN. Medicine in motion: Opportunities, challenges and data analytics-based solutions for traditional medicine integration into western medical practice. *J Ethnopharmacol*. 2021 Mar 1;267:113477. doi: 10.1016/j.jep.2020.113477. Epub 2020 Oct 21. PMID: 33098971; PMCID: PMC7577282.
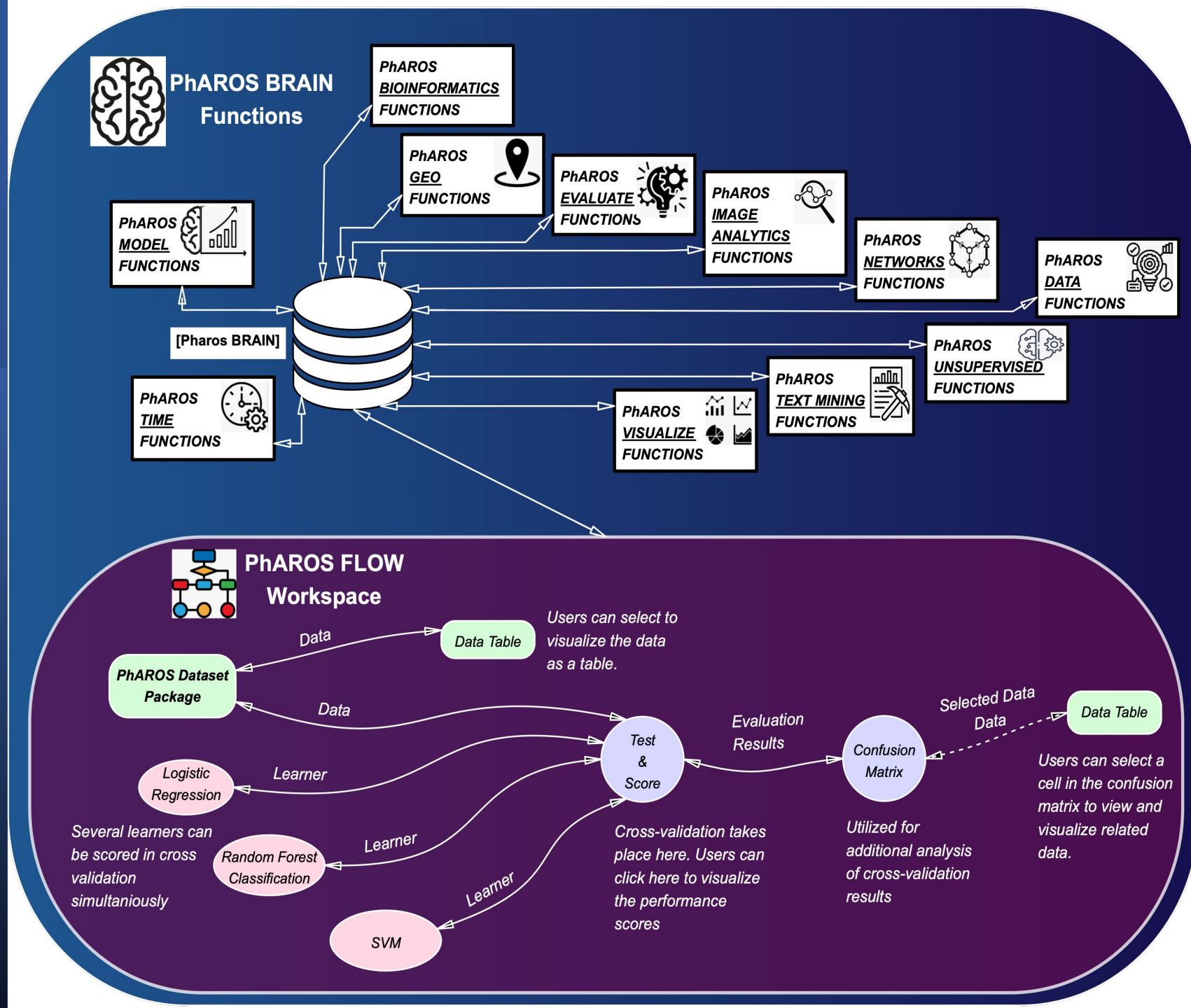
PhAROS™ Platform: Phytomedicine Analytics for Research Optimization at Scale
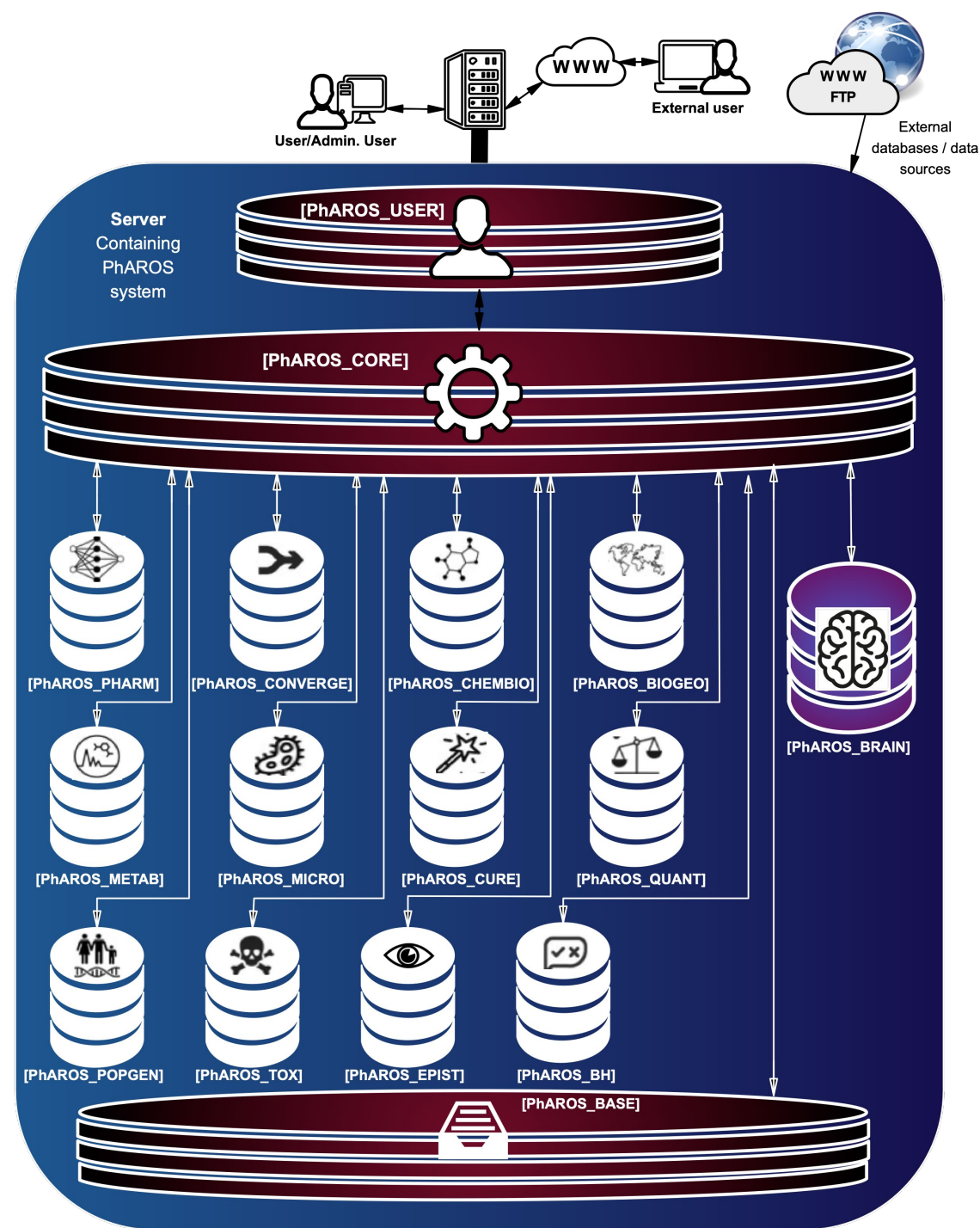
PhAROS_BRAIN houses many data analytics, AI/ML-functions & visualization tools

Diversity of Uses for PhAROS™

Phytomedicine Analytics for Research Optimization at Scale

Demonstration of Flexibility/Adaptability of PhAROS Drug Discovery Platform

INPUT(S)	PhAROS_XXX COMPONENTS & SUB-COMPONENTS																OUTPUT(S)
	USER	CORE	BRAIN			PHARM	CHEMBIO	BIOGEO	PHARM		CURE	QUANT	POPGEN	TOX	BASE	BH	
			CID	CONVERGE	EPIST				METAB	MICRO							
Medical Condition	X	X	X	X	X	X	X		X		X		X	X	X	X	Ranked Compounds & Ranked Minimum Essential Mixtures
Medical Condition, Desired Sub-type	X	X	X	X	X	X	X		X		X		X	X	X	X	Ranked Minimum Essential Mixtures by Clinical Sub-type
Medical Condition, Desired Organism(s)	X	X	X	X		X	X		X	X	X			X	X	X	Ranked Compounds & Ranked Minimum Essential Mixtures
Divergence Analysis, Overlapping Conditions	X	X	X	X	X	X	X							X	X	X	Ranked Compounds & Ranked Minimum Essential Mixtures
Medical Condition, Geographical Region	X	X	X	X	X	X	X	X				X		X	X	X	Ranked Formulas, Geo-Specific Alternate Plant Sources
Desired Compound(s)	X	X	X			X	X	X	X		X	X			X	X	Ranked Plant Sources, Relative Compound Abundance, Geography
Current Plant Source, Desired Component(s)	X	X	X			X	X	X	X	X	X				X	X	Alternative Plant Sources, Relative Compound Abundance, Geography

PhAROS™ Platform Objectives

1. MINIMUM ESSENTIAL MIXTURES (MEM):

- **<u>Improve Existing TMS Therapies</u> by reducing the numbers of components to the Minimum Essential**

- **<u>Substitution of Ingredients</u> across TMS (free from biogeographical & cultural boundaries) to increase efficacy/decrease side effects**

- **<u>De Novo Design</u> of a new class of 'Transcultural' Medicines, integrating phytomedical intelligence for a particular indication across geographically and culturally distinct pharmacopeias**

2. EFFICACY PREDICTIONS: IN SILICO CONVERGENCE ANALYSIS

3. SUPPLY CHAIN SOLUTIONS: 'BIOEQUIVALENT' PLANTS

PhAROS Drug Discovery Platform: Key Components

PHAROS_PHARM: NOVEL TRANSCULTURAL DATABASE

- **Multiple Traditional Medical Systems (TMS)**

- **Layers of Information (plant, compounds, indications, ratios, biogeography, epistemology, history, culture, toxicology, pharmacology, etc.)**

- **Created Clinical Indication Dictionaries (TMS to Western)**

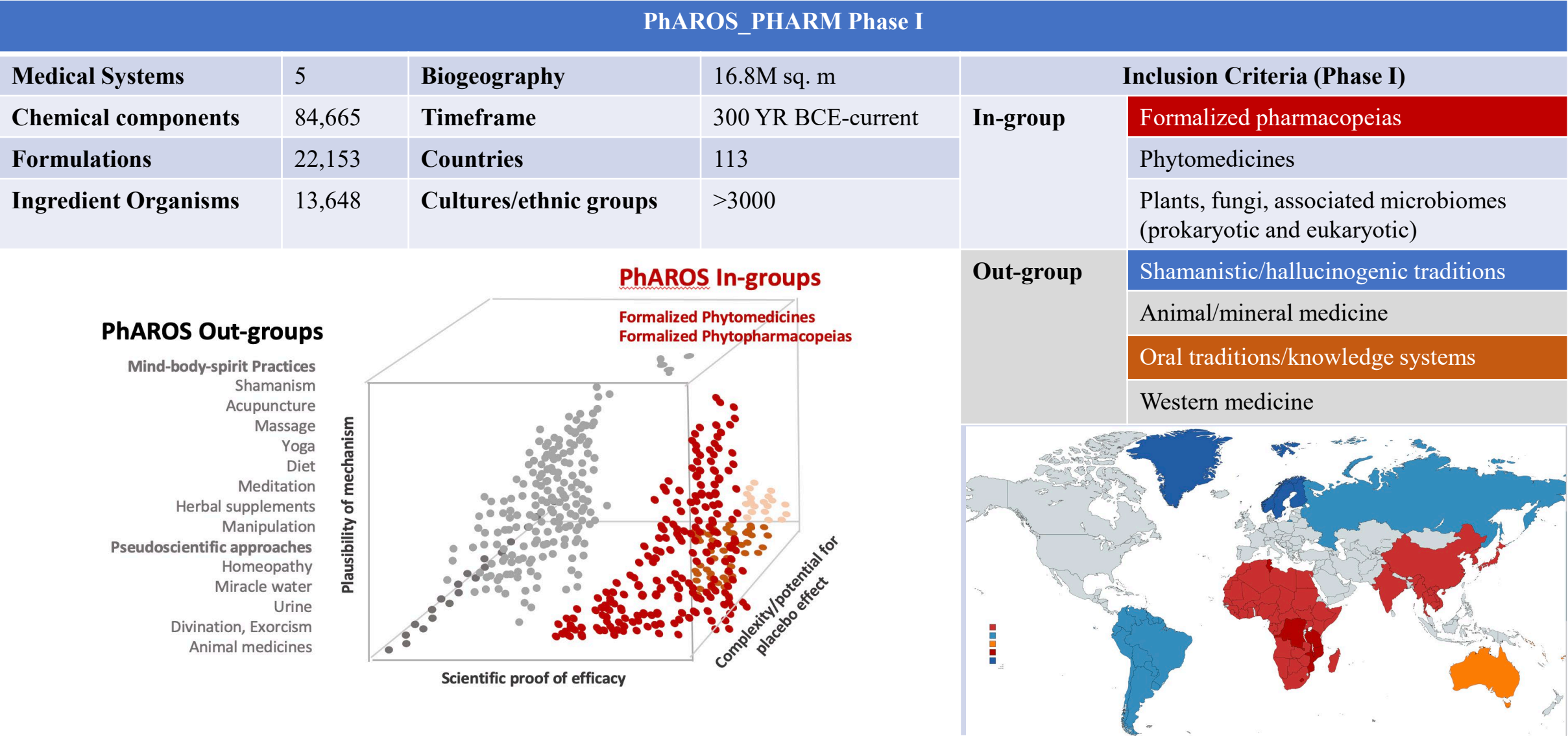**PhAROS_CONVERGE: IN SILICO CONVERGENCE ANALYSIS**

- **TMS have Geographically Isolated Data Sets**

- **Epistemological Considerations**

- **Greater Efficacy Predicted in Areas of Overlap between TMS**

PhAROS_PHARM: Transcultural Database

Figure A: PhAROS_PHARM is a single computational space comprised of multiple traditional medical (TMS) systems

PhAROS_PHARM Phase I					
Medical Systems	5	**Biogeography**	16.8M sq. m		**Inclusion Criteria (Phase I)**
Chemical components	84,665	**Timeframe**	300 YR BCE-current	**In-group**	Formalized pharmacopeias
Formulations	22,153	**Countries**	113		Phytomedicines
Ingredient Organisms	13,648	**Cultures/ethnic groups**	>3000		Plants, fungi, associated microbiomes (prokaryotic and eukaryotic)
				Out-group	Shamanistic/hallucinogenic traditions
					Animal/mineral medicine
					Oral traditions/knowledge systems
					Western medicine

PhAROS_PHARM: Layered Transcultural Database

Figure B. PhAROS_PHARM. PhAROS_PHARM is layered with multiple data layers for multidimensional interrogation using multiple axes of query.

Clinical Indication Dictionaries

Gb

Generate PAIN indication dictionary → **PhAROS_ PHARM**

```
Pain, inflam*, hurt, analges*, noci*, *ache
```

Generate CANCER indication dictionary → **PhAROS_ PHARM**

```
Cancer, tumor, swelling, growth, metasta*, leukemia, neuroblastoma, ,
onco* carcinoma, sarcoma, melanoma, fibroma, hepatoma, lymphoma,
papilloma, neuroblastoma, teratoma, glioma, gliobastoma, keratocanthoma,
myeloma, adenoma, mesothelioma, polyp, lump, outgrowth, neoplasm, cyst
```

Generate MIGRAINE indication dictionary → **PhAROS_ PHARM**

```
acute migraine; allay vexation and thirst headache; allergic headache; antimigraine; ardent fever with headache;
attack of  on the shaoyin channel characterized by association of headache with precordial pain and  legs;
cephalalgia; cluster headache; common  with headache; common  with headache and fever; common  with headache and
nasal congestion; concussional headache; diarrhea  common  with headache; distended head and headache; dizziness
and headache; draw out toxin and engender flesh common  with headache; expel roundworm  common  with headache;
expel worms headache; fever and headache; fever and headache due to external contraction; fever and headache in s
and influenza; gaseous headache; head wind headache; headache; headache accompanied by retching and  limbs;
headache and dizziness; headache and nasal congestion; headache and red eyes; headache and sore pharynx; headache
and thirst and sorethroat; headache caused by wind-heat toothache; headache disorders; headache due; headache due
to externally contracted wind-heat; headache due to febrile disease; headaches; hemicrania; hemicrania / migraine;
intractable headache with pulling sensation; liver fire headache; liver wind headache; migraine; migraine
disorders; migraine with aura; migraine without aura; neuralgic headache; quicken blood and disperse swelling
common  with headache; quicken blood and relieve pain  headache due to externally contracted wind-heat; recurrent
paroxysmal headache; relieve headache; resolve toxin common  with headache; senile vacuity weakness headache; sick
headache; sinusitis with headache; tension-type headache; upward invasion of phlegm causing headache accompanied
with dizziness; vascular headache; vascular migraine; vertex headache; wind- headache; wind-heat common  and
headache; wind-heat headache; yang brightness headache; yin summerheat and headache
```

Increasing need for non-Western epistemological terms

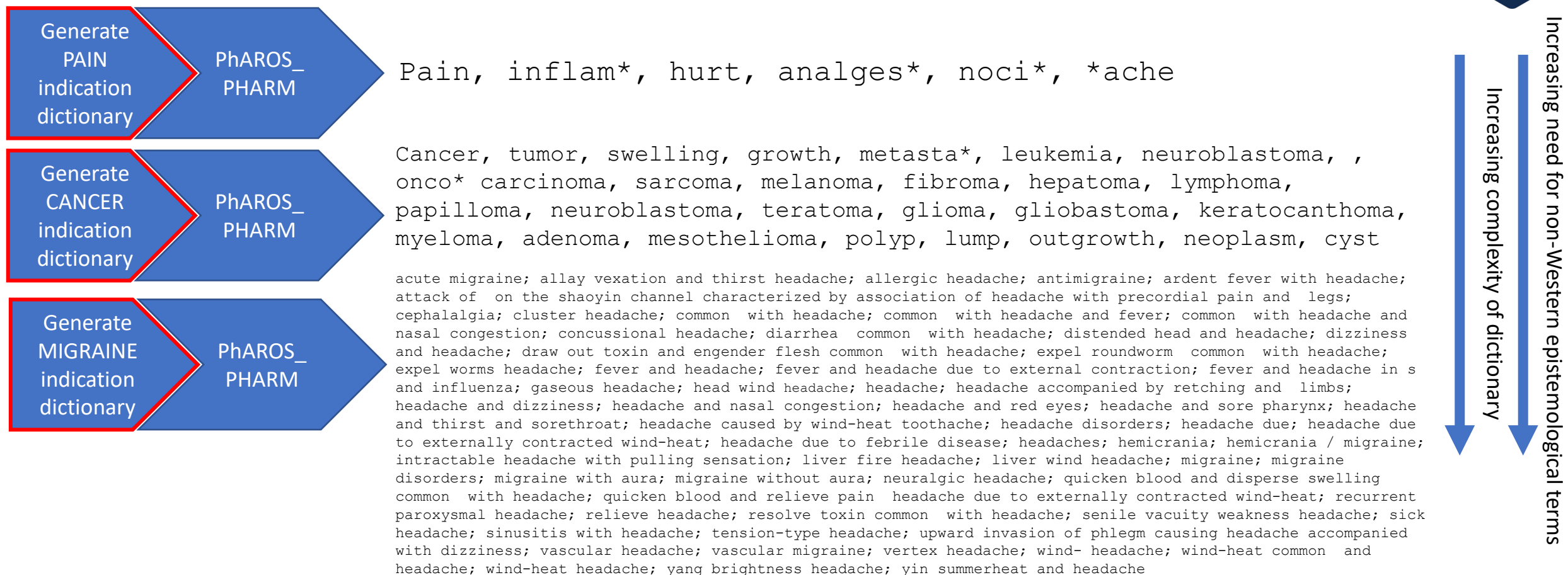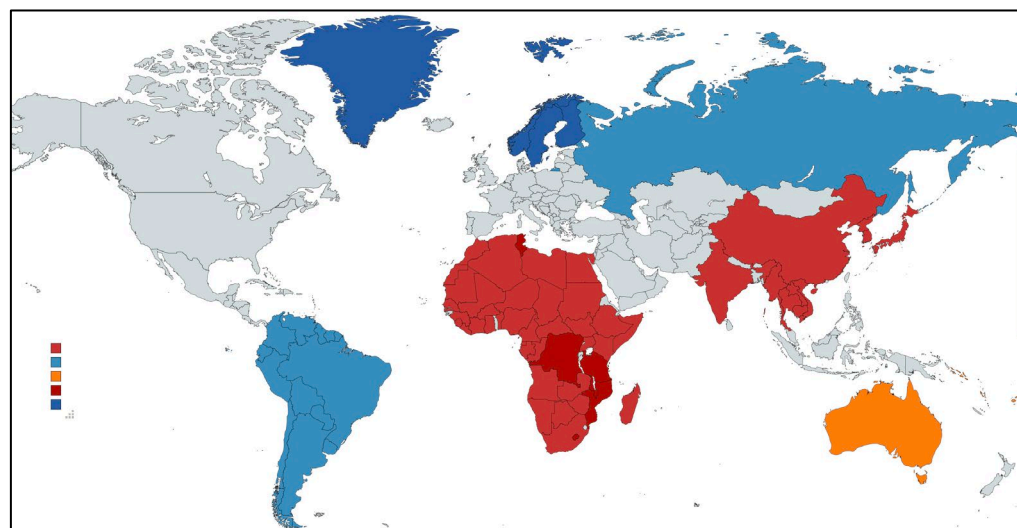Increasing complexity of dictionary

Figure C: Created Clinical Indication Dictionaries for database filtering and as features for subsequent AI/ML that reflect the knowledge systems underlying diagnosis. Indication definitions embedded in TMS reflect modern and historical terminology, Western and non-Western epistemologies.
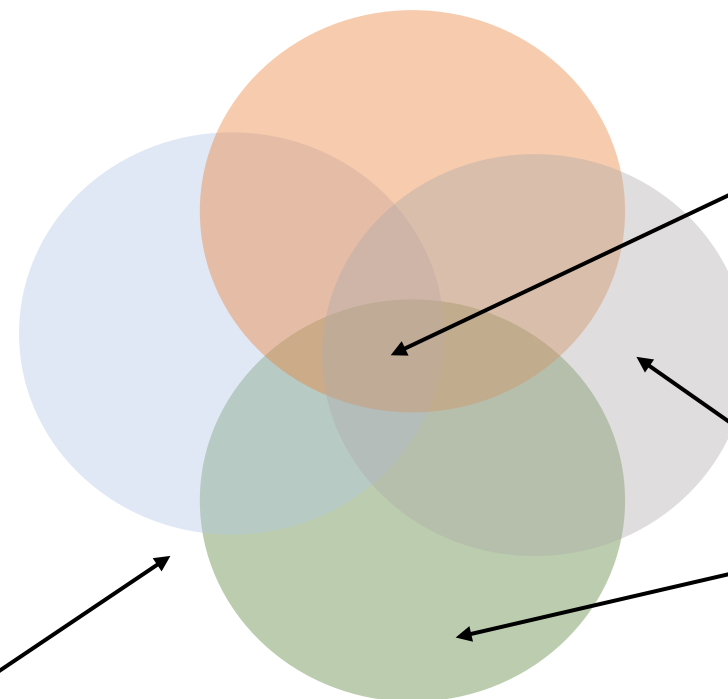
PhAROS_CONVERGE: ISCA Process

Convergence
Commonalities are de-risked/ pre-validated for entry into drug development pipeline

Divergence
Region-specific solutions that can be included in *de novo* designed formulations that overcome biogeocultural boundaries

TMS reflect local flora
TMS reflect shared disease burdens

Multiple formulation approaches to a given indication

Figure D. PhAROS_CONVERGE. In Silico Convergence Analysis (ISCA) reduces complexity and de-risks translation of phytomedical therapies from TMS to Western pipelines through identifying commonalities in approaches from biogeographically and culturally separated locales.

Proof of Concept: PAIN FORMULATIONS

PhAROS_CONVERGE Approach:

PAIN	_PHARM	TCM	TJM	TKM	TIM	TAM
Formulations	12500	3341	164	1162	424	592
Indications	8600	69	73	49	77	98
Organisms	3000	676	168	441	393	577
Chemicals	30000	7455	1345	7302	5239	14130

(TCM) SI MO TANG

(Kampo) Goshuyuto

(TCM) XIE XIN TANG

(Kampo) Goshajinkigan

121 convergent compounds (4 or more Medical Systems)
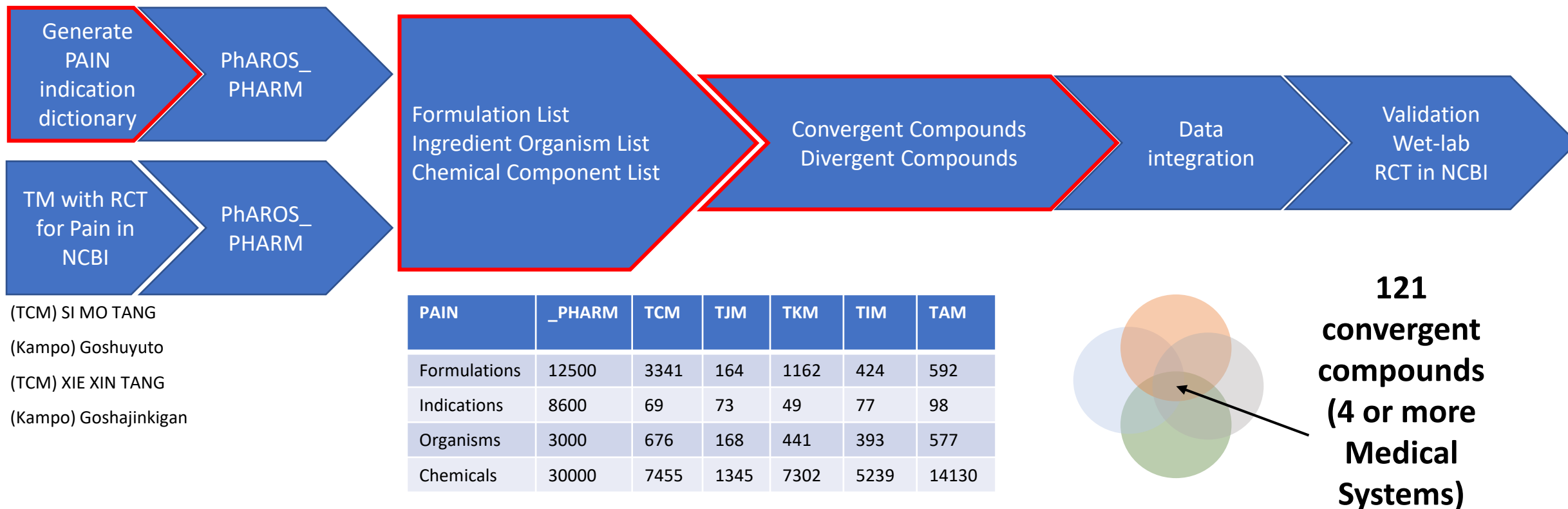
Figure E: We start by creating a Clinical Indication Dictionary for PAIN, then we use the PhAROS_CONVERGE in silico convergence analysis on the PhAROS_PHARM database to generate formulation, ingredient, and chemical composition lists. Both Convergent Compounds and Divergent Compounds are studied separately within a poly-pharmaceutical context to identify Minimum Essential Mixtures.

Proof of Concept: PAIN FORMULATIONS

PhAROS_CONVERGE Approach:

I1

Convergent Compounds
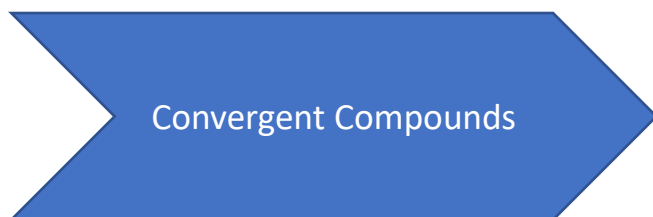
Figure F: We assessed the chemical characteristics of the convergent compounds from either 5 TMS or 4 TMS.

FREQUENCY RANKINGS
e.g., outputs ranked by co-incidence across specific TMS

| Output	Total	5 TMS	4 TMS
alkaloids	698	13: niacin, berberine, palmatine, trigonelline, jatrorrhizine, d-pseudoephedrine, candicine, protopine, stachydrine, harmane, liriodenine, caffeine, sinoacutine	25: ephedrine, niacinamide, 3-hydroxytyramine, anonaine, magnoflorine, sanguinarine, cryptopine, piperine, dihydrosanguinarine, papaverine, codeine, narcotoline, higenamine, roemerine, gentianine, xanthine, theophylline, ricinine, morphine, pelletierine, meconine, narceine, xanthaline, harmine, reserpine
terpenes	1545	47: alpha-pinene, linalool, terpineol, oleanolic acid, beta-sitosterol, p-cymene, myrcene, beta-bisabolene, beta-humulene, carvacrol, beta-caryophyllene, gamma-terpinene, geraniol, 1,8-cineole, alpha-farnesene, limonene, ursolic acid, beta-selinene, terpilene, spinasterol, beta-eudesmol, citral, sabinene.....	88: stigmasterol, limonene, beta-elemenene, d-cadinene, terpinene-4-ol, uralenic acid, borneol, beta-pinene, limonin, camphene, campesterol, citronellal, isocyperol, ruscogenin, crocetin, squalene, brassicasterol, piperitenone, lycopene, toralactone, phytofluene, alpha-carotene, ecdysone, neomenthol, auroxanthin, soyasapogenol-e, cyasterone, neodihydrocarveol, guaiazulene, alpha-pinene, crataegolic acid, violaxanthin, pathoulene...

PhAROS IMPACT: Use this information for reducing complexity and de-risking components for further evaluation

Proof of Concept: PAIN FORMULATIONS

Figure G: After identifying Convergent Compounds, Data integration modules are used to describe the set of convergent compounds & predict the most efficacious compounds for MEM based on target analyses, network pharmacology, etc.

PhAROS_CONVERGE Approach:

Convergent Compounds → Data integration

_CHEM-BIO
_TOX
_POPGEN
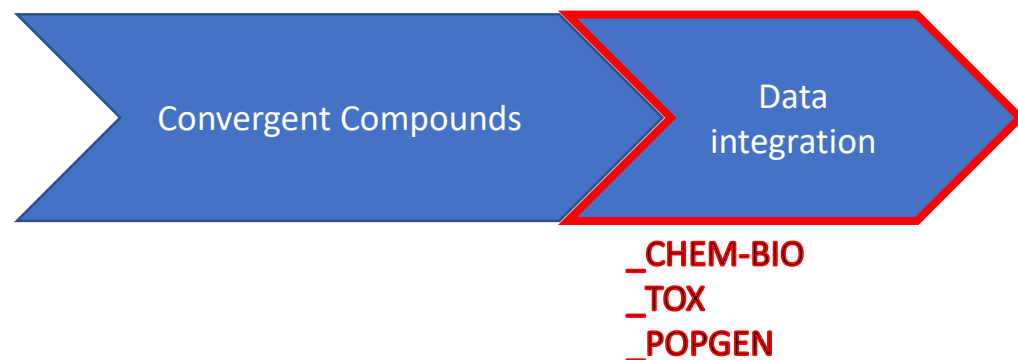
TYPE/TARGET ANALYSIS
opioid/alkaloid candidate analgesics
   alkaloids related to known opioid receptor ligands or ion channel ligands
   4 convergent compounds
potential ligands for nociceptive ion channels
   terpenes
   49 convergent compounds
components with other demonstrated neuroactivity
   15 convergent compounds
components with bioactivity indirectly related to pain
   anti-inflammatory, anti-oxidants
   16 convergent compounds
compounds with other types of bioactivity
   but no obvious link to analgesia (56 convergent compounds)

FREQUENCY RANKINGS
e.g., top 10 most convergent compounds, their targets and pathways

Nicotinic acid
Perlolyrine
Palmitine
Berberine
Jatrorrhizine
Coptisin
Lysicamine
Columbamine
Aconitine
Nicotine

Alkaloid/opioid receptor pathways

ACHE receptor pathways
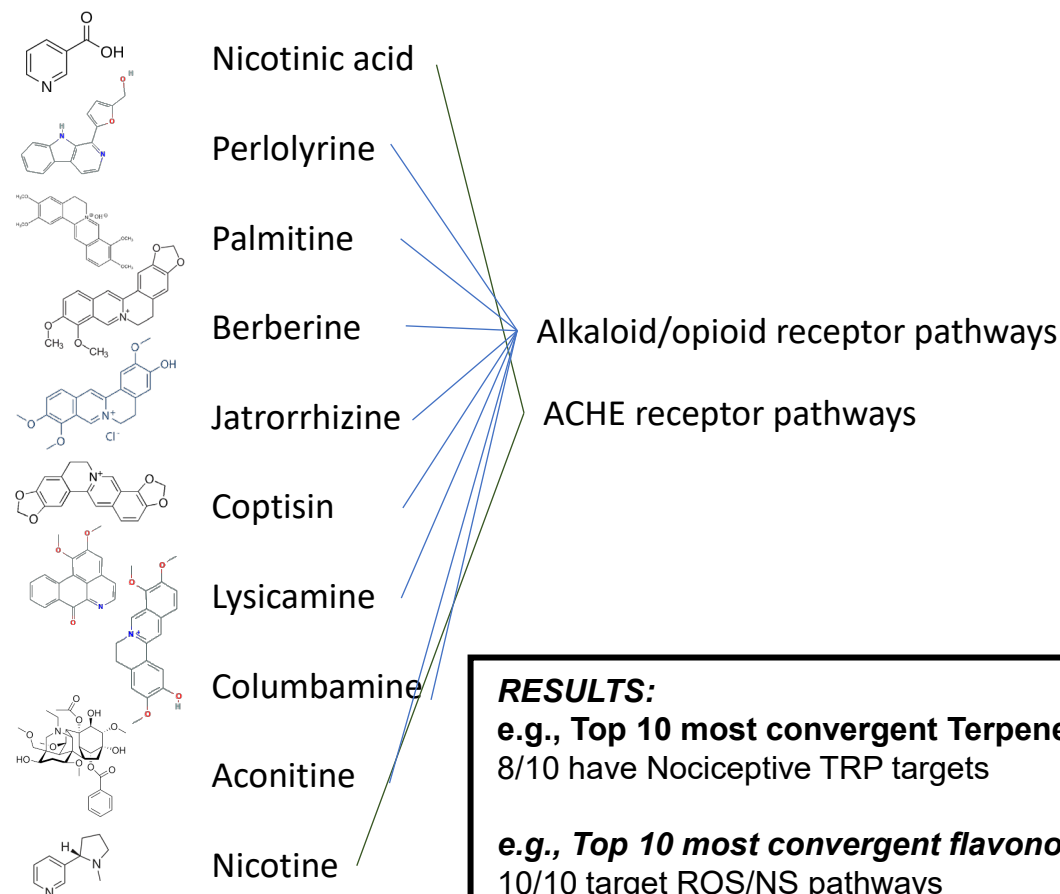
RESULTS:
e.g., Top 10 most convergent Terpenes
8/10 have Nociceptive TRP targets

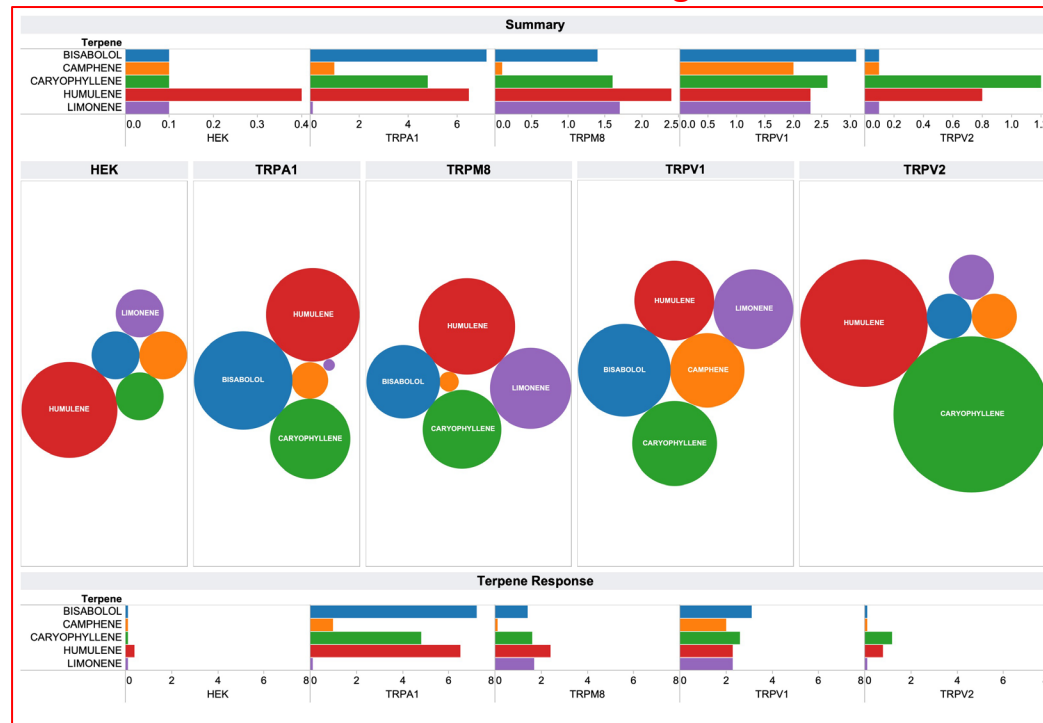*e.g., Top 10 most convergent flavonoids*
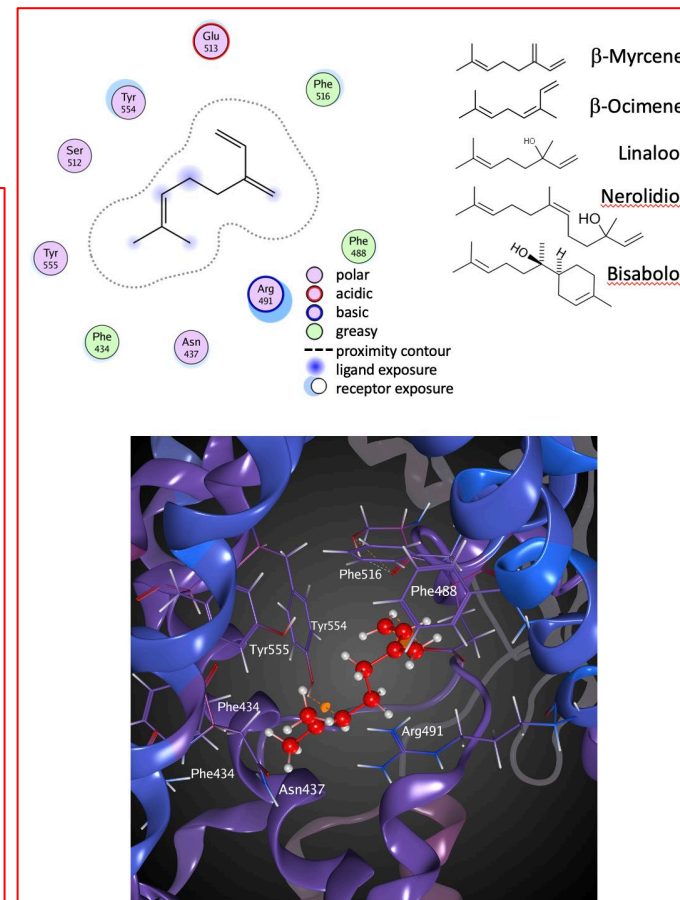10/10 target ROS/NS pathways

Validation: PAIN FORMULATIONS

Figure H: Validation of preliminary MEM predictions with wet lab data is a critical part of the drug development pathway.
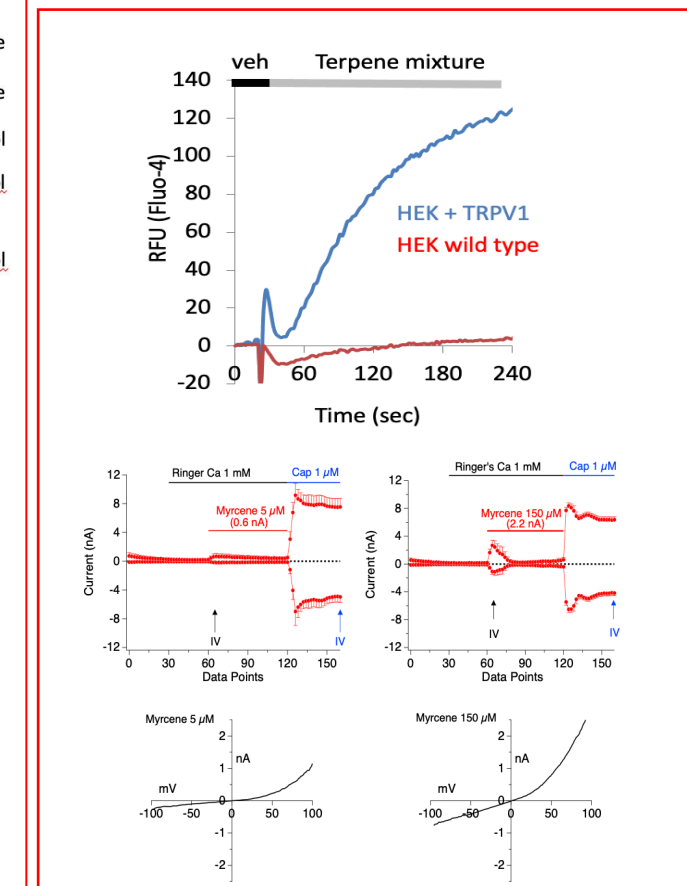
e.g., **Top 10 most convergent Terpenes**
8/10 have Nociceptive TRP targets

e.g., Top 10 most convergent flavonoids
10/10 target ROS/NS pathways

Proof of Concept: PAIN FORMULATIONS

Figure I. PhAROS. Transcultural Formulation Assembly of Minimum Essential Mixtures based on Epistemolgy
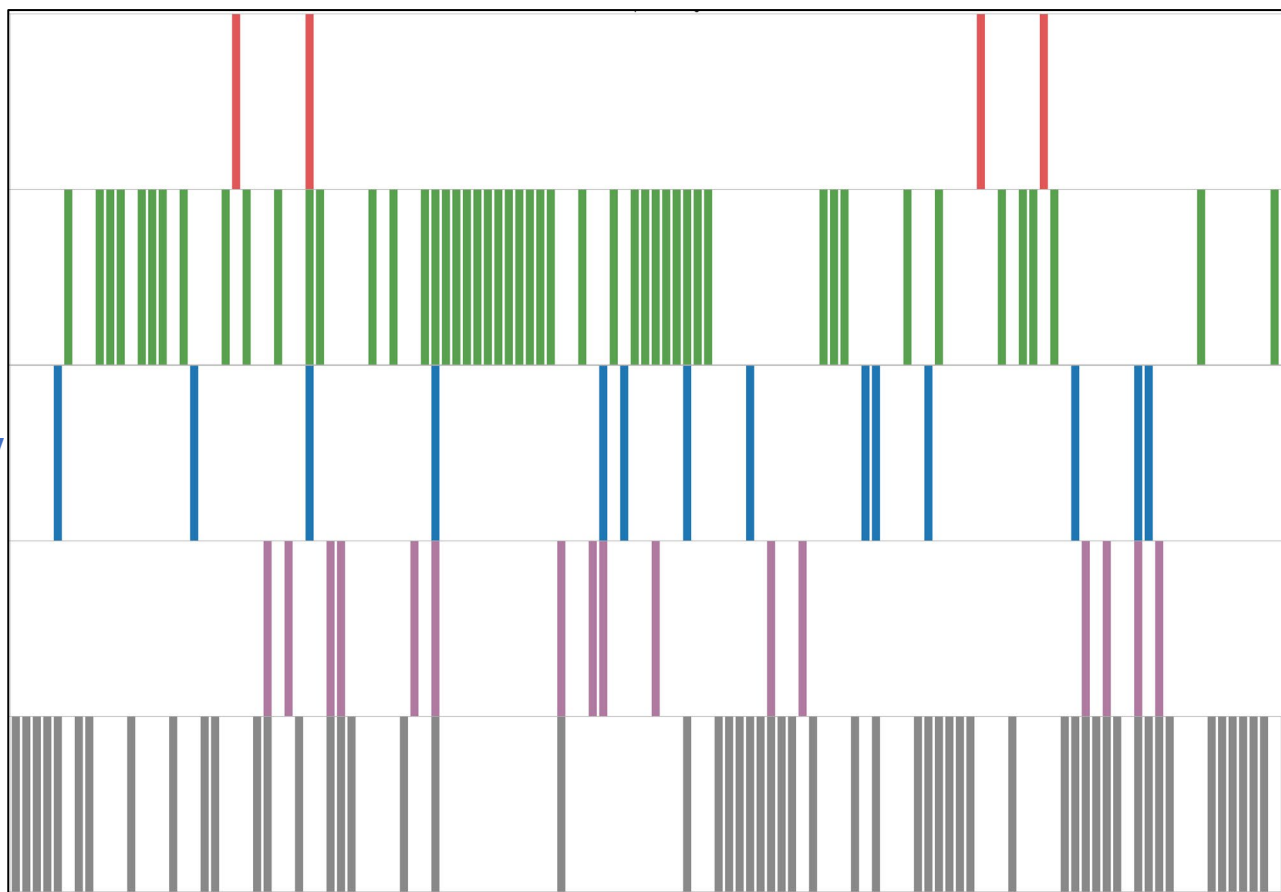

CATEGORIES

opioid/alkaloid candidate analgesics

ligands for nociceptive ion channels
e.g., terpene ligands for nociceptive TRPs

components with other demonstrated neuroactivity
e.g., NACHE pathways

components with bioactivity associated with pain
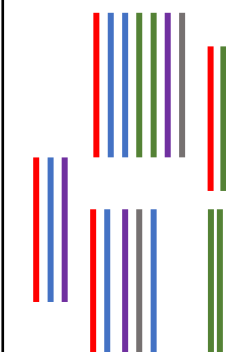e.g., ROS/RNS targeting anti-inflammatories

compounds with other types of bioactivity

PhAROS OUTPUT: CONVERGENT COMPOUNDS FOR PAIN ACROSS 5 TMS

Convergent compound CIDs

PhAROS IMPACT:

New formulations can be designed that are
- **Transcultural** *(result from integrated knowledge across cultures and biogeographies)*
- **Minimal essential** *(reduce complexity by including components from each part of the hierarchy)*
- **Polypharmaceutical** *(retain non-Western medical architecture and polypharmacy)*

Validation Wet-lab

Jansen C, Baker JD, Kodaira E, Ang L, Bacani AJ, Aldan JT, Shimoda LMN, Salameh M, Small-Howard AL, Stokes AJ, Turner H, Adra CN. Medicine in motion: Opportunities, challenges and data analytics-based solutions for traditional medicine integration into western medical practice. *J Ethnopharmacol.* 2021 Mar 1;267:113477. doi: 10.1016/j.jep.2020.113477. Epub 2020 Oct 21. PMID: 33098971;

Proof of Concept: PAIN FORMULATIONS

Gb

← PhAROS Output: Convergent compound CIDs →

List A. opioid/alkaloid candidate analgesics

List B. ligands for nociceptive ion channels e.g., terpene ligands for nociceptive TRPs

List C. components with other demonstrated neuroactivity e.g., NACHE pathways

List D. components with bioactivity associated with pain e.g., ROS/RNS targeting anti-inflammatories
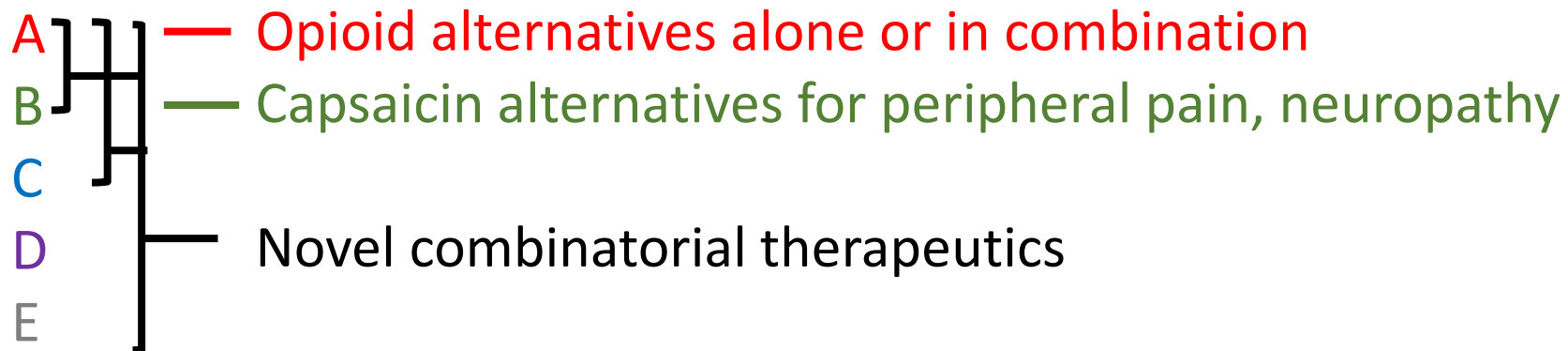
List E. compounds with other types of bioactivity

Human in the loop subject matter expertise   **AND**   **Machine Learning/AI**

Novel formulations

A
B — **Opioid alternatives alone or in combination**
— **Capsaicin alternatives for peripheral pain, neuropathy**
C
D   Novel combinatorial therapeutics
E

Validation
Wet-lab
Clinical

Diversity of Uses for PhAROS™

Phytomedicine Analytics for Research Optimization at Scale

Demonstration of Flexibility/Adaptability of PhAROS Drug Discovery Platform

INPUT(S)	USER	CORE	BRAIN: CID	BRAIN: CONVERGE	BRAIN: EPIST	PHARM	CHEMBIO	BIOGEO	PHARM: METAB	PHARM: MICRO	CURE	QUANT	POPGEN	TOX	BASE	BH	OUTPUT(S)
Medical Condition	X	X	X	X	X	X	X		X		X	X		X	X	X	Ranked Compounds & Ranked Minimum Essential Mixtures
Medical Condition, Desired Sub-type	X	X	X	X	X	X	X		X		X	X		X	X	X	Ranked Minimum Essential Mixtures by Clinical Sub-type
Medical Condition, Desired Organism(s)	X	X	X	X		X	X		X	X	X			X	X	X	Ranked Compounds & Ranked Minimum Essential Mixtures
Divergence Analysis, Overlapping Conditions	X	X	X	X	X	X	X							X	X	X	Ranked Compounds & Ranked Minimum Essential Mixtures
Medical Condition, Geographical Region	X	X	X	X	X	X	X	X				X		X	X	X	Ranked Formulas, Geo-Specific Alternate Plant Sources
Desired Compound(s)	X	X	X			X	X	X	X		X	X			X	X	Ranked Plant Sources, Relative Compound Abundance, Geography
Current Plant Source, Desired Component(s)	X	X	X			X	X	X	X	X	X				X	X	Alternative Plant Sources, Relative Compound Abundance, Geography

PhAROS™ OVERVIEW

- Science Gateway for Drug Discovery
- Multiple functional modules allow for flexibility in searches with many different possible inputs and outputs.
- PhAROS_PHARM = multiple TMS in a single searchable space with layers of data for sophisticated queries
- PhAROS_CONVERGE = ISCA to estimate efficacies of complex mixtures
- Applications for Global Health Initiatives
- Applications for novel polypharmaceutical medicines:
    1. Improved TMS therapies = Minimum Essential Mixtures (MEM)
    2. Substitution within TMS therapies = MEM with improved efficacy/side effects
    3. Transcultural Formulations = *de novo* drug development informed by TMS

Contact Information

Andrea Small-Howard, Ph.D., M.B.A.
President, Chief Science Officer & Director
GB Sciences, Inc.
3550 West Teco Avenue
Las Vegas, Nevada 89118
www.gbsciences.com
andrea@gbsciences.com

Michael Farley, Ph.D.
President & Director
GBS Global Biopharma Inc.
200-900 Morrison Drive
Ottawa, Ontario, **CANADA** K2H 8K7
www.gbsglobalbiopharma.com
michael@gbsglobalbiopharma.com