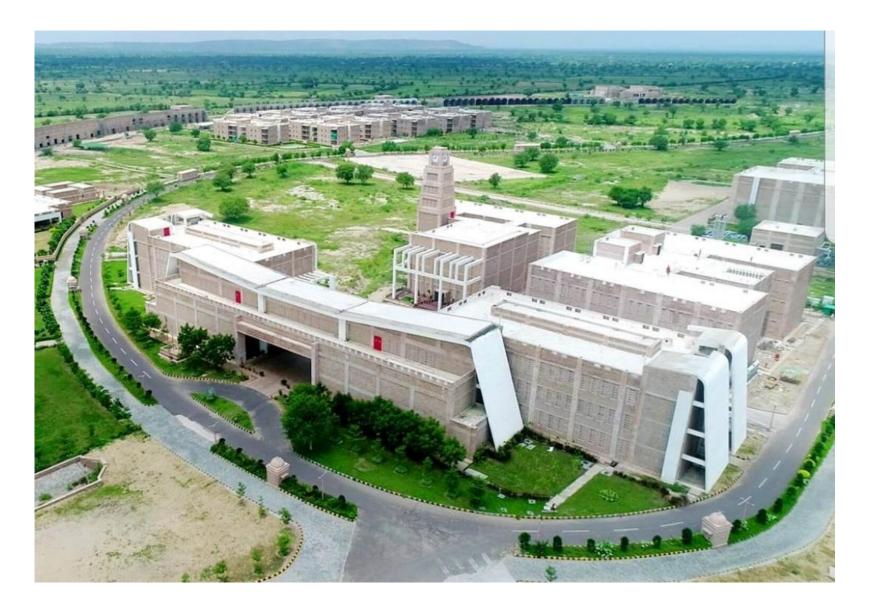
#### Development of frameworks for evidence-based practice of traditional medicine in integrative medicine settings



IntegratingTraditional Knowledge in Evidence Based Medicine pGI January 7-10 2024

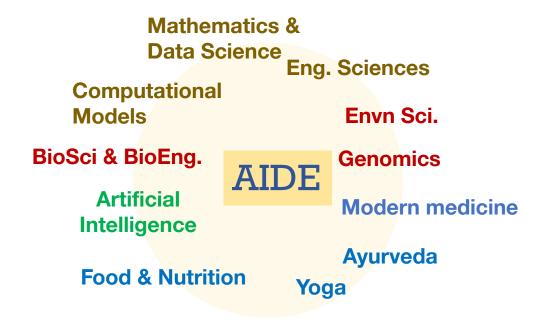
Mitali Mukerji, PhD, FASc, FNASc Professor & Head, Department of Bioscience & Bioengineering Affliate Faculty, School of Artificial Intelligence and Data Science (AIDE) Indian Institute of Technology Jodhpur



# Transdisciplinary Centre of Excellence in Integrative Precision Health

### <u>Aim</u>

Establishment of AI driven integrative framework for population and individual risk stratification and early actionable precision health interventions

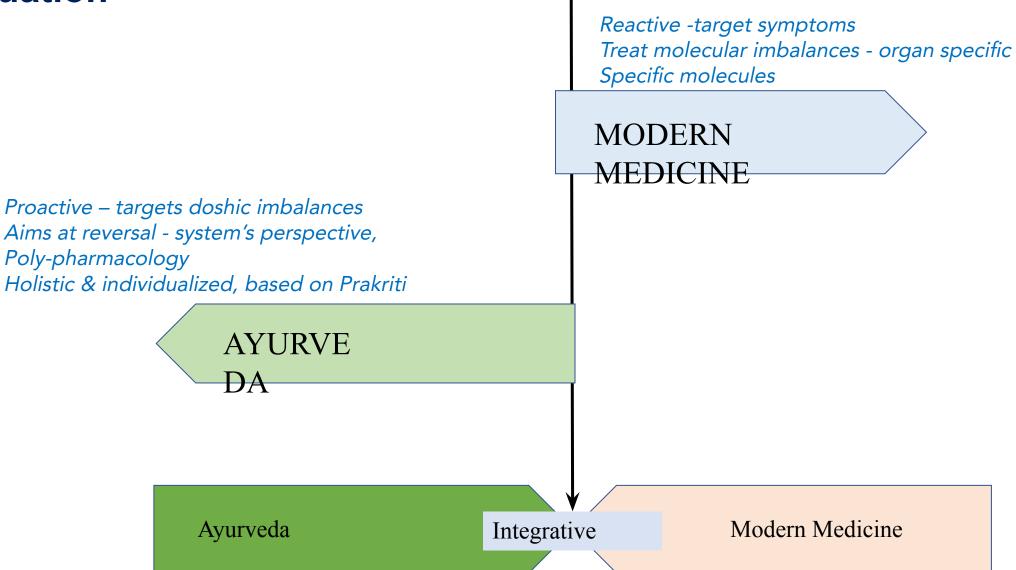


The School of <u>Artificial Intelligence & Data Scienc</u> (AIDE) would nucleate a transdisciplinary framework that would have application in:

- Phenomics based non-invasive risk stratification
- Integration of principles and practice of Ayurveda with other knowledge systems
- Management of rare disease and common disease
- Development of an objective framework for Integrative medicine
- Precision health with specific focus in arid regions

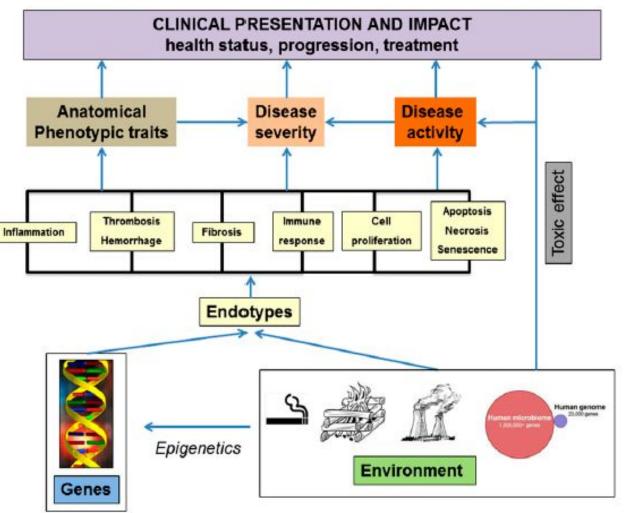
# Integrative medicine\_ a win-win

# situation

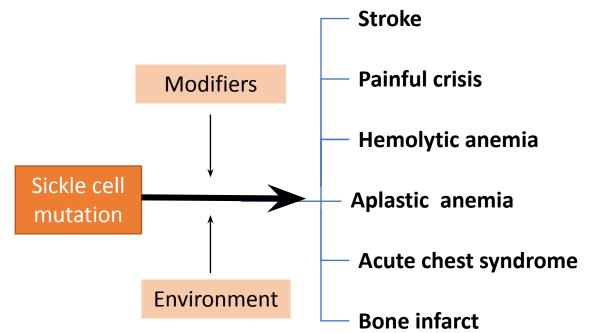


### Interoperable, complementary, synergistic, personalized options

# **Converging themes in diseases**







### Challenges

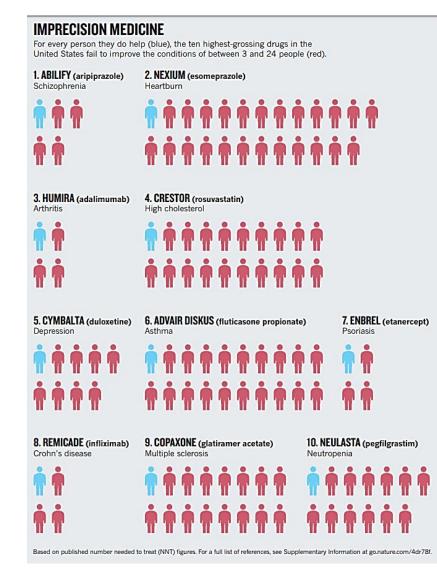
- Modifiers ?
- Endophenotypes?
- Targeted interventions ?

<mark>(Samprapti ?)</mark>

# A Paradigm shift from population based to individualized approach

### **Population response based**

### Personalised

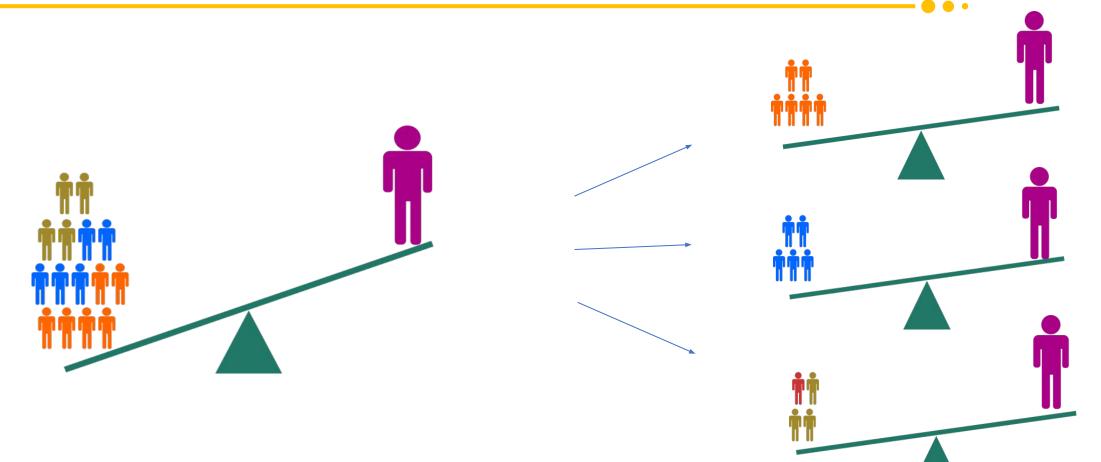




# Time for one-person trials

Precision medicine requires a different type of clinical trial that focuses on individual, not average, responses to therapy, says **Nicholas J. Schork**.

# Gap in knowledge : Health Stratification and Affordability





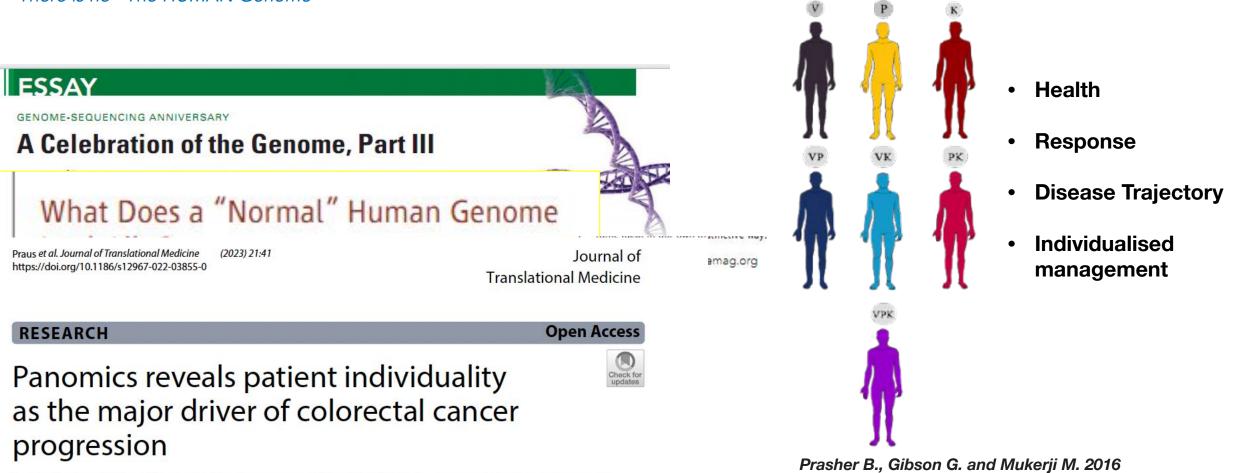
# **Definition of Genetic individuality - Modern vs**

# Ayurveda

Human Genome Project Surprises

There is no "The HUMAN Genome"

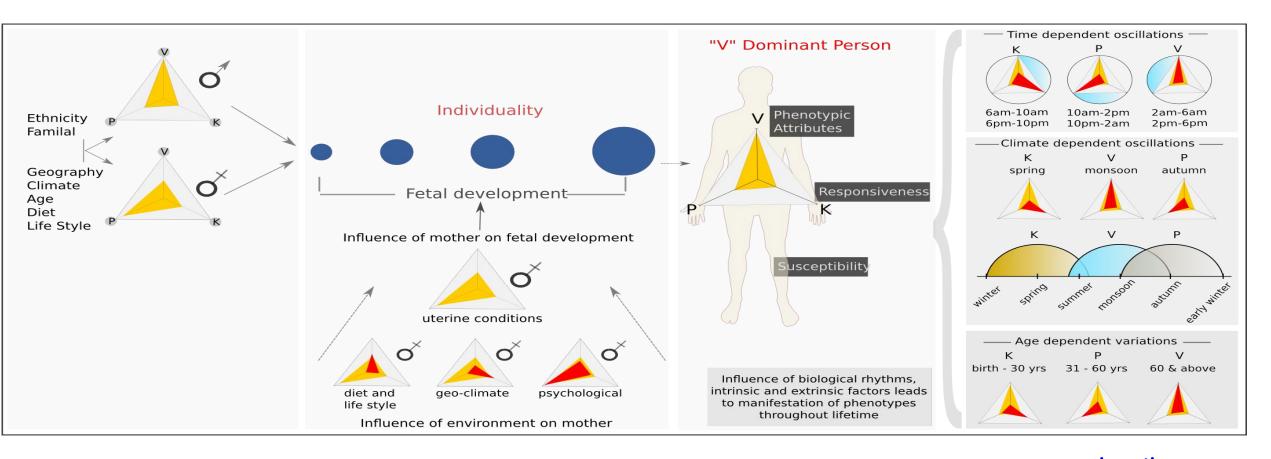
#### 7 Prakriti types in a population



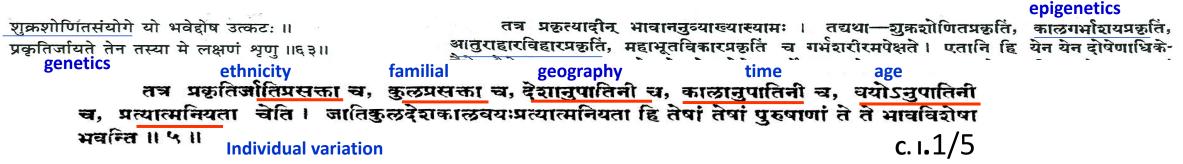
Friederike Praus<sup>1+</sup>, Axel Künstner<sup>2+</sup>, Thorben Sauer<sup>1</sup>, Michael Kohl<sup>1,2</sup>, Katharina Kern<sup>1</sup>, Steffen Deichmann<sup>3</sup>, Ákos Végvári<sup>4,5</sup>, Tobias Keck<sup>3</sup>, Hauke Busch<sup>2</sup>, Jens K. Habermann<sup>1,6</sup> and Timo Gemoll<sup>1\*</sup>

Prasher B., Gibson G. and Mukerji M. 2016 Genomic insights into ayurvedic and western approaches to personalized medicine. J. Genet. 95, 209–228

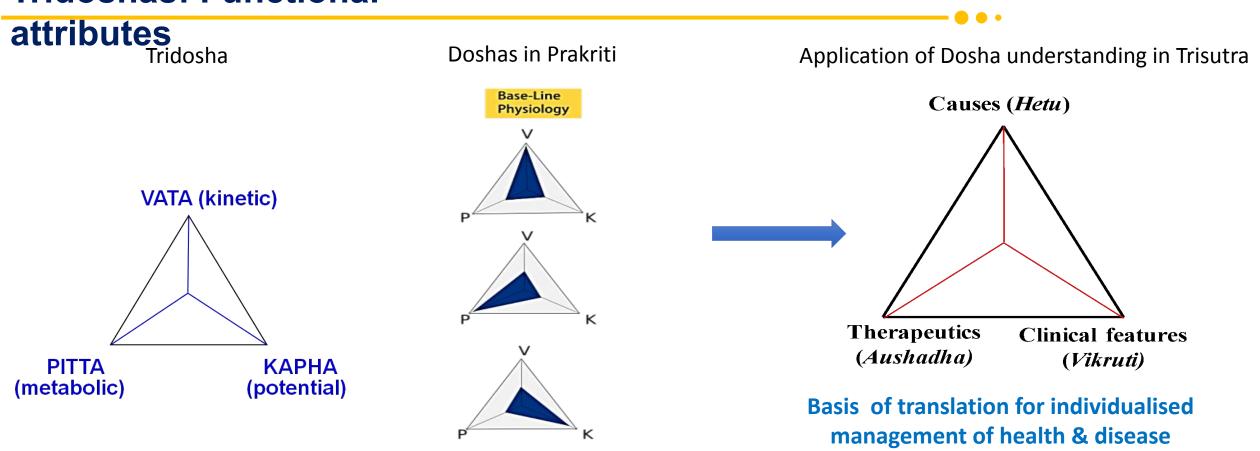
# **Prakriti - GIS of an individual**



• •



# **Tridoshas: Functional**



सर्वशरीरचरास्तु वातपित्तऋषमाणः सर्वस्मिञ्छरीरं कुपिताकुपिताः शुभाशुभानि कुर्वन्ति— प्रकृतिभूताः शुभान्युपचयवलवर्णप्रसादादीनि, अशुभानि पुनर्विकृतिमापन्ना विकारसंज्ञकानि ॥ ९ ॥ c.su.20/9

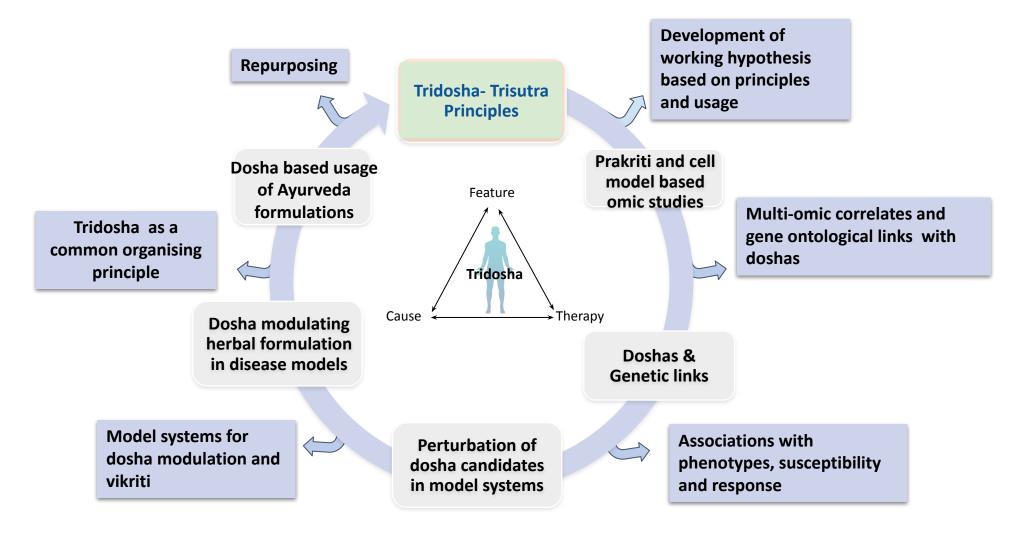
### Treatment evolved by "Yukti" (reasoning

Yukti ( युक्ति)-	State of the second second second second
मात्राकालाश्रया या	क्तिः, सिद्धिर्युक्तौ प्रतिष्ठिता  तिष्ठत्युपरि युक्तिज्ञो <u>द्रव्यज्ञानवतां</u> सदा  चरक सहिता सूत्र स्थान २/१६
3	चरक संहिता सूत्र स्थान २/१६
Therapeutic apt	tness or rational therapy depends on the matra (dose) and kala(time).
Success of the	treatment depends on yukti (rational therapeutics). But prior to the
application of yu	ukti (rational therapeutics) the physician should always possess comp

# **Operational framework for exploring "trisutra"**

### ayurveda

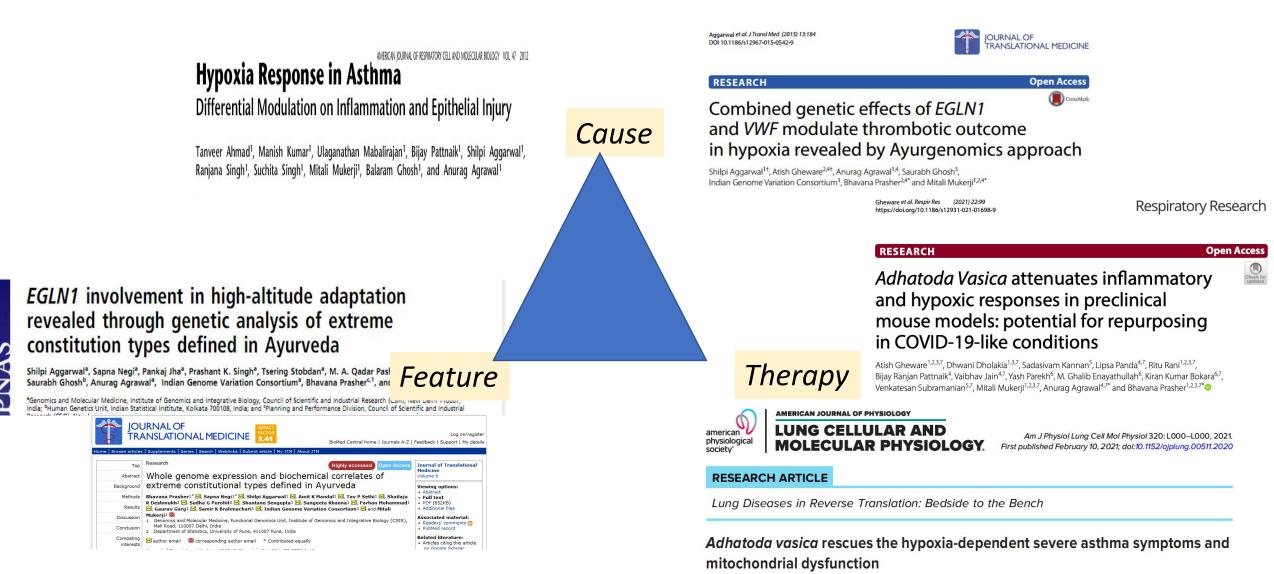
**Summary** 



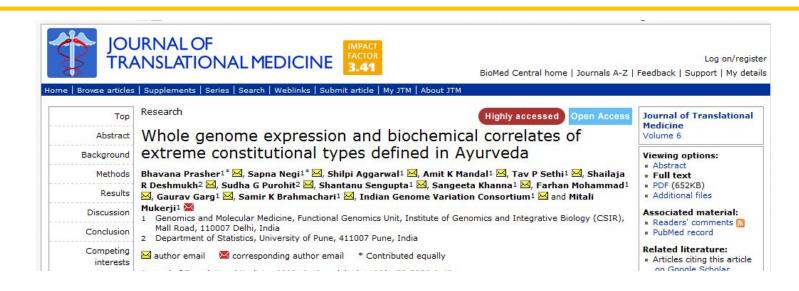
• •

# Molecular corelates of *Trisutra* framework : platform for translation

### Differences between constitution types - Hypoxia response



### Prakriti, dosha and cellular outcomes

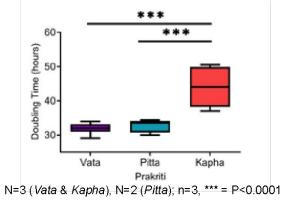


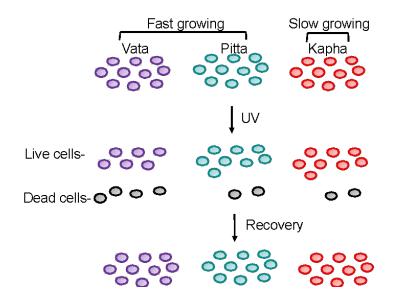


•

# Inter-individual variability in cell proliferation rates : Who

# cares?





CELL CYCLE https://doi.org/10.1080/15384101.2021.1909884



Check for updates



Baseline cell proliferation rates and response to UV differ in lymphoblastoid cell lines derived from healthy individuals of extreme constitution types

Sumita Chakraborty, Sunanda Singhmar, Dayanidhi Singh, Mahua Maulik, Rutuja Patil, Satyam Kumar Agrawal, Anushree Mishra, Madeeha Ghazi, Archana Vats, Vivek T Natarajan, Sanjay Juvekar, Bhavana Prasher, and Mitali Mukerji

\*Centre of Excellence for Applied Development of Ayurveda Prakriti and Genomics, CSIR-Institute of Genomic Delhi, India; \*CSIR Ayurgenomics Unit-TRISUTRA, CSIR-Institute of Genomics & Integrative Biology, New Delhi, Molecular Medicine, CSIR-Institute of Genomics & Integrative Biology, New Delhi, India; \*Academy of Scientifi (AcSIR), Ghaziabad, India; \*Department of Biological Sciences, Indian Institute of Science & Gucation & Researcl Nadia, West Bengal, India; \*Vadu Rural Health Program, KEM Hospital Research Centre, Pune, Maharashtra, Inc Emerging Sciences (SPES), Baddi University of Emerging Science and Technology (BUEST), Baddi, Himachal Pr

#### SCIENTIFIC REPORTS

```
natureresearch
```

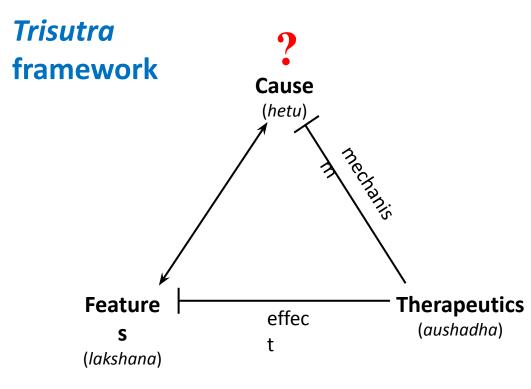
Check for updates

### Lithium response in bipolar disorder correlates with improved cell viability of patient derived cell lines

Pradip Paul<sup>®1</sup>, Shruti Iyer<sup>2</sup>, Ravi Kumar Nadella<sup>®1</sup>, Rashmitha Nayak<sup>1</sup>, Anirudh S. Chellappa<sup>1</sup>, Sheetal Ambardar<sup>2,3</sup>, Reeteka Sud<sup>1</sup>, Salil K. Sukumaran<sup>1</sup>, Meera Purushottam<sup>1</sup>, Sanjeev Jain<sup>1,3</sup>, ADBS Consortium (ADBS: The Accelerator program for Discovery in Brain disorders using Stem cells)\* & Biju Viswanath<sup>®1</sup>

Lithium is an effective, well-established treatment for bipolar disorder (BD). However, the mechanisms of its action, and reasons for variations in clinical response, are unclear. We used neural precursor cells (NPCs) and lymphoblastoid cell lines (LCLs), from BD patients characterized for clinical response to lithium (using the "Alda scale" and "NIMH Retrospective Life chart method"), to interrogate cellular phenotypes related to both disease and clinical lithium response. NPCs from two biologically related BD patients who differed in their clinical response to lithium were compared with healthy controls. RNA-Seq and analysis, mitochondrial membrane potential (MMP), cell viability, and cell proliferation parameters were assessed, with and without in vitro lithium. These parameters were also examined in LCLs from 25 BD patients (16 lithium responders and 9 non-responders), and 12 controls. MMP was lower in both NPCs and LCLs from BD; but it was reversed with in vitro lithium only in LCLs, and this was unrelated to clinical lithium response. The higher cell proliferation observed in BD was unaffected by in vitro lithium. Cell death was greater in BD. However, LCLs from clinical lithium responders could be rescued by addition of in vitro lithium. In vitro lithium also enhanced BCL2 and GSK3B expression in these cells. Our findings indicate cellular phenotypes related to the disease (MMP, cell proliferation) in both NPCs and LCLs; and those related to clinical lithium response (cell viability, BCL2/GSK3B expression) in LCLs.

# **Exploring molecular connectivity through Ayurveda based formulations**





Cissampelos pareira

# Ayurveda, folk-care and traditional use:

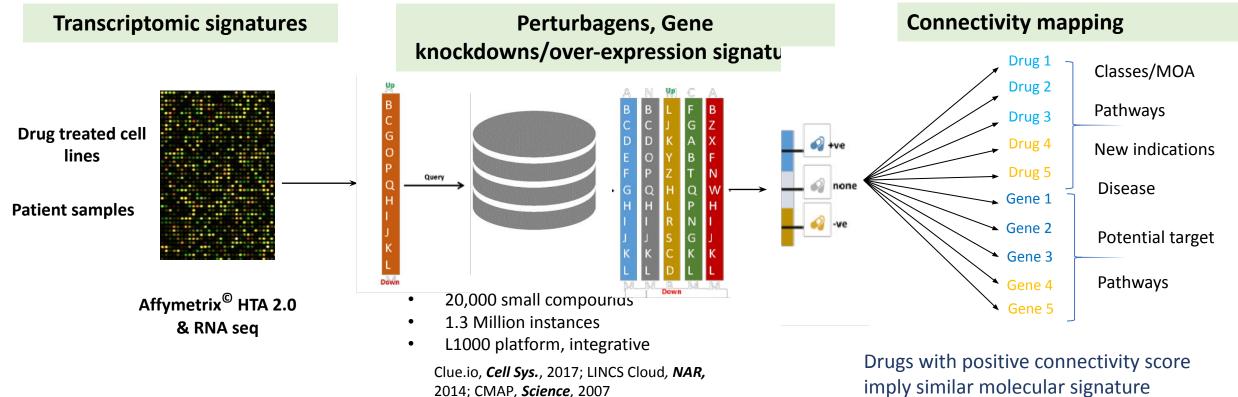
Against **snake bite**, hormonal disorders, Febrifuge, sepsis, bleeding disorders Fibroid tumours, Poor digestion, Dyspepsia and **malaria etc** 

- Repurposing of Ayurveda formulation in the norm?
- Is there a cross-talk between pathways ?
- Is there a molecular basis?
- Advantage of whole plant extract is being realized

## **Estrogen & viral inhibition link???**

# Connectivity Map platform : For understanding/repurposing of Ayurveda

### formulations



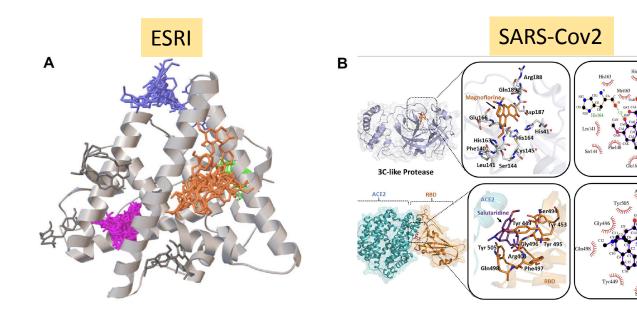
Traditional use of Cissampelos pareira L. for hormone disorder and fever provides molecular links of ESRI modulation to viral inhibition

Madiha Haider, Dhwani Dholakia, Aleksha Panwar, Parth Garg, Vivek Anand, Atish Gheware, Khushboo Singhal, Dayanidhi Singh, Shaunak A Burse, M. Ghalib Enayathullah, Yash Parekh, Sushma Ram, Surekha Kumari, Anmol Kumar, Arjun Ray, D Guruprasad R. Medigeshi, Kiran Kumar Bokara, Upendra Sharma, Bhavana Prasher, Mitali Mukerji

doi: https://doi.org/10.1101/2021.02.17.431579

This article is a preprint and has not been certified by peer review [what does this mean?].

### Ayurgenomics based framework : Application in exploring poly-pharmacology & repurposing



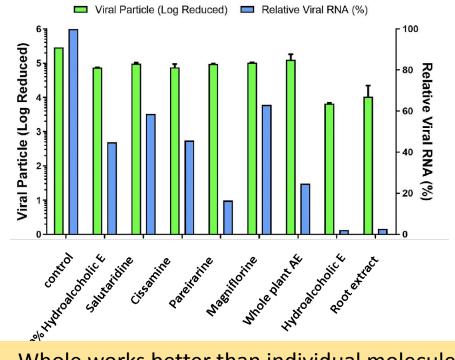
CIPA biomolecules binds ESRI & crucial SARS-CoV2 therapeutic targets

## Traditional use of Cissampelos pareira L. for hormone disorder and fever provides molecular links of ESRI modulation to viral inhibition

Madiha Haider, Dhwani Dholakia, Aleksha Panwar, Parth Garg, Vivek Anand, Atish Gheware, Khushboo Singhal, Dayanidhi Singh, Shaunak A Burse, M. Ghalib Enayathullah, Yash Parekh, Sushma Ram, Surekha Kumari, Anmol Kumar, Arjun Ray, <sup>10</sup> Guruprasad R. Medigeshi, Kiran Kumar Bokara, Upendra Sharma, Bhavana Prasher, Mitali Mukerji

doi: https://doi.org/10.1101/2021.02.17.431579

This article is a preprint and has not been certified by peer review [what does this mean?].



#### Whole works better than individual molecules

Haider et al. BMC Complementary Medicine and Therapies (2022) 22:114 https://doi.org/10.1186/s12906-022-03584-3 BMC Complementary Medicine and Therapies

**Open Access** 

#### RESEARCH



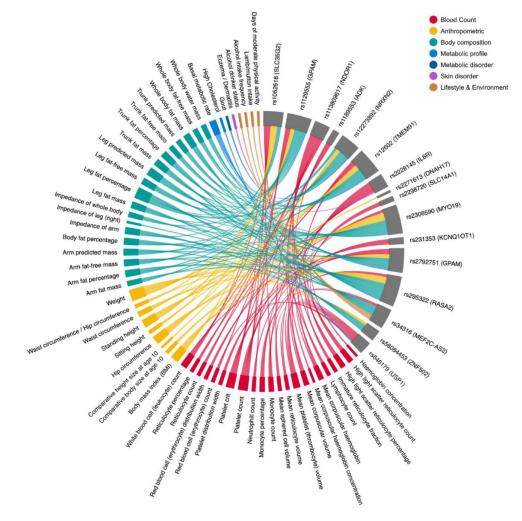
# Anti-SARS-CoV-2 potential of *Cissampelos* pareira L. identified by connectivity map-based analysis and in vitro studies

Madiha Haider<sup>1,2</sup>, Vivek Anand<sup>1,2</sup>, M. Ghalib Enayathullah<sup>3</sup>, Yash Parekh<sup>3</sup>, Sushma Ram<sup>3</sup>, Surekha Kumari<sup>4,2</sup>, Anmol<sup>2,4</sup>, Gayatri Panda<sup>5</sup>, Manjari Shukla<sup>6</sup>, Dhwani Dholakia<sup>1,2</sup>, Arjun Ray<sup>5</sup>, Sudipta Bhattacharyya<sup>6</sup>, Upendra Sharma<sup>2,4</sup>, Kiran Kumar Bokara<sup>3</sup>, Bhavana Prasher<sup>1,2,7\*</sup> and Mitali Mukerji<sup>1,2,6,7\*</sup>

# Non-invasive phenotyping for Risk stratification : insights from exome

#### Article

#### Whole Exome Sequencing in Healthy Individuals of Extreme Constitution Types Reveals Differential Disease Risk: A Novel Approach towards Predictive Medicine



	Variation details			alt allele frequency in cohorts				
				VADU		North		
Gene	dbSNP	alt allele	nature	Vata	Kapha	Vata	Kapha	profile
ANKLE1	rs8100241	А	missense (A to T)	0.611	0.333	0.6111	0.2941	
ANKLEI	rs8108174	А	missense (L to Q)	0.611	0.333	0.5833	0.2778	V vs K

#### ARTICLE

Received 16 Jun 2015 | Accepted 20 Jul 2016 | Published 7 Sep 2016

01: 10.1038/ncomms12675 OPEN

Check for updates

Functional mechanisms underlying pleiotropic risk alleles at the 19p13.1 breast-ovarian cancer susceptibility locus

Kate Lawrenson et al.#

#### ARTICLE

#### https://doi.org/10.1038/s42003-023-04611-w OPEN

ANKLE1 cleaves mitochondrial DNA and contributes to cancer risk by promoting apoptosis resistance and metabolic dysregulation

Piotr Przanowski [1] <sup>1,2 III</sup>, Róża K. Przanowska [1] <sup>1,2</sup> & Michael J. Guertin [1] <sup>3,4 III</sup>

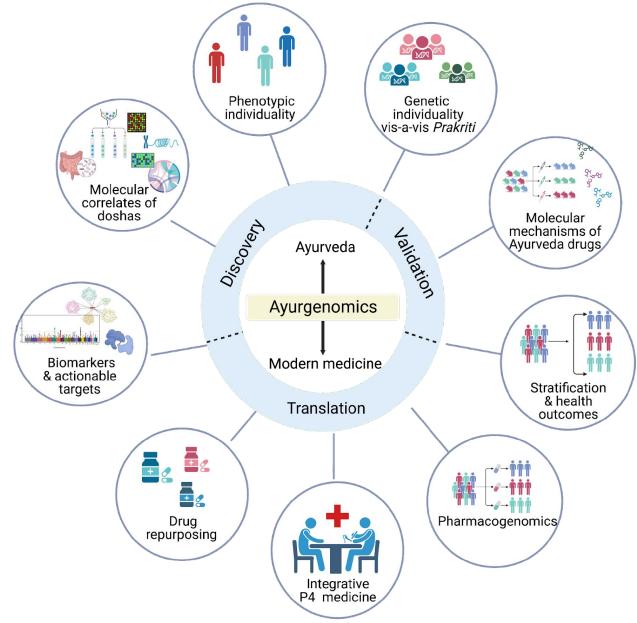
**Molecular corelates of doshas through Ayurgenomics** 

Mukerji M (2023).

Ayurgenomics-based frameworks in precision and integrative medicine: Translational opportunities. Cambridge

### Ayurgenomics – A framework for bridging Ayurveda with modern

### medicine





pubs.acs.org/acschemicalbiology

•

Ayurgenomics: A New Way of Threading Molecular Variability for Stratified Medicine

Tav Pritesh Sethi,<sup>†</sup> Bhavana Prasher,<sup>\*,‡</sup> and Mitali Mukerji<sup>\*,†</sup>

ACS Chem. Biol. 2011, 6, 875–880

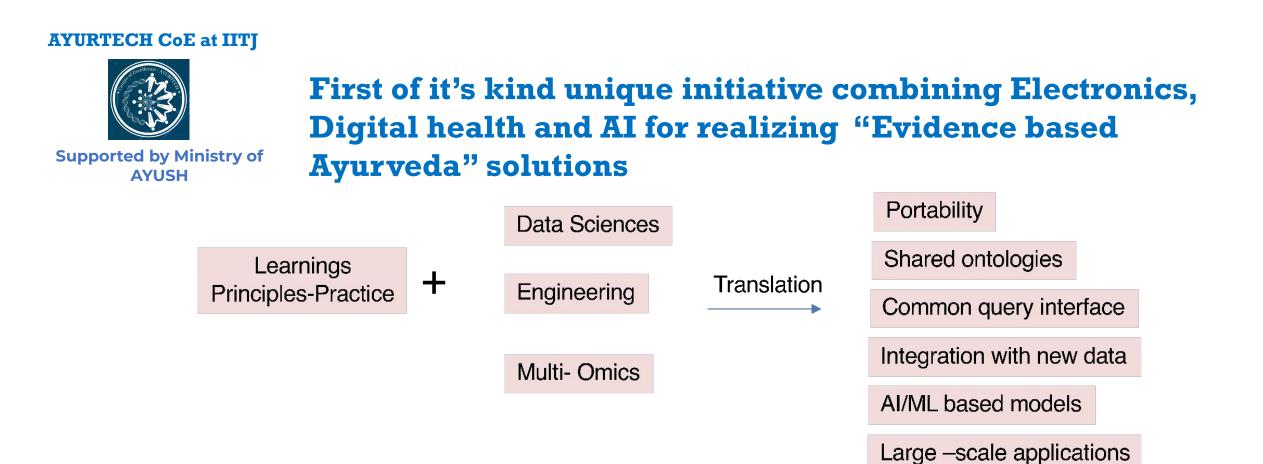
Ayurgenomics-based frameworks in precision and integrative medicine: Translational opportunities

Mitali Mukerji 回

Department of Bioscience and Bioengineering, Indian Institute of Technology Jodhpur, Karwar, India and School of Artificial Intelligence and Data Science (AIDE), Indian Institute of Technology Jodhpur, Karwar, India

Cambridge Prisms: Precision Medicine, 1, e29, 1–14

# Setting up : Trans-disciplinary Centre of Excellence in integrative precision health at IIT Jodhpur

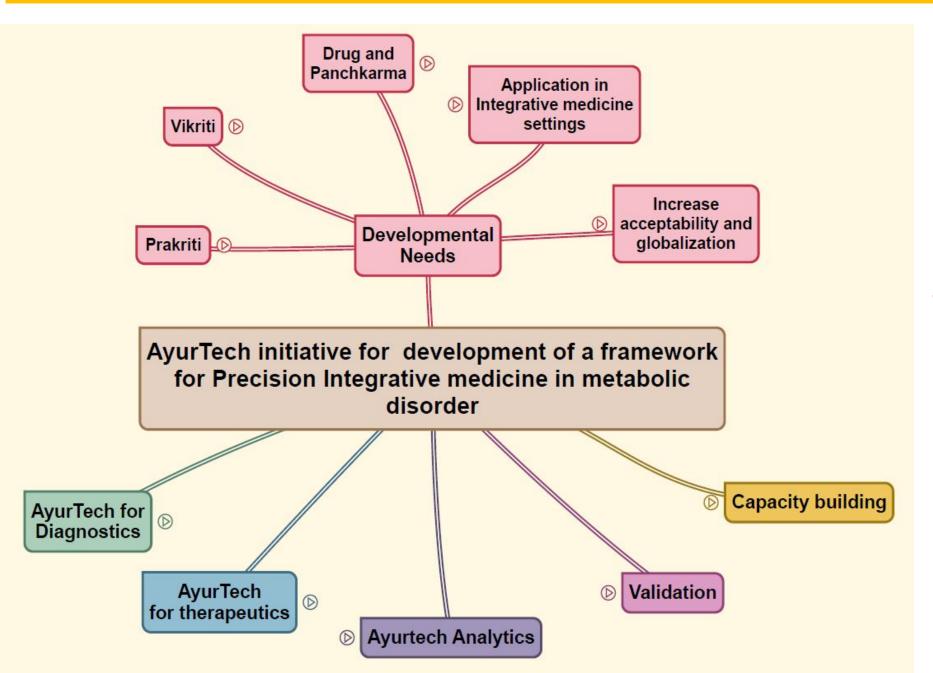


### **AYURTECH** Aims to Leverage **Ayurveda** to address **GAP** areas in current Precision Health Cohorts

- System's understanding through common organizing principle (*tridosha*) and network medicine for translation (*trisutra*)
- Individualized health baseline that inform response and trajectory in geo-spatio-temporal dimensions and pre-emptive management of lifestyle and nutrition
- Disease trajectories based on individual baselines
- Diseases treated in an individual centric manner and as moving targets
- Unique therapeutic modalities
  - Panchkarma
  - Multicomponent single and poly herbo-metallic formulations
  - Different preparations and mode of administrations for diverse therapies
  - Personalised dietary and yoga interventions
- Context of population, culture and habitat on individual baselines

### **Development of AyurTech Framework**





First of it's kind unique initiative combining Electronics, Digital health and AI for realizing "Evidence based Ayurveda" solutions

### Scenario : Patient A – approaches an Ayurveda doctor with a disease called Fanconi anemia

### The patient exhibits the following symptoms

HPO_TERM_NAME	CATEGORY
Deficient excision of UV-induced pyrimidin	e Metabolism/Laboratory abnormality
Prolonged G2 phase of cell cycle	Metabolism/Laboratory abnormality
Hearing impairment	Ear
Strabismus	Eye
Short stature	Growth
Ectopic kidney	Genitourinary system
Maleinfertility	Genitourinary system
Horseshoe kidney	Genitourinary system
Duplicated collecting system	Genitourinary system
Abnormal renal morphology	Genitourinary system
Leukemia	Neoplasm
Hypergonadotropichypogonadism	Endocrine

Abnormality of cardiovascular system morp	Cardiovascular
Bruising susceptibility	Skin, Hair, and Nails
Abnormal heart morphology	Cardiovascular
Complete duplication of thumb phalanx	Skeletal system
Intellectual disability	Nervous System
Microcephaly	Nervous System
Abnormality of skin pigmentation	Skin, Hair, and Nails
Chromosomal breakage induced by crosslin	Metabolism/Laboratory abnormality
Small for gestational age	Growth
Microphthalmia	Eye
Autosomal recessive inheritance	Inheritance
Absentthumb	Skeletal system
Reticulocytopenia	Blood and blood-forming tissues
Short thumb	Skeletal system
Thrombocytopenia	Blood and blood-forming tissues
Cryptorchidism	Genitourinary system
Pancytopenia	Blood and blood-forming tissues
Absentradius	Skeletal system
Renal ægenesis	Genitourinary system
Anemic pallor	Skin, Hair, and Nails
Neutropenia	Blood and blood-forming tissues

What would be the Ayurveda diagnosis?

What is the likely cause ??

Which features are informative for diagnosis??

What is the likely therapy ??

### Vata regulates cell division and morphogenesis

शरीरावयथास्तु परमाणुभेदेनापरिसंख्येया भवन्ति, अतिबहुत्वादतिसौक्ष्म्यादतीन्द्रियत्वाच । तेर्पा संयोगविभागे परमाणूनां कारणं वायुः कर्मस्वभावश्च ॥ १७ ॥

c.sa.7/17

#### Summary

Gene Location: 16q24.3

#### Definition

The Fanconi anemia complementation group (FANC) currently includes FANCA, FANCB, FANCC, FANCD1 (also called BRCA2), FANCD2, FANCE, FANCF, FANCG, FANCI, FANCJ (also called BRIP1), FANCL, FANCM and FANCN (also called PALB2). The previously defined group FANCH is the same as FANCA. Fanconi anemia is a genetically heterogeneous recessive disorder characterized by cytogenetic instability, hypersensitivity to DNA crosslinking agents, increased chromosomal breakage, and defective DNA repair. The members of the Fanconi anemia complementation group do not share sequence similarity; they are related by their assembly into a common nuclear protein complex. This gene encodes the protein for complementation group A. Alternative splicing results in multiple transcript variants encoding different isoforms. Mutations in this gene are the most common cause of Fanconi anemia. [provided by RefSeq, Jul 2008]

No. Descendants Hierarchy ⑦	Abnormality of the cell cycle HP:0011018			
Abnormal cellular physiology Abnormality of the cell cycle Prolonged G2 phase of cell cycle	An abnormality of the cell cycle.   Synonyms: Abnormality of the cell cycle   Cross References: UML5:C4023594			
	Disease Associations	Gene Associations		
	Disease Id	Disease Name	Associated Genes	

Fanconi anemia

Fanconi anemia, complementation group C

Fanconi anemia, complementation group D2

Fanconi anemia, complementation group E

OMIM:227650

OMIM:227645

OMIM:227646

OMIM:600901

FANCA [2175]

FANCC [2176]

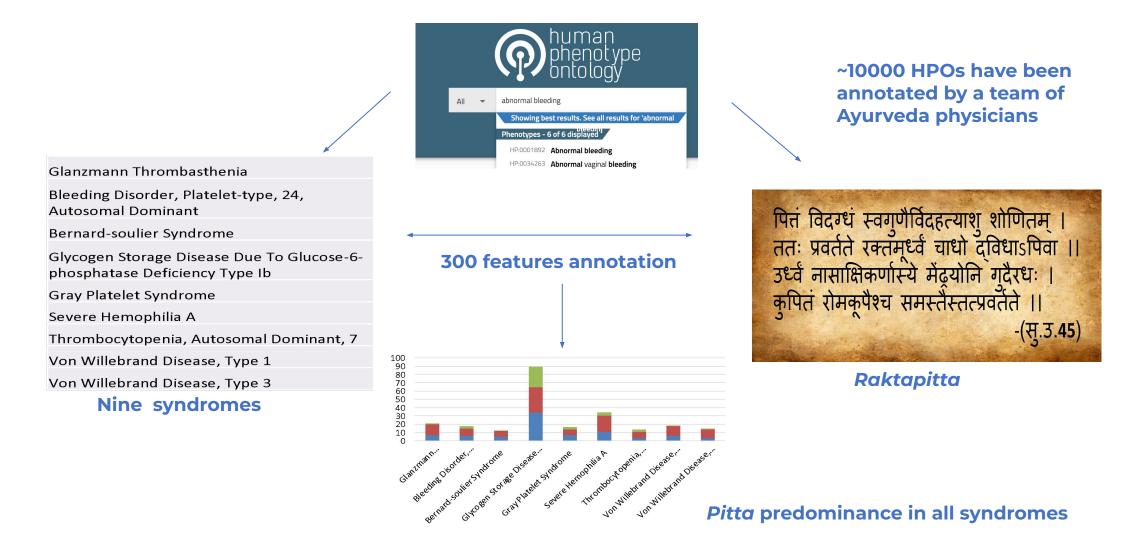
FANCD2 [2177]

FANCE [2178]

Displaying 4 out of 4.

# Building conversational language between Ayurveda and Modern medicine

Bridging the ontological gap



### Prof. Santanu Chaudhury: Director IITJ & Dept of Elcetrical Engineering Engineering IIT Delhi

Computer Vision, AI/ML, Big Data Science

#### Lead Coordinators:

Prof. Mitali Mukerji: Department Bioscience and Bio Engineering, IIT Jodhpur; Human genomics, personalized medicine, Ayurgenomics
 Prof. Ajay Agarwal: Department of Electrical engineering; Microelectronics professional, Nanotechnologies, MEMS, microfluidics & Micro-sensors

#### **BioScience and Bioengineering:**

Dr. Sudipta Bhattacharyya Structure-guided rational drug discovery, drug-protein interactions, biophysics, drug screening, & bioassay development
Dr. Raviraj Vankayala: nanotheranostics, biophotonics, and drug delivery

#### **Computer Science & Engineering:**

Dr. Dip Sankar Banerjee : high performance computing, data analytics, parallel computing and computer architecture.
Dr. Sumit Kalra : Software Architecture, Data Analytics, IoT and Smart Healthcare

#### **Electrical Engineering:**

Dr. Rajendra Nagar: Computer Vision, Computer Graphics, 3D
 Geometry Processing, and Machine Learning.
 Prof. Manoj Choudhary: Communications and computing, Wireless
 Communications & Networks (5G/6G/Next gen WLAN/UWB), AI, IOT,
 Connected and digital healthcare, Sensors, regulatory & standards
 frameworks, IPR management.

#### **Chemistry:**

Dr. Rohan Erande: synthetic organic chemistry, method development and total synthesis of bioactive natural products.

#### **Industry partners**

Dr. Bala Pesala: Professor of Practice, IIT Jodhpur and founder and CEO of Ayur.Al & CTO, Adiuvo Diagnostics and also.
 Next gen deep tech companies in the digital health and diagnostics, AI/ML
 Dr. Lipika Dey: TCS Research and Innovation and heads analytics and insights practices. NLP, text and data mining, information fusion, machine learning, and semantic search.

### **AYURTECH Lead Clinical Collaborators for framework development**

Dr. S. R. Rajasthan Ayurved University Nodal co-ordinator: Vice Chancellor,

Prof. Abhimanyu Kumar Dr. Sanjay Srivastava: Shalya Tantra, Dr. Prem Prakash Vyas: Bal Roga Dr. Rakesh Kumar Sharma: Rachana Shareer

S.No.	Group Name	Name of Faculty Member
1.		1. Dr. Rakesh Kumar Sharma
	Prakriti	2. Dr. Vinod Kumar Gautam
		3. Dr. Brahmanand Sharma
		4. Dr. Dinesh Chandra Sharma
		1. Dr. Govind Prasad Gupta
2.	AYURTECH	2. Dr. Gyan Prakash Sharma
		3. Dr. Sanjay Srivastav
		4. Dr. Ritu Kapoor
		5. Dr. Manisha Goel
3.	DESSERT Medicine	1. Dr. Prem Prakash Vyas
		2. Dr. Chandan Singh
		3. Dr. Manoj Adlakha

### Validation studies for integrative medicine: AYUSH Centre, AIIMS Jodhpur

Nodal Coordinator : Director AIIMS Jodhpur Dr Pankaj Bharadwaj : Additional Professor, Community Medicine & Family Medicine. Coordinator, School of Public Health. AIIMS Jodhpur. Dr Meenakshi Sharma

> Implementation studies: More partners have shown Expression of interest from different centres and hospitals.....

# **Ayurgenomics inter-disciplinary team**

Dr. Bhavana Prasher MD Ayurveda Principal Scientist TRISUTRA @IGIB & Co-PI

#### <u>Ayurveda</u>

Shilpi Aggarwal (PhD, BAMS) Bharat Krishna Khuntia (MD), Arvind Kumar (MD)

**Genome informatics** Dr Ankita Narang Dr Pradeep Tiwari Rintu Kutum (PhD) Dhwani Dholakia (PhD) Tahseen Abbas (PhD)

#### Modern medicine, Pharma and Physiology Tav Pritesh Sethi (PhD MBBS) Dr Atish Gheware (PhD Mpharm)

Ritu Rani (PhD)

#### Genomics Dr Sapna Negi Dr Binuja Varma, Dr Rajesh Pandey, Dr Pankaj Jha Dr Pramod Gautam Madiha Haider (PhD) Gaura Chaturvedi (PhD) Dayanidhi Singh (PhD) Sumita Chakravorty (PhD) Sunanda (PhD)



Prof Samir Brahmachari (mentor & vision)



#### **KEMHRC**: Sanjay Juvekar, Bhushan Girase, Ankita Shrivastava, Rutuja Patil, Dheeraj Aggarwal, **Bharat Choudhury**

### DST, CSIR, AYUSH for financial support

**Public health** 





Modern medicine







Ayurveda

**Collaborators** 

Dr. Anurag Agrawal (IGIB),

Dr Saurav Ghosh (ISI Kolkata),

Greg Gibson (Georgia Tech)

Dr Kiran Bokara CSIR-CCMB

Dr Upendra Sharma CSIR-IHBT,

Indian Genome Variation Consortium

**TRISUTRA Ayurgenomics Consortium** 

Dr Guruprasad Medigeshi THSTI,

Dr Nar Singh Chauhan, MDU, Rohtak

Dr. Qadar Pasha (IGIB),

Dr. Debasis Dash,

Dr Arjun Ray – IIITD

**CSIR-TRISUTRA Team @IGIB** 



*jeorgi* AIST











Thank You