Panel 3: TMD Research – Basic & Preclinical
Future Directions for Basic and Preclinical TMD Research

TMD research over the years – gaps, priorities, opportunities.

Allen W. Cowley, Jr., PhD.
Professor of Physiology
Medical College of Wisconsin
Chairman of TMJ Association Scientific Advisory Committee

Over the years - Eight Scientific Meetings of The TMJ Association

Sponsored by TMJ Association, NIDCR and other NIH Institutes and Offices.

www.tmj.org

- Meetings driven based upon an awareness that there was no coherent body of knowledge on the etiology and pathogenesis of TMD.
- Goals were to analyze the state of current research and bring new ideas and perspectives to the field.
- Resulted in recommendations to NIH regarding gaps and opportunities in TMD basic and clinical sciences.
- Patients and young investigators were an integral part of these meetings.

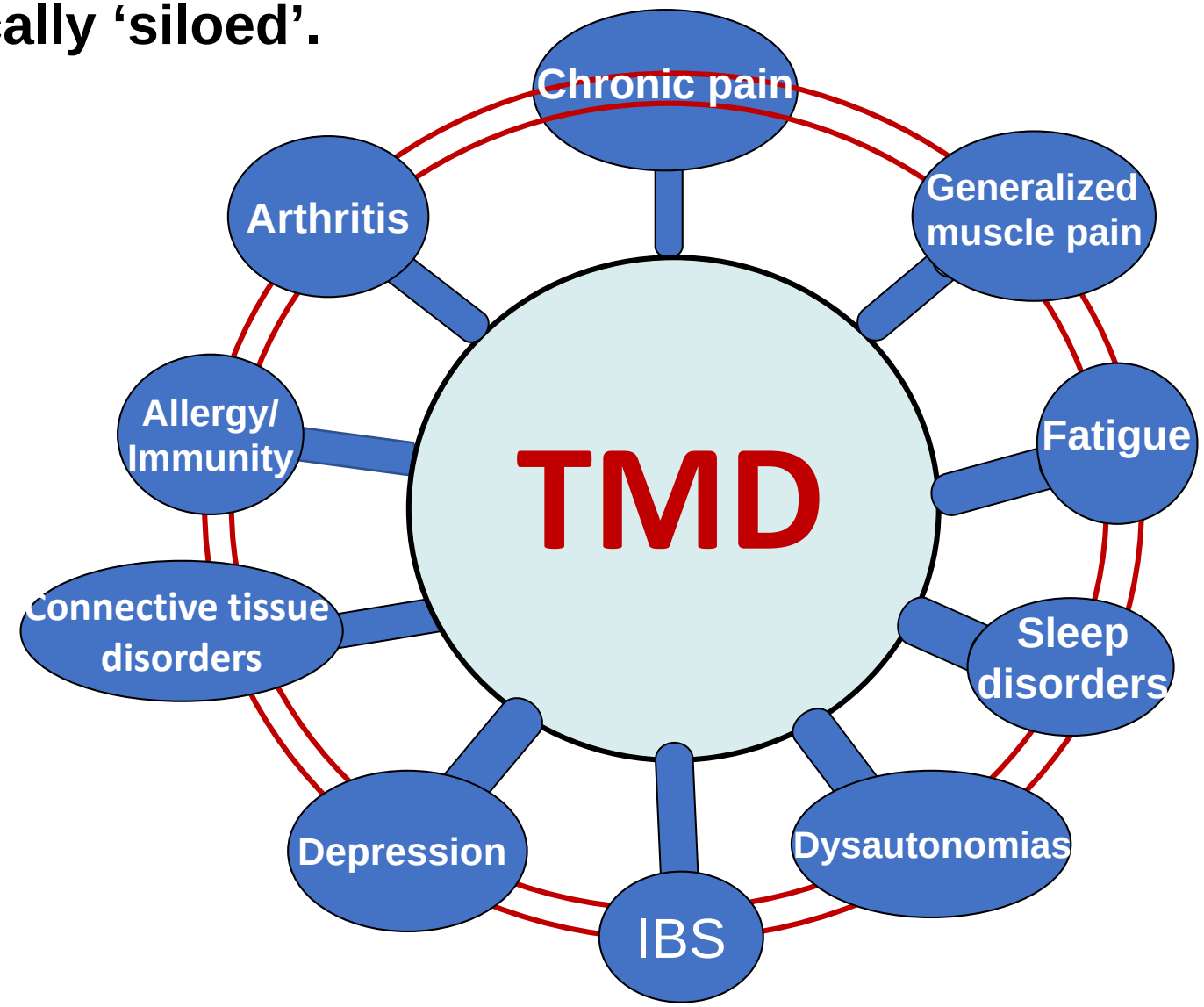
What did we learn?

- The pathophysiological basis of TMD remains an enigma.
- Found many hypotheses related to etiology but none validated.
- Found a lack of clinical definition: What is TMD? One or many diseases?
- Importantly, TMD was recognized as more than a problem of jaw dysfunction and pain in the jaw joint.

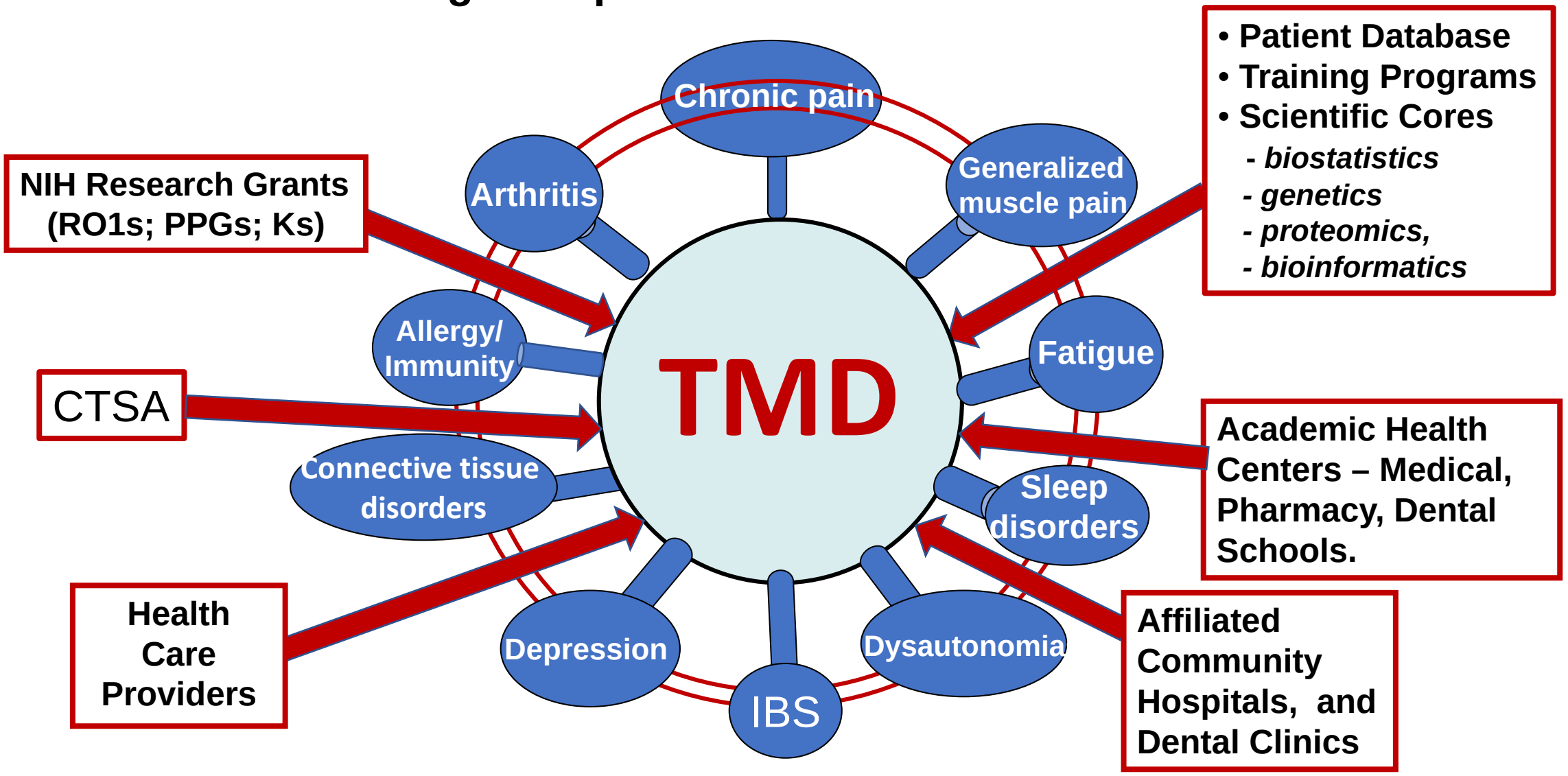
TMDs do not exist alone - collection of disorders/comorbidities – currently scientifically and clinically ‘siloed’.

“…temporomandibular joint and muscle disorders (TMJDs) do not exist alone. They are part of a collection of disorders that are both influenced by, as well as influence, other medical conditions such as chronic fatigue syndrome, cardiovascular disorders, hearing problems such as tinnitus, digestive and gastrointestinal disorders, and sleep disorders, to name a few. <u>In short, TMDs are part of a very complex system</u>.”

Lawrence A. Tabak, D.D.S., Ph.D.
Director, National Institute of Dental and Craniofacial Research
TMJ Science Vol 4, 2007



“Center concept” proposed – multidisciplinary, integrated patient care and research.



The TMJ Patient-Led RoundTable
(2016 – ongoing)

A public private partnership bringing together all stakeholders – **patients**, scientists, bioengineers, oral surgeons, device manufacturers, NIH, FDA, AHRQ, insurance industry, patient reported outcome experts and others - with interest in TMDs and with the common goal of improving the healthcare of patients.

Gaps/Opportunities Identified in Basic Science related to TMD

- Molecular genomics and epigenetics.
- TMD and Data Science/Informatics
- Mechanisms underlying chronic TMD pain and joint specific pain.
- Sex difference
- Neuro-endocrine system interactions
- Immune/Inflammatory mechanisms (CNS/systemic)
- TM joint tissues and mechanics
- TM joint tissue engineering and disk replacements.
- Animal models

Gaps/Opportunities Identified in Basic Science related to TMD

Molecular genomics and epigenetics.

- Integrated investigation of genetic polymorphisms, gene expression, epigenetic markers, nucleosome localization and genome interactions for cell populations and at the single-cell level in TMD relevant tissue types versus normal.
- NGS for genomic/epigenomic/proteomic/biomic/immune profiling.
- Associations of novel genetic loci and non-coding mutations with well-defined phenotypes of TMD subjects.

TMD and Data Science/Biomedical Informatics

- Data science/biomedical informatics for advanced data analysis; artificial intelligence, machine learning, novel clustering methods for precise ID of disease risk, therapeutic effectiveness and outcomes of TMD subjects.
- Bioinformatic approaches that vertically integrate pathway analysis.

Gaps/Opportunities Identified in Basic Science related to TMD

Mechanisms underlying chronic TMD pain and joint specific pain (animal models and humans).

- Quantitative sensory testing; mechanisms of peripheral and central sensitization.

Sex differences

- Effects of sex hormones upon disease initiation, progression and responses to drug treatments, surgical interventions and implants.

Neuro-endocrine system interactions

- Stress induced pathophysiological mechanisms and epigenetic responses related to TMD progression (PTSD, social isolation, etc.).

Gaps/Opportunities Identified in Basic Science related to TMD

Immune/Inflammatory mechanisms

- Role of innate and adaptive immunity; inflammation & cytokines in onset and progression of TMD; responses to surgical procedures and implant devices.

TM joint tissues and mechanics

- Developmental biology of the joint and related tissues.
- Unique characteristics of jaw joint and other tissues (ligaments/muscles/blood vessels/nerves/collagens/extracellular matrixes).
- Joint mechanics .

Tissue engineering of TM joint and disk replacements.

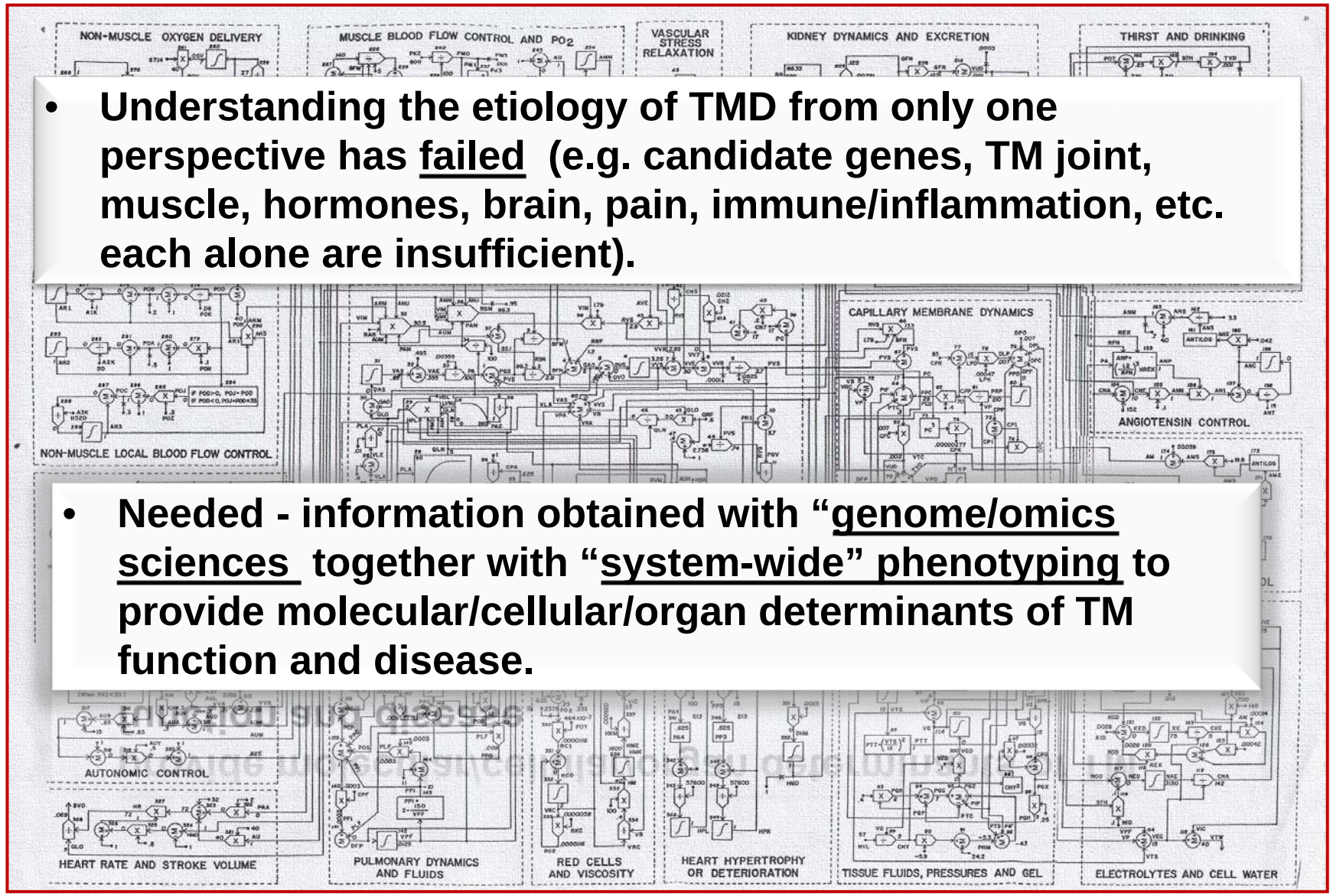
- Cellular models of TM joint tissues and TM muscles.
- Novel materials
- Regenerative medicine approaches

Gaps/Opportunities Identified in Basic Science related to TMD

Animal Models.

- Model organisms that mimic important aspects of the complex human condition.
- Genetically engineered models (rat/mouse; CRISPR-Cas9) based on GWAS associations in humans to study mechanisms.

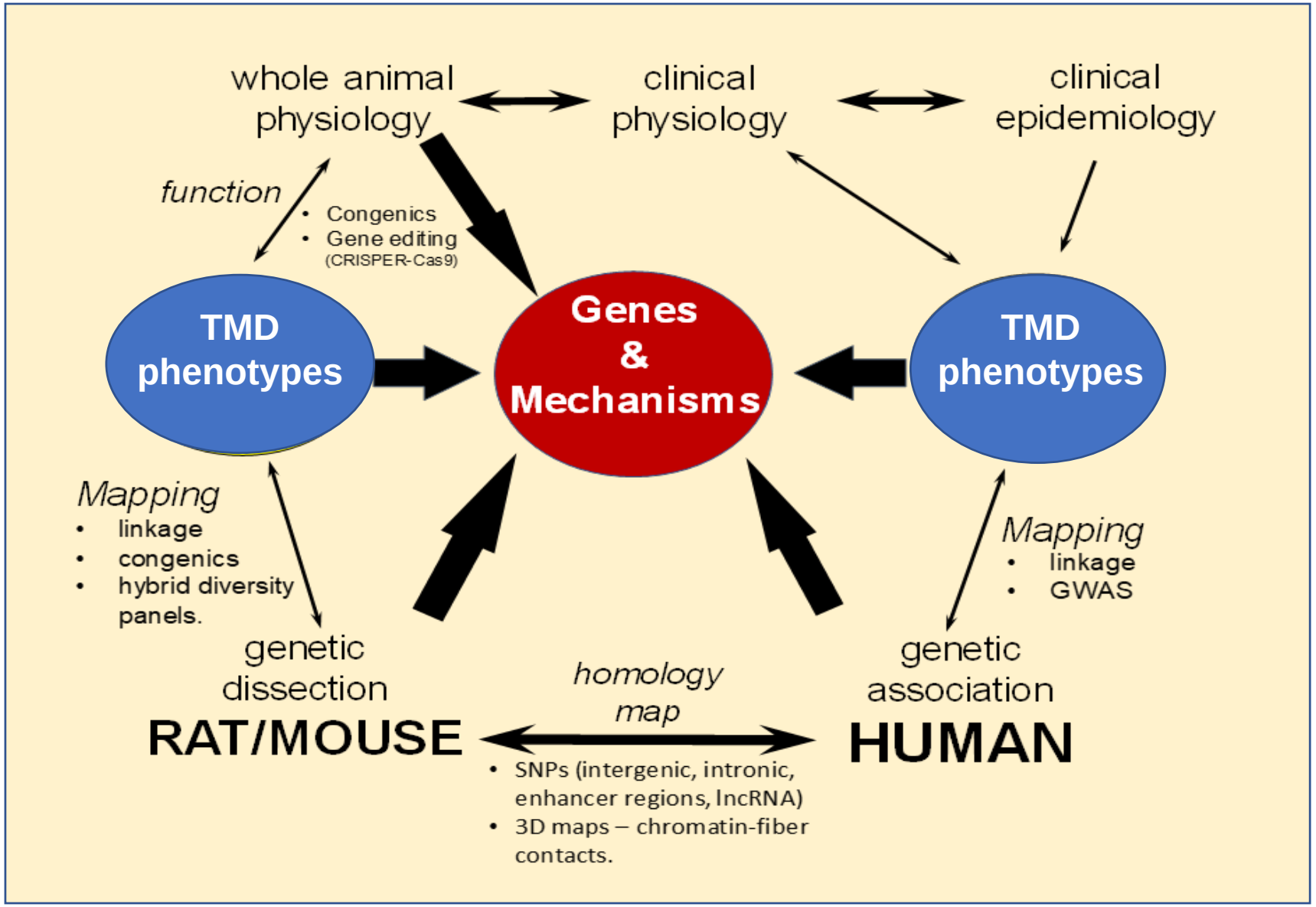
TMD must be studied as a complex disorder determined by interacting and redundant systems.



- Understanding the etiology of TMD from only one perspective has <u>failed</u> (e.g. candidate genes, TM joint, muscle, hormones, brain, pain, immune/inflammation, etc. each alone are insufficient).

- Needed - information obtained with "<u>genome/omics sciences</u> together with "<u>system-wide" phenotyping</u> to provide molecular/cellular/organ determinants of TM function and disease.

Big gap: basic-translational research = integrated functional genomics.



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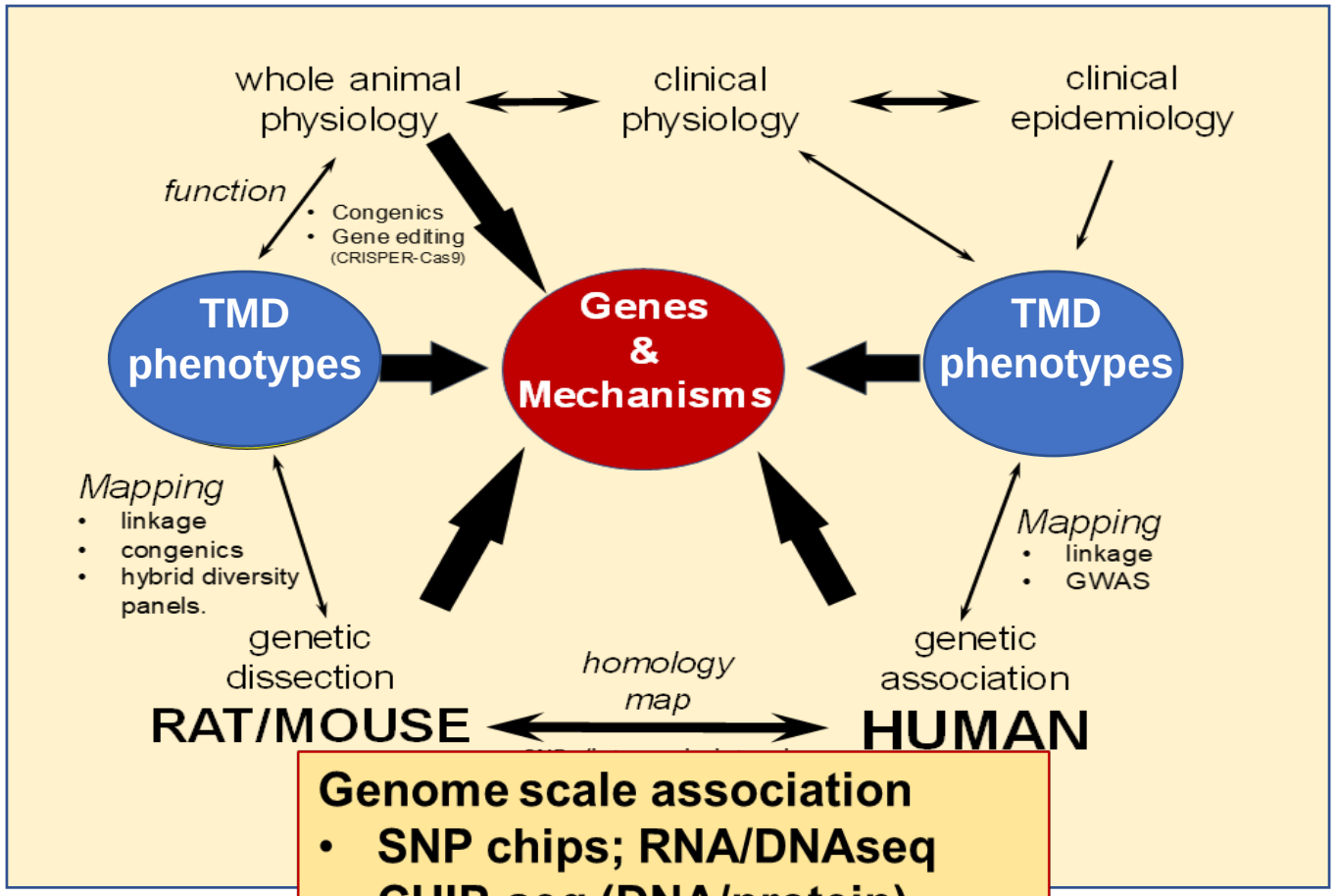
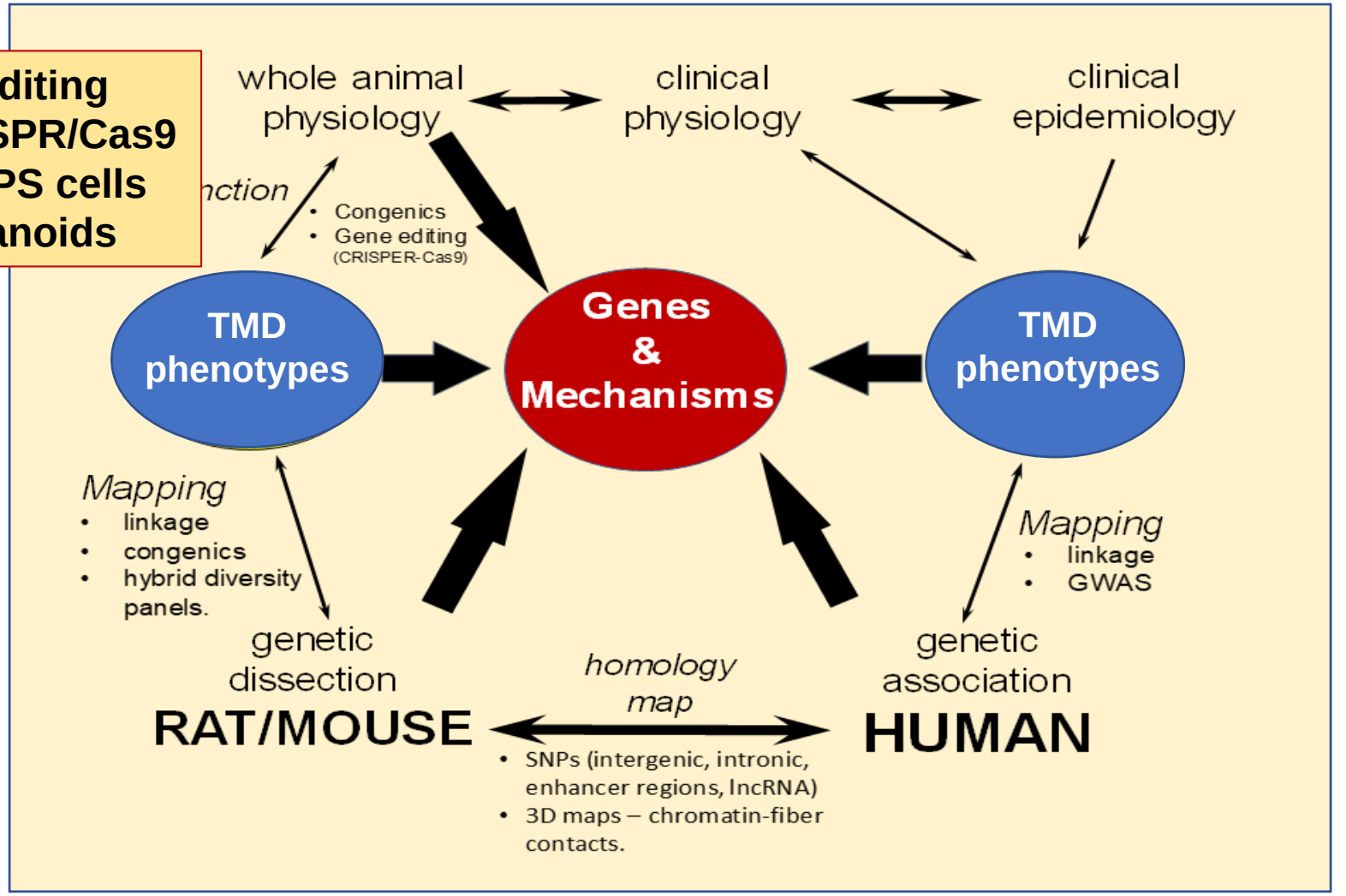


Genome scale association

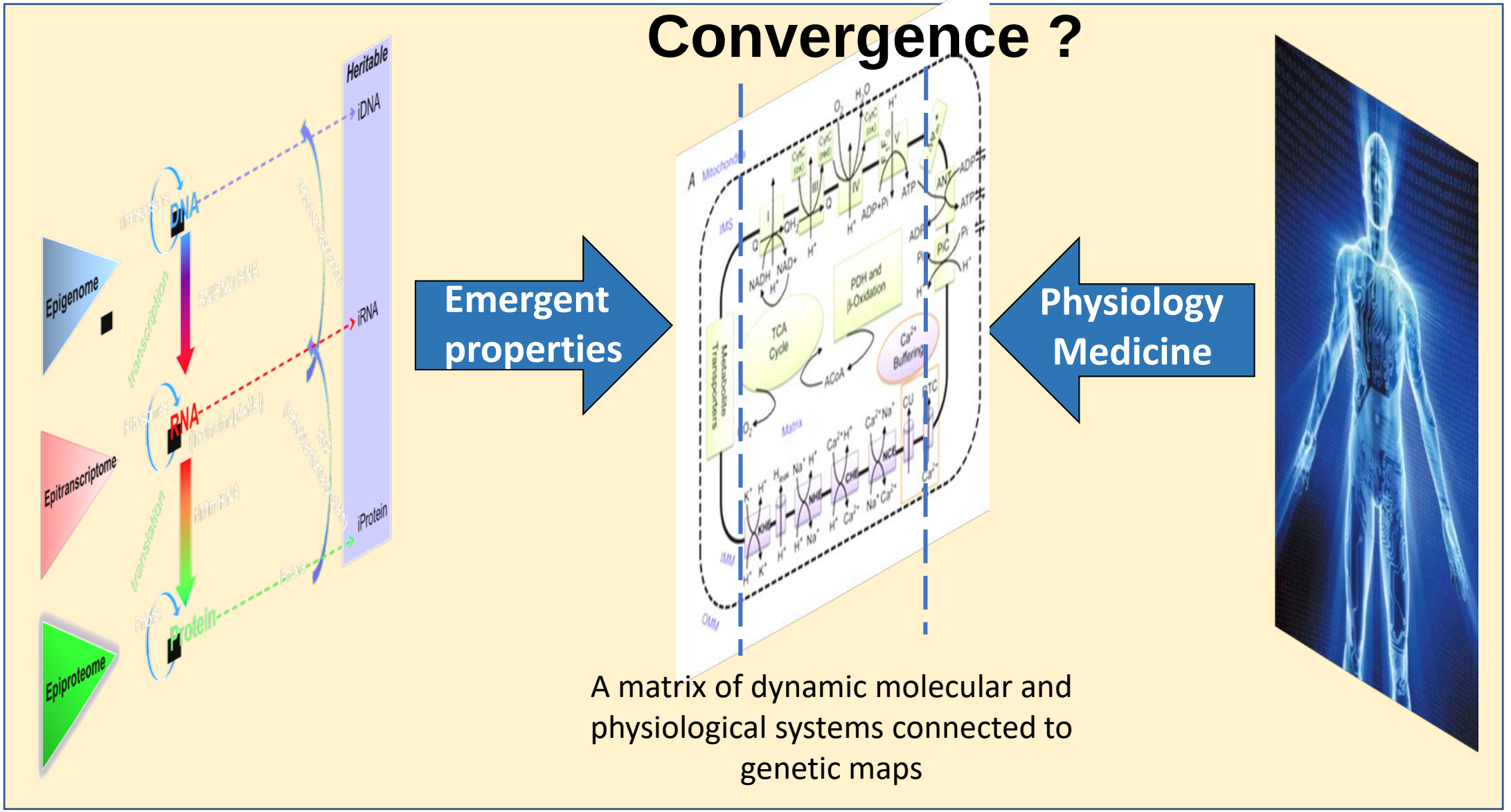
- **SNP chips; RNA/DNAseq**
- **CHIP-seq (DNA/protein)**
- **DNA 3D, 4D (nucleome)**
- **Hi-C maps (chromatin)**
- **TF regulation/databases**
- **KO mouse/rat (KOMP/KORC)**

Big gap: basic-translational research = integrated functional genomics.

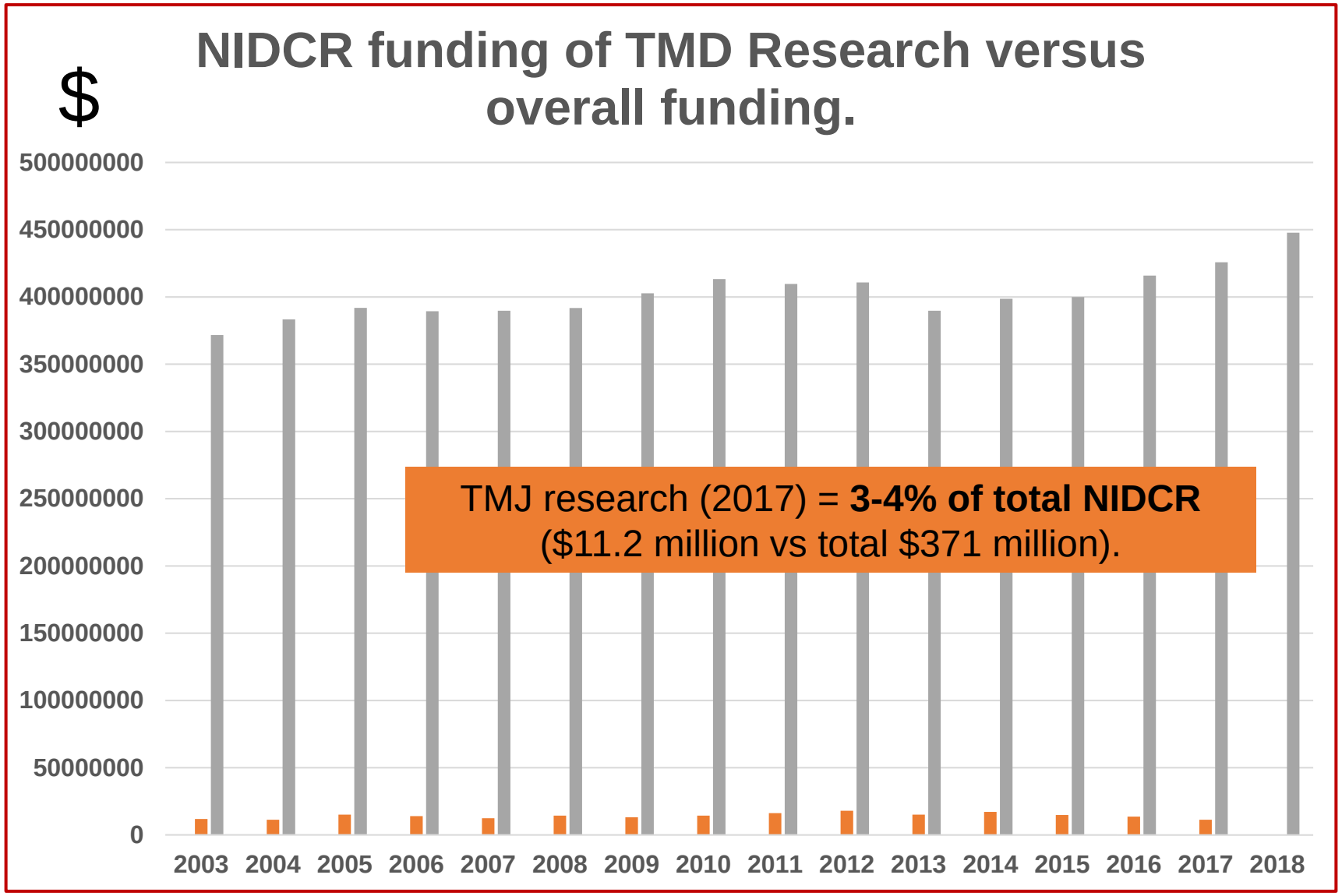
Gene editing
- **CRISPR/Cas9**
- **ES/IPS cells**
- **Organoids**



Integration and convergence of complex multiscale systems needed to achieve an understanding of the interacting molecular/cellular/organ determinants of TM functions and TMD.

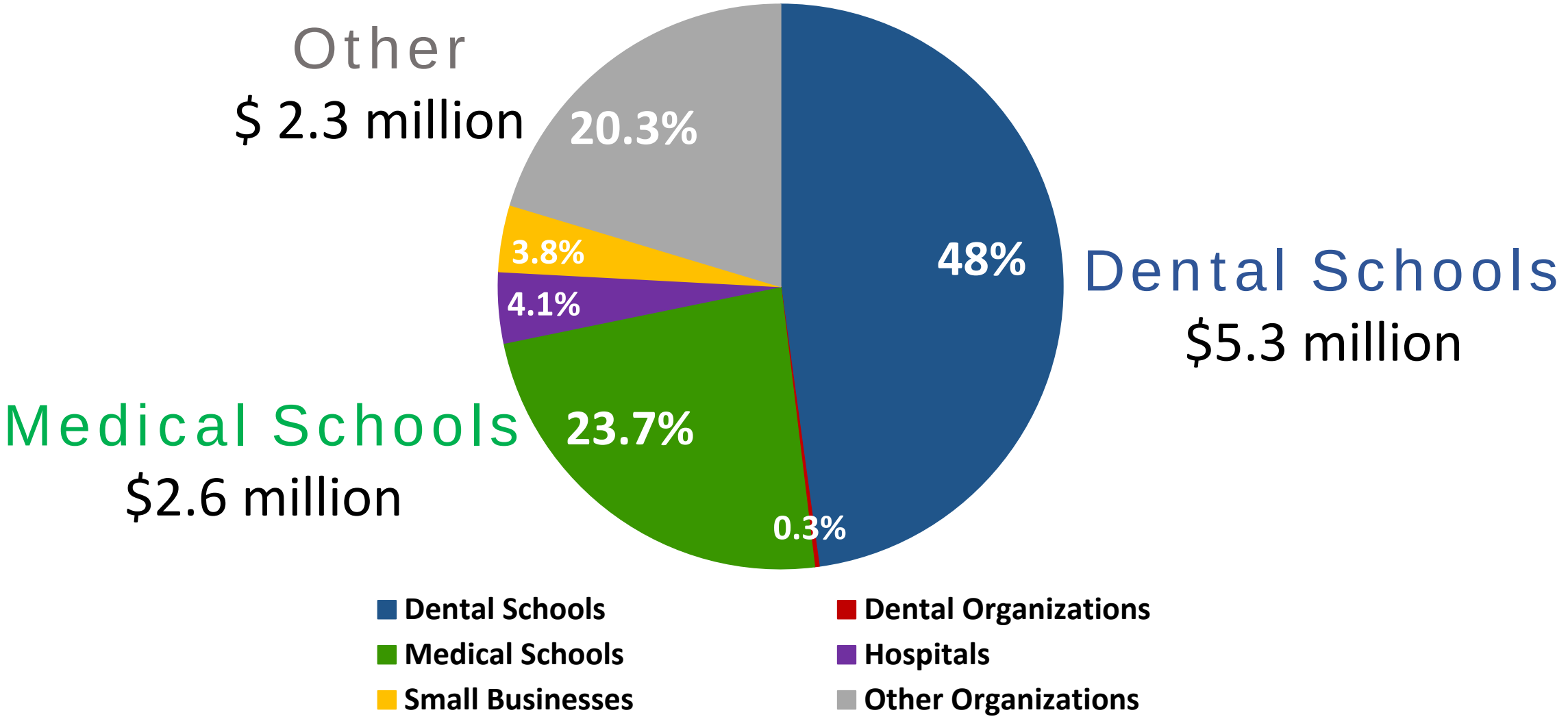


Facts



TMD affects approximately 36 million people in the U.S.

NIDCR Extramural Funding to All Organizations (2017)



NIDCR funded 36 TMD related research grants in FY 18

Pain – neural basis:……..n=11

Pain – sex differences:……..n=2

Emotion dysregulation/sleep/bruxism:……..n=3

Structure-function (ligaments/collagen/ECM elements/cartilage/chondrocyte/bone):……..n=4

TMJ disc regeneration/bioscaffolds/stem cells:…n=7

Genetics:……..n=2

Immune factors:……..n=1

Risk factors:……..n=1

Therapy/drug delivery:……..n=2

Training K-99:……..n=1

Other NIH Institutes funding of TMD (n=5)

Project titles

Project Title

The neural basis of touch and proprioception in the primate orofacial sensorimotor cortex
TMJ Disc Regeneration
Development of Drug Delivery Technology for Stem Cell-Based TMJ Regeneration

Modeling temporomandibular joint disorders pain: role of transient receptor potential ion channels
Genetic and post-translational modifications of TRPV1 in craniofacial pain

Chronic orofacial pain: genetics, cognitive-emotional factors, and endogenous modulatory systems

Structure-function relationships between human temporomandibular lateral capsule-ligament complex tensile stiffness, collagen ultrastructure and ECM composition: Investigation of sexual dimorphisms
Progenitor Regulation in Craniofacial Development and Regeneration
Investigation and Modulation of the Mu-Opioid Mechanism in Chronic TMD (in vivo)
Investigation and Modulation of the Mu-Opioid Mechanism in Chronic TMD (in vivo)
Investigation of Risk Factors for Development of TMJD Pathology
NIDCR Dentist Scientist K99:Improve TMJ Fibrocartilage Regeneration Strategies

Chondrocyte-derived bone cells determine the overall pattern of TMJ condyle and contribute to bone remodeling
Emotion Dysregulation and Sleep-Time Masticatory Muscle Activity in Sleep Bruxism
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Mechanism of Nociception Induced by Innocuous Cold in Trigeminal System
Mechanistic Characterization of Pain in Temporomandibular Disorders: Does Pain Centralization Influence Responsiveness to Peripherally Targeted Treatments?
Role of Descending Pain Modulation System in Orofacial Pain
Mechanisms of TMJ development and long-term function

Molecular Roles of Cdk5 in Neuronal Functions and Pain Signaling
TMJ Disc Regeneration by 3D-Printed Bioscaffolds in a Pre-Clinical Animal Model
Cellular and Mechanical Mechanisms Regulating Mandibular Distraction Osteogenesis
Brain Connectivity Patterns in Chronic Temporomandibular Joint Disorders

Chondrocyte-pericellular matrix derived signaling maintains tissue integrity in the temporomandibular joint
Immune activation of the endogenous control of persistent pain
Central mechanisms underlying sex differences in endogenous pain modulation

The Requirement of ADAMTS5-mediated Cleavage of Aggrecan in Temporomandibular Joint Development
Neuroplasticity and the role of sensorimotor cortex in control of orofacial funct
Mechanisms of Secondary Cartilage Induction and Maintenance in the Jaw
Endogenous stem cells in jaw joint cartilage and ligament regeneration

Effect of COMT genetic polymorphisms on response to propranolol therapy in Temporomandibular Disorder
The Temporomandibular Disc: Biology and Regeneration
Mechanism of BMP2 regulation of Mandibular Condylar Cartilage Growth

TMD research greatly lagging in molecular genomic fields.
Number of publications listed in PubMed (March 2019) indicating 'omic' research in TMD/TMJ research compared to cardiovascular, kidney and pain.

	Cardiovascular	Kidney	TMD/TMJ	Pain
genomics"	8232	4387	65	1050
proteomics"	3500	2288	32	444
metabolomics"	1425	917	2	241
epigenome"	247	97	0	20
biome"	1015	760	9	276
	14,419	8449	108	2013

Disconnect between Dental and Medical School Basic and Translational Research *

1. Generally there remains paltry basic research collaborations with Dental and Medical School researchers.

2. NIDCR funding for TMD related basic research is very limited even in the top 5 research ranked Dental Schools.

3. Aggressive efforts to stimulate an integrated approach to study TMD are lacking. The science and funding siloes represent a great impediment to progress in this field.

4. Little evidence of efforts to comprehensively integrate cell/tissue specific functions with those of the whole organism.

* Based on NIH grant titles and self-reported data from University web-sites.

Blue Ridge Institute for Medical Research (BRIMR.ORG)

3X more Medical Schools with 70 X more funded research.

US Medical Schools (n=147):	$14,328,627,745	(updated Feb 2019)
US Dental Schools (n=51):	$202,866,311	(updated Feb 2019)

- Far fewer Dental School faculty with NIH funded research.
- TMD is not a priority of Dental School research.
- NIH wide funding for TMD related basic research is difficult to obtain since reporting is not broken down in this manner.

Summary of Gaps & Needs for TMD Basic Science

- It is necessary to extend TMD basic and translational research beyond the narrow province of dentistry to include the basic scientific and clinical disciplines needed to study this complex disorder.

- Basic research in Dental Schools would greatly benefit from collaborations with Medical School faculty, Schools of Bioengineering, Pharmacy School, and related shared core facilities.

- Advances in the basic sciences related to TMD need to be coordinated via a trans-Institute/Agency research planning group to set goals based on exciting scientific and clinical missions that will attract basic, clinical, translational scientists and engineers to the field.

Summary of Gaps & Needs for TMD Basic Science

- Patients expertise should be sought to identify and help focus broad research areas of greatest relevance to them.

- Every aspect of basic and clinical TMD research needs a significant increase of funding to attract scientists from those disciplines essential to develop teams of experts to address the obvious gaps in this field.

Biggest gap: Lack of integration of knowledge from cell to organism.