

Revisiting inflammation: non-communicable disease and the wound healing process

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Introduction

- Non Communicable diseases (**NCDs**) include cancers and autoimmune maladies and have represented a **silent pandemic** long before the dramatic rise of covid-19.
- NCDs are well known to be characterized by **chronic inflammation** & **altered wound healing**,
- yet medical approaches leverage only on the former, with virtually no attention to the latter.
- Wound healing can be elicited by a number of **physical (i.e. non-pharmacological) stimuli**
- Investigation of the tight interaction of the role of wound healing in a broader inflammatory perspective may offer **additional entry points to treat and prevent** the progression of such **maladies**.

Synopsys

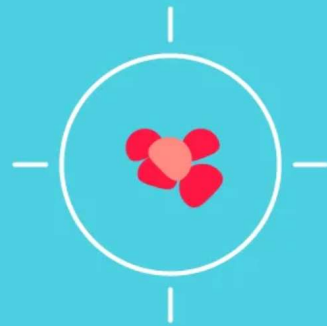
- **Introduction:**
 - Rheumatoid arthritis as a model
 - Wound healing (WH)
- **WH's dual nature (local/systemic)**
 - Animal Study
 - Human Pilot Study
- **Hypothesis: WH as a therapeutic act**
 - A molecular standpoint
 - An anthropological standpoint
- **Perspective**
 - 3d fast track
 - Greater inflammatory

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Rheumatoid arthritis: Model for chronic inflammatory diseases

Rheumatoid Arthritis (RA)

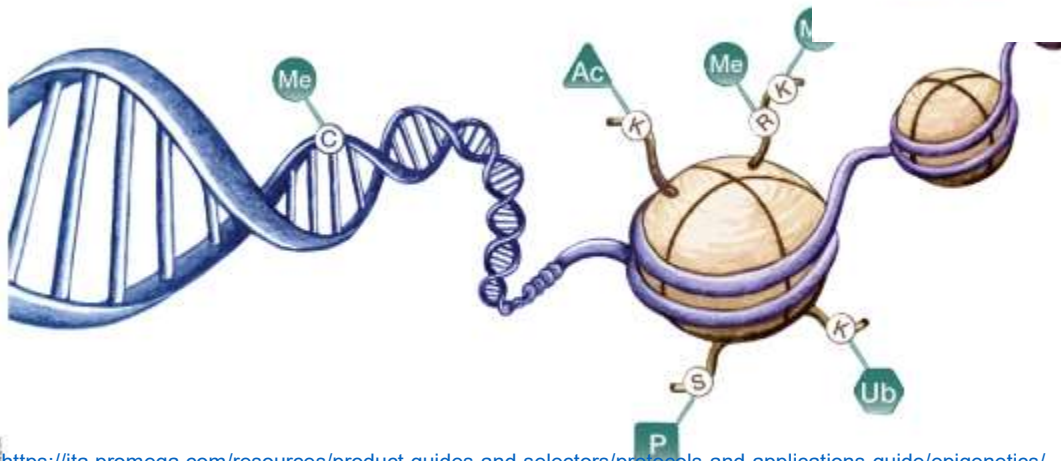
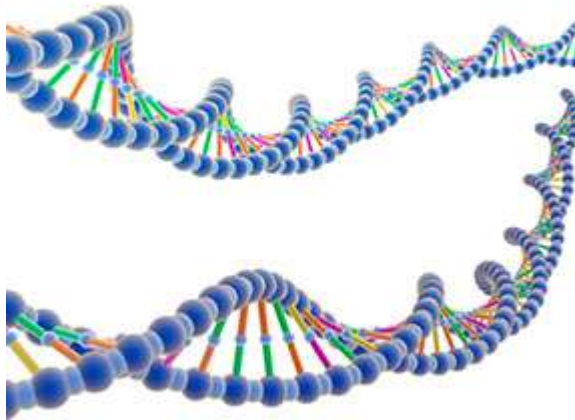


An autoimmune disease that attacks tissues near joints and other body parts.



RA causes chronic **swelling and pain** that is sometimes severe.

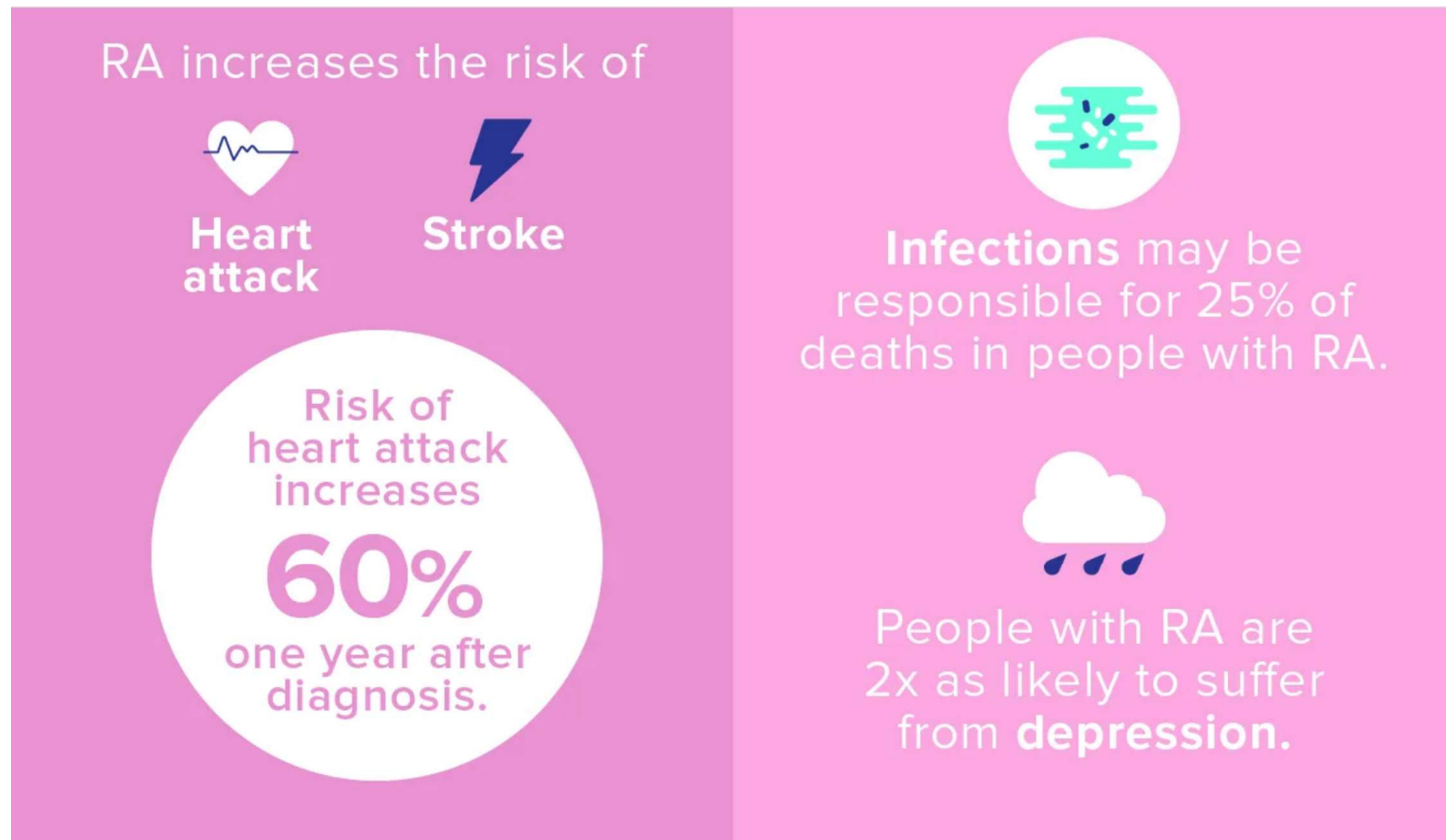
Genetic, epigenetic, metagenetic, environmental



<https://ita.promega.com/resources/product-guides-and-selectors/protocols-and-applications-guide/epigenetics/>

<https://noticias.medsbla.com/noticias-medicas/cirugia-general-y-del-aparato-digestivo/el-deterioro-del-sistema-inmune-se-asocia-a-disbiosis-intestinal/>

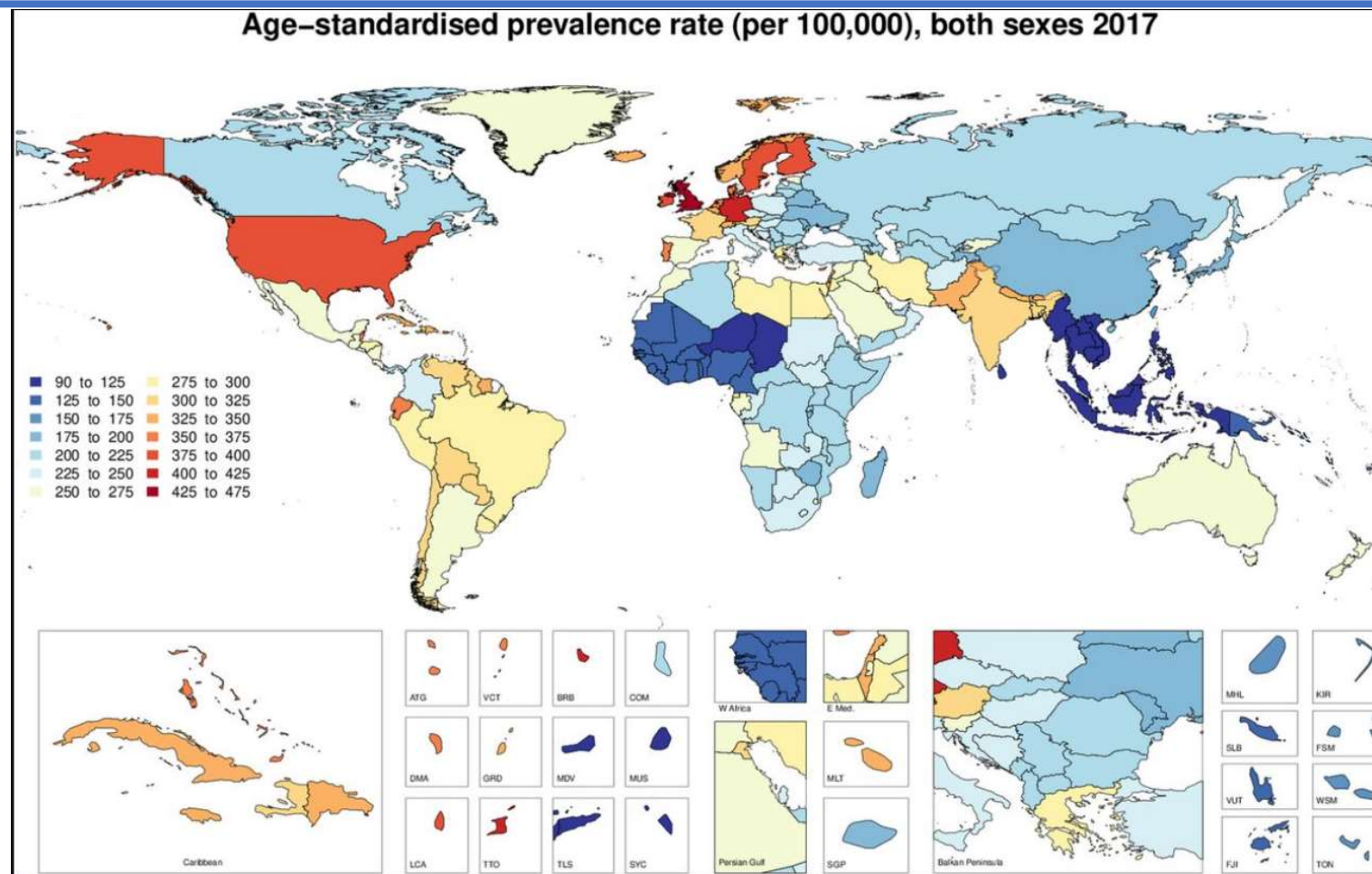
Rheumatoid arthritis: Model for chronic inflammatory diseases



Rheumatoid arthritis: Model for chronic inflammatory diseases



Rheumatoid arthritis: Model for chronic inflammatory diseases



Rheumatoid arthritis: Model for chronic inflammatory diseases



Drugs that treat RA include:

NSAIDs

DMARDs

Biologic DMARDs

Rheumatoid arthritis: Model for chronic inflammatory diseases



Drugs that treat RA include:
NSAIDs

Nonsteroidal anti-inflammatory drugs (NSAIDs), the mildest class of medications, primarily work to reduce pain by reducing inflammation, but don't effect the progression of RA.

Corticosteroids more powerfully work to quickly decrease inflammation, and are ideally for short-term usage.

Rheumatoid arthritis: Model for chronic inflammatory diseases



Drugs that treat RA include:

NSAIDs
DMARDs

Disease-modifying antirheumatic drugs (DMARDs), the most standard RA treatment, work to slow down the progression of RA, but may cause moderate to severe side effects.

Rheumatoid arthritis: Model for chronic inflammatory diseases



Drugs that treat RA include:

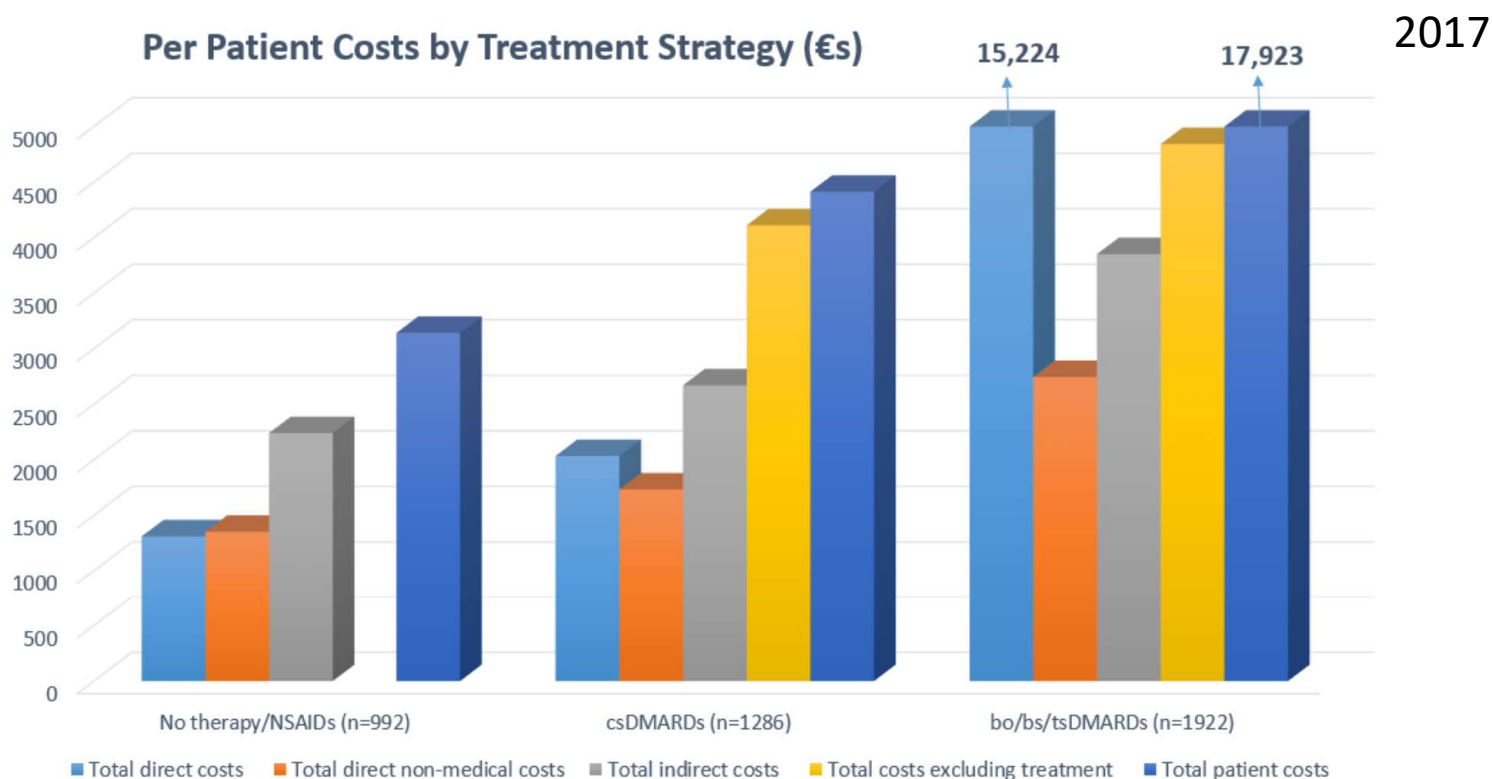
NSAIDs

DMARDs

Biologic DMARDs

Biologic response modifiers (biologic DMARDs), often used in combination with DMARDs, work to modify immune systems that have trouble responding to DMARDs.

Rheumatoid arthritis: Model for chronic inflammatory diseases



Treatment groups: No therapy or NSAIDs only (+/- steroids), Conventional synthetic DMARD(s) (+/- steroids), Biologic, biosimilar or targeted synthetic DMARD (+/- steroids, csDMARDs, NSAIDs)

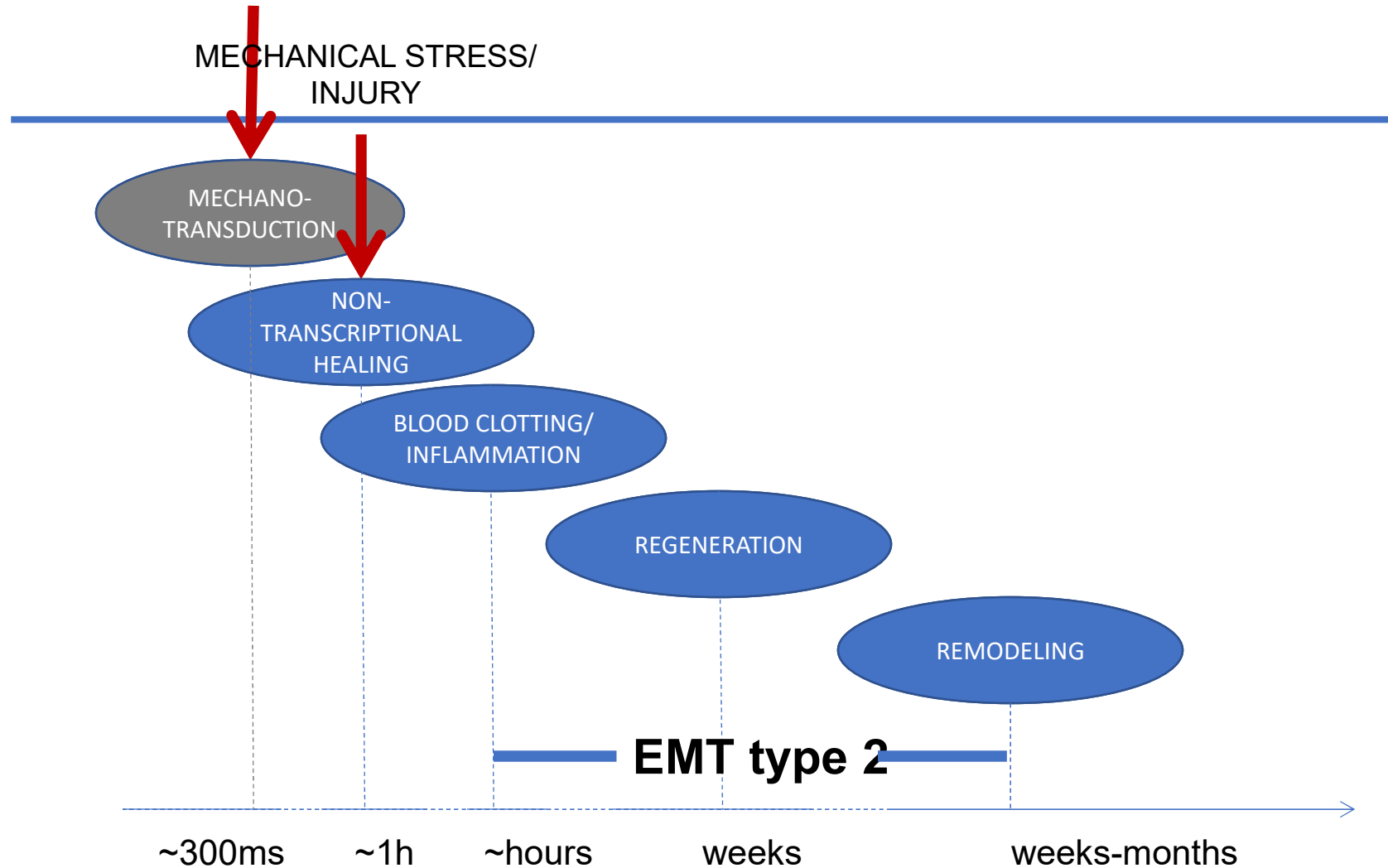
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WOUND HEALING – Evolution over time

TORSIONAL MECHANICAL STRESS

Langevin et al., 2010



A



Na et al.,
PNAS, 2008

Cordeiro et al.,
NATURE, 2011

NATURE

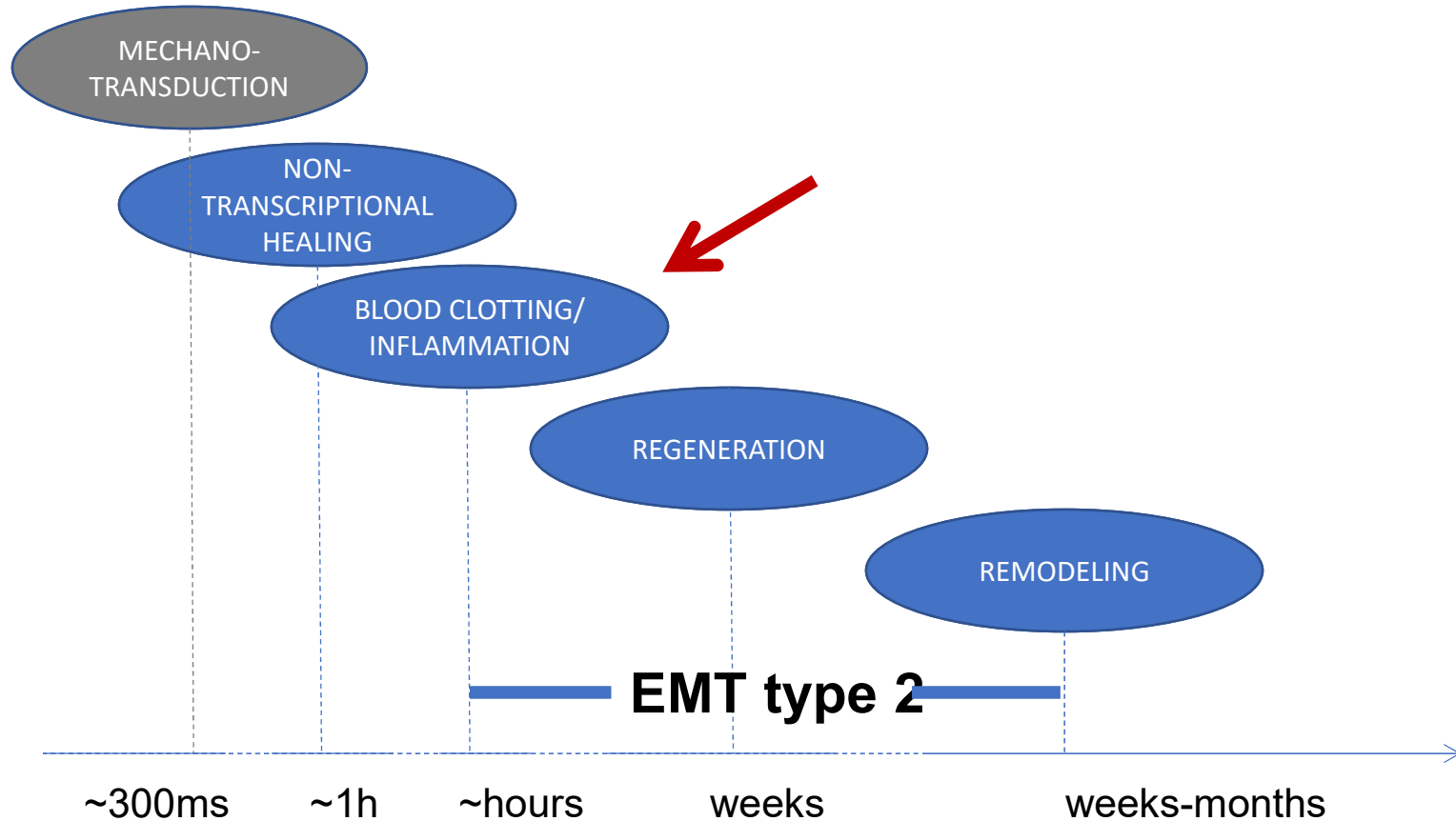


WOUND HEALING – Evolution over time

TORSIONAL MECHANICAL STRESS

Langevin et al., 2010

MECHANICAL STRESS/
INJURY



A



Na et al.,
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Cordeiro et al.,
NATURE, 2011

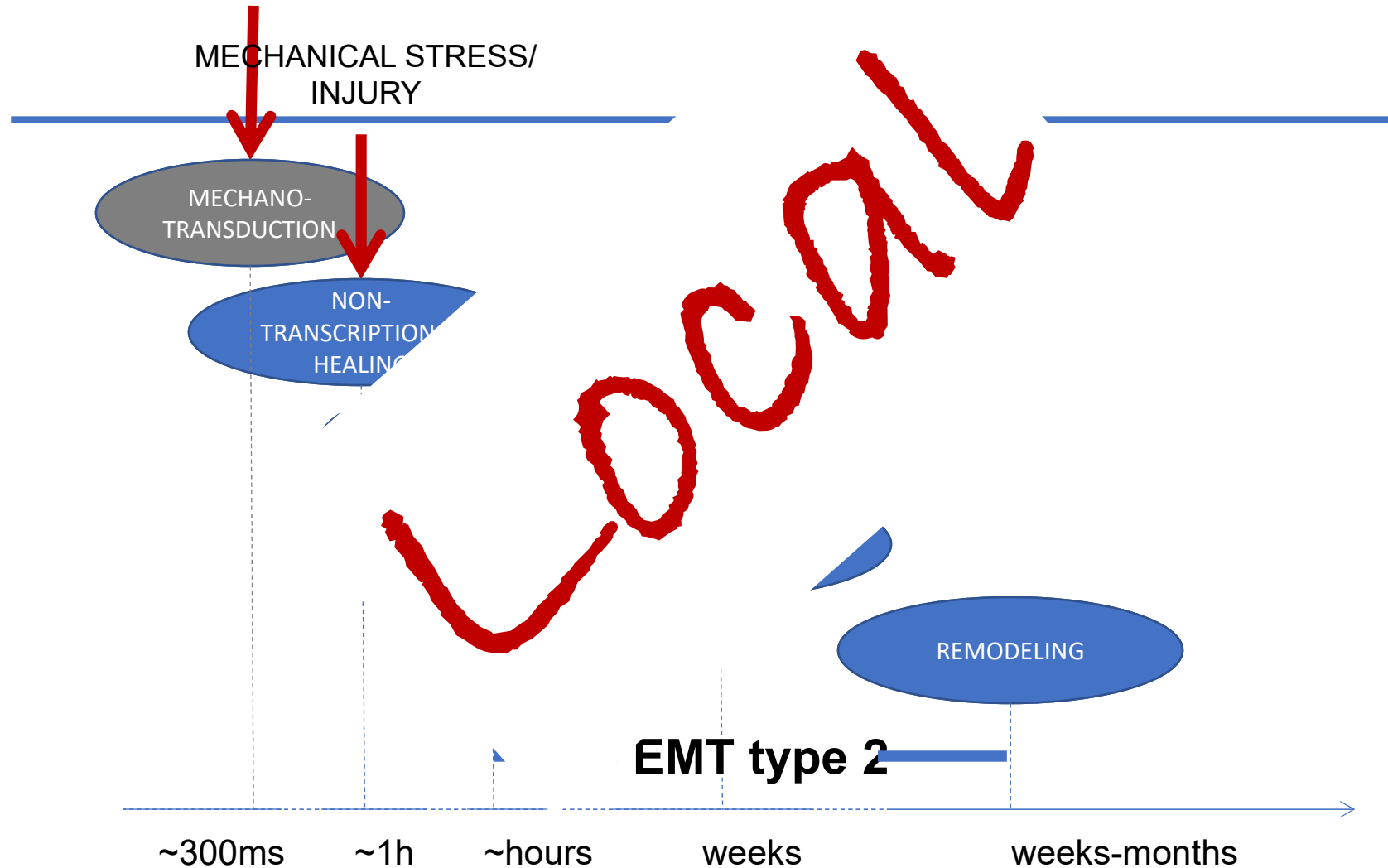
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Animal models

Experiments



Blood



Tissue



Feces

Prot



miRNA



mRNA



DNA



Original Aim:

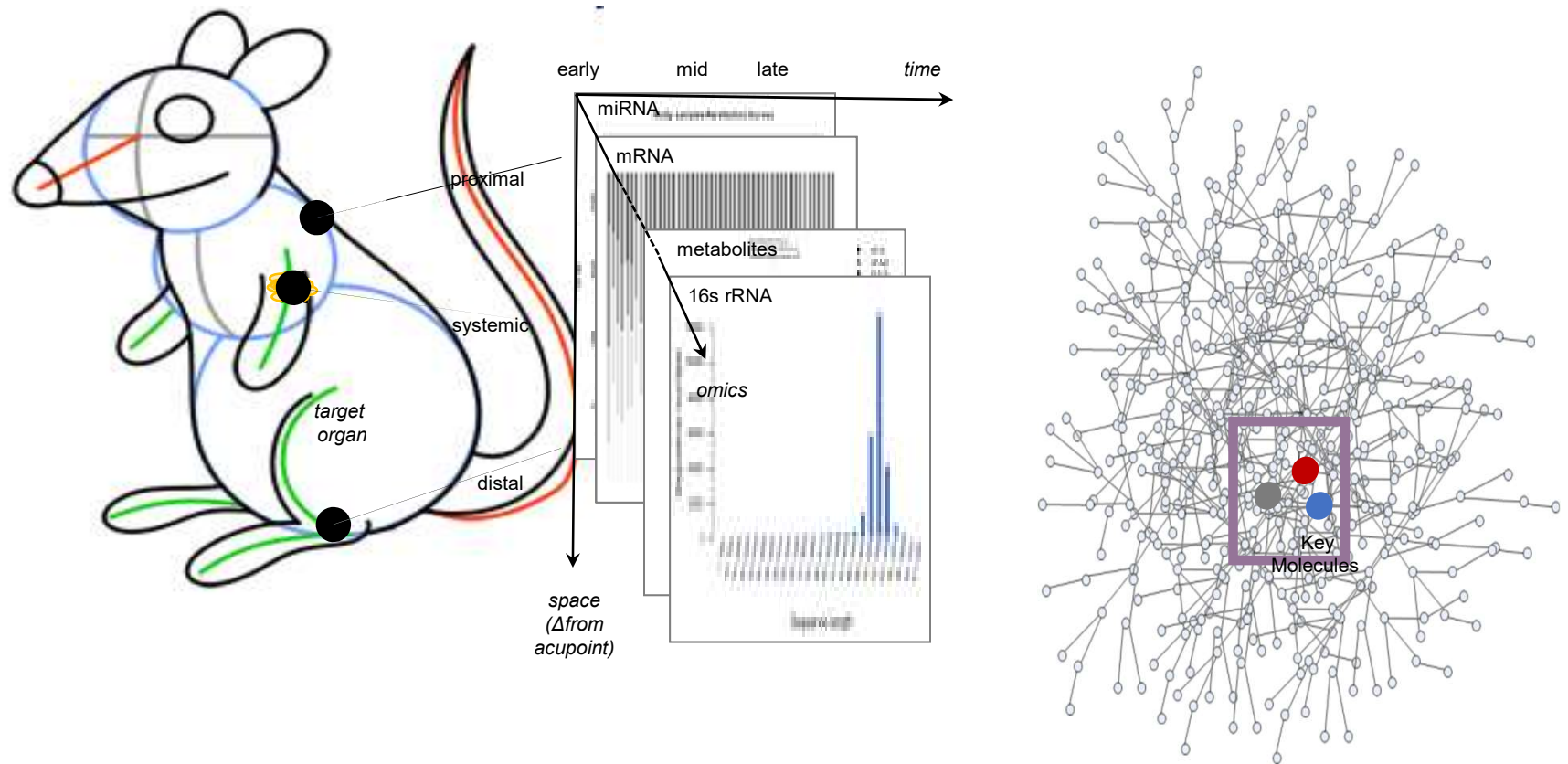
Assess and explore the systemic response of a local mechanical stimulation (MS)

Design:

- Study design: winstar rats, CIA, 4 arms
- 2 active arms: MS; DMARDs
- 2 control arms: placebo DMARDs; anesthetic control
- 1 supercontrol: no induction, no treatment

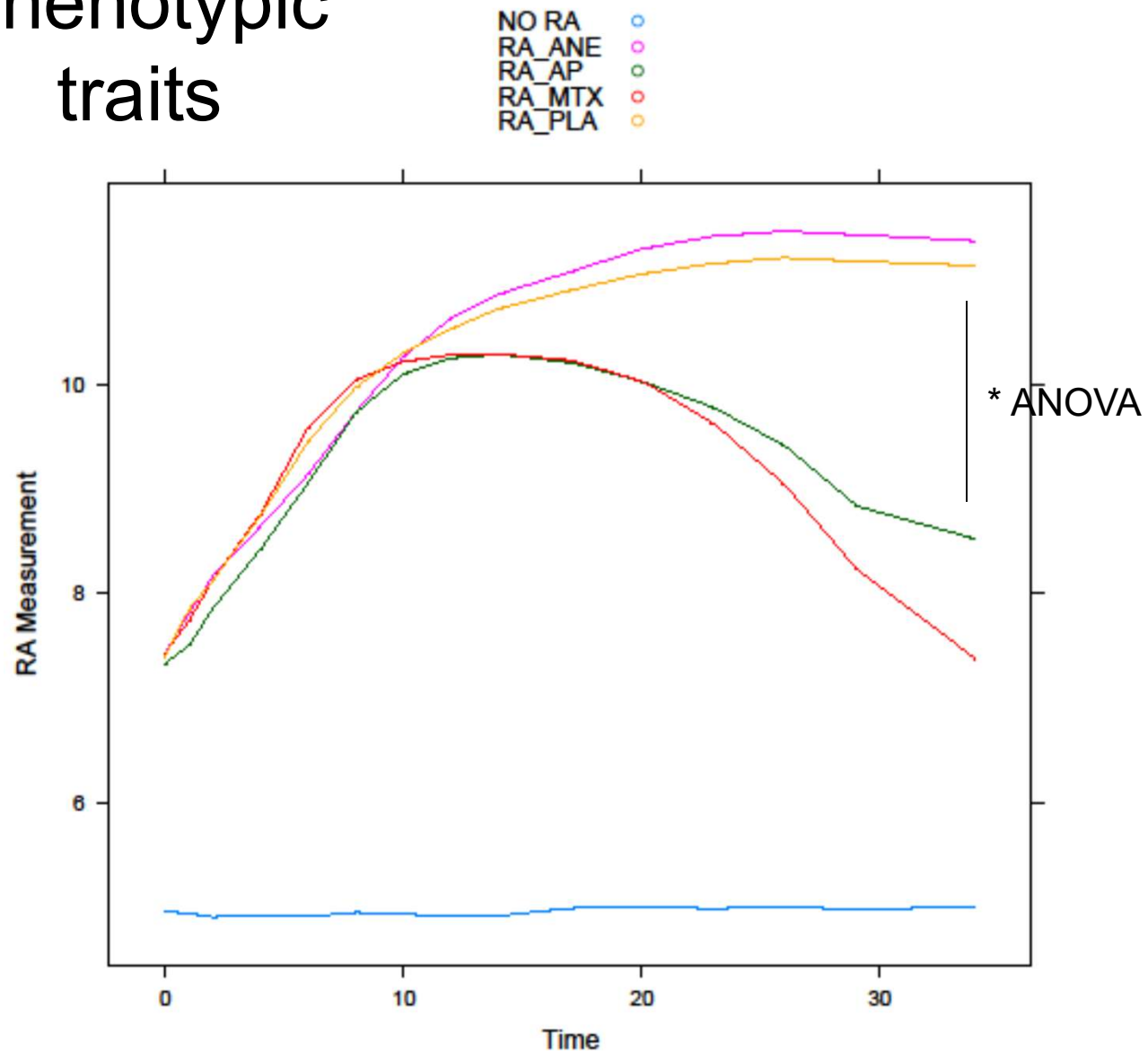
Spatio-temporal resolution

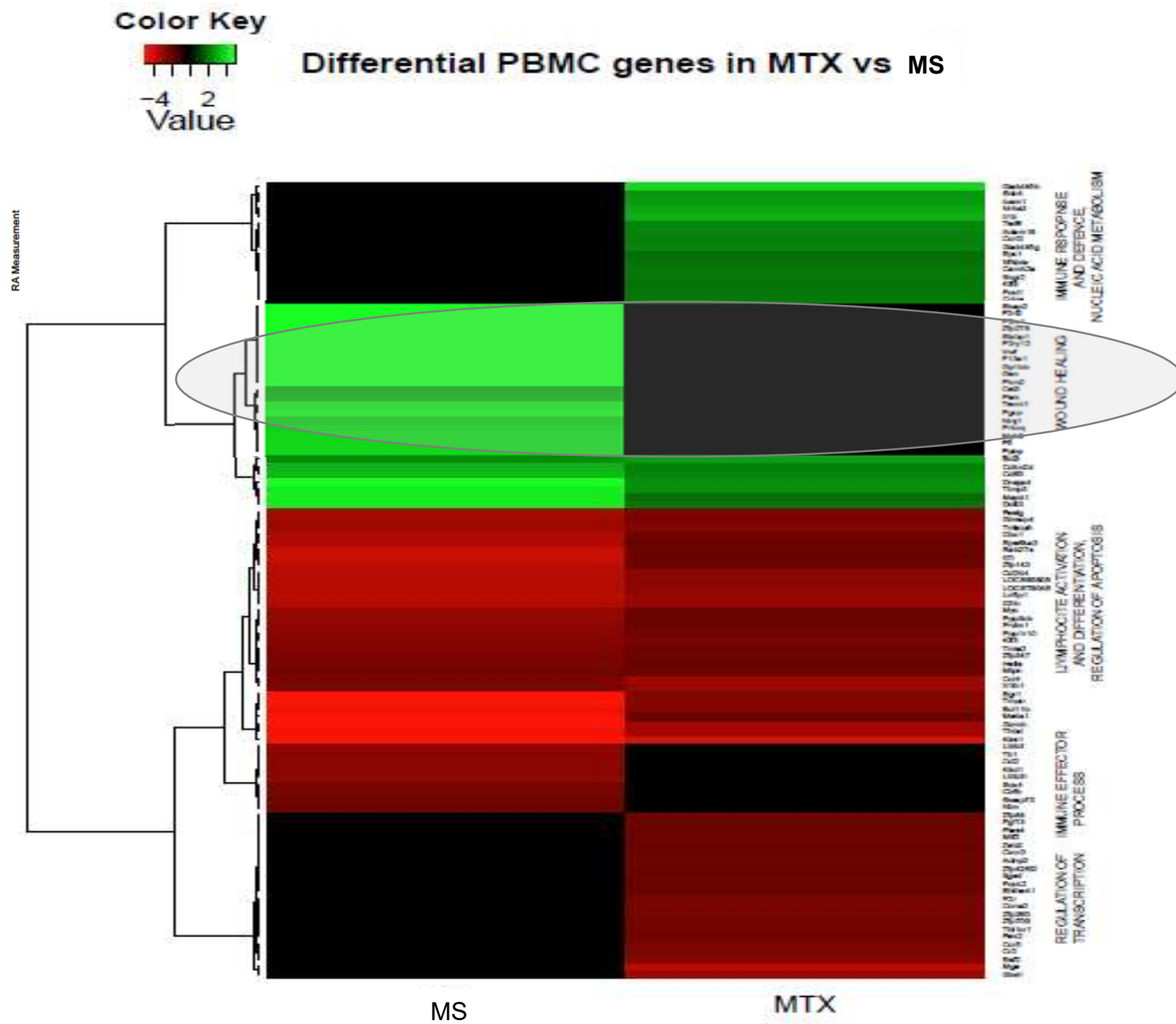
limited *a priori*: omics



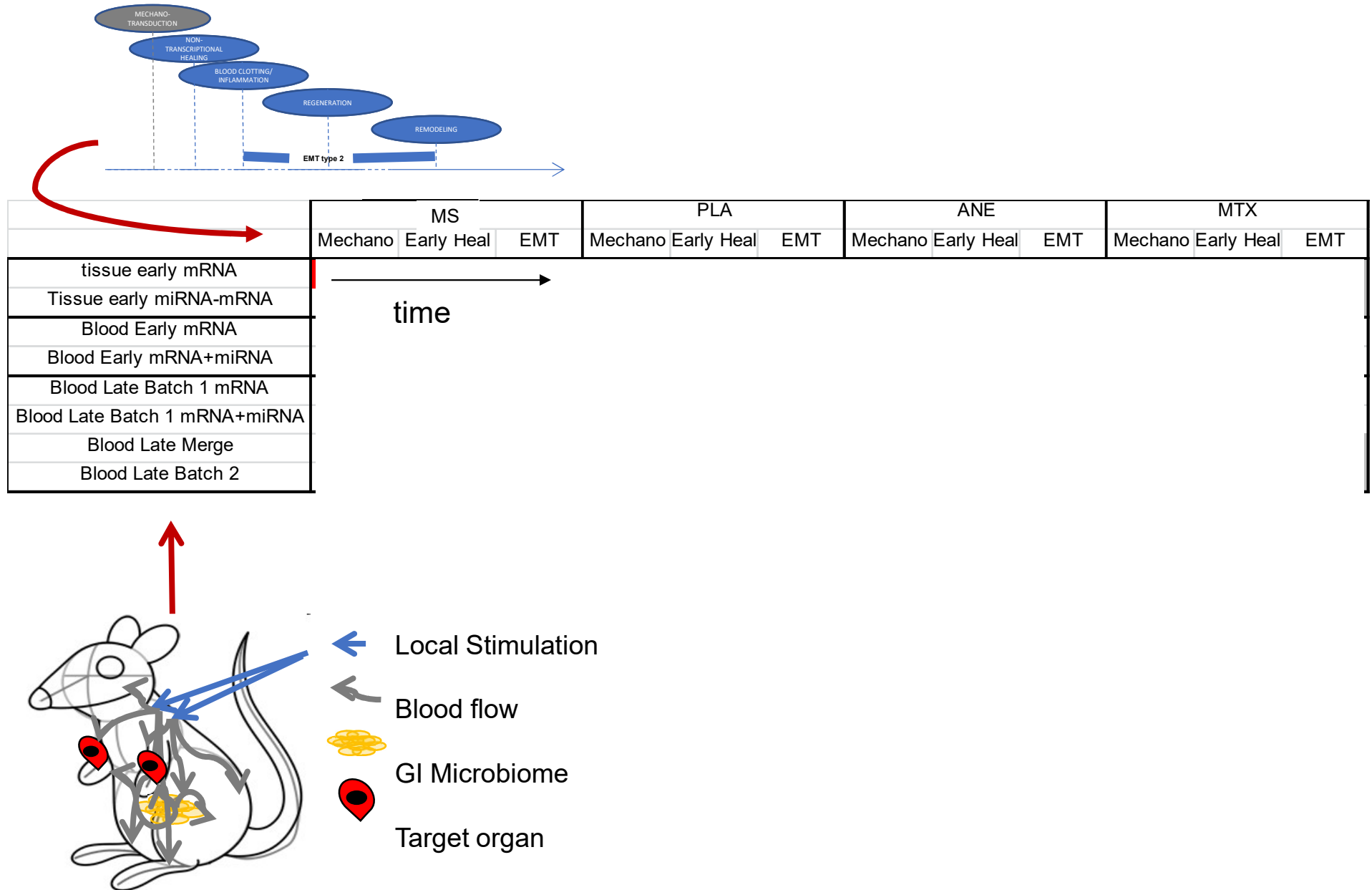
C. Nardini, et al., Science 346 (6216 Suppl), S21-S22 (2014).

Phenotypic traits

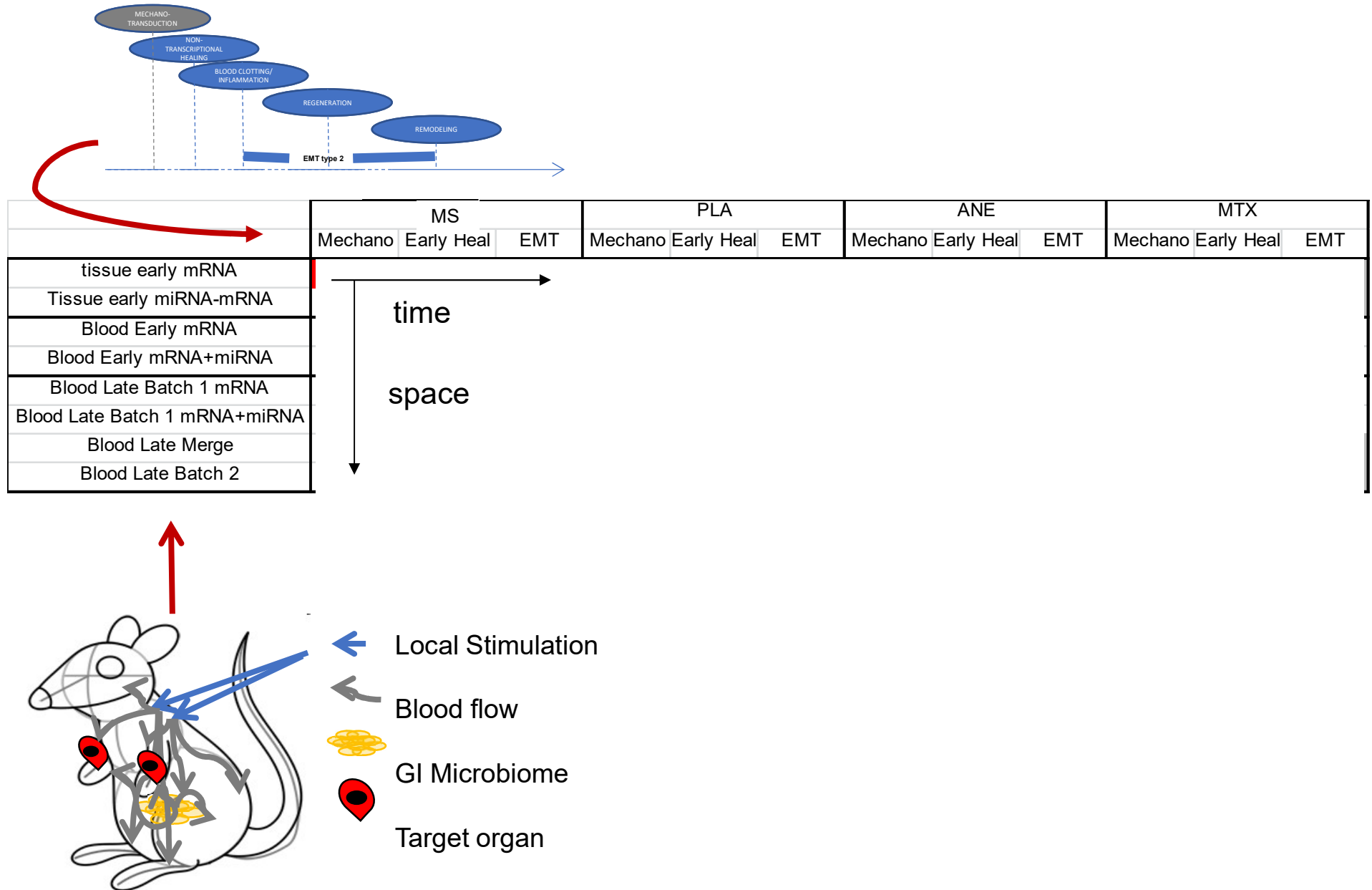




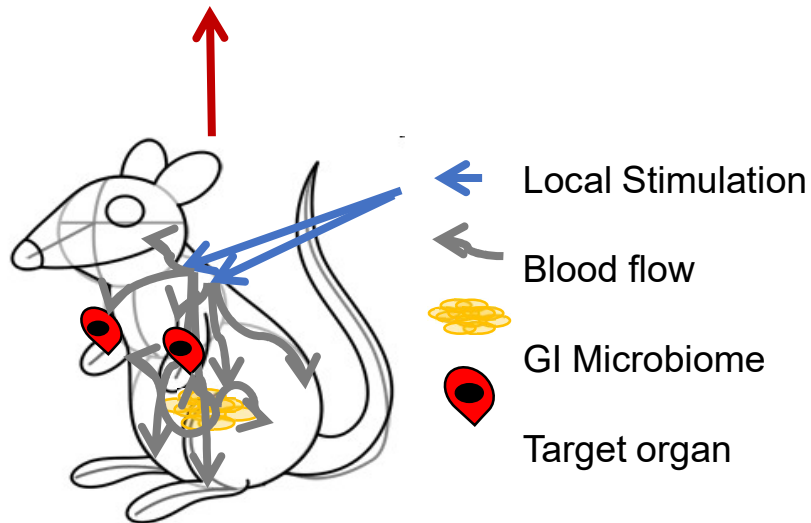
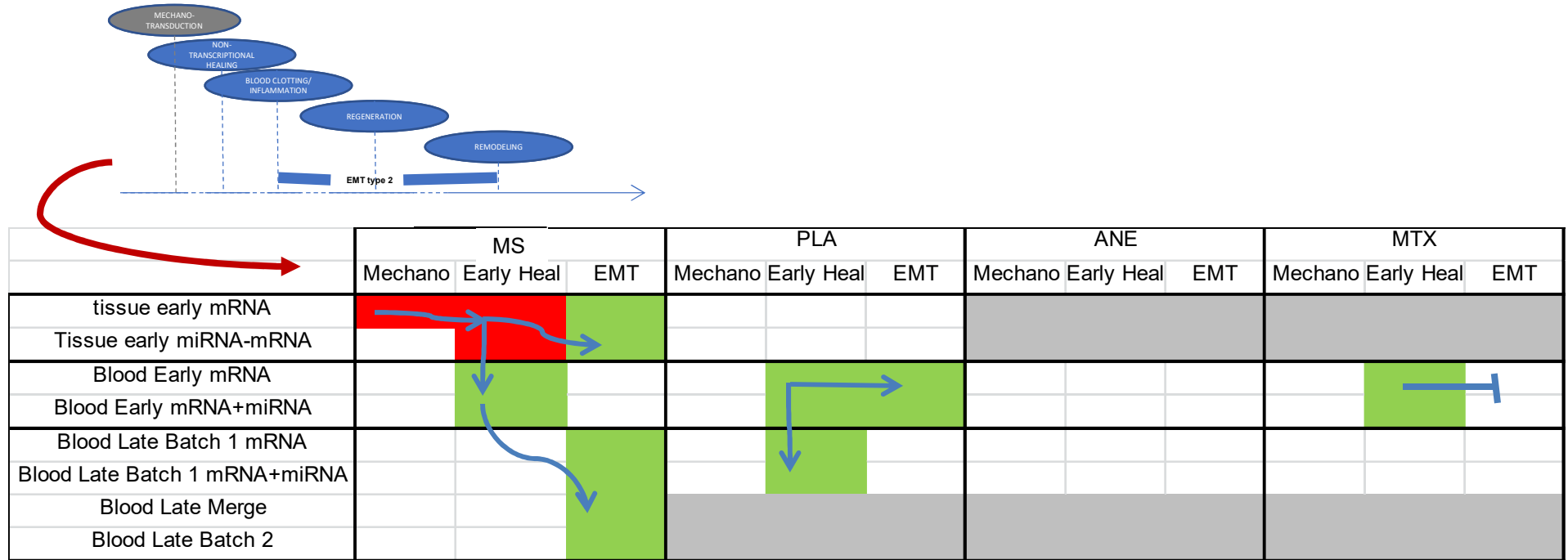
Molecular Signaling Spatio-Temporal Deconvolution

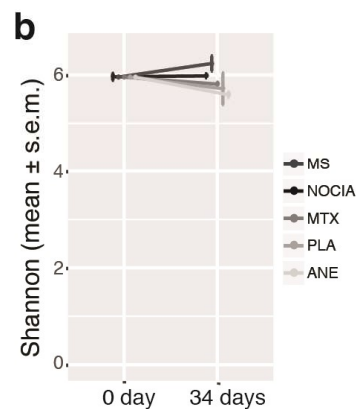
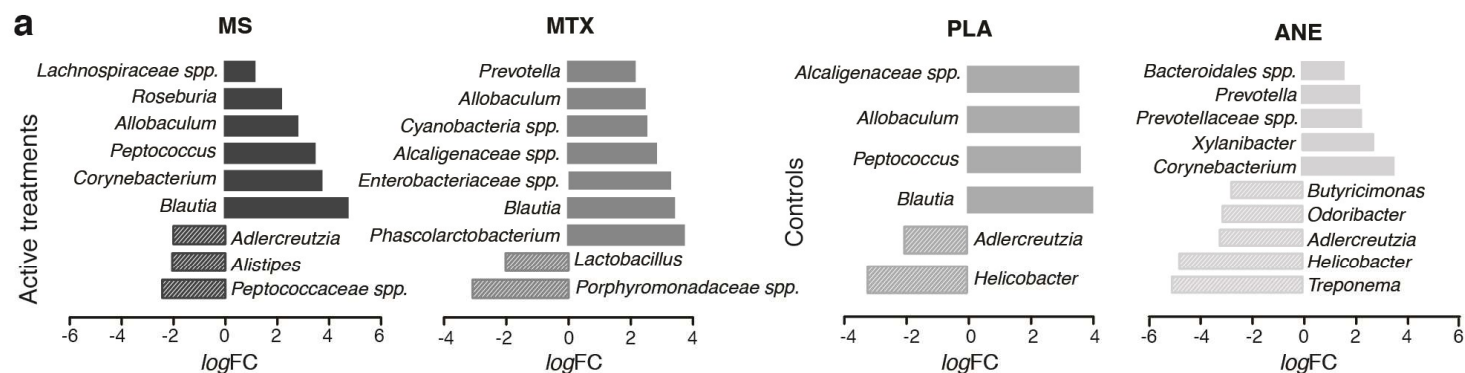
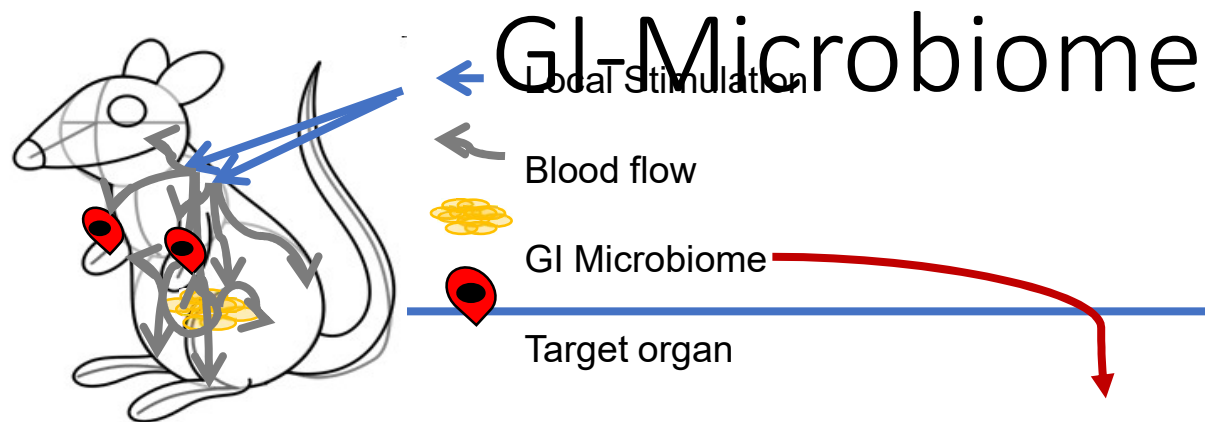


Molecular Signaling Spatio-Temporal Deconvolution



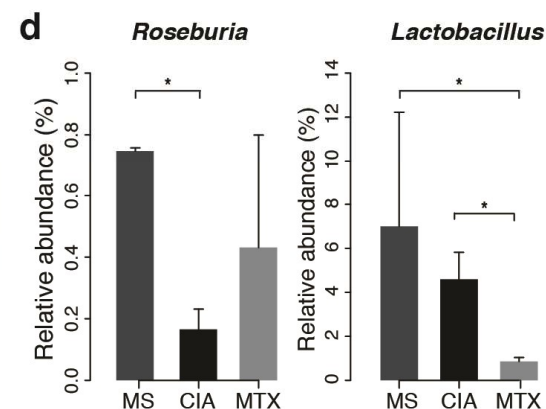
Molecular Signaling Spatio-Temporal Deconvolution





c

P values	MS	MTX	PLA	ANE	NOCIA
MS		1.21E-80	0.673	3.14E-06	3.66E-12
MTX	1		1	1	0.42
PLA	0.456	3.17E-52		1.94E-05	1.54E-11
ANE	1	7.95E-19	1		2.13E-05
NOCIA	1	0.721	1	1	



Host-microbiome interaction



MS Distinctive Mechanism: WOUND HEALING

over time

TORSIONAL MECHANICAL STRESS
Langevin et al., 2010

MECHANICAL STRESS/
INJURY

MECHANO-
TRANSDUCTION

NON-
TRANSCRIPTION
HEALING

Mole

relation

LOW

GI Microbiome

Target organ

B

REMODELING

EMT type 2

hours

weeks

weeks-months

A



Nature
PNAS,

Jeiro et al.,
NATURE, 2011

NATURE



SYSTEMIC

SCIENTIFIC REPORTS

OPEN

***Systemic* Wound Healing Associated with *local* sub-Cutaneous Mechanical Stimulation**

Received: 14 June 2016
Accepted: 17 November 2016

Christine Nardini^{1,2,*}, Valentina Devescovi^{1,*}, Yuanhua Liu^{1,3,*}, Xiaoyuan Zhou^{1,*}, Youtao Lu^{1,*}
& Jennifer E. Dent^{1,4,*}

Review | [Open Access](#) | Published: 03 March 2017

Impaired wound healing: facts and hypotheses for multi-professional considerations in predictive, preventive and personalised medicine

[Eden Avishai](#), [Kristina Yeghiazaryan](#) & [Olga Golubnitschaja](#) 

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Wound Healing Associated with sub-Cutaneous Electrical Stimulation

[Martina Devescovi](#)^{1,*}, [Yuanhua Liu](#)^{1,3,*}, [Xiaoyuan Zhou](#)^{1,*}, [Youtao Lu](#)^{1,*}

Synopsys

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In addition to Pharmacology?

- Non-pharmacological / biologic-free approaches

In addition to Pharmacology?

- Non-pharmacological / biologic-free approaches
- Example of biologic free approach:
 - FMT (fecal microbiota transplant):
 - used to successfully treat recurrent *Clostridium difficile* infection.
 - Studies on IBD (inflammatory bowel disease)

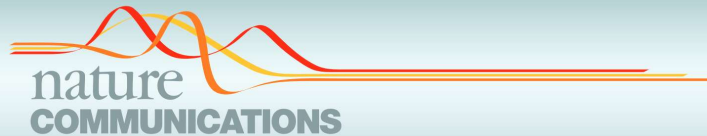
In addition to Pharmacology?

- Non-pharmacological / biologic-free approaches

- Examples

- FMT

- u
 - S





ARTICLE



<https://doi.org/10.1038/s41467-020-17180-x>

OPEN

An ecological framework to understand the efficacy of fecal microbiota transplantation

Yandong Xiao^{1,2}, Marco Tulio Angulo ^{3,4}, Songyang Lao¹, Scott T. Weiss² & Yang-Yu Liu ^{2,5}✉

In addition to pharmacology?

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- Example of biologic free approach:
 - FMT (fecal microbiota transplant):
 - used to successfully treat recurrent *Clostridium difficile* infection.
 - Studies on IBD (inflammatory bowel disease)->autoimmune
- Example of non-pharmacological approaches:

Exploitation of Mechano-transduction -repair

- Non-pharmacological approaches

- Examples

- FMT

- us

- St



Biologic-free mechanically induced muscle regeneration

Christine A. Cezar^{a,b}, Ellen T. Roche^{a,b}, Herman H. Vandenburg^c, Georg N. Duda^{d,e}, Conor J. Walsh^{a,b}, and David J. Mooney^{a,b,1}

^aSchool of Engineering and Applied Sciences, Harvard University, Cambridge, MA 02138; ^bWyss Institute for Biologically Inspired Engineering, Cambridge, MA 02138; ^cDepartment of Pathology and Lab Medicine, Brown University, Providence, RI 02912; ^dJulius Wolff Institute, Charité-Universitätsmedizin Berlin, 13353 Berlin, Germany; and ^eBerlin-Brandenburg Center for Regenerative Therapies, 13353 Berlin, Germany

Edited by Robert Langer, Massachusetts Institute of Technology, Cambridge, MA, and approved December 22, 2015 (received for review September 2, 2015)

Exploitation of sympathetic nervous circuits -inflammation

- No
- Exa
-

PNAS



Vagus nerve stimulation inhibits cytokine production and attenuates disease severity in rheumatoid arthritis

Frieda A. Koopman^a, Sangeeta S. Chavan^b, Sanda Miljko^c, Simeon Grazio^d, Sekib Sokolovic^e, P. Richard Schuurman^f, Ashesh D. Mehta^g, Yaakov A. Levine^h, Michael Faltys^h, Ralph Zitnik^h, Kevin J. Tracey^b, and Paul P. Tak^{a,1,2,3,4}

^aAmsterdam Rheumatology and Immunology Center, Department of Clinical Immunology and Rheumatology, Academic Medical Center, University of Amsterdam, 1105 AZ Amsterdam, The Netherlands; ^bLaboratory of Biomedical Science, Feinstein Institute for Medical Research, Manhasset, NY 11030; ^cUniversity Clinical Hospital, Mostar 88000, Bosnia and Herzegovina; ^dClinical Hospital Center Sestre Milosrdnice, Zagreb 10000, Croatia; ^eSarajevo University Clinical Center, Sarajevo 71000, Bosnia and Herzegovina; ^fDepartment of Neurosurgery, Academic Medical Center, University of Amsterdam, 1105 AZ Amsterdam, The Netherlands; ^gDepartment of Neurosurgery, Hofstra Northwell School of Medicine, Manhasset, NY 11030; and ^hSetPoint Medical Corporation, Valencia, CA 91355

Edited by Ruslan Medzhitov, Yale University School of Medicine, New Haven, CT, and approved June 1, 2016 (received for review April 18, 2016)

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Can we reframe non-pharmacological therapies as means to elicit WH?

1. TENS, Laser therapy, ultrasound, VIN, exploits as many electrical, optical, mechanical and thermal stimulations recollecting the panel of means used for WH assays*
2. The rationale for such therapies is very weak although observation on cytokines control accompany the rare attempts to explore the effectiveness relegating often these to palliative, complementary or alternative cures
3. Reading this in the light of WH enable an organic/systemic understanding of the phenomenon
4. Takes into account the dual nature of WH (local systemic)
5. Takes into account the potential (therapeutic vs physiologic) of the function

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A Social Human Science (SHS) standpoint

- Is there a difference in the approach to non-pharmacological treatment and pharmacology?
 - Mauro Turrini science sociologist Spanish National Research Council, Madrid, ES
 - Lucia Candelise anthropologist and historian of medicine University of Lausanne, CH

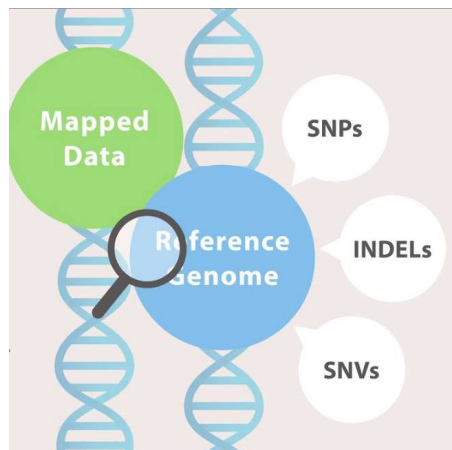
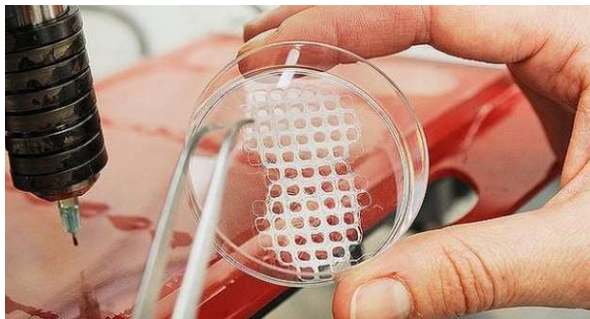
A Social Human Science (SHS) standpoint

MeSH	Search Query	Publications (Total)
Pharmacological Approach		
	Drug Therapy	1311 (("Arthritis, Rheumatoid/therapy"[Mesh]) AND "Review" [Publica
	anti inflammatory agents: S	1294 (((("Arthritis, Rheumatoid/therapy"[Mesh]) AND "Review" [Publica
	Anti inflammatory Drug The	258 (((("Arthritis, Rheumatoid/therapy"[Mesh]) AND "Review" [Publica
Autonomic nervous system		
	Vagus Nerve Stimulation	3 (("Arthritis, Rheumatoid/therapy"[Mesh]) AND "Review" [Publica
Gut Intestinal Microbiota		
	Gastrointestinal Microbiom	8 (((("Arthritis, Rheumatoid/therapy"[Mesh]) AND "Review" [Publica
	Anti-Bacterial Agents	121 (((("Arthritis, Rheumatoid/therapy"[Mesh]) AND "Review" [Publica
	Dietary Supplements (note:	49 (((("Arthritis, Rheumatoid/therapy"[Mesh]) AND "Review" [Publica
	Fecal Microbiota Transplant	0 (((("Arthritis, Rheumatoid/therapy"[Mesh]) AND "Review" [Publica
		https://clinicaltrials.gov/ct2/show/NCT03944096
Wound Healing		
	Mechanical Stimuli	
	Ultrasonic Therapy	5 (("Arthritis, Rheumatoid/therapy"[Mesh]) AND "Review" [Publica
	Massage	6 (((("Arthritis, Rheumatoid/therapy"[Mesh]) AND "Review" [Publica
	Acupuncture Therapy	22 (((("Arthritis, Rheumatoid/therapy"[Mesh]) AND "Review" [Publica
	Electrical Stimuli	
	Electric stimulation Therapy	13 (((("Arthritis, Rheumatoid/therapy"[Mesh]) AND "Review" [Publica
	Electromagnetic Stimuli	
	Electromagnetic Phenomena	5 (((("Arthritis, Rheumatoid/therapy"[Mesh]) AND "Review" [Publica
	Optical radiation	
	Laser	11 (((("Arthritis, Rheumatoid/therapy"[Mesh]) AND "Review" [Publica

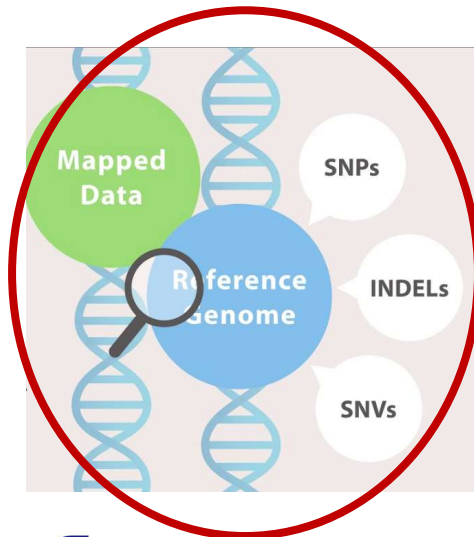
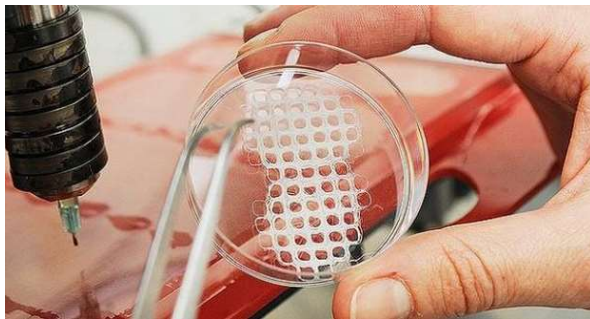
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Area Science Park & Politecnico di Torino & CNR



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Revisit the concept of inflammatory response



Review | [Published: 10 December 2019](#)

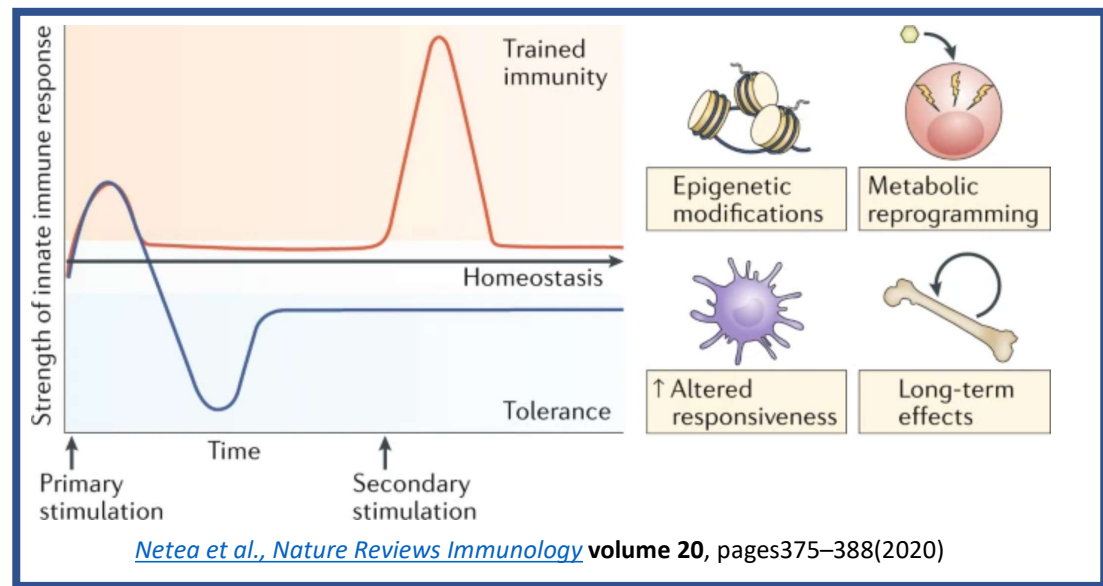
The greater inflammatory pathway—high clinical potential by innovative predictive, preventive, and personalized medical approach

[Maria Giovanna Maturo](#), [Marzia Soligo](#), [Greg Gibson](#), [Luigi Manni](#) & [Christine Nardini](#) 

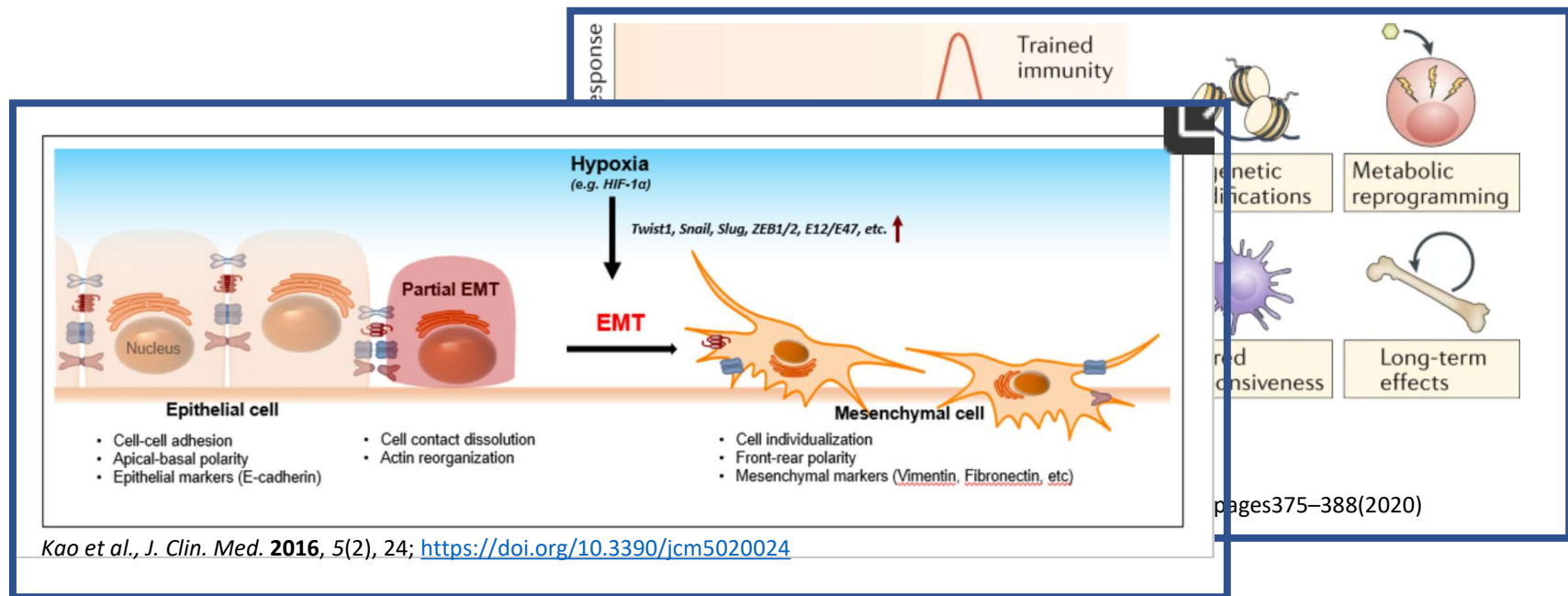
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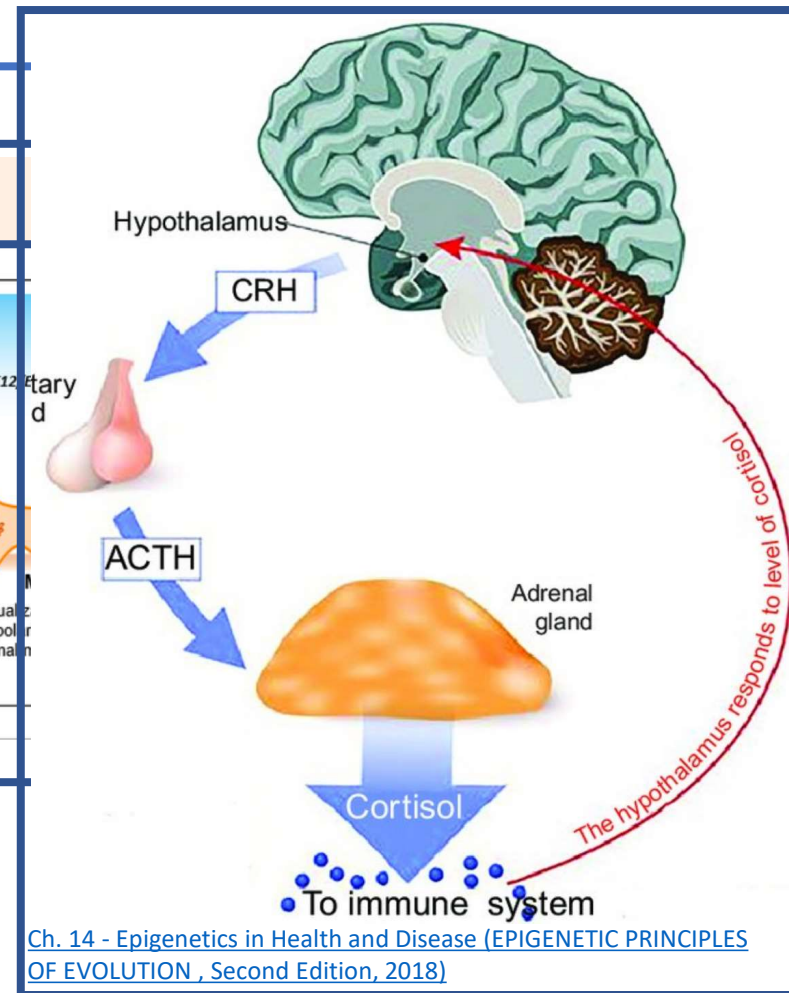
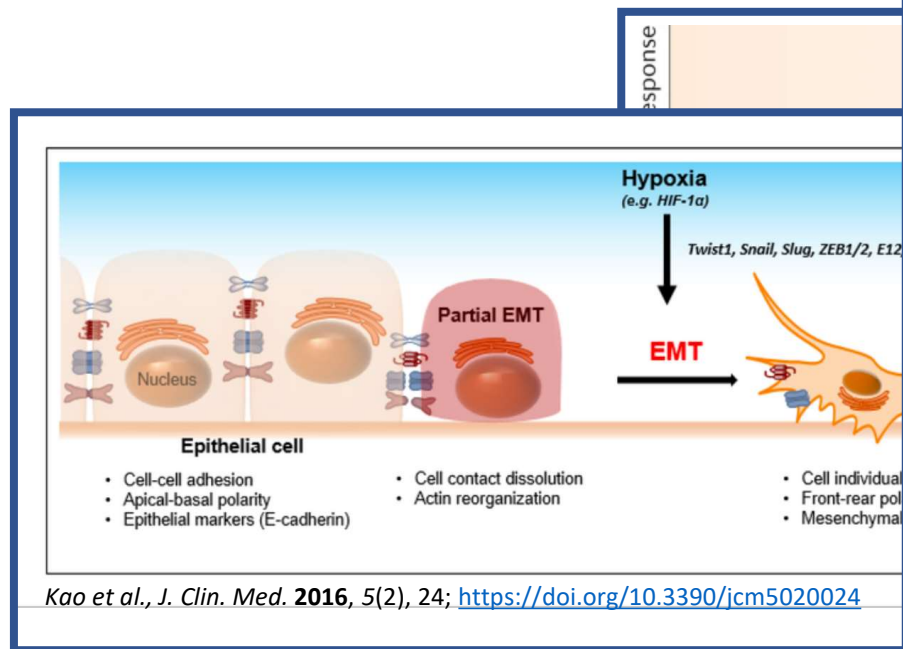
The Greater Inflammatory Pathway



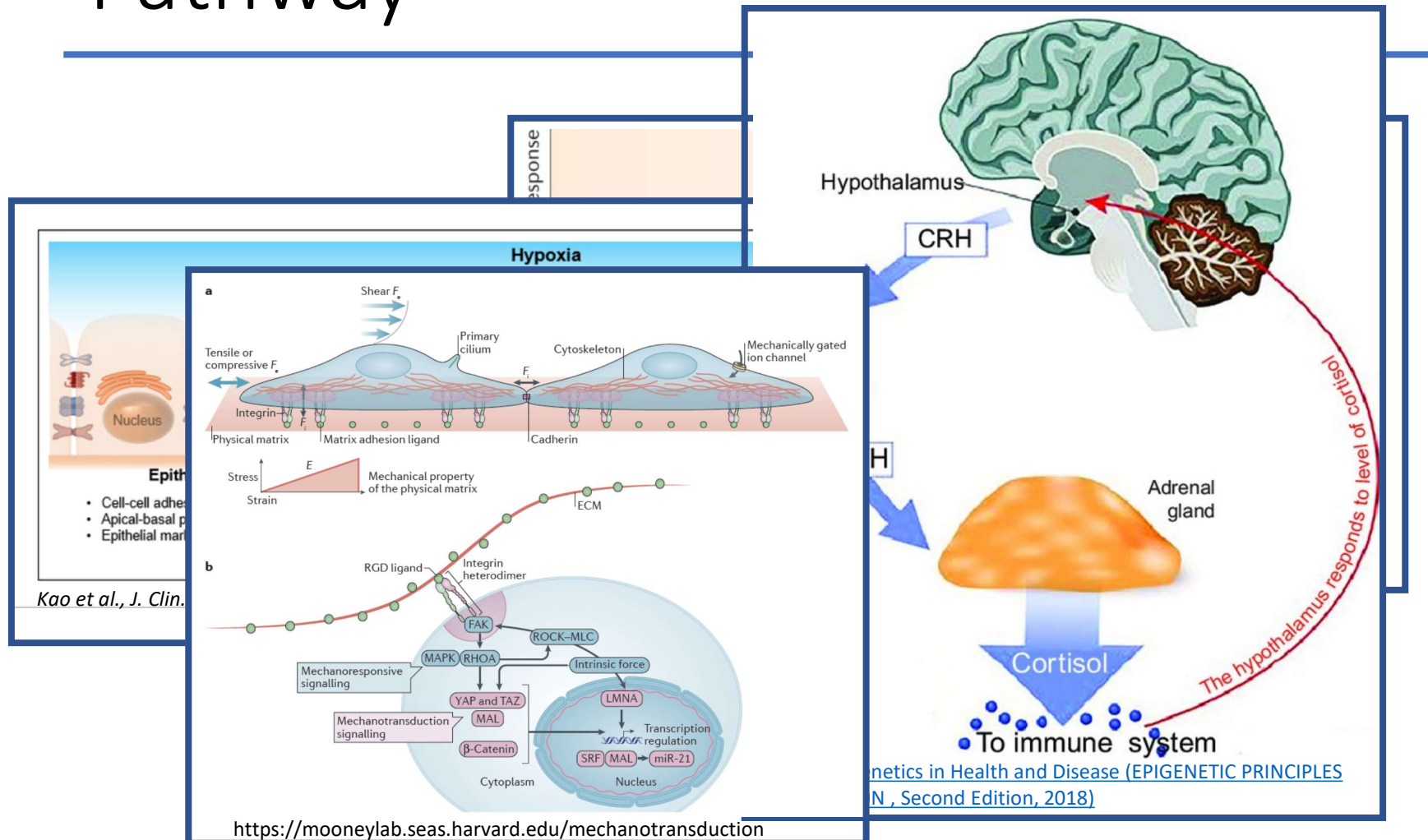
The Greater Inflammatory Pathway



The Greater Inflammatory Pathway



The Greater Inflammatory Pathway



Biological Pathways in Systems Biology

- Very often, low-level biological pathway's graphical representation are in the form of a **network**



NETWORK SCIENCE

Network

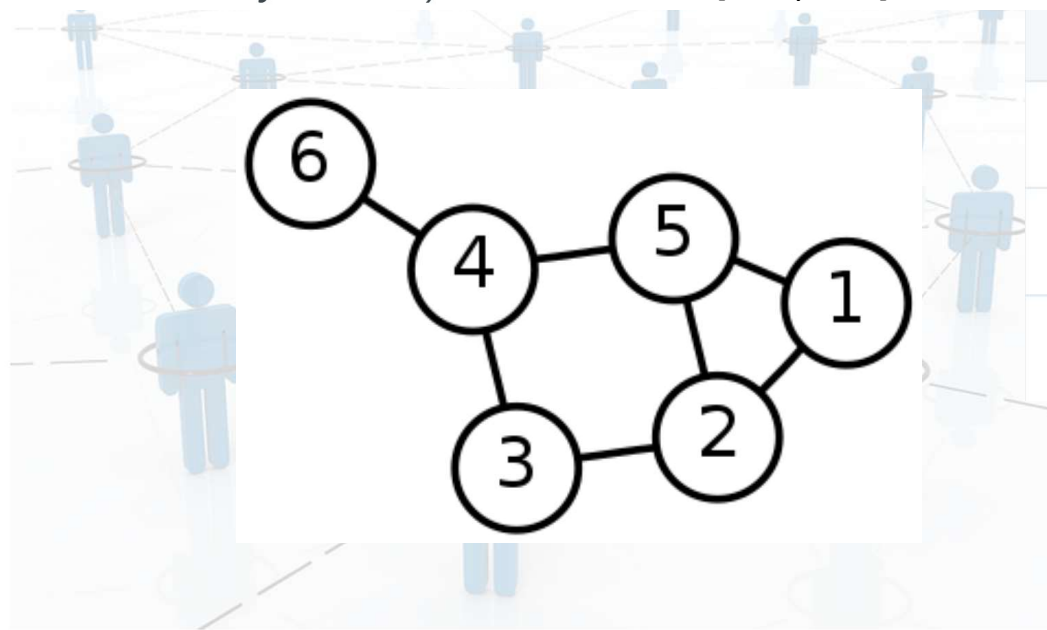
Node

Link

<https://bence.ferdinandy.com/2018/05/27/whats-the-difference-between-a-graph-and-a-network/>

Biological Pathways in Systems Biology

A graph G is an ordered pair $(V(G), E(G))$ consisting of a set $V(G)$ of vertices and a set $E(G)$, disjoint from $V(G)$, of edges, together with an incidence function Ψ_G that associates with each edge of G an unordered pair of (not necessarily distinct) vertices of G . [Wikipedia]



GRAPH THEORY	NETWORK SCIENCE
Graph	Network
Vertex	Node
Edge	Link

<https://bence.ferdinandy.com/2018/05/27/whats-the-difference-between-a-graph-and-a-network/>

Biological pathways are hypergraphs

In **mathematics**, a **hypergraph** is a generalization of a **graph** in which an **edge** can join any number of **vertices**. In contrast, in an ordinary graph, an edge connects exactly two vertices. Formally, a hypergraph H is a pair $H = (X, E)$ where X is a set of elements called *nodes* or *vertices*, and E is a set of non-empty subsets of X called *hyperedges* or *edges*. Therefore, E is a subset of $\mathcal{P}(X) \setminus \{\emptyset\}$, where $\mathcal{P}(X)$ is the **power set** of X . The size of the vertex set is called the *order of the hypergraph*, and the size of edges set is the *size of the hypergraph*.

Most common
& intuitive

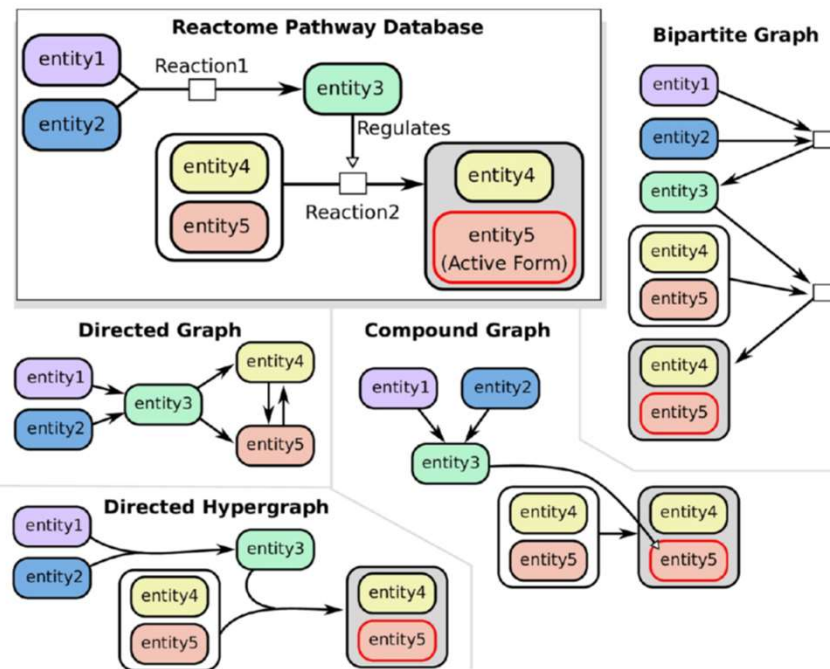
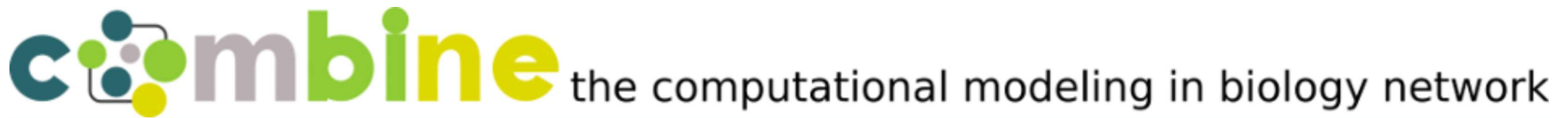


Fig 1. Representations of two toy reactions as directed graphs, compound graphs, directed hypergraphs, and bipartite graphs. In this work, we use "directed hypergraphs" and "hypergraphs" interchangeably.

<https://doi.org/10.1371/journal.pcbi.1007384.g001>

Combine

<https://co.mbine.org/standards>

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Standards covered by or related to COMBINE activities

One of the major goals of COMBINE is to improve the interoperability of existing standards, and to foster or support fledging efforts aimed at filling gaps or new needs. Below are listed some of the major community standard representation formats covered by or related to COMBINE activity.

COMBINE standards

The following standardization activities are open community efforts. The standards are described in freely available specifications, and associated tools (XML schemas, UML diagrams etc.). They are piloted by democratically elected editorial boards, sometimes assisted by scientific committees. A decent software support exist, including API implementations. The development is supported by central teams and/or funding sources. The different formats try to avoid overlapping but rather strive to interoperate, via interconversion, cross-linking, use of common metadata layers etc.

A [comprehensive list of specification documents](#) is also available, following the COMBINE [specification infrastructure](#).

Extensible Markup Language (XML)

- A *markup language* is a meta language that enables to define and control the meaning of elements contained in a document or a text.
- defines a set of rules for encoding documents in a format that is human- and machine-readable.
- It is **eXtensible** in that it enables the creation of personalized tags

BioPAX

BioPAX is a standard language that aims to enable integration, exchange and analysis of biological pathway data. It is expressed in [OWL](#).

The last specification is [BioPAX Level 3](#).

BioPAX development is [coordinated](#) by an elected editorial board and a Scientific Advisory Board.

BioPAX is supported by [many pathway database or processing tools](#). An API is available to help implementing support: [Paxtools](#)

[More information](#)



The [Systems Biology Graphical Notation \(SBGN\)](#), is a set standard graphical languages to describe visually biological knowledge. It is currently made up of three languages describing Process Descriptions, Entity Relationships and Activity Flows.

The [last specifications](#) are SBGN PD Level 1 Version 2.0, SBGN ER Level 1 Version 2 and SBGN AF Level 1 Version 1.2.

SBGN development is [coordinated](#) by an elected editorial board and a Scientific Committee.

Several [data resources and software claim support for SBGN](#). An API is available to help implementing support: [libSBGN](#)

[More information](#)



The [Systems Biology Markup Language \(SBML\)](#) is a computer-readable [XML format](#) for representing models of biological processes. SBML is suitable for, but not limited to, models using a process description approach.

The latest stable specification is [Level 3 Version 2 Core](#).

SBML development is [coordinated](#) by an elected editorial board and central developer team.

Over 250 software systems known to support SBML can be found in the [SBML software guide](#). APIs are available to help implementing support: [libSBML](#) in C++ and [JSBML](#) in Java.

[More information](#)



The [Simulation Experiment Description Markup Language \(SED-ML\)](#) is an XML-based format for encoding simulation experiments. SED-ML allows to define the models to use, the experimental tasks to run and which results to produce. It is a computer-readable format for representing the models of biological processes. SED-ML can be used with models encoded in several languages, as far as they are in XML.

The latest stable specification is [Level 1 Version 3](#).

SED-ML development is coordinated by an [elected editorial board](#).

APIs are available to help implementing support: [libSedML](#) in C#, [libSedML](#) in C++ with swig bindings for python, java, perl, R and ruby, and [libSedML](#) in Java.

[More information](#)



The [CellML language](#) is an XML markup language to store and exchange computer-based mathematical models. CellML is being developed by the Auckland Bioengineering Institute at the University of Auckland and affiliated research groups.

The latest stable specification is [Version 1.1](#).

CellML development is coordinated by an [elected editorial board](#).

APIs are available to help implementing support: [CellML API](#) in C.

[More information](#)



The [Synthetic Biology Open Language Data \(SBOL Data\)](#) is a language for the description and the exchange of synthetic biological parts, devices and systems.

The latest stable specification of SBOL Data is [2.2.0](#).

SBOL Data is developed by the [SBOL Developers Group](#). The development is coordinated by an [editorial board and the SBOL Chair](#).

SBOL data is supported by many software tools. [APIs](#) are available to help implement the support of this data standard.

[More information](#)



The [Synthetic Open Language Visual \(SBOL Visual\)](#) is an open-source graphical notation that uses schematic "glyphs" to specify genetic parts, devices, modules, and systems.

The latest stable specification of SBOL Visual is [2.0.0](#).

SBOL is developed by the [SBOL Developers Group](#) and [SBOL Visual Group](#). The development is coordinated by an [editorial board and the SBOL Chair](#).

SBOL Visual is supported by many [software tools](#).

[More information](#)



The [NeuroML](#) project focuses on the development of an XML based description language that provides a common data format for defining and exchanging descriptions of neuronal cell and network models.

The latest stable specification of NeuroML is [version 2 beta 4](#).

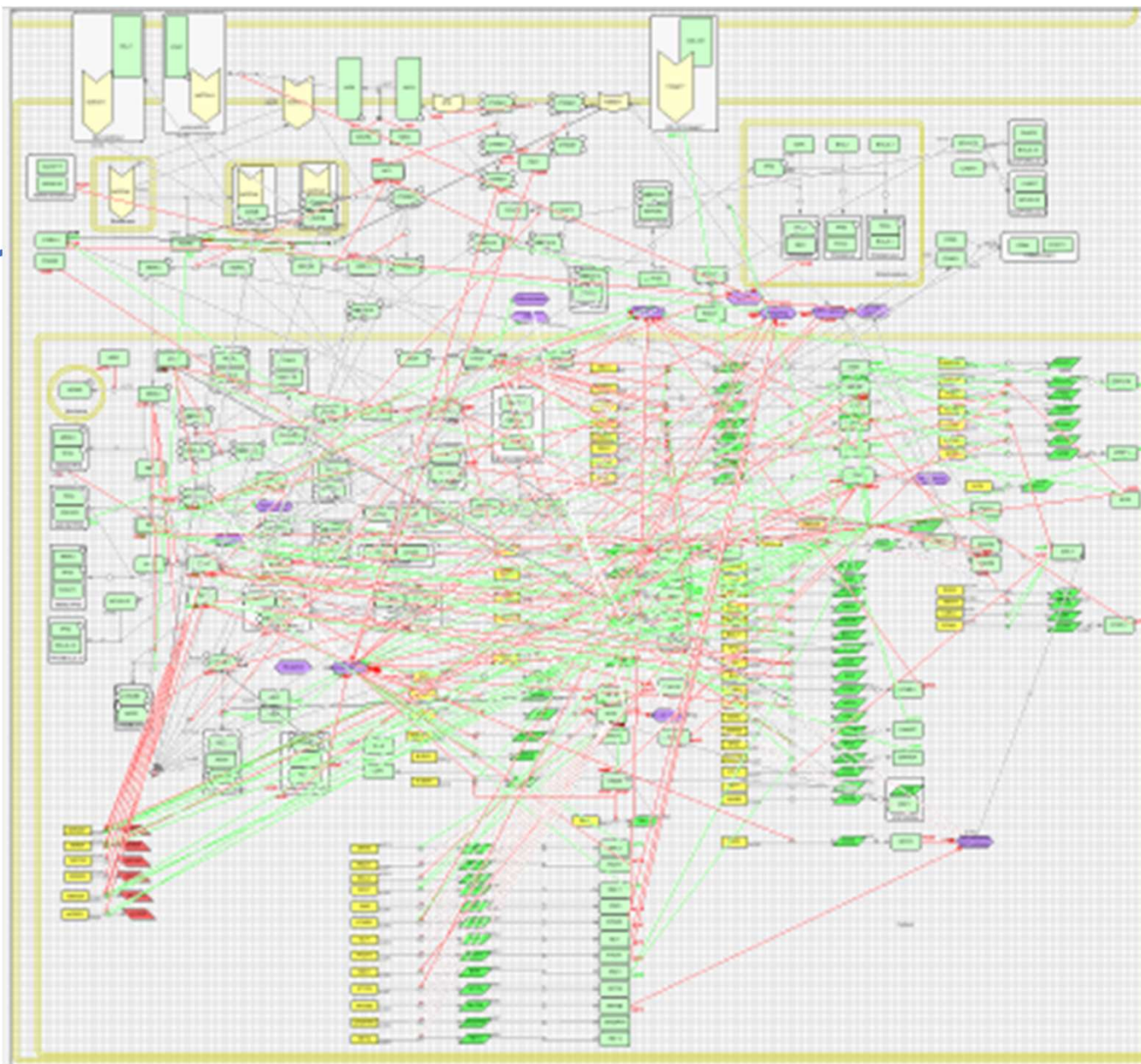
NeuroML development is coordinated by the [NeuroML Editorial Board](#).

NeuroML is supported by many software tools and databases, see [here](#).

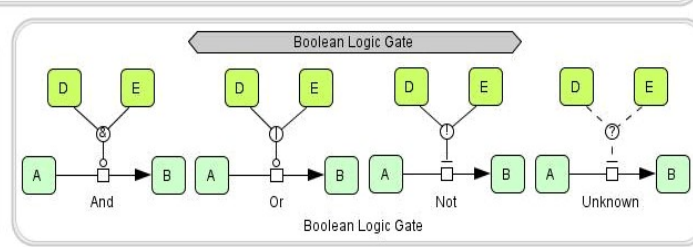
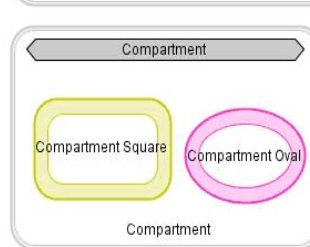
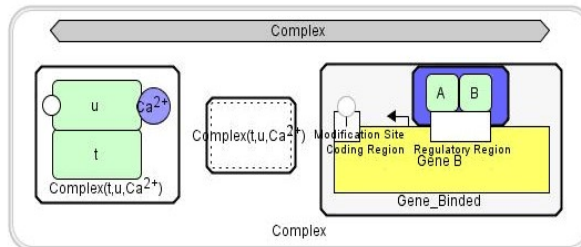
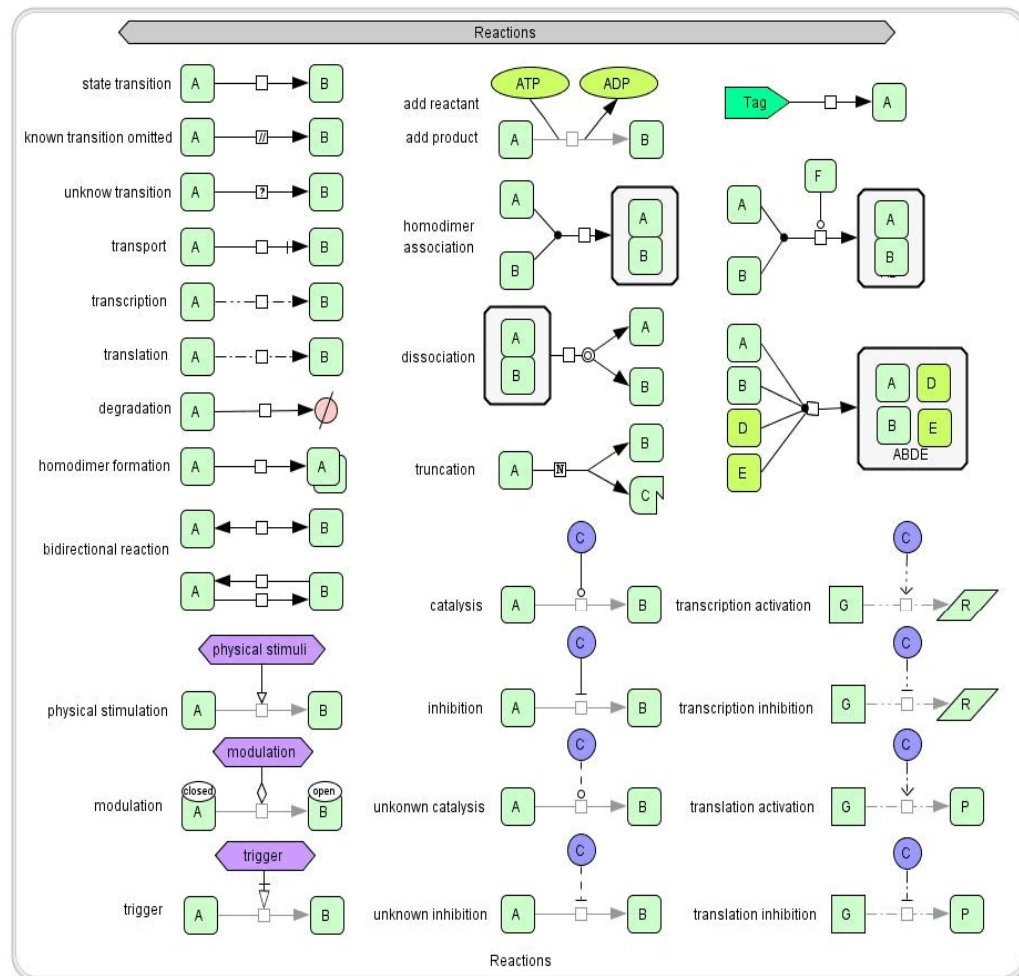
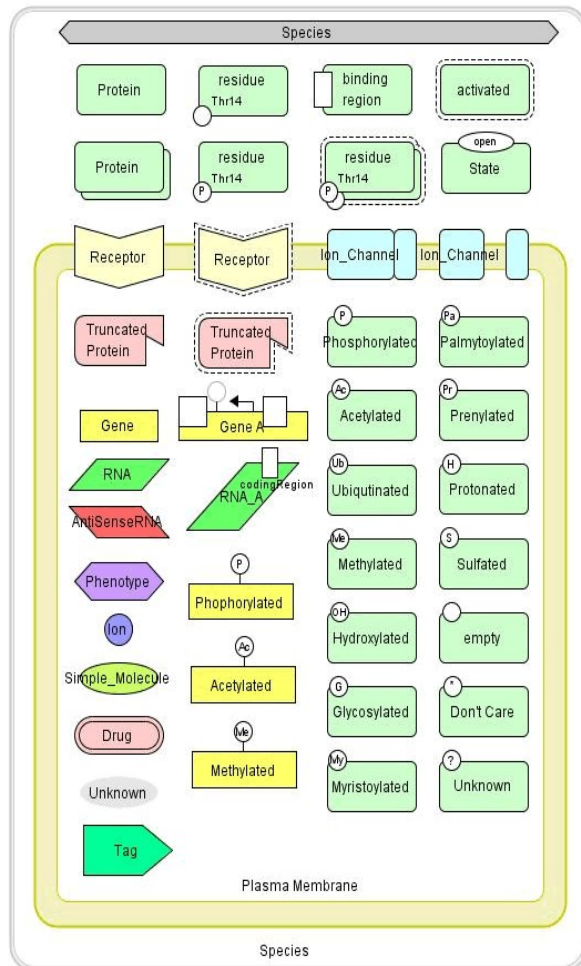
[More information](#)

Layout

- Proper visualization, including positioning of molecular entities, can greatly facilitate understanding of the entire system
- Manual or automatic layout can be chosen, as well as custom views to emphasize specific components or processes
- the network structure should be stored in a layout-aware format, i.e. a format allowing one to encode positions of molecular entities.







- Reactome
- Spike
- KEGG
- Wipathways
- Navicell



Mechanotransduction

Bioinformatics, 31(7), 2015, 1053–1059

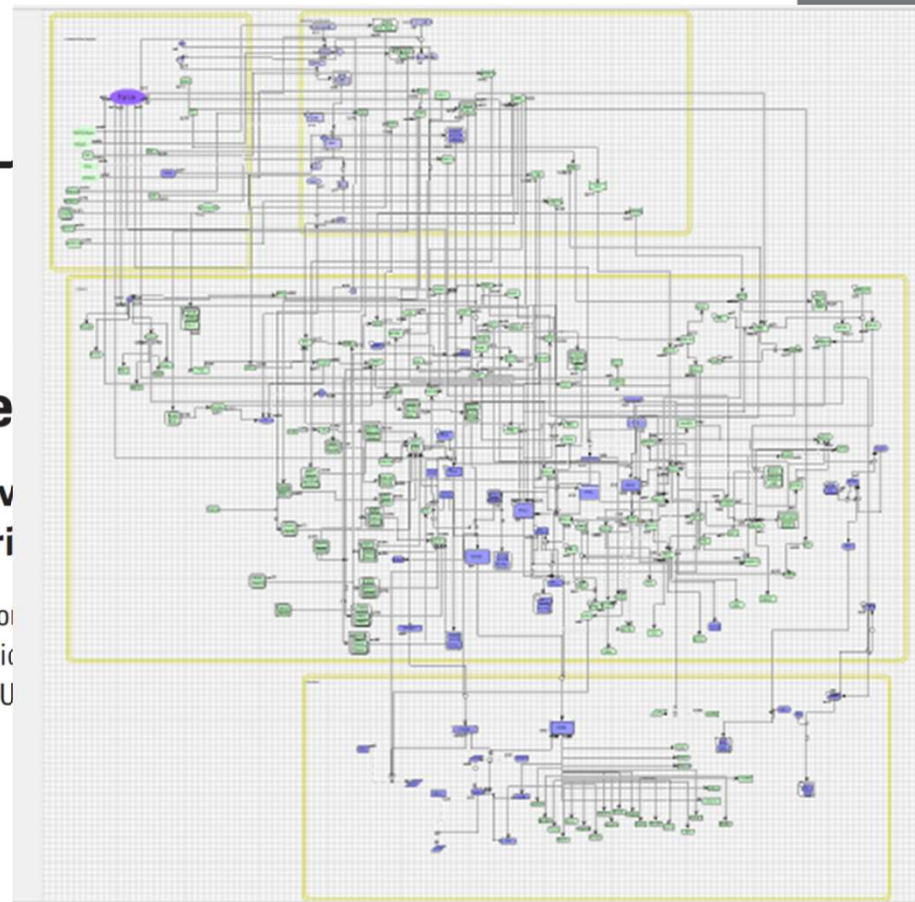
Systems biology

Mechanotransduction molecular pathway, ge

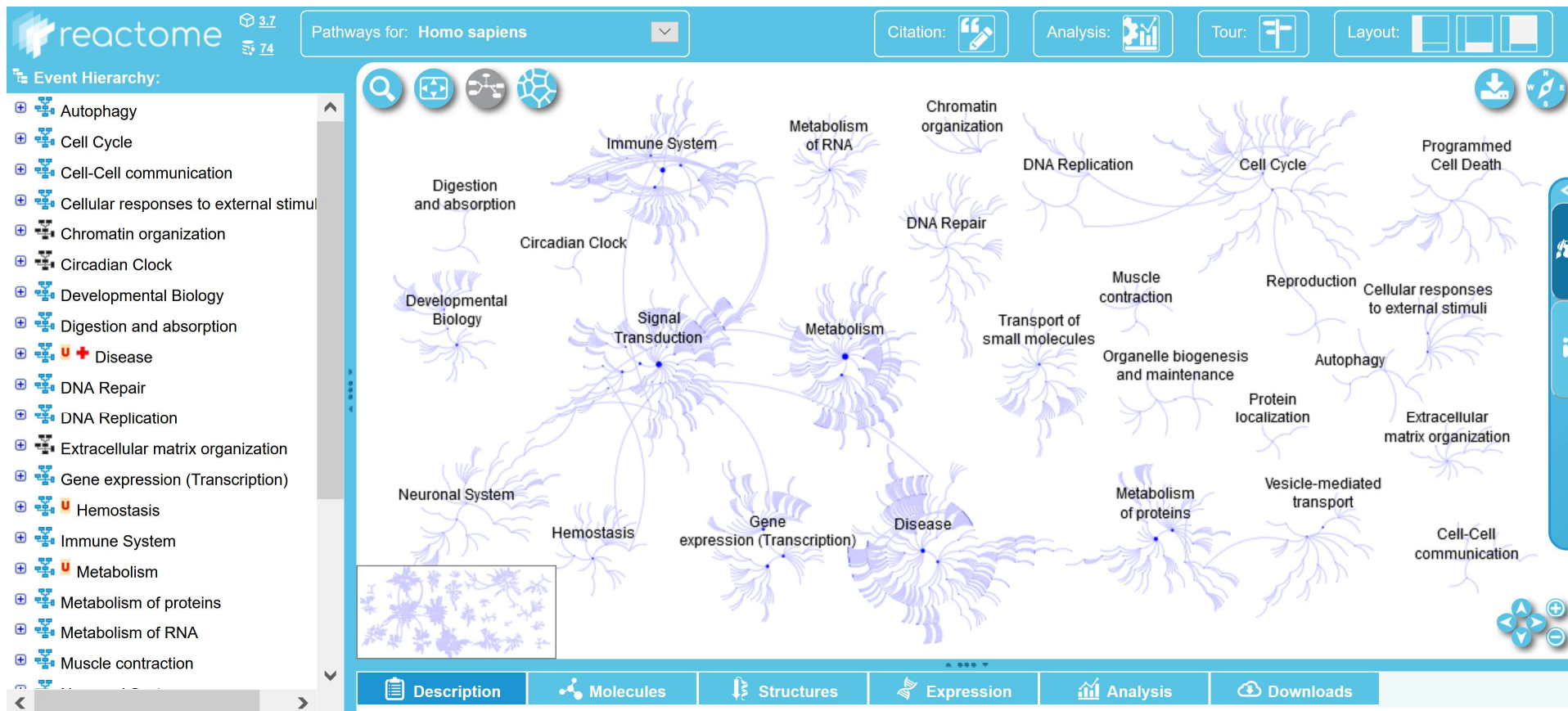
Jennifer E. Dent^{1,2,†}, Valentina Dev
Youtao Lu¹, Yuanhua Liu¹ and Chri

¹Group of Clinical Genomic Networks, Key Laboratory
Computational Biology, Shanghai Institutes for Bio

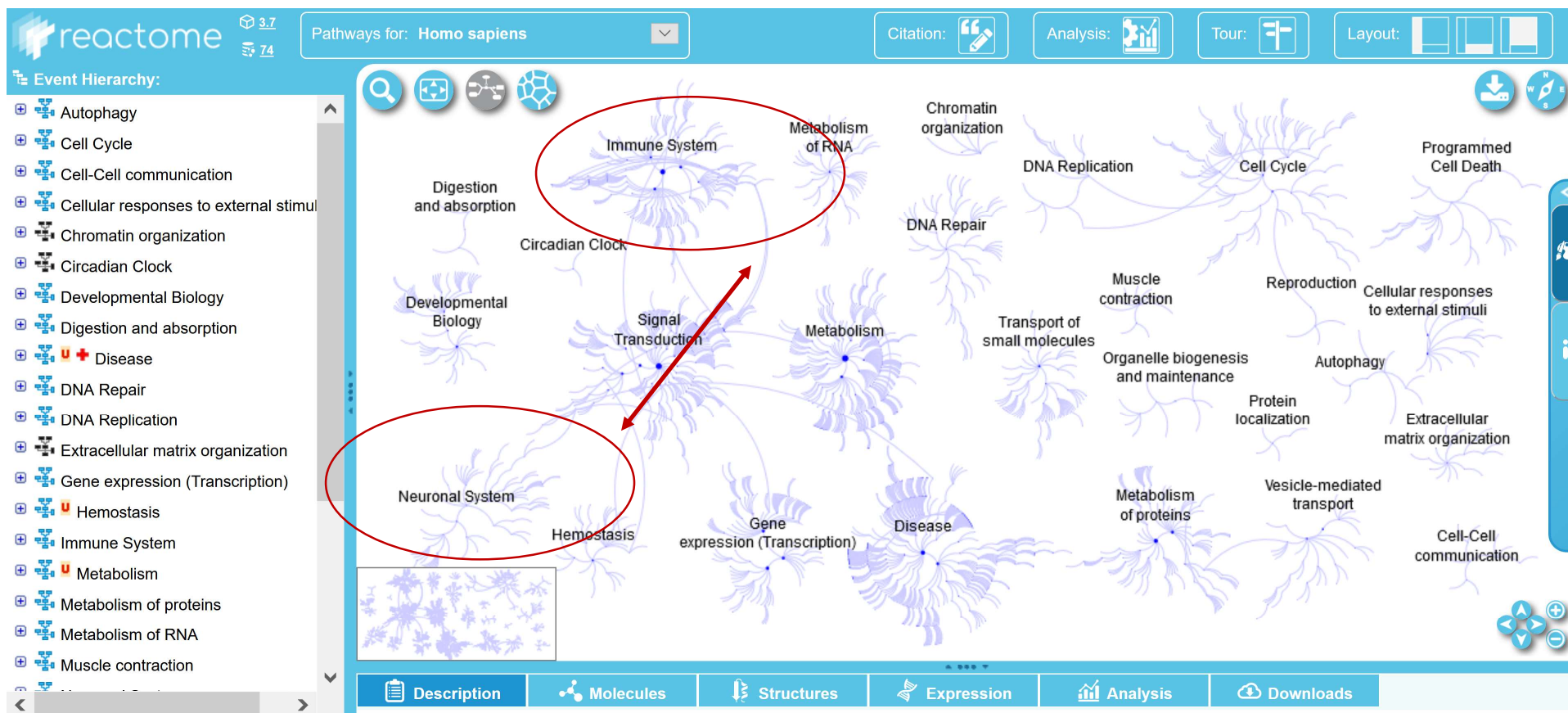
²Quintiles, Global Biostatistics, Reading, Berkshire, U
DISI, University of Bologna, Bologna, Italy



Inflammatory Reflex



Inflammatory Reflex



Davide Martelli Unibo

Immune Response



Overlap Merge & Analyze

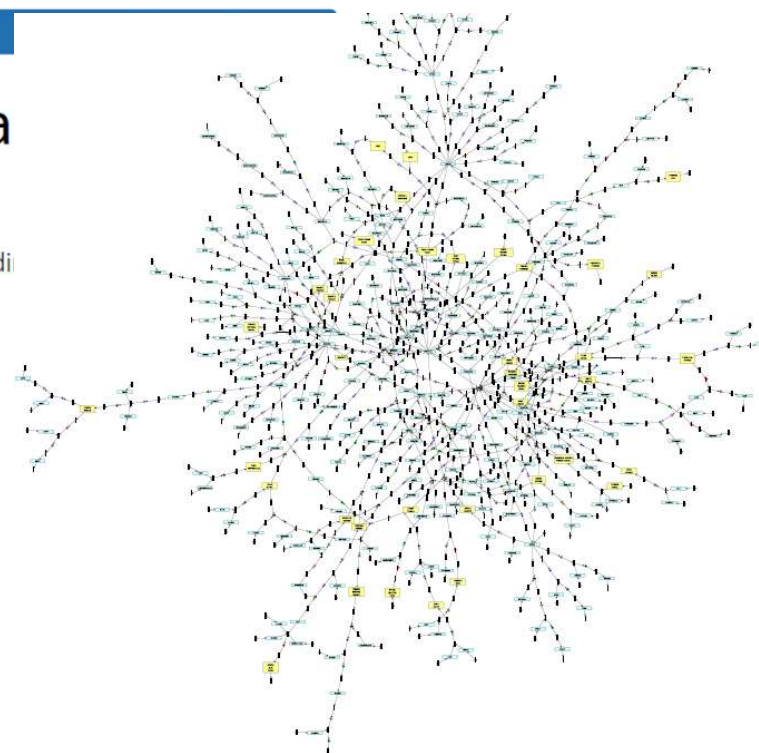
Di Lena et al. *BMC Bioinformatics* 2013, **14**:159
<http://www.biomedcentral.com/1471-2105/14/159>



SOFTWARE

MIMO: an efficient tool for molecular interaction maps overlap

Pietro Di Lena^{1,2*}, Gang Wu¹, Pier Luigi Martelli³, Rita Casadio³ and Christine Nardi



Thank you