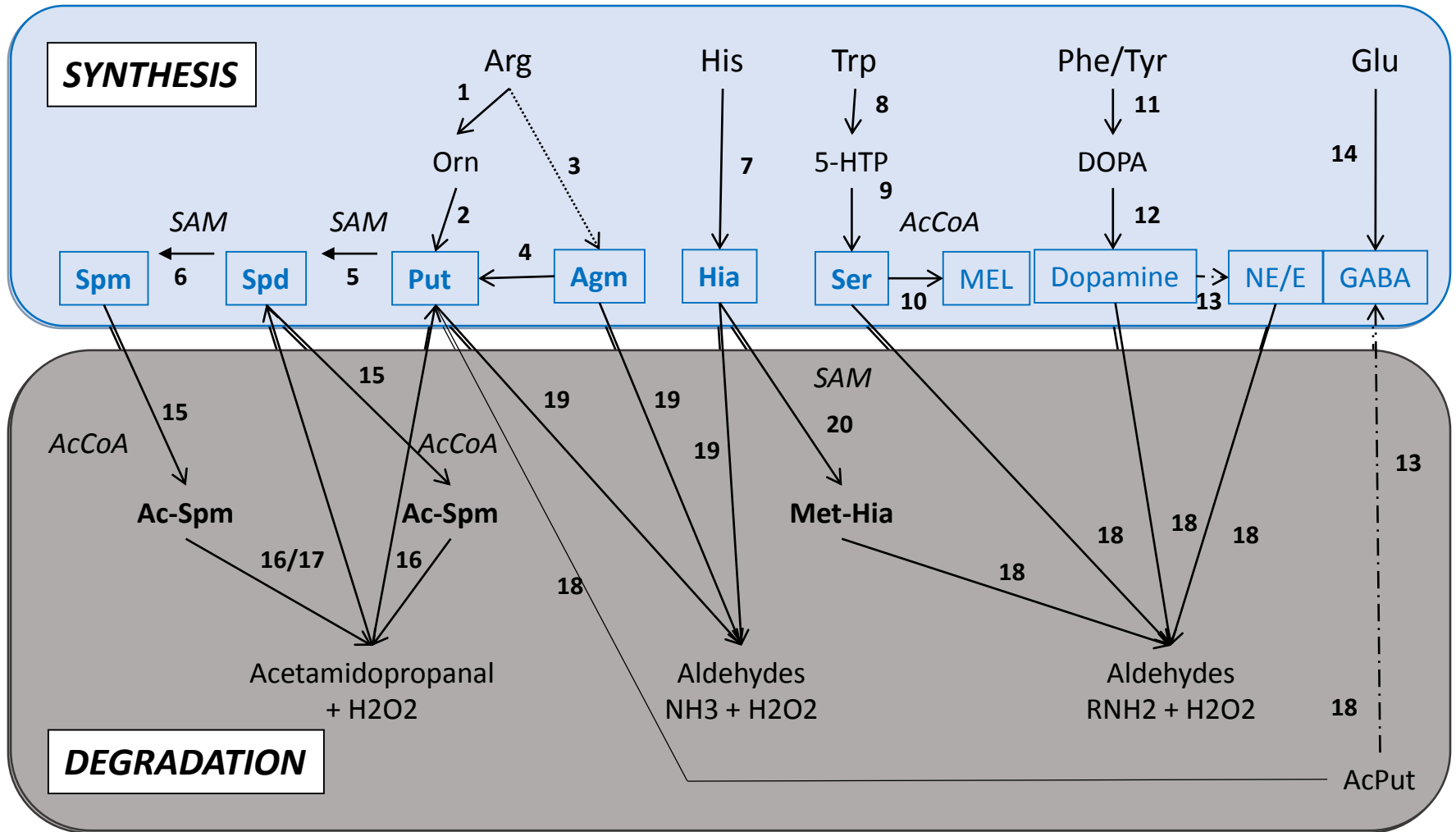




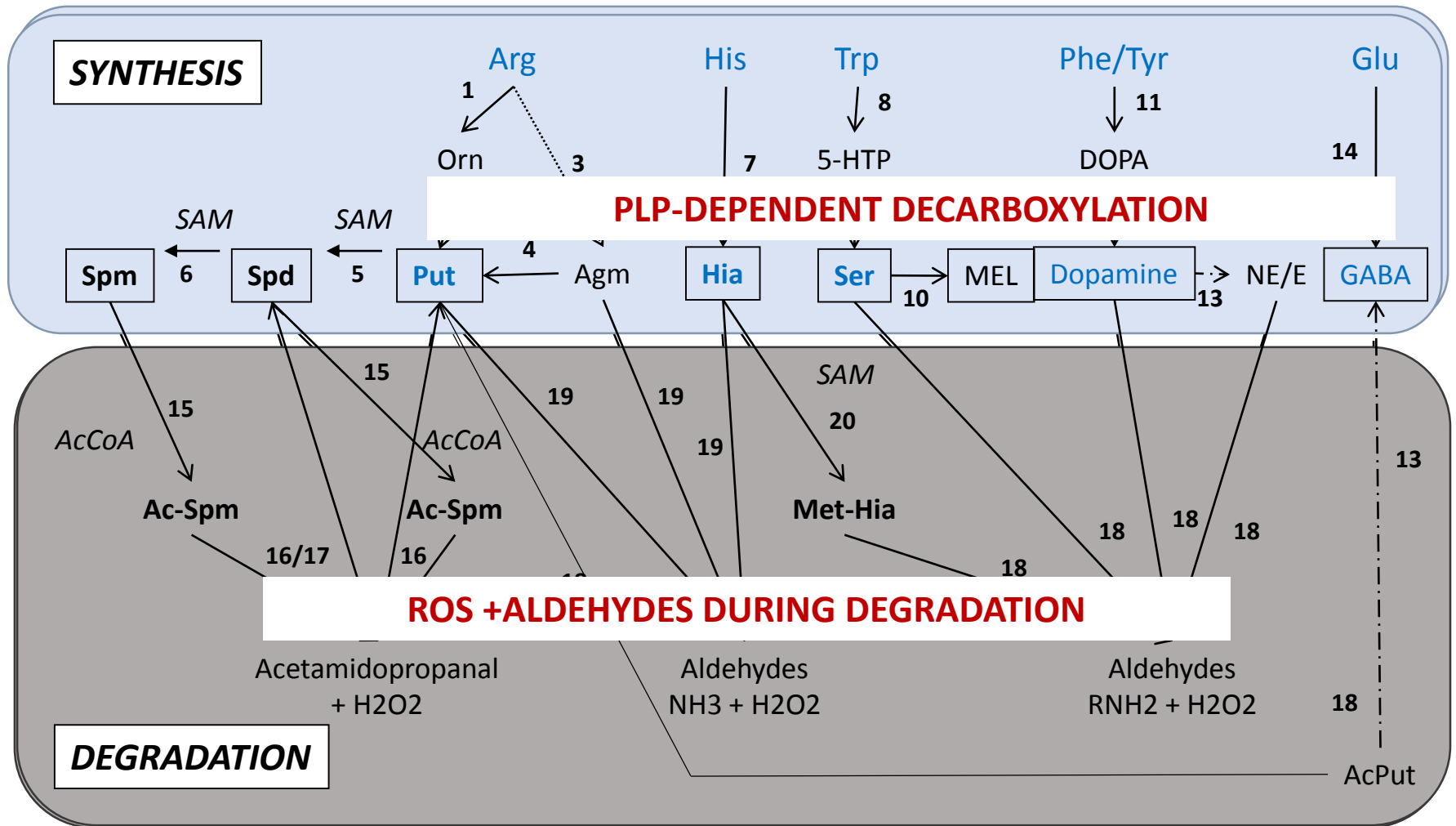
F. Sánchez-Jiménez
Dpt. Mol- Biol. & Biochem.
University of Malaga

**POLYAMINES AND OTHER BIOGENIC AMINES
AT THE MOLECULAR BASIS OF LOW PREVALENCE DISEASES**

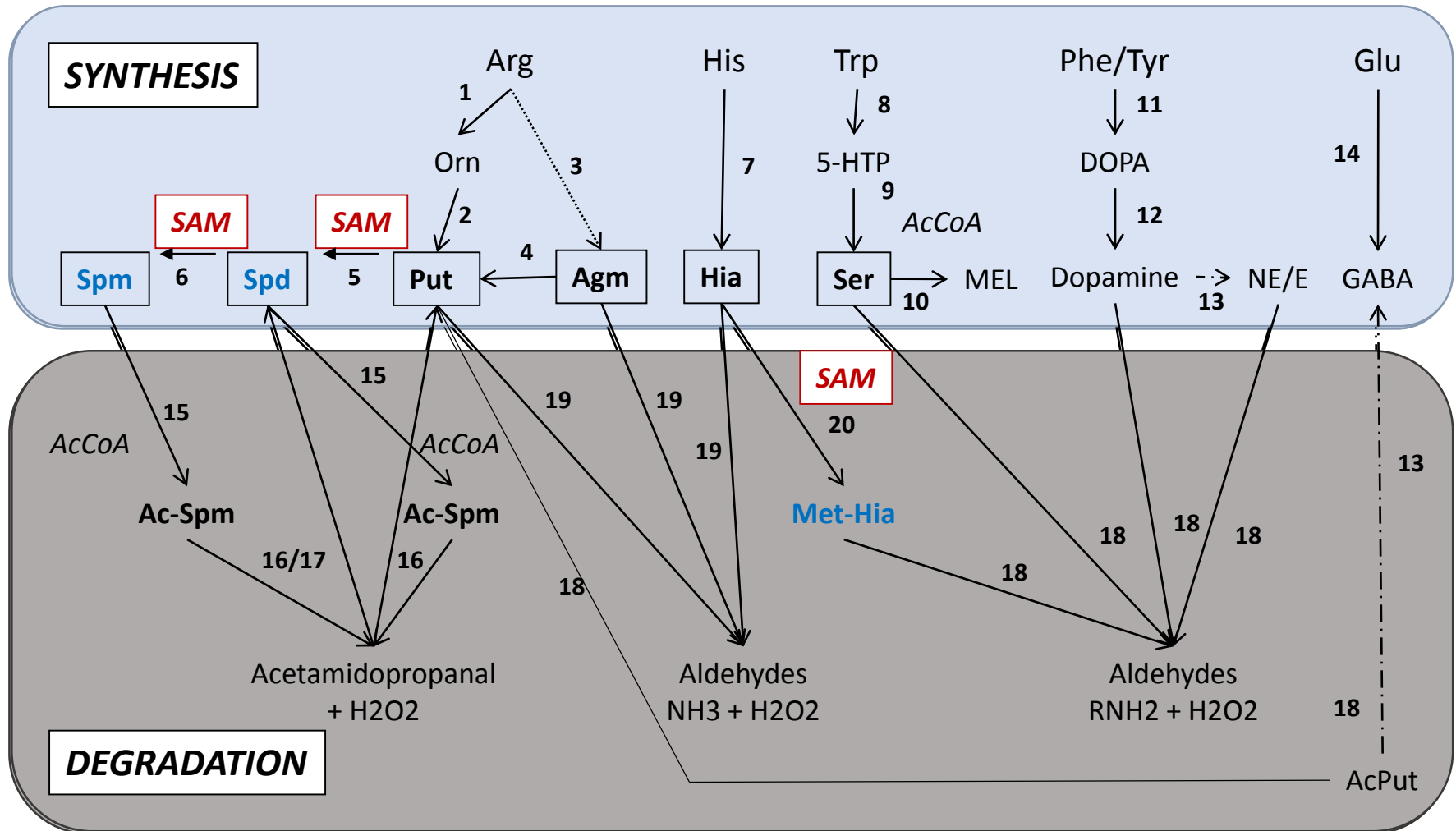
SCHEME OF BIOGENIC AMINE METABOLISM



COMMON FEATURES OF BIOGENIC AMINE METABOLISM

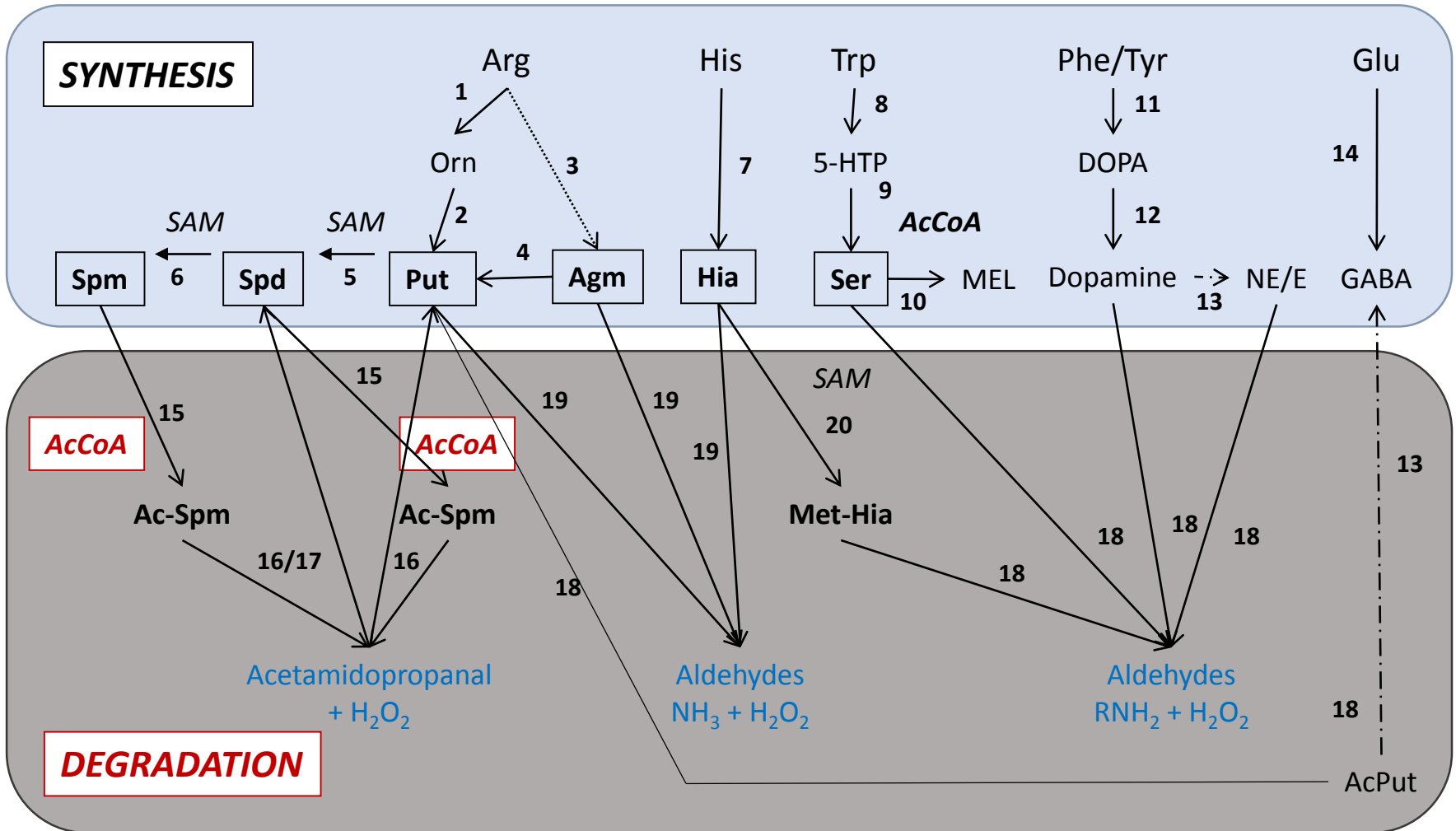


AMINE METABOLISM IS LINKED TO METHYL CYCLES BY SAM



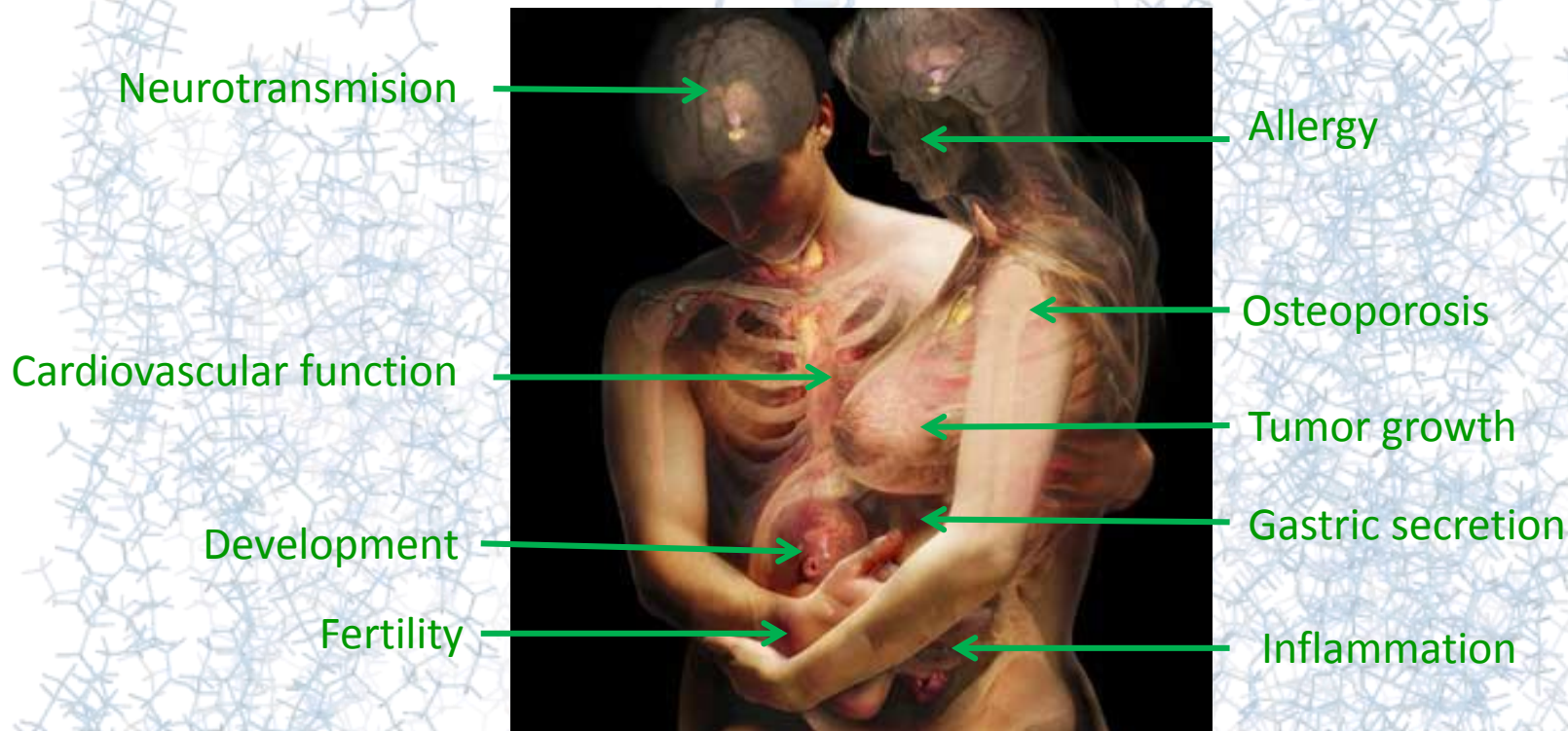
Rodríguez-Caso et al., 2006, *J Biol Chem.* 2006;281:21799-812

POLYAMINE METABOLISM IS LINKED TO ENERGY METABOLISM BY ACETYL-CoA (among other metabolites)



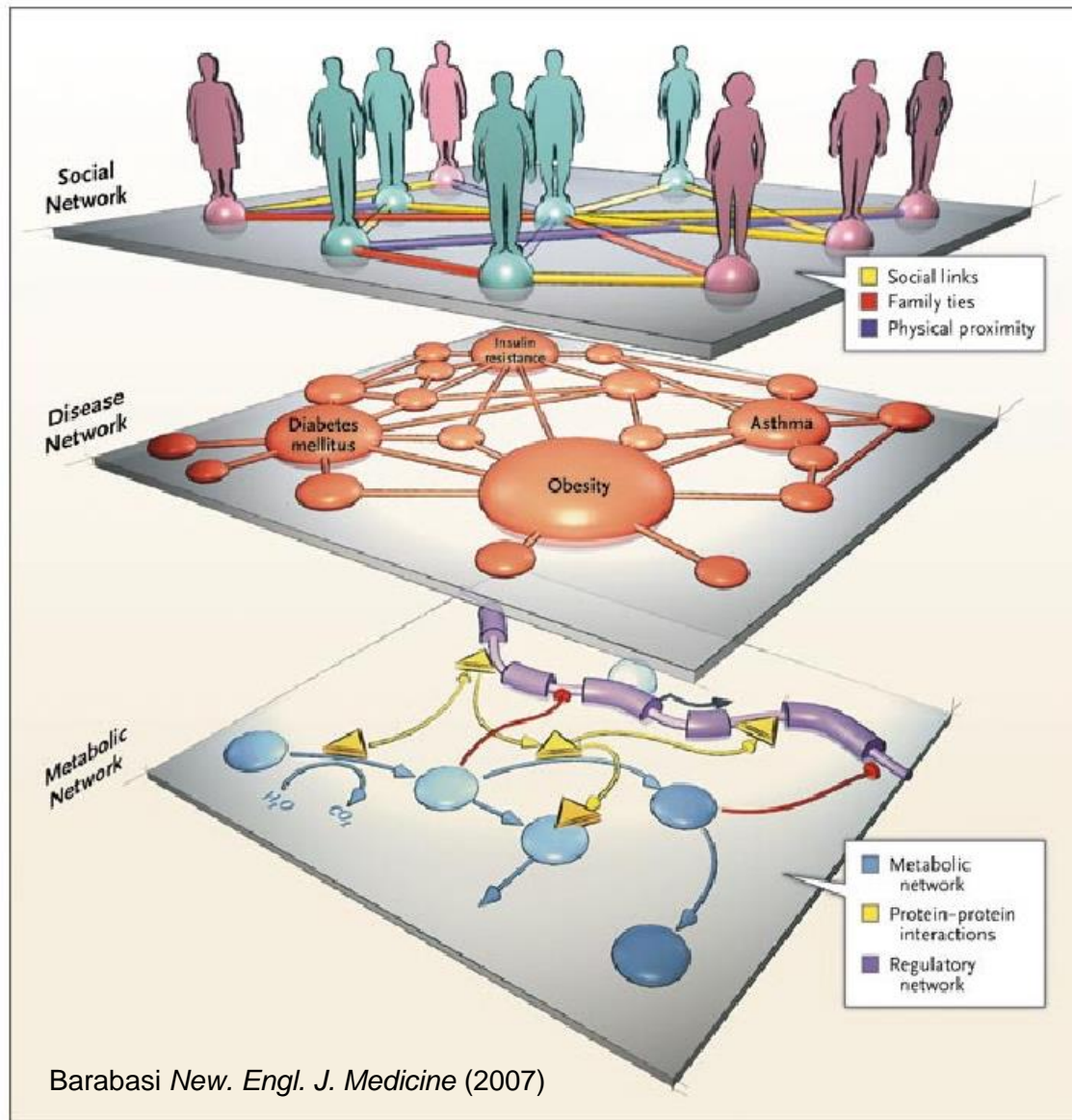
Rodríguez-Caso et al., 2006, *J Biol Chem.* 2006;281:21799-812

THE IMPORTANCE OF THE METABOLIC LINKS OF BIOGENIC AMINES IS REFLECTED ON THEIR INVOLVEMENT IN THE MOST IMPORTANT PHYSIOLOGICAL FUNCTIONS



Thus, imbalance of biogenic amine metabolism must be involved in many diseases. However, there are many difficulties for characterization of the roles of biogenic amines in health. Systems Biology techniques can help us to advance in this topic

LEVELS OF INFORMATION ON DISEASES



SOCIAL NETWORK

Social links
Symptoms
Prevalence

DISEASOME

Genetic relationships among diseases (genes shared among diseases)

BIOCHEMICAL NETWORKS

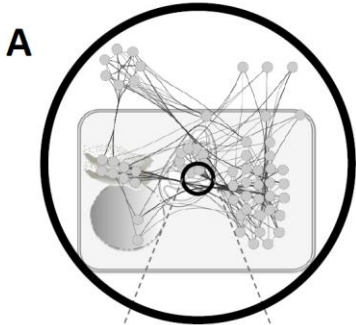
Disease genes and gene products distribution in functional pathways: modulatory effects, metabolic and signaling pathways, protein-protein interactions

DIFFERENT SYSTEMS BIOLOGY APPROACHES ARE NEEDED DEPENDING ON THE AIM

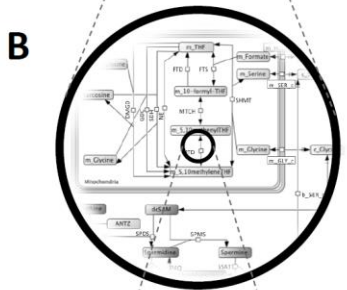


SYSTEMS

IN SILICO TECHNOLOGICAL SUPPORT



- Analysis of HTP experimental data
- Data mining
- Mathematical modeling of biological systems
- Predictive models



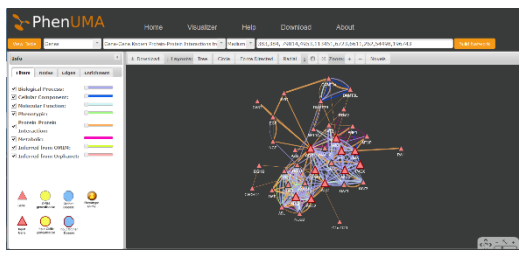
- Metabolic modeling based on:
 1. Kinetic data
 2. Flux balance analysis
- Network based models
- Pathway and modular analysis



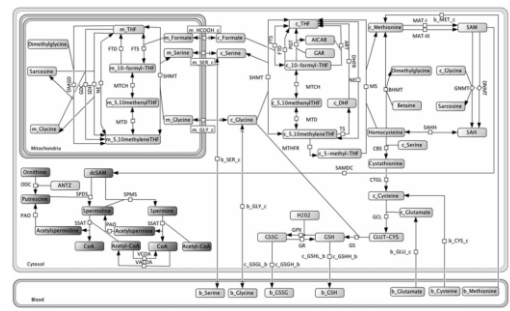
- Molecular modeling
- Docking
- Molecular Dynamics
- Virtual Screening
- QSAR

Sánchez-Jiménez et al., Curr Pharm Des. 2014;20:293-300

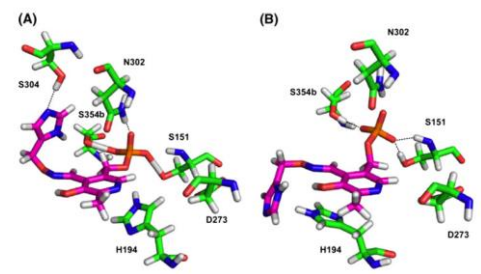
www.phenuma.uma.es



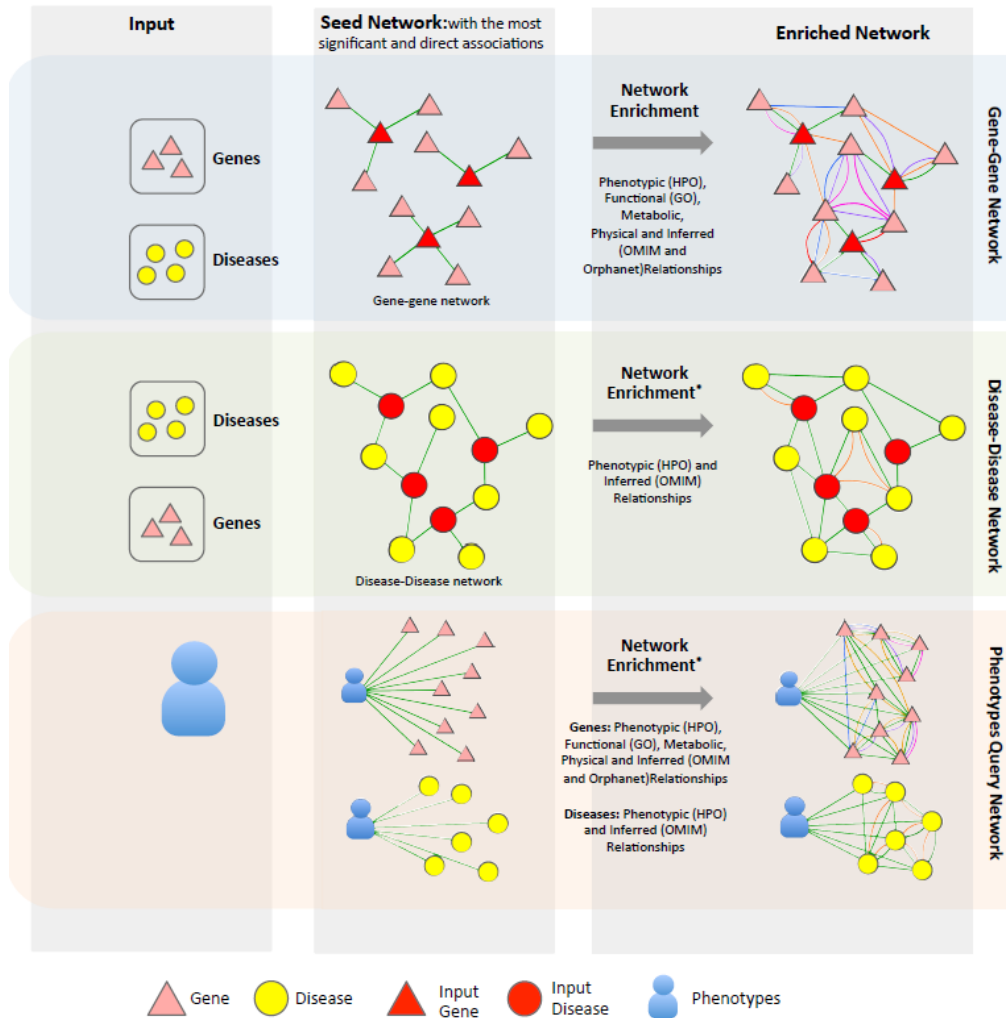
Reyes-Palomares et al., Amino Acids. 2012 42:597-610



Castro-Oropeza et al., Amino Acids. 2014 46: 621-31



PhenUMA STRATEGY AND INFORMATION SOURCES



The tool integrates information from:

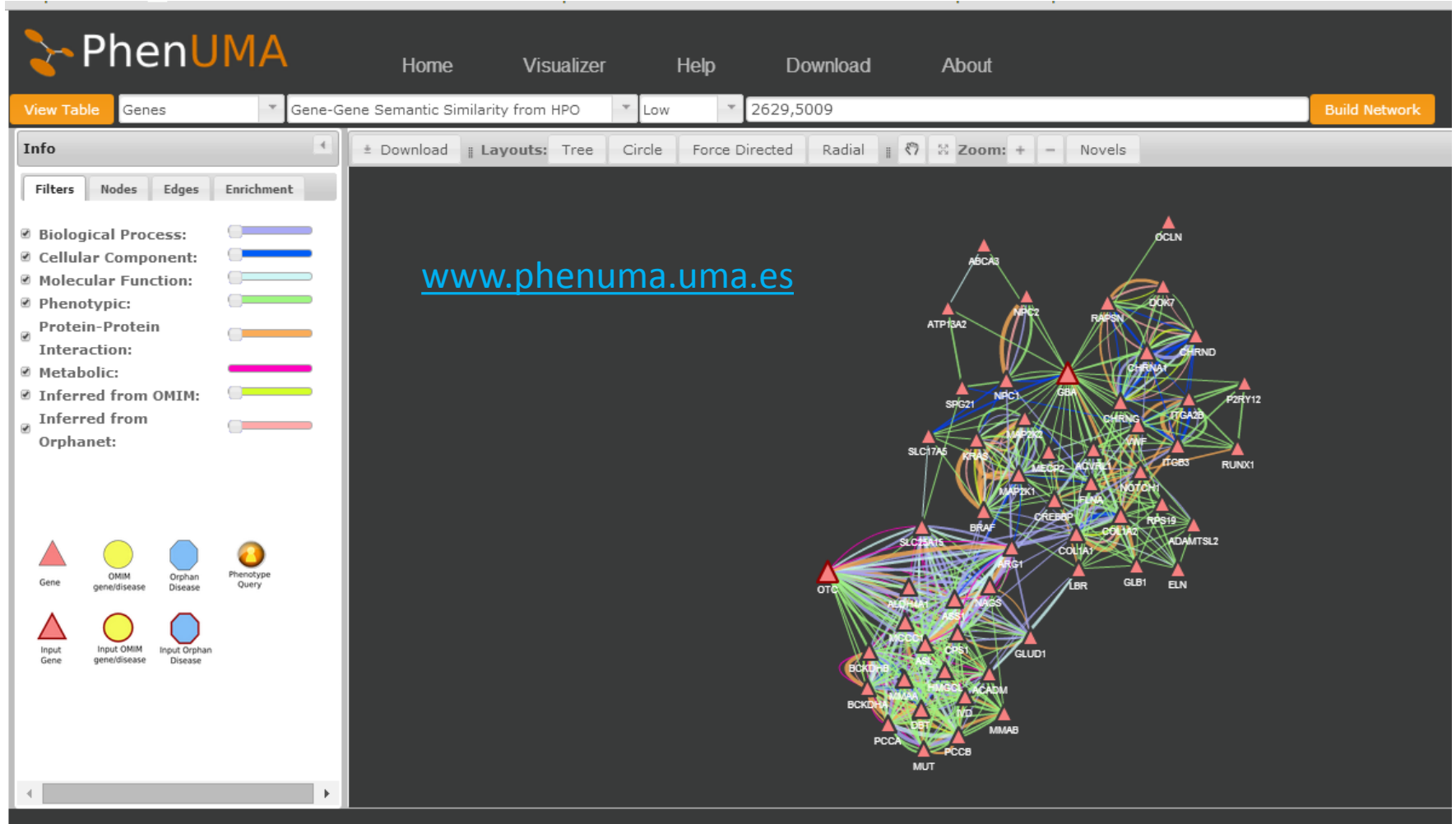


Integration provides emergent insights for:

- Diagnosis
- Prognosis
- Therapeutic strategies

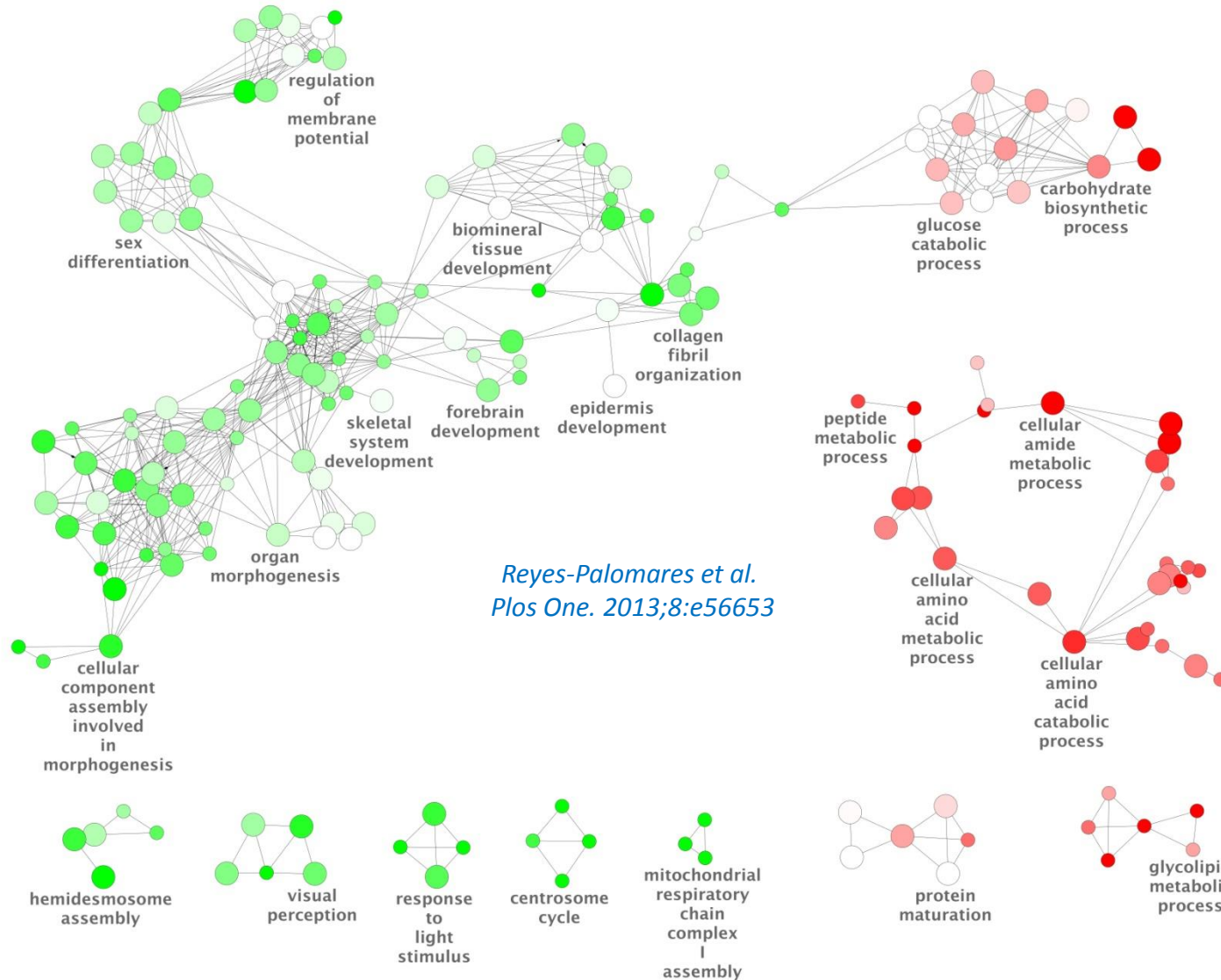


PHENUMA: A TOOL TO LOOK FOR FUNCTIONAL AND PHENOTYPIC RELATIONSHIPS AMONG HUMAN GENES AND DISEASES



PhenUMA 2.0 is an on-going Project that will be enriched in genetic variant data, metabolic information and drug-ligand information

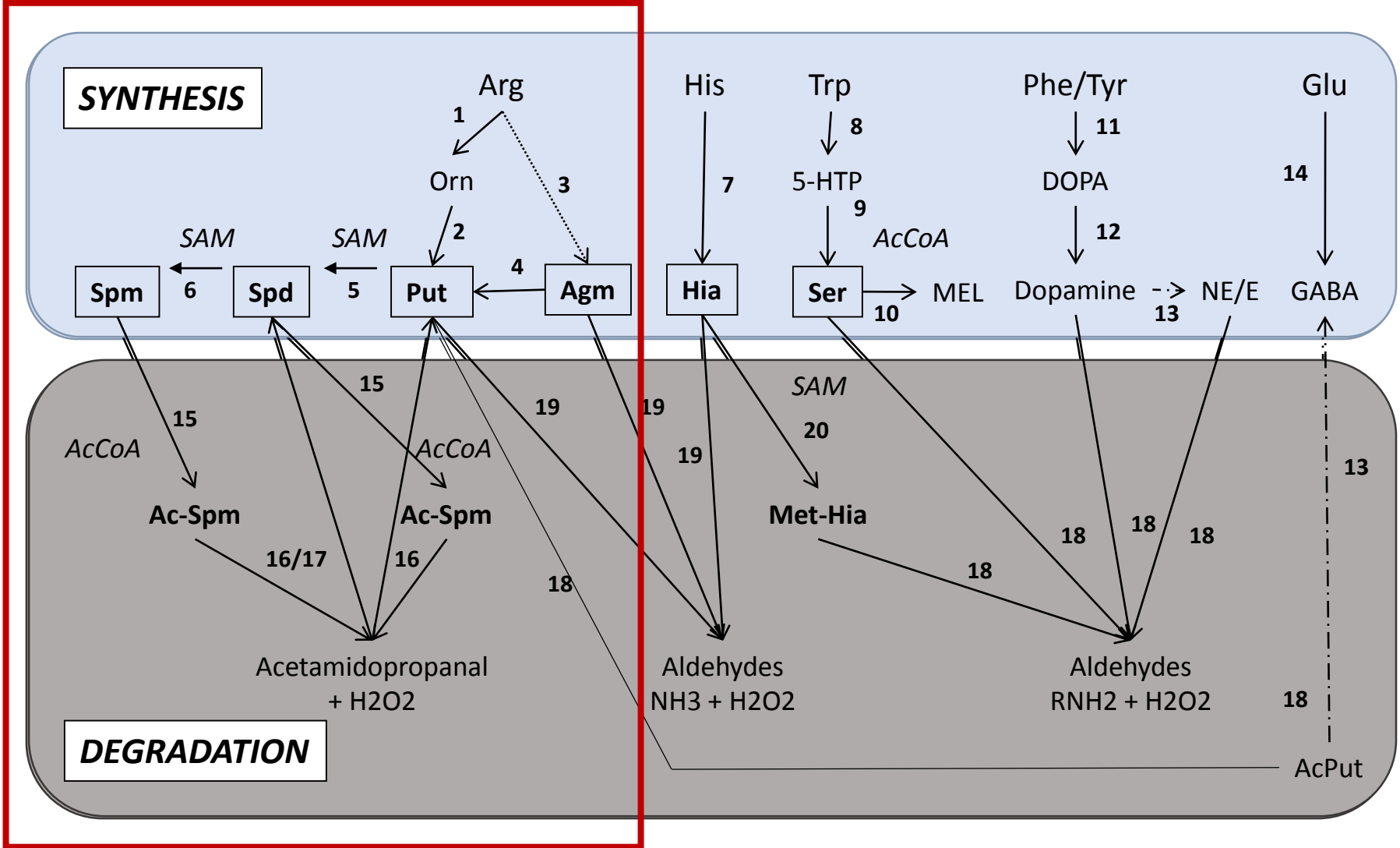
AMINE-RELATED DISEASES ARE DISTRIBUTED IN DIFFERENT MODULES OF THE HUMAN DISEASOME BUT MAINLY IN THE “DARK SIDE”



Polygenic/multiphenotypic diseases

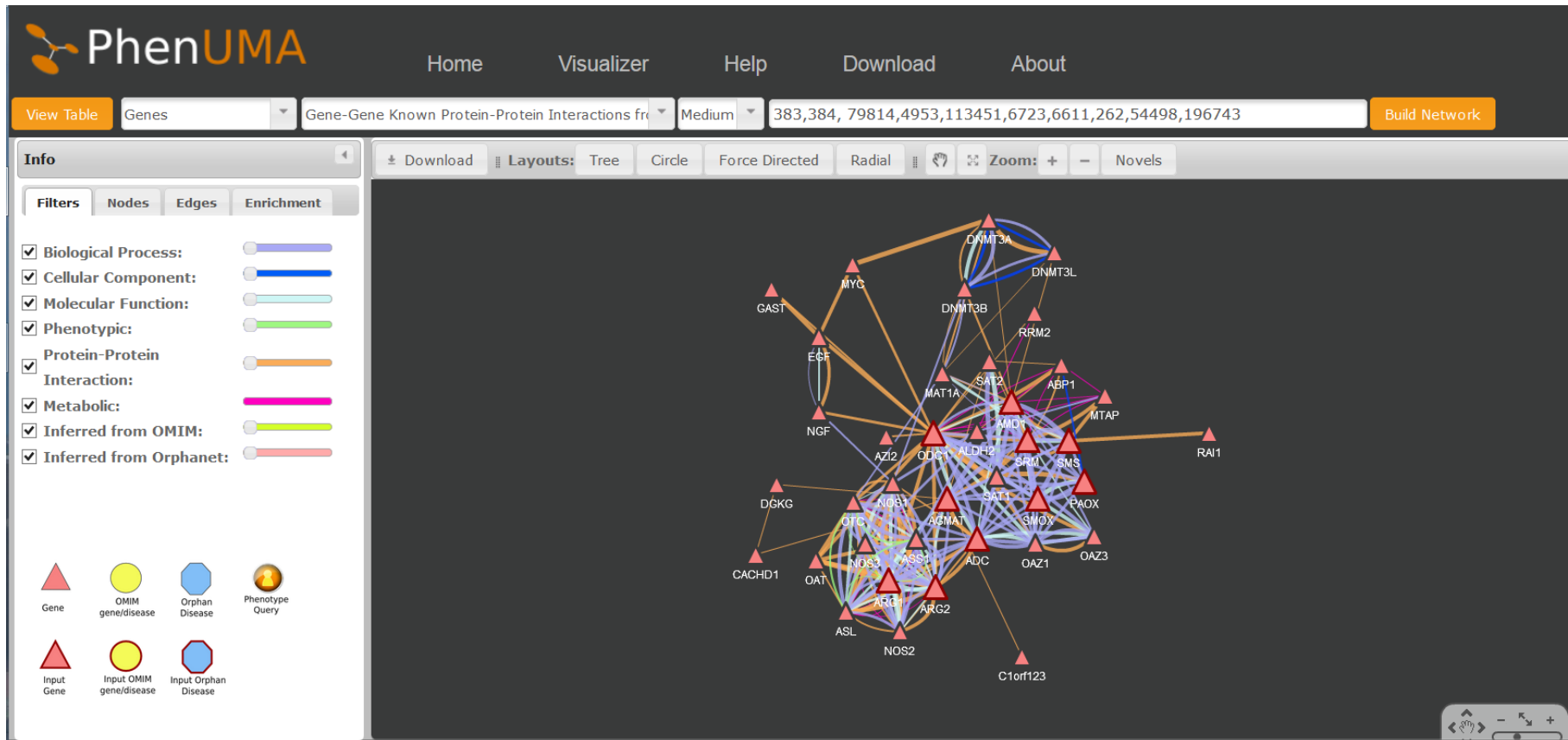
Monogenic diseases

POLYAMINE-RELATED ELEMENTS AND HUMAN DISEASOMES



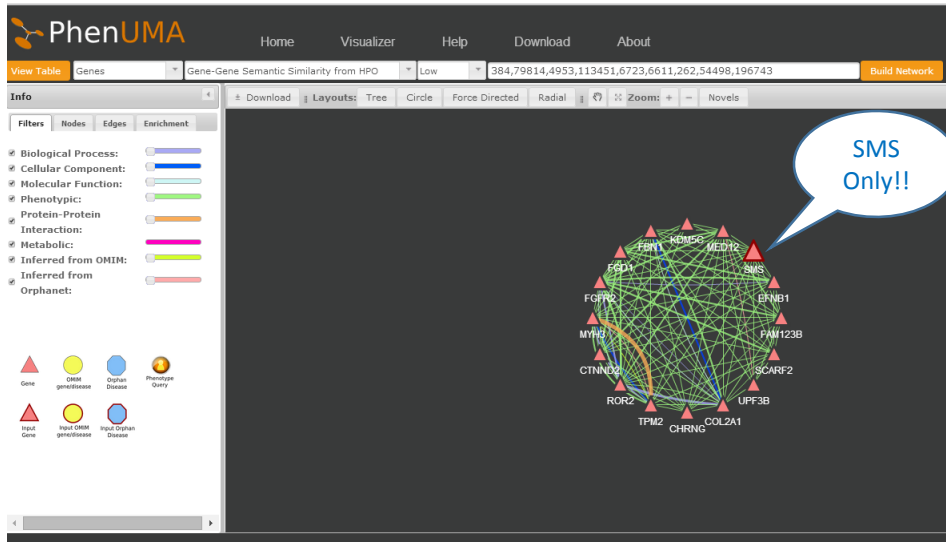
PHENUMA (www.phenuma.uma.es)

An example: asking for polyamine related genes

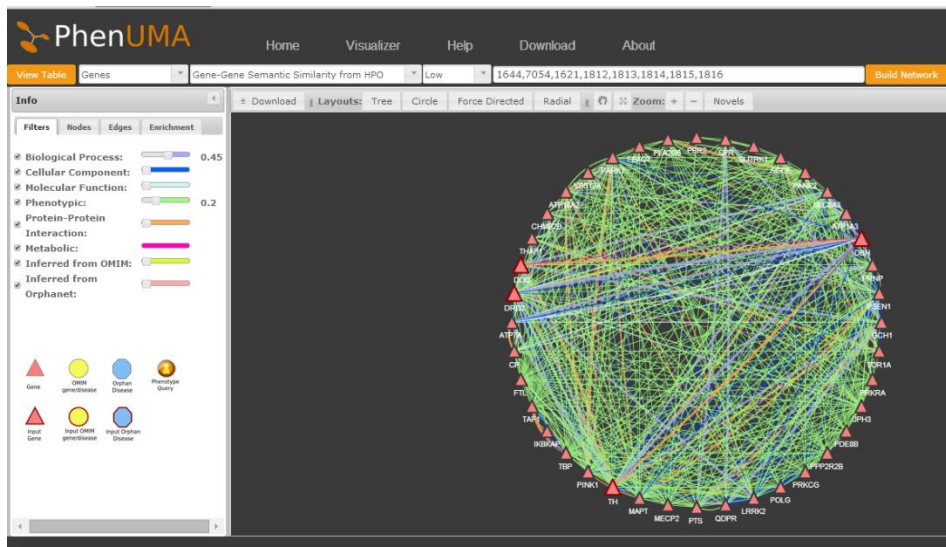


There is a lot of information on structural and functional relationships but scarce information on polyamine elements as genes involved in pathological conditions!!

COMPARISON BETWEEN THE PHENOTYPIC SIMILARITY NETWORK OF POLYAMINE-RELATED GENES AND DOPAMINE-RELATED ELEMENTS



It is not real but it is all we have annotated in databanks!

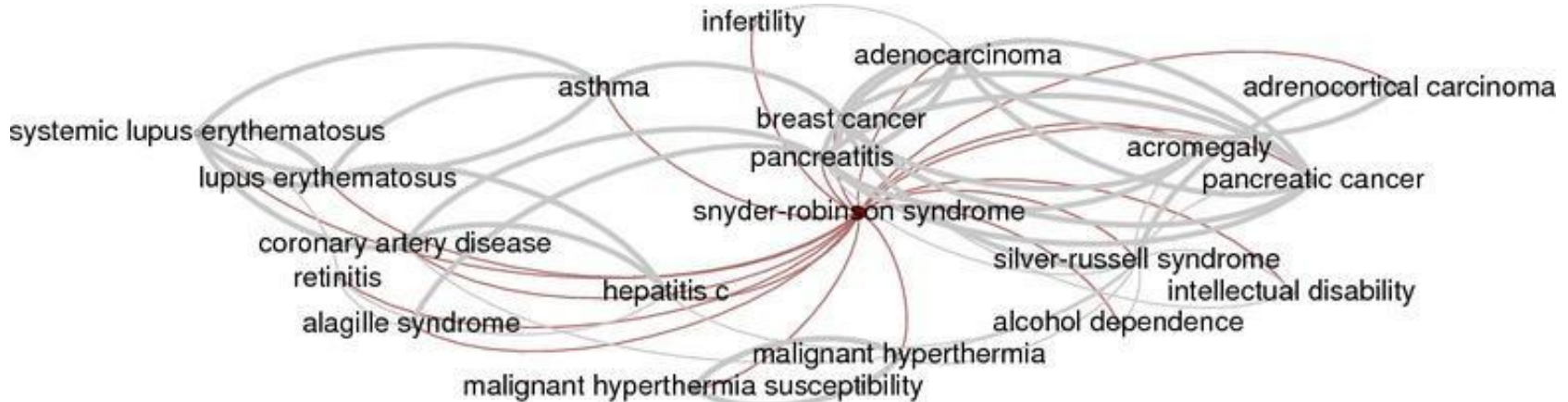


The opposite problem: a highly complex network, too many interactions!!



POLYAMINE RELATED DISEASES

Monogenic disease: Snyder-Robinson syndrome (Spermine synthase) **OMIM: 309583**



Copyright © Weizmann Institute of Science - www.malacards.org

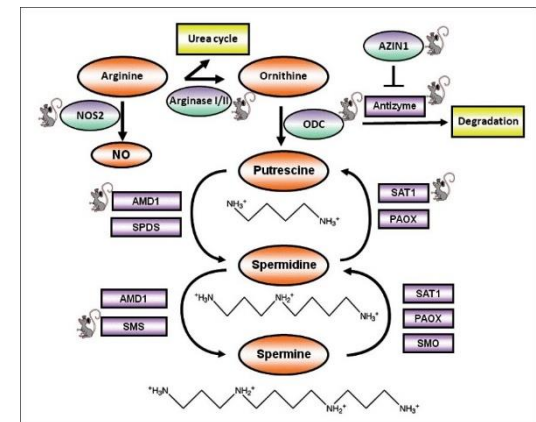
Other diseases:

Gene	Code	Diseases/Symptoms
Agmatinase	AGMAT,79814	Mood disorders
Ornithine DC	ODC, 4953	Colorectal cancer
SAM-DC	AMD1,262	Mood disorders, obesity, suicide behavior, psychosis, angiogenesis

The polyamine paradox:
 Polyamines are essential for cell life/death equilibrium; however, only a few diseases are clearly annotated as related to polyamine metabolism elements
Why?

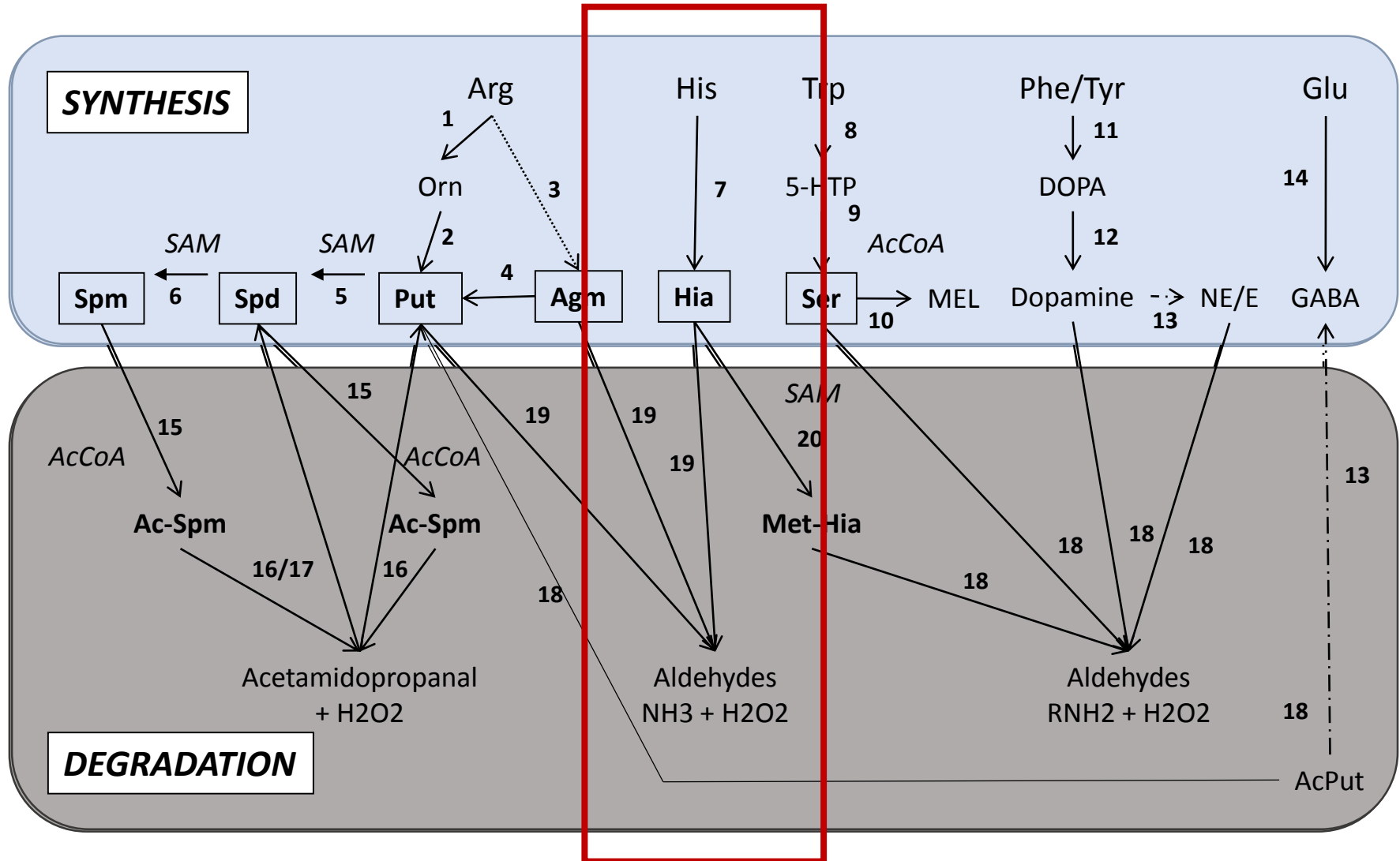
PUTATIVE CAUSES CONTRIBUTING FOR KEEPING POLYAMINES ALMOST OUT OF DISEASOMES

- Inherited diseases: PA homeostasis is so essential for cell survival that embryogenesis is not possible in case of PA-gene abnormalities.
- The robustness of polyamine metabolism makes difficult to alter PA metabolism homeostasis.
- Cancer: The lack of specific PA targets makes difficult to correlate PA-related elements to specific types of cancer in databases.
- Not much interest for visualization of our biomedical results in databases.

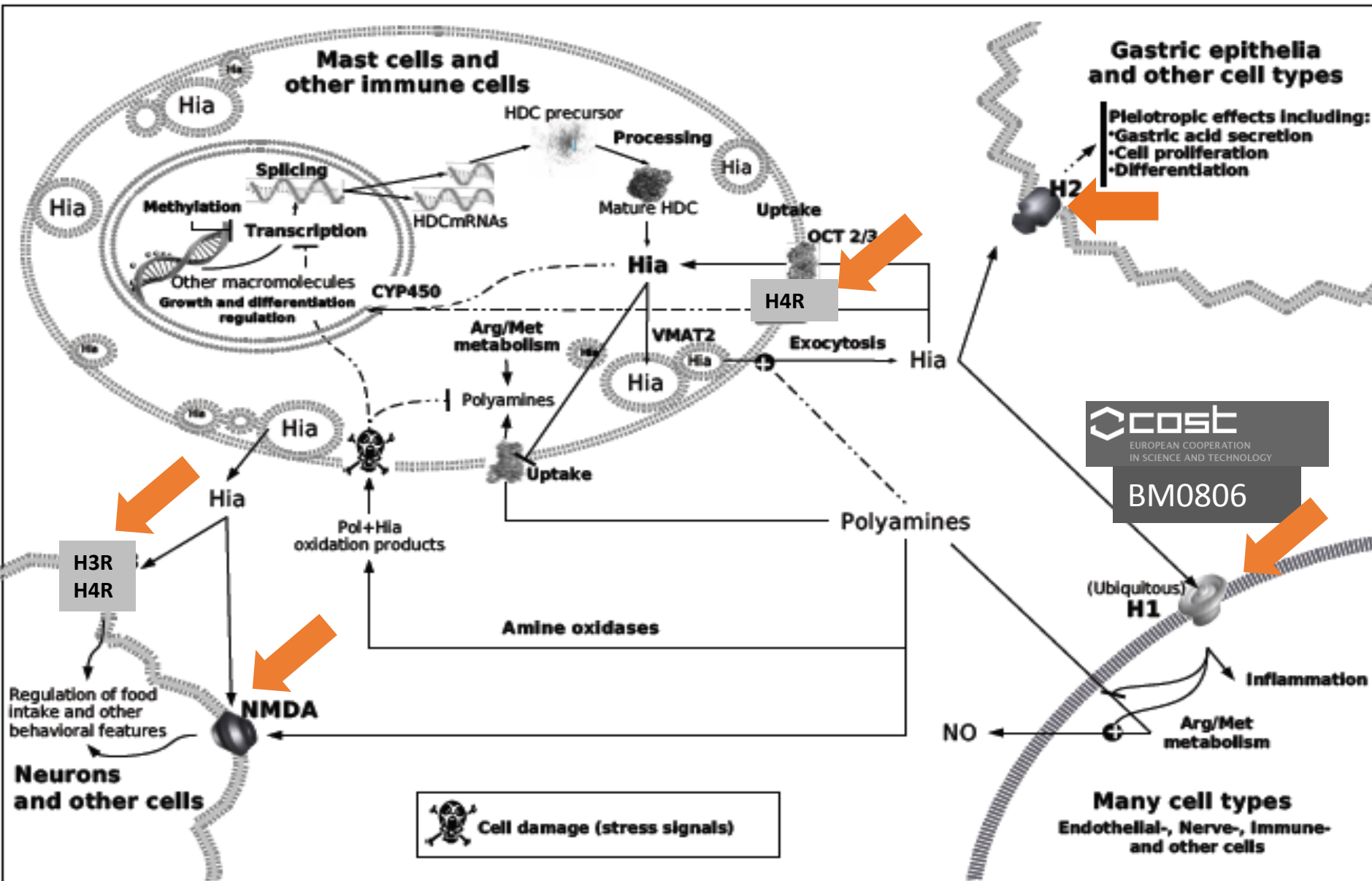


Ignatenko et al., JU. Carcinog. 2011, 10:10

HISTAMINE: THE MOST PLEITROPIC AMINE BUT ALMOST IGNORED BY HUMAN DISEASOMES

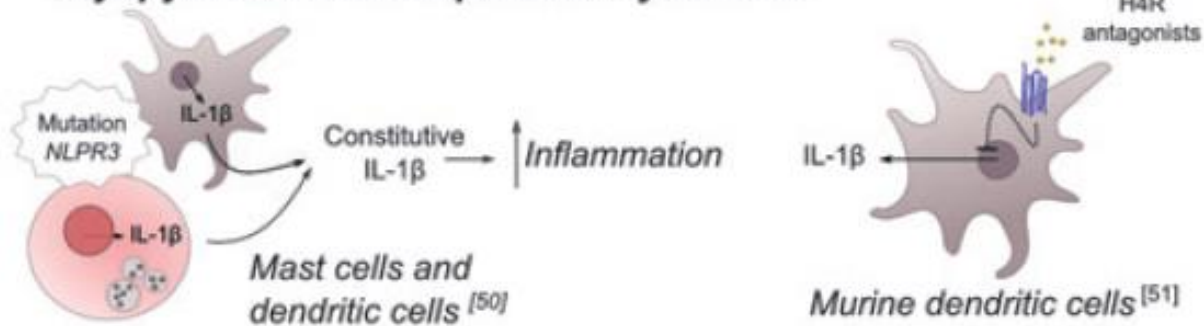


TISSUE-DEPENDENT EXPRESSION OF HISTAMINE RECEPTORS

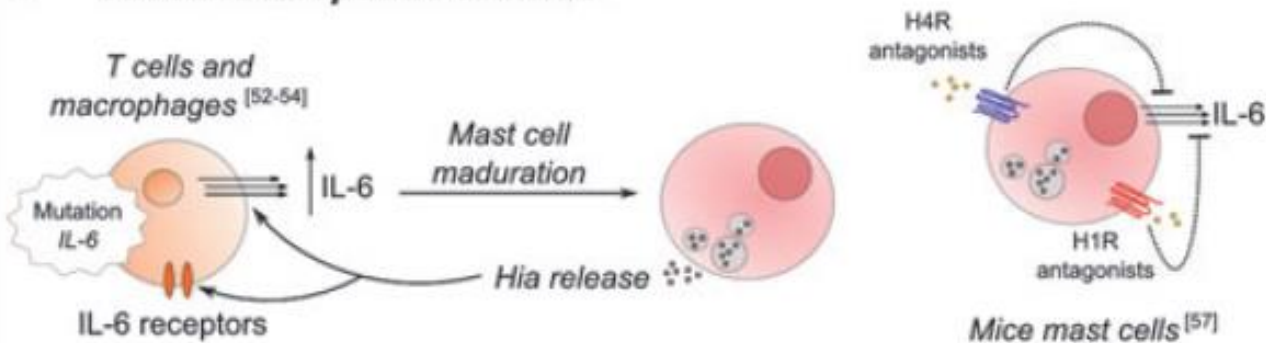


HISTAMINE AND RARE INFLAMMATORY DISEASES

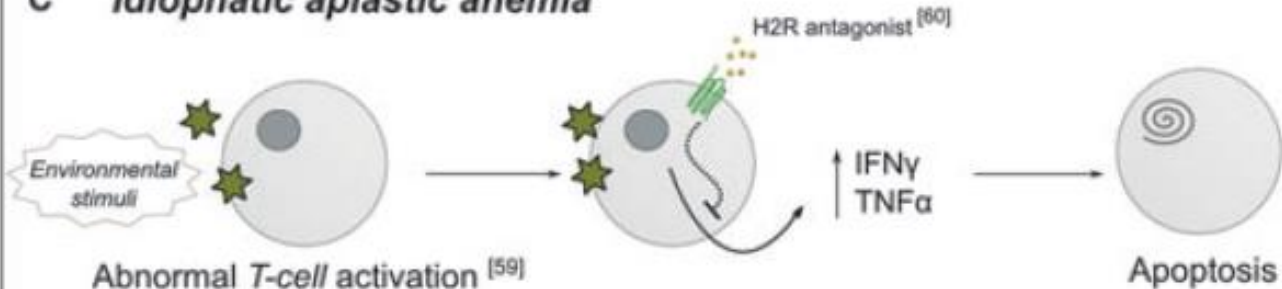
A Cryopyrin-associated periodic syndrome



B Juvenile idiopathic arthritis



C Idiopathic aplastic anemia



Pino-Ángeles et al.
J. Cell. Mol. Med. 2012,
 16: 1947-60

SciMiner

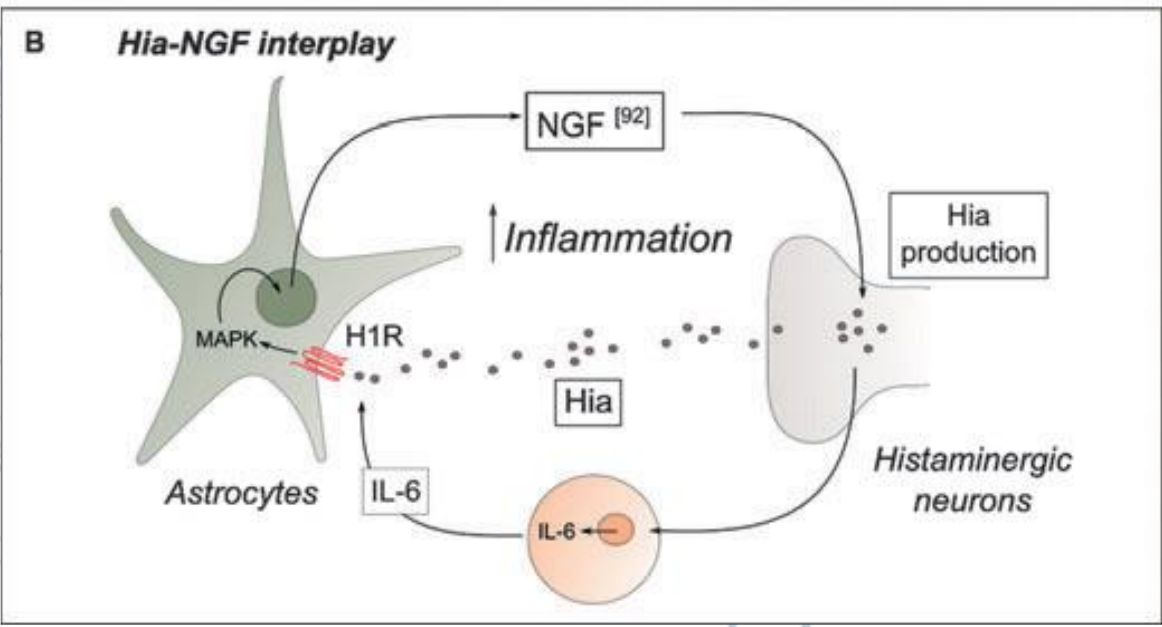
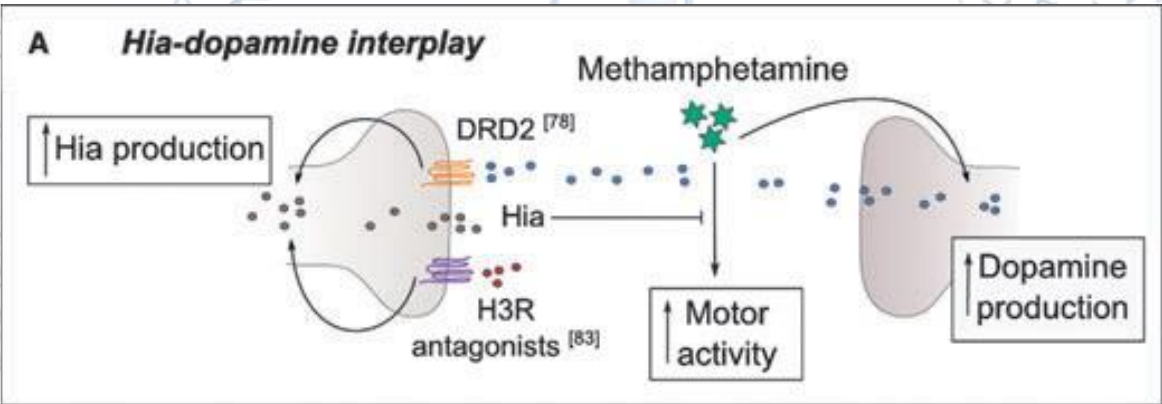
An on-line literature mining tool
 for target identification
 and functional enrichment
 analysis
<http://jdrf.neurology.med.umich.edu/SciMiner/>



Shpall, R.L., Jeffes, E.W.B., & Hoffman, H.M. A case of familial cold auto-inflammatory syndrome confirmed by the presence of a CIAS1 mutation. *British Association of Dermatologists, British Journal of Dermatology*, 2004, 150, 1028-1034.

HISTAMINE-RELATED ELEMENTS INTERACT WITH OTHER BIOGENIC AMINE-RELATED ELEMENTS AND GROWTH FACTORS IN NERVOUS SYSTEM

*Pino-Ángeles et al.
J. Cell. Mol. Med. 2012,
16: 1947-60*

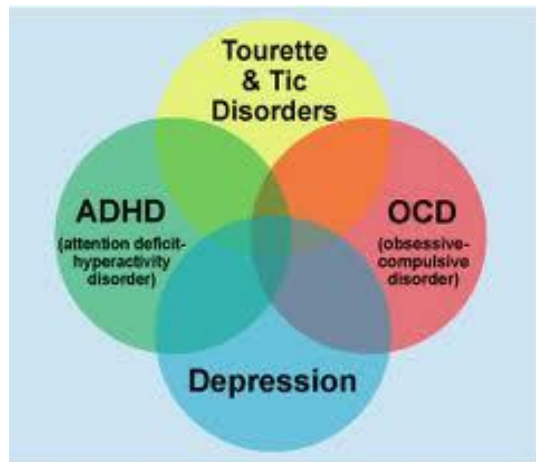


NEUROLOGICAL HISTAMINE RELATED DISEASES

DISEASE	MUTATED GENE/ORIGIN	ORPHANET ID	OMIM ID
Narcolepsy with cataplexy	HCRT	2073	161400
Tourette's syndrome	HDC, SLITRK2	856	137580
Hereditary essential tremor	DRD3, ETM2, ETM3	862	190300
Myoclonic dystonia	DRD2, SGCE	36899	159900



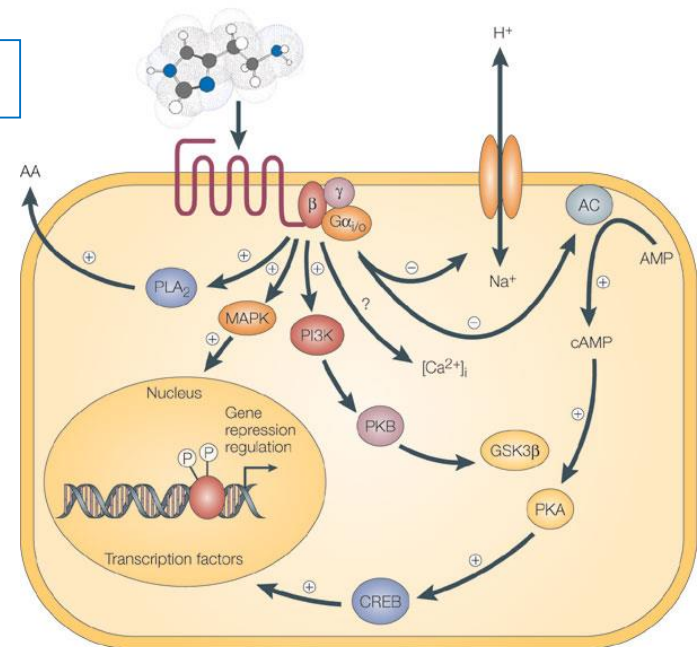
Receptor mosaic events adds unsolved complexity!



Moreno et al., J Biol Chem. 2011 Feb 18;286(7):5846-54

Wallace et al. Pharmacol. Biochem. Behav. 2011, 99: 130-45.

Ercan-Sencicek et al., 2010 N Engl. J. Med. 362: 1901-8

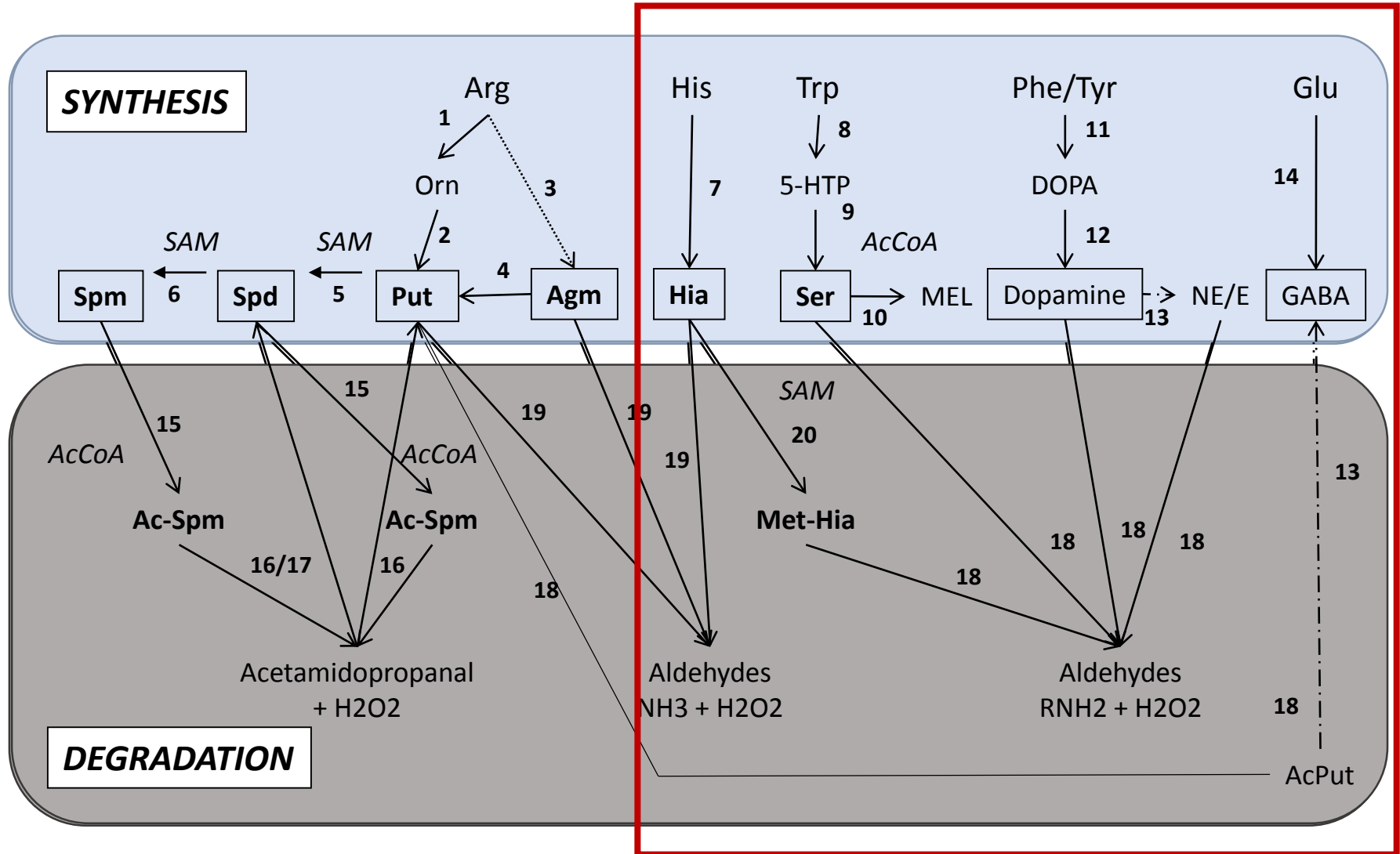


HUMAN DISEASES FOR WHICH HISTAMINE METABOLISM-RELATED ELEMENTS HAS A RELEVANT ROLE INCLUDE RARE NEOPLASIAS

Pino-Ángeles et al. J. Cell. Mol. Med. 2012, 16: 1947-60

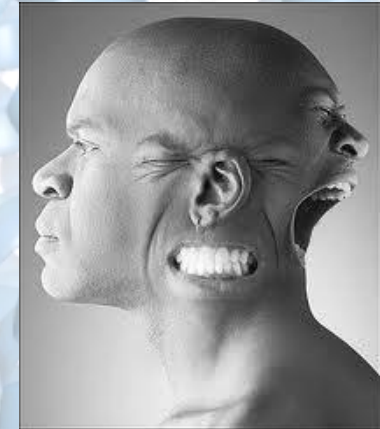
NEUROINFLAMMATORY DISEASES	MUTATED GENE(S)/ORIGIN	ORPHANET ID	OMIM ID
Myasthenia gravis	Autoimmune	589	159400*
Hereditary sensory and autonomic neuropathy, type IV	NTRK1	642	256800
Hereditary sensory and autonomic neuropathy, type V	NGFB	64752	608654
Multiple sclerosis	HLA genes on 6p21, MS2, MS3, MS4	802	126200
RARE NEOPLASIAS			
Acute myeloid leukaemia	Heterogeneous	519	252270
Zollinger-Ellison syndrome	Sporadic/associated to MEN1 mutation	913	131100
Mastocytosis	cKIT, TET2	98292	154800
OTHER DISEASES			
Vitamin D-dependent rickets type 2A	VDR	437	277440
Familial long QT syndrome	Potassium voltage-gated channels	768	152427
Brugada syndrome	Ionic voltage-gated channels	130	601144
von Willebrand disease	VWF	166078	193400
Metabolic syndrome	Heterogeneous	68367	–
Congenital adrenal hyperplasia	Heterogeneous	418	145295
Histidinaemia	HAL	2157	235800

OTHER BIOGENIC AMINES: ESSENTIAL ELEMENTS FOR OUR BEHAVIOR



NEUROLOGICAL DISORDERS ASSOCIATED TO OTHER BIOGENIC AMINE: Dopamine, Serotonin and GABA (It is not a full list)

Protein name	Gene Entrez ID	Disease/Phenotype	MIM code
Aromatic L-amino acid DC Tyr hydroxylase	DDC,1644 TH,7054	Deficiency 7p12.1 Sagawa syndrome	107930 191290
Dopamine β-oxigenase	DBH,1621	Schizophrenia, tobacco addiction, susceptibility to migraine	609312
Dopamine receptor D1	DRD1, 1812	A systolic blood pressure regulator associated to nicotine dependence and schizophrenia	126449
Dopamine receptor D2	DRD2, 1813	Myoclonic dystonia	126450
Dopamine receptor D3	DRD3, 1814	Susceptibility to essential tremor and schizophrenia	126451
Dopamine receptor D4	DRD4, 1815	Schizophrenia, Parkinson, other behavioral problems	126452
Dopamine receptor D5	DRD5, 1816	ADHD, schizophrenia, Lesch-Nyhan disease (ORPHA510)	126453
5-hydroxytryptamine (serotonin) receptor 1A	HTR1A, 3350	Menstrual cycle-dependent periodic fever, anxiety, stress. Related to risk for sudden infant death.	109760
5-hydroxytryptamine (serotonin) receptor 1B	HTR1B, 3351	Anxiety, depression, migraine	182131
5-hydroxytryptamine (serotonin) receptor 2A	HTR2A, 3356	Susceptibility to alcohol dependence, anorexia nervosa, schizophrenia, seasonal affective disorder, obsessive-compulsive disorder, major depressive disorder (response to citalopram).	182135
5-hydroxytryptamine (serotonin) receptor 2B	HTR2B, 3357	Regulator of cardiovascular functions and impulsive behavior. A polymorphism related to Alzheimer.	601122



An important part of our behavior depends on these elements

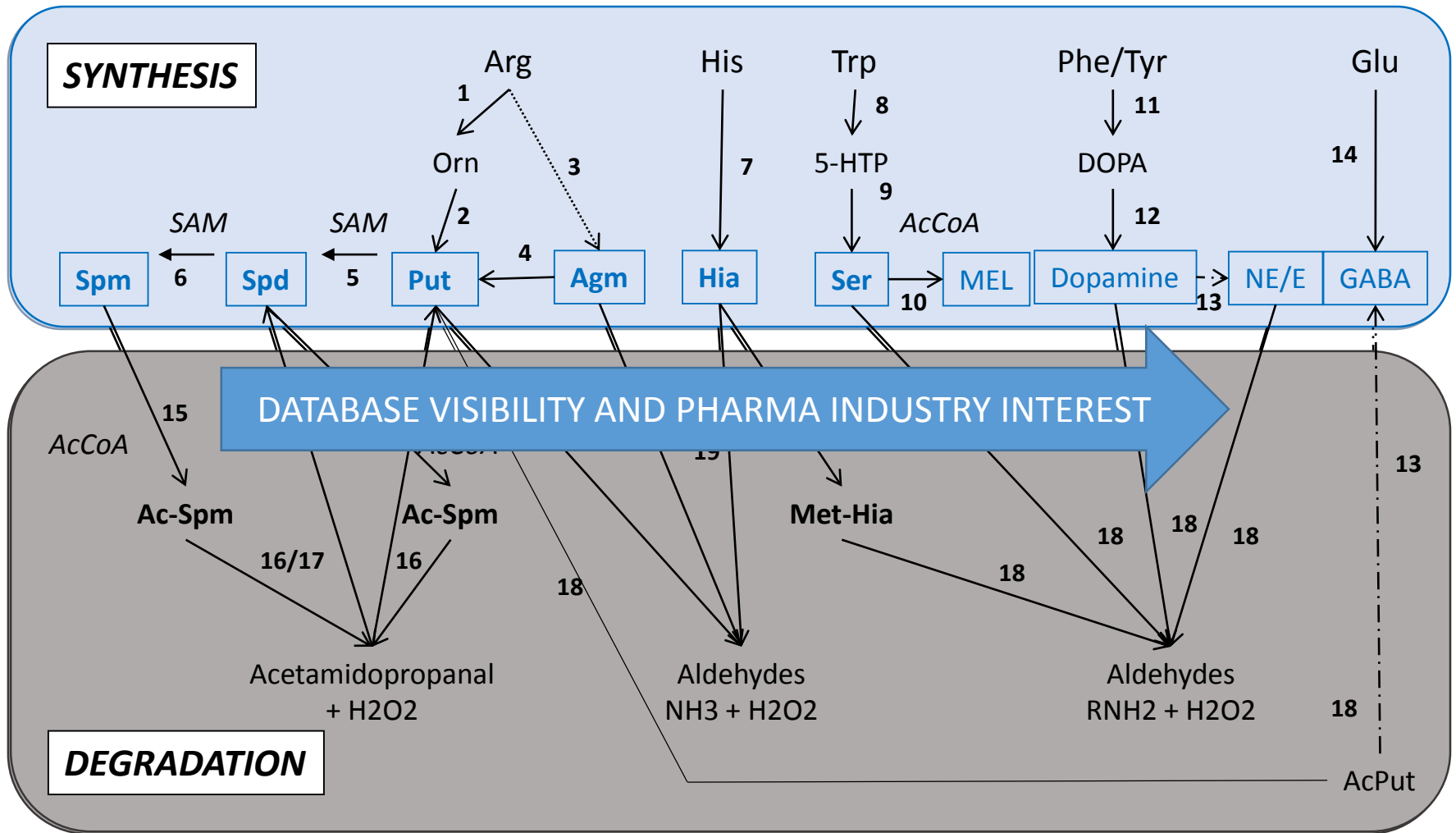
NEUROLOGICAL DISORDERS ASSOCIATED TO OTHER BIOGENIC AMINE: Dopamine, Serotonin and GABA (It is not a full list)

Protein name	Gene Entrez ID	Disease/Phenotype	MIM code
5-hydroxytryptamine (serotonin) receptor 2C	HTR2C, 3358	Related to Prader-Willi syndrome (ORPHA739), visual hallucinations, hyperphagia. A polymorphism related to Alzheimer.	312861
5-hydroxytryptamine (serotonin) receptor 4	HTR4, 3360	Bipolar disorder, schizophrenia	602164
Hydroxyindole O-methyl transferase	ASMT,438	Psychiatric disorders	402500
Glu DC 1	GAD1, 2571	Cerebral palsy, panic disorder, cortical thickness in the parahippocampal gyrus.	605363
Glu DC 2	GAD2, 2572	Autoimmune disease stiff person syndrome	138275
GABA receptor 1	GABBR1, 2550	Related to epilepsy and essential tremor and SSADH deficiency	603540
GABA receptor 2	GABBR2, 2566	Epilepsy, febrile seizures	137164
GABA receptor 3	GABBR3, 2556	A target for treatment of chronic pain	305660

In this cases there are much more information in data bases and more interest by pharma companies

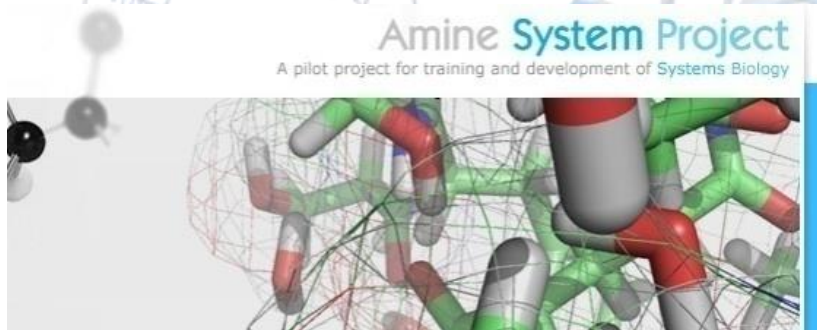


METABOLIC CROSSTALK & FUNCTIONAL CROSSTALK BUT...



It do not make much sense in terms of Biomedicine!!!

CHANGELLES FOR SYSTEMS MEDINE IN THE BIOGENIC AMINE FIELD

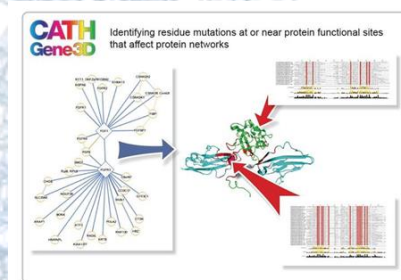


A PROPOSAL FOR A CONSENSUS AND INTERACTIVE AMINE METABOLISM DATABASE

Kuopio, June 26-30, 2008

- Enrichment of databases in functional and phenotypic data concerning BA-related elements.
- Enrichment of databases in genetic variants of BA-related genes and metabolic data coming from HTP projects and their correlations with patient phenotypes.
- Enrichment of basic knowledge on specific amine-target and amine analog-target interactions.
- Of course, systematic organization of BA-related information.

TEAM AND SUPPORT



SABIO-RK
Biochemical Reaction Kinetics Database





44th EHRS Annual Meeting
Hotel Amaragua
Torremolinos (Málaga)
May 6-9 2015



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